Novel therapeutic concepts

Triple antithrombotic therapy in cardiac patients: more questions than answers

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Many cardiac patients require combined antithrombotic therapy consisting of an anticoagulant and inhibition of platelet function. The most frequent indications are atrial fibrillation (AF) in combination with drug-eluting stent implantation and/or the presence of an acute coronary syndrome (ACS). Currently, the optimal combination of anticoagulants and anti-platelet therapy is unknown, but it is well established that the combination of regular doses and regimens as prescribed in AF or after ACS results in increased bleeding rates. In this review, we discuss the current literature and describe approaches to reduce the risk of bleeding hoping not to increase the rate of ischaemic events.

Keywords

Atrial fibrillation • Antithrombotic therapy • Triple therapy • Platelets • Acute coronary syndrome

Cardiac conditions requiring antithrombotic therapy

Many cardiac patients require combined antithrombotic therapy consisting of an anticoagulant and inhibition of platelet function. Typical indications for the inhibition of the coagulation cascade in cardiovascular diseases are: atrial fibrillation (AF), deep venous thromboembolism, pulmonary embolism, or mechanical valve surgery. On the other side, an acute coronary syndrome (ACS) or coronary stent implantation require ‘dual-anti-platelet therapy’ (DAPT), usually consisting of aspirin and a P2Y12 antagonist. ‘Triple therapy’ (TT) is usually referred to as a combination of an anticoagulant with two anti-platelet agents. Up to 30% of patients on vitamin K antagonist (VKA) for AF have the concomitant diagnosis of coronary artery disease (CAD) and are thus potential candidates for coronary stent implantation. Similarly, between 5 and 10% of patients undergoing coronary stent implantation (PCI) have been on VKA treatment. For these patients, triple therapy (TT) needs to be considered.

What are the thrombotic risks?

Coronary stent thrombosis

Stent thrombosis after elective stent implantation is a rare but serious event. Recent developments in stent technology resulted in further reduction of the stent-thrombosis rate. In the event of stent thrombosis it is still associated with an up to 70% rate of myocardial infarction (MI) and 20% mortality depending on the location of the respective stent within the coronary vascular tree and other circumstances.

In addition to this risk, an ACS carries intrinsic risks for recurrent ischaemic events and cardiovascular mortality. Even with up-to-date anti-platelet therapy the residual risk of recurrent MI, stroke, or cardiovascular death remains at ~10% per year.

What are the antithrombotic strategies to avoid stent thrombosis?

It is well established and recommended in the guidelines that DAPT comprising aspirin and a P2Y12 antagonist (usually clopidogrel) is currently the most effective strategy to prevent thrombosis after elective stent implantation. Using this approach stent-thrombosis rates are reduced to ~1% in the first month and to ~1–2% in the first year. The time window of susceptibility for stent thrombosis appears to be longer for drug-eluting stents (DESs) than for bare-metal stents (BMS). Thus current guidelines recommend DAPT for 1 month after elective BMS implantation and for 6 months to 1 year after DES implantation. Recent data suggest that, with newer stent technologies, extended duration of DAPT may not be as beneficial as with earlier stents. Although these data have not been accounted for in the guidelines they still provide some support for situations in which shorter DAPT is desired. After an

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ACS DAPT has been proven beneficial in several trials and as a consequence this strategy is recommended for the duration of 1 year after ACS in current guidelines independent of the coronary revascularization strategy.12 – 14

Although early trials have shown that VKA may also be effective to prevent recurrent events after a MI this approach is currently not recommended by the guideline committees. In the absence of platelet inhibitors the number of stent thrombosis is substantially increased and the bleeding rate with VKA is increased.15 In the STARS trial VKA, even when combined with aspirin, was not as effective as DAPT to prevent stent thrombosis at the time and with the stent technology when the study was performed.16 Thus VKA alone is not an alternative to DAPT therapy in patients with ACS and stent implantation. Nonetheless and in contrast to the STARS data more recent registries and one randomized trial suggest that the combination of one anti-platelet and VKA may be effective to prevent excessive stent thrombosis when used with modern DES types.17 – 19

Stroke and systemic embolism

In patients with AF the thrombo-embolic risk depends on the presence of additional risk factors being evaluated by scores such as the CHADS2- and the CHA2DS2-VASc score. High scores are related to a stroke and systemic embolism risk of up to 15% per year.20

What are the antithrombotic strategies to avoid stroke and systemic embolism in atrial fibrillation patients?

