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EDITORIAL

Is there equivalence between PCI and CABG surgery in long-term survival of patients with diabetes? Importance of interpretation biases and biological plausibility

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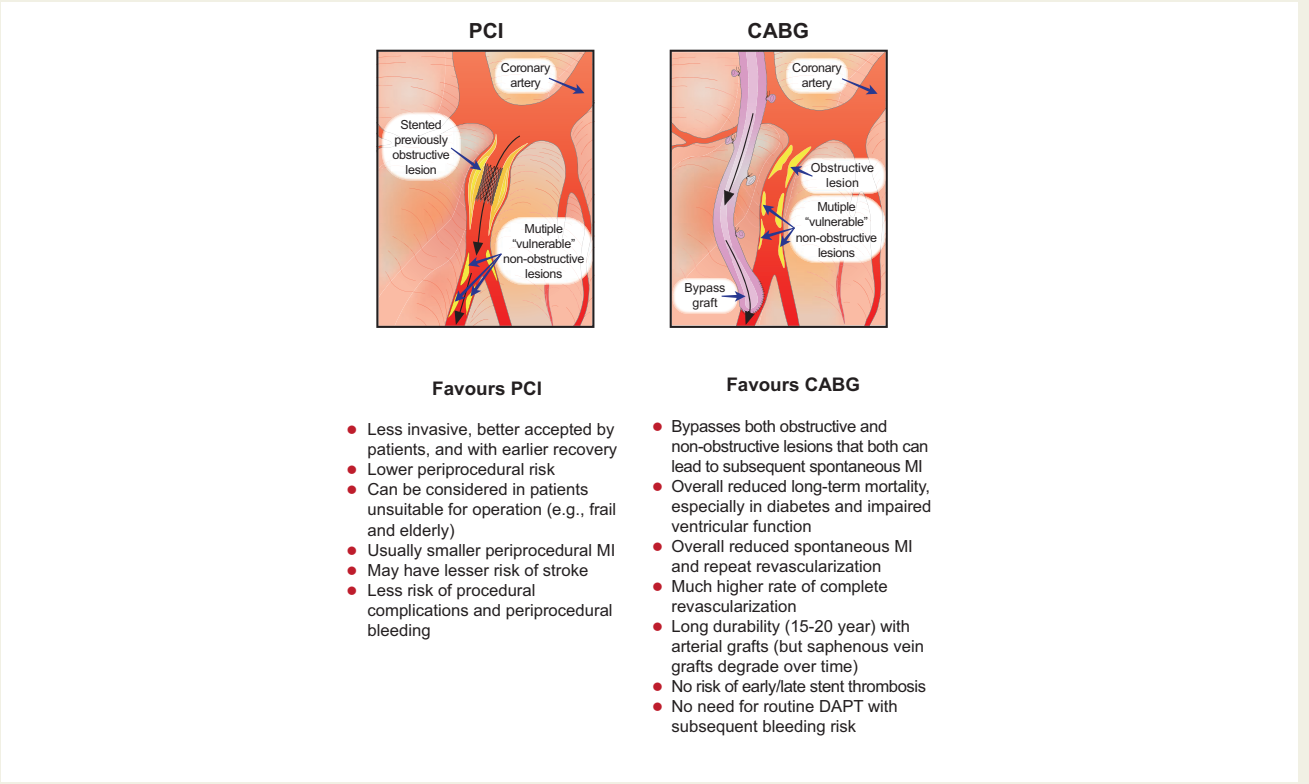
This editorial refers to 'Ten-year all-cause death after percutaneous or surgical revascularization in diabetic patients with complex coronary artery disease', by R. Wang *et al.*, doi:10.1093/eurheartj/ehab441.



Graphical Abstract CABG superiority over PCI on major adverse cardiovascular outcomes, including all-cause mortality, has been consistently proven in a number of comparative trials provided that the study cohorts are sufficiently powered and the highest risk patients are selected: this is the case for SYNTAX score ≥33 with or without diabetes, as shown in the overall 10-year report of SYNTAX and in the study of Wang *et al.* (see Supplementary material, figure S8).[13] CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery.

