Intracoronary brachytherapy is the first method which has been effective in two components of restenosis, intimal hyperplasia and negative remodelling. Several randomized studies have demonstrated that brachytherapy is effective in restenosis. Its subsequent approval for clinical use has made it a routine procedure for the treatment of in-stent restenosis. In Europe, intracoronary brachytherapy is performed in more than 150 sites. It is estimated that 4000 procedures were carried out in the year 2000, which is still a conservative attitude when compared with the 350 active sites and 30 000 procedures estimated for the United States. The initial studies used γ radiation[1–3] while more recent trials[4,5] have confirmed that similar benefit can be obtained with β radiation. The advantages of β sources include rapid attenuation of radiation, minimized exposure of physicians and staff, reduced shielding requirements and the usage of more intense sources allowing shorter dwell times. Almost all the European centres use β radiation with three systems: Novoste Beta-Cath, Guidant Galileo and Radiance RDX, which received the CE mark recently. The results obtained with brachytherapy in de novo lesions are more controversial and limited information is available for the application of this system in a wide range of indications. This explains the interest in the study presented in this issue by Regar et al.[6] with the Novoste system, applied in 108 consecutive de novo and restenotic lesions.

Is the news good? Yes indeed in terms of feasibility. Even with the stiff 5 Fr delivery catheter, already replaced by a 3.6 Fr more flexible catheter, the success rate of device insertion is 100% with some additional dissections (nine lesions, 8%) and an acceptable increase in procedure duration (dwell time of only 3.3 min).

What about late outcome? As a reviewer I was shocked by the contrasting messages from the first version of this study, limited to 6 months follow-up with the recent version, with a complete 1 year follow-up. The worst prophecies, that brachytherapy delays but does not solve problems, seem to be confirmed. Myocardial infarction occurred in nine patients (9%) during the first year following the procedure. Most of the events occurred between 6 months and 1 year and, as the follow-up was stopped at 1 year, it is possible that new events will occur later. The percentage of target lesion revascularization may appear lower than expected (23%) for this complex lesion selection, but two worrisome aspects must be considered. Restenosis is reported to have occurred proximal or distal to the treated segments. This was despite the fact that this skillful group of pioneers of vascular brachytherapy made every attempt to avoid incomplete coverage of the lesion, reported only in 8% of cases, using very long sources (60 mm) or pullback of the
source. Radiation appears to stimulate hyperplasia in the segment of dose fall-off.

The second and more alarming event is the development of stent thrombosis, often occurring months after treatment, despite the use of a combination of aspirin and clopidogrel for 3–7 months after irradiation. A 5.4% incidence of late thrombotic events after the application of the Novoste Beta Cath System was recently reported in the RENO (REgistry with the NOvoste Beta-Cath System) registry in which over 1000 patients with de novo and restenotic lesions were included[7]. More recent studies with brachytherapy have not confirmed this high incidence of thrombotic complications[8]. In the most recent brachytherapy studies of in-stent restenosis a prolonged treatment of aspirin and clopidogrel was sufficient to prevent thrombosis but these trials were limited to 6 months, included ‘ideal’ lesions and candidates, and double antiplatelet therapy was continued for 6 months, with no evidence that a persistent risk is not present at a later stage.

Does it make sense to trade hyperplasia for thrombosis? A similar dilemma may be faced with local stent-based delivery of high doses of aggressive anti-proliferative drugs. The SCORE (Study to COMPARE REStenosis Rate) study[9], a randomized trial of 243 patients treated with a high dose prolonged release eluting stents with a taxol derivative impregnated in polyethylene sleeves, showed a much greater inhibition of intimal hyperplasia than brachytherapy. The trial was stopped when the group with active treatment showed a 5.5% incidence of stent thrombosis, including late occlusions after per protocol discontinuation of clopidogrel 6 months after treatment[10].

