How Many Grails Do We Need?

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In a classic mixed metaphor of Greek and more recent continental lore, restenosis has been called the Achilles’ heel of interventional cardiology and the solution to restenosis has been called the holy grail. Restenosis itself has been the target of a multiplicity of initiatives, starting with trials of established drugs in the early 1980s, then moving more broadly to trials of many newer and different classes of drugs, and then finally to the application of a large number of widgets and gadgets. After initial promising animal trials and often small positive pilot human clinical experiences, larger scale randomized clinical trials were mounted only to fail the test of scientific trial design, the problems seemingly unmanageable.1

The combination of drugs and devices in a single (albeit expensive) package has revolutionized the field. There are now abundant data from large scale well-designed clinical trials and even larger “real world” registries that have documented definitively that restenosis, although not completely abrogated, is dramatically improved with clinical restenosis rates in the lower to mid single digit range.2,3 This formed the basis for the exceedingly rapid implementation of a specific drug-eluting stent code in the United States. The earliest and by far most robust data set is centered around sirolimus-eluting stents, which have been documented to be very safe and extremely effective in randomized blinded multicenter trials of selected patients, as well as in broader “real world” consecutive patient series.2,4–9 More recently, paclitaxel-eluting stents have been approved,10 and they also result in similar reductions in angiographic and clinical restenosis. There are, however, significant differences between the stents in terms of specific type and mechanism of action of the drug, the specific polymer used, the stent backbone itself, and differences in the arterial response to stent implantation, including specifically the neointimal thickness identified at the time of follow-up intravascular ultrasound studies.

This forms the background against which the new entrant to the party must be evaluated. Grube et al11 report on everolimus, an active immunosuppressive and antiproliferative compound of the same macrocyclic lactone family as sirolimus. In this first in human experience, a single-blind randomized trial design was followed in 42 patients undergoing treatment of de novo coronary lesions. There is only limited information available about the amount of drug or the specific characteristics of the bioabsorbable polymer, both of which may be important. We do know that the primary end point was safety free of major adverse cardiac events, with major adverse cardiac events including cardiac death, target vessel coronary bypass graft surgery, Q-wave and non–Q-wave myocardial infarction, and target lesion revascularization within 30 days. Efficacy was assessed with a secondary end point of quantitative coronary angiography and intravascular ultrasound, as well as clinical performance at 6 months.

A variety of patients makes up the follow-up in the study by Grube et al.11 Clinical follow-up at 12 months was available in 95% of patients, whereas angiographic follow-up at 6 months was only available in 36 of 42 patients, and 12-month angiographic follow-up in 8 patients who had received the drug-eluting stent. As can be seen from that article, procedural success rates were superb and were 100% for both groups, and 30-day major adverse cardiac events were nonexistent. At 6 months, there was only 1 death, and it was noncardiac. Only 2 patients, 1 in each group, had target lesion revascularization, but the numbers are so small that they do not allow for any real statistical assessment. Only 1 patient in the entire study had in-stent restenosis, and that patient was in the control group. Another single patient in each group had in-segment restenosis. Late loss was much higher in the control group at 0.85 mm compared with 0.11 mm in the everolimus patients; the magnitude and direction of this improvement in late loss mirrors that seen with the “predicate compound”—sirolimus.

What could one say about that pilot study?11 I echo the authors’ conclusion that the everolimus-eluting stent does show promise, with marked reduction in neointimal hyperplasia, although it must be said that the bare stent used as a control did very well by itself. If the bare stent results of that study11 held up in a larger series, they would be superb, with a restenosis rate of only 9%. This point illustrates the fact that although drug-eluting stents are changing, bare metal technology is also improving.

An obvious question is whether we need another grail if we already have 2—sirolimus and paclitaxel. The answer is that we do because neither of the current approved approaches is ideal. For example, in the Multicenter, Randomized, Double Blind Study of the Sirolimus-Coated Bx Velocity Balloon Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions (SIRIUS), the frequency of target lesion revascularization in diabetics at 2 years was markedly reduced at 10.5% with sirolimus versus 28.8% in the control...
limb (P=0.002), and the number of events prevented per 1000 patients treated was 183. In the Randomized Double-Blind Trial to Assess TAXUS Paclitaxel-Eluting Coronary Stents, Slow-Release Formulation, in the Treatment of High Risk De Novo Coronary Artery Lesions (TAXUS), in diabetic patients taking oral medications at 9 months, there was a reduction in target lesion revascularization at 9 months in the drug-eluting stent group from 17.4% to 14.8% (P=0.004) and in the insulin-treated patients from 13.0% to 5.9% (P=0.32). It must be remembered that the TAXUS and SIRIUS trials were relatively restricted in terms of lesion selection criteria; in the real world of all diabetic patients, which is characterized by diffuseness and aggressiveness of disease, the event rate with drug-eluting stents will still be significantly better than with bare metal stents but may result in clinical problems. In other patient subsets with complex disease, including bifurcation, multivessel disease, and small vessels, although the patients again treated with drug-eluting stents will have improved outcome compared with bare metal stents, there is still work to be done with either stent currently available.

Concern persists over the impact of the drug or polymer used on the potential for inflammation. In addition, the potential for subacute closure, hypersensitivity, and the bare metal backbone of both approved stents needs to be improved to make the stents more deliverable and more artery friendly with easier side branch access.

Not all coatings will be singular, and not all will be pharmacological. Multiple drugs in combination, growth factors, and cell therapy will be developed, evaluated, and tested to modulate local arterial function, perhaps improve coronary collaterals, or influence remodeling; the living stent capable of acting as a living local factory is no longer hypothetical. Finally, new entrants to the field are also needed because competition is healthy for the marketplace.

Will everolimus, this newer delivery vehicle, solve all the problems? Almost certainly not. Will it be superior to what we have? We may never know because the trials with predicate devices, for example one drug-eluting stent versus a different drug-eluting stent, may very easily be non-inferior in design, the end points low in each limb, and they may have limited power.

So what could we conclude about the field of drug-eluting stents and the mixed metaphor of the Achilles’ heel and the holy grail? Alexander Pope’s statement, “Neither you nor I are perfect. We suit each other admirably” could be modified to read “None of the drug-eluting stents is ideal but they are pretty tremendous.” The future starts tomorrow and is blindingly bright.

References

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