In this issue, Naranjo et al. [1] report on a patient who was off-label treated with dabigatran 110 mg twice daily after electric cardioversion and developed a large middle cerebral artery (MCA) ischemic stroke after having taken the third dose of dabigatran. Prior to cardioversion, the patient received enoxaparin at an unknown dose for 1 month. No transesophageal echocardiography for exclusion of intracardial thrombi was performed.

Thrombolysis with rtPA was initiated 190 min after onset of symptoms corresponding to approximately 6 h after the last dose of dabigatran, and the patient developed fatal intracerebral hemorrhage 12 h later.

In an earlier issue of Cerebrovascular Diseases, De Smedt et al. [2] described the use of rtPA for stroke thrombolysis in another patient with atrial fibrillation treated with dabigatran as participant of the RELY-ABLE study. In this case, rtPA was started 9 h after the last dose of dabigatran. There were no signs of intracranial hemorrhage in the control CT scan and no other bleeding complications. Matute et al. [3] treated a patient with rtPA receiving dabigatran 220 mg once daily for prevention of venous thromboembolism after knee surgery, who developed a left MCA ischemic stroke with right-sided hemiplegia and aphasia. The patient had received the last dose of dabigatran 15 h before treatment with rtPA and there were no hemorrhagic complications. In all three cases, prothrombin time (PT) and activated partial thromboplastin time (aPTT) were essentially normal at the time rtPA treatment was started.

The case reported by Naranjo et al. [1] differs from the other two cases in that it is the only one with stroke occurring shortly after cardioversion, the patient had not been on long-term dabigatran treatment, and rtPA was started at a time when relevant plasma concentrations of dabigatran are expected to be present.

Oral direct thrombin inhibitors like dabigatran and factor Xa inhibitors like rivaroxaban, apixaban or edoxaban have a reliable anticoagulant effect without the need of laboratory monitoring or repeated dose adjustments. Extensive clinical trials have demonstrated that these drugs are at least equally effective as vitamin K antagonists for the prevention of stroke and systemic embolism in patients with atrial fibrillation. Dabigatran at the higher dose of 150 mg twice daily was clearly superior to warfarin [4]. In the RELY study [4], the rate of ischemic or nonspecified stroke was 1.34% per year for the lower dose and 0.92% per year for the higher dose of dabigatran, i.e. significantly reduced. The rate of intracranial hemorrhage and especially hemorrhagic stroke was also significantly lower compared to warfarin. Rivaroxaban displayed superiority in the on-treatment analysis; the intention-to-treat analysis demonstrated non-inferiority [5]. Apixaban at a dose of 5 mg twice daily was superior to acetylsalicylic acid in the prevention of stroke and systemic embolism [6] (table 1).

In addition to prevention of stroke and systemic embolism in atrial fibrillation, the novel oral anticoagulant drugs are used for other indications, including prophylaxis and treatment of venous thrombosis and pulmonary embolism. It is to be expected that with more widespread use of the oral direct thrombin or factor Xa inhibitors, clinicians will be increasingly confronted with the question how to treat acute ischemic stroke in these patients.

Fibrinolytic therapy with TPA analogues is approved for treatment of acute ischemic stroke within 3 h after onset of neurological symptoms and has just been approved within 3–4.5 h according to the results of ECASS3 [7]. This therapy is associated with an increased risk of intracerebral hemorrhage combined with neurological worsening to 7.3% (range 6.7–7.9) according to the SITS–MOST registry similar to rates in randomized clinical trials [8]. Thus, thrombolytic therapy should be performed in properly equipped, specialized stroke centers and only in patients who meet strict inclusion and exclusion criteria. Patients developing stroke despite vitamin K antagonist therapy are generally excluded from fibrinolytic therapy because of the increased risk of bleeding imposed by low levels of vitamin-K-dependent coagulation factors regardless of the international normalized ratio (INR) [9]. On the other hand, rapid reversal of the anticoagulant effect by prothrombin complex concentrates is not recommended, presumably due to an anticipated thromboembolic risk.

The new oral anticoagulant drugs currently studied in large randomized clinical trials (table 1) differ from warfarin and the other vitamin K antagonists in that they do not reduce the levels of coagulation proenzymes but directly inhibit the active procoagulant enzymes thrombin or factor Xa. This inhibitory effect is directly dependent upon the plasma concentration of the active drug. After ingestion of the drug, maximal plasma levels are attained within approximately 1–2 h, followed by a continuous decline.

