Review Article

The Ever Increasing Role of Percutaneous Interventions in Coronary Revascularisation

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The time period between the first balloon angioplasty[1] and the advent of drug-eluting stents (DES)[2] was less than twenty five years.

Progress of percutaneous coronary interventions

Balloon angioplasty

Balloon angioplasty was developed as the first non-surgical method to treat coronary artery stenosis, thanks to the pioneering work by Andreas Gruentzig from 1977 to 1986.[1] The method is based on mechanical stenosis relief by balloon dilatation. Vessel wall stretch, as well as plaque compaction and redistribution, are the main mechanisms of angioplasty lumen gain.[3] The technique had a relatively high acute vessel closure rate that dictated its performance with standby emergency coronary artery bypass grafting (CABG).[4] Stenosis recurrence four to five months after a successful procedure was relatively frequent, and was common to balloon angioplasty as well as other means of percutaneous revascularisation that developed in parallel. Restenosis after balloon angioplasty was mainly attributed to passive recoil of the initially stretched vessel wall, although plaque increase, later defined as intimal hyperplasia, also played a role.[3] Despite all its shortcomings, percutaneous interventions in the 80s made modification of coronary stenosis with diseased vessel reformation possible for the first time in history. Thanks to this development, patients were offered the option of open arteries, at least in cases without restenosis.

Stents

Stents were introduced as a bailout procedure in cases of threatened vessel closure,[5] reducing the need for emergency CABG.[6] It soon became evident that stent implantation leads to greater acute lumen gain and a higher success rate for the initial procedure, as well as a lower restenosis rate at mid-term follow up.[7,8] A major drawback was the relatively common occurrence of stent thrombosis and the threat of acute myocardial infarction (AMI) in the first twenty-four hours following the procedure. Although potent antithrombotic treatment became routine, causing bleeding complications, stent thrombosis persisted.[9]

In 1995, the problem of thrombosis was overcome thanks to observations from intravascular ultrasound examination after stenting. It became evident that stents that appeared to be well expanded on coronary angiography were often poorly attached to the vessel wall, as evidenced by intravascular ultrasound interrogation.[10] Regular use of higher balloon pressures during stent implantation and double antiplatelet treatment[11] resulted in stent thrombosis rates as low as 0.5%.[12]

The overcoming of thrombosis resulted in the widespread use of stents. Completion of stenting in one day, with low morbidity and mortality, became an attractive alternative to CABG. The possibility of revascularisation during the same session as diagnostic coronary angiography simplified patients' treatment. Stent implantation became the most common coronary intervention.[13] Never before had so many patients benefited from open coronary arteries.

Even so the problem of restenosis lingered. Although its rate diminished in comparison to balloon angioplasty, the number of restenosis cases grew in parallel with the increasing numbers and the difficulty of lesions approached with stenting.[14] Restenosis affects patients' perception of disease and quality of life,[15] and may also affect cardiac mortality in a few cases where the location of the stenosis is critical, as in unprotected left main stenting.[16] Restenosis also resulted in a much greater need for repeat intervention compared to CABG, with widening differences in multivessel coronary artery disease.[17,18]

The mechanisms resulting in restenosis are partial elastic recoil of the vessel at the stenosis site and the development of intimal hyperplasia in response to vessel trauma. Although stents practically abolish the first of these, intimal hyperplasia is amplified post stenting and is responsible for lumen loss and eventual restenosis.[19]

