Clinical Trials Versus Clinical Practice:

When Evidence and Practice Diverge—Should Nondiabetic Patients With 3-Vessel Disease and Stable Ischemic Heart Disease Be Preferentially Treated With CABG?

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The planning of revascularization strategy for multivessel coronary artery disease (CAD) in nondiabetic patients is optimally made through considering the goals of improving survival and/or relieving symptoms. Existing clinical practice guidelines and appropriate use criteria (1–3) state that in nondiabetic patients with multivessel CAD and stable ischemic heart disease (SIHD), either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with drug-eluting stents may be used for those with low SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores, but CABG is preferred for those with intermediate or high SYNTAX scores. In the overall SYNTAX population (4–6), the rates of death and stroke were similar, but the risk of myocardial infarction (MI) and repeat revascularization were higher in PCI-treated patients. At 5-year follow-up, the rates of death/stroke/MI are 8.0% lower, and the rate of repeat revascularization is 12.8% lower in CABG-treated patients. In the low SYNTAX score tertile, these trends are not significantly different, but they are in the intermediate and high SYNTAX score subsets. When considering only survival in the 3 tertiles, there was a 0.9%, 6.7%, and 9.0% difference over 5 years, an average of 0.2% to 1.8% per year. Yet, PCI is more often performed in multivessel CAD patients, despite the guidelines and clinical evidence. Can this apparent divergence from the evidence base be supported? Drs. Weintraub and Tcheng and colleagues were asked to defend or critique the current guidelines.

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EVIDENCE FROM THE SYNTAX TRIAL

The SYNTAX trial provides the only multicenter, randomized comparison between CABG and drug-eluting stents among nondiabetic patients with left main artery (LM) and/or 3-vessel CAD (3VD) (4). The trial randomized 1,800 patients with 3VD or LM disease to undergo either PCI (n = 903) or CABG (n = 897), with a mean age of 65 years in both groups. Approximately 75% of patients did not have diabetes. The rate of patients at high surgical risk (EuroSCORE [European System for Cardiac Operative Risk Evaluation] 6) was ~20% in both groups. Almost 60% of the patients had 3VD (n = 1,095), and 39% of the patients in both groups had LM disease in addition to other vessel involvement. The primary endpoint of major adverse cardiac or cerebrovascular events (MACCE) (composite of death from any cause, MI, stroke, or repeat revascularization) and its components was compared with that in the CABG and PCI groups at 1-, 3-, and 5-year follow-up periods. Both groups were also compared according to low (score 22), intermediate (scores of 23 to 32), and high (scores 33) SYNTAX scores. The average SYNTAX score was 29.1 in the CABG group and 28.4 in the PCI group (p = 0.19) (3). The detailed comparison of clinical endpoints for the CABG group versus the PCI group for SIHD patients with LM or 3VD disease at 1-, 3-, and 5-year follow-up periods (Table 1).

Clinical outcomes at 1-year—At 1-year, the CABG group had fewer MACCE compared with the PCI group (4). This was largely driven by a decreased rate of repeat revascularization in the CABG group. Death and MI were comparable in the 2 groups. The SYNTAX score had significant interaction with the treatment groups (Table 1). MACCE were not significantly different between the CABG and PCI groups for low and intermediate SYNTAX scores. However, MACCE were lower in patients undergoing CABG with a high SYNTAX score (Table 1), but the stroke rate was higher in the CABG cohort.

Clinical outcomes at 3 years—The 3-year follow-up again demonstrated fewer MACCE in the CABG group compared with the PCI group, driven by a decreased rate of repeat revascularizations and fewer MIs in the CABG group compared with the PCI group (5). In contrast to 1-year follow-up, there was no longer a significant difference in the incidence of stroke between the CABG and PCI groups at 3 years (Table 1). MACCE were comparable between the CABG and PCI groups for low SYNTAX score (Table 1) (6). In LM/3VD patients with intermediate SYNTAX scores, the CABG group had fewer MACCE, fewer MIs, and a lower rate of repeat revascularization. In LM/3VD patients with a high SYNTAX score, the CABG group had fewer MACCE compared with the PCI group (Table 1).

Clinical outcomes at 5 years—Consistent with 1- and 3-year results, CABG remained favorable compared with PCI for LM/3VD with fewer MACCE and a lower rate of repeat revascularization (6). Death of any cause and stroke were not significantly different between the 2 groups (7). MACCE were comparable between the CABG and PCI groups for low

SYNTAX score and were significantly lower in the CABG group for intermediate and high SYNTAX scores compared with the PCI group (Table 1) (7). In a subgroup analysis of patients with 3VD, MACCE were significantly lower in the CABG group compared with the PCI group (24.2% vs. 37.5%, p < 0.0001) (7). The 3VD subgroup with a low SYNTAX score had comparable MACCE between the CABG and PCI groups (26.8% vs. 33.3%, p = 0.21). However, the 3VD subgroup with intermediate and high SYNTAX scores had lower MACCE with CABG compared with PCI (intermediate SYNTAX score: 25.8% vs. 36.0%, p = 0.008; high SYNTAX score: 26.8% vs. 44.0%, p < 0.0001) (7).