To reduce this risk oral anticoagulation (OAC) is recommended when a CHA2DS2-VASc score of 2 or higher is reached. Traditionally VKA is used for anticoagulation and has proven effective in AF patients providing a risk reduction of about 60% compared with placebo.21 In contrast aspirin alone appears not to have a specific antithromboembolic activity in AF as it results in a relative risk reduction of about 20% only—a number that is comparable to the stroke risk reduction achieved by aspirin in atherosclerotic patients without AF.22 Even when aspirin is combined with clopidogrel it is not as effective as VKA treatment.23 Recently, novel direct oral antagonists (NOAC) of coagulation factors Xa (rivaroxaban and apixaban) or llα (dabigatran) have demonstrated non-inferiority compared with VKA and have been approved for clinical use in stroke prevention.24 – 26 In the future these novel anticoagulants will most likely be used in the large majority of AF patients.

What is the risk of antithrombotic therapy?

It is well established, e.g. from the OASIS-5 dataset, that severe bleeding may have deleterious effects on mortality.27 Mechanistically, not only anaemia and hypovolemic shock contribute to mortality in bleeding patients but also ischaemic events which can be triggered by inflammatory responses to bleeding or by discontinuation of antithrombotic drug therapy. Notably, even the occurrence of minimal bleeding events may have fatal consequences: it has been demonstrated that the incidence of ‘nuisance’ bleeding is associated with clopidogrel therapy cessation in more than 10% of patients, which may then in turn result in an increased rate of stent thrombosis.28 Thus, bleeding events of any intensity should be avoided but efficacy of anticoagulation should be maintained. To achieve this critical goal the individual bleeding risk of the patient may serve as a basis for adapted antithrombotic therapy. Assessing the individual bleeding risk is a challenging task in clinical practice. Scores can be of limited help in this context. The HAS-BLED score has been recommended by the European Society of Cardiology (ESC) to assess bleeding risk in patients with AF. Three or more of the following criteria define a high bleeding risk: Hypertension, abnormal liver or renal function, stroke, bleeding history, labile INRs, elderly (>65 years) (anti-platelet), drug or alcohol use. If a patient is considered to have a high bleeding risk careful attention should be given to the choice of antithrombotic therapy. In clinical practice there is a large overlap between the HAS-BLED and the CHA2DS2-VASc score resulting in a dilemma. Patients who require effective anticoagulation frequently also have an increased bleeding risk. Thus individualized strategies balancing bleeding and thrombotic risks are needed. In some patients occlusion of the left atrial appendage should be considered.

Is there a benefit from triple antithrombotic therapy in patients with atrial fibrillation and coronary stent implantation or acute coronary syndrome?

VKA given alone is not effective to prevent stent thrombosis, whereas DAPT is inferior to VKA in the prevention of thromboembolism in AF patients. As a consequence, combinations of antithrombotic drugs need to be considered in patients with a coronary stent and AF.

It is not surprising that a combination of anticoagulants with antiplatelet drugs increases bleeding risk. The key challenge is to identify the best combination and dose to keep bleeding risk low while optimizing the antithrombotic effect for both thromboembolism in AF and prevention of stent thrombosis. A number of studies have been conducted using different strategic approaches (see Table 1). Triple therapy has been compared with DAPT and/or with a combination of VKA and a single-anti-platelet drug. Unfortunately there are almost no randomized, prospective trials to elucidate this important clinical problem.

Triple therapy vs. dual-anti-platelet therapy

In one study involving 426 patients with AF undergoing PCI, DAPT was reported in 41% and TT in 50% of all patients.29 In patients without VKA mortality rates were higher [28 vs. 18%; hazard ratio (HR) 3.43, 95% CI 1.61–7.54]. In another study 604 patients with AF undergoing PCI were registered and matched using propensity scores.30 It was reported that OAC at discharge reduced major cardiovascular adverse events (HR 0.40, 95% CI 0.22–0.74) and all-cause mortality (0.34, 95% CI 0.17–0.68). Moreover, in a retrospective study 478 patients with an indication for OAC mostly due to AF who underwent PCI were analysed. Patients treated with DAPT compared with patients treated with TT had a significantly higher rate of stroke (8.8 vs. 2.8%) or stent thrombosis (5.9 vs. 1.9%) at
### Table 1  Clinical data on patients with coronary stent implantation and the indication for anticoagulation.

