

Hotline Editorials

Benestent II, a remake of Benestent I? Or a step towards the era of stentoplasty?

'If dilation with balloon angioplasty can achieve a 'stent-like' result, the benefits of a large post-procedural luminal diameter should be conferred without the need for coronary stent placement.'

J. A. Bittl^[1]

'Benestent has already demonstrated that the primary strategy of elective stenting is superior to that of elective balloon angioplasty with the option of bailout stenting'. P. W. Serruys^[2]

Star Wars II, *Alien III* and *Rocky IV* failed to arouse enthusiasm among moviegoers who had unconditionally appreciated the 'seminal' version of these famous movies. ... However, Benestent II^[3] is neither a remake nor the continuing story of Benestent I^[4].

In 1990–91, some prominent European cardiologists, solicited for their collaboration, refused to participate in Benestent I for ethical reasons; stents were potentially dangerous and expensive devices necessitating complex anticoagulation and long hospitalization. These 'refusers' did not subscribe to the motto of Andreas Gruentzig 'if in doubt, let us randomize'. In their minds, stents were undoubtedly worse than balloons.

In 1994, after the publication of Benestent I in the *New England Journal of Medicine*, it was difficult to restrain the enthusiasm of investigators who wanted to be part of the Benestent II study. In the meantime the stent has proven to be superior to the balloon. In 1998 the medical community may have been tempted to see Benestent II as just a plain and self-evident confirmation of Benestent I. Today a 'BS lesion' (Benestent–Stress^[5] type of lesion) has an almost negative connotation and refers to a simple, easy to treat lesion almost never seen in the real world of clinical practice. Beyond these psychological and rather superficial considerations, the practitioner may have overlooked a few essential facts emerging from the Benestent II trial, which will influence our future practice.

Fact number 1: *in Benestent II, we were not treating 'BS' lesions in 'BS' patients.* In Benestent II, 55% of lesions were in AHA/ACC class B2 or C; 45% of the patients were unstable and 32% were in Braunwald

class II. Thirty-eight percent of the stents used were 20 mm long and 7% were multivessel. We were thus dealing with a population with more severe lesions than in Benestent I.

Fact number 2: *coated stents are safe and efficient, but we cannot prove that they are superior to uncoated stents.* We, interventional cardiologists, rapidly tend to become blasé about new technical developments. In 1996 we could not conceal our enthusiasm for a biological coating covalently attached to a metallic stent; today, we tend to deny that the principle of coating has any value. In doing so, we overlook the fact that, among the 721 patients with stable, unstable and acute myocardial infarction who had been treated with a heparin coated stent in the Benestent II pilot^[6], Benestent II and PAMI pilot^[7] trials, there was only one occurrence of subacute thrombosis angiographically demonstrated (an incidence of 0.12%). This result compares favourably with the 0.5% of subacute thrombosis observed in the randomized cohort of patients with optimal stenting treated with aspirin and ticlopidine in the STARS trial. However, among the 312 patients who did not undergo randomization the incidence of the combined primary end-point was 3.5%^[8]. Unfortunately, we will never be able to demonstrate statistically the value of the coating. Power calculations would necessitate a mega mammoth 'GUSCO' trial ('global use of stent coating') to demonstrate the significant difference between 0.12 and 0.5%.

Fact number 3: *balloon angioplasty has improved its score and performance thanks to stenting.* 'Stent-like' angioplasty, conditional and provisional stenting are all by-products and spin-offs of stenting. 'Bailout stenting' has been the escape road for failed and suboptimal balloon angioplasty for many years. It takes care of the complications of angioplasty and at the same time selects lesions which respond appropriately to the dilating force of the balloon. This double process has made balloon angioplasty safer and more efficient.

It is not surprising that, shortly after the presentation of the Benestent II results, prominent American interventional cardiologists published an editorial

entitled: 'The balloon is back'^[9]. Although the performance of balloon angioplasty has improved with the support of bailout stenting, it is incorrect to state that the outcome of optimal stent-like balloon angioplasty supercedes the results of elective stenting. In Benestent II, the cohort of patients treated by balloon angioplasty and with a post-procedural diameter stenosis <30% had a clinical outcome still 6% inferior to the stented patients. The additional value of stenting after optimal balloon angioplasty has so far never been addressed in a randomized trial^[10,11]. The Debate II trial^[12] is the first which specifically addresses this question. Preliminary results strongly suggest that the clinical outcome of patients receiving optimal balloon angioplasty may be further improved by additional stenting. This observation seriously undermines the value of provisional stenting and leads to the provocative conclusion that we should stent all our patients provided they belong to the type of patients (and lesion) included in Benestent II and Debate II.

