

Long-Term Outcome After Coronary Angioplasty: Where Do We Stand?

MICHAEL I. PAPAFAKLIS,¹ LAMPROS K. MICHALIS^{1,2}

¹Michaelideion Cardiac Centre, ²Cardiology Department, Medical School, University of Ioannina, Ioannina, Greece

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Address:

Lampros K. Michalis

Cardiology Department
Medical School,
University of Ioannina,
P.O. Box 45110
Ioannina, Greece
e-mail:
lmichalis@cc.uoi.gr

The pathogenic process of atherosclerosis is the principal cause of a reduced lumen and of thrombotic and vasoconstrictive mechanisms that all lead to chronic and acute manifestations of ischaemic heart disease, the leading cause of morbidity and mortality in western societies. More than 25 years have passed since Andreas Gruntzig changed the course of interventional cardiology by introducing percutaneous transluminal coronary angioplasty (PTCA) in the management of patients with coronary artery disease, and many advances have been witnessed during this time. Having entered the so called “golden era” of drug-eluting stents at the dawn of the 21st century, we should stand still for a moment and reflect on the long-term outcome of patients undergoing PTCA during the last two decades. Questions like, “What has been the impact of PTCA on survival and which are the major predictors of adverse cardiac events?” are of paramount importance and their answers determine the general contribution of PTCA.

Plain old balloon angioplasty

The first successful dilatation of the coronary arterial stenosis of a patient with ischaemic heart disease by Gruntzig et al¹ also led to the initiation of the first registry of patients undergoing coronary angioplasty. The results of the ten-year follow-up of these

169 first patients with attempted PTCA (10-year survival: 89.5%; angiographic restenosis: 38%) were quite satisfactory even by contemporary standards, while the angiographic success rate of 79% was impressive for a newly born procedure and application.² Even in this early phase of PTCA (1977-1980) a significant number of patients with multi-vessel disease (42%) were included, allowing the demonstration of noteworthy differences between the multi-vessel and the single-vessel group. The patients with multi-vessel disease had a lower primary success rate, a higher rate of death from cardiac disease, a lower long-term survival free from bypass surgery, and presented with angina more frequently.

The multi-centre registry, established by the National Heart, Lung, and Blood Institute in the late 70s, expedited a more meaningful evaluation of the new procedure at an early stage of its development and has constituted a continuing source of valuable information through the years. It prospectively followed two large cohorts of consecutive patients, those undergoing PTCA from 1977 to 1981 (1345 patients) and those undergoing PTCA from 1985 to 1986 (2136 patients), thereby providing comparative long-term clinical data from two different periods of time.³ Differences in baseline characteristics and PTCA strategy were more than apparent; patients from the more recent registry were older (5 years on aver-

age), had significantly more cardiac risk factors and were twice as likely to have double-vessel disease and three times as likely to have triple-vessel disease, while multi-lesion or multi-vessel PTCA was more frequent in this cohort. Advances in PTCA technology were also evident, since angiographic success was significantly lower in the first registry with a per lesion success (reduction of $\geq 20\%$ in luminal diameter stenosis and a post-PTCA stenosis of $<50\%$ luminal diameter narrowing) of 58% versus 82%, the difference being due primarily to the high percentage of lesions that could not be crossed with the “primitive” devices. Regarding clinical events, a large difference in favour of the second registry was found in the rate of coronary artery bypass graft surgery (CABG) during the initial hospitalisation (25% vs. 6%) and at 5 years (39% vs. 19%), whereas the unadjusted 5-year mortality was lower in the first registry (6.4% vs. 9.8%). After adjusting for the baseline differences, similar mortality rates were demonstrated, while major adverse cardiac events (MACE: myocardial infarction [MI], bypass surgery, need for repeat PTCA) were significantly lower in the more recent registry.

Data from the whole first decade of PTCA application, which included a very large number of patients undergoing PTCA and followed up for many years, also became available and consolidated the position of coronary angioplasty in the management of patients with coronary artery disease. Such an example is the decennial (1980-1991) experience at the Emory University Hospitals; after excluding patients who had a PTCA procedure performed acutely after a myocardial infarction, Weintraub et al⁴ reported the 8-year clinical course of 10,785 patients undergoing elective angioplasty. The procedure was angiographically successful (success in all lesions attempted) in 90% of the patients with an overall clinical success (angiographic success without the complications of MI, CABG or death during the same hospital admission) of 88.5%. Eight-year cumulative survival was 89%, while the cumulative rates of MI, CABG and repeat PTCA were 17%, 23% and 42%, respectively; advanced age, congestive heart failure, low ejection fraction, diabetes mellitus, multi-vessel disease and hypertension were found to be independent predictors of mortality, with age >70 being the strongest.

