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CURRENT OPINION
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Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization

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The 2018 ESC/EACTS guidelines on myocardial revascularization reflect the joint effort of the European Society of Cardiology (ESC) and the European Association of Cardiothoracic Surgery (EACTS) to provide up-to-date recommendations that are both evidence-based and clinically meaningful. Although the field of myocardial revascularization represents one of the best studied therapeutic technical interventions in medicine with >20 randomized clinical trials (RCT) comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) enrolling approximately 15 000 patients, there remain areas of controversy owing to imperfect or incomplete data that have accumulated over time. One of the major points of discussion surround the issue of choosing between the revascularization strategies based on clinically relevant subsets.

The appropriate treatment allocation among patients with left main and coronary artery disease (CAD) at estimated low surgical risk remains a complex decision process. It is best achieved in the context of the local Heart Team taking into consideration the operative risk as calculated by established risk scores, the complexity of the underlying CAD, intra- and extracardiac factors that may favour one revascularization technique over another as well as local expertise. The 2018 ESC/EACTS guidelines on myocardial revascularization recommend the use of the STS score (Class IB) or EuroSCORE II (IIb B) to estimate in-hospital CABG-related mortality,[1–3] the calculation of the Syntax score (Class IB) to assess anatomical complexity as well as the long-term risk of mortality and morbidity after PCI,[4–9] and emphasize the importance to achieve complete revascularization (Class IIa B) when considering the revascularization options.[10–13] In the absence of an accepted cut-off to define low surgical mortality, the 2018 ESC/EACTS guidelines advise individual decision taking and refer to the estimated risk that has been reported in major trial comparing PCI and CABG. A table to inform the reader is provide in Chapter 5.3.1.1 of the guideline document.[14]

The stratification of guideline recommendations between CABG and PCI in patients with stable multivessel CAD according to anatomical complexity with use of the SYNTAX score groups, diabetes, and left main disease was introduced in the 2010 ESC/EACTS Guidelines on Myocardial Revascularization[15] and maintained in the 2014 version.[16] Of note, the ACCF/AHA/SCAI 2011 guideline for

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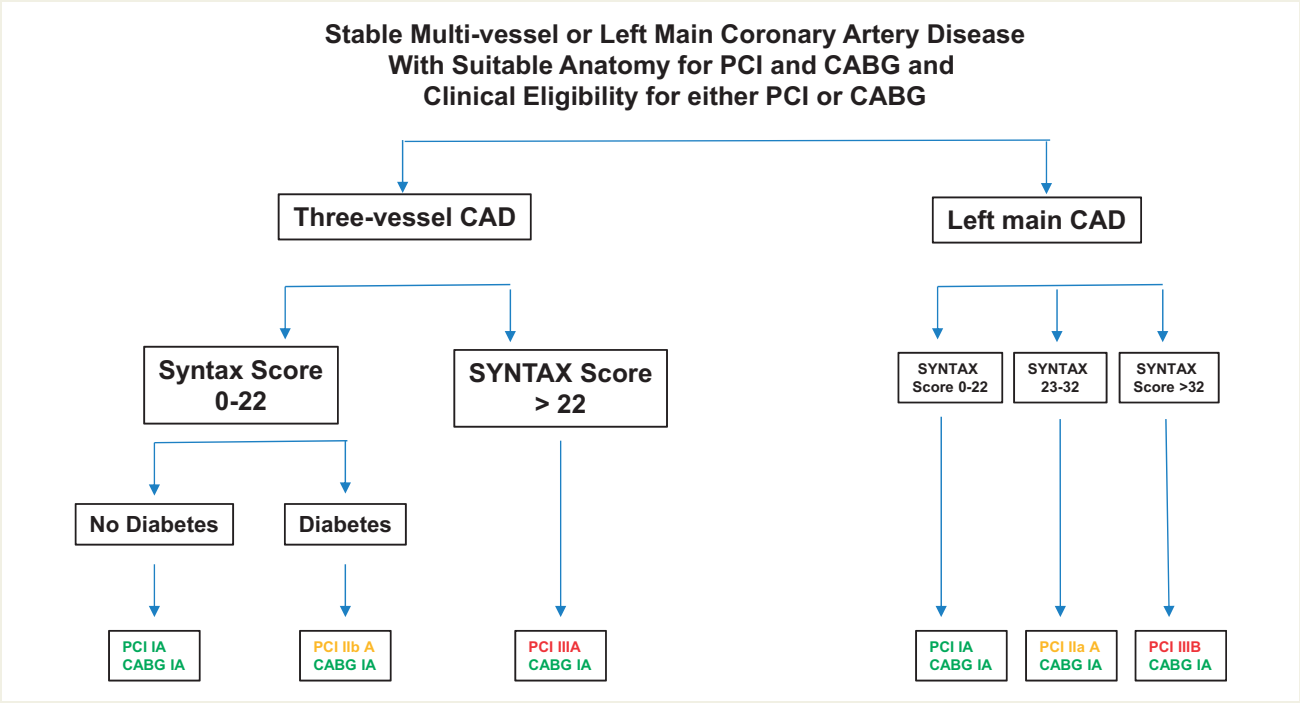