<table>
<thead>
<tr>
<th>Name/author</th>
<th>Design</th>
<th>n</th>
<th>Mean follow-up</th>
<th>Comparison</th>
<th>Efficacy endpoint</th>
<th>OR/HR (95% CI)</th>
<th>Bleeding endpoint</th>
<th>OR/HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>TT vs. DAPT</strong></td>
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<tr>
<td>Riuz-Nodar et al.</td>
<td>Retrospective, single-centre</td>
<td>426</td>
<td>594 days</td>
<td>DAPT vs. TT</td>
<td>Mortality: 27.8 vs. 17.8%</td>
<td>HR 3.43 (1.61–7.54); P = 0.002</td>
<td>Major bleeding: 14.9 vs. 9.0%</td>
<td>Not reported</td>
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<td></td>
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<td>MACE: 26.5 vs. 38.7%</td>
<td>HR 4.90 (2.17–11.10); P = 0.001</td>
<td>Minor bleeding 12.6 vs. 9.0%</td>
<td>Not reported</td>
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<tr>
<td>Ruiz-Nodar et al.</td>
<td>Retrospective, 2 centres</td>
<td>604</td>
<td>693 days</td>
<td>DAPT vs. TT</td>
<td>Mortality: not reported</td>
<td>HR 0.34 (0.17–0.68); P &lt; 0.01</td>
<td>Not reported</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>MACE: not reported</td>
<td>HR 0.40 (0.22–0.74); P &lt; 0.01</td>
<td>Not reported</td>
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</tr>
<tr>
<td>Karjalainen et al.</td>
<td>Retrospective, 6 centres</td>
<td>478</td>
<td>12 months</td>
<td>TT vs. DAPT</td>
<td>Stent thrombosis: 1.9 vs. 5.9%</td>
<td>Not reported</td>
<td>Major bleeding: 6.6 vs. 11.8%</td>
<td>Not reported</td>
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<td>Stroke: 2.8 vs. 8.8%</td>
<td>Not reported</td>
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<td><strong>TT vs. VKA + single anti-platelet</strong></td>
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<tr>
<td>Sambola et al.</td>
<td>Prospective, 3 centres</td>
<td>405</td>
<td>6 months</td>
<td>TT vs. VKA + single anti-platelet</td>
<td>CV events: 7.9 vs. 15.2%</td>
<td>Not reported</td>
<td>Major bleeding: 4.3 vs. 6.5%</td>
<td>Not reported</td>
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<tr>
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<td>Stent thrombosis: 4.0 vs. 8.7%</td>
<td>Not reported</td>
<td>Minor bleeding 11.2 vs. 6.5%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Karjalainen et al.</td>
<td>Retrospective, 6 centres</td>
<td>478</td>
<td>12 months</td>
<td>TT vs. VKA + ASA</td>
<td>Stent thrombosis: 1.9 vs. 15.2%</td>
<td>Not reported</td>
<td>Major bleeding: 6.6 vs. 6.1%</td>
<td>Not reported</td>
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<td>MI: 8.5 vs. 18.2%</td>
<td>Not reported</td>
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<td>Stent thrombosis: 1.9 vs. 0.0%</td>
<td>Not reported</td>
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<td>MI: 8.5 vs. 11.1%</td>
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<td><strong>Meta-analysis and registry data</strong></td>
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<tr>
<td>Gao et al.</td>
<td>Meta-analysis (9 trials)</td>
<td>5181</td>
<td>1–18 months</td>
<td>TT vs. non-TT</td>
<td>Ischaemic stroke: not reported</td>
<td>OR 0.29 (0.15–0.58); P = 0.0004</td>
<td>Major bleeding: not reported</td>
<td>OR 2.00 (1.41 to 2.83); P = 0.0001</td>
</tr>
<tr>
<td>Zhao et al.</td>
<td>Meta-analysis (9 trials)</td>
<td>1996</td>
<td>&gt; 3 months</td>
<td>TT vs. DAPT</td>
<td>Mortality: not reported</td>
<td>OR 1.20 (0.63–2.27); P = 0.56</td>
<td>Major bleeding: 4.1 vs. 1.9%</td>
<td>OR 2.12 (1.05–4.29); P = 0.04</td>
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<tr>
<td>Hensen et al.</td>
<td>Registry</td>
<td>118606</td>
<td>3.3 years</td>
<td>DAPT vs. VKA alone</td>
<td>MACE: 8.8% vs. 13.9</td>
<td>OR 0.60 (0.42–0.86); P = 0.005</td>
<td>Major bleeding: not reported</td>
<td>OR 2.12 (1.05–4.29); P = 0.04</td>
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<td>Mortality: 6.5 vs. 9.7%</td>
<td>OR 0.59; (0.39–0.90); P = 0.01</td>
<td>Major bleeding: not reported</td>
<td>OR 2.12 (1.05–4.29); P = 0.04</td>
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<td>Stroke: not reported</td>
<td>HR 1.66 (1.34–2.04); P not reported</td>
<td>Major bleeding: not reported</td>
<td>OR 2.12 (1.05–4.29); P = 0.04</td>
</tr>
<tr>
<td>Lamberts et al.</td>
<td>Registry</td>
<td>11480</td>
<td>288 days</td>
<td>TT vs. VKA + single anti-platelet</td>
<td>CV-death, MI, ischaemic stroke: 20.1 vs. 19.4%</td>
<td>HR 1.15 (0.95;1.40); not significant</td>
<td>Major bleeding: not reported</td>
<td>OR 2.12 (1.05–4.29); P = 0.04</td>
</tr>
</tbody>
</table>

