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REVIEW

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2022 Joint ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease in patients at low surgical risk and anatomy suitable for PCI or CABG

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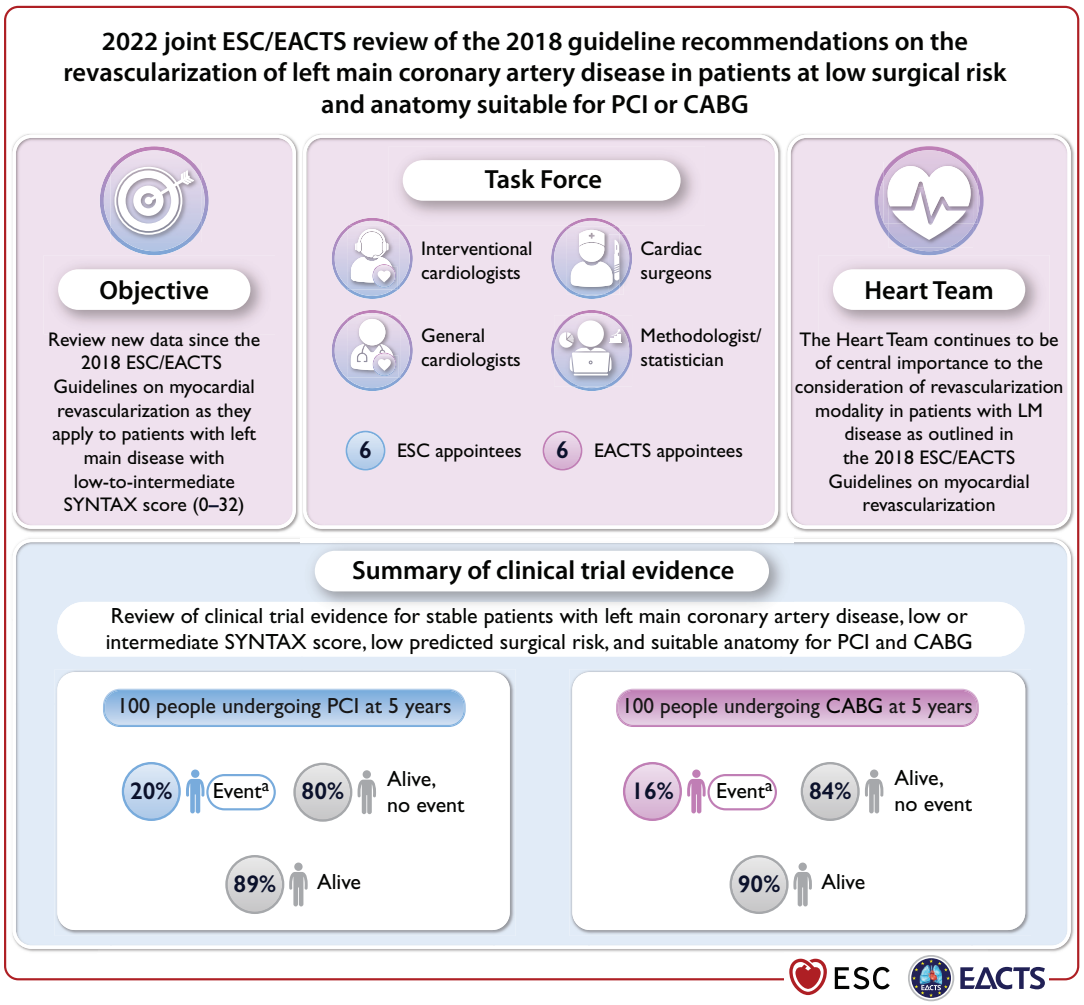

Task Force structure and summary of clinical evidence of 2022 ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LM, left main; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. [a]'Event' refers to the composite of death, myocardial infarction (according to Universal Definition of Myocardial Infarction if available, otherwise protocol defined) or stroke.

Abstract

In October 2021, the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) jointly agreed to establish a Task Force (TF) to review recommendations of the 2018 ESC/EACTS Guidelines on myocardial revascularization as they apply to patients with left main (LM) disease with low-to-intermediate SYNTAX score (0-32). This followed the withdrawal of support by the EACTS in 2019 for the recommendations about the management of LM disease of the previous guideline. The TF was asked to review all new relevant data since the 2018 guidelines including updated aggregated data from the four randomized trials comparing percutaneous coronary intervention (PCI) with drug-eluting stents vs. coronary artery bypass grafting (CABG) in patients with LM disease. This document represents a summary of the work of the TF; suggested updated recommendations for the choice of revascularization modality in patients undergoing myocardial revascularization for LM disease are included. In stable patients with an indication for revascularization for LM disease, with coronary anatomy suitable for both procedures and a low predicted surgical mortality, the TF concludes that both treatment options are clinically reasonable based on patient preference, available expertise, and local operator volumes. The suggested recommendations for revascularization with CABG are Class I, Level of Evidence A. The recommendations for PCI are Class IIa, Level of Evidence A. The TF recognized several important gaps in knowledge related to revascularization in patients with LM disease and recognizes that aggregated data from the four randomized trials were still only large enough to exclude large differences in mortality.

