

## 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery

### A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

*Developed in Collaboration With the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons*

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## Preamble

The medical profession should play a central role in evaluating the evidence related to drugs, devices, and procedures for the detection, management, and prevention of disease. When properly applied, expert analysis of available data on the benefits and risks of these therapies and procedures can improve the quality of care, optimize patient outcomes, and favorably affect costs by focusing resources on the most effective strategies. An organized and directed approach to a thorough review of evidence has resulted in the production of clinical practice guidelines that assist physicians in selecting the best management strategy for an individual patient. Moreover, clinical practice guidelines can provide a foundation for other applications, such as performance measures, appropriate use criteria, and both quality improvement and clinical decision support tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly produced guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force), charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, directs and oversees this effort. Writing committees are charged with regularly reviewing and evaluating all available evidence to develop balanced, patientcentric recommendations for clinical practice.

Experts in the subject under consideration are selected by the ACCF and AHA to examine subject-specific data and write guidelines in partnership with representatives from other medical organizations and specialty groups. Writing committees are asked to perform a formal literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected outcomes where such data exist. Patient-specific modifiers,

Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT												
		CLASS I <i>Benefit &gt;&gt;&gt; Risk</i> Procedure/Treatment <b>SHOULD</b> be performed/ administered	CLASS IIa <i>Benefit &gt;&gt; Risk</i> Additional studies with <i>focused objectives needed</i> <b>IT IS REASONABLE</b> to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed</i> ; additional registry data would be <i>helpful</i>  Procedure/Treatment <b>MAY BE CONSIDERED</b>	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i> <table><tr><th></th><th>Procedure/ Test</th><th>Treatment</th></tr><tr><td>COR III: No benefit</td><td>Not Helpful</td><td>No Proven Benefit</td></tr><tr><td>COR III: Harm</td><td>Excess Cost w/o Benefit or Harmful</td><td>Harmful to Patients</td></tr></table>		Procedure/ Test	Treatment	COR III: No benefit	Not Helpful	No Proven Benefit	COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients
	Procedure/ Test	Treatment												
COR III: No benefit	Not Helpful	No Proven Benefit												
COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients												
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated*  Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is useful/effective</li><li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation in favor of treatment or procedure being useful/effective</li><li>■ Some conflicting evidence from multiple randomized trials or meta-analyses</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation's usefulness/efficacy less well established</li><li>■ Greater conflicting evidence from multiple randomized trials or meta-analyses</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li><li>■ Sufficient evidence from multiple randomized trials or meta-analyses</li></ul>									
	LEVEL B Limited populations evaluated*  Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is useful/effective</li><li>■ Evidence from single randomized trial or nonrandomized studies</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation in favor of treatment or procedure being useful/effective</li><li>■ Some conflicting evidence from single randomized trial or nonrandomized studies</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation's usefulness/efficacy less well established</li><li>■ Greater conflicting evidence from single randomized trial or nonrandomized studies</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li><li>■ Evidence from single randomized trial or nonrandomized studies</li></ul>									
	LEVEL C Very limited populations evaluated*  Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is useful/effective</li><li>■ Only expert opinion, case studies, or standard of care</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation in favor of treatment or procedure being useful/effective</li><li>■ Only diverging expert opinion, case studies, or standard of care</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation's usefulness/efficacy less well established</li><li>■ Only diverging expert opinion, case studies, or standard of care</li></ul>	<ul style="list-style-type: none"><li>■ Recommendation that procedure or treatment is not useful/effective and may be harmful</li><li>■ Only expert opinion, case studies, or standard of care</li></ul>									
Suggested phrases for writing recommendations		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit  is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective	COR III: Harm  potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other								
Comparative effectiveness phrases†		treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B											

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

\*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and outcomes constitute the primary basis for the recommendations contained herein.

In analyzing the data and developing recommendations and supporting text, the writing committee uses evidence-based methodologies developed by the Task Force.<sup>1</sup> The Class of Recommendation (COR) is an estimate of the size of the treatment effect considering risks versus benefits in addition to evidence and/or agreement that a given treatment or procedure is or is not useful/effective or in some situations may cause harm. The Level of Evidence (LOE) is an estimate of the certainty or precision of the treatment effect. The

writing committee reviews and ranks evidence supporting each recommendation with the weight of evidence ranked as LOE A, B, or C according to specific definitions that are included in Table 1. Studies are identified as observational, retrospective, prospective, or randomized where appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and are ranked as LOE C. When recommendations at LOE C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues for which sparse data are available, a survey of current practice among the clinicians on the writing committee is the basis for LOE C recommendations, and no references are cited. The schema for COR and LOE is summarized in Table



1, which also provides suggested phrases for writing recommendations within each COR. A new addition to this methodology is separation of the Class III recommendations to delineate if the recommendation is determined to be of “no benefit” or is associated with “harm” to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment or strategy versus another have been added for COR I and IIa, LOE A or B only.

In view of the advances in medical therapy across the spectrum of cardiovascular diseases, the Task Force has designated the term *guideline-directed medical therapy (GDMT)* to represent optimal medical therapy as defined by ACCF/AHA guideline–recommended therapies (primarily Class I). This new term, GDMT, will be used herein and throughout all future guidelines.

Because the ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America, drugs that are not currently available in North America are discussed in the text without a specific COR. For studies performed in large numbers of subjects outside North America, each writing committee reviews the potential influence of different practice patterns and patient populations on the treatment effect and relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding the care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. As a result, situations may arise for which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient’s active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, where the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the writing committee. All writing committee

members and peer reviewers of the guideline are required to disclose all such current relationships, as well as those existing 12 months previously. In December 2009, the ACCF and AHA implemented a new policy for relationships with industry and other entities (RWI) that requires the writing committee chair plus a minimum of 50% of the writing committee to have no relevant RWI (Appendix 1 for the ACCF/AHA definition of relevance). These statements are reviewed by the Task Force and all members during each conference call and meeting of the writing committee and are updated as changes occur. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the voting members. Members are not permitted to write, and must recuse themselves from voting on, any recommendation or section to which their RWI apply. Members who recused themselves from voting are indicated in the list of writing committee members, and section recusals are noted in Appendix 1. Authors’ and peer reviewers’ RWI pertinent to this guideline are disclosed in Appendixes 1 and 2, respectively. Additionally, to ensure complete transparency, writing committee members’ comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement. Comprehensive disclosure information for the Task Force is also available online at [www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx](http://www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx). The work of the writing committee was supported exclusively by the ACCF and AHA without commercial support. Writing committee members volunteered their time for this activity.

In an effort to maintain relevance at the point of care for practicing physicians, the Task Force continues to oversee an ongoing process improvement initiative. As a result, in response to pilot projects, evidence tables (with references linked to abstracts in PubMed) have been added.

In April 2011, the Institute of Medicine released 2 reports: *Finding What Works in Health Care: Standards for Systematic Reviews* and *Clinical Practice Guidelines We Can Trust*.<sup>2,3</sup> It is noteworthy that the ACCF/AHA guidelines are cited as being compliant with many of the proposed standards. A thorough review of these reports and of our current methodology is under way, with further enhancements anticipated.

The recommendations in this guideline are considered current until they are superseded by a focused update or the full-text guideline is revised. Guidelines are official policy of both the ACCF and AHA.

Alice K. Jacobs, MD, FACC, FAHA  
Chair ACCF/AHA Task Force on Practice Guidelines

## 1. Introduction

### 1.1. Methodology and Evidence Review

Whenever possible, the recommendations listed in this document are evidence based. Articles reviewed in this guideline revision covered evidence from the past 10 years through January 2011, as well as selected other references through April 2011. Searches were limited to studies, reviews, and other evidence conducted in human subjects that were published in English. Key search words included but were not limited to the following: *analgesia*, *anastomotic techniques*, *antiplatelet*

agents, automated proximal clampless anastomosis device, asymptomatic ischemia, Cardica C-port, cost effectiveness, depressed left ventricular (LV) function, distal anastomotic techniques, direct proximal anastomosis on aorta, distal anastomotic devices, emergency coronary artery bypass graft (CABG) and ST-elevation myocardial infarction (STEMI), heart failure, interrupted sutures, LV systolic dysfunction, magnetic connectors, PAS-Port automated proximal clampless anastomotic device, patency, proximal connectors, renal disease, sequential anastomosis, sternotomy, symmetry connector, symptomatic ischemia, proximal connectors, sequential anastomosis, T grafts, thoracotomy, U-clips, Ventrica Magnetic Vascular Port system, Y grafts. Additionally, the committee reviewed documents related to the subject matter previously published by the ACCF and AHA. References selected and published in this document are representative but not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published, the absolute risk difference and number needed to treat or harm are provided in the guideline, along with confidence interval (CI) and data related to the relative treatment effects such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or incidence rate ratio.

The focus of these guidelines is the safe, appropriate, and efficacious performance of CABG.

## 1.2. Organization of the Writing Committee

The committee was composed of acknowledged experts in CABG, interventional cardiology, general cardiology, and cardiovascular anesthesiology. The committee included representatives from the ACCF, AHA, American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons (STS).

## 1.3. Document Review and Approval

This document was reviewed by 2 official reviewers, each nominated by both the ACCF and the AHA, as well as 1 reviewer each from the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and STS, as well as members from the ACCF/AHA Task Force on Data Standards, ACCF/AHA Task Force on Performance Measures, ACCF Surgeons' Scientific Council, ACCF Interventional Scientific Council, and Southern Thoracic Surgical Association. All information on reviewers' RWI was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACCF and the AHA and endorsed by the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and STS.

## 2. Procedural Considerations

### 2.1. Intraoperative Considerations

#### 2.1.1. Anesthetic Considerations: Recommendations

##### Class I

1. Anesthetic management directed toward early postoperative extubation and accelerated recovery of low- to medium-risk patients undergoing uncomplicated CABG is recommended.<sup>4–6</sup> (Level of Evidence: B)

2. Multidisciplinary efforts are indicated to ensure an optimal level of analgesia and patient comfort throughout the perioperative period.<sup>7–11</sup> (Level of Evidence: B)
3. Efforts are recommended to improve interdisciplinary communication and patient safety in the perioperative environment (eg, formalized checklist-guided multidisciplinary communication).<sup>12–15</sup> (Level of Evidence: B)
4. A fellowship-trained cardiac anesthesiologist (or experienced board-certified practitioner) credentialed in the use of perioperative transesophageal echocardiography (TEE) is recommended to provide or supervise anesthetic care of patients who are considered to be at high risk.<sup>16–18</sup> (Level of Evidence: C)

##### Class IIa

1. Volatile anesthetic-based regimens can be useful in facilitating early extubation and reducing patient recall.<sup>5,19–21</sup> (Level of Evidence: A)

##### Class IIb

1. The effectiveness of high thoracic epidural anesthesia/analgesia for routine analgesic use is uncertain.<sup>22–25</sup> (Level of Evidence: B)

##### Class III: HARM

1. Cyclooxygenase-2 inhibitors are not recommended for pain relief in the postoperative period after CABG.<sup>26,27</sup> (Level of Evidence: B)
2. Routine use of early extubation strategies in facilities with limited backup for airway emergencies or advanced respiratory support is potentially harmful. (Level of Evidence: C)

See Online Data Supplement 1 for additional data on anesthetic considerations.

Anesthetic management of the CABG patient mandates a favorable balance of myocardial oxygen supply and demand to prevent or minimize myocardial injury (Section 2.1.8). Historically, the popularity of several anesthetic techniques for CABG has varied on the basis of their known or potential adverse cardiovascular effects (eg, cardiovascular depression with high doses of volatile anesthesia, lack of such depression with high-dose opioids, or coronary vasodilation and concern for a “steal” phenomenon with isoflurane) as well as concerns about interactions with preoperative medications (eg, cardiovascular depression with beta blockers or hypotension with angiotensin-converting enzyme [ACE] inhibitors and angiotensin-receptor blockers [ARBs]<sup>28–30</sup>) (Sections 2.1.8 and 4.5). Independent of these concerns, efforts to improve outcomes and to reduce costs have led to shorter periods of postoperative mechanical ventilation and even, in some patients, to prompt extubation in the operating room (“accelerated recovery protocols” or “fast-track management”).<sup>5,31</sup>

High-dose opioid anesthesia with benzodiazepine supplementation was used commonly in CABG patients in the United States in the 1970s and 1980s. Subsequently, it became clear that volatile anesthetics are protective in the setting of myocardial ischemia and reperfusion, and this, in

combination with a shift to accelerated recovery or “fast-track” strategies, led to their ubiquitous use. As a result, opioids have been relegated to an adjuvant role.<sup>32,33</sup> Despite their widespread use, volatile anesthetics have not been shown to provide a mortality rate advantage when compared with other intravenous regimens (Section 2.1.8).

Optimal anesthesia care in CABG patients should include 1) a careful preoperative evaluation and treatment of modifiable risk factors; 2) proper handling of all medications given preoperatively (Sections 4.1, 4.3, and 4.5); 3) establishment of central venous access and careful cardiovascular monitoring; 4) induction of a state of unconsciousness, analgesia, and immobility; and 5) a smooth transition to the early postoperative period, with a goal of early extubation, patient mobilization, and hospital discharge. Attention should be directed at preventing or minimizing adverse hemodynamic and hormonal alterations that may induce myocardial ischemia or exert a deleterious effect on myocardial metabolism (as may occur during cardiopulmonary bypass [CPB]) (Section 2.1.8). This requires close interaction between the anesthesiologist and surgeon, particularly when manipulation of the heart or great vessels is likely to induce hemodynamic instability. During on-pump CABG, particular care is required during vascular cannulation and weaning from CPB; with off-pump CABG, the hemodynamic alterations often caused by displacement or verticalization of the heart and application of stabilizer devices on the epicardium, with resultant changes in heart rate, cardiac output, and systemic vascular resistance, should be monitored carefully and managed appropriately.

In the United States, nearly all patients undergoing CABG receive general anesthesia with endotracheal intubation utilizing volatile halogenated general anesthetics with opioid supplementation. Intravenous benzodiazepines often are given as premedication or for induction of anesthesia, along with other agents such as propofol or etomidate. Nondepolarizing neuromuscular-blocking agents, particularly nonvagolytic agents with intermediate duration of action, are preferred to the longer-acting agent, pancuronium. Use of the latter is associated with higher intraoperative heart rates and a higher incidence of residual neuromuscular depression in the early postoperative period, with a resultant delay in extubation.<sup>23,34</sup> In addition, low concentrations of volatile anesthetic usually are administered via the venous oxygenator during CPB, facilitating amnesia and reducing systemic vascular resistance.

Outside the United States, alternative anesthetic techniques, particularly total intravenous anesthesia via propofol and opioid infusions with benzodiazepine supplementation with or without high thoracic epidural anesthesia, are commonly used. The use of high thoracic epidural anesthesia exerts salutary effects on the coronary circulation as well as myocardial and pulmonary function, attenuates the stress response, and provides prolonged postoperative analgesia.<sup>24,25,35</sup> In the United States, however, concerns about the potential for neuraxial bleeding (particularly in the setting of heparinization, platelet inhibitors, and CPB-induced thrombocytopenia), local anesthetic toxicity, and logistical issues related to the timing of epidural catheter insertion and management have resulted in limited use of these tech-

niques.<sup>22</sup> Their selective use in patients with severe pulmonary dysfunction (Section 6.5) or chronic pain syndromes may be considered. Although meta-analyses of randomized controlled trials (RCTs) of high thoracic epidural anesthesia/analgesia in CABG patients (particularly on-pump) have yielded inconsistent results on morbidity and mortality rates, it does appear to reduce time to extubation, pain, and pulmonary complications.<sup>36–38</sup> Of interest, although none of the RCTs have reported the occurrence of epidural hematoma or abscess, these entities occur on occasion.<sup>38</sup> Finally, the use of other regional anesthetic approaches for postoperative analgesia, such as parasternal block, has been reported.<sup>39</sup>

Over the past decade, early extubation strategies (“fast-track” anesthesia) often have been used in low- to medium-risk CABG patients. These strategies allow a shorter time to extubation, a decreased length of intensive care unit (ICU) stay, and variable effects on length of hospital stay.<sup>4–6</sup> Immediate extubation in the operating room, with or without markedly accelerated postoperative recovery pathways (eg, “ultra-fast-tracking,” “rapid recovery protocol,” “short-stay intensive care”) have been used safely, with low rates of reintubation and no influence on quality of life.<sup>40–44</sup> Observational data suggest that physician judgment in triaging lower-risk patients to early or immediate extubation works well, with rates of reintubation <1%.<sup>45</sup> Certain factors appear to predict fast-track “failure,” including previous cardiac surgery, use of intra-aortic balloon counterpulsation, and possibly advanced patient age.

Provision of adequate perioperative analgesia is important in enhancing patient mobilization, preventing pulmonary complications, and improving the patient’s psychological well-being.<sup>9,11</sup> The intraoperative use of high-dose morphine (40 mg) may offer superior postoperative pain relief and enhance patient well-being compared with fentanyl (despite similar times to extubation).<sup>46</sup>

The safety of nonsteroidal anti-inflammatory agents for analgesia is controversial, with greater evidence for adverse cardiovascular events with the selective cyclooxygenase-2 inhibitors than the nonselective agents. A 2007 AHA Scientific statement presented a stepped-care approach to the management of musculoskeletal pain in patients with or at risk for coronary artery disease (CAD), with the goal of limiting the use of these agents to patients in whom safer therapies fail.<sup>47</sup> In patients hospitalized with unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI), these agents should be discontinued promptly and reinstituted later according to the stepped-care approach.<sup>48</sup>

In the setting of cardiac surgery, nonsteroidal anti-inflammatory agents previously were used for perioperative analgesia. A meta-analysis of 20 trials of patients undergoing thoracic or cardiac surgery, which evaluated studies published before 2005, reported significant reductions in pain scores, with no increase in adverse outcomes.<sup>49</sup> Subsequently, 2 RCTs, both studying the oral cyclooxygenase-2 inhibitor valdecoxib and its intravenous prodrug, parecoxib, reported a higher incidence of sternal infections in 1 trial and a significant increase in adverse cardiovascular events in the other.<sup>26,27</sup> On the basis of the results of these 2 studies (as well as other nonsurgical reports of increased risk with cyclooxygenase-2-selective agents), the U.S.



Food and Drug Administration in 2005 issued a “black box” warning for all nonsteroidal anti-inflammatory agents (except aspirin) immediately after CABG.<sup>50</sup> The concurrent administration of ibuprofen with aspirin has been shown to attenuate the latter’s inhibition of platelet aggregation, likely because of competitive inhibition of cyclooxygenase at the platelet-receptor binding site.<sup>51</sup>

Observational analyses in patients undergoing noncardiac surgery have shown a significant reduction in perioperative death with the use of checklists, multidisciplinary surgical care, intraoperative time-outs, postsurgical debriefings, and other communication strategies.<sup>14,15</sup> Such methodology is being used increasingly in CABG patients.<sup>12–14</sup>

In contrast to extensive literature on the role of the surgeon in determining outcomes with CABG, limited data on the influence of the anesthesiologist are available. Of 2 such reports from single centers in the 1980s, 1 suggested that the failure to control heart rate to  $\leq 110$  beats per minute was associated with a higher mortality rate, and the other suggested that increasing duration of CPB adversely influenced outcome.<sup>52,53</sup> Another observational analysis of data from vascular surgery patients suggested that anesthetic specialization was independently associated with a reduction in mortality rate.<sup>54</sup>

To meet the challenges of providing care for the increasingly higher-risk patients undergoing CABG, efforts have been directed at enhancing the experience of trainees, particularly in the use of newer technologies such as TEE. Cardiac anesthesiologists, in collaboration with cardiologists and surgeons, have implemented national training and certification processes for practitioners in the use of perioperative TEE (Section 2.1.7).<sup>164,165</sup> Accreditation of cardiothoracic anesthesia fellowship programs from the Accreditation Council for Graduate Medical Education was initiated in 2004, and efforts are ongoing to obtain formal subspecialty certification.<sup>18</sup>

### 2.1.2. Use of CPB

Several adverse outcomes have been attributed to CPB, including 1) neurological deficits (eg, stroke, coma, postoperative neurocognitive dysfunction); 2) renal dysfunction; and 3) the Systemic Inflammatory Response Syndrome (SIRS). The SIRS is manifested as generalized systemic inflammation occurring after a major morbid event, such as trauma, infection, or major surgery. It is often particularly apparent after on-pump cardiac surgery, during which surgical trauma, contact of blood with nonphysiological surfaces (eg, pump tubing, oxygenator surfaces), myocardial ischemia and reperfusion, and hypothermia combine to cause a dramatic release of cytokines (eg, interleukin [IL] 6 and IL8) and other mediators of inflammation.<sup>55</sup> Some investigators have used serum concentrations of S100 beta as a marker of brain injury<sup>56</sup> and have correlated increased serum levels with the number of microemboli exiting the CPB circuit during CABG. In contrast, others have noted the increased incidence of microemboli with on-pump CABG (relative to off-pump CABG) but have failed to show a corresponding worsening of neurocognitive function 1 week to 6 months postoperatively.<sup>57,58</sup> Blood retrieved from the operative field during on-pump CABG contains lipid material and particulate matter, which have been implicated as possible causes of post-

operative neurocognitive dysfunction. Although a study<sup>59</sup> reported that CPB-associated neurocognitive dysfunction can be mitigated by the routine processing of shed blood with a cell saver before its reinfusion, another study<sup>60</sup> failed to show such an improvement.

It has been suggested that CPB leads to an increased incidence of postoperative renal failure requiring dialysis, but a large RCT comparing on-pump and off-pump CABG showed no difference in its occurrence.<sup>61</sup> Of interest, this study failed to show a decreased incidence of postoperative adverse neurological events (stroke, coma, or neurocognitive deficit) in those undergoing off-pump CABG.

The occurrence of SIRS in patients undergoing CPB has led to the development of strategies designed to prevent or to minimize its occurrence. Many reports have focused on the increased serum concentrations of cytokines (eg, IL-2R, IL-6, IL-8, tumor necrosis factor alpha) and other modulators of inflammation (eg, P-selectin, sE-selectin, soluble intercellular adhesion molecule-1, plasma endothelial cell adhesion molecule-1, and plasma malondialdehyde), which reflect leukocyte and platelet activation, in triggering the onset of SIRS. A study showed a greater upregulation of neutrophil CD11b expression (a marker of leukocyte activation) in patients who sustained a  $\geq 50\%$  increase in the serum creatinine concentration after CPB, thereby implicating activated neutrophils in the pathophysiology of SIRS and the occurrence of post-CPB renal dysfunction.<sup>62</sup> Modulating neutrophil activation to reduce the occurrence of SIRS has been investigated; however, the results have been inconsistent. Preoperative intravenous methylprednisolone (10 mg/kg) caused a reduction in the serum concentrations of many of these cytokines after CPB, but this reduction was not associated with improved hemodynamic variables, diminished blood loss, less use of inotropic agents, shorter duration of ventilation, or shorter ICU length of stay.<sup>63</sup> Similarly, the use of intravenous immunoglobulin G in patients with post-CPB SIRS has not been associated with decreased rates of short-term morbidity or 28-day mortality.<sup>64</sup>

Other strategies to mitigate the occurrence of SIRS after CPB have been evaluated, including the use of 1) CPB circuits (including oxygenators) coated with materials known to reduce complement and leukocyte activation; 2) CPB tubing that is covalently bonded to heparin; and 3) CPB tubing coated with polyethylene oxide polymer or Poly (2-methoxyethylacrylate). Leukocyte depletion via specialized filters in the CPB circuits has been shown to reduce the plasma concentrations of P-selectin, intercellular adhesion molecule-1, IL-8, plasma endothelial cell adhesion molecule-1, and plasma malondialdehyde after CPB.<sup>65</sup>

Finally, closed mini-circuits for CPB have been developed in an attempt to minimize the blood–air interface and blood contact with nonbiological surfaces, both of which promote cytokine elaboration, but it is uncertain if these maneuvers and techniques have a discernible effect on outcomes after CABG.

### 2.1.3. Off-Pump CABG Versus Traditional On-Pump CABG

Since the first CABG was performed in the late 1960s, the standard surgical approach has included the use of cardiac arrest coupled with CPB (so-called on-pump CABG), thereby



optimizing the conditions for construction of vascular anastomoses to all diseased coronary arteries without cardiac motion or hemodynamic compromise. Such on-pump CABG has become the gold standard and is performed in about 80% of subjects undergoing the procedure in the United States. Despite the excellent results that have been achieved, the use of CPB and the associated manipulation of the ascending aorta are linked with certain perioperative complications, including myonecrosis during aortic occlusion, cerebrovascular accidents, generalized neurocognitive dysfunction, renal dysfunction, and SIRS. In an effort to avoid these complications, off-pump CABG was developed.<sup>58,66</sup> Off-pump CABG is performed on the beating heart with the use of stabilizing devices (which minimize cardiac motion); in addition, it incorporates techniques to minimize myocardial ischemia and systemic hemodynamic compromise. As a result, the need for CPB is obviated. This technique does not necessarily decrease the need for manipulation of the ascending aorta during construction of the proximal anastomoses.

To date, the results of several RCTs comparing on-pump and off-pump CABG in various patient populations have been published.<sup>61,67,68</sup> In addition, registry data and the results of meta-analyses have been used to assess the relative efficacies of the 2 techniques.<sup>69,70</sup> In 2005, an AHA Scientific statement comparing the 2 techniques concluded that both procedures usually result in excellent outcomes and that neither technique should be considered superior to the other.<sup>71</sup> At the same time, several differences were noted. Off-pump CABG was associated with less bleeding, less renal dysfunction, a shorter length of hospital stay, and less neurocognitive dysfunction. The incidence of perioperative stroke was similar with the 2 techniques. On-pump CABG was noted to be less technically complex and allowed better access to diseased coronary arteries in certain anatomic locations (eg, those on the lateral LV wall) as well as better long-term graft patency.

In 2009, the results of the largest RCT to date comparing on-pump CABG to off-pump CABG, the ROOBY (Randomized On/Off Bypass) trial, were published, reporting the outcomes for 2203 patients (99% men) at 18 Veterans Affairs Medical Centers.<sup>61</sup> The primary short-term endpoint, a composite of death or complications (reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure) within 30 days of surgery, occurred with similar frequency (5.6% for on-pump CABG; 7.0% for off-pump CABG;  $P=0.19$ ). The primary long-term endpoint, a composite of death from any cause, a repeat revascularization procedure, or a nonfatal myocardial infarction (MI) within 1 year of surgery, occurred more often in those undergoing off-pump CABG (9.9%) than in those having on-pump CABG (7.4%;  $P=0.04$ ). Neuropsychological outcomes and resource utilization were similar between the 2 groups. One year after surgery, graft patency was higher in the on-pump group (87.8% versus 82.6%;  $P<0.01$ ). In short, the ROOBY investigators failed to show an advantage of off-pump CABG compared with on-pump CABG in a patient population considered to be at low risk. Instead, use of the on-pump technique was associated with better 1-year composite outcomes and 1-year graft patency rates, with no difference in neuropsychological outcomes or resource utilization.

Although numerous investigators have used single-center registries, the STS database, and meta-analyses in an attempt to identify patient subgroups in whom off-pump CABG is the preferred procedure, even these analyses have reached inconsistent conclusions about off-pump CABG's ability to reduce morbidity and mortality rates.<sup>69,72–83</sup> A retrospective cohort study of 14 766 consecutive patients undergoing isolated CABG identified a mortality benefit (OR: 0.45) for off-pump CABG in patients with a predicted risk of mortality  $>2.5\%$ ,<sup>82</sup> but a subsequent randomized comparison of off-pump CABG to traditional on-pump CABG in 341 high-risk patients (a Euroscore  $>5$ ) showed no difference in the composite endpoint of all-cause death, acute MI, stroke, or a required reintervention procedure.<sup>78</sup> An analysis of data from the New York State Cardiac Surgery Reporting system did not demonstrate a reduction in mortality rate with off-pump CABG in any patient subgroup, including the elderly (age  $>80$  years) or those with cerebrovascular disease, azotemia, or an extensively calcified ascending aorta.<sup>69</sup>

Despite these results, off-pump CABG is the preferred approach by some surgeons who have extensive experience with it and therefore are comfortable with its technical nuances. Recently, published data suggested that the avoidance of aortic manipulation is the most important factor in reducing the risk of neurological complications.<sup>84,85</sup> Patients with extensive disease of the ascending aorta pose a special challenge for on-pump CABG; for these patients, cannulation or cross-clamping of the aorta may create an unacceptably high risk of stroke. In such individuals, off-pump CABG in conjunction with avoidance of manipulation of the ascending aorta (including placement of proximal anastomoses) may be beneficial. Surgeons typically prefer an on-pump strategy in patients with hemodynamic compromise because CPB offers support for the systemic circulation. In the end, most surgeons consider either approach to be reasonable for the majority of subjects undergoing CABG.

#### 2.1.4. Bypass Graft Conduit: Recommendations

##### Class I

1. If possible, the left internal mammary artery (LIMA) should be used to bypass the left anterior descending (LAD) artery when bypass of the LAD artery is indicated.<sup>86–89</sup> (*Level of Evidence: B*)

##### Class IIa

1. The right internal mammary artery (IMA) is probably indicated to bypass the LAD artery when the LIMA is unavailable or unsuitable as a bypass conduit. (*Level of Evidence: C*)
2. When anatomically and clinically suitable, use of a second IMA to graft the left circumflex or right coronary artery (when critically stenosed and perfusing LV myocardium) is reasonable to improve the likelihood of survival and to decrease reintervention.<sup>90–94</sup> (*Level of Evidence: B*)

## Class IIb

1. Complete arterial revascularization may be reasonable in patients less than or equal to 60 years of age with few or no comorbidities. (Level of Evidence: C)
2. Arterial grafting of the right coronary artery may be reasonable when a critical ( $\geq 90\%$ ) stenosis is present.<sup>89,93,95</sup> (Level of Evidence: B)
3. Use of a radial artery graft may be reasonable when grafting left-sided coronary arteries with severe stenoses ( $>70\%$ ) and right-sided arteries with critical stenoses ( $\geq 90\%$ ) that perfuse LV myocardium.<sup>96–101</sup> (Level of Evidence: B)

## Class III: HARM

1. An arterial graft should not be used to bypass the right coronary artery with less than a critical stenosis ( $<90\%$ ).<sup>89</sup> (Level of Evidence: C)

Arteries (internal mammary, radial, gastroepiploic, and inferior epigastric) or veins (greater and lesser saphenous) may be used as conduits for CABG. The effectiveness of CABG in relieving symptoms and prolonging life is directly related to graft patency. Because arterial and venous grafts have different patency rates and modes of failure, conduit selection is important in determining the long-term efficacy of CABG.

### 2.1.4.1. Saphenous Vein Grafts

Reversed saphenous vein grafts (SVGs) are commonly used in patients undergoing CABG. Their disadvantage is a declining patency with time: 10% to as many as 25% of them occlude within 1 year of CABG<sup>89,102,103</sup>; an additional 1% to 2% occlude each year during the 1 to 5 years after surgery; and 4% to 5% occlude each year between 6 and 10 years postoperatively.<sup>104</sup> Therefore, 10 years after CABG, 50% to 60% of SVGs are patent, only half of which have no angiographic evidence of atherosclerosis.<sup>104</sup> During SVG harvesting and initial exposure to arterial pressure, the endothelium often is damaged, which, if extensive, may lead to platelet aggregation and graft thrombosis. Platelet adherence to the endothelium begins the process of intimal hyperplasia that later causes SVG atherosclerosis.<sup>103,105</sup> After adhering to the intima, the platelets release mitogens that stimulate smooth muscle cell migration, leading to intimal proliferation and hyperplasia. Lipid is incorporated into these areas of intimal hyperplasia, resulting in atherosclerotic plaque formation.<sup>106</sup> The perioperative administration of aspirin and dipyridamole improves early ( $<1$  month) and 1-year SVG patency and decreases lipid accumulation in the SVG intima.<sup>103,106,107</sup>

### 2.1.4.2. Internal Mammary Arteries

Unlike SVGs, IMAs usually are patent for many years postoperatively (10-year patency  $>90\%$ )<sup>89,95,102,108–117</sup> because of the fact that  $<4\%$  of IMAs develop atherosclerosis, and only 1% have atherosclerotic stenoses of hemodynamic significance.<sup>118–120</sup> This resistance to the development of atherosclerosis is presumably due to 1) the nearly continuous internal elastic lamina that prevents smooth muscle cell migration and 2) the release of prostacyclin and nitric oxide, potent vasodilators and inhibitors of platelet function, by the endothelium of IMAs.<sup>119,121,122</sup>

The disadvantage of using the IMA is that it may spasm and eventually atrophy if used to bypass a coronary artery without a flow-limiting stenosis.<sup>89,95,118,123–130</sup> Observational studies suggest an improved survival rate in patients undergoing CABG when the LIMA (rather than an SVG) is used to graft the LAD artery<sup>86–88</sup>; this survival benefit is independent of the patient's sex, age, extent of CAD, and LV systolic function.<sup>87,88</sup> Apart from improving survival rate, LIMA grafting of the LAD artery reduces the incidence of late MI, hospitalization for cardiac events, need for reoperation, and recurrence of angina.<sup>86,88</sup> The LIMA should be used to bypass the LAD artery provided that a contraindication to its use (eg, emergency surgery, poor LIMA blood flow, subclavian artery stenosis, radiation injury, atherosclerosis) is not present.

Because of the beneficial influence on morbidity and mortality rates of using the IMA for grafting, several centers have advocated bilateral IMA grafting in hopes of further improving CABG results.<sup>90,91,94</sup> In fact, numerous observational studies have demonstrated improved morbidity and mortality rates when both IMAs are used. On the other hand, bilateral IMA grafting appears to be associated with an increased incidence of sternal wound infections in patients with diabetes mellitus and those who are obese (body mass index  $>30$  kg/m<sup>2</sup>).

### 2.1.4.3. Radial, Gastroepiploic, and Inferior Epigastric Arteries

Ever since the observation that IMAs are superior to SVGs in decreasing the occurrence of ischemic events and prolonging survival, other arterial conduits, such as the radial, gastroepiploic, and inferior epigastric arteries, have been used in an attempt to improve the results of CABG. Information about these other arterial conduits is sparse in comparison to what is known about IMAs and SVGs, however. The radial artery is a muscular artery that is susceptible to spasm and atrophy when used to graft a coronary artery that is not severely narrowed. Radial artery graft patency is best when used to graft a left-sided coronary artery with  $>70\%$  stenosis and worst when it is used to bypass the right coronary artery with a stenosis of only moderate severity.<sup>96–100</sup>

The gastroepiploic artery is most often used to bypass the right coronary artery or its branches, although it may be used to bypass the LAD artery if the length of the gastroepiploic artery is adequate. Similar to the radial artery, it is prone to spasm and therefore should only be used to bypass coronary arteries that are severely stenotic.<sup>131</sup> The 1-, 5-, and 10-year patency rates of the gastroepiploic artery are reportedly 91%, 80%, and 62%, respectively.<sup>132</sup>

The inferior epigastric artery is only 8 to 10 centimeters in length and therefore is usually used as a "Y" or "T" graft connected to another arterial conduit. On occasion it is used as a free graft from the aorta to a high diagonal branch of the LAD artery. Because it is a muscular artery, it is prone to spasm and therefore is best used to bypass a severely stenotic coronary artery. Its reported 1-year patency is about 90%.<sup>133,134</sup>

### 2.1.5. Incisions for Cardiac Access

Although the time-honored incision for CABG is a median sternotomy, surgeons have begun to access the heart via several other approaches in an attempt to 1) reduce the traumatic effects often seen with full median sternotomy, 2)

hasten postoperative recovery, and 3) enhance cosmesis. The utility and benefit of these smaller incisions has been evident in subjects undergoing valvular surgery, for which only limited access to the heart is required.

The most minimally invasive access incisions for CABG are seen with robotically assisted totally endoscopic CABG. A study showed that totally endoscopic CABG with robotic technology was associated with improved physical health, shorter hospital stay, and a more rapid return to the activities of daily living compared with traditional techniques. At present, direct comparisons of robotically assisted and conventional CABG are lacking.<sup>135</sup>

The use of minimally invasive cardiac access incisions for CABG is limited. The need for adequate exposure of the ascending aorta and all surfaces of the heart to accomplish full revascularization usually precludes the use of minimal access incisions, such as upper sternotomy, lower sternotomy, or anterolateral thoracotomy. Nevertheless, use of limited incisions may increase in the future with the advent of hybrid strategies that use a direct surgical approach (usually for grafting the LAD artery through a small parasternal incision) and percutaneous coronary intervention (PCI) of the other diseased coronary arteries. The benefit of hybrid revascularization and hybrid operating rooms, in which PCI and CABG can be accomplished in one procedure, is yet to be determined. In patients with certain comorbid conditions, such as severe aortic calcification, previous chest irradiation, and obesity in combination with severe diabetes mellitus, full median sternotomy may be problematic,<sup>136</sup> and hybrid revascularization may be preferable.

### 2.1.6. Anastomotic Techniques

At present, most coronary bypass grafts are constructed with hand-sewn suture techniques for the proximal and distal anastomoses, a practice that has resulted in good short- and intermediate-term patency rates. Because surgeons have different preferences with regard to the technical aspects of the procedure, a wide variety of suture configurations is used. Sewing of the proximal and distal anastomoses with a continuous polypropylene suture is commonly done, but techniques with interrupted silk sutures have been used, with similar results for graft patency and adverse events.

Certain clinical scenarios have precipitated an interest in alternative techniques of constructing coronary bypass anastomoses. Some surgeons and patients wish to avoid the potential morbidity and cosmetic results of a median sternotomy, yet the least invasive incisions usually are too small to allow hand-sewn anastomoses. To solve this problem, coronary connector devices have been developed for use with arterial or venous conduits to enable grafting without direct suturing. In addition, these devices have been used in subjects with diseased ascending aortas, in whom a technique that allows construction of a proximal anastomosis with minimal manipulation of the ascending aorta (typically by eliminating the need for aortic cross-clamping) may result in less embolization of debris, thereby reducing the occurrence of adverse neurological outcomes. In this situation, the operation is performed through a median sternotomy, and the proximal anastomoses are created with a connector (or may be hand-

sewn with the assistance of a device that provides a bloodless operative field) without partial or complete clamping of the ascending aorta.

### 2.1.7. Intraoperative TEE: Recommendations

#### Class I

1. Intraoperative TEE should be performed for evaluation of acute, persistent, and life-threatening hemodynamic disturbances that have not responded to treatment.<sup>137,138</sup> (Level of Evidence: B)
2. Intraoperative TEE should be performed in patients undergoing concomitant valvular surgery.<sup>137,139</sup> (Level of Evidence: B)

#### Class IIa

1. Intraoperative TEE is reasonable for monitoring of hemodynamic status, ventricular function, regional wall motion, and valvular function in patients undergoing CABG.<sup>138,140–145</sup> (Level of Evidence: B)

The use of intraoperative TEE in patients undergoing cardiac surgery has increased steadily since its introduction in the late 1980s. Although its utility is considered to be highest in patients undergoing valvular and complex open great-vessel/aortic surgery, it is commonly used in subjects undergoing CABG. TEE is most often used,<sup>146</sup> although epicardial and epiaortic imaging, performed under aseptic conditions, allows visualization of imaging planes not possible with TEE.<sup>147,148</sup> Specifically, epiaortic imaging allows visualization of the “blind spot” of the ascending aorta (caused by interposition of the trachea with the esophagus), the site of aortic cannulation for CPB, from which dislodgement of friable atheroma, a major risk factor for perioperative stroke, may occur (Section 5.2.1). In addition, epicardial probes allow imaging when TEE is contraindicated, cannot be performed, or produces inadequate images. It can facilitate the identification of intraventricular thrombi when TEE images are equivocal.

The “2003 ACC/AHA/ASE Guideline Update for the Clinical Application of Echocardiography” based its recommendations on those reported in the 1996 American Society of Anesthesiologists/Society of Cardiovascular Anesthesiologists practice guideline and considered the use of TEE in CABG patients.<sup>149</sup> The latter document was updated in 2010.<sup>139</sup> Because of the use of different grading methodologies in the American Society of Anesthesiologists/Society of Cardiovascular Anesthesiologists guideline relative to that of the ACCF/AHA, precise comparisons are difficult. However, it is noted that TEE “should be considered” in subjects undergoing CABG, to confirm and refine the preoperative diagnosis, detect new or unsuspected pathology, adjust the anesthetic and surgical plan accordingly, and assess the results of surgery. The strongest recommendation is given for treatment of acute life-threatening hemodynamic instability that has not responded to conventional therapies.

Observational cohort analyses and case reports have suggested the utility of TEE for diagnosing acute life-threatening hemodynamic or surgical problems in CABG patients, many of which are difficult or impossible to detect or treat without direct imaging. Evaluation of ventricular cross-sectional areas



and ejection fraction (EF) and estimation or direct measurement of cardiac output by TEE may facilitate anesthetic, fluid, and inotropic/pressor management. The utility of echocardiography for the evaluation of LV end-diastolic area/volume and its potential superiority over pulmonary artery occlusion or pulmonary artery diastolic pressure, particularly in the early postoperative period, has been reported<sup>150,151</sup> (Section 4.10). In subjects without preoperative transthoracic imaging, intraoperative TEE may provide useful diagnostic information (over and above that detected during cardiac catheterization) on valvular function as well as evidence of pulmonary hypertension, intracardiac shunts, or other complications that may alter the planned surgery.

In patients undergoing CABG, intraoperative TEE is used most often for the detection of regional wall motion abnormalities (possibly caused by myocardial ischemia or infarction) and their effect on LV function. Observational studies have suggested that regional wall motion abnormalities detected with TEE can guide surgical therapy, leading to revision of a failed or inadequate conduit or the placement of additional grafts not originally planned. The presence of new wall motion abnormalities after CPB correlates with adverse perioperative and long-term outcomes.<sup>143</sup>

Although the initial hope that an estimation of coronary blood flow with intramyocardial contrast enhancement visualized by TEE would facilitate surgical intervention has not been realized, technical advances in imaging of coronary arteries and grafts may ultimately provide reliable information. At present, the evaluation of graft flow with conventional nonimaging handheld Doppler probes appears adequate (Section 8). Intraoperative evaluation of mitral regurgitation may facilitate detection of myocardial ischemia and provide guidance about the need for mitral valve annuloplasty (Section 6.7). Newer technologies, including nonimaging methods for analyzing systolic and diastolic velocity and direction and timing of regional wall motion (Doppler tissue imaging and speckle tracking), as well as “real-time” 3-dimensional imaging, may facilitate the diagnosis of myocardial ischemia and evaluation of ventricular function. At present, however, their cost-effectiveness has not been determined, and they are too complex for routine use.<sup>152–154</sup>

Among different centers, the rate of intraoperative TEE use in CABG patients varies from none to routine; its use is influenced by many factors, such as institutional and practitioner preferences, the healthcare system and reimbursement strategies, tertiary care status, and presence of training programs.<sup>155</sup> The efficacy of intraoperative TEE is likely influenced by the presence of 1) LV systolic and diastolic dysfunction, 2) concomitant valvular disease, 3) the planned surgical procedure (on pump versus off pump, primary versus reoperative), 4) the surgical approach (full sternotomy versus partial sternotomy versus endoscopic or robotic), 5) its acuity (elective versus emergency); and 6) physician training and experience.<sup>137,138,140–142,144,145,156–163</sup>

The safety of intraoperative TEE in patients undergoing cardiac surgery is uncertain. Retrospective analyses of data from patients undergoing diagnostic upper gastrointestinal endoscopy, nonoperative diagnostic TEE imaging, and intraoperative imaging by skilled operators in high-volume cen-

ters demonstrate a low frequency of complications related to insertion or manipulation of the probe.<sup>164,165</sup> Nevertheless, minor (primarily pharyngeal injury from probe insertion) and major (esophageal perforation, gastric bleeding, or late mediastinitis) complications are reported.<sup>166,167</sup> A more indolent complication is that of acquired dysphagia and possible aspiration postoperatively. Although retrospective analyses of postoperative cardiac surgical patients with clinically manifest esophageal dysfunction have identified TEE use as a risk factor,<sup>168–170</sup> such dysfunction also has been reported in subjects in whom TEE was not used.<sup>171</sup> Advanced age, prolonged intubation, and neurological injury seem to be risk factors for its development. The significance of the incidental intraoperative detection and repair of a patent foramen ovale, a common occurrence, is controversial.<sup>172</sup> A 2009 observational analysis of 13 092 patients (25% isolated CABG; 29% CABG or other cardiac procedure), of whom 17% had a patent foramen ovale detected by TEE (28% of which were repaired), reported an increase in postoperative stroke in the patients who had patent foramen ovale repair (OR: 2.47; 95% CI: 1.02 to 6.0) with no improvement in long-term outcome.<sup>173</sup>

#### 2.1.8. Preconditioning/Management of Myocardial Ischemia: Recommendations

##### Class I

1. Management targeted at optimizing the determinants of coronary arterial perfusion (eg, heart rate, diastolic or mean arterial pressure, and right ventricular or LV end-diastolic pressure) is recommended to reduce the risk of perioperative myocardial ischemia and infarction.<sup>53,174–177</sup> (Level of Evidence: B)

##### Class IIa

1. Volatile-based anesthesia can be useful in reducing the risk of perioperative myocardial ischemia and infarction.<sup>178–181</sup> (Level of Evidence: A)

##### Class IIb

1. The effectiveness of prophylactic pharmacological therapies or controlled reperfusion strategies aimed at inducing preconditioning or attenuating the adverse consequences of myocardial reperfusion injury or surgically induced systemic inflammation is uncertain.<sup>182–189</sup> (Level of Evidence: A)
2. Mechanical preconditioning might be considered to reduce the risk of perioperative myocardial ischemia and infarction in patients undergoing off-pump CABG.<sup>190–192</sup> (Level of Evidence: B)
3. Remote ischemic preconditioning strategies using peripheral-extremity occlusion/reperfusion might be considered to attenuate the adverse consequences of myocardial reperfusion injury.<sup>193–195</sup> (Level of Evidence: B)
4. The effectiveness of postconditioning strategies to attenuate the adverse consequences of myocardial reperfusion injury is uncertain.<sup>196,197</sup> (Level of Evidence: C)

See Online Data Supplements 2 to 4 for additional data on preconditioning.

Perioperative myocardial injury is associated with adverse outcomes after CABG,<sup>198–200</sup> and available data suggest a direct correlation between the amount of myonecrosis and the likelihood of an adverse outcome<sup>198,201–204</sup> (Section 5.2.4).

The etiologies of perioperative myocardial ischemia and infarction and their complications (electrical or mechanical) range from alterations in the determinants of global or regional myocardial oxygen supply and demand to complex biochemical and microanatomic, systemic, or vascular abnormalities, many of which are not amenable to routine diagnostic and therapeutic interventions. Adequate surgical reperfusion is important in determining outcome, even though it may initially induce reperfusion injury. Various studies delineating the major mediators of reperfusion injury have focused attention on the mitochondrial permeability transition pore, the opening of which during reperfusion uncouples oxidative phosphorylation, ultimately leading to cell death.<sup>205</sup> Although several pharmacological interventions targeting components of reperfusion injury have been tried, none has been found to be efficacious for this purpose.<sup>182,184–189,205–207</sup>

The severity of reperfusion injury is influenced by numerous factors, including 1) the status of the patient's coronary circulation, 2) the presence of active ongoing ischemia or infarction, 3) preexisting medical therapy (Sections 4.3 and 4.5), 4) concurrent use of mechanical assistance to improve coronary perfusion (ie, intra-aortic balloon counterpulsation), and 5) the surgical approach used (on pump or off pump). CPB with ischemic arrest is known to induce the release of cytokines and chemokines involved in cellular homeostasis, thrombosis, and coagulation; oxidative stress; adhesion of blood cell elements to the endothelium; and neuroendocrine stress responses; all of these may contribute to myocardial injury.<sup>208,209</sup> Controlled reperfusion strategies during CPB, involving prolonged reperfusion with warm-blood cardioplegia in conjunction with metabolic enhancers, are rarely used in lieu of more routine methods of preservation (eg, asystolic arrest, antegrade or retrograde blood cardioplegia during aortic cross-clamping). Several studies suggest that the magnitude of SIRS is greater with on-pump CABG than with off-pump CABG.<sup>201,208,210–213</sup>

Initial studies of preconditioning used mechanical occlusion of arterial inflow followed by reperfusion via aortic cross-clamping immediately on institution of bypass or with coronary artery occlusion proximal to the planned distal anastomosis during off-pump CABG.<sup>190,191,214–217</sup> Because of concerns of the potential adverse cerebral effects of aortic manipulation, enthusiasm for further study of this technique in on-pump CABG patients is limited (Section 5.2.1). Despite intense interest in the physiology of postconditioning, few data are available.<sup>197</sup> A small 2008 study in patients undergoing valve surgery, which used repeated manipulation of the ascending aorta, reported a reduction in surrogate markers of inflammation and myonecrosis.<sup>196</sup> In lieu of techniques utilizing mechanical occlusion, pharmacological conditioning agents are likely to be used. An alternative approach that avoids much (but not all) of the safety concerns related to potential vascular injury is remote preconditioning of arterial inflow to the leg or (more commonly) the arm via blood pressure cuff occlusion.<sup>218</sup> Two studies of patients undergoing on-pump CABG at a single center, the first of which

used 2 different myocardial protection strategies and the second of which repeated the study with a standardized cold-blood cardioplegia routine, reported similar amounts of troponin release during the 72 hours postoperatively, with no apparent complications.<sup>193,195</sup> A larger trial was unable to confirm any benefits of a similar protocol, casting doubt on the utility of this approach.<sup>194</sup>

Volatile halogenated anesthetics and opioids have anti-ischemic or conditioning properties,<sup>32,33,219,220</sup> and propofol has antioxidant properties of potential value in subjects with reperfusion injury.<sup>221,222</sup> The salutary properties of volatile anesthetics during myocardial ischemia are well known. Their negative inotropic and chronotropic effects are considered to be beneficial, particularly in the setting of elevated adrenergic tone that is common with surgical stimulation. Although contemporary volatile agents demonstrate some degree of coronary arterial vasodilation (with isoflurane considered the most potent), the role of a “steal phenomena” in the genesis of ischemia is considered to be trivial.<sup>33</sup> In comparison to propofol/opioid infusions, volatile agents seem to reduce troponin release, preserve myocardial function, and improve resource utilization (ie, ICU or hospital lengths of stay) and 1-year outcome.<sup>223–227</sup> It is postulated that multiple factors that influence myocardial preservation modulate the potential impact of a specific anesthetic regimen.

Observational analyses have reported an association between elevated perioperative heart rates and adverse outcomes,<sup>228,229</sup> but it is difficult to recommend a specific heart rate for all CABG patients. Instead, the heart rate may need to be adjusted up or down to maintain an adequate cardiac output.<sup>230,231</sup> Similarly, controversy exists about management of blood pressure in the perioperative period,<sup>232</sup> particularly with regard to systolic pressure<sup>233</sup> and pulse pressure.<sup>234</sup> Intraoperative hypotension is considered to be a risk factor for adverse outcomes in patients undergoing many types of surgery. Unique to CABG are unavoidable periods of hypotension associated with surgical manipulation, cannulation for CPB, weaning from CPB, or during suspension and stabilization of the heart with off-pump CABG. Minimization of such periods is desirable but is often difficult to achieve, particularly in patients who are unstable hemodynamically.

## 2.2. Clinical Subsets

### 2.2.1. CABG in Patients With Acute MI: Recommendations

#### Class I

1. Emergency CABG is recommended in patients with acute MI in whom 1) primary PCI has failed or cannot be performed, 2) coronary anatomy is suitable for CABG, and 3) persistent ischemia of a significant area of myocardium at rest and/or hemodynamic instability refractory to nonsurgical therapy is present.<sup>235–239</sup> (*Level of Evidence: B*)
2. Emergency CABG is recommended in patients undergoing surgical repair of a postinfarction mechanical complication of MI, such as ventricular septal rupture, mitral valve insufficiency because of papillary muscle infarction and/or rupture, or free wall rupture.<sup>240–244</sup> (*Level of Evidence: B*)

3. Emergency CABG is recommended in patients with cardiogenic shock and who are suitable for CABG irrespective of the time interval from MI to onset of shock and time from MI to CABG.<sup>238,245–247</sup> (*Level of Evidence: B*)
4. Emergency CABG is recommended in patients with life-threatening ventricular arrhythmias (believed to be ischemic in origin) in the presence of left main stenosis greater than or equal to 50% and/or 3-vessel CAD.<sup>248</sup> (*Level of Evidence: C*)

#### Class IIa

1. The use of CABG is reasonable as a revascularization strategy in patients with multivessel CAD with recurrent angina or MI within the first 48 hours of STEMI presentation as an alternative to a more delayed strategy.<sup>235,237,239,249</sup> (*Level of Evidence: B*)
2. Early revascularization with PCI or CABG is reasonable for selected patients greater than 75 years of age with ST-segment elevation or left bundle branch block who are suitable for revascularization irrespective of the time interval from MI to onset of shock.<sup>250–254</sup> (*Level of Evidence: B*)

#### Class III: HARM

1. Emergency CABG should not be performed in patients with persistent angina and a small area of viable myocardium who are stable hemodynamically. (*Level of Evidence: C*)
2. Emergency CABG should not be performed in patients with noreflow (successful epicardial reperfusion with unsuccessful microvascular reperfusion). (*Level of Evidence: C*)

See Online Data Supplement 5 for additional data on CABG in patients with acute myocardial infarction.

With the widespread use of fibrinolytic therapy or primary PCI in subjects with STEMI, emergency CABG is now reserved for those with 1) left main and/or 3-vessel CAD, 2) ongoing ischemia after successful or failed PCI, 3) coronary anatomy not amenable to PCI, 4) a mechanical complication of STEMI,<sup>241,255,256</sup> and 5) cardiogenic shock (defined as hypotension [systolic arterial pressure <90 mm Hg for ≥30 minutes or need for supportive measures to maintain a systolic pressure ≥90 mm Hg], evidence of end-organ hypoperfusion, cardiac index ≤2.2 L/min/m<sup>2</sup>, and pulmonary capillary wedge pressure ≥15 mm Hg).<sup>245,247</sup> In the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, 36% of patients randomly assigned to early revascularization therapy underwent emergency CABG.<sup>245</sup> Although those who underwent emergency CABG were more likely to be diabetic and to have complex coronary anatomy than were those who had PCI, the survival rates of the 2 groups were similar.<sup>247</sup> The outcomes of high-risk STEMI patients with cardiogenic shock undergoing emergency CABG suggest that CABG may be preferred to PCI in this patient population when complete revascularization cannot be accomplished with PCI.<sup>236,238,246</sup>

The need for emergency CABG in subjects with STEMI is relatively uncommon, ranging from 3.2% to 10.9%.<sup>257,258</sup> Of the 1572 patients enrolled in the DANAMI-2 (Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction) study, only 50 (3.2%) underwent CABG within 30 days (30 patients initially treated with PCI and 20 given fibrinolysis), and only 3 patients (0.2%) randomly assigned to receive primary PCI underwent emergency CABG.<sup>257</sup> Of the 1100 patients who underwent coronary angiography in the PAMI-2 (Primary Angioplasty in Myocardial Infarction) trial, CABG was performed before hospital discharge in 120.<sup>258</sup>

The in-hospital mortality rate is higher in STEMI patients undergoing emergency CABG than in those undergoing it on a less urgent or a purely elective basis.<sup>239,257,259–264</sup> In a study of 1181 patients undergoing CABG, the in-hospital mortality rate increased as the patients' preoperative status worsened, ranging from 1.2% in those with stable angina to 26% in those with cardiogenic shock.<sup>265</sup>

Although patients requiring emergency or urgent CABG after STEMI are at higher risk than those undergoing it electively, the optimal timing of CABG after STEMI is controversial. A retrospective study performed before the widespread availability of fibrinolysis and primary PCI reported an overall in-hospital mortality rate of 5.2% in 440 STEMI patients undergoing CABG as primary reperfusion therapy. Those undergoing CABG ≤6 hours after symptom onset had a lower in-hospital and long-term (10 years) mortality rate than those undergoing CABG >6 hours after symptom onset.<sup>237</sup> Other studies have provided conflicting results, because of, at least in part, the lack of clear delineation between STEMI and NSTEMI patients in these large database reports.<sup>259,265</sup> In an analysis of 9476 patients hospitalized with an acute coronary syndrome (ACS) who underwent CABG during the index hospitalization, 1344 (14%) were STEMI patients with shock or intra-aortic balloon placement preoperatively.<sup>264</sup> These individuals had a mortality rate of 4% when CABG was performed on the third hospital day, which was lower than the mortality rates reported when CABG was performed earlier or later during the hospitalization.<sup>264</sup> In studies in which the data from STEMI patients were analyzed separately with regard to the optimal timing of CABG, however, the results appear to be different. In 1 analysis of 44 365 patients who underwent CABG after MI (22 984 with STEMI; 21 381 with NSTEMI), the inhospital mortality rate was similar in the 2 groups undergoing CABG <6 hours after diagnosis (12.5% and 11.5%, respectively), but it was higher in STEMI patients than in NSTEMI patients when CABG was performed 6 to 23 hours after diagnosis (13.6% versus 6.2%;  $P=0.006$ ).<sup>262</sup> The groups had similar in-hospital mortality rates when CABG was performed at all later time points (1 to 7 days, 8 to 14 days, and ≥15 days after the acute event).<sup>262</sup> Similarly, in a study of 138 subjects with STEMI unresponsive to maximal nonsurgical therapy who underwent emergency CABG, the overall mortality rate was 8.7%, but it varied according to the time interval from symptom onset to time of operation. The mortality rate was 10.8% for patients undergoing CABG within 6 hours of the onset of symptoms, 23.8% in those



undergoing CABG 7 to 24 hours after symptom onset, 6.7% in patients undergoing CABG from 1 to 3 days, 4.2% in those who underwent surgery from 4 to 7 days, and 2.4% after 8 days.<sup>266</sup> In an analysis of data from 150 patients with STEMI who did not qualify for primary PCI and required CABG, the in-hospital mortality rate increased according to the time interval between symptom onset and surgery.<sup>239</sup> The mortality rate was 6.1% for subjects who underwent CABG within 6 hours of pain onset, 50% in those who underwent CABG 7 to 23 hours after pain onset, and 7.1% in those who underwent CABG after 15 days.<sup>239</sup> Lastly, in another study, the time interval of 6 hours was also found to be important in STEMI patients requiring CABG. The mean time from symptom onset to CABG was significantly shorter in survivors versus nonsurvivors ( $5.1 \pm 2.7$  hours versus  $11.4 \pm 3.2$  hours;  $P < 0.0007$ ).<sup>235</sup> In patients with cardiogenic shock, the benefits of early revascularization were apparent across a wide time interval between 1) MI and the onset of shock and 2) MI and CABG. Therefore, although CABG exerts its most profound salutary effect when it is performed as soon as possible after MI and the appearance of shock, the time window in which it is beneficial is quite broad.

