New oral anticoagulant agents – general features and outcomes in subsets of patients

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Summary
During the past four years the phase III trials on stroke prophylaxis in atrial fibrillation and on treatment of venous thromboembolism have been completed for four new oral anticoagulants – dabigatran, apixaban, edoxaban and rivaroxaban. The studies have revealed advantages in terms of a reduced risk of bleeding, most importantly of intracranial bleeding. These anticoagulants also have favourable pharmacokinetics, eliminating the need for routine laboratory monitoring and dose adjustments. There are, however, some differences between the drugs in certain subsets of patients, according to patient characteristics or to indication for treatment. These features are reviewed here. The management of patients in association with invasive procedures or major bleeding is also discussed. Finally, a strategy of how to select patients for warfarin or the new anticoagulants and thereafter possibly also among the latter is outlined.

Keywords
Thrombin inhibitor, Xa inhibitor, atrial fibrillation, venous thromboembolism

Introduction
In 1945 the agricultural biochemist Karl Paul Link (1901-1978), with collaborators Stahlmann and Ikawa, patented warfarin, named after Wisconsin Alumni Research Foundation. Almost 70 years later some may now ask whether the widely used drug is ready to be downgraded to the single purpose of a rodenticide, as it was originally marketed.

The largest market portion of warfarin as a drug is for stroke prophylaxis in atrial fibrillation (SPAF). The proportion of these patients included in the recommendation to anticoagulate has grown during recent years with the expansion from a CHADS2 score (1 point each for Congestive heart failure, Hypertension, Age over 75 and Diabetes and 2 points for stroke or transient ischaemic attack)1 of ≥2 points to also include those with 1 point (2) and even further with a similar expansion of the CHA2DS2-VASc score (which gives 2 points for Age over 75, and one point each for Age 65-74, Vascular disease and female Sex)2 down to 1 point (2). It has become clear that not all patients with a CHADS2 score of 0 or 1 have “truly low risk” and the CHA2DS2-VASc score can provide better differentiation in this subset of patients (3). The number of patients with atrial fibrillation is currently approximately 6 million in the United States according to Miyasaka et al., based on data from Olmsted county and is projected to at least double by 2050 (4) with similar trends estimated for Europe by Krijthe et al. (5). The sole purpose of anticoagulation in atrial fibrillation is to protect the patient from the devastating consequence of an ischaemic stroke and at a population health level to reduce the appalling numbers, which in the United States amount to 795,000 strokes per year, out of which 140,000 are fatal. The only glimmer of hope for the females, who became overtly identified as having an additional stroke risk with the CHA2DS2-VASc-score that is below age of 75 their gender is not an independent risk factor (6). Atrial fibrillation and stroke are not confined to the Western world but constitute a global burden (7, 8). Deitelzweig et al. have predicted a similar expansion of the population affected by venous thromboembolism (VTE) from currently about 1 million to almost 2 million per year in 2050 (9).

Studies on new anticoagulants
It is with this scenario in the background that we are entering an entirely new era of anticoagulant therapy. During only four years (2009-2013) phase III trials with four target-specific oral anticoagulants including more than 70,000 patients with atrial fibrillation (AF) were published (10-13). Three of these new agents, dabigatran, rivaroxaban and apixaban, have already been approved for the SPAF-indication as well as for primary prophylaxis against VTE in many countries. Furthermore, rivaroxaban has been approved for treatment of VTE in a large number of countries. While this article was prepared an additional anticoagulant,
Stroke prevention in atrial fibrillation, dabigatran RE-LY

Acute coronary syndromes, rivaroxaban ATLAS ACS-2 TIMI 51

Primary VTE prevention (orthopaedic surgery), dabigatran RE-MODEL RE-MOBILIZE RE-NOVATE RE-NOVATE II

Primary VTE prevention (medically ill), rivaroxaban MAGELLAN rivaroxaban EINSTEIN-DVT EINSTEIN-PE rivaroxaban EINSTEIN-Extension

Initial treatment of VTE, apixaban ADVANCE I ADVANCE I ADVANCE III apixaban ADOPT apixaban AMPLIFY apixaban AMPLIFY-Extension

Extended treatment of VTE, edoxaban TIMI 48-ENGAGE edoxaban HOKUSAI-VTE

VTE, venous thromboembolism. *Studies with the oral thrombin inhibitor ximelagatran are not included since the drug was withdrawn from market in 2006.

