Stent thrombosis revisited

Background

Stent thrombosis has in some cardiologists’ view become something of a non-problem[1,2]. Although the incidence of stent thrombosis has decreased, this is not applicable to all patient subgroups. In the groups with a low thrombosis rate this may be related, at least in part, to the changing indication for stent deployment coupled with more widespread use of stents and better appreciation of the risk factors for stent thrombosis. Previously, we have outlined an antithrombotic strategy to prevent thrombotic stent occlusion[3]. This review aims to address recent changes in our understanding of stent thrombosis and suggests an updated antithrombotic regimen tailored to individual patient subgroups.

Risk factors for stent thrombosis

There is good evidence that certain patient-specific and lesion-specific factors contribute to the risk of stent thrombosis. Two reports in the early 1990s of the clinical results after stent deployment were largely responsible for convincing cardiologists of the need for systemic anticoagulation after stent implantation.

References

Serruys et al. reported a 24% incidence of stent thrombosis in the first 105 patients receiving a Wallstent and identified patients whose anticoagulation was interrupted, those with acute coronary syndromes and chronic total occlusions and those whose vessels were small (<3 mm in diameter) or had poor distal run-off as being at particular risk. Almost simultaneously, Schatz reported the results of elective stent implantation in 226 patients and found an 18% incidence of stent thrombosis in patients treated with antiplatelet agents alone but only 0.6% in those receiving both oral anticoagulants and antiplatelet agents.

A number of other studies identified lesion eccentricity, unstable angina and bailout (as opposed to elective) indication risk factors for thrombotic occlusion. These studies indicated that bailout stent implantation had a 10% to 20% risk of thrombosis and added to the enthusiasm for intense anticoagulation in all patients. Such intense anticoagulation contributed to the high (10%–30%) incidence of vascular complications reported in several series. Following bailout stent implantation, George et al. reported bleeding complications necessitating blood transfusion in 16.8% of 518 patients and a number of other groups reported vascular surgical repair rates of 6% to 11%.

Additionally, such aggressive anticoagulation regimes substantially prolong in-hospital stay. Although early discharge of patients receiving warfarin has been shown to be feasible using adjunctive self-administered low molecular weight heparin, this was in a relatively small series of patients undergoing elective stenting of large coronary arteries (reference vessel diameter >3 mm).

The high complication rates related to anticoagulation and the adverse cost-benefit effects of prolonged stay have understandably contributed to the desire for anticoagulant-free stenting.

**Approaches to anticoagulant-free stenting**

Two aspects of clinical practice changed almost simultaneously in the pursuit of this goal. Neither aspect has yet been fully evaluated in prospective randomized studies (although trials are ongoing); available data are thus based largely on observational studies.

(a) **Optimal stent deployment**

Colombo and others postulated that the risk of thrombosis after stent implantation may be due to haemodynamic factors such as turbulent flow caused by asymmetric stent expansion or gaps between the stent struts and the luminal surface of the artery. The limitations of angiography may thus contribute to the incidence of stent thrombosis since luminograms fail to identify poor stent apposition. Such 'dead spaces' were likely to be the site of thrombus formation. In patients undergoing Palmaz–Schatz stent implantation in native coronary arteries, Nakamura and colleagues demonstrated significant stent underexpansion by intracoronary ultrasound after an apparently optimal angiographic result in 80% of the 63 patients studied. Subsequently, Colombo and co-workers provided observational data suggesting that use of intravascular ultrasound combined, where necessary, with high pressure balloon inflation to optimize stent expansion can eliminate the need for anticoagulation whilst maintaining a low (1–4%) subacute thrombosis rate. Colombo's group have provided clear intravascular ultrasound criteria for stent deployment (intrastent lumen cross-sectional area equal to or greater than the distal reference lumen cross-sectional area and no significant lesion in the non-stented segments immediately adjacent to the stent).

