

# Reversal of Therapeutic Recommendations in the American College of Cardiology Coronary Artery Disease Guidelines

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## Abstract

**Background:** Medical reversal is defined as the discontinuation of a procedure's recommendation due to new evidence regarding its efficacy or safety. Cardiology is the specialty with the highest number of documented reversals, yet there is no information available about the probability of reversal.

**Objectives:** To describe the frequency of medical reversal in the ischemic heart disease guidelines published by the American College of Cardiology/American Heart Association (ACC/AHA), according to levels of evidence.

**Methods:** The most recent guidelines for stable coronary disease, non-ST-elevation acute coronary syndrome, and ST-elevation myocardial infarction were compared with the first version. Medical reversal was defined as a shift from a recommended procedure to a contraindicated one or the removal of the recommendation. The quality of evidence was categorized by the guidelines as high, moderate, or low.

**Results:** A total of 224 therapeutic recommendations were identified, with 19% based on high-quality evidence, 42% on moderate-quality evidence, and 39% on low-quality evidence. Forty-nine medical reversals were observed, constituting 22% of all therapeutic recommendations included in the first version of the guidelines. The probability of reversal for procedures based on high-quality evidence was 2%, compared with 25% for procedures with moderate-quality evidence and 30% for procedures with low-quality evidence.

**Conclusion:** In the ACC/AHA ischemic heart disease guidelines, medical reversal is common in recommendations based on moderate or low-quality evidence, but rare in those with high-quality evidence.

**Keywords:** Coronary Artery Disease; Acute Coronary Syndrome; Myocardial Infarction.

## Introduction

Over time, certain clinical practices are replaced by more advantageous ones, whereas others remain in use for extended periods until they are shown to be non-beneficial or even harmful; this phenomenon is known as medical reversal.<sup>1-9</sup> The primary consequence is harm to patients receiving medical practices lacking high-level scientific evidence.<sup>10,11</sup> Robust studies that challenge these practices are not promptly developed or published, leading to the implementation of medical practices based on low-quality evidence.<sup>12-14</sup>

A study summarizing 363 studies that evaluated medical practices in use over the last decade found that 146 (40.2%) yielded results that contradicted those practices.<sup>2</sup> Cardiology<sup>15</sup> was the specialty with the highest number of documented

reversals.<sup>6-9,16-18</sup> This may be linked to the weak scientific basis of certain recommendations, given that 48% of practices recommended in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines<sup>19</sup> are derived from low-quality evidence, whereas only 11% stem from high-quality evidence.<sup>20-25</sup> A recent study assessing a set of ACC/AHA guidelines across various clinical contexts found that 9.2% of the recommendations had been reversed.<sup>21</sup>

The objective of this study was to describe the frequency of reversal among therapeutic recommendations in ACC/AHA guidelines for symptomatic ischemic heart disease by comparing the initial versions with the most recent updates. Results were stratified according to the level of evidence.

## Methods

### Guideline selection

The search was conducted on the official website of the American Heart Association, within the "Guidelines & Statements" section.<sup>19</sup> Three clinical contexts were identified for which guidelines addressing symptomatic ischemic heart disease had been developed: stable angina,<sup>26,27</sup> non-ST-elevation acute coronary syndrome,<sup>28,29</sup> and ST-elevation

