Coagulation Factor IXa as a Target for Treatment and Prophylaxis of Venous Thromboembolism

John W. Eikelboom, Steven L. Zelenkofske, Christopher P. Rusconi

Abstract—Venous thromboembolism remains a frequent cause of vascular death. Despite advances in anticoagulant drug development, unmet needs remain, including limited treatment options for patients with severe renal impairment and the inability to fully reverse the effects of anticoagulants approved or in late-stage development. Because coagulation factor IXa plays a pivotal role in tissue factor-mediated thrombin generation, it represents an attractive target for anticoagulant development. This article discusses the rationale for factor IXa as an anticoagulant target and the potential role in venous thromboembolism prevention or management of the 2 factor IXa inhibitors that have undergone testing in phase 1 or 2 trials: TTP889, an oral, small-molecule compound, and RB006, an aptamer-based compound, the intravenous and subcutaneous formulations of which are the anticoagulant components of the REG1 and REG2 anticoagulation systems, respectively. (Arterioscler Thromb Vasc Biol. 2010;30:382-387.)

Key Words: anticoagulants ■ anticoagulant mechanisms ■ coagulation ■ deep vein thrombosis ■ platelets

Venous thromboembolism (VTE) affects 1 in 1000 adults yearly and is the third most common cause of vascular death after myocardial infarction and stroke.1-5 Unfractionated heparin (UFH) and warfarin effectively prevent and treat VTE, but their limitations have prompted the development of new anticoagulants.6 Low-molecular-weight heparins (LMWH) and fondaparinux have replaced UFH for most patients in VTE prevention and initial treatment because they can be administered subcutaneously without coagulation monitoring and are likely to replace warfarin for long-term management of VTE.7,8

Despite advances in anticoagulant drug development, unmet needs remain.6 LMWH and fondaparinux are cleared via the kidneys and therefore tend to accumulate in patients with renal failure. The anticoagulant effects of LMWH are only partly reversed with protamine sulfate, and fondaparinux lacks an antidote altogether. Dabigatran etexilate and rivaroxaban, new anticoagulants that have been approved in Europe and Canada for prevention of VTE, are in advanced stages of development for VTE treatment. These agents can be administered orally in fixed doses without coagulation monitoring and are likely to replace warfarin for long-term management of VTE.9,8

New anticoagulant drugs, review new FIXa inhibitors in clinical development, and consider the potential role of these new agents in VTE prevention and treatment.

Coagulation Factor IXa as a Target for VTE Treatment and Prophylaxis

In contrast to the traditional Macfarlane10 and Davie and Ratnoff11 “waterfall” models, our current view of the process leading to fibrin deposition in vivo acknowledges the important interplay between the protease-driven coagulation process and the cells or surfaces on which these reactions occur (Figure 1).12 In the cell-based coagulation model, the “extrinsic” and “intrinsic” pathways are merged into a staged series of events in which the tissue factor–factor VIIIa (FVIIIa) complex (extrinsic pathway) initiates coagulation, and the intrinsic, or contact activation, pathway drives propagation of thrombin generation and fibrin clot formation.

In the traditional and modern views of coagulation, amplification remains a common feature at every step from initiation to thrombin generation. Thus, 2 key considerations shape the choice of target for anticoagulant therapy. First, blocking the pathway before the significant amplification and positive feedback cycles should provide efficient blockade. Second, targeting the rate-limiting step should provide effective anticoagulation with the widest therapeutic window. The FVIIIa/FIXa complex drives propagation upstream of both the significant amplification and positive feedback cycles should provide efficient blockade. Furthermore, FVIIIa/FIXa-catalyzed activation of coagulation factor X appears to be the rate-limiting step for thrombin generation.13-15

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From Regado Biosciences, Inc. (S.L.Z., C.P.R.), Durham, NC; Department of Medicine (J.W.E.), McMaster University, Hamilton, Ontario, Canada.
Correspondence to Christopher P. Rusconi, PhD, Regado Biosciences, Inc., 318 Blackwell St, STE 130, Durham, NC 27701. E-mail crusconi@regadobio.com

