Review

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Contact phase inhibitors: the future of anticoagulation?

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Abstract: Thrombosis remains a major public health problem. Although traditional anticoagulants, vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) have been used with success over the last decades for prevention of venous thromboembolism (VTE) and stroke in non-valvular atrial fibrillation (AF), their use exposes the patient to an increased risk of bleeding. To overcome these limitations, new approaches are exploring contact phase inhibitors, specifically targeting factors XI, XIa, XII, and XIIa. Contact phase inhibitors including antisense oligonucleotides, monoclonal antibodies, small peptidomimetic molecules, aptamers and natural inhibitors seem promising in term of efficacy and safety. A common assay can be used to measure the anticoagulant activity of different drugs within a same pharmacological class (INR for VKAs) or even across different pharmacological classes (anti-Xa for all heparins and for direct factor Xa inhibitors). Because of the diversity of contact phase inhibitors, no specific common assay has been proposed so far. Activated partial thromboplastin time (aPTT) could play a role in the assessment of these new anticoagulants, but its relevance need to be confirmed. We aim at providing an overview of the pharmacological properties of contact phase inhibitors, the safety and efficacy outcomes from clinicals trials, as well as the possible coagulation assays relevant for patient follow-up.

Keywords: contact phase inhibitors; (activated) factor XI inhibitors; (activated) factor XII inhibitors; laboratory testing; anticoagulants

Introduction

Prevention and treatment of thrombosis have been successfully achieved first with the use of unfractionated heparin (UFH) and vitamin K antagonists (VKAs). Although effective in a wide array of indications, these medications require frequent monitoring and dose adjustments and their use increase the risk of potentially life-threatening bleeding. In the 1980s, low molecular weight heparins (LMWH) opened the way to safer treatments, requiring neither routine monitoring of anticoagulant activity nor dose adjustment in the majority of patients. LMWH replaced UFH in a large number of indications, limiting the use of the latter to specific patient populations, usually severe or fragile patients. Besides, direct factor IIa (thrombin) inhibitors (hirudin and its derivatives, argatroban) have been made available for management of patients in intensive care units using the parenteral route of administration. More recently, in the last 20 years, direct oral anticoagulants (DOACs), targeting activated factor X (apixaban, edoxaban, rivaroxaban) or thrombin (dabigatran) have replaced VKAs in most patients because of undeniable advantages; this includes an easier use with a fixed-dose regimen, the absence of need for routine laboratory monitoring and a significant reduction in the risk of major bleeding, intracranial bleeding, and fatal and clinically relevant nonmajor bleeding [1]. Despite the existing effective and relatively safe therapeutic arsenal, contact phase factors (factor XI and factor XII and their activated forms) have aroused interest and numerous works from both researchers and pharmaceutical companies.

The aims of this article is to review the rationale for developing contact phase inhibitors, to take stock of molecules in development in the pharmaceutical industry and of possible laboratory tests to measure the anticoagulant activity of these new drugs when necessary.

Rationale for targeting contact phase factors

Although VKAs and DOACs have been widely used with success over the last decades for prevention of venous thromboembolism (VTE) and stroke in non-valvular atrial

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fibrillation (AF), their use exposes the patient to an increased risk of bleeding, even if the latter have reduced the risk of severe haemorrhage compared to the former [1]. In addition, DOACs may be not as effective as VKAs in certain patient populations such as e.g. the anti-phospholipid syndrome, stroke prevention in patients with mechanical heart valves, prevention of cardiovascular events or death in patients with AF associated with rheumatic heart disease [2]. Contact phase inhibition has appeared as a potential safe anticoagulation path based on the observation that inherited factor XI (FXI) deficiency is associated to a limited bleeding risk and that factor XII (FXII) deficiency is not a bleeding risk factor. This concept was further supported by FXII deficient mice models showing that the mice did not exhibit bleeding after injury nor thrombosis after exposure to mechanical or chemical thrombosis stimuli [3]. Similarly, FXI-deficient animals were protected against FeCl3 triggered arterial thrombosis [4]; in contrast to FXII deficiency, low circulating FXI levels are associated with mild to moderate but unpredictable bleeding [5]. Historically, only exogenous compounds (kaolin, ellagic acid, dextran sulphate) were recognized as activators of contact phase factors (factors, XI and XII, high molecular weight kininogen). This formed the basis for the development of the activated partial thromboplastin time (aPTT). It was however recently shown that naturally occurring polyanions, including DNA, RNA, polyphosphates and denatured proteins, especially neutrophil extracellular traps also serve as potent activators [6]. Exposure to these compounds has emerged as a situation at risk of developing thrombosis in the concept of immunothrombosis [7].