Some considerations concerning fibrinolytic therapy in patients treated with thrombin or factor Xa inhibitors: TPA does not directly degrade fibrin but activates endogenous plasminogen, which then degrades the fibrin. Fibrin acts as cofactor in TPA-induced plasminogen activation [12], resulting in a 1,000-fold enhancement of the plasminogen activation rate in the presence of fibrin, compared to fibrinogen [13]. Enhancement of tPA-in-
The porosity of fibrin clots, including the direct thrombin and factor Xa inhibitors, increases resistance of the clots towards fibrinolysis. Anticoagulant drugs, which result in reduced clot permeability, and thus, further increases the effect on coagulation assays like PT and aPTT, but this may induce a procoagulant response. Consequently, ongoing treatment with vitamin K antagonists is considered a contraindication for fibrinolytic therapy with rtPA. The anticoagulant effect of the new direct thrombin and factor Xa inhibitors is dependent upon plasma concentration, and depending upon the pharmacokinetics, the anticoagulant effect disappears within 12–24 h after ingestion of the drug. At present, laboratory assays for measurement of the specific anticoagulant effects are not yet widely available but should be performed in all patients known or suspected to be on treatment with new anticoagulants before rtPA is administered, similarly to prothrombin time/INR measurement in patients on warfarin treatment.

Vitamin K antagonists can rapidly be antagonized by prothrombin complex concentrates, but this may induce a procoagulant response. Consequently, ongoing treatment with vitamin K antagonists is considered a contraindication for fibrinolytic therapy with rtPA. The anticoagulant effect of the new direct thrombin and factor Xa inhibitors is dependent upon plasma concentration, and depending upon the pharmacokinetics, the anticoagulant effect disappears within 12–24 h after ingestion of the drug. At present, laboratory assays for measurement of the specific anticoagulant effects are not yet widely available but should be performed in all patients known or suspected to be on treatment with new anticoagulants before rtPA is administered, similarly to prothrombin time/INR measurement in patients on warfarin treatment.

Thrombin inhibitors [35], as well as factor Xa inhibitors [36], have an effect on coagulation assays like PT and aPTT, but this effect is highly variable, depending on the reagent and laboratory instrument used for measurement [36, 37]. Although these assays may be used for detecting a possible overdose, levels within the lower therapeutic range are not accurately detected.

Direct thrombin inhibitors, such as dabigatran, strongly influence thrombin time. A normal-range thrombin time assay exists for the detection of dabigatran, but this assay may not be accurate for all dabigatran concentrations. The use of a normal-range thrombin time assay for the detection of dabigatran is therefore limited. However, the use of a modified normal-range thrombin time assay for the detection of dabigatran is more accurate and can be used for the detection of dabigatran concentrations between 30 and 150 ng/mL. This modified normal-range thrombin time assay is less accurate for the detection of dabigatran concentrations above 150 ng/mL.

Finally, tPA-induced plasminogen activation is dependent upon clot permeability (influencing the motion of tPA and plasminogen within the clot) and the availability of binding sites for both tPA and plasminogen. Clot permeability is strongly influenced by thrombin activity. A high thrombin concentration results in reduced clot permeability, and thus, further increases the resistance of the clots towards fibrinolysis. Anticoagulant drugs, including the direct thrombin and factor Xa inhibitors, increase the porosity of fibrin clots [32]. In the experiments of Blomback et al. [32], this effect was more pronounced at therapeutic levels of direct thrombin and factor Xa inhibitors than at therapeutic levels of vitamin K antagonists. According to the results of Ammollo et al. [25], clots generated in the presence of dabigatran were more permeable, less rigid and consisted of thinner fibers. In fibrin clots, plasmin appears to move laterally across fibers, the rate of lysis being faster for clots made up of thicker fibers than for clots consisting of thinner fibers [20]. The individual contribution of these mechanisms concerning the outcome of fibrinolytic therapy needs to be further investigated.

### Table 1. New oral anticoagulant drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study acronym</th>
<th>Patients</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg/150 mg b.i.d. versus warfarin INR 2–3</td>
<td>RELY</td>
<td>18,113</td>
<td>published [4]</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg q.d. versus warfarin INR 2–3</td>
<td>ROCKET-AF</td>
<td>14,264</td>
<td>published [5]</td>
</tr>
<tr>
<td>Apixaban 5 mg b.i.d. versus warfarin INR 2–3</td>
<td>ARISTOTLE</td>
<td>18,205</td>
<td>published [10]</td>
</tr>
<tr>
<td>Apixaban 5 mg b.i.d. versus aspirin 81–324 mg o.d.</td>
<td>AVERROES</td>
<td>5,599</td>
<td>published [6]</td>
</tr>
<tr>
<td>Edoxaban 30 mg/60 mg q.d. versus warfarin INR 2–3</td>
<td>ENGAGE-AF</td>
<td>20,500</td>
<td>ongoing [11]</td>
</tr>
</tbody>
</table>