**NOTES:**
- OR, odds ratio; HR, hazard ratio; TT, triple therapy; DAPT, dual-anti-platelet therapy; MACE, major adverse cardiovascular events; CV, cardiovascular; MI, myocardial infarction.
12 months.\textsuperscript{31} Taken together these data suggest that major cardiovascular adverse events after PCI occur more frequently when patients with an indication for OAC (usually AF) are not discharged on TT. However, definite conclusions cannot be based on these observational studies in which the possibility of bias is relatively high and patient numbers are low.

**Triple therapy vs. vitamin K antagonism + single anti-platelet**

Similarly to TT vs. DAPT the body of evidence for TT vs. VKA in combination with single-anti-platelet agent is small. In a prospective registry of 405 patients on VKA who underwent PCI, cardiovascular events occurred more frequently in the group that received VKA and single-anti-platelet agent (15.2\%) as compared with patients who received TT (7.9\%) or DAPT (1.2\%).\textsuperscript{32} Remarkably, bleeding rates were not significantly different between patients treated with TT vs. VKA + one anti-platelet agent (15.5 vs. 13.0\%).

However in the retrospective study mentioned above out of 478 patients with an indication for OAC who underwent PCI those treated with aspirin and warfarin had a higher risk for stent thrombosis (15.2 vs. 1.9\%) or MI (18.2 vs. 8.5\%) than those on TT.\textsuperscript{31} Notably, no differences were observed in major bleeding (6.1 vs. 6.6\%). When clopidogrel instead of aspirin was combined with VKA and compared with TT there was no significant difference in stent thrombosis (0 vs. 1.9\%) or MI (11.1 vs. 8.5\%) observed. These data would suggest that VKA combined with clopidogrel has a similar efficiency profile as TT but VKA combined with aspirin has not. This study must be interpreted with great caution not only because patient numbers are small and a stent-thrombosis rate of 15\% appears extraordinarily high, but also because data are not consistent, e.g. major bleeding rates for DAPT are higher than for TT.

**Meta-analysis and registry data**

Meta-analyses of these and other smaller studies have been published although comparability between the studies is hampered due to different control groups, antithrombotic strategies, and agents as well as bleeding definitions. In one meta-analysis involving nine trials the rate of ischaemic stroke was significantly reduced in TT patients compared with patients with other antithrombotic strategies (OR 0.29, 95\% CI: 0.15 to 0.58; \(P = 0.0004\)). Concurrently, there was a two-fold increased risk of major bleeding associated with TT (OR 2.00, 95\% CI 1.41 to 2.83; \(P = 0.0001\)). The overall incidence of death (OR 1.20, 95\% CI 0.63 to 2.27; \(P = 0.56\)) or MI (OR 0.84, 95\% CI 0.57 to 1.23; \(P = 0.38\)) were comparable between the regimens.\textsuperscript{33} In another meta-analysis Zhao et al came to similar conclusions analysing nine clinical trials including 1996 patients. Triple therapy was more effective than DAPT to prevent major adverse cardiovascular events (OR, 0.60; 95\% CI, 0.42–0.86; \(P = 0.005\)), even with regard to mortality (OR, 0.59; 95\% CI, 0.39–0.90; \(P = 0.01\)) although TT was accompanied by more major bleeding events in the first 6 months (OR, 2.12; 95\% CI, 1.05–4.29; \(P = 0.04\)).\textsuperscript{34}

