Reviews

Antithrombotic treatments for patients with atrial fibrillation and a requirement for a coronary artery stent

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Abstract

**Background:** Patients with atrial fibrillation and a coronary artery stent require anticoagulation to provide prophylaxis against stroke and dual antiplatelet therapy to provide prophylaxis against stent thrombosis (triple therapy). This combination increases the risk of major bleeding complications compared to either treatment alone. It is suggested that an alternative to triple therapy is high dose dual antiplatelet therapy (aspirin 325mg/day and clopidogrel 75mg/day), which would have similar efficacy to triple therapy in relation to prophylaxis against both stroke and stent thrombosis with a lower risk of bleeding complications.

**Summary:**
1. Patients with atrial fibrillation and a coronary artery stent require triple therapy, which is associated with increased bleeding risk.
2. In everyday practice 50% of patients do not receive this, because of the excess bleeding risk.
3. It is suggested that for patients at increased bleeding risk and for whom it is felt that triple therapy is not suitable, aspirin (325mg daily) and clopidogrel (75mg daily) should be considered.

**Key words:** Atrial fibrillation, Coronary artery stent, anticoagulation, dual antiplatelet therapy, triple therapy.

Introduction

The optimum antithrombotic treatment for patients with atrial fibrillation requiring a coronary artery stent is not clear. There have been no randomised controlled trials to address this issue. For the vast majority of patients with atrial fibrillation oral anticoagulation (OAC) is recommended to reduce the risk of stroke and systemic embolism. Patients with a CHADS2-VASc score of zero (aged under 65 years and no risk factors) do not require OAC, all other patients do. It has been established that the combination of aspirin 75mg and clopidogrel 75mg is not adequate to achieve this. For patients with a coronary artery stent dual antiplatelet treatment (aspirin 75mg and clopidogrel 75mg) is essential to reduce the risk of stent thrombosis to acceptable levels. For bare metal stents (BMS) at least one month is recommended and for drug eluting stents (DES) 12 months is recommended. Dual antiplatelet therapy is superior to aspirin alone and to the combination of aspirin and OAC for the reduction of risk of stent thrombosis. Thus it appears that patients with atrial fibrillation and a coronary artery stent require triple therapy (OAC, aspirin and clopidogrel) to reduce the risk of both stroke and stent thrombosis.

Triple therapy

Observational studies have demonstrated that triple therapy is associated with an increased risk of bleeding complications. Thus it is not surprising that in usual clinical practice less than half of patients with atrial fibrillation and a coronary artery stent are discharged on triple therapy. Cardiologists are therefore faced with a difficult dilemma. If triple therapy is given to provide optimal protection against both stroke and stent thrombosis, the patient will be at increased risk of bleeding complications, which are associated with a poorer outcome.

Conversely, if triple therapy is not given the patient will be at increased risk of stroke or stent thrombosis.

European guidelines based on expert opinion provide suggestions on how to balance these competing pressures. It is recommended that when considering coronary artery stents for patients with atrial fibrillation, alternative treatment strategies, such as medical treatment, CABG or balloon angioplasty should be considered to avoid the need for triple therapy. When a coronary artery stent is considered appropriate a BMS should be used in situations where restenosis is likely to be of a problem, and DES should be avoided in patients at high haemorrhagic risk. When deployment of a DES is considered to provide the most appropriate revascularisation strategy 3 to 6 months of triple therapy is recommended. Patients receiving a stent in the context of an ACS should generally have triple therapy for 6 months, although this may need to be reduced in patients with a high bleeding risk. In this context triple therapy consists of OAC with a target INR range of 2.0 to 2.5, aspirin <100mg/day and clopidogrel 75mg/day. For the remaining time up to 12 months post stent deployment treatment with OAC (INR 2.0 to 2.5) and clopidogrel (or aspirin), followed by OAC (INR 2.0 to 3.0) alone indefinitely is recommended.