It is unclear whether high pressure balloon inflation without ultrasound guidance would suffice, since Colombo et al. did not evaluate this strategy. In their series, patients who failed to meet the ultrasound criteria despite high pressure balloon inflation were subsequently anticoagulated with warfarin for 2 months. In a small series comparing high (n=28 patients) and low (n=24 patients) pressure inflation for coronary stent implantation, Görge et al. found, using intracoronary ultrasound, that echo-free spaces and stent asymmetry were still present in some patients in the high pressure group thus arguing against 'blind' high pressure balloon inflation. However, the authors did not present outcome data, particularly thrombosis rates. Clearly therefore a simple high pressure stent deployment strategy without ultrasound guidance needs to be evaluated in a prospective randomized study. Although intravascular ultrasound guidance may assist with choice of antithrombotic regime, the suggestion that intravascular ultrasound is essential for optimal stent deployment needs to be resisted in the absence of evidence from randomized trials; intravascular ultrasound is expensive, time-consuming, not entirely without risk and may not be universally available. We await the results of the MUSIC multicentre trial, applying the ultrasound criteria proposed by Colombo, which should be reported in 1996.

(b) **Newer antithrombotic regimes**

These have been introduced during the same period as the changes in stent deployment strategy; thus the
relative benefits of each are unclear. Endothelial denudation, an inevitable consequence of balloon-induced arterial damage, leads to platelet activation, deposition and aggregation. Extensive platelet coverage is also evident on stents implanted into animal models. In clinical studies after stent implantation platelet activation has been shown to occur using flow cytometry, a considerably more sensitive technique than ex-vivo aggregometry used in other studies. Using similar techniques, Neumann and colleagues have prospectively shown surface expression of the platelet fibrinogen receptor to be an independent predictor of subacute stent occlusion.

The newer antithrombotic regimes are based on the hypothesis that inhibiting platelet activation after stent deployment may reduce the incidence of stent thrombosis. This notion is supported by clinical trials showing a significant reduction in acute ischaemic complications in patients undergoing high-risk coronary angioplasty treated with monoclonal antibody directed against the platelet glycoprotein (GP) IIb/IIIa receptor, a potent inhibitor of platelet aggregation. The drawback of such systemically administered therapy is an increased risk of bleeding complications. At present, there are no published data evaluating the use of platelet (GP) IIb/IIIa antagonists following stent deployment. Available data from animal studies obtained using a canine ex-vivo femoral arteriovenous shunt model suggest that use of an intravenous bolus of monoclonal antibody m7E3 (directed against the platelet glycoprotein (GP) IIb/IIIa receptor) significantly reduces thrombus formation and prolongs bleeding time. These agents may therefore have additional prospects for preventing stent thrombosis in high-risk situations.

**Ticlopidine**

Ticlopidine is an antiplatelet agent that has been most extensively evaluated in patients suffering from strokes and transient ischaemic attacks. The precise mode of action of ticlopidine is unclear; it is known to inhibit ADP-induced platelet aggregation and has also been shown to block fibrinogen binding to the platelet GP IIb/IIIa receptor. Ticlopidine itself is, however, inactive; it is metabolised in the liver to four major products of which the 2-keto derivative is the most important. The onset of action of ticlopidine is delayed for up to 72 h, potentially leaving an early window of risk for stent thrombosis and making it difficult to fully explain some of the clinical findings which appear to support its use.

In clinical studies following stent implantation, ticlopidine has been evaluated as either sole antiplatelet therapy or in combination with aspirin or subcutaneous heparin. The French trials clearly demonstrate that thrombosis rates can be reduced using ticlopidine and aspirin together with subcutaneous low molecular weight heparin (dose 0.01 mg kg⁻¹ twice daily for up to 4 weeks). It is of interest, however, that univariate analysis of the 2901 patients treated in this manner showed small artery size (P<0.001) and stenting for occlusive dissection (P<0.001) to be independent predictors of thrombosis. In smaller trials, subcutaneous heparin appears to confer no significant additional benefit over the combination of ticlopidine and aspirin. Subgroups of these large trials evaluating bailout stent implantation have also demonstrated the benefits of ticlopidine in reducing stent thrombosis; however, thrombosis rates after bailout stenting continue to be reported at higher levels than after elective stenting.