Table 1: Overview of the phase III trials performed with the new oral anticoagulants* with study acronym and according to generic drug name.

<table>
<thead>
<tr>
<th>Stroke prevention in atrial fibrillation</th>
<th>Acute coronary syndromes</th>
<th>Primary VTE prevention (orthopaedic surgery)</th>
<th>Primary VTE prevention (medically ill)</th>
<th>Initial treatment of VTE</th>
<th>Extended treatment of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>dabigatran RE-LY</td>
<td>rivaroxaban</td>
<td>rivaroxaban RECORD I RECORD II RECORD III RECORD IV</td>
<td>rivaroxaban MAGELLAN</td>
<td>rivaroxaban EINSTEIN-DVT EINSTEIN-PE rivaroxaban EINSTEIN-Extension</td>
<td>apixaban ADVANCE I ADVANCE I ADVANCE III apixaban ADOPT apixaban AMPLIFY apixaban AMPLIFY-Extension</td>
</tr>
<tr>
<td>rivaroxaban ROCKET AF</td>
<td>rivaroxaban ATLAS ACS-2 TIMI 51</td>
<td>rivaroxaban RECORD I RECORD II RECORD III RECORD IV</td>
<td>rivaroxaban MAGELLAN</td>
<td>rivaroxaban EINSTEIN-DVT EINSTEIN-PE rivaroxaban EINSTEIN-Extension</td>
<td>apixaban ADVANCE I ADVANCE I ADVANCE III apixaban ADOPT apixaban AMPLIFY apixaban AMPLIFY-Extension</td>
</tr>
<tr>
<td>apixaban AVERROES ARISTOTLE</td>
<td>apixaban APPRAISE-2</td>
<td>apixaban ADVANCE I ADVANCE I ADVANCE III</td>
<td>apixaban ADOPT</td>
<td>apixaban AMPLIFY apixaban AMPLIFY-Extension</td>
<td>apixaban AMPLIFY-Extension</td>
</tr>
<tr>
<td>edoxaban TIMI 48-ENGAGE</td>
<td>apixaban</td>
<td>apixaban ADVANCE I ADVANCE I ADVANCE III</td>
<td>apixaban ADOPT</td>
<td>apixaban AMPLIFY apixaban AMPLIFY-Extension</td>
<td>apixaban AMPLIFY-Extension</td>
</tr>
</tbody>
</table>

Table 2: Important pre-clinical features of the new anticoagulants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/prodrug</td>
<td>Produg (dabigatran etexilate)</td>
<td>Drug</td>
<td>Drug</td>
<td>Drug</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6%</td>
<td>Almost 100% for 10 mg, less for higher doses</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Time to maximum effect (t_{max})</td>
<td>1.5–2 h</td>
<td>2 h</td>
<td>3–4 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Half-life (t½)</td>
<td>12–17 h</td>
<td>5–9 h*</td>
<td>8–15 h</td>
<td>9–10 h</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>35%</td>
<td>92–95%</td>
<td>87%</td>
<td>40–59%</td>
</tr>
<tr>
<td>Renal elimination of active drug</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>35–39%</td>
</tr>
<tr>
<td>Interactions mediated by</td>
<td>P-gp</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, (CYP3A4)</td>
</tr>
<tr>
<td>Food effect</td>
<td>Absorption delayed, not reduced</td>
<td>Required for absorption of doses &gt;10 mg</td>
<td>Not reported</td>
<td>No</td>
</tr>
</tbody>
</table>

P-gp, P-glycoprotein or permeability glycoprotein; CYP, cytochrome P450. *In elderly, the candidate population, the t½ is 11–13 h.
fect is that the activity of factor VII is depressed by warfarin but not by the new anticoagulants. With the latter, tissue factor that is present in high concentrations in brain tissue has a better chance in case of injury to activate the extrinsic pathway of coagulation.

