Late clinical events after drug-eluting stents: is there a problem?

Recent presentations at the joint meeting of the European Society of Cardiology and World Congress of Cardiology in Barcelona, Spain, highlighted the potential problem of very late stent thrombosis and increased non-cardiac death occurring in drug-eluting stents (DES) (see pages 317–18). The presentations received major publicity, not least because of the comments of the designated discussant Professor Salim Yusuf (McMaster University, Hamilton, Canada) at one of the conference Hot Line sessions.

These presentations and their content need careful assessment and debate. The manner in which the information was communicated also merits discussion. Finally, the interventional community should scientifically decide whether this is a major problem and, if so, what is required to solve it.

Two presentations at the Hot Line session concentrated on all-cause mortality, the incidence of death and Q-wave myocardial infarction (MI) (a surrogate end-point for stent thrombosis) following DES placement. These data were for randomised trials with the first-generation Cypher® (sirolimus-eluting) and Taxus® (paclitaxel-eluting) stents. The first presentation (the Nordmann meta-analysis) suggested an increase in non-cardiac deaths with DES compared to bare-metal stents (BMS) and implied this was because of increased cancer rates. The second presentation (the Camenzind meta-analysis) suggested a statistically significant increase in death and Q-wave MI (and by inference stent thrombosis) in DES, specifically with the Cypher® stent rather than the Taxus® stent, compared to BMS.

This led to Professor Yusuf commenting: "as clinicians we seem to have lost our clinical judgement, let alone our ability to view data and evidence. The whole field of angioplasty has been led astray by a preoccupation with restenosis for which study after study has shown, has no prognostic value". In addition, he suggested that angioplasty was being overused in stable angina and that there was an unhealthy relationship between interventionalists, money and industry (reported on www.theheart.org). All of these comments led to Professor Yusuf appearing on the front pages of much of the medical press.

These data require and deserve careful analysis. The interventional community understands that stent thrombosis is a major, recognised, complication of any stenting (DES or BMS) procedure. In addition, if an increase in non-cardiac mortality is the 'price' of a DES, this would have major consequences.

Martyn Thomas

All-cause mortality after DES: the Nordmann presentation

The Nordmann meta-analysis addressed the mortality rates up to four years in randomised trials of Cypher® and Taxus® stents. There was no reported difference in all-cause mortality or cardiac mortality but an increase in non-cardiac mortality (specifically with the Cypher® stent) at two and three years. This had disappeared at four years. There was a description of the causes of death in DES patients but no such description for BMS. In DES patients, a high proportion died of cancer (although in the absence of a cardiovascular death this would seem statistically obvious).

Professor Yusuf's suggestion that a rapid impairment of the immune system related to DES could be responsible for cancer deaths in DES patients appears unlikely. The maximum follow-up in this study was four years so any 'effect' of the drug would be huge and given there is no drug measurable in the systemic circulation, this seems highly unlikely. Much more data and peer review is required before any conclusions can be made from this meta-analysis. We will need to know the exact timing of events (including any diagnosis made before stent implantation!) in both DES and BMS patients. It

will be important to know whether any cancer patients had delay in any treatment because of the need for continued dual antiplatelet therapy. This may be the only plausible hypothesis for the mechanism. The conclusion, without the description of the causes of non-cardiac death in the BMS group, does not seem justified.

Death and Q-wave MI after DES: the Camenzind presentation

The Camenzind meta-analysis claims to show that stent thrombosis (defined as a sudden death or death due to cardiac failure after an MI; or a non-fatal Q-wave MI) was significantly higher in patients receiving a DES (specifically a Cypher® rather than a Taxus® stent) in the randomised trials. The data obtained for this meta-analysis were based on the published literature and there were no 'patient level' data available. The timing of events is a little difficult to follow in this presentation. Statistical significance is only reached for this combined end point at the 'latest follow-up data' time point of 18 months. At this time, the incidence of the combined end point was 6.3% and 3.9% in DES and BMS, respectively.

Once more, these data will require careful peer review and comparison with 'patient level' data. Such data should be available from the original case report forms and it has already been requested by the interventional community. Camenzind was not able to report on the separate incidence of death or non-fatal MI. Reporting from published literature also presents the possibility of 'double counting' of events. Defining clinical events is crucial to this type of meta-analysis. All end points, especially stent thrombosis, have differing definitions in the reported trials. Meta-analysis studies will therefore be difficult until a consensus on the definition of clinical end points is agreed.

Ongoing stent thrombosis in DES out to five years: the Wenaweser presentation

An important study suggested an on-going stent thrombosis rate in DES of 0.6% per year out to five years (Wenaweser). This data included 'allcomer' patients in the SIRTAX and post-SIRTAX registries in Bern, Switzerland, and the RESEARCH and T-SEARCH registries in Rotterdam, the Netherlands, using a variety of different DES. These data will be of concern to the interventional community but it should be remembered that many of the patients in these registries had stent implantation outside the indications demonstrating the benefits of DES in randomised trials. It would be interesting to know how many of the patients with adverse events in these registries had stent implantation for indications outside the current National Institute of Health and Clinical Excellence (NICE) guidelines (small vessels and long lesions, and hopefully the addition of diabetes in the near future). In addition, there are little data in the literature describing the on-going stent thrombosis rate to five years with BMS. The short-term data in the randomised trials show no statistical difference in the stent thrombosis rate between DES and BMS.

