JACC REVIEW TOPIC OF THE WEEK

PCI and CABG for Treating Stable Coronary Artery Disease

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Torsten Doenst, MD, PhD,[a] Axel Haverich, MD, PhD,[b] Patrick Serruys, MD, PhD,[c] Robert O. Bonow, MD, MS,[d] Pieter Kappetein, MD, PhD,[e] Volkmar Falk, MD, PhD,[f] Eric Velazquez, MD,[g] Anno Diegeler, MD, PhD,[h] Holger Sigusch, MD[i]

ABSTRACT

Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are considered revascularization procedures, but only CABG can prolong life in stable coronary artery disease. Thus, PCI and CABG mechanisms may differ. Viability and/or ischemia detection to guide revascularization have been unable to accurately predict treatment effects of CABG or PCI, questioning a revascularization mechanism for improving survival. By contrast, preventing myocardial infarction may save lives. However, the majority of infarcts are generated by non–flow-limiting stenoses, but PCI is solely focused on treating flow-limiting lesions. Thus, PCI cannot be expected to significantly limit new infarcts, but CABG may do so through providing flow distal to vessel occlusions. All comparisons of CABG to PCI or medical therapy that demonstrate survival effects with CABG also demonstrate infarct reduction. Thus, CABG may differ from PCI by providing "surgical collateralization," prolonging life by preventing myocardial infarctions. The evidence is reviewed here. (J Am Coll Cardiol 2019;73:964–76) © 2019 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Coronary artery disease (CAD) causes angina pectoris, myocardial infarction, and ischemic heart failure and thereby contributes significantly to cardiovascular disease being the leading cause of death worldwide (1). CAD is characterized by the development of atherosclerotic plaques inside the coronary vessel wall that stenose the vessel (causing ischemia) or that can rupture, which through thrombotic vessel occlusion represents the major mechanism for acute myocardial infarction (AMI) (2). Myocardial infarction or chronic ischemia through severely stenotic CAD may lead to heart failure and/or death (2). Treatment of CAD is therefore aimed at alleviating angina symptoms and preventing AMI or premature death (1). Next to medical therapy (MED), mainly consisting of angina control and prevention or reversal of plaque progression, 2 (more or less) invasive strategies are available, aimed at re-establishing adequate blood supply to undersupplied myocardial territories due to severe coronary stenosis

or vessel occlusion, that is, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) (1).

A plethora of trials have compared the 2 (or 3, if MED is included) treatment strategies for their ability to achieve the aforementioned treatment goals (Table 1). Several publications, comments, and reviews have addressed these comparisons and have come to 2 main (and possibly sobering) conclusions (Table 1) (3-21). First, PCI in stable CAD, independent of stent type used, has thus far failed to report an improvement in survival or a significant reduction in new myocardial infarctions (16). Second, improved survival and reductions in new myocardial infarctions has been consistently demonstrated for CABG in stable CAD, but this effect is not always detectable and seems to be dependent on the severity of CAD (15) (Table 1) and possibly the presence of diabetes mellitus (7,22,23).

These findings are somewhat surprising because both procedures have always been considered revascularization treatments (1) and should therefore have similar effects. However, the majority of AMIs are not caused by flow-limiting lesions (24-38), but our current revascularization strategy focusses more and more on treating only flow-limiting stenoses (38,39). In addition, the majority of deaths in this patient population are due to cardiac reasons, mainly AMI (22,23,40,41). Thus, protection against infarction may be an underappreciated mechanism although it had been suggested previously (22,42). Because native collateralization protects from infarction of acute vessel occlusion (24-28,32), CABG may do the same surgically.

We searched the published reports and looked for possible explanations of the difference in clinical impact of CABG and PCI. We present here a collection of (circumstantial) evidence to make the case that CABG, although a revascularization treatment and thereby comparable to PCI in treating angina, is able to provide a survival benefit by protecting against new myocardial infarctions (i.e., creating "surgical collateralization") (Central Illustration).

REVIEWING THE EVIDENCE

PATHOPHYSIOLOGY OF CAD. CAD is generally caused by atherosclerotic plaque formation. Plaques form inside the vessel and lead to varying degrees of lumen obstruction. Such a stenosis is considered to be hemodynamically relevant once the degree exceeds 70% (43). Since fractional flow-reserve (FFR) has emerged, the assessment of severity degree may differ compared with conventional eyeball

assessment. However, the number of stenoses determined as flow-limiting has not increased (31,39,44). Hemodynamically relevant flow obstructions can cause ischemia in the distal myocardium. The resulting symptoms are ischemic pain (classically angina pectoris) and/or dyspnea as expression of ischemic pump failure. (Of note, ischemic symptoms may appear in the absence of significant epicardial disease, but this is not the topic of this review). In the setting of epicardial disease with patients amendable for CABG or PCI, non-flow-limiting stenoses are generally asymptomatic. However, rupture of these plaques, often followed by thrombotic vessel occlusion, represents the main mechanism of myocardial infarction (1,24). Importantly, plaques can rupture without causing an infarct. In this case, the thrombus may either not fully occlude the vessel or collateral flow may protect the myocardium from infarction (45). The latter mechanism explains the relatively large number of coronary occlusions in clinical practice. In addition, CAD is a disease that migrates from proximal parts of the vessel system distally, and the vast majority of plaque burden is found in the first few centimeters of the coronary vessels (42,46).

Figure 1A shows the quantitative distribution of CAD in the human coronary system dependent on the degree of stenosis and at which rate it causes vessel occlusions within 5 years. The data come from a summary of a series of angiographic and/or pathological studies (25-28,32). Figure 1B demonstrates the percentage at which the different degrees of stenoses are the cause of myocardial infarction. It is evident that the higher the degree of stenosis, the greater the risk for this stenosis to occlude or cause an infarct. However, because the lesions with lower degrees of stenosis by far outnumber those with higher stenotic degrees, the majority of myocardial infarctions in real life are caused by stenoses with a stenotic degree of <70% (i.e., most likely non-flow-limiting lesions). This finding is illustrated in Figure 1C. It is an important recognition with respect to the expectations of current treatment strategies because the figure shows that the vast majority of new myocardial infarctions are caused by non-flow-limiting stenoses. Because PCI (more often supported by FFR or intravascular ultrasound nowadays [38]) focuses on treatment of primarily flow-limiting stenoses (38), one may ask, why do we actually expect a significant reduction of myocardial infarctions by PCI?