Drug eluting stents: challenging CABG

During the last decade we have witnessed the introduction of stents that caused a plummeting of restenosis rates through the local release of drugs that inhibit intimal hyperplasia.[20] Clinical practice has shifted towards non-surgical revascularisation since the need for repeat intervention reached single-digit numbers in multivessel coronary artery disease.[21] A drawback of these drug-eluting stents (DES) was late stent thrombosis, often associated with withdrawal of double antiplatelet treatment during a surgical intervention.[22] Safety concerns regarding DES became paramount after an announcement at the World Congress of Cardiology in 2006, pointing to increased non-cardiac deaths and AMIs in patients treated with sirolimus-eluting stents compared to bare metal stents (BMS). Although this announcement was based on clinical trials comparing DES with BMS, the actual meta-analyses did not confirm such a difference for either paclitaxel- or sirolimus-eluting stents.[23] Nevertheless, DES safety was scrutinised via the continued follow up of patients recruited in the initial DES trials,[24] registries comparing hard endpoint outcomes in patients treated with first generation DES and BMS in everyday clinical practice,[25,26] and the conduction of clinical trials comparing first generation DES and BMS in clinical scenarios where stent thrombosis may be more common, as in the setting of AMI.[27] All results gathered reinforce the improved outcome of first generation DES compared to BMS as regards restenosis and need for repeat intervention, expanding their benefits to reduced incidence of death or AMI.[25,26] The "paradox" of stents with late stent thrombosis not leading to higher AMI or cardiac death rates is explained by the much higher rates of BMS restenosis, a sequela not as benign as previously thought.[28] The resulting equilibrium is clearly depicted in a paper that reports the detailed follow up of patients recruited in four different TAX-US trials.[29]

In current clinical practice, implantation of multiple DES has become an alternative to CABG for severe multivessel coronary artery disease[30] (Figures 1 & 2). An attempt to delineate the limits of PCI has been the SYNTAX randomised trial. Use of the SYNTAX score[31] has helped define procedure outcomes with respect to lesion complexity. Results of the trial indicate that the need for re-intervention after PCI increases in parallel with lesion complexity, whilst it remains constant for patients treated with CABG. As a result, at twelve months' follow up PCI results in more than twice the events observed post CABG (23.4% vs. 10.9%, $p<0.001$) in patients at the highest lesion complexity level, expressed as a SYNTAX score 33 or greater.[32] In the same patient subset there is also a clinically meaningful difference in the composite of death, AMI and stroke in favour of CABG (7.6% vs. 11.9 for patients treated with PCI), although it did not reach statistical significance ($p=0.08$). Event rates, re-intervention included, are similar for either method of revascularisation in the majority of patients with a SYNTAX score lower than 33. The equivalence of the two methods in patients without very great anatomical complexity holds especially for patients with unprotected left main lesions. The relevant subgroup evaluation suggests that one out of three patients with unprotected left main stenosis may be treated with PCI with outcomes as good as CABG for a follow-up period up to two years.[33]

The results of the SYNTAX LEMANS angiographic sub-study suggest that the lack of a relationship between lesion complexity and the need for re-

