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EDITORIAL

Drug-eluting stents with biodegradable polymers: are enough data in for a final assessment?

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This editorial refers to 'Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis'†, by S.-H. Kang *et al.*, on page 1147

Polymers of drug-eluting coronary stents (DES) provide a stable matrix for drugs to be diffused into the damaged vessel wall and modulate drug release. They lose their function after all drug is released; however, by disintegration, all durable polymers carry the risk for local inflammation, neoatherosclerosis, and thrombosis. Although polymers are not the only reason for this pathophysiological cascade leading to late stent thrombosis (ST) with related cardiac death and myocardial infarction, it was obvious that new biocompatible or totally bioabsorbable polymers should be developed. The goals of such DES with biodegradable polymers (BP-DES) were therefore to reduce the risk of late or very late ST with no increased rate of target vessel revascularization compared with first-generation DES, thereby limiting the duration of dual antiplatelet therapy (DAPT) needed. In other words, BP-DES should be as effective as durable polymer DES (DP-DES) and, beyond 1 year after implantation, as safe as bare-metal stents (BMS).

Accordingly, BP-DES have been tested in several studies, showing non-inferiority compared with first-generation DES regarding efficacy and safety up to 9–12 months.[1,2] The first meta-analyses also including initial comparisons with second-generation DES confirmed these findings but pointed—perhaps surprisingly—to a higher rate of ST for BP-DES within the first year after implantation.[3] Results on very late ST, i.e. beyond 1 year, remained limited, but follow-up studies of patients enrolled in the pivotal trials were presented with conflicting results. One major problem of all these trials directly comparing BP-DES with other DP-DES is the low rate of ST events, particularly beyond 1 year, providing uncertain results with wide confidence intervals. Thus, a new meta-analysis should define the safety of currently available BP-DES relative to all other stents regarding ST.

With the specific aims to determine whether DES in fact generally differ in the risk of ST compared with BMS, whether the risk of ST beyond 1 year differs with different DP-DES, and how safe and effective BP-DES are compared with DP-DES and BMS, a multiple treatment network meta-analysis using a Bayasian framework is now presented by Kang *et al.*[4] Based on an electronic search, 113 trials with >90 000 patients treated with BMS, DP-DES, and BP-DES were analysed for definite or probable ST within 1 year. The results showed that all DES tested except for paclitaxel- and zotarolimus-eluting DP-DES proved to be superior to BMS with regard to definite or probable ST within 1 year. In individual comparisons, cobalt–chromium everolimus-eluting stents (CC-EES) were the safest stents regardless of timing of ST compared with BMS and all other DES including BP-DES. BP-DES also showed lower rates of ST compared with BMS, but not compared with CC-EES, mainly due to an increased risk of early ST. In addition, all DES reduced the need for repeat revascularization compared with BMS and all showed comparable clinical performance. Further results suggested that not only the biodegradability of the polymer but also the optimal combination of stent alloy, design, strut thickness, and drug, all combined, determine the safety of DES.

Kang *et al.* claim that their study is the most updated and comprehensive network meta-analysis comparing contemporary stents including BP-DES, with a greater statistical power compared with a meta-analysis with a similar design just published by Palmerini *et al.*[5] Still, it may be instructive to compare these two similar studies regarding the primary endpoint of the Kang study, i.e. ST (see *Figure 1*). If we concentrate on findings of BP-DES compared with CC-EES (as the 'gold standard' of all second-generation DP-DES[6]), then both analyses found that 'definite' ST within the first year occurred significantly more frequently with the newer BP-DES than with CC-EES. This was also true for the more comprehensive definition of 'definite or probable' ST based on the findings of Kang *et al.*[4] but no longer according to Palmerini *et al.*[5] Interestingly, such a difference between 'definite' and 'definite or probable' ST was also found beyond 1 year in both analyses: CC-EES were superior to BP-DES beyond 1 year for 'definite' but not for 'definite or probable' ST. However, both groups of investigators stressed the limited comparative long-term data with BP-DES. In fact, no study with BP-DES so

