New anticoagulants in combination with antiplatelet agents

The use of new, direct anticoagulants is increasing. Data from both controlled trials and clinical practice have shown that these drugs are as efficacious and safe as warfarin for deep vein thrombosis and pulmonary embolism, and as stroke prophylaxis for patients with atrial fibrillation. But what if platelet inhibition is also indicated? In the following, the combination of antiplatelets and the new anticoagulants is discussed for various indications.

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The new non-vitamin K oral anticoagulants (NOACs) or direct oral anticoagulants (DOACs) are included in the guidelines for thrombosis prophylaxis after hip and knee surgery, for preventing and treating venous thromboembolism (deep vein thrombosis and pulmonary embolism), for preventing stroke and TIA in connection with atrial fibrillation, and as secondary prophylaxis after mycoardial infarction (1). Apixaban, rivaroxaban and dabigatran are the three new drugs that have so far been approved for use in Norway. Edoxaban is approved in Europe, but not yet marketed in Norway (expected from the end of 2016).

Since no randomised trials exist of the risk of bleeding inherent in using the new drugs in combination with antiplatelet agents, the evidence basis for this treatment is based on post-hoc analyses of phase 3 studies and expert consensus. We will review the evidence base and safety of combination therapy for the indications in question.

The article is based on Norwegian, European and US guidelines (1–4), searches in PubMed for articles published from 1980 to November 2015 with combinations of relevant keywords, searches in the authors' own literature archives and our clinical experience. Several of the authors have been involved in working on the European and Norwegian guidelines for the use of new anticoagulants (4, 5).

Prevention of stroke and TIA in atrial fibrillation cases

Lifelong anticoagulation treatment is recommended for patients with atrial fibrillation and at least two risk factors for thromboembolism (CHA_2DS_2-VASc score ≥ 2). An individual evaluation should be made of those with only one risk factor (CHA_2DS_2-VASc score = 1). Female gender alone is not an indication for anticoagulation treatment (4).

Dabigatran, rivaroxaban and apixaban are approved in Norway as stroke prophylaxis for patients with non-valvular atrial fibrillation (5). The randomised controlled trials that formed the basis for the approval revealed lower incidences of stroke, systemic embolism and serious bleeding in connection with the use of the new anticoagulants compared with warfarin. This effect was also seen in the subgroups of patients with concomitant use of acetylsalicylic acid (aspirin). This is the reason that new drugs are now being recommended as the first choice for atrial fibrillation cases (4). However, concomitant use of anticoagulants and antiplatelet agents entails an extra risk of bleeding, and the underlying data are therefore discussed in more detail in the following.

The RE-LY study (6), in which dabigatran was compared with warfarin, revealed an approximately 50 % higher risk of clinically relevant bleeding in those who received both antiplatelet and anticoagulant, compared with those who only received an anticoagulant. Triple therapy, i.e. dual antiplatelet therapy with acetylsalicylic acid and clopidogrel in addition to an anticoagulant, doubled the risk of bleeding in both groups. There was no difference in risk of bleeding between the warfarin and dabigatran groups who received combination treatment with an antiplatelet agent. The use of aspirin was the most important independent and modifiable risk factor for intracranial haemorrhage (7).

Using aspirin concomitantly with new anticoagulants was also found to be a risk factor for severe haemorrhage in the ROCKET-AF trial, in which rivaroxaban and warfarin were compared.

In the ARISTOTLE trial, in which the efficacy and safety of apixaban were compared with warfarin, 24 % of the patients used aspirin (9). The incidence of severe haemorrhage was higher for those who used aspirin in addition to warfarin (3.9 %) or apixaban (3.1 %) than for those who used only one anticoagulant (2.7 % and 1.8 %, respectively). There was lower risk of stroke, sys-

MAIN POINTS

As a general rule, a combination of new anticoagulants and platelet inhibitors (antiplatelet agents) is only indicated in cases of acute coronary syndrome and a need for stents in coronary vessels in patients for whom anticoagulation treatment is indicated because of atrial fibrillation or venous thromboembolism.

For patients with atrial fibrillation who undergo percutaneous coronary intervention (PCI) and stent implantation, short-term (1–6 month) triple therapy is recommended followed by an anticoagulant combined with clopidogrel for up to 12 months, and then an anticoagulant alone.

Combination treatment of this kind should be avoided in most other cases because of the strong risk of bleeding.