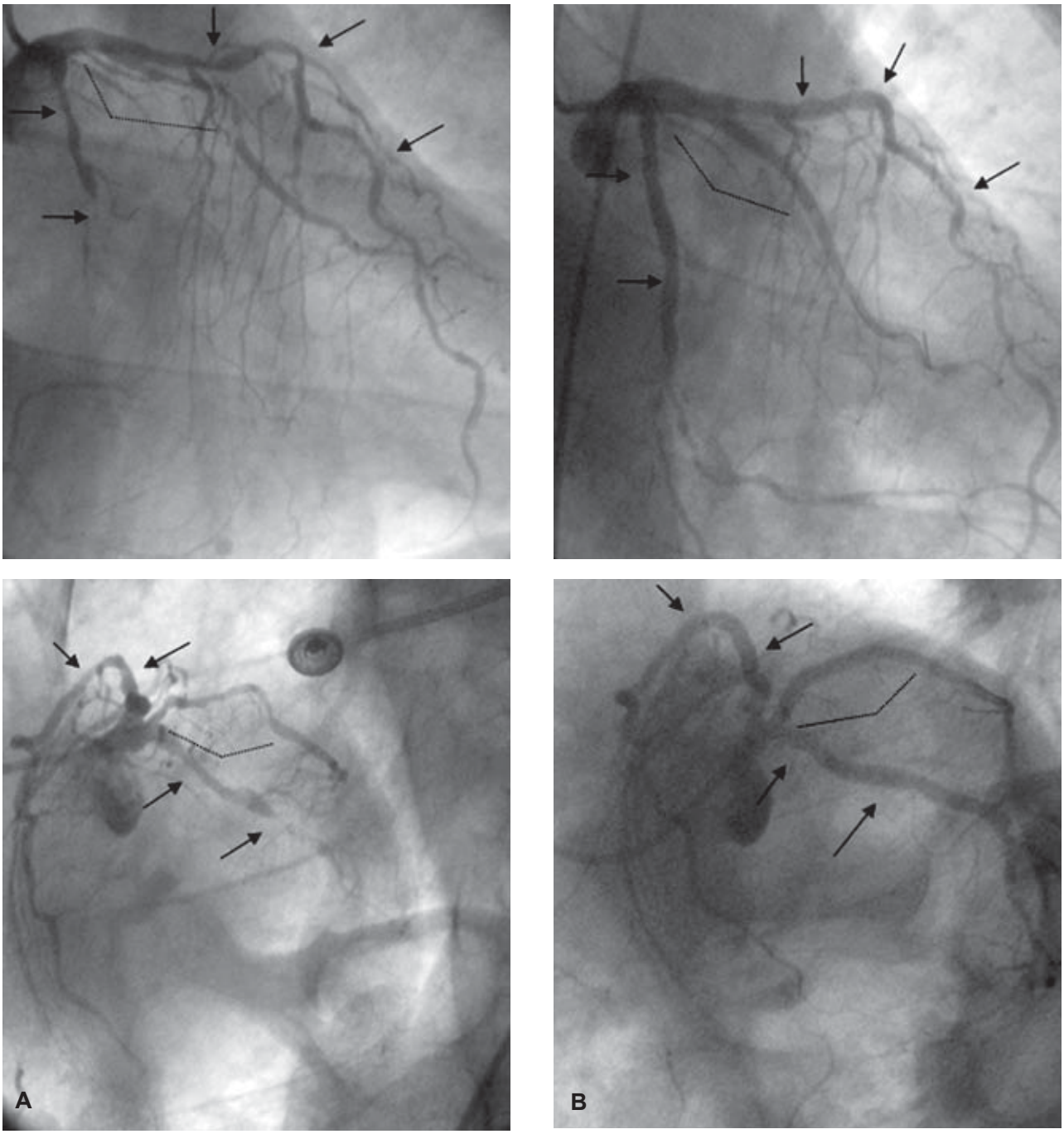

Figure 1. Successful recanalisation and reconstruction of chronically occluded left circumflex and stenting for discrete stenoses in the left anterior descending artery. Images are in right caudal (upper) and left caudal (lower) views. Arrows and bracket point to stented segments. A: Before intervention; B: Six months post-intervention, at the time of treatment of a diffusely diseased *ramus intermedius*.

intervention post CABG may be attributable to the fact that, although graft failure is quite high, patients are less likely to undergo follow-up angiography and revascularisation.[33] In any case, an increased need for re-intervention cannot be regarded *per se* as a good enough reason for denying patients the option of undergoing PCI. Everyday practice indicates that the vast majority of patients are willing to undergo re-intervention in case of restenosis, as long as they can avoid surgical revascularisation.[34] We will need to define differences in hard endpoints—such as the composite of death, AMI and stroke—for patients at

