contribution of this unique investigation that benefits everyone.[16] The scientific questions addressed by RERF are not yet fully answered; civilisation will hold us accountable if we fail to complete the work that began nearly 60 years ago.

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We have no conflict of interest to declare.

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Are drug-eluting stents a panacea for patients with coronary heart disease?

In patients with atherosclerotic coronary heart disease, dilation of the narrowed coronary artery with a catheter-borne balloon followed by a metal wire-mesh tube, called a stent, to scaffold the vessel segment has been the treatment of choice for well over a decade. This mechanical remedy usually re-establishes coronary blood flow, but does so at the cost of severe vessel wall injury. As with any biological system, the vessel wall responds to injury with a wound healing process including proliferation and migration of smooth-muscle cells to form a neointimal layer covering the stent struts. However, proliferative growth of smooth-muscle cells and the secretion of extracellular matrix can cause neointimal hyperplasia extending through the stent struts into the vessel lumen to obstruct coronary blood flow again.[1] Stent restenosis—a lumen re-narrowing of at least 50%—usually occurs within 6–9 months of stent placement and can affect up to 60% of patients. It is mediated by a variety of factors, such as the calibre of the diseased coronary vessel, the location and extent of the lesion, and the presence or absence of diabetes mellitus.

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To counteract the proliferative growth of smooth-muscle cells, current research is directed at the elution of specific pharmacological agents from the stent struts into the surrounding tissue. Two such agents, known from immunosuppressive and cancer therapy, are sirolimus and paclitaxel. Both drugs interfere with the smooth-muscle cells' natural ability to replicate—sirolimus, by blocking the target-of-rapamycin enzyme to ultimately induce cell-cycle arrest in the late G_1 phase; and paclitaxel, by promoting the formation of stable yet dysfunctional cellular microtubules.

Scientific evidence on the clinical efficacy and safety of sirolimus-eluting and paclitaxel-eluting coronary stents is emerging at an astounding rate. In this issue of *The Lancet*, Mohan Babapulle and colleagues present their meta-analysis of 11 major randomised clinical trials comparing three types of drug-eluting stent with bare-metal stents. The bottom line of their study is that controlled elution of sirolimus or paclitaxel from a polymer-drug matrix bound to the stent, for about 4 weeks, results in substantial angiographic and clinical efficacy. Compared with the bare-metal stents, the incidence of restenosis within the stented vessel segment, plus the adjacent 5 mm proximal and distal vessel segments (in-lesion restenosis), was reduced across the trials by 83% with the sirolimus stent and

by 70% with the polymer-based paclitaxel stent. Although no effect of either stent on all-cause mortality and rate of periprocedural myocardial infarction was observed, both types of stent were associated with major clinical benefit in terms of a significant reduction at 6–12 months in the need for repeat target lesion revascularisations. The results were less impressive with non-polymeric paclitaxel stents, which had no significant impact on target lesion revascularisation rates. Finally, in terms of safety, Babapulle and co-workers did not find differences between any drug-eluting stent included in their analysis and the bare-metal stents in the rate of stent thrombosis and late incomplete stent apposition, which was defined as new evidence at follow-up of blood flow between the stent struts and the vessel wall on intravascular ultrasound.

In essence, by the end of 2003, polymer-based drug-eluting stents had shown a clear superiority over bare-metal stents in the treatment of patients with atherosclerotic coronary artery disease in patients presenting with symptomatic coronary artery disease. As Babapulle and colleagues point out, the patients enrolled in the studies they analysed had a low to intermediate risk of developing restenosis. Most patients had a single coronary lesion that was not overtly long (on average $<$15 mm), treated for the first time (de novo), and located in a vessel not overtly small (on average $\geqslant$2·60 mm diameter). Because the study patients do not reflect the spectrum of patients seen by a cardiologist these days, the results of the present meta-analysis cannot be extrapolated to diabetic patients in general; those with acute myocardial infarction; or multivessel disease; or chronic total occlusions; or those with lesions located in the left main coronary artery, at a coronary bifurcation, or in a saphenous vein graft; nor to patients with restenotic lesions, very long lesions, or lesions in very small coronary arteries. Preliminary data from large real-world drug-eluting stent registries, such as e-CYPHER (sirolimus) and WISDOM (polymeric paclitaxel),[2,3] show that these higher-risk patients constitute about 40% of those receiving drug-eluting stent therapy in everyday practice, despite lack of scientific evidence. However, promising results with sirolimus or polymeric paclitaxel stents in some of these patient/lesion subsets have already been reported,[4–11] and various major trials of drug-eluting stents in ever more challenging clinical scenarios are ongoing.

Still looming over the current drug-eluting stent euphoria is the spectre of late failures. These have seriously compromised the excellent initial results of endoluminal radiation therapy for in-stent restenosis.[12] What if drug-eluting stents do not actually prevent restenosis but rather only delay it? Will there be late adverse events related to the polymer, which remains on the stent long after the drug has been eluted? To date, long-term clinical follow-up has only been reported for a handful of patients: the first 30 patients receiving the sirolimus stent in Brazil[13] and for the patient cohort enrolled in the randomised RAVEL trial.[14] Survival, free of target lesion revascularisations, was 97·2% at 4 years in the Brazilian cohort, and 95·0% at 3 years (compared with 85·6% with the bare-metal stent) in the RAVEL cohort. Although these results attest to the long-term efficacy and safety of the sirolimus-eluting stent, the patients enrolled in these two studies represent a low-risk cohort. Long-term outcomes in higher-risk patient/lesion cohorts are needed before drug-eluting stents deserve the term panacea.

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We have no conflict of interest to declare.

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Computer illustration of a stent being positioned in a narrowed artery