How contact phase inhibitors are different from the traditional anticoagulants

Different types of molecules

Contact phase inhibitors are characterized by diversity, in contrast to a relative uniformity of other anticoagulants.

Heparins (UFH and LMWHs) are heterogenous mixtures of glycosaminoglycans of various molecular weights obtained by extraction from porcine or bovine intestinal mucosa. LMWHs vary depending on their mean molecular weight resulting in variable anti-Xa/anti-IIa ratios across the different LMWH preparations. However all heparins have a common mechanism of action inhibiting factor Xa and thrombin by potentiating antithrombin activity [8]. VKAs are chemically defined compounds obtained by synthesis and belonging to different chemical families (coumarin derivatives – acenocoumarol, warfarin, phenprocoumon –, indane-dione – fluindione). They are all small molecules with a molecular weight in the range of 240–350 Daltons and share a similar mechanism of action. DOACs are also small molecules, with a molecular weight in the range of 500 Daltons, produced by chemical synthesis. Rivaroxaban, apixaban, and edoxaban inhibit directly factor Xa while dabigatran exerts its action directly on thrombin. A common assay can be used to measure the anticoagulant activity of different drugs within a same pharmacological class (e.g. INR for all VKAs) or even across different pharmacological classes for drugs sharing the same mechanism of action (e.g. anti-Xa for all heparins and for direct factor Xa inhibitors), even if the assay in the latter case may require specific features in terms of test set-up, calibration and internal quality controls.

In contrast, contact phase inhibitors are diverse from a structural standpoint: some of them are monoclonal antibodies (abelacimab, osocimab, xisomab, garadacimab, MK2060, REGN9933), while others are small molecules (asundexian, milvexian, SHR2285, ONO-7684, frunexian, BMS-962212), antisense oligonucleotides (IONIS-FXI$_{RX}$, fesomersen), natural inhibitor (IrCPI, fasxiator, acaNAP10), or aptamers (FELIAP, 11.16, 12.7, R4CxII-It). Each class Different mechanisms of action emerge from this diversity; inhibition of the biosynthesis of FXIa by antisense oligonucleotides, which reduce FXI mRNA expression in the liver [9], direct inhibition of FXI or FXIa by monoclonal antibodies, small molecules, aptamers, as well as natural inhibitors and direct inhibition of FXII or FXIIa by garadacimab (a monoclonal antibody), R4CxII-It (an aptamer) and IrCPI (a natural inhibitor). These differences may complicate the development of an adequate common assay.

Different pharmacological properties

Pharmacological features differ dramatically across the contact phase inhibitors. Table 1 summarizes the main pharmacologic and pharmacokinetic characteristics of the different class of contact phase inhibitors.

Traditional anticoagulants sometimes different exhibit onset and offset of actions but with minimal impact vis-à-vis their indications within a pharmacological class. In addition, they all are administered via the same route (parenteral for heparins, oral for VKAs and DOACs).

In contrast, contact phase inhibitors have very short (minutes, e.g. frunexian), intermediate (hours, e.g. xisomab, asundexian, milvexian, SHR2285, BMS-962212, FXI-ASO) to extended half-lives (weeks, e.g. abelacimab, osocimab,

Table 1: Main pharmacologic and pharmacokinetic characteristics of contact phase inhibitors.

Class	Mechanism of action	Target	Route	CYP450 metabolism	Renal elimination	Onset	Offset
ASO	Binds to the target mRNA blocking synthesis of FXI	– FXI: IONIS-FXI$_{RX}$ (ISIS 416858), fesomersen (BAY2976217)	Parenteral (SC)	No	25 %	Weeks	Weeks
Monoclonal antibodies	Binds to the target protein blocking FXIa generation or inhibiting FXIa/FXIIa activity	– FXIIa: Garadacimab (CSL312) – FXI: xisomab 3G3 (AB023), MK-2060, REGN 9933 – FXI/FXIa: Abelacimab (MAA868) – FXIa: Osocimab (BAY1213790)	Parenteral (IV, SC)	No	No	Hours to days	Weeks
Small molecules	Binds to the target protein inhibiting FXIa activity	– FXIa: Asundexian (BAY2433334), milvexian (BMS986177+ JNJ70033093), SHR2285, ONO-7684, frunexian EP-7041, BMS-962212	Oral (IV for Frunexian)	Yes	15–20 %	Mins to hours	Hours
Natural inhibitors	Binds to the target protein inhibiting FXIa activity	– FXIa/FXIIa: IrCPI – FXIa: Fasxiator, desmoralis, aca-NAP10, boophilin	Parenteral (IV)	No	No	Mins to hours	hours
Aptamers	Binds to the target protein inhibiting FXIa or FXIIa activity	– FXIa: FELIAP, 11.6 (29-nt), 12.7 (40-nt) – FXII/FXIIa: R4CxII-it	Parenteral (IV, SC)	No	No	Mins to hours	Mins to hours