A North American perspective on the management of patients with atrial fibrillation who require a coronary artery stent has also been published. The authors acknowledge the lack of trial evidence and the increased bleeding risk with triple therapy and state that the recommendations are based on expert opinion. The recommendations are similar (but not identical) to those from Europe, with greater emphasis being placed on the bleeding risk with triple therapy. An INR in the range 2.0 to 2.5 is recommended for triple therapy, although it is acknowledged...
that in ordinary clinical practice this may be hard to achieve.

The differences between the European and North American recommendations are a reflection of the lack of firm trial evidence. The table summarises each set of recommendations. It should be noted, however, that the two sets of recommendations are described differently making a direct comparison difficult. Firstly, the North American recommendation are for patients with a CHADS2 score of greater than zero because these recommendations suggest that patients with a CHADS2 score of zero do not require anticoagulation and therefore can have standard dual antiplatelet therapy. Whereas the European recommendations are for patients who require anticoagulation based on the 2010 European Guidelines1 which use the CHADS2-VASc score. Consequently for many patients whether they receive triple therapy or dual antiplatelet therapy will depend on their place of residence. For example a female patient with atrial fibrillation requiring a coronary artery stent aged between 65 and 74 and no other risk factors has a CHADS2 score of zero, so in North America would receive dual antiplatelet therapy. Whereas, in Europe she would receive triple therapy as the CHADS2-VASc score is three. Secondly, the North American recommendations are presented in terms of stent thrombosis risk, whereas the European recommendations are given in terms of elective and ACS associated procedures. In the table the North American approach has been adopted, with elective being considered low stent thrombosis risk and ACS procedures being considered high risk.

These recommendations are inevitably a compromise between providing adequate prophylaxis against both stroke and stent thrombosis while minimising bleeding complications. The optimum INR range with OAC alone is 2.0 to 3.0; INR values <2.0 are substantially less effective16. In the European Atrial Fibrillation Trial an INR< 2.0 did not confer any protection against stroke11. A case control study of stroke in patients with atrial fibrillation found that an INR of 1.7 doubled the risk of stroke compared to an INR of 2.027. In clinical practice a target INR range of between 2.0 and 2.5 will be difficult to achieve and will likely result in longer periods of time during which the INR will be less than 2.0 as compared to the usual broader target INR range of 2.0 to 3.0, with the associated increased risk of stroke. Even in highly monitored clinical trials with a target INR of between 2.0 and 3.0, the time in the therapeutic range is typically only 64%-72%. Consequently the recommendations provide suboptimal prophylaxis against stroke. The curtailed duration of dual antiplatelet treatment (3 to 6 months) rather than 12 months will similarly provide suboptimal prophylaxis against stent thrombosis. In an observational study following DES deployment all cases of stent thrombosis identified occurred in patients who had discontinued one of the components of dual antiplatelet therapy14. A further consideration that may impact on antiplatelet activity is the possibility of an interaction between OAC and clopidogrel. Clopidogrel is a pro drug that is metabolised to its active metabolite by the hepatic cytochrome p450 system. Oral anticoagulation treatments are also metabolised by this system, with the potential that they may affect the availability of the active clopidogrel metabolite. An observational study15 has found that the co administration of the OAC phenprocoumon (commonly used in Germany and some other European countries) significantly attenuates the antiplatelet effects of clopidogrel. It is not known whether other OAC, such as warfarin have similar effects.

