Active Online Assessment of Patients Using New Oral Anticoagulants: Bleeding Risk, Compliance, and Coagulation Analysis

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Abstract

Clinicians prescribing new oral anticoagulants (OACs; dabigatran, rivaroxaban, and apixaban) should be aware of the exclusion criteria related to bleeding risks defined in published clinical studies. At least a quarter of patients currently using warfarin have an exclusion criterion that may prevent easy transition to the new OACs. In the summary of product characteristics for dabigatran, as an example, the target populations appear generalized. Due to fixed dosing and predictable pharmacology, routine laboratory monitoring of new OACs is deemed unnecessary. Under special circumstances, however, understanding the extent of thrombin or factor (F) Xa inhibition may aid in evaluating compliance and handling emergency interventions, bleeding complications, or overdoses. Although commonly available global coagulation-time assessments (prothrombin time and activated partial thromboplastin time) are insensitive, they may assist clinical management by indicating a severe accumulation of OACs; moreover, a normal thrombin time (TT) excludes a thrombin-inhibitor effect. In particular circumstances, specific assays (diluted TT, Ecarin clotting time, anti-FIIa or anti-FXa activity) may quantify the anticoagulant effect, but therapeutic ranges for dose adjustment are not yet established. Laboratory results are also influenced by clinical situation: e.g. bleed (consumption of coagulation factors) versus postoperative state (activation of coagulation). Without specific antidotes and evidence-based treatment strategies, new OACs are clinically worrisome in patients with impaired renal or liver function. Postmarketing surveillance and recording of bleeding complications (ICD-10 D68.32) are therefore of major importance.

Keywords
► bleeding risk
► new oral anticoagulants
► laboratory measuring
► dabigatran
► rivaroxaban
► apixaban

One-fourth of all patients on vitamin K antagonist (VKA) therapy, when admitted to hospital for an infection would have been excluded from practically all clinical trials of oral anticoagulants (OACs) for atrial fibrillation (AF), for secondary prevention of venous thromboembolism (VTE), or for prevention of coronary atherothrombosis.1 Similar exclusion criteria occurred even more frequently among patients hospitalized for a bleeding complication while on VKA; at least one exclusion criterion emerged in 40% of such cases.1 It is noteworthy that six principal randomized studies for the present treatment guidelines on VKA for AF excluded 87% of the patients screened.1 The presence of at least one
Anticoagulation therapy with direct thrombin inhibitors (DTIs) or FXa inhibitors (DFXaIs) seems to show efficacy and safety than do low-molecular-weight heparins (LMWHs) and VKAs, but thus far only in highly selected patient populations. Anticoagulation with direct thrombin inhibitors (DTIs) or FXa inhibitors (DFXaIs) shows similar or even better efficacy and safety than that of VKA, the new OACs inhibit a targeted activated coagulation factor, that is, thrombin (dabigatran) or factor Xa (FXa) (rivaroxaban and apixaban). VKAs have many limitations, their therapeutic range may be achievable only 60% of the time, even in highly controlled and selected study populations.

The new OACs are emerging in clinical practice for prophylaxis of stroke in AF and for prophylaxis and treatment of VTE. Clinical experiences regarding new OACs among nonselected patient populations are scarce, because the initial official indications included only short-term prophylaxis after elective knee or hip replacement surgery. Stroke prevention in AF will become a new indication for dabigatran, rivaroxaban, and apixaban, where dabigatran is the first newcomer. Hence, clinicians should become acquainted with the specific safety characteristics of these drugs and of those patients most likely to gain the greatest long-term benefit from the new OACs.

### Bleeding Risk-Related Exclusion Criteria

Studies on new OACs for VTE treatment or stroke prevention in AF (Tables 1 and 2) excluded patients with another indication for VKA, or having active liver (or alanine aminotransferase >2 to 3 times upper normal limit) or kidney disease (an estimated creatinine clearance <30 mL/min; SBP >200 mm Hg or DBP >110 mm Hg).