Cost-effectiveness analysis of the SYNTAX trial—A cost-effectiveness analysis (CEA) of the SYNTAX trial was performed for 1- and 5-year outcomes. Although 1-year survival was comparable between the CABG and PCI groups, quality-adjusted life years (QALYs) were lower in the CABG group compared with the PCI group (0.80 vs. 0.82, p = 0.003) (7). PCI remained an economically dominant strategy with respect to QALYs gained at 1-year due to the lower cost and higher quality-adjusted survival. Due to the increased rate of repeat revascularization with PCI, CABG remained the approach to use to avoid repeat revascularization. Although the CEA will be limited at 1 year, there was an interaction between the SYNTAX score and the incremental cost-effectiveness ratio (ICER) measured in cost per QALY gained. PCI was found to be a dominant strategy in 3VD patients with low and intermediate SYNTAX scores. However, the ICER for 3VD with high SYNTAX scores was favorable for CABG even at 1 year (Table 1). The cost-effectiveness of CABG compared with PCI at 5-year follow-up demonstrated that the in-trial cost remained $5,619 higher in the CABG group at 5 years with 0.1 QALY gained compared with PCI (8). Lifetime estimates suggested 0.412 QALY gained for CABG, making CABG an economically attractive strategy with an ICER of $16,537/QALY gained for LM/3VD patients and $4,905/QALY gained for 3VD patients. The cost-effectiveness of CABG versus PCI based on SYNTAX score showed CABG as a favorable strategy for those with high SYNTAX scores (ICER for CABG: $8,219/QALY gained) and intermediate SYNTAX scores (ICER for CABG: $36,790/QALY). For low SYNTAX scores, PCI remained a dominant strategy (8).

In summary, the clinical and economic outcomes at 5 years in the SYNTAX trial demonstrated CABG to be superior compared with PCI in nondiabetic patients with 3VD and SIHD by reducing MACCE, MI, and repeat revascularization with an attractive ICER of $12,329/QALY gained. For patients with a high SYNTAX score (≥33), CABG lowered all-cause mortality at 5 years and still remained highly cost-effective with an ICER of $8,219/QALY gained compared with PCI.

Evidence from the registry data—Results similar to those of the SYNTAX trial were observed in ASCERT (American College of Cardiology Foundation and the Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies), the largest and the most comprehensive observational study. This was a comparative effectiveness study of CABG versus PCI, analyzing data in the American College of Cardiology Foundation National Cardiovascular Data Registry and the Society of Thoracic Surgeons Adult Cardiac Surgery Database linked to claims data from the Centers

for Medicare and Medicaid Services for stable multivessel disease in patients older than 65 years of age (9). Although the CABG and PCI groups had significant baseline differences, after adjusting with inverse probability weighting based on propensity score, the CABG (n = 86,244) and PCI (n = 103,549) groups were comparable for all baseline characteristics (mean age, 74 years; 65% without diabetes, 53% with 3VD in both groups). The follow-up ranged from 1 to 5 years (median follow-up, in years; 2.67 overall, 2.83 CABG group, and 2.53 PCI group). At 1 year, there was no significant difference in the adjusted mortality between the CABG and PCI groups. At 4-year follow-up, however, patients undergoing CABG had lower mortality compared with patients undergoing PCI (16.4% vs. 20.8%; risk ratio [RR]: 0.79; 95% confidence interval [CI]: 0.76 to 0.82). This survival difference persisted across a wide range of subgroup analyses including the presence or absence of diabetes and high or low surgical risk groups. The adjusted relative risk for patients with 3VD and no diabetes undergoing CABG was 0.81 (95% CI: 0.78 to 0.85).

At 4 years, the CABG group had a significantly lower adjusted incidence of MI compared with the PCI group (3.2% vs. 6.6%, RR: 0.49; 95% CI: 0.45 to 0.53) (10). Similarly, at 4 years, the CABG group had a significantly lower adjusted composite of death, MI, or stroke compared with the PCI group (21.6% vs. 26.7%, RR: 0.81; 95% CI: 0.78 to 0.83). In contrast to 5-year results from the SYNTAX trial, ASCERT showed that the CABG group continued to have a significantly higher stroke rate at 4 years compared with PCI (4.5% vs. 3.1%, RR: 1.43; 95% CI: 1.31 to 1.54). In the ASCERT, the incidence of stroke in both groups remained parallel after the initial periprocedural period. Two randomized clinical trials evaluating cognitive function at 1 and 5 years demonstrated no difference in the neuropsychological outcomes between patients undergoing CABG or PCI (11,12). Also, a systematic review of 23 randomized clinical trials showed a higher rate of procedure-related strokes in patients undergoing CABG compared with PCI (13). The reason for the difference in the adjusted stroke risk at 4 years between the CABG and PCI groups in the ASCERT compared with the convergence of risk in the randomized trials during long-term follow is unknown.