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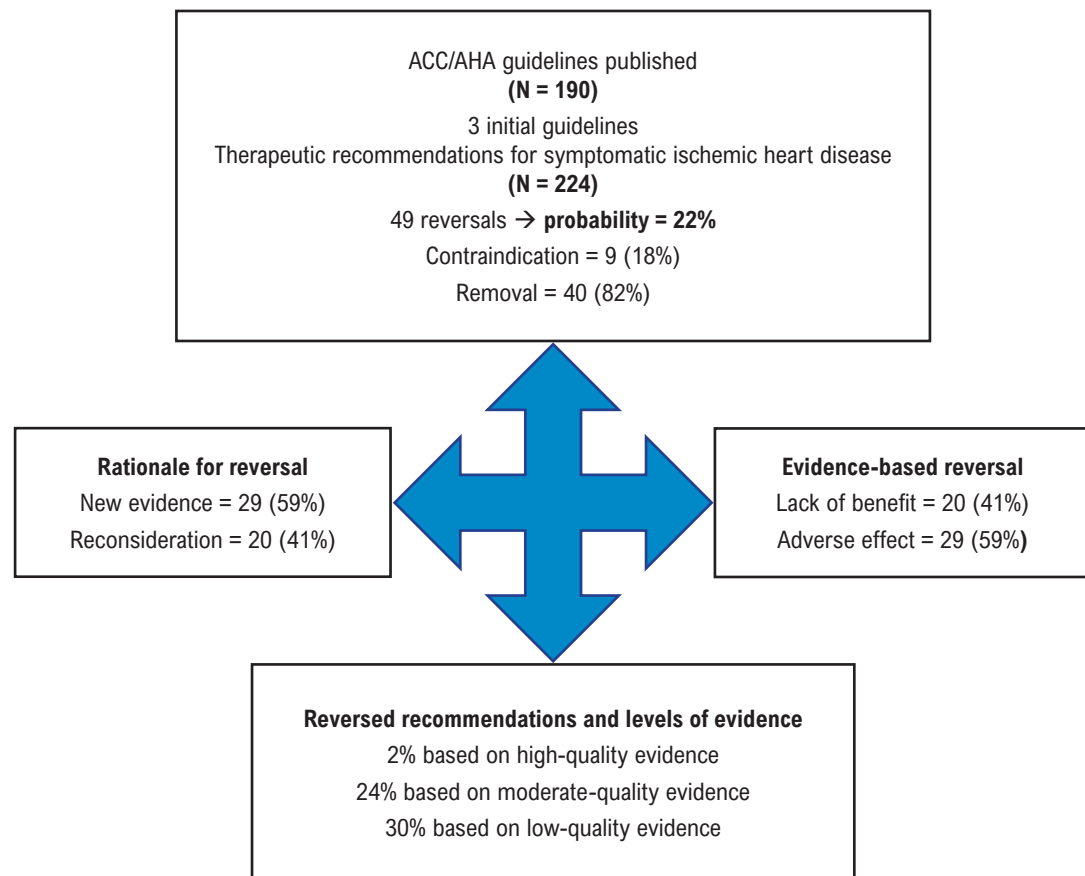
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**Central Illustration: Reversal of Therapeutic Recommendations in the American College of Cardiology Coronary Artery Disease Guidelines****Probability and rationale for medical reversal in ACC/AHA guidelines for symptomatic ischemic heart disease from 1999 to 2019**

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myocardial infarction.<sup>30,31</sup> The interval between the first and most recent versions of each guideline spanned 1999 to 2019.

#### Data extraction

Two researchers (ACC and DMDS) independently extracted the recommendations, which were entered into a spreadsheet and compared. Disagreements were resolved through discussion between the researchers. Extracted variables included guideline publication date; guideline classification by ischemic heart disease category (stable angina, non-ST-elevation acute coronary syndrome, and ST-elevation myocardial infarction); medical recommendations (pharmacological/interventional); levels of evidence (high, moderate, and low); number of recommendations; categories of medical reversals (evidence-based/rationale-based); and adverse effects (cardiovascular mortality, all-cause mortality,

major bleeding, malignant arrhythmia, and non-ST-elevation acute coronary syndrome).

#### Definitions

The recommendations contained in the initial version were tracked in the most recent version of the guidelines. Reversal was defined as a change from an indication to a contraindication or the removal of the recommendation. Intermediate versions were consulted to identify the timing of the reversal and possible justifications. Justifications were classified as supported by new scientific evidence contradicting previous beliefs or based on reconsideration by the authors. The evidence underpinning recommendations was classified according to study design. Practice-changing evidence was assessed to determine whether it was related to lack of benefit or to adverse effects.

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### Data analysis

This study describes the complete set of the three types of guidelines analyzed and does not aim to extrapolate the results to other guidelines or societies. Therefore, frequentist inference in the form of confidence intervals or p values does not apply. Frequencies are reported in absolute and relative terms.

Descriptive statistical analysis was performed using IBM SPSS Statistics Premium Grad Pack v14 software, licensed by the Bahiana School of Medicine and Public Health (EBMSP).

### Results

For the period from 1999 to 2019, 190 publications were identified on the ACC/AHA guidelines website,<sup>21</sup> with three topics addressing symptomatic ischemic heart disease. The initial versions were published in 1999,<sup>26</sup> 2000,<sup>28</sup> and 2004,<sup>30</sup> for stable angina, non-ST-elevation acute coronary syndromes, and ST-elevation myocardial infarction, respectively (Figure 1).