Keywords: Coronary artery disease • clinical practice guidelines • coronary artery bypass grafting • Heart Team • left main coronary artery • left main stenosis • meta-analysis • myocardial revascularization • percutaneous coronary intervention • randomized controlled trials

PREAMBLE

In October 2021, the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) agreed to establish a panel of experts to review the recommendations for revascularization of left main (LM) coronary artery disease (CAD) from the 2018 ESC/EACTS Guidelines on myocardial revascularization [1], and recommend revision, if appropriate, of the recommendations on the choice of treatment modality for the management of LM CAD for low Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) score (0-22) and intermediate SYNTAX score (23-32), as set out in the recommendation table (page 107) [1], and the accompanying text describing the evidence and recommendations for LM CAD (page 109) [1].

The panel members were selected by the ESC and EACTS to represent professionals involved with the medical care of patients with this pathology and to provide expertise in biostatistics. Panel members provided declaration of interest forms including all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules by both the ESC and EACTS. Declarations have been compiled in a report and published in a supplementary document simultaneously to this document.

This review did not follow a formal guideline development process. However, the level of evidence and the strength of recommendation of management options included in this document were weighed and graded according to agreed scales, and which applied to the prior recommendations or any suggested updated recommendations. All proposed recommendations were subject to a vote and required support from at least 75% of voting (i.e. non-abstaining) panel members to be recorded as agreed. Minutes of the three Task Force (TF) meetings are included as a supplement to this manuscript.

Upon validation of the content by all the experts involved in the panel, the document was peer-reviewed by members of the Boards of the ESC and EACTS. Both Boards provided final sign-off for the publication of this document.

This document aims to summarize and evaluate available evidence to assist health professionals in proposing the best management strategies for an individual patient with a given condition. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate. This ESC/EACTS document does not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is the healthcare professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription.

INTRODUCTION

In October 2021, the ESC and EACTS jointly agreed to establish a TF to review recommendations of the 2018 ESC/EACTS Guidelines on myocardial revascularization [1] as they apply to LM disease. This document represents a summary of the work of the TF and contains updated recommendations for the choice of revascularization modality in patients undergoing myocardial revascularization for LM disease.

In December 2019, EACTS withdrew their support of the recommendations for LM disease in low surgical risk patients with stable coronary artery disease—either chronic coronary syndrome or stabilized acute coronary syndrome—amenable to both coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI). This response followed the 2019 publication of the 5-year results of the Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial [2]. The primary outcome, the composite of death, stroke, or myocardial infarction (MI), was not statistically different after PCI or CABG [22.0% vs. 19.2%; odds ratio (OR) 1.19 (95% confidence interval, CI 0.95-1.50)], consistent with the conclusions from the 3-year EXCEL results [3], which informed the 2018 guidelines. However, all-cause mortality, a secondary outcome, was increased in patients allocated to PCI [13.0% vs. 9.9%; OR 1.38 (95% CI 1.03-1.85)]. In addition, there was controversy related to the reporting of periprocedural MI, which was initially reported only according to the protocol definition rather than also according to the Universal Definition (UDMI) [4]. Periprocedural MI according to the UDMI was later reported: while the incidence was similar to the protocol definition in the PCI arm (3.9% vs. 3.3%), it was markedly lower in the CABG arm (6.0% vs. 1.4%) [5].

In November 2021, an individual patient data meta-analysis by Sabatine and colleagues [6] was published providing important new information that can inform the LM management recommendations. This meta-analysis included data from the 4 randomized controlled trials (RCTs) comparing PCI using drug-eluting stents (DES) to CABG with at least 5 years of follow-up: SYNTAX [7], Bypass Surgery Versus Angioplasty Using Sirolimus Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) [8], Nordic-Baltic-British left main revascu larisation study (NOBLE) [9], and EXCEL [2].

The complete terms of reference for the TF are provided in the supplementary data online. The TF would have 12 members, with equal representation for the 2 societies (6 appointments each), with each society identifying one person to co-chair the proceedings. The panel was expected to review all new research and other relevant material published or presented publicly since the publication of the 2018 guidelines including the results on 5-year survival and procedural MI as defined by the UDMI in the EXCEL trial, and the individual patient data meta-analysis by Sabatine *et al.* (Graphical Abstract).

Overview of the 2018 ESC/EACTS guidelines on myocardial revascularization

The 2018 ESC/EACTS Guidelines on myocardial revascularization is a comprehensive document including recommendations about indications for myocardial revascularization, considerations regarding the modality of revascularization (PCI vs. CABG), considerations in special situations, and technical aspects of PCI and CABG. The reader is referred to the main document for detailed consideration on these general aspects of myocardial revascularization [1].

A patient-centred approach to informed consent is a cornerstone of clinical practice. In the 2018 ESC/EACTS Guidelines on myocardial revascularization, it is recommended that patients are

adequately informed about short- and long-term benefits and risks of the revascularization procedure with information about local experience and allowed enough time for informed decision-making (Class I recommendation, level of evidence C). Such informed decision-making necessarily and explicitly considers the preference of the patient for one or other of the treatment options available. It is recommended that institutional protocols are developed by the Heart Team to implement the appropriate revascularization strategy in accordance with current guidelines (Class I recommendation, level of evidence C). In PCI centres without on-site surgery, it is recommended that institutional protocols are established with partner institutions providing cardiac surgery (Class I recommendation, level of evidence C).