<table>
<thead>
<tr>
<th>Study, Mean Duration (n = Patients with New OAC)</th>
<th>Bleeding Risk-Related Exclusion Criteria</th>
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<tbody>
<tr>
<td>Dabigatran (RE-COVER) 163 ± 50 d (n = 1273)</td>
<td>High risk for bleeding</td>
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<td>Contraindication to heparin</td>
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<td>Requirement for long-term antiplatelet therapy</td>
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<td>ASA &gt;100 mg</td>
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<tr>
<td>Rivaroxaban (Einstein-DVT) 83–87 d (n = 405)</td>
<td>Active bleeding or high risk of bleeding</td>
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<td>Any other contraindication listed in the labeling of permitted anticoagulants</td>
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<tr>
<td></td>
<td>Treatment for &gt;36 h before randomization with therapeutic doses of UFH or LMWH, or receiving more than a single dose of a VKA SBP &gt;200 mm Hg or DBP &gt;110 mm Hg</td>
</tr>
<tr>
<td>Apixaban (Botticelli DVT) 80 ± 20 d (n = 392)</td>
<td>Active bleeding or high risk for bleeding contraindicating treatment with LMWH, fondaparinux, or VKA</td>
</tr>
<tr>
<td></td>
<td>Any other contraindication listed in the local labeling of enoxaparin, tinzaparin, fondaparinux, warfarin, acenocoumarol, or phenprocoumon</td>
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<tr>
<td></td>
<td>&gt;24 h of prerandomization treatment with therapeutic doses of UFH, LMWH, or fondaparinux</td>
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<tr>
<td></td>
<td>More than a single starting dose of VKA before randomization SBP &gt;200 mm Hg or DBP &gt;110 mm Hg</td>
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<tr>
<td></td>
<td>ASA &gt;165 mg</td>
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</table>

OACs, oral anticoagulants; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism; ASA, acetylsalicylic acid; UFH, unfractionated heparin; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Exclusion criterion elevated the bleeding risk up to 2.9-fold (95% CI, 2.2–3.9). This information is highly important when considering the use of new OACs.

In contrast to the multiple coagulation-factor targets of VKA, the new OACs inhibit a targeted activated coagulation factor, that is, thrombin (dabigatran) or factor Xa (FXa) (rivaroxaban and apixaban). VKAs have many limitations, and their therapeutic range may be achievable only 60% of the time, even in highly controlled and selected study populations.

Anticoagulation with direct thrombin inhibitors (DTIs) or FXa inhibitors (DFXaIs) seems to show similar or even better efficacy and safety than that of low-molecular-weight heparins (LMWHs) and VKAs, but thus far only in highly selected patient populations.

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### Bleeding Risk-Related Exclusion Criteria

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Assessment of the bleeding risk-related exclusion criteria on admission was subjective, with criteria varying between studies (Tables 1 and 2). One could argue that possibly 25 to 40% of the patients in clinical practice would have been excluded from these studies based on study trial-defined exclusion criteria. Avoidance of bleeding complications is extremely important; each bleeding event during antithrombotic treatments contributes to highly increased mortality. One particular challenge is that patients requiring anticoagulation often have simultaneous risk factors predisposing them to both bleedings and thrombosis, that is, diabetes, advanced age, and hypertension according to CHA2DS2-VASC score (Congestive heart failure, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65 to 74, and Sex Category [female]) and HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly).

Anticoagulation is necessary in various clinical situations. Need for active assessment among patients on new OACs can develop in various scenarios: (1) short-term thromboprophylaxis during acute illness, (2) after orthopedic or other surgery, (3) long-term secondary prophylaxis for stroke or VTE and onset of new disease or need of elective or emergency invasive intervention, (4) cancer patients with simultaneous bleeding and thrombosis risks, or (5) bleeding complication or severe trauma while on new OACs.
Short-Term Thromboprophylaxis

Short-term thromboprophylaxis is obviously less problematic than long-term use of the new OACs. Acute infection, transient renal or hepatic insufficiency, or postoperative or other inflammation or problems in drug absorbance can all modify coagulation. The effects of new OACs on measurements of fibrinogen and of other activity-based coagulation factors should thus be known in advance to ensure appropriate interpretation of test results.19-21