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Both the prevalence and incidence of type 2 diabetes mellitus have increased at alarming rates during the last three decades. Recent epidemiological data show that global and regional trends of diabetes have risen dramatically for all ages worldwide from ~100 million in 1990 to ~462 million individuals in 2017, corresponding to 6.3% of the world's population or a prevalence of 6059 cases per 100 000.[1] Global prevalence of diabetes is projected to increase to 7079 individuals per 100 000 by 2030, reflecting a sustained and nearly exponential rise across all regions of the world. These accelerating rates of diabetes pose an enormous healthcare risk and economic burden globally, and are occurring at a much faster rate in developed regions, such as Western Europe.[1,2] Cardiologists have long viewed patients with coronary artery disease (CAD) and diabetes as being at significantly increased risk for major adverse cardiovascular events, which in turn has fuelled the parallel belief that myocardial revascularization would improve clinical outcomes in such high-risk patients.

For decades, numerous randomized controlled trials (RCTs) have assessed comparative outcomes in patients with stable CAD—now referred to as chronic coronary syndrome (CCS)—undergoing percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery. The first RCT comparing balloon angioplasty and CABG in diabetic patients with CCS showed a mortality benefit with CABG.[3] With the advent of PCI, first with bare-metal stents and later with drug-eluting stents, the evolution of stent design held promise that such technological advancements would match outcomes of CABG, which has also evolved significantly over the last two decades with increasing utilization of multiple arterial grafts and more sophisticated surgical revascularization techniques. These developments, in turn, led to dedicated, prospective RCTs in diabetic patients, [4–7] where revascularization with CABG and/or PCI was compared with optimal medical therapy (OMT) alone. In aggregate, these trials, including a pooled, patient-level analysis of three trials in diabetic patients,[8] firmly established the superiority of CABG in reducing mortality and myocardial infarction (MI)—findings which became even more robust during late (5-year) follow-up.[8]

It cannot be overstated that several critical and fundamental pathophysiological distinctions between CABG and PCI revascularization approaches underlie the better survival and other clinical benefits of CABG: (i) the cardioprotective superiority of CABG is postulated to result from bypass grafts to the mid-coronary vessels that not only treat culprit lesions (even anatomically complex ones), but also afford prophylaxis against new proximal disease by mitigating the impact of plaque rupture and atherothrombosis on future events, whereas stents treat only suitable stenotic segments with otherwise no benefit against native CAD progression (*Graphical Abstract*); (ii) internal mammary artery conduits elute nitric oxide into the coronary circulation which promotes a vasoprotective endothelial effect;[9] and (iii) PCI more often results in incomplete revascularization. In essence, PCI treats only focal, stenotic lesions, whereas CABG treats the entire vessel. Nevertheless, attempts persist to portray an alternative narrative of 'equivalence' between PCI and CABG using selected post-hoc findings and meta-analyses.[10–12] It is likewise important to recognize that direct comparisons of outcomes between PCI and CABG in many trials are plagued by an assumption of putative equipoise between revascularization approaches, though in reality patients with more severe CAD deemed unsuitable for PCI underwent CABG while, conversely, frail patients and those considered too high an operative risk often received PCI. Thus, solely generalizing only randomized trial results to entire, unselected populations, who may be systematically different from the trial populations, is a well-recognized concern in assessing comparative revascularization outcomes.

In this issue of the *European Heart Journal*, Wang and co-workers now re-evaluate, in an analysis of the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, whether and how differences in surgical or percutaneous revascularization may affect long-term mortality in patients with or without diabetes using an 'all-comers' design of PCI with the first-generation paclitaxel-eluting stent vs. CABG surgery, and where all randomized patients were eligible for either revascularization approach.[13] The authors report that the 10-year all-cause mortality was not different in diabetic patients treated either with PCI using the paclitaxel drug-eluting stent or with CABG, and that diabetes did not discriminate any between-group differences in mortality. As expected, 10-year mortality was higher in diabetic than in non-diabetic patients after multivariable adjustment, and especially in insulin- vs. non-insulin-treated patients regardless of the revascularization modality. Importantly, in the 75% of non-diabetic SYNTAX patients with three-vessel CAD, death was significantly higher with PCI at both 5 years [12.8% vs. 9.3%; hazard ratio (HR) 2.04, 95% confidence interval (CI) 1.22–3.41, $P = 0.007$] and 10 years (25.9% vs. 17.3%; adjusted HR 1.57, 95% CI 1.28–2.60, $P = 0.001$). Of note, in diabetic patients, the authors observed lower mortality with CABG vs. PCI only in the subset with three-vessel CAD and the highest (≥33) SYNTAX score tertile, while mortality with CABG vs. PCI in insulin-treated patients was 'numerically lower'.[13] These data support the clinical benefit of CABG in both these highest risk anatomic and clinical subsets.