The major efficacy outcome in the AF studies was the composite of stroke and systemic embolism and the major safety outcome was major bleeding. The results differ somewhat here between the anticoagulants when evaluated against the comparator that always was warfarin (▶Table 3). It could be remarked that the design of the trials differed, with the dabigatran trial as the only one with open-label and blinded endpoint evaluation. In a recent analysis of phase III trials in SPAF there was no significant difference in event rates or in risk estimates of major outcomes according to study design (20). For patients at a high risk of stroke and bleeding there seems to be improved net clinical benefit with all three approved new anticoagulants compared to warfarin as shown in a modelling analysis (21). In various subsets of patients with lower risks there may be small advantages of one new anticoagulant over the others.

Subgroup analyses from the AF trials

Gender

The influence of gender on the results appears to be minimal. With dabigatran 150 mg twice daily the annual absolute risk reduction for the primary efficacy outcome was 0.39% for males and 0.89% for females, which was not a statistically significant difference. In the treatment studies for VTE there was a similar trend (18, 22). This could possibly be due to a lower body weight in females and thereby an increased effect (see also under Ethnicity or race regarding better effect in the Asian population). In contradiction, with apixaban there was a trend to lower risk of major bleeding among females (p=0.08) (11).

Age

For dabigatran with both dose regimens there is a trend to higher risk of major bleeding with age (▶Table 4) and the treatment-by-age interaction was found to be statistically significant (23). This tendency cannot be discerned for rivaroxaban, edoxaban and apixaban. It should be noted that for intracranial bleeding the relative risk remained very favorable in patients 75 years or older on dabigatran (110 mg – 0.37; 95% confidence interval [CI], 0.21-0.64, and for 150 mg 0.42; 95% CI, 0.25-0.70). Thus, whereas dabigatran has a very favorable risk profile for younger patients the factor Xa inhibitors appear to do better in the elderly when it comes to extracranial bleeding. This could be a reflection of their lower dependence on renal elimination. Nevertheless, if prophylaxis against ischaemic stroke is more important to the patient the differences in extracranial bleeding become less of a concern.

Ethnicity or race

There was usually a trend to better effect in the Asian countries although not at the cost of decreased safety (10-12). This is of clear importance to these countries where there has traditionally been an exaggerated caution with dosing of warfarin. Obviously, that could have been a contributing reason for the beneficial effect, since patients on warfarin were given suboptimal doses. Another possible reason for better effect of new anticoagulants in the Asian populations could be their lower body weight compared to Western populations. Nevertheless, since intracranial haemorrhage is more common in the Asian population in general and the risk reduction for this ominous event appeared even greater in the Asian than in the non-Asian population with dabigatran versus warfarin (24), the new anticoagulants should be an attractive alternative in these countries.

Renal dysfunction

In view of the renal dependence for drug elimination for all the new anticoagulants, albeit at different magnitudes, there was from the beginning of the trials a concern. Patients with a calculated creatinine clearance of less than 25 or 30 ml/minute (min) were not eligible, since that corresponds to severe renal failure. Furthermore, in the trials with rivaroxaban and apixaban there was a built-in reduction of the dose for renal impairment (rivaroxaban 20 → 15 mg daily for creatinine clearance 30-49 ml/min; apixaban 5 → 2.5 mg twice daily for a composite with creatinine >132 mmol/l as one of the components). This was not the case in the somewhat earlier RE-LY trial with dabigatran but the labelling has a recommendation to reduce the dose (220 → 150 mg daily) in patients receiving dabigatran as prophylaxis against VTE after ortho-

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Table 3: Major efficacy (analysed as intention to treat) and safety outcomes in the atrial fibrillation studies (10–12). Hazard ratios or relative risks are in relation to warfarin and are in bold type when showing a statistically significant reduction.

