CLINICAL PHARMACOLOGY

Triple antithrombotic management after stent implantation: when and how?

Albert Schömig, Nikolaus Sarafoff, Melchior Seyfarth

► Additional references are published online only at http://heart.bmj.com/content/vol95/issue15

Deutsches Herzzentrum München and 1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Germany

Correspondence to: Professor Albert Schömig, Deutsches Herzzentrum München, Lazarettstr. 36, 80636 Munich, Germany; aschoemig@dhm.mhn.de

Inhibition of platelet activation is a cornerstone of adjunctive medical treatment during and after percutaneous coronary interventions with stent implantation (PCI-S) in order to prevent acute and long term thrombotic complications. Dual antiplatelet therapy (DAT) with aspirin and clopidogrel has been proven to be very effective at preventing adverse events such as acute and subacute stent thrombosis, myocardial infarction, and death after coronary stenting, for both bare metal stents (BMS) and drug eluting stents (DES). Oral anticoagulation (OAC) is the recommended treatment for patients at risk of thromboembolic events due to atrial fibrillation, mechanical heart valves, deep vein thrombosis, pulmonary embolism and left ventricular thrombi. The number of patients who have an indication for both DAT and OAC is increasing, since more patients who are already on OAC are scheduled for percutaneous coronary interventions and some patients who are on DAT will develop a medical condition which requires OAC. Consequently, these patients need triple antithrombotic therapy, consisting of aspirin, clopidogrel and OAC. There is a concern, however, that this "triple therapy" leads to increased bleeding events and physicians are cautious in prescribing the combination of DAT and OAC.

In the first part of this article, we review the studies and present the evidence that have led to the current recommendations for either DAT or OAC in the specific medical conditions. We will evaluate when OAC and DAT might be interchangeable, and whether one or the other of these regimens might be temporarily discontinued. We will focus on patients requiring OAC with a recent stent implantation or who are scheduled for a PCI-S. The second part of this review focuses on the currently available data on triple therapy and will provide guidance on how to manage these patients and how long the duration of treatment should be.

INDICATION AND DURATION OF DUAL ANTIPLATELET THERAPY IN PATIENTS WITH PCI-S

Dual antiplatelet therapy with aspirin and clopidogrel for a minimum of 4 weeks is the recommended adjunctive treatment after coronary stenting in all patients. In the early years of coronary stenting, patients received only aspirin and OAC after stent implantation for the prevention of thrombotic occlusion of the stented vessel. This treatment had some serious limitations due to both a residual high incidence of stent thrombosis and a significant occurrence of haemorrhagic complications.[w1] Therefore, a superior adjunctive medical treatment was sought and was found in an increased inhibition of activated platelets by combining aspirin and a thienopyridine (ticlopidine, and later clopidogrel). Compared to the combination of aspirin and OAC, DAT is superior in reducing thrombotic events (stent thrombosis and myocardial infarction) and in reducing haemorrhagic complications.[1 w2 w3] Consequently, clopidogrel together with aspirin is the current recommendation for antithrombotic therapy after coronary stenting, regardless of the type of stent (DES or BMS).[2] The recommended duration of this DAT, however, depends on the type of stent.

In patients treated with a BMS, the recommended minimal duration of DAT after implantation of a coronary stent is 4 weeks.[3] After that time period, it is assumed that the stent struts are sufficiently endothelialised, and stent thrombosis is a rare event. Consequently, DAT can be discontinued and a single antiplatelet therapy with aspirin or clopidogrel can be continued. The rapid re-endothelialisation of BMS struts is often accompanied by a significant degree of neointimal hyperplasia which may predispose to restenosis and necessitate repeat coronary interventions. With DES the neointimal hyperplasia of the stented segment can be effectively inhibited and the need for repeat revascularisation procedures can be significantly reduced.[w4 w5] At the same time there is a need for a prolonged duration of DAT following DES implantation because of a delayed re-endothelialisation of the stented segment and the associated risk of stent thrombosis. There is ongoing debate regarding the optimal duration of DAT after DES. The current guidelines recommend at least 12 months of DAT after DES implantation.[3] However, some studies suggest that discontinuation of clopidogrel is a major determinant of stent thrombosis only in the first 6 months after stent placement.[4] Whether the optimal duration of DAT after DES placement will be 6 or 12 months (or even longer) is currently unclear and under investigation. One multicentre, randomised study has been started to compare prospectively 6 and