Additionally, while overall mortality in diabetic patients was substantially higher numerically with PCI compared with CABG at 5 years (19.6% vs. 13.3%; HR 1.53, 95% CI 0.96–2.43, $P = 0.075$), it was not between 5 and 10 years (20.8% vs. 24.4%; HR 0.82, 95% CI 0.52–1.27, $P = 0.366$). A landmark analysis in the subset with three-vessel CAD showed a significantly higher mortality with PCI than with CABG at 5 years (19.8% vs 11.3%; adjusted HR 2.27, 95% CI 1.14–4.52, $P = 0.020$),[13] consistent with all prior published studies in diabetic patients with CAD.[4–8,14] Yet, counterintuitively, the authors report that mortality became numerically higher with CABG vs. PCI between 5 and 10 years (21.7% vs. 24.3%; adjusted HR 0.70, 95% CI 0.36–1.37, $P = 0.295$). Thus, based on the small observational subset of diabetic patients in SYNTAX, the authors infer and extrapolate an apparent 'equivalence' between PCI and CABG on overall 10-year mortality and, notwithstanding the potential survival benefit from CABG in insulin-treated diabetic patients, appear to advocate for either revascularization approach in complex CAD cases.

This analysis raises several significant issues and concerns that warrant comment. First, with a planned 5-year follow-up, only 452 of 1800 patients (25%) had pharmacologically treated diabetes (with insulin or oral hypoglycaemic agents); thus, the trial, by predominantly including relatively low-severity CAD patients, was woefully underpowered to ascertain any differential treatment benefit of revascularization, particularly for mortality. Second, because SYNTAX lacked an OMT comparator,[14] the selection/intensity of pharmacological treatment was not protocol mandated, but left to the investigators' discretion. Most critically, after trial follow-up ended at 5 years, no

information is provided about subsequent treatments or procedures, including potential crossovers. Since many trials showed substantially lower rates of OMT use in CABG than in PCI patients,[15] such treatment disparities could have adversely impacted 10-year mortality and other clinical outcomes, and led to significant confounding. Third, prior comparative trials of PCI and/or CABG in diabetic patients were undertaken in homogeneous populations of CCS patients,[3–8] whereas SYNTAX enrolled a heterogeneous population comprising 55% with stable angina, 30% with unstable angina, and 15% with silent ischaemia (table 1 in Wang *et al.*);[13] co-mingling stable and unstable angina patients in comparison of revascularization modalities can also lead to confounding. Fourth, in trials with extended follow-up, it is often difficult to draw definitive treatment conclusions when cohorts become progressively smaller over time and when Kaplan–Meier curves may converge due to regression to the mean. Fifth, in diabetic patients, there were 4.7 stents/patient vs. only 2.8 surgical conduits/patient, of which just 1.4 were arterial. If a higher proportion of CABG-treated patients had received multiple arterial grafts, a more demonstrable mortality benefit favouring CABG would probably have emerged. Yet, despite this imbalance, significantly more diabetic patients undergoing CABG achieved complete revascularization (61%) compared with PCI ($P = 0.016$). Perhaps this also best explains why CABG was associated with lower mortality in insulin-treated diabetes (39.6%) than PCI (47.9%), with an 8% absolute between-group difference, though this was not nominally significant. Sixth, and most importantly, we should consider the totality of published medical evidence regarding durability of revascularization modalities, particularly in diabetic patients; in dedicated prospective RCTs, CABG surgery has been proven to result in superior outcomes compared with PCI. Accordingly, it must be emphasized that these SYNTAX findings in a small diabetes subset are discordant with the results of the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM trial),[5,6] the largest ($n = 1900$), prospective RCT of PCI vs. CABG in CCS patients pre-selected with diabetes, which showed a highly significant and continuously diverging survival advantage of CABG vs. PCI at 5 years (24.3% vs. 18.3%; HR 1.36; 95% CI 1.07–1.74; $P < 0.01$), and which remained durable at a median follow-up of 7.5 years (range 0–13.2 years).