Apart from the timing of CABG, the outcomes of STEMI patients undergoing CABG depend on baseline demographic variables. Those with mechanical complications of STEMI (eg, ventricular septal rupture or mitral regurgitation caused by papillary muscle rupture) have a high operative mortality rate.<sup>240–242,244,255,267</sup> In a study of 641 subjects with ACS, 22 with evolving STEMI and 20 with a mechanical complication of STEMI were referred for emergency CABG; the 30-day mortality rate was 0% in those with evolving STEMI and 25% in those with a mechanical complication of STEMI.<sup>268</sup> In those with mechanical complications, several variables were predictive of death, including advanced age, female sex, cardiogenic shock, the use of intra-aortic balloon counterpulsation preoperatively, pulmonary disease, renal insufficiency, and magnitude of elevation of the serum troponin concentration.<sup>235,239,263,265,266,269,270</sup>

### 2.2.2. Life-Threatening Ventricular Arrhythmias: Recommendations

#### Class I

1. CABG is recommended in patients with resuscitated sudden cardiac death or sustained ventricular tachycardia thought to be caused by significant CAD ( $\geq 50\%$  stenosis of left main coronary artery and/or  $\geq 70\%$  stenosis of 1, 2, or all 3 epicardial coronary arteries) and resultant myocardial ischemia.<sup>248,271,272</sup> (Level of Evidence: B)

#### Class III: HARM

1. CABG should not be performed in patients with ventricular tachycardia with scar and no evidence of ischemia. (Level of Evidence: C)

See Online Data Supplement 6 for additional data on life-threatening ventricular arrhythmias.

Most studies evaluating the benefits of CABG in patients with ventricular arrhythmias have examined survivors of

out-of-hospital cardiac arrest as well as patients with inducible ventricular tachycardia or fibrillation during electrophysiological study.<sup>272–274</sup> In general, CABG has been more effective in reducing the occurrence of ventricular fibrillation than of ventricular tachycardia, because the mechanism of the latter is usually reentry with scarred endocardium rather than ischemia. Observational studies have demonstrated a favorable prognosis of subjects undergoing CABG for ischemic ventricular tachycardia/fibrillation.<sup>248</sup>

In survivors of cardiac arrest who have severe but operable CAD, CABG can suppress the appearance of arrhythmias, reduce subsequent episodes of cardiac arrest, and result in a good long-term outcome.<sup>271–273</sup> It is particularly effective when an ischemic cause of the arrhythmia can be documented (for instance, when it occurs with exercise).<sup>275</sup> Still, because CABG may not alleviate all the factors that predispose to ventricular arrhythmias, concomitant insertion of an implantable cardioverter-defibrillator is often warranted.<sup>276</sup> Similarly, continued inducibility or clinical recurrence of ventricular tachycardia after CABG usually requires an implantable cardioverter-defibrillator implantation.

Patients with depressed LV systolic function, advanced age, female sex, and increased CPB time are at higher risk for life-threatening arrhythmias in the early postoperative period. Given the poor short-term prognosis of those with these arrhythmias, mechanical and ischemic causes should be considered in the postoperative setting.<sup>277–279</sup>

### 2.2.3. Emergency CABG After Failed PCI: Recommendations

#### Class I

1. Emergency CABG is recommended after failed PCI in the presence of ongoing ischemia or threatened occlusion with substantial myocardium at risk.<sup>280,281</sup> (Level of Evidence: B)
2. Emergency CABG is recommended after failed PCI for hemodynamic compromise in patients without impairment of the coagulation system and without a previous sternotomy.<sup>280,282,283</sup> (Level of Evidence: B)

#### Class IIa

1. Emergency CABG is reasonable after failed PCI for retrieval of a foreign body (most likely a fractured guidewire or stent) in a crucial anatomic location. (Level of Evidence: C)
2. Emergency CABG can be beneficial after failed PCI for hemodynamic compromise in patients with impairment of the coagulation system and without previous sternotomy. (Level of Evidence: C)

#### Class IIb

1. Emergency CABG might be considered after failed PCI for hemodynamic compromise in patients with previous sternotomy. (Level of Evidence: C)

#### Class III: HARM

1. Emergency CABG should not be performed after failed PCI in the absence of ischemia or threatened occlusion. (Level of Evidence: C)

## 2. Emergency CABG should not be performed after failed PCI if revascularization is impossible because of target anatomy or a no-reflow state. (Level of Evidence: C)

See Online Data Supplement 7 for additional data on CABG after failed PCI.

With widespread stent use as well as effective antiplatelet and antithrombotic therapies, emergency CABG after failed PCI is not commonly performed. In a 2009 analysis of data from almost 22 000 patients undergoing PCI at a single center, only 90 (0.4%) required CABG within 24 hours of PCI.<sup>281</sup> A similarly low rate ( $\leq 0.8\%$ ) of emergency CABG after PCI has been reported by others.<sup>284–286</sup> The indications for emergency CABG after PCI include 1) acute (or threatened) vessel closure, 2) coronary arterial dissection, 3) coronary arterial perforation,<sup>281</sup> and 4) malfunction of PCI equipment (eg, stent dislodgement, fractured guidewire). Subjects most likely to require emergency CABG after failed PCI are those with evolving STEMI, cardiogenic shock, 3-vessel CAD, or the presence of a type C coronary arterial lesion (defined as  $>2$  cm in length, an excessively tortuous proximal segment, an extremely angulated segment, a total occlusion  $>3$  months in duration, or a degenerated SVG that appears to be friable).<sup>281</sup>

In those in whom emergency CABG for failed PCI is performed, morbidity and mortality rates are increased compared with those undergoing elective CABG,<sup>287–289</sup> resulting at least in part from the advanced age of many patients now referred for PCI, some of whom have multiple comorbid conditions and complex coronary anatomy. Several variables have been shown to be associated with increased perioperative morbidity and mortality rates, including 1) depressed LV systolic function,<sup>290</sup> 2) recent ACS,<sup>290,291</sup> 3) multivessel CAD and complex lesion morphology,<sup>291,292</sup> 4) cardiogenic shock,<sup>281</sup> 5) advanced patient age,<sup>293</sup> 6) absence of angiographic collaterals,<sup>293</sup> 7) previous PCI,<sup>294</sup> and 8) a prolonged time delay in transfer to the operating room.<sup>293</sup> In patients undergoing emergency CABG for failed PCI, an off-pump procedure may be associated with a reduced incidence of renal failure, need for intra-aortic balloon use, and reoperation for bleeding.<sup>283,295</sup>

If complete revascularization is achieved with minimal delay in patients undergoing emergency CABG after failed PCI, long-term prognosis is similar to that of subjects undergoing elective CABG.<sup>280,282,296</sup> In-hospital morbidity and mortality rates in women<sup>297</sup> and the elderly<sup>298</sup> undergoing emergency CABG for failed PCI are relatively high, but the long-term outcomes in these individuals are comparable to those achieved in men and younger patients.

### 2.2.4. CABG in Association With Other Cardiac Procedures: Recommendations

#### Class I

1. CABG is recommended in patients undergoing non-coronary cardiac surgery with greater than or equal to 50% luminal diameter narrowing of the left main coronary artery or greater than or equal to 70%

luminal diameter narrowing of other major coronary arteries. (Level of Evidence: C)

#### Class IIa

1. The use of the LIMA is reasonable to bypass a significantly narrowed LAD artery in patients undergoing noncoronary cardiac surgery. (Level of Evidence: C)
2. CABG of moderately diseased coronary arteries ( $>50\%$  luminal diameter narrowing) is reasonable in patients undergoing noncoronary cardiac surgery. (Level of Evidence: C)

## 3. CAD Revascularization

Recommendations and text in this section are the result of extensive collaborative discussions between the PCI and CABG writing committees, as well as key members of the Stable Ischemic Heart Disease (SIHD) and UA/NSTEMI writing committees. Certain issues, such as older versus more contemporary studies, primary analyses versus subgroup analyses, and prospective versus post hoc analyses, have been carefully weighed in designating COR and LOE; they are addressed in the appropriate corresponding text. The goals of revascularization for patients with CAD are to 1) to improve survival and 2) to relieve symptoms.

Revascularization recommendations in this section are predominantly based on studies of patients with symptomatic SIHD and should be interpreted in this context. As discussed later in this section, recommendations on the type of revascularization are, in general, applicable to patients with UA/NSTEMI. In some cases (eg, unprotected left main CAD), specific recommendations are made for patients with UA/NSTEMI or STEMI.

Historically, most studies of revascularization have been based on and reported according to angiographic criteria. Most studies have defined a “significant” stenosis as  $\geq 70\%$  diameter narrowing; therefore, for revascularization decisions and recommendations in this section, a “significant” stenosis has been defined as  $\geq 70\%$  diameter narrowing ( $\geq 50\%$  for left main CAD). Physiological criteria, such as an assessment of fractional flow reserve, has been used in deciding when revascularization is indicated. Thus, for recommendations on revascularization in this section, coronary stenoses with fractional flow reserve  $\leq 0.80$  can also be considered “significant.”<sup>299,300</sup>

As noted, the revascularization recommendations have been formulated to address issues related to 1) improved survival and/or 2) improved symptoms. When one method of revascularization is preferred over the other for improved survival, this consideration, in general, takes precedence over improved symptoms. When discussing options for revascularization with the patient, he or she should understand when the procedure is being performed in an attempt to improve symptoms, survival, or both.

Although some results from the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) study are best characterized as subgroup analyses and “hypothesis generating,” SYNTAX nonetheless represents the latest and most comprehensive comparison of contemporary PCI and CABG.<sup>301,302</sup> There-

fore, the results of SYNTAX have been considered appropriately when formulating our revascularization recommendations. Although the limitations of using the SYNTAX score for certain revascularization recommendations are recognized, the SYNTAX score is a reasonable surrogate for the extent of CAD and its complexity and serves as important information that should be considered when making revascularization decisions. Recommendations that refer to SYNTAX scores use them as surrogates for the extent and complexity of CAD.

Revascularization recommendations to improve survival and symptoms are given in the following text and summarized in Tables 2 and 3. References to studies comparing revascularization with medical therapy are presented when available for each anatomic subgroup.

*See Online Data Supplements 8 and 9 for additional data regarding the survival and symptomatic benefits with CABG or PCI for different anatomic subsets.*

### 3.1. Heart Team Approach to Revascularization Decisions: Recommendations

#### Class I

1. A Heart Team approach to revascularization is recommended in patients with unprotected left main or complex CAD.<sup>302–304</sup> (*Level of Evidence: C*)

#### Class IIa

1. Calculation of the STS and SYNTAX scores is reasonable in patients with unprotected left main and complex CAD.<sup>301,302,305–310</sup> (*Level of Evidence: B*)

One protocol used in RCTs<sup>302–304,311</sup> often involves a multidisciplinary approach referred to as the Heart Team. Composed of an interventional cardiologist and a cardiac surgeon, the Heart Team 1) reviews the patient's medical condition and coronary anatomy, 2) determines that PCI and/or CABG are technically feasible and reasonable, and 3) discusses revascularization options with the patient before a treatment strategy is selected. Support for using a Heart Team approach comes from reports that patients with complex CAD referred specifically for PCI or CABG in concurrent trial registries have lower mortality rates than those randomly assigned to PCI or CABG in controlled trials.<sup>303,304</sup>

The SIHD, PCI, and CABG guideline writing committees endorse a Heart Team approach in patients with unprotected left main CAD and/or complex CAD in whom the optimal revascularization strategy is not straightforward. A collaborative assessment of revascularization options, or the decision to treat with GDMT without revascularization, involving an interventional cardiologist, a cardiac surgeon, and (often) the patient's general cardiologist, followed by discussion with the patient about treatment options, is optimal. Particularly in patients with SIHD and unprotected left main and/or complex CAD for whom a revascularization strategy is not straightforward, an approach has been endorsed that involves terminating the procedure after diagnostic coronary angiography is completed; this allows a thorough discussion and affords

both the interventional cardiologist and cardiac surgeon the opportunity to discuss revascularization options with the patient. Because the STS score and the SYNTAX score have been shown to predict adverse outcomes in patients undergoing CABG and PCI, respectively, calculation of these scores is often useful in making revascularization decisions.<sup>301,302,305–310</sup>

### 3.2. Revascularization to Improve Survival: Recommendations

#### Left Main CAD Revascularization

##### Class I

1. CABG to improve survival is recommended for patients with significant ( $\geq 50\%$  diameter stenosis) left main coronary artery stenosis.<sup>312–318</sup> (*Level of Evidence: B*)

##### Class IIa

1. PCI to improve survival is reasonable as an alternative to CABG in selected stable patients with significant ( $\geq 50\%$  diameter stenosis) unprotected left main CAD with: 1) anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score [ $\leq 22$ ], ostial or trunk left main CAD); and 2) clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality  $\geq 5\%$ ).<sup>301,305,307,311,319–336</sup> (*Level of Evidence: B*)
2. PCI to improve survival is reasonable in patients with UA/NSTEMI when an unprotected left main coronary artery is the culprit lesion and the patient is not a candidate for CABG.<sup>301,324–327,332,333,335–337</sup> (*Level of Evidence: B*)
3. PCI to improve survival is reasonable in patients with acute STEMI when an unprotected left main coronary artery is the culprit lesion, distal coronary flow is less than Thrombolysis In Myocardial Infarction grade 3, and PCI can be performed more rapidly and safely than CABG.<sup>321,338,339</sup> (*Level of Evidence: C*)

##### Class IIb

1. PCI to improve survival may be reasonable as an alternative to CABG in selected stable patients with significant ( $\geq 50\%$  diameter stenosis) unprotected left main CAD with: 1) anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (eg, low-intermediate SYNTAX score of  $< 33$ , bifurcation left main CAD); and 2) clinical characteristics that predict an increased risk of adverse surgical outcomes (eg, moderate-severe chronic obstructive pulmonary disease, disability from previous stroke, or previous cardiac surgery; STS-predicted risk of operative mortality  $> 2\%$ ).<sup>301,305,307,311,319–336,340</sup> (*Level of Evidence: B*)

##### Class III: HARM

1. PCI to improve survival should not be performed in stable patients with significant ( $\geq 50\%$  diameter stenosis) unprotected left main CAD who have unfavorable



**Table 2. Revascularization to Improve Survival Compared With Medical Therapy**

Anatomic Setting	COR	LOE	References
<b>UPLM or complex CAD</b>			
CABG and PCI	I—Heart Team approach recommended	C	302–304
CABG and PCI	IIa—Calculation of the STS and SYNTAX scores	B	301, 302, 305–310
<b>UPLM*</b>			
CABG	I	B	312–318
PCI	IIa—For SIHD when both of the following are present <ul style="list-style-type: none"> <li>Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score of <math>\leq 22</math>, ostial or trunk left main CAD)</li> <li>Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality <math>\geq 5\%</math>)</li> </ul> IIa—For UA/NSTEMI if not a CABG candidate	B	301, 305, 307, 311, 319–336
	IIa—For STEMI when distal coronary flow is TIMI flow grade $< 3$ and PCI can be performed more rapidly and safely than CABG	C	301, 324–327, 332, 333, 335–337
	IIb—For SIHD when <i>both</i> of the following are present <ul style="list-style-type: none"> <li>Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and intermediate to high likelihood of good long-term outcome (eg, low-intermediate SYNTAX score of <math>&lt; 33</math>, bifurcation left main CAD)</li> <li>Clinical characteristics that predict an increased risk of adverse surgical outcomes (eg, moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality <math>&gt; 2\%</math>)</li> </ul> III: Harm—For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B	301, 305, 307, 311, 319–336, 340
		B	301, 305, 307, 312–320
<b>3-vessel disease with or without proximal LAD artery disease*</b>			
CABG	I	B	314, 318, 341–344
	IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (eg, SYNTAX $> 22$ ) who are good candidates for CABG	B	320, 334, 343, 359–360
PCI	IIb—Of uncertain benefit	B	314, 341, 343, 370
<b>2-vessel disease with proximal LAD artery disease*</b>			
CABG	I	B	314, 318, 341–344
PCI	IIb—Of uncertain benefit	B	314, 341, 343, 370
<b>2-vessel disease without proximal LAD artery disease*</b>			
CABG	IIa—With extensive ischemia	B	348–351
	IIb—Of uncertain benefit without extensive ischemia	C	343
PCI	IIb—Of uncertain benefit	B	314, 341, 343, 370
<b>1-vessel proximal LAD artery disease</b>			
CABG	IIa—With LIMA for long-term benefit	B	87, 88, 318, 343
PCI	IIb—Of uncertain benefit	B	314, 341, 343, 370
<b>1-vessel disease without proximal LAD artery involvement</b>			
CABG	III: Harm	B	318, 341, 348, 349, 382–386
PCI	III: Harm	B	318, 341, 348, 349, 382–386
<b>LV dysfunction</b>			
CABG	IIa—EF 35% to 50%	B	318, 352–356
CABG	IIb—EF $< 35\%$ without significant left main CAD	B	318, 352–356, 371, 372
PCI	Insufficient data		N/A
<b>Survivors of sudden cardiac death with presumed ischemia-mediated VT</b>			
CABG	I	B	271, 345, 347
PCI	I	C	345
<b>No anatomic or physiological criteria for revascularization</b>			
CABG	III: Harm	B	318, 341, 348, 349, 382–386
PCI	III: Harm	B	318, 341, 348, 349, 382–386

\*In patients with multivessel disease who also have diabetes, it is reasonable to choose CABG (with LIMA) over PCI<sup>350,362–369</sup> (Class IIa/LOE: B).

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; COR, class of recommendation; EF, ejection fraction; LAD, left anterior descending; LIMA, left internal mammary artery; LOE, level of evidence; LV, left ventricular; N/A, not applicable; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; STS, Society of Thoracic Surgeons; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction; UPLM, unprotected left main disease; and VT, ventricular tachycardia.

**Table 3. Revascularization to Improve Symptoms With Significant Anatomic ( $\geq 50\%$  Left Main or  $\geq 70\%$  Non-Left Main CAD) or Physiological (FFR  $\leq 0.80$ ) Coronary Artery Stenoses**

Clinical Setting	COR	LOE	References
$\geq 1$ significant stenoses amenable to revascularization and unacceptable angina despite GDMT	I—CABG I—PCI	A	370, 387–396
$\geq 1$ significant stenoses and unacceptable angina in whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences	Ila—CABG Ila—PCI	C	N/A
Previous CABG with $\geq 1$ significant stenoses associated with ischemia and unacceptable angina despite GDMT	Ila—PCI Iib—CABG	C	374, 377, 380 381
Complex 3-vessel CAD (eg, SYNTAX score $>22$ ) with or without involvement of the proximal LAD artery and a good candidate for CABG	Ila—CABG preferred over PCI	B	320, 343, 359–361
Viable ischemic myocardium that is perfused by coronary arteries that are not amenable to grafting	Iib—TMR as an adjunct to CABG	B	397–401
No anatomic or physiologic criteria for revascularization	III: Harm—CABG III: Harm—PCI	C	N/A

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COR, class of recommendation; FFR, fractional flow reserve; GDMT, guideline-directed medical therapy; LOE, level of evidence; N/A, not applicable; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and TMR, transmyocardial laser revascularization.

**anatomy for PCI and who are good candidates for CABG.<sup>301,305,307,312–320</sup> (Level of Evidence: B)**

#### *Non-Left Main CAD Revascularization*

##### **Class I**

1. CABG to improve survival is beneficial in patients with significant ( $\geq 70\%$  diameter) stenoses in 3 major coronary arteries (with or without involvement of the proximal LAD artery) or in the proximal LAD plus 1 other major coronary artery.<sup>314,318,341–344</sup> (Level of Evidence: B)
2. CABG or PCI to improve survival is beneficial in survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant ( $\geq 70\%$  diameter) stenosis in a major coronary artery. (CABG Level of Evidence: B<sup>271,345,347</sup>; PCI Level of Evidence: C<sup>345</sup>)

##### **Class IIa**

1. CABG to improve survival is reasonable in patients with significant ( $\geq 70\%$  diameter) stenoses in 2 major coronary arteries with severe or extensive myocardial ischemia (eg, high-risk criteria on stress testing, abnormal intracoronary hemodynamic evaluation, or  $>20\%$  perfusion defect by myocardial perfusion stress imaging) or target vessels supplying a large area of viable myocardium.<sup>348–351</sup> (Level of Evidence: B)
2. CABG to improve survival is reasonable in patients with mild-moderate LV systolic dysfunction (EF 35% to 50%) and significant ( $\geq 70\%$  diameter stenosis) multivessel CAD or proximal LAD coronary artery stenosis, when viable myocardium is present in the region of intended revascularization.<sup>318,352–356</sup> (Level of Evidence: B)
3. CABG with a LIMA graft to improve survival is reasonable in patients with significant ( $\geq 70\%$  diameter) stenosis in the proximal LAD artery and evi-

dence of extensive ischemia.<sup>87,88,318,343</sup> (Level of Evidence: B)

4. It is reasonable to choose CABG over PCI to improve survival in patients with complex 3-vessel CAD (eg, SYNTAX score  $>22$ ), with or without involvement of the proximal LAD artery, who are good candidates for CABG.<sup>320,334,343,359–360</sup> (Level of Evidence: B)
5. CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery.<sup>350,362–369</sup> (Level of Evidence: B)

##### **Class IIb**

1. The usefulness of CABG to improve survival is uncertain in patients with significant ( $\geq 70\%$ ) stenoses in 2 major coronary arteries not involving the proximal LAD artery and without extensive ischemia.<sup>343</sup> (Level of Evidence: C)
2. The usefulness of PCI to improve survival is uncertain in patients with 2- or 3-vessel CAD (with or without involvement of the proximal LAD artery) or 1-vessel proximal LAD disease.<sup>314,341,343,370</sup> (Level of Evidence: B)
3. CABG might be considered with the primary or sole intent of improving survival in patients with SIHD with severe LV systolic dysfunction (EF  $<35\%$ ) whether or not viable myocardium is present.<sup>318,352–356,371,372</sup> (Level of Evidence: B)
4. The usefulness of CABG or PCI to improve survival is uncertain in patients with previous CABG and extensive anterior wall ischemia on noninvasive testing.<sup>373–381</sup> (Level of Evidence: B)

##### **Class III: HARM**

1. CABG or PCI should not be performed with the primary or sole intent to improve survival in patients with SIHD with 1 or more coronary stenoses that are

not anatomically or functionally significant (eg, <70% diameter non-left main coronary artery stenosis, fractional flow reserve >0.80, no or only mild ischemia on noninvasive testing), involve only the left circumflex or right coronary artery, or subtend only a small area of viable myocardium.<sup>318,341,348,349,382–386</sup> (*Level of Evidence: B*)

### 3.3. Revascularization to Improve Symptoms: Recommendations

#### Class I

1. CABG or PCI to improve symptoms is beneficial in patients with 1 or more significant ( $\geq 70\%$  diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite GDMT.<sup>370,387–396</sup> (*Level of Evidence: A*)

#### Class IIa

1. CABG or PCI to improve symptoms is reasonable in patients with 1 or more significant ( $\geq 70\%$  diameter) coronary artery stenoses and unacceptable angina for whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences. (*Level of Evidence: C*)
2. PCI to improve symptoms is reasonable in patients with previous CABG, 1 or more significant ( $\geq 70\%$  diameter) coronary artery stenoses associated with ischemia, and unacceptable angina despite GDMT.<sup>374,377,380</sup> (*Level of Evidence: C*)
3. It is reasonable to choose CABG over PCI to improve symptoms in patients with complex 3-vessel CAD (eg, SYNTAX score >22), with or without involvement of the proximal LAD artery, who are good candidates for CABG.<sup>320,334,343,359–360</sup> (*Level of Evidence: B*)

#### Class IIb

1. CABG to improve symptoms might be reasonable for patients with previous CABG, 1 or more significant ( $\geq 70\%$  diameter) coronary artery stenoses not amenable to PCI, and unacceptable angina despite GDMT.<sup>381</sup> (*Level of Evidence: C*)
2. Transmyocardial laser revascularization (TMR) performed as an adjunct to CABG to improve symptoms may be reasonable in patients with viable ischemic myocardium that is perfused by arteries that are not amenable to grafting.<sup>397–401</sup> (*Level of Evidence: B*)

#### Class III: HARM

1. CABG or PCI to improve symptoms should not be performed in patients who do not meet anatomic ( $\geq 50\%$  left main or  $\geq 70\%$  non-left main stenosis) or physiological (eg, abnormal fractional flow reserve) criteria for revascularization. (*Level of Evidence: C*)

### 3.4. CABG Versus Contemporaneous Medical Therapy

In the 1970s and 1980s, 3 RCTs established the survival benefit of CABG compared with contemporaneous (although

minimal by current standards) medical therapy without revascularization in certain subjects with stable angina: the Veterans Affairs Cooperative Study,<sup>402</sup> European Coronary Surgery Study,<sup>344</sup> and CASS (Coronary Artery Surgery Study).<sup>403</sup> Subsequently, a 1994 meta-analysis of 7 studies that randomized a total of 2649 patients to medical therapy for CABG<sup>318</sup> showed that CABG offered a survival advantage over medical therapy for patients with left main or 3-vessel CAD. The studies also established that CABG is more effective than medical therapy at relieving anginal symptoms. These studies have been replicated only once during the past decade. In MASS II (Medicine, Angioplasty, or Surgery Study II), patients with multivessel CAD who were treated with CABG were less likely than those treated with medical therapy to have a subsequent MI, need additional revascularization, or experience cardiac death in the 10 years after randomization.<sup>392</sup>

Surgical techniques and medical therapy have improved substantially during the intervening years. As a result, if CABG were to be compared with GDMT in RCTs today, the relative benefits for survival and angina relief observed several decades ago might no longer be observed. Conversely, the concurrent administration of GDMT may substantially improve long-term outcomes in patients treated with CABG in comparison with those receiving medical therapy alone. In the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial of patients with diabetes mellitus, no significant difference in risk of mortality in the cohort of patients randomized to GDMT plus CABG or GDMT alone was observed, although the study was not powered for this endpoint, excluded patients with significant left main CAD, and included only a small percentage of patients with proximal LAD artery disease or LV ejection fraction (LVEF) <0.50.<sup>404</sup> The PCI and CABG guideline writing committees endorse the performance of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, which will provide contemporary data on the optimal management strategy (medical therapy or revascularization with CABG or PCI) of patients with SIHD, including multivessel CAD, and moderate to severe ischemia.

### 3.5. PCI Versus Medical Therapy

Although contemporary interventional treatments have lowered the risk of restenosis compared with earlier techniques, meta-analyses have failed to show that the introduction of bare-metal stents (BMS) confers a survival advantage over balloon angioplasty<sup>405–407</sup> or that the use of drug-eluting stents (DES) confers a survival advantage over BMS.<sup>407,408</sup>

No study to date has demonstrated that PCI in patients with SIHD improves survival rates.<sup>314,341,343,370,404,407,409–412</sup> Neither COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)<sup>370</sup> nor BARI 2D,<sup>404</sup> which treated all patients with contemporary optimal medical therapy, demonstrated any survival advantage with PCI, although these trials were not specifically powered for this endpoint. Although 1 large analysis evaluating 17 RCTs of PCI versus medical therapy (including 5 trials of subjects with ACS) found a 20% reduction in death with PCI



compared with medical therapy,<sup>411</sup> 2 other large analyses did not.<sup>407,410</sup> An evaluation of 13 studies reporting the data from 5442 patients with nonacute CAD showed no advantage of PCI over medical therapy for the individual endpoints of all-cause death, cardiac death or MI, or nonfatal MI.<sup>412</sup> Evaluation of 61 trials of PCI conducted over several decades shows that despite improvements in PCI technology and pharmacotherapy, PCI has not been demonstrated to reduce the risk of death or MI in patients without recent ACS.<sup>407</sup>

The findings from individual studies and systematic reviews of PCI versus medical therapy can be summarized as follows:

- PCI reduces the incidence of angina.<sup>370,387,392,395,396,413</sup>
- PCI has not been demonstrated to improve survival in stable patients.<sup>407,409,410</sup>
- PCI may increase the short-term risk of MI.<sup>370,409,413,414</sup>
- PCI does not lower the long-term risk of MI.<sup>370,404,407,409,410,414</sup>

### 3.6. CABG Versus PCI

The results of 26 RCTs comparing CABG and PCI have been published: Of these, 9 compared CABG with balloon angioplasty,<sup>363,393,415–429</sup> 14 compared CABG with BMS implantation,<sup>376,430–447</sup> and 3 compared CABG with DES implantation.<sup>302,448,449</sup>

#### 3.6.1. CABG Versus Balloon Angioplasty or BMS

A systematic review of the 22 RCTs comparing CABG with balloon angioplasty or BMS implantation concluded the following<sup>450</sup>:

1. Survival was similar for CABG and PCI (with balloon angioplasty or BMS) at 1 year and 5 years. Survival was similar for CABG and PCI in subjects with 1-vessel CAD (including those with disease of the proximal portion of the LAD artery) or multivessel CAD.
2. Incidence of MI was similar at 5 years after randomization.
3. Procedural stroke occurred more commonly with CABG than with PCI (1.2% versus 0.6%).
4. Relief of angina was accomplished more effectively with CABG than with PCI 1 year after randomization and 5 years after randomization.
5. During the first year after randomization, repeat coronary revascularization was performed less often after CABG than after PCI (3.8% versus 26.5%). This was also demonstrated after 5 years of follow-up (9.8% versus 46.1%). This difference was more pronounced with balloon angioplasty than with BMS.

A collaborative analysis of data from 10 RCTs comparing CABG with balloon angioplasty (6 trials) or with BMS implantation (4 trials)<sup>451</sup> permitted subgroup analyses of the data from the 7812 patients. No difference was noted with regard to mortality rate 5.9 years after randomization or the composite endpoint of death or MI. Repeat revascularization and angina were noted more frequently in those treated with balloon angioplasty or BMS implantation.<sup>451</sup> The major new observation of this analysis was that CABG was associated with better outcomes in patients with diabetes mellitus and in those >65 years old. Of interest, the relative outcomes of

CABG and PCI were not influenced by other patient characteristics, including the number of diseased coronary arteries.

The aforementioned meta-analysis and systematic review<sup>450,451</sup> comparing CABG and balloon angioplasty or BMS implantation were limited in several ways.

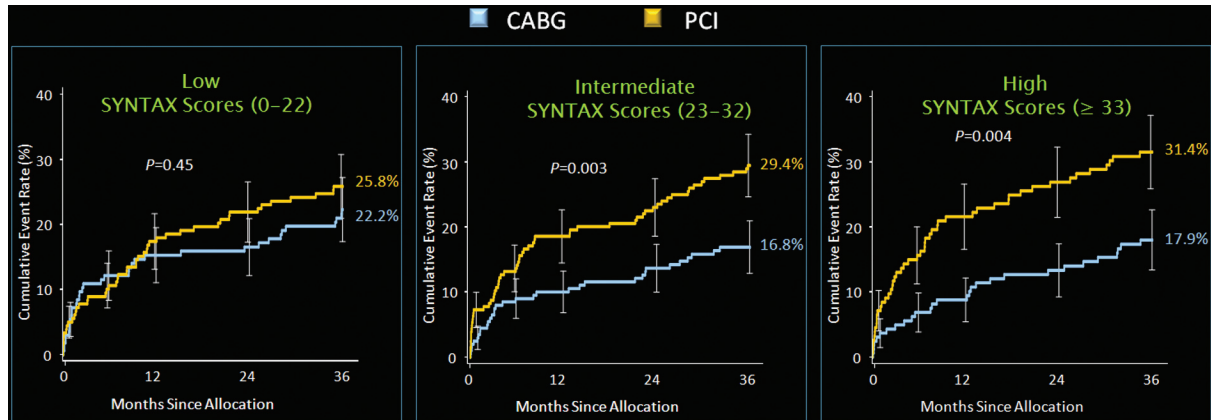
1. Many trials did not report outcomes for other important patient subsets. For example, the available data are insufficient to determine if race, obesity, renal dysfunction, peripheral artery disease (PAD), or previous coronary revascularization affected the comparative outcomes of CABG and PCI.
2. Most of the patients enrolled in these trials were male, and most had 1- or 2-vessel CAD and normal LV systolic function (EF >50%)—subjects known to be unlikely to derive a survival benefit and less likely to experience complications after CABG.<sup>318</sup>
3. The patients enrolled in these trials represented only a small fraction (generally <5% to 10%) of those who were screened. For example, most screened patients with 1-vessel CAD and many with 3-vessel CAD were not considered for randomization.

*See Online Data Supplements 10 and 11 for additional data comparing CABG with PCI.*

#### 3.6.2. CABG Versus DES

Although the results of 9 observational studies comparing CABG and DES implantation have been published,<sup>320,452–459</sup> most of them had short (12 to 24 months) follow-up periods. In a meta-analysis of 24 268 patients with multivessel CAD treated with CABG or DES,<sup>460</sup> the incidences of death and MI were similar for the 2 procedures, but the frequency with which repeat revascularization was performed was roughly 4 times higher after DES implantation. Only 1 large RCT comparing CABG and DES implantation has been published. The SYNTAX trial randomly assigned 1800 patients (of a total of 4337 who were screened) to receive DES or CABG.<sup>302,334</sup> Major adverse cardiac events (MACE), a composite of death, stroke, MI, or repeat revascularization during the 3 years after randomization, occurred in 20.2% of CABG patients and 28.0% of those undergoing DES implantation ( $P<0.001$ ). The rates of death and stroke were similar; however, MI (3.6% for CABG; 7.1% for DES) and repeat revascularization (10.7% for CABG; 19.7% for DES) were more likely to occur with DES implantation.<sup>334</sup>

In SYNTAX, the extent of CAD was assessed using the SYNTAX score, which is based on the location, severity, and extent of coronary stenoses, with a low score indicating less complicated anatomic CAD. In post hoc analyses, a low score was defined as  $\leq 22$ ; intermediate 23 to 32; and high,  $\geq 33$ . The occurrence of MACE correlated with the SYNTAX score for DES patients but not for those undergoing CABG. At 12-month follow-up, the primary endpoint was similar for CABG and DES in those with a low SYNTAX score. In contrast, MACE occurred more often after DES implantation than after CABG in those with an intermediate or high SYNTAX score.<sup>302</sup> At 3 years of follow-up, the mortality rate was greater in subjects with 3-vessel CAD treated with PCI than in those treated with CABG (6.2% versus 2.9%). The differences in MACE between those



**Figure 1.** Cumulative incidence of MACE in patients with 3-vessel CAD based on SYNTAX score at 3-year follow-up in the SYNTAX trial treated with either CABG or PCI. CABG indicates coronary artery bypass graft; CAD, coronary artery disease; MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention; and SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. Adapted with permission from Kappetein.<sup>334</sup>

treated with PCI or CABG increased with an increasing SYNTAX score (Figure 1).<sup>334</sup>

Although the utility of using a SYNTAX score in everyday clinical practice remains uncertain, it seems reasonable to conclude from SYNTAX and other data that outcomes of patients undergoing PCI or CABG in those with relatively uncomplicated and lesser degrees of CAD are comparable, whereas in those with complex and diffuse CAD, CABG appears to be preferable.<sup>334</sup>

See Online Data Supplements 12 and 13 for additional data comparing CABG with DES.

### 3.7. Left Main CAD

#### 3.7.1. CABG or PCI Versus Medical Therapy for Left Main CAD

CABG confers a survival benefit over medical therapy in patients with left main CAD. Subgroup analyses from RCTs performed 3 decades ago included 91 patients with left main CAD in the Veterans Administration Cooperative Study.<sup>316</sup> A meta-analysis of these trials demonstrated a 66% RR reduction in mortality with CABG, with the benefit extending to 10 years.<sup>318</sup> The CASS Registry<sup>312</sup> contained data from 1484 patients with  $\geq 50\%$  left main CAD initially treated surgically or nonsurgically. Median survival duration was 13.3 years in the surgical group and 6.6 years in the medical group. The survival benefit of CABG over medical therapy appeared to extend to 53 asymptomatic patients with left main CAD in the CASS Registry.<sup>317</sup> Other therapies that subsequently have been shown to be associated with improved long-term outcome, such as the use of aspirin, statins, and IMA grafting, were not widely used in that era.

RCTs and subgroup analyses that compare PCI with medical therapy in patients with “unprotected” left main CAD do not exist.

#### 3.7.2. Studies Comparing PCI Versus CABG for Left Main CAD

Of all subjects undergoing coronary angiography, approximately 4% are found to have left main CAD,<sup>463</sup> >80% of

whom have significant ( $\geq 70\%$  diameter) stenoses in other epicardial coronary arteries.

Published cohort studies have found that major clinical outcomes are similar with PCI or CABG 1 year after revascularization and that mortality rates are similar at 1, 2, and 5 years of follow-up; however, the risk of needing target-vessel revascularization is significantly higher with stenting than with CABG.

In the SYNTAX trial, 45% of screened patients with unprotected left main CAD had complex diseases that prevented randomization; 89% of these underwent CABG.<sup>301,302</sup> In addition, 705 of the 1800 patients who were randomized had revascularization for unprotected left main CAD. The majority of patients with left main CAD and a low SYNTAX score had isolated left main CAD or left main CAD plus 1-vessel CAD; the majority of those with an intermediate score had left main CAD plus 2-vessel CAD; and most of those with a high SYNTAX score had left main CAD plus 3-vessel CAD. At 1 year, rates of all-cause death and MACE were similar for the 2 groups.<sup>301</sup> Repeat revascularization rates were higher in the PCI group than the CABG group (11.8% versus 6.5%), but stroke occurred more often in the CABG group (2.7% versus 0.3%). At 3 years of follow-up, the incidence of death in those undergoing left main CAD revascularization with low or intermediate SYNTAX scores ( $\leq 32$ ) was 3.7% after PCI and 9.1% after CABG ( $P=0.03$ ), whereas in those with a high SYNTAX score ( $\geq 33$ ) the incidence of death after 3 years was 13.4% after PCI and 7.6% after CABG ( $P=0.10$ ).<sup>334</sup> Because the primary endpoint of SYNTAX was not met (ie, noninferiority comparison of CABG and PCI), these subgroup analyses need to be considered in that context.

In the LE MANS (Study of Unprotected Left Main Stenting Versus Bypass Surgery) trial,<sup>311</sup> 105 patients with left main CAD were randomized to receive PCI or CABG. Although a low proportion of patients treated with PCI received DES (35%) and a low proportion of patients treated with CABG received IMA grafts (72%), the outcomes at 30 days and 1 year were similar between the groups. In the PRECOMBAT (Premier of Randomized Comparison of By-

pass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease) trial of 600 patients with left main disease, the composite endpoint of death, MI, or stroke at 2 years occurred in 4.4% of patients treated with PCI and 4.7% of patients treated with CABG, but ischemia-driven target-vessel revascularization was more often required in the patients treated with PCI (9.0% versus 4.2%).<sup>340</sup>

The results from these 3 RCTs suggest (but do not definitively prove) that major clinical outcomes in *selected* patients with left main CAD are similar with CABG and PCI at 1- to 2-year follow-up, but repeat revascularization rates are higher after PCI than after CABG. RCTs with extended follow-up of  $\geq 5$  years are required to provide definitive conclusions about the optimal treatment of left main CAD. In a meta-analysis of 8 cohort studies and 2 RCTs,<sup>329</sup> death, MI, and stroke occurred with similar frequency in the PCI- and CABG-treated patients at 1, 2, and 3 years of follow-up. Target-vessel revascularization was performed more often in the PCI group at 1 year (OR: 4.36), 2 years (OR: 4.20), and 3 years (OR: 3.30).

*See Online Data Supplements 14 to 19 for additional data comparing PCI with CABG for left main CAD.*

### 3.7.3. Revascularization Considerations for Left Main CAD

Although CABG has been considered the “gold standard” for unprotected left main CAD revascularization, more recently PCI has emerged as a possible alternative mode of revascularization in carefully selected patients. Lesion location is an important determinant when considering PCI for unprotected left main CAD. Stenting of the left main ostium or trunk is more straightforward than treating distal bifurcation or trifurcation stenoses, which generally requires a greater degree of operator experience and expertise.<sup>464</sup> In addition, PCI of bifurcation disease is associated with higher restenosis rates than when disease is confined to the ostium or trunk.<sup>327,465</sup> Although lesion location influences technical success and long-term outcomes after PCI, location exerts a negligible influence on the success of CABG. In subgroup analyses, patients with left main CAD and a SYNTAX score  $\geq 33$  with more complex or extensive CAD had a higher mortality rate with PCI than with CABG.<sup>334</sup> Physicians can estimate operative risk for all CABG candidates by using a standard instrument, such as the risk calculator from the STS database. The above considerations are important factors when choosing among revascularization strategies for unprotected left main CAD and have been factored into revascularization recommendations. Use of a Heart Team approach has been recommended in cases in which the choice of revascularization is not straightforward. As discussed in Section 3.9.7, the ability of the patient to tolerate and comply with dual antiplatelet therapy (DAPT) is also an important consideration in revascularization decisions.

The 2005 PCI guidelines<sup>466</sup> recommended routine angiographic follow-up 2 to 6 months after stenting for unprotected left main CAD. However, because angiography has limited ability to predict stent thrombosis and the results of SYNTAX suggest good intermediate-term results for PCI in subjects

with left main CAD, this recommendation was removed in the 2009 STEMI/PCI focused update.<sup>467</sup>

Experts have recommended immediate PCI for unprotected left main CAD in the setting of STEMI.<sup>339</sup> The impetus for such a strategy is greatest when the left main CAD is the site of the culprit lesion, antegrade coronary flow is diminished [eg, Thrombolysis In Myocardial Infarction flow grade 0, 1, or 2], the patient is hemodynamically unstable, and it is believed that PCI can be performed more quickly than CABG. When possible, the interventional cardiologist and cardiac surgeon should decide together on the optimal form of revascularization for these subjects, although it is recognized that these patients are usually critically ill and therefore not amenable to a prolonged deliberation or discussion of treatment options.

### 3.8. Proximal LAD Artery Disease

A cohort study<sup>341</sup> and a meta-analysis<sup>318</sup> from the 1990s suggested that CABG confers a survival advantage over contemporaneous medical therapy for patients with disease in the proximal segment of the LAD artery. Cohort studies and RCTs<sup>318,420,432,433,435,448,468–470</sup> as well as collaborative- and meta-analyses<sup>451,471–473</sup> showed that PCI and CABG result in similar survival rates in these patients.

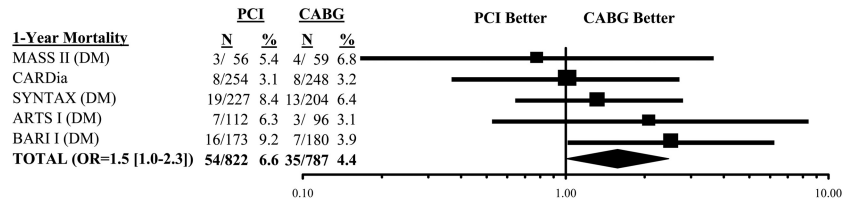
*See Online Data Supplement 20 for additional data regarding proximal LAD artery revascularization.*

### 3.9. Clinical Factors That May Influence the Choice of Revascularization

#### 3.9.1. Diabetes Mellitus

An analysis performed in 2009 of data on 7812 patients (1233 with diabetes) in 10 RCTs demonstrated a worse long-term survival rate in patients with diabetes mellitus after balloon angioplasty or BMS implantation than after CABG.<sup>451</sup> The BARI 2D trial<sup>404</sup> randomly assigned 2368 patients with type 2 diabetes and CAD to undergo intensive medical therapy or prompt revascularization with PCI or CABG, according to whichever was thought to be more appropriate. By study design, those with less extensive CAD more often received PCI, whereas those with more extensive CAD were more likely to be treated with CABG. The study was not designed to compare PCI with CABG. At 5-year follow-up, no difference in rates of survival or MACE between the medical therapy group and those treated with revascularization was noted. In the PCI stratum, no significant difference in MACE between medical therapy and revascularization was demonstrated (DES in 35%; BMS in 56%); in the CABG stratum, MACE occurred less often in the revascularization group. One-year follow-up data from the SYNTAX study demonstrated a higher rate of repeat revascularization in patients with diabetes mellitus treated with PCI than with CABG, driven by a tendency for higher repeat revascularization rates in those with higher SYNTAX scores undergoing PCI.<sup>364</sup> In summary, in subjects requiring revascularization for multivessel CAD, current evidence supports diabetes mellitus as an important factor when deciding on a revascularization strategy, particularly when complex or extensive CAD is present (Figure 2).





**Figure 2.** 1-year mortality after revascularization for multivessel disease and diabetes mellitus. An OR of  $>1$  suggests an advantage of CABG over PCI. ARTS I indicates Arterial Revascularization Therapy Study I<sup>474</sup>; BARI I, Bypass Angioplasty Revascularization Investigation I<sup>362</sup>; CARDia, Coronary Artery Revascularization in Diabetes<sup>475</sup>; CI, confidence interval; DM, diabetes mellitus; MASS II, Medicine, Angioplasty, or Surgery Study II<sup>366</sup>; OR, odds ratio; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and W, weighted.<sup>364</sup>

See Online Data Supplements 21 and 22 for additional data regarding diabetes mellitus.

### 3.9.2. Chronic Kidney Disease

Cardiovascular morbidity and mortality rates are markedly increased in patients with chronic kidney disease (CKD) when compared with age-matched controls without CKD. The mortality rate for patients on hemodialysis is  $>20\%$  per year, and approximately 50% of deaths among these patients are due to a cardiovascular cause.<sup>476,477</sup>

To date, randomized comparisons of coronary revascularization (with CABG or PCI) and medical therapy in patients with CKD have not been reported. Some, but not all, observational studies or subgroup analyses have demonstrated an improved survival rate with revascularization compared with medical therapy in patients with CKD and multivessel CAD,<sup>478–480</sup> despite the fact that the incidence of periprocedural complications (eg, death, MI, stroke, infection, renal failure) is increased in patients with CKD compared with those without renal dysfunction. Some studies have shown that CABG is associated with a greater survival benefit than PCI among patients with severe renal dysfunction.<sup>479–485</sup>

### 3.9.3. Completeness of Revascularization

Most patients undergoing CABG receive complete or nearly complete revascularization, which seems to influence long-term prognosis positively.<sup>486</sup> In contrast, complete revascularization is accomplished less often in subjects receiving PCI (eg, in  $<70\%$  of patients), but the extent to which the absence of complete initial revascularization influences outcome is less clear. Rates of late survival and survival free of MI appear to be similar in patients with and without complete revascularization after PCI. Nevertheless, the need for subsequent CABG is usually higher in those whose initial revascularization procedure was incomplete (compared with those with complete revascularization) after PCI.<sup>487–489</sup>

### 3.9.4. LV Systolic Dysfunction

Several older studies and a meta-analysis of the data from these studies reported that patients with LV systolic dysfunction (predominantly mild to moderate in severity) had better survival with CABG than with medical therapy alone.<sup>318,352–356</sup> For patients with more severe LV systolic dysfunction, however, the evidence that CABG results in better survival compared with medical therapy is lacking. In the STICH (Surgical Treatment for Ischemic Heart Failure) trial of subjects with LVEF  $<35\%$  with or without viability

testing, CABG and GDMT resulted in similar rates of survival (death from any cause, the study's primary outcome) after 5 years of follow-up. For a number of secondary outcomes at this time point, including 1) death from any cause or hospitalization for heart failure, 2) death from any cause or hospitalization for cardiovascular causes, 3) death from any cause or hospitalization for any cause, or 4) death from any cause or revascularization with PCI or CABG, CABG was superior to GDMT. Although the primary outcome (death from any cause) was similar in the 2 treatment groups after an average of 5 years of follow-up, the data suggest the possibility that outcomes would differ if the follow-up were longer in duration; as a result, the study is being continued to provide follow-up for up to 10 years.<sup>371,372</sup>

Only very limited data comparing PCI with medical therapy in patients with LV systolic dysfunction are available.<sup>356</sup> In several ways, these data are suboptimal, in that many studies compared CABG with balloon angioplasty, many were retrospective, and many were based on cohort or registry data. Some of the studies demonstrated a similar survival rate in patients having CABG and PCI,<sup>359,451,490–492</sup> whereas others showed that those undergoing CABG had better outcomes.<sup>320</sup> The data that exist at present on revascularization in patients with CAD and LV systolic dysfunction are more robust for CABG than for PCI, although data from contemporary RCTs in this patient population are lacking. Therefore, the choice of revascularization in patients with CAD and LV systolic dysfunction is best based on clinical variables (eg, coronary anatomy, presence of diabetes mellitus, presence of CKD), magnitude of LV systolic dysfunction, patient preferences, clinical judgment, and consultation between the interventional cardiologist and the cardiac surgeon.

### 3.9.5. Previous CABG

In patients with recurrent angina after CABG, repeat revascularization is most likely to improve survival in subjects at highest risk, such as those with obstruction of the proximal LAD artery and extensive anterior ischemia.<sup>373–381</sup> Patients with ischemia in other locations and those with a patent LIMA to the LAD artery are unlikely to experience a survival benefit from repeat revascularization.<sup>380</sup>

Cohort studies comparing PCI and CABG among post-CABG patients report similar rates of mid- and long-term survival after the 2 procedures.<sup>373,376–379,381,493</sup> In the patient with previous CABG who is referred for revascularization for medically refractory ischemia, factors that may support the choice of repeat CABG include vessels unsuitable for PCI,

number of diseased bypass grafts, availability of the IMA for grafting, chronically occluded coronary arteries, and good distal targets for bypass graft placement. Factors favoring PCI over CABG include limited areas of ischemia causing symptoms, suitable PCI targets, a patent graft to the LAD artery, poor CABG targets, and comorbid conditions.

### 3.9.6. Unstable Angina/Non-ST-Elevation Myocardial Infarction

The main difference between management of the patient with SIHD and the patient with UA/NSTEMI is that the impetus for revascularization is stronger in the setting of UA/NSTEMI, because myocardial ischemia occurring as part of an ACS is potentially life threatening, and associated anginal symptoms are more likely to be reduced with a revascularization procedure than with GDMT.<sup>494–496</sup> Thus, the indications for revascularization are strengthened by the acuity of presentation, the extent of ischemia, and the ability to achieve full revascularization. The choice of revascularization method is generally dictated by the same considerations used to decide on PCI or CABG for patients with SIHD.

### 3.9.7. DAPT Compliance and Stent Thrombosis: Recommendation

#### Class III: HARM

1. PCI with coronary stenting (BMS or DES) should not be performed if the patient is not likely to be able to tolerate and comply with DAPT for the appropriate duration of treatment based on the type of stent implanted.<sup>497–500</sup> (*Level of Evidence: B*)

The risk of stent thrombosis is increased dramatically in patients who prematurely discontinue DAPT, and stent thrombosis is associated with a mortality rate of 20% to 45%.<sup>497</sup> Because the risk of stent thrombosis with BMS is greatest in the first 14 to 30 days, this is the generally recommended minimum duration of DAPT therapy for these individuals. Consensus in clinical practice is to treat DES patients for at least 12 months with DAPT to avoid late (after 30 days) stent thrombosis.<sup>497,501</sup> Therefore, the ability of the patient to tolerate and comply with at least 30 days of DAPT with BMS treatment and at least 12 months of DAPT with DES treatment is an important consideration in deciding whether to use PCI to treat patients with CAD.

### 3.10. TMR as an Adjunct to CABG

TMR has been used on occasion in patients with severe angina refractory to GDMT in whom complete revascularization cannot be achieved with PCI and/or CABG. Although the mechanism by which TMR might be efficacious in these patients is unknown,<sup>502,503</sup> several RCTs of TMR as sole therapy demonstrated a reduction in anginal symptoms compared with intensive medical therapy alone.<sup>397–399,504–506</sup> A single randomized multicenter comparison of TMR (with a holmium:YAG laser) plus CABG and CABG alone in subjects in whom some myocardial segments were perfused by arteries considered not amenable to grafting showed a significant reduction in perioperative mortality rate (1.5% versus 7.6%, respectively), and the survival benefit of the TMR–CABG combination was present after 1 year of follow-up.<sup>400</sup>

At the same time, a large retrospective analysis of data from the STS National Cardiac Database, as well as a study of 169 patients from the Washington Hospital Center who underwent combined TMR–CABG, showed no difference in adjusted mortality rate compared with CABG alone.<sup>401,507</sup> In short, a TMR–CABG combination does not appear to improve survival compared with CABG alone. In selected patients, however, such a combination may be superior to CABG alone in relieving angina.

### 3.11. Hybrid Coronary Revascularization: Recommendations

#### Class IIa

1. Hybrid coronary revascularization (defined as the planned combination of LIMA-to-LAD artery grafting and PCI of  $\geq 1$  non-LAD coronary arteries) is reasonable in patients with 1 or more of the following<sup>508–516</sup> (*Level of Evidence: B*):
  - a. Limitations to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI);
  - b. Lack of suitable graft conduits;
  - c. Unfavorable LAD artery for PCI (ie, excessive vessel tortuosity or chronic total occlusion).

#### Class IIb

1. Hybrid coronary revascularization (defined as the planned combination of LIMA-to-LAD artery grafting and PCI of  $\geq 1$  non-LAD coronary arteries) may be reasonable as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk–benefit ratio of the procedures. (*Level of Evidence: C*)

Hybrid coronary revascularization, defined as the planned combination of LIMA-to-LAD artery grafting and PCI of  $\geq 1$  non-LAD coronary arteries,<sup>515</sup> is intended to combine the advantages of CABG (ie, durability of the LIMA graft) and PCI.<sup>516</sup> Patients with multivessel CAD (eg, LAD and  $\geq 1$  non-LAD stenoses) and an indication for revascularization are potentially eligible for this approach. Hybrid revascularization is ideal in patients in whom technical or anatomic limitations to CABG or PCI alone may be present and for whom minimizing the invasiveness (and therefore the risk of morbidity and mortality) of surgical intervention is preferred<sup>510</sup> (eg, patients with severe preexisting comorbidities, recent MI, a lack of suitable graft conduits, a heavily calcified ascending aorta, or a non-LAD coronary artery unsuitable for bypass but amenable to PCI, and situations in which PCI of the LAD artery is not feasible because of excessive tortuosity or chronic total occlusion).

