Stent thrombosis: who’s guilty?

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This editorial refers to ‘Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period”1, by S. Schulz et al., on page 2714

Stent thrombosis is a devastating complication of percutaneous coronary intervention (PCI) which remains unsolved as it is poorly predicted and prevented. Its frequency appears to be low (0.8–2%) but most evaluations come from registries that are likely to underestimate the real prevalence. The mortality associated with stent thrombosis is high, within a range of 25–40%, comparable with that of many cancers. Because of its low incidence, stent thrombosis has been neglected for too long by the interventional community. Recent understanding of the underlying mechanisms has reactivated our consciousness and opened up new avenues for dedicated preventive approaches.

The patient

Some of the explanations for stent thrombosis will be found in relation to the patient. A number of simple clinical traits have been identified as risk factors for stent thrombosis including diabetes, active smoking, prior or ongoing myocardial infarction, heart failure, recent cancer, or renal insufficiency.1 Angiographic characteristics have also been associated with stent thrombosis including small arteries, long lesions, bifurcations, thrombotic or ulcerated lesions, or low TIMI flow. Among biological factors, the markers of necrosis, inflammation, and high platelet reactivity on double antiplatelet therapy, have frequently been associated with stent thrombosis. However, evidence has accumulated to suggest that the strongest factor associated with stent thrombosis is the discontinuation of clopidogrel treatment. This is again highlighted in the study of Schulz and colleagues who report the powerful preventive effect of clopidogrel within the first 6 months of drug-eluting stent (DES) implantation.2 The causal relationship between clopidogrel discontinuation and stent thrombosis during this period cannot be demonstrated but is suggested by the average 9-day delay between interruption and stent thrombosis, an estimated time frame for platelet functional recovery. The average time to stent thrombosis of 104 days if discontinuation occurs >6 months after DES placement and the much lower frequency of stent thrombosis in that period provide further support for the critical role of clopidogrel in the prevention of stent thrombosis in the first 6 months. These findings are consistent with those of Eisenberg and colleagues who reported a delay of 122 days from clopidogrel discontinuation to stent thrombosis when discontinuation occurred late after stent implantation in patients who still were on aspirin.3 However, many confounding variables, often not reported, could pollute this type of analyses, in particular the reasons for interruption (tolerance, bleeding complication, scheduled surgery, compliance, etc.). Poor compliance to clopidogrel may well be associated with poor compliance to aspirin, statins, β-blockers, or angiotensin-converting enzyme (ACE) inhibitors, all drugs being associated with survival in coronary disease patients. Indeed, studies have shown, for example, that interruption of statins or aspirin is also associated with recurrent ischaemic events.4,5 Drug discontinuation is a solid indicator of risk, as shown recently in a subset analysis of the CHARISMA trial in which patients who permanently discontinued the study drug (n = 2999) had increased rates of both ischaemic and bleeding events, as well as mortality.6 However, there was a long average time from drug discontinuation to the recurrent event (>200 days), suggesting that it was due more to the lack of chronic antiplatelet protection than to a rebound effect.

The stent

Stent thrombosis was born with bare metal stents and was a more frequent complication in the early stent era than it is today; and it almost condemned the device to disappear. The interventional cardiologists realized that the initial combination of aspirin and heparin was inappropriate. After unsuccessful experiences with other agents (dextran or warfarin), the time came for the P2Y12 inhibitor class to show its strong preventive effect on thrombosis with an antiplatelet agent which had almost no background in cardiology (ticlopidine). Improvements in stent design, stent/artery ratio, and stent delivery helped reduce stent thrombosis. A new challenge was faced with the advent of DESs associated with
proinflammatory drugs and polymers, delay or absence of endothelialization, and more complex cases. Recent multiple studies, meta-analyses, and registries have shown reassuring results on the short-term safety of DESs, including in the most thrombotic milieu of primary PCI. Future challenges, currently being tested in ongoing trials, include timing of P2Y$_12$ antagonist discontinuation with regards to the potential risk of still having incomplete stent coverage, and development of new therapeutic strategies that promote endothelial coverage or early disappearance of the stent scaffolding, such as bioabsorbable stents.

