Twelve Months Dual Antiplatelet Therapy after Drug-eluting Stents – Too Long, too Short or Just Right?

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Abstract

Dual Antiplatelet Therapy (DAPT) remains a cornerstone in the secondary prevention of coronary artery disease. Further, in contemporary practice, a period of DAPT is considered a mandatory requirement after intracoronary stents to prevent stent thrombosis (ST), a complication associated with heart attack and a mortality rate of up to 40%. In current clinical practice, the default strategy in most centres is 12 months’ DAPT followed by aspirin alone for life. However, the optimal duration of DAPT, particularly given the rapid iterative turnover of drug-eluting stents (DES) is the subject of discrepant evidence and clinical uncertainty. In particular, the 12-month regimen is based upon relatively weak evidence. A series of fairly small randomised trials, not powered to look specifically at ST as an endpoint, have recently indicated that there is no apparent disadvantage to shorter versus longer duration DAPT (including several trials of >12 months versus 12 months) when looking at various composite clinical endpoints. By contrast, the 9,961 patient DAPT trial, published in the New England Journal of Medicine at the end of 2014, demonstrated clinical outcome benefit, including a significantly lower rate of ST as a predefined primary endpoint, in DES patients randomised to 30 months’ DAPT compared to stopping at 12 months. Here, the authors to assess the data, including the most recent meta-analyses, in an attempt to answer the question: DAPT after DES...12 months, longer or shorter?

Keywords

Dual anti-platelet therapy, duration of anti-platelet therapy, coronary artery disease, percutaneous coronary intervention, drug-eluting stents, stent thrombosis

Antiplatelet therapy (APT) represents a major cornerstone in the secondary prevention of coronary artery disease, along with modifying patients’ risk factors. Furthermore, it has been clear, since early unsuccessful regimens, including warfarin and dipyridamole with aspirin, that it is APT that stops coronary stents from clotting off and causing stent thrombosis. Specifically, the requirement for aspirin plus a second antiplatelet drug (thus, dual-antiplatelet therapy [DAPT]) to minimise the risk of ST was quickly established. Initially the second agent was ticlopidine, which despite being effective at its primary task was poorly tolerated and associated with an unwelcome incidence of blood dyscrasias. Subsequently, following randomised trial evidence of beneficial clinical outcome with fewer adverse effects, clopidogrel became the P2Y12 inhibitor of choice to accompany aspirin. Concerns about inter-individual variations in the response to clopidogrel led to the development of apparently more potent and rapidly acting agents in the form of prasugrel and ticagrelor. Specifically, the latter agents have been shown to have clinical outcome benefit compared to clopidogrel in terms of reducing some ischaemic events in heterogeneous populations of patients with acute coronary syndromes, albeit at the expense of increased bleeding.

The concept that DAPT is necessary to prevent ST in coronary stents has been dominant for at least two decades. However, the optimal duration of that DAPT therapy always has been, and remains, uncertain and recently, in particular, has attracted considerable debate. Put simply, the question frontline interventional cardiologists face is this: how much DAPT do you need, and for how long, in order to prevent ST but minimise major bleeding?

In most interventional centres, the default DAPT regimen for most patients receiving stents consists of 12 months followed by aspirin monotherapy for life. A forensic assessment of the basis for this default unveils (perhaps surprisingly) shaky foundations. Studying the evolution of our APT to this default DAPT regimen is valuable to what is currently customarily prescribed by default and may shed some light on the current state of knowledge and practice. By way of introduction, the role of aspirin in secondary prevention is discussed, followed by an overview of the history and development of the antiplatelet regimens used in contemporary practice. On the basis of such an overview, the current role of aspirin and considerations for the duration of DAPT are considered.

Antiplatelet Therapy for Bare-metal (BMS) and First-generation Drug-eluting (DES 1) Stents

When bare-metal stents were first studied, initial therapy consisted of aspirin and dipyridamole. Subsequent to this, DAPT was recommended for 1 month in stable patients with BMS. The original comparative trials of DES 1 versus BMS employed DAPT for between 2 and 6 months only, admittedly in relatively stable and low-risk populations.

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However, as has been the case consistently since those early days, in patients with acute coronary syndromes (ACS) receiving stents there are competing indications for DAPT, since the evidence suggests a benefit from DAPT as a medical therapy in this setting. CURE was the first randomised trial to show that in a population of non-ST elevation ACS patients DAPT (using clopidogrel with aspirin) significantly decreased the rate of recurrent ischaemic events compared with aspirin monotherapy with placebo at a mean duration of therapy of 9 months. Importantly, 64% of the 12,562 patients in this trial did not undergo revascularisation after randomisation. Specifically, there was a 20% relative risk reduction in myocardial infarction, stroke or cardiovascular death with long-term DAPT use with no increase in life-threatening bleeds. In the CURE-PCI sub-study, there was a 25% relative risk reduction in the composite of myocardial infarction or cardiovascular death with DAPT (≤12 months) compared with aspirin and placebo.

