The 2021 ACC/AHA/SCAI guideline for coronary artery revascularization. A worldwide call for consistency and logic.

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The 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization

The 2021 ACC/AHA/SCAI guideline for coronary artery revascularization raised significant controversy, with recommendations dissonant from best evidence.

These issues are worrisome for the worldwide cardiovascular community, who routinely treat patients with advanced coronary artery disease (CAD).

The current recommendations potentially place the patients with advanced CAD at risk.

A revision of the recommendations is both mandatory and urgent.
The 2021 ACC/AHA/SCAI guideline for coronary artery revascularization.

A worldwide call for consistency and logic.

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Glossary of Abbreviations

ACC: American College of Cardiology
AHA: American Heart Association
CABG: coronary artery bypass surgery
CAD: coronary artery disease
COR: class of recommendation
EF: left ventricular ejection fraction
MT: medical treatment
PCI: percutaneous coronary intervention
RCT: randomized control trials
SCAI: Society for Cardiac Angiography and Interventions

Central Message
The recommendations of the 2021 ACC/AHA/SCAI guideline for coronary artery revascularization are dissonant from evidence. The issued recommendations may leave patients at risk. A revision is needed.

Perspective Statement
The 2021 ACC/AHA/SCAI guideline for coronary artery revascularization raised significant controversy, with interpretation and recommendations dissonant from best evidence. These issues are worrisome for the worldwide cardiovascular community, who routinely treat patients with advanced coronary artery disease (CAD). The current
recommendations potentially place the patients with advanced CAD at risk. A revision of
the recommendations is both mandatory and urgent.

Keywords: Coronary artery bypass grafting, percutaneous coronary intervention,
coronary artery disease, guideline.
The publication of the 2021 ACC/AHA/SCAI guideline for coronary artery revascularization\(^1\) replaced the 2011 coronary artery bypass graft (CABG) surgery\(^2\), the 2011 and 2015 percutaneous coronary intervention (PCI) guidelines\(^3,4\), and the sections on revascularization from the 2012 stable ischemic heart disease guideline.\(^5\) However, the statements raised significant controversy, with interpretation and recommendations dissonant from best existing evidence and self-contradictory, uncommonly seen in guidelines, customarily issuing evidence-based and balanced statements. This has understandably caused concern in the wider cardiovascular community.

In particular, CABG was downgraded from a class of recommendation (COR) 1 to 2b in patients with stable 3-vessel (3VD) CAD with preserved left ventricular (LV) function and no left main (LM) coronary artery disease. The previous evidence, based on registry studies, a meta-analysis which included seven randomized control trials (RCT), and an additional RCT (MASS II)\(^2\), supporting the Class 1 recommendation and showing a convincing mortality benefit for CABG in patients with 3VD, were deemed outdated and removed from the guideline assessment. This change in COR follows a clear statement that "studies have shown that CABG confers a survival benefit over medical therapy in multiple subsets of patients, including left main CAD (Figure 3), triple vessel CAD, and ischemic cardiomyopathy". Additionally, CABG was downgraded from COR 1 to class 2a (moderate) in improving survival in patients with 3VD and mild to moderate left ventricular dysfunction (LV ejection fraction 35 to 50%).

The main reasoning behind the changes was that the trials supporting the former COR for CABG vs. medical treatment (MT) were completed >20 to 40 years ago and no longer represented modern optimal medical treatment (OMT), and additionally by inference from analysis of the CABG subgroup of the ISCHEMIA trial.\(^6\) We believe this is misguided for the following reasons:
Firstly, the MASS-II trial, the sole trial ever to compare CABG, PCI, and MT in patients with multivessel coronary artery disease, stable angina, and preserved ventricular function, reported in 2010 the 10-year follow up, reinforced the results of earlier studies while adding new insights.