In considering the modality of revascularization, for patients with a stable presentation, with suitable coronary anatomy for both PCI and DES and low predicted surgical mortality, recommendations are discussed separately for patients with one-vessel, two-vessel, three-vessel and LM CAD. In patients with LM CAD, recommendations are considered according to anatomic disease complexity as determined by the SYNTAX score. In patients with low or intermediate SYNTAX scores, CABG received a Class I, level of evidence A recommendation, while PCI received Class I and IIa recommendations for low and intermediate SYNTAX scores, respectively (level of evidence A for both recommendations.) Note that in patients with high SYNTAX scores, CABG is indicated (Class I recommendation, level of evidence A) whereas PCI is not recommended (Class III recommendation, level of evidence B). The latter recommendations for patients with LM CAD and high SYNTAX scores were not reviewed by the current TF as per its terms of reference.

New data from clinical trials

Since the publication of the 2018 ESC/EACTS Guidelines on myocardial revascularization, four additional relevant reports, one from each of the four prospective RCTs comparing PCI with DES vs. CABG in patients with LM disease—the previously mentioned NOBLE, EXCEL, PRECOMBAT and SYNTAXES—were identified [2, 9–11]. The additional reports included data from longer-term follow-up in each case; a summary of the main results is replicated below and in the evidence table in the supplementary data online, Supplementary Tables S1-S3.

NOBLE randomized 1201 patients with LM disease 1:1 to PCI or CABG. The primary outcome, a composite of death, non-procedural MI, repeat revascularization, and stroke, at 5 years, had occurred in 28% of the PCI group and 19% of the CABG group [hazard ratio (HR) 1.58 (95% CI 1.24-2.01), P = .0002] [9]. The components of the primary outcome were all-cause mortality [9% vs. 9%, HR 1.08 (95% CI 0.74-1.59)], non-procedural MI [8% vs. 3%, HR 2.99 (95% CI 1.66-5.39)], repeat revascularization [17% vs. 10%, HR 1.73 (1.25-2.40)] and stroke [4% vs. 2%, HR 1.75 (0.86-3.55)].

EXCEL randomized 1905 patients with LM disease of low or intermediate anatomical complexity 1:1 to PCI or CABG. The primary outcome, a composite of death, stroke, or MI, at 5 years, had occurred in 22.0% of the PCI group and 19.2% of the CABG group [odds ratio (OR) 1.19 (95% CI 0.95-1.50), P = .13] [2]. The components of the primary outcome were all-cause mortality [13.0% vs. 9.9%, OR 1.38 (95% CI 1.03-1.85)], stroke [2.9% vs. 3.7%, OR 0.78 (95% CI 0.46-1.31)] and MI [10.6% vs. 9.1%, OR 1.14 (95% CI 0.84-1.55)]. The secondary outcome of ischaemia-driven revascularization was more frequent after PCI than after CABG [16.9% vs. 10.0%; OR 1.84 (95% CI 1.39-2.44)]. Using the UDMI definition rather than the protocol MI definition, the cumulative incidence of MI at 5 years was later reported to be 9.6% vs. 4.7% [5].

PRECOMBAT randomized 600 patients with LM disease 1:1 to PCI or CABG. The primary outcome, a composite of death, MI, stroke, or ischaemia-driven target-vessel revascularization, at 10 years, had occurred in 29.8% of the PCI group and 24.7% of the CABG group [HR 1.25 (95% CI 0.93-1.69)] [10]. The components of the primary outcome were all-cause mortality [14.5% vs. 13.8%, HR 1.13 (95% CI 0.75-1.70)], MI [3.2% vs. 2.8%, HR 0.76 (95% CI 0.32-1.82)], stroke [1.9% vs. 2.2%, HR 0.71 (95% CI 0.22-2.23)] and ischaemia-driven target-vessel revascularization [16.1% vs. 8.0%, HR 1.98 (95% CI 1.21-3.21)]. A secondary composite endpoint of death, MI, or stroke occurred in 18.2% of the PCI group and 17.5% of the CABG group [HR 1.00 (95% CI 0.70-1.44)].

SYNTAX randomized 1800 patients with *de-novo* three-vessel or LM disease 1:1 to PCI or CABG (1095 patients with three-vessel disease and 705 patients with LM disease). The primary endpoint of the extended follow-up (SYNTAXES study) was 10-year all-cause mortality [11]. Vital status information at 10 years was complete for 93% in the PCI group and 95% in the CABG group. Among patients with LM disease, 27% of the PCI group and 28% of the CABG group died by 10 years [HR 0.92 (95% CI 0.69-1.22)].

New data related to risk scores

In patients with LM disease, suitable coronary anatomy for both PCI and CABG, and low predicted surgical mortality, risk stratification relies on individual clinical and anatomical considerations. As recommended by the 2018 ESC/EACTS Guidelines on myocardial revascularization, the STS-PROM risk model is preferred to EuroSCORE II to predict the risk of mortality and morbidity of bypass surgery [1] and showed satisfactory discrimination for all-cause mortality at 30 days in patients undergoing CABG but not PCI according to subgroup analysis from the EXCEL trial [12].

The SYNTAX score, an anatomical grading system that aids the quantification of the overall burden of CAD, provides meaningful risk stratification for patients undergoing PCI but not for those undergoing CABG. In patients with disease undergoing revascularization, the low- (≤22 points), intermediate- (23-32 points) and high- (≥33 points) risk categories have been historically defined by tertiles of SYNTAX score distribution in the landmark SYNTAX trial [13]. A reported limitation of the SYNTAX score is inter-observer variability [14, 15]. High SYNTAX score—an exclusion criterion of the EXCEL trial—was present according to core laboratory review in approximately a quarter of the enrolled EXCEL patients; SYNTAX score was not a significant treatment modifier of the primary outcome according to local or central readings. In the NOBLE trial, no significant heterogeneity in the treatment effect for the primary composite outcome by SYNTAX score tertiles was reported at 5 years [9]. Similarly, no significant interactions were reported for the primary composite endpoint and individual outcomes in the PRECOMBAT trial at 10 years [16], and no significant gradient in all-cause mortality was observed in the SYNTAX Extended Study at 10 years [11]. The findings related to SYNTAX score from the individual patient

data meta-analysis by Sabatine and colleagues are discussed in more detail later in this review [6].