Hybrid coronary revascularization may be performed in a hybrid suite in one operative setting or as a staged procedure (ie, PCI and CABG performed in 2 different operative suites, separated by hours to 2 days, but typically during the same hospital stay). Because most hospitals lack a hybrid operating room, staged procedures are usually performed. With the staged procedure, CABG before PCI is preferred, because this approach allows the interventional cardiologist to 1)

verify the patency of the LIMA-to-LAD artery graft before attempting PCI of other vessels and 2) minimize the risk of perioperative bleeding that would occur if CABG were performed after PCI (ie, while the patient is receiving DAPT). Because minimally invasive CABG may be associated with lower graft patency rates compared with CABG performed through a midline sternotomy, it seems prudent to angiographically image all grafts performed through a minimally invasive approach to confirm graft patency.<sup>510</sup>

To date, no RCTs involving hybrid coronary revascularization have been published. Over the past 10 years, several small, retrospective series of hybrid revascularization using minimally invasive CABG and PCI have reported low mortality rates (0 to 2%) and event-free survival rates of 83% to 92% at 6 to 12 months of follow-up. The few series that have compared the outcomes of hybrid coronary revascularization with standard CABG report similar outcomes at 30 days and 6 months.<sup>508–514</sup>

## 4. Perioperative Management

### 4.1. Preoperative Antiplatelet Therapy: Recommendations

#### Class I

1. Aspirin (100 mg to 325 mg daily) should be administered to CABG patients preoperatively.<sup>517–519</sup> (*Level of Evidence: B*)
2. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery<sup>520–522</sup> (*Level of Evidence: B*) and prasugrel for at least 7 days (*Level of Evidence: C*) to limit blood transfusions.
3. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications.<sup>521,523–525</sup> (*Level of Evidence: B*)
4. In patients referred for CABG, short-acting intravenous glycoprotein IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before surgery<sup>526,527</sup> and abciximab for at least 12 hours beforehand<sup>528</sup> to limit blood loss and transfusions. (*Level of Evidence: B*)

#### Class IIb

1. In patients referred for urgent CABG, it may be reasonable to perform surgery less than 5 days after clopidogrel or ticagrelor has been discontinued and less than 7 days after prasugrel has been discontinued. (*Level of Evidence: C*)

Nearly all patients with UA or recent MI in whom CABG is performed will be taking aspirin; CABG can be performed safely in these individuals, with only a modest increase in bleeding risk. Preoperative aspirin use reduces operative morbidity and mortality rates.<sup>517,518</sup>

Although the use of thienopyridines (clopidogrel or prasugrel) is associated with improved outcomes in subjects with UA or NSTEMI,<sup>305,306</sup> their use is associated with an increase in post-CABG bleeding and need for transfusions.<sup>520,522,529–533</sup> The

risk of major bleeding complications (ie, pericardial tamponade or reoperation) is increased when CABG is performed <24 hours after clopidogrel's discontinuation.<sup>524,525</sup> Conversely, no increase in bleeding or transfusions is noted when CABG is performed >5 days after clopidogrel has been stopped.<sup>529,532</sup> The magnitude of bleeding risk when CABG is performed 1 to 4 days after the discontinuation of clopidogrel is less certain. Although the incidence of life-threatening bleeding does not appear to be significantly increased during this time, an increase in blood transfusions is likely.<sup>523,524,529,531</sup> Accordingly, from the perspective of blood conservation, it is reasonable to delay elective CABG for ≥5 days after discontinuing clopidogrel. For patients requiring more urgent CABG, it can be performed >24 hours after clopidogrel has been stopped with little or no increased risk of major bleeding. Approximately two thirds of clopidogrel-treated patients undergo CABG <5 days after clopidogrel discontinuation,<sup>529,532</sup> driven largely by concerns for patient stability, resource utilization, patient preference, and the confidence of the surgical team in managing hemostasis. Little experience with CABG in patients treated with prasugrel has been reported. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction) trial, the incidence of CABG-related major bleeding was higher in prasugrel-treated patients than in those on clopidogrel (13.4% versus 3.2%;  $P<0.001$ ).<sup>533</sup> When possible, therefore, CABG should be delayed for ≥7 days after prasugrel is discontinued.<sup>533</sup>

Ticagrelor, an oral agent that binds reversibly to the platelet P2Y<sub>12</sub> receptor, provides faster, more effective, and more consistent inhibition of platelet aggregation and more rapid recovery of platelet function after discontinuation than clopidogrel.<sup>534</sup> In the PLATO (Platelet Inhibition and Patient Outcomes) trial, 632 patients in the ticagrelor group and 629 in the clopidogrel group underwent CABG within 7 days of the last dose of study drug.<sup>521</sup> Although the study protocol recommended waiting ≥5 days after stopping clopidogrel and 24 to 72 hours after ticagrelor, many patients underwent surgery before the recommended waiting times. The rates of major bleeding (59.3% with ticagrelor, 57.6% with clopidogrel) and transfusion requirements (55.7% with ticagrelor, 56.5% with clopidogrel) were similar. Furthermore, no difference in bleeding was noted between ticagrelor and clopidogrel with respect to time from last dose of study drug, even when CABG was performed 1, 2, or 3 days after discontinuation. On the basis of these data, it does not appear that the more rapid recovery of platelet function seen in ticagrelor pharmacokinetic studies translates to a lower risk of bleeding or less need for transfusion compared with clopidogrel when CABG is performed early (ie, <5 days) after drug discontinuation.

### 4.2. Postoperative Antiplatelet Therapy: Recommendations

#### Class I

1. If aspirin (100 mg to 325 mg daily) was not initiated preoperatively, it should be initiated within 6 hours postoperatively and then continued indefinitely to



**reduce the occurrence of SVG closure and adverse cardiovascular events.<sup>519,535,536</sup> (Level of Evidence: A)**

#### Class IIa

1. For patients undergoing CABG, clopidogrel 75 mg daily is a reasonable alternative in patients who are intolerant of or allergic to aspirin. (Level of Evidence: C)

See Online Data Supplement 23 for additional data on postoperative antiplatelet therapy.

Aspirin significantly improves SVG patency rates, particularly during the first postoperative year. Because arterial graft patency rates are high even in the absence of antiplatelet therapy, the administration of such therapy has not shown an improvement. Aspirin administration before CABG offers no improvement in subsequent SVG patency compared with its early postoperative initiation.<sup>535</sup> Prospective controlled trials have demonstrated a graft patency benefit when aspirin was started 1, 7, or 24 hours after operation<sup>103,537</sup>; in contrast, the benefit of postoperative aspirin on SVG patency was lost when it was initiated >48 hours after surgery.<sup>538</sup>

Dosing regimens ranging from 100 mg daily to 325 mg 3 times daily appear to be efficacious.<sup>539</sup> As the grafted recipient's coronary arterial luminal diameter increases, SVG patency rates improve, and the relative advantage of aspirin over placebo is reduced.<sup>540</sup> Although aspirin doses of <100 mg daily have been used for prevention of adverse events in patients with CAD, they may be less efficacious than higher doses in optimizing SVG patency.<sup>541</sup> Enteric-coated aspirin, 75 mg, has been associated with suboptimal inhibition of platelet aggregation in 44% of patients with stable cardiovascular disease, suggesting that soluble aspirin may be preferred if low-dose aspirin is used.<sup>542</sup> When given within 48 hours after CABG, aspirin has been shown to reduce subsequent rates of mortality, MI, stroke, renal failure, and bowel infarction.<sup>519</sup>

Although ticlopidine is efficacious at inhibiting platelet aggregation, it offers no advantage over aspirin except as an alternative in the truly aspirin-allergic patient.<sup>543</sup> In addition, its use may be associated with potentially life-threatening neutropenia, a rare adverse effect, such that white blood cell counts should be monitored repetitively after initiating it. Dipyridamole and warfarin add nothing to the effect of aspirin on SVG patency,<sup>544,545</sup> and use of the latter may be associated with an increased risk for bleeding compared with antiplatelet agents.<sup>546</sup>

Clopidogrel is associated with fewer adverse effects than ticlopidine. Severe leukopenia occurs very rarely.<sup>546,547</sup> A subset analysis of CABG patients from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial suggested that clopidogrel reduced the occurrence of cardiovascular death, MI, and stroke (14.5%) compared with placebo (16.2%). This benefit occurred primarily before surgery, however, and after CABG a difference in primary endpoints between groups was not demonstrable. Clopidogrel was stopped a median of 10 days before surgery and was restarted postoperatively in 75.3% of patients assigned to receive it. All patients received aspirin, 75 mg to

325 mg daily, but the details of aspirin administration in the study groups were not described.<sup>530</sup>

### 4.3. Management of Hyperlipidemia: Recommendations

#### Class I

1. All patients undergoing CABG should receive statin therapy, unless contraindicated.<sup>545,548–559</sup> (Level of Evidence: A)
2. In patients undergoing CABG, an adequate dose of statin should be used to reduce LDL cholesterol to less than 100 mg/dL and to achieve at least a 30% lowering of LDL cholesterol.<sup>548–552</sup> (Level of Evidence: C)

#### Class IIa

1. In patients undergoing CABG, it is reasonable to treat with statin therapy to lower the LDL cholesterol to less than 70 mg/dL in very high-risk\* patients.<sup>549–551,561–563</sup> (Level of Evidence: C)
2. For patients undergoing urgent or emergency CABG who are not taking a statin, it is reasonable to initiate high-dose statin therapy immediately.<sup>564</sup> (Level of Evidence: C)

#### Class III: HARM

1. Discontinuation of statin or other dyslipidemic therapy is not recommended before or after CABG in patients without adverse reactions to therapy.<sup>565–567</sup> (Level of Evidence: B)

See Online Data Supplement 24 for additional data on management of hyperlipidemia.

In patients with CAD, treatment of hyperlipidemia with therapeutic lifestyle changes and medications reduces the risk of nonfatal MI and death. The goal of such therapy is to reduce the LDL cholesterol level to <100 mg/dL.<sup>563</sup> Statins are the most commonly prescribed agents for achieving this goal.<sup>563</sup>

Studies of lipid-lowering therapy in CABG patients have demonstrated that lowering LDL cholesterol with statins influences post-CABG outcomes, and “aggressive” LDL cholesterol lowering (to 60 to 85 mg/dL) is associated with a reduced rate of graft atherosclerosis and repeat revascularization compared with only “moderate” lowering (130 to 140 mg/dL).<sup>545,556</sup> In the latter study, both groups of subjects initially received lovastatin at different doses (40 mg in the “aggressive” lowering group versus 2.5 mg in the “moderate” group), and cholestyramine was added if LDL cholesterol goals were not met with lovastatin alone. Of note, patients were maintained on therapy for ≥1 year, and as many as 11 years, after CABG.

The PROVE IT TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction) trial randomly assigned patients with ACS, a

\*Presence of established cardiovascular disease plus 1) multiple major risk factors (especially diabetes), 2) severe and poorly controlled risk factors (especially continued cigarette smoking), 3) multiple risk factors of the metabolic syndrome (especially high triglycerides ≥200 mg/dL plus non-high-density lipoprotein cholesterol ≥130 mg/dL with low high-density lipoprotein cholesterol [ $<40$  mg/dL]), and 4) acute coronary syndromes.

minority of whom had previous CABG, to intensive (LDL cholesterol goal <70 mg/dL) versus standard (LDL cholesterol goal <100 mg/dL) lipid-lowering therapy. The benefit of intensive therapy (a reduction in death, MI, recurrent UA, repeat revascularization, or stroke) was observed within 30 days.<sup>561</sup> In the occasional subject who cannot take statins, alternative hypolipidemic agents, such as bile acid sequestrants, niacin, and fibrates, should be considered, in accordance with National Cholesterol Education Program: Adult Treatment Panel III guidelines.<sup>563</sup>

#### 4.3.1. Timing of Statin Use and CABG Outcomes

As noted, the benefits of post-CABG LDL lowering with statins have been reported previously, but no prospective studies of the impact of preoperative LDL cholesterol lowering on post-CABG outcomes are available. One small randomized comparison of preoperative placebo and a statin (initiated 1 week before CABG) showed a reduction in elevated perioperative cardiac biomarkers with statin therapy.<sup>554</sup> Several nonrandomized, retrospective studies have noted an association between preoperative statin use and reduced rates of postoperative nonfatal MI and death.<sup>553,555,557–559</sup> In addition, preoperative statin use has been associated with reduced rates of postoperative atrial fibrillation (AF),<sup>571,572</sup> neurological dysfunction,<sup>555,573,574</sup> renal dysfunction,<sup>575</sup> and infection.<sup>576</sup> Untreated hyperlipidemic patients have been shown to have a higher risk of post-CABG events than that of treated hyperlipidemic patients and those with normal serum lipid concentrations.<sup>567</sup> In patients undergoing CABG who are not on statin therapy or at LDL goal, it seems reasonable to initiate intensive statin therapy preoperatively (ie, no later than 1 week before surgery).

Postoperatively, statin use should be resumed when the patient is able to take oral medications and should be continued indefinitely. Patients in whom statins were discontinued after CABG have been shown to have a higher mortality rate than those in whom statins were continued postoperatively.<sup>566</sup>

##### 4.3.1.1. Potential Adverse Effects of Perioperative Statin Therapy

The most common adverse effects reported with statin use are myopathy and hepatotoxicity. Muscle aches have been reported in about 5% of patients treated with statins, although several pooled analyses of RCTs have shown a similar rate of muscle aches with placebo.<sup>577</sup> Myositis, defined as muscle pain with a serum creatine kinase >10 times the upper limit of normal, occurs in 0.1% to 0.2% of statin users, and rhabdomyolysis occurs in 0.02%.<sup>578,579</sup> In addition, approximately 2% of patients are observed to have elevated liver enzymes (ie, alanine and aspartate transaminases) in the weeks to months after statin initiation, but no data are available to suggest that these elevations are associated with permanent hepatotoxicity or an increased risk of hepatitis. Nonetheless, the presence of active or chronic liver disease is a contraindication to statin use, and patients initiated on a statin should be monitored for the development of myositis or rhabdomyolysis, either of which would mandate its discontinuation.<sup>580</sup>

## 4.4. Hormonal Manipulation: Recommendations

### Class I

1. Use of continuous intravenous insulin to achieve and maintain an early postoperative blood glucose concentration less than or equal to 180 mg/dL while avoiding hypoglycemia is indicated to reduce the incidence of adverse events, including deep sternal wound infection, after CABG.<sup>581–583</sup> (*Level of Evidence: B*)

### Class IIb

1. The use of continuous intravenous insulin designed to achieve a target intraoperative blood glucose concentration less than 140 mg/dL has uncertain effectiveness.<sup>584–586</sup> (*Level of Evidence: B*)

### Class III: HARM

1. Postmenopausal hormonal therapy (estrogen/progesterone) should not be administered to women undergoing CABG.<sup>587–589</sup> (*Level of Evidence: B*)

#### 4.4.1. Glucose Control

Hyperglycemia often occurs during and after CABG, particularly when CABG is performed on pump. Intraoperative hyperglycemia is associated with an increased morbidity rate in patients with diabetes<sup>590</sup> and with excess mortality in patients with and without diabetes.<sup>591</sup> Hyperglycemia during CPB is an independent risk factor for death in patients undergoing cardiac surgery. A retrospective observational study of 409 cardiac surgical patients identified intraoperative hyperglycemia as an independent risk factor for perioperative complications, including death, and calculated a 34% increased likelihood of postoperative complications for every 20-mg/dL increase in blood glucose concentration >100 mg/dL during surgery.<sup>592</sup> An RCT of critically ill patients, many of whom had high-risk cardiac surgery, found reduced morbidity and mortality rates in those whose blood glucose was tightly controlled,<sup>583</sup> and follow-up of these subjects showed that this benefit persisted for up to 4 years.<sup>582</sup>

The Portland Diabetes Project, begun in 1992, was the first large study to elucidate the detrimental effects of hyperglycemia in relation to CABG outcomes. This prospective observational study described the evolution in management of cardiac surgical patients with diabetes mellitus from a strategy of intermittent subcutaneous injections of insulin to one of continuous intravenous insulin infusion with decreasing target glucose concentrations. As this management strategy evolved, the upper target serum glucose concentrations declined from 200 mg/dL to 110 mg/dL, with which significant reductions in operative and cardiac-related death (arrhythmias and acute ventricular failure) were noted.<sup>581</sup> In addition, continuous intravenous insulin to maintain a serum glucose concentration of 120 mg/dL to 160 mg/dL resulted in a reduced incidence of deep sternal wound infection.<sup>593,594</sup> As a result, most centers now emphasize tight glucose control (target serum glucose concentration ≤180 mg/dL, accomplished with a continuous intravenous insulin infusion) during surgery and until the morning of the third postoperative day.

Whether extremely tight intraoperative glucose control can further reduce morbidity or mortality rate is controversial. A prospective trial from the Mayo Clinic randomly assigned 400 patients to intensive treatment (continuous insulin infusion during surgery) or conventional treatment (insulin given only for a glucose concentration  $>200$  mg/dL).<sup>586</sup> Postoperative ICU management was similar in the 2 groups. Although no difference was noted between groups in a composite endpoint of death, deep sternal wound infection, prolonged ventilation, cardiac arrhythmias, stroke, or renal failure within 30 days of surgery, intensive treatment caused an increased incidence of death and stroke, thereby raising concerns about this intervention.<sup>586</sup> In a prospective RCT in 381 CABG patients without diabetes, those with an intraoperative blood glucose concentration  $>100$  mg/dL were assigned to an insulin infusion or no treatment.<sup>584</sup> Those receiving insulin had lower intraoperative glucose concentrations, but no difference between groups was observed in the occurrence of new neurological, neuro-ophthalmologic, or neurobehavioral deficits or neurology-related deaths. Of note, no difference in need for inotropic support, hospital length of stay, or operative mortality rate was seen between the groups.<sup>584</sup> A retrospective analysis of intraoperative and postoperative ICU glucose concentrations in  $>4300$  patients undergoing cardiac surgery at the Cleveland Clinic observed that a blood glucose concentration  $>200$  mg/dL in the operating room or ICU was associated with worse outcomes, but intraoperative glucose concentrations  $\leq 140$  mg/dL were not associated with improved outcomes compared with severe hyperglycemia, despite infrequent hypoglycemia. Diabetic status did not influence the effects of hyperglycemia.<sup>585</sup> In short, until additional information is available, extremely tight intraoperative glucose control is not recommended.

Although the management of blood glucose before surgery in patients with and without diabetes mellitus is not well studied, an increased incidence of adverse outcomes has been noted in patients with poor preoperative glycemic control.<sup>593,595</sup> As a result, most centers now attempt to optimize glucose control before surgery, attempting to achieve a target glucose concentration  $\leq 180$  mg/dL with continuous intravenous insulin. Measuring preoperative hemoglobin A1c concentrations may be helpful in assessing the adequacy of preoperative glycemic control and identifying patients at risk for postoperative hyperglycemia.<sup>596</sup>

#### 4.4.2. Postmenopausal Hormone Therapy

Postmenopausal hormone therapy was shown previously to reduce the risk of cardiac-related death. However, more contemporary published RCTs have suggested that it may have adverse cardiovascular effects. The Women's Health Initiative randomly assigned  $>16\,000$  healthy postmenopausal women to placebo or continuous combined estrogen-progestin therapy. Hormone therapy was discontinued early because of an increased risk of breast cancer in those receiving it. Additionally, subjects receiving it had an increased incidence of cardiac ischemic events (29% increase, mainly nonfatal MI), stroke, and venous thromboembolism.<sup>588</sup> A secondary prevention trial, HERS (Heart and Estrogen/Progestin Replacement Study), randomly assigned

2763 postmenopausal women with known CAD to continuous estrogen/progestin or placebo, after which they were followed up for a mean of 4.1 years.<sup>587</sup> No difference in the primary endpoints of nonfatal MI and CAD death was noted, but those receiving hormone therapy had a greater incidence of deep venous thrombosis and other thromboembolic events. This predisposition to thrombosis has raised concerns that hormone therapy may cause adverse events at the time of CABG. A prospective RCT comparing hormone therapy to placebo in postmenopausal women after CABG was initiated in 1998 but was stopped when the Women's Health Initiative trial results were reported.<sup>589</sup> Eighty-three subjects were enrolled, and 45 underwent angiographic follow-up at 42 months. Angiographic progression of CAD in nonbypassed coronary arteries was greater in patients receiving hormone therapy, although less progression of disease was observed in SVGs. Postoperative angioplasty was performed in 8 hormone therapy patients and only 1 placebo subject ( $P<0.05$ ). On the basis of these data, it is not recommended that post-menopausal hormone therapy be initiated in women undergoing CABG, and it may be reasonable to discontinue it in those scheduled for elective CABG.

#### 4.4.3. CABG in Patients With Hypothyroidism

Subclinical hypothyroidism (thyroid-stimulating hormone concentration, 4.50 mIU/L to 19.9 mIU/L) occurs commonly in patients with CAD. In a meta-analysis of  $>55\,000$  subjects with CAD, those with subclinical hypothyroidism did not have an increase in total deaths, but the CAD mortality rate was increased, particularly in those with thyroid-stimulating hormone concentrations  $>10$  mIU/L.<sup>597</sup>

The risks of CABG in hypothyroid patients are poorly defined. A retrospective study of hypothyroid patients undergoing CABG had a higher incidence of heart failure and gastrointestinal complications and a lower incidence of postoperative fever than did members of a matched euthyroid group.<sup>598</sup> Patients with subclinical hypothyroidism may be at increased risk for developing AF after CABG,<sup>599</sup> and 1 study even suggested that triiodothyronine supplementation in patients undergoing CABG (including those who are euthyroid) decreased the incidence of postoperative AF.<sup>600</sup> Conversely, controlled studies of triiodothyronine in subjects undergoing CABG have shown no benefit.<sup>601,602</sup> Rarely, patients may develop severe hypothyroidism after CABG, which manifests as lethargy, prolonged required ventilation, and hypotension.<sup>603</sup> Thyroid replacement is indicated in these individuals.

### 4.5. Perioperative Beta Blockers: Recommendations

#### Class I

1. Beta blockers should be administered for at least 24 hours before CABG to all patients without contraindications to reduce the incidence or clinical sequelae of postoperative AF.<sup>604–608,608a–608c</sup> (Level of Evidence: B)
2. Beta blockers should be reinstituted as soon as possible after CABG in all patients without contraindications to reduce the incidence or clinical sequelae of AF.<sup>604–608,608a–608c</sup> (Level of Evidence: B)



3. Beta blockers should be prescribed to all CABG patients without contraindications at the time of hospital discharge. (*Level of Evidence: C*)

#### Class IIa

1. Preoperative use of beta blockers in patients without contraindications, particularly in those with an LVEF greater than 30%, can be effective in reducing the risk of in-hospital mortality.<sup>609–611</sup> (*Level of Evidence: B*)
2. Beta blockers can be effective in reducing the incidence of perioperative myocardial ischemia.<sup>612–615</sup> (*Level of Evidence: B*)
3. Intravenous administration of beta blockers in clinically stable patients unable to take oral medications is reasonable in the early postoperative period.<sup>616</sup> (*Level of Evidence: B*)

#### Class IIb

1. The effectiveness of preoperative beta blockers in reducing inhospital mortality rate in patients with LVEF less than 30% is uncertain.<sup>609,617</sup> (*Level of Evidence: B*)

See Online Data Supplement 25 for additional data on beta blockers.

Because beta blockers have been shown to reduce the incidence of postoperative AF in CABG patients who are receiving them preoperatively<sup>604,605,608</sup> (Section 5.2.5), the STS and AHA recommend that they be administered preoperatively to all patients without contraindications and then be continued postoperatively.<sup>618,619</sup> Despite this recommendation, uncertainty exists about their efficacy in subjects not receiving them preoperatively; in this patient population, their use appears to lengthen hospital stay and not to reduce the incidence of postoperative AF.<sup>604,607</sup> Their efficacy in preventing or treating perioperative myocardial ischemia is supported by the results of observational studies and small RCTs.<sup>612–614</sup> Although a meta-analysis of available data did not show an improvement in outcomes with perioperative beta blockers,<sup>615</sup> observational analyses suggest that preoperative beta-blocker use is associated with a reduction in perioperative deaths.<sup>609–611</sup> Another analysis of data from 629 877 patients reported a mortality rate of 2.8% in those receiving beta blockers versus 3.4% in those not receiving them.<sup>609</sup>

Few data are available on the pharmacokinetic disposition of beta blockers in the early postoperative period, when an alteration in gastrointestinal perfusion may adversely affect their absorption after oral administration. An RCT demonstrated a significant reduction in the incidence of postoperative AF when a continuous intravenous infusion of metoprolol was used rather than oral administration.<sup>616</sup>

The efficacy of beta-blocker use in CABG patients after hospital discharge is uncertain, as data from 2 RCTs and 1 large detailed observational analysis suggest that they exert no benefit over 2 years postoperatively.<sup>621–623</sup> In contrast, some observational analyses have reported that they are, in fact, efficacious in high-risk subgroups (eg, those with perioperative myocardial ischemia or elderly subjects with heart failure).<sup>624</sup> A contempor-

rary analysis of prescription data from 3,102 Canadian patients, 83% of whom were prescribed a beta blocker at the time of discharge, reported that those receiving beta blockers had a reduced mortality rate during a mean follow-up of 75 months.<sup>625</sup> Of note, improved survival was noted in all patient subgroups receiving beta blockers, even including those without perioperative myocardial ischemia or heart failure.

### 4.6. ACE Inhibitors/ARBs: Recommendations

#### Class I

1. ACE inhibitors and ARBs given before CABG should be reinstituted postoperatively once the patient is stable, unless contraindicated.<sup>622,626,627</sup> (*Level of Evidence: B*)
2. ACE inhibitors or ARBs should be initiated postoperatively and continued indefinitely in CABG patients who were not receiving them preoperatively, who are stable, and who have an LVEF less than or equal to 40%, hypertension, diabetes mellitus, or CKD, unless contraindicated.<sup>622,627,627a,627b</sup> (*Level of Evidence: A*)

#### Class IIa

1. It is reasonable to initiate ACE inhibitors or ARBs postoperatively and to continue them indefinitely in all CABG patients who were not receiving them preoperatively and are considered to be at low risk (ie, those with a normal LVEF in whom cardiovascular risk factors are well controlled), unless contraindicated.<sup>622,627–630</sup> (*Level of Evidence: B*)

#### Class IIb

1. The safety of the preoperative administration of ACE inhibitors or ARBs in patients on chronic therapy is uncertain.<sup>631–636</sup> (*Level of Evidence: B*)
2. The safety of initiating ACE inhibitors or ARBs before hospital discharge is not well established.<sup>622,628,630,640</sup> (*Level of Evidence: B*)

See Online Data Supplements 26 and 27 for additional data on ACE inhibitors.

ACE inhibitors and ARBs are known to exert cardiovascular-protective actions, particularly in subjects with LV systolic dysfunction, hypertension, diabetes mellitus, or chronic renal insufficiency.<sup>626</sup> Nonetheless, the safety and effectiveness of preoperative ACE inhibitors and ARBs in patients undergoing cardiac or noncardiac surgery is uncertain<sup>638</sup> because their administration has been associated with intraoperative hypotension as well as a blunted response to pressors and inotropic agents after induction of anesthesia. Of particular concern during cardiac surgery is their reported association with severe hypotension after CPB (so-called vasoplegia syndrome) and postoperative renal dysfunction.<sup>631,639</sup>

Although it has been postulated that these agents may protect against the development of postoperative AF, published studies have reached conflicting conclusions in this regard.<sup>634,636</sup> The safety and efficacy of ACE inhibitors and ARBs after CABG in previously naïve low- to moderate-risk patients (ie, subjects without diabetes mellitus or renal insufficiency and with or

without asymptomatic moderate LV systolic dysfunction) are uncertain; furthermore, ACE inhibitors and ARBs must be used with caution in these subjects. They should not be instituted in the immediate postoperative period if the systolic arterial pressure is <100 mm Hg or if the patient develops hypotension in the hospital after receiving them. The IMAGINE (Ischemia Management With Accupril Post Bypass Graft via Inhibition of Angiotensin Converting Enzyme) study failed to show a beneficial effect of postoperative ACE inhibitor therapy 3 years after CABG, instead noting an increase in adverse events, particularly recurrent angina in the first 3 months of therapy.<sup>630</sup> A subanalysis of the data from patients enrolled in EUROPA (European Trial on the Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) with previous revascularization (CABG or PCI no sooner than 6 months before enrollment) suggested a primary and secondary prevention benefit over a 4.2-year follow-up period; however, an analysis of the data from almost 3000 patients in the PREVENT IV (PROject of Ex-vivo Vein graft ENGINEERING via Transfection) trial, all of whom were taking either ACE inhibitors or ARBs at the time of hospital discharge, failed to demonstrate a significant reduction in death or MI after 2 years of follow-up in “ideal” candidates (based on ACCF/AHA/HRS guidelines) (HR: 0.87; 95% CI: 0.52 to 1.45;  $P=NS$ ), whereas significance was achieved in “non-ideal” candidates (HR: 1.64; 95% CI: 1.00 to 2.68;  $P=0.05$ ).<sup>608,622,628,640</sup>

#### 4.7. Smoking Cessation: Recommendations

##### Class I

1. All smokers should receive in-hospital educational counseling and be offered smoking cessation therapy during CABG hospitalization.<sup>642–644</sup> (*Level of Evidence: A*)

##### Class IIb

1. The effectiveness of pharmacological therapy for smoking cessation offered to patients before hospital discharge is uncertain. (*Level of Evidence: C*)

See Online Data Supplement 28 for additional data on smoking cessation.

Smoking cessation after CABG is associated with a substantial reduction in subsequent MACE, including MI and death. Data from the randomized portion of the CASS study showed 10-year survival rates of 82% among the 468 patients who quit smoking after CABG and only 77% in the 312 who continued to smoke ( $P=0.025$ ).<sup>645</sup> Those who continued to smoke were more likely to have recurrent angina and to require repeat hospitalization. Data from the CASS registry demonstrated 5-year mortality rates of 22% for those who continued to smoke and only 15% for those who successfully quit smoking after CABG (RR: 1.55; 95% CI: 1.29 to 1.85).<sup>646</sup> Similar favorable outcomes with smoking cessation were reported from the MRFIT (Multiple Risk Factor Intervention Trial), in which the impact of smoking cessation on MACE was assessed after 10.5 years of follow-up in 12 866 men; the risk of death was greater among smokers than non-smokers (RR: 1.57).<sup>647</sup> Notably, the risk of dying from cardiac causes was lower for those who successfully quit than for nonquitters after only 1 year of smoking cessation (RR: 0.63),

and it remained so in those who quit for at least the first 3 years of the study (RR: 0.38).<sup>647</sup> The beneficial effects of smoking cessation after CABG seem to be durable during long-term follow-up (ie, even 30 years postoperatively).<sup>648–650</sup> In fact, smoking cessation was associated with a reduction in mortality rate of greater magnitude than that resulting from any other treatment or intervention after CABG.<sup>649</sup> In these long-term follow-up studies, patients who continued to smoke had significantly higher rates of MI, reoperation, and death.

Smoking is a powerful independent predictor of sudden cardiac death in patients with CAD (HR: 2.47; 95% CI: 1.46 to 4.19). It has been associated with accelerated disease and occlusion of SVGs as well as endothelial dysfunction of arterial grafts.<sup>651–653</sup> Compared with nonsmokers, subjects who are smoking at the time of CABG more often have pulmonary complications that require prolonged postoperative intubation and a longer ICU stay as well as postoperative infections.<sup>654–656</sup> Even smokers who quit just before CABG have fewer postoperative complications than those who continued to smoke.<sup>654</sup> As a result, all smokers referred for CABG should be counseled to quit smoking before surgery.

Smoking cessation seems to be especially beneficial for patients hospitalized with ACS who then require CABG.<sup>644,657</sup> Independent predictors of continued nonsmoking 1 year after CABG included <3 previous attempts to quit (OR: 7.4; 95% CI: 1.9 to 29.1), >1 week of preoperative nonsmoking (OR: 10.0; 95% CI: 2.0 to 50), a definite intention to quit smoking (OR: 12.0; 95% CI: 2.6 to 55.1), and no difficulty with smoking cessation while in the hospital (OR: 9.6; 95% CI: 1.8 to 52.2).<sup>658</sup> Aggressive smoking cessation intervention directed at patients early after post-CABG discharge appears to be more effective than a conservative approach.<sup>642</sup> In a systematic review of 33 trials of smoking cessation, counseling that began during hospitalization and included supportive contacts for >1 month after hospital discharge increased the rates of smoking cessation (OR: 1.65; 95% CI: 1.44 to 1.90), whereas the use of pharmacotherapy did not improve abstinence rates.<sup>643</sup> These findings are supported by a 2009 RCT comparing intensive or minimal smoking cessation intervention in patients hospitalized for CABG or acute MI.<sup>644</sup> In this trial, the 12-month self-reported rate of abstinence was 62% among patients randomly assigned to the intensive program and 46% among those randomly allocated to the minimal intervention (OR: 2.0; 95% CI: 1.2 to 3.1). Overall, a higher rate of continuous abstinence was observed in patients undergoing CABG than in those who had sustained an MI. Interestingly, the rates of abstinence were lower in subjects who used pharmacotherapy regardless of the intervention group (OR: 0.3; 95% CI: 0.2 to 0.5).<sup>644</sup>

Seven first-line pharmacological treatments are available for smoking cessation therapy, including 5 nicotine-replacement therapies; the antidepressant bupropion; and varenicline, a partial agonist of the  $\alpha_4\beta_2$  subtype of the nicotinic acetylcholine receptor.<sup>659–661</sup> The data supporting the use and timing of nicotine-replacement therapy after CABG are unclear. One study from a large general practice database reported no increased risk of MI, stroke, or death with nicotine-replacement therapy,<sup>662</sup> whereas a retrospective

case-control study of critically ill patients reported a higher in-hospital mortality rate in those receiving nicotine replacement (20% versus 7%;  $P=0.0085$ ). Despite adjusting for the severity of illness, nicotine-replacement therapy was an independent predictor of in-hospital mortality (OR: 24.6; 95% CI: 3.6 to 167.6;  $P=0.0011$ ).<sup>663</sup> Similarly, in a cohort study of post-CABG patients, nicotine-replacement therapy was shown to be an independent predictor of in-hospital mortality after adjusting for baseline characteristics (OR: 6.06; 95% CI: 1.65 to 22.21).<sup>663,664</sup> Additional studies are needed to determine the safety of nicotine-replacement therapy in smokers undergoing CABG as well as the optimal time at which to begin such therapy postoperatively.

#### 4.8. Emotional Dysfunction and Psychosocial Considerations: Recommendation

##### Class IIa

1. Cognitive behavior therapy or collaborative care for patients with clinical depression after CABG can be beneficial to reduce objective measures of depression.<sup>665–669</sup> (Level of Evidence: B)

The negative impact of emotional dysfunction on risk of morbidity and mortality after CABG is well recognized. In a multivariate analysis of elderly patients after CABG, the 2 most important predictors of death were a lack of social participation and a lack of religious strength.<sup>670</sup> Social isolation is associated with increased risk of death in patients with CAD,<sup>671</sup> and treatment may improve outcomes.<sup>672</sup> The most carefully studied mood disorder, depression, occurs commonly after CABG. Several studies have shown that the primary predictor of depression after CABG is its presence before CABG and that only rarely does CABG cause depression in patients who were not depressed beforehand. In 1 report, half the patients who were depressed before CABG were not depressed afterward, and only 9% of subjects who were not depressed before CABG developed depression postoperatively.<sup>673</sup> The prevalence of depression at 1 year after CABG was 33%, which is similar to the prevalence in those undergoing other major operations. Patients with stronger perceptions of control of their illness were less likely to be depressed or anxious after CABG.<sup>674</sup> No difference in the incidence of mood disturbances was noted when off-pump and on-pump CABG were compared.<sup>675</sup>

##### 4.8.1. Effects of Mood Disturbance and Anxiety on CABG Outcomes

Depression is an important risk factor for the development and progression of CAD. In fact, it is a more important predictor of the success of cardiac rehabilitation than many other functional cardiac variables.<sup>676</sup> Both the presence of depressive symptoms before CABG and the postoperative worsening of these symptoms correlate with poorer physical and psychosocial functioning and poorer quality of life after CABG.<sup>677</sup> In a study of 440 patients who underwent CABG, the effects of both preoperative anxiety and depression (as defined by the Depression Anxiety and Stress Scale) on mortality rate were assessed for a median of 5 years postoperatively.<sup>678</sup> Interestingly, preoperative anxiety was associ-

ated with a significantly increased risk of death (HR: 1.88; 95% CI: 1.12 to 3.37;  $P=0.02$ ), whereas preoperative depression was not.<sup>678</sup> In a multivariate analysis of 817 patients at Duke University Medical Center, severe depression (assessed using the Center for Epidemiological Studies–Depression scale before surgery and 6 months postoperatively<sup>665</sup> was associated with increased risk of death (HR: 2.4; 95% CI: 1.4 to 4.0), as was mild or moderate depression that persisted at 6 months (HR: 2.2; 95% CI: 1.2 to 4.2). In another study of 309 subjects followed up for  $\leq 1$  year after CABG, those with diagnostic criteria for a major depressive disorder before discharge were nearly 3 times as likely to have a cardiac event, such as heart failure requiring hospitalization, MI, cardiac arrest, PCI, repeat CABG, or cardiac death.<sup>666</sup> Finally, depression after CABG is an important predictor of the recurrence of angina during the first 5 postoperative years.<sup>666,673</sup>

##### 4.8.2. Interventions to Treat Depression in CABG Patients

The Bypassing the Blues investigators identified 302 patients who were depressed before CABG and 2 weeks after discharge.<sup>668</sup> They were randomly assigned to 8 months of telephone-delivered collaborative care (150 patients) or “usual care” (152 patients). The 2 groups were compared with each other and also to another group of 151 randomly selected nondepressed post-CABG patients. At 8 month follow-up, the collaborative care group showed an improvement in quality of life and physical functioning and were more likely to report a  $>50\%$  decline in the Hamilton Rating Score for Depression than the usual care group (50.0% versus 29.6%;  $P<0.001$ ). Men were more likely to benefit from the intervention.<sup>668,669</sup> In another study, 123 patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, criteria for major or minor depression within 1 year of CABG were randomly assigned to 12 weeks of cognitive behavior therapy, 12 weeks of supportive stress management, or usual care.<sup>667</sup> Both interventions were efficacious for treating depression after CABG, and cognitive behavior therapy had the most durable effects on depression and several secondary psychological outcome variables.<sup>667</sup> Thus, both collaborative intervention and cognitive behavior therapy are effective for treating depression in patients after CABG. Given that depression is associated with adverse outcomes after CABG, it is likely that these interventions also may lead to reduced rates of morbidity and mortality.

#### 4.9. Cardiac Rehabilitation: Recommendation

##### Class I

1. Cardiac rehabilitation is recommended for all eligible patients after CABG.<sup>679–681,681a–681d</sup> (Level of Evidence: A)

See Online Data Supplement 29 for additional data on cardiac rehabilitation.

Cardiac rehabilitation, including early ambulation during hospitalization, outpatient prescriptive exercise training, and education, reduces risk of death in survivors of MI.<sup>682–684</sup> Beginning 4 to 8 weeks after CABG, 3-times-weekly education and exercise sessions for 3 months are associated with a



35% increase in exercise tolerance ( $P=0.0001$ ), a slight (2%) ( $P=0.05$ ) increase in high-density lipoprotein cholesterol, and a 6% reduction in body fat ( $P=0.002$ ).<sup>421</sup> Exercise training is a valuable adjunct to dietary modification of fat and total caloric intake in maximizing the reduction of body fat while minimizing the reduction of lean body mass. Aerobic training improves volume of maximum oxygen consumption at 6 months compared with moderate continuous training ( $P<0.001$ ).<sup>685</sup>

After hospital discharge, CABG patients were randomly assigned to standard care ( $n=109$ ) or standard care plus rehabilitation ( $n=119$ ). At 5 years, the groups were similar in symptoms, medication use, exercise capacity, and depression scores, but rehabilitated patients reported better physical mobility, better perceived health, and better perceived overall life situation. A larger proportion of the rehabilitated patients were working at 3 years, although this difference disappeared with longer follow-up.<sup>679</sup> Subjects who sustained an MI followed by CABG had greater improvement in exercise tolerance after rehabilitation than did those who had an MI alone. Improvement was sustained for 2 years.<sup>686</sup> Observational studies have reported that cardiac events are reduced with rehabilitation after revascularization.<sup>680</sup>

In many CABG patients, initiation of rehabilitation is a substantial hurdle. Medically indigent patients seem to have rehabilitation compliance and benefit rates similar to those of insured or private-paying patients if rehabilitation is initiated promptly and is structured appropriately.<sup>687</sup> In addition to contributing to a patient's sense of well-being, participation in cardiac rehabilitation offers an economic benefit. During a 3-year (mean: 21 months) follow-up after CABG or another coronary event, per capita hospitalization charges were \$739 lower for rehabilitated patients compared with nonparticipants.<sup>688</sup> Post-CABG patients are more likely to resume sexual activity than are survivors of MI. Anticipatory and proactive advice by the physician or surgeon on the safety of resumption of sexual activity as the patient reengages in other daily activities is beneficial.<sup>682</sup>

Recommendations for intensive risk-reduction therapies for patients with established coronary and other atherosclerotic vascular disease are detailed in the "AHA/ACC Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Vascular Disease: 2011 Update."<sup>689</sup> This updated guideline includes recommendations on smoking, blood pressure control, lipid management, physical therapy, weight management, type 2 diabetes management, antiplatelet agents and anticoagulants, renin-angiotensin-aldosterone system blockers (ACE inhibitors and ARBs), beta blockers, influenza vaccination, depression, and cardiac rehabilitation.

## 4.10. Perioperative Monitoring

### 4.10.1. Electrocardiographic Monitoring: Recommendations

#### Class I

1. Continuous monitoring of the electrocardiogram for arrhythmias should be performed for at least 48 hours in all patients after CABG.<sup>606,690,691</sup> (Level of Evidence: B)

#### Class IIa

1. Continuous ST-segment monitoring for detection of ischemia is reasonable in the intraoperative period for patients undergoing CABG.<sup>53,692–694</sup> (Level of Evidence: B)

#### Class IIb

1. Continuous ST-segment monitoring for detection of ischemia may be considered in the early postoperative period after CABG.<sup>613,690,695–698</sup> (Level of Evidence: B)

### 4.10.2. Pulmonary Artery

#### Catheterization: Recommendations

#### Class I

1. Placement of a pulmonary artery catheter (PAC) is indicated, preferably before the induction of anesthesia or surgical incision, in patients in cardiogenic shock undergoing CABG. (Level of Evidence: C)

#### Class IIa

1. Placement of a PAC can be useful in the intraoperative or early postoperative period in patients with acute hemodynamic instability.<sup>699–704</sup> (Level of Evidence: B)

#### Class IIb

1. Placement of a PAC may be reasonable in clinically stable patients undergoing CABG after consideration of baseline patient risk, the planned surgical procedure, and the practice setting.<sup>699–704</sup> (Level of Evidence: B)

### 4.10.3. Central Nervous System Monitoring: Recommendations

#### Class IIb

1. The effectiveness of intraoperative monitoring of the processed electroencephalogram to reduce the possibility of adverse recall of clinical events or for detection of cerebral hypoperfusion in CABG patients is uncertain.<sup>705–707</sup> (Level of Evidence: B)
2. The effectiveness of routine use of intraoperative or early postoperative monitoring of cerebral oxygen saturation via near-infrared spectroscopy to detect cerebral hypoperfusion in patients undergoing CABG is uncertain.<sup>708–710</sup> (Level of Evidence: B)

See Online Data Supplement 30 for additional data on central nervous system monitoring.

Requirements for basic perioperative monitoring in patients undergoing CABG, including heart rate, blood pressure, peripheral oxygen saturation, and body temperature, are well accepted. Additional intraoperative standards established by the American Society of Anesthesiologists, including the addition of end-tidal carbon dioxide measurement in the intubated patient, are uniformly applied.<sup>711</sup> Specialized monitoring of cardiac and cerebral function varies among centers and includes the use of PACs, TEE, or other forms of echocardiography (Section 2.1.7); noninvasive monitors of cardiac output; processed electroencephalographic monitoring; and cerebral oximetry with near-infrared spectroscopy. Given the added expense and potential hazards of such

monitors (eg, pulmonary artery rupture with PAC, false-positive changes with cerebral oximetry or processed electroencephalogram), substantial controversy exists about indications for their use. None of these monitoring methods is routinely recommended.

Electrocardiographic monitoring includes an assessment of heart rate and rhythm as well as the morphology and deviation of the QRS complex and ST segments for evidence of ischemia, infarction, or abnormal conduction.<sup>690</sup> Continuous telemetric monitoring of cardiac rate and rhythm is recommended for 48 to 72 hours after surgery in all patients because of the high incidence of post-CABG AF, which most often occurs 2 and 4 days after surgery.<sup>606,613,690,691,697,698</sup> In addition, other arrhythmias and conduction abnormalities may occur in patients with ischemia because of incomplete revascularization or in those undergoing concurrent valve replacement.

Uncertainty continues with regard to the utility of PAC in low-risk patients undergoing CABG.<sup>712</sup> Several observational studies suggest that such patients can be managed only with monitoring of central venous pressure, with insertion of a PAC held in reserve should the need arise. In fact, it has even been suggested that patients in whom a PAC is placed incur greater resource utilization and more aggressive therapy, which may lead to worse outcomes and higher costs. The reported rates of PAC use range from <10% in a combined private-academic setting to >90% in patients in the Department of Veterans Affairs health system.<sup>61,639,701,702,713</sup>

Aside from providing an indirect assessment of left atrial pressure and the presence and severity of pulmonary hypertension, PAC can be used to measure cardiac output (by thermodilution) and to monitor the mixed venous oxygen saturation—information that may be helpful in the management of high-risk patients.<sup>712,714</sup> The need for careful consideration of baseline patient risk, the planned procedure, and the patient setting before use of a PAC are outlined in several opinion pieces, consensus documents, the “Practice Guidelines for Pulmonary Artery Catheterization: An Updated Report by the American Society of Anesthesiologists,” and the “2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery.”<sup>699,712,714–716</sup> Pulmonary artery perforation or rupture is fatal in >50% of patients in whom it occurs. This complication usually can be avoided by 1) withdrawal of the catheter tip into the main pulmonary artery before initiation of CPB; 2) withdrawal of the catheter into the pulmonary artery before balloon inflation, especially if the pressure tracing suggests damping; and 3) avoiding routine measurement of the pulmonary artery wedge pressure, reserving this maneuver as a specific diagnostic event.

Perioperative monitoring of cerebral function (primarily with an electroencephalogram) has been used in certain high-risk patients, such as those undergoing neurosurgery or carotid vascular surgery.<sup>717</sup> In the setting of cardiac surgery, the potentially deleterious effects of CPB on cerebral hypofusion or embolic events (ie, air or aortic calcific debris) have been investigated via transcranial Doppler techniques, with a lesser emphasis on the electroencephalogram (in part because

of excessive artifact in this setting).<sup>57,718</sup> Although processed electroencephalographic monitors and bifrontal cerebral oximetry have been available for more than 2 decades, controversy remains about their clinical effectiveness.<sup>719,720</sup> Processed electroencephalographic monitoring is aimed primarily at assessing the risk of conscious recall of intraoperative events, but it also has been used to gauge the depth of anesthesia, theoretically allowing more precise titration of the anesthetic.<sup>721,722</sup> Although a variety of electroencephalographic variables are commonly accepted as markers of cerebral ischemia, the ability of current commercial devices to detect or quantify ischemia is limited.<sup>706,707,717,718</sup>

Given the intuitive link between reflectance oximetry (ie, for peripheral oxygen or mixed venous oxygen saturation) and clinical interventions (ie, manipulating hemodynamic variables, the fraction of inspired oxygen, etc.), there is considerable interest in the use of bifrontal cerebral oximetry as a measure of brain perfusion.<sup>723</sup> Two RCTs in CABG patients suggest that bifrontal cerebral oximetry may be helpful in predicting early perioperative cognitive decline, stroke, noncerebral complications, and ICU and hospital length of stay.<sup>709,710</sup> A 2011 observational cohort (1178 CABG patients) suggested that a patient’s preoperative response to breathing oxygen for 2 minutes ( $\text{ScO}_2 \leq 50\%$ ) is an independent predictor of death at 30 days and 1 year after surgery.<sup>724</sup>

## 5. CABG-Associated Morbidity and Mortality: Occurrence and Prevention

Several comprehensive data registries for CABG have been developed in the United States, the largest being the STS Adult Cardiac Database. For >20 years, these registries have collected data on all aspects of the procedure.<sup>306,725,727</sup> A detailed analysis of these data and their correlation to outcomes has facilitated the creation of risk-assessment models that estimate the rates at which various adverse events occur. On the basis of these models, risk-adjusted outcomes for hospitals and surgeons have been calculated and, in some instances, publicly reported.

### 5.1. Public Reporting of Cardiac Surgery Outcomes: Recommendation

#### Class I

1. Public reporting of cardiac surgery outcomes should use risk-adjusted results based on clinical data.<sup>728–735</sup>  
(Level of Evidence: B)

*See Online Data Supplement 31 for additional data on public reporting of cardiac surgery outcomes.*

To address the need for valid and reliable risk-adjusted outcomes data, cardiac surgery registries were developed by the STS,<sup>306,725,727</sup> Veterans Administration,<sup>306,736–738</sup> Northern New England Cardiovascular Disease Study Group,<sup>739,740</sup> and the state of New York.<sup>741,742</sup> These have been the basis for several performance assessment and improvement strategies, including public report cards,<sup>742–744</sup> confidential feedback to participants showing their performance relative to national benchmarks,<sup>306,737,745–748</sup> and state or regional col-

laboratives that identify and disseminate best-practices information.<sup>749</sup> Public report cards are the most controversial of these 3 approaches. Although they provide transparency and public accountability, it is unclear if they are the only or best way to improve quality. Reductions in the CABG mortality rate after the publication of such report cards in New York were encouraging,<sup>742,750–752</sup> but subsequent studies revealed comparable reductions in other states, regions, and countries that used confidential feedback with or without performance improvement initiatives.<sup>752–754</sup> These findings suggest that the common denominator among successful performance improvement strategies is the implementation of a formal quality assessment and feedback program benchmarked against regional or national results.<sup>755</sup> The incremental value of public (as opposed to confidential) reporting is controversial.

Although providers fear the potential negative impact of public reporting on referrals and market share, this concern seems to be unfounded.<sup>756–765</sup> Even when such impact has been observed, it has generally been modest, transient, and limited to areas populated by more affluent and educated subjects.<sup>760–762,766</sup> With implementation of healthcare reform legislation that increases access of consumers and payers to objective data and more easily understood data presentations, the influence of public report cards is likely to increase in the future.<sup>762,767–771</sup> As this occurs, it will be important to monitor unintended negative consequences, such as “gaming” of the reporting system<sup>772</sup> and avoidance of high-risk patients (risk aversion), the precise group of patients who are most likely to benefit from aggressive intervention.<sup>773–776</sup>

Methodological considerations are important for provider profiling and public reporting. Numerous studies have shown the superiority of clinical over administrative data for these purposes.<sup>728–731,733,734</sup> The latter data lack critical clinical variables that are necessary for adequate risk adjustment,<sup>732,735</sup> they may confuse comorbidities and complications, and they may contain inaccurate case numbers and mortality rates. Outcomes measures, such as mortality, should always be adjusted for patient severity on admission (ie, “risk-adjusted” or “risk-standardized”)<sup>777–780</sup>; otherwise, providers will be hesitant to care for severely ill patients, who are more likely to die from their disease. In addition, if a hospital or surgeon is found to be a low-performing outlier on the basis of unadjusted results, the hospital or surgeon may claim that their patients were sicker. Statistical methodologies should account for small sample sizes and clustered patient observations within institutions, and hierarchical or random-effects models have been advocated by some investigators.<sup>743,781–787</sup> Point estimates of outcomes should always be accompanied by measures of statistical uncertainty, such as CIs. The units of analysis and reporting for provider profiling also have implications. Surgeon-level reports are published together with hospital reports in several states, but their smaller sample sizes typically require data aggregation over several years. Surgeon-level reporting may also increase the potential for risk aversion, as the anticipated worse results of the highest-risk patients are not diluted by the larger volume of a hospital or group. Finally, because the distribution of patient severity may vary substantially among providers, direct comparison of the results of one surgeon or hospital

with those of another, even by using indirectly risk-standardized results, is often inappropriate.<sup>788</sup> Rather, these results should be interpreted as comparisons of a provider’s outcomes for his or her specific patient cohort versus what would have been expected had those patients been cared for by an “average” provider in the benchmark population.

Although risk-adjusted mortality rate has been the dominant performance metric in cardiac surgery for 2 decades, other more comprehensive approaches have been advocated.<sup>789</sup> The STS CABG composite illustrates one such multidimensional approach, consisting of 11 National Quality Forum–endorsed measures of cardiothoracic surgery performance grouped within 4 domains of care.<sup>619,790</sup>

### **5.1.1. Use of Outcomes or Volume as CABG Quality Measures: Recommendations**

#### **Class I**

- 1. All cardiac surgery programs should participate in a state, regional, or national clinical data registry and should receive periodic reports of their risk-adjusted outcomes. (Level of Evidence: C)**

#### **Class IIa**

- 1. When credible risk-adjusted outcomes data are not available, volume can be useful as a structural metric of CABG quality.<sup>309,751,791–798,800–804,807,818</sup> (Level of Evidence: B)**

#### **Class IIb**

- 1. Affiliation with a high-volume tertiary center might be considered by cardiac surgery programs that perform fewer than 125 CABG procedures annually. (Level of Evidence: C)**

*See Online Data Supplement 32 for additional data on outcomes or volume as CABG quality measures.*

Numerous studies have demonstrated an association between hospital or individual practitioner volume and outcome for a variety of surgical procedures and some medical conditions.<sup>805–831</sup> CABG was one of the original procedures for which this volume–outcome association was investigated.<sup>309,751,791–798,800–804,807,818</sup> The CABG volume–outcome association is generally weaker than that of other procedures, such as esophagectomy or pancreatectomy, which are performed less often. In addition, the results of volume–outcome studies vary substantially according to methodology. The apparent strength of the volume–outcome association often diminishes with proper risk adjustment based on clinical (as opposed to administrative) data.<sup>802,808</sup> It is also weaker in more contemporary studies, presumably because of improved techniques and increasing experience.<sup>795,802</sup> Finally, volume–outcome associations appear weaker when hierarchical models are used that properly account for small sample sizes and clustering of observations.<sup>832</sup> The impact of CABG volume was studied in an observational cohort of 144 526 patients from 733 hospitals that participated in the STS Adult Cardiac Surgery Database in 2007.<sup>309</sup> In this analysis, a weak association between volume and unadjusted mortality rate was noted (2.6% unadjusted mortality rate for hospitals perform-



ing <100 procedures versus 1.7% for hospitals performing  $\geq 450$  procedures).<sup>309</sup> Using multivariate hierarchical regression, the largest OR (1.49) was found for the lowest-volume (<100 cases) group versus the highest-volume group. Desirable processes of care (except for use of the IMA) and morbidity rates were not associated with volume. The average STS-CABG composite score for the lowest-volume group (<100 cases per year) was significantly lower than that of the 2 highest-volume groups, but volume explained only 1% of variation in the composite score.<sup>619,790</sup>

In general, the best results are achieved most consistently by high-volume surgeons in high-volume hospitals and the worst results by low-volume surgeons in low-volume hospitals.<sup>793,794</sup> However, many low-volume programs achieve excellent results, perhaps related to appropriate case selection; effective teamwork among surgeons, nurses, anesthesiologists, perfusionists, and physician assistants; and adoption of best practices derived from larger programs.<sup>833,834</sup>

As a quality assessment strategy, participation in a state, regional, or national clinical data registry that provides regular performance feedback reports is highly recommended for all cardiac programs. Random sampling variation is greater at low volumes,<sup>309,797,798,803,827,834,835</sup> which complicates performance assessment of smaller programs. Several strategies may be considered to mitigate this measurement issue, including analysis over longer periods of time; appropriate statistical methodologies, such as hierarchical (random-effects) models; composite measures, which effectively increase the number of endpoints; and statistical quality control approaches, such as funnel plots<sup>835</sup> and cumulative sum plots.<sup>836–838</sup> Small programs may benefit from direct supervision by a large tertiary center.<sup>834</sup> Ultimately, state or national regulatory authorities must decide whether the lower average performance of very small programs and the added difficulty in accurately measuring their performance are outweighed by other considerations, such as the need to maintain cardiac surgery capabilities in rural areas with limited access to referral centers.<sup>834</sup>

Volume, a structural quality metric, is an imperfect proxy for direct measurement of outcomes.<sup>822,839</sup> Risk-adjusted outcomes based on clinical data are the preferred method of assessing CABG quality except in very low-volume programs, in which performance is generally weakest and small sample size makes accurate assessment of performance difficult.

