Routine angiographic surveillance for risk stratification in PCI-treated patients: fact or fiction?

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This editorial refers to ‘Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting’, by S. Cassese et al. on page 94

Patients with restenosis after coronary artery stent implantation may present with recurrent ischaemia, stable angina, and acute coronary syndromes. Restenosis may also be asymptomatic (without ischaemia), detected only on repeat angiography. Previous studies have demonstrated that angiographic measures including both in-stent and in-segment late loss and percentage diameter stenosis are valid surrogates for subsequent target lesion revascularization (TLR).1 Cassese and co-workers now raise the issue of whether routine surveillance angiography and the detection of asymptomatic restenosis might have clinical utility.2 Specifically, employing a strategy of routine follow-up angiography at 6–8 months after stenting, the authors identified angiographic restenosis in 2643 (26.4%) of 10 004 patients. After adjustment for clinical differences between groups, restenosis was an independent predictor of subsequent 4-year mortality [hazard ratio (HR) 1.23, 95% confidence interval (CI) 1.03–1.46; \( P = 0.02 \)], even if patients were asymptomatic (HR 1.40, 95% CI 1.06–1.87; \( P = 0.01 \)). Should routine surveillance angiography be considered after coronary stent implantation to detect asymptomatic restenosis and trigger repeat revascularization on the basis of this provocative study?

It is well known that routine follow-up angiography results in a marked increase in TLR procedures in otherwise asymptomatic patients.3 In this regard, the angiographic restenosis rate of 26.4% in the series reported by Cassese et al.2 is substantially higher than the typical 5–10% rates of clinically driven restenosis found in most studies.1 Although routine angiographic surveillance is frequently performed to compare the efficacy of different stent systems,2 no prospective randomized trials have been performed to examine whether restenosis detected at routine angiographic follow-up has prognostic utility. In this regard, a meta-analysis of studies comparing outcomes of non-randomized patients assigned either to routine angiographic follow-up or to clinical follow-up alone demonstrated that the strategy incorporating routine angiographic surveillance was associated with increased ‘oculostenotic’ TLR of intermediate lesions without affecting subsequent rates of cardiac death or myocardial infarction.5

Restenosis: risk factor or risk marker for worse prognosis?

Patients with restenosis of major coronary vessels have a worse prognosis at long-term follow-up.4 However, the numerous clinical characteristics, genetic and epigenetic mechanisms, and lesion- and procedure-related factors which have been associated with restenosis may also in parallel fashion (but without an inter-relating mechanism) affect survival (i.e. epiphenomena). For example, previous reports from the patients investigated in the study by Cassese et al.2,8 identified smaller vessel size, total stented length, complex lesion morphology, presence of diabetes mellitus, history of bypass surgery, and the type of stent [bare metal stent (BMS) vs. first-generation drug-eluting stent (DES) vs. second-generation DES] as being independently associated with restenosis. Most of these factors are also predictive of cardiovascular and all-cause mortality (Figure 1). The extent of atherosclerosis, in particular, is often not measured and strongly correlates with subsequent mortality.9,10 In the study by Cassese and colleagues, information regarding non-cardiac co-morbidities and concomitant medications during the follow-up period is limited.2 The extent to which unmeasured confounders contribute to the associations observed in non-randomized data must always be carefully considered.

If restenosis per se has a causal effect on subsequent mortality, interventions to reduce restenosis should enhance survival. A DES substantially reduces both angiographic restenosis and clinical revascularization rates compared with a BMS. However, randomized trials

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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Published online 2014.
have shown that DESs compared with BMSs do not reduce mortality. Similarly, all-comers randomized controlled trials including SORTOUT III, ISAR-TEST 2, and ZEST have not reported greater long-term mortality despite higher rates of binary restenosis and TLR in one of the comparator groups. In addition, the decision to perform target vessel revascularization (TVR) in the study by Cassese et al. did not impact the 4-year mortality risk.

Restenosis vs. recurrent ischaemia

Angiographic restenosis after percutaneous coronary intervention (PCI) is more common than recurrent angina. Approximately 50% of patients with angiographic restenosis have no symptoms. Clinically silent restenosis is associated with greater reference diameter and lesser lesion severity on follow-up angiography.