<table>
<thead>
<tr>
<th>Efficacy (reduction of stroke or systemic embolism)</th>
<th>Safety (major bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best</strong></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>Edoxaban 30 mg daily</td>
</tr>
<tr>
<td>RR 0.66 (95% CI, 0.53–0.82)</td>
<td>HR 0.47 (97.5% CI, 0.41–0.55)</td>
</tr>
<tr>
<td>Apixaban 5 mg BID</td>
<td></td>
</tr>
<tr>
<td>HR 0.79 (95% CI, 0.66–0.95)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60 mg daily</td>
<td>Dabigatran 110 mg BID</td>
</tr>
<tr>
<td>HR 0.87 (97.5% CI, 0.73–1.04)</td>
<td>HR 0.80 (95% CI, 0.69–0.93)</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg daily</td>
<td></td>
</tr>
<tr>
<td>RR 0.88 (95% CI, 0.74–1.03)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110 mg BID</td>
<td></td>
</tr>
<tr>
<td>RR 0.91 (95% CI, 0.74–1.11)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30 mg daily</td>
<td>Rivaroxaban 20 mg daily</td>
</tr>
<tr>
<td>HR 1.13 (97.5% CI, 0.96–1.34)</td>
<td>HR 1.04 (95% CI, 0.90–1.20)</td>
</tr>
</tbody>
</table>

*Note that “worst” risk estimate is still non-inferior to warfarin.
paediatric surgery in case of a creatinine clearance of 30-49 ml/min. For the AF population it is the age criterion (80 years or older) rather than moderate renal impairment that qualifies for a reduction (150 → 110 mg twice daily) of the dose. However, in case of a creatinine clearance of 30-49 ml/min it is recommended to treat “with caution” and to monitor renal function annually – keeping in mind that in many elderly there is a concomitant reduction of renal function. These recommendations for dabigatran are not applicable in the United States, where the labelling is 150 mg twice daily for all with a creatinine clearance over 30 ml/min and a 75 mg twice daily regimen is proposed in case of a clearance of 15-30 ml/min.

In the AF studies there was an increase in the risk of bleeding among those with moderate renal impairment with all the new anticoagulants – despite the dose reduction mandated for rivaroxaban and apixaban – but this was also the case in the warfarin groups (Table 5).

### Stroke risk stratification

The patients in the AF trials were characterised according to their risk of stroke with the CHADS<sub>2</sub> score. For eligibility at least a score of 1 was required except for the rivaroxaban trial, where 2 was the minimum (12). Results of efficacy according to the CHADS<sub>2</sub> score did not show any clear trends – the effect was similar across all scores (data not shown).

#### Concomitant antiplatelet therapy

A substantial proportion of patients with AF have a history of coronary artery disease and have an indication for antiplatelet therapy. In the RE-LY trial 20% had concomitant treatment with aspirin and 38% had received aspirin or clopidogrel at some point (10). In the ROCKET-AF trial 35% were on aspirin treatment (12). There does not appear to be any treatment-by-antiplatelet interaction but aspirin seems to add a similar risk of bleeding to each regimen of dabigatran as to anticoagulation with warfarin, as demonstrated in a subgroup analysis by Dans et al. (25).

#### Anticoagulation for VTE

Patients with deep vein thrombosis or pulmonary embolism are typically treated for 3-6 months for their first event. In about half of the cases the VTE was unprovoked and in additional patients it was provoked by a permanent risk factor. For these patients it is...
desirable to extend the prevention of recurrent events, which otherwise is high. Extended treatment is by no means routine and therefore placebo was an ethically acceptable comparator in this particular population.

The primary efficacy outcome, which was recurrent, symptomatic VTE or related death, occurred in the studies on the initial treatment with a similar rate with the new anticoagulants as with vitamin K antagonists (Table 6) (15-18, 22). Thus, for this indication it has not been possible to achieve superiority with any of the new agents. On the other hand, several of the risk estimates for bleeding outcomes show a statistically significant advantage for the new anticoagulants, which is one of the important requirements for considering indefinite duration of anticoagulation after VTE. The second requirement is convenience, which is achieved with drugs that do not require routine laboratory monitoring and dose adjustments. Several trials were performed to study the extended treatment after VTE. One was with warfarin as active comparator and although there was not a statistically significant reduction in the risk of major bleeding the event rate was numerically reduced by half and consistent with the significant reduction of major and clinically relevant non-major bleeding rate (19). In three placebo-controlled trials the new anticoagulants always gave a substantial reduction of risk for recurrence without a significant increase of major bleeding (16, 19, 26). Whether it is possible to fine-tune the dose of dabigatran or rivaroxaban so that also minor bleedings are kept as low as with placebo might be addressed in future trials.