## 5.2. Adverse Events

### 5.2.1. Adverse Cerebral Outcomes

#### 5.2.1.1. Stroke

The incidence of stroke after CABG ranges from 1.4% to 3.8%,<sup>840</sup> depending on the patient population and the criteria for diagnosis of stroke. Risk factors for stroke include advanced age, history of stroke, diabetes mellitus, hypertension,<sup>841</sup> and female sex,<sup>842</sup> with newer research emphasizing the importance of preoperative atherosclerotic disease (including radiographic evidence of previous stroke or aortic atheromatous disease).<sup>843</sup> Although macroembolization and microembolization are major sources of stroke, hypoperfu-

sion,<sup>844</sup> perhaps in conjunction with embolization,<sup>845</sup> is a risk factor for postoperative stroke. The mortality rate is 10-fold higher among post-CABG patients with stroke than among those without it, and lengths of stay are longer in stroke patients.<sup>846</sup>

Although off-pump CABG was introduced in large part to reduce stroke and other adverse neurological outcomes associated with CPB, several RCTs comparing on-pump and off-pump CABG have shown no difference in stroke rates.<sup>61,68,78,846a,846b,1069,1259</sup>

*See Online Data Supplement 33 for additional data on stroke rates.*

#### 5.2.1.1.1. Use of Epiaortic Ultrasound Imaging to Reduce Stroke Rates: Recommendation

##### Class IIa

1. **Routine epiaortic ultrasound scanning is reasonable to evaluate the presence, location, and severity of plaque in the ascending aorta to reduce the incidence of atheroembolic complications.**<sup>847–849</sup> (*Level of Evidence: B*)

Identification of an atherosclerotic aorta is believed to be an important step in reducing the risk of stroke after CABG.<sup>850</sup> Intraoperative assessment of the ascending aorta for detection of plaque by epiaortic ultrasound imaging is superior to direct palpation and TEE.<sup>851,852</sup> Predictors of ascending aortic atherosclerosis include increasing age, hypertension, extracardiac atherosclerosis (peripheral artery and cerebrovascular disease), and elevated serum creatinine concentrations.<sup>853–855</sup> Prospective RCTs to evaluate the role of epiaortic scanning in assessing stroke risk have not been reported, but several observational studies reported stroke rates of 0 to 1.4%<sup>847–849,853,856,857</sup> when surgical decision making was guided by the results of epiaortic scanning. Separate guidelines for the use of intraoperative epiaortic ultrasound imaging in cardiac surgery were endorsed and published in 2008 by the American Society for Echocardiography, Society of Cardiovascular Anesthesiologists, and STS.<sup>147</sup>

#### 5.2.1.1.2. The Role of Preoperative Carotid Artery Noninvasive Screening in CABG Patients: Recommendations

##### Class I

1. **A multidisciplinary team approach (consisting of a cardiologist, cardiac surgeon, vascular surgeon, and neurologist) is recommended for patients with clinically significant carotid artery disease for whom CABG is planned.** (*Level of Evidence: C*)

##### Class IIa

1. **Carotid artery duplex scanning is reasonable in selected patients who are considered to have high-risk features (ie, age >65 years, left main coronary stenosis, PAD, history of cerebrovascular disease [transient ischemic attack [TIA], stroke, etc.], hypertension, smoking, and diabetes mellitus).**<sup>858,859</sup> (*Level of Evidence: C*)

2. **In the CABG patient with a previous TIA or stroke and a significant (50% to 99%) carotid artery stenosis, it is reasonable to consider carotid revascularization in conjunction with CABG. In such an individual, the sequence and timing (simultaneous or staged) of carotid intervention and CABG should be determined by the patient's relative magnitudes of cerebral and myocardial dysfunction. (Level of Evidence: C)**

#### Class IIb

1. **In the patient scheduled to undergo CABG who has no history of TIA or stroke, carotid revascularization may be considered in the presence of bilateral severe (70% to 99%) carotid stenoses or a unilateral severe carotid stenosis with a contralateral occlusion. (Level of Evidence: C)**

Because the presence of extracranial disease of the internal carotid artery is a risk factor for adverse neurological events after CABG,<sup>860</sup> one might argue for use of carotid noninvasive scanning (duplex ultrasonography or noninvasive carotid screening) in all patients scheduled for CABG. At issue is the effectiveness of noninvasive carotid screening in identifying carotid artery stenoses of hemodynamic significance. Alternatively, the identification of preoperative risk factors known to be associated with the presence of carotid artery disease could be used to stratify patients into high- and low-risk categories, thereby allowing for a more selective use of noninvasive carotid screening. A retrospective analysis of 1421 consecutive CABG patients identified the following as risk factors for significant carotid artery disease: age >65 years, presence of a carotid bruit, and a history of cerebrovascular disease.<sup>858</sup> In so doing, they reduced preoperative testing by 40%, with only a “negligible” impact on surgical management or neurological outcomes. Similarly, the following risk factors have been identified as predicting the presence of >50% reduction in internal diameter of the internal carotid artery: smoking, diabetes mellitus, hypertension, a previous cerebrovascular event, PAD, left main CAD, and a history of cervical carotid disease.<sup>859</sup> All subjects found to have significant carotid disease were noted to have  $\geq 1$  of these criteria. In addition, the probability of detecting significant carotid disease increased almost 3 times for each additional criterion that was present. The authors noted that the presence of a single preoperative risk factor increased the sensitivity of the screening test to 100% and increased the specificity to 30%. As a result, they strongly recommend a selective approach to the use of preoperative noninvasive carotid screening, allowing for a decrease in the number of unnecessary tests but exerting little effect on the detection of significant carotid disease.

In patients undergoing carotid endarterectomy, the rates of periprocedural stroke have been reported to be as high as 2.5% in those with asymptomatic carotid stenoses<sup>861</sup> and 5% in those with previous cerebrovascular symptoms.<sup>862</sup> In CABG patients with >50% unilateral carotid stenoses in whom carotid endarterectomy is not performed concomitantly with CABG, the peri-CABG stroke rate is reportedly

3%, rising to 5% in those with bilateral carotid artery stenoses and 11% in those with an occluded carotid artery.<sup>860</sup> In light of these data, the issue of combined carotid and coronary revascularization (performed simultaneously or in a staged, sequential fashion) as a strategy to reduce the postoperative stroke risk in CABG patients with known carotid artery disease has received substantial attention. The lack of clarity about the optimal approach to the management of such patients is the result of several factors:

- To date, no published randomized, prospective study has addressed this important clinical scenario.<sup>863</sup>
- The etiology of postoperative stroke often is multifactorial (eg, ascending aortic calcifications with resultant atherothrombotic embolization, preexisting carotid artery disease, air or debris cerebral embolization associated with CPB, episodes of transient intraoperative hypotension).
- Many risk factors for stroke coexist in CABG patients.
- The rates for postoperative stroke and death for carotid endarterectomy and for CABG, independent of or in conjunction with one another, vary considerably in different patient populations (eg, young versus old, male versus female, etc.).
- More than half of all post-CABG strokes occur after uneventful recovery from CABG and are believed to be caused by supraventricular arrhythmias, low cardiac output, or postoperative hypercoagulability.<sup>863</sup>
- A substantial proportion of post-CABG strokes occur in patients without significant carotid artery disease or in an anatomic distribution not consistent with a known significant carotid arterial stenosis.

Advances in technologies for carotid and coronary revascularization make the decision-making process for the procedures even more complex. In addition to conventional CABG with CPB, the surgeon may choose an off-pump technique in certain patients (eg, those with a heavily calcified ascending aorta). Likewise, carotid artery stenting provides an alternative to endarterectomy, which may reduce the risk of postoperative stroke. Still, the ultimate impact of such stenting on postoperative stroke rates in CABG patients awaits the results of properly designed trials. At present, carotid artery stenting is reserved for CABG patients in whom a contraindication to open endarterectomy exists.

When combined carotid and coronary revascularization is indicated, an awareness of the stroke and mortality rates for different patient subgroups will help to guide decision making. Several factors favor combined revascularization, including (but not limited to) 1) severe carotid artery disease, 2) unfavorable morphological characteristics of the carotid lesion(s) (eg, ulcerated lesions), 3) the presence of related symptoms, and 4) a history of TIA or stroke. In those with a history of TIA or stroke who have a significant carotid artery stenosis (50% to 99% in men or 70% to 99% in women), the likelihood of a post-CABG stroke is high; as a result, they are likely to benefit from carotid revascularization.<sup>863</sup> Conversely, CABG alone can be performed safely in patients with asymptomatic unilateral carotid stenoses, because a carotid

revascularization procedure offers no discernible reduction in the incidence of stroke or death in these individuals. Men with asymptomatic bilateral severe carotid stenoses (50% to 99%) or a unilateral severe stenosis in conjunction with a contralateral carotid artery occlusion may be considered for carotid revascularization in conjunction with CABG. Little evidence exists to suggest that women with asymptomatic carotid artery disease benefit from carotid revascularization in conjunction with CABG.<sup>864</sup> Whether the carotid and coronary revascularization procedures are performed simultaneously or in a staged, sequential fashion is usually dictated by the presence or absence of certain clinical variables. In general, synchronous combined procedures are performed only in those with both cerebrovascular symptoms and ACS.

The optimal management of patients with coexisting carotid artery disease and CAD is poorly defined. Several therapeutic approaches can be used, including staged carotid endarterectomy and CABG, simultaneous carotid endarterectomy and CABG, or similar variations that use endovascular stenting as the primary carotid intervention. At present, no prospective RCTs comparing neurological outcomes after these different treatment strategies in patients with coexisting carotid artery disease and CAD have been reported.<sup>865</sup>

#### 5.2.1.2. Delirium

The incidence of postoperative delirium after CABG is <10%, similar to that reported after noncardiac surgery.<sup>866–868</sup> The risk factors for postoperative delirium are similar for cardiac and noncardiac surgery and include advanced age, preexisting cognitive impairment, and vascular disease.<sup>866,868,869</sup> The burden of intraoperative cerebral microemboli does not predict the presence or severity of postoperative delirium.<sup>870</sup> The development of postoperative delirium has been linked to functional decline at 1 month, short-term cognitive decline,<sup>871</sup> and risk of late mortality.<sup>867,872</sup>

#### 5.2.1.3. Postoperative Cognitive Impairment

Short-term cognitive changes occur in some patients after on-pump CABG.<sup>873–875</sup> The precise incidence depends on the timing of the postoperative assessment and the choice of criteria for cognitive decline.<sup>876,877</sup> Similar short-term cognitive changes also are noted in elderly patients receiving general anesthesia for noncardiac surgery.<sup>878–880</sup> Risk factors for short-term postoperative cognitive decline include preexisting risk factors for cerebrovascular disease,<sup>881</sup> preexisting central nervous system disease,<sup>882</sup> and preexisting cognitive impairment.<sup>75</sup> Up to 30% of candidates for CABG have been shown to have cognitive impairment before surgery.<sup>75</sup> A few studies have reported a lower incidence of short-term cognitive decline after off-pump CABG than on-pump CABG,<sup>883</sup> but most studies have shown no difference in cognitive outcomes between them.<sup>884</sup> Studies with appropriate comparison groups have demonstrated that most patients do not suffer cognitive decline after CABG.<sup>885,886</sup> For those who do, the postoperative cognitive changes are generally mild, and for most patients, they resolve within 3 months of surgery.<sup>887</sup>

Long-term cognitive decline after CABG has been reported,<sup>888,889</sup> but other studies have shown that a similar degree of late cognitive decline occurs in comparison groups of demographically similar patients with CAD but without

surgery, suggesting that the late decline is not related to the use of CPB.<sup>890</sup> An RCT comparing late cognitive outcomes after on-pump and off-pump CABG has reported no difference between them.<sup>891</sup>

See Online Data Supplement 34 for additional data on the role of perioperative cognitive impairment.

### 5.2.2. Mediastinitis/Perioperative Infection: Recommendations

#### Class I

1. Preoperative antibiotics should be administered to all patients to reduce the risk of postoperative infection.<sup>892–897</sup> (Level of Evidence: A)
2. A first- or second-generation cephalosporin is recommended for prophylaxis in patients without methicillin-resistant *Staphylococcus aureus* colonization.<sup>897–905</sup> (Level of Evidence: A)
3. Vancomycin alone or in combination with other antibiotics to achieve broader coverage is recommended for prophylaxis in patients with proven or suspected methicillin-resistant *S. aureus* colonization.<sup>900,906–908</sup> (Level of Evidence: B)
4. A deep sternal wound infection should be treated with aggressive surgical debridement in the absence of complicating circumstances. Primary or secondary closure with muscle or omental flap is recommended.<sup>909–911</sup> Vacuum therapy in conjunction with early and aggressive debridement is an effective adjunctive therapy.<sup>912–921</sup> (Level of Evidence: B)
5. Use of a continuous intravenous insulin protocol to achieve and maintain an early postoperative blood glucose concentration less than or equal to 180 mg/dL while avoiding hypoglycemia is indicated to reduce the risk of deep sternal wound infection.<sup>583,586,590,591,922,923</sup> (Level of Evidence: B)

#### Class IIa

1. When blood transfusions are needed, leukocyte-filtered blood can be useful to reduce the rate of overall perioperative infection and in-hospital death.<sup>924–927</sup> (Level of Evidence: B)
2. The use of intranasal mupirocin is reasonable in nasal carriers of *S. aureus*.<sup>928,929</sup> (Level of Evidence: A)
3. The routine use of intranasal mupirocin is reasonable in patients who are not carriers of *S. aureus*, unless an allergy exists. (Level of Evidence: C)

#### Class IIb

1. The use of bilateral IMAs in patients with diabetes mellitus is associated with an increased risk of deep sternal wound infection, but it may be reasonable when the overall benefit to the patient outweighs this increased risk. (Level of Evidence: C)

See Online Data Supplements 35 and 36 for additional data on mediastinitis and perioperative infection.

Nosocomial infections occur in 10% to 20% of cardiac surgery patients. To prevent surgical site infections in CABG patients, a multimodality approach involving several periop-



erative interventions must be considered. Preoperative interventions include screening and decolonization of patients with methicillin-resistant and methicillin-sensitive *S. aureus* colonization and adequate preoperative preparation of the patient. Nasal carriage of *S. aureus* is a well-defined risk factor for subsequent infection. In proven nasal carriers of *S. aureus*, intranasal mupirocin reduces the rate of nosocomial *S. aureus* infection, but it does not reduce the rate of surgical site infection with *S. aureus*.<sup>928,929</sup> Preoperative patient bathing, the use of topical antiseptic skin cleansers (chlorhexidine gluconate),<sup>930–932</sup> and proper hair removal techniques (using electric clippers or depilatories rather than razors)<sup>933–937</sup> are important measures with which to prepare the patient for surgery.

Intraoperative techniques to decrease infection include strict adherence to sterile technique, minimization of operating room traffic, less use of flash sterilization of surgical instruments, minimization of electrocautery<sup>933,936</sup> and bone wax,<sup>938</sup> use of double-gloving,<sup>938–943</sup> and shorter operative times. Identification of patients at high risk for preoperative infection allows the clinician to maximize prevention strategies. Superficial wound infection occurs in 2% to 6% of patients after cardiac surgery,<sup>656,944–946</sup> and deep sternal wound infection occurs in 0.45% to 5%, with a mortality rate of 10% and 47%.<sup>947–953</sup>

The etiology of deep sternal wound infection is multifactorial. Risk factors for deep sternal wound infection are diabetes mellitus,<sup>25,27,28</sup> obesity (body mass index >30 kg/m<sup>2</sup>),<sup>947,949,950,953,954</sup> chronic obstructive pulmonary disease,<sup>950</sup> prolonged CPB time, reoperation, prolonged intubation time, and surgical reexploration.<sup>945,947,955</sup> Potentially modifiable risk factors are smoking cessation, optimized nutritional status, adequate preoperative glycemic status (with hemoglobin A1c <6.9%), and weight loss. The use of bilateral IMAs has been a subject of investigation as a risk factor for deep sternal wound infection. Each IMA provides sternal branches, which provide 90% of the blood supply to each hemisternum. As a result, IMA harvesting can compromise sternal wound healing. Although no RCTs assessing the risk of deep sternal wound infection after bilateral IMA grafting have been reported, the use of bilateral IMAs in patients with diabetes and those with other risk factors for surgical site infection increases the incidence of deep sternal wound infection.<sup>956,957</sup> Skeletonization of the IMA may be associated with a beneficial reduction in the incidence of sternal wound complications, more evident in patients with diabetes mellitus.<sup>958</sup>

Transfusion of homologous blood is a risk factor for adverse outcomes after cardiac surgery. Blood transfusions after CABG are correlated in a dose-related fashion to an increased risk of transfusion-related infection, postoperative infection, postoperative morbidity, and early and late death.<sup>959–962</sup> In addition, they have been associated with a higher incidence of sternal wound infections.<sup>949,963,964</sup> In a retrospective analysis of 15 592 cardiovascular patients, the risk of septicemia/bacteremia and Superficial and deep sternal wound infections increased incrementally with each unit of blood transfused.<sup>961</sup> The leukocytes that are present in packed red blood cells induce the immunomodulatory effects associated with blood transfusions.

Allogenic transfusions of blood containing leukocytes induce higher concentrations of proinflammatory mediators (such as interleukins 6 and 10) than does the transfusion of leukocyte-depleted blood.<sup>924–927,965</sup> In patients undergoing cardiac surgery, RCTs have shown that those receiving leukocyte-filtered blood have lower rates of perioperative infection and in-hospital death than those receiving non-leukocyte-filtered blood.<sup>924–927</sup> An RCT showed that those receiving leukocyte-depleted blood had a reduced rate of infection (17.9% versus 23.5%;  $P=0.04$ ) and 60-day mortality (transfused/nonfiltered patient mortality rate, 7.8%; transfused/filtered at the time of donation, 3.6%; and transfused/filtered at the time of transfusion, 3.3% [ $P=0.019$ ]).<sup>927</sup> Leukodepletion can be accomplished by the blood bank at the time of donation or at the bedside at the time of transfusion (with the use of an inexpensive in-line transfusion filter). Preoperative antibiotics reduce the risk of postoperative infection 5-fold.<sup>892</sup> Interest has grown in administering antibiotic prophylaxis as a single dose rather than as a multiple-dosing regimen for 24 to 48 hours, because single-dose antibiotic prophylaxis reduces the duration of prophylaxis, its cost, and the likelihood of antimicrobial resistance.

*Staphylococcus* coagulase-negative epidermidis or *S. aureus* (including methicillin-resistant *S. aureus*) account for 50% of surgical site infections. Other organisms that are often involved are *Corynebacterium* and enteric gram-negative bacilli.<sup>966–968</sup> Antibiotic prophylaxis against these organisms should be initiated 30 to 60 minutes before surgery, usually at the time of anesthetic induction, except for vancomycin, which should be started 2 hours before surgery and infused slowly to avoid the release of histamine.<sup>903,969,970</sup> In patients without methicillin-resistant *S. aureus* colonization, a cephalosporin (cefazolin, 1 g given intravenously every 6 hours, or cefuroxime, 1.5 g given intravenously every 12 hours) is the agent of choice for standard CABG.<sup>897–905</sup> Antibiotic redosing is performed if the operation lasts >3 hours.<sup>970</sup> Vancomycin is reserved for the patient who is allergic to cephalosporins or has known or presumed methicillin-resistant *S. aureus* colonization.<sup>900,906–908</sup>

The incidence of deep sternal wound infection has decreased over the past 15 years despite an increased risk profile of patients undergoing cardiac surgery (ie, increased comorbidities, obesity, diabetes mellitus, and advanced age).<sup>971</sup> Several options are available for the treatment of deep sternal wound infection. The main treatment is surgical debridement with primary or delayed reconstruction with vascularized soft tissue (pectoral muscle or omentum).<sup>909–912,972</sup> Conventional treatment with pectoralis flap muscle or omentum is associated with procedure-related morbidities, such as destabilization of the thoracic cage, surgical trauma, and potential failure of the flap. In current practice, the vacuum-assisted closure system is often used in the treatment of mediastinitis.<sup>913</sup> With it, local negative pressure is applied to the open wound, accelerating granulation tissue formation and increasing blood supply. Such vacuum-assisted closure therapy, which is less invasive than conventional surgical treatment, has been used as standalone therapy, as a bridge to flap advancement, or as sternal preconditioning and preservation

followed by titanium plate sternal osteosynthesis.<sup>913,914,973</sup> Although several studies have suggested that vacuum-assisted closure therapy can be a successful alternative to conventional standard therapy,<sup>913–921,973</sup> the data are from single-center retrospective studies of patients with heterogeneous disease processes. As a result, it seems reasonable to suggest that both conventional and vacuum-assisted closure therapy can be used in the treatment of mediastinitis.

### 5.2.3. Renal Dysfunction: Recommendations

#### Class IIb

1. In patients with preoperative renal dysfunction (creatinine clearance <60 mL/min), off-pump CABG may be reasonable to reduce the risk of acute kidney injury (AKI).<sup>974–978</sup> (Level of Evidence: B)
2. In patients with preexisting renal dysfunction undergoing on-pump CABG, maintenance of a perioperative hematocrit greater than 19% and mean arterial pressure greater than 60 mm Hg may be reasonable. (Level of Evidence: C)
3. In patients with preexisting renal dysfunction, a delay of surgery after coronary angiography may be reasonable until the effect of radiographic contrast material on renal function is assessed.<sup>979–981</sup> (Level of Evidence: B)
4. The effectiveness of pharmacological agents to provide renal protection during cardiac surgery is uncertain.<sup>982–1004</sup> (Level of Evidence: B)

See Online Data Supplements 37 to 39 for additional data on CABG and renal dysfunction.

Depending on the definition used, the incidence of AKI (defined in various studies as an increase in serum creatinine concentration and/or decrease in calculated glomerular filtration rate of a certain magnitude) after isolated CABG is 2% to 3%, and the incidence of AKI requiring dialysis is 1%.<sup>1005</sup> Risks factors for developing AKI after CABG are preoperative renal dysfunction, LV systolic dysfunction, PAD, advanced age, race, female sex, type of surgery, diabetes mellitus requiring insulin, emergency surgery, preoperative intraaortic balloon support, and congestive heart failure or shock.<sup>1005–1013</sup>

The pathogenesis of postoperative AKI is usually multifactorial. The identification and effective management of modifiable variables can minimize its occurrence. CPB can lead to renal dysfunction if renal perfusion is not adequately maintained. In addition, CPB leads to a systemic inflammatory response, with the release of 1) inflammatory cytokines (eg, kallikrein, bradykinin), 2) catecholamines, and 3) other hormones (eg, renin, aldosterone, angiotensin II, vasopressin), all of which influence renal function. The effects of hypothermia during CPB on renal function are uncertain. Two RCTs<sup>1014,1015</sup> showed no effect of CPB temperature on renal function in patients undergoing CABG, whereas a 2010 observational study<sup>1016</sup> of 1072 subjects identified a relationship between a CPB temperature <27°C and the development of AKI (OR: 1.66; 95% CI: 1.16 to 2.39;  $P=0.005$ ). Although off-pump CABG may theoretically avoid CPB-related renal injury, the cardiac manipulation that is often required to obtain adequate exposure may cause transient decreases in cardiac output, increased peripheral vasoconstriction,

and decreased renal perfusion.<sup>1017</sup> A meta-analysis of 6 RCTs and 16 observational studies (encompassing data from 27 806 patients) suggested a modest beneficial effect of off-pump CABG in reducing the incidence of AKI but no advantage in reducing the incidence of AKI–dialysis.<sup>977</sup> These findings were confirmed by another published RCT of 2203 patients, in which the incidence of AKI–dialysis was similar among those undergoing off-pump and on-pump CABG (0.8% for off pump; 0.9% for on pump;  $P=0.82$ ).<sup>61</sup> Considering the low (approximately 1%) incidence of AKI–dialysis in subjects undergoing CABG, available RCTs are underpowered to detect a difference in outcome. In patients with renal dysfunction preoperatively, it might be reasonable to perform off-pump CABG to reduce the risk of AKI.<sup>974–976,978,996</sup> During CPB, hemodilution is induced to reduce blood viscosity and plasma oncotic pressure to improve regional blood flow in the setting of hypothermia and hypoperfusion. However, an excessively low hematocrit on CPB is associated with increased adverse events and in-hospital deaths.<sup>1018</sup> In patients undergoing isolated CABG, it has been reported that the mortality rate of patients with a single hematocrit value <19% was twice that of those with a hematocrit of 25%.<sup>1019</sup> On the basis of these data, a hematocrit <19% on CPB should be avoided.

No drugs have been identified that prevent or alleviate CABG-associated AKI. N-acetylcysteine reduces proinflammatory cytokine release, oxygen free radical generation, and reperfusion injury, but a review of 10 RCTs containing data from 1163 patients<sup>982</sup> showed that it did not reduce the incidence of AKI and AKI–dialysis.<sup>987</sup> In several RCTs, atrial natriuretic peptide was shown to reduce peak postoperative serum creatinine concentrations, increase urine output, and reduce the need for dialysis in individuals with normal renal function preoperatively, but it did not prevent AKI–dialysis in patients with preexisting renal dysfunction.<sup>996</sup>

Fenoldopam, a selective dopamine D<sub>1</sub> receptor agonist that causes vasodilatation and increases renal cortical and outer medullary blood flow, seems to exert protective renal effects in critically ill patients.<sup>994,995</sup> A meta-analysis of the data from 1059 patients reported in 13 randomized and case-matched studies showed that fenoldopam exerts a beneficial effect on renal function. Compared with standard therapy, fenoldopam reduced the need for renal replacement therapy (5.7% versus 13.4%; OR: 0.37; 95% CI: 0.23 to 0.59;  $P<0.001$ ) and lowered the peak value for serum creatinine concentration. Nevertheless, this beneficial effect was counterbalanced by an increased rate of hypotension and vasopressor requirements (15% versus 10.2%; OR: 1.94; 95% CI: 1.19 to 3.16;  $P=0.008$ ). Dopamine at low doses increases renal blood flow and blocks the tubular reabsorption of sodium. A meta-analysis on the use of low-dose dopamine reported that it increased urine output and improved serum creatinine concentrations without influencing the need for renal replacement therapy or the rates of adverse events or death.<sup>990</sup>

Diltiazem and mannitol have been used to prevent AKI after cardiac surgery.<sup>988</sup> Diltiazem may inhibit the inflammatory response that occurs with CPB,<sup>992</sup> whereas mannitol produces an osmotic diuresis.<sup>1000</sup> The role of mannitol in preventing AKI is unclear.<sup>983,1004</sup> Diltiazem does not prevent

renal dysfunction.<sup>983</sup> Contrast-induced nephropathy is a common cause of AKI. It is usually self-limited and manifests its peak effect 3 to 5 days after the administration of contrast material. In patients with preoperative renal dysfunction, it is reasonable to delay surgery for several days after coronary angiography to reduce the incidence of AKI.<sup>979–981</sup>

#### 5.2.4. Perioperative Myocardial Dysfunction: Recommendations

##### Class IIa

1. In the absence of severe, symptomatic aorto-iliac occlusive disease or PAD, the insertion of an intraaortic balloon is reasonable to reduce mortality rate in CABG patients who are considered to be at high risk (eg, those who are undergoing reoperation or have LVEF <30% or left main CAD).<sup>1021–1026</sup> (Level of Evidence: B)
2. Measurement of biomarkers of myonecrosis (eg, creatine kinase-MB, troponin) is reasonable in the first 24 hours after CABG.<sup>200</sup> (Level of Evidence: B)

Intraaortic balloon counterpulsation is an established mechanical cardiac support procedure that has been demonstrated to increase cardiac output and to improve coronary blood flow.<sup>1025,1026</sup> In several RCTs, its preoperative initiation and perioperative use have been shown to reduce the mortality rate in CABG patients who are considered to be at high risk (ie, those undergoing repeat CABG, those with an LVEF <30%, or those with left main CAD)<sup>1022–1024</sup> despite its known associated vascular complications.<sup>1021</sup> In contrast, its routine use in subjects who are not thought to be high risk has not been demonstrated.<sup>1027</sup>

Some myocyte necrosis often occurs during and immediately after CABG, caused by cardiac manipulation, inadequate myocardial protection, intraoperative defibrillation, or acute graft failure. A determination of the frequency and magnitude with which postoperative myonecrosis occurs has been difficult. In 2007, the European Society of Cardiology/ACC/AHA/World Heart Federation Task Force for the Redefinition of Myocardial Infarction stated, “[B]iomarker values more than 5 times the 99th percentile of the normal reference range during the first 72 h following CABG, when associated with the appearance of new pathological Q-waves or new [left bundle branch block], or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium should be considered as diagnostic of a CABG-related myocardial infarction (type 5 myocardial infarction).”<sup>203</sup>, p. 2183 Until 2000, the conventional biomarker for myonecrosis was creatine kinase-MB, but at present cardiac-specific troponin is the preferred indicator of myonecrosis.<sup>198,200</sup> The higher the serum concentrations of biomarkers after CABG, the greater the amount of myonecrosis and, therefore, the greater the likelihood of an adverse outcome.

Published data from the PREVENT IV trial suggest, first, that serum biomarkers for myonecrosis are elevated postoperatively even in roughly 10% of CABG subjects who are considered to be low risk for the procedure and, second, that short-term (30-day) and long-term (2-year) outcomes were

worse in these patients than in those without a postoperative biomarker elevation. Similarly, a direct correlation has been noted between the presence and magnitude of biomarker elevations postoperatively and both intermediate- and long-term risk of death.<sup>1028</sup>

#### 5.2.4.1. Transfusion: Recommendation

##### Class I

1. Aggressive attempts at blood conservation are indicated to limit hemodilutional anemia and the need for intraoperative and perioperative allogeneic red blood cell transfusion in CABG patients.<sup>1029–1032</sup> (Level of Evidence: B)

Numerous large observational studies have identified perioperative allogeneic red blood cell transfusion(s) as an independent risk factor for adverse outcomes, including death.<sup>1029–1032</sup> A prospective observational study of 8004 patients demonstrated that the transfusion of allogeneic red blood cells in CABG patients was associated with an increased risk of low-output heart failure irrespective of the extent of hemodilutional anemia.<sup>1030</sup> An adverse outcome may be caused by immunomodulation (known to occur with red blood cell transfusion), initiation of a systemic inflammatory response and its associated direct negative myocardial effects, reduced red blood cell capacity for adequate oxygen delivery<sup>1031,1032</sup> (diphosphoglycerate function in “banked” blood may cause tissue hypoxia), and changes in red blood cell morphology of transfused blood. Regardless of etiology, myocardial depression is observed consistently after allogeneic red blood cell transfusion, and this effect appears to be dose dependent. Even risk-adjusted survival rates after CABG in patients transfused with allogeneic red blood cells are reduced.<sup>1029–1032</sup>

#### 5.2.5. Perioperative Dysrhythmias: Recommendations

##### Class I

1. Beta blockers should be administered for at least 24 hours before CABG to all patients without contraindications to reduce the incidence or clinical sequelae of postoperative AF.<sup>604–608,608a–608c</sup> (Level of Evidence: B)
2. Beta blockers should be reinstituted as soon as possible after CABG in all patients without contraindications to reduce the incidence or clinical sequelae of AF.<sup>604–608,608a–608c</sup> (Level of Evidence: B)

##### Class IIa

1. Preoperative administration of amiodarone to reduce the incidence of postoperative AF is reasonable for patients at high risk for postoperative AF who have contraindications to beta blockers.<sup>1036</sup> (Level of Evidence: B)
2. Digoxin and nondihydropyridine calcium channel blockers can be useful to control the ventricular rate in the setting of AF but are not indicated for prophylaxis.<sup>606,1037–1041</sup> (Level of Evidence: B)



AF immediately after CABG, occurring in 20% to 50% of patients, is often difficult to manage and is associated with a substantially increased risk of morbidity (particularly disabling embolic events) and mortality. A prospective observational study of 1878 consecutive subjects undergoing CABG noted that post-CABG AF was associated with a 4-fold increased risk of disabling embolic stroke and a 3-fold increased risk of cardiac-related death.<sup>607</sup>

The incidence of postoperative AF is increased in the presence of advanced patient age, male sex, PAD, chronic lung disease, concomitant valvular heart disease, left atrial enlargement, previous cardiac surgery, preoperative atrial tachyarrhythmias, pericarditis, and elevated postoperative adrenergic tone. However, many subjects have none of these factors, yet they develop AF in the immediate postoperative period. Postoperative AF almost always occurs within 5 days postoperatively, with a peak incidence on the second postoperative day.<sup>608</sup> Numerous trials have assessed the efficacy of various pharmacologic agents in preventing post-CABG AF, including beta-adrenergic-blockers, various antiarrhythmic agents, glucocorticosteroids, hormonal agents (eg, triiodothyronine), and even statins. Preoperative and postoperative beta blockers (or possibly amiodarone) are most effective at reducing its incidence, with several RCTs showing that they effectively accomplish this goal. In contrast, glucocorticosteroids, hormonal agents, and statins are not effective at decreasing its occurrence.<sup>604–606,608b,608c,1042</sup> In subjects without pre-CABG AF, post-CABG AF usually resolves spontaneously within 6 weeks of surgery. As a result, the preferred management strategy of post-CABG AF in such patients often consists of control of the ventricular rate (with beta blockers) in anticipation of spontaneous reversion to sinus rhythm within a few weeks. In addition, if the patient is considered to be at risk for a thromboembolic event while in AF, anticoagulation (with heparin and then warfarin) is warranted. For a more detailed description of the management of subjects with postoperative AF, the reader is referred to the 2011 ACCF/AHA/HRS guidelines for the Management of Patients with Atrial Fibrillation.<sup>608</sup>

### 5.2.6. Perioperative Bleeding/Transfusion: Recommendations

#### Class I

1. Lysine analogues are useful intraoperatively and postoperatively in patients undergoing on-pump CABG to reduce perioperative blood loss and transfusion requirements.<sup>1044–1051</sup> (*Level of Evidence: A*)
2. A multimodal approach with transfusion algorithms, point-of-care testing, and a focused blood conservation strategy should be used to limit the number of transfusions.<sup>1052–1057</sup> (*Level of Evidence: A*)
3. In patients taking thienopyridines (clopidogrel or prasugrel) or ticagrelor in whom elective CABG is planned, clopidogrel and ticagrelor should be withheld for at least 5 days<sup>520,521,523,524,531,1058–1063</sup> (*Level of Evidence: B*) and prasugrel for at least 7 days<sup>533</sup> (*Level of Evidence: C*) before surgery.
4. It is recommended that surgery be delayed after the administration of streptokinase, urokinase, and

tissue-type plasminogen activators until hemostatic capacity is restored, if possible. The timing of recommended delay should be guided by the pharmacodynamic half-life of the involved agent. (*Level of Evidence: C*)

5. Tirofiban or eptifibatide should be discontinued at least 2 to 4 hours before CABG and abciximab at least 12 hours before CABG.<sup>526–528,1049,1050,1064–1068</sup> (*Level of Evidence: B*)

#### Class IIa

1. It is reasonable to consider off-pump CABG to reduce perioperative bleeding and allogeneic blood transfusion.<sup>67,1069–1074</sup> (*Level of Evidence: A*)

See Online Data Supplements 40 to 42 for additional data on bleeding/transfusion.

Approximately 10% of allogeneic blood transfusions in the United States are given to subjects undergoing cardiac surgery.<sup>1075</sup> Allogeneic transfusion carries the risks of transfusion reactions, airborne infections, and increased hospital costs. In patients undergoing isolated CABG, transfusions are associated with reduced long-term survival and worse quality of life.<sup>1029,1076</sup>

About 10% to 20% of the cardiac patients who are transfused receive roughly 80% of the transfusions that are administered.<sup>1075,1078</sup> These high-risk patients often can be identified preoperatively to facilitate measures directed at blood conservation. Several reports have identified risk factors for blood transfusions,<sup>1079–1082</sup> including advanced age, preoperative anemia, small body size, reoperative CABG, priority of operation, duration of CPB, presence of preoperative coagulopathy, and preoperative antithrombotic therapy.<sup>1080,1083–1088</sup> A multimodal approach that includes transfusion algorithms, point-of-care testing, and a focused blood conservation strategy can limit the percentage of patients requiring transfusion and the amount of blood transfusions per patient.<sup>1052–1057</sup>

About 60% to 70% of CABG patients are taking aspirin at the time of the procedure.<sup>536,1089,1090</sup> Although aspirin increases perioperative blood loss and blood transfusion requirements,<sup>1091–1098</sup> the amount of blood loss can be minimized by avoiding CPB<sup>1099</sup> and by using blood conservation techniques. In a meta-analysis of data from 805 patients,<sup>1100</sup> doses of preoperative aspirin >325 mg were associated with increased bleeding (mean difference, 230 mL), whereas those who received <325 mg preoperatively did not have a significant increase in blood loss (mean difference: 65.3 mL; 95% CI: 20.2 to 150.8;  $P=0.134$ ).

Some subjects undergoing CABG are receiving DAPT. Multiple studies have shown that the preoperative use of aspirin and clopidogrel is associated with increased perioperative bleeding, transfusions, and required reexploration for bleeding.<sup>522–524,531,1058–1062,1101–1107</sup> In a study of 350 CABG patients at 14 centers, the risk of reexploration for bleeding was increased 3-fold in patients who were exposed to clopidogrel within 5 days of surgery; half of these patients required transfusions.<sup>520</sup> In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld

for 5 to 7 days before surgery. In subjects taking DAPT because of previous placement of a DES, clopidogrel can be stopped 1 year after the most recent DES placement. If CABG cannot be postponed, some operators have suggested that the patient be hospitalized for conversion of thienopyridine therapy to short-acting glycoprotein IIb/IIIa inhibitors for several days before surgery<sup>497,1063,1108,1109</sup>; however, no data are available demonstrating the efficacy of such a management strategy. Streptokinase, urokinase, and tissue-type plasminogen activator should be stopped before CABG; in these individuals, the timing of CABG depends on the pharmacodynamic half-life of the agent involved.<sup>1110</sup>

The use of unfractionated heparin has not been associated with increased perioperative blood loss; it can be continued until a few hours before CABG. Low-molecular-weight heparin can be administered safely  $\leq 12$  hours preoperatively and does not result in excessive perioperative blood loss.<sup>1064–1068</sup> Lysine analogues, such as epsilon-aminocaproic acid and tranexamic acid, inhibit fibrinolysis by binding to the plasminogen molecule. Several trials have shown that both epsilon-aminocaproic acid and tranexamic acid reduce blood loss and blood transfusions during cardiac surgery, but they do not reduce the rate of reexploration for bleeding.<sup>1044–1051</sup> Both drugs appear to be safe and do not increase the risk of death.<sup>1111</sup>

Erythropoietin is a glycoprotein hormone that stimulates red blood cell production. Recombinant human erythropoietin is used in combination with iron supplementation to treat anemic patients (hemoglobin levels  $<13$  g/dL) with renal failure and those undergoing chemotherapy. The use of erythropoietin in cardiac surgery has been studied in 12 RCTs and has been shown to be associated with significant risk reduction in allogeneic blood transfusion after cardiac surgery.<sup>1112–1122</sup> However, the data from the RCTs are heterogeneous, with different doses of erythropoietin administered for 1 to 3 weeks preoperatively; as a result, further studies are needed to define more precisely the patient subgroups who may benefit from this therapy.<sup>1123</sup> In patients who refuse blood transfusions during cardiac surgery, a short-term course of preoperative erythropoietin, to produce a high hematocrit preoperatively, may be administered.<sup>1124,1125</sup> Alternatively, autologous blood donation may be used, which consists of extracting 1 to 3 units during the 30 days preoperatively and then reinfusing it during or postoperatively. However, such a practice is uncommon because of the increased risk of hemodynamic instability.

Off-pump CABG may avoid CPB-related coagulopathy caused by exposure of blood to artificial surfaces, mechanical trauma, alterations in temperature, and hemodilution. Some evidence suggests that off-pump CABG is associated with less bleeding and fewer blood transfusions.<sup>67,1069–1074</sup>

## 6. Specific Patient Subsets

### 6.1. Elderly

The term “elderly” in CABG patients is usually defined as  $\geq 80$  years of age. Compared with younger subjects, the elderly are more likely to have severe (left main or multivessel) CAD, LV systolic dysfunction, concomitant valvular disease, and previous sternotomy. In addition, they often have

comorbid conditions, such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, PAD, and azotemia. As a result, the elderly have a higher perioperative risk of morbidity and mortality than do younger patients receiving CABG. The operative mortality rate among the elderly ranges from 2.6% (in a population  $>75$  years of age) to 11% (in a population  $>80$  years of age undergoing urgent or emergency surgery).<sup>298,1126</sup> Retrospective studies have observed a substantially higher in-hospital mortality rate among octogenarians than among younger patients.<sup>1127–1130</sup> A report from the National Cardiovascular Network of outcomes in 67 764 patients undergoing cardiac surgery, of whom 4743 were octogenarians, showed that the in-hospital mortality rate for the octogenarians was substantially higher (3.0% versus 8.1%;  $P<0.001$ ).<sup>1127</sup>

Several retrospective studies of patients undergoing CABG have reported a higher incidence of neurological complications, renal failure, respiratory failure, and gastrointestinal complications among octogenarians than among younger subjects.<sup>298,1127,1128</sup> In addition, the elderly have longer lengths of stay and are less likely to be discharged home. An analysis of the New York State Department of Health Cardiac Reporting System registry revealed that length of stay after CABG was 8.5 days in patients  $<50$  years of age and 14.1 days in those  $>80$  years of age, with discharge-to-home rates of 96% and 52%, respectively.<sup>1126</sup>

Despite higher rates of in-hospital morbidity and mortality, the majority of octogenarians achieve functional improvement after CABG. Two studies of patients  $\geq 80$  years of age demonstrated improvements in quality of life, as assessed by the Seattle Angina Questionnaire.<sup>1131,1132</sup> In 1 of these, angina relief and quality-of-life improvement scores after CABG did not differ between patients  $>75$  and  $\leq 75$  years of age.<sup>1126</sup> Of 136 octogenarians who underwent CABG, 81% felt that they were left with little or no disability in their daily activities, and 93% reported substantial symptomatic improvement an average of 2.1 years postoperatively.<sup>1131</sup>

### 6.2. Women

Data on the influence of sex on CABG outcomes are limited. The BARI (Bypass Angioplasty Revascularization Investigation) study compared the outcomes of 1829 patients with multivessel CAD randomly assigned to receive CABG or PCI; 27% were women.<sup>1133</sup> Most information on the efficacy of CABG comes from studies done primarily in men, with extrapolation of the results to women. Although long-term outcomes with CABG in women are similar to or even better than those in men, women have higher rates of periprocedural morbidity and mortality.<sup>1133–1139</sup> Several hypotheses have been suggested to explain this increased morbidity and mortality, including older age at presentation, more frequent need for urgent revascularization, more comorbid conditions, smaller body surface area and coronary arterial dimensions, and increased risk of bleeding. The fact that women on average are older than men at the time of CABG is thought, at least in part, to be due to the loss of the protective effects of estrogen with menopause.<sup>1134,1138,1140–1148</sup> In studies of age-matched men and women undergoing CABG, in-hospital

mortality rates were similar, even among the elderly ( $\geq 70$  years of age).<sup>1149,1150</sup>

In addition to being older, women undergoing CABG are more likely than men to have ACS and cardiogenic shock<sup>1140</sup> and, therefore, to require urgent revascularization.<sup>1138,1141–1143,1146,1148</sup> Sex disparity in the diagnosis and treatment of CAD may contribute to the more complex and delayed presentations in women compared with men.<sup>1151</sup> In comparison to men, women are less likely to be referred for coronary angiography and revascularization and are more likely to have refractory ischemia and repeated hospitalizations.<sup>1152</sup>

Compared with men undergoing CABG, women have more comorbid conditions, including diabetes mellitus, hypertension, hyperlipidemia, chronic renal insufficiency, chronic obstructive pulmonary disease, and concomitant valvular disease.<sup>1153</sup> In some studies, no significant difference in outcomes between women and men undergoing CABG was noted when the data were adjusted for age and comorbidities,<sup>1136–1138,1154–1156</sup> whereas in others, female sex remained an independent predictor of a worse outcome.<sup>1141,1157,1158</sup> In a systematic review of sex differences and mortality after CABG, early mortality differences were reduced but not eliminated after adjustment for comorbidities, procedural characteristics, and body habitus.<sup>1139</sup> Some investigators have shown that smaller body surface area, a surrogate for coronary arterial size, is associated with higher risk of perioperative mortality, whereas others have not.<sup>1140</sup>

Women use more hospital resources in the perioperative period than do men, including intra-aortic balloon counterpulsation,<sup>1137</sup> vasopressors, mechanical ventilation, dialysis, and blood products,<sup>1154,1159</sup> all of which are associated with higher mortality rates.<sup>1146,1160,1161</sup> Women are more likely to have wound complications and longer ICU and hospital stays.<sup>1162–1165</sup> Lastly, the operative procedure itself appears to be different in women than in men, in that women are less likely to be completely revascularized<sup>1166,1167</sup> and less likely to have IMA grafting, especially bilateral,<sup>1168</sup> although bilateral IMA grafting in women is associated with low rates of in-hospital morbidity and mortality.<sup>1169</sup>

### 6.3. Patients With Diabetes Mellitus

The prevalence of diabetes mellitus in CABG patients has increased markedly over the past 30 years. In the late 1970s, only 10% to 15% of CABG patients had diabetes<sup>1170</sup>; by 2005, the incidence had risen to 35%.<sup>308</sup> Patients with diabetes, especially those who are insulin dependent, have higher rates of perioperative morbidity and mortality and a reduced long-term survival rate than those without diabetes.<sup>308,1171,1172</sup> In the STS Registry, patients with diabetes on oral therapy had an adjusted OR of 1.15 for death within 30 days of CABG (95% CI: 1.09 to 1.21) as well as a greater likelihood of stroke, renal failure, and deep sternal wound infection than those without diabetes.<sup>308</sup> For subjects receiving insulin, the adjusted OR for death within 30 days was 1.50 (95% CI: 1.42 to 1.58), and the risks for other complications were correspondingly higher. The poorer short-term outcome in patients with diabetes is only partly explained by a greater frequency of other comorbid conditions, such as obesity, hypertension, renal insufficiency, PAD, and cerebro-

vascular disease. The reduced long-term survival rate after CABG in patients with diabetes is likely due to a combination of more rapid progression of atherosclerosis, a lower long-term patency rate of SVGs,<sup>1173</sup> and a greater burden of comorbid conditions. As in patients without diabetes, long-term outcome after CABG is better when an IMA is used as a conduit than when CABG is performed with only SVGs.<sup>362</sup>

A subgroup analysis of data from the BARI trial suggested that patients with diabetes who underwent CABG with 1 arterial conduit had improved survival compared with those who underwent PCI.<sup>516</sup> Several subsequent observational and cohort studies also showed that CABG results in better long-term outcome in patients with diabetes and multivessel CAD compared with balloon angioplasty or BMS implantation.<sup>361,451,1174</sup> A meta-analysis of 10 RCTs comparing CABG with balloon angioplasty ( $n=6$ ) or BMS implantation ( $n=4$ ) concluded that the mortality rate was substantially lower in patients with diabetes undergoing CABG.<sup>451</sup>

Little information is available about CABG versus PCI with DES in patients with diabetes mellitus. The results of CARDia (Coronary Artery Revascularisation in Diabetes), the first RCT comparing CABG and PCI in a population consisting entirely of subjects with diabetes, suggested that PCI with DES (used in 69% of the PCI patients) and CABG achieved similar outcomes.<sup>475</sup> Of the 1,800 subjects enrolled in the SYNTAX trial, which compared CABG and PCI with paclitaxel-eluting stents, 452 had medically treated diabetes.<sup>364</sup> At 1-year follow-up, the 2 treatments exerted a similar effect on survival, MI, and the composite endpoint of death, MI, or stroke. As in the entire SYNTAX cohort, patients with diabetes randomly assigned to receive PCI had a higher rate of repeat revascularization (20.3% after PCI versus 6.4% after CABG;  $P<0.001$ ), and those with highly complex lesions (ie, SYNTAX score  $\geq 33$ ) had a higher mortality rate with PCI (13.5% versus 4.1%;  $P=0.04$ ). The FREEDOM (Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial, an ongoing randomized comparison of CABG and PCI with DES in 1900 patients with diabetes and multivessel CAD, should shed further light on the preferred therapy for these patients.<sup>1175</sup>

Few comparisons of CABG and contemporary medical therapy in patients with diabetes mellitus are of sufficient size to allow meaningful conclusions. The largest such trial, BARI 2D, randomly assigned 2368 patients with type 2 diabetes mellitus to revascularization plus intensive medical therapy or intensive medical therapy alone,<sup>404,1176</sup> with patients in the medical therapy group to undergo revascularization during follow-up only if such therapy were clinically indicated by the progression of angina or the development of an ACS or severe ischemia. The planned method of revascularization, PCI or CABG, was determined before randomization by the treating physicians. No significant difference in primary endpoints was evident between the PCI group and the medical therapy group. No difference in survival rate between those undergoing CABG and those receiving only medical therapy was noted. Acute MI occurred less often in those assigned to CABG plus intensive medical therapy than in those given intensive medical therapy alone (10% versus



17.6%;  $P=0.003$ ), and the composite endpoints of death or MI (21.1% versus 29.2%;  $P=0.01$ ) and cardiac death or MI also occurred less often.<sup>1176</sup> Compared to those selected for PCI, the CABG patients had more 3-vessel CAD (52% versus 20%), more totally occluded arteries (61% versus 32%), more proximal LAD artery stenoses >50% (19% versus 10%), and a higher myocardial jeopardy score.

Elevated fasting blood glucose concentrations before CABG and persistently elevated glucose concentrations afterward are associated with increased risk of morbidity and mortality.<sup>592,1177,1178</sup> The complications most closely linked to postoperative hyperglycemia are infections, including deep sternal wound infection and mediastinitis. Achieving glyce-mic control perioperatively in patients with diabetes decreases this risk.<sup>581,593</sup> Because the risk of deep sternal wound infection in patients with diabetes is increased when both IMAs are harvested and used, bilateral IMA grafting is not recommended in this patient cohort unless the overall benefit to the patient outweighs this increased risk.<sup>957</sup>

#### 6.4. Anomalous Coronary Arteries: Recommendations

##### Class I

1. Coronary revascularization should be performed in patients with:
  - a. A left main coronary artery that arises anomalously and then courses between the aorta and pulmonary artery.<sup>1179–1181</sup> (*Level of Evidence: B*)
  - b. A right coronary artery that arises anomalously and then courses between the aorta and pulmonary artery with evidence of myocardial ischemia.<sup>1179–1182</sup> (*Level of Evidence: B*)

##### Class IIb

1. Coronary revascularization may be reasonable in patients with a LAD coronary artery that arises anomalously and then courses between the aorta and pulmonary artery. (*Level of Evidence: C*)

Several variations and anatomic courses of anomalous coronary arteries have been described, some benign and others associated with sudden cardiac death. The most life-threatening variants involve anomalous origin of the left main coronary artery from the right sinus of Valsalva or of the right coronary artery from the left sinus of Valsalva, after which the anomalous artery travels to its normal area of perfusion between the ascending aorta and the main pulmonary artery. In a review of consecutive echocardiograms in 2388 asymptomatic children and young adolescents, the incidence of anomalous coronary arteries arising from the opposite sinus of Valsalva was 0.17%.<sup>1183</sup> Anomalous coronary arteries (particularly those traversing between the aorta and the main pulmonary artery) are associated with exercise-related sudden death in young ( $\leq 35$  years of age) athletes.<sup>1184–1190</sup> A consecutive series of 27 young athletes with sudden death who were found to have such anomalous coronary arteries at autopsy had inducible myocardial ischemia and complained of cardiac symptoms before their demise.<sup>1179</sup> Isolated case reports of other coronary arterial anomalies in subjects with

syncope or sudden death emphasize the need for careful anatomic and functional evaluation of all individuals with anomalous coronary arteries.<sup>1191–1194</sup> The method of revascularization employed in adults with anomalous coronary arteries has been 1) CABG or, more recently, 2) PCI with stenting.<sup>1195</sup> When CABG is employed, consideration should be given to the presence of competitive flow in the native coronary circulation.<sup>1196</sup> In children and some adults, an unroofing procedure or coronary arterial reimplantation may provide the best long term results.<sup>1197,1198</sup> The risk associated with these coronary anomalies if they are left untreated and the existing operative experience make corrective surgery reasonable in these individuals.<sup>1180</sup>

#### 6.5. Patients With Chronic Obstructive Pulmonary Disease/Respiratory Insufficiency: Recommendations

##### Class IIa

1. Preoperative intensive inspiratory muscle training is reasonable to reduce the incidence of pulmonary complications in patients at high risk for respiratory complications after CABG.<sup>1199</sup> (*Level of Evidence: B*)

##### Class IIb

1. After CABG, noninvasive positive pressure ventilation may be reasonable to improve pulmonary mechanics and to reduce the need for reintubation.<sup>1200,1201</sup> (*Level of Evidence: B*)
2. High thoracic epidural analgesia may be considered to improve lung function after CABG.<sup>37,1202</sup> (*Level of Evidence: B*)

See Online Data Supplement 43 for additional data on patients with chronic obstructive pulmonary disease/respiratory insufficiency.

In the STS Adult Cardiac Database predictive algorithms, the presence of chronic obstructive pulmonary disease preoperatively was an independent predictor of mortality, the need for prolonged postoperative ventilator support, and renal failure.<sup>1203</sup> Furthermore, most rehospitalizations following CABG are related to pulmonary dysfunction and/or infection or volume overload. The incidence of complications increases with patient age and the severity of chronic obstructive pulmonary disease, as measured with pulmonary function testing.<sup>1204,1205</sup> None of these studies, however, address the relative risks and benefits of CABG in subjects with chronic obstructive pulmonary disease, thereby precluding a specific recommendation regarding the performance of CABG in these patients. In preparation for CABG, optimizing pulmonary function is imperative.<sup>1206</sup> An RCT of 279 patients<sup>1199</sup> showed that preoperative respiratory muscle training reduced postoperative pulmonary complications (including pneumonia) and length of stay in patients at high risk for such complications after CABG. Such muscle training is indicated in all patients before CABG, especially those with impaired baseline pulmonary function.

Two prospective RCTs have shown that prophylactic nasal continuous positive airway pressure after CABG improves pulmonary function and offers protection from

postoperative pulmonary complications.<sup>1200,1201</sup> However, the applicability of these results to patients with impaired pulmonary function is uncertain, because those with severe underlying lung disease and other comorbid conditions were not enrolled. Although noninvasive positive pressure ventilation may be useful in subjects with borderline pulmonary function postoperatively, its overuse should be avoided, because it may cause gastric distention, thereby increasing the risk of vomiting and aspiration. Improved lung function has been achieved with the use of high thoracic epidural anesthesia in patients undergoing CABG,<sup>36,37</sup> but its application has been limited by concerns about paraspinal and epidural hemorrhage related to epidural catheter insertion.

