Multivessel Disease from Reasonably Incomplete to Functionally Complete Revascularization

Running title: De Bruyne; Functionally complete revascularization

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Soon after the introduction of coronary artery bypass surgery, the “completeness” of revascularization became a matter of concern. Several early surgical studies confirmed the belief that better clinical outcomes were obtained when each and every angiographically visible stenosis was bypassed by a distal anastomosis.\(^\text{1,2}\) Similarly, among patients with multivessel disease treated with percutaneous coronary intervention (PCI), complete revascularization was found to provide a significant advantage over incomplete revascularization in terms of re-intervention, myocardial infarction and death.\(^\text{3,4}\) However, a careful analysis of surgically treated multivessel disease patients in the BARI trial showed that one graft to any system other than the LAD confers no long-term advantage over PCI and may actually be deleterious.\(^\text{5}\)

More recently, the results of large surgical registries supported strategies of “reasonably incomplete” revascularization.\(^\text{6-8}\) In addition, the FAME trial indicated that, in patients with multivessel disease, approximately one third of angiographically ‘significant’ stenoses were actually hemodynamically not significant.\(^\text{9}\) Stenting limited to stenoses with a fractional flow reserve (FFR) value below 0.80 yielded better clinical outcomes than stenting based on treating every visible lesion, introducing the concept of “functionally complete” rather than “anatomically complete” revascularization.

Several factors contribute to the marked variability in prognostic value of “incomplete revascularization” reported. First, the definition of incomplete revascularization has varied from study to study\(^\text{10}\), making the results difficult to compare. Second, in all studies, the definition of incomplete revascularization was based on percent diameter stenoses derived from visual estimation. This simple metric is misleading, especially in coronary segments portending as high a prognostic value as the left main.\(^\text{11}\) The poor correlation between the angiogram and the presence of vessel-related ischemia clouds the relationship between the degree of
revascularization and clinical outcome. Third, the end-points, as well as the quality of their monitoring and adjudication, differed across studies. Fourth, selection biases make it difficult to generalize the conclusions of most of these non-randomized studies. Although recent investigations have used multivariate and propensity score analysis to account for differences in baseline characteristics, capturing some of these characteristics remains difficult. Factors including, but not limited to, patient frailty, vessel tortuosity and calcification, total coronary atherosclerotic burden, presence of viability and/or ischemia, problems of vascular access and presence and extent of mitral regurgitation, are frequent residual confounders. These factors may be more common among patients treated by incomplete revascularization and are a marker of poor outcome. Finally, the reasons for incomplete revascularization as well as the extent of residual ischemia are different in stable patients (whether treated by bypass surgery or by PCI) than in patients with acute coronary syndromes (ACS) undergoing PCI. Incomplete revascularization in stable patients is dictated by anatomic factors and tends to leave behind small territories of myocardium at risk. In contrast, incomplete revascularization in patients with acute coronary syndromes is generally intentional per guidelines and often leaves behind substantial myocardial territories depending on the location of the so-called non-culprit lesions. Since residual vessel-related ischemia is difficult to assess non-invasively, especially early after an acute coronary syndrome, these patients are often discharged without knowing whether or not the non-culprit lesions are in fact hemodynamically significant.

The study by Rosner at al published this week in Circulation is important in many respects. First, the trial focuses on a clinically relevant problem, namely incomplete revascularization in patients with moderate to high-risk non-ST elevation myocardial infarction NSTEMI-ACS undergoing early PCI. In many catheterization laboratories, acute coronary
syndromes represent more than half of the indications for PCI. The current guidelines recommend treating only the culprit lesion, which leads in many instances to angiographically incomplete revascularization. Second, the study overcomes many of the shortcomings of previous studies on incomplete revascularization. The patient population is homogenous and the study was conducted according to contemporary quality standards for clinical trials. In addition, quantitative coronary angiography of the entire coronary tree was performed as part of the trial protocol. This quantitative approach allows a nuanced definition of incomplete revascularization and provides a unique means of characterizing global coronary atherosclerotic burden.

The results of this investigation may have significant consequences for our treatment strategy. They indicate - expectedly - that the more stringent the definition of incomplete revascularization, the lower its prevalence, and the higher the chance of any individual patients with incomplete revascularization to experience an event. More importantly, the data convincingly show that, irrespective of its definition, incomplete revascularization is associated with a significant increase in myocardial infarction and of repeat revascularization and a trend towards increased mortality. Even though the present study was limited to patients with NSTEMI-ACS, its conclusions are likely to be applicable to the full range of ACS, including ST elevation myocardial infarctions (STEMI). In patients with STEMI undergoing primary PCI in the HORIZONS-AMI trial, the presence of stenoses of more than 50% in non-infarct-related arteries was associated with a 40% relative increase in the risk of death at 3 years. When one of these non-infarct-related arteries happened to be a chronic occlusion, this risk was 2.5 times higher. These results leave little doubt about the detrimental effect of extensive residual atherosclerosis.

As discussed by Rosner et al, showing that incomplete revascularization is associated...
with a poor prognosis does not necessarily imply that revascularization of residual stenoses visible on the angiogram improves prognosis. Much like in the FAME trial, obtaining functional information with high spatial resolution about the residual stenoses will be critical to distinguishing lesions that should be revascularized from those that should be left alone. FFR has been proven accurate in assessing non-culprit stenosis severity even when performed in the setting of primary angioplasty of a myocardial infarction. Taken together, these data suggest an important role for FFR measurements in patients with acute coronary syndromes. After stenting of the infarct-related artery, non-culprit stenoses can be assessed immediately. Thus, when leaving the catheterization laboratory, the diagnostic work-up of patients with MVD admitted for an ACS should be complete i.e. left ventricular- and coronary angiogram, and FFR when needed. This simplification of the post-ACS diagnostic work-up would render non-invasive testing superfluous, since all the information needed for clinical decision making about additional revascularization will have been obtained in the catheterization laboratory.

Rosner et al. convincingly confirmed the poor prognosis of ACS patients in whom angiographically significant non-culprit lesions are left unrevascularized. Which of these stenoses may benefit from revascularization and when this procedure should be performed are the next questions. As it can be obtained ‘on the spot’ and has an unsurpassed spatial resolution, FFR appears to be the method of choice to guide functionally complete revascularization - also in acute coronary syndromes.

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**References:**


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