A number of other studies were presented suggesting a problem with increased late and very late stent thrombosis with DES mainly with the Cypher® stent (e.g. RAVEL, BASKET LATE, TAXUS II). One must be very careful about the interpretation of these data, however. None of these studies had statistical power to show difference in stent thrombosis. The BASKET trial, in particular, was designed as a health economics study, yet has gained the highest publicity for its reporting of stent thrombosis at follow-up. The trial was never powered or designed to assess this end point.

How should this data be interpreted?

End points

All trials are designed with a primary end point for which they are statistically powered. Other secondary end points often have not been statistically powered and these data should be interpreted with great caution (e.g. BASKET LATE). Finally, post-hoc subgroup analysis is interesting for hypothesis generation but little else. Definitions of stent thrombosis (at various time-points) vary throughout the stent literature. Recently a group of experts including clinicians, regulatory bodies (the US Food and Drug Administration [FDA] included) and industry gathered to agree definitions of end points associated with DES trials: 'the Dublin definitions'. These definitions should be used in all future reports of the data and, ideally, re-analysis of these current trials and registries should be performed using the new definitions.

Major adverse events should also be independently adjudicated in all trials and registries. This, in itself, can be difficult. The most rigid definition of stent thrombosis requires angiographic proof and undoubtedly will under-report the event; while the looser definitions will almost certainly result in some non-stent-related events being classed as stent thrombosis. Uniformity of definition should at least allow this problem to equally apply for DES and BMS. Little attention has been placed on the analysis of late and very late stent thrombosis in BMS but much of the randomised literature suggests there is no statistical difference between BMS and DES.

Peer review

All of the discussed presentations should be subject to stringent peer review prior to publication. The publicity these data have been given may be inappropriately high and relate to the 'front page' comments of Professor Yusuf.

Data

'Patient-level' data should be obtained to allow more detailed discussion of the Camenzind meta-analysis.

Preventing stent thrombosis

It should be remembered that the majority of stent thrombosis occurs early. Much of this is related to stent deployment and the continuation of dual antiplatelet therapy. Interventionalists should ensure excellent results of the primary procedure by stringent attention to detail. In addition, we should stay within the current NICE guidelines and deploy DES in small vessels or long lesions (with the proposed future addition of all patients with diabetes). At a recent meeting of the British Cardiovascular Intervention Society (BCIS) in Manchester, there was a consensus view for the use of one-year dual antiplatelet therapy for all DES procedures. Individual high-risk patients may be advised to continue dual antiplatelet therapy long-term.

Guidelines

The Wenaweser data does indicate a continued event rate to five years with DES. It should be remembered that this was a registry of 'allcomers' and many patients would probably be outside the current NICE guidelines. In addition, similar data are not available for BMS. These data may well indicate the need to adhere to current guidelines when deciding on the use of DES.

Registries

Large-scale registries are needed to define the risk of very late stent thrombosis. Many of these are already underway or in the planning phase. Data should be collected and adjudicated to five-year follow-up and beyond. Evidence of increased non-cardiac mortality in patients with DES is not compelling but all-cause, cardiac and non-cardiac mortality should always be reported in future trials and registries.

Conclusion

There may be a small but important excess of very late stent thrombosis in DES compared to BMS. However, further scientific data are required to confirm this. Large-scale registries may define the risk of very late stent thrombosis if adequate data are collected and adjudicated at five-year follow-up and beyond. Evidence of increased non-cardiac mortality in patients with DES is not compelling but in future trials and registries all-cause, cardiac and non-cardiac mortality should always be reported. Patients should be advised to continue dual antiplatelet therapy for one year following DES placement with some individual cases being advised to continue in the long term.

Some of the headlines seen recently in the medical and non-medical press on this subject have been unhelpful and could be seen as opportunistic on some individual's parts. These are important issues and we must ensure that they are addressed in a robust and scientific manner so that we can ensure we continue to treat our patients with ischaemic heart disease in the optimal manner.

Conflict of interest

MT has received research support from Boston Scientific, Medtronic and Cordis.

Further information

The BCIS Council have recently produced a 'position statement' on this topic which may be found at: www.bcis.org.uk. The FDA have recently produced a statement on this topic which may be found at: www.fda.gov/cdrh/news/091406.html

Martyn Thomas
Interventional Cardiologist, and President of the
British Cardiovascular Intervention Society
King's College Hospital, Denmark Hill,
London, SE5 9RS.
(email: MTTWINS@aol.com)

Br J Cardiol 2006;**13**:313–16