

Review Article

Triple Antithrombotic Therapy with Aspirin, a Thienopyridine Derivative Plus Oral Anticoagulation in Patients with Atrial Fibrillation Undergoing Coronary Stenting

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Key words:

Antithrombotic therapy, coronary stenting, bleeding, clopidogrel, aspirin, atrial fibrillation.

Manuscript received:

August 20, 2009;

Accepted:

January 10, 2010.

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According to current guidelines, all patients with a recent coronary artery stent placement should receive double antiplatelet therapy with a combination of aspirin plus clopidogrel to reduce the likelihood of acute and subacute stent thrombosis.¹ The length of treatment depends on the type of the stent, with drug-eluting stents requiring at least 6-12 months of both antiplatelet drugs. Atrial fibrillation (AF) carries a high risk for thromboembolic events and any patient with at least two moderate risk factors (or probably even one) should be on oral anticoagulation (OAC) with a vitamin K antagonist.² Since AF and coronary artery disease with stent placement are common, it is not infrequent to treat patients with both these conditions, where triple antithrombotic therapy with aspirin, clopidogrel and OAC would be needed. However, concerns about increased bleeding risk do exist and clinicians are uncertain about how to manage this difficult clinical situation – especially since there are no large randomised trials to guide clinical practice regarding this particular issue.

Antiplatelet therapy in patients with coronary stents

Dual antiplatelet therapy with aspirin and

clopidogrel has been proven to be beneficial for patients with acute coronary syndromes and those undergoing percutaneous coronary interventions (PCI) in the short and long term.^{3,4} Especially in patients undergoing PCI with stenting, short term aspirin treatment plus a thienopyridine derivative results in a substantially lower rate of cardiovascular ischaemic events than does either aspirin alone or warfarin.⁵ In a meta-analysis of 4 trials including 25,000 patients with stent implantation, the combination of aspirin plus a thienopyridine was superior to the combination of aspirin plus warfarin; the combined endpoint of death, myocardial infarction or revascularisation procedures was reduced by 60%; the incidence of acute or subacute stent thrombosis was reduced (non-significantly) but at the cost of increased major bleeding (similarly non-significantly).⁶

On the basis of randomised clinical trial protocols, and according to the current guidelines, the administration of aspirin and clopidogrel should comply with the following scheme: aspirin 162 mg to 325 mg daily (100 mg is considered adequate according to ESC guidelines) should be given for at least 1 month after implantation of a bare-metal stent (BMS), 3 months after

implantation of a sirolimus-eluting stent (SES), and 6 months after implantation of a paclitaxel-eluting stent (PES).^{1,4} After this early period, long-term use of aspirin should be continued indefinitely at a low dose of 75 mg to 162 mg daily. Likewise, clopidogrel 75 mg daily should be given for a minimum of 1 month after implantation of a BMS (minimum 2 weeks for patients at significantly increased risk of bleeding) and for 12 months after implantation of a SES or PES if the risk of bleeding is not considered high. Under circumstances that prevent the use of clopidogrel for 1 year, the duration can be shortened to 3 months for a SES and 6 months for a PES. The continuation of clopidogrel therapy beyond 1 year is not established and should depend on the judgment of the risk-benefit ratio for the individual patient. It should be emphasised that the risk of overt gastrointestinal bleeding with dual antiplatelet therapy can be as high as 1.3% within the first 30 days of therapy.³

Late (day 30 to 1 year) or very late (beyond 1 year) stent thrombosis has been reported in both DES and BMS, but mainly concerns DES (where it is likely to appear as a primary thrombosis with extremely high mortality) and represents another growing and major safety concern related to stent implantation.⁷ Late stent thrombosis accounts for 40% of all stent thromboses and is reported to occur at an annual rate of 0.6% up to 3 years (or even later) after DES implantation.⁸⁻¹⁰ Late stent thrombosis is more frequent with PES (1.8%) as compared with SES (1.4%). Premature discontinuation of antiplatelet agents is one of the predictors of late stent thrombosis.^{11,12} It is obvious that patients should be informed about the need for prolonged dual antiplatelet therapy, especially if a DES is implanted, and their consent concerning strict compliance should be obtained.

