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Appropriate myocardial revascularization: a joint viewpoint from an interventional cardiologist and a cardiac surgeon*

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Two landmarks, contemporary trials on mechanical revascularization therapies in patients with multivessel coronary artery disease (CAD) have been presented, discussed and published recently.[1-4] This common viewpoint explores the potential impact of these trials on clinical decision making and how this may affect the interaction between interventional cardiologists and cardiac surgeons.

Lessons from SYNTAX

SYNTAX stands for SYNergy between percutaneous coronary intervention (PCI) with TAXus and cardiac surgery. The trial compared the outcome of surgical and catheter-based revascularization in 3075 patients with multivessel and/or left main CAD. At each of the 85 participating sites (62 in Europe, 23 in USA), a team involving cardiac surgeon(s) and interventional cardiologist(s) evaluated both the coronary lesions and the clinical data for treatment suitability either by PCI using drug-eluting stents (DES) or by coronary artery bypass grafting (CABG). When both approaches were deemed feasible, a 1:1 randomization to either therapy was proposed (PCI = 903, CABG = 897). If not, two prospective registries of preferred PCI (n = 198) or preferred CABG (n = 1077) were constructed. Severity and extent of CAD were quantified prospec-tively by the newly designed SYNTAX score.[5]

At 1 year follow-up, the trial failed to confirm the non-inferiority hypothesis with respect to the composite endpoint of death, non-fatal myocardial infarction, cerebro-vascular accident, repeat revascularization by PCI or CABG. While the pre-specified margin of non-inferiority was 6.6%, the observed difference in major adverse cardiac and cerebro-vascular events (MACCE) rate was 5.7%, with a 95% confidence interval at 8.3% (P = 0.0015 in favour of surgery). With respect to individual components of the primary endpoint, death and myocardial infarction were neutral (P = 0.37 for all cause mortality, P = 0.11 for myocardial infarction), cerebro-vascular accident favoured PCI (0.06% after PCI, 2.2% after CABG, P = 0.003) while repeat revascularization was significantly less after CABG (5.9% vs. 13.7% after PCI, $P < 0.001$), driving the rate of MACCE well outside the non-inferiority margin.

Extensive *post hoc* subset analyses have been presented, which is problematic since the trial is essentially negative and confirms the value of CABG as the standard of care for the majority of patients with extensive CAD. With PCI, outcome was inversely related to the extent and severity of the disease, as captured by the SYNTAX score. The MACCE rates per tertiles of SYNTAX score (≤22, 23-32, ≥33) showed a stepwise increase: 13.5, 16.6, 23.3% (P = 0.007). The lower tertile subset of SYNTAX scores included patients with left main disease in the absence of diffuse distal involvement. The fewer DES were implanted, the shorter the vessel length covered by stents, the better the outcome. In retrospect, denying PCI attempts in cases with the most complex anatomy, based on a pre-intervention SYNTAX score ≥33, would most likely have resulted in a positive trial. With CABG, results were more predictable across tertiles of SYNTAX scores, as well as in patients with diabetes. By multivariable analysis in the randomized cohort, poor outcome with surgery was associated primarily with the presence of clinical markers of increased risk such as unstable angina, chronic obstructive lung disease, poor left ventricular function, or prior myocardial infarction. These observations were confirmed by the registry data. Percutaneous coronary intervention was deemed not feasible more often than CABG (5:1), essentially because of excessive lesion complexity. Coronary artery bypass grafting was deemed not feasible because of co-morbidities in 70.7% and lack of suitable conduits for bypass in 9.1% of cases.