The SYNTAX score II, a model combining into a single risk scoring system anatomical and clinical information that might be relevant for decision making regarding revascularization in LM patients, has been recently redeveloped and validated [17]. The initial iteration of the SYNTAX score II showed an overestimation of all-cause mortality at 4 years and modest discrimination in patients from the EXCEL trial [18]. A newer iteration of the SYNTAX score II, also known as SYNTAX score 2020, was externally validated in a pooled dataset of the FREEDOM, PRECOMBAT and Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease (BEST) trial, with evidence of acceptable discrimination for the prediction of all-cause mortality at 10 years and modest discrimination for the prediction of major adverse cardiac events at 5 years [17]. In a further validation study, the score showed acceptable discrimination for all-cause mortality at 5 years in a Japanese cohort of patients with LM disease and/or multivessel disease [19]. However, the TF agreed that there is still limited meaningful prospective data to support a more prominent role of the SYNTAX score II or SYNTAX 2020 for decision making in patients with LM disease.

In patients with LM disease and an indication for revascularization, the evidence that the SYNTAX score identifies the best candidates for PCI when CABG is an option is not robust. However, the TF also agreed that there is insufficient new evidence to modify the current structure of the table of recommendations (i.e. based on SYNTAX score categories), and acknowledged that this frame is broadly adopted by local Heart Teams and provides unambiguous guidance for each type of patient that is likely to be encountered in daily practice.

Individual patient data meta-analysis of trials comparing PCI and CABG for left main disease

One of the key sets of data reviewed by the TF was the individual patient data meta-analysis [6] of the SYNTAX, PRECOMBAT, NOBLE and EXCEL trials [2, 9–11]. The key inclusion criteria for the meta-analysis were randomized trials comparing outcomes of patients treated with PCI with DES and CABG and at least 5 years of follow-up. Both the SYNTAX and PRECOMBAT studies also had 10 years of follow-up [10, 11]. The primary outcome of this review was mortality over 5 years. Secondary endpoints included cardiovascular death, spontaneous MI, procedural MI, stroke, and repeat revascularization, while a variety of composite outcomes were also reported as tertiary outcomes. The total sample size was 4394 patients. The median age was 66 years, the proportion of female patients was 23.3%, the median SYNTAX score was 25.0% and 22.9% had a SYNTAX score >33.

Mortality over 5 years was not statistically different between patients treated with PCI or with CABG [11.2% vs. 10.2%; HR 1.10 (95% CI 0.91-1.32), P = .33; absolute risk difference of 0.9%]. A similar treatment effect was observed for 10-year mortality [22.4% vs. 20.4%, HR 1.10 (95% CI 0.93-1.29), P = .25, absolute risk difference 2.0%]. According to Bayesian analysis, there was an 85.7% probability that death at 5 years was greater with PCI than with CABG, although the magnitude of this difference, if it existed, is likely to be small, < 1.0% over 5 years or <2% over 10 years (i.e. < 0.2%/year).

Of the subgroups assessed, the treatment effect was consistent. SYNTAX score tertile was not a significant treatment effect modifier for all-cause mortality, acknowledging that there were few patients with a higher SYNTAX score. Similarly, when analysed as a continuous variable using splines, SYNTAX score was not a significant treatment effect modifier for all-cause mortality or cardiovascular death.

Spontaneous MI was lower in the CABG arm [6.2% vs. 2.6%; HR 2.35 (95% CI 1.71-3.23), P < .0001; absolute risk difference 3.5)]. The results for procedural MI differed according to whether the analysis used the protocol definition or the UDMI definition. Using the protocol definition, procedural MI was statistically lower with PCI [3.2% vs. 4.7%, OR 0.65 (95% CI 0.47-0.92), P = .013; absolute risk difference 1.5%.]; according to the UDMI definition, procedural MI was non-significantly higher in the PCI group [3.2% vs. 2.3%, OR 1.42 (95% CI 0.88-2.30), P = .15; absolute risk difference 0.9%]. Data for this endpoint were available for only 46% of the patients enrolled in the NOBLE trial, and data according to UDMI were reported only for the SYNTAX and EXCEL trials.

Stroke was not statistically different overall [2.7% vs. 3.1%; HR 0.84 (95% CI 0.59-1.21), P = .36; absolute risk difference -0.4%]. However, in a pre-specified analysis of the first 12 months of follow-up, stroke was lower after PCI than after CABG [0.6% vs. 1.6%, HR 0.37 (95% CI 0.19-0.69), P = .002); absolute risk difference -1.0%].