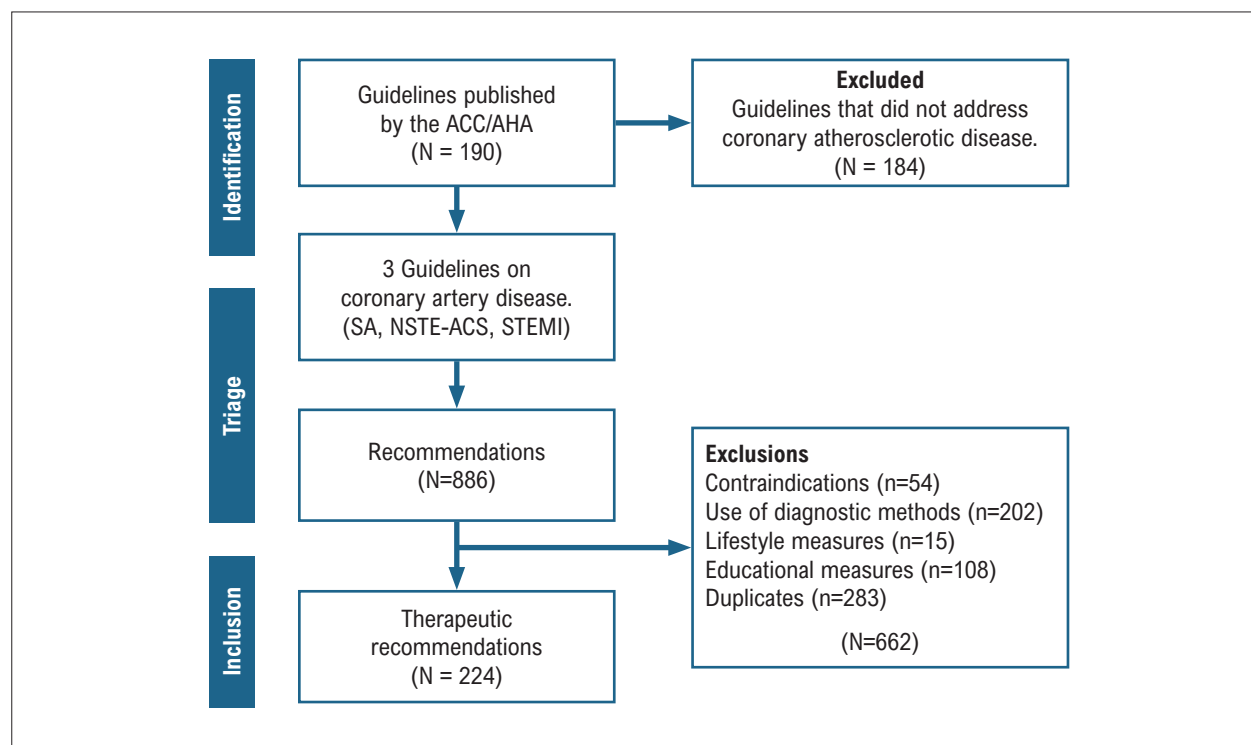
The most recent guidelines used to assess medical reversals were published in 2012,<sup>27</sup> 2013,<sup>29</sup> and 2013,<sup>31</sup> respectively. Among a total of 886 recommendations identified in the initial versions, 224 were therapeutic recommendations: 25 for stable angina, 42 for ST-elevation acute coronary syndrome, and 157 for non-ST-elevation myocardial infarction. With respect to levels of evidence, 45 (20%) were based on high-quality evidence, 100 (45%) on moderate-quality evidence, and 79 (35%) on low-quality evidence (Table 1).

Forty-nine medical reversals were identified (Table 2), indicating a 22% probability of reversal. Among these, 18%

**Table 1 – Characteristics of therapeutic recommendations in ACC/AHA guidelines for symptomatic ischemic heart disease from 1999 to 2019**

| Characteristics                   | N (%)     |
|-----------------------------------|-----------|
| <b>Clinical condition</b>         | 224       |
| STEMI                             | 157 (70%) |
| Non-ST-elevation ACS              | 42 (19%)  |
| Stable angina                     | 25 (11%)  |
| <b>Treatment type</b>             |           |
| Pharmacological                   | 131 (58%) |
| Interventional                    | 93 (42%)  |
| <b>Strength of recommendation</b> |           |
| Strong                            | 126 (56%) |
| Moderate                          | 98 (44%)  |
| <b>Quality of evidence</b>        |           |
| High                              | 45 (20%)  |
| Moderate                          | 100 (45%) |
| Low                               | 79 (35%)  |

ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction.



