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"Cherry-Picking" Patients for Randomized, Controlled Trials—Reliving the Past. . .

We read with interest the VA CARDS (Veterans Affairs Coronary Artery Revascularization in Diabetes) study (1) comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in subjects with diabetes. In our opinion, the most notable finding of the study is not the outcome of the trial, but the actual study design itself, that is, the stringent angiography- and clinically based inclusion and exclusion criteria, which makes application of the study's findings to real-world contemporary clinical practice highly questionable. Notably, of the 6,678 diabetic patients screened for this study, a staggering 6,080/6,678 (91%) of screened subjects did not meet angiographic requirements for the study, and only 198 subjects (3%) were randomly assigned to either CABG (n = 97, 1.5%) or PCI with drug-eluting stents (DESs) (n = 101, 1.5%) and completed the 2-year follow-up. Such a trial design is reminiscent of the PCI versus CABG randomized trials undertaken before the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial (2,3), where "cherry-picking" of patients before randomization was a major confounding issue (2% to 12% of screened patients were randomized in most trials) that effectively invalidated the results of these trials (4,5). The SYNTAX trial was designed to overcome these limitations by incorporating an all-comers design in which practically no patient was refused entry, with subjects either randomized (if determined by the Heart Team to achieve "equivalent anatomical revascularization" between CABG and PCI) or nested in registries (2,3). This was at the insistence of 7 cardiac surgeons (dubbed the "magnificent 7") during the design of SYNTAX to prevent selection bias, a view that was fully endorsed by the clinical and interventional cardiologists at the time. To give an example of the potential dangers of using highly selected populations in a clinical trial design, a recent meta-analysis of randomized trials undertaken before SYNTAX comparing PCI with CABG (6) showed CABG to be favored in older subjects and PCI to be favored in younger subjects, findings that have since been directly contradicted by the all-comers SYNTAX trial (where the opposite was shown) (7). In addition, the analyses demonstrating the anatomic SYNTAX score in the VA CARDS study not to show any treatment effect between CABG and PCI warrant specific mention in that they were severely underpowered to draw any conclusions, even if considered hypothesis generating (8). Specifically, the majority of subjects in the VA CARDS study had low (≤22) (CABG: n = 47 vs. PCI: n = 59) SYNTAX scores, with few subjects in the intermediate (23 to 32) (CABG: n = 33 vs. PCI: n = 24) or high (≥33) (CABG: n = 13 vs. PCI: n = 12) SYNTAX scores, presumably due to the overwhelmingly restrictive angiographic inclusion and exclusion criteria of the study as described earlier, thus making any comparisons of the low with the higher SYNTAX score tertiles practically meaningless. Even within the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, (9) analyses based on the SYNTAX score tertiles appear to have been limited by power and were contradicted by those reported in the pre-stratified and powered diabetic subgroup of SYNTAX (10). The real lesson of the VA CARDS study is that randomization of subjects in a clinical trial is not enough and that an all-comers clinical trial design is warranted. Anything less will take us back to the confusing era of randomized trials performed before SYNTAX and will serve to cloud the medical literature.

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Please note: Steven Nissen, MD, served as Guest Editor for this letter.

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Reply

In the letter about our paper (1), Drs. Farooq and Serruys make the assertion that the VA CARDS (Veterans Affairs Coronary Artery Revascularization in Diabetes) study is not applicable to contemporary coronary revascularization based on: 1) the angiographic inclusion criteria being too strict; 2) the small percentage of screened patients who were enrolled; and 3) that our study was underpowered to evaluate SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) scores. The letter completely misses important aspects of our study.

Our angiographic criteria were based on subsets of patients known to have better survival with surgery than with medical treatment. We deliberately excluded patients when the primary role of revascularization would be symptom relief. These patients were extensively studied in COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) and BARI 2D (Bypass versus Angioplasty Revascularization Intervention 2 Diabetes) (2,3). Including these subsets would have increased enrollment but also would have diluted the power of the study to find survival differences.

Our screened patients included *all patients* with diabetes referred for a diagnostic angiogram *for any reason*. To compare VA-CARDS to SYNTAX, we need to know the total number of patients having diagnostic angiography at the 85 sites over their 2-year enrollment (4). An average of 500 diagnostic angiograms per year per SYNTAX site would yield a total of 85,000 diagnostic coronary angiograms. The 1,800 patients enrolled in SYNTAX would then represent 2.1% of this total, which is *lower* than our study.

Our study was not designed or powered to examine SYNTAX score subgroups. The SYNTAX scores in our study merely show that there was no systematic bias in the distribution of scores to explain the observed survival difference. If anything, low SYNTAX scores were more frequent for PCI than surgery. It is important to note in this discussion that the SYNTAX trial itself was not powered to compare small subgroups based on SYNTAX terciles. There is no SYNTAX score that leads to an absolute improvement in outcome for percutaneous coronary intervention over surgery among patients with 3-vessel coronary disease. The failure to find a significant p value in the subanalysis of 352 patients with low SYNTAX scores and 3-vessel coronary artery disease is likely to represent a type II error (5). The SYNTAX investigators need to report a power analysis of each of the subgroups that they analyze. The assumption that the failure to find a difference means that there is no difference is misleading.

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