In the MASS II trial, all patients were placed on an optimal medical regimen at baseline until the end of follow-up, consisting of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, nitrates, and lipid-lowering agents, along with a low-fat diet, on an individual basis. All medications were dispensed free of charge to all patients throughout the 10-year follow-up to ensure protocol adherence. Proximal left anterior descending (LAD) coronary artery disease was present in 89% of patients in the MT group and 93% of the CABG patients. Although the study design was insufficiently powered for assessing individual components of the composite endpoint, a significantly lower incidence of non-fatal MI with CABG versus OMT was seen at 10-year (20.7 versus 10.3, P=0.010) but not at 5-year (P=0.785). Cardiac death was significantly higher with OMT versus CABG (20.7% versus 10.8%, P=0.019), but at 5-years was non-significant at 12.3% vs. 7.9%, P=0.631. Overall mortality was reduced with CABG vs. OMT (25.1% vs. 31.0%, P=0.089), although not reaching statistical significance, at 5–year was 12.8% vs. 16.2%, P=0.824. The pairwise comparison analysis showed a significant 2.02- and 2.77-fold increased risk of cardiac death and subsequent MI with MT versus CABG, respectively, demonstrating the progressively better long-term prognosis of surgical patients.

The results of the MASS-II trial parallel the findings of STICH<sup>8</sup>, FREEDOM<sup>9</sup>, and SYNTAX<sup>10</sup> trials, where additional and robust benefits from CABG were progressively increasing at longer-term follow-up beyond the 5-years scrutiny.
Secondly, the ISCHEMIA trial was neither designed nor statistically powered to compare CABG with OMT. In particular, the CABG stratum was not powered for potential mortality differences, and the follow-up was restricted to a median of 3.2 years. The primary outcome was the composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. The key secondary outcomes were the composite of death from cardiovascular causes or myocardial infarction and angina-related quality of life. The method of revascularization in the invasive group, percutaneous or surgical, was not randomized in the ISCHEMIA trial. In fact, CABG represented only 26% of all revascularization procedures, and actually performed in 20% of patients in the initial invasive strategy, and indicated only when PCI was not the best option due to the extent and severity of CAD. Therefore, it is inappropriate to compare CABG vs. MT from ISCHEMIA due to a strong selection bias. The patients enrolled in the ISCHEMIA trial were not representative of patients with multivessel CAD meriting guideline based CABG, fewer than half had proximal stenosis of the left anterior descending coronary artery. The overall analysis of the ISCHEMIA trial therefore cannot be applied to this subset of more complex patients who received CABG. There is no reasonable way to match CABG and OMT patients by anatomy, and even this comparison would not provide any high-quality causal inference, as it would be underpowered, not pre-specified, or randomized. It is illogical that such implied effects or unpublished data, which goes against previously validated published recommendations, were used to guide the revision recommendations while discounting prior published RCT. Therefore, the ISCHEMIA trial did not provide any new or consistent evidence to invalidate the previous Class 1 LOE A for CABG in multivessel coronary disease.
Further analysis of the ISCHEMIA trial revealed that more severe CAD was associated with increased risk of MI (both spontaneous and periprocedural MI subtypes), higher risk of cardiovascular death, the trial primary composite endpoint, and cardiovascular death or MI. The outcomes of the typical multivessel CABG patient contemporarily referred by heart teams, i.e., 3-vessel severe stenosis (≥70%) or 2-vessel severe stenosis with proximal LAD (defined by the authors as modified Duke Prognostic Index score of 6), showed a significant reduction in the 4-year rate of cardiovascular death or myocardial infarction in the invasive strategy group (difference, 6.3% [95% CI, 0.2%–12.4%]).\textsuperscript{11,12} The ISCHEMIA trial included less than one-third of the patients in this category. Additionally, the anatomic completeness of revascularization in the CABG group was 34% and the functional was 48.5%, clearly below the expected rate.

While the guideline states that CABG as a revascularization strategy versus MT alone "may be reasonable" to improve survival in stable patients with 3-vessel CAD, the writing committee concluded that the ability of PCI to improve survival, compared with MT alone in patients with multivessel CAD, remains uncertain. Nonetheless, both procedures receive the same COR 2b.

This recommendation is in contrast with evidence supporting PCI. While PCI has consistently been shown in RCT (as in COURAGE and BARI-2D), and meta-analyses to have no benefit compared to MT in terms of MI and death in patients with multivessel coronary disease.\textsuperscript{13} CABG has been demonstrated to afford superior results compared to PCI with hard endpoints over the long-term in patients with advanced CAD.\textsuperscript{14} PCI has only been shown to offer better results than MT when it is combined as a common "revascularization" group with CABG. However, performing such analyses is incorrect since both revascularization strategies are different, should not be grouped together as
equivalent revascularization procedures and should not be considered part of evidence-based recommendations.