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The earliest evidence of the critical role of FIXa as the limiting protease in thrombin generation comes from animal modeling. Using purified, activated coagulation proteases, Gitel et al investigated the thrombogenicity of FIXa, FXa, and thrombin in the Wessler model of venous thrombosis. Factor IXa was 7-fold more thrombogenic than FXa and 60-fold more thrombogenic than thrombin. Similarly, inhibition of venous thrombosis initiated by FIXa required heparin doses that were 2- to 4-fold lower than those required to inhibit clot formation when venous thrombus was initiated by FXa or thrombin. Thus, FIXa is rate-limiting in thrombus generation and, based on the relative sensitivities to heparin, inhibition of FIXa vs FXa or thrombin might provide a wider therapeutic window.

Multiple orthogonal studies have confirmed these early discoveries. In vivo and in vitro investigations of the thrombogenicity of prothrombin-complex concentrates demonstrated that FIXa levels determined the thrombogenic potential of these factor-replacement concentrates. Molecular genetic studies using FIX-deficient mice have shown that FIXa is a critical regulator of thrombin generation, and that in vivo FIXa activity determines susceptibility to occlusive venous thrombus formation in a murine model of saphenous vein thrombosis. Similarly, loss of the intrinsic pathway protects mice from pulmonary embolism induced by polyphosphate, a recently described molecular trigger linking coagulation initiation and platelet activation to coagulation propagation.

Further evidence for FIXa as a viable target for anticoagulant therapy resides in the manifestations of FIX deficiency in patients with and carriers of hemophilia B. The clinical phenotype of hemophilia B depends on the plasma FIX level. Spontaneous bleeding occurs in patients with severe hemophilia (<1% FIX activity), whereas bleeding occurs only with trauma or surgery in those with moderate hemophilia (1%–5% FIX activity). The tendency to bleed from small wounds and during surgery decreases as factor levels increase in patients with mild hemophilia (5%–50% FIX activity) and hemophilia B carriers (median FIX activity, 60%). Mild FIX deficiency may not prolong activated partial thromboplastin time or require prophylaxis to prevent bleeding during minor procedures, but in epidemiological studies it has been associated with fewer cardiovascular events. The narrow window for clinically important bleeding with a wider window for reduced cardiovascular events in hemophilia B carriers lends further support for FIXa as an attractive target for anticoagulant therapy.

Generation of FIXa inhibitors using traditional active-site, small-molecule approaches is challenging because the active site of FIXa does not adopt its functional structure until allosteric activation on complex formation with FVIIIa. Consequently, most FIX/FIXa inhibitors evaluated in preclinical models have been designed to block protein–protein or other macromolecular interactions, such as active site-inhibited FIXa, which blocks formation of the FVIIa/FIXa complex; monoclonal antibodies against the FIX/IXa gla-domain, which block binding of FIX/IXa to cell surfaces; or nucleic acid aptamers, which block the interaction of FX with the FIXa/FVIIa complex.

Consistent with mechanistic, molecular genetic, and epidemiological data, evaluations of anti-FIXa agents in arterial thrombosis models have validated FIXa as an effective target for treatment and prophylaxis of arteriothrombotic indications. Results of preclinical evaluations in venous thrombosis models, although more rare, are consistent with those conducted in arterial thrombosis models and suggest that FIX/FIXa inhibition is as efficacious as UFH treatment and might have a wider therapeutic window.

**Factor IXa/IXa Inhibitors in Clinical Development**

Two FIXa inhibitors have undergone testing in phase 1 or 2 clinical trials. TTP889 (Transtech Pharma) is an oral, small-molecule FIXa inhibitor that has been evaluated for extended venous prophylaxis after hip fracture surgery. RB006 is a parenteral, aptamer-based agent. The intravenous formulation of RB006 is the anticoagulant component of the REG1 (Regado Biosciences) anticoagulation system, and the subcutaneous formulation of RB006 is the anticoagulant component of the REG2 (Regado Biosciences) anticoagulation system.