It is to be expected that clots developing in the presence of dabigatran, rivaroxaban, apixaban, edoxaban or other direct thrombin or factor Xa inhibitors are more responsive to fibrinolytic therapy. This may result in increased risk of intracranial hemorrhage associated with fibrinolytic therapy, although it is a matter of speculation if the anticoagulant drug needs to be present already during clot formation to cause the effect or if presence of the drug during fibrinolysis is sufficient.

An enhanced profibrinolytic effect leading to a drop in plasma fibrinogen levels due to plasmin proteolysis [33], or to increased levels in fibrinogen degradation products [34], has been shown to be associated with an increased rate of intracranial hemorrhage during rtPA treatment.
cludes the presence of relevant plasma concentrations of dabiga-
tran. For accurate determination of dabigatran plasma levels, the
thrombin time assay needs to be modified, and specific dabiga-
tran calibrators are needed. Direct factor Xa inhibitors do not
influence thrombin time but have a strong effect on antifactor Xa
assays similar to those used for monitoring of low-molecular-
weight heparin or fondaparinux therapy [38, 39]. Again, drug-
specific calibrators are needed for determination of plasma con-
centration of the drugs, and the reference curves used for low-
molecular-weight heparins cannot be used [40].

In emergency situations, such as the occurrence of acute neu-
rological symptoms in patients treated with dabigatran, rivaroxa-
ban, apixaban, edoxaban or other direct thrombin or factor Xa
inhibitors, thrombin time (for thrombin inhibitors) or an anti-
factor Xa assay (for direct factor Xa inhibitors) should be per-
formed before invasive procedures, such as surgery or fibrino-
lytic therapy.

Concerning the case report of Naranjo et al. [1], it needs to be
mentioned that cardiovascular is associated with a relevant risk of
embolic stroke, and pretreatment with anticoagulant drugs in
the therapeutic dose range is recommended. The authors neither
mention the dose of enoxaparin given before cardioversion nor
was transesophageal echocardiography performed prior to car-
dioversion to exclude the presence of atrial thrombi. In a sub-
group analysis of the RELY study patients had been treated with
a study drug (dabigatran or warfarin) for at least 3 weeks before
performing cardioversion. The study protocol recommended
against cardioversion of patients with left atrial thrombus [4].
Stroke and systemic embolism rates at 30 days were 0.8% for dab-
igatran 110 mg twice daily, 0.3% for dabigatran 150 mg twice
daily, and 0.6% for warfarin (dabigatran 110 mg vs. warfarin, p =
0.71; dabigatran 150 mg vs. warfarin, p = 0.40) [41]. Consequent-
ly, the case can only be interpreted with caution concerning the
possible relation between fibrinolytic therapy performed at a
time when a therapeutic level of dabigatran must have been pres-
ent as well as a possibly spontaneous occurrence of intracranial
hemorrhage as the result of a large MCA territory ischemia and
tPA treatment.

Summary

Fibrinolytic therapy with rtPA in patients with dabigatran,
and presumably also in patients treated with other novel oral an-
ticoagulant drugs such as rivaroxaban, apixaban or edoxaban,
should not be performed when therapeutic plasma levels of anti-
cogulant are present. As elimination kinetics may vary, depend-
ing on renal and hepatic function, body mass and age, measure-
ment of the anticoagulant effect of the drug by functional assays,
or measurement of drug levels, must be recommended before at-
tempting rtPA treatment. For direct thrombin inhibitors, throm-
bin time or related assays provide the most reliable information
but take time to become available (approximately 20 min). Simi-
larly, for direct factor Xa inhibitors, antifactor Xa assays (chro-
mosomic assays, but also clotting assays) can be used but require
specific calibration, as the conventional calibrators based on low-mo-
olecular-weight heparin cannot be used.

The novel oral anticoagulant drugs influence PT and aPTT,
but the effect is highly variable and a normal range of PT or aPTT
does not exclude the presence of relevant concentrations of the
anticoagulant in the blood. The PT or INR limits used for estima-
tion of bleeding risk connected to vitamin K antagonist therapy
cannot be applied. Cardioversion in patients treated with the new
sufficient phase of reliable anticoagulation and exclusion of intracar-
dial thrombus.

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Fibrinolytic Treatment, Acute Ischemic Stroke and New Oral Anticoagulants


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