The composite of death, MI, or stroke was not statistically different between treatment arms using protocol defined MIs [19.6% vs. 17.1%; HR 1.14 (95% CI 0.99-1.31), P = .069], but was higher following PCI using UDMI defined procedural MIs [19.7% vs. 15.5%; HR 1.29 (95% CI 1.12-1.49), P = .0005]. Repeat revascularizations were more common in the PCI-treated patients than in the CABG-treated patients [18.3% vs. 10.7%; HR 1.78 (95% CI 1.51-2.10), P < .0001; absolute risk difference 7.6%]. Composite outcomes including repeat revascularization favoured CABG whether procedural MIs were included [30.6% vs. 23.9%; HR 1.31 (95% CI 1.16-1.47), P < .0001] or not included [29.0% vs. 21.6%; HR 1.39 (95% CI 1.24-1.57), P < .0001].

The key findings of the individual patient meta-analysis are reproduced in the supplementary data online. A summary of the rates of events in the PCI and CABG treatment groups is presented in Figure 1.

Consideration on the strengths and limitations of different outcome measures to inform guideline recommendations in coronary revascularization

The TF separately evaluated the strengths and weaknesses of the different outcomes in cardiovascular trials, given that the trials usually report several endpoints, and for feasibility, frequently rely on composite outcomes. There is no agreement about the best outcome to use in coronary revascularization trials [20, 21]. All-cause mortality is arguably the most important and most objective of all outcomes [22]; however, because of the low rate, powering a trial for mortality would require a very large sample size (see **section Gaps in knowledge)** [6, 23].

The use of all-cause vs. cause-specific (cardiac, cardiovascular) mortality is a matter of debate [22, 24–26]. In general, the TF noted that all-cause mortality was less likely to be affected by ascertainment or adjudication bias. Cause-specific mortality rates are, of course, lower than all-cause mortality rates, making

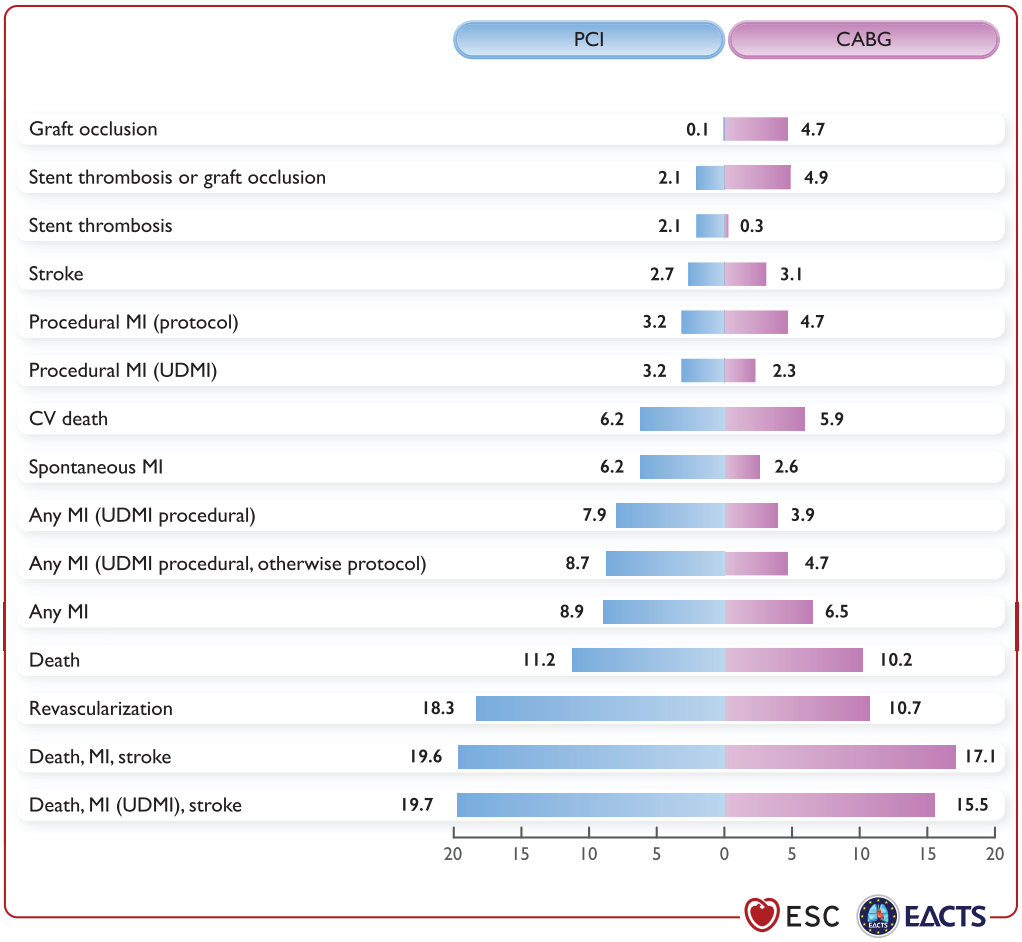

Figure 1: 5-year clinical outcomes with PCI vs. CABG in pooled analysis of randomized trials. CABG, coronary artery bypass grafting; CV, cardiovascular; MI, myocardial infarction; PCI, percutaneous coronary intervention; UDMI, Universal Definition of Myocardial Infarction.

statistical power concerns even more important. However, the treatment effect size for cause-specific mortality may be larger (as treatment may not affect non-cardiac/non-cardiovascular mortality, diluting the overall treatment effect on all-cause mortality) and the use of cause-specific mortality may then maximize the chances of detecting a treatment effect. On the other hand, cause-specific mortality (cardiac or cardiovascular) may ignore procedure-related deaths, e.g. death from bleeding, kidney failure, infection—technically non-cardiovascular but may be related to the procedure (especially immediately post-operatively). Also, adjudication of the cause of death is often problematic and there is no agreement about how to categorize deaths where the cause is unknown/uncertain [22, 25].