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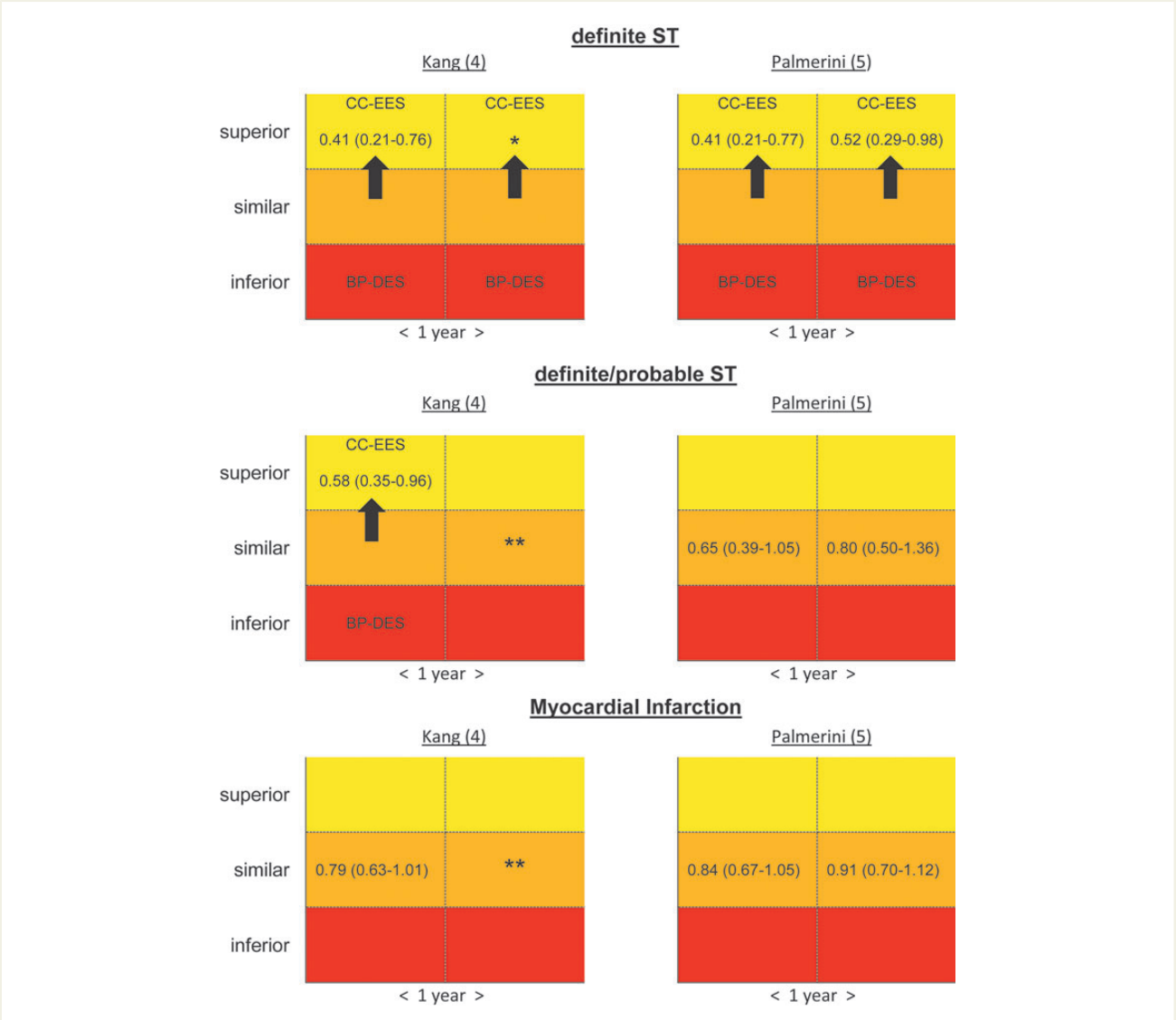

Figure 1 Comparison (odds ratios and 95% confidence intervals) of cobalt–chromium everolimus-eluting stents (CC-EES) vs. biodegradable polymer drug-eluting stents (BP-DES) for definite stent thrombosis (ST), definite or probable ST and myocardial infarction within and beyond the first year in the two meta-analyses by Kang *et al.*[4] and Palmerini *et al.*[5] Note that there were no differences in death or cardiac death between the two stents at any time in both studies. Arrows indicate 'in favour of the stent' they are pointing to; asterisks indicate that findings (* = difference; ** = no difference) were described without corresponding odds ratios presented.