Long-Term Treatment: Lessons from the Last Decade

At present, data on the new OACs are based on clinical trials with selected patient populations; no postmarketing safety analyses are yet available. In the RE-LY study, having the longest longitudinal follow-up of patients on new OACs, the AF patients were on dabigatran for only a median 2 years.6 Thus, its long-term safety remains unknown during lifelong indications for OAC. Side effects are more common in unselected populations due to aging and comorbidities, such as cancer and renal or liver impairment. Even recently many new drugs with great expectations have been withdrawn from the market due to unexpected off-target side effects, such as hepatotoxicity (the anticoagulant melagatran/ximelagatran and anti-inflammatory nimesulide), cardiotoxicity (the anti-inflammatory rofecoxib and valdecoxib and the antiobesity drug sibutramine), depression (the antiobesity drug rimonabant), or progressive multifocal leukoencephalopathy (the psoriasis drug efalizumab).22-27 In addition, dronedarone was newly marketed
for rate control in AF without the need for laboratory checks, but soon after its use in real-world populations, new recommendations were given for monthly laboratory tests during the first 6 months, to survey for liver toxicity. The coadministration of new OACs and dronedarone in AF patients cannot be recommended.

Long-term use of DTIs and FXaIs needs further attention as both thrombin and FXa have other key roles beyond coagulation, such as regulatory functions during inflammation and cell renewal. At present caution seems a better approach toward the new OACs than an overoptimistic reliance on, or extrapolation of, the data available.

**Need for Elective or Emergency Intervention**

Discontinuation of the new OACs before elective surgery due to obvious bleeding risk is the recommendation, based on pharmacological data. Especially among the elderly with slow drug elimination or for those undergoing surgical procedures requiring intact hemostasis (e.g., neurosurgery), laboratory assessment must demonstrate a reverted anticoagulant effect. In the clinical trials, recent or planned elective surgery was one exclusion criterion. In emergency situations, recent or planned elective surgery was one exclusion criterion. In emergency situations, recent or planned elective surgery was one exclusion criterion. In emergency situations, recent or planned elective surgery was one exclusion criterion. In emergency situations, recent or planned elective surgery was one exclusion criterion.

**Bleeding While on New OACs**

In addition to the current lack of specific antidotes, information is only suggestive without clinical evidence as to the roles of blood products, hemostatic (prothrombin complex concentrates [PCC], activated PCC, or recombinant FVIIa), or antifibrinolytic agents in management of bleeds associated with the new OACs. The rapid evolution of the antidote is thus most welcome. Only dabigatran can be eliminated by dialysis, in contrast to rivaroxaban and apixaban—which due to their binding to proteins cannot Charcoal may be a possibility, at less than 2 hours after the last dose of dabigatran. Completely unknown is the management and outcome in association with surgery due to a severe bleed, such as aortic aneurysm rupture or gastric ulcer. Avoiding bleeding complications is vital; some may be avoided with targeted patient selection and surveillance (exclusion of developing concomitant anemia, thrombocytopenia, or renal or liver failure; Table 3) and individualized choice of anticoagulant.

Comparison of the data available on OACs is difficult due to the lack of uniform criteria for evaluation of bleeding complications. In future, the use of International Society on Thrombosis and Haemostasis definitions will harmonize this evaluation of the current and newer anticoagulants.

**Assessment of Anticoagulation Effect**

Routine laboratory monitoring of the anticoagulation effect is unnecessary, because DTIs and FXaIs have low interindividual variability, relatively short half-lives (<17 hours), and

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**Table 3** Patient Monitoring to Rule Out Ongoing Bleeding or Tendency to Bleed While on an OAC

<table>
<thead>
<tr>
<th>Clinical Risk Assessment</th>
<th>Rationale/Aim</th>
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<tbody>
<tr>
<td>Blood cell count</td>
<td>Exclusion of anemia and/or thrombocytopenia</td>
</tr>
<tr>
<td>Renal function</td>
<td>Exclusion of risk for drug accumulation (e.g., Clcr)</td>
</tr>
<tr>
<td>Liver function</td>
<td>Exclusion of liver impairment (e.g., PT, ALT, prealbumin)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normotension</td>
</tr>
<tr>
<td>Comedications</td>
<td>Evaluation of possible interactions or additive effects (platelet inhibitors, NSAID, SSRI, SNRI, large doses of omega-3 fatty acid)</td>
</tr>
<tr>
<td>Head or other severe trauma (especially in elderly patients)</td>
<td>Emergency assessment and follow-up</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>Peri- and postoperative management plan</td>
</tr>
<tr>
<td>Active cancer</td>
<td>Evaluation of benefit–risk ratio</td>
</tr>
<tr>
<td>HAS-BLED18 or other bleeding score</td>
<td>Evaluation of benefit–risk ratio</td>
</tr>
</tbody>
</table>