TABLE 1   Summary Information for All Current Prospective Randomized Controlled Trials Comparing CABG and PCI

Trial Name Follow-Up Period (Year) (Ref. #)	Primary Endpoint	Degree of CAD	Mortality PCI vs. CABG (%)	New MI PCI vs. CABG (%)	Cardiac Death PCI vs. CABG (%)
ARTS	Freedom from MACCE	Multivessel disease (>60% 2-vessel, >30% 3-vessel)			
1 yr (2005) (3)			2.5 vs. 2.8	6.0 vs. 4.6	n. a.
3 yrs (2005) (3)			3.7 vs. 4.6	7.3 vs. 5.7	n. a.
5 yrs (2005) (3)			8.0 vs. 7.6	8.5 vs. 6.6	n. a.
BEST	Composite of death, MI, or target-vessel revascularization at 2 yrs	Multivessel disease (>70% 3-vessel)			
2 yrs (2015) (4)			6.6 vs. 5.0	4.8 vs. 2.7	4.1 vs. 3.7
CARDia	Composite of all-cause mortality, MI and stroke	Symptomatic multivessel disease (>60% 3-vessel)			
1 yr (2010) (5)			3.2 vs. 3.2	9.8 vs. 5.7	n. a.
EXCEL	Composite of death from all cause, stroke, or MI	Left main coronary artery stenosis of at least 70%			
3 yrs (2016) (6)			8.2 vs. 5.9	8.0 vs. 8.3	4.4 vs. 3.7
FREEDOM	Composite of all-cause mortality, nonfatal MI, or stroke	Multivessel disease (>80% 3-vessel)			
2 yrs (2012) (7)			6.7 vs. 6.3	6.7 vs. 4.7	0.9 vs. 1.3
5 yrs (2012) (7)			16.3 vs. 10.9	13.9 vs. 6.0	10.9 vs. 6.8
MASS II	Total mortality, Q-wave MI or refractory angina requiring revascularization	Multivessel disease (>40% 2-vessel, >55% 3-vessel)			
5 yrs (2007) (8)			15.5 vs. 12.8	11.2 vs. 8.3	11.6 vs. 7.9
NOBLE	Freedom from MACCE at 5 yrs	Left main coronary artery disease of at least 50%			
1 yr (2016) (9)			2.0 vs. 3.0	2.0 vs. 1.0	1.0 vs. 2.0
5 yrs (2016) (9)			12.0 vs. 9.0	7.0 vs. 2.0	3.0 vs. 3.0
PRECOMBAT	Freedom from MACCE	Unprotected left main coronary artery stenosis			
5 yrs (2015) (10)			5.7 vs. 7.9	2.0 vs. 1.7	n. a.
SoS	Comparison of the rates of repeat revascularization	Multivessel disease (>50% 2-vessel, >35% 3-vessel)			
2 yrs (2002) (11)			5.0 vs. 2.0	4.0 vs. 7.0	n. a.
SYNTAX	Noninferiority of major adverse cardiac and cerebral events	3-vessel disease			
1 yr (2009) (12)			4.4 vs. 3.5	4.8 vs. 3.3	3.7 vs. 3.1
3 yrs (2011) (13)			8.6 vs. 6.7	7.1 vs. 3.6	6.0 vs. 3.6
5 yrs (2014) (14)			14.6 vs. 9.2	10.6 vs. 3.3	9.2 vs. 4.0

ARTS = Arterial Revascularization Therapies Study; BEST = Bypass Surgery Versus Everolimus-Eluting Stent Implantation for Multivessel Coronary Artery Disease study; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CARDia = Coronary Artery Revascularization in Diabetes; EXCEL = EXCEL Clinical Trial; FREEDOM = Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes study; MACCE = major adverse cardiac and cerebrovascular events; MASS II = Medicine, Angioplasty, or Surgery Study; MI = myocardial infarction; n. a. = not available; NOBLE = PCI vs. CABG in the Treatment of Unprotected Left Main Stenosis study; PCI = percutaneous coronary intervention; PRECOMBAT = Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease study; SoS = Stent or Surgery Trial; SYNTAX = TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries study.

RISKS AND CAUSES OF DEATH IN STABLE CAD. Every invasive treatment method carries a certain risk. For proper decision-making, the risks of the natural cause of the disease (or in case of CAD, the risks associated with CAD under optimal medical treatment) need to be known.

Figure 2 shows an image modified from the current European Society of Cardiology guidelines on myocardial revascularization, illustrating the risk of dying under optimal MED within 1 year, dependent on the degree of CAD. Accordingly, patients with single-vessel disease have a 1.4% yearly risk of dying from this problem, whereas it increases to >8%

per year in patients with triple-vessel disease including the left main artery. It is currently generally accepted that the main causes of death in these patients are of cardiac origin (1,40), specifically in patients with diabetes mellitus (7,22,23,41).

Thus, myocardial infarction appears to be a major mechanism for death from CAD. Treatments reducing the occurrence of myocardial infarction should therefore potentially be able to reduce mortality from CAD, but the "visibility" of this effect is related to the inherent risk of the treatment itself. Statistically speaking, the detectability of a treatment impact on survival depends on 3 factors: periprocedural

CENTRAL ILLUSTRATION Infarct Prevention Through Bypass Grafting

Percutaneous Coronary Intervention

- Stent in coronary artery
- Stent
- Flow-limiting lesion
- Not-flow-limiting lesion
- Potential cause for rupture and thrombotic occlusion

Coronary Artery Bypass Grafting

- Bypass graft
- Bypass graft
- Bypass graft
- Bypass graft
- Flow-limiting lesion
- Not-flow-limiting lesion
- CABG provides protection against vessel occlusion through surgical collateralization

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Schematic illustration of mechanistic differences between percutaneous coronary intervention and coronary artery bypass grafting (CABG). Although both stents and bypass grafts provide revascularization to vascular territories affected by flow-limiting stenoses, only CABG also provides protection against vessel occlusions (i.e., myocardial infarctions) from non–flow-limiting stenoses, because the majority of bypass graft insertions are performed distal to the plaque location.

mortality, length of the observation period, and natural risk of the disease. Thus, periprocedural risks and treatment effects need to be evaluated against the duration of the observation period, which may explain several of the concurrent possibly contradictory findings from current CABG versus PCI trials.

