QRS duration alone to select patients for cardiac resynchronization therapy: flying in the face of the evidence? reply

I thank Hawkins et al. for their interest in my editorial on the question of detecting dysynchrony and its relation to outcome after biventricular pacing or cardiac resynchronization therapy (CRT). Their response is not responsive because my comments on their previous paper were provocative, as much as theirs were in the first place.2 I assume that they would agree to the proposition that not all patients improve with biventricular pacing (perhaps at least 30–40% in most large clinical trials) and indeed some may deteriorate.3,4 Therefore, by definition, selection for CRT is not good using the current ECG-based criteria. Hence, there are unnecessary costs, waste of valuable resources, and risks for patients; there must be a better way. Furthermore, devices are not the same as pills, and should not be treated as such, as they suggest.2 Biventricular pacing is associated with significant risks that are mainly up-front at the time of implantation as are the costs, unlike medical therapy that can be stopped at any time removing any further risks and saving money. Thus, for a device therapy identifying patients who will not respond is vitally important. Dismissing all echocardiographic techniques that appear to do this because they were not part of the inclusion criteria in the major clinical trials is pedantic.

Many studies have shown that the degree of mechanical dyssynchrony by Doppler-echocardiography is related to the success of CRT whether that is assessed by symptoms or the degree of reverse remodelling.4 Remodelling is a major process in heart failure and all treatments that have been shown to reduce mortality and improve quality of life prevent or reduce remodelling.5 And, after CRT, Yu et al.6 have shown that reverse remodelling (a reduction of end-systolic volume of 10%) predicts long-term survival. It is true that a number of indices of dyssynchrony have been proposed but in a thorough analysis of regional functional indices. Yu et al. have shown that those based on a 12-segment model appear to be most reliable.7 Using a global functional measurement, Duncan et al. were able to gain good separation of responders from non-responders defined by clinical criteria (not volumes alone). As suggested in my editorial, a combination of both regional and global indices would probably be the best.1 Obviously, these new methods for selection need to be tested in larger trials, which was also stated in the editorial. In particular, we need to know if CRT can produce benefit in those who do not have mechanical dyssynchrony despite a widened QRS (which occurs in 30%),8 or in those with a normal QRS duration and dysynchrony who have been excluded from previous trials. After all, the QRS duration criteria are just a historical accident because it was the only available measure of abnormal activation at the time. Finally, no one is against guidelines but they are not just guidelines; they are not immutable. They can change quickly with new information and progress is often made when guidelines are challenged. The history of medicine is littered with examples of erroneous guidelines.

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Lack of efficacy and cost-effectiveness of drug-eluting stents

The findings of the meta-analysis about the comparative efficacy of drug-eluting stents (DESs) compared with bare-metal stents (BMSs) by Nordmann et al.1 both re-affirm and enhance those observed in previous research. Katritsis et al.2 have also demonstrated the lack of any efficacy superiority of DES over BMS, during the relatively short-term follow-up of between six and 12 months from intervention.4

Unsurprisingly for a health intervention with questionable clinical efficacy, the cost-effectiveness ratios of the current practice of nearly routine use of DES represent poor use of available resources. A study using high-quality ‘real-world’ registry data has indicated that at current pricing levels, DESs are likely to be cost-effective for a much smaller minority of patients than originally thought (probably <5%).5 Someone would have expected that DES manufacturers may have changed their pricing policies in response to this health economics evidence, but there is little evidence or information about any such change.

Unlike the opinion expressed by Nordmann et al., their findings do not question DES’s safety—the issue is one of lack of efficacy. The hypothesis that DES may, during a short follow-up period of up to 5 years, produce the necessary genomic changes required for the development of cancer is biologically
highly implausible. Cancer-related deaths observed in their study are much more likely to represent small numbers chance effects. The lack of any DES efficacy superiority persists, even when non-cardiac deaths are excluded. Patients need, and deserve, reassurance that although the evidence questions whether DES work any better than BMSs, they are actually safe. Moreover, the findings do not question the superiority of angioplasty with stenting (of whatever type) compared with angioplasty alone. Policy-makers should also not lose sight of the fact that primary coronary intervention may, by an overall small degree, be more cost-effective compared with coronary artery bypass grafting.

Some authorities as well as members of the interventional cardiology community appear to be in a state of denial about the increasing body of evidence questioning both DES’s effectiveness and cost-effectiveness. This is disappointing in the era of evidence-based medicine. Moreover, the British Cardiovascular Intervention Society Council recommends Clopidogrel usage, in combination with aspirin, for up to 12 months after DES placement. This consensus-based recommendation has a poor evidence basis, and the only current certainty about its impact is that it may produce a small but appreciable excess number of otherwise avoidable haemorrhagic events and an even worse cost-effectiveness ratio for DES usage.

References


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Lack of efficacy and cost-effectiveness of drug-eluting stents: reply

We agree with Lyratzopoulos that drug-eluting stents (DES) lack any survival benefit compared with bare-metal stents (BMSs) for patients with chronic coronary heart disease. In addition, we believe that the higher rate of intra-stent restonias associated with DES during longer periods of follow-up is a matter of concern and indicates a safety issue of currently used DES.

In our meta-analysis, odds ratios after 2 and 3 years indicated a significant increase in non-cardiac mortality associated with sirolimus-eluting stents (SES). Although we still lack cause-specific mortality data of patients treated with BMSs at these time points (because the manufacturer felt unable to release this information), we agree that it is highly unlikely and biologically implausible that DES may induce cancer. Thus, the observed increase in non-cardiac mortality may reflect a chance finding. Nevertheless, the results of our meta-analysis stress the importance of obtaining 5-year long-term follow-up of all patients enrolled in DES trials to clarify the benefit of DES based on hard endpoints. An individual patient data meta-analysis is needed to identify patient subgroups that may eventually profit from the current generation of DES. In our view, only full transparency and data analysis independent of any potential conflict of interest will definitely demonstrate whether SES can be considered to be safe.

References


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