MI is an important outcome, but its incidence and prognostic relevance are dependent on the definition used, particularly for periprocedural MI. For the latter, the incidence and prognosis differ according to whether PCI or CABG was performed and the definition used [27, 28].

Stroke is a very important clinical outcome especially if severe, but its severity is rarely reported in clinical trials. Its incidence is dependent on the time frame (early vs. later after the procedure) and assessment method used (clinical reporting, brain imaging, neurology vs. non-neurology assessment, etc.) and is generally low in modern series, leading to the same power issues described for mortality [20–22]. The TF acknowledges the important role of early stroke in informing patient choice between revascularization modalities. Available evidence demonstrates a lower risk of stroke at 12 months after PCI vs. CABG with an absolute risk difference of 1.0% [6]. Moreover, while risk of stroke was not significantly different between PCI and CABG at later follow- up, this was due to an excess of stroke with PCI after one year in one of the four trials that does not have a strong mechanistic explanation and may represent a chance finding.

Repeat revascularization is a procedure, not a clinical outcome, and may not always be symptom or ischaemia driven. There may be asymmetric ascertainment methods and clinical threshold for repeat revascularization after PCI and CABG, introducing biases. Also, while repeat revascularization by PCI or CABG has different clinical implications, they are generally grouped together as the same outcome. Importantly, due to its high frequency, repeat revascularization dominates other outcomes and in a composite time-to-first event analysis may mask more important outcomes. The weighting of the importance of components in composite outcomes, especially when a composite is dominated by one component, is important and must be considered [22, 24, 29].

Given the above considerations regarding repeat revascularization and the lack of consensus regarding the diagnosis and prognosis with procedural MI (see **section Gaps in knowledge),** the TF considered death, spontaneous MI, or stroke as the preferred composite outcome in this patient cohort when comparing the different modes of revascularization.

Quality of life is a very important clinical outcome for patients, but it has not been used as the primary outcome of any revascularization trial and there are methodological and analytic challenges when incorporating it in composite outcomes [20, 21, 30].

Suggested recommendations of the TF for revascularization modality in patients with left main disease

In patients with chronic coronary syndrome or stabilized acute coronary syndrome with an indication for revascularization for LM disease, with coronary anatomy suitable for both procedures, with a low predicted surgical mortality, and with a SYNTAX score of 0-32, based on the available evidence from RCTs and meta-analysis of individual data from all 4 trials comparing PCI using DES with CABG among patients with LM disease, the TF concludes that both treatment options are clinically reasonable based on available expertise and local operator volumes. The suggested recommendations of the TF for each modality are shown in Table 1. Recommendations for type of revascularization facilitate shared decision-making in accordance with patient preference, available clinical expertise and local operator volumes.

The totality of the evidence shows similar results for overall mortality at 5 years, without evidence of a large difference in trials with follow-up extended to 10 years. There is a higher rate of spontaneous MI with PCI with an absolute risk difference of 3.5% and a number need to treat with CABG to prevent one MI of 29 (95% CI 21-44). Similar rates of stroke are seen with both treatments, although there is an excess risk of stroke of 1.0% in the first year with CABG. Repeat revascularization is more common after PCI with an absolute risk difference of 7.6% over 5 years and a number needed to treat with CABG to prevent one repeat revascularization of 14 (95% CI 11-19).

In relation to the safety composite of death, MI or stroke, the risk tended to be higher with PCI compared with CABG but varied depending on the definition used in the trials to determine procedural MI. With the protocol definitions of procedural MI, the estimated risk difference for this composite outcome was 2.5% (95% CI 0.1-4.8) in favour of CABG whereas with the UDMI definition the estimated risk difference was 4.2% (95% CI 1.9-6.4) in favour of CABG (Figure 2).

Evidence comparing quality of life after revascularization with PCI or CABG in patients with LM disease is modest. A secondary publication from EXCEL highlighted that both modalities of revascularization were associated with improved and equivalent disease-specific quality of life at 1 year, and much faster physical recovery after PCI [31].

In relation to the SYNTAX score, the TF noted an absence of evidence to suggest a significant difference in treatment effect between tertiles one and two for either PCI or CABG. Consequently, the suggested class of recommendation does not differ between low and intermediate SYNTAX scores for PCI in these guidelines or CABG patients.

The TF noted that there is residual uncertainty about the treatment effects for several outcome measures. Moreover, robust evidence on differences in quality of life is a notable scientific gap. Similarly, data synthesis in the meta-analysis of Sabatine and colleagues did not capture differences in early morbidity between the treatments, though upfront morbidity is significantly higher early after CABG than following PCI; for example in the EXCEL trial major periprocedural adverse events at 30 days occurred in 12.4% of PCI patients vs. 44.0% of CABG patients ($P < .001$), with the difference driven mainly by a higher rate of major arrhythmias, infections that required antibiotics, and blood transfusions in patients treated with CABG.

For the choice of treatment modality, compared to the recommendations included in the 2018 Guidelines, there is no change in class or level of evidence for CABG. The suggested recommendations for PCI represent a downgrade from Class I to IIa for patients with low SYNTAX scores, unchanged for intermediate SYNTAX scores and the level of evidence continues to be considered A.

