Drug-Eluting Stents

Life Insurance With a Better Death Benefit*

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The phrase “off-label use” has been much overused, often in a negative sense. This is unfortunate. It is especially unfortunate in the case of drug-eluting stents, which are one of the greatest achievements of cardiovascular medicine. Clinical trials used for the approval of drug-eluting stents have been necessarily restricted to clearly defined subsets of a much larger population of diseased patients. Label indications, if they are strictly derived only from these clinical trials, will then inevitably be a small and imperfect reflection of a larger reality.

On the other hand, practitioners of evidence-based medicine recognize that randomized clinical trials are only a part of the “evidence base” regarding any clinical topic. As the evidence base grows, then recommendations and practices change. It was never to be expected that use of coronary stents would always conform to so-called “label indications.” Clinical medicine doesn’t work that way and never has. The important issue is whether the clinical community continuously reevaluates the disease entity with all its treatment options and outcomes. And this the cardiology community does zealously and extremely well. In this issue of the Journal, there are 2 new reports (1,2) adding to the substantial evidence base regarding the safety and efficacy of drug-eluting stents. Both reports are timely and noteworthy.

Complex coronary disease. Inasmuch as drug-eluting stents were approved based upon clinical trials involving relatively “simple” coronary lesions, anything other than a simple lesion is supposedly off-label. Unfortunately, clinicians are confronted every day with complex coronary disease, and it has been estimated that somewhat more than one-half of all stents, both bare-metal as well as drug-eluting, are implanted for coronary lesions that do not conform to the label indications for either one (3–8). The outcomes of intervention in patients with complex lesions are not as good as the outcomes in simple ones. This is no surprise.

Kelbaek et al. (9) with the SCANDSTENT (Stenting Coronary Arteries in Non-Stress/Benestent Disease) collaborative group have conducted an important randomized trial that has helped with the complex lesion issue. The original SCANDSTENT report contained angiographic results at 6 months and clinical outcomes at 7 months in 322 patients treated with either drug-eluting stents or bare-metal stents for complex lesions. The SCANDSTENT trial was similar to 3 other randomized clinical trials that focused on complex lesions (10–12). Outcomes in all 4 trials were reported at 7 to 9 months and were quite similar, consistently revealing short-term superiority for drug-eluting stents. One major difference was that, in SCANDSTENT, the 4 subsets of “complex” (off-label) lesions were clearly enumerated. In descending order of frequency these were: chronic total occlusions, bifurcation lesions, ostial lesions, and angulated lesions.

The SCANDSTENT group has published separately their analyses of both of the first 2 (the largest) of these subgroups (13,14). For both chronic occlusions and bifurcation lesions, the SCANDSTENT results have contributed important findings that are consistent with other contemporary data. For example, in the 127 patients in SCANDSTENT with chronic occlusions, the binary restenosis rates were 0% for drug-eluting stents and 38% for bare-metal stents. In the 200 patients in the PRISON (Primary Stenting of Totally Occluded Native Coronary Arteries) II randomized trial (15), the binary restenosis rates were 7% and 36%, respectively. Similar consistency was found in the results for bifurcation lesions (16,17).

The new SCANDSTENT report (1) extends the original follow-up to 3 years. Overall, the Kaplan-Meier estimates of event-free survival at 7 months in the initial report were 95.7% for drug-eluting stents and 70.1% for bare-metal stents, and these estimates declined slightly but steadily in parallel to 87.7% and 62.4%, respectively, at 3 years. The durability of the results is important and gratifying. Interestingly, the occurrence of stent thrombosis according to Academic Research Consortium definitions at 3 years in SCANDSTENT was lower in the drug-eluting stent group compared with the bare-metal stent group (3.1% vs. 4.4%), which is similar to the findings in the RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) trial at 5 years (3.3% vs 6.8%) (18), although neither difference was significant because of the small numbers of events.

Elderly patients. After its introduction in 1977, coronary balloon angioplasty was applied in all age groups. Its success in elderly patients was not as great as in younger ones (19). Procedural complication rates and in-hospital and short-
term mortality were greater in the elderly. Many studies noted that these greater complication rates and lower success rates were associated with the greater burden of diseases generally found in older people, including more multivessel coronary disease, higher incidence of previous infarctions, worse left ventricular function, more calcified lesions, and greater numbers of comorbid conditions such as renal impairment and lung disease. The elderly, then, constitute a higher risk group, which helps explain in part why elderly patients have been underrepresented in clinical trials. The perception by physicians of greater risk in the elderly also helps explain, but does not excuse, the fact that elderly patients in general do not always receive recommended therapies according to guidelines (20).