**Figure 1 – Study selection flowchart.** CAD: atherosclerotic coronary artery disease; SA: stable angina; NSTEMI: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction. Source: Author.

**Table 2 – ACC/AHA guideline recommendations for symptomatic ischemic heart disease that were subsequently reversed**

| Guideline            | Original recommendation                                                                                                                                                            | Modification     |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| Stable angina        | Mild anticoagulation with warfarin and aspirin<br>(Moderate recommendation with moderate-quality evidence)                                                                         | Removal          |
| Stable angina        | Postmenopausal hormone replacement<br>(Moderate recommendation with moderate-quality evidence)                                                                                     | Contraindication |
| Stable angina        | Folate therapy associated with elevated homocysteine<br>(Moderate recommendation with low-quality evidence)                                                                        | Contraindication |
| Stable angina        | Vitamin C and E supplementation<br>(Moderate recommendation with moderate-quality evidence)                                                                                        | Contraindication |
| Stable angina        | PTCA or CABG for single- or double-vessel CAD<br>(Strong recommendation with moderate-quality evidence)                                                                            | Contraindication |
| Stable angina        | PTCA, CABG, or PTCA for recurrent stenosis<br>(Moderate recommendation with moderate-quality evidence)                                                                             | Removal          |
| Non-ST-elevation ACS | PCI for focal and multiple lesions in inoperable patients<br>(Moderate recommendation with moderate-quality evidence)                                                              | Contraindication |
| Non-ST-elevation ACS | Repeat CABG for multiple saphenous vein graft stenoses<br>(Moderate recommendation with moderate-quality evidence)                                                                 | Removal          |
| Non-ST-elevation ACS | Gemfibrozil or niacin for HDL < 40 and a triglyceride level of > 200 mg/dL<br>(Moderate recommendation with moderate-quality evidence)                                             | Removal          |
| Non-ST-elevation ACS | PTCA in diabetic patients with single-vessel disease and ischemia<br>(Moderate recommendation with moderate-quality evidence)                                                      | Contraindication |
| Non-ST-elevation ACS | Abciximab in patients with DM treated with stents<br>(Moderate recommendation with moderate-quality evidence)                                                                      | Removal          |
| Non-ST-elevation ACS | Repeat CABG for saphenous vein graft stenoses<br>(Moderate recommendation with low-quality evidence)                                                                               | Removal          |
| Non-ST-elevation ACS | Nitroglycerin and calcium channel blockers for ST-segment elevation or depression and chest pain<br>(Strong recommendation with low-quality evidence)                              | Removal          |
| Non-ST-elevation ACS | Beta-blockers for arterial hypertension or tachycardia<br>(Moderate recommendation with low-quality evidence)                                                                      | Contraindication |
| Non-ST-elevation ACS | Therapy with nitrates, beta-blockers, and calcium channel antagonists<br>(Strong recommendation with moderate-quality evidence)                                                    | Removal          |
| Non-ST-elevation ACS | Hormone replacement therapy in women<br>(Moderate recommendation with low-quality evidence)                                                                                        | Contraindication |
| Non-ST-elevation ACS | Imipramine for persistent pain<br>(Moderate recommendation with low-quality evidence)                                                                                              | Removal          |
| STEMI                | Oxygen therapy during the first 6 hours<br>(Moderate recommendation with low-quality evidence)                                                                                     | Removal          |
| STEMI                | Morphine for pain<br>(Strong recommendation with low-quality evidence)                                                                                                             | Removal          |
| STEMI                | Fresh plasma, cryoprecipitate, protamine, and platelets for severe bleeding<br>(Moderate recommendation with low-quality evidence)                                                 | Removal          |
| STEMI                | Preventive reperfusion therapy with abciximab at half the dose of reteplase or tenecteplase in patients < 75 years old<br>(Moderate recommendation with moderate-quality evidence) | Removal          |