OAC, oral anticoagulant; Clcr, estimated creatinine clearance; PT, prothrombin time; ALT, alanine aminotransferase; NSAID, nonsteroidal anti-inflammatory drugs; SSRI, serotonin selective reuptake inhibitors; SNRI, selective noradrenaline reuptake inhibitors; HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly).
only a few drug-drug interactions based on pharmacokinetic and pharmacodynamic studies.\textsuperscript{11,34,38–40} Criteria for appropriate laboratory monitoring require intra- and interindividual variability of the drug, suitable assay methods, and proven value of therapeutic drug monitoring.\textsuperscript{41} A recent debate on laboratory monitoring of new OACs reached a consensus: In unselected patient populations, measurement of the anticoagulation effect after a therapeutic dose may be necessary in special circumstances.\textsuperscript{41,42}

### Special Circumstances and Patient Monitoring

Special circumstances in which measurement of pharmacodynamic effects of the new OACs could aid in clinical judgment are listed in Table 4. For planning thrombolysis, emergency evaluation of an unconscious patient with a stroke who is on a new OAC would benefit from a qualitative test of compliance and bleeding risks. In turn, a quantitative method could distinguish between a spontaneous bleed due to a tissue defect versus an excessive drug concentration due to accumulation or overdose. Certain individual clinical features initially and during surveillance must be recognized to avoid complications and difficulties during emergency situations (Table 3). Mild or moderate renal failure and transient renal impairment are common, especially among elderly and medical patients. Dabigatran mainly (≈80%) and rivaroxaban (up to 66%) are excreted by the kidneys; severe renal insufficiency is thus a contraindication (estimated creatinine clearance $[\text{CL}_\text{CR}] < 30 \text{ mL/min}$) due to risk of drug accumulation.\textsuperscript{34,43} Apixaban is metabolized by multiple elimination pathways but only 25% of it via the kidneys.\textsuperscript{40} The multiple elimination pathways of apixaban may present an advantage for patients with kidney or liver insufficiency, but more data are necessary. Patient education is important to ensure early contact with physicians on occurrence of any complication such as fatigue, or head or blunt trauma. The same applies to disrupted compliance, such as with vomiting, diarrhea, or other problems. Patient monitoring must improve the safety and effectiveness of treatment under special circumstances, and this requires further experience.

### Timing of Blood Sampling and Laboratory Measurements

Preanalytical factors such as patient-related issues (a stable vs. postoperative or bleeding patient) and timing of the last dose before blood collection all impact the interpretation of coagulation measures. The relatively short half-lives of the new OACs require defined timing of sampling related to their administration. Peak levels occur within 1.25 to 3 hours after administration with dabigatran, 2 to 4 hours with rivaroxaban, and 1 to 3 hours with apixaban.\textsuperscript{11,34} Stabilization of a drug’s effect may be impaired shortly after surgery or during gastroenteric diseases. Mean half-lives of the new OACs are: 12 to 14 hours for dabigatran, 7 to 13 hours for rivaroxaban, and 8 to 13 hours for apixaban.\textsuperscript{11,34} Proper interpretation of the coagulation test results requires knowledge of the time of sampling after drug administration, dosage, and patient’s clinical status. This applies also to activity-based thrombophilia testing (e.g., activated protein C-resistance methods).\textsuperscript{20,21}

### Global Coagulation versus Substance-Specific Tests

Options for measurement of the pharmacodynamic effects of the anticoagulants include clotting assays (activated partial thromboplastin time [APTT], prothrombin time [PT], and thrombin time [TT] and its dilution), tests measuring the inhibition of FIIa or FXa activity, and functional thrombin-generation tests.\textsuperscript{44} In coagulation-based assays, the reagents and coagulation analyzers are likely to induce significant variation, interfering with comparison between laboratories.\textsuperscript{20,21} Validation of reagent- and method-specific issues is crucial.