### Mechanical heart valves – another ball game

Dabigatran for prevention of stroke or systemic embolism in mechanical heart valves was first evaluated in animal models and subsequently in the phase II study (27). Patients were monitored for plasma levels of dabigatran and attempts were made to keep those above 50 ng/ml at the trough level, which turned out difficult in the first few months after the heart surgery. Two of the three dose regimens were higher (220 mg and 330 mg twice daily) than chosen for dabigatran in AF or VTE. Unfortunately, there was not sufficient efficacy for stroke protection despite increased risk of bleeding and the study was prematurely discontinued. Mechanical heart valves are therefore a contraindication for the use of new anticoagulants.

### Table 6: Primary efficacy outcomes and major bleeding in the trials in venous thromboembolism (15–19, 22, 26). Significant risk reductions are in bold type.

<table>
<thead>
<tr>
<th>Drug, trial</th>
<th>Primary efficacy outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>Absolute difference in risk</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran RE-COVER</td>
<td>1.10 (0.65–1.84)</td>
<td>0.4%</td>
<td>0.82 (0.45–1.48)</td>
<td>0.63 (0.47–0.84)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran RE-COVER II</td>
<td>1.08 (0.64–1.8)</td>
<td>0.2%</td>
<td>0.69 (0.36–1.32)</td>
<td>0.62 (0.45–0.84)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban EINSTEIN DVT</td>
<td>0.68 (0.44–1.04)</td>
<td>-0.9%</td>
<td>0.65 (0.33–1.30)</td>
<td>0.97 (0.76–1.22)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban EINSTEIN PE</td>
<td>1.12 (0.75–1.68)</td>
<td>0.3%</td>
<td>0.49 (0.31–0.79)</td>
<td>0.90 (0.76–1.07)</td>
<td></td>
</tr>
<tr>
<td>Apixaban AMPLIFY</td>
<td>0.84 (0.60–1.18)</td>
<td>-0.4%</td>
<td>0.30 (0.17–0.55)</td>
<td>0.44 (0.36–0.55)</td>
<td></td>
</tr>
<tr>
<td>Edoxaban HOKUSAI VTE</td>
<td>0.89 (0.70–1.13)</td>
<td>-0.4%</td>
<td>0.84 (0.59–1.21)</td>
<td>0.81 (0.71–0.94)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran vs warfarin, RE-MEDY</td>
<td>1.44 (0.78–2.64)</td>
<td>0.5%</td>
<td>0.52 (0.27–1.02)</td>
<td>0.54 (0.41–0.71)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran vs P RE-SONATE</td>
<td>0.08 (0.02–0.25)</td>
<td>-5.2%</td>
<td>Not estimable (2 vs 0 events)</td>
<td>2.92 (1.52–5.60)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban vs P EINSTEIN Extension</td>
<td>0.18 (0.09–0.39)</td>
<td>-5.8%</td>
<td>Not estimable (4 vs 0 events)</td>
<td>5.19 (2.3–11.7)</td>
<td></td>
</tr>
<tr>
<td>Apixaban 5 mg vs P</td>
<td>0.36 (0.25–0.53)</td>
<td>-7.4%</td>
<td>0.25 (0.03–2.24)</td>
<td>1.62 (0.96–2.73)</td>
<td></td>
</tr>
<tr>
<td>Apixaban 2.5 mg vs P AMPLIFY-EXT</td>
<td>0.33 (0.22–0.48)</td>
<td>-7.8%</td>
<td>0.49 (0.09–2.64)</td>
<td>1.20 (0.69–2.10)</td>
<td></td>
</tr>
</tbody>
</table>

CRNMB, clinically relevant non-major bleeding; CI, confidence interval; P, placebo.
Perioperative management

The main differences between the new anticoagulants and warfarin in this setting are the shorter times for onset and offset of effect of the former. This means that the new anticoagulants can be stopped shorter before surgery, usually 1-2 days before the procedure. For dabigatran in patients with moderate renal failure (creatinine clearance 30-49 ml/min) together with a high-risk procedure an interval of four days is recommended. Furthermore, the anticoagulant effect comes almost momentarily after resumption of treatment and therefore no bridging anticoagulation with heparin is required. The exception would be when oral medication cannot be administered due to bowel paralysis or other reasons.

