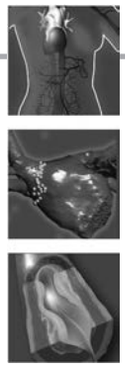

Drug-eluting stents in patients on long-term oral anticoagulation therapy: a mission impossible?

It is estimated that 5% of patients undergoing coronary stenting are on long-term oral anticoagulation therapy. This patient group presents unique challenges in navigating the delicate balance of preventing ischemic events with dual antiplatelet treatment, while mitigating the risk of stroke and other embolic events with oral anticoagulation, without a resultant unacceptably high bleeding risk. Stent selection and concomitant antithrombotic strategies are the key considerations when finding the best balance between these opposite threats. Drug-eluting stents should be avoided or strictly limited to those situations where a significant net benefit is expected as compared with bare-metal stents. Triple therapy of oral anticoagulation plus aspirin and clopidogrel or dual antiplatelet therapy is recommended for the initial prevention of thrombotic complications, but its duration should be individualized according to the stent type and bleeding risk of the patient. These recommendations are based on limited evidence and there is a definite need for large-scale registries and prospective clinical studies to determine the optimal management of this patient group. A continuous focus on educating physicians to tailor antithrombotic therapy according to the patient's risk profile is also needed.

KEYWORDS: antithrombotic treatment ▪ bleeding ▪ clopidogrel ▪ coronary artery ▪ stent ▪ warfarin

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Percutaneous coronary intervention (PCI) with drug-eluting stents (DES) has markedly reduced restenosis and the subsequent need for repeat revascularization procedures and has become common practice [1,2]. However, the risk of late stent thrombosis with these devices has led to the recommendation of prolonged dual antiplatelet therapy (DAT) [3,4].

It is estimated that 5% of patients undergoing PCI are on long-term oral anticoagulation (OAC) therapy owing to underlying chronic medical conditions such as atrial fibrillation (AF) or mechanical heart valve. This chronic OAC patient group presents unique challenges in navigating the delicate balance of preventing ischemic events with DAT, while mitigating the risk of stroke and other embolic events with OAC, without a resultant unacceptably high bleeding risk [5,6]. Stent selection and concomitant antithrombotic strategies are key considerations when finding the best balance between these opposite threats.

In this article, we first focus on the available reports on current stenting practice in OAC-treated patients and continue with an analysis of the available evidence on the magnitude of the competing risks of restenosis, stent thrombosis, stroke and bleeding events in this complex patient population. Last, we present practical suggestions for the treatment of this growing patient population at high risk of bleeding events.

Previous studies on the use of DES in patients on OAC

We conducted literature searches in PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry) on English language articles and found 16 studies describing outcomes in OAC patients undergoing coronary stenting and providing information on stent use (Table 1). Most publications reported retrospective analyses of single-center consecutive patient series undergoing PCI in different settings. No randomized trials were available. The data are heterogeneous, and the reporting of clinical parameters associated with thrombotic or bleeding events are even more so.

The use of DES ranged from 2 to 100% between the reports and centers. Only two of the trials presented data on comparison of DES versus bare-metal stents (BMS) (Table 1) [7,8]. Rogacka *et al.* showed no significant difference between DES or BMS with respect to major bleeding or major adverse cardiac events (MACE) [7], whereas Ruiz-Nodar *et al.* concluded that the routine use of DES in this patient population does not appear to be justified on the basis of adverse outcome in the DES-treated patients [8]. At the other end of the spectrum, Sarafoff *et al.* demonstrated that the

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Table 1. Studies analyzing patients on oral anticoagulation undergoing coronary stenting.