In the absence of solid randomized, controlled clinical trials, apart from meta-analyses registries provide useful real world information about combined antithrombotic strategies.

In the CRUSADE registry, out of 5673 patients enrolled with NSTE-ACS who were previously on warfarin a subset of only 1247 patients underwent PCI with coronary stenting. Out of these patients the majority of 60\% received TT at discharge and 31\% were on DAPT. A minority of 3\% were treated with warfarin combined with aspirin without clopidogrel after PCI. Despite this small number, the CRUSADE registry demonstrates that therapy with one anti-platelet and VKA may be at least as effective to prevent ischaemic end-points in patients with NSTE-MI and AF, but is associated with less bleeding complications compared with TT.\textsuperscript{18}

More support for this strategy can be derived from the GRACE registry. This is a multinational registry of patients with ACS comparing ischaemic events at 6 months in patients discharged on VKA and one anti-platelet with patients discharged on VKA and two-anti-platelets (see Figure 1). Although the number of patients who received a DES is small this registry supports the notion that ST rates do not increase excessively when patients are treated with one anti-platelet in combination with VKA.

In a nationwide registry from Denmark 118 606 patients with AF were followed for the occurrence of clinical events.\textsuperscript{35} In terms of stroke prevention regimens without VKA were less effective compared with VKA alone. But the risk of bleeding during a mean follow-up of 3.3 years was more than three-fold elevated in TT treated patients compared with VKA alone. As patients were not randomized it is difficult to interpret potential differences between the various regimens because a selection bias is likely in this type of study. For example, patients at increased bleeding risk may not have been treated with TT although formally indicated. Thus, bleeding in TT patients may be underestimated in this registry.

In another analysis of the Danish nationwide registry comprising 11 480 AF patients with acute MI (76.4\%) or elective PCI (23.6\%) only 17.3\% of all MI patients underwent PCI within 1 week. Out of all patients 13\% were treated with TT.\textsuperscript{36} These data demonstrate that TT is part of our clinical everyday practice. But in some instances the fear of the potential need for a TT may prevent physicians from referring anticoagulated patients presenting with an ACS to undergo invasive coronary therapy.

**Vitamin K antagonism + single-anti-platelet vs. triple therapy**

In the Danish registry mentioned above bleeding events were recorded according to antithrombotic regimen.\textsuperscript{36} Both early (within 90 days) and delayed (90–360 days) bleeding risk for patients with TT compared with patients receiving VKA and one anti-platelet was increased (HR 1.47 [CI: 1.04–2.08] and 1.36 [0.95–1.95], respectively). No significant differences in thrombo-embolic risk were observed for TT vs. VKA combined with one anti-platelet drug (HR: 1.15 [0.95;1.40]). Taken together registry data support the notion that TT is feasible but the combination of an anticoagulant with only one anti-platelet is an alternative.

**Can antithrombotic therapy be individualized?**

One approach of reducing bleeding events while maintaining antithrombotic effectiveness may be to individualize antithrombotic treatment. In one study clinical and echocardiographic criteria were used to decide whether a patient receiving a stent should be treated with DAPT or TT.\textsuperscript{37} No significant differences in terms of
major cardiovascular adverse outcomes were observed during the time of DAPT or at 2 years suggesting that this approach may be useful to balance risks and benefits. In another study 590 patients with AF and stent implantation were grouped according to their bleeding risk as assessed by the HAS-BLED score. It turned out that more than 70% of patients had a score of 3 or higher. Notably, even in these patients with a high bleeding risk the use of treatment strategies involving VKA were associated with a reduced death rate although bleeding rates were higher. But due to their design and size both of these studies do not provide definitive conclusions and larger trials are warranted to test the hypothesis that individualized therapy can optimize the net clinical data on TT.