Fact number 4: *the oculo-stenotic reflex, a major determinant in clinical outcome and an eye opener for future trials.* In Benestent II, patients were sub-randomized and assigned either to clinical follow-up or angiographic and clinical follow-up. The clinical outcome of these two subarms was drastically different; the need for reintervention in the clinical arm was reduced by 50% when compared to the angiographic arm, indicating that visualization of a partially restenotic lesion at 6 months triggered unnecessary intervention, which was not clinically driven. Obviously, cost-effectiveness could only be properly evaluated in the cohort of patients not requiring angiographic follow-up as mandated per protocol. In future trials, if we want angiographic follow-up, we will have to take into account this major bias, by training and filtering objectively the indications for reintervention. Prospective declaration of intention to re-treat based on symptoms and signs of ischaemia, quantitative angiography on line, and functional and invasive evaluation of lesion severity, are all means to justify the need for reintervention.

Fact number 5: *Benestent tested the hypothesis that elective stenting was more clinically effective and as cost-effective as balloon angioplasty.* These two goals were achieved, which implies that in our daily practice all patients fulfilling the inclusion criteria of this trial should be stented. In the final analysis a new mode of therapy may be preferred if it fulfils the following criteria, (1) if it is as safe or safer than the currently applied treatment, (2) if it is more efficacious than current treatment, (3) if it is as cost effective or more cost effective than the old treatment. In the case of stenting, our ignorance on the long-

term follow-up (10 years and more) remains a deterrent to a strategy of elective stenting. Once implanted, the metallic cage will permanently preclude any spontaneous or therapeutically induced positive remodelling. Having acknowledged this fact, we have to emphasize that the 5 year follow-up of Benestent I seems to be reassuring (to be published). The Benestent II subgroup analysis (unstable angina, vessel size >3 mm, left anterior descending coronary artery) clearly indicated that stenting is more cost effective than balloon angioplasty and in patients presenting with all the unfavourable features combined, stenting is not only more cost-effective but even cost saving^[13,14]. Stent-like results obtained with balloon angioplasty appear to be more cost effective than a strategy of elective stenting but remain less effective (event free survival 6% less than with a strategy of elective stenting). It is still debatable whether the importance society places on the financial cost of a procedure should supercede the clinical benefit to a patient as an individual.

In conclusion, although a fast and superficial reader may have concluded that Benestent II was just a remake of Benestent I, the future will tell whether the cost-effectiveness strategy of elective stenting described in Benestent II is not simply heralding a era of generalized stentoplasty.

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European Heart Journal (1999) **20**, 781–783

The United Kingdom Prospective Diabetes Study — everything you needed to know about diabetes but were afraid to ask?

As risk factors go, diabetes mellitus ranks well below the big three — smoking, cholesterol and hypertension — in most European countries. Yet the population prevalence of around 3–5% belies its importance to cardiologists. In most hospital series, diabetic patients represent around 10–15% of those admitted with myocardial infarction, and up to 20% of those who die^[1]. And, despite the potential for major improvements in the outcome of diabetic patients with myocardial infarction (using insulin therapy, aspirin, thrombolysis, beta-blockers and ACE inhibitors^[2,3]) important questions remain around primary prevention.

Diabetes is, self-evidently, a hyperglycaemic condition. Moreover, in a number of population studies, the degree of hyperglycaemia predicts the risk of cardiovascular disease, with each 1% increase in glycated haemoglobin increasing risk by around 10%^[4]. The United Kingdom Prospective Diabetes Study (UKPDS) was designed, some 20 years ago, to answer the question as to whether improved glycaemic control reduces that risk^[5]. Furthermore, by comparing treatment with insulin, sulphonylureas, or (in overweight patients) metformin^[6], it also tackled the question of whether any particular therapy might augment, rather than diminish, cardiovascular risk. In particular, the potential effect of sulphonylureas on the cardiac K_{ATP} channel might adversely affect outcome after myocardial infarction^[7]. This has been suggested as potentially responsible for the observa-

tions of the University Group Diabetes Program, in which tolbutamide, a sulphonylurea, was suggested to increase cardiovascular mortality in type 2 diabetes^[8].

The UKPDS recruited 5102 patients with type 2 diabetes, randomizing patients either to conventional treatment — based initially on diet, with the addition of additional therapy if glycaemia substantially deteriorated — or to intensified treatment — in which oral hypoglycaemic agents or insulin were used to try to maintain fasting plasma glucose concentration under $6 \text{ mmol} \cdot \text{l}^{-1}$. Over a median follow-up period of 10 years, a mean difference in HbA_{1C} was achieved of just under 1%. This was despite the deterioration in glycaemic control with increased duration of follow-up in both groups, exemplifying how difficult it is to pull out all the glycaemic stops in an ageing population group.

As might be predicted from the results of the Diabetes Control and Complications Trial in type 1 diabetes^[9], the UKPDS showed a major impact on microvascular disease — around a 25% reduction^[5]. However, for the major large vessel end-point, acute myocardial infarction, the benefit of intensified control just failed to achieve significance — a 16% reduction with a *P* value of 0.052. With intensified treatment, there was absolutely no evidence for adverse effects on myocardial infarction risk of either insulin or sulphonylureas. In overweight patients, metformin as initial treatment produced substantially greater benefits on risk of myocardial infarction than