Stent thrombosis

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INTRODUCTION

Cardiovascular disease is the major source of mortality in the Western world, killing around one-third of all individuals.[1,2] Coronary artery disease is the source of half of cardiovascular deaths, and kills 3.8 million men and 3.4 million women every year worldwide.[1]

Percutaneous coronary intervention (PCI) and coronary stenting is the most common intervention in the treatment of coronary artery disease, but has the two major drawbacks of restenosis and stent thrombosis. In late 2006, drug-eluting stents, hailed as a breakthrough for the treatment of restenosis, were reported to have increased rates of stent thrombosis.[3]

This review will investigate the controversy surrounding drug-eluting stent thrombosis.

BACKGROUND

Percutaneous coronary intervention was developed in the late 70's.[4] It was thought to be an interesting but esoteric intervention, suitable for maybe 5% of those who would have otherwise had coronary artery bypass grafting. However, it's use expanded beyond the simplest lesions and in ten years, the volume of procedures matched that of CABG, around 250,000 in the USA.[5] The success of plain balloon angioplasty was limited by two main factors, acute thrombosis from arterial injury, and restenosis, the re-closure of treated lesions by elastic recoil and negative remodelling,[6] requiring revascularization in up to 50% of those treated.[7]

These limitations were addressed with the development of the coronary stent, introduced in 1987.[8] Coronary stents are metal cages which prop treated arteries open, practically eliminating the elastic recoil and negative remodelling which dogged balloon angioplasty.[6]

Coronary stenting had it's drawbacks as well, with rates of thrombosis of up to 24%,[9] and clinical restenosis rates of around 20%, although by a different mechanism.[6] These problems were attacked and with improved anti-platelet therapy, thrombosis rates dropped to about 1.2%.[9] Restenosis was resistant to treatment and rates remained similar. With the addition of a permanent foreign body to arterial injury, inflammation was increased, probably due to fibrin deposition on the stent surface and the mismatch between the compliance of the artery and the rigid stent. With increased inflammation, increased arterial repair was noted.[10] This is manifest by the migration of vascular smooth muscle cells to the intima, the inner layer of the artery, and their proliferation once there. They then differentiate into a synthetic phenotype, producing a collagenous "scar", neo-intimal hyperplasia, approximately a 50:50 fibrocellular lesion.[11,12] This lesion grew in between the stent struts re-narrowing the arterial lumen.

Despite this, during the nineties and early this decade stenting became increasingly popular, with close to one million stents being placed worldwide annually.[5]

DRUG-ELUTING STENTS

Fast forwarding to 2003, the first drug-eluting stent (DES), Cordis' Cypher (J&J), was approved by the US FDA[13] on the basis of the SIRIUS trial, a multi-centre, prospective, randomized, double-blind trial of 533 participants with Cypher and 525 with bare metal stents (BMS). The outcome of reduction of the composite endpoint, target lesion revascularisation, MI and cardiac death, at 9 months was achieved. Target lesion failure was significantly reduced from 20.0% in the BMS group to 4.9% in the DES group,[14] however the only significant individual outcome was target lesion revascularisation, there was no significant difference in MI or cardiac death. Multiple studies agreed with the SIRIUS trial - Cypher was efficacious at reducing intimal hyperplasia. One year later, Boston Scientific's Taxus DES was also approved, although there were no significant differences between the two with respect to clinical outcome.[15] Both stents release cytostatic drugs, previously approved in cancer therapies, which broadly inhibit cell function.[16] Preclinical studies showed delayed endothelization with paclitaxel eluting stenting, with an increase of inflammation, postulated to be from a reaction to the polymer.[17] Early after FDA approval of Cypher, a number of cases of both stent thrombosis and hypersensitivity reactions were reported. The FDA responded by requesting that Cordis perform a 2000 participant post approval study,[18] and based on this they concluded that there was no significant difference in stent thrombosis or hypersensitivity compared to bare metal stenting.[19]

With fears allayed, drug-eluting stenting became increasingly popular, growing to around 90% of the stenting market in the US,[20] and around 80% in Europe, with around one and a half million stents placed annually worldwide.

There were a few sceptics - one group of pathologists in Washington published extensively on the pathology of DES. They described delayed endothelialization,[17,21] persistent incomplete endothelialization[22] and a lack of neo-intimal coverage of stent struts,[23] as well as reporting on hypersensitivity reactions[24] and stent thrombosis;[25] mostly poor healing

and the consequences. However, no significant increase of adverse events was noticed in clinical trials, and the suspicion did not influence clinical practice much.

