Understanding causes of death in trials of coronary artery bypass grafting versus percutaneous coronary intervention

Entendiendo las causas de muerte en estudios de cirugía de revascularización miocárdica frente angioplastia coronaria con *stents*

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Despite recent evidence that managing coronary artery disease with an initial invasive strategy may not improve cardiovascular outcomes in the long term (1), selected groups of patients still benefit of a revascularization procedure along the course of their disease. Although coronary artery bypass grafting (CABG) surgery and percutaneous coronary intervention with stent (PCI) share the same intent of providing coronary revascularization, these methods are considerably different on their approach (2).

CABG bypasses a large portion of the diseased coronary artery, treating not only the flow-limiting obstructions but also other adjacent smaller lesions that might become unstable and lead to future cardiovascular events (3). PCI is a focal procedure, targeted only at the perceived high-risk or symptom-generating lesion, leaving untreated the other segments. Both strategies are meant to be combined with optimal medical therapy, including adequate control of cholesterol, blood pressure, glycemia, smoking cession, and weight loss (4). Medical therapy acts systemically, including in the coronary territories not directly treated by the revascularization procedure. In fact, the role of these therapies post-PCI seems to be even more important than post-CABG, likely due to the aforementioned differences (5).

Numerous clinical trials have compared CABG and PCI in diverse populations. The findings usually indicate that in patients with chronic coronary artery disease, CABG, compared to PCI, reduces the combined incidence of major cardiovascular events, through reductions mainly in myocardial infarction, and the need of a new revascularization procedure (6). On the other hand, in patients with diabetes from the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, it was observed an excess of periprocedural stroke following CABG, but this was not consistent across all revascularization trials (7,8). Individual trials are generally not powered to detect differences in all-cause mortality between the two strategies, at least within the first few years of follow-up (9). An individual-patient level pooled analysis of 11 randomized studies and 11,518 patients showed a mortality increase following PCI compared to CABG over a mean follow-up of 3.8 years (HR: 1.20; 95% CI: 1.06 to 1.37; p=0.0038) (10). This result was significant particularly in the subgroups of patients with diabetes and multivessel coronary artery disease.

It would be logical to think that the mortality benefit of CABG over PCI is derived from reductions in cardiovascular mortality, but this has not been extensively investigated. A recently reported meta-analysis by Gaudino *et al* sought to evaluate the differences in cardiac versus non-cardiac mortality following the two procedures. (11) A total of 23 trials were included and, similarly to the patient-level analysis, PCI was associated with increased all-cause mortality (incidence rate ratio [IRR]: 1.17; 95% CI: 1.05 to 1.29) (11). Moreover, this study revealed that PCI was linked to excess both in cardiac and non-cardiac mortality (IRR: 1.24; 95% CI: 1.05 to 1.45 and IRR: 1.19; 95% CI: 1.00 to 1.41, respectively) (11).

More granular data regarding cardiovascular mortality after CABG and PCI was obtained in a sub-analysis of the TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries (SYNTAX) trial, involving 1,676 patients (12). Half (49.4%) of the deaths after CABG were cardiovascular, with the most prominent causes being heart failure and arrhythmia. After PCI, most deaths were also cardiovascular (67.5%), but predominantly due to myocardial infarction. The hazard rate of dying due to a myocardial infarction was 8 times greater in PCI versus CABG patients (HR: 8.43; 95% CI: 2.99 to 23.67) (12). A similar observation was inferred from the Bypass Angioplasty Revascularization Investigation (BARI) trial using a different statistical approach (multi-state modelling) (13). This study compared CABG vs percutaneous old balloon angioplasty (POBA) and significantly more patients who develop a myocardial infarction following POBA ended up dying compared to those after CABG (13). As discussed above, CABG leads to a more complete coronary revascularization compared to PCI, which may explain these reductions in cardiovascular and myocardial infarction-related death.

The reductions in non-cardiac death found in the meta-analysis by Gaudino *et al* are perplexing and need to be further investigated. This study, being a trial-level meta-analysis, cannot provide more detailed data on specific causes of death, preventing additional inference into a still unknown mechanism through which PCI would increase (or CABG would decrease) non-cardiac death (11). It seems likely that mis-categorization of cardiac deaths as non-cardiac deaths might be the case (14). Interestingly, initial results of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial identified an increase in non-cardiovascular death due to cancer in patients undergoing an invasive strategy with coronary revascularization (74% of which with PCI), compa-

red to a conservative strategy with optimal medical therapy (adjusted HR: 2.11, 95% CI: 1.24 to 3.61) (15). The significance of these results remain unknown and more studies are warranted.