Heart 2009;**95**:1280–1285. doi:10.1136/hrt.2008.160457

12 months of DAT after DES in 6000 patients (ISAR-SAFE, Intracoronary Stenting and Antithrombotic Regimen: Safety And eFficacy of a 6-month DAT after drug-Eluting stenting).

INDICATION AND DURATION OF ORAL ANTICOAGULATION

There are different indications as to why patients scheduled for PCI-S are on OAC. In general OAC is the recommended regimen to prevent arterial and venous thromboembolism. However, the intensity and the duration of OAC differ from indication to indication and OAC may be substituted by DAT in some patients.

Atrial fibrillation

Atrial fibrillation is the most frequent reason for long term OAC, accounting for 70% of the patients on OAC scheduled for PCI-S.[5] The overall prevalence of atrial fibrillation in patients over 60 years is 4%. The prevalence rises to 9% in patients over 80 years. It is forecast that, due to an increasing population age profile, the number of patients with atrial fibrillation will have more than doubled by 2050.[w6]

Multiple randomised trials have evaluated the efficacy and safety of OAC or aspirin for stroke prophylaxis in atrial fibrillation and have shown that OAC is superior to aspirin in reducing stroke in patients with atrial fibrillation.[6] This reduction of strokes was significantly higher than the increase in major bleedings by OAC. OAC has also been compared to DAT in a large randomised trial and has been shown to have superior efficacy in preventing strokes.[7] However, the net benefit of OAC in patients with atrial fibrillation strongly depends on the individual absolute risk for stroke and bleeding. The $CHADS_2$ score, which includes cardiac failure, arterial hypertension, age, diabetes mellitus, and previous stroke, is the most commonly used model to risk stratify patients (table 1).[w7] Patients with a $CHADS_2$ score $\leqslant 1$ are at low risk for stroke and can be treated with aspirin (or DAT in case of PCI-S). Patients with a $CHADS_2$ score $\geqslant 2$ may be expected to derive incremental benefit from OAC (international normalised ratio (INR) 2.0–3.0), since the individual risk for stroke gradually outweighs the annual risk for major bleeding, which may be assumed to be 1–2% (table 1).[8 w8 w9]

Venous thromboembolism

The current treatment for prevention of venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is OAC.[w10] There are no studies demonstrating that aspirin or DAT is equivalent to OAC in the prevention of venous thromboembolism. However, in contradistinction to atrial fibrillation, the recommended duration of OAC for venous thromboembolism is limited in many patients. In these patients, an elective PCI-S may be postponed to avoid the need for DAT and OAC at the same time. Current recommendations suggest that OAC should be maintained for 3–6 months in patients with transient risk factors for venous thromboembolism (for example, immobilisation) and for more than 12 months for recurrent venous thromboembolism. While the appropriate duration of OAC for idiopathic or recurrent thromboembolism is not definitely known, there is evidence of substantial benefit for extended duration treatment.[9] Patients with inherited thrombophilias should receive lifelong anticoagulation in the case of life threatening thromboembolic events or recurrent thrombosis.

Mechanical heart valves

Patients with mechanical heart valves are among those with the highest risk for thromboembolic events without OAC. The event rates for systemic embolism per 100 patient-years is 8.6 without antithrombotic therapy, 7.5 with aspirin alone, and 1.8 with coumarins.[10] Only one study has so far assessed the safety and efficacy of DAT compared to OAC and was terminated early because of a higher rate of valve thrombosis in the DAT group.[11] Therefore, the current recommended treatment to prevent thromboembolic events in patients with mechanical valves is OAC.