Despite some evidence that oral corticosteroids improve pulmonary function after cardiac surgery,<sup>1207,1208</sup> their use has not been adopted widely in subjects undergoing CABG. Finally, a consistent reduction in postoperative pulmonary complications has not been shown when off-pump (as opposed to on-pump) CABG is performed.<sup>1209</sup>

## 6.6. Patients With End-Stage Renal Disease on Dialysis: Recommendations

### Class IIb

1. CABG to improve survival rate may be reasonable in patients with end-stage renal disease undergoing CABG for left main coronary artery stenosis of greater than or equal to 50%.<sup>479</sup> (*Level of Evidence: C*)
2. CABG to improve survival rate or to relieve angina despite GDMT may be reasonable for patients with end-stage renal disease with significant stenoses ( $\geq 70\%$ ) in 3 major vessels or in the proximal LAD artery plus 1 other major vessel, regardless of LV systolic function.<sup>1210</sup> (*Level of Evidence: B*)

### Class III: HARM

1. CABG should not be performed in patients with end-stage renal disease whose life expectancy is limited by noncardiac issues. (*Level of Evidence: C*)

Rates of cardiovascular morbidity and mortality are increased in patients with CKD compared with age-matched controls without CKD, and the magnitude of the increase is directly related to the severity of CKD. About half of those on maintenance dialysis die from a cardiovascular cause.<sup>476</sup> At present, the prevalence of CKD in the general population of the United States is estimated to be 13%, with approximately 5.8% of these having Stage III–V disease (ie, glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>).<sup>1211</sup> In 2009,  $> 525$  000 Americans were receiving maintenance hemodialysis.<sup>1212</sup>

To date, randomized comparisons of CABG and medical therapy in patients with CKD (irrespective of its severity) have not been reported. Observational studies have demonstrated an improved survival rate with CABG (compared with medical therapy) in patients with CKD and multivessel CAD.<sup>57,479</sup> At the same time, these observational studies as well as other registries have demonstrated a markedly reduced long-term survival rate

in patients with CKD undergoing CABG compared with non-dialysis CABG patients,<sup>1213–1216</sup> with the magnitude of the decrease directly related to the severity of CKD. In these reports, subjects with CKD undergoing CABG had an increased incidence of periprocedural complications, including mediastinitis, need for blood transfusion, prolonged ventilation, reoperation, stroke, and increased length of hospital stay.<sup>1210</sup>

## 6.7. Patients With Concomitant Valvular Disease: Recommendations

### Class I

1. Patients undergoing CABG who have at least moderate aortic stenosis should have concomitant aortic valve replacement.<sup>1217–1220</sup> (*Level of Evidence: B*)
2. Patients undergoing CABG who have severe ischemic mitral valve regurgitation not likely to resolve with revascularization should have concomitant mitral valve repair or replacement at the time of CABG.<sup>1221–1226</sup> (*Level of Evidence: B*)

### Class IIa

1. In patients undergoing CABG who have moderate ischemic mitral valve regurgitation not likely to resolve with revascularization, concomitant mitral valve repair or replacement at the time of CABG is reasonable.<sup>1221–1226</sup> (*Level of Evidence: B*)

### Class IIb

1. Patients undergoing CABG who have mild aortic stenosis may be considered for concomitant aortic valve replacement when evidence (eg, moderate–severe leaflet calcification) suggests that progression of the aortic stenosis may be rapid and the risk of the combined procedure is acceptable. (*Level of Evidence: C*)

## 6.8. Patients With Previous Cardiac Surgery: Recommendation

### Class IIa

1. In patients with a patent LIMA to the LAD artery and ischemia in the distribution of the right or left circumflex coronary arteries, it is reasonable to recommend reoperative CABG to treat angina if GDMT has failed and the coronary stenoses are not amenable to PCI.<sup>380,1227</sup> (*Level of Evidence: B*)

### 6.8.1. Indications for Repeat CABG

RCTs comparing medical therapy to CABG in subjects with SIHD demonstrated that those with specific angiographic findings, such as left main disease, 3-vessel disease, and 2-vessel disease that includes the proximal LAD artery, derive a survival benefit from CABG.<sup>318</sup> At the same time, it is unknown if CABG provides a survival benefit compared with medical therapy in patients with these anatomic findings who have had previous CABG. It is logical to assume that subjects with previous CABG and these anatomic findings would, in fact, derive a survival benefit from repeat CABG provided that CABG could be performed with an acceptable risk. The importance of recurrent MI in the distribution of the

LAD artery has been shown to be associated with a poor prognosis in patients with previous CABG. The long-term outcomes of 723 patients with diseased SVGs who did not undergo reoperation or PCI within 1 year of angiography were reviewed.<sup>1228</sup> A stenosis of a graft to the LAD artery was associated with decreased rates of survival, reoperation-free survival, and event-free survival. On the basis of these data, these authors suggest that a >50% stenosis in a graft to the LAD artery is an indication for reoperation. In contrast, patients without ischemia in the LAD artery distribution do not derive a survival benefit from repeat CABG. In an observational study from the Cleveland Clinic, the survival rate of 4640 patients with patent LIMA grafts to the LAD artery and ischemia in the distribution of the right and/or left circumflex arteries who were treated with repeat CABG, PCI, or medical therapy was examined.<sup>380</sup> No improvement in survival was observed in either revascularization group compared with those treated medically.

### 6.8.2. Operative Risk

Because of the technical difficulty of repeat CABG and the high risk profiles of these patients, reoperative CABG is associated with higher rates of morbidity and mortality than is primary CABG.<sup>945,1229–1235</sup> With advances in surgical techniques, some groups have reported a decline in mortality rate for patients undergoing repeat CABG.<sup>1233,1236</sup> An observational study suggested that the higher operative risk with reoperation is related to the higher patient risk profiles and not to the technical challenges of the operation itself, thereby suggesting that improvements in surgical techniques have neutralized the risk associated with the complexity of repeat CABG,<sup>1233</sup> but others continue to suggest that technical issues are still important in causing the higher mortality rate in these individuals.

### 6.8.3. Long-Term Outcomes

The survival rate after repeat CABG is lower than that after primary CABG. A multicenter study from Australia reported 1, 3, 5, and 6 year survival rates in reoperative CABG patients of 93.1%, 90.5%, 85.9%, and 80.5%, respectively<sup>1235</sup>—survival results that were significantly lower than those observed after primary CABG. However, after adjusting for differences in risk profiles between primary and reoperative CABG patients, no difference in long-term survival rate was apparent. The variables associated with decreased late survival rate included advanced age, hypertension, elevated serum cholesterol, diabetes mellitus, PAD, renal failure, left main CAD, LV systolic dysfunction, and emergency status.<sup>1235</sup>

Compared with primary CABG, repeat CABG is less successful at relieving angina,<sup>1237,1238</sup> although a 2004 quality-of-life analysis reported that repeat CABG was as effective as primary CABG in relieving angina and improving functional capacity and quality of life.<sup>1239</sup>

### 6.9. Patients With Previous Stroke

Patients with a previous stroke or TIA are at higher risk for a perioperative stroke during CABG than those without such a history. A meta-analysis of the data from several studies observed a perioperative stroke risk of 8.5% in patients with previous stroke (compared with 2.2% in those without a

previous neurological event) ( $P<0.0001$ ).<sup>860</sup> When subjects with a history of stroke or TIA were analyzed separately (ie, stroke only or TIA only), the increased perioperative risk in comparison with neurologically asymptomatic patients was present in both groups. In a multivariate logistic regression analysis of 16 194 cardiac surgery patients, a history of cerebrovascular disease was identified as an independent predictor of perioperative stroke.<sup>1240</sup> The STS National Cardiac Surgery Database demonstrated an increased risk of perioperative death, perioperative stroke, and prolonged length of stay in patients with a history of stroke who underwent isolated CABG from 2002 to 2006.<sup>308</sup>

### 6.10. Patients With PAD

CAD and PAD, generally defined as atherosclerotic disease of the aorta, its visceral arterial branches (renal and mesenteric), and the arteries of the lower extremities, often coexist. The presence of PAD is an independent predictor of early<sup>1241</sup> and late death in CABG patients. In the STS National Cardiac Surgery Database, 774 881 patients underwent isolated CABG over a 5-year period, of whom 15.5% had PAD. The presence of PAD was an independent risk factor for in-hospital death or death within 30 days of CABG. In addition, PAD was an independent risk factor for perioperative stroke and subsequent need for post-CABG limb revascularization or amputation. Potential but unproven explanations for the adverse effects of PAD on long-term survival after CABG include: 1) The presence of PAD may lead to vascular events (ie, cerebrovascular events) that adversely affect post-CABG survival; 2) PAD may be a marker for more severe CAD, which may lead to an increased rate of post-CABG death from cardiac causes despite revascularization; and 3) PAD may contribute to noncardiovascular death in the long term. Revascularization of PAD before CABG is not known to improve post-CABG outcomes.

## 7. Economic Issues

### 7.1. Cost-Effectiveness of CABG and PCI

In the United States, it is estimated that the annual hospital costs of CABG are approximately \$10 billion.<sup>1242</sup> Despite the increasing risk profile of CABG candidates, it nonetheless is becoming more cost-effective. Hospital charges from the Nationwide Inpatient Sample of nearly 5.5 million patients who had isolated CABG in the United States from 1988 to 2005 were examined.<sup>1243</sup> A decrease in risk-adjusted mortality rate, from 6.2% to 2.1% ( $P<0.0001$ ), was noted. When hospital costs were corrected for inflation, they declined from \$26 210 in 1988 to \$19 196 in 2005 (\$1988) ( $P<0.0001$ ).

Several factors tend to increase the cost of CABG, including advanced patient age, female sex, African-American ethnicity, postoperative complications, longer hospital stay, and multiple comorbidities, particularly CKD.<sup>1244–1247</sup> The National Health Service Foundation Trust in Britain found that patients >75 years of age undergoing CABG had higher rates of postoperative complications and greater resource utilization than their younger counterparts.<sup>1244</sup> Similarly, the Maryland Health Services Cost Review Commission reported an increased total cost and length of hospital stay with increasing age in patients undergoing CABG.<sup>1245</sup> The same



phenomenon was not present with PCI until the patients were >80 years old. In an examination of data from 12 016 subjects undergoing CABG in New York State in 2003, it was determined that older age, female sex, and African-American ethnicity were associated with higher costs.<sup>1247</sup> Clinical characteristics, such as a lower LVEF, number of diseased vessels, previous open-heart operations, and numerous comorbidities, further increased costs. Larger hospitals were associated with higher CABG discharge costs, whereas costs significantly decreased with higher CABG volumes.

Not surprisingly, perioperative complications lead to increased costs. An examination of the Medicare Provider Analysis and Review file of data from 114 223 Medicare beneficiaries who survived CABG in 2005 showed the mean cost of hospitalization associated with CABG to be \$32 201 ± \$23 059 for a mean length of stay of 9.9 ± 7.8 days. Those with complications (13.6% of patients) consumed significantly more hospital resources (incremental cost, \$15 468) and had a longer length of stay (average additional stay, 1.3 days).<sup>1246</sup>

Evidence for the role of off-pump versus on-pump CABG in decreasing costs is conflicting. In a randomized study comparing off-pump and on-pump CABG, the mean total hospitalization cost per patient was \$2272 less for off-pump CABG at hospital discharge and \$1955 less at 1 year.<sup>1248</sup> Another study of 6665 patients who underwent CABG between 1999 and 2005 determined that off-pump CABG provided a small short-term gain,<sup>1249</sup> although off-pump patients had increased long-term risks of repeat revascularization and major vascular events, especially if they were considered to be high risk. In the long run, in fact, off-pump patients utilized more resources.

#### 7.1.1. Cost-Effectiveness of CABG Versus PCI

Medical costs and quality of life were examined 10 to 12 years after patients were randomly assigned to receive angioplasty or CABG in the BARI trial.<sup>1250</sup> Although CABG costs initially were 53% higher, the gap closed to <5% by the end of 2 years. After 12 years, the average cost was \$123 000 in CABG patients and \$120 000 for PCI patients. Cumulative costs were significantly higher among patients with diabetes mellitus, heart failure, and comorbid conditions, and they were higher in women. CABG was deemed to be as cost-effective as PCI in patients with multivessel CAD.

The cost of coronary artery revascularization in 6218 patients with and without CKD whose data were available in the Duke database was examined.<sup>1251</sup> CABG was an economically attractive alternative to PCI or medical therapy for all patients with left main or 3-vessel CAD without concomitant CKD as well as those with 2-vessel CAD with concomitant CKD. For subjects with 3-vessel CAD and concomitant CKD, 2-vessel CAD without CKD, and 1-vessel CAD regardless of renal function, medical therapy was an economically attractive strategy compared with CABG or PCI. This analysis concluded that CABG is most economically attractive compared with PCI and medical therapy in patients to whom it confers the greatest survival advantage and for whom the cost of alternative treatments is greatest (ie, those with the most severe CAD). Although CABG was more expensive than medical therapy for all patients, the

survival benefits associated with it were of such magnitude in some subjects that it was economically attractive.

The cost-effectiveness of CABG and PCI in high-risk patients was analyzed in the AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) study,<sup>446</sup> in which costs were assessed at 3 and 5 years. After 3 years, the average total cost was \$63 896 for PCI and \$84 364 for CABG, a difference of \$20 468. After 5 years, the average total cost was \$81 790 for PCI and \$100 522 for CABG, a difference of \$18 732. The authors concluded that PCI was less costly and at least as effective for urgent revascularization in high-risk patients with medically refractory angina.

#### 7.1.2. CABG Versus PCI With DES

The use of DES for PCI will require a reassessment of cost-effectiveness. Although the initial procedure is considerably more expensive than the use of balloon angioplasty or BMS, equaling the cost of CABG in many patients with multivessel CAD, the cost of reintervention for restenosis may be reduced. The cost-effectiveness will depend on the pricing of stents, utilization rates of the more expensive stents, and efficacy. In a 2010 study from Japan comparing the total costs at 2 years of CABG and DES implantation in patients with left main CAD, the total costs were significantly lower for those undergoing CABG than for those receiving a DES.<sup>1252</sup>

### 8. Future Research Directions

With improvements in percutaneous techniques and medical therapy, on-pump CABG and off-pump CABG will increasingly be reserved for patients with extensive CAD, many of whom have had previous PCI. The future of CABG will be directed at improving its results in high-risk patients and making CABG less invasive for elective revascularization. Minimally invasive techniques, with the use of robotics and anastomotic connectors, intraoperative imaging, hybrid procedures, and protein and gene therapy, appear promising. Robotic technology in minimally invasive CABG leads to less traumatic harvesting of the LIMA for minimally invasive direct coronary artery bypass procedures compared with nonrobotic techniques.<sup>1253</sup> The ultimate goal of robotic CABG is totally endoscopic CABG, but its use has been limited, at least partly because of a substantial learning curve, cost considerations, and few data demonstrating noninferior graft patency and outcomes compared with standard CABG.

Anastomotic connectors may enable more routine application of totally endoscopic anastomoses in subjects undergoing minimally invasive CABG. Because hand-sewn anastomoses are technically challenging when performed endoscopically, consideration has been given to the concept of anatomic connectors to facilitate more reproducible and less technically demanding procedures and ultimately to allow widespread use. Both proximal and distal connectors may be used. Several options are being developed, some only available outside the United States, and the evidence base supporting their use is evolving.<sup>1254</sup> The PAS-Port proximal device has been associated with acceptable outcomes. In two prospective studies, its angiographic graft patency 9 months after CABG was similar to that of hand-sewn anastomoses.<sup>1255,1256</sup> With this device, the proximal anastomoses must be constructed

before the distal ones. At present, only 1 distal device, the Cardica C-Port, has been approved for use in the United States. The prospective studies<sup>1257,1258</sup> demonstrated a 6-month overall patency of 96% in 102 subjects. These devices increase the cost of the operation.

Over the past 20 years, the patency rate of all graft types has improved gradually, so that the present failure rate of LIMA grafts at 1 year is about 8% and of SVGs roughly 20%.<sup>1259</sup> Many patients being referred for CABG nowadays have far advanced CAD, which is often diffuse and exhibits poor vessel runoff. Technical issues at the time of surgery may influence graft patency, and intraoperative imaging may help to delineate technical from nontechnical issues. Because coronary angiography is rarely available intraoperatively, other techniques have been developed to assess graft integrity at this time, most often the transit-time flow and intraoperative fluorescence imaging. The transit-time flow is a quantitative volume-flow technique that cannot define the severity of graft stenosis or discriminate between the influence of the graft conduit and the coronary arteriolar bed on the mean graft flow. Intraoperative fluorescence imaging, which is based on the fluorescent properties of indocyanine green, provides a “semiquantitative” assessment of graft patency with images that provide some details about the quality of coronary anastomoses.<sup>1260</sup> Although both methods are valuable in assessing graft patency, neither is sufficiently sensitive or specific to allow identification of more subtle abnormalities.<sup>1260</sup> It is hoped that such imaging may help to reduce the occurrence of technical errors.

The hybrid suite can be used as an operating room and a catheterization laboratory. It allows the performance of an angiogram after CABG so that one can identify abnormal grafts, providing the opportunity to revise them (with PCI or surgery) before leaving the operating room. Until completion angiography becomes more routine (in a hybrid suite), cardiac surgeons must rely on reasonably accurate, albeit imperfect, methods to identify problems with a recently implanted graft.

### 8.1. Hybrid CABG/PCI

Advances in surgical techniques and the introduction of DES have provided a platform for a “hybrid revascularization strategy” that combines grafting the LAD artery with the LIMA and stenting the non-LAD arteries with DES (instead of bypassing them with SVGs). Although preliminary data<sup>1261</sup> have indicated that a hybrid strategy may be a reasonable alternative in some patients with multivessel CAD, its real effect will not be known until results of RCTs are available.<sup>1261</sup> The primary purpose of performing hybrid CABG is to decrease the morbidity rate of traditional CABG in high-risk patients. Although hybrid revascularization is most often performed in a staged fashion, a simultaneous hybrid procedure can be performed in a hybrid suite, offering several potential advantages, including improving the efficiency and cost-effectiveness of therapy as well as condensing therapy into 1 patient encounter. If a staged approach is chosen, minimally invasive CABG performed first, followed days later by PCI, is probably preferable, so as to enable surgery without the unwanted effects of antiplatelet therapy as well as

to enable complete angiography of the LIMA graft at the time of PCI. The major disadvantage of this approach is that if complications occur with PCI, a third procedure may be necessary. Even with a hybrid suite, one of the most substantive barriers to simultaneous minimally invasive CABG and PCI is the management of antiplatelet therapy. The role of hybrid CABG–PCI compared with sole PCI and sole conventional CABG awaits the results of the ongoing observational study of hybrid coronary revascularization by the National Heart, Lung, and Blood Institute.

### 8.2. Protein and Gene Therapy

Several proteins, such as vascular endothelial growth factor, acidic fibroblast growth factor, and basic fibroblast growth factor, induce angiogenesis<sup>1262</sup>; as a result, interest has grown in using these substances to stimulate myocardial perfusion. One RCT found that patients who were given 100 mcg of basic fibroblast growth factor became angina free, and nuclear perfusion testing appeared to show improved perfusion.<sup>1262</sup> Another RCT has suggested that the intracoronary injection of high-dose angiogenic molecules yields improvement in symptoms, exercise time, functional capacity, and myocardial perfusion.<sup>1263</sup> Alternatively, gene therapy may be used to induce angiogenesis, but conceptual concerns with intravascular gene therapy, such as peripheral uptake into nontarget tissues and subsequent unintended effects, have been raised.

### 8.3. Teaching CABG to the Next Generation: Use of Surgical Simulators

Over the past decade, pressure on hospitals and physicians to ensure high quality and safety has increased. Public reporting of outcomes, common in many states, has been endorsed by the STS. In addition, healthcare reform has placed great emphasis on the efficiency of care. These factors, coupled with the increased complexity of patients referred for CABG, the decreased number of qualified physicians specializing in cardiac surgery, and the restrictions on resident work hours, make the teaching of surgical techniques to the next generation a substantial challenge.

Given the success of simulator training of airline and military personnel, it has the potential to have a major impact on surgical training paradigms. With surgical simulators, a trainee’s first distal anastomosis in an actual patient will occur only after mastering the technique on a simulator.<sup>1264</sup> The mastery of basic skills will allow the trainee to focus on more complex tasks as well as to understand the conduct of the operation more thoroughly and quickly. The fundamentals of simulator training are based on the learning principle of “deliberate practice,” in which an individual practices a finite task until it is mastered. Still, before this method of training can be incorporated into a formal curriculum, several issues must be addressed. Trainees must have adequate supervision and instruction to ensure appropriate technique, which will require that attending surgeons have time away from clinical and academic duties to provide simulator training. This poses a considerable challenge under current reimbursement requirements, and a reimbursement system that provides an incentive to active surgeons to teach residents in the simula-

tion laboratory will be required. As an alternative, training programs may opt to hire recently retired surgeons to teach in the simulation laboratory. Finally, simulators must become more robust, with perhaps computer-enhanced clinical scenarios, before the residents who train on them are qualified to care for patients.

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KEY WORDS: AHA Scientific Statements ■ acute coronary syndromes ■ anticoagulants ■ antiplatelet agents ■ arrhythmias, cardiac ■ coronary angiography ■ coronary artery revascularization interventions: stents ■ drug therapy ■ heart diseases ■ myocardial revascularization ■ platelet aggregation inhibitor ■ ultrasound

**Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery**

Committee Member	Employer/Title	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section Numbers*
L. David Hillis ( <i>Chair</i> )	University of Texas Health Science Center at San Antonio—Professor and Chair of the Department of Medicine	None	None	None	None	None	None	None
Peter K. Smith ( <i>Vice Chair</i> )	Duke University Medical Center: Private Diagnostic Clinic—Professor of Surgery; Chief of Thoracic Surgery	• Eli Lilly • Baxter BioSurgery	None	None	None	None	None	2.2.3 4.1 4.2 5.2.6
Jeffrey L. Anderson	Intermountain Medical Center—Associate Chief of Cardiology	• BMS/sanofi-aventis	None	None	• AstraZeneca • Gilead Pharma • Toshiba†	None	None	2.1.6 2.2.3 4.1 4.2 4.3 5.2.6
John A. Bittl	Ocala Heart Institute Munroe Regional Medical Center—Interventional Cardiologist	None	None	None	None	None	None	None
Charles R. Bridges	University of Pennsylvania Medical Center—Chief of Cardiothoracic Surgery	• Baxter BioSurgery† • Zymogenetics	• Bayer Pharmaceuticals	None	None	None	• Plaintiff, alleged mitral valve dysfunction, 2009 • Defendant, retinal artery occlusion (stroke) after CABG, 2009 • Defendant, timely insertion of IABP after CABG, 2009 • Defendant, timely transport after acute aortic dissection, 2009 • Plaintiff, unexpected intra-abdominal hemorrhage and death after AVR, 2009	2.2.3 4.1 4.2 5.2.6
John G. Byrne	Vanderbilt University Medical Center: Division of Cardiac Surgery—Chairman of Cardiac Surgery	None	None	None	None	None	None	None
Joaquin E. Cigarroa	Oregon Health and Science University—Associate Professor of Medicine	None	None	None	None	None	None	None
Verdi J. DiSesa	John Hopkins Hospital, Division of Cardiac Surgery—Clinical Associate	None	None	None	None	None	None	None
Loren F. Hiratzka	Cardiac, Vascular and Thoracic Surgeons, Inc.—Medical Director of Cardiac Surgery	None	None	None	None	None	None	None
Adolph M. Hutter, Jr.	Massachusetts General Hospital—Professor of Medicine	None	None	None	None	None	None	None
Michael E. Jessen	UT Southwestern Medical Center—Professor of Cardiothoracic Surgery	• Quest Medical†	None	None	None	None	None	2.1.8
Ellen C. Keeley	University of Virginia—Associate Professor of Internal Medicine	None	None	None	None	None	None	None
Stephen J. Lahey	University of Connecticut—Professor and Chief of Cardiothoracic Surgery	None	None	None	None	None	• Defendant, mitral valve replacement, 2009	None

(Continued)



## Appendix 1. Continued

Committee Member	Employer/Title	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section Numbers*
Richard A. Lange	University of Texas Health Science Center at San Antonio—Professor of Medicine	None	None	None	None	None	None	None
Martin J. London	University of California San Francisco, Veterans Affairs Medical Center—Professor of Clinical Anesthesia	None	None	None	None	None	None	None
Michael J. Mack	The Heart Hospital Baylor Plano—Cardiovascular Surgery, Medical Director	<ul style="list-style-type: none"> <li>• Cordis</li> <li>• Marquett</li> <li>• Medtronic</li> <li>• Edwards Lifesciences†</li> </ul>	None	None	None	None	None	2.1.3 2.2.1 5.2.1.1 5.2.1.2
Manesh R. Patel	Duke University Medical Center—Associate Professor of Medicine	None	None	None	None	None	None	None
John D. Puskas	Emory University/Emory Healthcare—Chief of Cardiac Surgery	<ul style="list-style-type: none"> <li>• Marquett</li> <li>• Medtronic</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Marquett‡</li> <li>• Medtronic‡</li> </ul>	None	None	2.1.3 2.2.1 2.2.2
Joseph F. Sabik	Cleveland Clinic Foundation—Professor of Surgery	<ul style="list-style-type: none"> <li>• Edwards Lifesciences</li> <li>• Medtronic</li> </ul>	None	None	None	None	None	2.2.2 5.2.1.1 5.2.1.2
Ola Selnes	John Hopkins Hospital, Department of Neurology—Professor of Neurology	None	None	None	None	None	None	None
David M. Shahian	Massachusetts General Hospital—Professor of Surgery	None	None	None	None	None	None	None
Jeffrey C. Trost	John Hopkins School of Medicine—Assistant Professor of Medicine	None	None	None	<ul style="list-style-type: none"> <li>• Toshiba‡</li> </ul>	None	None	2.1.7 4.10 4.10.1 4.10.2 4.10.3 5.2.1.1.1 5.2.1.1.2
Michael D. Winniford	University of Mississippi Medical Center—Professor of Medicine	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$10\,000$  of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

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\*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.

†No financial benefit.

‡Significant relationship.

AVR indicates aortic valve replacement; CABG, coronary artery bypass graft surgery; and IABP, intraaortic balloon pump.

# Appendix 2. Reviewer Relationships With Industry and Other Entities (Relevant)—2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery

Peer Reviewer	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Robert Guyton	Official Reviewer—ACCF/ AHA Task Force on Practice Guidelines	None	None	None	• Edwards Lifesciences	None	None
Jeffrey Jacobs	Official Reviewer—ACCF/ AHA Task Force on Data Standards	None	None	None	None	None	None
L. Kristin Newby	Official Reviewer—AHA	• AstraZeneca	None	None	• Eli Lilly* • GlaxoSmithKline†	None	None
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AATS indicates American Association for Thoracic Surgery; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; SCA, Society of Cardiovascular Anesthesiologists; STEMI, ST-elevation myocardial infarction; and STS, Society of Thoracic Surgeons.

## Appendix 3. Abbreviation List

ACE=angiotensin-converting enzyme	LIMA=left internal mammary artery
ACS=acute coronary syndrome	LV=left ventricular
AF=atrial fibrillation	LVEF=left ventricular ejection fraction
AKI=acute kidney injury	MACE=major adverse coronary events
ARB=angiotensin-receptor blockers	MI=myocardial infarction
BMS=bare-metal stent	NSTEMI=non-ST-elevation myocardial infarction
CABG=coronary artery bypass graft surgery	PAC=pulmonary artery catheter
CAD=coronary artery disease	PAD=peripheral artery disease
CKD=chronic kidney disease	PCI=percutaneous coronary intervention
CPB=cardiopulmonary bypass	RCT=randomized controlled trial
DAPT=dual antiplatelet therapy	SIHD=stable ischemic heart disease
DES=drug-eluting stent	SIRS=systemic inflammatory response system
EF=ejection fraction	STEMI=ST-elevation myocardial infarction
GDMT=guideline-directed medical therapy	SVG=saphenous vein graft
ICU=intensive care unit	TEE=transesophageal echocardiography
IMA=internal mammary artery	TIA=transient ischemic attack
LAD=left anterior descending	TMR=transmyocardial laser revascularization
LDL=low-density lipoprotein	UA=unstable angina

## 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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# Correction

In the article by Hillis et al, “2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines,” which published ahead of print on November 7, 2011, and appears in the December 6, 2011, issue of the journal (*Circulation*. 2011;124:e652–e735), a correction was needed.

On page e689, in the second column, under “5.2.2. Mediastinitis/Perioperative Infection: Recommendations,” the second recommendation under Class I read,

2. **A second-generation cephalosporin is recommended for prophylaxis in patients without methicillin-resistant *Staphylococcus aureus* colonization.**<sup>897–905</sup> (*Level of Evidence: A*)

It has been changed to read,

2. **A first- or second-generation cephalosporin is recommended for prophylaxis in patients without methicillin-resistant *Staphylococcus aureus* colonization.**<sup>897–905</sup> (*Level of Evidence: A*)

This correction has been made to the current online version of the article, which is available at <http://circ.ahajournals.org/cgi/reprint/124/23/e652>.

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**2011 ACCF/AHA Coronary Artery Bypass Graft Surgery Data Supplements**

**Data Supplement 1. Anesthetic Considerations**

Author	Drug	Number of Patients	Number of patients with ≥1 SAE (%)	RR (95% CI)	P-Value	Mortality Number of Patients (%)	RR (95% CI)	P-Value	Number of Patients with CV events (%)	RR (95% CI)	P-Value	Sternal Infection in Patients (%)	RR (95% CI)	P-Value
<a href="#">Ott et. al. 2003 (1)</a>	Standard Care	151	15 (9.9)			0 (0)			4 (2.6)			0 (0)		
	Parecoxib/vald ecoxib	311	59 (19.0)		0.015	4 (1.3)		0.31	17 (5.4)			10 (3.2)		0.035
<a href="#">Nussmeier et al. 2005 (2)</a>	Placebo	560	22 (4.0)			1 (0.2)			3 (0.5)			16 (2.9)		
	Placebo+Vald ecoxib	556	40 (7.4)	1.9 (1.1 to 3.2)	0.02	3 (0.6)	3.0 (0.3 to 29.3)	0.31	6 (1.1)	2.0 (0.5 to 8.1)	0.31	27 (5.0)	1.7 (0.9 to 3.3)	0.08
	Parecoxib/vald ecoxib	555	40 (7.4)	1.9 (1.1 to 3.2)	0.02	4 (0.7)	4.1 (0.5 to 36.4)	0.18	11 (2.0)	3.7 (1.0 to 13.5)	0.03	20 (3.7)	1.3 (0.7 to 2.5)	0.48
	Both COX-2 Groups	1,088	1,088 (7.4)	2.9 (0.8 to 9.9)	0.08	7 (0.6)	3.6 (0.4 to 29.1)	0.2	17 (1.6)	2.9 (0.8 to 9.9)	0.08	47 (4.3)	1.5 (0.8 to 2.7)	0.15

CI indicates confidence interval; COX-2; cyclooxygenase-2 inhibitors; CV, cardiovascular; N, number of patients; RR, relative risk; and SAE, serious adverse events.

**Data Supplement 2. Preconditioning: Table 1**

Author	Study Population	Comparison	Protocol	Primary Outcome	Comments
<a href="#">De Hurt et al. 2009 (3)</a>	Elective CABG, 8 centers Belgium, 2002 to 2004	TIVA only n=145; SEVO n=132; DES n=137	Minimum end-tidal volatile concentration 0.5 MAC starting at least 30 min prior to cross-clamping continued until at least 10 min after the release of the cross-clamp on CPB otherwise anesthesia not controlled	Peak postoperative troponin T release: TIVA 0.30 ng/ml (0.00 to 4.79); SEVO 0.33 ng/ml (0.02 to 3.68); DES 0.39 ng/ml (0.08 to 3.74); p=NS between groups	Only variable associated with elevated troponin was use of >2 distal anastomoses; volatile assignment associated with shorter LOS; only significant predictor of 1 y mortality was EUROSCORE >2

<a href="#">Frassdorf et al 2009</a> (4)	Elective CABG, single center	TIVA only n=10, SEVO group I n=10, SEVO group II n=10	10 min prior to CPB onset, SEVO group I received 1.0 MAC SEVO for 5 min; SEVO group II received (2 times) 5 min of SEVO, with 5 min washout 10 min before CPB.	Peak postoperative troponin I release: TIVA only 14±3 ng/ml; SEVO group I 14±3 ng/ml; SEVO group II group 7±2 ng/ml; TIVA only and SEVO group I vs. SEVO group II; p<0.001	Translocation of PKC epsilon observed in SEVO group II from cytosol to nuclear fraction consistent with preconditioning
<a href="#">Flier 2010</a> (5)	Elective CABG, single center	Group I: n=51; Group P: n=49	Group I: ISO 0.5 to 1.0 MAC with SUF Group P: PROP 2 to 4 mg/kg/h with SUF throughout surgery	Peak postoperative troponin I release: Group I: 2.72 mg/ml (95% CI: 1.78 to 5.85) vs. Group P: 2.64 mg/ml (95% CI: 1.67 to 4.83); p=0.11	No differences in in-hospital mortality or morbidity, 1 y-mortality

CI, confidence interval; CPB indicates cardiopulmonary bypass; CV, cardiovascular; DES, desflurane; EUROSCORE, European System for Cardiac Operative Risk Evaluation; ISO, isoflurane; LOS, length of stay; MAC, minimum alveolar concentration; NS, non significant; PKC, protein kinase C; PROP, propofol; RCT, randomized controlled trial; RR, relative risk; SEVO, sevoflurane; SUF, sufentanil; and TIVA, total intravenous anesthesia.

Data Supplement 3. Preconditioning: Table 2

Author	Study Population	Study Drug	Proposed Mechanism	Patients With Event/Total Patients for Placebo	%	Patients With Event/Total Patients Treated	%	ARR	RR	95% CI	P-Value	Comments
<a href="#">Mangano et al. 2006</a> (6)	Subanalysis of 2 y outcome of 100 patients sustaining perioperative MI in larger RCT (Acadesine Trial 1024 conducted in 2,695 CABG patients at 54 centers from 1993 to 1994 evaluating efficacy in reduction of cardiac death, MI or stroke by POD 4) stopped for futility.	Acadesine	Purine analog increases local adenosine levels, inhibit mPTP opening	Death 15/54 Periop MI 54/1358	Death 27.8% Periop MI 4.0%	Death 3/46 Periop MI 46/1337	Death 6.5% Periop MI 3.4%	Death 0.213 Periop MI 0.005	Death 0.765 Periop MI 0.135	Death 0.239 to 0.928 Periop MI 0.273 to 0.412	Death 0.013 MI 0.53	Subsequent large scale RCT: RED-CABG (Effect of Acadesine on Reducing Cardiovascular and Cerebrovascular Adverse Events in Coronary Artery Bypass Graft) (NCT00872001) with planned enrollment of 7,500 patients was terminated for futility by sponsor Oct. 2010

<a href="#">Mentzer et al 2008</a> (EXPEDITION Study) (7)	5,761 CABG patients at high-risk for perioperative ischemic events at 235 centers in 26 countries from 2001 to 2002 (terminated early due to mortality from increased cerebrovascular events)	Cariporide	Inhibitor of sodium hydrogen exchanger (isoform 1) limits intracellular calcium overload	Periop MI 562/2891 6 m Cerebrovascular Events 86/2839	Periop MI 19.4% Cerebrovascular Events 3.0% Periop Death 1.5%	Periop MI 439/2870 Cerebrovascular Events 146/2870	Periop MI 15.3% Cerebrovascular Events 5.2% Periop Death 2.2%	Periop MI 0.041 Cerebrovascular Events 0.021	Periop MI 0.213 Cerebrovascular Events 0.679	Periop MI 0.118 to 0.298 Cerebrovascular Events 1.181 to 0.293	Periop MI 0.003 Cerebrovascular Events 0.0001	No difference in mortality noted at 6 mo follow-up, beneficial effects persisted.
<a href="#">MEND-CABG II Investigators 2008</a> (8)	3,023 intermediate to high risk CABG patients at 130 sites in 3 countries from 2006 to 2007	MC-1	Purinergic receptor antagonist preventing cellular calcium overload	Periop CV death or MI 133/1,486	9.00%	Periop CV death or MI 140/1,510	9.30%	-0.003	-0.036	"-0.299 to 0.174"	0.809	
<a href="#">Smith et al. 2010</a> (PRIMO-CABG I and II trials) (9)	Discrete and combined analyses of PRIMO I (3,099 CABG patients at 205 centers in North American and Europe from 2002 to 2003) and PRIMO II (4,254 CABG patients at 249 centers from 2004 to 2005)	Pexelizumab	Monoclonal antibody binding to C5 complement aimed at inhibiting formation of the membrane attack complex responsible for cell lysis	PRIMO II 30 d death or MI 323/2130 Combined 30 d mortality	PRIMO II 30 d death or MI 15.3%	PRIMO II 30 d death or MI 341/2098	PRIMO II 30 d death or MI 16.3%	PRIMO II 30 d death or MI -0.011	PRIMO II 30 d death or MI -0.072	PRIMO II 30 d death or MI -0.233 to 0.068	PRIMO II 30 d death or MI 0.2	Combined analysis of pooled studies stratifying patients by < or ≥2% expected STS mortality noted significant reduction in 30 d mortality in treated pts (5.7 vs. 8.1%; p=0.024)

ARR indicates absolute risk ratio; CABG, coronary artery bypass graft; CI, confidence interval; CV, cardiovascular; EXPEDITION, Expanding Alzheimer’s Disease Investigators; MC-1, pyridoxal 5’-phosphate; MEND-CABG II, MC-1 to Eliminate Necrosis and Damage in Coronary Artery Bypass Graft Surgery Trial; MI, myocardial infarction; mPTP, mitochondrial permeability transition pore; NS, nonsignificant; Periop, perioperative; POD, Postoperative Day; PRIMO , Pexelizumab for Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery; RCT, randomized controlled trial; and REDCABG, Reduction in Cardiovascular and Cerebrovascular Events in High-Risk Subjects Undergoing Coronary Artery Bypass Graft Surgery Using Cardiopulmonary Bypass; RR, relative risk; and STS, Society of Thoracic Surgeons.



**Data Supplement 4. Preconditioning: Table 3 (Comparison of Meta-Analyses of Potential Cardioprotective Effects of Volatile Anesthetics for Patients Undergoing CABG)**

Author	Inclusions	No. Studies/ No. Patients	MI; OR; 95% CI; P-Value	Troponin Release; OR; 95% CI; P-Value	Mortality; OR; 95% CI; P-Value
<a href="#">Symons et al. 2006</a> (10)	HALO, ENF, ISO, SEVO, DES; on-/ off-pump	27/2979	WMD OR: -3.87; 95% CI: -8.75,1.03; p=0.12	OR -1.44 (95% CI: -2.34 to -0.55); p=0.002	OR 0.68 (95% CI: 0.32 to 1.47); p=0.33
<a href="#">Yu et al. 2006</a> (11)	HALO, ENF, ISO, SEVO, DES; on-pump	32/2841	OR: 1.34; 95% CI: 0.68 to 2.64; p=0.40	WMD: (SEVO,DES) OR: -1.45; 95% CI: -1.73 to -1.16; p<0.00001	OR: 0.65; 95% CI: 0.36 to 1.18; p=0.16
<a href="#">Landoni et al. 2007</a> (12)	SEVO, DES; on-/off-pump	22/1922	OR: 0.51; 95% CI: 0.32 to 0.84; p for effect=0.008	Not reported	OR: 0.31; 95% CI: 0.12 to 0.80; p for effect=0.02
<a href="#">Yao et al. 2009</a> (13)	SEVO; on-/off-pump	13/696	Not reported	WMD: OR: -0.82; 95% CI: -0.87 to -0.85; p=0.0002	OR: 0.32; 95% CI: 0.03 to 3.19; p=0.33

CI indicates confidence interval; DES indicates desflurane; ENF, enflurane; HALO, halothane; ISO, isoflurane; MI, myocardial infarction; OR, odds ratio; SEVO, sevoflurane; and WMD, weighted mean difference.

**Data Supplement 5. CABG in Patients With Acute MI**

Study Name	Study Type	Patient Population Sample Size	Findings	Statistical Significance
<a href="#">Thielmann et al. 2007</a> (14)	Observational Study	138 STEMI unresponsive to nonsurgical therapy	In-hospital mortality: 23.8% when CABG was performed between 7 to 23 h 6.7% when performed at 1 to 3 d 4.2% when performed at 4 to 7 d 2.4% when performed at 8 to 14 d Independent predictors of in-hospital death were female gender and preoperative cTnI level	p<0.01
<a href="#">Alexiou et al. 2008</a> (15)	Observational Study	220 with ACS; 35 (15.9%) with STEMI	In-hospital mortality was 8.5% Mean time from onset of symptoms to CABG differed between survivors (5.1±2.7 h) and nonsurvivors (11.4±3.2 h) Independent predictors of mortality were age >75 y (OR: 5.36; 95% CI: 1.64 to 21.68; p=0.028), COPD (OR: 23.04; 95% CI: 4.33 to 158.61; p=0.003), and renal disease (OR: 7.01; 95% CI: 1.81 to 34.62; p=0.007)	p<0.0007
<a href="#">Filizcan et al. 2011</a> (16)	Observational Study	150 (114 survived, 36 died)	Overall in-hospital mortality was 22% patients who underwent CABG ≤6 h (6.1%) 7 to 23 h (50%) 15 to 30 d (7.1%) Predictors of in-hospital mortality were age (OR: 1.049; 95% CI: 1.013 to 1.087; p=0.008), preoperative IABP (OR: 4.386; 95% CI: 1.381 to 13.933; p=0.012), and preoperative cTnI (OR: 1.019; 95% CI: 1.002 to 1.036; p=0.027).	

<a href="#">Lee et al. 2001</a> (17)	Observational Study	22,984 with STEMI; 21,381 with NSTEMI	In-hospital mortality was similar in STEMI and NSTEMI groups undergoing CABG <6 h after diagnosis (12.5% and 11.5%, respectively) In-hospital mortality was significantly higher in STEMI patients compared to NSTEMI patients when CABG was performed 6 to 23 h after diagnosis (13.6% vs. 6.2%; p=0.006) Both groups had similar in-hospital mortality rates when CABG was performed at all other later time-points (1 to 7 d; 8 to 14 d and ≥15 d).	
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ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; COPD, chronic obstructive pulmonary disease; cTnI, cardiac troponin I TnI; d, day; h, hour; IABP, intra aortic balloon pump; MI; myocardial infarction; NSTEMI, non-ST myocardial infarction; OR, odds ratio; and STEMI, ST myocardial infarction.

Data Supplement 6. Life-Threatening Ventricular Arrhythmias

Study Name	Study Type	Patient Population Sample Size	Findings	Statistical Significance
<a href="#">Kelly et al. 1990</a> (18)	Observational Study	50 survivors of out of hospital cardiac arrest with multivessel CAD	Inducible ventricular arrhythmia preoperatively was strongest predictor of suppression post-CABG	p=0.001
<a href="#">Ngaage et al. 2008</a> (19)	Observational Study	93 consecutive patients (75 male, 81%) presented with ischemic VF/VT (21% surviving and undergoing CABG)	5-y survival 88% - similar to controls without VT/VF	
<a href="#">Every et al. 1992</a> (20)	Observational Study	265 survivors of cardiac arrest (85 CABG, 180 medical treatment)	CABG reduced subsequent cardiac arrest (RR: 0.48; 95% CI: 0.24 to 0.97)	p<0.04
<a href="#">Cook et al. 2002</a> (21)	Subanalysis of AVID Registry for ICD	3,117 patients with life threatening arrhythmias, 218 (17%) underwent CABG	Improved survival HR: 0.67. Mean follow-up 24.2±13.5 mo, Death rates were 21.4% ±4.8% in the revascularization group and 29.4% ±2.0% in the medically treated group	p=0.002

AVID indicates Antiarrhythmics Versus Implantable Defibrillators; CABG, coronary artery bypass graft; CAD, coronary artery disease; HR, hazards ratio; ICD, implantable cardioverter-defibrillator; RCT, randomized controlled trial; RR, relative risk; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Data Supplement 7. CABG After Failed PCI

Study Name	Study Type	Patient Population Sample Size	Findings
<a href="#">Roy et al. 2009</a> (22)	Observational Study	21,957	90 patients (0.41%) required emergent CABG; independent predictors included acute MI (OR: 2.7; 95% CI: 1.4 to 5.3; p=0.003), cardiogenic shock (OR: 4.8; 95% CI: 2.3 to 9.7; p<0.001), 3-vessel disease (OR:1.7; 95% CI: 1.2 to 2.4; p=0.004), and Type C lesion (OR: 2.8; 95% CI: 1.5 to 5.2; p=0.001)
<a href="#">Andreassen et al. 2000</a> (23)	Observational Study	8,620	132 patients (1.5%) required emergent CABG; mortality rate was 12%
<a href="#">Tally et al. 1990</a> (24)	Observational Study	430	Presence of preoperative myocardial ischemia, pre-PTCA diameter stenosis <90%, and multivessel disease correlated with death or nonfatal MI at 5 y
<a href="#">Craver et al. 1992</a> (25)	Observational Study	9,860	699 patients required emergent CABG; mortality rate was 3.1%; multivessel disease and age >60 at time of emergent CABG were independent predictors of death at 5-y follow-up
<a href="#">Stamou et al. 2006</a> (26)	Observational Study	2,273 off-pump CABG 3,487 on-pump CABG	Off-pump CABG was associated with abbreviated LOS (OR: 0.6; 95% CI: 0.47 to 0.64; p<0.01); less renal failure (OR: 0.5; 95% CI: 0.37 to 0.72; p<0.01); and less need for IABP (OR: 0.5; 95% CI: 0.3 to 0.71; p<0.01)

CABG indicates coronary artery bypass graft; CI, confidence interval; IABP, intra aortic balloon pump; LOS, length of stay; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; and PTCA, percutaneous transluminal coronary angioplasty.



Tables 8 to 22 pertain to the Revascularization Section

Data Supplement 8. Evidence for Survival Benefit After PCI or CABG (with LIMA Grafting to the LAD) in Patients With SIHD Who Are Receiving Medical Therapy and Are Suitable Candidates for Revascularization

Anatomic Subgroups	Evidence Supporting CABG for Survival	Evidence Supporting PCI for Survival	Evidence Supporting Superiority of Either CABG or PCI for Survival	Evidence Supporting Equivalence of CABG and PCI for Survival
Unprotected left main CAD	CASS Registry*( <a href="#">27</a> , <a href="#">28</a> ) <a href="#">CASS</a> † (29) VA Cooperative† ( <a href="#">30</a> , <a href="#">31</a> ) <a href="#">Yusuf et al.</a> † (32) <a href="#">Dzavik et al.</a> * (33)	None found	CABG better: <a href="#">Wu</a> * (34)  PCI better: None found	<a href="#">SYNTAX</a> † (36) <a href="#">LE MANS</a> † (37) <a href="#">Boudriot et al.</a> † (38) Chieffo et al.*( <a href="#">39</a> , <a href="#">40</a> ) <a href="#">Lee et al.</a> * (41) <a href="#">Lee et al.</a> § (42) <a href="#">Naik et al.</a> § (43) <a href="#">White et al.</a> * (44) <a href="#">Palmerini et al.</a> * (45) <a href="#">Park et al.</a> * (46) <a href="#">Sanmartín et al.</a> * (47) <a href="#">Brener et al.</a> * (48) <a href="#">Mäkikallio et al.</a> * (49)
SYNTAX score <33			<a href="#">SYNTAX</a> † (35)	
SYNTAX score ≥33			<a href="#">SYNTAX</a> † (35)	
3-vessel disease with or without proximal LAD disease	For: <a href="#">Dzavik et al.</a> * (33) <a href="#">ECSS</a> † (50) <a href="#">Jones et al.</a> * (51) <a href="#">MASS II</a> * (52) <a href="#">Myers et al.</a> † (53) <a href="#">Smith et al.</a> * (54) <a href="#">SYNTAX</a> † (55) <a href="#">Yusuf et al.</a> †(32)	For: <a href="#">Dzavik et al.</a> * (33) <a href="#">Smith et al.</a> * (54)  Against: <a href="#">Boden et al.</a> † (56)	CABG better: <a href="#">Bair et al.</a> * (57) <a href="#">Booth et al.</a> † (58) <a href="#">Hannan et al.</a> * (59) <a href="#">Hannan et al.</a> * (60) <a href="#">Jones et al.</a> * (51) <a href="#">MASS II</a> * (52) <a href="#">Malenka et al.</a> * (61)	<a href="#">Bravata et al.</a> † (62) <a href="#">Daemen et al.</a> † (63) <a href="#">Dzavik et al.</a> * (33) <a href="#">ERACI II</a> † (64) <a href="#">Mercado et al.</a> † (65) <a href="#">RITA I</a> † (66) <a href="#">Van Domburg et al.</a> * (67)

2-vessel disease with proximal LAD disease	<i>For:</i> <a href="#">ECSS</a> † (50) <a href="#">Jones et al.</a> * (51) <a href="#">Smith et al.</a> * (54) <a href="#">Yusuf et al.</a> † (32)	<i>For:</i> <a href="#">Dzavik et al.</a> * (33) <a href="#">Jones et al.</a> * (51) <a href="#">Smith et al.</a> * (54)  <i>Against:</i> <a href="#">Boden et al.</a> † (56)	<i>CABG better:</i> <a href="#">Hannan et al.</a> * (59) <a href="#">Hannan et al.</a> * (60) <a href="#">Hannan et al.</a> * (68) <a href="#">Jones et al.</a> * (51)	<a href="#">Berger et al.</a> † (69) <a href="#">ERACI II</a> † (64) <a href="#">Malenka et al.</a> * (61)
2-vessel disease without proximal LAD disease	<i>For:</i> <a href="#">Smith et al.</a> * (54)	<i>For:</i> <a href="#">Jones et al.</a> * (51) <a href="#">Smith et al.</a> * (54)  <i>Against:</i> <a href="#">Boden et al.</a> † (56) <a href="#">Cecil et al.</a> † (70) <a href="#">Pitt et al.</a> † (71)	<i>CABG better:</i> <a href="#">Bair et al.</a> * (57) <a href="#">Booth et al.</a> † (58) <a href="#">Dzavik et al.</a> * (33) <a href="#">Hannan et al.</a> * (68) <a href="#">Hannan et al.</a> * (60) <a href="#">Jones et al.</a> * (51)	<a href="#">Bravata et al.</a> † (62) <a href="#">Daemen et al.</a> † (63) <a href="#">Dzavik et al.</a> * (33) <a href="#">Jones et al.</a> * (51) <a href="#">Mercado et al.</a> † (65) <a href="#">van Domburg et al.</a> * (67)
Single-vessel proximal LAD disease	<i>For:</i> <a href="#">Smith et al.</a> * (54)  <i>Against:</i> <a href="#">Greenbaum et al.</a> * (72)	<i>For:</i> <a href="#">Jones et al.</a> * (51) <a href="#">Smith et al.</a> * (54)  <i>Against:</i> <a href="#">Greenbaum et al.</a> * (72)	<i>CABG better:</i> <a href="#">Hannan et al.</a> (59)	<a href="#">Aziz et al.</a> † (73) <a href="#">Ben-Gal et al.</a> * (74) <a href="#">Bravata et al.</a> † (62) <a href="#">Cisowski et al.</a> § (75) <a href="#">Diegeler et al.</a> † (76) <a href="#">Drenth et al.</a> † (77) <a href="#">Fraund et al.</a> * (78) <a href="#">Goy et al.</a> † (79, 80) <a href="#">Greenbaum et al.</a> * (72) <a href="#">Hong et al.</a> † (81) <a href="#">Jaffery et al.</a> † (82) <a href="#">Jones et al.</a> * (51) <a href="#">Kapoor et al.</a> † (83) <a href="#">MASS I</a> † (84)
Single-vessel disease without proximal LAD involvement	<i>Against:</i> <a href="#">Jones et al.</a> * (51) <a href="#">Smith et al.</a> * (54) <a href="#">Yusuf et al.</a> † (32)	<i>Against:</i> <a href="#">Jones et al.</a> * (51)	<i>PCI better:</i> <a href="#">Hannan et al.</a> * (59) <a href="#">Jones et al.</a> * (51)	<a href="#">Jones et al.</a> * (51)

Multivessel CAD, diabetes present	<p><i>For:</i>  <a href="#">MASS II</a>† (85)  <a href="#">Sorajja et al.</a>* (86)</p> <p><i>No benefit:</i>  <a href="#">BARI 2D</a>† (87)</p>	<p><i>For:</i>  <a href="#">MASS II</a>† (85)</p> <p><i>No effect:</i>  <a href="#">BARI 2D</a>† (87)  <a href="#">Sorajja et al.</a>* (86)</p>	<p><i>CABG better:</i>  BARI I† (<a href="#">88</a>, <a href="#">89</a>)  <a href="#">Brener et al.</a>* (90)  <a href="#">Hlatky et al.</a>† (91)  <a href="#">Javaid et al.</a>* (92)  <a href="#">Malenka et al.</a>* (61)  <a href="#">Niles et al.</a>* (93)  <a href="#">Pell et al.</a>* for 3-V CAD (94)  <a href="#">Weintraub et al.</a>† (95)</p>	<p><a href="#">ARTS I</a>* (96)  <a href="#">Bair et al.</a>* (57)  <a href="#">Barsness et al.</a>* (97)  <a href="#">Bravata et al.</a>† (62)  <a href="#">CARDia</a>† (98)  <a href="#">Dzavik et al.</a>* (33)  <a href="#">MASS II</a>† (85)  <a href="#">Pell et al.</a>* for 2-V CAD (94)</p>
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\*Observational study, including articles on long-term follow-up, clinical trials not specified as randomized, comparative registry studies, comparative studies, prospective cohort studies, prospective observational studies, prospective registries, and prospective studies. †Randomized controlled trials, including meta-analyses. ‡Reviews (systematic or not). §Unknown study design.

ARTS indicates Arterial Revascularization Therapies Study Part; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; BARI I, Bypass Angioplasty Revascularization Investigation I; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CAD, coronary artery disease; CARDIA, Coronary Artery Revascularization in Diabetes; DM, diabetes mellitus; ECSS, European Coronary Surgery Study; ERACI II, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease II; LAD, left anterior descending; MASS, Medicine, Angioplasty, or Surgery Study; RITA, Randomised Intervention Treatment of Angina; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; V, vessel; and VA, Veterans Administration.

**Data Supplement 9. Evidence for Relief of Unacceptable Angina in Subsets of Patients With SIHD Who are Receiving GDMT and Have Anatomy Suitable for Revascularization**

Anatomic Subgroup	Evidence Supporting CABG + GDMT for Angina	Evidence Supporting PCI + GDMT for Angina	Evidence Supporting Superiority of Either CABG or PCI for Angina	Evidence Supporting Equivalence of CABG and PCI for Angina
Multivessel CAD	<p><i>Benefit:</i>  <a href="#">Benzer et al.</a>* (99)  <a href="#">Bonaros et al.</a>* (100)  <a href="#">Favaroto et al.</a>† (101)  <a href="#">Hofer et al.</a>* (102)  <a href="#">Lukkarinen et al.</a>* (103)  <a href="#">MASS II</a>† (52)  <a href="#">RITA I</a>† (104)</p>	<p><i>No benefit:</i>  <a href="#">Lukkarinen et al.</a>* (103)</p> <p><i>Benefit:</i>  <a href="#">Benzer et al.</a>* (99)  COURAGE† (<a href="#">56</a>, <a href="#">105</a>)  <a href="#">Hambrecht</a>‡ (106)  <a href="#">Hofer et al.</a>* (102)  <a href="#">MASS II</a>† (52)  <a href="#">RITA I</a>† (104)  <a href="#">RITA II</a>† (107)  <a href="#">Wijeysundera et al.</a>‡ (108)</p>	<p><i>CABG better:</i>  <a href="#">Benzer et al.</a>* (99)  <a href="#">Bonaros et al.</a>* (100)  <a href="#">Lukkarinen et al.</a>* (103)  <a href="#">RITA I</a>† (66)</p> <p><i>PCI better:</i>  None found</p>	<p><a href="#">Hofer et al.</a>* (102)  <a href="#">MASS II</a>† (52)  <a href="#">Takagi et al.</a>‡ (109)</p>
1-vessel CAD excluding the proximal LAD	No data found	<p><a href="#">Hambrecht et al.</a>† (106)  <a href="#">Parisi et al.</a>† (110)  <a href="#">Pitt et al.</a>† (71)  <a href="#">Pocock et al.</a>† (107)</p>	No data found	No data found

Anatomic Subgroup	Evidence Supporting CABG + GDMT for Angina	Evidence Supporting PCI + GDMT for Angina	Evidence Supporting Superiority of Either CABG or PCI for Angina	Evidence Supporting Equivalence of CABG and PCI for Angina
1-vessel CAD involving the proximal LAD	<a href="#">MASS I</a> † (84)	<a href="#">Hambrecht et al.</a> † (106) <a href="#">Parisi et al.</a> † (110) <a href="#">Pitt et al.</a> † (71) <a href="#">Pocock et al.</a> † (107)	<i>CABG better:</i> <a href="#">Ben-Gal et al.</a> * (74) <a href="#">Cisowski et al.</a> † (75) <a href="#">Diegeler et al.</a> ‡ (76) <a href="#">Goy et al.</a> † (79) <a href="#">Herz et al.</a> * (130) <a href="#">MASS I</a> † (84)	<a href="#">Cisowski et al.</a> † (111) <a href="#">Drenth et al.</a> § (112) <a href="#">Thiele et al.</a> † (113)
Special Circumstances				
Patients with prior CABG and small or moderate sized area of ischemia	No data found	<a href="#">Gurfinkel et al.</a> § (114) <a href="#">Pfausch et al.</a> * (115) <a href="#">Subramanian et al.</a> * (116)	<i>CABG better:</i> <a href="#">Weintraub et al.</a> † (117)	<a href="#">Stephan et al.</a> * (118)

\*Observational study, including articles on long-term follow-up, clinical trials not specified as randomized, comparative registry studies, comparative studies, prospective cohort studies, prospective observational studies, prospective registries, and prospective studies. †Randomized controlled trials, including meta-analyses. ‡Reviews (systematic or not). §Unknown study design.  
 ARTS indicates Arterial Revascularization Therapies Study Part; AWESOME, Angina With Extremely Serious Operative Mortality Evaluation; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass graft; CAD, coronary artery disease; CARDia, Coronary Artery Revascularization in Diabetes; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; GDMT, guideline-directed medical therapy; LAD, left anterior descending artery; LOE, level of evidence; MASS, Medicine, Angioplasty or Surgery Study; PCI, percutaneous coronary intervention; RITA, Randomised Intervention Treatment of Angina; and TIME, Trial of invasive versus medical therapy in elderly patients.