Take home figure Algorithm to guide the choice of revascularization procedure across major categories in patients with multivessel or left main coronary artery disease. Class recommendations correspond to the 2018 ESC/EACTS Guidelines on myocardial revascularization. CABG, coronary artery bypass grafting; CAD, coronary artery disease; LAD, left anterior descending artery; PCI, percutaneous coronary intervention.

PCIs[17] and American College of Cardiology (ACC)/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria[18] have embraced the same criteria for stratification of treatment decisions on CABG vs. PCI. Here, we will review the rationale and new evidence in support of this stratification scheme (*Take home figure*). We also point to the lack of acceptable alternative stratification systems since none of them have been investigated in prospective studies. This article is a companion article to the 2018 ESC/EACTS guidelines on myocardial revascularization expanding on details that are introduced in the chapter revascularization in stable CAD.[14]

Anatomical complexity of multivessel coronary artery disease and SYNTAX score

Ample evidence from observational and controlled studies indicate that extent and severity of coronary artery stenoses impact prognosis. The seminal individual patient data meta-analysis of seven RCTs comparing CABG with medical therapy by Yusuf *et al.*[19] firmly established a survival benefit of surgical revascularization over medical therapy. Of note, the relative benefit of CABG over medical therapy increased according to disease severity being greatest among patients with left main, intermediate among patients with three-vessel and least among patients with one- or two-vessel CAD.

In 2007, Bravata *et al.*[20] reported the results of a meta-analysis of 23 RCTs comparing CABG and PCI (balloon angioplasty and bare metal stents) among approximately 10 000 patients. The data showed similar survival throughout 10 years, but a higher risk of stroke, better relief of angina, and a lower risk of repeat revascularization with CABG. The failure to demonstrate significant differences in terms of survival during long-term follow-up was thought to be related to the fact that these trials included highly selected patients (10% of screened patients) and excluded patients with complex and advanced CAD (three-vessel or left main disease). In contrast, several non-randomized observational studies comparing CABG and PCI using large health record data sets reported better survival with CABG than PCI in the overall cohort with subgroup analyses suggesting a gradient of benefit particularly among patients with three-vessel disease.[21–25]

The SYNTAX trial was the first multicentre RCT comparing CABG with PCI using drug-eluting stents (DES) that employed a heart-team based, all-comer approach, and succeeded to include 41% of screened patients increasing its external validity.[26] All patients were required to have severe CAD by limiting inclusion to patients with three-vessel and left main CAD. Of note, it prospectively validated the SYNTAX score, an angiography based index of anatomical complexity among patients with multivessel and left main disease using evaluation by an independent core laboratory.

The SYNTAX score had not been derived from a specific data set, but rather developed by an international group of expert cardiac surgeons and interventional cardiologists in an effort to optimize several previously proposed CAD scoring systems including the American Heart Association (AHA) classification modified for the ARTS (Arterial Revascularization Therapy Study) study, the Leaman score,