Author (year)	n	Mean age (years)	AF (%)	ACS (%)	DES (%)	Triple therapy (%)	Length of triple therapy (months)	Follow-up (months)	Outcome measures (%)	Ref.
Khurram *et al.* (2006)	107	69	80	NA	50	100	NA	12	Major bleeding: 6.6	[44]
Lip *et al.* (2006)	35	71	100	94	14	17	1	1	Bleeding: 0	[45]
Karjalainen *et al.* (2007)	239	70	70	54	42	48	4	12	Major bleeding: 8.2 MACE: 22	[5]
Rubboli *et al.* (2007)	49	69	60	6	2	41	1	1	Bleeding: 10	[28]
DeEugenio *et al.* (2007)	97	70	59	NA	25	100	NA	6	Major bleeding: 14.4	[46]
Nguyen *et al.* (2007)	800	65	37	100	16	73	NA	6	Triple therapy vs warfarin + ASA/Clop Death: 5.1 vs 6.5 Stroke: 0.7 vs 3.4 MI: 3.3 vs 4.5	[22]
Rogacka *et al.* (2008)	127	70	59	26	56	100	DES vs BMS 8 vs 3	21	Major bleeding: DES vs BMS 5.6 vs 3.6 MACE: DES vs BMS 19.7 vs 28.6	[7]
Rossini *et al.* (2008)	102	68	67	78	47	100	5	18	Major bleeding: 2.9 MACE: 5.8	[41]
Sarafoff *et al.* (2008)	306	71	67	33	100	100	3	24	Major Bleeding: 1.4 MACE: 14.1	[9]
Manzano-Fernandez *et al.* (2008)	104	72	100	95	66	49	12	12	Major bleeding:12.5	[47]
Ruiz-Nodar *et al.* (2008)	426	72	100	84	40	50	NA	20	Major bleeding: 12.3 MACE: 32.2	[48]
Manzano-Fernandez *et al.* (2008)	166	71	63	90	64	46	NA	17	Major bleeding: 15.7	[49]
Ruiz-Nodar *et al.* (2009)	414	71	100	83	50	45	NA	36	Major bleeding: DES vs BMS 16.9 vs 7.9 MACE: DES vs BMS 37.0% vs 34.0	[18]
Halbfass *et al.* (2009)	117	72	100	NA	47	45	NA	28	Major bleeding: 11.5	[50]
Hälg *et al.* (2009)	44	71	NA	57	80	100	6	36	Major bleeding: 20.5	[51]
Gilard *et al.* (2009)	359	72	69	46	30	35	12	12	Triple therapy vs ASA + Clop Major bleeding: 5.6 vs 2.1 Stroke: 0.8 vs 3.0	[52]

Triple therapy was a combination of aspirin, thienopyridine and warfarin.
ACS: Acute coronary syndrome; AF: Atrial fibrillation; ASA: Aspirin; BMS: Bare-metal stent; Clop: Clopidogrel; DES: Drug-eluting stent; GI: Gastrointestinal; MACE: Major adverse cardiac events; MI: Myocardial infarction.

use of DES was feasible and safe in 515 patients receiving either a triple therapy of OAC plus aspirin and clopidogrel or DAT [9]. In this trial, the choice of DAT or triple therapy with a low target international normalized ratio (INR) of 2.0–2.5 was made on the basis of an individual assessment of thromboembolic risk in each patient.

Data on antithrombotic therapy after stenting was variable and no data on bleeding risk assessment were reported. Generally, major bleeding with triple therapy increased by 3.2–6.6-fold compared with DAT alone. The incidence of stroke and stent thrombosis was rarely reported, but when it was, it was lowest with the triple therapy. One study argued against the use of DAT in stroke prevention and also reported a high incidence of stent thrombosis with the combination OAC and aspirin [5].

Risk of restenosis & stent thrombosis

Percutaneous coronary intervention with stenting compared with balloon angioplasty alone has markedly reduced the rates of restenosis. At present, the incidence of clinically driven restenosis is approximately 3–10% with BMS and 2–5% with DES in large registry studies, varying according to the lesion and patient characteristics [1,2,10,11].

The well-known downside of stenting is the risk of stent thrombosis, which has received special attention due to the high mortality and morbidity of the complication. With the current antithrombotic strategies, most (~1%) stent thromboses occur early (<30 days), but late thrombosis is reported to occur at an annual rate of approximately 0.6% up to 4 years after DES implantation [12,13]. A higher rate of late stent thrombosis has been observed after acute coronary syndrome than in stable patients in post-mortem analysis of patients who died after DES implantation [14]. Premature DAT discontinuation has been the most important predisposing factor for stent thrombosis [15]. Recent data has suggested that patient-related factors such as age, hypertension, diabetes, smoking, renal failure, low ejection fraction and female gender are independently associated with stent thrombosis [16].