It was largely based on this evidence that 12 months’ DAPT became the recommended default for stents post-ACS. However, given that there was a 4% per year incidence of significant bleeding in the CURE study in the cohort on DAPT, there was clearly a balance to be struck between longer DAPT to reduce ischaemic events and shorter DAPT to minimise bleeding, which itself has been shown to be an independent risk factor for worse prognosis. That tension between ischaemic and bleeding events is indeed the driver for our current debate, just as it has been since stents were first implanted. In addition, the suspicion that patients receiving stents in elective, stable settings need DAPT for less time than patients presenting with ACS consistently remains a driver for reducing duration of DAPT therapy. Finally, the consistent iterative technologically-driven evolutions in the design of stents represent a further confounding factor in determining the optimal duration of DAPT.

**DAPT in DES Patients – a Moving Target!**

The main limitation of BMS was an exaggerated inflammatory healing response, leading to excessive neointimal proliferation and restenosis. Clinically, this led to around 10% of patients representing with recurrent symptoms. Randomised trials demonstrating the dramatic reduction in target vessel revascularisation, due to restenosis, with DES compared with BMS has revolutionised patient care. However, the cost of this clinical benefit was a demonstrably higher risk of ST compared with BMS has revolutionised patient care. The cost of this clinical benefit was a demonstrably higher risk of ST, death or myocardial infarction, stroke or cardiovascular death compared with BMS. The implications of this trial are not yet as clear as they first seem. There is concern about committing all DES patients to a longer regimen associated with more severe bleeding. But also, despite the temptation to put the increased incidence of non-cardiovascular death down to statistical quirk, this raises alarm bells given the large number of patients worldwide being treated in this way. The meta-analysis by Palmerini et al., which includes the DAPT trial, just published in *The Lancet,* confirms that we should indeed take a cautious approach to a universal switch to prolonged DAPT after DES. The analysis includes more than 32,000 patients and confirms that there is a 33% lower rate of non-cardiovascular mortality in the shorter duration DAPT arm compared with longer duration, and this actually drives a hazard ratio of 0.82 for all-cause mortality in the shorter duration group. On the other side of the coin, a meta-analysis by Elmariah et al., which involved 14 studies including the DAPT study, showed that extended-duration was not associated with a difference in the risk of all-cause, cardiovascular or non-cardiovascular death compared with aspirin alone or short-duration.

**DAPT after DES – What Should We Do Now?**

Although the evidence apparently presents a chaotic and discrepant picture, some themes regarding our DAPT strategy for DES patients are manifest. First, that if DAPT is used for longer, the risk of ischaemic events, including ST, will be reduced. Second, that this reduction will be at the expense of increased bleeding. Third, strong circumstantial evidence suggests that if DAPT is used for more than a year, non-CV mortality is higher – perhaps because of the excess in important bleeding.

Taking these concepts together, it seems sensible to stick, for now, with a default of 12 months’ DAPT for most patients, pending further specific data.
DAPT after DES – What Do We Need to Know for the Future?

In order to make progress in this field, we need to address more precisely some unanswered questions. These questions cannot be answered in trials that recruit patients with a variety of elective and ACS presentations using different generations of stent and different DAPT constituents. We need answers to these questions via appropriately powered randomised trials:

1. Using specific DES 2 (i.e. only one type in each trial), can DAPT be safely employed for 6, 3 or 1 month(s) in elective patients?
2. Using specific DES 2, can DAPT be safely employed for 6 or even 3 months in ACS patients?
3. Do we actually need DAPT anyway? The results of trials like GLOBAL LEADERS, randomising DES patients to ticagrelor alone compared with DAPT after a certain period of aspirin plus ticagrelor, could revolutionise our thinking about this field completely.

Finally, what shines out of a forensic assessment of the current evidence about DAPT after DES is this: the concept that we can have wholesale strategies for APT for large groups of patients is fundamentally flawed. The real challenge is to develop personalised pathways of care that take into account individual risk of ischaemic events, bleeding and, probably, also their response to APT using point-of-care tests of platelet reactivity. It is time to discard our palpably inadequate “one-size-fits-all” approach and develop patient-specific strategies. Such an individualised approach might well eliminate many of the adverse effects we currently witness.