Based on the previous studies in patients with complex chronic coronary artery disease, CABG, compared to PCI, leads to reductions in long-term all-cause mortality, primarily due to reductions in cardiovascular death and, more specifically, reductions in myocardial infarction-related death. But what would be the importance of studying causes of death after a coronary revascularization procedure? On a research level, it is important to note that all the aforementioned analyses utilized clinical trial data, and events were usually ascertained by adjudication committees, having medical experts assigning cause of death. This approach is more accurate than public health surveillance data where causes of death are extracted from death certificates (16-18). Even in these adjudication committees, however, it may be difficult to determine the exact cause of death, particularly if reliable source documentation is pending. As pointed out by Gaudino *et al*, all-cause death is easier to be ascertained than cardiovascular death, constituting a less biased and more reliable endpoint (11). Additionally, the effects of a coronary revascularization intervention are not mitigated if we include all-cause death as a component of the primary outcome (rather than cardiovascular death) (11). This should be considered to be the standard approach in clinical trials of coronary revascularization going forward.

On a population level, the main utility of death surveillance is to plan risk mitigation strategies, aiming to reduce the most responsible specific components of all-cause death. Applied to the post-coronary revascularization setting, these data reinforce the importance of secondary prevention in preventing new cardiovascular events particularly in post-PCI patients, a population at greater risk of having a myocardial infarction-related death.

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REFERENCES

1. *Maron DJ, Hochman JS, Reynolds HR, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. N Engl J Med 2020;382:1395-407.*
2. *Domanski MJ, Farkouh ME. Type 1 Diabetes, Coronary Disease Complexity, and Optimal Revascularization Strategy. J Am Coll Cardiol 2017;70:1452-4.*
3. *Doenst T, Haverich A, Serruys P, et al. PCI and CABG for Treating Stable Coronary Artery Disease: JACC Review Topic of the Week. J Am Coll Cardiol 2019;73:964-76.*
4. *Bittner V, Bertolet M, Barraza Felix R, et al. Comprehensive Cardiovascular Risk Factor Control Improves Survival: The BARI 2D Trial. J Am Coll Cardiol 2015;66:765-73.*
5. *Farkouh ME, Godoy LC, Brooks MM, et al. Influence of LDL-Cholesterol Lowering on Cardiovascular Outcomes in Patients With Diabetes Mellitus Undergoing Coronary Revascularization. J Am Coll Cardiol 2020;76:2197-207.*
6. *Godoy LC, Tavares CAM, Farkouh ME. Weighing Coronary Revascularization Options in Patients With Type 2 Diabetes Mellitus. Can J Diabetes 2020;44:78-85.*
7. *Head SJ, Milojevic M, Daemen J, et al. Stroke Rates Following Surgical Versus Percutaneous Coronary Revascularization. J Am Coll Cardiol 2018;72:386-98.*
8. *Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.*
9. *Farkouh ME, Domanski M, Dangas GD, et al. Long-Term Survival Following Multivessel Revascularization in Patients With Diabetes: The FREEDOM Follow-On Study. J Am Coll Cardiol 2019;73:629-38.*
10. *Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391:939-48.*
11. *Gaudino M, Hameed I, Farkouh ME, et al. Overall and Cause-Specific Mortality in Randomized Clinical Trials Comparing Percutaneous Interventions With Coronary Bypass Surgery: A Meta-analysis. JAMA Internal Medicine 2020;180:1638-46.*
12. *Milojevic M, Head SJ, Parasca CA, et al. Causes of Death Following PCI Versus CABG in Complex CAD: 5-Year Follow-Up of SYNTAX. J Am Coll Cardiol 2016;67:42-55.*
13. *Zhang X, Li Q, Rogatko A, et al. Analysis of the Bypass Angioplasty Revascularization Investigation Trial Using a Multistate Model of Clinical Outcomes. Am J Cardiol 2015;115:1073-9.*
14. *Medical Examiners' and Coroners' Handbook on Death Registration and Fetal Death Reporting. Department of Health and Human Service, Center for Disease Control and Prevention, National Center for Health Statistics, 2003.*
15. *Sidhu MS, Alexander KP, Huang Z, et al. Abstract 13030: Causes of Cardiovascular and Non-cardiovascular Mortality in the Ischemia Trial. Circulation 2020;142:A13030-A13030.*
16. *Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. Ann Intern Med 1998;129:1020-6.*
17. *Coady SA, Sorlie PD, Cooper LS, Folsom AR, Rosamond WD, Conwill DE. Validation of death certificate diagnosis for coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. J Clin Epidemiol 2001;54:40-50.*
18. *Olubowale OT, Safford MM, Brown TM et al. Comparison of Expert Adjudicated Coronary Heart Disease and Cardiovascular Disease Mortality With the National Death Index: Results From the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. J Am Heart Assoc 2017;6:e004966.*