ASO, antisense oligonucleotide; FELIAP, factor XI inhibitory aptamer; IV, intravenous; mRNA, messenger RNA; FXI, factor XI; FXIa, activated factor XI; FXII, factor XII; FXIIa, activated factor XII; Mins, minutes; SC, subcutaneous.

garadacimab) [10, 11]. These inhibitors can be administered intravenously (for monthly, weekly or daily dose), subcutaneously (for monthly or weekly dose) or orally (for daily dose). They have distinct pharmacokinetics properties, particularly regarding metabolism and elimination. Monoclonal antibodies are degraded into small peptides and amino acids by the reticuloendothelial system [12]. Antisense oligonucleotides bind to plasma protein, limiting the contribution of the kidney to their elimination [13]. As these molecules are not substrates for CYP450 or P-gp, drug-drug interactions are unlikely [14]. In contrast small peptidomimetic molecules are P-gp substrates and are metabolized by CYP3A4, making them susceptible to drug-drug interactions [15].

Due to these diverse pharmacological properties, contact phase inhibitors address various patient populations in various clinical settings. This add difficulties in developing the right assay format as bed-side (point of care) testing might be a preferable option for drugs used in acute care while core lab testing appears more suitable for long-term anticoagulation.

Different clinical outcomes

Ionis pharmaceuticals and Bayer first conducted pivotal trials with IONIS-FXI$_{RX}$ to demonstrate its safety and efficacy in major orthopaedic surgery compared to enoxaparin [9]. This indication, because patients are exposed to a double risk of thrombosis and bleeding, because patients are treated while being hospitalized and for a short period of time, offers advantages over other indications to get fast approval. Indeed, the main other indication, stroke prevention in AF, requires trials in ambulatory patients, treated long term, therefore possibly more difficult to control and possibly exposed to drug-drug interferences and other conditions that may impact drug metabolism or clearance. Abelacimab, asundexian, milvexian, the most advanced drugs in clinical trials, have been studied for these indications.

Pivotal trials have also focused on patients with end-stage renal disease (ESRD) for drugs which do not undergo renal elimination, including monoclonal antibodies (osocimab, xisomab 3G3, MK-2060), and antisense oligonucleotides (IONIS FXI$_{RX}$, fesomersen) [16–19]. Results in ESRD patients who are at increased risk of thromboembolic and bleeding events, highlight a real improvement compared to DOACs, especially dabigatran, which may accumulate and expose the patients to bleeding risks due to their renal clearance. Contact phase inhibitors appear promising in patients with biomaterials such as catheters or extracorporeal membrane oxygenation (ECMO), who are at risk of coagulopathy. Xisomab 3G3 shows a lower incidence of catheter-related thrombosis [20], and FXIa inhibition could be an effective alternative to UFH in ECMO [21]. The activated form of FXII (FXIIa) triggers thrombosis and inflammatory reactions [22]. Pharmacologic inhibition of FXIIa limit thrombo-inflammation without increasing the bleeding risk [23].

Although still in the early stage of development phase FXII inhibitors (phase 3 for garadacimab, and phase 2 for IrCPI) show significant potential in the treatment of COVID-19 and hereditary angioedema [24].