The ability of drug eluting stenting to reduce intimal hyperplasia and therefore restenosis led to use in a broader range of patients than BMS were generally used for.[26] While BMS had similar outcomes to CABG for simple lesions, DES were used in far more complex lesions without any rigorous evaluation. However, from clinical anecdotes this appeared to be successful. Studies that looked at known risk factors, such as left main disease and diabetes were hopeful.[27]

Cost effectiveness has been a weak point. Drug eluting stents appear to be less cost effective than CABG in unselected patients.[28] In the US, use is unselected but in New Zealand, the use is restricted to around 20% of those eligible for stenting.(Chu, JSW. Personal communication)

It was in the long-term follow-up for one of the cost effectiveness studies that a difference in stent thrombosis was first seen. Presented at the 2006 American College of Cardiology Scientific Sessions in Atlanta, the BASKET LATE study,[29] investigators saw a statistically significant rise in cardiac death/non-fatal MI in the DES group, with 1.3% of the BMS group suffering cardiac deaths and non-fatal MIs, and 4.9 % in the DES group, excluding results outside of the months 7 - 18.[28] The results of this analysis galvanised the interventional cardiology community into action.

The first step was to perform a meta-analysis of all trials currently available. This was performed and presented in September that year, at the European Society of Cardiology Annual Meeting/World Congress of Cardiology Meeting.[29] The results were that at 12 months onward, there was a significant rise in thrombotic events in both Cypher and Taxus groups compared with BMS.[3]

So how did the stent thrombosis phenomenon escape detection before?

The most important answer is the statistical power (the probability of a sample actually showing a significant difference when one is present) of all of the trials. The primary outcome the trials were designed to test was a reduction of target lesion revascularisation. With the 20% of BMS recipients and 5% of DES recipients suffering restenosis, only a sample size of 120 for a power of 80% (the recommended level), whereas to see a rate of stent thrombosis which is 1% for BMS and 1.5% for DES, upwards of ten thousand participants would be needed for the same power.[30] Even with meta-analyses of all trials, the power levels sit somewhere around 30%, with less than 50 events experienced by trial participants and a difference is probably only seen because of the different time frames of the thrombotic events, which is the second answer. It may be that the group of Washington pathologists were vindicated after all. They noted that there was persistent incomplete re-endothelialization with DES, which is a plausible pathological mechanism for thrombosis.[22] The time frame of BMS thrombosis was up to thirty days, as the lesion was re-endothelialized,[31,32] and consequently anti-platelet therapy was maintained over that period. Anti-platelet therapy was extended to 3 to 6 months in DES, as it was known that poor endothelialization, which could lead to thrombosis, was an issue. DES thrombosis seems to appear after 12 months, and many of the approval trials were for only one year, thus excluding them from being able to detect stent thrombosis.

However, it was noted that the definition of stent thrombosis was variable between trials. A group of medical and stent industry experts proposed a comprehensive definition of stent thrombosis. They included definite thrombosis, with angiographic or autopsy evidence; probable thrombosis, an unexplained event which is likely to be stent thrombosis; and possible thrombosis, an unexplained event which is consistent with stent thrombosis. They then reworked the original data from the original approval trials. With these more robust definitions, the difference between groups disappeared.[33]

To sort out what was actually happening, the FDA organised a conference of many of the world experts to meet on the 7th and 8th of December 2006 to discuss the issue of stent thrombosis. They reviewed existing evidence as well as new data, with the most significant findings published in a special edition of the New England Journal of Medicine.

Firstly, re-workings of the original randomised clinical trials with thorough definitions of stent thrombosis showed no difference of stent thrombosis rates with Cypher versus bare metal stenting,[34] no difference in stent thrombosis between DES and BMS[35] and no difference in mortality between DES and BMS.[33,36]