Numerous clinical studies have shown that the presence of untreated myocardial ischaemia is associated with adverse outcomes and a higher risk of death. Reduction of ischaemia by the addition of revascularization to optimal medical therapy (OMT) as compared with OMT alone may result in improved event-free survival. Ischaemia-guided revascularization has been associated with a reduction of major adverse events in patients with multivessel coronary artery disease.

In patients with objective signs or symptoms of recurrent myocardial ischaemia after PCI, repeat coronary angiography should be performed. If myocardial ischaemia has not been confirmed non-invasively prior to the invasive procedure, fractional flow reserve (FFR) measurement can be performed during diagnostic angiography to assess the functional significance of coronary lesions with ‘intermediate’ diameter reduction. A strategy of repeat angiography only for patients with progressive symptoms or recurrent ischaemia and functional assessment of lesions with undetermined significance can minimize repeat revascularization procedures of non-ischaemic intermediate stenoses, and is thus currently recommended in the European and American guidelines.

Recurrent symptoms vs. recurrent ischaemia

Recurrent angina due to restenosis is only one of the many causes for recurrent chest pain after PCI. Other causes include stent thrombosis, incomplete revascularization, and progression of coronary artery disease not involving the target lesion. In addition, non-coronary cardiovascular causes have to be considered as causes of recurrent chest pain after PCI, including left ventricular hypertrophy, microvascular dysfunction, valvular heart disease, pericarditis, and acute aortic syndromes. Non-cardiovascular causes may also mimic recurrent angina due to restenosis.

Ongoing or recurrent chest pain at the time of routine follow-up angiography at the previous treatment site may be misleading and may prompt ‘oculostenotic’ TLR of non-ischaemic intermediate lesions in the absence of FFR. Assessment of symptoms and anginal status early after PCI may thus improve diagnostic accuracy in the case of recurrent chest pain.
Does treatment of asymptomatic restenosis detected at routine angiographic follow-up improve outcomes in high-risk patients?

Mancini and colleagues have suggested that the angiographic extent of disease correlates more strongly with prognosis than does baseline ischaemia. Routine surveillance angiography after PCI of a lesion supplying a large amount of myocardium [the left main coronary artery (LMCA) being the ultimate example] may therefore appear reasonable. However, there are no data from prospective randomized trials to demonstrate the safety and efficacy of this approach (let alone its cost-effectiveness). In the non-randomized CASS Registry, 53 of the 1477 patients with LMCA disease were identified as being asymptomatic. However, coronary angiography was performed in these patients because of a recent acute coronary syndrome or positive non-invasive stress test. Thus, most patients in this registry were not truly asymptomatic but had some degree of ischaemia. Routine surveillance angiography after PCI of the unprotected LMCA has not been demonstrated to predict the occurrence of major adverse cardiac events (MACE) or sudden stent thrombosis, and is not recommended in current guidelines.

Conclusions

The unique study by Cassese et al suggests that angiographic restenosis demonstrated on routine follow-up angiography in asymptomatic patients might be a risk factor for subsequent mortality. However, given the absence of a control group (asymptomatic patients without routine follow-up angiography), we cannot infer whether the follow-up angiography strategy per se in asymptomatic patients may provide a clinical benefit. Moreover, because of the concern regarding unmeasured confounders, we cannot be confident that the correlation between angiographic restenosis and mortality is causal. We are also not provided data on the presence of ischaemia in the asymptomatic cohort with restenosis—it may be that ischaemia is the risk factor, and not the angiographic narrowing per se. Thus, while further studies are warranted to determine whether routine surveillance angiography might be useful in patients with large myocardial territories at risk, in the vast majority of PCI patients risk stratification can be based on patient-associated factors, lesion-specific characteristics, and procedural variables, with repeat angiography confined to those with recurrent ischaemia or progressive symptoms (Figure 2).

Such a strategy minimizes repeat revascularization of non-ischaemic low-grade or intermediate lesions and may be expected to optimize long-term event-free survival after PCI.

Conflict of interest: within the last 36 months J.A. has served as a consultant to Medtronic; within the last 36 months G.W.S. has served as a consultant to Abbott Vascular, Boston Scientific, Medtronic, and Reva Corp.

References