**Data Supplement 10. RCTs of CABG Versus Balloon Angioplasty**

					Acute Outcome		Late Outcome						
					Death %	Q wave MI %	Death %	Q wave MI %	Angina %	RepeatRevasc %	Primary Endpoint	Primary Endpoint Reached	Follow-Up (y)
Trial	No. of Patients	Avg. Age (y)	Female	CAD	CABG/ PCI	CABG/ PCI	CABG/ PCI	CABG/ PCI	CABG/ PCI	CABG/ PCI		CABG/ PCI	
BARI ( <a href="#">89</a> , <a href="#">119</a> , <a href="#">120</a> , <a href="#">121</a> )	1829	61	26%	MV	1.3/1.1	4.6/2.1	26.5/29	36/36	NA/NA	20/77*	D	26.5/29	10
EAST ( <a href="#">122</a> , <a href="#">123</a> )	392	61	26%	MV	1.0/1.0	10.3/3.0*	17/21	19.6/16.6	12/20*	27/65*	D+MI+T	27.3/28.8	8 <sup>a</sup>
<a href="#">GABI</a> (124)	359	NA	20%	MV	2.5/1.1	8/2.3*	22/25	9.4/4.5	26/29	59/83*	A	26/29	13 <sup>b</sup>
<a href="#">Toulouse</a> (125)	152	67	23%	MV	1.3/1.3	6.6/3.9	10.5/13.2	1.3/5.3	5.3/21.1*	9/29*	A	5.2/21.1*	5



RITA I ( <a href="#">66</a> , <a href="#">104</a> , <a href="#">126</a> )	1011	57	19%	SV/MV	1.2/0.8 RR: 0.88 (95% CI: 0.59 to 1.29)	2.4/3.5	9.0/7.7	7.4/10.8	52/78*	11/44*	D+MI+T	8.6/9.8	5
ERACI ( <a href="#">127</a> , <a href="#">128</a> )	127	58	13%	MV	4.6/1.5	6.2/6.3	4.7/9.5	7.8/7.8	3.2/4.8	6/37*	D+MI+A+Rep Revasc	23/53*	3
MASS ( <a href="#">84</a> , <a href="#">129</a> )	142	56	42%	SV (LAD)	1.4/1.4	1.4/0	2.9/5.7	7/11	23/25	0/30*	D+MI+Rep Revasc	3/24*	3
<a href="#">Lausanne et al.</a> (79)	134	56	20%	SV (LAD)	0/0	0/0	2/9	4/15* RR: 2.6 (95% CI: 1.1 to 5.4; p=0.00004) <sup>c</sup>	29/26	9/38*	D+MI+Rep Revasc	7.6/36.8*	5
CABRI ( <a href="#">130</a> , <a href="#">131</a> )	1054	60	22%	MV	1.3/1.3	NA/NA	2.7/3.9 RR: 1.42 (95% CI: 0.731 to 2.76l; p=0.297)	3.5/4.9 RR: 1.42 (95% CI: 0.80 to 2.54, p=0.234)	10.1/13.9* RR: 1.54 (95% CI: 1.09 to 2.16; p=0.012)	9/36* RR: 5.23 (95% CI: 3.90 to 7.03; p<0.001)	D	2.7/3.9	1

\*Statistically significant; <sup>a</sup>Mortality and repeat revascularization at 8 y, other end points at 3 y; <sup>b</sup>Mortality and repeat revascularization at 13 y, other end points at 1 y; <sup>c</sup>Relative risk for combined endpoint cardiac death and myocardial infarction. A indicates angina; BARI, Bypass Angioplasty Revascularization Investigation; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CABRI, Coronary Angioplasty versus Bypass Revascularization Investigation; CI, confidence interval; D, death; EAST, Emory Angioplasty versus Surgery Trial; ERACI, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease; GABI, German Angioplasty Bypass Surgery Investigation; LAD, left anterior descending; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; MV, multivessel; NA, not available; No., number; PCI, percutaneous coronary intervention; RITA, Randomized Intervention Treatment of Angina; Rep Revasc, repeat revascularization; RR, relative risk; SV, single-vessel; and T, thallium defect.

### Data Supplement 11. RCTs of CABG Versus BMS

						Death %	Q Wave MI %	Angina %	Repeat Revascularization %	Primary Endpoint	Primary Endpoint Reached (%)	Follow-Up (Y)
Trial	No. of Patients	Average Age (y)	Female	CAD	Enrollment Period	CABG/ PCI	CABG/ PCI	CABG/ PCI	CABG/PCI		CABG/ PCI	
<a href="#">SIMA</a> (132)	121	59	21%	SV	1994-1998	4/2	4/5	5/9	8/24	D+MI+Rep Revasc	7/31*	2.4
AWESOME ( <a href="#">133</a> , <a href="#">134</a> )	454	67	NA	MV	1995-2000	21/18	NA	NA	22/43*	D	21/20	5
<a href="#">MASS II</a> (52)	408	60	32%	MV	1995-2000	25/24	10/13	NA	7.5/41.9	D+MI+Rep Revasc HR: 1.85 (95% CI: 1.39 to 2.47)	33/42*	10
ERACI II ( <a href="#">128</a> , <a href="#">135</a> )	450	62	21%	MV	1996-1998	11.6/7.2	6.2/2.8	18/14	7.2/28.4*	D+MI+CVA+RR	23.6/34.7*	5

<a href="#">SoS</a> (136)	988	61	21%	MV	1996-1999	6.8/10.9* HR: 2.91 (95% CI: 1.29 to 6.53); p=0.01	8.2/4.9	NA	6/21* HR: 3.85 (95% CI: 2.56 to 5.79); p<0.0001	Rep Revasc	6/21*	6
<a href="#">ARTS I</a> (137)	1205	61	24%	MV	1997-1998	7.6/8.0 RR: 1.05 (95% CI: 0.71 to 1.55); p=0.83	5.6/6.7 RR: 1.19 (95% CI: 0.76 to 1.85); p=0.47	NA	8.8/30.3* RR: 3.46 (95% CI: 2.61 to 4.60); p<0.001	D+MI+CVA+Rep Revasc	21.8/41.7* RR: 1.91 (95% CI: 1.60 to 2.28); p<0.001	5
Drenth et al. ( <a href="#">77</a> , <a href="#">112</a> )	102	61	24%	SV	1997-1999	2/0	2/10	15/33	4/16	D+MI+CVA+Rep Revax	14/29	4
Leipzig ( <a href="#">76</a> , <a href="#">138</a> )	220	62	25%	SV	1997-2001	12/10 RR: 0.85 (95% CI: 0.37 to 1.93); p=0.54	7/5 RR: 0.71 (95% CI: 0.20 to 2.43); p=0.46	NA	10/32* RR: 3.18 (95% CI: 1.67 to 6.39); p<0.001	D+MI+Rep Revasc	29/47* RR: 1.64 (95% CI: 1.13 to 2.42); p=0.02	5
<a href="#">Myoprotect</a> (139)	44	70	30%	MV	1998-2001	24/22	0/4	NA	5/30	D+MI+Rep Revasc	29/48*	1
<a href="#">Octostent</a> (140)	280	60	29%	MV	1998-2000	2.8/0	4.9/4.4	13/22	4.2/15.2	D+MI+CVA+Rep Revasc	9.5/14.5 RR: 0.93 (95% CI: 0.86 to 1.02)	1
<a href="#">AMIST</a> (141)	100	57	22%	SV	1999-2001	25/30	0/4	8/10	0/4	D+MI+Rep Revasc+T	28/34	1
Cisowski et al. ( <a href="#">75</a> , <a href="#">111</a> )	100	54	17%	SV	2000-2001	0/3.6	0/0	0/20	0/20	D+MI	0/4	1
<a href="#">Kim et al.</a> (142)	100	62	35%	SV	2000-2001	4.0/4.0	NA	6/19	2/14	NA	NA	1

\*Statistically significant. AMIST indicates Angioplasty versus Minimally Invasive Surgery Trial; ARTS, Arterial Revascularization Therapies Study; AWESOME, Angina with Extremely Serious Operative Mortality Evaluation; BMS, bare-metal stents; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CVA, cerebrovascular accident; D, death; ERACI, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease; HR, hazard ratio; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass; MV, multivessel; NA, not available; No., number; Octostent, Long-term comparison of stenting versus off-pump; PCI, percutaneous coronary intervention; RITA, Randomized Intervention Treatment of Angina; RR, relative risk; Rep Revasc, repeat revacularization; SIMA , Stenting versus Internal Mammary Artery Study; SoS, Stent or Surgery; SV, single-vessel; T, thallium defect and Y, year.

Data Supplement 12. RCTs of CABG Versus DES

						Death %	MI %	Repeat Revascularization %	Primary Endpoint		RR and 95% CI	Follow-Up in Months
Trial	No. of Patients	Avg. Age (y)	Female Patients	CAD	Enrollment Period	CABG/PCI	CABG/PCI	CABG/PCI		CABG/PCI		
<a href="#">Hong et al.</a> (81)	189	61	36%	SV	2003	2.9/0	2.9/1.7	5.9/1.7	D, MI, Rep Revasc	11.7/4.3	n/a	6
<a href="#">Leipzig</a> (113)	130	66	30%	SV	2003-2007	0/0	7.7/1.5*	0/6.2	D+MI+Rep Revasc	7.7/7.7	n/a	12
SYNTAX ( <a href="#">143</a> , <a href="#">144</a> )	1800	65	22%	MV	2005-2007	6.7/8.6	3.6/7.1	10.7/19.7	D+MI+CVA+Rep Revasc	20.2/28.0	MACCE 12 mo follow-up; RR: 1.44 (95% CI: 1.15 to 1.81)	36

\*Statistically significant. CABG indicates coronary artery bypass; CAD, coronary artery disease; CI, confidence interval; CVA, cerebrovascular accident; D, death; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; N/A, not applicable; No., number of patients; mo, month; MV, multivessel; PCI, percutaneous coronary intervention; RR, relative risk; Rep Revasc, repeat revascularization; SV, single vessel; and SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Data Supplement 13. Hazard Ratios in Observational Studies Comparing PCI-DES to CABG

Study	Location	No. Patients (CABG/PCI)	Age (y)	Female	CAD	Enrollment Period	Combined Death/MI/CVA HR and 95% CI)*	Repeat Revascularization HR and 95% CI*	MACCE HR and 95% CI	Follow-Up in Months
<a href="#">Park et al.</a> (145)	Korea	1,495/1,547	62	29%	MVD	2003-2005	0.7* 0.53-0.91	2.56* 1.96-3.4	1.37* 1.16-1.63	31
<a href="#">Hannan et al.</a> (60)	USA	7,437/9,964	66	30%	MVD	2003-2004	0.99 0.89-1.098	5.88* 5.31-6.51	2.89* 2.72-3.08	19
<a href="#">Briguori et al.</a> (146)	Italy	149/69	65	29%	MVD	2002-2004	1.03 0.53-1.99	4.01* 1.67-9.60	1.48* 0.91-2.43	12
<a href="#">Yang et al.</a> (147)	China	231/235	65	22%	MVD	2003-2004	0.7 0.33-1.49	13.26* 4.15-42.34	3.09* 1.80-5.30	25
<a href="#">Lee et al.</a> (148)	USA	103/102	68	35%	MVD	2003-N/A	1.29 0.68-2.46	6.73* 2.06-21.95	2.25* 1.36-3.72	12
<a href="#">Yang et al.</a> (149)	Korea	390/441	63	29%	MVD	2003-2004	0.75 0.43-1.31	4.26* 1.78-10.15	1.41* 0.93-2.13	12
<a href="#">Javaid et al.</a> (92)	USA	701/979	65	33%	MVD	N/A	1.93 1.37-2.73	2.43* 1.73-3.41	2.44* 1.87-3.19	12
<a href="#">Varani et al.</a> (150)	Italy	95/111	65	31%	MVD	2003-2005	0.47* 0.16-1.37	5.91* 1.39-25.6	1.52* 0.70-3.28	12

<a href="#">Tarantini et al.</a> (151)	Italy	127/93	66	18%	MVD	2005-2005	0.56 0.20-1.56	1.91* 0.62-5.83	0.96* 0.48-1.92	24
Pooled HR							0.94	4.06	1.86	
							p=0.66	p<0.001	p<0.001	

\*Statistically significant. CABG indicates coronary artery bypass surgery; CAD, coronary artery disease; CI, confidence interval; CVA, cerebrovascular accident; DES, drug-eluting stent; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; Mo, months; MVD, multivessel disease; N/A, not available; PCI, percutaneous coronary intervention and Y, year.

Data Supplement 14. Evidence From RCTs and Cohort Studies Comparing PCI With CABG for Unprotected Left Main CAD

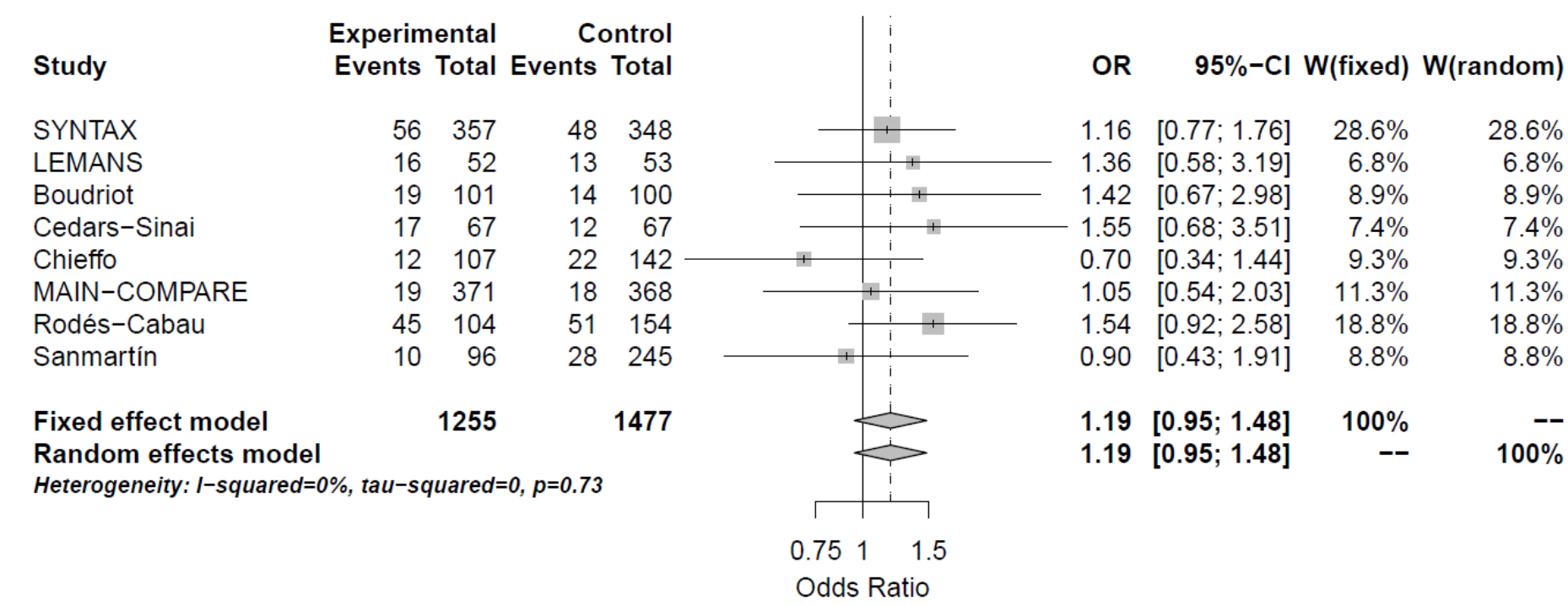
Study	Type of Study/ Years of Recruitment	PCI/CABG Number of Patients	Early Results for PCI Versus CABG	1 to 5-Y Results for PCI Versus CABG
<a href="#">SYNTAX</a> (36)	Randomized/2005-2007 45% of screened patients with LM disease not randomized, 89% of these had CABG	357/348	30-d outcomes not reported	3-y follow-up: MACCE 13.0% vs. 14.3% (p=0.60), repeat revascularization 20.0% vs. 11.7% (p=0.004), all-cause 7.3% PCI vs. 8.4% (change -0.2% (p=0.64).
<a href="#">LE MANS</a> (37)	Randomized/2001-2004 65% of screened patients excluded as not suitable for both procedures	52/53	30-d outcomes: death 0% vs. 0%, MI 2% vs. 4% (p=NS) MACCE 2% vs. 14% (p=0.01); MAE RR: 0.78; p=0.006; MACCE RR: 0.88; p=0.03	1-y follow-up: death 2% vs. 8% (p=NS), MI 2% vs. 6%) (p=NS); revascularization 30% vs. 10% (p=0.01); MACCE 32% vs. 26% (p=NS); MACCE RR: 1.09 (95% CI: 0.85 to 1.38); MAE RR: 0.89 (95% CI: 0.64 to 1.23)
<a href="#">Boudriot et al.</a> (38)	Randomized/2003-2009 53% of screened patients excluded	100/201	Early outcomes not reported	12 mo outcomes: death 2.0% vs. 5.0% (p<0.001 for noninferiority); death, MI or revascularization 19.0% vs. 13.9% (p=0.19 for noninferiority)
<a href="#">Brener et al.</a> (48)	Cohort/1997-2006	97/190	In hospital outcomes: death 3% vs. 4% (p=NS)	3-y follow-up: survival 80% vs. 85% (OR: 1.42, 95% CI: 0.56 to 3.63; p=0.14)
Cedars-Sinai ( <a href="#">41</a> , <a href="#">43</a> , <a href="#">44</a> )	Cohort/2003-2005	67/67	30-d outcomes: death 2% vs. 5% (p=NS), MI: 0% vs. 2% (p=NS); stroke 0% vs. 8% (p=0.03), MACCE: 17% vs. 2%; (p<0.01)	1-2-y follow-up: propensity-adjusted HR for death HR: 1.93 (95% CI: 0.89 to 4.19); p=0.10), MACCE HR: 1.83 (95% CI: 1.01 to 3.32); p=0.05)
Chieffo et al. ( <a href="#">39</a> , <a href="#">40</a> )	Cohort/2002-2004	107/142	In-hospital outcomes: death 0% vs. 2.1% (p=NS), MI 9.3% vs. 26.1% (p=0.0009), stroke 0% vs. 2% (p=NS)	5-y adjusted cardiac death (OR: 0.50; 95% CI: 0.16 to 1.46; p=0.24), cardiac death or MI (OR: 0.41; 95% CI: 0.15 to 1.06; p=0.06), death, MI, or stroke (OR: 0.40; 95% CI: 0.15 to 0.99; p=0.04), TVR (OR: 4.41; 95% CI: 1.83 to 11.37; p=0.0004), MACCE (OR: 1.58; 95% CI: 0.83 to 3.05; p=0.18)



MAIN-COMPARE ( <a href="#">46</a> , <a href="#">152</a> )	Cohort/2000-2006	1,102/1,138	30-d outcomes not reported	5-y adjusted risk of death (HR: 1.13; 95% CI: 0.88 to 1.44; p=0.35), combined adjusted risk of death, Q-wave MI, or stroke (HR: 1.07, 95% CI: 0.84 to 1.37; p=0.59, TVR (HR: 5.11, 95% CI: 3.52 to 7.42; p<0.001)
<a href="#">Mäkikallio et al.</a> (49)	Cohort/2005-2207	49/238	30-d outcomes: death 2% vs. 7% (p=0.13)	1-y follow-up: death 4% vs. 11% (p=0.14). CABG vs. PCI (using 1° and 2° endpoint) HR: 2.1 95% CI: 0.7 to 5.8; p 0.180
<a href="#">Palmerini et al.</a> (45)	Cohort/2002-2005	157/154	30-d outcomes: death 3.2% vs. 4.5% (p=NS), MI 4.5% vs. 1.9%; (p=NS), revascularization: 0.6% vs. 0.6% (p=NS)	1-2-y follow-up: death 13.4% vs. 12.3% (p=0.8); MI: 8.3% vs. 4.5% (p=0.17), revascularization 25.5% vs. 2.6% (p=0.0001). CABG vs. PCI: mortality HR: 0.95; 95% CI: 0.51 to 1.77; p=0.861; cardiac mortality HR: 0.99; 95% CI: 0.49 to 2.04; p=0.994; MI HR: 0.53; 95% CI: 0.21 to 1.32; p=0.170
<a href="#">Rodés-Cabau et al.</a> (153)	Cohort/2002-2008	104/145	30- outcomes: MACCE 18.3% vs. 27.6%; death 6.7% vs. 8.3%; MI 12.5% vs. 17.2%; stroke 1.0% vs. 5.5% (all p=NS)	1-2-y follow-up: MACCE 43.3% vs. 35%, death 16.3% vs. 12.4%, MI 23.1% vs. 19.3%, revascularization 9.6% vs. 4.8%, stroke 8.75 vs. 6.2% (all NS). Survival free of cardiac death or MI adjusted HR: 1.28; 95% CI: 0.64 to 2.56; p=0.47; MACCE-free survival adjusted HR: 1.11 95% CI: 0.59 to 2.0; p=0.73
<a href="#">Sanmartín et al.</a> (47)	Cohort/2000-2005	96/245	30-d outcomes: MACCE after surgery 2.1% vs. 9.0% (p=0.03).	1-y follow-up: MACCE (10.4% vs. 11.4%; p=0.50), repeat revascularization (5.2% vs. 0.8%; p=0.02)
<a href="#">Wu et al.</a> (34)	Cohort/2000-2004	135/135	30-d outcomes: death 5.2% vs. 2.2% (p=0.33)	1-y follow-up: death 16.1% vs. 5.9% (OR: 3.06, 95% CI: 0.99 to 9.45). 2 y follow-up: death 18.0% vs. 5.9% (HR: 3.1, 95% CI: 1.42 to 7.14; p=0.005), revascularization 37.3% vs. 6.3% (HR: 6.7; 95% CI: 3.0 to 14.3; p<0.001)

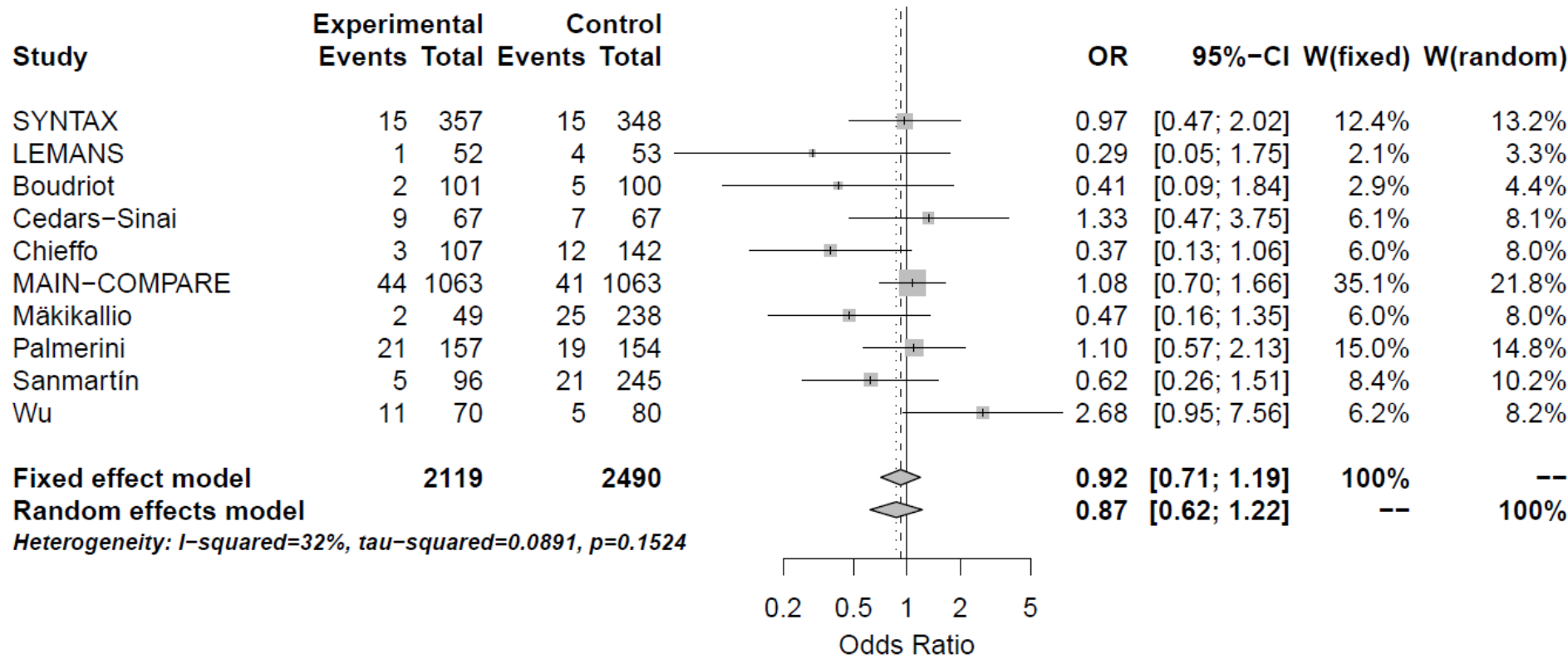
CABG indicates coronary artery bypass grafting; CI, confidence interval; d, day; HR, hazard ratio; LEMANS, Study of Unprotected Left Main Stenting Versus Bypass Surgery; LM, left main; MACCE, Major adverse cardiac and cardiovascular events; MAE, major adverse events; MAIN-COMPARE, Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization; MI, myocardial infarction; No., number; NS, not significant; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TVR, target vessel revascularization; and y, year.

Data Supplement 15. Forest Plot of 1-Year MACCE Rates After PCI or CABG for Unprotected Left Main CAD



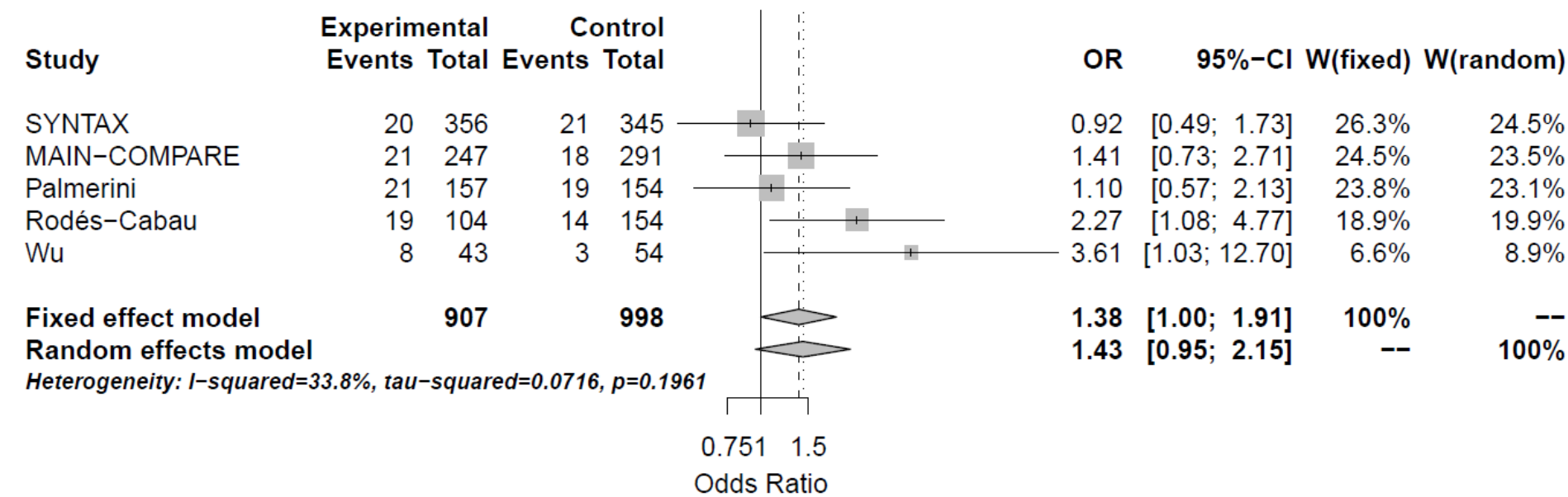
References: (36-41, 43, 44, 46, 152, 153). OR >1 suggest an advantage of CABG over PCI.  
CABG indicates coronary artery bypass surgery; CAD, coronary artery disease; CI, confidence interval; LEMANS, Study of Unprotected Left Main Stenting Versus Bypass Surgery; MACCE, major adverse cardiac and cerebrovascular event; MAIN-COMPARE, Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization; OR, odds ratio; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and W, weighted.

Data Supplement 16. Forest Plot of 1-Year Mortality Rates After PCI or CABG for Unprotected Left Main CAD



References: (34, 36-41, 43-46, 49, 152, 153). OR >1 suggest an advantage of CABG over PCI.  
CABG indicates coronary artery bypass surgery; CAD, coronary artery disease; CI, confidence interval; LEMANS, Study of Unprotected Left Main Stenting Versus Bypass Surgery; MAIN-COMPARE, Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization; OR, odds ratio; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and W, weighted.

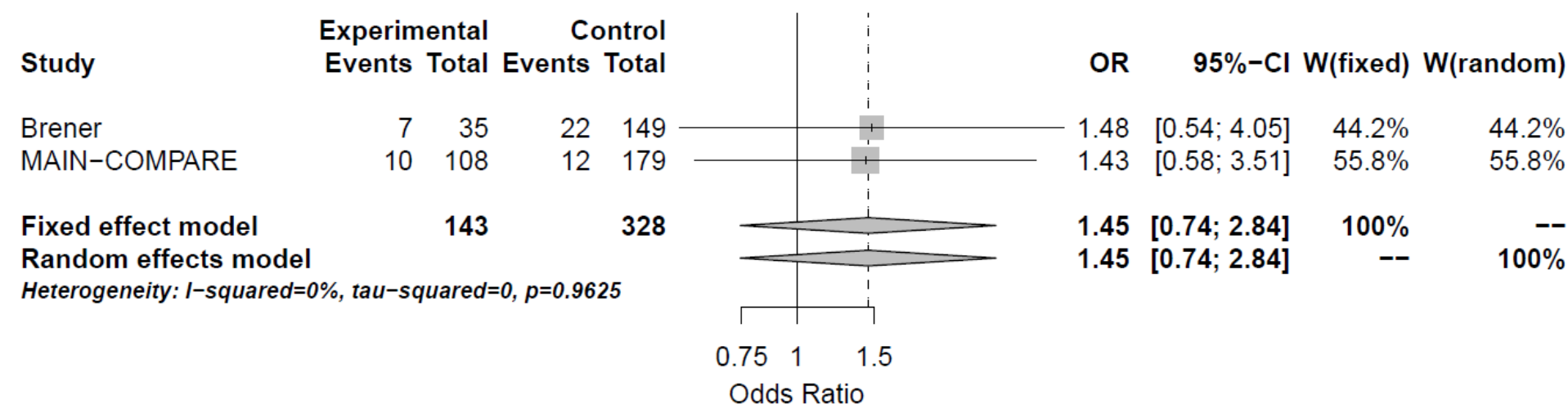
Data Supplement 17. Forest Plot of 2-Year Mortality Rates After PCI or CABG for Unprotected Left Main CAD



References: (34, 37, 45, 46, 152-154). OR >1 suggest an advantage of CABG over PCI.  
CABG indicates coronary artery bypass surgery; CAD, coronary artery disease; CI, confidence interval; MAIN-COMPARE, Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization; OR, odds ratio; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and W, weighted.

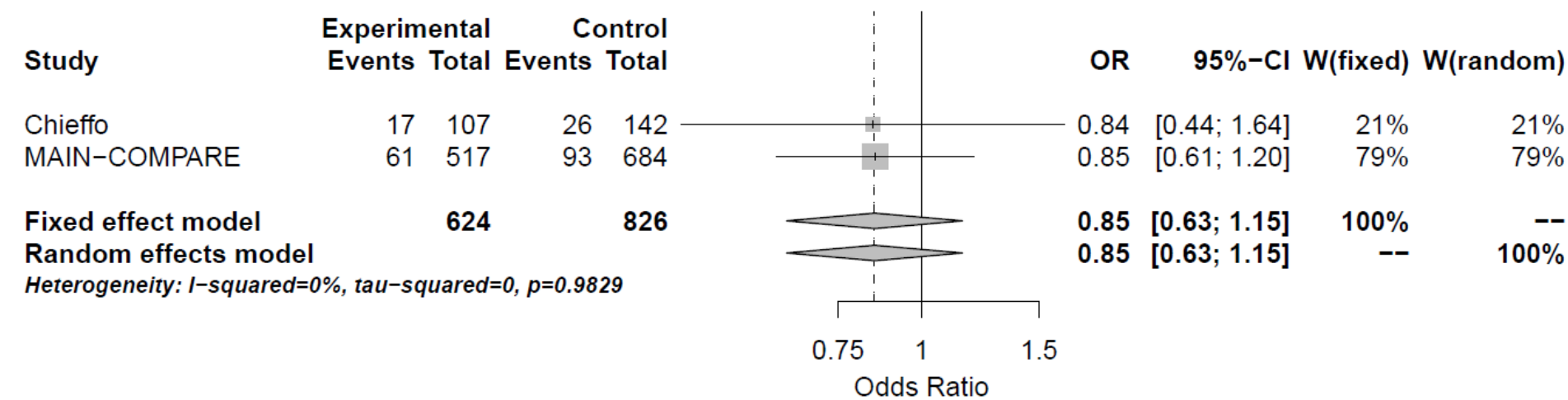


Data Supplement 18. Forest Plot of 3-Year Mortality Rates After PCI or CABG for Unprotected Left Main CAD



References: (46, 48). OR >1 suggest an advantage of CABG over PCI.  
CABG indicates coronary artery bypass surgery; CAD, coronary artery disease; CI, confidence interval; MAIN-COMPARE, Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization; OR, odds ratio; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and W, weighted.

Data Supplement 19. Forest Plot of 5-Year Mortality Rates After PCI or CABG for Unprotected Left Main CAD



References: (40, 46). OR >1 suggest an advantage of CABG over PCI.  
CABG indicates coronary artery bypass surgery; CAD, coronary artery disease; CI, confidence interval; MAIN-COMPARE, Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty versus Surgical Revascularization; OR, odds ratio; PCI, percutaneous coronary intervention; and W, weighted.

**Data Supplement 20. Outcomes of PCI Versus CABG for Patients with Single-Vessel Coronary Disease Involving the Proximal Left Anterior Descending Artery**

Author	Type of Study/ Years of Recruitment	Number of Patients PCI/CABG	Short-Term Results for PCI Versus CABG	Long-Term Results for PCI Versus CABG
<a href="#">Greenbaum et al.</a> (72)	Retrospective cohort 1986-1994	754/149	At 1 y, HR for event-free survival for CABG to PCI: 0.20; p<0.0001	At 2-7 y, HR for event-free survival for CABG to PCI: 0.62; p=NS
Goy et al. ( <a href="#">79</a> , <a href="#">80</a> , <a href="#">155</a> )	Randomized 1994-1998	68/66	At 2.4 y: death, MI, revascularization 31% vs. 7% (p<0.001); death or MI 12% vs. 7%	At 5 y: death 9% vs. 3% (p=0.09). At 10 y: death 10% vs. 10% (p=1.0)
<a href="#">Cisowski et al.</a> (75)	Randomized 2000-2001	50/50	At 6 mo: death or MI 0% vs. 0%; revascularization 12% vs. 2% (p<0.05)	N/A
<a href="#">Diegeler et al.</a> (76)	Randomized 1997- 2001	110/110	At 6 mo: death or MI 3% vs. 6% (p=NS); revascularization 29% vs. 8% (p=0.02)	N/A
Drenth et al. ( <a href="#">77</a> , <a href="#">112</a> )	Randomized 1997-99	51/51	At 6 mo: death or MI 6% vs. 10% (p=NS); revascularization 4% vs. 8% (p=NS)	N/A
<a href="#">Reeves et al.</a> (141)	Randomized 1999-2001	50/50	In-hospital: death or MI 0% vs. 0%	At 1.5 y: death 0% vs. 2% (p=NS); MI 4% vs. 0% (p=NS); revascularization 4% vs. 0% (p=NS). Survival analysis for MIDCAB versus PTCA HR: 0.77 (95% CI: 0.38 to 1.57; p=0.47)
<a href="#">Thiele et al.</a> (113)	Randomized 1997-2001	110/110	N/A	At 5 y: death 10% vs. 12% (p=0.54); MI 5% vs. 7% (p=0.46); revascularization 32% vs. 10% (p<0.001)
<a href="#">Hong et al.</a> (81)	Randomized 2003	119/70	In-hospital: death or MI 5.1% vs. 4.3% (p=1.00)	At 6 mo: death or MI: 6.8% vs. 10.1% (p=NS); revascularization 5.9% vs. 1.7% (p=NS)
MASS I ( <a href="#">84</a> , <a href="#">156</a> )	Randomized	72/70	N/A	At 3 y: death, MI or revascularization 24% vs. 3% (p=0.006)
<a href="#">Fraund et al.</a> (78)	Cohort 1998-2001	256/206	In-hospital death or MI 0.8% vs. 2% (p=NS)	At 3 y: death or MI 4.7% vs. 5.8% (p=NS); revascularization 7.8% vs. 28.9% (p<0.01)
<a href="#">Ben-Gal et al.</a> (74)	Matched cases from prospective cohort 2002-2003 (PCI were all DES)	83/83	30-d death: 0% vs. 1.1% (p=NS)	At 22 mo: death 1.1% vs. 5.5% (p=NS); revascularization 16.8% vs. 3.6% (p=0.005). Independent predictors of MACE (Cox analysis) were assignment to the Cypher group (HR: 4.1; 95% CI: 1.26 to 13.16), multivessel disease (HR: 4.3; 95% CI: 1.44 to 13.16), and prior PCI (HR: 4.36; 95% CI: 1.28 to 14.90)

<a href="#">Toutouzas et al.</a> (157)	Cohort	147/110	In-hospital death or MI or revascularization 0% vs. 0%	At 2 y: death: 2.0% vs. 1.8% (p=NS); MI 0% vs. 0.9%; (p=NS), revascularization 2% vs. 0% (p=0.51)
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CABG indicates coronary artery bypass graft; CI, confidence interval; d, day; DES, drug-eluting stents; HR, hazard ratio; MACE, major adverse cardiac events; MASS, Medicine, Angioplasty, or Surgery Study; MIDCAB, minimally invasive direct coronary artery bypass; MI, myocardial infarction; mo, month; NS, not significant; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty, and y, year.

**Data Supplement 21. Cohort Studies Comparing CABG to PCI in Patients With Diabetes**

Author	Type of Study/ Year of Recruitment	Number of Patients PCI/CABG	Long-Term Results for PCI Versus CABG
<a href="#">Barsness et al.</a> (97)	Retrospective cohort 1984-90	770 patients with total	At 5 y: similar mortality for PCI and CABG patients: unadjusted 86% vs. 89%; p=NS; adjusted 92% vs. 93%
<a href="#">Weintraub et al.</a> (95)	Cohort 1981-94	834/1805	At 10 y: death: 64% vs. 53%, p=0.045 for insulin-requiring diabetics ONLY Insulin-requiring subgroup multivariate HR: 1.35, 95% CI: 1.01 to 1.79 for PTCA vs. CABG
<a href="#">Niles et al.</a> (93)	Retrospective cohort 1992-96	2766 patients total	At 2 y: higher mortality in PCI patients (HR: 2.0; p=0.038) with 3-vessel disease. Trend to higher mortality in PCI patients (HR: 1.3; p=0.2) with 2-vessel disease, compared to CABG
<a href="#">Van Domburg et al.</a> (67)	Cohort 1970-1985	76/82	At 20 y: survival similar for PCI vs. CABG patients Mortality for PTCA vs. CABG, RR: 1.03; 95% CI: 0.87 to 1.24
<a href="#">Brener et al.</a> (90)	Retrospective cohort 1995-1999	265/2,054	At 6 y: deaths for NIDDM: 21% vs. 17%; p=0.008 Deaths for IDDM: 31% vs. 23%; p<0.0001 Unadjusted HR: 1.13; 95% CI: 1.0 to 1.4; p=0.07
<a href="#">Javaid et al.</a> (92)	Retrospective cohort DES era	601 patients total 344/257	At 1 y: death, stroke, MI, revascularization HR: 3.5 (p<0.001) for 2-vessel CAD HR: 4.8 (p<0.001) for 3-vessel CAD
<a href="#">Hueb et al.</a> (85)	Cohort 1995-2000	120/221	At 5 y: incidence of cardiac death 11.1% vs. 11.8% (p=NS), revascularization 27.5% vs. 3.2% (p<0.001) The incidence of cardiac death was NS different between PCI and MT groups
<a href="#">Bair et al.</a> (57)	Subset of large cohort 1992-2000	353/1,267	At 15 y: death HR: 0.81; p=0.03
<a href="#">Hannan et al.</a> (60)	Subset of large cohort 2003-2004	2,844/3,256	At 18 mo: death HR: 1.03; p=0.75; death or MI HR: 1.19; p=0.07

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; IDDM, insulin dependent diabetes mellitus; MT, medical therapy; MI, myocardial infarction; NIDDM, non-insulin dependent diabetes mellitus; NS, not significant; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angiography; RR, relative risk; and y, year.



**Data Supplement 22. RCTs of PCI With CABG in Patients With Multivessel CAD and Diabetes**

Author	Type of Study in Year of Recruitment	Number of Patients PCI/ CABG	Primary Endpoint for PCI and CABG	Comments
<a href="#">SYNTAX</a> (158)	Randomized 2005-2007	Overall 903/897 DM 231/221	DM: 12-mo death, stroke, MI, or revascularization: 26.0% vs. 14.2% (HR: 1.83, 95% CI: 1.22 to 1.73; p=0.003)	Criterion for noninferiority of PCI to CABG was not met in overall study.
<a href="#">CARDIA</a> (98)	Randomized 2002-2007	DM 256/254	DM: 1-y death, stroke or MI: 13.0% vs. 10.5% (OR: 1.25, 95% CI: 0.75 to 2.09; p=0.39)	Criterion for noninferiority of PCI to CABG was not met.
<a href="#">BARI 2D</a> (87)	Prestratified/randomized to revascularization-medical therapy	DM 798/807	DM: 5-y freedom from MACE: PCI vs. medical 77.0% vs. 78.9; p=0.15 CABG vs. medical 77.6% vs. 69.5%; p=0.01; interaction p=0.002	No benefit associated with PCI as compared with medical therapy.
ARTS I ( <a href="#">96</a> , <a href="#">137</a> , <a href="#">159</a> )	Randomized 1997-1998	Overall 600/605 DM 112/96	Overall: 5-y overall freedom from death, stroke, or MI 18.2% vs. 14.9% (RR: 1.22; 95% CI: 0.95 to 1.58; p=0.14) DM: 1-y freedom from death, stroke, MI, or revascularization 63.4% vs. 84.4%; p< 0.001	
<a href="#">MASS II</a> (85)	Randomized 1995-2000	Overall 205/203 DM 56/59	DM: 1-y death 5.3% vs. 6.8% (p=0.5)	

ARTS indicates Arterial Revascularization Therapies Study; BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes; CABG, coronary artery bypass graft; CAD, coronary artery disease; CARDIA, Coronary Artery Revascularization in Diabetes; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; LAD, left anterior descending artery; MACE, major adverse cardiovascular events; MASS, Medicine, Angioplasty, or Surgery Study; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; and y, year.

**Data Supplement 23. Antiplatelet Therapy**

Study Reference	Study Type	Patient Population Sample Size	Findings	Statistical Analysis
<a href="#">Hongo</a> 2002 (160)	Single center observational study	CABG within 7 d of stopping clopidogrel (59 patients) vs. CABG with no prior clopidogrel (165 patients)	Reoperation for bleeding in 6.8% in clopidogrel group vs. 0.6% in no clopidogrel group	p=0.018
<a href="#">Mehta</a> 2006 (161)	Subgroup analysis of CRUSADE	Timing of CABG: ≤5 d after clopidogrel (739 patients) >5 d after clopidogrel (113 patients)	Increased risk of transfusion when CABG ≤5 d after clopidogrel	OR: 1.36; 95% CI: 1.10 to 1.68
<a href="#">Berger et al.</a> 2008 (162)	Retrospective cohort study	Timing of CABG: ≤5 d after clopidogrel (298 patients) >5 d or no prior clopidogrel (298 patients)	Reoperation rate higher in ≤5 d group than >5d or no prior clopidogrel group (6.4% vs. 1.7%) Major bleeding rate higher in ≤5 d group than >5 d or no prior clopidogrel group (35% vs. 26%)	p=0.004  p=0.049

<a href="#">Kim</a> 2008 (163)	Duke Database Logistic Regression Analysis	Clopidogrel $\leq$ 5 d before CABG (332 patients) vs. No clopidogrel $\leq$ 5 d before CABG (4,462 patients)	Clopidogrel <5 d associated with: Increased need for transfusion No increase in reoperation rate	OR: 1.40; 95% CI: 1.04 to 1.89 OR: 1.24; 95% CI: 0.63 to 2.41
<a href="#">Mehta</a> 2009 (164)	STS database logistic regression	12,652 CABG patients requiring reoperation for bleeding out of 528,686 total CABG patients	Clopidogrel use $\leq$ 24 h of CABG is an independent risk factor for need for reoperation	OR: 1.46; 95% CI: 1.37 to 1.56
<a href="#">Herman</a> 2010 (165)	Single center observational study	CABG and/or valve surgery performed with (n=999 patients) or without (n=2,780 patients) preoperative clopidogrel therapy	Higher transfusion rate and hemorrhagic complications in clopidogrel group than without preoperative clopidogrel therapy (34.1% vs. 4.1%) Clopidogrel use within 24 h was independent predictor of transfusion and hemorrhagic complications	Transfusion OR: 2.4; 95% CI: 1.8 to 3.3 Hemorrhagic complication OR: 2.1; 95% CI: 1.3 to 3.6
<a href="#">Ebrahimi</a> 2009 (166)	Subgroup analysis of ACUTY	Timing of CABG: <5 d after clopidogrel (524 patients) $\geq$ 5 d after clopidogrel (249 patients)	Increased risk of transfusion when CABG <5 d after clopidogrel vs. $\geq$ 5 d after clopidogrel (41.8% vs. 31.3%, respectfully). No increased risk of major bleeding or reoperation for bleeding.	p=0.005
<a href="#">Firanescu</a> 2009 (167)	Randomized trial	Clopidogrel stopped: On d of CABG (40 patients) 3 d before (40 patients) 5 d before (38 patients)	Postoperative blood loss higher in d of CABG group (929+471 mL) than in 3 d before (767+471 mL) or 5 d before (664+312 mL) groups	d of CABG vs. 5 d before; p=0.022 3 d before vs. 5 d before; p=NS
<a href="#">Wiviott</a> 2007 (168)	Subgroup analysis of TRITON – TIMI 38	CABG performed in: 179 patients on prasugrel 189 patients on clopidogrel	TIMI major bleeding rate higher in prasugrel group than clopidogrel group (13.4% vs. 3.2%)	p<0.001
<a href="#">Held</a> 2010 (169)	Post-randomization analysis	1,261 (6.8%) patients underwent CABG receiving study drug <7days before surgery (632 patients in ticagrelor group; 629 patients in clopidogrel group).	Relative reduction of primary composite endpoint at 12 mo (10.6% [66 of 629 patients] with ticagrelor vs. 13.1% [79 of 629 patients] with clopidogrel.  Total mortality reduced from 9.7% (58 of 629 patients) to 4.7% (29 of 629 pts)  CV death reduced from 7.9% (47 of 629 patients) to 4.1% (25 of 629 patients)  No significant difference in CABG-related major bleeding between ticagrelor vs. clopidogrel groups.	HR: 0.84; 95% CI: 0.60 to 1.16; p=0.29  HR: 0.49; 95% CI: 0.32 to 0.77; p<0.01  HR: 0.52; 95% CI: 0.32 to 0.85; p<0.0; and non-CV death numerically from 2.0% to 0.7%; p=0.07

ACUTY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CABG, coronary artery bypass graft; CI, confidence interval; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines; CV, cardiovascular; d, day; HR, hazard ratio; NS, non significant; OR, odds ratio; STS, Society of Thoracic Surgeons; TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38; and TIMI, Thrombolysis in Myocardial Infarction.

Data Supplement 24. Management of Hyperlipidemia

Study Name	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P-Values & 95% CI	OR / HR / RR	Study Summary	Study Limitations	Other Information
				Inclusion Criteria	Exclusion Criteria	Primary Endpoint	Secondary Endpoint OR/HR: (95% CI)						
<a href="#">The Post Coronary Artery Bypass Graft Trial Investigators.</a> 1997 (170)	To compare 2 strategies of lipid-lowering and their effect on bypass graft disease	RCT	1,192	1) Patients 1 to 11 y post-CABG; 2) Baseline LDL 130 to 175 mg/dL 3) ≤1 patent vein graft on baseline angiogram	1) Likelihood of revascularization/death within 5 y; 2) UA/MI within 6 mo; 3) Severe angina; 4) HF; 5) Contraindication to prescription with medication	Percent of grafts with angiographic evidence of atherosclerotic progression: 27% (intensive) vs. 39% (moderate)	Lipid lowering: mean 93 to 97 mg/dL (intensive) vs. 132 to 136 mg/dL (moderate)	Intention-to-treat	p<0.001	N/A	Reduced rate of SVG atherosclerotic progression with intensive lipid-lowering (statin) therapy	Not powered to detect difference in clinical events	Mean follow-up 4.3 y
							Rate of repeat revascularization: 6.5% (intensive) vs. 9.2% (moderate)		p=0.03				
<a href="#">Dotani</a> 2000 (171)	To examine effect of preoperative statins on 60 d and 1 y post-CABG outcomes	Retrospective case-control	323	Consecutive patients admitted for CABG over 10 mo period in 1997	None	60 d death/MI/recurrent angina: 9% (nonstatin) vs. 1% (statin)	None	N/A	p<0.001	OR: 0.28	N/A	N/A	N/A
						60 d any adverse outcome (death, MI, UA, CHF, arrhythmia, CVA): 37% (nonstatin) vs. 15% (statin use)			p<0.0001	OR: 0.31			

						1 y any adverse outcome: 45% (nonstatin) vs. 18% (statin)			p<0.001	OR: 0.26	Preoperative statin therapy associated with reduced CV events at 60 d and 1 y	Nonrandomized , retrospective (may be unmeasured factors that account for difference between statin and nonstatin outcomes)	
<a href="#">Pan</a> 2004 (172)	To examine effect of statin therapy on perioperative CABG mortality	Retrospective case-control	1,663	Consecutive patients undergoing CABG at single institution from 2000 to 2001	N/A	N/A	N/A	30 d all cause mortality: 3.75% (nonstatin) vs. 1.8% (preoperative statin)	p<0.05; 95% CI: 0.28 to 0.99	OR: 0.53	Preoperative statin therapy may reduce early mortality of CABG	Nonrandomized , retrospective (may be unmeasured factors that account for difference between statin and nonstatin outcomes)	Confirmed in a propensity-matched cohort of 1,362 patients
<a href="#">Collard</a> 2006 (173)	To assess preoperative statin therapy on postoperative mortality/MI	Retrospective case-control	2,663	Patients undergoing CABG in 70 centers/17 countries from 1996 to 2000	N/A	Risk of early cardiac death post-CABG: 0.3% (statin-treated) vs. 1.4% (not-statin treated)	No difference in postoperative nonfatal, in-hospital MI	N/A	p<0.03; 95% CI: 0.07 to 0.87	OR: 0.25; for early cardiac death	Preoperative statin use is associated with reduced cardiac mortality after CABG	Retrospective, nonrandomized	Postoperative statin discontinuation associated with increased in-hospital mortality : 1.9% (discontinued) vs. 0.5% (continued) (OR: 2.95 for death; 95% CI:



													1.31 to 6.66; p<0.01)
<a href="#">Clark</a> 2006 (174)	To assess statin therapy on postoperative surgical outcomes (included CABG alone, valve alone or combined)	Retrospective case-control	3,113 with CABG ± valve	Consecutive cardiac surgery patients over 8 y period	N/A	30 d mortality/morbidity (risk-adjusted): mortality OR: 0.55; (95% CI: 0.32 to 0.93); morbidity OR: 0.76 (95% CI: 0.62 to 0.94) favoring statin users	N/A	N/A	p<0.05	N/A	Preoperative statin use confers a "protective effect" with regard to postoperative outcomes	Nonrandomized , retrospective	N/A
<a href="#">Kulik</a> 2008 (175)	To assess early postoperative statin use vs. no early postoperative statin use and post-CABG outcome	Retrospective case-control	7,503	Medicare patients undergoing CABG from 1995 to 2003	N/A	All cause mortality (median follow-up 4 y) HR: 0.82 favoring statin users within 1 m (95% CI: 0.72 to 0.94); p=0.004	MACE HR: 0.89; (95% CI: 0.81 to 0.98); p=0.02	Intention-to-treat	N/A	N/A	Postoperative statin use within 1 mo of discharge reduces all-cause mortality and MACE following CABG	Nonrandomized , retrospective	N/A

CABG indicates coronary artery bypass graft; CHF, congestive heart failure; CI, confidence interval; CVA, cerebral vascular accident; CV, cardiovascular; d, day; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; m, month; MACE, major adverse cardiac events; MI, myocardial infarction; N/A, not applicable; OR, odds ratio; RR, relative risk; SVG, saphenous vein graft; UA, unstable angina; and y, year.

Data Supplement 25. Beta Blockers

Author (Trial)	Drug	Number of Patients	AF Episode (Percent)	RR (95% CI)	ARR (95% CI)	P-Value	Comments
<a href="#">Halonen et al.</a> 2006 (176)	IV metoprolol administration (1 to 3 mg/h)	119	20 (17%)	0.4 (0 .02 to 0.63)	0.11 (0.01 to 0.22)	p=0.04	Dosing started on the first postoperative morning; Continued for 48 h; No difference in onset of AF in h after surgery (26.5 h IV vs. 30.1 h oral); IV metoprolol temporarily discontinued for ≥1 h due to hypotension or bradycardia in 15.1%

<a href="#">Halonen et al.</a> 2006 (176)	Oral metoprolol administration (25 mg bid up to 50 mg bid titrated to heart rate)	121	34 (28%)				
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AF indicates atrial fibrillation; ARR, absolute risk reduction; bid, twice daily; IV, intravenous; mg, milligram; and RR, relative risk.

Data Supplement 26. ACE Inhibitors: Table 1

Author	Definition	Inclusion	Exclusion	Statistical Methods	Primary Outcome	Secondary Outcomes	Primary Results OR (95% CI); P-Value	Secondary Results [OR (95% CI); P-Value]
<a href="#">Miceli</a> et al. 2009 (177)	Use of ACE inhibitors within 24 h of surgery	10,023 isolated CABG, single site, 1996 to 2008	Unknown ACE inhibitor status, preoperative shock	Propensity matching 3,052 patients per group, OPCAB 49%	30 d mortality, overall rate 1%	Renal dysfunction, AF, MI, stroke, inotrope use	OR: 2.0 (1.2 to 3.4); p=0.01, ACE inhibitor vs. Non-ACE inhibitor	Renal dysfunction OR 1.4; (1.1 to 1.7); p=0.006 AF: OR: 1.3; 1.2 to 1.5; p<0.0001 Inotrope: OR: 1.2 (1.1 to 1.4); p<0.0001 No difference in MI or stroke
<a href="#">Rader</a> et al. 2010 (178)	Use of ACE or ARB (ABDT) prescription within 30 d and last dose within 24 h of surgery	10,552 CABG ± valve, single site, 1997 to 2003	Preoperative AF or paced rhythm (prior history of AF allowed)	Propensity matching (6,744 patients, 70% cohort)	<u>Postoperative AF</u>	VT, VF, cardiac arrest, inotrope use, stroke, in hospital death, renal failure, pulmonary embolism, LOS	<u>Unadjusted OR: 1.13 (1. 05 to 1.25); p&lt;0.01</u>  <u>OR: 1.05 (0.95 to 1.16); p=0.38</u>	Trend towards longer LOS (p=0.07), however no evidence found an association between preoperative angiotension blockade and occurrence of POAF.