Colombo's group have also demonstrated that use of ticlopidine and aspirin can result in acceptable (1.4%) subacute thrombosis rates. However, the authors relied on strict intravascular ultrasound criteria to ensure optimal stent deployment, their patients had large vessels (reference diameter 3.19 ± 0.34 mm) and the great majority (95%) of stents were deployed for elective (as opposed to bailout) indication. Subsequently, the same group published data suggesting that aspirin alone may be as effective as a combination of ticlopidine and aspirin. Once again intravascular ultrasound criteria were relied upon to ensure optimal deployment in patients with relatively large vessels (reference diameter 3.01–3.06 mm) primarily (90%) having elective stent implantation. Furthermore, this small study (226 patients) was not sufficiently powered to detect a difference between the two therapies given the low overall thrombosis rates so the question remains unanswered.

A recently published randomized comparison of antiplatelet therapy alone vs conventional anticoagulation following stent deployment also supports the hypothesis that effective inhibition of platelet function may be superior to anticoagulant therapy in preventing stent thrombosis. The 257 patients randomized to antiplatelet (aspirin plus ticlopidine) therapy had a significantly lower incidence (0.8%) of stent occlusion than the 260 patients randomized to conventional anticoagulation (5.4%). The antiplatelet group also had an 82% lower risk of myocardial infarction and 78% lower need for repeat intervention. It is noteworthy, however, that patients enrolled in this study all had relatively large vessels (reference diameter 3.14 ± 0.52 mm) and although more than 50% of patients had 'dissection before stenting' the
severity of this in terms of flow reduction or actual vessel closure was not detailed by the authors\(^{[35]}\).

Although ticlopidine is presently available only on a named patient basis in the U.K., side effects are uncommon. Of the 321 patients treated by Colombo et al. only seven developed a problem, and only two were for neutropenia which reversed after stopping the drug\(^{[18]}\). It is recommended, however, that 15 days after starting the drug a full blood count and platelet count be taken and again, after finishing therapy. Despite the encouraging data on ticlopidine there are still unanswered questions about its true value since high pressure alone following stenting has not been tested separately. Additionally, the relatively slow onset of action means that there would appear to be several days following stent implantation when there is no protection. Results of the MUST trial, evaluating combined ticlopidine and aspirin treatment without intravascular ultrasound, are awaited.

(c) **Heparin-coated stents**

Currently available metal stents may possess adverse surface characteristics which make them thrombogenic. Thus there is intense interest in using surface coatings to enhance the thromboresistance of stents. One example is the heparin-bonded, polymer coating (Palmaz-Schatz) coronary stent currently undergoing clinical trials to assess the feasibility of anticoagulant-free stent implantation (Benestent II study). Early outcome results from the pilot phase of this study indicate that no stent thrombosis occurred despite progressive reduction in systemic anticoagulation and eventual replacement with antiplatelet agents (aspirin and ticlopidine) alone. There was also a progressive reduction in hospital stay and vascular complications during the four phases of the study. Although these data are encouraging, they do not provide evidence about the specific thromboresistant properties of heparin-coated stents.

A number of factors, other than the heparin coated stent itself, may account for the improvement in outcome compared with the Benestent I study. Thus patients had slightly larger vessels (reference vessel diameter 3.38 ± 0.37 mm vs 3.17 ± 0.42 mm) and attained a better postprocedure minimal luminal diameter (2.77 ± 0.37 vs 2.51 ± 0.36) in the Benestent II compared with Benestent I study. Additional factors such as greater operator experience, increasing use of intravascular ultrasound or on-line quantitative angiography and high-pressure balloon inflations may have led to better stent deployment in Benestent II\(^{[56]}\). Furthermore, it is apparent from a number of observational studies that de novo stenting in large native coronary arteries, even with uncoated stainless steel stents, carries a low risk of stent thrombosis\(^{[8,10]}\). Thus it is unclear whether the Benestent II results can be attributed to the heparin-coated stent. The lack of a 'control' group of patients receiving uncoated stents is a serious omission from this study and the efficacy of heparin-coated stents will also need to be evaluated in more thrombogenic situations such as bailout stenting and smaller vessels. It remains to be established therefore whether heparin-bonded stents are truly non-thrombogenic.