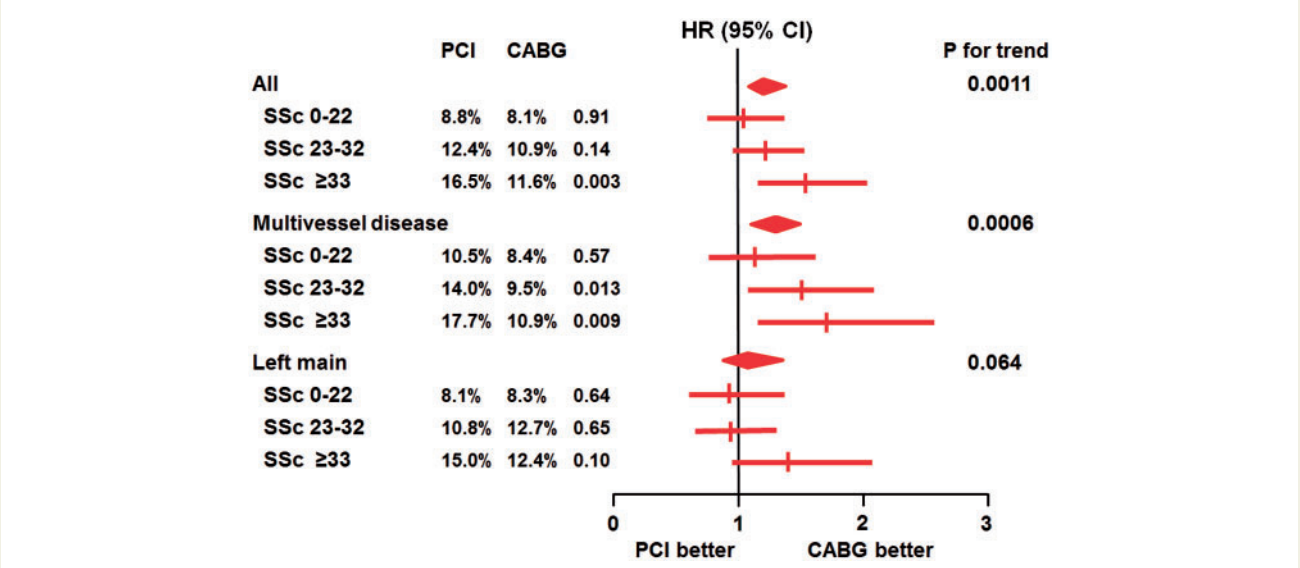

Figure 1 All-cause mortality among patients with multivessel and left main coronary artery disease (All) and separate for multivessel coronary artery disease and left main coronary artery disease stratified by SYNTAX score. Data [rates, hazard ratios (HR), 95% confidence intervals (CI), and *P*-values] are derived from the individual-pata data meta-analysis by Head *et al.*[29]

the ACC/AHA lesion classification system, the total occlusion classification system, and the Duke and ICPS classification systems for bifurcation lesions. Assuming that the number of diseased vessels was not the only marker for CAD severity, the SYNTAX score systematically addressed other lesion-based factors including the location of lesions, the degree of coronary stenosis, calcification, the specific complexity of left main, bifurcations, total occlusions, thrombus, and small vessels.[27] The SYNTAX score was first validated in the ARTS II study showing that the lowest SYNTAX tertile was associated with significantly higher freedom from major adverse cardiac events than the intermediate and high SYNTAX tertiles.[28] In multivariable analyses, the SYNTAX score emerged as independent predictor of MACE at 5 years suggesting a potential role of baseline assessment of the SYNTAX score in the risk stratification of patients undergoing PCI. Moreover, it proved superior in terms of long-term outcome prediction compared with the traditional ACC/AHA classification system.

Results of the SYNTAX trial at 1 and 5 years failed to demonstrate non-inferiority of PCI compared with CABG for the primary composite endpoint of major adverse cardiac and cerebrovascular events (MACCE).[8,26] However, pre-specified subgroup analyses of the primary endpoint MACCE according to SYNTAX tertiles stratified according to low (0–22), intermediate (23–32), and high (>32) SYNTAX tertiles showed that the relative efficacy of CABG over PCI was dependent on anatomical complexity of CAD with a significant *P*-value for interaction.[26] Accordingly, the SYNTAX score as angiographic marker of anatomical disease complexity was associated with a significant interaction effect on clinical outcomes for PCI (predictive) but not CABG (not predictive). The statistical analysis plan of the SYNTAX trial implemented a hierarchical approach whereby subgroup analyses would only be allowed if the primary endpoint would be met. From a statistical point of view, the stratified outcome analysis of the SYNTAX trial was therefore formally hypothesis generating. Of note, the American Food and Drug Administration (FDA) subsequently adopted the SYNTAX score to define inclusion criteria for trials comparing PCI and CABG.

