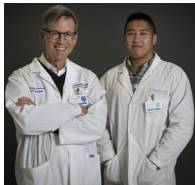


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### REPLY: GOING FROM STABLE TO UNSTABLE

Reply to the Editor:



We thank Dr Gomes for his letter to the editor and his nuanced discussion on the pathophysiology of complex coronary artery disease (CAD),

particularly as it relates to left main stenosis.<sup>1</sup> This letter, in response to a commentary by Gaudino and colleagues,<sup>2</sup> further expands on the idea that left main disease should not be considered a separate entity, either from a statistical basis as described by Gaudino and colleagues or from a pathophysiologic perspective as highlighted by Dr Gomes.

The recent publication of the ISCHEMIA trial showed no difference in the primary outcome of a composite of cardiovascular death, myocardial infarction, or heart failure rehospitalization in those with stable CAD and moderate or severe ischemia treated with medical therapy or invasive angiography and revascularization.<sup>3</sup> Although many of these patients had stable multivessel disease (31.4% had double-vessel whereas 45.1% had triple-vessel disease), patients who had significant left main disease on coronary computed tomography angiography were excluded.<sup>4</sup> The extent of CAD was associated with both all-cause mortality and myocardial infarction. Furthermore, ISCHEMIA investigators recently presented a subgroup analysis comparing patients with intermediate left main lesions (25%-49%) versus those without intermediate left main lesions and found that the incidence of the primary outcome was greater in those with intermediate left main lesions, suggesting that the burden of CAD is also greater in this group.<sup>5</sup> Early work in the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) subgroup of left main patients suggest that lower SYNTAX score left main patients had similar number of major adverse cardiac

and cerebrovascular events after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) whereas major adverse cardiac and cerebrovascular events were much greater in those with high SYNTAX scores after PCI compared with CABG.<sup>6</sup> The development of the SYNTAX II score suggests that the incorporation of anatomical complexity with patient factors help predict long-term mortality.<sup>7</sup> All this evidence reinforces the notion that the extent of CAD is prognostically important. As Dr Gomes elegantly points out, those with left main disease may have a greater total burden of CAD throughout the coronary tree that are at risk for plaque rupture leading to acute coronary syndrome (ACS) and death—the incidence of true isolated left main disease is likely low.<sup>1</sup>

Thus, it is not uncommon for patients with left main disease to present as ACS. In the trials comparing CABG with PCI in left main disease, the proportion of patients with ACS varied: in EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and PRECOMBAT (Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease), about 60% of patients presented with stable angina or silent ischemia whereas the remaining patients presented with a recent myocardial infarction (within 7 days) or unstable angina. The numbers were lower in the NOBLE (Nordic-Baltic-British left main revascularisation study), only 18% of patients presented with ACS whereas the remaining had stable angina. Overall, the majority of randomized evidence comparing PCI with CABG in left main patients was derived predominantly from patients with stable CAD. Although many guidelines indicate that stable ischemic heart disease and ACS should be managed similarly, PCI, in general may be more appropriate than CABG for most patients.<sup>8,9</sup> However, in those with left main and multivessel CAD, CABG should be the preferred treatment for both patients with stable CAD and ACS.

The evidence landscape around coronary revascularization is rapidly evolving, yet we are tasked with optimally managing the patients in front of us. The management of these patients in the face of uncertainty highlights the ever-growing importance of the heart team. While CABG should be the preferred strategy in those who are surgical candidates, the personalization and tailoring of treatment strategies for those who are less than ideal for surgery in a heart team discussion can help optimize these decisions.<sup>10</sup>

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## REPLY: BEHIND ENEMY LINES: PRESERVING THE MYOCARDIUM SUPPLIED BY THE LEFT MAIN

Reply to the Editor:

In a recent letter, Gomes<sup>1</sup> discussed the concept that left main coronary artery (LMCA) stenosis is not a unique entity, but shares the same pathophysiologic characteristics as non-left main coronary artery disease (CAD). This hypothesis is also based on the recent evidence drawn from

the ISCHEMIA trial, in which invasive treatment of ischemia did not significantly affect survival relative to medical treatment alone.<sup>2</sup>

As Gomes<sup>1</sup> states, the prognosis of patients with CAD is mostly affected by acute coronary syndromes that occur as a result of rupture or erosion of non-flow limiting stenosis, rather than by the extent of ischemia. This justifies the hypothesis that LMCA stenosis is only a marker of diffuse CAD that might be associated with the presence of multiple unstable atherosclerotic plaques. It must be noted, however, that patients with LMCA stenosis were excluded from the ISCHEMIA trial, and its conclusions cannot be generalized.

In accordance with what has been elegantly discussed by Gaudino and colleagues,<sup>3</sup> LMCA should be considered a “clinical entity” in which the atherosclerosis process can involve not only the LMCA territory but also other coronary arteries. The clinical recommendation for the treatment of LMCA has historically treated LMCA disease as a unique “anatomic entity” rather than a “clinical entity,” because the LMCA supplies two-thirds of the myocardium (Figure 1).

In our recent meta-analysis, we found that percutaneous coronary intervention is associated with an increased risk of myocardial infarction at 5-year follow-up compared with CABG (odds ratio, 2.32; 95% confidence interval, 1.62-3.31;  $P < .001$ ) and with an increase in the number of repeat revascularizations (odds ratio, 1.89; 95% confidence interval, 1.58-2.26;  $P < .001$ ).<sup>4</sup> A subanalysis of the EXCEL trial showed that repeat revascularization was independently associated with increased risks for 3-year all-cause mortality and cardiovascular mortality and that most of the repeat revascularizations were the result of target lesion failure.<sup>5</sup> Our meta-analysis found no significant difference in all-cause mortality at 5 years.<sup>4</sup> None of the randomized clinical trials (including the EXCEL and NOBLE trials) were powered to assess mortality, but a pooled analysis of the EXCEL and NOBLE trials showed a survival benefit in the CABG group.<sup>3</sup>

Therefore, we would like to emphasize a “pathophysiologic concept”: LMCA stenosis as an anatomic entity puts a large amount of myocardium at risk and as a clinical entity is a marker of more extensive CAD. Acute myocardial infarction as a result of LMCA occlusion is a dramatic event because of the key anatomic role played by the LMCA in supplying the left ventricle.

The heart team’s mission should be to protect and save the myocardium. CABG, by achieving more complete revascularization and by protecting proximal segments of coronary arteries from the progression of the disease, is a valuable option in reducing the risk of repeat revascularization, myocardial infarction, and therefore mortality in patients with LMCA stenosis.

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