Figure 1 *Overview of conditions that indicate anticoagulation therapy or platelet inhibition as monotherapy or in combination*

Clinical picture		Acute coronary syndrome	Stable coronary disease	Myocardial infarction	Cerebral infarction/TIA with arterial stenoses and stent implantation in pre- and intra-cerebral vessels
	Standard therapy	Acetylsalicylic acid (aspirin) + P2Y12 inhibitor	Aspirin monotherapy	Aspirin + dipyridamole or clopidogrel	Aspirin + clopidogrel
Atrial fibrillation	Anticoagulant monotherapy	Antikcoagulation therapy and dual platelet inhibition 1–6 months after stent implantation, followed by anticoagulant plus clopidogrel for up to 1 year, followed by anti-coagulant as monotherapy	Without stent implanta-tion: Anticoagulant as monotherapy With stent implantation: Anticoagulant and dual platelet inhibition for 1 month after stent implantation, followed by anticoagulant plus clopi-dogrel for up to 1 year, followed by anticoagulant as monotherapy	Anticoagulation monotherapy	Anticoagulant and aspirin/ clopidogrel
Venous throm-bosis – initial treatment (first 3 months)	Anticoagulant monotherapy[1]	Anticoagulation therapy and dual platelet inhibition for 1–3 months (metal stent) or 3–6[2] months (drugeluting stent)	Anticoagulant monotherapy	Anticoagulant monotherapy	Anticoagulant and aspirin and clopidogrel
Venous thrombosis – secondary prophylaxis (treatment after 3 months)	Anticoagulant monotherapy[1]	As above for cases of high risk of recurring venous thrombosis, or dual platelet inhibition without anticoagulant	Anticoagulant monotherapy	Anticoagulant monotherapy in cases of high risk of recurring venous thrombosis, other-wise either aspirin and dipyridamole or clopidogrel	Anticoagulant in cases of high risk of recurring venous thrombosis, or aspirin and clopidogrel
Thrombosis prophylaxis for hip / knee graft opera-tions	Anticoagulant monotherapy[3]	Aspirin + P2Y12 inhibitor normally adequate, or thrombosis prophylaxis with DOAC in addition	Can continue with aspirin during DOAC prophylaxis	Can continue with aspirin during DOAC prophylaxis	Aspirin and clopidogrel may be adequate, short-term thrombosis prophylaxis may be administered in addition

[1] Three months of anticoagulation therapy are recommended for patients with a high risk of bleeding, patients with deep vein thrombosis and patients with venous thrombosis triggered by a transient cause. For patients with a second thrombosis or first idiopathic thrombosis, anticoagulation therapy for an indefinite period is recommended if the risk of bleeding is not high (1)

[2] A period of 1–6 months can also be considered for any patients with drug-eluting stents who are at very high risk of bleeding.

[3] A reduced dose of anticoagulant should be given for 2–5 weeks as thrombosis prophylaxis (1).

temic embolism and major bleeding in the apixaban group than in the warfarin group. This difference was independent of whether the patients took aspirin or not (10).

Peripheral vascular and cerebrovascular disease without atrial fibrillation

Antiplatelet agents (in this patient group aspirin and clopidogrel) are recommended as prophylactic treatment for peripheral vascular disease, symptomatic carotid stenoses and other types of cerebral infarction/TIA without detected atrial fibrillation.

No randomised, controlled trials have yet been conducted to study the efficacy and safety of the new anticoagulants for this patient group (Fig. 1) (11, 12).

Coronary disease

New anticoagulants for acute coronary disease

Patients with both acute and stable coronary disease who have stent implantation are normally treated with aspirin and a class P2Y12 antiplatelet agent (clopidogrel, prasugrel or ticagrelor) for a period, depending on the revascularisation strategy that has been chosen, the stent type and comorbidity/risk of haemorrhage (13). Despite dual antiplatelet therapy, a substantial proportion of patients nonetheless experience new ischaemic events (approximately 10 % within a year) (14).

It is well known that anticoagulation therapy with warfarin in addition to antiplatelet agents results in fewer new ischaemic events

in coronary disease patients, but the combination entails a significant risk of bleeding (15). The role of the new anticoagulants after acute coronary disease is subject to debate.