Four early randomized trials showed that DAT cannot be safely replaced by a warfarin plus aspirin combination in preventing stent thrombosis [17]. The recommended duration of DAT is at least 1 month in patients receiving BMS, 3 months in patients receiving DES from limus family and 6 months of aspirin and clopidogrel in patients receiving paclitaxel-eluting DES. DAT has been proven to be beneficial in patients with both non-ST-elevation myocardial infarction [18] and ST-elevation myocardial infarction [19], and should be maintained for up to 12 months in these indications. The major problem with the use of DES is that premature stopping of the longer clopidogrel treatment may cause a tenfold increased risk of stent thrombosis [15].

Risk of stroke

Devastating, irreversible consequences of stroke have been self-evident for the clinicians. AF is the most common risk factor for stroke, increasing the incidence of embolic stroke from 1% to over 10% per year depending on concomitant risk factors. In addition to AF, other conditions may put patients at a high risk of thromboembolic complications and, for example, patients with mechanical valve prosthesis confer an annual risk of 10–91% depending on the position and type of prosthesis and concomitant risk factors [20].

Oral anticoagulation reduces the risk of stroke by two-thirds, as demonstrated by well-designed clinical trials for the primary and secondary prevention of stroke and thromboembolism in a wide spectrum of clinical conditions. The greatest benefit is seen in those people who are in the high-risk category for having a stroke. The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) trial showed that DAT cannot replace OAC in stroke prevention in patients with AF [21], and recent observational studies on clinical practice also support this conclusion in patients on home warfarin undergoing PCI [5,8,22].

Risk of bleeding complications

The annual risk of major bleedings among 'real world' patients on OAC is estimated to be approximately 3%. The bleeding risk seems to be even higher in the first year of treatment and in the elderly population [23]. Adding aspirin to warfarin therapy confers a 1–2% absolute increase in major bleeding per year compared with warfarin alone [24]. In a recent Danish study, triple therapy of OAC, aspirin and clopidogrel was associated with a threefold increase in bleeding complications compared with OAC alone [25]. Strikingly, the bleeding risk of clopidogrel plus OAC, which has been recommended as a potentially safer combination than triple therapy, was only slightly lower than the combination of all three drugs.

Bleeding complications are the most frequent nonischemic complications of PCI, especially in the treatment of acute coronary syndromes. It is estimated that the annual frequency of

major bleeding ranges from 2 to 15% across the spectrum of PCI and greatly depends on the type of antithrombotic treatment and use of invasive procedures. Most of the bleeding events occur early during the hospital phase. In the large CRUSADE Registry (an ongoing, voluntary, observational data collection and quality improvement initiative), the incidence of in-hospital major bleeding events was as high as 9.4% [26]. The incidence of bleeding events seems to be even higher when these patients are on long-term OAC and need concomitant potent antiplatelet agents owing to PCI [6,27]. Triple therapy is the most frequently used drug regimen in this scenario. The downside of triple therapy is the high incidence of bleeding complications, ranging up to 21% in small single-center registries (Table 1). According to a pooled analysis, the incidence of major bleeding increased from 4.6 to 10.3% when the treatment period increased from 1 month to 6–12 months or more [28]. On the basis of these considerations, the duration of triple therapy is critical for the bleeding events and should be minimized after individual assessment of risk for ischemic, thromboembolic and bleeding events resulting from available treatment choices (Figure 1).