## The drug

Clopidogrel results in considerable variation in the degree of inhibition of platelet function. On clopidogrel, high platelet reactivity is associated with recurrent ischaemic events after PCI, including stent thrombosis, and this was viewed as drug failure for a non-negligible proportion of patients (a quarter) exposed to the complication because of a lack of optimal biological response to the drug. In another study, Michelson and colleagues report on the extent of platelet inhibition following the administration of the new thienopyridine agent prasugrel compared with clopidogrel in a substudy of the randomized TRITON-TIMI 38 trial. Their major finding is that the number of patients with platelet hyporesponsiveness was dramatically reduced with prasugrel compared with clopidogrel in an acute coronary syndrome (ACS) population, confirming previous information from another ACS study. Although this difference was particularly evident in the early phase (1–2 h) after PCI (43% vs 4% of patients with a VASP index <50%), it is noteworthy that the degree and/or speed of inhibition 1–2 h after prasugrel administration was lower than expected (from previous studies in healthy volunteers or stable patients), confirming that with prasugrel, as with clopidogrel, pre-treatment platelet hyper-reactivity of ACS patients has a direct impact on post-treatment platelet reactivity. This may well explain the different risk/benefit ratio observed among the different subsets of the TRITON population where patients with the most hyperactive platelets (diabetics and those with ST-segment elevation myocardial infarction) had the best risk/benefit ratio with prasugrel compared with clopidogrel in an acute coronary syndrome (ACS) population, confirming previous information from another ACS study.

## The gene

Prasugrel and clopidogrel are both pro-drugs that require biotransformation to produce finally the same active metabolite. However, the in vivo generation of the active metabolite is much more efficient after prasugrel administration. The main explanation for this difference is the requirement for the polymorphic hepatic enzyme CYP2C19 for clopidogrel activation while prasugrel is much less dependent on this enzyme. In coronary patients who are carriers of a genetic variant associated with a loss of function of the CYP2C19 enzyme, the risk of stent thrombosis on clopidogrel treatment is 3- to 6-fold higher depending on the population. The meta-analysis of the published studies is reported in Figure 1. It was performed with a fixed effect model, using available data and the odds ratio (OR) to report the results. The meta-analysis calculation (association test) and heterogeneity were performed with EasyMa software. It confirms the excess risk of stent thrombosis [OR 3.03; 95% CI 1.19–4.80, P < 0.001]. More importantly, it demonstrates for the first time the impact of this single gene variant (CYP2C19*2) on cardiovascular mortality (OR 1.79; 95% CI 1.10–1.79, P < 0.019). The analysis for heterogeneity was non-significant (P = 0.43).
It is an attractive addition to platelet function testing and it could guide therapy just as well as platelet function testing. However, the clinical relevance of genetic testing or platelet function testing has not been tested yet prospectively in adequately powered randomized studies. This is the goal of ongoing studies such as the ARCTIC study performed in patients receiving a DES. Is genetics going to play a role when prasugrel enters the market? It is uncertain, but the new option represented by prasugrel will undoubtedly create new strategies of switching from one drug to the other, strategies not tested so far, except in small studies.\textsuperscript{16,27} Hopefully, switching will be either event driven or based on a well-tuned risk stratification. The role of genetic profiling and pharmacodynamic assessment remains to be established in this context.

The physician

The blame for stent thrombosis may also be put on the interventional cardiologist as the key person indicating and carrying out the procedure. How many excessive or inadequate decisions for percutaneous interventions are taken? How relevant are the complex procedures with multiple stents? How frequently do deficient implantations occur? With all this uncertainty about the procedure itself, where do we go from here, having all the biological information, knowing the potential consequences, but lacking the clinical trials on which all recommendations are based? Basic knowledge increases and technical developments of bedside tests occur faster than clinical research, and subsequently the basic knowledge is delivered in simple and easy-to-catch messages by the lay press to the patient-consumers. Meanwhile, bedside tests to evaluate the individual response to oral antplatelet agents are put on the market for the physician-care providers, although there is no demonstration that such a strategy of monitoring to guide therapy can improve patient outcome. Immediate generalization of such testing cannot be considered, at least in most European countries, for many reasons, one being the lack of reimbursement. However, some patients who can afford the extra cost for this vital information have started asking for the tests and their interpretation! This is one more example of the dawning ‘two-speed’ medicine that our social security systems have tried to avoid for many years in our ‘old European countries’. Among us, the most conservative physicians may think that ‘no golden randomized demonstration’ means ‘no use at all’, and they should never ask for the information, including for themselves. The most liberal may think that we should apply the rules of the free market to our healthcare systems (a revolution for most countries) and make the information available to everyone if they can pay for it (‘high-speed’ medicine for the rich). The left alone physician may decide to use his common sense and allocate a limited part of his budget to pay for these non-reimbursed tests in selected cases, while waiting for strong official recommendations. Then he would use the tests wisely, in those patients with a strong suspicion of resistance or already with failure of the drug (e.g. stent thrombosis). Then, he would adjust the antplatelet therapy to the genetic profile and/or platelet function measures just like he is used to do with statins and LDL, insulin and HBA\textsubscript{1c}, β-blockers and heart rate.\textsuperscript{27} With such a strategy, he would do a better job than just apply the ‘one size fits all’ approach, especially if this approach has already failed once in his patient. Thus, while waiting for stronger clinical data, the physician would consider the available scientific information and would not betray his patient asking for a second chance.

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