The STICH (Surgical Treatment for Ischemic Heart Failure) trial is a perfect example for this statement. The trial compared CABG to optimal MED in patients with ischemic heart failure. There was no statistically significant survival improvement at the 5-year endpoint (47) but there was at 10 years (resulting in an 18 months longer average survival in the operated patients) (48). Another trial may be the SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) study, in which patients with triple-vessel disease either received PCI or CABG. **Figure 3** shows the cumulative event rate at 5 years for the 2 patient groups according to their SYNTAX score. The figure illustrates that CABG is superior to PCI if the SYNTAX score is high, and PCI is comparable to CABG if the SYNTAX score is low. Yet, extrapolating the curves to 10 years may possibly also show superiority for CABG. However, despite the absence of long-term follow-up

in most trials, reviewing the evidence from concurrent trials is already revealing.

EVIDENCE FROM TRIALS. A plethora of investigations has addressed the potential of PCI to improve survival and to reduce myocardial infarctions in patients with stable CAD compared with MED alone (1,16). The sobering finding was that PCI has consistently failed to improve survival or to reduce new myocardial infarction in stable CAD. A recent network meta-analysis suggested a survival benefit of new-generation drug-eluting stents over MED, giving a rate ratio of 0.75 (95% confidence interval [CI]: 0.59 to 0.96) for everolimus-eluting stents (EES) and of 0.65 (95% CI: 0.42 to 1.00) for Resolute zotarolimus-eluting stents (R-ZES) (Medtronic, Dublin, Ireland) (49). However, the actual trial comparing EES to MED (39) demonstrated equal rates of all-cause mortality (p = 0.31), and a comparison of R-ZES with MED has never been conducted. In addition, the recent NORSTENT (Trial of Drug Eluting Stent Versus Bare Metal Stent to Treat Coronary Artery Stenosis) demonstrates equal survival rates for patients with exactly this everolimus-eluting stent compared with concurrent bare-metal stents (50). By contrast, comparisons of PCI to CABG have consistently

FIGURE 1 Coronary Occlusion/MI as Function of CAD Stenosis Severity
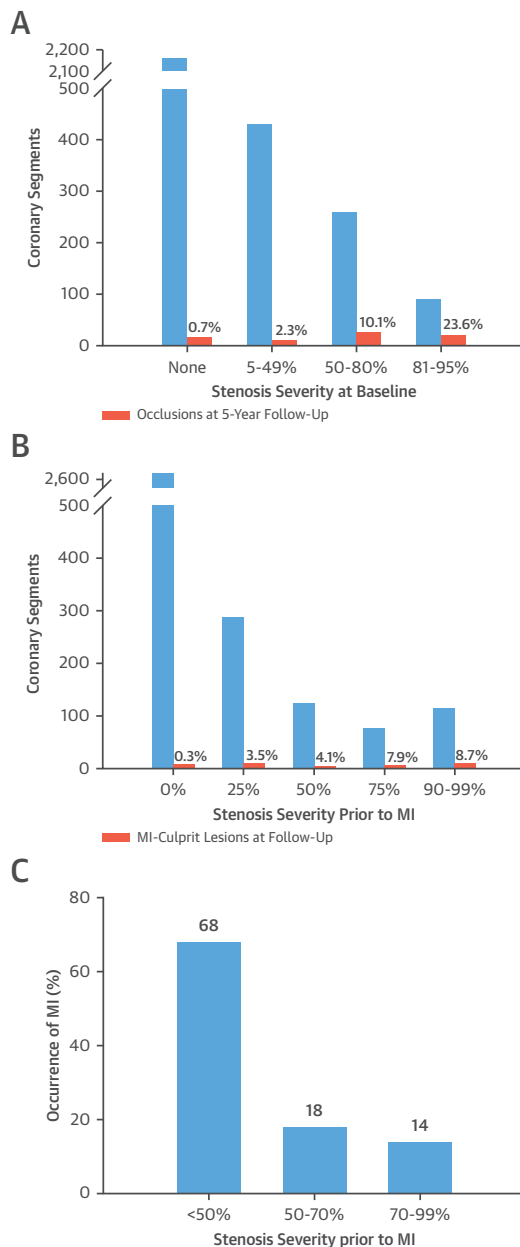
Bar graphs showing stenosis severity and associated risk of coronary oc-
clusion and myocardial infarction (MI) as evaluated by serial angiographic
examination. The more stenotic an individual coronary segment is at base-
line, the more frequently it progresses to occlusion **(A)** and/or gives rise to
infarction **(B)**. Because less-obstructive plaques by far outnumber severely
obstructive plaques, most occlusions and infarctions result from progres-
sion of the less-obstructive plaques. Thus, myocardial infraction evolves
most frequently from plaques that are only mildly to moderately
obstructive **(C)**. Bar graphs are constructed from data published by **(A)**
Alderman et al. (26); **(B)** Nobuyoshi et al. (32); and **(C)** Ambrose et al. (27),
Little et al. (25), Nobuyoshi et al. (32), and Giroud et al. (28). CAD = coronary
artery disease.

demonstrated potential superiority of CABG, inde-
pendent of stent type used (4,29,41).

In addition, all trials comparing PCI and CABG have
been performed in patients without previous PCI. PCI
per se may disturb the coronaries' inherent vaso-
motor function, possibly causing adverse events (51),
and increase perioperative risk if CABG is needed (52).

Table 1 displays a summary of all important pro-
spective randomized controlled trials having
compared CABG and PCI in the last 15 years. Note that
77% of trials suggest a better survival with CABG.
Although the effects of CABG appear to be most
prevalent in patients with diabetes mellitus (1,7,23),
the therapeutic impact may be similar in patient
populations with lower percentages of diabetic pa-
tients (14). There are only a few investigations
comparing coronary bypass grafting to MED alone
without including coronary interventions (26,35). The
STICH trial is the most recent and largest trial of such
kind. As already mentioned, CABG provided a
significant survival benefit over MED alone after 10
years. Importantly, the treatment effect could not be
predicted by assessing pre-operative viability (53) or
the presence of ischemia (54).