far published had a primary endpoint at 2 years or later. Accordingly, no significant differences between these two stents were found for very late ST assessed by landmark analyses. Also, no direct comparisons of BP-DES with BMS, presumed to be the 'standard' for low very late ST risk, have been reported. The differences between these two meta-analyses seem small, but are relevant and may be due to methodological differences, to differences in definitions, or to limitations of the meta-analyses themselves: these meta-analyses assume that patients included in the different studies could have come from one single study which was obviously not true even if in sensitivity analyses data of specific subgroups were excluded. In addition, meta-analyses assume that similar comparisons in different trials have a consistent risk–benefit ratio which may not be true either: just think of the different DAPT regimes used in the various trials, treatments to reduce ST, the primary outcome of interest, or the known influence of mandatory follow-up angiographies on event rates in some pivotal studies. Thus, meta-analyses remain important to put low rate events into a broader perspective but they have to be interpreted with caution due to inherent limitations. In addition, one may question the clinical relevance of differences which become significant with >90 000 patients only.

Therefore, one has to look at individual stent comparisons again. For events occurring beyond 1 year, the LEADERS investigators carefully followed their patients up to 5 years and, in fact, found lower rates of very late 'definite' ST of BP-DES compared with the first-generation sirolimus-eluting DP-DES.[7] These findings were confirmed recently when results were combined with 4-year follow-up results of two ISAR studies.[8] However, these analyses compared

BP-DES with the first-generation sirolimus-DP-DES—which itself has been shown to be associated with increased ST rates beyond 1 year—and not with the 'gold-standard' CC-EES. In fact, only one study directly compared the DP-DES CC-EES with BP-EES, limited to patients with acute myocardial infarction and a 1-year follow-up;[9] with further follow-ups pending. In addition, it should be noted that follow-up studies are secondary goals of randomized trials only, unblinded, with information gathered by telephone contact or questionnaires rather than by rigid prospective examinations. To make very late assessments even less asserting, two recent studies demonstrated that progression of coronary disease becomes as relevant as late stent-related problems 3–5 years after stent implantation[10,11] when these late follow-ups are performed.

Additional problems with follow-up studies focusing on ST may lie in the difficulty in detecting 'true' 'definite', 'probable', or even 'possible' ST. Only carefully performed prospective evaluations including autopsies in all patients who die and acute angiographies in all infarction patients could ensure that 'true' ST events are not missed. Only on the basis of such meticulous late investigations was it possible to describe the patho-anatomy of very late ST. Note that a cancer death may also be due to coronary ST in view of the prothrombotic state associated with certain cancers. Thus, >50% of 'possible' ST were most likely to be due to true ST based on a detailed retrospective analysis.[12] Note also that risk differences in ST among different DES are associated with different rates of death and myocardial infarction. Therefore, it is important to report ST not just alone but also in the context of these events which are most important to patients. In fact, it is of interest that both meta-analyses found no significant differences in death or myocardial infarction between BP-DES and CC-EES, an unexplained but clinically important discrepancy compared with single ST results!

Thus, the findings of Kang *et al.* put the current trial results of BP-DES in perspective with the available data of DP-DES and BMS with regard to ST. The results also show that more long-term data comparing BP-DES with DP-DES, particularly CC-EES, are needed, as well as very late comparisons with BMS, the 'standard' for low rates of very late ST. If polymer degradation was found to be the reason for the increased 1-year ST rates of BP-DES noted, then this could become a 'killer' argument for current BP-DES. The effect of different DAPT regimes on these outcomes and the effect of stent outcomes on the need for prolonged DAPT will have to be defined. Other aspects as highlighted by Kang *et al.*, such as stent design and drug load, will also be important. Corresponding studies with newer BP-DES are running or planned, such as with the ORSIRO™ stent (Biotronik, Germany), the SYNERGY™ stent (Boston Scientific, USA), and others[13–15] as presented at the Transcatheter Cardiovascular Therapeutics Meetings in 2013. However, this situation will continue—calling for the patience of researchers, physicians, patients, and industry—until a more final assessment of BP-DES is possible! Follow-ups of at least 2 years and a large number of patients or multiple studies are needed to ascertain whether BP-DES really improve late outcomes by enhancing healing and getting rid of thrombogenic polymer materials such that DAPT duration may be shortened.

Conflict of interest: none declared.

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