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|       |                                                                                                                                                                                |         |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| STEMI | Preventive reperfusion therapy with abciximab at half the dose of reteplase or tenecteplase before angiography and PTCA<br>(Moderate recommendation with low-quality evidence) | Removal |
| STEMI | Emergency CABG within the first 18 hours of cardiogenic shock<br>(Moderate recommendation with moderate-quality evidence)                                                      | Removal |
| STEMI | Bivalirudin with streptokinase for thrombocytopenia within the first 12 hours<br>(Moderate recommendation with moderate-quality evidence)                                      | Removal |
| STEMI | Thienopyridine for patients with aspirin intolerance<br>(Strong recommendation with low-quality evidence)                                                                      | Removal |
| STEMI | Magnesium replacement when levels are reduced<br>(Moderate recommendation with low-quality evidence)                                                                           | Removal |
| STEMI | Magnesium sulfate for torsades de pointes<br>(Moderate recommendation with low-quality evidence)                                                                               | Removal |
| STEMI | Intravenous nitroglycerin within the first 48 hours for persistent ischemia<br>(Strong recommendation with moderate-quality evidence)                                          | Removal |
| STEMI | Subcutaneous LMWH for prolonged hospitalizations and high risk of DVT<br>(Strong recommendation with high-quality evidence)                                                    | Removal |
| STEMI | Oxygen therapy for pulmonary congestion with saturation > 90%<br>(Strong recommendation with low-quality evidence)                                                             | Removal |
| STEMI | Early reperfusion for right ventricular infarction and ischemic dysfunction<br>(Strong recommendation with low-quality evidence)                                               | Removal |
| STEMI | Aneurysmectomy and CABG for ventricular aneurysm with tachyarrhythmias and lack of therapeutic response<br>(Strong recommendation with moderate-quality evidence)              | Removal |
| STEMI | Electrical shock for ventricular fibrillation or pulseless VT<br>(Strong recommendation with moderate-quality evidence)                                                        | Removal |
| STEMI | Potassium replacement to > 4.0 mEq/L and magnesium replacement to > 2.0 mg/dL<br>(Moderate recommendation with low-quality evidence)                                           | Removal |
| STEMI | Electrical shock for sustained VT or hemodynamic instability<br>(Strong recommendation with moderate-quality evidence)                                                         | Removal |
| STEMI | Potassium replacement to > 4.0 mEq/L and magnesium replacement to > 2.0 mg/dL in refractory VT<br>(Moderate recommendation with low-quality evidence)                          | Removal |
| STEMI | Intravenous digoxin for nodal reentrant tachycardia<br>(Strong recommendation with low-quality evidence)                                                                       | Removal |
| STEMI | Corticosteroids for pericarditis refractory to aspirin and NSAID<br>(Moderate recommendation with low-quality evidence)                                                        | Removal |
| STEMI | PTCA with carotid stent for > 50% stenosis after ischemic stroke in high-risk patients<br>(Moderate recommendation with low-quality evidence)                                  | Removal |
| STEMI | Niacin or fibrate for HDL-C < 40 mg/dL when LDL-C < 100 mg/dL and non-HDL-C < 130 mg/dL<br>(Moderate recommendation with moderate-quality evidence)                            | Removal |
| STEMI | Clopidogrel or ticlopidine in cases of aspirin allergy<br>(Strong recommendation with low-quality evidence)                                                                    | Removal |
| STEMI | Warfarin in cases of aspirin allergy as an alternative to clopidogrel<br>(Strong recommendation with low-quality evidence)                                                     | Removal |

|       |                                                                                                                                                                                                  |         |
|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| STEMI | ARB as an alternative to ACEI in clinical CHF or LVEF < 40%<br>(Moderate recommendation with moderate-quality evidence)                                                                          | Removal |
| STEMI | ACEI and ARB in symptomatic CHF and LVEF < 40%<br>(Moderate recommendation with moderate-quality evidence)                                                                                       | Removal |
| STEMI | Beta-blocker in moderate to severe left ventricular failure<br>(Strong recommendation with low-quality evidence)                                                                                 | Removal |
| STEMI | Blood pressure < 140/90 mmHg with pharmacotherapy and < 130/80 mmHg<br>in patients with diabetes and CKD<br>(Strong recommendation with moderate-quality evidence)                               | Removal |
| STEMI | Hypoglycemic therapy to maintain HbA1c < 7%<br>(Strong recommendation with moderate-quality evidence)                                                                                            | Removal |
| STEMI | Anticoagulation with warfarin combined with clopidogrel for patients with<br>aspirin allergy undergoing PTCA with stenting<br>(Strong recommendation with low-quality evidence)                  | Removal |
| STEMI | Warfarin or warfarin combined with aspirin for patients undergoing PTCA<br>without stenting who have an indication for anticoagulation<br>(Strong recommendation with moderate-quality evidence) | Removal |