Being an observational study, the ASCERT has the important limitation of potential residual treatment selection bias, even after adjusting the CABG and PCI groups for significant baseline differences. The probability of a patient being selected for either CABG or PCI, based on clinical and hospital characteristics and after adjusting for significant between-group differences, was estimated by the propensity score (9). The performance of a propensity model was verified by comparing the distribution of propensity scores and covariates. It showed that patients undergoing PCI had a lower probability of being selected for CABG compared with patients undergoing CABG. Although there was an excellent balance between the CABG and PCI groups, after adjustment with the use of propensity score–derived inverse probability weighting, there remains a possibility of unmeasured confounders such as complexity of coronary disease, chronic total occlusions, and patient frailty.

CEA of ASCERT

The CEA of ASCERT was recently reported (14). It demonstrated that the adjusted cost of CABG was higher for the index hospitalization, 4-year follow-up, and for lifetime. The quality-adjusted survival was calculated based on published data on health utilities and adjusted survival. Patients undergoing CABG gained an average survival of 0.25 years for the 4-year observational study period and 0.38 years over the lifetime compared with patients undergoing PCI. The lifetime ICER for CABG over PCI was $30,454/QALY gained for overall study population, $36,298/QALY gained for patients with no diabetes, and $27,080/QALY gained for patients with 3VD (well below the conventional threshold of $50,000/QALY gained).

Evidence from the meta-analysis—A meta-analysis of 10 randomized trials (N = 7,812, PCI performed with balloon angioplasty in 6 trials and with bare metal stents in 4 trials (drug-eluting stents were not used in these trials) compared the clinical effectiveness of CABG with that of PCI on long-term mortality in the management of stable multivessel disease with a median follow-up of 5.9 years. The results showed a trend for decreased mortality with CABG compared with PCI for multivessel disease (overall: hazard ratio [HR]: 0.91, 95% CI: 0.82 to 1.02, p = 0.12; nondiabetic patients: HR: 0.98, 95% CI: 0.86 to 1.12, p = 0.014) (15). The study population included 84% of patients with no diabetes, 34% 65 years of age or older, and 37% with 3VD. There was a significant interaction between patient age (65 years) and the treatment effect on mortality. CABG improved survival in patients 65 years of age and older compared with PCI (HR: 0.82, 95% CI: 0.70 to 0.97) but did not have any impact on mortality for patients younger than 65. CABG improved the composite of 5-year event rate (death, myocardial infarction, or repeat revascularization) compared with PCI (20.1% vs. 36.4%, HR: 0.52, 95% CI: 0.49 to 0.57, p < 0.0001) Another recent meta-analysis included a total of 6 randomized trials comparing long-term mortality of CABG versus PCI for multivessel disease (N = 6,055 patients) with a median follow-up of 4.1 years (16). In 4 of these 6 trials (n = 3,665: ARTS, MASS II, SoS, SYNTAX), the majority of the patients were nondiabetic with a mean age of 60 or older. Here, CABG was noted to have improved survival compared with PCI (RR: 0.72, 95% CI: 0.58 to 0.89, p = 0.003).

CONCLUSIONS

Oftentimes, the decision to perform PCI as a revascularization strategy is considered first when the stenosis appears to be easily approachable. However, the best strategy for long-term outcomes is only partly dependent on technical considerations. The available clinical evidence demonstrates a decreased rate of repeat revascularization and MI with CABG compared with PCI. CABG improves long-term survival of patients with a high SYNTAX score. Patients older than 65 years of age appear to have favorable long-term outcomes with CABG compared with PCI. The increased risk of stroke with CABG during the initial periprocedural period seems to decrease during long-term follow-up in the randomized studies, except in the ASCERT. Overall, CABG appears to be a cost-effective strategy, especially for patients with intermediate or high SYNTAX scores compared with PCI. The clinical evidence regarding mortality and morbidity after CABG or PCI should be discussed

in a "heart team" approach for the optimal management of SIHD with 3VD in nondiabetic patients.