Assessment of thromboembolic & bleeding risk

The risk factors and consequences of restenosis and stent thrombosis are well known for the interventional cardiologists from the everyday practice. The $CHADS_2$ score successfully stratifies AF patients according to risk of stroke [29]. $CHADS_2$ is measured using five common risk factors: heart failure, hypertension, age over 75 years, diabetes and previous stroke/transient ischemic attack (1 point for each risk factor except 2 points for stroke). A score of 4–6 identifies patients at high risk, a score of 2–3 an

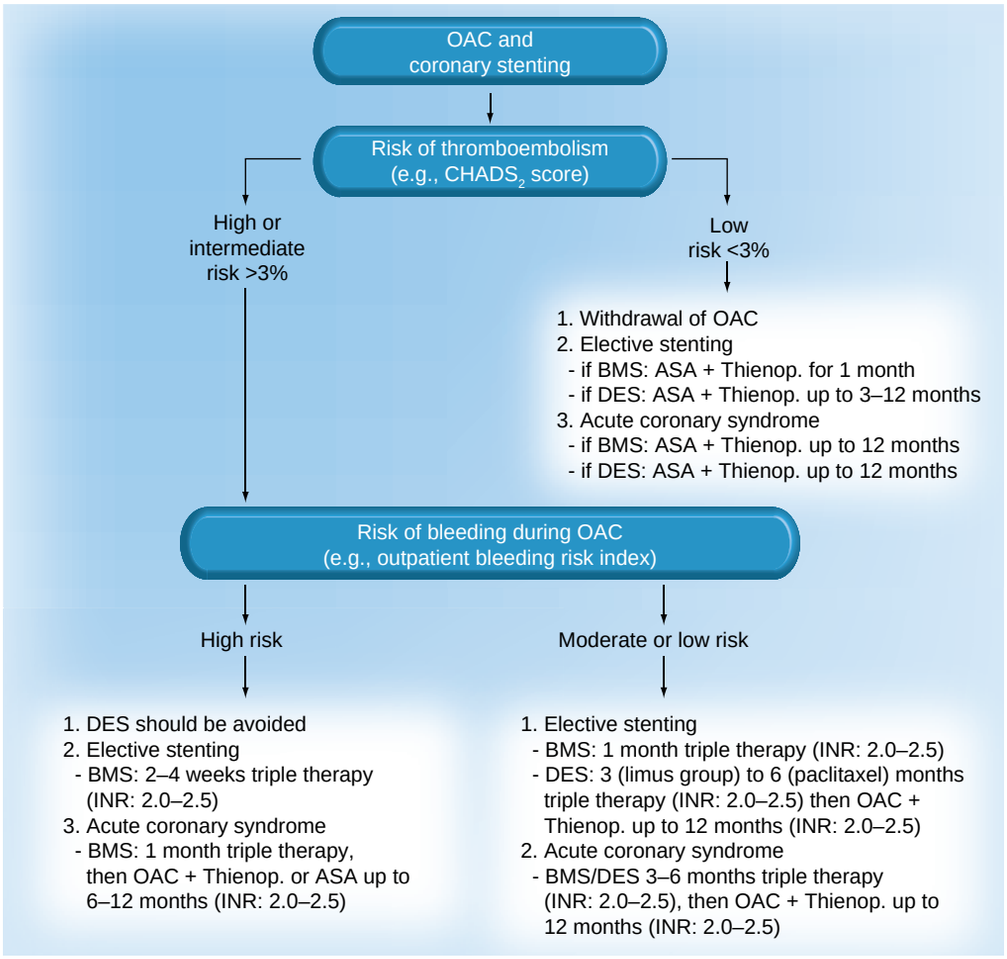

Figure 1. Antithrombotic treatment of patients on oral anticoagulation undergoing coronary stenting. Triple therapy was a combination of ASA, Thienop. and warfarin.
ASA: Aspirin; BMS: Bare-metal stent; DES: Drug-eluting stent; INR: International normalized ratio; OAC: Oral anticoagulation; Thienop.: Thienopyridine.

intermediate risk, and a score of 0–1 indicates low-risk patients. Other conditions may also put patients at a high risk of stroke, for example, patients with a mechanical valve prosthesis confer a very high risk of thromboembolic complications depending on the position and type of prosthesis and concomitant risk factors if they are not treated with OAC [20].