ABDT, indicates angiotensin-blocking drug therapy ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass graft; CI, confidence interval; h, hour; LOS, length of stay; MI, myocardial infarction; OPCAB, off-pump coronary artery bypass; OR, odds ratio; POAF, postoperative atrial fibrillation, VF, ventricular fibrillation; and VT, ventricular tachycardia.

**Data Supplement 27. ACE Inhibitors: Table 2**

Author (Trial)	Intervention	Number	Inclusion/Exclusion	Dates	Outcome	Results; HR (95% CI)
<a href="#">Kjoller-Hansen</a> et. al. 2000 (APRES) (179)	Ramipril 5 to 10 mg, 5 to 7 d post uncomplicated CABG, median follow-up 33 mo, 82% post-CABG (vs. PCI)	80	Key inclusion: preoperative LVEF 0.3 to 0.5 and uncomplicated postoperative course. Exclusion: hx recent MI, clinical heart failure, or valve disease.	1994 to 1996, single Danish site, terminated early (lack of enrollment)	Triple (cardiac death, MI, CHF) or quadruple composite outcome (recurrent angina)	Reduction in triple composite only (58% risk reduction), (7% to 80%). Trend to higher incidence recurrent angina first 6 mo. No interaction with EF.
	Placebo	79				
<a href="#">Oosterga et. al.</a> 2001 (Quo Vadis) (180)	Quinapril (40 mg), 4 wkspreoperative, prescription 1 y postoperative	75	Key inclusion: exercise induced ischemia. Key exclusions: clinical heart failure, severe renal disease, severe hypertension, AF, diuretic prescription	1994 to 1997; 2 sites, Dutch	Clinical ischemic events, Ischemia on ETT, Holter	Reduction of clinical ischemic events only HR: 0.2; (95% CI: 0.06 to 0.87)
	Placebo	73				
<a href="#">Rouleau et al.</a> 2008 (IMAGINE) (181)	Quinapril (titrate up to 40 mg), 7 to 10 d postoperative, Prescription 6 to 43 mo	1,280	Key exclusion: insulin-dependent diabetes mellitus, or type 2 diabetes with microalbuminuria, significant renal disease, microalbuminuria, preoperative LVEF <40%, perioperative MI.	1999 to 2004; 57 sites, 4 countries	Composite MACE, CVA; drug AEs	Primary outcome NS (HR: 1.15; 95% CI: 0.92 to 1.42; p=0.212); first 3 mo postoperative worse outcome treated group (HR: 1.60; 95% CI: 0.73 to 3.52; p=0.240), more AE's
	Placebo	1,273				
<a href="#">Fox et al.</a> 2007 (182)	Perindopril 8 mg after 4 wk run in period. Prescription for at least 3 wk.	3,340	Key inclusion: CAD without heart failure. Key Exclusions: renal insufficiency; revascularization within 6 mo of enrollment	1997 to 2000, multicenter European 24 countries	Primary (cardiovascular death, nonfatal MI or cardiac arrest) at 4.2 y of follow-up	CABG only in 3,136 patients, CABG and PCI in 451, PCI only in 3122 pts. RRR 17.3% (95% CI: 1.3 to 30.8; p=0.035) (vs. 20% in entire EUROPA trial); RRR in pts without prior MI 23% (95% CI: 2.7 to 42.2, p=0.074); RRR for fatal or nonfatal outcome alone 23% (95% CI: 4.9 to 37.6%; p=0.015).
	Placebo	3,369				

AE indicates adverse event; AF, atrial fibrillation; APRES, Angiotension-converting Enzyme Inhibition Post Revascularization Study; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CVA, cerebral vascular accident; d, day; EF, ejection fraction; ETT, exercise tolerance test; HTN, hypertension; HR, hazard ratio; hx, history; IMAGINE, Ischemia Management with Accupril post-bypass Graft via Inhibition of the converting Enzyme; LV, left ventricular; LVEF, left ventricular ejection fraction; m, month; MACE, major adverse cardiac events; MI, myocardial infarction; NS, non significant; PCI, percutaneous coronary infection; Quo Vadis, QUinapril on Vascular Ace and Determinants of Ischemia; RRR, relative risk reduction; w, week, and y, year.

**Data Supplement 28. Smoking Cessation**

Study Name	Study Type	Patient Population Sample Size	Findings	Statistical Significance
<a href="#">Cavender et al.</a> 1992 (183)	Randomized Study	780	Increased survival in nonsmokers vs. smokers (82% and 77%, respectively)	p=0.025
<a href="#">Vlietstra et al.</a> 1986 (184)	Observational Study	4,165	Lower mortality in quitters vs. those who continued to smoke (15% vs. 22% respectively) RR: 1.55; 95% CI: 1.29 to 1.85	N/A
<a href="#">Voors et al.</a> 1996 (185)	Observational Study	415	No difference in survival; compared to nonsmokers, smokers were at increased risk for MI, repeat CABG and recurrent angina	N/A
<a href="#">van Domburg et al.</a> 2000 (186)	Observational Study	985	Nonsmokers were less likely to undergo repeat CABG or PCI RR: 1.41; 95% CI: 1.02 to 1.94	N/A
<a href="#">van Domburg et al.</a> 2008 (187)	Observational Study	1,041	Smoking cessation was an independent predictor of lower mortality HR: 0.60; 95% CI: 0.48 to 0.72	N/A

CABG indicates coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; N/A, not applicable; OR, odds ratio; PCI, percutaneous coronary intervention; and RR, relative risk.

**Data Supplement 29. Cardiac Rehabilitation**

Study Name	Study Type	Patient Population Sample Size	Findings	Statistical Significance
<a href="#">Engbloom et al.</a> 1997 (188)	Randomized Trial	Post-CABG n=119 randomized to rehabilitation vs. n=109 usual hospital treatment	5 y rates of physical mobility, health status improved	p=0.002
<a href="#">Millani et al.</a> 1998 (189)	Observational Study	500 consecutive patients entering rehabilitation following cardiac event (MI, PCI, CABG)	Decrease body fat 5% from 26.2±8.0 to 24.8±7.5	p<0.0001
<a href="#">Hansen et al.</a> 2009 (190)	Observational Study	PCI n=194 and CABG n=149 undergoing rehabilitation compared to controls	CABG and PCI patients getting rehabilitation had lower 2 y mortality compared to controls	p<0.005
<a href="#">Moholdt et al.</a> 2009 (191)	Randomized Trial	59 CABG randomized to AIT vs. MCT	4 wk and 6 mo follow-up with improved VO <sub>2</sub> max in AIT group	p<0.001

AIT indicates aerobic interval training; CABG, coronary artery bypass graft; MCT, moderate continuous training; MI, myocardial infarction; mo, month; PCI, percutaneous coronary intervention; VO<sub>2</sub> max, oxygen uptake maximum; wk, week; and y, year.



**Data Supplement 30. Central Nervous System Monitoring**

Author	Aim of Study	N of Patients	Patients With ≥1 MOMM Outcome N (%)	Relative RR; (95% CI)	Absolute RR; (95% CI)	P-Value	Number of Patients With ≥1 any STS 30-d Outcomes N (%)	RR; (95% CI)	Absolute RR (95% CI) (%)	P-Value	Comments
<a href="#">Murkin et al. 2007</a> (192)	Active intraoperative rSO <sub>2</sub> cerebral oximetry monitoring with treatment	100	3 (3%)	0.73; (95% CI: 0.05 to 0.92)	0.08; (95% CI: 0.01 to 0.15)	0.048	23 (23%)	0.25 (95% CI: -0.10 to 0.49)	0.10; (95% CI: -0.03 to 0.23)	NS	MOMM variables: death, ventilation >48 h, stroke, MI, return for reexploration; alarm threshold of 75% of resting rSO <sub>2</sub> used for intervention; concomitant procedure or OPCAB in 12 control vs. 7 intervention patients
	Active intraoperative rSO <sub>2</sub> cerebral oximetry monitoring with treatment	100	11 (11%)				30 (30%)				
			Postoperative Cognitive Decline				Other major postoperative complications				
<a href="#">Slater et al. 2009</a> (193)	Active intraoperative rSO <sub>2</sub> cerebral oximetry monitoring with treatment	125	73 (58%)	0.05 (95% CI: 0.17 to 0.23)	0.03 (95% CI: -0.09 to 0.15)	NS	6 (5%)	0 (95% CI: -202 to 67)	0 (95% CI: -0.06 to 0.06)	NS	Other complications=CVA, MI, renal insufficiency, reoperation; prolonged rSO <sub>2</sub> was higher in pooled cognitive decline patients (33% vs. 20%; p=0.02) and was associated with hospital stay >6 d (25%) OR: 2.71 (95% CI 1.3 to 5.6); p=0.007
	Active intraoperative rSO <sub>2</sub> cerebral oximetry monitoring with treatment	115	70 (61%)				6 (5%)				

CI indicates confidence interval; CVA, cerebral vascular accident, MI, myocardial infarction; MOMM, major organ morbidity and mortality; N, number; NS, non-significant; OPCAB, off-pump coronary artery bypass; RR, relative risk; rSO<sub>2</sub>, regional oxygen saturation; and STS, Society of Thoracic Surgeons.

**Data Supplement 31. Performance**

Article Name	Aim of Study	Study Design	Study Size	Patient Population	Endpoints	Results
<a href="#">Comparing hospitals that perform CABG: the effect of outcome measures and data sources.</a> 1994 (194)	To determine if hospital quality comparisons impacted by use of administrative vs. clinical data	Observational	2,867 CABG patients	10 WI hospitals, April 1990 to June 1991	Risk-adjusted mortality and morbidity	Low correlations between adjusted hospital rankings derived from the clinical and administrative databases were 0.48 for mortality, 0.21 for major complications, and - 0.14 for any complication.  Assessing provider quality using administrative data may not be adequate.
<a href="#">Using Medicare claims data to assess provider quality for CABG: does it work well enough?</a> 1997 (195)	Determine adequacy of administrative claims data for profiling.	Observational, comparing risk models and provider performance based on Medicare vs. NY clinical data registry.	13,577 CABG patients	Isolated CABG patients, NY state, 1991 to 1992	Model performance, outcomes, outlier determination.	Performance of administrative models diminished substantially when complications separated from co-morbidities (from c-index=0.78 to c-index=0.71 and c-index=0.73).  NY clinical registry-based model based on all patients had best performance (c-statistic=0.813).  Different risk-adjusted mortality rates and outliers using administrative vs. clinical data.  Clinical database better for profiling  Performance of administrative models improved by adding a few clinical variables
<a href="#">Clinical versus administrative data bases for CABG. Does it matter?</a> 1992 (196)	To compare the ability of clinical and administrative databases to predict CABG mortality and assess provider performance.	Observational, comparing NY clinical and administrative databases.	22, 827 CABG patients	NY CABG patients, 1989 to 1990	Risk factor coding, observed and risk-adjusted mortality, outlier determination.	Substantial differences between databases in risk factor coding.  For some hospitals, substantial differences between risk-adjusted mortality rates and ranking determined by administrative model and clinical model (the gold standard).  Clinical data much better at predicting mortality and for use in profiling.  Administrative model can be improved with the addition of some clinical variables.
<a href="#">Does reporting of</a>	To assess accuracy of CABG	Observational,	1,121 confirmed	Single hospital isolated	Case volumes and mortality rates	Case volumes over-reported as much as 21% in

<a href="#">coronary artery bypass grafting from administrative databases accurately reflect actual clinical outcomes?</a> 2005 (197)	outcomes from administrative databases	comparing STS database results with those from 4 administrative data sources and risk models.	CABG patients	CABG 1999 to 2001		<p>all patients, underreported up to 16% or more in Medicare patients</p> <p>Mortality in administrative data exceeded that in clinical data by 21%.</p> <p>Different administrative data-derived risk models had risk-adjusted mortality rates that exceeded STS rates by as much as 61%</p>
<a href="#">Comparison of clinical and administrative data sources for hospital coronary artery bypass graft report cards.</a> 2007 (198)	To compare the accuracy of administrative and clinical data sources for public report cards.	Observational, comparing audited, clinical registry and state administrative data.	4,440 isolated CABG in audited clinical registry, 5,657 “CABG” in state administrative data.	MA CABG patients, FY 2003	Observed and risk-adjusted mortality, outliers.	<p>27% higher number of patients (5,657 vs. 4,440 actual) in administrative data due to inappropriate inclusion of nonisolated CABG cases.</p> <p>Administrative data in-hospital mortality 2.88% vs. 2.05% in audited clinical registry.</p> <p>Differences in risk-adjusted mortality rates and outliers between administrative and clinical data based-models.</p> <p>Recommend clinical data for profiling.</p>
<a href="#">Mortality after cardiac bypass surgery: prediction from administrative versus clinical data.</a> 2005 (199)	To compare mortality prediction and outlier determination from administrative vs. clinical data.	Observational	15,288 CABG patients	43 VA hospitals, October 1, 1993, to March 30, 1996	Model performance, risk-adjusted mortality rates, outliers.	<p>Administrative model c-index=0.698, clinical model c-index=0.761.</p> <p>6 hospitals (14%) changed more than 2 deciles in rank when using administrative vs. clinical data.</p> <p>Administrative models identified only 2 of 6 high and 1 of 4 low outlier hospitals determined by the clinical model.</p> <p>Clinical models have better performance, but administrative models can be improved by adding clinical variables</p>
<a href="#">Assessing the outcomes of coronary artery bypass graft: how many risk factors are enough?</a> 1997 (200)	To determine the impact of number of risk factors on the accuracy of risk-adjusted mortality rates.	Observational, comparing the results of models using an increasing number of risk factors.	5,517 isolated CABG patients.	Ontario, FY 1993, 9 hospitals.	Model performance, risk adjusted mortality rates, and rankings.	<p>Model performance stable after the inclusion of 6 core clinical variables (c-index=0.77).</p> <p>In comparison with unadjusted results, 6-variable clinical model resulted in a change in risk-adjusted mortality rates and rankings for</p>

						most hospitals.
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CABG, coronary artery bypass graft; FY; fiscal year; MA, Massachusetts; NY, New York; STS, Society of Thoracic Surgeons; VA, Veterans Administration; and WI, Wisconsin.

Data Supplement 32. Outcomes or Volume as CABG Quality Measures

Article Name	Aim of Study	Study Design	Study Size	Patient population/Year/Hospital	Endpoints	Results
<a href="#">Should operations be regionalized? The empirical relation between surgical volume and mortality.</a> 1979 (201)	To determine the impact of volume on mortality.	Observational	34,505 CABG patients	CABG patients/1974 to 1975/The Professional Activity Study Database.	Adjusted mortality	Mortality 5.7% for ≤200 CABG; 3.4% for >200 CABG.
<a href="#">Hospital volume and surgical mortality in the United States.</a> 2002 (202)	To determine the association between procedural volume and mortality.	Observational	901,667 CABG patients	Medicare CABG patients/ 1994 to 1999/1,068 hospitals.	Adjusted mortality	Continuous inverse association between volume and outcome.  Adjusted mortality 5.6% for <230 procedures vs. 4.5% for >849 procedures.  Relatively weak association compared to other procedures.
<a href="#">Association of volume with outcome of CABG. Scheduled vs. nonscheduled operations.</a> 1987 (203)	To determine volume-outcome association for scheduled vs. nonscheduled operations.	Observational	18,986 CABG patients	CA CABG patients/1983/ 77 hospitals	Adjusted mortality	Patients undergoing CABG in hospitals with volume >350 cases had lowest mortality, and this effect was most pronounced in nonscheduled cases.
<a href="#">Regionalization of cardiac surgery in the United States and Canada. Geographic access, choice, and outcomes.</a> 1995 (204)	To determine the impact of CABG regionalization.	Observational	116,593 CABG patients	CABG patients in NY, Canada, and CA/1987 to 1989.	Adjusted mortality	Highest adjusted mortality rate (4.7%) in CA CABG patients having surgery at hospitals with annual volume <100 CABG.
<a href="#">CABG: the relationship between in-hospital mortality rate and surgical volume after controlling for clinical risk factors.</a> 1991 (205)	To determine association of hospital and surgeon volume with CABG outcome.	Observational	12,448 CABG patients	NY isolated CABG patients/1989/126 surgeons, 30 hospitals  Cardiac Surgery Reporting System.	Risk-adjusted mortality	Overall crude mortality rate 3.68%.  Crude mortality rates decrease monotonically from 5.38% for hospital volumes 1 to 199 to 3.08% for hospital volumes ≥890.  Hospital risk-adjusted mortality rates decrease



						<p>monotonically from 7.25% to 2.85%.</p> <p>Crude mortality rates decrease monotonically from 9.09% for annual surgeon volumes between 1 to 54 to 2.89% for annual surgeon volumes <math>\geq 260</math>.</p> <p>Risk-adjusted rates decrease from 8.14% for patients of surgeons with volumes <math>&lt;55</math> to 2.43% for patients of surgeons with volumes <math>\geq 260</math>.</p> <p>Best results (risk-adjusted mortality 2.18%) in hospitals performing <math>\geq 890</math> cardiac operations in 1989 and from surgeons performing <math>\geq 260</math> cardiac operations.</p>
<a href="#">The decline in CABG mortality in New York State. The role of surgeon volume.</a> 1995 (206)	<p>To examine the longitudinal relationship between surgeon volume and in-hospital mortality for CABG in NY.</p> <p>To explain changes in mortality over time.</p>	Observational	57,187 isolated CABG patients	1989 to 1992/30 NY CABG hospitals	Risk adjusted mortality	<p>Risk-adjusted in-hospital mortality decreased for all surgeon volume categories.</p> <p>Low-volume surgeons (<math>\leq 50</math> CABG/y) had largest reduction (60%) in risk-adjusted mortality over 4-y.</p> <p>Highest-volume surgeons (<math>&gt;150</math> CABG/y) had 34% reduction.</p> <p>Percentage of patients having CABG by low-volume surgeons decreased from 7.6% in 1989 to 5.7% in 1992 (25% reduction).</p> <p>Part of decrease due to exodus of low-volume surgeons with high risk-adjusted mortality; better performance of surgeons who were new to the system; and performance of surgeons who were not consistently low-volume surgeons.</p>
<a href="#">Volume and outcome in CABG: true association or artifact?</a> 1995 (207)	To assess impact of case-mix on CABG volume-outcome studies	Systematic review		<p>1972 to 1992</p> <p>7 studies of CABG volume-outcome association</p> <p>US data</p>	CABG mortality	<p>All 7 studies reported reduced mortality with increased volume.</p> <p>Studies with better case-mix adjustment indicated less reduction in mortality with increased volume (<math>p=0.04</math>).</p> <p>Apparent advantages of higher volume decreased over time (<math>p&lt;0.001</math>).</p>
<a href="#">Do hospitals and surgeons with higher CABG volumes still have lower risk-adjusted</a>	To investigate the CABG volume outcome association with	Observational	57,150 isolated CABG patients	NY CABG patients/1997 to 1999	Risk-adjusted in-hospital mortality	Significantly lower risk-adjusted mortality rates observed above all annual hospital volume thresholds between 200 to 800 and above all surgeon volume

<a href="#">mortality rates?</a> 2003 (208)	contemporary data.			Cardiac Surgery Reporting System		<p>thresholds between 50 to 200.</p> <p>Risk-adjusted mortality rate for surgeons with volumes of <math>\geq 125</math> in hospitals with volumes of <math>\geq 600</math> was 1.89%. Risk-adjusted mortality significantly higher (2.67%) for surgeons with volumes of <math>&lt;125</math> in hospitals with volumes of <math>&lt;600</math>.</p>
<a href="#">Is the impact of hospital and surgeon volumes on the in-hospital mortality rate for CABG limited to patients at high risk?</a> 2004 (209)	To determine if volume-outcome association only valid for high-risk patients.	Observational	57,150 isolated CABG patients	NY CABG patients (Cardiac Surgery Reporting System)/1997 to 1999.	Risk-adjusted in-hospital mortality	<p>For annual hospital volume thresholds between 200 and 600 cases, adjusted ORs of mortality for high-volume to low-volume hospitals =0.45 to 0.77 (all significant) for low-risk group.</p> <p>For moderate- to high-risk group, OR: 0.62 to 0.91 (most significant).</p> <p>As annual surgeon volume threshold increased from 50 to 150 cases, ORs for high- to low-volume surgeons increased from 0.43 to 0.74 for low-risk group.</p> <p>For the moderate- to high-risk group, ORs ranged from 0.79 to 0.86. Compared with patients treated by surgeons with volumes of <math>&lt;125</math> in hospitals with volumes of <math>&lt;600</math>, patients treated by higher-volume surgeons in higher-volume hospitals had significantly lower risk of death (OR: 0.52 for low-risk group).</p> <p>Higher volume associated with better outcomes for all risk groups.</p>
<a href="#">Outcome as a function of annual CABG volume.</a> 1996 (210)	To determine association between risk-adjusted CABG mortality and volume.	Observational	124,793 CABG patients	<p>Isolated CABG patients/1991 to 1993/<math>&gt;600</math> US hospitals.</p> <p>STS-NCD</p> <p>1,200 surgeons</p>		<p>Variability of outcome was significant in lower volume practices (<math>&lt;600</math> cases/y) and varied little at <math>&gt;600</math> cases/y.</p> <p>No practice volume category had an observed/expected ratio of less than 0.8 or <math>&gt;1.2</math> if annual volume was <math>&gt;100</math>.</p> <p>Practices of <math>&lt;100</math> cases/y had an observed/expected ratio of 1.6.</p>
<a href="#">No continuous relationship between Veterans Affairs hospital coronary artery</a>	To determine association between CABG volume and outcome in VA	Observational	23,986 CABG	CABG patients/April 1987 to September 1992/44 VA hospitals.	30-d risk-adjusted mortality	No statistically significant relationship between CABG volume and risk-adjusted operative mortality ( $p=0.10$ ).

<a href="#">bypass grafting surgical volume and operative mortality.</a> 1996 (211)	hospitals.					<p>Using ANOVA, hospitals with <math>\leq 100</math> cases per y have higher observed to expected mortality ratios than hospitals performing <math>&gt;100</math> cases per y (<math>p=0.03</math>).</p> <p>Using Poisson regression models, volume threshold not found.</p>
<a href="#">Hospital CABG volume and patient mortality, 1998 to 2000.</a> 2004 (212)	To assess the volume-outcome association for CABG	Observational	228,738 CABG patients	1998 to 2000 Nationwide Inpatient Sample	In-hospital mortality by hospital CABG volume group (low=12 to 249 cases/y, medium=250 to 499 cases/y, high $\geq 500$ cases/y)	<p>Crude in-hospital mortality rates=4.21% in low volume hospitals, 3.74% in medium-volume hospitals, and 3.54% in high-volume hospitals (trend <math>p&lt;0.001</math>).</p> <p>Compared with high-volume hospitals, patients at low-volume hospitals had increased adjusted mortality risk (OR: 1.26; 95% CI: 1.15 to 1.39), as did medium volume hospitals (OR: 1.11; 95% CI: 1.01 to 1.21).</p> <p>Considerable outcomes heterogeneity at every volume level.</p> <p>207 of 243 (85%) low-volume and 151 of 169 (89%) medium-volume hospital-y had risk-standardized mortality rates that were statistically lower or comparable to expected.</p> <p>Only 11 of 169 (6%) high-volume hospital-y had outcomes that were statistically better than expected and 18 of 161 (11%) high-volume hospital-y had worse than expected risk-standardized mortality rates.</p> <p>“Volume is not a reliable marker of hospital CABG quality”.</p>
<a href="#">Limitations of Hospital Volume as a Measure of Quality of Care for CABG.</a> 2005 (213)	To assess the association between CABG volume and outcomes	Observational	948,093 CABG procedures	Medicare CABG Patients/1996 to 2001/870 US hospitals.	Risk-adjusted mortality	<p>Considerable mortality heterogeneity at all volume levels.</p> <p>Volume alone a poor predictor of mortality (c-index=0.52), similar to “coin toss.”</p> <p>253 of 660 hospitals (38%) with volume <math>&lt;450</math> cases annually had risk-adjusted mortality rates similar to or lower than the overall risk-adjusted mortality of high-volume hospitals (5.2%).</p>

<a href="#">Association of hospital coronary artery bypass volume with processes of care, mortality, morbidity, and the STS Surgeons composite quality score.</a> 2010 (214)	To examine the association of CABG volume and mortality, morbidity, processes of care, and STS CABG composite score.	Observational	144,526 isolated CABG patients	Isolated CABG patients/2007/733 hospitals participating in the STS-NCD.	Risk-adjusted mortality, morbidity, NQF process measure adherence.	<p>Unadjusted mortality decreased across volume categories (2.6% for &lt;100 cases, 1.7% for &gt;450 cases; p&lt;0.0001).</p> <p>After multivariable adjustment, mortality OR: 1.49 (lowest vs. highest volume).</p> <p>Most care processes and morbidity not associated with volume.</p> <p>Lowest volume group (&lt;100 cases) had lowest composite scores but volume only explained 1% of latter.</p> <p>Considerable performance heterogeneity at low volumes, and low volume did not preclude excellent performance.</p>
<a href="#">Volume and outcome of CABG: are more and less the same?</a> 2004 (215)	To assess changes in the CABG volume-outcome association over time.	Systematic review		<p>16 CABG volume-outcome studies (1980 to 2002).</p> <p>High and low volume cohorts (200 case cut-point).</p>		<p>Progressive increase of OR favoring high volume hospitals from 0.55 in 1972 to 0.95±0.07.</p> <p>All OR estimates per 100 patients close to 1.0, suggesting minimal effect of volume on mortality.</p>
<a href="#">The role of hospital volume in coronary artery bypass grafting: is more always better?</a> 2001 (216)	To determine if low risk patients have improved outcomes at high volume hospitals.	Observational study	<p>2,029 CABG patients at 25 low-volume hospitals.</p> <p>11,615 CABG patients at 31 high-volume (≥200 annual cases) hospitals.</p>	<p>1997 administrative and clinical data from Solucient EXPLORE.</p> <p>Patients classified into 5 surgical risk groups: minimal (&lt;0.5%), low (0.5% to 2%), moderate (2% to 5%), high (5% to 20%), and severe (≥20%).</p>	In-hospital mortality, costs and LOS	<p>Significant differences in in-hospital mortality between low- and high-volume facilities in moderate (5.3% vs. 2.2%; p=0.007) and high risk (22.6% vs. 11.9%; p=0.0026) but not minimal, low- or severe-risk patients.</p> <p>Hospital costs and LOS similar across risk groups.</p> <p>Targeted regionalization for moderate to higher risk patients feasible.</p>
<a href="#">Procedural volume as a marker of quality for CABG.</a> 2004 (217)	To determine the association between CABG volume and outcomes in a large clinical data registry.	Observational	267,089 isolated CABG procedures	January 1, 2000 to December 31, 2001/439 US hospitals participating in the STS-NCD.	Adjusted operative mortality	<p>Adjusted rates of operative mortality decreased with increasing hospital CABG volume (0.07% for every 100 additional CABG procedures; adjusted OR: 0.98; 95% CI: 0.96 to 0.99; p=0.004).</p> <p>Volume-mortality not observed in patients &lt;65 y or in those at low operative risk.</p>



						<p>Limited ability of hospital volume to discriminate performance due to the wide variability in risk-adjusted mortality among hospitals with similar volume.</p> <p>“...hospital procedural volume is only modestly associated with CABG outcomes and therefore may not be an adequate quality metric for CABG surgery.”</p>
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ANOVA indicates analysis of variance; CABG, coronary artery bypass graft; CA, California; HR, hazard ratio; LOS, length of stay; NQF, National Quality Forum; NY, New York; OR, odds ratio; STS, Society of Thoracic Surgeons; STS-NCD, Society of Thoracic Surgeons-National Cardiac Database; US, United States; VA, Veterans Affairs; and y, year.

**Data Supplement 33. Use of Epiaortic Ultrasound Imaging to Reduce Stroke Rates**

Study	Sample Characteristics	Sample Size	Stroke Rate: On-Pump	Stroke Rate: Off-Pump	P-Value	Interval Between Surgery and Outcome
<a href="#">ROOBY</a> 2009 (218)	All male	2203	0.7%	1.3%	p=0.28 (NS)	30 d
<a href="#">Nathoe et al.</a> , 2003 (Octopus) (219)	Low-risk patients	281	1.4%	0.7%	p=0.55 (NS)	1 y
<a href="#">SMART</a> 2004 (220)	Single surgeon	197	2.0%	1.0%	(NS)	30 d
<a href="#">Best Bypass Surgery trial</a> 2010 (221)	High-risk patients	341	3.7%	4.0%	p=1.00 (NS)	>30 d
<a href="#">BHACAS 1 / 2</a> 2002 (222)	Single institution	401	3%/ 3%	2%/ 1%	(NS)	>30 d
<a href="#">Legare</a> 2004 (223)	Single-center trial	300	0.0%	1.3%	p=0.50 (NS)	In-hospital
<a href="#">Muneretto</a> 2003 (224)	Low-risk	176	2.2%	0.0%	(NS)	“early” outcome

BHACAS indicates Beating heart against cardioplegic arrest studies; d, day; NS, non-significant; Rooby, Randomized On/Off Trial; SMART, Surgical Management of Arterial Revascularization Therapies and y, year.

**Data Supplement 34. Randomized Trials Comparing Cognitive Outcomes After On-Pump And Off-Pump Surgery: Postoperative Cognitive Impairment**

Study	Year Published	Sample Characteristics	Sample Size	Follow-Up Interval	Incidence of Decline		P-Value/Comments
					On-Pump/Off-pump		
Van Dijk D et al. (Octopus Trial) ( <a href="#">225</a> , <a href="#">226</a> )	2002	Low risk Patients	281	3 mo	29%	21%	NS
	2007			12 mo	34%	31%	NS
				5 y	35%	33%	NS

<a href="#">St. Francis Medical Center</a> (227)	2003	Single center	60	2 wk	15%	16%	NS
				12 mo	15%	19%	NS
<a href="#">Lund</a> (228)	2005	Single center	120	3 mo	23%	20%	NS
				12 mo	23%	24%	NS
Jenson (substudy of Best Bypass Surgery trial) ( <a href="#">229</a> , <a href="#">230</a> )	2006	High-risk patients	120	3 mon	24%	20%	NS
	2008			1 y	19%	9%	NS
<a href="#">Ernest</a> (231)	2006	Single institution	107	2 mo	N/A	N/A	No difference in incidence of cognitive impairment
				6 mo	N/A	N/A	Lower incidence of cognitive impairment in off-pump group for 1 test (word fluency)
<a href="#">Al-Ruzzeh</a> (232)		Single institution	168	6 wk	N/A	N/A	Off-pump performed significantly better in 3/15 tests (p≤0.001)
				6 mo	N/A	N/A	Off-pump group performed significantly better in 2/15 tests (p<0.001)
<a href="#">Vedin</a> (233)	2006	Single institution	70	1 wk	57%	58%	NS
				1 mo	30%	12%	NS
				6 mo	19%	15%	NS
<a href="#">Motallebzadeh</a> (234)	2007	Single institution	212	Discharge	N/A	N/A	Higher global composite cognitive score (0.25 standard deviation) in the off-pump group (p=0.01)
				6 mo	N/A	N/A	No SD in global composite score between on-pump and off-pump groups
				6 mo	N/A	N/A	No SD in global composite score between on-pump and off-pump groups
<a href="#">Hernandez</a> (235)	2007	Single institution	201	Discharge	62%	52%	NS
				6 mo	47%	44%	NS
<a href="#">ROOBY</a> (218)	2009	VA Medical Centers	2203	1 y	N/A	N/A	No difference between on- and off-pump in change in global z-score from baseline to follow-up

Mo indicates month; N/A, not applicable; NS, not significant; Rooby indicates Randomized On/Off Trial; SD, significant difference; VA, Veteran Affairs; wk, week and y, year.

**Data Supplement 35. Mediastinitis and Perioperative Infection**

Study Name	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P Values & 95% CI	OR / HR / RR	Study Summary
				Inclusion Criteria	Exclusion Criteria	Primary Endpoint	Secondary Endpoint				
<a href="#">Impact of DSWI management with VAC therapy followed by sternal osteosynthesis: a 15-y review of 23,499 sternotomies. 2010 (236)</a>	To examine the outcome of patients with DSWI now treated with VAC therapy as a bridge to sternal osteosynthesis with horizontal titanium plate fixation	Part of the data was collected retrospectively, and part - prospectively	23,499 total number of patients (267 patients with DSWI)	All patients undergoing open heart surgery	Patients undergoing thoracic aortic surgery or heart transplantation as well as congenital cases were all excluded from the present study	DSWI rate	Early hospital mortality, hospital stay, DSWI recurrence, 1-, 2- and 3-y survival	VAC therapy (n=125) was associated with a lower mortality (4.8% vs. 14.1%, p=0.01). Early adjusted survival for patients with DSWI treated with VAC therapy was 92.8%, 89.8% and 88.0%, respectively, at 1-, 2- and 3-y, compared with 83.0%, 76.4% and 61.3%, respectively, for patients with DSWI treated without VAC (p=0.02).	p=0.01 (mortality), p=0.02 (1-, 2- and 3-survival)	N/A	DSWI remains a major and challenging complication of OHS. VAC therapy with sternal preservation followed by delayed sternal osteosynthesis and pectoralis myocutaneous flaps has been recently proposed as a new therapeutic strategy. Most patients treated with VAC therapy showed decreased perioperative mortality and increased survival.
<a href="#">VAC of DSWI in high-risk patients after cardiac surgery. 2005 (237)</a>	To examine the effect of VAC on sternal wounds	Prospective	22	All cardiac surgery patients who developed DSWI	N/A	Reduction of wound size	Need for secondary surgical intervention, LOS, VAC complications	VAC induced granulation of 71% of the sternal wound area by 7 d. By 14 d, there was a 54% reduction in wound size, and patients were discharged after approximately 19.5 d and placed on home therapy. VAC was discontinued at approximately 36.7 d with an average reduction in sternal wound size of 80%. Extensive secondary surgical closure, requiring muscle flaps, was avoided in 64% of patients, whereas 28% of patients required	p<0.05 (reduction of wound size)	N/A	Adjunctive VAC therapy markedly reduced required surgical interventions, reoperation for persistent infections, and the hospitalization period. VAC provides a viable and efficacious adjunctive method by which to treat postoperative wound infection after medial sternotomy.

								no surgical reconstruction for wound closure.			
<a href="#">The VAC system for the treatment of DSWI after cardiac surgery.</a> 2002 (238)	To report an experience with the VAC system (KCI Inc., San Antonio, TX) as an adjunct in the treatment of DSWI after cardiac surgery	Prospective	11	Patients with DSWI after cardiac surgery	N/A	Length of ICU and hospital stay	In-hospital mortality, 30-d survival, complication rate	Median ICU stay of patients treated with pectoralis muscle flap closure without pretreatment with the VAC system was 9.5 d (range 4 to 26 d), whereas patients with VAC treatment had an ICU stay of median 1 d (range 1 to 4 d).	N/A	N/A	In-hospital mortality was 0%, and 30-d survival was 100%. Median hospital stay ranged from 13 to 45 d (median 30 d). Most importantly, there were no VAC device–related complications.
<a href="#">VAC as a treatment modality for infections after cardiac surgery.</a> 2003 (239)	To assess the impact of VAC on the management of sternal wound infections in terms of wound healing, duration of VAC, and cost of treatment	Prospective	27	Patients who underwent cardiac surgery through a median sternotomy and acquired sternal wound infections	N/A	Mortality	Healed scar (%), duration of VAC, LOS, cost of treatment	VAC-group mortality was 28.6% vs. 7.7% in VAC+ second procedure group. A satisfactorily healed scar was achieved in 64% of VAC-cases and in 77% of VAC+ second procedure cases. Median durations of VAC in VAC-group were 13.5 d (interquartile range 8.8 to 32.2 d), and median hospital stay was 20 d (interquartile range 16.7 to 25.2 d). Median duration of vacuum-assisted closure in VAC+ second procedure group was 8 d (interquartile range 5.5 to 18 d), and median hospital stay was 29 d (interquartile range 25.8 to 38.2 d). The total cost (hospitalization and treatment) per patient for VAC was \$16,400, compared with \$20,000 for the closed irrigation	N/A	N/A	VAC, used alone or before other surgical treatment strategies, is an acceptable treatment modality for infections in cardiac surgery with reasonable morbidity, mortality, and cost.



								system treatment.			
<a href="#">The concept of NPWT after poststernotomy mediastinitis--a single center experience with 54 patients.</a> 2009 (240)	To report an experience of using NPWT followed by muscular pectoralis plasty in treatment of DSIs after cardiac surgery procedures	Prospective	3,668 total number of patients/54 patients with DSI	Patients with DSI after cardiac surgery procedures.	N/A	DSI rate	LOS, time from operation to detection of mediastinitis, time from the start of the NPWT therapy until date of discharge, complication rate	The detection of DSI and subsequent treatment with NPWT of the patients is clearly prolonged: the period of time that patients stayed in hospital ranged from 22 d up to 185 d (median 64.5 d). The time period from the date of operation until detection of mediastinitis ranged from 5 d to 155 d (19 d). Time period from the start of the NPWT therapy until date of discharge from hospital ranged from 7 d until 99 d with a median at 35 d. No complications were found in 74% of patients.	N/A	N/A	In line with the mentioned articles and reviews we come to the conclusion, that negative pressure wound treatment is a relatively new option for treatment of devastating wounds after sternotomy in cardiac surgery. As many institutions have presented their own approaches, it is important to find a strategy which may be used as a "standard NPWT approach" if identified in the future.
<a href="#">Management of the infected median sternotomy wound with muscle flaps. The Emory 20-y experience.</a> 1997 (241)	To report on morbidity and mortality in patients treated for DSWI with sternal debridment and flap	Retrospective	409	Patients who developed DSWI after cardiac surgery	N/A	Mortality/morbidity	N/A	Mean hospital stay after sternal wound reconstruction declined from 18.6 d (1988 to 1992) to 12.4 d (1993 to 1996)	(p=0.005)	N/A	With aggressive early debridment and flap the mortality and hospital stay after DSWI has decreased over time
<a href="#">Prospective trial of catheter irrigation and muscle flaps for sternal wound infection.</a> 1998 (242)	To determine the appropriate roles of closed-chest catheter irrigation and muscle flap closure for sternotomy infection	Prospective	43	Patients with sternal dehiscence or infection	N/A	Wound resolution	LOS, rate of complications	N/A	N/A	N/A	Irritation alone failed in 88% of patients with DSWI. All patients treated with flap had a successful outcome.
<a href="#">Two-stage</a>	To report on	Retrospective	68	Patients with	N/A	Mortality/mor	N/A	91% survival at 1 y and	N/A		N/A

<a href="#">management of sternal wound infection using bilateral pectoralis major advancement flap</a> . 2006 (243)	morbidity and mortality in patients treated for DSWI with sternal debridment and flap	ve		DSWI after cardiac surgery		bidity		0% mortality for patients treated with flap after DSWI .			
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CI, indicates confidence interval; d, day; DSI, deep sternal infection; DSWI, deep sternal wound infection; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; N/A, not applicable; NPWT, negative pressure wound therapy; OHS, open heart surgery; OR, odds ratio; RR, relative risk; and VAC, vacuum-assisted closure.

Data Supplement 36. Mediastinitis and Perioperative Infection

Study Name	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P-Values & 95% CI	OR / HR / RR (95% CI)	Study Summary
				<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>Primary Endpoint</i>	<i>Secondary Endpoint</i>				
<a href="#">Glycopeptides are no more effective than beta-lactam agents for prevention of SSI after cardiac surgery: a meta-analysis</a> . 2004 (244)	To investigate whether a switch from beta-lactams to glycopeptides for cardiac surgery prophylaxis should be advised.	Meta-analysis	5,761	Trials that compared SSI in subjects receiving glycopeptide prophylaxis with SSI in those who received beta-lactam prophylaxis were pooled	N/A	Occurrence of SSI at 30 d	Chest SSI, Deep-chest SSI, Leg SSI, SSI due to different microorganism s	N/A	N/A	SSI RR: 1.14; (95% CI: 0.91 to 1.42) Chest SSI RR: 1.47; (95% CI: 1.11 to 1.95) Deep-chest SSI RR: 1.33; (95% CI: 0.91 to 1.94) Leg SSI RR: 0.77; (95% CI: 0.58 to 1.01) SSI due to gram positive bacteria RR: 1.36; (95% CI: 0.98 to 1.91) SSI due to meticillin-resistant gram-positive bacteria RR: 0.54; (95% CI: 0.33 to 0.90) SSI due to other organism RR: 1.08; (95% CI: 0.75 to 1.55)	Neither agent proved to be superior for prevention of the primary outcome, occurrence of SSI at 30 d. In subanalyses, beta-lactams were superior to glycopeptides for prevention of chest SSI and approached superiority for prevention of deep-chest SSI and SSI caused by gram-positive bacteria. Glycopeptides approached superiority to beta-lactams for prevention of leg SSI and were superior for prevention of SSI caused by methicillin-resistant gram-positive bacteria. Standard prophylaxis for cardiac surgery should continue to be beta-lactams in most circumstances.
<a href="#">Vancomycin versus cefazolin prophylaxis for</a>	This study was undertaken to	RCT	885	All adult patients (≥18 y) scheduled for cardiac	Exclusion criteria included the	SSI rates	Duration of postoperative hospitalizatio	The overall SSI rates were similar in the 2	p=0.8 (overall SSI)	N/A	The durations of postoperative hospitalization and the mortalities were

<a href="#">cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections.</a> 2002 (245)	compare the efficacy of vancomycin prophylaxis with that of cefazolin in preventing SSI in a tertiary medical center with a high prevalence of methicillin-resistant staphylococcal infections.			surgery requiring sternotomy were considered eligible for the trial.	presence of active infection, the use of antibiotics within 2 wk before the operation, and a previous cardiac operation requiring sternotomy within 1 y of enrollment in this trial.		n, mortality, characteristic s of microorganisms isolated from the infection site	groups (43 cases in the vancomycin group, 9.5%, vs. 39 cases in the cefazolin group, 9.0%, p=0.8). Superficial and deep incisional SSI rates were also similar in the 2 groups. SSI caused by methicillin-susceptible staphylococci were significantly more common in the vancomycin group (17 cases, 3.7%, vs. 6 cases, 1.3%; p=0.04).			similar in the 2 groups. This trial suggests that vancomycin and cefazolin have similar efficacy in preventing SSI in cardiac surgery.
<a href="#">Comparative study of cefazolin, cefamandole, and vancomycin for surgical prophylaxis in cardiac and vascular operations: a double-blind randomized trial.</a> 1992 (246)	To compare 3 regimens, using intravenous cefazolin, cefamandole, or vancomycin for prophylaxis against SSI.	RCT	321	Adult patients undergoing cardiac or major vascular operations who did not have renal disease or evidence of infection at the time of operation and had not had a known adverse reaction to a beta-lactam antibiotic or vancomycin were eligible for participation in	Patients with renal disease or evidence of infection at the time of operation and with a known adverse reaction to a beta-lactam antibiotic or vancomycin were excluded.	The prevalence of surgical wound infection	The mean duration of postoperative hospitalization, adverse effects	The prevalence of surgical wound infection was lowest with vancomycin (4 infections [3.7%] vs. 14 [12.3%] and 13 [11.5%] in the cefazolin and cefamandole groups, respectively; p=0.05); there were no thoracic wound infections in	p=0.05 (prevalence of surgical wound infections in vancomycin group vs. cefazolin and cefamandole)	N/A	Vancomycin deserves consideration for inclusion in the prophylactic regimen (1) for prosthetic valve replacement and prosthetic vascular graft implantation, to reduce the risk of implant infection by methicillin-resistant coagulase-negative staphylococci and enterococci; (2) for any cardiovascular operation if the patient has recently received broad-spectrum antimicrobial therapy; and (3) for all CV operations in centers with a high

				this study.				cardiac operations in the vancomycin group (p=0.04). The mean duration of postoperative hospitalization was lowest in the vancomycin group (10.1 d; p<0.01) and highest in the cefazolin group (12.9 d). Thus, administration of vancomycin (approximately 15 mg/kg), immediately preoperatively, provides therapeutic blood levels for surgical prophylaxis throughout most cardiac and vascular operations, resulting in protection against postoperative infection superior to that obtained with cefazolin or cefamandole.			prevalence of surgical infection with methicillin-resistant staphylococci or enterococci.
<a href="#">Comparative efficacy of teicoplanin and</a>	The primary objective of the study was	RCT	3,027	Adult (≥18 y of age) patients undergoing	Exclusion criteria included the	SSI rates at hospital discharge, 30 d	Bacteremia, respiratory infections,	Thirty day postoperatively, there was a	p=0.032 (DSWI at 6 mo)	N/A	Cefazolin was more effective prophylaxis than teicoplanin against



<a href="#">cefazolin for cardiac operation prophylaxis in 3,027 patients.</a> 2000 (247)	to compare the efficacy of single-dose teicoplanin with multiple-dose cefazolin in the prophylaxis of SSI 1 mo after elective cardiac operations. Secondary objectives were to compare both drugs in the prevention of SSI at the time of hospital discharge and 6 mo postoperatively; to compare both drugs in the prevention of nonsurgical infections, noninfectious complications, and mortality at discharge, 1 mo, and 6 mo after the operation; to compare the microorganisms			elective CABG, valve operations (replacement or repair), or both were eligible for the trial.	following: patients who were pregnant and those who had previously undergone sternotomy procedures; patients with severe concomitant diseases, such as the immunocompromised; patients who were morbidly obese; and individuals with osteotomies. Medically unstable patients and those with VAD and/or requiring IABPs, transplant, or total artificial hearts were not enrolled. Patients who had received systemic antibiotics in the preoperative w and those	postoperatively, 6 mo postoperatively	UTI at hospital discharge, 30 d postoperatively, 6 mo postoperatively	trend to more deep sternotomy wound infections in the teicoplanin group (31 vs. 18, p=0.087), which became significant by 6 m (36 vs. 19; p=0.032). Infection rates were low with either treatment.			postoperative wound infections after elective cardiac operations.
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	responsible for infections after operations; and to compare the safety of the 2 drugs.				allergic to glycopeptides , penicillins, or cephalosporins were not eligible. Active bacterial infections precluded entry into the study, but asymptomatic bacteriuria was allowed. Patients with serum creatinine levels of 250 μmol/L or more (2.8 mg/dL) or neutropenia of 1,000 cells/mm <sup>3</sup> or less were excluded. Use of an investigational drug or device in the 30 d before the operation was not allowed nor was prior participation in a trial with teicoplanin. Patients of mental						
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					capacity so limited as to preclude informed consent were not enrolled.						
<a href="#">Ceftriaxone versus vancomycin prophylaxis in CV surgery.</a> 1999 (248)	This study compared the efficacy of this narrow-spectrum glycopeptide 4 with a single dose of ceftriaxone.	RCT	200	All patients undergoing elective heart surgery	Patients with serum creatinine levels higher than 17 mg/L were excluded.	Overall rate of infections (wound infections, mediastinitis, asymptomatic bacteriuria, respiratory infections)	N/A	The overall infection rate was 13.4% in the ceftriaxone and 10.7% in the vancomycin group. 4 (4%) wound infections, including one mediastinitis, occurred in the ceftriaxone group and 5 (5%) in the vancomycin group, with no statistically significant difference.	NS	N/A	The findings of this study support the adequacy of a simple single dose of ceftriaxone prophylaxis in cardiac surgery, at least in hospitals with low incidence of vancomycin-resistant staphylococcal infections.
<a href="#">Comparison of vancomycin and cefuroxime for infection prophylaxis in coronary artery bypass surgery.</a> 1998 (249)	To investigate clinically significant differences between vancomycin and cefuroxime for perioperative infection prophylaxis in CABG.	RCT	884	All patients scheduled for CABG without valvular surgery	Patients with a known allergy to cephalosporins or vancomycin, an active infection, or who had received prescribed antibiotic within the previous 2 wk, were excluded, as	Rate of in-hospital and late (1 mo) SSI	N/A	The overall immediate SSI rate was 3.2% in the cefuroxime group and 3.5% in the vancomycin group (difference, - 0.3; 95% CI: - 2.6 to 2.1).	NS	difference between proportions - 0.3 (95% CI: -2.6 to 2.1)	The data suggest that vancomycin has no clinically significant advantages over cephalosporin in terms of antimicrobial prophylaxis. We suggest that cefuroxime (or first-generation cephalosporins, which were not studied here) is a good choice for infection prophylaxis in connection with CABG in institutions without methicillin-resistant <i>Staphylococcus aureus</i> problems. In addition to the

					were patients undergoing a repeat bypass						increasing vancomycin-resistant enterococci problem, the easier administration and usually lower price of cefuroxime make it preferable to vancomycin.
<a href="#">Antibiotic prophylaxis in cardiac surgery: a prospective comparison of 2 dosage regimens of teicoplanin with a combination of flucloxacillin and tobramycin.</a> 1998 (250)	In this present study, the development of wound infection following cardiac surgery has been examined with a scoring method that measures the clinical appearance of the wound and any changes in management related to infection. In the paper there are 2 trials described, both compared different regimens of teicoplanin vs. flucloxacillin +tobramycin.	RCT (2 trials in 1 paper)	Trial 1: 314; Trial 2: 203	All patients undergoing cardiac surgery involving CPB were to be considered for the trial.	Exclusion criteria of age under 18 y, pregnancy, history of allergy to penicillin or vancomycin, serum creatinine over 150/anol/l, active infection or antibiotic treatment within the last 7 d, were agreed. Midstream urine specimens would be taken preoperatively and patients with more than 10 <sup>5</sup> Gramnegative bacteria per ml of urine were to be excluded unless a repeat	Wound scores	Rates of bacteremia, respiratory and urinary infections	Teicoplanin prophylaxis resulted in a significantly greater number of sternal wound infections (p<0.01), due to gram-positive bacteria. In the second trial the teicoplanin dose regimen was changed to three doses of 400 mg but this did not improve the rates of infection.	p<0.01	N/A	In the first trial, teicoplanin (400 mg on induction of anaesthesia and 200 mg 24 h later), was compared with tobramycin and flucloxacillin. Gram-negative bacteria were responsible for more respiratory and urinary infections after teicoplanin prophylaxis.



					specimen was shown to be sterile.						
<a href="#">Intraoperative and postoperative effects of vancomycin administration in cardiac surgery patients: a prospective, double-blind, randomized trial.</a> 1993 (251)	To compare 2 surgical population randomized to receive antibiotic prophylaxis consisting of either cefazolin or both cefasolin and vancomycin. In these groups norepinephrin use was compared.	RCT	58	Adult patients requiring elective CABG	Valvular heart disease requiring surgical repair or replacement, a history of prior open-heart surgery, LVEF of <0.4, emergency surgery, chronic renal insufficiency (creatinine of >1.8 mg/dL) or renal failure, a history of allergic or adverse reaction to cephalosporin antibiotics or vancomycin, chronic administratio n of calcium entry blockers (due to effects on the peripheral vascular system), pregnancy, prisoners, and the mentally impaired.	The rate and frequency of norepinephrine infusions	Hemodynami c data	In the vancomycin group, 50% of patients received a norepinephrine infusion in the intraoperative and/or postoperative period as compared with 14% in the normal saline group (p<0.01).	p<0.01	Not reported	The results show that a significantly greater number of patients who received vancomycin required a norepinephrine infusion and that, despite norepinephrine infusion therapy, systemic vascular resistance was not normalized in this group of patients. The study supports the conclusion that perioperative administration of vancomycin in cardiac surgery patients may result in hypotension requiring the use of a vasopressor in an attempt to normalize hemodynamic indices.

<a href="#">Clinical trial of cefamandole, cefazolin, and cefuroxime for antibiotic prophylaxis in cardiac operations.</a> 1993 (252)	<p>To compare 3 cephalosporins (cefazolin, cefamandole, cefuroxime) for antibiotic prophylaxis in cardiac surgery.</p>	RCT	1,641	N/A	N/A	Number of sites of infection	The depth of tissue involvement	<p>Of the 1,641 participants, 141 (8.6%) had <math>\geq 1</math> operative site infections: 46 of 549 (8.4%) cefamandole recipients, 46 of 547 (8.4%) cefazolin recipients, and 49 of 545 (9.0%) cefuroxime recipients (p=0.92). The sites of infection and the depth of tissue involvement were NS different across groups.</p>	NS	N/A	<p>Because no differences in effectiveness in preventing postoperative site infections were demonstrated in a rigorously designed trial, the costs of the drugs, including the costs of their preparation and delivery, may be the only variables by which to choose among these 3 antibiotic prophylaxis regimens.</p>
<a href="#">Efficacy of cefazolin, cefamandole, and gentamicin as prophylactic agents in cardiac surgery. Results of a prospective, randomized, double-blind trial in 1,030 patients</a> (253).	<p>To compare cefazolin vs cefamandole for antibiotic prophylaxis in cardiac surgery.</p>	RCT	1,030	<p>All adult patients scheduled for elective median sternotomy incision who were free of infection and not receiving any therapeutic antibiotics were considered eligible for inclusion in the study.</p>	<p>Patients who received antibiotics or patients with infections</p>	Sternal and donor site infection rates	Cost of hospitalization	<p>Patients receiving cefamandole-gentamicin had a significantly lower sternal wound infection rate than those receiving cefazolin-gentamicin (0% and 2.4%, respectively; p&lt;0.02). Patients receiving cefamandole</p>	<p>p&lt;0.02 (sternal wound infection rate with gentamicin added), p&lt;0.05 (sternal wound infection rate with or without gentamicin), p&lt;0.02 (donor site infection</p>	N/A	<p>These data suggest that , compared with cefamandole, cefazolin offers unreliable prophylaxis against deep infection at both the sternal and donor sites, and that gentamicin has no role as a prophylactic antibiotic in cardiac surgery.</p>

								with or without gentamicin had a significantly lower infection rate than patients receiving cefazolin with or without gentamicin at both the sternal (0.4% vs. 1.8%, p<0.05) and donor sites (0% vs.1.3%, p<0.02).	rate with or without gentamici n)		
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CABG indicates coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; CV, cardiovascular; d, day; DSWI, deep sternal wound infection; HR, hazard ratio; IABP, intra aortic balloon pump; LVEF, left ventricular ejection fraction; mon, month; N/A, not applicable; NS, non-significant; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SSI, surgical site infection; UTI, urinary tract infection; and VAD, ventricular assist device.

Data Supplement 37. Renal Dysfunction

Article Title	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P-Values & 95% CI	OR / HR / RR	Study Summary
				<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>Primary Endpoint</i>	<i>Secondary Endpoint</i>				
<a href="#">Efficacy of NAC in preventing renal injury after heart surgery: a systematic review of RCTs.</a> 2009 (254)	To assess the potential efficacy and adverse effects of perioperative NAC administration in adults undergoing cardiac surgery.	Systematic review and meta-analysis	1,163	RCTs of adults undergoing cardiac surgery, in which at least 1 of the treatment groups received NAC, administered orally or intravenously, immediately before, during, or immediately after cardiac surgery at any dose, for any length of time, with reported preoperative		Incidence of ARI	Maximum change in serum creatinine from baseline within 5 d following surgery, need for postoperative haemodialysis, all-cause mortality, and LOS in the ICU and the hospital.	Compared with placebo, NAC did not provide a statistically significant reduction in any of the assessed outcomes. There was no difference in the incidence of ARI [35% NAC vs. 37% placebo; RR: 0.91; 95% CI: 0.79 to 1.06; p=0.24] or maximum change in serum creatinine from baseline (0.32 mg/dL ±0.51 vs. 0.32 mg/dL	p=0.24 (incidence of ARI)	RR: 0.91; 95% CI: 0.79 to 1.06 (incidence of ARI)	NAC did not statistically reduce the length of ICU or hospital stay. However, there was a trend towards reduced ARI incidence among patients with baseline CKD randomized to NAC (RR: 0.86; 95% CI: 0.70 to1.05; p=0.14), particularly if NAC preparations were administered intravenously (RR: 0.80; 95% CI: 0.64 to 1.01; p=0.06).

