ensure that core items are also placed on controlled-trials.com where everyone can see them (box).

The foundation will review progress in six months and challenge the European Commission to follow through its repeated calls for trials to be registered. In the meantime, what should the rest of us be doing? Lobbying politicians. It worked in the United States where a sustained campaign by patient groups led to a change in the law. Patient groups should be urging European politicians to open up the planned European database or pay for another more accessible initiative. Ethics committees should apply pressure to researchers at the ethical review stage. Finally, editors of medical journals should ask authors to register their trials and commit to publishing a trial's international standard randomised controlled trial number alongside the published paper.

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Drug eluting coronary stents

May sound the death knell for restenosis

Percutaneous coronary revascularisation has revolutionised the treatment of ischaemic heart disease during the past two decades. Despite technical refinements, however, long term results after using standard techniques remain limited by the phenomenon of restenosis—a process whereby elastic recoil and neointimal hyperplasia occur at the site of endothelial injury, often resulting in recurrent symptoms within six months of the procedure. Although the use of coronary stents is associated with lower rates of restenosis than balloon angioplasty alone,[1] rates of up to 40% have been reported in some series, and treatment options are often unsatisfactory, with high recurrence rates after further intervention.[2]

Neointimal hyperplasia begins soon after coronary intervention as a result of platelet activation, inflammation, and proliferation of smooth muscle cells. Pharmacological inhibition of these processes by using drugs administered systemically has had little success in preventing restenosis. A platelet IIb/IIIa receptor antagonist, abciximab, has shown a modest benefit for patients with diabetes mellitus undergoing stent implantation,[3] but trials of other drugs have often failed spectacularly despite promising preliminary work in animal models. Intravascular radiation (brachytherapy) using sources emitting γ rays or β rays is an effective way of treating established restenosis,[4 5] although its use for the prevention of restenosis has been disappointing. Furthermore, several important safety issues are associated with brachytherapy, and owing to strict regulation the procedure is currently restricted to specialist centres.

Previous pharmacological trials focused on giving a systemic drug and may have failed in part because adequate local concentrations of the drug were not achievable without systemic toxicity. A novel solution to this problem has been the recent development of drug eluting stents, allowing controlled release of a drug directly to the injured endothelium.

In the RAVEL study (randomised study with the sirolimus coated BX velocity balloon expandable stent in the treatment of patients with de novo native coronary artery lesions)[6] the first prospective randomised trial, patients undergoing angioplasty of simple lesions received a stent that was either coated with sirolimus or made from bare metal. Sirolimus, also known as rapamycin, inhibits proliferation of smooth muscle cells by preventing progression through of the cell cycle. The trial showed not only a treatment benefit but also the complete absence of detectable restenosis in the patients receiving coated stents, compared with a rate of 28.8% in the standard stent group.

More recently, the SIRIUS study (multicentre randomised double blind study of the sirolimus coated BX velocity stent) reported preliminary results in 400 randomised patients receiving sirolimus coated stents for longer lesions, at higher risk of restenosis, and including more patients with complex stenoses, diabetes mellitus, and multivessel disease (Paris Course on Revascularisation, May 2002). Nine months' data showed an in-stent restenosis rate of 2% compared with 32.3% in the standard stent group, but a higher incidence of restenosis at the stent margins (total restenosis rate 9.2%, target vessel revascularisation rate 6.8%).

Paclitaxel coated stents, which slow microtubule degradation after cell division, have also been investigated in a parallel series of trials; the initial TAXUS-I (paclitaxel) study reported no instances of restenosis in 61 randomised patients at nine months, and the later ELUTES (European evaluation of paclitaxel eluting stent) trial reported a target lesion revascularisation rate of 5% at 12 months compared with 16% in the standard stent group.[7 8]

These impressive preliminary results have generated enormous expectations and clinical demand for drug eluting stents. All completed trials to date have, however, been small, and none have specifically

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enrolled patients at high risk, such as those with diabetes mellitus, bifurcation lesions, occlusions, calcified vessels, degenerative vein grafts, unprotected left main stem lesions, or acute myocardial infarction.

Many of these issues are being addressed in ongoing studies (for example, the DELIVER-II study—prospective non-randomised multicentre evaluation of the achieve paclitaxel eluting coronary stent system in the treatment of lesions with high risk of revascularisation due to restenosis). Long term follow up data to exclude late restenosis due to delayed neointimal proliferation are unavailable, and theoretical safety issues persist regarding the potential for late thrombosis due to delayed endothelialisation, the necessary duration of antiplatelet treatment (currently 2-6 months), and the possibility of late arterial thinning and aneurysm formation.

The issue of cost effectiveness remains difficult. A bare metal stent costs about £380 ($585; €600) in the United Kingdom, whereas the only commercially available drug eluting stent costs about £1200. Based on an average of 1.4 stents per case, the excess cost of a comprehensive drug eluting stent programme would therefore be £1150 per patient, compared with the total current procedural cost of about £5700. At the current rate of reintervention after angioplasty in the United Kingdom of 6% (British Cardiovascular Intervention Society, www.bcis.org.uk), the cost per intervention saved would be £19 000. Equivalent costs assuming clinical recurrence rates of 15% and 30%, as might be expected in more complex disease, would be £7600 and £3800, respectively.

These financial issues provide a challenge to the introduction of this new technology into the United Kingdom's health system. Many trusts have taken the view that drug eluting stent programmes should await formal review by the National Institute for Clinical Excellence (NICE) or agreed funding by primary care trusts, thereby delaying the introduction of this major breakthrough. For the time being, many centres will target use of drug eluting stents to patients at high risk of restenosis or those presenting with in-stent restenosis. Ironically, these are the very groups of patients for whom benefit is undefined by the trials to date.

Nevertheless, it is likely that the forthcoming ARTS-2 (arterial revascularisation therapies) study will show comparable or improved outcomes for patients with multivessel disease who are revascularised by using drug eluting stents rather than bypass surgery. In reality, many patients will remain unsuitable for percutaneous revascularisation because of diffuse disease or unfavourable anatomy, and predictions of the demise of coronary artery surgery are almost certainly premature. With respect to restenosis after angioplasty, however, the death knell tolls.

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