EuroIntervention

Coronary stenting in warfarin treated patients

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Abstract

Dual antiplatelet therapy is standard treatment following coronary stent implantation. An important minority of patients also require chronic anticoagulation, most commonly for atrial fibrillation. There are no prospective trials to guide the selection of therapy in this situation. In this paper we review the available data and present practice recommendations. It appears that in patients who are not at high risk of bleeding, and in whom both coronary stenting and anticoagulation are considered necessary after careful consideration, drug eluting stents should be avoided as much as possible. Triple therapy with aspirin, clopidogrel and warfarin for one month, followed by the combination of aspirin and warfarin for life is the most reasonable approach.

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Introduction

A 70 year old man is admitted to the coronary care unit for an acute anterior myocardial infarction. His known risk factors include hypertension and dyslipidaemia. He has been in permanent atrial fibrillation for five years and has been treated with metoprolol, atorvastatin and warfarin. On admission, the patient is taken to the cardiac catheterisation laboratory where his mid-left anterior descending coronary artery is found to be totally occluded. A bare metal stent is successfully implanted and normal arterial flow is restored. Echocardiography shows moderate left ventricular dysfunction. The patient recovers uneventfully. Prior to discharge you are consulted about his anti-thrombotic regimen. The attending physician is uncertain which combination of aspirin, clopidogrel and warfarin would be best.

Dual antithrombotic therapy (DAT) with aspirin and a thienopyridine is standard therapy following coronary stent implantation. An important minority of patients who undergo coronary stenting also require chronic oral anticoagulation (OAC), most commonly for atrial fibrillation, prosthetic heart valves or venous thromboembolism. The optimal nature and duration of the antithrombotic and antiplatelet combination in such patients is unknown and poses a serious dilemma since it involves significant risks of both thrombosis and bleeding. Unfortunately, no randomised data are available to guide the clinician in this dilemma. The available sources of data are retrospective, subject to selection bias and often derived from patient groups whose risk of thrombosis and bleeding are not directly comparable to the population of interest. However, until better data are available, clinicians are faced daily with the kind of dilemma presented above.

In this review we will examine the possible approaches which could be considered in such patients in view of the existing literature and try to formulate practical recommendations.

Prospective studies

Warfarin + aspirin vs dual antiplatelet therapy

In four clinical trials[1-4], randomised patients who underwent coronary stenting to either aspirin plus warfarin or ticlopidine plus aspirin. The size, endpoints and main findings of these trials are given in Table 1. A meta-analysis of these four trials[5] found DAT to be associated with a significant 59% reduction in the risk of cardiac death, nonfatal myocardial infarction (MI) or need for urgent revascularisation. None of these studies was blinded and follow-up was limited to a few weeks. Importantly, eligible patients did not have another indication for OAC. Taken together, the above mentioned trials indicate that in patients undergoing coronary stenting DAT is superior to the combination of aspirin and warfarin in reducing ischaemic endpoints, stent thrombosis and major bleeding, as judged within 4-6 weeks.

Dual antithrombotic therapy vs warfarin alone

Since DAT seems to be the best strategy following coronary stenting, as shown above, it was of interest to assess whether this combination might be an adequate substitute for OAC in patients who have an indication for such therapy. The ACTIVE-W study included 6,706 patients who had atrial fibrillation and at least one additional risk factor for stroke. Patients were randomised to either warfarin or aspirin plus clopidogrel. The primary endpoint was the composite of vascular death, stroke, MI or systemic embolism. The trial was prematurely discontinued due to evidence of superiority of warfarin. The primary endpoint was reduced by OAC as compared to DAT (3.9% vs 5.6%, p=0.0003) as was the rate of stroke (1.4% vs 2.4%, p=0.001). Therefore, DAT cannot be recommended as an alternative to OAC in patients with AF who are at moderate – high risk of embolism.

Warfarin + clopidogrel

No prospective study evaluated the combination of warfarin and clopidogrel following coronary stenting.

