Randomised trials comparing drug-eluting (DES) to bare-metal stents (BMS) have unequivocally demonstrated a reduced incidence of restenosis and need for revascularisation with various types of DES. However, most of those trials were not sufficiently powered to address whether DES have any effect on hard clinical endpoints, such as mortality and acute myocardial infarction, or whether they have a higher or lower propensity to thrombosis compared with conventional BMS. These issues are of high clinical importance, particularly since there have been concerns about delayed healing and polymer-related hypersensitivity reactions, with consequent risks of delayed, potentially fatal thrombosis. Given the low incidence of these important clinical events, large sample sizes are certainly required to rule out differences between drug-eluting and conventional stenting and the tool of meta-analysis has been employed to address this important issue.

In 2004, the initial two meta-analyses of DES appeared. Both studies considered various types of DES (such as sirolimus, paclitaxel, everolimus, actinomycin and 7-hexanolytaxol) and found no differences in mortality and overall myocardial infarction rate between DES and BMS. Stent thrombosis, in particular, was examined by Babapulle et al, but no significant difference was detected between the two types of stents. At the same time we published our meta-analysis on the same issue, but considering only sirolimus- (SES) and paclitaxel-eluting stents (PES). This review of 10 randomised trials with 5,066 patients also confirmed that DES with paclitaxel or sirolimus are largely equivalent to BMS in terms of survival or the overall rate of myocardial infarction. However, despite this general picture of equivalence, we found some hints that these new stents may be associated with an increase in the risk of Q-wave myocardial infarction. There was a modest increase in the risk of Q-wave myocardial infarction with DES (0.36%, 95% CI: -0.04% to 0.77%, p=0.080). The trend for increased risk of Q-wave myocardial infarction was seen for both paclitaxel and sirolimus stents (risk differences 0.28% and 0.58%, respectively). DES also had a non-significant trend for higher risk of thrombosis (0.29%, 95% CI: -0.08% to 0.66%, p=0.13). This difference did not reach full statistical significance and it may well have been due to chance. However, the trend for increased myocardial infarction requires attention. If true, the observed hazard might correspond to almost a doubling of the risk of Q-wave myocardial infarction in these study populations. In absolute terms, the observed excess risk translates to one additional Q-wave myocardial infarction over 6-12 months of follow-up among 280
patients given a DES. Two recent meta-analyses have also focused on the issue of DES thrombosis. Both studies reached the conclusion that DES do not increase the risk of stent thrombosis compared to BMS, at least under appropriate anti-platelet therapy.

At the recent 2006 ESC meeting, two novel meta-analyses of first generation DES drew considerable attention among attendees. Camenzind et al evaluated all available data from company-supported randomised trials, including a total of 878 SES patients who were compared to 870 BMS controls and 1,685 PES patients compared to 1,675 BMS controls. The focus was on rates of death or Q-wave myocardial infarction, as these were thought to reflect the incidence of stent thrombosis best. Based on the latest available follow-up (up to 4 years), the incidence of death or myocardial infarction was 6.3% for the sirolimus stent and 3.9% for the control BMS stent (p=0.03). For the paclitaxel stent, rates were 2.6% compared to 2.3% for the BMS stent (p=0.68). Thus, death or Q-wave myocardial infarction was 61% higher with sirolimus-eluting stents and 13% higher with paclitaxel-eluting stents, compared to BMS. In the second study, Nordmann et al undertook a meta-analysis of all randomised, controlled, first-generation DES trials comparing cardiac and non-cardiac deaths in DES versus BMS. At four years follow-up, there was a trend towards increased total mortality in DES patients. At two and three years, non-cardiac mortality was significantly higher in patients treated with sirolimus stents compared to patients treated with BMS. Of the 36 non-cardiac deaths identified, 15 were due to cancer, including lymphoma and cancers of the lung, prostate, pancreas, gastrointestinal tract, kidney and rectum. This evidence is too weak to prove a causal relationship beyond a statistical association. However, it was speculated that the increase in cancer might be due to a rapid impairment of the immune system.

