Antioxidants and Prevention of Restenosis After Directional Coronary Atherectomy

To the Editor:

The negative results obtained with carvedilol in the European Carvedilol Atherectomy Restenosis (EUROCARE) trial led Serruys et al.\(^1\) to question the value of antioxidants for the prevention of restenosis after coronary angioplasty. An important flaw in study design, however, invalidates the conclusions reached by the authors.

The antioxidant probucol has been shown to prevent restenosis in several clinical studies, including the MultiVitamins and Probucol (MVP) trial\(^2\) and the Probucol Angioplasty Restenosis Trial (PART). Indeed, the only study in which probucol did not prevent restenosis after coronary balloon angioplasty allowed for only 24 hours of pretreatment. There is a massive release of reactive oxygen species very early after balloon injury,\(^3\) and adequate accumulation of a powerful antioxidant needs to have occurred at the time of angioplasty to control this oxidative stress. This was the basis for the pretreatment phase with probucol and for the bolus before angioplasty in MVP. In contrast, the duration of pretreatment in EUROCARE was not tailored to the pharmacokinetic profile of carvedilol. Angioplasty was performed 2 hours after the third dose of carvedilol in EURO CARE and no bolus was administered. Plasma levels of carvedilol were not at steady-state at the time of angioplasty, a critical factor that is not contested by the authors. It follows that the antioxidant protection afforded by carvedilol at tissue level was suboptimal after such a short duration of pretreatment. Animal studies have shown that carvedilol prevents neointimal formation following vascular injury after 72 hours of pretreatment. In contrast to the authors contention, however, carvedilol did not inhibit neointima formation at the site of restenosis (cross-section 1 in each animal) when given only 2 hours before angioplasty.\(^4\)

When LDLs are incubated with macrophages to assess the oxidation induced by biologically derived reactive oxygen species, the inhibitory concentrations of probucol and carvedilol are 0.8 and 3.8 \(\mu\text{mol/L}\), respectively.\(^5\) Interestingly, the inhibitory concentration is reduced to 1.8 \(\mu\text{mol/L}\) when carvedilol is added to the cell culture medium for 72 hours before the addition of LDL, which again denotes the importance of long-term exposure of cells to carvedilol. EUROCARE confirmed that the duration of pretreatment needs to be tailored to the pathophysiology and to the pharmacokinetic profile of the antioxidant agent.

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Response

Drs Tardif and Grégoire make some interesting and relevant points in their letter on the EUROCARE trial.\(^1\) However, they inappropriately focused on the antioxidant properties of carvedilol, probably because they believe probucol exerts a positive effect on restenosis after balloon angioplasty via an antioxidant effect.\(^2\) We used carvedilol for its generalized potential to inhibit restenosis (eg, a direct inhibitor of the migration of vascular myofibroblasts) and its antioxidant properties, which are equivalent to probucol, with some of its metabolites being 30 to 80 times more potent than probucol.\(^3,4\)

As discussed in the report, there are many potential explanations for the lack of clinical effect on restenosis, including too brief a pretreatment period. By prevailing European angioplasty practice, pretreatment for >1 day would jeopardize recruitment, so a compromise was reached—a minimum of 24 hours of pretreatment, with the fourth 25 mg tablet administered = 2 hours before atherectomy. This allowed for peak plasma levels at the time of atherectomy. Although steady-state plasma levels may not have been consistently reached (this requires 35 hours\(^3\)), carvedilol is known to accumulate rapidly in cell membranes.\(^5\) Because plasma levels were not measured, adequacy to exert a preventative effect on intimal hyperplasia or vessel remodeling is speculative.

If the predominant cause of treatment failure was inadequate pretreatment, a new trial would be needed after establishing an optimal pretreatment regimen (eg, bolus intravenous infusion at intervention in addition to oral pretreatment) by measuring plasma and tissue levels in a pilot study. Because carvedilol, unlike probucol, is a safe, approved, well tolerated, and widely used agent in patients with cardiovascular disease, such further evaluations might well be worthwhile.

However, pretreatment for >24 hours, at least in European centers, is logistically difficult because (1) many interventions take place directly after diagnostic angiography (ad hoc intervention), (2) many patients are transferred from a referring center to the intervention center on the day of intervention, and (3) many interventions are performed for myocardial infarction. Requiring a long pretreatment time would remove a huge number of patients who would be most likely to benefit from an effective “anti-restenosis” agent.

We do not foresee any change in this pattern of intervention, and we think the future of anti-restenosis therapy lies mainly in the realm of the “local delivery” of agents to the site of intervention, such as with coated stents (Rapamycin or Taxol coating) or catheter-based radiation, to name a few areas undergoing intensive clinical investigation.

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