The importance of avoiding bleeding complications has become more evident, since they have turned out to be highly predictive of mortality across a broad spectrum of patients undergoing PCI [30–32]. The best documented bleeding risk factors in patients using OAC include old age, high blood pressure and history of bleeding or cerebrovascular disease. Anemia, renal failure, female gender, recent myocardial infarction and simultaneous use of antiplatelet therapy also appear to have predictive value, at least in certain clinical situations. There are four published bleeding risk scores that have been validated for bleeding risk in patients on OAC [33]. Of these models, the most often used is the outpatient bleeding risk index, which was developed based on a study that identified independent risk factors for major bleeding, including history of stroke, age over 65 years, history of GI tract bleeding, and the presence of one or more comorbid conditions (recent myocardial infarction, renal insufficiency, severe anemia or diabetes). Based on this classification, the patient is considered to be at a low (zero risk factors), moderate (one or two risk factors) or high risk (three or four risk factors) for bleeding. This index has been validated prospectively and demonstrated to reach acceptable discrimination among the risk categories. In the original report, it was found that the cumulative rates for major bleeding at 1 year varied from 3 to 12 to 48% according to the risk category [34,35].

How to avoid bleeding complications?

Evaluation of patient's propensity to ischemic, thromboembolic and bleeding complications is the basis of all individual treatment decisions (Figure 1 & Box 1). If there is a clear indication for OAC, triple therapy is the current recommendation for patients undergoing PCI [36–39]. Since the duration of triple therapy seems to be crucial in the prevention of bleeding events, it should be minimized by limiting DES to those clinical and/or anatomical situations where a significant net benefit is expected as compared with BMS. This pre-requisite leaves little space for the use of DES, especially in patients with clinical bleeding risk factors (as described previously). When using BMS in stable coronary artery disease, the recommended duration of triple therapy is 2–4 weeks according to the individual risks of bleeding complications, followed by long-term OAC therapy or a combination of OAC plus clopidogrel or aspirin (up to 12 months) in patients with a lower bleeding risk.

Optimal duration of triple therapy is still a question of debate in acute coronary syndromes and when using DES, but the general recommendation is to continue treatment up to 12 months [6,39]. However, it seems that the risk of stent thrombosis declines more rapidly than the risk of bleeding complications, rendering the net outcome unfavorable with lengthy use of triple therapy when the patient is at high risk of bleeding [5]. In selected patients at high risk for bleeds, triple therapy may be replaced by a combination of clopidogrel and OAC [5,22], although its safety relative to triple therapy has been questioned.

The risk of bleeding during OAC is related to the intensity of anticoagulation [40]. Thus, it is reasonable to adjust the OAC intensity and target to a lower therapeutic range of INR (2.0–2.5).

Box 1. How to avoid bleeding complications after percutaneous coronary intervention in patients on long-term oral anticoagulation.

- Is there a definite net advantage for percutaneous coronary intervention (PCI) compared with conservative strategy?
- Evaluate the indication of oral anticoagulation (OAC) and risk of thromboembolism:
  - Interruption of OAC possible in atrial fibrillation, if $CHADS_2$ score ≤1.
  - Postpone elective PCI if the indication for OAC is temporary (e.g. venous thromboembolism).
- Evaluate bleeding risk and the risks for restenosis and stent thrombosis and their consequences.
- Try to avoid using drug-eluting stents, especially if bleeding risk is high.
- Try to minimize the duration of triple therapy.
- Arrange careful and frequent international normalized ratio (INR) controls during concomitant antiplatelet therapy.
- Target low therapeutic international normalized ratio range (2.0–2.5) in atrial fibrillation patients.
- Use gastric protection.
- Avoid glycoprotein inhibitors during OAC when possible.
- Use radial approach and uninterrupted OAC whenever possible.

This strategy has been shown to lead to a low incidence of bleeding complications in patients on triple therapy after PCI, without compromising the efficacy against stroke and ischemic complications (Table 1) [9,41]. Furthermore, wide fluctuations and overshoots in INR are known to predispose to bleeding complications, underscoring the importance of frequent INR controls preferably in dedicated OAC clinics. If a patient belongs to the low-risk category ($CHADS_2$ score ≤1), the indication for OAC is relative, and it can usually (at least temporarily) be replaced by DAT (1 month after BMS and up to 12 months after DES). Gastric protection with proton-pump inhibitors is considered useful during triple therapy in spite of the potential attenuation of clopidogrel effects, at least with omeprazole [42,43]. Major bleeding events should be treated aggressively, but inadvertent stopping of antithrombotic treatment owing to minor bleeding events is not wise.