Ventricular thrombi

The presence of a left ventricular thrombus may be an indication for OAC to prevent systemic emboli. The risk of systemic embolisation can be reduced with OAC.[w11] To our knowledge, there are no data on the use of DAT to prevent systemic embolisation in patients with ventricular thrombi. The guidelines state that OAC should be prescribed for at least 3 months, and indefinitely in patients without an increased risk of bleeding.[12] In the case of PCI-S and the need for DAT, the benefit of OAC should be estimated taking into account the probable age of the ventricular thrombus and any prior history of systemic emboli.

Heart failure

Some studies have shown that aspirin as well as OAC reduce stroke in patients with low ejection fraction, while others could not demonstrate

Table 1 Stroke risk in patients with non-valvular atrial fibrillation not treated with anticoagulation according to the $CHADS_2$ score[8]

$CHADS_2$ score	Stroke rate (%/year)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

The $CHADS_2$ score is calculated by giving 1 point for cardiac failure, arterial hypertension, age>75 or diabetes mellitus, respectively, and 2 points for prior stroke or transient ischaemic attack.[w7]

Table 2 Recommendations for antithrombotic treatments for various medical conditions

Medical condition	Recommended treatment
Coronary stent implantation	DAT for 1 month after BMS; 6–12 months after DES
Atrial fibrillation	For $CHADS_2 \geqslant 2$: OAC indefinitely
Mechanical heart valves	OAC indefinitely
Venous thromboembolism	OAC at least 3 months (see text)
Left ventricular thrombus	OAC at least 3 months (see text)
Heart failure	Routine use of anticoagulation/antithrombotic therapy not well established (see text)

BMS, bare metal stent; DAT, dual antiplatelet therapy consisting of aspirin and clopidogrel; DES, drug eluting stent; OAC, oral anticoagulation with a coumarin derivate.

a beneficial effect with either agent.[w12 w13] Accordingly, the current guidelines for heart failure do not support the general use of OAC in those patients with heart failure and no history of atrial fibrillation or a prior thromboembolic event.[13]

An overview of these recommendations in the various medical conditions discussed above is presented in table 2.

STUDIES ON TRIPLE THERAPY

The prevalence of patients on OAC scheduled for a percutaneous coronary intervention strongly depends on the population screened. In one retrospective analysis of more than 4000 patients, 6% required long term OAC.[5] At our institution, 5–10% of all patients scheduled for percutaneous coronary intervention were on OAC. Since the mean age of patients undergoing PCI-S is likely to become progressively older, and the prevalence of atrial fibrillation—the principal indication for OAC—is strongly related to the age of the patients, we expect to encounter an increasing number of patients scheduled for PCI-S who have an indication for OAC.

Therefore, at least for a certain time period, these patients have an indication for both DAT and OAC. As demonstrated in 6706 patients of the ACTIVE W (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) study, DAT and OAC treatment are each associated with nearly 15% risk of major or minor bleeding per year.[7] As each regimen impairs haemostasis by a different mechanism, there is a concern that adding OAC to DAT may increase bleeding rates. On the other hand, temporary discontinuation of either antiplatelet or anticoagulation therapy in this subset of patients may increase the risk of either stent thrombosis or thromboembolic events, as discussed above. Therefore, the benefit and risk of triple therapy for patients undergoing PCI-S while on OAC is an important consideration. For some patients, concomitant treatment with OAC and DAT may be avoided by delaying PCI-S to a time point when OAC will be no longer indicated. For most patients, however, OAC is a lifelong recommendation, and therefore postponing PCI-S is not an option.