Recently, Head *et al.*[29] reported the results of a collaborative individual patient data meta-analysis of 11 RCTs among 11 518 patients with multivessel or left main CAD who did not present with acute coronary syndromes and were randomly allocated to CABG or PCI with the primary outcome all-cause mortality. Results in the overall group of patients with multivessel or left main CAD demonstrated superiority of CABG over PCI for all-cause mortality during a mean follow-up of 3.8 ± 1.4 years. Stratified analyses according to SYNTAX score confirmed a gradient of benefit between PCI and CABG across SYNTAX tertiles with similar mortality among patients with low SYNTAX score (8.8% vs. 8.1%, $P = 0.91$) but increased rates of mortality among patients treated by PCI in the intermediate (12.4% vs. 10.9%, $P = 0.14$) and high SYNTAX tertiles (16.5% vs. 11.6%, $P = 0.003$) (*Figure 1*).

There were formally negative tests for interaction between subgroups of patients with low, moderate, or high SYNTAX scores and hazard ratios (HRs) of death. However, the investigators tested for subgroup by treatment interactions across unordered subgroups defined by SYNTAX tertiles, even though the clinically most plausible hypothesis is that HRs comparing CABG with PCI will increase with increasing SYNTAX tertiles. This hypothesis can be examined in a test for linear trend of log HRs across ordered SYNTAX tertiles.[30] Head *et al.* performed such a test for linear trend of log HRs across ordered SYNTAX tertiles using the same approach as for the primary analysis, a random-effects Cox model with shared frailty reflected by a random intercept to account for variation in baseline risk between trials. This test for trend of HRs of death across

ordered SYNTAX tertiles was positive in the overall population at $P = 0.00114$ and positive for the population with multivessel disease (in the absence of left main disease) at $P = 0.00055$. These data therefore also satisfy statistical criteria of significance for the interaction between SYNTAX tertiles and outcomes between PCI and CABG.

Based on the review above, the SYNTAX score currently remains the best tool to gauge the anatomical complexity of advanced CAD and is helpful to appraise the relative benefit of choosing between revascularization strategies among patients with multivessel disease. Despite its proven validity, the SYNTAX score cannot prevail as the sole criterion for decision making on the revascularization strategy. Apart from anatomical complexity a number of clinical characteristics that modify the peri-operative and peri-interventional risk need to be considered. To account for this, several risk scores combining clinical variables with the SYNTAX score have been developed. Yet, none of these scores have been validated in a prospective study. Among them, the SYNTAX II score is the most intensively studied. The SYNTAX II score was derived retrospectively from the SYNTAX cohort and was subsequently externally validated in several pre-existing cohorts.[7,31–33] Although discrimination and calibration were mostly adequate in these analyses, the SYNTAX II score failed to predict the outcome in the surgical arm of EXCEL. In aggregate, there is currently no sufficiently validated score that combines anatomical complexity with relevant clinical variables.

In summary, the SYNTAX score remains the best tool to guide evidence-based decisions on the revascularization strategy (*Take home figure* and *Figure 1*). With low SYNTAX scores PCI and CABG achieve similar long-term outcomes with respect to survival and the composite of death, myocardial infarction (MI), and stroke. Thus, PCI may be preferred as the more convenient and less resource-consuming treatment modality. Conversely, in patients with intermediate or high SYNTAX score, the lower mortality after CABG in conjunction with lower incidence of MI precludes PCI as an alternative to CABG in patients who are good surgical candidates.

Left main disease

Left main CAD has been recognized as specific disease entity since its first description by Herrick and the advent of coronary angiography in the 1960s[34–36] and is observed in 4–7% of patients undergoing diagnostic coronary angiography.[37] Due to its proximal location in the coronary artery tree, lesions of the left main may jeopardize blood flow subtending up to 60–90% of the myocardium. There are also important anatomico-pathological considerations owing to the differences between aorto-ostial lesions and the distal left main with involvement of the bifurcation in >60% of cases.