Retrospective analyses

A number of investigators analysed the course and outcome of patients who had an indication for OAC and received various antithrombotic combinations following coronary stenting. Lip and Karpha documented the substantial variability in management strategies which exists in these patients and highlighted the need for an accepted strategy[6]. In the Mayo Clinic[7], 66 consecutive patients were discharged on triple antithrombotic therapy (TAT) with aspirin, clopidogrel and warfarin following implantation of a bare metal stent. Most patients were treated for stable disease. The observation period was 30 days, which was also the duration of clopidogrel treatment. Six patients had a bleeding event, two of whom required a transfusion. There were no life-threatening bleeds, deaths or cases of stent thrombosis, myocardial infarction or target vessel revascularisation during the study period.

Buresly et al analysed a database of 21,443 elderly survivors of myocardial infarction in Quebec and compared the bleeding risk in patients discharged on various antithrombotic regimens[8]. Most patients received 300-325 mg of aspirin daily. The authors reported that warfarin, either alone or combined with aspirin, was associated with an increased risk of bleeding but the absolute risk was not prohibitive: 3.2% per year with aspirin alone and 6-8% per year on warfarin alone, warfarin plus aspirin or aspirin plus a thienopyridine. Only 12 patients received TAT in this cohort and thus the risk associated with this regimen could not be analysed.

Konstantino and coworkers analysed data from the bi-annual Israeli ACSIS survey, which includes all patients admitted to all coronary care units in the country over a two month period[9]. Seventy-six patients who received TAT were compared to 2,661 patients who received DAT. Major bleeding in hospital was observed in 2.6% and 0.6% of patients in the two groups, respectively (p=0.03). Adjusted one year mortality was not different between groups. The authors concluded that TAT is associated with a higher risk of bleeding than DAT but the risk is acceptable and is not associated with increased mortality.

Porter and coworkers from Rabin Medical Center in Israel reported their experience of TAT post coronary stenting[10]. Among 180 patients so treated over a five year period, 20 (11%) suffered a bleeding episode within 30 days, two of which were major.

Table 1. Studies comparing the combination of aspirin and warfarin to aspirin and ticlopidine following coronary stent implantation.

	ISAR	FANTASTIC	STARS	MATTIS
N	257	473	1653	350
Follow-up	30d	6 weeks	30d	30d
Primary endpoint	Death+MI+ CABG+re-PCI	Bleeding	Death+MI+ TVR+stent thrombosis	Death+MI+re-PCI
Primary endpoint: DAT vs aspirin + warfarin	1.6% vs 6.2%, (p=0.01)	13.5% vs 21.0% (p=0.03)	2.7% vs 0.5% (p=0.001)	5.6% vs 11.0% (p=0.07)
Bleeding (DAT vs aspirin + warfarin)	0 vs 6.5% (P<0.0001)	see above	5.5% vs 6.2%	1.7% vs 6.9% (p=0.02)
Stent thrombosis (DAT vs aspirin + warfarin)	0 vs 5.0% (P<0.0001)	2.8% vs 3.9% (p=0.58)	0.5% vs 2.7% (p=0.005)	NA

MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; TVR: target vessel revascularisation; DAT: dual antiplatelet therapy

The GRACE investigators analysed data from 800 patients who had coronary stenting (drug eluting stents in 16%) for an acute coronary syndrome and had, in addition, an indication for warfarin. The authors compared patients who were discharged on dual (n=580) or single (n=220) anti platelet therapy in addition to warfarin[11]. The rates of major bleeding in hospital and myocardial infarction and death at six months did not differ significantly between groups, but data on six months bleeding rates were not available. Outcomes among patients given aspirin or a thienopyridine (in addition to warfarin) were similar. The authors concluded that a regimen of warfarin + a single antiplatelet agent (either aspirin or a thienopyridine) may be reasonable in patients who require OAC following coronary stenting.

The above mentioned retrospective studies presented outcome data that were complete for 30 days follow-up. Longer follow-up regarding the risk of bleeding and stent thrombosis is greatly needed in this population but such data are almost non-existent. In a small (N=82) retrospective study from Royal Oak, MI, USA, the authors compared one year outcomes among patients who presented with ST elevation myocardial infarction and were subsequently discharged on either DAT or TAT[12]. The authors report an alarming rate of bleeding in the TAT group: 21% of patients required transfusion during follow up, as compared to 3.5% among patients given DAT. However, the small size of the study, and substantial differences in baseline characteristics between groups, make interpretation difficult.