Anticoagulation in patients with AF

Patients with AF are at risk of developing stroke or systemic embolism. The risk depends on the presence of several risk factors, which are classified as high risk (previous stroke, transient ischaemic attack [TIA] or other embolic event, mitral stenosis, prosthetic heart valve) or moderate risk (age over 75, hypertension, heart failure, ejection fraction [EF] <35% and diabetes mellitus). According to the current ESC/AHA/ACC guidelines any patient with AF and any high risk factor or more than one moderate risk factor should be anticoagulated with a vitamin K antagonist, aiming at an international normalised ratio (INR) target

2.0-3.0.² Patients without risk factors could be treated with aspirin (or even no antithrombotics at all), at a dose of 81-325 mg daily, while in patients with only one moderate risk factor there is a choice between either aspirin or oral anticoagulation. The CHADS-2 score is a simple scoring system with prior stroke or TIA counting as 2 points, and age >75, hypertension, diabetes and heart failure each counting as 1 point.¹³ Patients with a score of 0 or 1 have a sufficiently low annual embolic risk (less than 4% per year) and could be treated with aspirin alone, while patients with CHADS-2 score 2-6 (annual risk 4-30%) should be anticoagulated with vitamin K antagonists.¹⁴

Recently, the ACTIVE-W trial randomised patients with AF and at least 2 stroke risk factors to treatment with warfarin (as recommended by the guidelines) or a combination of aspirin 75 mg/day plus clopidogrel 75 mg/day.¹⁵ The study was stopped prematurely as the double antiplatelet combination was inferior to warfarin. Therefore, if patients with AF and a recent stent placement receive only double antiplatelet therapy for the recommended time period according to the type of stent (DES or BMS) they may not be sufficiently protected against AF-related embolism. With an average annual embolic risk of 5-15% it could be assumed that if warfarin therapy is discontinued, the AF-related risk would be 0.4-1.2% per month (or somewhat smaller, since aspirin and clopidogrel would confer partial protection).

The clinical importance of major bleeding

In any clinical trial with antithrombotic therapies, clinical effectiveness is weighed against risk. Effectiveness is measured as a reduction in mortality, reinfarction and recurrent ischaemia, whilst risk is measured as an increase in major and minor bleeding. An antithrombotic regimen that reduces mortality would make an increased bleeding risk look acceptable. Recently, more attention has been drawn to the long-term prognostic significance of major bleeding. From the GRACE registry and the OASIS-5 trial it was evident that a major bleed in hospital resulted in increased mortality at 6 months.¹⁶⁻¹⁸ In fact, major bleeding has the same long-term prognostic impact as a non-fatal (re)infarction. Consequently, an antithrombotic regimen that reduces just reinfarction or recurrent ischaemia, but not mortality, would make an increased major bleeding risk look unacceptable.

In studies of acute coronary syndromes the main risk factors that are associated with increased bleed-

ing risk are the use of platelet glycoprotein IIb/IIIa inhibitors, advanced age, renal failure, female gender, history of haemorrhage, whilst in studies of chronic OAC therapy the main factors are advanced age, prior stroke, history of bleeding, low haematocrit, diabetes and increased serum creatinine level. One of the problems is that patients at high risk for bleeding are at the same time at high risk for ischaemic events (since some of the risk factors apply to both conditions) and therefore require increased antithrombotic therapy despite bleeding risk.^{16,19} Every effort must be made to avoid bleeding.²⁰ To justify the use of triple antithrombotic therapy with aspirin, clopidogrel plus OAC and accept the inevitable increased risk of bleeding, strong indications for all three drugs should be present: early period after stenting and high risk AF.

Triple therapy

At present, solid evidence regarding the management of patients with AF undergoing stent implantation is lacking. There are no randomised clinical trials and the management of these patients is left to the discretion of the individual physician. Indeed, triple therapy with OAC, aspirin and a thienopyridine derivative is the main antithrombotic strategy prescribed over the medium term after PCI with stent implantation in patients with an indication for OAC. In the GRACE registry, among 800 patients with an acute coronary syndrome and an indication for warfarin (40% AF), 580 were discharged on warfarin plus dual antiplatelet therapy and 220 on warfarin and single antiplatelet therapy.²¹ Similarly, in the CRUSADE registry, among 1247 patients who underwent stent implantation and were previously on warfarin, 60% were discharged on triple therapy, 31% on dual antiplatelet without warfarin, and 3% on warfarin plus aspirin without clopidogrel.²²

Clinical studies evaluating the combination of aspirin, thienopyridines, and anticoagulants