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Not unexpectedly, criticism has been voiced from both sides. Some surgical colleagues have argued that the early risk of CABG was unnecessarily high (on-pump surgery in 85% of cases and frequent use of aortic anastomoses) and that the potential late benefit of CABG will not be fully exercised (complete arterial revascularization in 18.9%, use of at least one vein graft in 81.1% of cases). Many surgeons indicated that implementation of more advanced surgical techniques, such as off-pump CABG, avoidance of aortic anastomoses, and use of multiple arterial conduits would be expected to increase the gap between treatment arms even further. Others argued that the benefits of off-pump surgery remain to be fully demonstrated and that full arterial revascularization is often hampered by the limits to available conduits. From the percutaneous corner, it has been emphasised that the number of implanted stents (4.6 ± 2.3 per patient) and the length of the stented segments (86.1 ± 47.9 mm with stent length above 100 mm in 33.2% of patients) were the largest ever. Although symptomatic stent thrombosis was not more frequent than symptomatic graft closure, absolute rate of definite stent thrombosis at 1 year reaches 3.3%, a figure observed only after 4 years of follow-up with conventional indications for PCI.[6] Given the rather high rates of death (4.3%) and non-fatal myocardial infarction (4.8%), PCI with DES at 1 year was equivalent to CABG in terms of hard events. Although extensively advertised as a demonstration of safety, this should rather be seen as a sobering observation. Indeed the time domain of the risk function is different for CABG (highest initially, very low for several years, higher again at the time of vein graft failure) and for PCI with DES (lowest initially, low but stable for several years, unknown in the very long term). Equivalence in hard events at 1 year implies limited tolerance, if any, for death or non-fatal myocardial infarctions that would proceed from (very) late DES thrombosis, possibly a significant risk given the 'heavy metal' load.

Lessons from FAME

FAME stands for Fractional flow reserve vs. Angiography for Multivessel Evaluation.[3-4] Although practice guidelines recommend functional evaluation prior to elective revascularization, results of non-invasive functional testing were shown to be available in only 26-45% of patients submitted to elective PCI.[7] An alternative is to use the pressure-derived fractional flow reserve (FFR), a functional test that can be applied in the catheterization laboratory for estimation of the haemodynamic significance of individual lesions. Proof of concept was demonstrated in the DEFER trial.[8,9] With FFR guidance, resource utilization was reduced, outcome was equivalent up to 5 years with death and non-fatal myocardial infarction rate at 3.3% (not different from 7.9% in patients randomized to PCI despite normal FFR, $P = 0.21$). Because the diagnostic performance of non-invasive functional testing for the evaluation of lesion significance in patients with multivessel disease is limited, FAME was designed to compare FFR-guided PCI using DES with angiography-guided PCI in patients with double and triple vessel disease, at the exclusion of left main stenosis and primary PCI for acute myocardial infarction. Once all stenoses ≥50% in diameter were identified, 1005 patients were randomized 1:1 to either standard PCI as planned ($n = 496$) or to prior FFR interrogation of all lesions deemed significant by angiography ($n = 509$). In patients randomized to FFR guidance, PCI using DES was eventually performed only for lesions with FFR ≤ 0.80 (taken as the threshold for stress-inducible ischaemia). Fractional flow reserve was successfully measured as planned in 98% of non-totally occlusive lesions, without complications. Although the number of angiographically significant stenoses was identical between groups (2.7 ± 0.9 vs. 2.8 ± 1.0), FFR was reduced in 63%, resulting in fewer lesions treated (819 vs. 1,237 with angiographic guidance) and reduced resource utilization (980 vs. 1359 DES with angiographic guidance). At 1 year follow-up, results of the FAME trial confirm the superiority of FFR-guided PCI with respect to the composite of death, non-fatal myocardial infarction, repeat revascularization by PCI, or CABG (18.4 vs. 13.2%, $P = 0.02$). Effect was consistent across the individual components of the primary endpoint: death (15 vs. 9, $P = 0.19$), myocardial infarction (43 vs. 29, $P = 0.07$), repeat revascularization (47 vs. 33, $P = 0.08$). Functional status and quality of life were equivalent, with 78 and 81% of patients free of angina for angiography- vs. FFR-guided PCI, respectively ($P = 0.20$).