More than 12,500 participants have been involved in phase 2 studies to demonstrate the safety and efficacy of contact phase inhibitors compared to current anticoagulants therapies (LMWH, apixaban, rivaroxaban) or placebo in patients with TKA, ESRD, AF, catheter-associated thrombosis, COVID-19, ischemic stroke (IS), acute myocardial infarction (AMI), intracerebral haemorrhage. Results show favourable safety and efficacy profiles. Phase 3 studies, aiming to better determine efficacy and confirm the benefit/risk ratio will recruit over 80,000 participants, focusing on VTE prophylaxis, AF, cancer associated thrombosis, IS, and acute coronary syndrome (ACS), especially for abelacimab, garadacimab, asundexian, and milvexian. A phase 3 study of asundexian in AF patients at risk of stroke was stopped by Bayer due to a lack of efficacy compared to apixaban, although safety was in line with phase 2 results [25, 26]. The OCEANIC-AF trial showed a similar adverse event rates between the two groups and fewer major bleeding with asundexian (0.2 %) than with apixaban (0.7 %) [26]. However, stroke or systemic embolism occurred in 1.3 % of patients receiving asundexian compared to 0.4 % with apixaban. This higher incidence of cardioembolic events may reflects an inadequate dose of asundexian; the PACIFIC-AF study showed a 92 % reduction of FXI with a dose of 50 mg once daily while a greater inhibition of FXI activity might be required in this indication [25, 27].

A meta-analysis by Galli et al. including 9,216 patients showed a decrease in any type of bleeding with FXI inhibitors compared to enoxaparin, a trend towards reduction compared to DOACs, but an increase compared to placebo with a relative risk of 1.25 (95 % CI:1.08–1.43) [28]. Due to their low risk of bleeding, FXI and FXII inhibitors with short half-time may not require specific antidote. However some contact phase inhibitors with half-life of weeks may necessitate reversal agents in case of emergency situations.

For patients with inherited FXI deficiency undergoing surgery, factor replacement (fresh frozen plasma or FXI concentrate) or non-specific reversion (rFVIIa) combined or not with antifibrinolytic agents (tranexamic acid or Ɛ-aminocaproic acid) can restore the coagulation and stabilize clots then reducing bleeding [29]. Salomon et al. demonstrated that surgeries with a single dose of rFVIIa 10–15 μg/kg in addition of tranexamic acid were safe in FXI-deficient patients [30]. As this reversal therapy works for FXI deficiency it has been proposed to antagonise FXI inhibitors [31]. The wide variety of contact phase inhibitors complicates the development of specific reversal agents. However, it appears possible to produce an antidote capable of neutralizing the effects of an entire class of therapeutic agents, DNA and RNA aptamers. Oney et al. describe how protamine and β-cyclodextrin–containing polycation can reverse the activity of aptamers *in vivo* [32]. Available data on indication, efficacy and safety outcomes of contact phase inhibitors currently under development are compiled in Table 2.

Contact phase inhibitor anticoagulant activity measurement

Historical anticoagulants, UFH and VKAs, had a narrow therapeutic window and therefore required frequent monitoring of their anticoagulant activity and dose adjustments. A big step forward was made with LMWHs, which, because of a much more predictable pharmacodynamics compared to UFH, only require anticoagulant activity assessment in selected patients possibly at risk of drug accumulation and overdose (pregnancy, elderly, patients with extreme body weight or renal insufficiency). A breakthrough innovation was reached with DOACs which were approved by regulatory agencies, because of their highly predictable pharmacokinetics and safety profile, with fixed-dose regimen and without any requirement for laboratory testing. Nevertheless, because patients may require urgent invasive procedures or owing the fact that DOAC may accumulate in specific situations (severe renal impairment, drug-drug interactions), the need for tests emerged when DOACs emerged in real life. As contact phase inhibitors are associated with a very low risk of bleeding it is likely that the need for laboratory testing will be even lower than for DOACs. However, it cannot be firmly excluded that the assessment of the anticoagulant activity of contact phase inhibitors or even simply testing for the presence of contact phase inhibitors may be required in some very specific settings.

Inherited deficiencies of contact phase coagulation factors are associated with a prolonged aPTT and a normal PT [49]. Sensitivity of aPTT to FXI and FXII deficiencies varies across aPTT reagents, depending on the nature of the contact phase activator and the phospholipid content [50]. In their investigation, Toulon et al. found variable responsiveness to single factor deficiency of five different aPTT reagents with activity ranging, for the same plasma sample, from 38 to 52 IU/dL for FXI and from 29 to 50 IU/dL for FXII [51].

Available data on contact phase inhibitors under development show a dose-dependent prolongation of aPTT. Prolongation of aPTT is more pronounced with contact

Table 2: Efficacy and safety outcomes of Contact phase inhibitors currently under clinical development.