The TF considered that the role of the Heart Team is of central importance to the consideration of revascularization modality in patients with LM disease. The TF endorses the recommendation in relation to institutional protocols for guideline implementation from the 2018 ESC/EACTS Guidelines on myocardial revascularization in this report.

The suggested recommendations regarding LM revascularization are for stable patients with coronary anatomy suitable for both procedures and low predicted surgical mortality (Graphical Abstract). Surgical risk is predicted by the STS score plus additional factors not captured by the STS risk score (Graphical Abstract). Additional factors that may influence the choice of revascularization are included in Table 2 and differ for the two revascularization modalities. These additional factors are for consideration of the Heart Team but are not meant to be prescriptive.

Table 1: Suggested recommendation for type of revascularization in stable patients with left main disease, coronary anatomy suitable for both procedures and low predicted surgical mortality

Recommendation	CABG		PCI	
	Class[a]	Level[b]	Class[a]	Level[b]
Left main disease with low or intermediate SYNTAX score (0–32).	**I**	**A**	**IIa**	**A**

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

[a]Class of recommendation.

[b]Level of evidence.

Gaps in knowledge

The TF recognized several important gaps in knowledge related to revascularization in patients with LM disease. Firstly, the aggregated sample size of the 4 RCTs included in the meta-analysis by Sabatine and colleagues [6] was still only large enough to exclude large differences in mortality. Based on an expected all-cause mortality of approximately 10% over 5 years, a well-powered study (90%) to test for modest differences in survival (HR 0.80-0.85) would require a total sample size of approximately 7800-14 800 patients, 2p = 0.05. It is unlikely that such a trial for this clinical question is feasible.

The issue about ascertainment of periprocedural MI was recognized as particularly problematic. The incidence of periprocedural MI is clearly dependent on the definition used—this was seen in secondary analyses of EXCEL [27] and SYNTAXES [28]. According to its terms of reference, the TF was instructed to focus on UDMI defined MIs but these were only reported by the

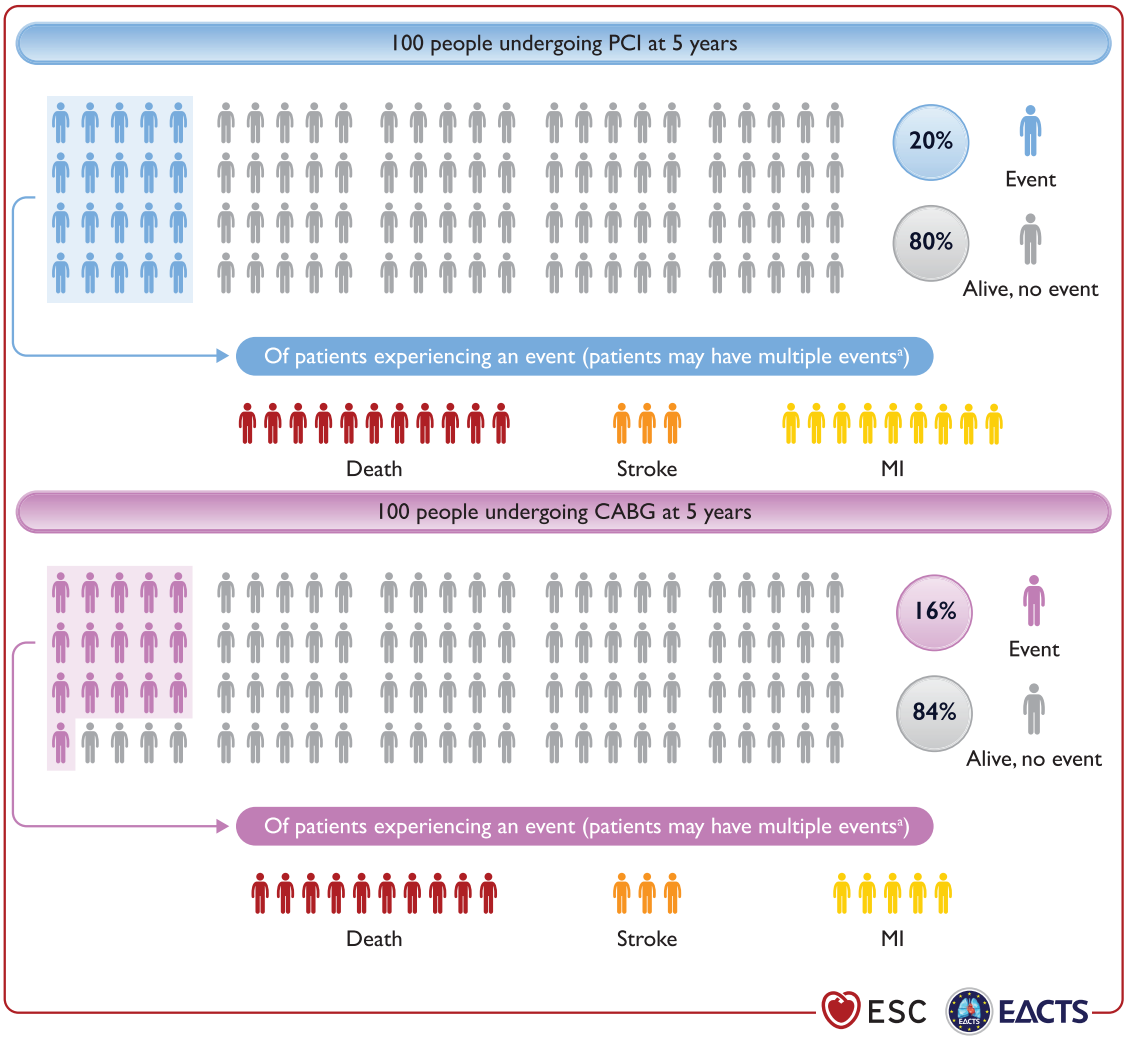

Figure 2: Visual representation of patient outcomes at 5 years after PCI or CABG. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention. [a] 'Event' refers to the composite of death, MI (according to Universal Definition of MI if available, otherwise protocol defined) or stroke.