Thus, FAME shows that routine measurement of FFR during DES stenting in patients with multivessel disease is superior to the currently applied angiographic guidance by efficacy, safety, and cost-effectiveness criteria.

Crossfire between trials and clinical implications

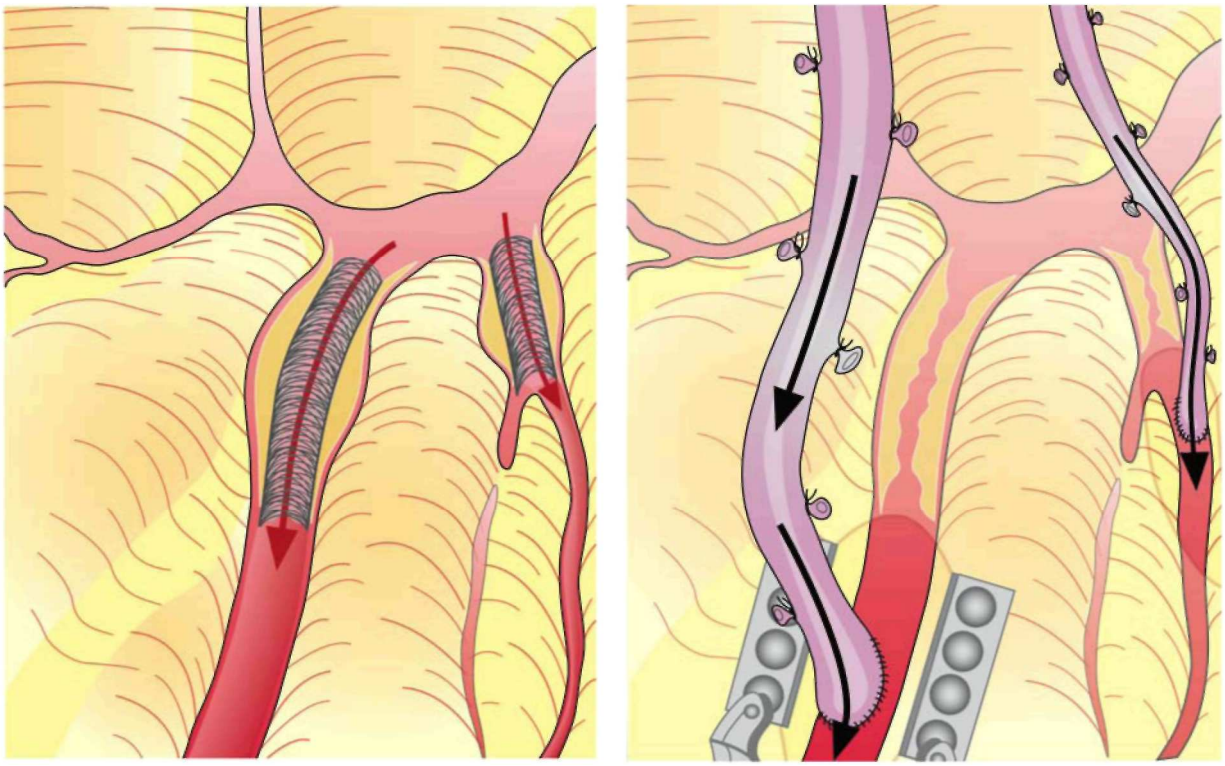
The results of both trials question the concept of 'complete revascularization' based exclusively on anatomic metrics. Instead, DEFER and FAME support the use of a combined anatomic and functional standard as the appropriate decision-maker for revascularization by PCL This new paradigm challenges both the design and the implications of recent trials such as SYNTAX or even COURAGE.[10]

Whenever revascularization decisions are based solely on angiographic guidance, it is unavoidable that a number of haemodynami-cally non-significant stenoses will be stented, while a number of seemingly mild stenoses will

be deferred inappropriately.[11] COURAGE substudy[12] confirms that the outcome benefit from revascularization therapy is largest when demonstrable ischaemia is present prior to—and relieved by—intervention. No benefit is to be expected from stenting of haemodynamically non-significant lesions, rather the opposite. Indeed, like any intervention, PCI with DES carries risks, both peri-procedural and at longer term. The outcome results of revascularization trials using exclusively angiographic guidance, including SYNTAX and COURAGE, are thus likely contaminated by side effects related to unnecessary stent implants. As a consequence, the potential benefit of PCI will be underestimated.