The first RCTs comparing CABG with medical therapy observed a survival benefit in favour of revascularization, findings that were synthesized in the individual patient data meta-analysis by Yusuf *et al.*[19] reporting the greatest relative benefit of CABG over medical therapy in the specific subset of patients with left main disease. Since then, it has been generally accepted that patients with left main disease should undergo expeditious revascularization by CABG, a recommendation that was sustained in guidelines over years as untreated left main disease is associated with poor prognosis.[26,38,39]

While PCI of left main disease was regarded contraindicated during the balloon angioplasty era, the advent of stents led to several dedicated RCTs assessing PCI in the specific setting of patients with left main disease.[40–43] Two recent RCTs compared PCI with the use of new generation DES and CABG in the specific setting of left main disease. The EXCEL trial compared CABG with PCI using new generation DES [Everolimus-Eluting Stent (EES)] among 1905 patients with left main CAD with evidence of invasive or non-invasive ischaemia.[42] Although complex left main CAD defined as SYNTAX score of >32 constituted a formal exclusion criterion, the distribution of SYNTAX score tertiles according to the Core laboratory evaluation were 36%, 40%, and 24% for low (<22), intermediate (23–32), and high (>32) SYNTAX score, respectively. At 3 years of follow-up, the primary endpoint of death, stroke, or MI occurred with similar frequency in the CABG and PCI group [14.7% vs. 15.4%, HR 1.00, 95% confidence interval (CI) 0.79–1.26; $P = 0.98$] without significant differences in the individual components. Repeat revascularization (which unlike in previous trials was not included as an endpoint in the MACE analysis) was less common with CABG than PCI (12.9% vs. 7.6%, $P < 0.001$). The trial used as definition of peri-procedural (within 72 h of the procedure) MI an increase in CK-MB >10 upper limit of normal (ULN) or CK-MB >5ULN in the presence of angiographically documented graft/stent occlusion, new pathological Q-waves in 2 contiguous leads or imaging evidence of new loss of viable myocardium. Peri-procedural MI was recorded in 3.6% of patients undergoing PCI and 5.9% of patients undergoing CABG (HR 0.61, 95% CI 0.40–0.93; $P = 0.02$) and ST-segment-elevation MI was noted in 0.7% of patients undergoing PCI and 2.3% of patients undergoing CABG within 30 days of the procedure (HR 0.32, 95% CI 0.14–0.74, $P = 0.005$). As a result, the primary endpoint within 30 days was in favour of PCI (4.9% vs. 7.9%, HR 0.61, 95% CI 0.42–0.88; $P = 0.008$). However, CABG was associated with a trend towards fewer spontaneous MIs throughout 3 years (4.3% vs. 2.7%, $P = 0.07$) and the preplanned landmark analysis from 30d to 3 years showed a significant difference for the primary endpoint in favour of surgery (7.9% vs. 11.5%, $P = 0.02$).

The NOBLE trial compared CABG with PCI using new generation DES (Biolimus-Eluting Stent-BES) among 1201 patients with left main CAD (mean SYNTAX score of 23) treated between 2008 and 2015.[43] At a median follow-up of 3.1 years, the primary endpoint of death, non-procedural MI, stroke and repeat revascularization occurred more frequently in the PCI than CABG group (29% vs. 19%, HR 1.48, 95% CI 1.11–1.96; $P = 0.007$). While there were no differences in the incidence of all-cause and cardiac death, PCI was associated with a higher incidence of non-procedural MI (7% vs. 2%, $P = 0.004$) and repeat revascularization (16% vs. 10%, $P = 0.03$). The trial failed to demonstrate non-inferiority of PCI for the primary endpoint and CABG was found superior to PCI ($P = 0.0066$).

The most recent synthesis of available evidence stems from the individual patient pooled analysis by Head *et al.* including 4478 patients with left main CAD randomly assigned to CABG or PCI with a mean follow-up of 3.4 ± 1.4 years.[29] The authors reported similar risks for the primary outcome all-cause mortality (PCI: 10.7% vs. CABG 10.5%, HR 1.07, 95% CI 0.87–1.33; $P = 0.52$) throughout 5 years.[29] There were no significant differences in mortality between PCI and CABG in subgroup analyses according to SYNTAX score (*Figure 1*). Although the proportion of patients with high SYNTAX score was limited in view of the inclusion criteria of the respective studies, there

was a trend towards better survival with CABG in this subset (*P* for trend 0.064). Of note, considering life expectancy of patients included in the latest trials investigating revascularization in the setting of left main CAD, longer follow-up results of these trials are awaited.

Based on the available evidence as established in dedicated RCTs and the distinct anatomico-pathophysiological properties of this lesion, left main CAD needs to be considered as a separate clinical and anatomical entity in practice guidelines.