Taken together, the available retrospective and non-randomized data suggest that TT is more effective than DAPT or VKA combined with one anti-platelet but at the expense of increased bleeding rates. When compared with DAPT the bleeding risk is increased by about two- to five-fold by TT. Therefore, it is recommended to keep the duration of TT as short as possible.

**Guidelines**

The ESC guidelines recommend TT with aspirin, clopidogrel, and VKA in patients with an indication for therapeutic anticoagulation and ACS and/or coronary stent implantation (see Figure 1). The recommended duration of TT ranges from 2–4 weeks through 6 months depending on individual bleeding risk, type of stent, and circumstances of stent implantation (ACS or elective). Triple therapy is recommended for the duration of 1 month after BMS implantation and should be prolonged to 3 months in the case of implantation of a DES or to 6 months in the case of implantation of a paclitaxel-eluting stent. In the case of ACS, TT should be also prolonged to 6 months irrespective of the stent type implanted. To reduce bleeding complications the INR should be maintained at a lower target range of 2–2.5 instead of 2–3. Aspirin and clopidogrel are given in the usual doses as recommended for stent implantation.

The 2012 American College of Chest Physicians (ACCP) guidelines on antithrombotic therapy for AF gave similar recommendations also using aspirin, clopidogrel, and VKA as antithrombotic drugs. The duration of TT ranges from 1 month (BMS) to 3–6 months (DES) depending on the stent type (see Figure 1).

Both guidelines agree that after 1 year anti-platelet therapy can be stopped and VKA continued as a single long-term prevention of thromboembolism in AF. A major difference between these two guidelines is the recommended INR during combination of VKA and anti-platelet therapy. The ESC guidelines recommend maintaining a reduced INR 2.0–2.5 during combination of VKA and anti-platelet therapy whereas the ACCP guidelines stay with the INR of 2.0–3.0.
It must be noted that the guideline recommendations for TT are not based on randomized trials and that there remains a great deal of uncertainty about the optimal therapy in these patients.

**WOEST trial**

Recently, the first randomized prospective trial addressing the issue of an optimal antithrombotic strategy for patients with AF after coronary stenting was published. In the WOEST multicenter, open-label trial 573 patients who were on OAC for at least 1 year and were scheduled for PCI and stent implantation were randomized to TT with 80 mg aspirin per day, 75 mg clopidogrel per day and VKA or to 75 mg clopidogrel per day and VKA. Treatment was continued for 1 month after bare-metal stenting (35% of patients) or for 1 year after drug-eluting-stent placement (65% of patients). The investigator-driven study was conducted in 15 hospitals in the Netherlands and Belgium. Follow-up time was 1 year. The primary end point of all types of TIMI bleeding including minimal, minor, and major was significantly reduced in the dual-therapy arm [19.5 vs. 44.9%; HR 0.36 (0.26–0.50); P < 0.001]. In particular minimal and minor bleedings were significantly reduced, while major bleeding events were numerically lower but did not reach statistical significance. Intracranial bleeding was unchanged. Although the trial was not powered for the analysis of ischaemic events it is notable that MI, stroke, and stent thrombosis were numerically lower and mortality was significantly lower in the dual-therapy group (see also Figure 1).

**Ongoing trials**

Relevant clinical trial databases (http://www.who.int/trialsearch, http://clinicaltrial.gov; search term ‘atrial and fibrillation and stent’) list two interventional trials currently enrolling patients. In MUSICA-2 304 patients are randomly assigned to receive TT or DAPT. The primary endpoint is ischaemic while the secondary endpoint consists of bleeding complications. In the ISAR-TRIPLE trial 600 patients will be enrolled to compare a TT over 6 weeks vs. TT over 6 months. The primary endpoint is a composite of death, MI, definite stent thrombosis, stroke, or major bleeding.

**What can we do to prevent bleeding?**

**Optimal dosing of antithrombotic drugs**

As bleeding is the major limitation of antithrombotic therapy but efficient antithrombotic treatment is necessary to prevent stent thrombosis or stroke preventive measures need to be considered to optimize the risk/benefit ratio particularly in patients who are at risk for both—stroke and stent thrombosis. Dosing of the antithrombotic drugs should be kept as low as possible. Aspirin—if given at all should be dosed at ≤100 mg per day. It is well established that low doses of aspirin are effective and reduce the bleeding risk compared with higher doses. When VKA are combined with anti-platelet drugs, INR should be kept between 2.0 and 2.5 instead of 2.0 to 3.0. It has been demonstrated that the lower target INR is associated with a significant reduction of bleeding risk in the setting of TT compared with higher target INRs and brings bleeding rates down to the level of DAPT. It may be necessary to shorten the intervals of INR testing in order to increase the time in therapeutic range and reduce bleeding risk.