Relevant published studies describing outcomes in patients receiving dual antiplatelet therapy in combination with OAC were recently reviewed and are summarised in Table 1.^{21,23-35} These studies were performed most often in patients who had additional indications for chronic anticoagulation following an acute coronary syndrome or PCI (AF in 40-100% of cases). Doses of aspirin used in the studies ranged from 81 mg/day to 325 mg/day, while the target INR varied by indication

and was reported in only 2 of the studies. It should be noted that each study was affected by various important limitations such as: small sample size (only 3 studies with more than 400 patients), unspecified doses of medications, absence of information on the duration of treatments, inconsistent efficacy outcomes concerning rates of stent thrombosis and recurrent myocardial ischaemic events, retrospective design, and absence of a control group. Although bleeding was invariably reported in these studies the severity of the bleeding and the timing of its occurrence were not consistently reported.

Among the aforementioned studies, two retrospective ones are selected on the basis of their methodology, clinical interest and limitations and will be described in more detail herein. The first one is the study of Ruiz-Nodar et al, which is the largest study reported to date in patients receiving triple antithrombotic therapy, where clinical outcomes of both bleeding and ischaemic events are reported.³⁴ This study was designed to review outcomes in relation to antithrombotic therapy management strategies for patients with AF who underwent PCI with stenting. The authors reviewed retrospectively 426 patients (70.9% men, mean age 71.5 ± 8.5 years) for whom clinical and demographic characteristics, stroke risk factors and antithrombotic therapy use before PCI and at discharge were recorded. Clinical follow up was performed, and all bleeding episodes, thromboembolic, and major adverse cardiac events (MACE) (i.e. death, acute myocardial infarction, or target lesion revascularisation) were reported. The most commonly associated comorbidities were hypertension (74.5%), diabetes mellitus (40.2%), chronic renal failure (14.9%), and congestive heart failure (26.7%); 80% of patients had more than 2 stroke risk factors. According to the study results, the combination of antithrombotic drugs prescribed at discharge was aspirin plus clopidogrel in 174 patients (40.8%) and triple therapy (OAC, aspirin plus clopidogrel) in 213 patients (50%). Complete follow up was achieved in 87.5% (median 594 days; range 0 to 2190). The incidence of adverse events was high (36.6%, with major bleeding in 12.3%); thromboembolic events occurred in 4.2%, and MACE in 32.3%. All-cause mortality was also high (22.6%). In a multivariate analysis, non-anticoagulation with OAC was found to be associated with increased mortality (17.8% vs. 27.8%; hazard ratio [HR]: 3.43, $p=0.002$) and MACE (26.5% vs. 38.7%; HR: 4.9, $p<0.01$). In a Cox-regression analysis, non-anticoagulation ($p<0.01$) and age ($p=0.02$) were independent predictors of MACE. The authors concluded that patients with AF undergoing PCI with

Table 1. Overview of clinical studies evaluating the combination of anticoagulants with aspirin and thienopyridines (triple therapy).