Along with the report of long-term survival data emerged the necessity to risk stratify patients undergoing coronary angioplasty, so that post-procedure management and follow-up could be improved and alternative forms of therapy or revascularisation could be tak-

en into consideration. An elaborate multivariate analysis of 5000 patients undergoing elective PTCA for unstable or stable angina was undertaken by Mick et al,⁵ aiming to provide a risk-stratification score. The 5-year survival free from death, MI, CABG or repeat PTCA was 52% and the corresponding independent negative correlates were age >70 , multi-vessel disease, diabetes mellitus, congestive heart failure, hypertension, male gender and a history of prior PTCA. It is worth noting that triple-vessel disease received the highest weighted score among all the other predictors.

The end of the 20th century also marked the completion of more than 20 years since PTCA was first applied, thereby allowing the follow-up of patients over a very long period of time, equivalent to that of many epidemiological studies investigating the survival of the general population. The first 856 consecutive patients treated by PTCA from 1980 through 1985 at the Erasmus University Hospital were followed up for more than 15 years, providing substantial information.⁶ Survival at 17 years was 58%, with a relatively constant mortality rate throughout all the years, whereas 17-year survival free from death, MI, CABG or repeat PTCA was 19%, with an impressively low and stable annual incidence after the first year, during which 30% of the patients experienced at least one MACE. Of note is that a low-risk group (younger non-diabetic patients with single-vessel disease and normal left ventricular function) had a 17-year survival similar to that of the general Dutch population.

Percutaneous coronary intervention with stent implantation

By the end of the eighties, PTCA had proven its short- and long-term efficacy and had become a widely used alternative to CABG and an adjunct to the medical management of coronary artery disease. However, recurrence of stenosis and the need for repeat revascularisation, mainly during the first 6 to 12 months after angioplasty, led to the introduction of metallic stents, a momentous advance that almost rivals the earlier introduction of balloon angioplasty itself.

It has been more than 10 years since the first randomised trials directly comparing coronary stenting with balloon angioplasty were completed.^{7,8} Although patients who underwent randomisation were rather select (e.g. stable angina, single de novo lesions) and do not represent “real world” practice, a noteworthy difference of 10% in target lesion revascularisation (TLR) in favour of the stent group in the Benestent-I trial be-

came evident during the first year of follow-up and remained unchanged at five years.⁹ Cumulative survival and event-free survival of the 259 patients in the stent arm of the trial were 94.1% and 65.6%, respectively, at 5 years.

Long-term results after coronary stenting from registries including larger numbers of consecutive patients confirmed the favourable outcomes of the randomised trials. Van Domburg et al¹⁰ described the clinical outcome up to 11 years of 1000 patients who underwent a first stent implantation between 1986 and 1996. TLR rate was approximately 20% and the need for any revascularisation reached 30% 7 years after the index procedure, while 7-year survival was 81%. Similar findings were reported for 405 patients with successful stenting in native coronary arteries from 1990 to 1993.¹¹ In this study, which also included angiographic follow-up information, target lesion repeat PTCA was 19% at 8 years; data from a subset of 131 patients with complete serial angiographic follow-up further revealed a late re-narrowing phase occurring beyond 4 years, apart from the early restenosis phase of the first 6 months. Cumulative 8-year mortality was 24% (10% for cardiac-related mortality) and the corresponding rate of MACE was 37%. Better results at 8 years following coronary stenting were reported recently from a registry of 3399 patients, 2456 of whom underwent stent deployment in the second half of the 90s (the majority of the rest were treated with balloon angioplasty).¹² Eight-year mortality and MACE rate in the stent group were 18% and 36.2%, respectively, and after pooling of the data stenting was found to affect both of them independently. The observed improvement, mostly in the MACE rate, in this later registry mainly reflects the continuous changes in antiplatelet therapy (i.e. ticlopidine, clopidogrel) and the introduction of IIb/IIIa inhibitors during the 90s.

As stenting became a standard in clinical practice, the intriguing question of “whether they are needed in all situations where they are being used” arose and led to the hypothesis that balloon angioplasty could be sufficient, provided the procedural result was good enough or “stent-like”. Therefore, either attempts were made in order to optimise the result of balloon angioplasty or a strategy of balloon angioplasty plus provisional stenting was followed. Holmes et al¹³ reported the 10-year clinical outcome of successfully treated patients with and without an initial “stent-like” result (≥ 1 lesion dilated to $\leq 10\%$ stenosis) after balloon angioplasty. The 10-year rate of death (22.2% in

the “stent-like” group) was similar in the two groups and there was less TLR in the “stent-like” group (30.2% vs. 36.8%). However, after adjustment there was only a non-significant trend for patients with an initial “stent-like” result to be at lower risk for CABG and TLR at 10 years of follow-up.