In addition to this, data from a large registry from Sweden was published. Nearly all patients receiving a stent from the beginning of 2003 until the end of 2004 were recruited, 19,771 patients. Recipients of BMS (n=13,738) were significantly different in many areas from those who received DES (n=6,033) with DES recipients having more stents, more triple vessel disease, longer lesions, indication and geographic location. A propensity score, analysing the likelihood that a particular variable was associated with treatment was used to reduce bias from non-randomization. The mortality outcomes for the BMS and DES groups were similar at 6 months but diverged after that, favouring the BMS group. Having a DES was associated with a relative risk for mortality of 1.32 (95% CI, 1.11 - 1.57).[37] While this result does not necessarily suggest that rates of stent thrombosis or even mortality are higher with drug eluting stenting, as the treatment groups still are not comparable, it is compelling to see real world data with long term follow up and large numbers. The result does bring up the need for trials of DES in patients with more severe disease. The trials designed to show the efficacy of DES, and approve them for use excluded patients with all but very simple disease. It is these patients who DES are FDA approved for, but it is estimated that 60% of use is in patients with more severe disease. This registry data suggests that outcomes for DES are significantly worse than BMS in "real world" usage.[38]

In addition to the papers published by the New England Journal of Medicine, the Lancet, another of the high impact medical journals published an article of a smaller registry, n=8,146. Angiographically documented stent thrombosis was noted at a steady rate, around 0.6% a year, with no evidence of dropping off. This is consistent with the biology of incomplete healing. This is an observational trial with no BMS group, so it is more difficult to draw definite conclusions, but the result adds to evidence demanding larger trials.[39]

Low powered studies and short-term follow up prevented the early detection, despite some suspicion. It seems likely that the BASKET LATE trial saw a real result by chance, and the re-working of the trials saw no effect because either in that patient population, those with simple lesions, there is no difference, or merely because of low power.

The registry data are compelling, because the studies are powered to see differences in the region of the magnitude stent thrombosis and differences in mortality are likely to appear in, <1%. In addition, they speak of the real world usage, which the approval trials do not. One plausible explanation is that the differences noted are related to discontinuation of anti-platelet therapy, a large known risk factor of stent thrombosis.[40,41] One group looked at mortality with respect to stent type as well as use of the universally used anti-platelet agent, clopidogrel. Their results suggest that perhaps the differences seen in the clinical trials and the registries could be due to medication with clopidogrel - the group with the highest mortality, 5.8%, are those who received DES but were not on clopidogrel at 6 months. However, the group with the lowest mortality, 1.6%, are those who received DES and were on clopidogrel at 6 months. Mortality for BMS was not significantly different with respect to clopidogrel at 6 months, at 3.9% with and 4.5% without clopidogrel. Again, this is an observational study and does not compare identical groups, but it does reflect what is happening in actual clinical practice.[42]

The FDA concluded that drug-eluting stents are associated with a "clinically important excess" of stent thromboses later than one year after stent placement, although the magnitude was unknown. Based on data from the approval trials, there appeared to be no increase in MI or cardiac death, although that may be because of small sample size or due to restenosis related death in BMS recipients. The panel agreed that there was insufficient evidence to certainly say whether one stent was superior

but safety concerns appeared to be justified equally in both. It was agreed that there was no increase in all cause mortality, and that when used according to the FDA approved guidelines[13,15] the benefits outweigh the risks. The recommendation for clopidogrel was increased to 12 months, while acknowledging that the optimal length of treatment was not known.

It was recognised that follow up was too short, and treatment groups too small, with the panel calling for bigger, longer trials for both approval and safety studies, taking care to look at compliance with treatment.[3]

Lastly, the panel agreed that off-label use should be limited.[3]

A recent Nature Clinical Practice article by top cardiology experts reflected on the controversy.[43] Farkouh et al. admit that the widespread adoption of DES was not based on the same rigorous analysis that other cardiovascular technologies were received. While most commonly used cardiovascular therapies were first evaluated in high risk groups, then evaluated in low risk groups, DES were tested in low risk individuals and use then broadened into high risk patients, for whom no data existed. Current views on DES range from disregarding stent thrombosis as an important outcome and promotion of unrestricted use to a panic reaction and widespread restriction of use.

However, individualized therapy could minimize restenosis while minimizing stent thrombosis, by weighing up risks and benefits. In addition, it is noted that widespread adoption is not as cost-effective as use in selected populations.

Key variables that should be taken into account include the cumulative risk of stent thrombosis, the risk of bleeding associated with long-term clopidogrel and the risk of in-stent restenosis.[43]

CONCLUSION

Stent thrombosis occurs at a very low, but clinically significant increased rate with drug-eluting stents compared with bare metal stents. Optimal use of drug eluting stents will be based on the risks and benefits to individual patients, and cost effectiveness will be increased.

Use of drug-eluting stents in high-risk patients should be limited until prospective, randomized trials give data on their efficacy in such situations.

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