**Oral: TTP889**

TTP889 is a selective, small-molecule, orally available, partial FIXa inhibitor (Table 1). Information regarding the specific structure and mechanism of action of TTP889 has not been published. The maximum reported level of FIXa inhibition achievable by TTP889 is ~90%, although primary data supporting this conclusion also remain unpublished.
TTP889 reduced thrombus formation in rat and porcine arteriovenous shunt models. In the latter model, TTP889 0.3 mg/kg was as effective as UFH 150 μg/kg and did not prolong bleeding time, activated partial thromboplastin time, or activated clotting time.

Data from phase 1 studies of TTP889 are unavailable, but results of a randomized, multicenter, double-blind, placebo-controlled study of TTP889 in extended VTE prophylaxis after major orthopedic surgery have been reported. Patients undergoing hip fracture surgery received UFH or LMWH for 5 to 9 days, after which they were randomized to receive TTP889 300 mg daily or placebo for another 3 weeks. Rates of the primary efficacy end point—total VTE, comprising venographic deep vein thrombosis, symptomatic deep vein thrombosis, or pulmonary embolism—did not differ (P = 0.58) with TTP889 (35/109; 32.1%) vs placebo treatment (29/103; 28.2%). No patients had major bleeding. Clinically relevant nonmajor bleeding occurred in 2 patients treated with TTP889 and in 1 placebo-treated patient. Biomarkers of thrombin generation (prothrombin fragment 1.2 and thrombin–antithrombin complex) and fibrin degradation (D-dimer) did not differ significantly by treatment. Consistent exposure to TTP889 throughout treatment was confirmed by plasma TTP889 measurements on treatment days 1, 7, and 21, but the absence of published data precludes correlation of these drug concentrations with expected anticoagulant effect.

Given the preclinical data supporting FIXa as a target for anticoagulant therapy, at least a trend toward efficacy was expected for TTP889 compared with placebo for VTE prevention. However, both the absence of activated partial thromboplastin time prolongation and changes in markers of thrombin generation suggest that the TTP889 dose used in this study may have been inadequate. Further evaluation of TTP889 in dose-ranging studies might be warranted to adequately evaluate its potential utility. Considering its long half-life, TTP889 might emerge as an ideal agent for long-term VTE treatment.

### Parenteral

REG1 and REG2 are both anticoagulant-active control-agent pair systems derived from the same novel technology platform. We briefly describe this technology before reviewing their development (Table 2).

Aptamers are small nucleic acid molecules that function as direct protein inhibitors, much like monoclonal antibodies. They are isolated via systematic evolution of ligands by exponential enrichment (SELEX). The SELEX process starts with random nucleic acid sequences (RNA, DNA, or nuclease-stabilized RNA) from which high-affinity aptamers to a target protein are isolated through iterative purification and amplification. Aptamers have been generated for numerous proteins representing most protein classes, including, most recently, other antithrombotic targets such as von Willebrand factor and prohemostatic targets such as tissue factor pathway inhibitor.

Aptamers have favorable toxicological properties, with low inherent toxicity because of their molecular size and target specificity. Under the right conditions, these agents may be able to replace or augment the use of long-acting parenteral anticoagulants.

### Table 1. Pharmacology of TTP889 and Established/Emerging Oral Anticoagulants for VTE Prevention and Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TTP889</th>
<th>Warfarin</th>
<th>Dabigatran Etxilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor IXa</td>
<td>VKOR</td>
<td>Factor IIa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Not reported</td>
<td>100%</td>
<td>6%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Dosing</td>
<td>Fixed, once daily</td>
<td>Variable, once daily</td>
<td>Fixed, once or twice daily</td>
<td>Fixed, once daily</td>
<td>Fixed, twice daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>21–25 hr</td>
<td>40 hr</td>
<td>12–14 hr</td>
<td>7–11 hr</td>
<td>12 hr</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>Not reported</td>
<td>None</td>
<td>80%</td>
<td>66%*</td>
<td>25%</td>
</tr>
<tr>
<td>Routine coagulation monitoring</td>
<td>Not reported</td>
<td>Numerous</td>
<td>Potent inhibitors of P-gp†</td>
<td>Potent inhibitors of CYP3A4 and P-gp‡</td>
<td>Potent inhibitors of CYP3A4§</td>
</tr>
</tbody>
</table>