COUNTERPOINT: NONDIABETIC PATIENTS WITH ADVANCED CORONARY DISEASE SHOULD PREFERENTIALLY BE CONSIDERED FOR PCI

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The current guidelines favoring CABG over PCI, although based on a large body of evidence, have a number of inherent limitations, including the following: 1) the rapid and ongoing evolution of PCI techniques and technologies, rendering PCI-specific outcomes potentially outdated even before being considered in the creating of guidelines; and 2) the difficulties of applying general guidelines to decision making at the individual patient level. Regarding the body of evidence, in an analysis of 2,711 American College of Cardiology/ American Heart Association guideline recommendations spanning 53 guidelines across 22 topic areas, recommendations regarding CABG were found to have only 19% Level of Evidence: A strength (17). Even then, a number of Level of Evidence: A guidelines are based on data more than 10 years old. Regarding the application of guidelines to the individual patient, the concept of external validity (or generalizability) of the trials that provide the basis for guidelines must be considered (18). Randomized, controlled trials (RCTs) are designed to assay the overall standard of treatment of a population of patients rather than delineate individualized recommendations. In applying guidelines, the clinician must aggregate and integrate multiple dimensions (e.g., comorbidities, psychological and social characteristics, operator proficiency and competency, health care setting factors) in addition to determining whether the specific guideline in question precisely fits the clinical context of the treatment decision.

Another issue is the relevance of the component endpoints comprising clinical trial composite endpoints to the clinical care objectives. The PCI strategy purposefully relies on limited treatment of only the coronary segments with the greatest disease. This targeted strategy anticipates the potential for repeat intervention given the progressive nature of atherosclerosis rather than considering repeat intervention as an adverse outcome. Given this anticipation, should repeat revascularization be graded as a failure of the PCI strategy in clinical trials, while not counting graft failure as a CABG endpoint equivalent to (or perhaps worse than that of) repeat revascularization?

A critical drawback is the lack of representation of symptom relief in the composite endpoints of clinical trials. The durability of PCI has remarkably improved with the evolution of drug-eluting stents. This salutary benefit is arguably of greater importance to the patient than a Kaplan-Meier demonstration of a reduction in mortality. Obviously, PCI is a much less physically traumatic procedure than CABG and, where used appropriately, results in effective and sustained symptomatic relief. Moreover, composite endpoints are heavily biased when a PCI revascularization procedure is assigned the same weight as MI and even death in trial endpoint calculations.

Only in the past 5 years have drug-eluting stent platforms evolved to the level of commodity. Dramatic technology improvements now permit complex multivessel CAD to be approached via PCI with high procedural success rates. This has rekindled the debate of the role of CABG versus PCI in the management of the patient with advanced coronary artery disease, particularly when both surgical and percutaneous interventions appear to be viable revascularization strategies. A key element is the recognition that the expression of CAD varies from patient to patient, from 3 discrete noncalcified lesions that can be easily treated primarily with PCI to calcified bifurcation disease and chronic total occlusions that carry a lower probability of PCI success. Unfortunately, clinical trials have generally not differentiated anatomy at this level, and even the definitions of clinical risk factors (e.g., diabetes and its various severity levels) vary from trial to trial.

There are no large randomized trials to date of CABG versus drug-eluting stents limited to patients without diabetes. The most relevant trial is SYNTAX (5–7), which randomized both diabetics and nondiabetic patients to either CABG or PCI with the paclitaxel-eluting TAXUS stent (Boston Scientific, Natick, Massachusetts). To further augment external validity, SYNTAX was designed as an "all-comers" trial. To reduce selection bias, consecutive patients were enrolled. A heart team approach was encouraged, and patients were enrolled only if equivalent anatomic revascularization could be achieved with CABG or PCI. Patients who were suitable for only 1 treatment option were enrolled in parallel CABG and PCI registries; those thought to be too high risk for surgery were offered PCI, and patients with complex disease not amenable to PCI were offered CABG. The exclusion of these groups of patients renders current guideline recommendations valid only in randomizable patients: although 4,337 patients with multi-vessel disease were identified, only 1,800 patients (41.5%) were randomized; 1,275 (29.4%) were enrolled in the parallel, nested registries and 1,262 were ineligible for various reasons such as treatment preference or the declining of informed consent. Guidelines based on SYNTAX and similar trials are thus a priori applicable to less than one-half of patients with multivessel disease.

The results of the SYNTAX trial demonstrated that at 12 months, all-cause mortality was 4.4% and 3.5% for PCI and CABG, respectively (p = 0.37). MI occurred in 4.8% versus 3.3% (p = 0.11), whereas stroke occurred in 0.6% versus 2.2% (p = 0.003). Evaluating the composite of all-cause mortality, stroke, or MI, rates were similar at 7.6% versus 7.7% (p = 0.98). The rates of symptomatic graft occlusion and stent thrombosis were also similar at 3.3% versus 3.4% (p = 0.89). It was not until the endpoint of repeat revascularization (13.5% for PCI versus 5.9% for CABG, p < 0.001) was included in the primary endpoint of MACCE (17.8% for PCI vs. 12.4% for CABG, p = 0.002) that PCI failed to meet the noninferiority margin specified as the primary analysis.