So what are we left with after all this? Are DES thrombogenic? First, it should be remembered that coronary intervention, regardless of the means employed, has been associated with an increased risk of iatrogenic myocardial infarction. Second, all stents are thrombogenic, at least for a given period of time. Previous studies on BMS have reported a 0.4 to 2.3% incidence of stent thrombosis; high-pressure deployments and dual antiplatelet therapy have been advocated to minimise this complication. Sirolimus and paclitaxel effectively reduce restenosis by inhibiting neointimal hyperplasia, but they also delay the healing process far beyond the 3- to 6-month period usually required with bare metal stents. Data from Virmani’s laboratory have shown that even beyond 40 months post-implantation, DES are not fully endothelialised, whereas BMS are completely covered by 6 to 7 months. SES produced more inflammation, consisting of eosinophils and giant cells, compared to PES (about a 10-fold difference), whereas PES had more fibrin deposits around them. Impaired intimal healing is a recognised cause of late stent thrombosis in humans. Furthermore, the role of polymer coatings used in commercially available DES has not been completely clarified. Polymers are long-chain molecules that serve as medication reservoirs and facilitate prolonged drug delivery. Prior animal studies have indicated that polymer toxicity may result in marked intimal inflammation and these observations have also recently been substantiated in humans. Chronic inflammation and hypersensitivity reactions to polymer coatings have been demonstrated in patients both with sirolimus and paclitaxel-eluting stents. In a recent angioscopy study, the frequency of persistence of thrombus was 86% in SES as opposed to 29% of BMS (p=0.031), six months after stent implantation. In the sirolimus-eluting group, six of seven thrombi found at baseline remained at the 6-month follow-up, and one thrombus was newly recognised at follow-up. In the BMS group, two of seven thrombi found at baseline remained at the 6-month follow-up, and there was no thrombus formation during the 6-month follow-up period.

DES thrombosis can result from various factors. In large observational studies of 2,000-3,000 patients who underwent DES implantation, premature cessation of antiplatelet therapy, renal failure, bifurcation lesions (treated with one or two stents), diabetes, low ejection fraction and stent length were significant predictors of stent thrombosis. Early discontinuation of antiplatelet medication is the strongest predictor of stent thrombosis in the setting of drug-eluting stenting. Following premature cessation of antiplatelet therapy the incidence of DES thrombosis rises to 7.8%. Results from the Late Clinical Events Related to Late Stent Thrombosis After Stopping Clopidogrel (BASKET LATE) trial have shown a significantly greater incidence of cardiac death or myocardial infarction in DES patients (n=499) compared to BMS patients (n=244) following discontinuation of clopidogrel. Although the difference did not reach statistical significance, late stent thrombosis occurred twice as frequently among the DES as among
BMS patients (2.6% vs. 1.3%, p=0.23). Median time to a late thrombotic event was 116 days after clopidogrel discontinuation, but events occurred throughout the 12-month follow-up. Stent length and bifurcation stenting are other important iatrogenic causes of stent thrombosis. It has been estimated that for each 1 mm increase in stent length, there is a 1.03 times greater risk of thrombosis. Resistance to antiplatelet therapy, aspirin or clopidogrel, has also been described and may play a significant role.

Clinical implications

Is the accumulated information enough to condemn DES?

The answer is that existing evidence is too weak for definitive conclusions. Meta-analyses on DES suffer inherent limitations due to heterogeneity in drug dosages, formulations and mode of liberation (most prominently in the paclitaxel trials referred to here), and variable time of antiplatelet medication administration. Both meta-analyses presented in Barcelona this year were based on trials not adequately powered to address long-term clinical end-points such as myocardial infarction or death. They based their conclusions on data gathered from trials with different protocols, various periods of antiplatelet medication, and different definitions of stent thrombosis. Indeed, no universal definition for stent thrombosis exists. Reported trials have used myocardial infarction and cardiac death as surrogate markers but these may not necessarily denote underlying angiographically proven stent thrombosis. However, the thrombosis issue has certainly emerged and further data are needed before definitive conclusions can be reached regarding the long-term safety of these useful devices.

Are sirolimus-eluting stents less safe than paclitaxel-eluting stents?