**VIABILITY OR ISCHEMIA TESTING AND ITS EFFECT
ON OUTCOME AFTER PCI AND CABG.** There is an
ongoing debate whether diagnostic tools detecting
ischemia and/or viability/scar should be used for
decision-making in PCI and CABG. It is recommended
that for any revascularization strategy, the presence
of viable, but ischemic, myocardium is determined
(1). Although the rationale is convincing and the ef-
fect of this approach can be witnessed by the disap-
pearance or alleviation of ischemia symptoms, the
ability of this strategy to improve survival or reduce
new myocardial infarctions has thus far not been
demonstrated in a prospective randomized trial (1).
The guidelines currently suggest that revasculariza-
tion is useful for mortality reduction if the ischemic
territory is >10%. This suggestion is based on 2 pub-
lications on nearly the same patient population
(55,56) that evaluated the impact of ischemia and scar
assessment on the therapeutic benefit from myocar-
dial revascularization. Although the data are
convincing, the authors compared a large group of
medically treated patients (n ≈ 12,000) to those
having received revascularization (n = 1,226). How-
ever, roughly 40% of revascularized patients received
CABG and the other part received PCI. The papers do
not differentiate the treatments any further. The
authors show that revascularization lowered mortal-
ity rates in patients with ischemic territories
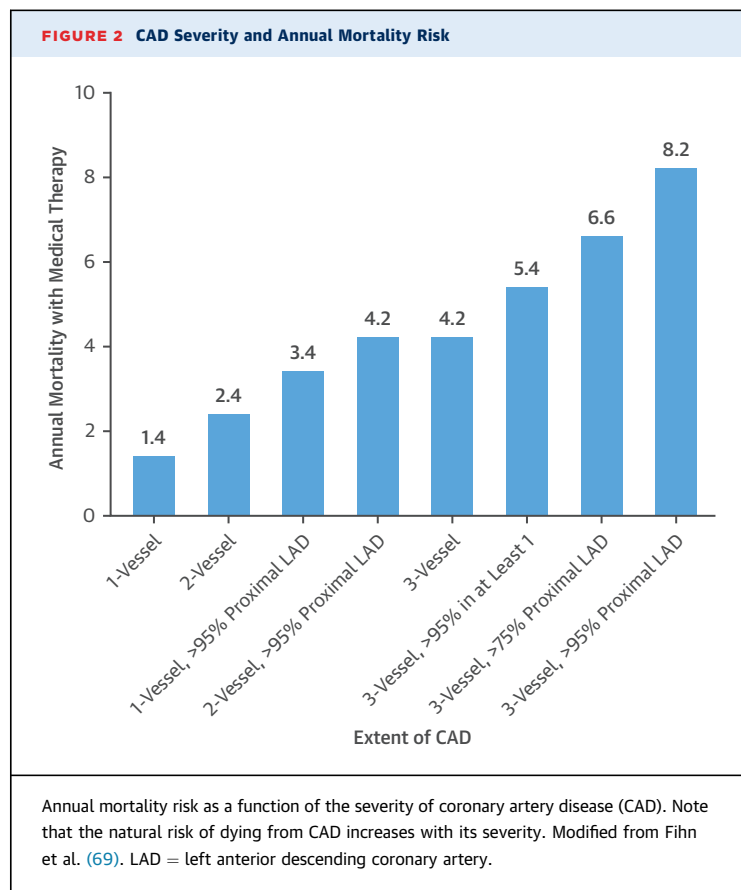on single-photon emission computed tomography

imaging of >10%. They also demonstrate that mortality with revascularization may even be higher with small ischemic territories (<5%). These data were taken to conclude, that revascularization of significantly ischemic myocardium improves survival (1). However, our present rationale would require differentiating the data further into outcomes of patients having undergone CABG or PCI. Although the overall mortality rate for both invasive strategies were similar in these reports, it is conceivable that CABG was primarily performed in patients with more severe CAD (i.e., more triple-vessel disease and therefore more ischemic territories and natural risk) and PCI was primarily performed in those with less severe CAD patients (i.e., single- and double-vessel disease, subsequently smaller ischemic territories, and lower natural risk) (**Figure 4A**). Thus, it is well conceivable that the outcomes may not be dependent on the degree of ischemic territory, but instead on the type of revascularization. The currently ongoing ISCHEMIA trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; NCT01471522) will hopefully clarify whether treating ischemia in stable CAD affects survival. However, the trial also combines PCI and CABG as revascularization for the comparison to MED.

The evidence from the STICH trial demonstrates that both viability testing and ischemia detection serve well to predict prognosis (i.e., patients with viability and/or ischemia live longer than those without it), but they are not helpful for decision-making for the performance of CABG (**Figure 4B**). In other words, CABG still appears to prolong life in patients without acutely ischemic or viable myocardium.

The STICH findings and the methodological concerns regarding the main evidence currently applied for predicting the revascularization effect on mortality suggest that revascularization may not be a main mechanism for mortality reduction. Thus, the finding of infarct reductions and reduced cardiac deaths with CABG may therefore represent a known (22,42), but underappreciated, mechanism to explain the survival impact (14). Thus, CABG may be considered as infarct-reducing treatment by bypassing diseased coronary territories (i.e., providing "surgical collateralization" in addition to revascularization).

It is important to state in this context again that myocardial infarction is a major, but not the only, cause of cardiovascular mortality. Assessing the data presented here suggests that CABG may reduce infarcts and cardiovascular mortality up to a maximum of 50% (average 30%) (**Table 1, Figure 5**). Thus, there is

FIGURE 2 CAD Severity and Annual Mortality Risk

Annual mortality risk as a function of the severity of coronary artery disease (CAD). Note that the natural risk of dying from CAD increases with its severity. Modified from Fihn et al. (69). LAD = left anterior descending coronary artery.

plenty of room for other causes of cardiovascular mortality and mechanisms of cardiovascular protection (57). However, in light of the mechanistic differences between CABG and PCI, CABG's ability to prevent new infarctions deserves further examination.