A key observation of the SYNTAX trial was the interaction between the SYNTAX score and outcomes by revascularization strategy. MACCE rates with PCI at 12 months increased incrementally with SYNTAX score; conversely, MACCE rates decreased with CABG. In patients with a low SYNTAX score (scores: 0 to 22), the rate of MACCE with PCI was 13.6% versus 14.7% with CABG (p = 0.71); with a SYNTAX score of 23 to 32, 16.7% with PCI versus 12.0% with CABG (p = 0.10); and with a high SYNTAX score (33), 23.4% versus 10.9% (p < 0.001). Importantly, at 5 years, patients with a low SYNTAX score

continued to have similar MACCE rates with PCI and CABG (32.1% and 28.6%, respectively, p = 0.43) (20). Patients with an intermediate SYNTAX score had similar rates of the composite of death, stroke, and MI (20.7% vs. 18.0%, p = 0.42), although MACCE rates (36.0% vs. 25.8%, p = 0.008) favored CABG due to an increasing need for repeat revascularization in the PCI arm. Thus, one-third of patients with advanced multivessel coronary disease, specifically SYNTAX-eligible patients with a low SYNTAX score, are good candidates for a PCI first approach. An additional one-third of patients, those with an intermediate score, could be expected to have similar rates of death, stroke, and MI while potentially requiring additional revascularization subsequent to the index intervention. Only in those with a high SYNTAX score is the benefit of a CABG first approach clearly manifest.

Specific to patients without diabetes in the SYNTAX trial, analysis of the 1-year data (5) reveals several key observations (Table 2) (19–21). First, the MACCE rates for CABG (11.8%) and PCI (15.1%) approximate those of patients with a low SYNTAX score (14.7% and 13.6%, respectively). Second, the difference in MACCE rates between CABG and PCI at 1- and 3-year follow-up is not statistically significant. Critically, the composite of death, stroke, and MI is no different between the 2 approaches, even at 5 years. Only repeat revascularization favors the CABG approach, and that difference is driven predominantly by the need for repeat PCI. At 1 year, 30 patients would need to be treated with CABG rather than PCI to prevent 1 MACCE, with that additional event being (most often) a PCI revascularization procedure. The post-procedure hospital stay was 3.4 ± 4.5 days in the PCI group versus 9.5 ± 8.0 days in the CABG group, clearly favoring PCI, even without considering postoperative surgical recovery at home. At longer term follow-up, while the differences in outcomes (in particularly MACCE, cardiac death, and repeat revascularization) favoring CABG did increase, this likely reflected progression of the underlying disease. The reticence to refer patients for a redo CABG is apparent; no patient underwent redo CABG over the 5-year period of observation once the 1-year anniversary had been achieved. Finally, Table 3 (21) illustrates that the SYNTAX score remains predictive of long-term outcome, even in patients without diabetes; as with the overall trial results, the differential between PCI and CABG widens as the SYNTAX score increases. When evaluated from the perspective of patients destined to do well—specifically patients without diabetes and with a low SYNTAX score—CABG arguably should be reserved only for the management of progressive disease once it can no longer be managed by PCI.

Finally, the incidence of restenosis and the need for repeat revascularization have substantially decreased since the SYNTAX experience with the paclitaxel-eluting stent. The COMPARE (Comparison of the Everolimus Eluting XIENCE-V Stent with the Paclitaxel Eluting TAXUS LIBERTE Stent) trial randomized 1,800 patients to PCI with either the everolimus-eluting stent (EES) or paclitaxel-eluting stent. At 2 years, the primary endpoint of death, nonfatal MI, and target vessel revascularization was 9.0% versus 13.7% (p = 0.002) in favor of EES. The rates of target vessel revascularization were also lower at 3.2% versus 8.0% (p < 0.001) (22). It could be hypothesized that, were the SYNTAX trial repeated today using an EES, the pre-specified noninferiority margin in SYNTAX trial would have been met. In 1 analysis, a subgroup of patients in the COMPARE trial who underwent PCI for multivessel and/or LM disease (N = 466, with 234 treated with paclitaxel-eluting stents and

232 with EES) were studied (23). The results were then stratified by complexity according to the SYNTAX score and suggest that patients with low SYNTAX scores may have lower MACCE rates with PCI using EES than with CABG (18.0% vs. 24.7% projected). In patients with intermediate scores, MACCE rates with PCI using EES and CABG would still favor PCI (18.6% vs. 22.1% projected). It is not until the SYNTAX score is high that CABG becomes superior (36.4% vs. 22.4% projected).