Karjalainen et al reported on 239 patients who had an indication for OAC and also had coronary stent implantation[13]. Drug eluting stents were used in 42% of cases. These patients were compared to a matched control group who had coronary stenting but did not have an indication for OAC. The authors further analysed outcomes according to the antithrombotic regimen selected by the attending physicians: 48% of patients had TAT and 15-20% each were treated by aspirin plus clopidogrel, aspirin plus warfarin or clopidogrel plus warfarin. This study offers a number of important observations: 1) Patients who have an indication for OAC are a much higher risk group than those who do not: Mortality at 12 months was 8.7% vs 1.8%, respectively (p=0.003). The risk of myocardial infarction and major bleeding was also significantly increased; 2) Following coronary stenting the risk of stent thrombosis declines rapidly over time whereas the risk of stent thrombosis bleeding remains stable during the first year. This observation suggests that a relatively short course of clopidogrel might reduce the risk of bleeding without increasing the risk of stent thrombosis; 3) Major bleeding occurs in 6-12% of patients and does not seem to be increased by TAT as compared to other combinations; 4) The risk of stroke is markedly elevated in the absence of warfarin; 5) The risk of stent thrombosis and myocardial infarction is markedly elevated in the absence of clopidogrel; 6) The combination of clopidogrel plus warfarin compares reasonably well with either aspirin plus clopidogrel or warfarin plus aspirin.

The largest study to date addressing this issue was published by Ruiz – Nodar et al[14]. This registry from two Spanish hospitals included 426 patients who had atrial fibrillation and underwent coronary stenting (40% drug eluting stents). Half of the cohort was discharged on TAT and 40.8% were discharged on DAT alone. Median follow-up was 595 days. Similar to previous reports, the authors found that this group of patients was at high risk of future complications. Overall mortality was 22.6%, 12.3% of patients had major bleeding and 32.3% experienced a major adverse cardiovascular event (MACE). The authors found that the use of warfarin was associated with significantly lower rates of mortality (17.8% vs 27.8%, p=0.002) and of MACE (26.5% vs 38.7%, p-0.001). Major bleeding was increased by the use of warfarin, but this did not reach statistical significance (14.98% vs 9.0%, p=0.19). Multivariate analysis showed that non-use of warfarin and age were the only independent predictors of MACE. This large study strongly supports the use of TAT in patients with AF at high risk of embolism (as were most patients in this cohort) who undergo coronary stenting but demonstrates again that these patients are at a particularly high risk of death and adverse events. The same group published later the same year data from a different cohort of patients with atrial fibrillation who underwent coronary stenting using DES in 69% of patients[15]. In this report, the authors differentiated between early (within 48 hours) and late major bleeding and observed a significant increase in late major bleeding among patients given TAT without a significant difference in ischaemic endpoints between patients given DAT or TAT. This was a cohort at high risk of bleeding (mean age: 72, chronic renal failure: 59%) and the authors conclude that the risk of bleeding with TAT in such patients is substantial. This conclusion is strongly supported by two additional retrospective comparisons of TAT and DAT both showing that TAT is associated with an increased risk of major bleeding[16-17].

Minimising the risk of bleeding

Patients who require OAC following coronary stenting should usually receive bare metal stents to avoid the prolonged requirement for dual antiplatelet therapy after drug eluting stent implantation. The risk of bleeding can be lowered further in these patients by reconsidering the need for OAC, maintaining a relatively low INR, using low doses of aspirin and shortening the duration of clopidogrel therapy.

Patients with mechanical heart valves should always be given OAC. When anticoagulation is deemed necessary for other indications a reassessment of the indication is warranted. In patients who require OAC following venous thromboembolism the need for anticoagulation depends on the context of the thromboembolic event (i.e. whether there has been a reversible predisposition), the time since the event and the presence of thrombophilia. Atrial fibrillation is the most common indication for OAC in patients who had coronary stenting. Current guidelines for the management of atrial fibrillation mandate the use of warfarin in patients who have high risk features (prior stroke, mitral stenosis or a prosthetic heart valve) or in those who have more than one moderate risk factor (age >75, diabetes, heart failure, left ventricular dysfunction or hypertension)[18]. Patients who have less than two moderate risk factors may be managed with aspirin. If a decision has been made to use OAC in a patient who is on TAT special care should be taken to maintain the INR at the lowest effective range, typically 2.0-2.5 for patients with atrial fibrillation.