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Table 4: Special Situations Making Assessment of Anticoagulant Effects of New OACs Necessary

<table>
<thead>
<tr>
<th>Case Scenarios</th>
<th>Underlying Causes</th>
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</thead>
<tbody>
<tr>
<td>Thrombosis, e.g., unconscious patient with a stroke</td>
<td>Adequate anticoagulant effect, Compliance and safety of possible thrombolysis</td>
</tr>
<tr>
<td>Bleeding complication</td>
<td>Spontaneous, due to a tissue defect, Accumulation of drug (e.g., kidney dysfunction), Overdose of drug (accidental or deliberate)</td>
</tr>
<tr>
<td>Severe trauma</td>
<td>Ensuring sufficient hemostasis during surgery and recovery</td>
</tr>
<tr>
<td>Elderly patients</td>
<td>Risk of accumulation and increased vulnerability to bleeding risk</td>
</tr>
<tr>
<td>Progressive renal failure</td>
<td>Kidney-dependent metabolism; risk for drug accumulation</td>
</tr>
<tr>
<td>Progressive liver insufficiency</td>
<td>Increased risk for bleeding complications</td>
</tr>
<tr>
<td>Main drug-drug interactions</td>
<td>P-glycoprotein-mediated pharmacokinetics (dabigatran), CYP3A4 or P-glycoprotein-mediated pharmacokinetics (rivaroxaban and apixaban)</td>
</tr>
</tbody>
</table>

OACs, oral anticoagulants; CYP3A4, cytochrome P450 3A4.
In the absence of data on the new DTIs, data for earlier DTIs offer valuable information on laboratory measurement options. In our studies, in contrast to APTT, both chromogenic methods, the Ecarin chromogenic assay (ECA) and the anti-FIIa activity assay (hirudin activity assay) linearly depicted lepirudin and bivalirudin concentrations (unpublished data) across a wide therapeutic range. Furthermore, the benefit of these chromogenic methods appears to be that they remain intact in the presence of either lupus anticoagulant or warfarin in DTI-spiked plasma. This is in contrast to APTT and prothrombinase-induced clotting time (PiCT®, Pefak, Pentapharm, Basel, Switzerland). Diluted TT could also assess therapeutic levels of the DTI lepirudin, even in lupus anticoagulant- and warfarin-containing plasma.

**Dabigatran**

Plasma concentrations of dabigatran can be reflected in routine coagulation-based tests, because dabigatran inhibits thrombin-mediated formation of fibrin from fibrinogen. PT (or international normalized ratio; INR) is insensitive, and thus cannot exclude a dabigatran effect, whereas INR over 1.5 (Owren PT)/2.0 (Quick PT) may already imply a supratherapeutic dabigatran concentration. APTT plateaus out with increasing dabigatran, which predisposes to underestimation of dabigatran concentrations. Activated clotting time is also insensitive to increasing amounts of dabigatran.

Dabigatran can be best assessed with thrombin-specific TT and ECT-based measures. TT is a highly sensitive indicator of the dabigatran effect and can exclude dabigatran use if normal, whereas quantitative assessment may be achieved by a diluted TT assay such as Hemoclot® thrombin inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France). This test needs further evaluation, but a linear correlation between clotting time and dabigatran levels is obtained. ECT, a specific-thrombin generation test, linearly depicts plasma concentrations of DTIs, but this assay is cumbersome and needs validation for dabigatran. ECA overcomes the limitation of possible prothrombin deficiency when compared with ECT, and it is capable of linear, quantitative measurement of other DTIs, but again no data are available for dabigatran. Neither ECT nor ECA is affected by other OACs.

In summary, TT seems to be a sensitive qualitative indicator of dabigatran and can ensure the absence of a relevant dabigatran effect. The traditional APTT is less sensitive and PT is too insensitive, but both should be included in an evaluation of hemostatic status. Diluted thrombin clotting time (Hemoclot) appears promising for quantitative assessment in addition to ECT, but all methods should be validated and standardized for dabigatran.