Furthermore, two recent trials comparing CABG and PCI in 3VD patients provide insights, that the writing committee appears to have overlooked. In the five-year analysis of the SYNTAX trial, of patients with 3VD and mostly preserved EF, CABG was associated with a significant reduction in cardiovascular and cardiac death, primarily from a decrease in MI-related death with CABG compared with PCI. In contrast, treatment with PCI vs. CABG was an independent predictor of cardiac death. The difference in MI-related death was seen mainly in patients with diabetes, 3VD, or high SYNTAX scores. SYNTAX reported a 40% higher mortality rate in 3VD patients with PCI than CABG.\textsuperscript{15,16}

At 10-year follow-up, the SYNTAX Extended Survival (SYNTAXES) reported a significantly lower all-cause death with CABG than PCI with a significant survival benefit in patients with three-vessel disease, with the survival curves continuously diverging over time.\textsuperscript{10}

The writing committee, given time constraints, missed the report of recent evidence from the FAME-3 non-inferiority trial one-year results, which randomized 3VD patients with predominantly preserved LV function (> 80% of patients had EF >50%) and no LM disease to either CABG or fractional flow reserve (FFR)-guided PCI with current-generation zotarolimus-eluting stents. In the 1-year analysis of the composite primary endpoint, the most cutting-edge PCI technology was not effective in reducing major adverse cardiovascular and cerebrovascular events compared with CABG, reinforcing the advantages of CABG in 3VD patients. The incidence of spontaneous myocardial infarction (3.3% vs. 2.3%), death from any cause (1.6% vs. 0.9%), and cardiovascular death (0.8% vs. 0.5%) were higher with PCI vs. CABG, respectively, although not reaching statistical significance. The findings are notable as the benefit of CABG was
evident at the very early stage of the study, with just 1-year follow-up, in contrast to previous studies where favorable results for CABG were only observed after longer-term follow-up. Subgroup analysis showed patients with EF>50% fared better than patients with EF 30–50% concerning the primary composite endpoint. The better outcomes seen with CABG in the trial were attributed to the improvements in operative techniques and more effective medical therapy.\textsuperscript{17} However, the generalizability of this trial may be limited since FFR-guided PCI is not the standard of care across the US or the world.

One of the most significant differences between the new 2021 guidelines and the replaced 2012 guidelines is that the current guideline is not endorsed by either the American Association for Thoracic Surgeons or the Society of Thoracic Surgeons\textsuperscript{18,19}. Considering that CAD is a clinical entity with broad therapeutic approaches, it represents an essential deviation from the Heart Team approach for CAD management, which is given a COR 1, "In patients for whom the optimal treatment strategy is unclear, a Heart Team approach that includes representatives from interventional cardiology, cardiac surgery, and clinical cardiology is recommended to improve patient outcomes."

Therefore, the 2021 ACC/AHA/SCAI guideline seems controversial and inconsistent with an impartial analysis of the evidence, resulting in inaccurate recommendations potentially damaging to patients with advanced CAD at risk. These may also unduly interfere with professional judgments and the appraisal and recommendation of the Heart Team.

Although primarily aimed to guide American medical practice, this guideline has far-reaching implications, influencing the treatment of advanced CAD all over the world. Consequently, if widely adopted, the current recommendations could potentially harm patients with advanced CAD worldwide. Furthermore, the healthcare budgets of poor,
emergent, or even rich nations will unnecessarily be strained by inappropriate procedures carrying higher costs in the years to come, diverting precious resources.

A revision of these guideline recommendations, including evidence from existing validated and new recent trials and an objective interpretation and correlation between evidence and recommendations, is imperative. This would align with the guideline's text, where it is clearly stated that "to ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections or knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science". The time has come for a thorough and impartial realignment between evidence and commensurate guideline recommendations.

References


3. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and


**Central Picture**

![Central Picture](image)

**Central Picture Legend:**

A worldwide call for consistency and logic.

**Graphical Abstract**
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Figure 1 Legend: A necessary realignment between evidence and commensurate guideline recommendations.
2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization
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