*Of drug cleared by the kidneys, half is unchanged drug and the remainder is inactive metabolites.
†Includes quinidine and amiodarone.
‡Potent inhibitors of both CYP3A4 and P-gp include azole antifungals and protease inhibitors.
§Potent inhibitors of CYP3A4 include azole antifungals, macrolide antibiotics, and protease inhibitors.
CYP indicates cytochrome P450; P-gp, P-glycoprotein; VKOR, vitamin K epoxide reductase.

### Table 2. Pharmacology of REG1/2 and Parenteral Anticoagulants for VTE Prevention and Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RB006</th>
<th>Heparin</th>
<th>LMWH</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>FIXa</td>
<td>Fila, FIXa, FXa, FXIa</td>
<td>FXa, Fila</td>
<td>FXa</td>
</tr>
<tr>
<td>Antithrombin-dependent route</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Administration route</td>
<td>Intravenous, subcutaneous</td>
<td>Intravenous, subcutaneous</td>
<td>subcutaneous</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>Half-life</td>
<td>30–150 min*</td>
<td>3–6 hr</td>
<td>12–17 hr</td>
<td></td>
</tr>
<tr>
<td>Renal clearance</td>
<td>None</td>
<td>Minimal</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Routine coagulation monitoring</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Antidote</td>
<td>RB007</td>
<td>Protamine</td>
<td>Protamine (partial)</td>
<td>None</td>
</tr>
<tr>
<td>Potential for immune HIT</td>
<td>No</td>
<td>High</td>
<td>Low</td>
<td>No</td>
</tr>
</tbody>
</table>

*Dose-dependent.
HIT indicates heparin-induced thrombocytopenia.
specificity, and no apparent immunogenic potential.\textsuperscript{40} Formulation of aptamers as high-molecular-weight polyethylene glycol conjugates prevents renal clearance; the primary mechanism of metabolism is organ-independent degradation by plasma-compartment nucleases. Degradation products, even from stabilized aptamers, present little safety risk, given that the main modifications used to stabilize aptamers (eg, 2'-omethyl substitutions) are endogenous nucleotides, and the non-natural modifications used for stabilization (eg, 2'-fluoro substitutions) have been shown to pose no genetic toxicology risk.\textsuperscript{43} Conjugation of aptamers to high-molecular-weight polyethylene glycol also limits extravasation from the plasma compartment, leading to compounds with predictable pharmacokinetic profiles and long durations of effect when administered intravenously.\textsuperscript{31}

A unique feature of aptamers is their ability to generate active control agents. These take the form of complementary oligonucleotides that hybridize to the aptamer by Watson-Crick base pairing.\textsuperscript{28,44} These active control agents fundamentally change the aptamers' active structure and thereby neutralize their pharmacological activity. Because the mechanism of action of the active control agents is 1:1 direct binding, the level of aptamer reversal by an active control agent can be finely tuned by varying the dose ratio of control agent to aptamer.\textsuperscript{33} Recent interest in short interfering RNA and its potential immune-stimulating side effects\textsuperscript{45} have raised questions about the potential for aptamer-control agent duplexes formed in the body to induce immune-stimulatory side effects. However, because of their size (<21 base pairs) and composition, aptamer-control agent duplexes do not activate the Toll-like family of receptors and are not immunostimulatory.\textsuperscript{46}

\textbf{REG1}

The REG1 anticoagulation system consists of intravenously administered RB006 and its matched, intravenously administered active control agent, RB007.\textsuperscript{31} RB006 has a unique mechanism of action, blocking thrombin generation by blocking association of FX with the FVIIa/FXa enzyme complex.\textsuperscript{28}