Several studies have so far assessed patients on OAC who underwent PCI-S. Triple therapy was one treatment option in these patients. Most of the studies were retrospective studies or post hoc analyses of prospective registries.[5 14 15 16 w14–19] Some of the studies included a control group which was treated with DAT. However, in all of these studies neither the patients with an indication for OAC were uniquely treated with triple therapy nor the control group was treated in a standard manner. When discussing the evidence for patients on triple therapy it is important to realise that none of the studies prospectively evaluated the treatment options for patients with stent implantation on OAC in a *randomised* manner.

Bleeding events

Combined major and minor bleeding events in these studies varied from 9.2–27.5% for patients on triple therapy.[14 w14 w15 w17] The rates for bleeding events varied from study to study, as follow-up times, bleeding definitions and baseline characteristics of patients on triple therapy were different. Whether these rates for bleeding events in patients on triple therapy are significantly "increased" depends on the definition of the control group. Does it comprise patients on warfarin alone, warfarin + aspirin, warfarin + clopidogrel, or DAT? Some of the studies included a control group without an indication for OAC.[5 w15 w16] In only three studies, patients on triple therapy as well as the control group had an indication for OAC.[14–16] Since only patients with an indication for OAC are candidates for triple therapy, the results of these latter three studies are of the greatest relevance (table 3). One study[16] reported similar in-hospital rates for major bleeding in patients with triple therapy (5.9%) compared to warfarin plus a single antiplatelet drug (4.6%); in agreement with this, another study[15] reported similar rates for major and minor bleeding after 2 years in patients with triple therapy (9.1%) versus DAT (11.5%); and one study[14] showed a non-significant trend towards increased major as well as minor bleedings after a median follow-up of 595 days in patients on OAC (27.5%) versus DAT (18.0%). A recent review article on triple therapy has also included the studies with matched control groups and has found that the bleeding risk with triple therapy was consistently higher at 1, 6 and 9 months.[17] Most of the bleeding occurred in the gastrointestinal tract. Taken together, the risk for bleeding in patients on triple therapy might be increased when compared to DAT. It is not possible, however, to calculate a "relative risk" for bleeding on the basis of the published data.

Cardiovascular events

With regard to efficacy, stent thrombosis as well as thromboembolic events should be taken into account when comparing triple therapy with other treatment options for patients on OAC undergoing PCI-S. In the two studies comparing triple therapy with DAT for more than 30 days, thromboembolic events and death were increased when patients were on DAT instead of triple therapy, while subacute or late stent thrombosis were not

Table 3 Selected studies comparing triple with dual therapy (studies including a control group with an indication for oral anticoagulation)

	Number of patients on triple therapy	Clinical end point	Major bleeding
Nguyen *et al*, 2007[16]	580	No difference*	No difference§
Ruiz-Nodar *et al*, 2008[14]	195	Triple significant better†	Dual trend better
Sarafoff *et al*, 2008[15]	307	Triple trend better‡	No difference

*No combined end point: no difference in death, myocardial infarction; significantly fewer strokes with triple therapy.
†Death, myocardial infarction, target vessel revascularisation, stroke, and/or major bleeding.
‡Death, myocardial infarction, stent thrombosis or stroke.
§Only in hospital bleeding monitored.

different.[14 15] In another study in which multiple antithrombotic treatment strategies were evaluated for 12 months in patients with stent implantation and an indication for OAC, the patients on DAT had the highest incidence of stroke (8.8% *vs* 2.8% in patients on triple therapy) and the patients on warfarin and aspirin had the highest incidence of stent thrombosis (15.2% *vs* 1.9% in patients on triple therapy).[5] At least for longer follow-up periods (>30 days), the efficacy of triple therapy to prevent thromboembolic events appears to be significantly higher compared to DAT, and the efficacy of triple therapy to prevent subacute stent thrombosis seems to be higher compared to warfarin without DAT.

MANAGEMENT OF PATIENTS RECEIVING TRIPLE THERAPY

Managing patients on triple therapy is a difficult task and the following issues should be considered: What kind of stent should be used? Which target INR should be aimed for? Is there a benefit for adding proton pump inhibitors to protect against gastrointestinal bleeding?