Drug	Indication	Study	Outcomes
Abelacimab (MAA868)	TKA	ECT 2019-003756-37 [33] (phase 2, n=412)	VTE occurred in 13 , 5 and 4 % with abelacimab 30, 75 and 100 mg vs. in 22 % with enoxaparin 40 mg. CRB occurred in 2 , 2, 0 % with abelacimab 30, 75 and 100 mg vs. in 0 % with enoxaparin 40 mg. SAE occurred in 1 , 3, and 1 % with abelacimab 30, 75 and 100 mg vs. in 0 % with enoxaparin 40 mg.
	AF	NCT04755283 [34] (pase 2, n=1,200)	Ongoing.
	AF	NCT04213807 [35] (phase 2, n=28)	No CRB or SAE reported.
	AF	NCT05712200 [34] (phase 3, n=1900)	Ongoing.
	Cancer-AT	NCT05171075 [34] (phase 3, n=2,700)	Ongoing.
	Cancer-AT	NCT05171049 [34] (phase 3, n=1,655)	Ongoing.
Asundexian (BAY2433334)	NVAF	NCT04218266 [25] (phase 2, n=755)	Thrombotic and CV events occurred in 0.8 % and in 1.5 % with asundexian 20 and 50 mg vs. in 1.2 % with apixaban 5 mg twice daily. CRB occurred in 1.2 %, 0.4 % with asundexian 20 and 50 mg vs. in 2.4 % with apixaban. SAE occurred in 8.8 %, 7.9 % with asundexian 20 and 50 mg vs. in 8.0 % with apixaban.
	NCIS	NCT04304508 [36] (phase 2 b, n=1808)	IS occurred in 19 , 22, 20 % with asundexian 10, 20, 50 mg vs. in 19 % with placebo. CRB occurred in 4 , 3 and 4 % with asundexian 10, 20 and 50 mg vs. in 2 % with placebo.
	AMI	NCT04304534 [37] (phase 2, n=1,601)	CV death, MI, IS or stent thrombosis occurred in 6.80 , 5.99, 5.47 % with asundexian 10, 20 and 50 mg vs. in 5.49 % with placebo. CRB occurred in 7.6 , 8.1, 10.5 % with asundexian 10, 20, 50 mg vs. in 9.0 % with placebo. SAE occurred in 20 , 21.2, 17.7 % with asundexian 10, 20 and 50 mg vs. in 21.3 % with placebo.
	AF	NCT05643573 [26] (phase 3, n=14,830)	Inferior efficacy of asundexian 50 mg.
	IS/TIA	NCT05686070 [34] (phase 3, n=12,300)	Ongoing.
BMS-962212	Healthy	NCT03197779 [38] (phase 1, n=691)	No CRB or SAE reported.
Fesomersen (BAY2976217)	ESRD	NCT04534114 [19, 39] (phase 2 b, n=307)	MI occurred in 1.3 % with fesomersen 40 mg vs. in 1.3 % with placebo. IS occurred in 1.3 % with fesomersen 80 mg. Acute limb ischemia occurred in 1.3 % with fesomersen 120 mg. CRB occurred in 6.5 , 5.1, 3.9 % with fesomersen 40, 80, 120 mg vs. 4.0 % with placebo. No SAE occurred.
Frunexian (EP-7041)	Healthy	NCT02914353 [21] (phase 1, n=80)	No SAE reported.
	Healthy	NCT05742126 [10] (phase 1, n=54)	No CRB or SAE reported.
Garadacimab (CSL312)	Healthy	NCT04580654 [34] (phase 1, n=38)	No SAE reported.
	Healthy	NCT05306275 [34] (phase 1, n=132)	Ongoing.
	COVID-19	NCT04409509 [24] (phase 2, n=124)	TI occurred in 22.2 % with garadacimab 700 mg vs. in 26.2 % with placebo. All-cause mortality occurred in 17.5 % with garadacimab vs. in 18.0 % with placebo. No CRB reported. SAE occurred in 34 patients with garadacimab 700 mg vs. in 45 patients with placebo.
IONIS-FXI_{RX} (ISIS 416858)	TKA	NCT01713361 [9] (phase 2, n=315)	VTE occurred in 27 %, 4 % with FXI-ASO 200, 300 mg vs. in 30 % with enoxaparin 40 mg. CRB occurred in 3 % with FXI-ASO in 8 % with enoxaparin.
	ESRD	NCT02553889 [18] (phase 2, n=49)	CRB occurred in 0 %, 6.7 % with IONIS-FXI_{RX} 200, 300 mg vs. in 7.7 % with placebo. SAE occurred in 20 % with IONIS-FXI_{RX} vs. in 30.8 % with placebo.
	ESRD	NCT03358030 [34] (phase 2, n=213)	Ongoing.
Ir-CPI	Healthy	NCT04653766 [40] (phase 1, n=32)	SAE occurred in 16.67 % with Ir-CPI 1.5 mg/kg and 6.0 mg/kg vs. in 0 % with placebo.
	ICH	NCT05970224 [34] (phase 2a, n=8)	Ongoing.