In an analysis of the 4,591 surgical procedures performed during the RE-LY trial there was no increase in bleeding risk among patients randomised to dabigatran compared to warfarin, neither for elective surgery nor for emergency procedures (28). Thus, the lack of an antidote for dabigatran did not result in more perioperative bleeding.

With the much faster off-set and on-set of anticoagulant effect of the new anticoagulants in comparison with warfarin no bridging anticoagulation with heparin is needed or recommended. The main exception would be when oral intake of medication is delayed postoperatively.

Management of bleeding

The recommendations in common for the new anticoagulants in case of major bleeding is to start with general supportive measures:
- Withhold all antithrombotic agents as long as appropriate
- Treat symptomatically, including fluid replacement, oxygenation, haemodynamic support, blood transfusion as required
- Haemostasis by local compression if feasible, endoscopic or surgical intervention to find and treat the source of bleeding.

For dabigatran there is also evidence that active charcoal can adsorb and inactivate drug if, for example still in the stomach after recent ingestion (29). Furthermore, dabigatran due to its low degree of plasma protein binding – but not the factor Xa inhibitors – can be removed with haemodialysis during at least 4-6 hours (30, 31). Obviously, the lack of a fast-acting antidote for the new anticoagulants has generated some concern among physicians. There are some encouraging data emerging that for dabigatran the use of activated prothrombin complex concentrate may be useful to control life-threatening bleeding (32, 33) and a specific monoclonal Fab fragment removes dabigatran rapidly from the circulation (34) and is now evaluated in a phase II study. For the factor Xa-inhibitors a decoy factor Xa, andexanet-alpha, reverses the anticoagulant effects of rivaroxaban and apixaban in healthy volunteers and is also being studied in humans now (35, 36).

In an attempt to analyse the consequences of major bleeding the five phase III treatment trials with dabigatran versus warfarin were recently reviewed, and there was no evidence for more hospital resources used for the dabigatran patients (37). Proportion of patients hospitalised, length of stay and surgical interventions were similar in the two groups. Major bleeds on dabigatran were treated with more red cells, well balanced by fewer plasma transfusions and they had significantly fewer nights in intensive care units. Outcomes after the bleeding were also analysed and there was a trend to lower 30-day all-cause mortality for the dabigatran patients (odds ratio 0.44; 95% confidence interval, 0.44-1.00; p=0.051) (37). No differences were seen in proportions of patients discharged home, to rehabilitation or to long-term care or in improvement of neurological function, as assessed with the modified Rankin Scale. Somewhat surprisingly, patients in the warfarin group, most of whom had open-label treatment (RE-LY trial) did not receive prothrombin complex concentrate in more than a few cases and even vitamin K was not routinely given. One can therefore also conclude that for a drug that has been available for 60 years there is still suboptimal management of major bleeding.

Target groups for the new anticoagulants

Warfarin is effective to prevent stroke in patients with a high proportion of time in the therapeutic range (38). Patients in question for starting on a new anticoagulant belong to two principal groups – the warfarin experienced and the warfarin-naïve.

A patient who has been on warfarin and has experienced an intracranial bleeding may be very reluctant to resume anticoagulation. If otherwise eligible and with a high risk of stroke, the patient should be introduced to the impressive data from all AF trials that the new anticoagulants reduced the risk of intracranial bleeding by about 50% compared to warfarin. It should also be mentioned that there are no studies that specifically addressed this subset of patients to provide evidence for a reduced risk of recurrent intracranial haemorrhage on new anticoagulants versus warfarin.