ASCERT (9) demonstrated that at 4 years, in Medicare patients with multivessel disease who did not require emergency treatment, mortality was 16.4% for patients who underwent CABG versus 20.8% for patients who underwent PCI. However, as would be expected, the baseline patient characteristics were quite different, necessitating the use of propensity scores and inverse-probability weighting to statistically compensate for these differences and for missing data. Importantly, the differences that could be addressed were largely in the realm of clinical risk factors and other clinical characteristics; the only anatomic data were the number of diseased coronary arteries and the presence of proximal left anterior descending disease. Although exceedingly well conducted, this observational study remains largely in the realm of hypothesis generation, particularly given the lack of in-depth knowledge about the other dimensions of non-captured information that contribute to the decision of PCI versus CABG in multivessel disease.

In conclusion, many patients with multivessel CAD can be appropriately managed with a PCI-first strategy. Seemingly applicable clinical trials to address the revascularization strategy question (and the guidelines derived thereof) have limited external validity and do not reflect the latest in interventional technologies. Careful case selection and consideration of technical details are crucial in choosing the right strategy for the right patient.

SUMMARY AND CONCLUSIONS

Lloyd W. Klein, MD

This discussion highlights an important clinical dilemma: in developing a revascularization strategy, there is a significant divergence in clinical practice from the existing guidelines. Results from the SYNTAX trial would suggest that only the least complex one-third of patients with 3VD might be candidates for PCI and that CABG should be preferentially considered for the majority. However, actual practice suggests that PCI is more often selected. This is confirmed in ASCERT (9), in which the Medicare PCI population in institutions that collected data for both National Cardiovascular Data Registry and Society of Thoracic Surgeons registries was almost twice as large as the CABG population.

This apparent discrepancy is connected to the recognition that patients who are enrolled in RCTs are a select subgroup of those who are seen in practice. Often, patients seen in actual practice do not meet a relevant study's inclusion or exclusion criteria, and, hence, it is ambiguous whether the trial results pertain to them because the benefits of any treatment option are usually not homogeneous, are useful for some subgroups, and negligible (or even harmful) for others.

In particular, frailty and severe comorbid conditions are not evaluated in RCTs or captured in registries, but are always taken into account in clinical practice.

Patients who are selected for PCI in clinical practice are frequently dissimilar to those who have CABG. For example, ASCERT showed that Medicare patients with multivessel CAD undergoing revascularization do not have the same propensity to undergo the 2 procedures: The propensity distribution curve shows a bimodal distribution with little overlap at a nadir between 0.4 and 0.6.

Why does CABG outperform PCI in RCTs? There are 3 main factors: 1) The high patency rate of the left internal mammary artery graft; 2) stents treat only the segment in which they are placed, but a graft bypasses all proximal segments, including vulnerable plaque that has not produced a significant luminal narrowing; and 3) complete revascularization is more commonly achieved with CABG. The latter reason is especially of interest: in SYNTAX, almost 5 stents per patient were placed, for a total length of ~9 cm, with incomplete revascularization in 43.3%. In the CABG group, ~3 grafts/patient were placed, with an incomplete revascularization rate of 36.8%. This significant difference was associated with increased adverse events (24). Such a critical factor in making individual decisions must be accounted for in evaluating medical judgments, and the "residual SYNTAX score" may be of enormous value in shared decision making. It has been estimated, using a residual score of 8 as criterion, that 71% of SYNTAX patients are best treated with CABG, whereas for the remainder, PCI is a reasonable alternative (6). In patients in whom a complete, or similar degree of incomplete, revascularization is anticipated with both techniques, there is insufficient analysis to conclude whether there may be equivalent outcomes in some subgroups.

Moreover, the absolute survival differences are small enough that a sensible physician can reasonably advise, or a patient intelligently desire, multivessel stenting or optimal medical therapy, in some cases. An approximate 1% per year survival advantage is not so overwhelming as to exclude additional apposite considerations. In particular, the relatively higher 30-day mortality in CABG in patients with significant left ventricular dysfunction might rationally affect decision making in some patients even when longer term outcomes favor CABG (25). In both SYNTAX and ASCERT, there was no difference in survival at 1 year overall, a finding that emphasizes that the longer term benefits of CABG can only be enjoyed if the patient survives the operation. Moreover, the relative differences in the rate of periprocedural MI after CABG or PCI may well be ascribed to differences in definition or reporting standards and includes many silent troponin leaks after MI of questionable significance in the PCI group.

Patients who are turned down for CABG represent a complex subgroup. When surgery is declined, PCI becomes the alternative for these patients who pose the highest risk; yet registries and RCTs do not capture this measure. In such cases, surgeons "preserve" their mortality statistics, but interventionists are not afforded this luxury.

