Drug-eluting stents

In their recent systematic review, Suzanne Ligthart and associates compared analyses of the cost-effectiveness of drug-eluting stents.[1] They found that in most studies in which an incremental cost-effectiveness ratio greater than $50 000 per quality-adjusted life-year was calculated the study authors recommended against the widespread use of drug-eluting stents. However, we believe that previously published cost analyses of drug-eluting stents, including those mentioned by Ligthart and associates, may have failed to consider the potential costs of lifetime therapy with clopidogrel.

Recent evidence suggests that cessation of clopidogrel therapy in patients with drug-eluting stents can lead to severe adverse outcomes such as in-stent thrombosis and may pose an increased mortality risk.[2] As a result, the duration of clopidogrel therapy in these patients has become controversial, leading most physicians to treat these patients indefinitely. A cost analysis of 1 year of clopidogrel therapy in the PCI-CURE and CREDO trials showed diminishing returns after 4 weeks of therapy and that an expenditure ranging from $70 000 to $350 000 was required to avoid a single myocardial infarction.[3]

Given that the only proven benefit of drug-eluting stents over conventional bare-metal stents is the reduction in target vessel restenosis,[4] we feel that the additional cost of lifetime clopidogrel therapy makes drug-eluting stents even less desirable. In a publicly funded health care system with limited resources, such as ours, interventions that provide marginal benefit at a high cost should be carefully scrutinized.

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The results of the cost-effectiveness study by Suzanne Ligthart and associates[1] bring into question the independence and validity of the science generated by health services researchers working with industry support, even in cases in which the support is unrestricted and the research is performed without any direct input from the funder. We suggest that important biases might have affected the authors' conclusions.

It is possible that the quality rating of the studies was biased by knowledge of the studies' conclusions and funding source. Indeed, it is surprising that some cost-effectiveness studies published in high-impact journals, especially the one by Cohen and colleagues,[2] were rated poorly by the reviewers. In addition, researchers may have undisclosed relationships with the government agencies that support some of their cost-effectiveness research. Interestingly, most of the highly rated cost-effectiveness analyses were requested and financed by health technology assessment agencies, whose mandate is to provide policy guidance to third-party payers. We believe such funding may influence studies' conclusions about cost-effectiveness, given that researchers are expected to provide responsible policy statements in the name of the health technology agency. Therefore, an alternative conclusion to that proposed by Ligthart and associates could be that publicly funded studies of the cost-effectiveness of drug-eluting stents are not likely to encourage widespread adoption of this technology unless it is expected to save costs. Finally, other factors such as geographic variation in the pricing of drug-eluting stents and repeat procedure costs (which are very different in the United States and Canada) or variations in the baseline risk of clinical restenosis in the population of interest may have had at least as much impact on the studies' conclusions as the source of funding.

In a 2006 industry-sponsored study[3] based on the results of the C-SIRIUS trial,[4] which was not included in the study by Ligthart and colleagues, we concluded that the cost-effectiveness of drug-eluting stents was borderline in high-risk patients. We clearly stated that drug-eluting stents would only be cost-effective in Canada in patients with a 12% or higher risk of repeat procedures. This is a clear example of responsible and unbiased conclusions reached by independent researchers who work with various sources of funding, including the medical device industry.

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Our interest in the systematic review by Suzanne Ligthart and colleagues of published studies evaluating the cost-effectiveness of drug-eluting stents[1] was not dispassionate, as we are coauthors of 4 of the 19 published studies cited. We have several concerns about the analysis in this review.

The authors stipulated that each study included in the review had to be an "original cost-effectiveness analysis" and "from an unrestricted patient population." We do not believe that any of our included studies meet these criteria. References 17 and 19 are review articles that briefly describe the results of models that were presented at scientific symposia. Neither of these papers was intended to fully convey the underlying methods or assumptions of the models. In fact, these 2 papers describe virtually the same cost-effectiveness analysis. References 20 and 29 describe prospectively conducted empirical cost-effectiveness analyses that were performed alongside the SIRIUS and TAXUS-IV trials, respectively. As noted in the published articles, each of these studies' conclusions apply only to the highly selected types of patients in the trials. It is well-recognized that only approximately 40% of current recipients of drug-eluting stents (and a smaller proportion of all patients with stents) meet the inclusion criteria for the SIRIUS and TAXUS-IV trials, and thus we do not believe that our conclusions constitute a recommendation for widespread use of drug-eluting stents.

Second, we are concerned about potential errors in determining the funding sources for the cost-effectiveness studies. In the case of our own studies, Ligthart and colleagues categorized reference 17 as being unfunded (the journal in which the paper was published did not request information on conflicts of interest) and they categorized reference 19 as being funded by industry (because 1 of the authors reported having received grant support from several manufacturers of drug-eluting stents). Reference 19 was directly solicited by the journal's editors and the cost-effectiveness analysis it describes was entirely unfunded. Ligthart and colleagues state that "studies were considered to be sponsored if the original publications indicated that funding was provided directly by the manufacturer of a drug-eluting stent." Neither study meets this criterion. Had we been approached by the authors to clarify the funding sources for our studies, we would have been happy to provide the relevant details. Whether there were similar errors in categorizing other publications cited in the systemic review is unknown.

Third, we are concerned about the main outcome variable of the study: whether the conclusion of the study favoured widespread use of drug-eluting stents. The term "widespread" means different things to different people. Although Ligthart and colleagues were apparently able to reach consensus on this point, it is almost impossible to interpret the results of a study when the primary outcome measure is subjective and not well-defined. Given these 3 concerns and the small number of studies included in their sample, we suggest that the findings of Ligthart and colleagues may have several alternative interpretations beyond the ones they proposed.

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[One of the authors responds:]

We appreciate the interest in our recent article.[1] We echo the concern of Liana Falcone and Navdeep Tangri that the cost-effectiveness of drug-eluting stents should be scrutinized; our desire to understand the variability in research conclusions prompted our study.

We thank Stéphane Rinfret and Erick Schampaert for their observation that publicly funded studies were of higher quality, but we find it difficult to reconcile this statement with their specious suggestion of a bias pertaining to authors' undisclosed relationships with government agencies as this completely lacks face validity. We can only speculate how they were able to identify such funding. We identified their study in our literature search but excluded it as it involved only a subgroup of patients with drug-eluting stents whereas our outcome was the recommendation (or not) of widespread use. Their assertions that the authors of publicly funded studies are unlikely to encourage widespread adoption of an intervention unless it is expected to save costs and allow responsible policy statements to be produced reflect a misunderstanding of the role of these agencies. Very few medical advances save costs; the metric for this form of health services research is not cost savings but value for investment. Moreover, such research seeks to inform policy-making, not usurp its role in decision-making.

Rinfret and Schampaert also worry that our quality rating was biased by knowledge of the studies' conclusions and source of funding. Our quality rating was based on the clear, unambiguous and objective criteria found in the appendices of our article. The 4 evaluators of the conclusions and 1 of the 2 quality evaluators were blinded to the source of funding, and there were few discrepancies among the evaluators. We invite others, including Rinfret and Schampaert, to validate our findings.

In addition, they state that as a consequence of our publication "the independence and validity" of the work of researchers with industry support is compromised, "even in cases in which the support is unrestricted and the research is performed without any direct input from the funder." We had no way