Another target group is the patients with repeatedly unstable prothrombin times for other reasons than poor adherence. A clue in this respect can be obtained from their adherence to the laboratory monitoring on warfarin. Patients with difficulties managing this monitoring for geographical reasons, for other reasons for difficult access to the laboratory, or with problematic venous access (for all of whom self-testing was not an acceptable option) may enjoy a great relief by switching to a new anticoagulant. There are patients who make all attempts to manage their warfarin treatment as instructed but due to frequent antibiotic courses for recurrent infections or due to intermittent need for strong analgesic medication they cannot achieve acceptable stability. With the limited spectrum of drug-drug interactions for the new anticoagulants they could be a good choice here. A similar situation occurs when patients have congestive heart failure with intermittent decompensation and associated impaired liver function and metabolism of warfarin.

On the contrary, the new anticoagulants are contraindicated for patients with mechanical heart valves, those with severe renal failure (calculated creatinine clearance less than 25-30 ml/min), and for the Xa inhibitors also in combination with azole antifungycotics or ritonavir. The reason for the latter is their strong inhibition of
P-glycoprotein, resulting in substantially higher blood levels of the anticoagulants.

Patients that might be unsuitable for the new anticoagulants are those with poor adherence to warfarin therapy since without monitoring the adherence will probably be even worse. Furthermore, a tendency to lower gastrointestinal bleeding is likely to deteriorate, at least with dabigatran and rivaroxaban, for which the concentration of active drug is high in the stools (39, 40).

Patients that are warfarin-naïve may in some countries have a private drug plan that covers the new anticoagulants and they are then free to request this alternative. For patients covered by a provincial or national health insurance there are in certain jurisdictions restrictions requiring that the patients first have a trial period and demonstrate “failure” on warfarin, e.g. low proportion of time in therapeutic range, or that laboratory monitoring is inaccessible. It is mostly impossible to predict what patient will be stable on warfarin and therefore it is reasonable to give the majority of patients a trial period of a few months on warfarin and then bring them back for reassessment.

Choice of new anticoagulant

With three and soon perhaps four new oral anticoagulants it may be a daunting task for some general practitioners to decide on which one to prescribe. Keeping in mind the total lack of head-to-head comparisons it is acceptable for a physician to know one drug well and use that consistently. For haematologists, cardiologists, neurologists and some other specialists it is probably more desirable to try and tailor the treatment to the specific needs and preferences of the patients.

- Reduce risk of ischaemic stroke. This should be the primary goal of anticoagulation in AF and the only alternative that provided a significant reduction of ischaemic stroke compared to warfarin was dabigatran at 150 mg twice daily.
- Minimise risk of bleeding. Patients with previous bleeds or who have refused to start on warfarin due to fear of bleeding can choose between dabigatran at 110 mg or apixaban 5 mg, both twice daily, which were associated with a significantly lower risk of bleeding than warfarin.
- Concern about acute coronary syndromes. There has been a signal of lower protection against myocardial infarction with dabigatran than with warfarin in some clinical trials (41, 42), although this was not confirmed in registry studies (43). For patients developing AF after myocardial infarction it may feel that they are not protected, although this was not confirmed in registry studies (43).
- History of dyspepsia. Dabigatran is clearly associated with a risk of dyspepsia (10) that can be expressed as reflux, abdominal pain, gas, nausea or diarrhea. Again, rivaroxaban or apixaban could be preferable for patients already frequently suffering from such symptoms.
- Twice-daily medication does not work. This is unusual but a few patients are indeed unable to cope with such a regimen and rivaroxaban, which is given once daily, is the natural choice here.

Conclusions

The choices between oral anticoagulants have increased from 1 to 4 during the past four years, and it is important for the physicians treating patients with such drugs to learn about the advantages and specific features. Patients starting on any of these drugs need to be taught about the benefits and risks so that they can take part in an informed decision on the choice of anticoagulant. Once treatment has been started, an appointment should be booked for reassessment after a few months. Some patients may have decided on their own to discontinue the medication due to side-effects and now they can be offered other alternatives. Studies are still needed on management of patients in special situations such as surgery or major bleeding and on real-world efficacy, safety and adherence.

Conflicts of interest

The author has received honoraria for work in study committees from Boehringer Ingelheim and Bayer Healthcare. The author is director of an anticoagulation clinic for warfarin.

References


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