**Patient selection and current antithrombotic strategies**

The definitions of 'poor angioplasty result' and 'bail-out' have always been subjective and may have changed as operators no longer wait until impending disaster before deploying a stent. It may thus be inappropriate to use ticlopidine alone when the vessel has closed or when there is true threatened closure with poor TIMI flow, since most of the data published are on de novo stenting with little description of what 'bail out' means when this is the indication.

The publication from Colombo's group exemplifies this point. In his study, 359 patients were considered for ticlopidine ± aspirin. The dose given was 250 mg twice daily for initially 2 and then, half way through the study, for only 1 month. The headline figure for stent thrombosis was 1.4%; more detailed review of the data shows that 20 patients were excluded on the basis of no intravascular ultrasound procedure, unsuccessful intravascular ultrasound or failure to achieve the intravascular ultrasound criteria. Twelve patients had unsuccessful stent implantation and six suffered complications associated with intravascular ultrasound optimization. In those patients with inadequate intravascular ultrasound \((n=20)\) full anticoagulation with warfarin was administered for 2 months\(^{[18]}\). Thus only patients who met the stringent intravascular ultrasound criteria were considered suitable for antiplatelet agents alone by Colombo and colleagues.

**Who should have what?**

There appears to be good evidence that for de novo stenting in large arteries ticlopidine plus aspirin is sufficient to reduce stent thrombosis to acceptable levels. Aspirin alone may not be so effective\(^{[18,34]}\), although some operators have applied the available observational data to employ such a strategy.

For higher risk patients, such as those in whom there is a small dissection treated by stenting, or where the stent has been placed for poor...
angiographic result, there may be an empiric argument for covering the first few post procedure days with subcutaneous low molecular weight heparin. Depending on the stent result this can be stopped at discharge or continued for one month.

For those patients where there has been major vessel disruption, poor TIMI flow and/or unsatisfactory post stent result there is little evidence to suggest that full anticoagulation should not be employed; these patients should probably still be treated with warfarin for one month with intravenous heparin cover until the appropriate international normalized ratio has been achieved[3]. In these patients there may be a role for aggressive inhibition of platelet function using antibody directed against the platelet GPIIb/IIIa receptor (abciximab [Reopro]), though this remains to be evaluated in clinical studies. Small vessel stenting still carries a high risk for thrombosis. In the Benestent data subgroup analysis the thrombosis rate for vessel size greater than 3 mm was 0-9%, compared with 6-9% for vessels <3 mm[3]. Stents eluting antiplatelet agents, which have shown promise both in vitro[36] and in aggressive models of stent thrombosis[37], may prove to be useful if their efficacy is confirmed in man; meanwhile there remains at least an argument for full anticoagulation in such patients.

Summary

The choice of antithrombotic regimes after stent implantation has increased. Complication rates have improved and in-hospital stay is reduced with the less aggressive regimes. For de novo stenting in large vessels with a good result, ticlopidine plus aspirin or even aspirin alone appears attractive. The successful use of such a regimen may depend on complying with published intravascular ultrasound criteria. For patients who are at higher risk, the option appears to be ticlopidine and aspirin either alone or combined with subcutaneous low molecular weight heparin. In patients selected for established or threatened vessel closure, the old regimen using full anticoagulation should still be considered. Operators should delay stents earlier to avert the need for true bailout stenting.

We still await the truly non-thrombogenic stent that can be used in small vessels under any circumstances.

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