Synthesis of the available evidence suggests that PCI is an appropriate alternative to CABG in left main CAD (*Take home figure* and *Figure 1*) Among patients with low to intermediate complexity left main CAD, clinical outcomes with respect to major adverse cerebrovascular events and ischaemic endpoints are similar for PCI and CABG and both revascularization strategies can be considered in this patient population. Conversely, the number of patients with high complexity studied in RCTs is low due to exclusion criteria and the risk estimates and CIs remain imprecise. Therefore, PCI in this setting cannot be endorsed as long-term outcomes are likely to be similar to patients with multivessel disease. With an increasing extent of the underlying CAD CABG is hence likely to provide improved long-term outcomes in patients with left main CAD.

Diabetes mellitus

Diabetes mellitus is not just a risk factor but rather a distinct disease entity that is critical for the selection between myocardial revascularization strategies in patients with multivessel disease. Diabetes mellitus, which is observed in 20–30% of patients requiring revascularization, is associated with systemic endothelial dysfunction, accelerated atherosclerosis and more diffuse pattern of CAD.[44,45] These disease properties are associated with a more pronounced progression of CAD after revascularization as well as neointimal hyperplastic response after PCI and may explain at least in part the differences in outcomes between CABG and PCI in patients with diabetes and multivessel CAD as compared to patients without diabetes.

The randomized BARI trial comparing PCI with use of balloon angioplasty and CABG in selected patients with multivessel CAD reported similar mortality for both revascularization strategies at 5 and 10 years.[46,47] In 1992, the Data Safety and Monitoring Board recommended to monitor outcomes among diabetic patients, a subgroup that had not been *a priori* defined as subgroup in the original protocol. Stratified analyses according to diabetes mellitus revealed improved survival among patients allocated to CABG compared with those allocated to PCI at 5 years and 10 years of follow-up. Conversely, In the SYNTAX trial stratified analyses of primary and secondary outcomes according to diabetic status did not reveal a relevant interaction[48] although event rates were consistently higher among patients with diabetes.

In 2009, Hlatky *et al.*[49] reported the results of an individual patient data meta-analysis of 10 RCTs (6 RCTs with balloon angioplasty, 4 RCTs with bare metal stents) including 7812 patients comparing PCI and CABG among patients with multivessel CAD with a mean follow-up of 5.9 years. In stratified analyses according to diabetes status, a significant interaction ($P = 0.014$) by treatment modality was identified with substantially higher mortality among patients with diabetes allocated to PCI (20% vs. 12.3%; HR 0.70, 95% CI 0.56–0.87), whereas mortality was similar for PCI and CABG among patients without diabetes (8.1% vs. 7.6%; HR 0.98, 95% CI 0.86–1.12).

In the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, the largest randomized study in diabetics, PCI with use of early-generation DES was compared with CABG in diabetic patients undergoing elective revascularization for multivessel CAD.[50]

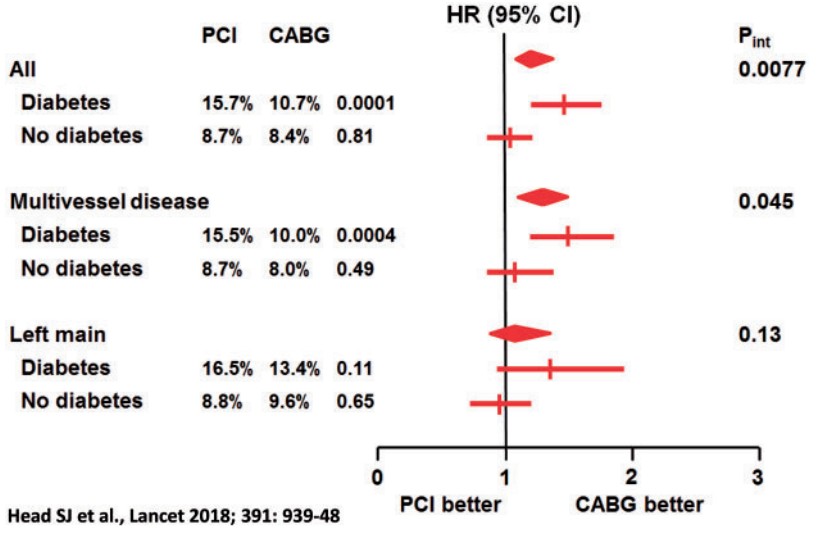

Figure 2 All-cause mortality among patients with multivessel and left main coronary artery disease (All) and separate for multivessel coronary artery disease and left main coronary artery disease stratified by diabetes mellitus. Data [rates, hazard ratios (HR), 95% confidence intervals (CI) and *P*-values] are derived from the individual-pata data meta-analysis by Head *et al.*[29]