In summary, the methodology used by Wang *et al.* in this SYNTAX analysis raises several major concerns that seriously challenge their conclusions that 10-year all-cause mortality was not different in diabetic patients treated with either PCI or CABG, and that diabetes did not discriminate any between-group differences in mortality. It is essential that medical decisions, particularly those relating to revascularization in high-risk CAD patients, are both informed and objective. They should be based on sound scientific evidence derived from carefully conducted, prospective RCTs in homogeneous populations with appropriate study design, execution, and follow-up. All too often it seems we are besieged with studies that challenge us on how to interpret subgroup analyses, post-hoc findings, and biased meta-analyses attempting to promote equivalence of PCI and CABG. We should be reminded that adherence to scientific truth demands respect for the highest methodological standards in weighing medical evidence that impacts the optimal care of our patients, particularly high-risk patients with diabetes.

Conflict of interest: none declared.

References

1. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes—global burden of disease and forecasted trends. *J Epidemiol Glob Health* 2020;**10**:107–111.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017;**128**:40–50.
3. Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;**335**:217–225.
4. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chaitman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE, BARI 2D Study GroupA randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;**360**:2503–2515.
5. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S, 3rd, Bertrand M, Fuster V, FREEDOM Trial InvestigatorsStrategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012;**367**:2375–2384.
6. Farkouh ME, Domanski M, Dangas GD, Godoy LC, Mack MJ, Siami FS, Hamza TH, Shah B, Stefanini GG, Sidhu MS, Tanguay JF, Ramanathan K, Sharma SK, French J, Hueb W, Cohen DJ, Fuster V, FREEDOM Follow-On Study Investigators Long-term survival following multivessel revascularization in patients with diabetes: the FREEDOM Follow-On Study. *J Am Coll Cardiol* 2019;**73**:629–638.
7. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, Baumbach A, Angelini G, de Belder A, Oldroyd KG, Flather M, Roughton M, Nihoyannopoulos P, Bagger JP, Morgan K, Beatt KJ. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol* 2010;**55**:432–440.
8. Mancini GB, Farkouh ME, Brooks MM, Chaitman BR, Boden WE, Vlachos H, Hartigan PM, Siami FS, Sidhu MS, Bittner V, Frye R, Fuster V. Medical treatment and revascularization options in patients with type 2 diabetes and coronary disease. *J Am Coll Cardiol* 2016;**68**:985–995.
9. Lüscher TF, Diederich D, Siebenmann R, Lehmann K, Stulz P, von Segesser L, Yang ZH, Turina M, Grädel E, Weber E, Bühler FR. Difference between endothelium-dependent relaxation in arterial and in venous coronary bypass grafts. *N Engl J Med* 1988;**319**:462–467.
10. Schömig A, Dibra A, Windecker S, Mehilli J, Suárez de Lezo J, Kaiser C, Park SJ, Goy JJ, Lee JH, Di Lorenzo E, Wu J, Jüni P, Pfisterer ME, Meier B, Kastrati A. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol* 2007;**50**:1373–1380.
11. Jeremias A, Kaul S, Rosengart TK, Gruberg L, Brown DL. The impact of revascularization on mortality in patients with nonacute coronary artery disease. *Am J Med* 2009;**122**:152–161.
12. Navarese EP, Lansky AJ, Kereiakes DJ, Kubica J, Gurbel PA, Gorog DA, Valgimigli M, Curzen N, Kandzari DE, Bonaca MP, Brouwer M, Umińska J, Jaguszewski MJ, Raggi P, Waksman R, Leon MB, Wijns W, Andreotti F. Cardiac mortality in patients randomized to elective coronary revascularization plus medical therapy or medical therapy alone: a systematic review and meta-analysis. *Eur Heart J* 2021;**42**:4638–4651.
13. Wang R, Seeruys PW, Gao C, Hara H, Takahashi K, Ono M, Kawashima H, O'Leary N, Holmes DR, Witkowski A, Curzen N, Burzotta F, James S, van Geuns RJ, Kappetein AP, Morel MA, Head SJ, Thuijs DJ, Davierwala PM, O'Brien T, Fuster V, Garg S, Onuma Y. Ten-year all-cause death after percutaneous or surgical revascularization in diabetic patients with complex coronary artery disease. *Eur Heart J* 2022;**43**:56–67.
14. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Ståhle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW. SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;**360**:961–972.
15. Pinho-Gomes AC, Azevedo L, Ahn JM, Park SJ, Hamza TH, Farkouh ME, Serruys PW, Milojevic M, Kappetein AP, Stone GW, Lamy A, Fuster V, Taggart DP. Compliance with guideline-directed medical therapy in contemporary coronary revascularization trials. *J Am Coll Cardiol* 2018;**71**:591–602.