We will briefly discuss the rationale for each of these measures and provide guidance on how to implement them in the management of an individual patient.

Low INR levels

There is some evidence that maintaining INR at the lowest possible level will significantly reduce the risk for bleeding in patients on triple therapy, without losing the efficacy to prevent thromboembolic events. Our own data suggest that an INR of 2.5–3.0 in patients with mechanical valves and an INR of 2.0–2.5 for all other indications may lead to comparable rates of major bleeding in patients with triple therapy compared to DAT.[15] Another study has shown that aiming for a target INR of 2.0–2.5 leads to a significant decrease in major and minor bleeding events in patients treated with triple therapy.[18] Therefore, it is our practice and the recommendation of the current guidelines[3] to recommend an INR at the lowest possible level during the time period of triple therapy. An important implication of this practice is that the frequency of blood sampling should be increased if the INR is to be safely maintained in this narrower range.

Proton pump inhibitors

Since gastrointestinal bleeding accounts for about 30–40% of haemorrhagic events in patients on triple therapy,[w20] consideration of approaches to reduce the risk of gastrointestinal bleeding is relevant.[19] For the period that triple therapy is needed, the risk of gastrointestinal bleeding should be reduced by a concomitant treatment with proton pump inhibitors.[19] It has been shown that omeprazole has a negative effect on clopidogrel mediated platelet reactivity.[20] Although the impact of this effect on clinical end points has so far not been investigated, the use of proton pump inhibitors other than omeprazole for patients on triple therapy might be advisable.

DES versus BMS in triple therapy

While the bleeding risk of patients on triple therapy remains the same over time, the risk of stent thrombosis diminishes with time (fig 1). This is supported by an observational study which demonstrated a continuous risk for bleeding, while the stent thrombosis events mostly occurred early after percutaneous coronary intervention.[5] Since DES and BMS differ in terms of endothelialisation and the recommended duration of DAT to prevent subacute stent thrombosis, it has been proposed that BMS should be the preferred stent type so that the duration of triple therapy might be limited to 4 weeks.[17] So far no study has primarily addressed the outcome of patients with BMS compared to DES and an indication for OAC. In general, target lesion revascularisation is significantly reduced with DES compared to BMS. While all reinterventions carry an additional risk, especially in patients on OAC, it is unclear what the net effect is when it comes to a reduced duration of triple therapy compared to a reduced rate of target lesion revascularisation. As long as this question has not

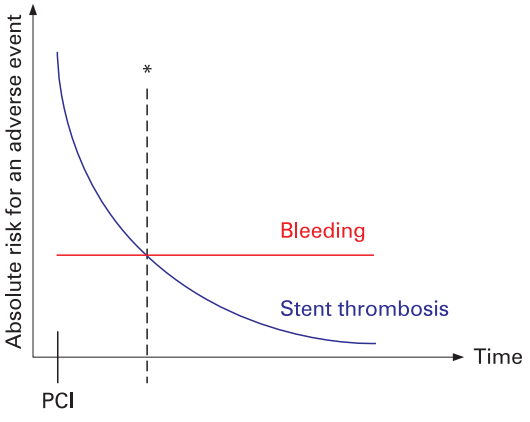

Figure 1 The bleeding risk of patients on triple therapy is grossly time independent, while the risk for stent thrombosis diminishes clearly over time. The asterisk marks a theoretical time point, at which the absolute bleeding risk exceeds the risk of stent thrombosis. At this time point, triple therapy could be reduced to oral anticoagulation (OAC) + single agent antiplatelet therapy in patients with an indication for lifelong OAC. PCI, percutaneous coronary intervention.