For coronary interventions, the situation began to change in the mid-1990s when bare-metal coronary stents began to have an impact in reducing acute complication rates (21). The elderly benefited from this too, but the anticoagulation regimens used with coronary stenting in that early era were associated with much greater rates of bleeding in the elderly. The development of the modern dual-antiplatelet regimens in place of warfarin, smaller catheters and sheaths, and weight-based heparin dosing finally reduced bleeding complications in elderly patients to levels at which substantial net benefits could be realized. A signal publication in this regard was from a French Registry on stenting without warfarin, which reported favorable 30-day outcomes in patients ≥75 years old (22).

By the time that drug-eluting stents were introduced in 2003, it had become established that elderly patients could benefit from coronary stenting (bare-metal), including even multivessel coronary stenting, even though their in-hospital complication rates and short- and long-term mortality rates still remained slightly greater than those found in younger patients (23–25). At about that same time, it was also discovered, somewhat surprisingly, that long-term outcomes of elderly patients with chronic angina were improved with an early invasive approach that included revascularization (26).

Once the acute complications issues were overcome, the problem with bare-metal stenting in the elderly then became the same problem as that found with stenting in younger patients: restenosis. Clark et al. (27) analyzed a random sample of Medicare patient data from 1998 (9,868 patients, 28% with acute MI, 80% received stents). From these data, they calculated that elderly patients had restenosis rates of approximately 15% after coronary intervention and that elderly patients, along with the Medicare system as a whole, stood to gain substantially by treatments that could reduce this restenosis rate. Almost simultaneously with this, the very first report appeared on the use of drug-eluting stents in octogenarians, revealing a repeat revascularization rate of 4.2% at 1 year (28).

In this issue of the Journal, Groeneveld et al. (2) report a long-term mortality benefit with drug-eluting stents compared with bare-metal stents in elderly patients. In previous reports from randomized trials, including follow-up to 4 years, the only significant difference to emerge was in repeat revascularization procedures (due to reduction in restenosis), whereas neither death nor myocardial infarctions were reduced (29,30). Nevertheless, the randomized trials included mostly the simpler, “lower-risk” coronary patients, with average ages in the 50s and 60s, for which the trials were designed to get clear answers on restenosis. When larger registries of actual clinical practice are examined, where there are substantial amounts of complex coronary disease and complex patients that are beyond the reach of randomized trials, then a mortality benefit “signal” may begin to be detected.

Tu et al. (31) in Ontario, Canada, used a propensity score-matching technique with elimination of unmatched patients, similar to that performed by Groeneveld et al. In 7,500 patients with 3 years’ follow-up, the mortality rate was significantly lower in the drug-eluting stent group compared with the bare-metal stent group (5.5% vs. 7.8%, p < 0.001). The absolute difference in mortality of 2% to 3% was similar to the difference in the elderly cohorts of Groeneveld et al. (2).

On the other hand, the authors of SCAAR (Swedish Coronary Angiography and Angioplasty Registry) (19,000 patients) (32) and the REAL (Registro Angioplastiche dell’Emilia Romagna) Multicenter Registry in Italy (10,000 patients) (33) did not find mortality differences at 3 years and 2 years, respectively, although the propensity score matching techniques were different in these last 2 studies and might have permitted poorly matched outliers to be included.

The National Heart, Lung, and Blood Institute Dynamic Registry recently reported an analysis of on-label versus off-label use of both drug-eluting as well as bare-metal stents (8). For off-label use, the unadjusted 1-year mortality was lower for drug-eluting stents compared with bare-metal stents (3.7% vs. 6.4%, p < 0.001). After multivariate risk adjustment, but without propensity score matching, the mortality difference was no longer significant (adjusted hazard ratio 0.94, 95% confidence interval 0.64 to 1.38). Even so, for most of the off-label subgroups examined (e.g., total occlusions, bifurcation lesions), the National Heart, Lung, and Blood Institute analysis indicated superiority for drug-eluting stents, based upon reductions in repeat revascularizations.

Conclusions. Drug-eluting coronary stents were introduced into clinical practice 5 years ago as a way to inhibit neointimal hyperplasia and reduce recurrences above and beyond what could be achieved with bare-metal stents. They have succeeded at this mission, both in the simple coronary lesions in which they were originally tested, as well as in the more complex lesions and more complex patients that constitute the greater bulk of clinical practice. In addition to reducing restenosis, it now seems possible that a mortality benefit is beginning to be signaled. The fact that this signal is emerging from the more complex (i.e., “off-label”) sets of coronary lesions and from elderly patients is
deliciously ironic. Whether these findings will withstand additional intense scrutiny and be confirmed with future analyses still remains to be seen. If they do stand up, then it will be a huge advance. We will still need an explanation of how the reduction in neointimal hyperplasia can translate into a reduction in fatal events, especially within the brief period of 1 year as suggested by the Groeneveld et al. analysis (2). Meanwhile, in the everyday world of clinical practice, whenever coronary stents are required for revascularization, drug-eluting stents are the superior devices, and nothing is off-label any longer.

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REFERENCES