Although Camenzind’s analysis suggested a significantly higher rate of the composite end-point of death and myocardial infarction only in SES, as opposed to PES, compared to conventional stents, randomised comparisons between sirolimus- and paclitaxel-eluting stents have produced different results. In the TAXi, SIRTAX, ISAR-DESIRE, and BASKET trials no difference was detected between the two types of stents as far as thrombosis or myocardial infarction was concerned, whereas in the REALITY trial there was a difference in favour of sirolimus, although it did not eventually reach statistical significance (0.7 vs. 1.9, p=0.06). It should be stressed, however, that in all these trials the reported follow-up ranged from 6 months to 1 year. On the other hand, recent evidence from extensive series still provides an incidence of sirolimus stent thrombosis over long-term follow-up (2 years) of approximately 0.9%. In a recent report by the eCYPHER Registry in 15,157 patients the rates of acute, subacute, and late stent thrombosis were 0.13%, 0.56%, and 0.19%, respectively, representing a 12-month actuarial incidence of 0.87%, although 48% of patients were taking only aspirin at 12 months. Our experience, derived from a series of 504 patients in whom 710 lesions were treated with DES, is similar. Stent thrombosis over an average 2-year follow-up occurred in 0.4% of patients treated with sirolimus-eluting stents.

The issue of non-cardiac mortality is even more complex and further data are needed before we can reach any conclusions. It should be remembered that statistical association does not necessarily imply causal relationship.

Should our routine practice change following recent evidence?

In certain aspects probably yes. First, systematic use of drug-eluting stenting in all angioplasties is not justified. Second, late loss or even angiographic restenosis as sole criteria for assessing the clinical usefulness of DES are far from adequate. Results of clinical trials and registries should be better interpreted according to “hard” clinical outcomes, such as myocardial infarction, cardiac death and total mortality. Third, drug-eluting stenting with two stents for bifurcation lesions, use of very long or multiple adjacent stents for lesion “cover”, as well as stenting of large diameter vessels (>3 mm), should be adopted only after careful consideration of the anticipated benefit to risk ratio on an individual patient basis. Last but not least, antiplatelet medication should be prescribed for longer than currently recommended. The 2005 updated ACC/AHA guidelines recommend aspirin 325 mg daily for at least 1 month after BMS implantation (unless there is a risk of bleeding, in which case it should be given for 2 weeks), for 3 months after sirolimus stent implantation, and 6 months after paclitaxel stent implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg. Clopidogrel 75 mg daily is recommended for at least 1 month after BMS implantation, 3 months after sirolimus stent implantation.
placement, 6 months after paclitaxel stent implantation and, ideally, up to 12 months in patients who are not at high risk of bleeding. To reduce the incidence of bleeding complications associated with dual antiplatelet therapy, the guidelines recommend lower-dose aspirin (75 to 162 mg daily) for long-term therapy. However, late (> 30 days post-procedure) stent thrombosis may account for up to 50% of all thrombosis cases and stent thromboses as late as 375 days after paclitaxel stent implantation have been described. sirolimus stent implantation and 442 days following stent implantation and 8 months after clopidogrel discontinuation. It seems that at least one year combined antithrombotic therapy, the guidelines recommend lower-dose aspirin (75 to 162 mg daily) for long-term therapy. For the time being, DES still represent a useful device that has dramatically altered current practice and helped many patients to avoid surgical revascularisation. Second generation DES are expected to overcome the problems mentioned above, offering a safer approach to the transluminal treatment of coronary artery disease.

Conclusions
1. Long-term stent thrombosis and myocardial infarction may be higher with first generation DES compared to BMS, if antiplatelet medication is prescribed according to current guidelines.
2. Sirolimus-eluting stents may be associated with higher stent thrombosis compared to BMS, if antiplatelet medication is prescribed according to current guidelines.
3. However, current evidence supporting these statements is weak. Further data are urgently needed so that we may reach definitive conclusions regarding the long-term safety of DES. Till then, the only reassuring measure is the complete compliance of both patients and doctors with a longer period of combined antiplatelet therapy.

References
17. Camenzind E, Wijns W; Safety of Drug Eluting Stents: a