**Duration of anti-platelet therapy**

At the moment there is insufficient data available about the optimal duration of TT. Most recommendations advise to continue TT for 3–6 months depending on the type of stent and bleeding risk of the patient, but it is unknown whether shorter periods of TT are also effective. Recently, the duration of DAPT after DES in general is under critical discussion. In a large clinical trial in patients receiving new generation zotarolimus eluting stents no differences were observed between 3 months duration of DAPT vs. 12 months. Some recent DES types have obtained clinical approval for only 3 months of DAPT. These data provide support for a shorter duration of TT after elective implantation of this third-generation olimus eluting stents.

**Other measures to reduce bleeding risk**

Most bleeding events in patients on TT occur in the gastrointestinal tract. Therefore, measures should be taken to reduce the risk of gastrointestinal bleeding. The administration of a proton pump inhibitor seems reasonable to achieve this goal. The rates of intracranial bleeding events in AF trials have been falling over the past decades. This is certainly related to the lower INR targets that have been implemented meanwhile, but also to better awareness to accompanying conditions such as arterial hypertension. Optimal control of arterial hypertension contributes to the reduction of bleeding events and thus tight control of blood pressure is also mandatory in TT patients. The patients should be aware that the use of over-the-counter NSAIDs increases the risk of bleeding in particular in TT patients.

**Is there a preferred stent type for triple therapy?**

The type of stent is of critical importance for the duration of TT. After BMS implantation the duration until the struts are covered by endothelium is considered to last 4 weeks. As a consequence, DAPT is required only for this time period. For DES implantation the guidelines currently recommend a prolonged duration of 3 months in the case of implantation of an mTOR-inhibitor-eluting stent or to 6 months in the case of implantation of a paclitaxel-eluting stent 1 year of DAPT. One retrospective study compared the outcomes of anticoagulated patients undergoing PCI with either BMS or DES. DES implantation was associated with a significantly increased risk of major bleeding in the follow-up period. The incidence of ischaemic events and all-cause mortality were similar. As a consequence and in order to reduce the duration of TT, BMS is the preferred stent-type for patients with an additional indication for anticoagulation.

It is notable that the risk of stent thrombosis is highest early after implantation while the risk of bleeding stays at similar levels after the very initial invasive phase. This is another argument in favour of limiting the duration of TT to the early phase and to continue with VKA and one anti-platelet drug later on. The case is different for patients who have survived stent thrombosis. In these patients special emphasis should be put on the prevention of recurrent
stent thrombosis rather than on reducing bleeding risk, therefore, TT should be maintained for longer periods.

**What is the role for modern antithrombotic drugs in triple therapy?**

**Third-generation P2Y12 antagonists**

The current standard of secondary prevention of atherothrombotic events includes anti-platelet therapy with aspirin and a P2Y12 receptor (ADP-receptor) antagonist (clopidogrel, prasugrel, and ticagrelor). The third-generation P2Y12 receptor antagonists provide faster, stronger, and more reliable anti-platelet activity compared with clopidogrel. Based on the TRITON and PLATO trial, respectively, prasugrel, and ticagrelor have been approved for the treatment of ACS and have Class I recommendations by the guidelines for this indication. For stroke prevention in AF patients DAPT with aspirin and clopidogrel has tested inferior compared with VKA. Currently, we do not know if a combination with prasugrel or ticagrelor would be more effective than clopidogrel for this indication. But we do know that prasugrel and ticagrelor cause more bleeding events than clopidogrel. Recently, prasugrel was compared with clopidogrel as an alternative in TT by an observational trial. TIMI major and minor bleeding occurred significantly more often in the prasugrel group compared with the clopidogrel group (adjusted HR 3.2 [1.1–9.1]; P = 0.03). No significant difference in ischaemic endpoints was observed. In line with the results of this study, current guidelines do not recommend the use of these third-generation P2Y12 antagonists in the context of triple therapy.