Whether the same paradigm of 'complete revascularization' based on functional standards is valid for CABG remains to be tested, as data are scarce.[13] While PCI aims at restoring the normal conductance of the native epicardial coronary vessels, CABG is providing extra conduits, thereby multiplying the sources of nutrient blood flow to the myocardium. However, this could potentially reduce flow across the native conduit and therefore make the vessel more dependent on graft patency for the long term (*Figure 1*). Given this fundamental difference in mechanisms of action between both techniques, no inference should be made as to the implications of FAME for the practice of CABG, but this hypothesis remains to be tested. As to the practice of PCI, there is now mounting evidence that this form of therapy provides best results when focusing on the relief of ischaemia, implying that stents should be targeted at haemodynamically significant stenoses. In patients presenting with unstable angina and myocardial infarction, ischaemia is obvious and culprit lesions are easily identified by angiography in the vast majority of cases. In patients with stable CAD, in particular in the presence of multivessel disease, identification of the culprit(s) requires anatomic orientation by angiography combined with functional evaluation, be it obtained by non-invasive imaging prior to catheterization, or during the invasive procedure using pressure-derived FFR. Voicing these common sense statements could be perceived as slamming open doors. The reality is that common sense and good clinical judgment supported by evidence need to overrule cosmetics as the main drivers of interventional behaviour.

Figure 1 *Anatomical representation of stenting (left) and aorto-coronary bypass (right).*



Appropriateness criteria

A coalition of American Scientific Societies has recently published a consensus document on the appropriateness of revascularization.[14] Whenever expected benefits in terms of survival or health outcomes exceed negative

consequences of the procedure, revascularization is declared appropriate. No less than 180 (!) clinical scenarios are identified, and for each of those, revascularization is deemed appropriate, uncertain, or inappropriate. The decision-making process incorporates clinical presentation, severity of angina, extent of ischaemia by non-invasive functional testing, medical therapy, and extent of anatomic disease by angiography. The panel recognizes that many patients with stable ischaemic heart disease undergo angiography without prior testing. Presence of left main and proximal left anterior descending (LAD) disease carries a strong prognostic weight. Clinicians are encouraged to grade stenosis severity between ≥50%, ≥70%, or ≥95% luminal narrowing. Fractional flow reserve or intravascular ultrasound imaging is recommended prior to revascularization of moderate stenoses in the absence of non-invasive testing. Coronary artery bypass grafting is deemed appropriate for all anatomic subsets with advanced CAD, whereas appropriateness of PCI is restricted to two-vessel disease with proximal LAD involvement. The appropriateness of PCI for triple vessel disease is deemed uncertain, and PCI is seen as inappropriate for treatment of left main disease, in isolation or with additional disease. The hypothesis-generating *post hoc* analysis of the left main subset from SYNTAX now challenges this statement.