Patient preference is especially worthy of consideration. The expected benefit associated with a particular therapy varies widely from patient to patient. The evidence base is not

sufficiently granular to make this assessment for every patient and ideally should be individualized. Additionally, there are endpoints important to physicians and patients that are not studied in RCTs but that may be more important, and occasionally even imperative, than death/ MI/stroke. Quality of life, relief from angina, recuperation time, and concern for permanent neurological damage are not easy to objectify and are not typically the endpoints of RCTs, but undeniably are important to consider. In particular, elderly patients frequently prefer treatments that tend to preserve quality rather than quantity of life. Physicians also tend to downplay complications of procedures that are not catastrophic; for example, the incidence of postoperative atrial fibrillation, pericarditis, and infection might reasonably be considered in treatment choice; conversely, post-PCI procedural bleeding and the need for more frequent follow-up and additional procedures might alter another patient's inclination. Such trade-offs are not simple but require the patient to thoughtfully consider the expected benefits and the risks before making a decision. They need to be able to choose their own priorities and values and should not be compelled by a "one-size-fits-all" inference: repeat procedures, for example, may be an acceptable downside for many.

An innovative approach to making the best decision for each patient is to consider the concept of value, which is defined as quality achieved per dollar spent. By evaluating each treatment modality by both its provision of results as well as its cost, a reasoned approach is ensured. A promising tactic (26) is to combine value with appropriateness. By including clinically defined outcomes, patient-expected outcomes, and relative cost in the equation, the "real value" of a procedure to that patient might be objectively appraised.

One significant obstacle to the value proposition is that cost, the denominator, tends to overwhelm consideration of the clinical benefit (27). Cost is a critical component from the societal perspective, but it is not the patient's concern: he or she seeks the best advice for his or her situation. What advice do we give if the most effective treatment is also the most costly? What weight should cost receive relative to outcomes? How much improved effectiveness is worth how much incremental cost? Is differential value based *only* on cost ethical? Several analyses have shown that along with the benefits of CABG comes a substantially higher cost (8,14). Moreover, these analyses fail to consider that when the PCI strategy is selected, usually repeat procedures are not required, and then it is significantly less expensive than CABG. In other cases, multiple PCI procedures or cases with greater equipment use (i.e., mechanical circulatory support such as intra-aortic balloon pump and left ventricular support devices) can be quite expensive: should PCI be denied solely because of increased cost?

The controversy highlighted in this discussion is a direct consequence of how guidelines are developed and interpreted. Guideline committees develop recommendations based on the evidence derived from the "uncomplicated" case. However, their conclusions are applied to patients beyond those who would have been potential enrollees in RCTs. Moreover, the economic and social consequences of using these guidelines and appropriate use criteria as reasons to deny payment for a judiciously selected alternate strategy are troubling and scientifically completely unjustifiable. For these reasons, future panels should avoid making strong recommendations when the best treatment strategy heavily depends on the patient's context, goals, values, and preferences and should be reserved for evidence that

demonstrates that 1 treatment option is definitely superior. When the evidence is conditional or less definitive, panels should indicate so and produce a provisional recommendation. These should explicitly describe how patient preferences and perspective may affect the choice between the relevant options (28). Although it is probably impossible to construct a decision tree that covers every conceivable situation, future iterations of the guidelines and appropriate use criteria must do a better job of simulating the decision-making process, defining elements that appropriately influence the application of the recommendation, and acknowledging "gray zones."

ABBREVIATIONS AND ACRONYMS

ASCERT	American College of Cardiology Foundation and the Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CEA	cost-effectiveness analysis
CI	confidence interval
EES	everolimus-eluting stent(s)
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
LM	left main artery
MACCE	major adverse cardiac or cerebrovascular event(s)
MI	myocardial infarction
PCI	percutaneous coronary intervention
QALY	quality-adjusted life year
RCT	randomizedcontrolled trial
RR	risk ratio
SIHD	stable ischemic heart disease
SoS	The Stent or Surgery Trial
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
3VD	3-vessel coronary artery disease

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TABLE 1

Comparison of the Clinical Endpoints in the CABG Group Compared With the PCI Group for SIHD Patients With LM or 3VD From the SYNTAX Trial (4–8)