Table 2: (continued)

Drug	Indication	Study	Outcomes
Milvexian (BMS986177+ JNJ70033093)	TKA	NCT03891524 [41] (phase 2, n=1,242)	VTE occurred in 25 , 24, 7 % with milvexian 25, 50 and 200 mg daily and in 21 , 11, 9, 8 % with milvexian 25, 50, 100, 200 mg twice daily vs. in 21 % with enoxaparin 40 mg. CRB occurred in 1 % with milvexian vs. in 2 % with enoxaparin. SAE occurred in 2 % with milvexian vs. in 4 % with enoxaparin.
	Hepatic impairment	NCT02982707 [42] (phase 1, n=26)	No CRB or SAE reported.
	IS/TIA	NCT03766581 [43] (phase 2, n=2,366)	IS or covert brain infarcts occurred in 16.7 % with milvexian 25 mg daily, 16.6 , 15.6, 14.4, and 15.3 % with 25, 50, 100, 200 mg twice daily vs. in 16.8 % with placebo. CRB occurred in 1 % with milvexian 25 mg daily, 1 , 2, 2, and 1 % with 25, 50, 100, 200 mg twice daily vs. in 1 % with placebo.
	AF	NCT05757869 [34] (phase 3, n=15,500)	Ongoing.
	ACS	NCT05754957 [34] (phase 3, n=16,000)	Ongoing.
	IS/TIA	NCT05702034 [34] (phase 3, n=15,000)	Ongoing.
MK-2060	ESRD	NCT05027074 [34] (phase 2, n=489)	Ongoing.
ONO-7684	Healthy	NCT03919890 [44] (phase 1, n=72)	No SAE reported.
Osocimab (BAY1213790)	Healthy	ECT 2014-003816-35 [45] (phase 1, n=83)	No CRB or SAE reported.
	TKA	NCT03276143 [46] (phase 2, n=813)	Postoperatively VTE occurred in 23.7 % 15.7 , 16.5 and 17.9 % with osocimab 0.3, 0.6, 1.2 and 1.8 mg/kg. Preoperatively VTE occurred in 29.9 , 11.3, 11.3 % with 0.3 and 1.8 mg/kg vs. in 26.3 % with enoxaparin 40 mg and 14.5 % with apixaban 2.5 mg twice daily. Postoperatively CRB occurred in 2 , 0, 1, 3 % with osocimab 0.3, 0.6, 1.2 and 1.8 mg/kg. Preoperatively CRB occurred in 1.9 and 4.7 % with osocimab 0.3 and 1.8 mg/kg vs. in 5.9 % with enoxaparin and in 2 % with apixaban.
	ESRD	NCT04523220 [16] (phase 2 b, n=704)	AVF and graft thrombosis occurred in 1.7 and 2.68 % with osocimab 105/52.5 and 210/105 mg vs. in 3.91 % with placebo. CRB occurred in 4.3 and 3.57 % with osocimab 105/52.5 and 210/105 mg vs. in 6.09 % with placebo.
REGN 9933	Healthy	NCT05102136 [34] (phase 1, n=56)	Ongoing
SHR2285	Healthy	NCT03769831 [47] (phase 1, n=28)	No CRB reported.
	Healthy	NCT04945616 [48] (phase 1, n=52)	No SAE reported.
Xisomab 3G3 (AB023)	Healthy	NCT03097341 [11] (phase 1, n=21)	No SAE reported.
	ESRD	NCT03612856 [17] (phase 2, n=27)	Clotting that required dialyzer change occurred in 12,5 %, 29 % with predose of 0.25, 0.5 mg/kg xisomab 3G3 vs. in 4 % with placebo. No CRB or SAE reported.
	Catheter-AT	NCT04465760 [20] (phase 2, n=22)	CAT occurred in 12.5 % with xisomab 3G3, 2 mg/kg, vs. in 40 % in the control group. No CRB or SAE reported.

ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ASO, antisense oligonucleotides; AT, associated thrombosis; AVF, arteriovenous fistula; CRB, clinically relevant bleeding; CV, cardiovascular; ECMO, extracorporeal membrane oxygenation; ESRD, end stage renal disease; HD, hemodialysis; ICH, intracerebral hemorrhage; IrCPI, Ixodes Ricinus Contact Phase Inhibitor; IS, ischemic stroke; MI, myocardial infarction; NCIS, non-cardioembolic ischemic stroke; NVAF, non-valvular atrial fibrillation; SAE, serious adverse event; TI, tracheal intubation; TIA, transient ischemic attack; TKA, total knee arthroplasty; VTE, venous thromboembolism.

phase inhibitors than direct FXa inhibitors although it varies amongst the different drugs [2]. It could be limited with values remaining close to the cut-off (e.g. low/high dose of oscocimab) or peak at three times the baseline level (e.g. high dose of milvexian) [16, 41]. The importance of the aPTT reagent chosen in the interpretation of results has also been demonstrated for certain drugs, such as the dose-dependent increases in aPTT ratio following IV administration of BAY 1213790 that peak at 1.85 with a silica-triggered method and 2.17 with a kaolin-triggered method [45]. Time to aPTT

prolongation correlates with time to peak drug levels for most of the drugs except for antisense oligonucleotides that reach their maximum levels after a few hours while their mechanism of action is responsible for a delayed aPTT prolongation of several weeks [18]. One advantage of these new anticoagulants, particularly ASO and monoclonal antibody, is their long duration of action. This allows for a reduction in the frequency of injections but is also responsible for an aPTT prolongation sometimes persisting for several weeks [52]. This can complicate the management of patients in urgent situations, such as acute haemorrhage and interventions with high bleeding risk. Mailer et al. have suggested that the use of an antibody against a specific segment PR-III of FXII C-terminal proline rich region can induce FXII contact activation in solution and in a controlled manner. This approach, antibody-activated partial thromboplastin time assays, has been used in a modified aPTT which in contrast with traditional aPTT assays, enables a precise measurement of FXI activity. This would permit a more reliable monitoring of contact phase inhibitors and a safer antithrombotic therapy [22].

Due to their highly specific binding, contact phase inhibitors lack effects on PT and other components of the intrinsic pathway such as FVIII and FIX [9]. aPTT has been used as a pharmacodynamic biomarker in most, if not all, studies evaluating contact phase inhibitors. It provides an approximation of the drug effect but the drug-dependent aPTT prolongation, inter-reagent variability and numerous factors that can interfere with the aPTT (e.g. lupus anticoagulant, factor deficiency, other anticoagulants, acute-phase

Table 3: Assays possibly used for the monitoring of anticoagulants.

Assay	VKA	UFH	LMWH	DXai	Dabigatran	Argatroban	XI(a)i/XII(a)i
PT INR	Yes (INR[c])	No (heparin neutralizer)	No (heparin neutralizer)	No (sensitivity varies across reagents and DXai)	No (sensitivity varies across reagents)	No (sensitivity varies across reagents)	No (not affected)
aPTT[a]	No (prolonged)	Yes (sensitivity varies across reagents)	No (usually moderately prolonged[b])	No (sensitivity varies across reagents and DXai)	No (sensitivity varies across reagents)	Yes (sensitivity varies across reagents)	Yes? (Sensitivity varies across reagents and DXI(a)i)
ACT	No (prolonged)	Yes (usually limited to monitoring during cardiac surgery)	No (usually moderately prolonged[b])	No (moderately prolonged)	No (moderately prolonged)	Yes	No (likely to be prolonged as it reflects contact phase activation)
TT	No (not affected)	Possible (dedicated test set-up)	No (usually moderately prolonged[b])	No (not affected)	No (too sensitive but can be used qualitatively)	No (too sensitive)	No (not affected)
Anti-Xa	No (not affected)	Yes[c]	Yes[c]	Yes (dedicated test set-up and calibrator)	No (not affected)	No (not affected)	No (not affected)
dTT	No (not affected)	No (prolonged)	No (usually moderately prolonged[b])	No	Yes (specific calibrator)	Yes (specific calibrator)	No (not affected)
ECT ECA	No (not affected)	No (not affected)	No (not affected)	No (not affected)	Yes (specific calibrator)	Yes (specific calibrator)	No (not affected)
aaPTT	No	No	No	No	No	No	Yes? (Could be more efficient than aPTT)
FXI FXIa FXII	No	No	No	No	No	No	Yes? (Possible surrogate marker of drug level)