				(baseline) and postoperative (within 5 d after surgery) creatinine levels or the incidence of ARI after heart surgery in each treatment group were included.				±0.47; p=0.95). Overall, 3.3% of patients required haemodialysis (NAC vs. placebo; RR: 1.13; 95% CI: 0.59 to 2.17) and 3% of patients died (RR: 1.10; 95% CI: 0.56 to 2.16).			
<a href="#">Effect of intravenous NAC on outcomes after CABG: a randomized, double-blind, placebo-controlled clinical trial.</a> 2007 (255)	To evaluate the effects of intravenous NAC on clinical and biochemical outcomes after CABG with CPB.	RCT	100	Patients undergoing primary CABG with CPB	Exclusion criteria were emergency operations, acute MI within <3 wk, prior cardiac surgery, age >80 y, EF<20%, and concomitant procedures.	The mean postoperative release of cardiac troponin T levels between the 2 groups (1-, 2-, 4-, 8-, 12-, and 24-h postoperatively, then 2-, 3-, and 4-d postoperatively)	The rate of MI (as defined by CK-MB level >50 and/or new Q wave on electrocardiogram in a given territory), renal function (creatinine), bleeding, low cardiac output syndromes, arrhythmias, and mean levels of CK-MB.	N/A	p=NS	N/A	No differences were noted in the incidence of renal dysfunction over a 4-d period after CPB comparing NAC-group and placebo-group.
<a href="#">Phase II, randomized, controlled trial of high-dose NAC in high-risk cardiac surgery patients.</a> 2007 (256)	To assess the effect of high-dose NAC on renal function in cardiac surgery patients at higher risk of postoperative renal failure	RCT	60	Patients at high-risk of postoperative renal dysfunction (age >70, preexisting renal impairment, NYHA 3/4, valve surgery or complex surgery, redo cardiac surgery, insulin-dependent diabetes mellitus) who were scheduled for elective or urgent cardiac surgery necessitating the use of CPB at 2 tertiary referral hospitals.	Exclusion criteria were age <18, allergy or hypersensitivity to NAC, emergency operations, planned off-pump surgery, enrolled in conflicting study. Known blood-borne infectious disease, chronic inflammatory	The absolute change in serum creatinine from baseline to peak level within the first 5 postoperative d.	The relative change in serum creatinine, the peak serum creatinine, the absolute and relative change in serum cystatin C, and the urinary output (to calculate the AKI rate), the use of renal replacement therapy, duration of ventilation, chest tube drainage, need for	There was no significant attenuation in the increase in serum creatinine from baseline to peak when comparing NAC with placebo (64.5±91.2 and 38.0±42.4 μmol/L, respectively; p=0.15). Also, there was no attenuation in the increase in serum cystatin C from baseline to peak for NAC compared with placebo (0.45±0.43	p=NS	N/A	There was no evidence for differences in any other clinical outcome.



					disease on immunosuppression, chronic moderate to high-dose corticosteroid therapy, ESRD, patients receiving IV nitrates.		return to operating room, prevalence of postoperative atrial fibrillation, and the duration of stay in the ICU and hospital	and 0.30±0.33 mg/L, respectively; p=0.40).			
<a href="#">The role of natriuretic peptide administration in CV surgery-associated renal dysfunction: a systematic review and meta-analysis of RCTs.</a> 2009 (257)	To systematically review these trials to ascertain the role of natriuretic peptide administration in the management of CV surgery-associated renal dysfunction.	Systematic review and meta-analysis	974	RCTs that compared any form or dose of natriuretic peptide with placebo in adult (age >18 y) patients undergoing CV surgeries, and that reported at least 1 of the following prespecified renal outcomes: ARF requiring dialysis, peak postsurgery serum creatinine levels, or postsurgery urine output.	The following studies were excluded: (1) nonrandomized trials, (2) duplicate publications, (3) those evaluating the role of natriuretic peptides in a noncardiovascular surgical setting (i.e., major abdominal surgery and radiocontrast nephropathy prevention), (4) experimental animal studies, and (5) those that did not report the prespecified renal outcomes (including those in which information on renal outcomes	ARF requiring dialysis, 30-d or in-hospital mortality	Peak postsurgery serum creatinine levels, postsurgery urine output, postsurgery serum aldosterone levels, duration of mechanical ventilation, and length of ICU stay.	A pooled estimate showed that the use of natriuretic peptide was associated with a reduction in ARF requiring dialysis (OR: 0.32; 95% CI: 0.15 to 0.66; p=0.002). Other benefits were a reduction in postsurgery peak serum creatinine levels (WMD/OR: -0.27; 95% CI: -0.38 to -0.16; p<0.002), an increase in postsurgery urine output (WMD/OR: 600; 95% CI: 330 to 870; p<0.001), a reduction in postsurgery serum aldosterone levels, and reductions in mechanical ventilation duration and ICU stay length.	p=0.002 for AKI requiring dialysis	OR: 0.32; 95% CI: 0.15 to 0.66 for AKI requiring dialysis	A pooled estimate showed that natriuretic peptide administration was not associated with a statistically significant reduction in mortality (OR: 0.59; 95% CI: 0.31 to 1.12; p=0.53).

					was not available despite contacting the original study authors).						
<a href="#">Beneficial impact of fenoldopam in critically ill patients with or at risk for ARF: a meta-analysis of randomized clinical trials.</a> 2007 (258)	To determine the impact of fenoldopam on AKI, patient mortality, and length of hospital stay in critically ill patients	Systematic review and meta-analysis	1,290	The following inclusion criteria were used for potentially relevant studies: (1) random allocation to treatment, (2) comparison of fenoldopam vs. control treatment, and (3) performed in surgical or intensive care patients (thus not including patients administered radiocontrast dye).	Exclusion criteria were: (1) studies selecting only patients undergoing procedures with angiographic contrast media, (2) nonparallel design (i.e., crossover) randomized trials, (3) duplicate publications (in this case, only the article reporting the longest follow-up was abstracted), (4) nonhuman experimental studies, and (5) no outcome data.	The number of patients progressing to AKI that requires at least 1 episode of RRT, the incidence of in-hospital mortality	The incidence of AKI and hypotension, peak serum creatinine levels, long-term survival, and the duration of ICU and hospital stays	Fenoldopam use decreased the risk of RRT (6.5% in the fenoldopam group vs. 10.4% in the control arm; OR: 0.54; 95% CI: 0.34 to 0.84; p=0.007) and of all-cause mortality (15.1% vs. 18.9%; OR: 0.64; 95% CI: 0.45 to 0.91; p=0.01), as well as AKI (16.0% vs. 28.3%; OR: 0.43; 95% CI: 0.32 to 0.59; p<0.001).	p=0.007 (for AKI requiring RRT); p=0.01 (for mortality); p<0.001 (for AKI).	OR: 0.54; 95% CI: 0.34 to 0.84 (for AKI requiring RRT); OR: 0.64; 95% CI: 0.45 to 0.91 (mortality), OR: 0.43; 95% CI: 0.32 to 0.59 (AKI).	N/A
<a href="#">Fenoldopam mesylate in early acute tubular necrosis: a randomized, double-blind,</a>	To study whether administration of low-dose fenoldopam during early ATN would decrease the	RCT	155	ICU patients with a serum creatinine level increasing to 50% > a normal baseline level (creatinine >1.5 mg/dL [ $>133 \mu\text{mol/L}$ ]) or a 25%	Exclusion criteria were a clinical diagnosis of ARF from causes other than ATN, ARF after renal	The incidence of dialysis therapy and/or all-cause mortality at 21 d.	N/A	Overall in critically ill patients, 27.5% in the fenoldopam group developed ATN compared with 38.7% in the placebo group (p=0.235). Similarly, there was no	p=0.049 for the incidence of ATN in cardiac surgery patients	N/A	There was no statistically significant difference in 21-d mortality rates between the 2 groups. However, fenoldopam reduced the incidence of ATN in postoperative cardiothoracic surgery patients with early ATN (17.6% vs. 38.8%; p=0.049).

<a href="#">placebo-controlled clinical trial.</a> 2005 (259)	need for dialysis therapy and/or incidence of death at 21 d.			increase > a baseline level >1.5 mg/dL (>133 µmol/L) during a single 24-h period were considered to have a diagnosis of ATN. Patients with ATN and MAP >70 mm Hg with adequate central venous pressure and administered no more than 2 vasopressors were eligible for study enrollment.	transplantation, and pregnancy			difference in the incidence of dialysis therapy between patients randomly assigned to fenoldopam.			
<a href="#">Fenoldopam infusion for renal protection in high-risk cardiac surgery patients: a randomized clinical study.</a> 2007 (260)	To evaluate the renoprotective effects of fenoldopam in patients at high risk of postoperative AKI undergoing elective cardiac surgery requiring CPB.	RCT	193	Patients were included if at least 1 of the following risk factors was present: preoperative serum creatinine >1.5 mg/dL, age >70 y, diabetes mellitus on insulin treatment, or prior cardiac surgery	Exclusion criteria were defined by age <18 y, preoperative use of inotropes, preoperative dialysis, and known allergy to fenoldopam mesylate.	AKI	Need for RRT	AKI developed in 12.6% patients receiving fenoldopam and in 27.6% patients receiving placebo (p=0.02), whereas renal replacement therapy was not required in fenoldopam group, but it was started in 8.2% patients in placebo group (p=0.004). Serum creatinine was similar at baseline (1.8±0.4 mg/dL vs. 1.9±0.3 mg/dL) in the fenoldopam and placebo groups but differed significantly (p<0.001 and p<0.001) 24 h (1.6±0.2 mg/dL vs. 2.5±0.6 mg/dL) and	p=0.02 (ATN rate), p=0.004 (need for RRT)	N/A	N/A

								48 h (1.5±0.3 mg/dL vs. 2.8±0.4 mg/dL) after the operation.			
<a href="#">Effects of fenoldopam infusion in complex cardiac surgical operations: a prospective, randomized, double-blind, placebo-controlled study.</a> 2010 (261)	To determine the effects of fenoldopam in a population of patients undergoing complex cardiac operations.	RCT	80	Patients scheduled for elective cardiac operations on CPB, over 18 y, and who had planned complex cardiac operation (coronary and valve operation, double/triple valve operation, ascending aorta operation) requiring a predictable CPB time of >90 min were included	Exclusion criteria: absence of written consent and allergy to femoldopam.	The adequacy of perfusion	Renal function during and after CPB (incidence of AKI, changes in urine output, changes in serum creatinin), in-hospital mortality, major morbidity	There was a significantly higher rate of AKI in the placebo group (10% vs. 0%; p=0.045). Urine output during and after CPB did not differ between groups, nor did the renal function parameters.	p=0.045 for the rate of AKI	N/A	Patients in the fenoldopam group had higher oxygen delivery during CPB and a significantly lower perfusion pressure, although this parameter was still within the normal range. Blood lactate concentrations during CPB were similar in the 2 groups.
<a href="#">Fenoldopam reduces the need for renal replacement therapy and in-hospital death in CV surgery: a meta-analysis.</a> 2008 (262)	To determine the efficacy of fenoldopam in the prevention of ARF, the authors performed a systematic review of RCTs and propensity-matched studies in patients undergoing CV surgery.	Meta-analysis	1,059	The following inclusion criteria were used for potentially relevant studies: (1) clinical trial comparing fenoldopam with control treatment, (2) clinical trial using random allocation or adjustment for covariates (for nonrandomized studies), and (3) clinical trial in patients undergoing CV surgery.	The exclusion criteria were (1) nonparallel design (i.e., crossover) randomized trials, (2) duplicate publications (in this case only the article reporting the longest follow-up was abstracted), (3) nonhuman experimental studies, and (4) no outcome data as far as RRT or death are concerned.	The number of patients requiring at least 1 episode of RRT, the incidence of in-hospital mortality	Peak serum creatinine levels, and the duration of mechanical ventilation, ICU and hospital stay, hypotension, or the use of vasoconstrictors.	Pooled estimates showed that fenoldopam consistently and significantly reduced the need for renal replacement therapy (5.7% vs.13.4%; OR: 0.37; 95% CI: 0.23 to 0.59; p<0.001 and in-hospital death (OR: 0.46; 95% CI: 0.29 to 0.75; p=0.01). These benefits were associated with shorter ICU stay (WMD=-0.93 d [-1.27; to 0.58]; p=0.002).	p<0.001 (need for RRT); p<0.01 (mortality)	OR: 0.37; 95% CI: 0.23 to 0.59 (need for RRT), OR: 0.46; 95% CI: 0.29 to 0.75 (for mortality)	N/A
<a href="#">Meta-analysis:</a>	To evaluate the effects of	Meta-analysis	3,359	Inclusion criteria: parallel-group RCTs	N/A	Mortality	Need for RRT, adverse effects	There was no effect of low-dose dopamine	p=NS	RR: 0.93; 95% CI:	Improvements in serum CrCl (4% relative decrease [CI: 1% to



<a href="#">low-dose dopamine increases urine output but does not prevent renal dysfunction or death.</a> 2005 (263)	low-dose dopamine ( $\leq 5$ $\mu\text{g/kg}$ of body weight per min) compared with placebo or no therapy in patients with or at risk for ARF.			that included any pt. sample, compared low-dose dopamine ( $\leq 5$ $\mu\text{g/kg}$ of body weight per min) with placebo or no therapy, and recorded any of the following outcomes: all-cause mortality, requirement for renal replacement therapy, renal physiologic variables (urine output, serum CrCl, or measured CrCl on d 1-, 2-, or 3- after starting therapy), or adverse effects. We also included trials in which patients were allocated in alternating fashion or by hospital registry number (quasi-randomization) and trials with pharmacologic co-interventions (such as mannitol, diuretics, or diltiazem) that were equally applied to both groups.				on mortality (RR: 0.96; 95% CI: 0.78 to 1.19), need for renal replacement therapy (RR: 0.93; 95% CI: 0.76 to 1.15), or adverse events (RR: 1.13; 95% CI: 0.90 to 1.41). Low-dose dopamine increased urine output by 24% (CI: 14% to 35%) on d 1.		0.76 to 1.15 (need for RRT)	7%]) and measured CrCl (6% relative increase [CI: 1% to 11%]) on d 1 were clinically insignificant.
<a href="#">Mannitol, furosemide, and dopamine infusion in postoperative renal</a>	To study whether the need for dialysis can be avoided by infusion of the solution of	Prospective	100	Patients who manifested either acute oliguric or anuric renal failure in the postoperative period, with adequate	Excluded from the study were patients with ARF associated with inadequate cardiac output and tissue	Need for RRT	Peak serum CrCls	Diuresis occurred in 93.3% of mannitol-furosemide-dopamine group vs. 10% in diuretics group. 90% of diuretics group required dialysis	N/A	N/A	N/A

<a href="#">failure complicating cardiac surgery.</a> 2000 (264)	mannitol, furosemide, and dopamine in the early postoperative period in oliguric renal failure.			postoperative cardiac output and tissue perfusion were prospectively evaluated and, in 100 patients, such acute renal dysfunction was recognized in the postoperative period.	perfusion, patients who required preoperative dialysis and patients who depended on dialysis.			versus only 6.7% of mannitol-furocemide-dopamine group.			
<a href="#">Diltiazem may preserve renal tubular integrity after cardiac surgery.</a> 2003 (265)	To evaluate the influence of dopamine and diltiazem on renal function and markers for ARF, including urinary alpha-glutathion s-transferase (alpha-GST), alpha-1-microglobulin (alpha (1)-MG) and N-acetyl-ss-glucosaminidase (ss-NAG) after extracorporeal circulation.	RCT	60	Patients undergoing elective cardiac surgery	Ex ante exclusion criteria (screened the d before surgery) were severe LV dysfunction (EF <25%), renal insufficiency (creatinine >177 µmol·L <sup>-1</sup> ), liver dysfunction (aspartate aminotransferase >40 U·L <sup>-1</sup> or alanine aminotransferase >40 U·L <sup>-1</sup> ), repeat cardiac surgery, known allergy to dopamine or diltiazem, anemia (hemoglobin <9.0 g·dL <sup>-1</sup> ), insulin-dependent diabetes mellitus and	Urine output	Excretion of alpha-GST, alpha(1)-MG, ss-NAG, and CrCl	Cumulative urine output in the diltiazem group (9.0±2.8 L) increased significantly compared with placebo (7.0±1.6 L), but not compared with dopamine (7.8±1.8 L). CrCl showed no significant intergroup differences. There were no significant intergroup differences in alpha (1)-MG excretion. Alpha-GST increased significantly in the placebo (2.1 ± 1.8 to 11.4 ± 8.6 micro g x L(-1)) and in the dopamine groups (2.7 ± 1.8 to 13.6 ±14.9 micro g x L(-1)), but not in the diltiazem group (1.8 ± 1.4 to 3.2 ± 3.2 micro g x L(-1)). Forty eight h postoperatively alpha-GST was significantly lower in the diltiazem	p<0.001 (excretion of alpha-GST)	N/A	Diltiazem stimulates urine output, reduces excretion of alpha-GST and ss-NAG and may be useful to maintain tubular integrity after cardiac surgery.

					use of diuretics or calcium antagonists. Ex post exclusion criteria were perioperative MI, death, and low output syndrome requiring IABP and the use of aminoglycosides during the study period or an intolerance to the study drug.			group than in both other groups.			
<a href="#">Diltiazem treatment does not alter renal function after thoracic surgery.</a> 2001(266)	To determine whether diltiazem treatment alters renal function in patients undergoing major thoracic surgery.	RCT	330	To be included in the study, patients' hearts had to be in sinus rhythm and the patients had to be at increased risk for developing postoperative arrhythmias, either because they were scheduled to undergo a pneumonectomy or were >60 y of age and scheduled to have a lobectomy.	Patients were excluded if they had a history of chronic atrial arrhythmias or second-degree atrioventricular block or were taking class I or class III antiarrhythmic drugs or calcium-channel blockers for ischemic heart disease. Patients who developed new signs of myocardial ischemia or infarction or who required	The incidence of renal failure, mortality rate	LOS, serum creatinine or BUN levels	During the first 5 d postoperative d, the 2 groups did not differ in terms of serum creatinine or BUN levels. The incidence of renal failure was 0.6% in the diltiazem group and 1.2% in the placebo group (difference was not significant). There was no difference in the length of hospitalization or mortality rate.	p=NS	N/A	N/A

					inotropic support on arrival to the postanesthesia care unit were also excluded.						
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AKI indicates acute kidney injury; alpha-GST, alpha-glutathion s-transferase; ARF, acute renal failure; ARI, acute renal injury; ATN, acute tubular necrosis; BUN, blood urea nitrogen;CI, confidence interval; CKD, chronic kidney disease; CK-MB, creatinine-kinase myocardial band; CPB, cardiopulmonary bypass; CrCl, Creatinine Clearance; CV, cardiovascular; d, day; EF, ejection fraction; ESRD, end-stage renal disease; IABP, intra aortic balloon pump, ICU, intensive care unit; IV, intravenous; LOS, length of stay; LV, left ventricular; MAP, mean arterial pressure; MI, myocardial infarction; N/A, not applicable; NAC, N-Acetylcysteine; NS, non significant; NYHA, New York Heart Association; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; RRT, renal replacement therapy; ss-NAG, N-acetyl-ss-glucosaminidase; U, unit; and WMD, weighted mean difference.

**Data Supplement 38. Renal Dysfunction**

Article Title	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P Values & 95% CI	OR / HR / RR	Study Summary
				<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>Primary Endpoint</i>	<i>Secondary Endpoint</i>				
<a href="#">OPCAB and AKI: a meta-analysis of randomized and observational studies.</a> 2009 (267)	To critically evaluate the outcomes and conduct of clinical trials addressing the impact of OPCAB on AKI during the postoperative period.	Meta-analysis	27,806	RCTs and observational studies comparing OPCAB with CAB in adult (>18 y) patients. To be included, studies had to report at least 1 of the following renal outcomes: AKI, AKI requiring RRT, or postoperative serum creatinine/Crcl. For studies that reported data from the same trial in multiple publications, only the largest study was included.	Studies involving patients with ESRD on long term RRT were excluded. Studies for which exclusion of RRT-dependent patients with ESRD could not be verified were also excluded.	Incidence of overall AKI (as reported by individual study definitions), incidence of AKI requiring RRT.	Peak postoperative serum creatinine level, nadir postoperative Crcl, and change in postoperative serum creatinine and Crcl from corresponding preoperative values.	The pooled effect from both RCT and observational studies showed a significant reduction in overall AKI (OR: 0.57; 95% CI: 0.43 to 0.76; p<0.001) and AKI requiring RRT (OR: 0.55; 95% CI: 0.43 to 0.71; p<0.001) in the OPCAB group compared with the CAB group. In RCTs, overall AKI was significantly reduced in the OPCAB group (OR: 0.27; 95% CI: 0.13 to 0.54; p<0.001); however, no statistically significant difference was noted in AKI requiring RRT (OR: 0.31; 95% CI: 0.06 to 1.59; p=0.2).	p<0.001 for both incidence of overall AKI and incidence of AKI requiring RRT.	OR: 0.61; 95% CI: 0.45 to 0.8 for incidence of AKI, OR: 0.54; 95% CI: 0.40 to 0.73 for incidence of AKI requiring RRT.	In the observational cohort, both overall AKI (OR: 0.61; 95% CI: 0.45 to 0.81; p<0.001) and AKI requiring RRT (OR: 0.54; 95% CI: 0.40 to 0.73; p<0.001) were significantly less in the OPCAB group.

<a href="#">Coronary artery bypass grafting with or without CPB in patients with preoperative nondialysis dependent renal insufficiency: A randomized study.</a> 2007 (268)	This study was designed to compare the effect of off-pump and on-pump techniques on renal function in patients with nondialysis-dependent renal insufficiency with a GFR of $60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ or less undergoing primary, elective CABG	RCTs	116	Patients with nondialysis-dependent renal insufficiency with a GFR of $60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ or less undergoing primary, elective CABG	N/A	Changes in renal function	Clinical outcomes	N/A	Serum creatinine, $p<0.000$ ; GFR, $p<0.000$	N/A	This study suggests that on-pump as compared with OPCAB is more deleterious to renal function in diabetic patients with nondialysis dependent renal insufficiency.
<a href="#">Renal Dysfunction in High-Risk Patients After On-Pump and Off-Pump Coronary Artery Bypass Surgery: A Propensity Score Analysis.</a> 2005 (269)	To compare the incidence of postoperative renal dysfunction in patients with preoperative renal dysfunction	Observational	2,869 (158 OPCAB)	(Preoperative CrCl $<60 \text{ mL/min}$ ) and who underwent isolated CABG	Patients on dialysis.	Decrease in postop Crcl $>25\%$ or need for RRT	N/A	Propensity match.	$p=0.2$	N/A	No difference in renal outcomes between on and off-pump.



	n (OPACB vs.on- pump)										
<a href="#">Coronary revascularization with or without CPB in patients with preoperative nondialysis-dependent renal insufficiency.</a> 2001 (270)	To compare the incidence of postoperative renal dysfunction in patients with preoperative nondialysis-dependent renal insufficiency (OPCAB vs.onpump)	Observational	253	Preoperative serum creatinine more than 150 µmol/L	Patients on dialysis, PVD, emergency operation, and reoperation were excluded	Changes in renal function	N/A	N/A	p<0.05 Greater increase in creatinine and urea in the on-pump group vs. OPCAB	N/A	Incidence of RRT same but reduced increased serum creatinine in OPCAB vs. on-pump.
<a href="#">Does Off-Pump Coronary Surgery Reduce Postoperative ARF? The Importance of Preoperative Renal Function.</a> (271)	To evaluate the impact of CPB on the incidence of postoperative ARF.	Observational	215	CABG , baseline creatinine>1.5 mg/dL	N/A	Changes in renal function	N/A	N/A	p=0.499		ARF incidence same between on-pump and OPCAB.

AKI indicates acute kidney injury; ARF, acute renal failure; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; Crcl, creatinine clearance; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; N/A, not applicable; OPCAB, off-pump coronary artery bypass; OR, odds ratio; PVD, peripheral vascular disease; RCT, randomized controlled trial; RR, relative risk; and RRT, renal replacement therapy.

Data Supplement 39. Renal Dysfunction

Study Name	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P-Values & 95% CI	OR / HR / RR	Study Summary
				Inclusion Criteria	Exclusion Criteria	Primary Endpoint	Secondary Endpoint				
<a href="#">Renal failure after cardiac surgery: timing of cardiac catheterization and other perioperative risk factors.</a> 2007 (272)	Identify the relationship between timing of preoperative cardiac catheterization and incidence of postoperative ARF	Retrospective single center	649	All cardiac surgery patients on dialysis, cardiac transplant, VAD, emergency, aortic dissection.	N/A	ARF, ARF-D, hospital mortality	N/A	Multivariate	Cardiac catheterization within 5 d; p=0.010; 95% CI: 1.17 to 2.84; baseline GFR <60 mL/min; p=0.047; 95% CI: 1.09 to 2.62	Cardiac catheterization within 5 d OR: 1.82; baseline GFR <60 mL/min 1.69.	Cardiac catheterization within 5 d of cardiac operation, baseline preoperative renal dysfunction, prolonged CPB time are significant risk factors for ARF.
<a href="#">The effect of cardiac angiography timing, contrast media dose, and preoperative renal function on ARF after CABG.</a> 2010 (273)	To assess the effect of timing of cardiac angiography and prevalence of ARF after cardiac surgery	Single center retrospective	395	CABG on-pump	Patients on dialysis and salvage operations, referred from OSH.	ARF	Perioperative mortality, ICU and hospital stay	Multivariate	1 d interval p=0.07; 95% CI: 1.4 to 8.3; CrCl <60 mL/min; 95% CI: 3 to 16; p<0.001	<1 d interval OR: 3.7; eCrCl <60 mL/min; OR: 7.1	CABG should be delayed in the presence of high contrast dose and preoperative renal dysfunction for at least 5 d after cardiac catheter
<a href="#">Influence of the Timing of Cardiac Catheterization and the Amount of Contrast Media on Acute Renal Failure After</a>	Identify the influence of timing of cardiac catheter and ARF after cardiac surgery	Single center retrospective	423	Elective on-pump cardiac surgery	Preop dialysis, emergent/urgent surgery/off-pump	ARF		Multivariate	Same day cardiac catheterization/surgery p=0.039; 95% CI: 1.06 to 8.78	Same day cardiac catheterization /surgery; OR: 3.05	Cardiac surgery and catheterization same d increased risk 3-fold for ARF

<a href="#">Cardiac Surgery.</a> 2008 (274)											
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ARF, acute renal failure; ARF-D, acute renal failure-dialysis; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; d, day; eCrCl, estimated creatinine clearance; GFR, glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; N/A, not applicable; OR, odds ratio; RR, relative risk; and VAD, ventricular assist device.

**Data Supplement 40. Perioperative Bleeding/Transfusion**

Study Name	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P Values & 95% CI	OR / HR / RR	Study Summary	Study Limitations
				<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>Primary Endpoint</i>	<i>Secondary Endpoint</i>					
<a href="#">Preoperative Use of Enoxaparin increases the Risk of Postoperative Bleeding and reexploration in cardiac surgery patients.</a> 2005 (275)	To investigate if the use of LMWH or PLT inhibitors increased the risk of bleeding in CABG.	Retrospective	111	CABG patients	Not CABG patients	Bleeding events	N/A	Greater percentage of patients on LMWH required mediastinal re-exploration for nonsurgical bleeding versus control (17% vs. 0% , respectively).	p=0.001	N/A	Increased blood loss and reoperative for bleeding in the LMWH group.	Median time interval for discontinued LMWH was 21 h.

<a href="#">Preoperative use of enoxaparin compared with UFH increases the incidence of re-exploration for postoperative bleeding after open-heart surgery in patients who present with an ACS: clinical investigation and reports. 2002 (276)</a>	To investigate if the use of LMWH compared with UFH increased the risk of bleeding in cardiac surgery	Retrospective	1159	Patients presented with a diagnosis of UA or non Q-wave MI and (2) the patient received antithrombotic therapy with either UFH or enoxaparin within 48 h before proceeding to surgery	1) The patient received no antithrombotic therapy (UFH or enoxaparin) within 48 h of the surgical procedure and 2) follow-up clinical data were not available	Bleeding events		Re-exploration was 7.9% in the enoxaparin group and 3.7% in the UFH group.	p=0.03	HR: 2.6	Enoxaparin administration within 48 h of surgery increases the risk of reoperative bleeding.	N/A
<a href="#">Effects of preoperative enoxaparin vs. UFH on bleeding indices in patients undergoing CABG. 2003 (277)</a>	To investigate the effects of LMWH on bleeding indices and transfusion rates in patients undergoing cardiac surgery	Retrospective	161	CABG patients	Not CABG patients	Bleeding events		Compared with UFH group, LMWH, <12 group had higher transfusion rate (73.5% vs. 50.7%, respectively),	p<0.05	N/A	LMWH given <12 h increased the transfusion rate and number of PRBC transfused per patient	N/A
<a href="#">Preoperative use of enoxaparin is not a risk factor for postoperative bleeding after CABG. 2003 (278)</a>	To investigate if the use of LMWH increased the risk of bleeding in CABG	Retrospective	64	CABG patients	Not CABG patients	Bleeding events	N/A	62% of pts transfused in the LMWH vs. 60% in the control	p=0.8	N/A	LMWH given <10 h does not increase the transfusion rate and number of PRBC transfused per patient	Number of patients receiving LMWH was only 21. High transfusion rate in the control group.

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; h, hour; HR, hazard ratio; LMWH, low molecular weight heparin; MI, myocardial infarction; N, number; N/A, not applicable; OR, odds ratio; PLT, platelet inhibitors; PRBC, packed red blood cells; RR, relative risk; UFH, unfractionated heparin; and UA, unstable angina.

Data Supplement 41. Perioperative Bleeding/Transfusion

Article Title	Aim of Study	Study Type	Patient Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	95% CI; P-Values	OR/HR/ RR	Study Summary
				Inclusion Criteria	Exclusion Criteria	Primary Endpoint	Secondary Endpoint				
<a href="#">A randomized comparison of off-pump and on-pump multi-vessel CABG.</a> 2004 (279)	To compare graft-patency rates and clinical outcomes in off-pump surgery with conventional, "on-pump" surgery.	RCT	50	Patients who were referred for isolated, first-time coronary-artery surgery and who required at least 3 grafts were eligible.	An age of <30 y or >80 y; an indication for additional surgical procedures; documented stroke within the preceding 6 mo; carotid-artery stenosis of more than 70%; documented MI in the preceding 3 mo; poor LV function, with an EF <20%; pregnancy and breast-feeding; an inability to provide written informed consent; and a history of complications after diagnostic angiography.	Graft patency	Clinical outcomes	Patients in the on-pump group were more likely to receive packed-cell transfusion (p=0.004) or clotting-product transfusion (p=0.002). The mean blood loss was not significantly different between the 2 groups (898 mL in the on-pump group and 1,031 mL in the off-pump group).	p=0.004	N/A	N/A
<a href="#">Early outcome after off-pump vs. on-pump coronary bypass surgery: results from a randomized study.</a> 2001 (280)	To compare the short term clinical outcomes of OPCAB with standard on-pump CABG.	Random ized Multice nter Trial	281	Patients were eligible if referred for first-time isolated coronary bypass surgery and an off-pump procedure was deemed technically feasible.	Patients were excluded in case of emergency or concomitant major surgery, Q-wave MI in the previous 6 w, or poor LV function or if they were unlikely to complete 1 y of follow-up or unable to give informed consent. There were no restrictions as to age.	Cardiac outcome 1 mo after surgery (defined as survival free of CV events, which included stroke, MI, and coronary intervention).	Improvement in quality of life at 1 mo.	The intraoperative use of blood products was reduced in the off-pump group. The proportion of patients in whom blood products were used during surgery was almost 4 times lower in the off-pump group (3% for OPCAB vs. 13% for on-pump CABG, p<0.01).	95% CI: 4 to 17; p<0.01	N/A	Concluded that in selected patients, off-pump CABG is safe and yields a short-term cardiac outcome comparable to that of on-pump CABG.



<a href="#">Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS1 and 2): a pooled analysis of 2 RCTs, 2002 (222)</a>	To pool the results of 2 RCT to assess midterm outcomes of OPCAB.	Pooled outcome of 2 RCT (which compared short term morbidity of OPCAB vs. on-pump CABG) to assess midterm outcomes.	401	Patients undergoing off-pump or on-pump CABG.	Recent MI within 1 mo; had a history of supraventricular arrhythmia; had a previous CABG; had renal or respiratory impairment; or had a previous stroke, TIA, or coagulopathy present.	The primary endpoint for this pooled analysis was all cause mortality or a cardiac-related event at midterm follow-up (1 to 3 y after surgery).	Noncardiac events, such as chest or wound infection, and neurological events.	Analyses of combined data from both trials showed transfusion of red blood was 31% lower in OPCAB pages compared to on-pump CABG.	95% CI: 0.26 to 0.51;p<0.0001	RR: 0.36	In general, study concluded off-pump coronary surgery significantly lowers in-hospital morbidity without compromising outcome in the first 1 to 3 y after surgery compared with conventional on-pump coronary surgery.
<a href="#">OPCAB grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and LOS: a prospective randomized comparison of 200 unselected patients undergoing off-pump vs. conventional coronary artery</a>	To compare completeness of revascularization, clinical outcomes, and resource use in unselected patients referred for elective, primary CABG randomly assigned to undergo OPCAB with an Octopus tissue stabilizer (Medtronic, Inc, Minneapolis,	RCT	200	Patients referred for elective primary CABG	Patients in cardiogenic shock and those requiring preoperative IABP counterpulsation were excluded from the study for cardiac reasons. Patients who had chronic renal insufficiency with a creatinine level greater than 2.5 mg/dL were eligible for enrollment in the study but were exempt from having postoperative cardiac angiography performed.	Completeness of revascularization.	In-hospital and 30-d outcomes, LOS, transfusion requirements, and extent of myocardial injury.	Patients undergoing OPCAB received fewer units of blood, were more likely to avoid transfusion altogether and had a higher hematocrit at discharge. CPB was an independent predictor of transfusion (OR: 2.42; p=0.0073) by multivariate analysis.	p=0.0073	OR: 2.42	In general, when compared with conventional CABG with CPB, OPCABG achieved similar completeness of revascularization, similar in-hospital and 30-d outcomes, shorter LOS, reduced transfusion requirement, and less myocardial injury.

<a href="#">bypass grafting</a> (281).	Minn) or CABG with CPB.										
<a href="#">Complete revascularization in coronary artery bypass grafting with and without CPB.</a> 2001 (282)	To evaluate the feasibility of CABG without CPB to achieve complete revascularization as compared with the standard operation with CPB in selected low-risk patients.	RCT	80	Inclusion criteria were a normal or almost unimpaired LVEF and presence of coronary multivessel disease.	Diffuse disease, ventricular hypertrophy, and cardiac enlargement	Completeness of revascularization	Parameters of clinical outcome	Although no significant differences in bleeding complications were reported, 1 (2.5%) reexploration occurred because of bleeding in a patient without CPB and 2 (5.0%) reexplorations occurred in patients with CPB.	p=NS	N/A	In general, the study concluded OPCAB is effective for complete revascularization in the majority of selected low-risk patients, although the rate of incomplete revascularization in this early series of CABG without CPB was higher.
<a href="#">Does OPCAB reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials.</a> 2005 (283)	To determine whether OPCAB reduces mortality, morbidity, or resource utilization when compared with standard CABG.	Meta-Analysis	3,369	Studies were included if they met each of the following conditions: randomized allocation to OPCAB on the beating heart vs. conventional CABG on the asystolic heart with CPB circuit, adult patients undergoing single- or multiple-vessel bypass, and reporting at least 1 pertinent clinical or economic outcome. Off-pump studies using minimally invasive direct coronary artery bypass with thoracotomy and	Hybrid (i.e., OPCAB plus balloon angioplasty) and robotically assisted surgery studies were excluded.	All-cause mortality at 30 d, 6 mon, and >1 y.	Postoperative incidence of stroke, acute MI, AF, renal failure, need for inotropes, need for intraaortic balloon pump, mediastinitis/wound infection, respiratory infections, angina recurrence, reintervention for ischemia, restenosis, need for transfusions, reexploration for bleeding, neurocognitive dysfunction, duration of ventilation, ICU LOS, hospital LOS, hospital costs, and QOL.	OPCAB significantly decreased transfusion requirements.	95% CI: 0.29 to 0.65; p<0.0001	OR: 0.43	In general, selected short-term and mid-term clinical and resource outcomes were improved compared with conventional CABG.

				studies allowing for ventricular assist devices were included with the intent of subanalyzing these groups. Blinded and unblinded studies were included.							
<a href="#">Impact of off-pump CABG on postoperative bleeding: current best available evidence.</a> 2006 (284)	To evaluate current best available evidence from RCTs to assess the impact of OPCAB on postoperative blood loss and transfusion requirements.	Review article on RCT's.	N/A	All blinded or unblinded RCTs comparing OPCAB or MIDCAB on the beating heart with conventional CABG on CPB using cardioplegic arrest, recruiting adult patients undergoing single- or multiple-vessel bypass, and reporting at least 1 pertinent clinical or economic outcome were retrieved. Out of these, RCTs reporting on postoperative blood loss were included for this systematic review.	Studies reporting on outcomes of hybrid (i.e., OPCAB plus balloon angioplasty) procedures, robotically assisted surgery or using circulatory assist devices were excluded.	Blood loss.	Transfusion requirements	N/A	N/A (values for individual studies reported)	N/A	Evidence clearly suggests that there is less bleeding with off-pump procedures compared with CPB and there is less need for blood products.

AF indicates atrial fibrillation; CI, confidence interval; CPB, cardiopulmonary bypass; CV, cardiovascular; EF, ejection fraction; HR, hazard ratio; IABP, intra aortic balloon pump; LOS, length of stay; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MIDCAB, minimally invasive directed coronary artery bypass; N/A, not applicable; OPCAB, off-pump coronary artery bypass; OR, odds ratio; QOL, quality of life; RCT, randomized controlled trial; and RR, relative risk..

**Data Supplement 42. Perioperative Bleeding/Transfusion**

Study Name	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	P Values & 95% CI	OR / HR / RR	Study Summary
				<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>Primary Endpoint</i>	<i>Secondary Endpoint</i>				
<a href="#">Blood conservation in coronary artery surgery.</a> 1994 (285)	To define strict transfusion criteria as the sole blood conservation strategy.	Comparison of prospective data with retrospective data (data is regarding blood product usage).	1,261	Patients undergoing isolated primary CABG.	Patients not undergoing isolated primary CABG.	Incidence of postoperative transfusion.	ICU and hospital LOS and reoperation for bleeding.	N/A	p<0.001	N/A	Adherence to defined transfusion criteria alone is a simple, safe, and effective strategy for decreasing blood product utilization.
<a href="#">Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after CPB.</a> 2001 (286)	To determine if coagulation test-based algorithms may reduce transfusion of nonerythrocyte allogeneic blood in patients with abnormal bleeding.	RCT	92	Adult men and nonpregnant adult women scheduled for elective cardiac surgery requiring CPB.	Patients undergoing nonelective surgery or undergoing surgery without CPB.	Transfusion requirements.	ICU blood loss.	Adherence to a coagulation test-based transfusion algorithm in cardiac surgery patients with abnormal bleeding after CPB reduced nonerythrocyte allogeneic transfusions in the operating room and ICU blood loss. The transfusion algorithm group received less allogeneic fresh frozen plasma in the operating room after CPB (median: 0 units; range: 0 to 7 units) than the control group (median: 3 units; range: 0 to 10 units) (p=0.0002). The median number of platelet units transfused in the operating room after CPB was 4 (range: 0 to 12) in the algorithm group compared with 6 (range: 0 to 18) in the control group (p=0.0001).	p=0.0002 (for FFP transfusion); p=0.0001 (for platelet transfusion)	N/A	ICU mediastinal blood loss was significantly less in the algorithm group. Multivariate analysis demonstrated that transfusion algorithm use resulted in reduced ICU blood loss. The control group also had a significantly greater incidence of surgical reoperation of the mediastinum for bleeding (11.8% vs. 0%; p=0.032).

<a href="#">Reduced haemostatic factor transfusion using heparinase-modified thrombelastography during CPB.</a> 2001 (287)	Determine if the heparinase-modified thrombelastogram using anticoagulated blood from patients during cardiac surgery could guide treatment with haemostatic components.	Pilot study to investigate the use of an algorithm.	60	Patients undergoing cardiac surgery.	Patients not undergoing cardiac surgery.	Reduced total exposure to hemostatic component therapies.	Chest tube output	Ten patients in the regular clinical group received a total of 16 units of FFP and 9 platelet concentrates compared with 5 patients transfused with 5 units of FFP and 1 platelet concentrate in the algorithm group. 12-h chest tube losses [algorithm group 470 (295 to 820) mL, clinically managed group 390 (240 to 820) ml (median, quartile values)] were not significantly different between groups despite the 3-fold reduction in the use of haemostatic products, showing that intraoperative monitoring of coagulation in the anticoagulated patient can be used to guide treatment.	p<0.005	N/A	Concluded that intraoperative monitoring of coagulation in the anticoagulated patient can be used to guide treatment.
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<a href="#">Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgment in the management of bleeding after cardiac surgery.</a> 2004 (288)	To test the hypothesis that a mgmt algorithm based on near-patient tests would reduce blood loss and blood component use after routine coronary artery surgery with CPB when compared with an algorithm based on routine laboratory assays or with clinical judgment.	RCT	102	Sequential patients for elective, first time CABG surgery with CPB treated by the same surgical, intensivist and anaesthetic teams	Patients with preoperative abnormal clotting tests, including INR >1.5, APTT ratio >1.5 or platelet count <150 X 10 E(9)/litre, were excluded. Any medication affecting coagulation within 72 h of surgery, including warfarin, heparin, low molecular weight heparin, aspirin and clopidogrel, was also an exclusion criterion.	Postoperative blood loss and the transfusion of PRBCs and blood components	Differences in the POC test results between the groups using POC hemostatic assessment and the group using standard haematology laboratory tests LAG.	The median blood loss was not significantly different among the groups in this study. Patients in the clinician discretion group received significantly more (p<0.025) transfusions of blood components (PRBCs, FFP and pooled platelets) compared with those in the LAG and POC groups. There were no significant differences in this regard between the LAG and POC groups.	p<0.025	N/A	Concluded that algorithms based on POC tests or on structured clinical practice with standard laboratory tests do not decrease blood loss, but reduce the transfusion of PRBCs and blood components after routine cardiac surgery, when compared with clinician discretion.
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<a href="#">The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery.</a> 1994 (289)	To evaluate the effect of a transfusion decision algorithm based on intraoperative coagulation monitoring of physicians' transfusion practice and the transfusion outcome.	RCT	66	Cardiac surgical patients determined to have microvascular bleeding at the cessation of CPB were assigned to the study.	Cardiac surgical patients who were not found to have microvascular bleeding at the cessation of CPB.	Red cell volume lost and the red cell volume transfused.	Nonred cell units transfused and total number of blood components transfused	Patients treated according to a transfusion algorithm, based on on-site coagulation data available within 4 m, received fewer hemostatic blood component units (p=0.008) and had fewer total donor exposures (p=0.007) during the entire hospitalization period compared to patients treated at physician discretion. Linear regression analysis of the differences in slopes (between the 2 groups) of the relationships between the red cell volume lost and the red cell volume transfused (p<0.03), nonred cell units transfused (p<0.0001), and total number of blood components transfused (p<0.0001) demonstrated that physicians' transfusion practice was significantly altered by the use of a transfusion algorithm with on-site coagulation data, independent of surgical blood losses.	p=0.008	N/A	N/A
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<a href="#">Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery.</a> 1999 (290)	To determine if a transfusion algorithm to is effective in reducing transfusion requirements in cardiac surgical patients at moderate to high risk of transfusion..	RCT	105	Adult patients were recruited if they were undergoing a cardiac surgical procedure that had a moderate to high risk for requiring a transfusion. Thus, the current study included patients undergoing single valve replacement, multiple valve replacement, combined coronary artery bypass plus valvular procedure, cardiac reoperation, or thoracic aortic	Patients were excluded from enrollment if they had significant preexisting hepatic disease (transaminase levels >2 times control) or renal disease requiring dialysis, or if they required preoperative inotropic support.	Intraoperative transfusion rate, postoperative transfusion rates and total transfusion rates.	Mediastinal tube drainage.	Intraoperative transfusion rates did not differ, but there were significantly fewer postoperative and total transfusions in the transfusion algorithm group. The proportion of patients receiving FFP was 4 of 53 in the algorithm group compared with 16 of 52 in the control group (p<0.002). Patients receiving platelets were 7 of 53 in the algorithm group compared with 15 of 52 in the control group (p<0.05). Patients in the algorithm group also received less volume of FFP (36±142 vs. 217±463 mL; p<0.04). Mediastinal tube drainage was not statistically different at 6, 12, or 24 h postoperatively. POC coagulation monitoring using the algorithm resulted in fewer transfusions in the postoperative period.	p<0.002 (for proportion of patients receiving FFP), p<0.04 (for volume of FFP), p<0.05 (for number of patients receiving platelets)	N/A	Concluded that in comparing a transfusion algorithm using POC coagulation testing with routine laboratory testing, the algorithm was effective in reducing transfusion requirements.
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APTT indicates activated partial thromboplastin time; CABG, coronary artery bypass graft; CI, confidence interval; CPB, cardiopulmonary bypass; ICU, intensive care unit; FFP, fresh frozen plasma; HR, hazard ratio; ICU, intensive care unit; INR, international normalization ratio; LAG, laboratory guided algorithm; LOS, length of stay; N/A, not applicable; OR, odds ratio; POC, point of care; PRBC, packed red blood cells; RCT, randomized controlled trial; and RR, relative risk.

**Data Supplement 43. CABG in Patients With COPD/Respiratory Insufficiency**

Article Title	Aim of Study	Study Type	Study Size	Patient Population/Inclusion & Exclusion Criteria		Endpoints		Statistical Analysis Reported	95% CI; P-Values	OR	Study Summary	Study Limitations
				<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>Primary Endpoint</i>	<i>Secondary Endpoint</i>					
<a href="#">Prophylactic nasal continuous positive airway pressure following cardiac surgery protects from postoperative pulmonary complications: a prospective, RCT in 500 patients.</a> 2009 (291)	Demonstrate benefit of prophylactic positive airway pressure for the prevention of pulmonary complications after CABG	Prospective, randomized	500	Patients undergoing elective CABG	Lack of consent, age <18, emphysema with bullae, steroid treatment, LVEF <40%, perioperative MI, postoperative catecholamines, reoperative surgery, postoperative ventilation for >18 h.	Hypoxemia, pneumonia, reintubation	Hospital re-admission to ICU or intermediate care unit	Intention-to-treat; ANOVA; Chi-square	p=0.03	N/A	Application of positive airway pressure improves oxygenation and reduces incidences of pneumonia, reintubation, and readmission to the ICU and the intermediate care unit	Exclusion of high-risk patients; did not assess comparative benefit of non-invasive ventilation.
<a href="#">Incentive spirometry with expiratory positive airway pressure reduces pulmonary complications, improves pulmonary function and 6-m walk distance in patients undergoing CABG.</a> 2008 (292).	Assess whether incentive spirometry with expiratory positive airway pressure prevents postoperative pulmonary complications after CABG	Prospective, randomized	34	Patients undergoing CABG with history of tobacco use, age >50, and use of mammary artery graft.	CHF, diabetes, peripheral neuropathy, obesity, neurologic or musculoskeletal diseases, requirement for mechanical ventilation for >24 h or reintubation.	Respiratory muscle strength, lung function, 6-mon walk, chest x-ray	N/A	Maximal inspiratory pressure significantly higher in IS+EPAP group compared to controls at 1 week and 1 month (p<0.001)  Maximal expiratory pressure		N/A	In patients undergoing CABG, incentive spirometry + expiratory positive airway pressure result in improved pulmonary function and 6-m walk distance and reduction in post-operative pulmonary complications.	Exclusion of patients with severe lung disease, CHF, diabetes, peripheral neuropathy, obesity, and neurologic or musculoskeletal disease; patient limitations in ambulation for 6-m walk; inability to supervise respiratory treatments done at the patients' homes.

								<p>significantly higher at 1 month compared to 1 week in IS+EPAP group (p&lt;0.01).</p> <p>Forced vital capacity and forced expiratory volume in 1 second significantly higher in IS+EPAP group compared to controls at 1 month (p&lt;0.05).</p> <p>Inspiratory capacity higher at 1 month in IS +EPAP group compared to controls (p&lt;0.05).</p> <p>Distance walked in 6 minute walk test was higher at 1 month in IS +EPAP group (p&lt;0.001) compared to</p>				
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								controls. Radiological injury score at 1 week was lower in IS+EPAP group compared to controls (p<0.004).				
<a href="#">Effects of perioperative central neuraxial analgesia on outcome after CABG: a meta-analysis.</a> 2004 (293)	Assess effects of perioperative thoracic epidural analgesia on outcomes after CABG	Meta-analysis	15 trials enrolling 1,178 patients	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Thoracic epidural analgesia affords faster time to extubation, decreased pulmonary complications and cardiac dysrhythmias, and reduces pain scores	N/A
<a href="#">Epidural analgesia improves outcome in cardiac surgery: a meta-analysis of randomized controlled trials.</a> 2010 (294)	Assess advantages of epidural analgesia in patients undergoing cardiac surgery	Meta-analysis	33 trials enrolling 2,366 patients	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Epidural analgesia reduces the incidence of ARF, time on mechanical ventilation, and the composite endpoint of mortality and MI in patients undergoing cardiac surgery	N/A
<a href="#">Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG: a randomized clinical trial.</a> 2006 (295)	Evaluate the efficacy of preoperative inspiratory muscle training on the incidence of postoperative pulmonary complications in high-risk patients undergoing elective	Prospective, single-blind, randomized	279 patients	Patients with high risk of pulmonary complications undergoing elective CABG.	Surgery performed within 2 wk of initial contact, history of cerebrovascular accident, immunosuppressive medication for 30 d before surgery, neuromuscular disorder, CV instability, or aneurysm	Incidence of pulmonary complication.	Duration of postoperative hospitalization.	Intent-to-treat; OR; Pearson chi-square; Mann-Whitney U; Student t; ANOVA	p=0.02	Postoperative pulmonary complications OR: 0.52; 95% CI: 0.30 to 0.92; Pneumonia OR: 0.40; 95% CI:	Preoperative inspiratory muscle training reduces postoperative pulmonary complications and postoperative length of stay in patients at high risk for pulmonary complications after CABG	Unrealistic that all patients were trained by the same physical therapist; Hawthorne effects may have played a role in results; randomization not perfect as some variables (cigarette smoking) distinguished the 2 groups.

	CABG.									0.19 to 0.84		
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ANOVA indicates analysis of variance; ARF, acute renal failure; CABG, coronary artery bypass graft s; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; EPAP, expiratory positive airway pressure; h, hour; HR, hazard ratio; ICU, intensive care unit; IS, incentive spirometry; LVEF, left ventricular ejection fraction; N/A, not applicable; PPC, plasma protein concentration, OR, odds ratio; and RR, relative risk.

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**2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery—ONLINE AUTHOR LISTING OF COMPREHENSIVE RELATIONSHIPS WITH INDUSTRY AND OTHERS (October 2011)**

<b>Committee Member</b>	<b>Employer/Title</b>	<b>Consultant</b>	<b>Speaker's Bureau</b>	<b>Ownership/ Partnership/ Principal</b>	<b>Personal Research</b>	<b>Institutional, Organizational, or Other Financial Benefit</b>	<b>Expert Witness</b>
L. David Hillis (Chair)	University of Texas Health Science Center at San Antonio—Professor and Chair of the Department of Medicine	None	None	None	None	None	None
Peter K. Smith (Vice Chair)	Duke University Medical Center: Private Diagnostic Clinic—Professor of Surgery; Chief of Thoracic Surgery	<ul style="list-style-type: none"> <li>• Eli Lilly</li> <li>• Baxter BioSurgery</li> </ul>	None	None	None	None	None
Jeffrey L. Anderson	Intermountain Medical Center—Associate Chief of Cardiology	<ul style="list-style-type: none"> <li>• Sanofi-aventis /BMS</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• AstraZeneca</li> <li>• Gilead Pharma</li> <li>• TIMI-48, 51, 52, and 54</li> <li>• Toshiba‡</li> </ul>	<ul style="list-style-type: none"> <li>• COAG Study</li> <li>• CoumaGenII Study</li> <li>• CORAL Study</li> <li>• DSMB: CANVAS Study</li> <li>• GIFT Study</li> </ul>	<ul style="list-style-type: none"> <li>• Defendant, Stroke after ablation for AF, 2010</li> </ul>
John A. Bittl	Munroe Regional Medical Center—Interventional Cardiologist	None	None	None	None	None	None
Charles R. Bridges	University of Pennsylvania Medical Center—Chief of Cardiothoracic Surgery	<ul style="list-style-type: none"> <li>• Baxter‡ BioSurgery</li> <li>• Zymogenetics</li> </ul>	<ul style="list-style-type: none"> <li>• Bayer Pharmaceuticals</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• Plaintiff, Alleged mitral valve dysfunction, 2009</li> <li>• Defense, Retinal artery occlusion (stroke) following CABG, 2009</li> <li>• Defense, Timely insertion of IABP following CABG, 2009</li> <li>• Defense, Timely transport after acute aortic dissection, 2009</li> <li>• Plaintiff, Unexpected intra-abdominal</li> </ul>

							hemorrhage and death following AVR, 2009
John G. Byrne	Vanderbilt University Medical Center: Division of Cardiac Surgery—Chairman of Cardiac Surgery	None	None	None	None	None	None
Joaquin E. Cigarroa	Oregon Health and Science University—Associate Professor of Medicine	None	None	None	None	None	None
Verdi DiSesa	John Hopkins Hospital: Division of Cardiac Surgery—Clinical Associate	None	None	None	None	None	None
Loren Hiratzka	Cardiac, Vascular and Thoracic Surgeons, Inc—Medical Director of Cardiac Surgery	None	None	None	None	None	None
Adolph M. Hutter	Massachusetts General Hospital—Professor of Medicine	None	None	None	None	None	None
Michael E. Jessen	UT Southwestern Medical Center—Professor of Cardiothoracic Surgery	• Quest Medical‡	None	None	None	None	None
Ellen C. Keeley	University of Virginia—Associate Professor of Internal Medicine	None	None	None	None	None	None
Stephen J. Lahey	University of Connecticut—Professor and Chief of Cardiothoracic Surgery	None	None	None	None	None	• Defense, mitral valve replacement, 2009
Richard A. Lange	University of Texas Health Science Center at San Antonio—Professor of Medicine	None	None	None	None	None	None
Martin J. London	University of California: San Francisco, Veterans Affairs Medical Center—Professor of Clinical Anesthesia	None	None	None	None	None	None

Michael J. Mack	The Heart Hospital Baylor Plano—Director	<ul style="list-style-type: none"> <li>• Cordis</li> <li>• Marquett</li> <li>• Medtronic</li> <li>• Edwards Lifesciences‡</li> </ul>	None	None	None	None	None
Manesh R. Patel	Duke University Medical Center—Associate Professor of Medicine	None	None	None	None	None	None
John D. Puskas	Emory University/ Emory Healthcare—Chief of Cardiac Surgery	<ul style="list-style-type: none"> <li>• Marquett</li> <li>• Medtronic</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Marquett†</li> <li>• Medtronic†</li> </ul>	None	None
Joseph F. Sabik	Cleveland Clinic Foundation—Professor of Surgery	<ul style="list-style-type: none"> <li>• Edwards Lifesciences</li> <li>• Medtronic</li> </ul>	None	None	None	None	None
Ola Selnes	John Hopkins Hospital: Department of Neurology—Professor of Neurology	None	None	None	None	None	None
David M. Shahian	Massachusetts General Hospital—Professor of Surgery	None	None	None	None	None	None
Jeffrey C. Trost	John Hopkins School of Medicine—Assistant Professor of Medicine	None	None	None	<ul style="list-style-type: none"> <li>• Toshiba†</li> </ul>	None	None
Michael D. Winniford	University of Mississippi Medical Center—Professor of Medicine	None	None	None	None	None	None

This table represents all healthcare relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of  $\geq 5\%$  of the voting stock or share of the business entity, or ownership of  $\geq \$10\,000$  of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer <http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx> for definitions of disclosure categories or additional information about the ACCF/AHA Disclosure Policy for Writing Committees.

†Indicates significant relationship.

‡No financial benefit.

AF indicates atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass graft surgery; CANVAS, CANagliflozin cardioVascular Assessment Study; COAG, Clarification of Optimal Anticoagulation Through Genetics; CORAL, Cardiovascular Outcomes with Renal Atherosclerotic Lesions; DSMB, data safety monitoring board; GIFT, Genetic Informatics Trial of Warfarin to Prevent Deep Vein Thrombosis; and IABP: Intra-aortic balloon pump.