ACEI: angiotensin-converting enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass graft; CAD: coronary artery disease; CHF: congestive heart failure; CKD: chronic kidney disease; DM: diabetes mellitus; DVT: deep vein thrombosis; HbA1c: glycated hemoglobin; LMWH: low-molecular-weight heparin; LVEF: left ventricular ejection fraction; NSAID: nonsteroidal anti-inflammatory drugs; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty; STEMI: ST-elevation myocardial infarction; VT: ventricular tachycardia.

became contraindications, whereas the remainder were no longer recommended in the latest version of the guidelines. Reversals stemmed from new evidence in 59% of cases, and 41% resulted from reconsideration by the authors. Among the evidence-based reversals, 35% originated from randomized controlled trials and 65% from non-experimental studies. This evidence influenced the reversals by demonstrating adverse effects in 59% of cases and a lack of benefit in the remaining 41%. Regarding levels of evidence, reversals were observed in only one of the 45 (2%) therapeutic recommendations originally based on high-quality evidence, 24% of those based on moderate-quality evidence, and 30% of those based on low-quality evidence (Central Illustration).

## Discussion

This metascientific study assessed the evolution of ACC/AHA guidelines on stable angina, non-ST-elevation acute coronary syndromes, and ST-elevation myocardial infarction between 1999 and 2019. The study demonstrates that medical reversal was a frequent phenomenon in ACC/AHA guidelines on symptomatic ischemic heart disease. This observation held true for subgroups of recommendations based on low- or moderate-quality evidence; however, the phenomenon was rare when the practice was supported by a high level of scientific evidence.

According to our review, only one previous study assessed the probability of reversal in cardiovascular disease guidelines.<sup>21</sup> Similar to our study, Neuman et al.<sup>21</sup> evaluated 11 ACC/AHA guidelines across various clinical contexts. Our data complement their findings by focusing specifically on symptomatic ischemic heart disease.

It had previously been reported that moderate or low levels of evidence predominated in ACC/AHA guideline recommendations; however, the association with medical reversal had not been demonstrated.<sup>20,22-25</sup> A recent study evaluated 11 ACC/AHA guidelines across various clinical contexts and reported a 20% rate of medical reversal.<sup>21</sup> Our data complement these findings by focusing specifically on symptomatic ischemic heart disease, demonstrating a similar probability of reversal.

Our data reinforce the idea that recommendations on procedures or therapies should be based on a high level of evidence, with the aim of minimizing unintended consequences arising from ineffective procedures or treatments.<sup>10,11</sup> It is possible that hasty recommendations stem from a fear of omission.<sup>32</sup> This concern may be mitigated when considering the marginal benefit of the majority of current therapeutic innovations, which can be counterbalanced by the unintended consequences of issuing recommendations prematurely.<sup>32-36</sup>

Caution is necessary when generalizing these conclusions to guidelines for other clinical conditions, medical societies, or countries. From the perspective of medical practice, we do not see strong reasons for heterogeneity; nevertheless, regional variations in medical practice have been documented, and these may also differ according to healthcare systems.

## Conclusion

In ACC/AHA guidelines for symptomatic ischemic heart disease, medical reversal was common among

recommendations based on moderate- or low-quality evidence, but rare among those based on high-quality evidence.

## Author Contributions

Conception and design of the research: Caldas AC, Correia LCL; acquisition of data: Caldas AC, Medina D; analysis and interpretation of the data: Caldas AC, Matias D, Medina D, Correia LCL; statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Caldas AC, Matias D, Correia LCL.

## Potential conflict of interest

No potential conflict of interest relevant to this article was reported.

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## Study association

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## Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

## Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

## Data Availability Statement

The underlying content of the research text is contained within the manuscript.

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