Patient Groups	Endpoint	1-Year Follow-Up	3-Year Follow-Up	5-Year Follow-Up
Overall study population	MACCE	12.4% vs. 17.8%, p = 0.002	20.2% vs. 28.0%, p < 0.001	26.9% vs. 37.3%, p < 0.0001
	Death from any cause	3.5% vs. 4.4%, p = 0.37	6.7% vs. 8.6%, p = 0.13	11.4% vs. 13.9%, p = 0.10
	MI	3.3% vs. 4.8%, p = 0.11	3.6% vs. 7.1%, p = 0.002	3.8% vs. 9.7%, p < 0.0001
	Stroke	2.2% vs. 0.6%, p = 0.003	3.4% vs. 2.0%, p = 0.07	3.7% vs. 2.4%, p = 0.09
	Repeat revascularization	5.9% vs. 13.5%, p < 0.001	10.7% vs. 19.7%, p < 0.001	13.7% vs. 25.9%, p < 0.0001
	CEA (ICER/QALY gained)	PCI dominant (in-trial period)	–	$12,329/QALY gained (lifetime)
Patients with a low SYNTAX score [*]	MACCE	14.7% vs. 13.6%, p = 0.71	22.7% vs. 22.5%, p = 0.98	28.6% vs. 32.1%, p = 0.43
	Death from any cause	–	–	10.1% vs. 8.9%, p = 0.64
	MI	–	–	4.2% vs. 7.8%, p = 0.11
	Stroke	–	–	4.0% vs. 1.8%, p = 0.11
	Repeat revascularization	–	–	16.9% vs. 23.0%, p = 0.056
	CEA (ICER/QALY gained)	PCI dominant (in-trial period)	–	PCI dominant (life-time)
Patients with an intermediate SYNTAX score [*]	MACCE	12.0% vs. 16.7%, p = 0.10	18.9% vs. 27.4%, p = 0.02	25.8% vs. 36.0%, p = 0.008
	Death from any cause	–	–	12.7% vs. 13.8%, p = 0.68
	MI	–	3.2% vs. 7.6%, p = 0.02	3.6% vs. 11.2%, p = 0.0009
	Stroke	–	–	3.6% vs. 2.0%, p = 0.25
	Repeat revascularization	–	10.1% vs. 17.4%, p = 0.01	12.7% vs. 24.1%, p = 0.0005
	CEA (ICER/QALY gained)	PCI dominant (in-trial period)	–	$36,790/QALY gained (lifetime)
Patients with a high SYNTAX score [*]	MACCE	10.9% vs. 23.4%, p < 0.001	19.5% vs. 34.1%, p < 0.001	26.8% vs. 44.0%, p < 0.0001
	Death from any cause	–	–	11.4% vs. 19.2%, p = 0.005
	MI	–	–	3.9% vs. 10.1%, p = 0.004
	Stroke	–	–	3.7% vs. 3.5%, p = 0.80
	Repeat revascularization	–	–	12.1% vs. 30.9%, p < 0.0001
	CEA (ICER/QALY gained)	$43,486/QALY gained (in-trial)	–	$8,219/QALY gained (lifetime)

[*] SYNTAX score: low (22), intermediate (23 to 32), high (33).

CABG = coronary artery bypass grafting; CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; LM = left main artery; MACCE = major adverse cardiac and cerebrovascular events (composite of death from any cause, MI, stroke, or repeat revascularization); MI = myocardial infarction; PCI = percutaneous coronary intervention; QALY = quality-adjusted life years; SIHD = stable ischemic heart disease; 3VD = 3-vessel disease.

TABLE 2

SYNTAX Trial Outcomes in Nondiabetic Patients (N = 1,348) (19–21)

Clinical Outcome	1-Year			3-Year			5-Year		
	CABG, %	PCI, %	p Value	CABG, %	PCI, %	p Value	CABG, %	PCI, %	p Value
Composite MACCE	11.8	15.1	0.08	19.3	24.9	0.014	26.3	34.1	0.002
Death/CVA/MI	6.8	6.8	0.97	11.4	13.4	0.293	15.9	19.8	0.069
All-cause death	2.6	3.0	0.68	6.1	6.9	0.519	10.9	12.0	0.48
Cardiac death	1.6	2.6	0.20	3.1	5.0	0.087	4.9	7.7	0.035
CVA	2.2	0.5	0.006	3.3	1.9	0.096	3.5	2.2	0.15
MI	2.9	4.8	0.08	3.2	7.5	<0.001	3.4	9.9	<0.001
Graft occlusion/stent thrombosis	3.8	3.4	0.72	3.4	4.3	0.345	3.9	5.6	0.14
Repeat revascularization	5.7	11.1	<0.001	10.0	16.9	<0.001	13.4	22.8	<0.001
PCI	4.8	9.6	<0.001	9.2	14.3	0.003	12.9	19.3	0.001
CABG	1.1	2.4	0.07	1.1	3.9	0.002	1.1	5.8	<0.001

CVA = cerebrovascular accident; other abbreviations as in Table 1.

TABLE 3

SYNTAX Trial Outcomes at 5 Years in Nondiabetic Patients by SYNTAX Score (N = 1,348) (21)

Clinical Outcome	SYNTAX Score 0–22			SYNTAX Score 23–33			SYNTAX Score ≥33		
	CABG, %	PCI, %	p Value	CABG, %	PCI, %	p Value	CABG, %	PCI, %	p Value
Composite MACCE	27.1	28.7	0.75	24.8	34.2	0.037	27.2	39.6	0.004
Death/CVA/MI	13.4	15.0	0.68	16.8	20.2	0.38	17.5	24.4	0.065
Revascularization	16.4	17.8	0.62	12.4	23.2	0.004	11.9	27.4	<0.001

Abbreviations as in Tables 1 and 2.