INFARCT REDUCTION AS POTENTIAL CAUSE FOR IMPROVING SURVIVAL WITH CABG. **Table 1** also displays a summary for rates of nonlethal myocardial infarctions and cardiac deaths for the aforementioned trials. It is striking to note that the overall lower mortality with CABG from these trials was accompanied also by reductions in nonlethal myocardial infarction and cardiac death. **Figure 5** shows a graphic illustration of the difference in mortality between CABG and PCI of these trials as a function of the difference in nonlethal myocardial infarction versus all-cause mortality (**Figure 5A**) or cardiac death (**Figure 5B**). The highly significant correlation is striking. Although this association does not prove that CABG's ability to prolong life is caused by its ability to reduce infarctions, the notion, however, is strong and is supported further by the following circumstantial evidence.

FIGURE 3 Outcome of PCI Versus CABG by SYNTAX Score
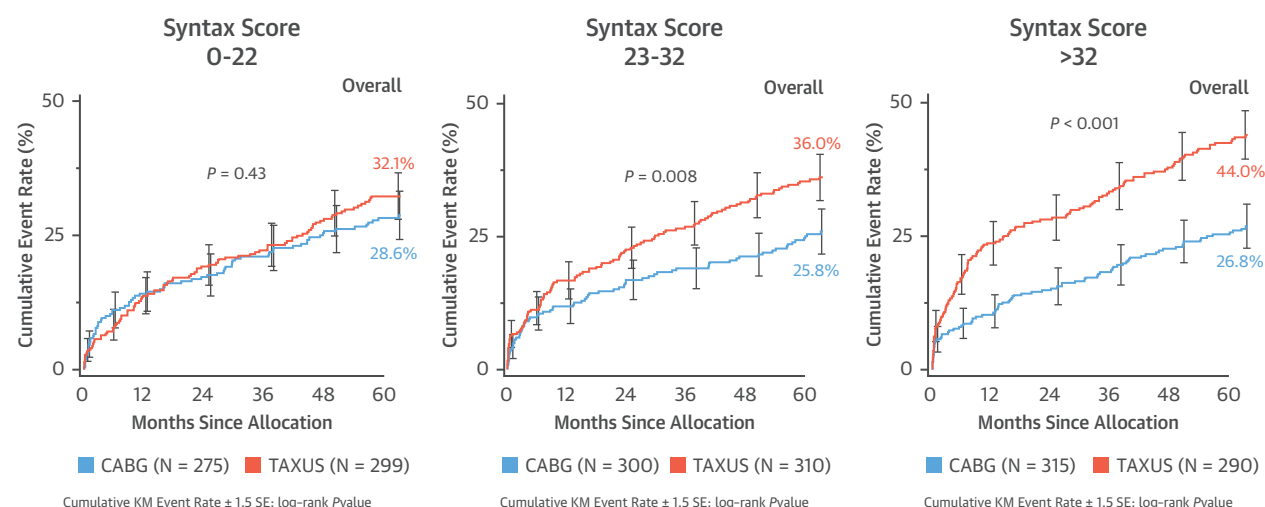
Cumulative event rates for PCI and CABG according to the 3 SYNTAX score groups from the SYNTAX trial. Note that the event rates increase with PCI with increasing SYNTAX scores and are stable with CABG. Note also that in the low SYNTAX group (0 to 22, **left**) the curves cross between 12 and 24 months. Reproduced with permission from Head et al. (14). CABG = coronary artery bypass grafting; KM = Kaplan-Meier; PCI = percutaneous coronary intervention; SYNTAX = TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries study.
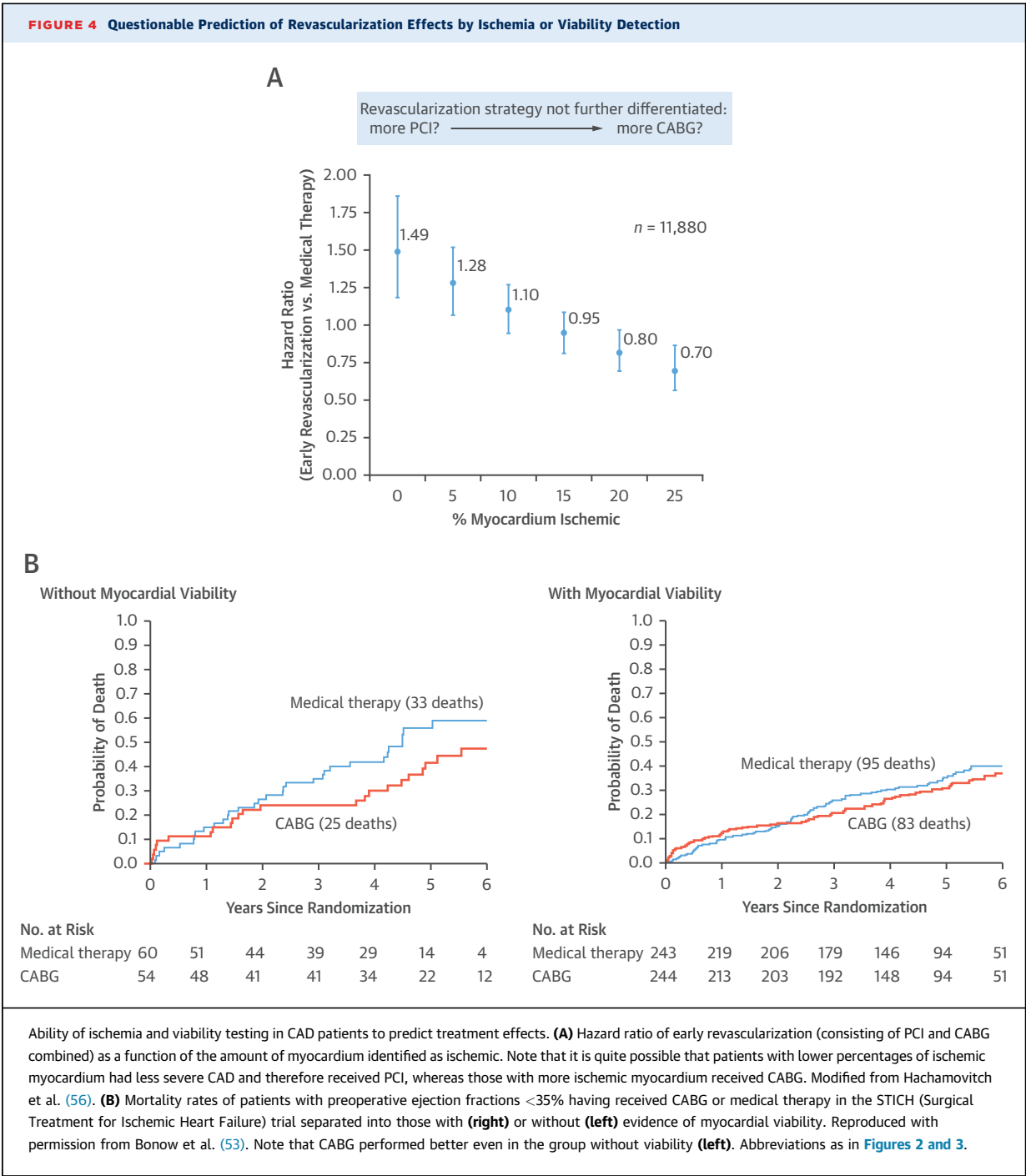
Mushtaq et al. (58) have addressed the impact of atherosclerotic burden on prognosis in patients with suspected CAD. They evaluated the Leaman score to quantify plaque load determined by computed tomography (CT) and found that patients with a high plaque load have more cardiac events than those low plaque load. Note in **Figure 6A** that patients with large atherosclerotic burden (CT Leaman score >5) and non–flow-limiting coronary stenosis (CAD <50%) have the same event rate as those patients with significantly flow-limiting stenoses. Thus, plaque load seems to be an important contributor to CAD morbidity and mortality, which underscores the discussion earlier in the text on infarct-inducing stenoses (**Figure 2**).