Reference/(Design)	Population in TT	Duration of TT	Bleeding risk	Outcome
Orford J, et al. ²⁵ (Retrospective)	66	NR	9.2% (3% major)	NR
Buresly K, et al. ²⁶ (Case-control)	141	5-1551 days (mean 654)	0.7%	NR
Mattichak S, et al. ²⁷ (Retrospective)	40	NR	15% GI bleeding in TT vs. 9% in DT, p: NS	Non-significant trend toward reinfarction at 6 and 12 months in W treated pts
Konstantino Y et al. ²⁸ (Retrospective)	76	NR	Major bleeding 2.6% in TT vs. 0.6% in DT, p=0.03	No differences in adjusted 30-day and 6-month mortality between TT and DT
Porter A, et al. ²⁹ (Case series)	180	30 days	11% (1% major, 10% minor)	All cause mortality 10% after 476 days follow up
Khurram Z, et al. ³⁰ (Retrospective)	107	211 ± 114 days	Major bleeding 6.6% in TT vs. 0% in DT; p= 0.03) and minor bleeding 14.9% vs. 3.8% respectively, p=0.01)	NR
DeEugenio et al. ³¹ (Retrospective)	97	182 days (range 0-191 days)	Major bleeding 14% in TT vs. 3% in DT; p=0.012)	NR
Karjalainen P et al. ³² (Retrospective)	106	4.1 months	Major bleeding was similar between groups (6.6% TT vs. 6.1% W+ASA vs. 11.1% W+C vs. 11.8% ASA+C). Major bleeding was more common in the W group (p=0.01).	At 12 months death, MI, TLR, or stent thrombosis was higher in the W group (p=0.003), mainly driven by a difference in mortality (p=0.003), but also the incidence of MI was higher in the W group (p=0.04).
Nguyen M, et al. ²¹ (Retrospective)	580	NR	No differences in major bleeding were observed in hospital between pts in TT and those in W+single antiplatelet agent (5.9% vs. 4.6%). Follow-up data on bleeding events NR.	At 6 months, a significant reduction in stroke was observed in patients receiving TT (0.7% vs. 3.4%, p=0.02) whereas no differences in death (5.1% vs. 6.5%) and (re)infarction were found (3.3% vs. 4.5%)
Nguyen M, et al. ³³ (Retrospective)	86	30 days	Major bleeding 1.2% in TT vs. 0.3% in DT, p=NS; minor bleeding 0% in TT vs. 0.4% in DT, p: NS	NR
Ruiz-Nodar J et al. ³⁴ (Retrospective)	213	594 days (0-2190)	The rates of major bleeding in AC and non-AC pts were 14.9% and 9% respectively (p: NS), while the relevant rates of minor bleeding were 12.6 and 9% (p: NS)	The incidence of death was 17.8% in AC pts and 27.8% in those non-AC (p=0.02). No significant differences were observed concerning AMI and TLR. The incidence of MACE was 26.5% and 38.7%, p<0.01 in AC and non-AC pts, respectively
Rogacka R et al. ³⁵ (Retrospective)	127	5.6 months	7.1% (4.7% major)	At 21 months DES had less TLR than BMS (14.1% vs. 26.8%, p<0.05)

AC – anticoagulation; AMI – acute myocardial infarction; ASA – aspirin; C – clopidogrel; DT – dual therapy (ASA+thienopyridine); GI – gastrointestinal; MACE – major adverse cardiac events; NR – Not reported; pts – patients; TLR – target lesion revascularisation; TT – triple therapy; W – warfarin.

stenting represent a high-risk population because of age, comorbidities, and the presence of stroke risk factors. These patients have a high mortality and MACE rate, which is reduced by anticoagulation therapy.

In the second relevant study, Karjalainen et al evaluated the safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting.³² The investigators analysed retrospectively all consecutive patients on warfarin therapy (n=239, mean age 70 years, men 74%) who underwent PCI in 2003-2004 in six hospitals. An age- and sex-matched control group with similar disease presentation (unstable or stable symptoms) was selected during the same study period. The primary endpoint was defined as the occurrence of death, myocardial infarction, target vessel revascularisation, or stent thrombosis at 12 months. Triple therapy with aspirin and clopidogrel was the most common (48%, 106 patients) option in stented patients in the warfarin group. Among the 4 possible drug combinations, warfarin+aspirin+clopidogrel, warfarin+aspirin, warfarin+clopidogrel and aspirin+clopidogrel, the rates of major bleeding were 6.6%, 6.1%, 11.1% and 11.8%, respectively; the rates of stroke 2.8%, 3%, 0%, and 8.8%; the rates of stent thrombosis 1.9%, 15.2%, 0%, and 5.9%; whereas the rates of myocardial infarction were 8.5%, 18.2%, 11.1% and 5.9%. It is emphasised that most of the events in the subgroup receiving triple therapy occurred at a time when the triple drug regimen was discontinued. Warfarin treatment was an independent predictor of both the primary endpoint (OR 1.7, p=0.05) and major bleeding (OR 3.4, p=0.02). Observing the above results, in patients who for some reason were considered ineligible for the triple regimen, a combination of warfarin plus clopidogrel seems more appropriate in terms of efficacy and safety. The final conclusion of the authors was that after coronary stenting the prognosis is unsatisfactory in warfarin-treated patients, irrespective of the drug combination used. Aspirin plus warfarin combination seems to be inadequate to prevent stent thrombosis.