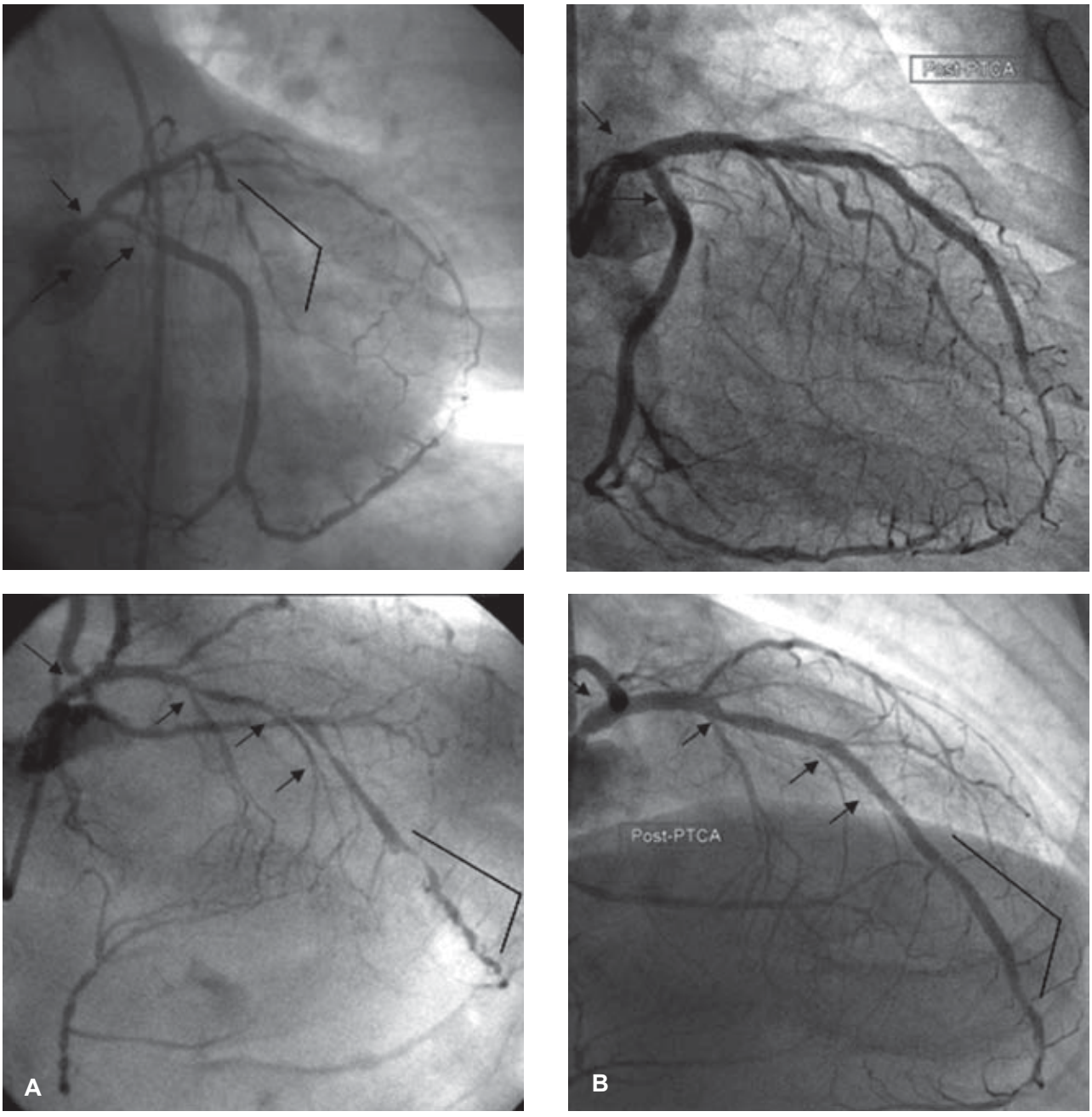

Figure 2. Use of drug-eluting stents to treat (unprotected) left main, ostial left circumflex and diffusely diseased left anterior descending arteries, with stenoses extending to the outermost distal part of the left anterior descending artery, making questionable the effectiveness of surgical revascularisation. Images are in right caudal (upper) and left cranial (lower) views. Arrows and bracket point to stented segments. Images pre (A) and post (B) staged percutaneous coronary intervention.

different levels of SYNTAX score, in order to delineate the limits of PCI. This may prove to be a moving target, given the constant, rapid evolution of materials and techniques of percutaneous revascularisation. Second generation DES have already been proven to reduce the composite of death, AMI and re-intervention by as much as 45% compared to the first generation DES used in the SYNTAX trial.[35]

Conclusions

Percutaneous coronary interventions have come a

long way since the early days of balloon angioplasty. The option of PCI is currently being offered to patients with severe coronary artery disease, who were previously amenable only to surgical revascularisation. The continuous evolution of materials and techniques forms the foundation for the constantly increasing use of non-surgical revascularisation for coronary artery disease patients.

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