Comprehensive phase 1 studies evaluated single and repeat escalating doses of REG1 in healthy volunteers and single escalating doses of REG1 in patients with stable cardiovascular disease who were receiving oral, dual antiplatelet therapy. The phase 1 study population included 177 exposures to RB006 and 170 exposures to RB007. Both components administered alone or in staggered fashion were well-tolerated. RB006 showed an onset of action within minutes and dose-linear pharmacokinetics and pharmacodynamics independent of the study population or number of exposures.\textsuperscript{31–34} At RB006 doses approaching therapeutic levels, the duration of effect exceeded 24 hours after a single intravenous bolus.\textsuperscript{33} The anticoagulant activity of RB006 can be monitored by activated partial thromboplastin time or activated clotting time, although activated partial thromboplastin time prolongation better reflects the degree of RB006-induced anticoagulation compared with activated clotting time measures.\textsuperscript{33} Single RB006 doses of 0.6 to 0.75 mg/kg inhibited >99% of FIX activity—the intended level of inhibition for treatment of acute coronary syndromes.\textsuperscript{47} Lower doses result in less FIX inhibition. The RB007 dose is administered as a weight-to-weight ratio of RB006 dose. RB007 dose ratios ≥1:1 result in complete, stable reversal of RB006 anticoagulation within 1 to 2 minutes of administration.\textsuperscript{31–34} Doses of RB007 <1:1 result in graded, partial reversal of RB006, consistent with the mechanism of action of RB007.\textsuperscript{33}

A phase 2a study of the REG1 system evaluated its feasibility vs UFH plus glycoprotein IIb/IIIa inhibition in patients undergoing elective percutaneous coronary intervention (PCI).\textsuperscript{34} For subjects assigned to REG1, RB006 1 mg/kg was used during PCI, and RB007 (2 mg/kg total dose) was administered to fully reverse RB006 anticoagulation after PCI (either step-wise over 4 hours or immediately), followed by sheath removal 10 minutes after full reversal of RB006 anticoagulation. The RB006 dose was selected to yield substantial (>99%) inhibition of FIX activity during PCI, with RB007 used to partly or completely reverse RB006-induced anticoagulation after the procedure.

A roll-in group (n=2) treated with REG1 plus glycoprotein IIb/IIIa inhibition with step-wise administration of RB007 was followed by 2 groups randomized 5:1 to receive REG1 (1 mg/kg RB006) or UFH. In group 1 (n=12), RB006 was reversed in a step-wise fashion, with a partly reversing dose of RB007 administered immediately after PCI, and the remaining fully reversing dose was administered 4 hours later, followed by immediate sheath removal. In group 2 (n=12), RB006 was fully reversed with RB007 on completion of PCI, followed by immediate sheath removal. All 22 PCIs conducted using REG1 were successful, with a final Thrombolysis in Myocardial Infarction (TIMI) flow grade of 3. Clinical events included 1 myocardial infarction and 1 target vessel revascularization in the REG1 groups, and 1 myocardial infarction and 1 major bleeding event in subjects treated with UFH. RB007 rapidly reversed RB006 in a dose-dependent manner. Both reversal strategies allowed scheduled sheath removal. REG1 is currently being evaluated in a phase 2 study in acute coronary syndromes (NCT 00932100).

REG1 is not being developed for VTE prevention in patients because the need for intravenous administration would be inconvenient. However, its long half-life (>24 hours with a single bolus), nonrenal clearance, availability of a simple, safe, rapid-acting control agent, and ability to rapidly reanticoagulate if reversal is required make REG1 an attractive option for initial treatment of VTE.

\textbf{REG2}

The key role of FIXa in the propagation of thrombus formation and the attractive pharmacological properties of intravenously administered RB006 prompted the development of a higher-concentration, longer-acting RB006 formulation that can be administered subcutaneously. RB006 has a molecular weight of ∼50 kDa, and absorption after subcutaneous administration is expected to be predominantly via the lymphatic system.\textsuperscript{48} Because lymphatic absorption of HMW compounds is slow, subcutaneously administered RB006 is expected to have a long absorption phase.\textsuperscript{31} RB007 remains the active control agent for REG2.