The interventional strategy according to which coronary lesions are initially managed with balloon angioplasty and stents are used in case of a complication or a suboptimal result was common in the 90s and became known as balloon angioplasty with provisional stenting. The 9-year clinical course of unselected patients treated in our catheterisation laboratory according to the above principle was reported recently.¹⁴ Despite the unfavourable baseline characteristics – high percentages of multi-vessel disease (55%), patients presenting with an acute MI (20%) and diabetics (27%) – of our cohort, cumulative 9-year survival (78%) and event-free survival (55%) were good. Moreover, younger patients (age ≤ 65) without diabetes and multi-vessel disease who did not undergo PTCA for an acute MI were found to have a very high survival rate of 92% at 9 years, which was similar to the expected survival rate of the general population in Greece, matched for age and gender (93% at 9 years). Other studies were designed to compare routine stenting itself to balloon angioplasty with provisional stenting, but their results were limited to one year of follow-up.^{15,16} Briefly, in these randomised trials, where additional technology (on-line QCA, Doppler CFR) was used for defining an optimal result, there was a trend for higher TLR (e.g. 10.9% vs. 7.2% in the DEBATE-II trial¹⁶) and MACE (e.g. 15.9% vs. 13.4% in the DEBATE-II trial¹⁶) rates in the provisional arm, and it was also reported that the provisional strategy was more expensive in the end.

Drug-eluting stents

At the beginning of the 21st century PTCA has become the main method of coronary revascularisation, accounting for more than 1,500,000 procedures worldwide every year.¹⁷ Undoubtedly, coronary stents have been the most significant technical advancement and have demonstrated good results in the long term, but restenosis remains the major problem that hampers the procedure's efficacy. Localised delivery of immunosuppressive agents using drug-eluting stents emerged as an alternative in order to inhibit the pathogenic path of restenosis occurring in the early phase of 6 months after

stent implantation. The impressive results of sustained suppression of neointimal proliferation up to one-year in the first in man (FIM) sirolimus-eluting stent safety and feasibility study¹⁸ led to the conduction of randomised trials comparing sirolimus-eluting stents with bare metal stents, while randomised trials with paclitaxel-eluting stents followed soon thereafter. Nowadays, more than 1.5 million patients have been treated with drug-eluting stents worldwide.

Long-term results up to 3 years of follow-up have just become available for both of the two leading drug-eluting stents at the recent 2005 Transcatheter Cardiovascular Therapeutics (TCT) scientific meeting.^{19,20} Briefly, pooled data from the randomised trials of either sirolimus-eluting stents (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS) or paclitaxel-eluting stents (TAXUS II, IV, V, VI) demonstrated an unquestionable superiority of drug-eluting stents over their bare metal counterparts regarding angiographic in-stent restenosis at 6 to 9 months (sirolimus trials: 3.1% vs. 38.5%; paclitaxel trials: 8.4% vs. 27.5%) and TLR (sirolimus: 6.3% vs. 22.8%; paclitaxel: 9.4% vs. 19.9%) or MACE (sirolimus: 12.6% vs. 27.8%) rates at 3 years of follow-up. It is of interest that this superiority seems to extend to some high-risk patient populations as well, since a significant number of diabetics (20-25%), patients with multivessel disease (>35%) or complex (B2/C) lesions (>60%) were included in the randomisation. However, no difference was observed in survival free from cardiac death or MI, and as far as the problematic topic of stent thrombosis is concerned drug-eluting stents appeared to be associated with a higher risk for thrombosis at 3 years (a difference of 0.5% on average) but not at a significant p level.

After almost 4 years of experience with drug-eluting stents in the marketplace, their immediate and longer term results regarding the need for repeat revascularisation procedures are remarkable; thus drug-eluting stents constitute quite an improvement compared to bare metal ones. If their efficacy is also proven adequately in the field of special high-risk patient groups (e.g. very small vessels, long lesions, chronic total occlusions, bifurcations, left main disease, acute MI) for which there is not yet an approved indication, they could be fairly considered as the third revolution in interventional cardiology.

Conclusion

Percutaneous transluminal coronary angioplasty, which was introduced by the simple inflation of a balloon and

in less than 30 years has evolved to the elaborate and precise implantation of drug-eluting stents using high-quality devices, has been a boon to patients with coronary artery disease. It has offered the alternative of a low-risk intervention with good long-term outcome, which can even reach the expected long-term survival of the general population in selected cases, and has become for the majority of patients the method of choice for the management of coronary atherosclerosis.

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