Two other investigations have addressed the spatial distribution of coronary vessel occlusions from CAD (46) and the site of bypass graft insertion (42). The vast majority of infarct-inducing vessel occlusions occur in the proximal one-third of the 3 main vessels (46), and the majority of bypass grafts are placed distal to a potential vessel occlusion from CAD (42) (**Figure 6B**). These studies fully support our main conclusion by stating that coronary bypass grafts may protect against infarction by covering anatomic zones at risk for ST-segment elevation myocardial infarction.

Considering these findings, it is interesting to re-review the main findings of the SYNTAX trial. **Figure 3** also shows that dependent on SYNTAX score, the event rate continuously increases in the PCI groups but not in the CABG groups. Thus, the severity of coronary artery disease only appears to be a risk factor for PCI. Because the main mechanism of death is cardiac (7,23,40,41) and perioperative risk appears similar, independent of the SYNTAX score, this finding also suggests that infarct reduction is the main reason for the difference in all-cause mortality.

This line of reasoning is further supported by studies demonstrating improved survival of CABG compared with PCI in patients with dialysis-dependent renal failure (30,59). Although it is undebated that renal failure increases perioperative risk, long-term survival is still consistently better with CABG (36). Importantly, myocardial infarction and cardiac death are the main causes of death in patients with severe renal failure (30,36,59).
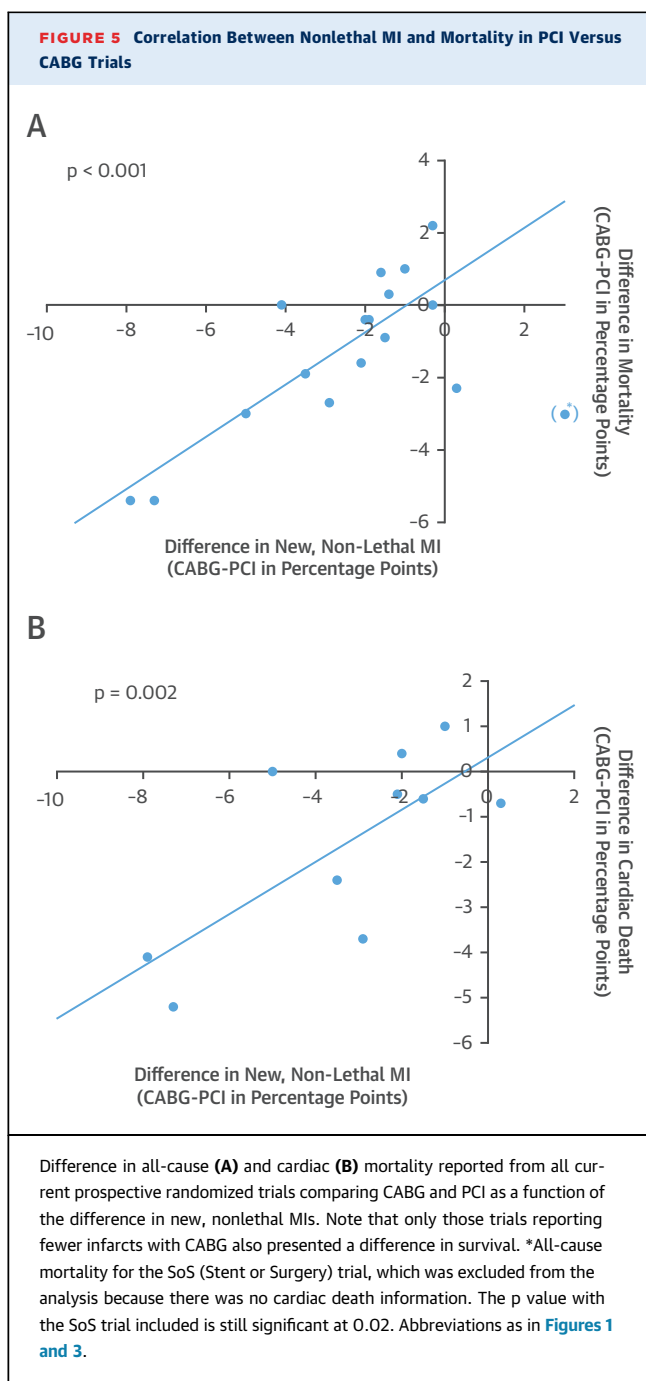
Finally, our argument is even supported by the aforementioned network meta-analysis that suggested a survival benefit for the new drug-eluting stents through sophisticated statistics (49), without direct evidence (39). However controversial this finding may be, it is interesting to note that the

FIGURE 4 Questionable Prediction of Revascularization Effects by Ischemia or Viability Detection