Out of a total of 33 966 patients screened, 1900 patients (6%) with a mean SYNTAX score of 26 ± 9 were enrolled. During 5-year follow-up, CABG significantly reduced the risk of the primary endpoint death, MI, or stroke compared with PCI. Consistent with the reports above, the individual patient data meta-analysis of 11 RCTs by Head *et al.*[29] reported a significant interaction by revascularization allocation in stratified analysis according to diabetes mellitus. In patients with diabetes, mortality was higher among patients allocated to PCI compared with CABG (15.7% vs. 10.7%, HR 1.44, 95% CI 1.20–1.74; $P = 0.001$), whereas mortality was comparable for PCI and CABG among patients without diabetes (8.7% vs. 8.2%, HR 1.02, 95% CI 0.86–1.21; $P = 0.81$, P for interaction 0.0077, *Figure 2*).

It has been argued that the *P*-value for interaction in the work by Head *et al.* would have to be adjusted for multiple testing, resulting in an adjusted *P*-value for significance of 0.005 based on the 10 comparisons reported in the original publication. However, only three of the subgroup analyses, namely diabetes status, tertiles of SYNTAX score, and left main disease would be considered key interactions and primary in nature, backed by prior pathophysiological, clinical and/or anatomical concepts, while the other subgroup analyses with interaction tests would be considered hierarchically subordinate and secondary in nature.

Thus, based on current evidence diabetes mellitus is the strongest predictor of a survival benefit of CABG as compared with PCI in patients with multivessel CAD. Particularly, in patients with intermediate or high SYNTAX scores this survival benefit is substantial and considerably more pronounced than in the absence of diabetes. Only, with low SYNTAX score it may be justified to consider PCI as an alternative to CABG (*Take home figure*).

Future perspective

Revascularization aims to improve myocardial blood flow thereby reducing ischaemia.[51] An important pre-requisite to achieve this goal is the comprehensive assessment and treatment planning of lesions requiring revascularization including treatment optimization. Although anatomical classification of CAD extent has been the foundation to guide revascularization and risk stratification among patients with multivessel CAD, intracoronary physiology-derived parameters [fractional flow reserve (FFR) and instantaneous wave-free ratio (iwFR)] provide incremental value by virtue of lesion reclassification[52–54] resulting in both deferral of intervention or identification of previously unrecognized ischaemia-producing lesions. Moreover, complete anatomical and physiological revascularization among patients with multivessel CAD is associated with improved outcomes irrespective of the revascularization strategy but has been less complete in case of PCI particularly among patients with chronic total occlusions (CTO).[10,11,13,55] In addition, pre-interventional physiologic lesion mapping[56] and intracoronary imaging (intravascular ultrasound (IVUS) and optical coherence tomography (OCT))[57–60] as well as post-procedural assessment translate into improved outcomes particularly among patients with left main and multivessel disease. Of note, none of the intracoronary physiology or imaging parameters have been prospectively investigated in trials comparing PCI and CABG and represent an important gap of evidence. Notwithstanding, observational data from the recent SYNTAX II trial indicate that a multimodal strategy incorporating guideline-based medical treatment, a heart-team based patient selection with use of the SYNTAX score II, intracoronary physiology-guided PCI using a hybrid assessment using iwFR and FFR combined with IVUS-guided stent implantation and contemporary CTO lesion management result in improved clinical outcomes throughout 1 year as compared to a historical PCI cohort derived from the SYNTAX I trial.[61] These procedural and technological improvements deserve consideration and further evaluation in appropriately designed revascularization trials.

Summary

Myocardial revascularization as adjunct to guideline-based medical therapy remains the mainstay in the treatment of patients with symptomatic or ischaemia-producing CAD. Patients with left main and multivessel CAD require individual decision making by the local Heart Team guided by assessment of the operative risk, complexity of the underlying CAD, and likelihood to achieve complete revascularization. The choice between PCI and CABG is informed by carefully weighing the benefits and risks inherent to the respective revascularization technique as well as local expertise. The SYNTAX score remains the best tool to guide decisions on the revascularization strategy among patients with multivessel CAD complemented by considerations in the presence of left main CAD and diabetes.

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