Of the two prospective (but with *post hoc* analysis) registries, GRACE has studied patients who received a stent after an acute coronary syndrome and were also prescribed warfarin (for AF or other indications), and reported interesting findings.²¹ When comparing patients on triple therapy (warfarin, aspirin plus clopidogrel) versus patients on dual therapy (warfarin plus aspirin or clopidogrel) at 6 months' follow up there were no significant differences in death (5.1% vs. 6.5%; p=0.47) or (re) infarction (3.3% vs. 4.5%; p=0.49), while major bleeding

in hospital was similar (5.9% vs. 4.6%; p=0.46). Unfortunately, there are no data on bleeding after discharge, which would be of great importance.

Risk of bleeding or transfusion is the principal concern associated with triple therapy. Overall, major bleeding varies between <1% and 15% and up to 21% of patients need a transfusion (Table 1). Bleeding most commonly involves the gastrointestinal tract.²³ In general, the relative risk of major bleeding in patients receiving triple therapy is 3 to 5-fold higher than that observed in patients receiving dual antiplatelet therapy alone. Risk factors for bleeding include age >65, history of stroke, history of bleeding (for example peptic ulcer or cerebral bleeding), specific comorbid conditions (renal insufficiency, recent myocardial infarction or severe anaemia), multiple drug regimen (polypharmacy), uncontrolled hypertension.^{36,37} The incidence of major bleeding varies from 1% in patients with no risk factor to 30% in patients with 3 or more risk factors.³⁷

The frequency of haemorrhage increases with a longer duration of triple therapy. A shorter use of triple therapy for only 1 month is probably safer and thus the use of DES in patients needing OAC should be discouraged – especially since a DES does not seem to be a superior treatment in terms of death and infarction, but only prevents restenosis and target lesion revascularisation.³⁸⁻⁴⁰

Recommendations

Indirect recommendations for the use of triple therapy can be found in the current guidelines on PCI, on acute coronary syndromes and on AF. In fact, the AHA guidelines for PCI in patients requiring warfarin, clopidogrel, and aspirin therapy after the procedure recommend an INR of 2.0 to 2.5 with low-dose aspirin (75 mg to 81 mg) and a 75 mg dose of clopidogrel (class IC).⁴ Guidelines on the management of non ST-elevation myocardial infarction recommend that a triple regimen should only be given if a compelling indication exists, in which case the lowest efficacious INR and shortest duration of the triple regimen should be targeted (Class IIa-C).⁴¹ Guidelines on the management of acute myocardial infarction with persistent ST-segment elevation recommend low dose aspirin (<100 mg daily) and/or clopidogrel concurrently with OAC (class IIb-C), while in the ESC/AHA/ACC guidelines on AF the authors even propose the combination of warfarin plus clopidogrel initially and then warfarin alone in

patients with a stent, although such policy is not supported by any reference.^{2,42}

In order to make some practical clinical recommendations the following parameters should be considered:²⁴

- what is the thromboembolic risk of AF?
- what is the risk of bleeding?
- what is the type of the stent implanted?
- what is the clinical situation (elective or acute coronary syndrome)?

If the risk of AF is considered small (CHADS-2 score 0 or 1), and since aspirin may be adequate, we can avoid triple therapy and use aspirin plus clopidogrel for the early period after stent implantation.

If the risk of AF is at least moderate (CHADS-2 score ≥ 2) we have to continue OAC. In this situation, if the patient's risk for bleeding is considered low we could use triple therapy, but the length of treatment depends upon the type of stent and the clinical situation: a) with a BMS triple therapy for one month, and then only OAC; b) with a DES triple therapy for 6 months, combination of clopidogrel plus OAC for the period 6-12 months, and then just OAC; c) after an acute coronary syndrome regardless of the type of stent triple therapy for 6 months, clopidogrel plus OAC for the period 6-12 months and then just OAC.

If the patient's risk for bleeding is considered high, then DES should be avoided. In an elective implantation of a BMS triple therapy should be used with caution for a month (minimum of 15 days), followed by OAC. In the setting of an acute coronary syndrome with BMS implantation, triple therapy should be used for one month (minimum 15 days), double therapy with clopidogrel plus OAC for the period 1-6 months, and then just OAC (Figure 1 summarises the above mentioned practical recommendations).