Ability of ischemia and viability testing in CAD patients to predict treatment effects. **(A)** Hazard ratio of early revascularization (consisting of PCI and CABG combined) as a function of the amount of myocardium identified as ischemic. Note that it is quite possible that patients with lower percentages of ischemic myocardium had less severe CAD and therefore received PCI, whereas those with more ischemic myocardium received CABG. Modified from Hachamovitch et al. (56). **(B)** Mortality rates of patients with preoperative ejection fractions <35% having received CABG or medical therapy in the STICH (Surgical Treatment for Ischemic Heart Failure) trial separated into those with **(right)** or without **(left)** evidence of myocardial viability. Reproduced with permission from Bonow et al. (53). Note that CABG performed better even in the group without viability **(left)**. Abbreviations as in **Figures 2 and 3**.

demonstration of a possible survival impact through low-risk ratios for drug-eluting stents versus MED is directly related to similarly low-risk ratios for infarct reduction (risk ratios, 95% CI for all cause-mortality: EES vs. MED: 0.75; 0.59 to 0.96, R-ZES vs. MED: 0.65; 0.42 to 1.00; for myocardial infarction: EES vs. MED: 0.75; 0.55 to 1.01, R-ZES vs. MED: 0.82; 0.52 to 1.26) (49).

"IDEAL STENT" VERSUS "IDEAL BYPASS GRAFT" AND A "REAL-WORLD-SOLUTION INCLUDING MED". Taking all the aforementioned considerations into account, the ideal stent would be free of thrombosis, not require re-revascularization, and maintain vasomotor/vascular function. Then, in theory, all plaques could be stented, and a reduction of infarcts and improved survival could be expected. The real

FIGURE 5 Correlation Between Nonlethal MI and Mortality in PCI Versus CABG Trials

Difference in all-cause **(A)** and cardiac **(B)** mortality reported from all current prospective randomized trials comparing CABG and PCI as a function of the difference in new, nonlethal MIs. Note that only those trials reporting fewer infarcts with CABG also presented a difference in survival. *All-cause mortality for the SoS (Stent or Surgery) trial, which was excluded from the analysis because there was no cardiac death information. The p value with the SoS trial included is still significant at 0.02. Abbreviations as in **Figures 1 and 3**.

occlusion rates of up to 25% at 1 year (61), and even arterial grafts occlude at a rate that appears to be dependent on the degree of collateral flow (62). If the current trend to graft target vessels guided by FFR measurements (34,63) is continued, the impact of CABG to reduce survival may even be reduced because fewer target vessels are likely to be grafted.

In addition, the impact of MED and primary prevention measures may not be underestimated. That includes MED to control symptoms as well as strategies to prevent or reverse plaque progression (64). The recently published SCOT HEART trial (Scottish COmputed Tomography of the HEART) (57) is well suited to illustrate the magnitude of these measures on cardiac events. The pure knowledge about the extent of CAD (based on a CT coronary angiogram) allowed the treating physicians to achieve around 40% reduction in infarcts. This reduction must have been due to primary prevention measures, because the fraction of patients having received invasive diagnosis and therapy has been identical. This finding, in concert with the illustrated inability of ischemia and scar detection methods to predict revascularization outcomes, underscores our conclusion that the reported difference in survival between CABG and PCI must be due to effects beyond revascularization. It also leads to the need of optimal MED in both PCI and CABG patients, which has been underscored by the most recent European Society of Cardiology revascularization guidelines (1).

Because in real life, the conditions are rarely ideal, individualization based on obeying current evidence may have the potential to achieve the best patient outcome. Such individualized decision-making requires a true heart team including a noninterventional, nonsurgical cardiovascular expert.

For the available invasive treatment options, Stanetic et al. (65) illustrated the possible impact of a heart team approach in today's practice. The authors used the validated SYNTAX II score and applied it to 651 consecutive patients with triple-vessel CAD from a hospital without cardiac surgery onsite. The authors compared actual outcomes based on the selected treatment (CABG or PCI) to the suggested treatment recommendation based on the SYNTAX II score. The authors found that one-third of the patients were referred for CABG and two-thirds received PCI. According to SYNTAX II score, only 4 of the CABG patients (1.65%) would have received a primary PCI recommendation, whereas 35% (n = 144) of the PCI patients would have received a primary recommendation for CABG. Comparing mortality rates in the PCI patients, the highest mortality rate (12.5%) was found in those patients who had a primary recommendation