Another strategy to decrease the risk of bleeding is to use low dose (75-100 mg/d) aspirin. The CURE investigators showed that increasing the dose of aspirin beyond this range, whether with or without clopidogrel, is associated with increased bleeding but does not improve efficacy[19].

The recommendation to aim at relatively low INR values and use low dose aspirin is supported by the recently updated ACC/AHA 2007 guidelines for PCI[20].

Current ESC guidelines call for at least one month of clopidogrel therapy following bare metal stent implantation. Treatment should ideally be continued for 9-12 months, especially in patients with acute coronary syndromes[21]. However, in patients who require TAT it seems prudent to limit the duration of clopidogrel treatment to the minimum of one month.

In patients in whom discontinuation of anticoagulation should be kept to the minimum (i.e. patients with prosthetic valves) performing angiography by the radial approach has the advantage of near elimination of the risk of puncture site bleeding, allowing for earlier resumption of intravenous and then oral anticoagulation.

Recommendations (see Figure 1)

Due to the relative paucity of evidence there is no clear recommendations given in current American and European guidelines regarding the antithrombotic strategy in patients who require OAC post coronary stenting. The atrial fibrillation guidelines only give a IIb recommendation for either TAT or the combination of warfarin and clopidogrel in this setting[17].

Based on the available literature the following recommendations can be made: when stenting is considered in a patient who requires chronic anticoagulation the indication for stenting as well as the need for warfarin should be reassessed in view of the guidelines. Medical and surgical alternatives to percutaneous intervention should be carefully considered. Patients with atrial fibrillation who have less than two moderate risk factors for stroke can be managed without warfarin. If both coronary stenting and warfarin are necessary, drug eluting stents should be avoided as much as possible. In patients who are not at a high bleeding risk triple anticoagulation is probably the best choice. The bleeding risk in patients who require triple therapy may be reduced by selecting a very low dose (75-80 mg/d) of aspirin and by limiting the duration of clopidogrel therapy to one month. If bleeding risk is high, the combination of warfarin and clopidogrel may be considered. Patients should be thoroughly educated regarding the need for careful INR monitoring and the risk of bleeding and thrombosis. Prospective, randomised studies are clearly needed to better define the best therapeutic strategy for patients who require chronic anticoagulation post coronary stenting.

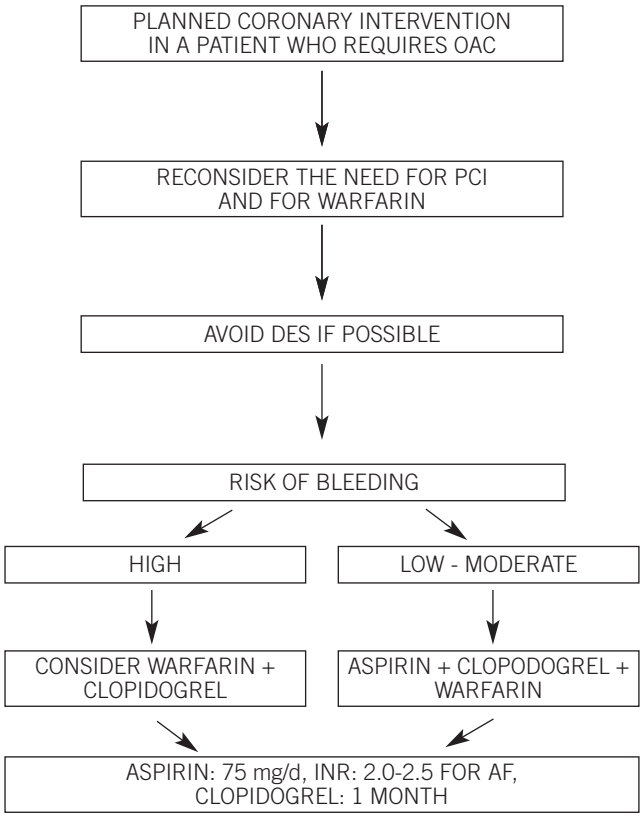

Figure 1. A proposed algorithm for the management of patients who have required coronary stenting and have an indication for chronic anticoagulation. OAC: oral anticoagulation. PCI: percutaneous coronary intervention. DES: drug eluting stents.

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