Should we avoid brachytherapy if a new stent is implanted? In general yes: in the largest randomized trial of brachytherapy for de novo lesions (β-CATH, 1600 patients) the brachytherapy group showed higher restenosis and adverse events if a stent was implanted with no significant benefit in the PTCA arm. It is then hard to support this method even for high risk population subsets. Conversely, diffuse in-stent restenosis remains a lesion with a high recurrence after conventional percutaneous revascularization, but with convincing evidence of a beneficial long-term effect of brachytherapy and a low risk of thrombosis if a prolonged combined antiplatelet treatment is performed. It is then hard to argue that brachytherapy should be offered to these patients.

Will brachytherapy finally become a standard indication for at least the most severe recurrent in-stent restenosis, a big ‘niche’ with more than 200 000 procedures expected worldwide? Short-term, possibly yes, long-term probably no. The news coming from the first trials with rapamycin and paclitaxel coated stents suggest that brachytherapy has a good chance of an early retirement[11–15]. If an alternative is a technique which is easier to handle and which solves the problem of restenosis more permanently and with fewer complications, nobody will cry too much.

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Amiodarone: pearl or peril?

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In this issue Dr Lumer and co-authors present the economic analysis from the Canadian Trial of Atrial Fibrillation (CTAF)[1]. This trial studied 403 patients with persistent or paroxysmal atrial fibrillation, demonstrating convincing evidence that amiodarone had greater efficacy than sotalol or propafenone in prevention of recurrent atrial fibrillation[2]. The 1 year maintenance of sinus rhythm was 69% in the amiodarone group compared to 39% for sotalol or propafenone. Flowing from this marked difference in efficacy, the authors found lower costs related to atrial fibrillation in the amiodarone group; $532 Canadian dollars in the amiodarone group compared to $898 in the sotalol/propafenone group. This was largely explained by a 40% reduction in cardioversions and a 56% reduction in admissions to hospital with a primary diagnosis of atrial fibrillation in the amiodarone group. It comes as little surprise that a significant reduction in atrial fibrillation results in a significant reduction in resource utilization related to atrial fibrillation care. Unfortunately, the overall cost of care was not significantly different between the two groups because of the nature of the ageing population with significant competing co-morbidities. Atrial fibrillation was responsible for only 28% of the overall cost of care in the study, making the beneficial effect of amiodarone unlikely to impact on overall cost over the time frame of the current study.

The authors are to be commended for providing prospective randomized data that give a concrete clinical and economic basis for use of amiodarone in atrial fibrillation. Other studies in the area have been hampered by relatively small numbers, or cost modelling based on retrospective data collected from multiple small case series or trials that have not provided a ‘head to head’ comparison of amiodarone to other therapies[3,4]. However, even the compelling cost and efficacy data from this trial may not affect most physicians’ decisions to defer the use of amiodarone as a first line drug in most patients with atrial fibrillation. Relatively small cost differences for a short period of follow-up are unlikely to change the culture of antiarrhythmic drug prescription for atrial fibrillation.

Both patients and physicians are wary of ongoing non-cardiac adverse effects related to amiodarone, which can be life-threatening. Open label amiodarone was discontinued in 18% of patients in CTAF, a 64% higher rate of discontinuation than the 11% seen in the sotalol/propafenone group. Although the reason for discontinuation of amiodarone was largely due to reversible or minor side effects, 3% of patients developed pulmonary or neurological findings consistent with toxicity within 1 year of initiation of therapy, which raised concern regarding irreversible organ damage. This rate of amiodarone toxicity and discontinuation is consistent with the results of previous pooled analyses of complications of low dose amiodarone[5,6]. The one exception to clinician avoidance of amiodarone as first line therapy is in patients with poor ventricular function, or those at high risk of proarrhythmia from other antiarrhythmic agents. In these patients, the potential downsides of amiodarone are outweighed by its safety and efficacy.

The second major limitation of the current study is the duration of follow-up. The relatively short 1-year follow-up period in a condition that certainly constitutes a chronic disease raises concern about the long-term confidence in the finding of cost effectiveness. On the one hand, longer follow-up may allow reduced atrial fibrillation in the amiodarone group to result in a reduction in direct costs related to atrial fibrillation, but may also indirectly lead to less progression of underlying heart disease and development of stroke, improving the overall cost benefit of amiodarone. The mortality and stroke impact of maintenance of sinus rhythm is being addressed in the Atrial