Finally, some special considerations are useful in making clinical decisions and the following points should be kept in mind: when triple therapy is used it is important to check INR levels frequently (weekly) and keep the intensity at low levels (2.0-2.5). Similarly, the aspirin dose should be kept at 100 mg daily. Since most bleeding events with triple therapy are related to gastrointestinal haemorrhages, the use of proton pump inhibitors seems reasonable, despite the possibility of an interaction with clopidogrel resulting in reduced antiplatelet activity.⁴³ Among DES it seems that sirolimus coated stents require a shorter time for endothelialisation than paclitaxel ones.⁴⁴ In the case of an acute coronary syndrome, after the

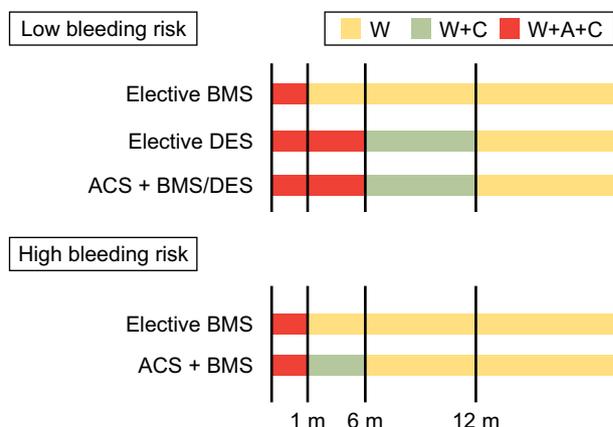


Figure 1. Recommended combination and length of antithrombotic therapy according to bleeding risk, type of stent and clinical setting. W – warfarin; C – clopidogrel; A – aspirin; DES – drug eluting stent; BMS – bare metal stent; ACS – acute coronary syndrome.

initial mandatory period of triple therapy and up to the completion of 12 months, a choice between OAC plus aspirin or OAC plus clopidogrel must be made. There are no hard data to support either policy, although the latter combination seems more appropriate in terms of efficacy and safety.³² After 12 months from stent placement or an acute coronary syndrome, stable patients with AF can continue on OAC alone with the target INR level being 2.0-3.0.

New antithrombotic therapies and new stents with rapid endothelialisation are being tested and therefore new practices may arise in the future. For example, recently, the results of the RE-LY randomised trial, which compared fixed doses of the new oral direct thrombin inhibitor dabigatran (110 mg and 150 mg twice daily) with adjusted-dose warfarin in patients with AF, were published.⁴⁵ Both dabigatran doses were non-inferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150 mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism and the 110 mg dose was superior to warfarin with respect to major bleeding. Therefore, this new antithrombotic agent, which notably does not require INR determination, might be safer in combination with antiplatelets in patients with AF and recent stent implantation. At present, a careful consideration of the risks of bleeding against the risk of recurrent ischaemia or stent thrombosis is needed and a rational use of antiplatelets and OAC in patients with AF undergoing stent placement is mandatory.

