Effectiveness of drug-eluting balloons: Quantifying the information size from clinical trials

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Numerous clinical studies have investigated the effectiveness of drug eluting balloons (DEBs) in de novo coronary lesions, in-stent restenosis, and peripheral artery disease, and each of these uses of DEBs has been assessed by a "traditional" meta-analysis [1–3]. According to these meta-analyses, DEBs are not superior to standard therapies in treating de novo coronary lesions [1], but on the other hand are superior to standard balloon intervention in patients with in-stent restenosis [2] and also in patients with peripheral artery disease [3].

Only in recent times the issue of quantifying the information size in meta-analytic studies has been investigated [4–9]. In this area, trial sequential analysis (TSA) has emerged as a specific statistical tool; in fact, interpretation of meta-analyses can be improved by TSA because TSA classifies the meta-analysed results into one of four mutually exclusive categories: a) superiority; b) inferiority; c) futility; and d) inconclusive. Interestingly enough, inconclusive meta-analyses have proven to be much more frequent than is generally thought [7,8].

In an attempt to clarify the uncertainty surrounding the effectiveness of DEBs in these three disease conditions, we undertook three separate TSA aimed at re-examining the same clinical trials included in the aforementioned meta-analyses [1–3]. The reference treatment was represented by drug-eluting stent (DES) for de novo coronary lesions (Analysis A, 6 trials [1]) and by standard balloon interventions for both in-stent restenosis (Analysis B, 5 trials [2]) and peripheral artery disease (Analysis C, 6 trials [3], 4 of which reported the appropriate outcome information).

The event rates (ERs) were based on a composite end-point represented by major adverse cardiac events (MACE) in the case of de novo coronary lesions and of in-stent restenosis and by major adverse events in the case of peripheral artery disease. The main assumptions of our analysis included two-sided testing, risk of type 1 error = 5%, and power = 80%. In Analyses A, B, and C, the ER in the control group was assumed to be 13.6%, 40.5%, and 36.5%, respectively; these three control ERs were drawn from the overall arithmetic rates in the control groups of the respective clinical trials. The intervention effect was set at an anticipated relative risk reduction (RRR) of 30%. As usual, the main result of TSA was expressed through the graph of cumulative z-curve. With reference to this graph, the boundaries for concluding superiority or inferiority or futility were calculated according to the O’Brien-Fleming alpha-spending function. Our analysis employed a specific statistical software (TSA Viewer, User Manual, Copenhagen Trial Unit 2011).

Fig. 1 shows the results of our three analyses. It should be recalled that the assumption of an anticipated RRR of −30% was a common parameter for the three analyses, and so the different interpretations that TSA suggests for individual analyses must always be referred to this assumption.
In Analysis A, the results were inconclusive: in fact, while a total of 3638 enrolled patients would be needed to draw a conclusion, only 636 were actually enrolled in the 6 trials. On the basis of these 6 trials, the z-curve remained far from the boundary of superiority or inferiority; the futility boundaries were not reported in this analysis because, according to the statistical algorithm, the information available for this purpose was insufficient.

In Analysis B, superiority of DEBs vs standard balloons was clearly achieved. Although the optimal information size would be 1044 patients, the results from the 5 trials available were sufficient to draw the aforesaid conclusion.

Also in Analysis C, the results were conclusive; the optimal information size was estimated at 561 enrolled patients, but the 4 trials available (totaling 324 patients) permitted to demonstrate superiority (as indicated by the z-curve that, after 4 trials, reached the area of superiority).

In conclusion, numerous clinical studies have been completed to evaluate the effectiveness of DEBs. As expected, the robustness of the therapeutic evidence of DEBs varies across the different therapeutic uses of these devices. On the one hand, the superiority of DEBs vs standard balloon is by now proven for both in-sentient restenosis and peripheral artery disease; on the other hand, the role of these devices in de novo coronary lesions is still far from a sufficient information size.

References


Letters to the Editor

Magnesium, sex and cardiovascular mortality

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Magnesium has a number of significant effects on the cardiovascular system. A recent meta-analysis [1] showed an inverse association between magnesium intake and cardiovascular mortality. Another important finding was that the effect was confined to women. The authors speculated about favorable effects of magnesium on blood pressure, endothelial function, inflammation, and platelet aggregation. However, we would like to remind of two additional protective cardiovascular mechanisms, each potentially helpful for explaining the two most important findings of the study [1]. First, there is a possibility of beneficial magnesium effect on serum lipid profile. Itoh et al. [2] performed a double blind placebo controlled study which compared oral magnesium supplementation with placebo. A significant decrease in the serum LDL cholesterol was found in the magnesium group, whereas there was no notable difference in the serum HDL cholesterol levels [2].

Two additional studies [3,4] have also shown a decrease in serum LDL levels with peroral magnesium therapy. Although none of these studies have suggested possible mechanisms for such effects, a correlation between magnesium and serum lipid metabolism seems worthy of future research.

The second group of mechanisms may regard to the fact that women more often have longer QTc interval [5,6]. Prolonged QTc interval is associated with an increased risk of life threatening cardiac arrhythmias such as polymorphic ventricular tachycardia [7] and may be involved in approximately two thirds of sudden cardiac death cases [8]. It has been suggested that magnesium has a protective effect against malignant cardiac arrhythmias. Intravenous magnesium has been used for treatment and prevention of ventricular tachyarrhythmias such as ventricular tachycardia [9,10], ventricular fibrillation [11] and especially polymorphic ventricular tachycardia [7,12]. In addition, a similar benefit has been shown for supraventricular arrhythmias such as atrial fibrillation [13,14], multifocal atrial tachycardia [15] and paroxysmal supraventricular tachycardia [16,17]. These arrhythmias are not malignant in nature but may initiate a pathophysiological cascade which occasionally may have a fatal outcome. Electrophysiological effects of intravenously applied magnesium have been mainly associated with the heart conduction system and ectopy suppression. The most important suggested effects include calcium antagonism at the L- and T-type calcium channels [18], membrane

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