In the APPRAISE II trial, full-dose apixaban (5 mg × 2) was added to aspirin or aspirin in combination with P2Y12 inhibitor for high-risk patients with acute coronary syndrome. The trial was stopped prematurely because of the increased incidence of major haemorrhages without a corresponding reduction in the number of ischaemic events (16).

In the ATLAS-ACS 2 trial, rivaroxaban (2.5 mg × 2 or 5 mg × 2) was added to aspirin and clopidogrel following acute coronary syndrome, and rivaroxaban was found to reduce the risk of the combined end-point death due to cardiovascular causes, myocardial infarction or stroke (hazard ratio 0.84). Only the low dose 2.5 mg × 2 daily resulted in significantly reduced all-cause mortality (17).

New anticoagulants for acute coronary syndrome and atrial fibrillation

The potential role of the new drugs for patients with acute coronary syndrome and atrial fibrillation has not been investigated in separate trials. Available data are limited to post-hoc analyses of randomised, controlled trials of the new drugs in cases of non-valvular atrial fibrillation and follow-up data from randomised, controlled trials of new anticoagulants and antiplatelet agents for acute coronary syndrome (18).

If patients undergoing treatment with new anticoagulants develop myocardial infarction with ST elevation, percutaneous coronary intervention (PCI) is recommended rather than thrombolysis (3). In patients with unstable angina pectoris or non-ST-elevation myocardial infarction, a switch to low-molecular heparin is recommended in the acute phase, and reversion to the new drugs either after five days, or immediately after successful revascularisation (13). Low-molecular heparin can be administered 12 hours after the last dose of new anticoagulants.

There are no studies in which new anticoagulants have been combined with the newer, more potent, P2Y12 inhibitors (ticagrelor and prasugrel), so the primary recommendation is aspirin and clopidogrel when anticoagulation therapy (warfarin or new anticoagulants) is indicated in addition (Fig. 1) (5).

New anticoagulants with stable coronary disease

At present, new anticoagulants are not indicated for stable coronary disease (> 12 months since acute coronary syndrome) alone.

The new European guidelines propose using anticoagulation therapy (new anticoagulants or warfarin) alone, without the addition of antiplatelet agent, for stable coronary disease and concurrent atrial fibrillation, except in quite special cases, such as main stem stenosis, poor stent apposition, complex bifurcation stenosis, first- generation stents or repeated myocardial infarctions despite secondary prophylaxis (3).

Venous thromboembolism – treatment and prophylaxis

Treatment of venous thromboembolism

Patients with acute venous thromboembolism (deep vein thrombosis or pulmonary embolism) should receive anticoagulation therapy for at least three months. If the risk of bleeding is regarded as high, it is recommended that treatment be terminated after three months (Fig. 1) (1).

Clinical trials to study the efficacy and safety of the new anticoagulants in cases of venous thromboembolism allowed combination therapy with new anticoagulants and dual platelet inhibition (Einstein trials) or aspirin (Amplify, Amplify-Extension, RE-COVER trials). There was increased incidence of clinically relevant (hazard ratio 1.81) and severe haemorrhages (hazard ratio 1.50) in both the rivaroxaban and the warfarin group in the Einstein trial in patients who used aspirin in addition (19). The efficacy and risk of bleeding in patients who used aspirin concomitantly was not analysed in the other trials.

Prophylactic treatment for orthopaedic patients

Approximately 4 % of the participants in the thromboprophylaxis trials with dabigatran and enoxaparin for patients undergoing knee and hip arthroplasty were taking aspirin concomitantly. Post-hoc analyses revealed no significantly increased risk of bleeding with concomitant aspirin compared with anticoagulation treatment as monotherapy, but the follow-up time was short – only 28–35 days (20).

Nor did sub-group analyses of the RECORD trials reveal any significant difference between rivaroxaban and enoxaparin in terms of bleeding risk (21). The risk of bleeding in connection with short-term use of a low-dose new anticoagulant in combination with aspirin accordingly appears to be limited.

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New information

Since the acceptance of the manuscript, new guidelines have been published (27 August 2016) by the European Society of Cardiology (ESC) for the treatment of patients with atrial fibrillation (1). They contain a few changes in the recommendations for stroke prophylaxis for atrial fibrillation patients. It is particularly important to note that there are now more detailed recommendations regarding CHA_2DS_2-VASc scores (the recommendation for women with only one additional risk factor has been downgraded from Class I to Class IIa). The article must therefore be read and interpreted in light of these new recommended classifications.

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