The non coumarin OAC, Dabigatran, Rivaroxaban and Apixaban have been demonstrated to be non-inferior to Warfarin for the reduction of the risk of stroke in patients with atrial fibrillation13,15,17. There is, however, no experience with these agents in patients with atrial fibrillation and a requirement for a coronary artery stent. The use of Rivaroxaban 2.5mg or 5mg bd and dual antiplatelet therapy in the context of patients with acute coronary syndromes (many of whom will have had a DES) results in an increased risk of major bleeding compared to dual antiplatelet therapy alone18. The recommended dose of Rivaroxaban for patients with atrial fibrillation is 20mg od19. Similarly, the use of Apixaban 5mg bd (the recommended dose for patients with atrial fibrillation) combined with dual antiplatelet therapy in the context of acute coronary syndromes resulted in an excess of major bleeds20. Consequently, when these agents are combined with dual antiplatelet therapy in the context of atrial fibrillation and a coronary artery stent there are likely to be problems with an increased bleeding risk, just as there are with the coumarin OAC.

High dose dual antiplatelet therapy as an alternative to triple therapy

Traditionally aspirin at doses of 75mg to 325mg daily has been considered to be less effective than warfarin for stroke prophylaxis in patients with atrial fibrillation, although better than control. This assumption has recently been re evaluated20. A network meta analysis has shown that the efficacy of aspirin for primary stroke prophylaxis is dose dependant. For daily doses of <150mg, aspirin is inferior to OAC and is no better than control for stroke prophylaxis. Whereas a daily dose of 325mg of aspirin is superior to control in reducing the risk of both stroke and death (all cause) and is comparable to OAC in reducing the risk of both these outcomes. Nevertheless, the weight of evidence supports OAC as a first choice antithrombotic treatment for the reduction of the risk of stroke with aspirin 325mg daily as a good second choice if there are reasons to avoid OAC.

These findings suggest that the combination of aspirin 325mg/day and clopidogrel 75mg/day (high dose dual antiplatelet therapy) would provide stroke prophylaxis similar to OAC and stent thrombosis prophylaxis similar to traditional dual antiplatelet therapy. Further, this treatment could be continued for the traditional 12 months currently recommended for dual antiplatelet therapy, thus avoiding the increased risk of stent thrombosis following early discontinuation of aspirin after 3 to 6 months. The absence of OAC treatment avoids the need to maintain the INR in a narrow therapeutic range and the concern of a possible interaction with clopidogrel. It is possible that bleeding complications may be greater than with standard dual antiplatelet therapy, but likely less than with triple therapy. In the CURRENT-OASIS 721 trial of ACS patients scheduled for an invasive strategy, high dose aspirin with clopidogrel resulted in no more major bleeding complications than low dose aspirin with clopidogrel. In particular there was no excess of intracranial bleeds. Minor bleeding complications, however, were more common with high dose aspirin. In the MATTIS trial22 of high dose dual antiplatelet therapy (aspirin 250mg and ticlopidine 500mg daily) against warfarin plus aspirin in high risk patients following coronary stent implantation, there were more bleeding complications in the later group than the former. There are no randomised controlled trials to support the use of high dose dual antiplatelet therapy in patients with atrial fibrillation and a coronary stent, but neither is there for triple therapy. High dose dual antiplatelet therapy has been used in clinical trials previously23,27, but has not been compared to triple therapy in patients with atrial fibrillation. High dose dual antiplatelet
therapy is an alternative to triple therapy that may be suitable for selected patients. In observational studies of real world clinical practice up to 50% of patients with atrial fibrillation and a DES are discharged on standard dual antiplatelet therapy without anticoagulation8,23, presumably because it is felt that there is a contraindication to triple therapy. Such patients would be ideally suited to high dose dual antiplatelet therapy. The management of patients at increased haemorrhagic risk who are in sinus rhythm at the time of DES deployment, but subsequently develop atrial fibrillation is not discussed in the recommendations8,10. Such patients currently present a difficult management problem and would also be good candidates for high dose dual antiplatelet therapy. These suggestions do not apply to patients in whom OAC therapy is mandatory, such as patients with a previous stroke or a mechanical heart valve.

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Table Comparison of European and North American Guidelines of antithrombotic treatments for patients with atrial fibrillation and a requirement for a coronary artery stent. ST-Stent thrombosis risk, BD- Bleeding risk.