As often the case in clinical practice, the proposed decision process is heavily dependent on the estimation of stenosis severity from coronary angiography. Yet, the inaccuracy of angiography in depicting stenosis severity as well as variability in the interpretation of coronary angiograms have been recognized and illustrated by numerous reports. Intravascular ultrasound imaging performs much better with this respect but is recommended only for the evaluation of moderate stenoses. Above all, even the most detailed cross-sectional evaluation of coronary stenoses does not provide a reliable estimate of their haemodynamic significance, because anatomy fails to account for the presence and efficiency of collateral circulation. The evidence accumulating from both non-invasive imaging and FFR trials, such as **FAME,** demonstrates that anatomy cannot reliably predict function, yet health outcomes after revascularization are driven by the extent and severity of pre-procedural ischaemia and its post-procedural reversal. Therefore, in patients with stable CAD, granting the appropriateness label to revascularization decisions taken in the absence of combined anatomic and functional evaluation of individual lesions is deemed... inappropriate.

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References

1. Ong AT, Serruys PW, Mohr FW, Morice MC, Kappetein AP, Holmes DR Jr, Mack MJ, van den Brand M, Morel MA, van Es GA, Kleijne J, Koglin J, Russell ME. The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study: design, rationale, and run-in-phase. *Am Heart J* 2006;151:1194-1204.

2. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, Stahle E, Feldman TE, van den Brand M, Bass EJ, Van Dyck N, Leadley K, Dawkins KD, Mohr FW, for the SYNTAX Investigators. Percutaneous Coronary ntervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. *N Engl J Med* 2009:360:961-972.

3. Fearon WF, Tonino PA, De Bruyne B, Siebert U, Pijls NH, FAME Study Investigators. Rationale and design of the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study. *Am Heart J* 2007;154:632-636 Erratum in: *Am Heart J* 2007:154:1243.

4 Tonino AL, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Verlee PN, Mac Carthy PA, Fearon WF. Fractional Flow Reserve versus Angiography for guiding Percutaneous Coronary Interventions. *N Engl J Med* 2009;360:213-224

5. Valgimigli M, Serruys PW, Tsuchida K Vaina S, Morel MA, van den Brand MJ, Colombo A, Morice MC, Dawkins K de Bruyne B, Kornowski R, de Servi S, Guagliumi G, Jukema JW, Mohr FW, Kappetein AP, Wittebols K, Stoll HP, Boersma E, Parrinello G, ARTS II. Cyphering the complexity of coronary artery disease using the SYNTAX score to predict clinical outcome in patients with three-vessel lumen obstruction undergoing percutaneous coronary intervention. *Am J Cardiol* 2007;99:1072-1081.

6. Wenaweser P, Daemen J, Zwahlen M, van Domburg R, Jüni P, Vaina S, Hellige G, Tsuchida K Morger C, Boersma E, Kukreja N, Meier B, Serruys PW, Windecker S. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol* 2008; 52:1134-1140.

7. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *J Am Med Assoc* 2008;300:1765-1773.

8. Bech GJW, De Bruyne B, Pijls NHJ, de Muinck ED, Hoorntje JC, Escaned J, Stella PR, Boersma E, Bartunek J, Koolen JJ, Wijns W.

Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. *Circulation* 2001;103:2928-2934.

9. Pijls NHJ, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study. *J Am Coll Cardiol* 2007;49:2105-2111.

10. Boden WE, O'Rourke RA, Teo KK Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS, COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-1516.

11. Wijns W, De Bruyne B, Vanhoenacker PK What does the clinical cardiologist need from noninvasive cardiac imaging: is it time to adjust practices to meet evolving demands? *J Nucl Cardiol* 2007;14:366-370.

12. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK Boden WE, COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008;117:1283-1291.

13. Botman KJ, Pijls NH, Bech JW, Aarnoudse W, Peels K van Straten B, Penn O, Michels HR, Bonnier H, Koolen JJ. Percutaneous coronary intervention or bypass surgery in multivessel disease? A tailored approach based on coronary pressure measurement. *Catheter Cardiovasc Interv* 2004;63:184-191.

14. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK Spertus JA. ACCF/SCAI/STS/ AATS/AHA/ASNC 2009 Appropriateness criteria for coronary revascularization: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology: Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. *Circulavon* 2009;119:1330-1352. Erratum in: *Circulation* 2009;119:e488.