Triple antithrombotic management after stent implantation: key points

- Triple therapy consisting of aspirin, clopidogrel and oral anticoagulation (OAC) is feasible and safe in patients with an indication for OAC who undergo coronary stenting.
- The intensity of OAC should be lowered in the case of a triple therapy to a target INR of 2.5–3.0 for mechanical heart valves and 2.0–2.5 for other indications.
- The duration of triple therapy depends on the stent that is used: after bare metal stent implantation the recommended duration for triple therapy is 4 weeks, and after drug eluting stent implantation the duration might be 3 months.
- After triple therapy is finished, treatment with OAC and one antiplatelet agent is recommended.

been assessed in a prospective way, we advise the use of BMS in all lesions with an expected low risk of restenosis and the use of DES in patients with an expected high risk of restenosis (diabetes, complex lesions).

Duration of triple therapy after DES implantation is a difficult issue where the risk of bleeding has to be weighed against possible thromboembolic complications. While there is no doubt regarding the superiority of DAT during the first 4 weeks after coronary stent placement, there are currently no data as to whether late stent thrombosis (30 days to 1 year) can also be prevented by OAC and one antiplatelet agent alone. Mainly based on the time course of stent thrombosis, we believe that the excess in bleeding risk does not justify in general the extension of triple therapy beyond 3 months after DES. However, this recommended duration of 3 months for triple therapy is not based on evidence and, therefore, should be individually adapted. If the consequences of a stent thrombosis are assumed to be high because of a large amount of myocardium at risk, the benefit of triple therapy for even more than 6 months might be justified. On the other hand, if the consequences of an occluded vessel caused by a stent thrombosis are low, since the jeopardised myocardium is small, an even shorter duration of triple therapy of 4 weeks might be justified. Until prospective data are available, triple therapy after DES is limited to 3 months in our institution, followed by OAC plus aspirin or clopidogrel in patients with a strong indication for lifelong OAC.

You can get CPD/CME credits for Education in Heart

Education in Heart articles are accredited by both the UK Royal College of Physicians (London) and the European Board for Accreditation in Cardiology—you need to answer the accompanying multiple choice questions (MCQs). To access the questions, click on **BMJ Learning: Take this module on BMJ Learning** from the content box at the top right and bottom left of the online article. For more information please go to: http://heart.bmj.com/misc/education.dtl

- **RCP credits:** Log your activity in your CPD diary online (http://www.rcplondon.ac.uk/members/CPDdiary/index.asp)—pass mark is 80%.
- **EBAC credits:** Print out and retain the BMJ Learning certificate once you have completed the MCQs—pass mark is 60%. EBAC/ EACCME Credits can now be converted to AMA PRA Category 1 CME Credits and are recognised by all National Accreditation Authorities in Europe (http://www.ebac-cme.org/newsite/?hit=men02).

Please note: The MCQs are hosted on BMJ Learning—the best available learning website for medical professionals from the BMJ Group. If prompted, subscribers must sign into *Heart* with their journal's username and password. All users must also complete a one-time registration on BMJ Learning and subsequently log in (with a BMJ Learning username and password) on every visit.

CONCLUSION

When and how should physicians prescribe triple antithrombotic therapy—consisting of warfarin, aspirin, and clopidogrel—after stent implantation? Triple therapy is the best treatment option in patients with an indication for OAC and an intermediate to high risk for thromboembolic events who undergo coronary stenting. Indications for OAC with an intermediate to high risk for thromboembolic events include atrial fibrillation with a $CHADS_2$ score >1, mechanical heart valves, recent venous thromboembolism, or new ventricular thrombi. When DES are used, the duration of triple therapy might be limited to 3 months. BMS implantation with triple therapy for 1 month is an alternative in patients who have an excessive risk for bleeding. To reduce bleeding complications, a low INR (2.5–3.0 for mechanical heart valves and 2.0–2.5 for other indications) should be targeted during triple therapy, with the recommendation for more frequent monitoring. Proton pump inhibitors are recommended in patients who receive triple therapy.