References

- Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. *Eur Heart J.* 2005; 26: 804-847.
- Fuster V, Rydén L, Cannon DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. *Europace.* 2006; 8: 651-745.
- Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001; 345: 494-502.
- King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol.* 2008; 51: 172-209.
- Mehta SR, Yusuf S. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J.* 2000; 21: 2033-2041.
- Rubboli A, Milandri M, Castelvetti C, Cosmi B. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting. Clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. *Cardiology.* 2005; 104: 101-106.
- Serruys PW, Daemen J. Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents. *Circulation.* 2007; 115: 1433-1439.
- Wenaweser P, Daemen J, Zwahlen M, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. *J Am Coll Cardiol.* 2008; 52: 1134-1140.
- Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet.* 2007; 369: 667-678.
- Korovesis S, Katritsis DG. Stent thrombosis four and a half years after implantation of a sirolimus-eluting stent. *Hellenic J Cardiol.* 2009; 50: 423-425.
- Grines CL, Bonow RO, Casey DE, et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *J Am Coll Cardiol.* 2007; 49: 734-739.
- Iakovou I, Mehra R, Dangas G. Thrombosis after implantation of drug-eluting stents. *Hellenic J Cardiol.* 2006; 47: 31-38.
- Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA.* 2003; 290: 1049-1056.
- van Walraven C, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med.* 2003; 163: 936-943.
- Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet.* 2006; 367: 1903-1912.
- Moscucci M, Fox KAA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J.* 2003; 24: 1815-1823.
- Yusuf S, Mehta S, Chrolavicius S, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. The OASIS-5 Investigators. *N Engl J Med.* 2006; 354: 1464-1476.
- Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KAA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation.* 2006; 114: 774-782.
- Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med.* 1998; 105: 91-99.
- Potsis TZ, Katsouras C, Goudevenos JA. Avoiding and managing bleeding complications in patients with non-ST-segment elevation acute coronary syndromes. *Angiology.* 2009; 60: 148-158.
- Nguyen MC, Lim YL, Walton A, et al. Combining warfarin and antiplatelet therapy after coronary stenting in the Global Registry of Acute Coronary Events: is it safe and effective to use just one antiplatelet agent? *Eur Heart J.* 2007; 28: 1717-1722.
- Wang TY, Robinson LA, Ou F-S, et al. Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: physician practice in the CRUSADE registry. *Am Heart J.* 2008; 155: 361-368.
- Holmes DR, Kerciakes DJ, Kleiman NS, Moliterno DJ, Patti G, Grines CL. Combining antiplatelet and anticoagulant therapies. *J Am Coll Cardiol.* 2009; 54: 95-109.
- Rubboli A, Halperin JL, Airaksinen KEJ, et al. Antithrombotic therapy in patients treated with oral anticoagulation undergoing coronary artery stenting. An expert consensus document with focus on atrial fibrillation. *Ann Med.* 2008; 40: 428-436.
- Orford JL, Fasseas P, Melby S, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J.* 2004; 147: 463-467.
- Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med.* 2005; 165: 784-789.
- Mattichak SJ, Reed PS, Gallagher MJ, Boura JA, O'Neill WW, Kahn JK. Evaluation of safety of warfarin in combination with antiplatelet therapy for patients treated with coronary stents for acute myocardial infarction. *J Interv Cardiol.* 2005; 18: 163-166.
- Konstantino Y, Iakobishvili Z, Porter A, et al. Aspirin, warfarin and a thienopyridine for acute coronary syndromes. *Cardiology.* 2006; 105: 80-85.
- Porter A, Konstantino Y, Iakobishvili Z, Shachar L, Battler A, Hasdai D. Short-term triple therapy with aspirin, warfarin, and a thienopyridine among patients undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv.* 2006; 68: 56-61.
- Khurram Z, Chou E, Minutello R, et al. Combination thera-

- py with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol.* 2006; 18: 162-164.
31. DeEugenio D, Kolman L, DeCaro M, et al. Risk of major bleeding with concomitant dual antiplatelet therapy after percutaneous coronary intervention in patients receiving long-term warfarin therapy. *Pharmacotherapy.* 2007; 27: 691-696.
 32. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J.* 2007; 28: 726-732.
 33. Nguyen MC, Murphy SA, Mega JL, et al. Triple therapy: ASA, thienopyridine and oral anticoagulation therapy following ST elevation myocardial infarction (STEMI): is it safe? (abstract 2221). *Circulation.* 2007; 116 (suppl II): II-483.
 34. Ruiz-Nodar JM, Marvn F, Hurtado JA, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. *J Am Coll Cardiol.* 2008; 51: 818-825.
 35. Rogacka R, Chieffo A, Michev I, et al. Dual antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients taking chronic oral anticoagulation. *JACC Cardiovasc Interv* 2008; 1: 56-61.
 36. Lip GYH, Karpha M. Anticoagulant and antiplatelet therapy use in patients with atrial fibrillation undergoing percutaneous coronary intervention: the need for consensus and a management guideline. *Chest.* 2006; 130: 1823-1827.
 37. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med.* 1989; 87: 144-152.
 38. Babapulle MN, Bélisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug -cluting stents. *Lancet.* 2004; 364: 583-591.
 39. Voudris V. Drug-eluting stents in coronary interventions. *Hellenic J Cardiol.* 2004; 45: 140-144.
 40. Alidoosti M, Salarifar M, Haji-Zeinalli AM, Kassaian SE, Dehkordi MR, Fathollahi MS. Clinical outcomes of drug-eluting stents compared with bare metal stents in our routine clinical practice. *Hellenic J Cardiol.* 2008; 49: 132-138.
 41. Anderson J, Adams C, Antman E, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction. *J Am Coll Cardiol.* 2007; 50: e1-e157.
 42. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J.* 2008; 29: 2909-2945.
 43. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA.* 2009; 301: 937-944.
 44. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol.* 2006; 47: e1-e121.
 45. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; 361: 1139-1151.