Conclusion

Current guidelines and expert opinions recommend that DES should be avoided or strictly limited to those situations where a significant benefit is expected as compared with BMS [27,44]. Triple therapy is recommended for the prevention of stent thrombosis, but its duration should be individualized according to the stent type and bleeding risk of the patient. These recommendations are largely based on limited evidence obtained from small, single-center and retrospectively analyzed cohorts. Consequently, there is a definite need for large-scale registries and prospective clinical studies to determine the optimal management of patients on home OAC undergoing coronary interventions. A continuous focus on educating physicians to tailor antithrombotic therapy according to the patient's risk profile is also needed.

Future perspective

All these recommendations are based on weak evidence obtained from small, single-center and retrospectively analyzed cohorts; the present practice in this field is highly variable and appears to be based on local opinions as shown by Table 1. Thus, there is a definite need for large-scale registries and prospective clinical studies assessing the optimal management of patients with a concomitant need for OAC who are undergoing coronary stenting. Until then, debate over the optimal management strategy of this increasing patient group is likely to continue. The availability of new drugs (dabigatran, prasugrel and ticagrelor), new-generation DES and bioactive stents may further complicate treatment decisions, since data on their performance in this patient population are lacking.

A prospective, multicenter registry – Management of Patients with Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) – aiming at prospectively evaluating antithrombotic and stenting strategies has been launched in several European countries [101]. The first results of this study will hopefully contribute to shedding some light on this common issue in early 2010. Another registry sponsored by the Working Group on Thrombosis – the Real Life Antithrombotic Stent Evaluation Registry (LASER) [102] – has just begun.

Executive summary

Current practice

- Approximately 5% of patients referred for coronary stenting are on long-term oral anticoagulation.
- Use of drug-eluting stents in this patient group varies from 2 to 100% according to local practice.
- Geographical and interhospital variation in the use of antithrombotic treatments is wide.
- Triple therapy with oral anticoagulation plus aspirin and clopidogrel is the most often used initial therapy.

Risks of restenosis, stent thrombosis, stroke & major bleeding

- Risks of restenosis and stent thrombosis do not appear to be abnormally high.
- Annual risk of stroke ranges from 1 to 90% depending on the underlying conditions.
- Continuous oral anticoagulation is the cornerstone of stroke prevention.
- Bleeding events are the major preventable problem in this fragile patient group.

How to avoid excessive bleeding risk

- Evaluate the indications for percutaneous coronary intervention and oral anticoagulation.
- Evaluate the bleeding and stroke risk of the individual patient.
- Use drug-eluting stents only if they have significant net advantage over bare-metal stents.
- Minimize the duration of triple therapy.
- Target international normalized ratio to the low therapeutic level of 2.0–2.5.
- Arrange careful and frequent international normalized ratio controls.
- Use a radial approach and uninterrupted oral anticoagulation if possible.
- Avoid glycoprotein inhibitors when possible.
- Use gastric protection.

The Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) trial will provide an answer to the hypothesis that reducing the duration of clopidogrel therapy from 6 months to 6 weeks after DES implantation is associated with improved clinical outcomes in patients on aspirin and an oral anticoagulant [103]. The What is the Optimal Antiplatelet and Anticoagulant in Patients With Oral Anticoagulation and Stenting (WOEST) study [104] will assess the hypothesis that the combination of warfarin and clopidogrel 75 mg/day is superior to triple therapy (warfarin + clopidogrel 75mg/day + aspirin 80 mg/day) with respect to bleeding complications, while equally safe with respect to the prevention of thrombotic complications in patients with both indications for warfarin use and DAT (clopidogrel 75 mg/day + aspirin 80 mg/day). These trials are expected to run until 2011–2012.

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