Little is known regarding the pharmacological behavior of subcutaneously administered high-molecular-weight polyethylene glycol conjugated aptamers in humans, but some
data exist from animal studies. Subcutaneous administration of the high-molecular-weight polyethylene glycol conjugated anti-vascular endothelial growth factor (VEGF) aptamer NX1838 in monkeys was associated with slower onset of action compared with intravenous dosing, but it was not associated with a substantially longer duration of effect.49 In contrast, subcutaneous RB006 administration in monkeys led to a substantially longer duration of effect compared with intravenous dosing (Figure 2), with little loss of anticoagulant activity 12 to 48 hours after dosing. This likely reflects the higher level of nuclease stabilization of RB006 vs NX1838. Intravenous RB007 administration neutralized absorbed, plasma-compartment RB006 (Figure 2) but did not affect RB006 remaining at the subcutaneous injection site, which remains physiologically inactive until its absorption into the plasma compartment. Thus, prolonged infusion or intermittent RB007 redosing might be necessary to maintain reversal of subcutaneously administered RB006 during its absorption phase.

Phase 1 studies of REG2 are ongoing to evaluate its safety, pharmacokinetic, and pharmacodynamic profiles and to investigate optimal dosing schedules of RB007 to reverse and maintain reversal of subcutaneously administered RB006. Given the longer effect duration for intravenous RB006 in humans vs in monkeys, the duration of effect for subcutaneous RB006 is also expected to be longer in humans than in monkeys.

Although the profile of REG2 requires elucidation in humans, its long half-life after subcutaneous administration in preclinical studies, its nonrenal clearance, and the ability to promptly reverse anticoagulant effects with RB007 suggest a potential role in primary VTE prevention in surgical and medical inpatients. REG2 might also have a role in bridging patients at high risk for VTE during temporary interruption of oral anticoagulant therapy.

Conclusions

The introduction of LMWH and fondaparinux as alternatives to UFH and the development of oral anticoagulants to replace warfarin have reduced unmet needs for VTE prevention and treatment. However, almost all heparin/warfarin alternatives are problematic in patients with severe renal impairment, and fondaparinux and oral anticoagulants in development lack antidotes. Furthermore, the need for daily or twice-daily dosing of current and future therapies makes their use inconvenient, especially for the treatment of VTE.

Coagulation FIXa comprises the rate-limiting step for thrombin generation and thrombus formation, and thus it is an attractive target for new anticoagulants for VTE prevention and treatment. To date, few FIX/FIXa inhibitors have been developed because of intrinsic difficulties in accessing the FIXa active site. The oral active-site FIXa inhibitor TTP889 did not reduce the risk of VTE compared with placebo when used for extended prophylaxis in patients undergoing hip fracture surgery in a phase 2 study, but the drug might have been suboptimally dosed for adequate FIXa inhibition. Future development of TTP889 is uncertain.

Intravenous and subcutaneous formulations of the aptamer-based FIXa inhibitor RB006, plus the active control agent RB007, constitute the new REG1 and REG2 anticoagulation systems. The nonrenal clearance of RB006 and the ability to rapidly reverse its anticoagulant effects by intravenous RB007 administration might overcome the remaining limitations of LMWH and fondaparinux for VTE prevention and treatment. Intravenous RB006 provides rapid onset of activity and >24-hour duration of effect, potentially beneficial in acute VTE treatment. Subcutaneous RB006 provides slower onset of activity and longer effect duration, potentially beneficial in VTE prevention and treatment. Continued studies of these agents will determine whether the theoretical advantages of targeting FIXa, compared with other anticoagulation targets such as factors Xa and thrombin, will translate into improved outcomes.

Disclosures

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References


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**Initiation**

- TF
- VII (VIIa)
- Xa
- TF-VII (VIIa)

**Activated platelet**

**Propagation**

- IX
- VIIIa
- IXa
- VIII
- X

- VaXa
- V
- Fg
- Fn
- II
- IIa
- IIa IIa IIa