[a]aPTT, is sensitive to multiple interferences including elevated factor levels (FVIII, fibrinogen), elevated CRP, and LA presence. [b]Prolongation of the assay is inversely proportional to the anti-Xa/anti-IIa, ratio of the LMWH, preparation. [c]Current WHO, International Standards for VKA, monitoring by INR: 5th International Standard 2016 Thromboplastin, Rabbit, Plain (NIBSC, code: RBT/16) and 5th International Standard 2016 Thromboplastin, Human, Recombinant (NIBSC, code: rTF/16) (future WHO, International Standard: 6th International Standard Thromboplastin, Human, Recombinant); Current WHO, International Standards UFH, monitoring by anti-Xa: 6th International Standard for Unfractionated Heparin (NIBSC, code: 07/328); Current WHO, International Standards LMWH, monitoring by anti-Xa: 2nd International Standard Low Molecular Weight Heparin (NIBSC, code: 05/112). ACT, activated clotting time; aaPTT, antibody activated partial thromboplastin time; aPTT, activated partial thromboplastin time; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECT, ecarin clotting time; DXai, direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban); FXI, Factor XI; FXIa, activated Factor XI; FXII, factor XII; LMWH, low molecular weight heparin; NIBSC, National Institute for Biological Standards and Controls (UK); TT, thrombin time; UFH, unfractionated heparin; VKA, vitamin K antagonists; WHO, World Health Organization; XI(a)I, Factor XI/Factor Xia inhibitors; XII(a)I, Factor XII/Factor XIIa inhibitors.

reactants) makes it use in clinical practice unreliable. The measurement of FXI, FXIa and FXII levels could be used as a surrogate marker but their correlation with the anticoagulant effect of contact phase inhibitors remains unclear [53]. Measurement of FXIa has been a matter of concern in intravenous IgG preparations as it may be responsible for thrombotic manifestations in patients receiving this kind of therapy [54]. Specific assays are proposed for the measurement of FXIa in this setting; FXIa inhibitors could benefit from an assay developed on the same principle [53]. Development of anti-FXI assays is an alternative worth exploring although the need for drug-specific calibration curves may hinder its possible large-scale use, unless a common calibrator could be used.

Global coagulation assays, such as thrombin generation assays and viscoelastic testing, may better reflect the actual coagulation profile in patients taking one of the contact phase inhibitors [55]. An investigation including 76 patients with FXI deficiency enrolled over a period of nine years revealed significantly lower endogenous thrombin potential (ETP) in patients with FXI deficiency in comparison with healthy controls while this parameter was not able to differentiate bleeders and non-bleeders [56]. In contrast, Pike et al. found significantly lower ETP and Peak height in FXI-deficient subjects with haemorrhagic phenotype than those with no bleeding [57]. Differences in methodology seems to explain such discrepancies; indeed both studies employed low tissue factor concentration but the former used platelet-poor plasma without corn trypsin inhibitor whereas the latter used platelet-rich plasma with corn trypsin inhibitor to prevent contact activation *in vitro*. Table 3 provides an overview of the assays possibly used for the monitoring of anticoagulants, including contact phase inhibitors.

Conclusions

Minimizing the incidence of thrombosis is pivotal in modern medicine. Since the initiation of antithrombotic therapy with heparin and VKA, efforts have been put to develop safer anticoagulants with an easier management. The success of DOACs, which have replaced VKA for most patients confirms the accuracy of this approach. However, current DOACs are still associated with an increased risk of bleeding, especially in certain patient populations, such as e.g. renal insufficiency. Based on the observation that FXI and FXII deficiencies are associated with minimal or even no bleeding manifestations, these factors emerged as potential target for newer anticoagulants. Multiple research programs have led to the development of a new class of anticoagulants, the contact phase inhibitors. This new class is composed of various compounds differing by their chemical structure, pharmacokinetic profile (delay of onset, half-life), route of administration and potential clinical indications. This makes this new class of anticoagulants a much more diverse family of anticoagulants than the historical or contemporary anticoagulants, heparin, VKA or DOACs. This diversity may pave the way for broader indications, but may also limit the development of a universal assay. Indeed, although likely to show a safe profile, contact phase inhibitors may require an assessment of the actual hemostasis profile of the patient, especially in emergency situations. Development and validation of an accurate and reliable assay remains today a need for a safe widespread of these new anticoagulant candidates and a perspective for research.

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