**Novel oral anticoagulants**

Vitamin K antagonists come with several disadvantages. Bleeding rates, particularly intracranial bleeding rates are relatively high and frequent controls of the INR are necessary. They are associated with drug and food interactions. Maintenance of target INR can sometimes be challenging. Of course all of this applies also to the use of VKA in TT. Novel direct oral anticoagulants (NOACs) have been developed and demonstrated their superior risk/benefit ratio in large trials in patients with AF. One may hypothesize that TT with DAPT combined with one of the NOACs would also improve the risk/benefit ratio of this therapeutic strategy. Indeed the NOACs have been tested in combination with DAPT but for the indication of secondary prevention after ACS. The direct thrombin inhibitor dabigatran and the direct factor Xa antagonist apixaban have been administered at the same dose that has been shown to be effective in AF patients. The outcomes of the respective trials suggest that in ACS patients and when combined with ASS and clopidogrel, the chosen doses—or the specific anticoagulants—were not suited for this indication as they resulted in excessive bleeding without any anti-ischaemic benefit. In contrast, the direct factor Xa antagonist rivaroxaban demonstrated an additional protective effect against stent thrombosis. It would be particularly interesting with regard to the WOEST data to test if rivaroxaban and clopidogrel without aspirin may have sufficient antithrombotic activity to prevent stent thrombosis and stroke in patients with AF and DES and/or ACS without causing excessive bleeding rates. The PIONEER trial (NCT01830543) will test the hypothesis that these encouraging results from ACS patients can be transferred to patients with AF needing stent therapy. Until these data are known the use of NOACs for this patients with a coronary stent and atrial fibrillation can not be recommended.

**Personal opinion and recommendations for future trials**

Based on published data and taking into consideration the guidelines but also the WOEST trial and the fact that stent thrombosis using new
generation stents is a rare event that occurs predominantly early but in contrast that the bleeding risk remains elevated even at later time points, we suggest the following strategies for patients with AF and coronary stent implantation/ACS (see also Figure 2) for trial testing:

- During times of combined anti-platelet and anticoagulant therapy patients should be treated with a proton pump inhibitor to reduce the risk of gastrointestinal bleeding.
- In patients with AF and the need for coronary stent implantation either in ACS or for an elective indication BMS should be preferred in particular when the patient has an elevated bleeding risk or when surgery is planned. With BMS TT should be maintained for 1 month and can be followed by OAC (INR 2–3) alone (preferred) or in combination with aspirin at the discretion of the treating physician.
- If a DES is implanted in AF patients the duration of TT should be kept as short as possible to reduce the bleeding risk. While in patients with low to intermediate bleeding risk the guidelines recommend TT for up to 6 months recent data from the WOEST trial suggest that aspirin may not be necessary in these patients. We are not convinced from the WOEST data that aspirin should be abandoned completely. Instead, we believe that the duration of aspirin and thus TT should be shortened to 1 month. It should also be kept in mind that patients with indications for a stent who suffer from AF in about 70% intrinsically have an elevated bleeding risk, which would further support the notion to reduce TT to one month.
- When triple therapy is completed, clopidogrel combined with VKA should be continued for a total of 1 year with a reduced INR of 2.0–2.5. Thereafter, anticoagulation for AF can be continued as usual.
- Target INR during TT or during combination of VKA with clopidogrel should be maintained at a reduced INR of 2.0 to 2.5. Frequent controls are usually necessary to maintain the INR within these therapeutic windows.
- TT using NOACs is currently not recommended. In the case that the patient and the treating physician nonetheless decide to use NOACs in triple therapy rivaroxaban in a reduced dose may be preferred, but currently only an extrapolation from existing data is available for this approach.
- Third-generation P2Y12 antagonists should be avoided when TT is necessary as bleeding risk may be unforeseeably high. Further trials are needed for combination with these drugs.
- For AF patients with a low thromboembolic risk it should be kept in mind that in a subgroup of the negative study ACTIVE W patients who were naïve to VKA had similar ischaemic event rates but strongly reduced bleeding rates during the first 6 months when treated with DAPT vs. VKA. Thus for these selected patients with a short treatment period, low CHA2DS2-VASc score (0–1) who have not been treated with VKA before stent implantation DAPT may be an alternative strategy to TT.

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**References**