These recommendations for triple therapy are based on the limited data that are available thus far. The current European and US guidelines for percutaneous coronary intervention do not comment in detail on patients with an indication for OAC due to the lack of published evidence on what the optimal management strategy is for these patients. Therefore, further prospective clinical trials are needed in order to evaluate the best treatment strategy for patients on OAC who undergo percutaneous coronary interventions. Some of them are already under way (AFCAS, ISAR-TRIPLE).

Competing interests: In compliance with EBAC/EACCME guidelines, all authors participating in Education in *Heart* have disclosed potential conflicts of interest that might cause a bias in the article. The authors have no competing interests.

REFERENCES

1. **Schomig A,** Neumann FJ, Kastrati A, *et al*. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996;**334**:1084–9.
   - **The first trial that showed the superiority of DAT over OAC after coronary stent implantation.**
2. **Grines CL,** Bonow RO, Casey DE Jr, *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. *Circulation* 2007;**115**:813–8.
3. **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.

4. **Airoldi F,** Colombo A, Morici N, *et al*. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation* 2007;**116**:745–54.
   - ► **This study showed that discontinuation of clopidogrel is a determinant of stent thrombosis only in the first 6 months after stent placement.**
5. **Karjalainen PP,** Porela P, Ylitalo A, *et al*. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J* 2007;**28**:726–32.
6. **Hart RG,** Benavente O, McBride R, *et al*. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**:492–501.
7. **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**:1903–12.
   - ► **Large randomised trial that showed for the first time that patients with atrial fibrillation have better outcomes with OAC compared to DAT.**
8. **Fuster V,** Ryden LE, Cannom DS, *et al*. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;**48**:854–906.
9. **Snow V,** Qaseem A, Barry P, *et al*. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2007;**146**:204–10.
10. **Cannegieter SC,** Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation* 1994;**89**:635–41.
    - ► **Meta-analysis of risk for thromboembolic complications in patients with mechanical heart valves with various antithrombotic regimens.**
11. **Schlitt A,** von Bardeleben RS, Ehrlich A, *et al*. Clopidogrel and aspirin in the prevention of thromboembolic complications after mechanical aortic valve replacement (CAPTA). *Thromb Res* 2003;**109**:131–5.
    - ► **The only trial in humans that compared DAT to OAC in patients with mechanical heart valves. The study was stopped prematurely after one patient on DAT developed aortic valve thrombosis.**
12. **Antman EM,** Anbe DT, Armstrong PW, *et al*. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). *Circulation* 2004;**110**:588–636.
13. **Hunt SA.** ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;**46**:e1–82.
14. **Ruiz-Nodar JM,** Marin 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**:818–25.
15. **Sarafoff N,** Ndrepepa G, Mehilli J, *et al*. Aspirin and clopidogrel with or without phenprocoumon after drug eluting coronary stent placement in patients on chronic oral anticoagulation. *J Intern Med* 2008;**264**:472–80.
    - ► **First study that analysed safety and efficacy of triple therapy compared to DAT in patients receiving drug eluting stents only.**
16. **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**:1717–22.
    - ► **Largest number of patients on triple therapy that have been analysed in one study.**
17. **Rubboli A,** Halperin JL, Juhani Airaksinen KE, *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**:428–36.
    - ► **Excellent review of studies on triple therapy and recommendations for management of patients with atrial fibrillation undergoing coronary stenting.**
18. **Rossini R,** Musumeci G, Lettieri C, *et al*. Outcomes of long-term triple therapy with aspirin, clopidogrel, and warfarin in patients undergoing coronary stenting [abstract]. *Eur Heart J* 2008;**29**(Suppl):328.
19. **Bhatt DL,** Scheiman J, Abraham NS, *et al*. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008;**118**:1894–909.
20. **Gilard M,** Arnaud B, Cornily JC, *et al*. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;**51**:256–60.

Heart

Triple antithrombotic management after stent implantation: when and how?

Albert Schömig, Nikolaus Sarafoff and Melchior Seyfarth

Heart 2009 95: 1280-1285
doi: 10.1136/hrt.2008.160457