**Rivaroxaban**

Routine coagulation tests are unsuitable for measuring rivaroxaban concentrations. Both PT and APTT, the latter less than the former, are prolonged in a concentration dependent, but insensitive manner as a response to rivaroxaban. Prolongation may be only transient and its length depends on timing after drug administration. Additionally, both the PT and APTT results varied greatly depending on the reagent used. PT methods should be calibrated in each laboratory for rivaroxaban and the results displayed as rivaroxaban concentration (µg/mL). Application of the international sensitivity index (ISI)/INR calibration for rivaroxaban seemed feasible in a single-center calibration study, but multicenter studies are necessary to confirm the results.

Incubation times for the HepTest (a clot-based anti-FXa assay) and PiCT test had to be shortened to overcome the paradoxical shortening of clotting times at trough rivaroxaban levels. PiCT is insensitive to rule out noncompliance despite having a higher sensitivity than PT for rivaroxaban. Rivaroxaban produced a concentration-dependent prolongation of the clotting parameters in thromboelastography and an inhibition of thrombin generation by platelets when measured with endogenous thrombin potential. Rivaroxaban reduced the peak of thrombin generation, and high concentrations almost completely suppressed thrombin generation in a calibrated automated thrombogram. Chromogenic anti-FXa activity assays calibrated specifically for rivaroxaban are under further evaluation but seem able to assess linearly a wide concentration range of rivaroxaban with high sensitivity.

**Apixaban**

Apixaban only minimally prolonged APTT. PT was unsuitable for assessment of apixaban due to its relative lack of sensitivity and its assay-dependent variability. Conversion of PT to INR by using the ISI of thromboplastin reagent further increased measurement variability. In contrast, anti-FXa activity assays linearly covered the relevant plasma concentration ranges of apixaban. Strong and nearly equivalent correlations appeared between plasma apixaban concentrations and anti-FXa activity, with standard curves constructed by either apixaban or even commercial LMWH standards. Wide availability of the LMWH standards may aid in emergency assessment of apixaban effects, but the methods need to be locally validated.

**Conclusions**

Great expectations have arisen for new OACs to permit redirection of the always-limited clinical resources. Even if INR visits can be omitted, outpatient visits cannot. Inevitably, reevaluation of a patient’s clinical condition is necessary from time to time while that patient is anticoagulated. This includes ruling out any development of hypertension, anemia, thrombocytopenia, or kidney or liver failure to avoid bleeding complications. Furthermore, launching of the new OACs should be carefully controlled and occur in step-wise fashion. Taking into account the lengthy clinical experience, low costs, and the available antidotes, it would be wise to continueVKAs at least among patients in whom INRs appear stable. However, patients with unstable INRs are not necessary the best candidates for new OACs either, if the underlying reason is poor compliance, particularly as the new OACs have relatively...
short half-lives and omission of doses can be catastrophic. Finally, patients having artificial heart valves with need of anticoagulation should continue with VKA exclusively due to lack of evidence of the new OACs in this indication.

Most likely the safety profile of the new OACs will change or cautions will be added as their use widens; some rare but severe complications can be predicted to occur when exposing hundreds of thousands of “unselected” patients to new drugs that have been trialed in selected patients. All clinicians, but especially general physicians, surgeons, cardiologists, anesthesiologists, and hematologists, when contemplating or facing the side effects of the new OACs, have the responsibility to report expected or unexpected side effects for the sake of future patient safety. Manufacturers are responsible for rapid distribution of easily accessible and timely drug safety data as well as management strategies. Clinicians should develop local and global guidelines for special situations requiring laboratory assessment of new OACs and plan subsequent management and follow-up. We suggest the documenting of any bleeding complications by using the ICD-10 (D68.32) to aid in their systematic analysis.

New OACs are most welcome to overcome the high unmet need of simplified, effective, and safe anticoagulant therapies in comparison with the limitations related to VKAs. In the future, more individualized antithrombotic treatment may become a clinical reality. Individualizing the anticoagulation strategy according to patient-related factors is likely to enhance treatment compliance, safety, and efficacy, but only when the questions related to assessment of the anticoagulant effects, need of antidotes and reversal strategies are answered.

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