EXCEL and SYNTAX/SYNTAXES trials included in the meta-analysis by Sabatine et al. However, we also refer throughout to the incidence of death, MI and stroke using the protocol definition of MI from each trial. Also, investigators from EXCEL and SYNTAXES reached different conclusions regarding the long-term prognostic importance of UDMI and biomarker-based definitions in PCI and CABG treated patients [27, 28]. Furthermore, recent cohort studies failed to show the prognostic importance of current biomarker-based definitions of perioperative MIs in patients undergoing bypass surgery [32, 33]. Recent cohort studies in patients undergoing PCI have reached differing conclusions on the prognostic importance of post-PCI cardiac troponin rise [34, 35]. The ESC has published a consensus document for periprocedural MI following PCI which supports isolated biomarker elevations (high-sensitivity troponin elevations greater than 5 times the upper limit of normal) as prognostically important [36].

The TF recognizes that there is little high-quality evidence comparing quality of life after revascularization in patients with LM coronary disease and chronic coronary syndromes [31]. Moreover, the incidence of procedural stroke is likely underreported in clinical trials in the absence of specific adjudication protocols and involvement of neurologists in clinical event committees.

Left ventricular systolic dysfunction is an important prognostic factor for patients with ischaemic heart disease, and patients with left ventricular systolic dysfunction, especially with a left ventricular ejection fraction <35% were excluded from the RCTs comparing revascularization modalities in LM patients. In aggregate, only 12% of patients in the review by Sabatine and associates included patients with an ejection fraction <50% [6].

Procedural imaging guidance for left main PCI is a IIa recommendation from the 2018 ESC/EACTS and the 2021 ACC/AHA/SCAI revascularization guidelines [1, 37]. PCI with image guidance using intravascular ultrasound was associated with a lower incidence of cardiac outcomes in complex coronary disease [38]. Image guidance of LM PCI was associated with reduced cardiac outcomes in the MAIN-COMPARE registry (The Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) [39]. Approximately two-thirds of the patients in the PCI arms had intravascular ultrasound imaging in the meta-analysis by Sabatine et al. In a NOBLE substudy, LM PCI with imaging guidance was associated with reduced LM target vessel revascularization [40].

Table 2: Practical recommendation and clinical situations favouring percutaneous coronary intervention or coronary artery bypass grafting in patients with left main disease

		Favours PCI	Favours CABG
Clinical characteristics	Advanced age/frailty/reduced life expectancy	✓	
	Severe co-morbidity (not adequately reflected by scores)	✓	
	High surgical risk	✓	
	Reduced LVEF <35%		✓
	Diabetes		✓
	Contraindication for DAPT		✓
	Recurrent diffuse in-stent restenosis		✓
	Prior CABG with patent LIMA-LAD graft	✓	
Anatomical and Technical aspects	Ostial or mid-shaft lesion	✓	
	Distal or bifurcation lesion		✓
	Presence of multivessel disease		✓
	High anatomic complexity (e.g. SYNTAX score >32)		✓
	Anatomy likely resulting in incomplete revascularization with PCI		✓
	Occluded dominant graftable right coronary artery		✓
	Severely calcified coronary artery lesions limiting lesion expansion		✓
	Sequelae of chest radiation	✓	
	Severe chest deformity	✓	
	Porcelain aorta (if local expertise with OPCAB with anaortic grafting not available)	✓	
	Need for concomitant cardiac surgery or surgery of ascending aorta		✓

CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; LAD, left anterior descending artery; LIMA, left internal mammary artery; LVEF, left ventricular ejection fraction; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery. A visual representation of patient outcomes at 5 years after PCI or CABG based on the individual patient data meta-analysis of Sabatine *et al.* [6] is shown in Figure 2.

Radial artery and bilateral internal thoracic artery grafting are Class I and Class IIa recommendations in both the 2018 ESC/EACTS and the 2021 ACC/AHA/SCAI revascularization guidelines [1, 37]. Arterial revascularization was used in more than 20% of CABG patients in the meta-analysis by Sabatine *et al*, much greater than contemporary results in the United States [41]. Bilateral internal thoracic artery grafting was not associated with lower cardiac events in adjusted analyses in a secondary analysis of CABG patients from the EXCEL trial [42].

Finally, there are no modern trials comparing revascularization with guideline-directed medical therapy in LM patients—only high-quality trials comparing different modalities of revascularization. The trials which compared revascularization (primarily with PCI) with guideline- directed medical therapy in patients with chronic coronary syndrome and preserved left ventricular function excluded LM patients. Aggregated data from these trials do not support an overall survival benefit with routine revascularization as an initial strategy [43], although death due to cardiac causes or spontaneous MI may be reduced [44]. The TF acknowledges that there is no modern high-quality evidence supporting routine revascularization rather than initial medical therapy in LM patients with chronic coronary syndrome by either PCI or CABG.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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DATA AVAILABILITY

No new data were generated or analysed in support of this research.

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