world of PCI for stable CAD lacks a measurable impact on survival or infarction. That statement is true for the continuously renewed drug-eluting stents (14,17,18,38,39,50), as well as for the new bioabsorbable stents (37,60).
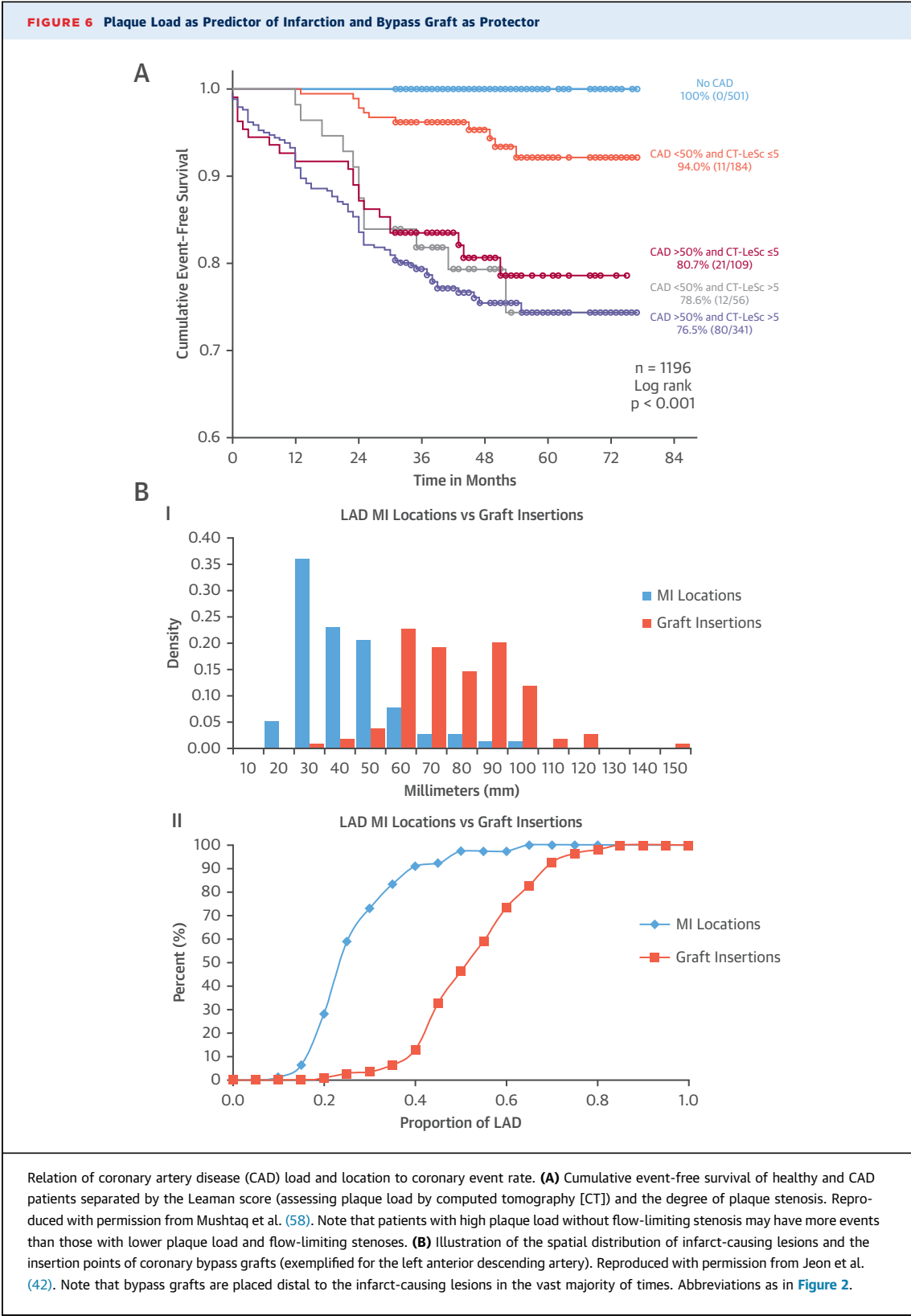
In analogy, the ideal bypass graft would not occlude. CAD would be treated by grafting all areas with CAD, and the treatment effect would be larger than it already is. The real world, however, shows

FIGURE 6 Plaque Load as Predictor of Infarction and Bypass Graft as Protector

Relation of coronary artery disease (CAD) load and location to coronary event rate. **(A)** Cumulative event-free survival of healthy and CAD patients separated by the Leaman score (assessing plaque load by computed tomography [CT]) and the degree of plaque stenosis. Reproduced with permission from Mushtaq et al. (58). Note that patients with high plaque load without flow-limiting stenosis may have more events than those with lower plaque load and flow-limiting stenoses. **(B)** Illustration of the spatial distribution of infarct-causing lesions and the insertion points of coronary bypass grafts (exemplified for the left anterior descending artery). Reproduced with permission from Jeon et al. (42). Note that bypass grafts are placed distal to the infarct-causing lesions in the vast majority of times. Abbreviations as in **Figure 2**.

for CABG according to SYNTAX II. Mortality for those patients treated consistent with SYNTAX II score recommendations was significantly lower (6.9% PCI or CABG, and 0% only PCI). The authors calculated that adherence to the SYNTAX II score recommendations could have reduced actual mortality by 5.6% with a number needed to treat of 18. They discuss that U.S. compliance rates with guidelines for CAD treatment are only 53%. (65).

IMPACT OF "SURGICAL COLLATERALIZATION" ON CURRENT PRACTICE. The aforementioned evidence piece by piece suggests that CABG provides "a collateralization effect" over revascularization by bypassing diseased territories and preventing symptoms in case of plaque rupture and vessel occlusion. Only the revascularization part may be comparable to PCI. It may be sobering to note that we continue to choose PCI over CABG in the "real world" management of stable CAD, despite the robust scientific evidence in support of CABG and the current clinical practice guidelines (1). Although the realization of mechanistic differences, as illustrated here, may require time, treatment decisions in real life may, however, be influenced by other factors than the extent of CAD. Advanced age and comorbidities may increase operative risk, and the need for symptomatic control may overcome a potential long-term benefit. Whether these reasons are always responsible is beyond this review, but they underscore the need for individual decision-making by a group of experts (heart team). In light of this discussion, several things may require revision for daily practice.

First and foremost, the terminology needs to change. CABG should no longer be considered a method of revascularization alone. It adds a mechanism of myocardial protection that explains its ability to prolong life (which may be less detectable if the disease is not associated with greater natural risk). Consenting patients, which is already suboptimal if it comes to addressing CABG as a revascularization option for CAD treatment (66), needs to change. Patients

should be informed that they can be treated for their symptoms with PCI and that they can obtain revascularization plus protection against new infarction from CABG.

For the conduct of CABG, the role of complete versus incomplete revascularization needs to be revisited and the mechanisms for early graft failure would need to be studied in more detail. For the conduct of PCI, restenosis and stent thrombosis would need to be solved before less stenotic lesions can be addressed, hoping for an impact of elective PCI on new myocardial infarctions and possibly survival.

Our current practice, however, suggests that treatment decisions are not always consistent with the currently available evidence (65) and recommendations (1). One potential solution may have arrived with the noninvasive imaging of even severe coronary artery disease using CT, potentially including functional flow assessments (33,67), allowing the objective discussion of risk-benefit tradeoffs (68) for CABG or PCI, independent of the need for a potential second intervention.

CONCLUSIONS

Coronary bypass surgery appears to bypass diseased coronary vessel segments (creating "surgical collateralization") in addition to revascularization, a condition that allows vessels to occlude without causing a lethal or nonlethal myocardial infarction. The mechanism of CABG is therefore different from that of PCI. This recognition has the potential to significantly alter our current routine of decision-making in patients with stable CAD.

ADDRESS FOR CORRESPONDENCE: Prof. Torsten Doenst, Department of Cardiothoracic Surgery, Friedrich-Schiller-University of Jena, Am Klinikum 1, 07747 Jena, Germany. E-mail: doenst@med.uni-jena.de.

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