A novel rationale for targeting FXI: Insights from the hemostatic miRNA targetome for emerging anticoagulant strategies

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Abstract

Therapeutic targeting of blood coagulation is a challenging task as it interferes with the delicate balance of pro- and anticoagulant activities. Anticoagulants are employed in millions of thrombophilic patients worldwide each year. The treatment and prevention of venous thromboembolism has changed drastically with the replacement of traditional anticoagulant vitamin K antagonists by direct oral anticoagulants (DOACs), which selectively target coagulation factors Xa or IIa. However for a growing population with comorbidities satisfying therapeutic options are still lacking and the quest for novel therapeutics continues. Recently targeting factors XI or XII have emerged as new therapeutic strategies. As these factors play important roles in thrombosis, nevertheless are practically functionally dispensable for hemostasis, they may potentially overcome the functional obstacle of treating or preventing thrombosis without affecting hemostasis. Based on the recent elucidation of the hemostatic miRNA targetome, we introduce and discuss a hitherto unrecognized rationale for the therapeutic targeting of factor XI. This is based on mimicking endogenous factor XI expression control by therapeutic delivery of miRNA mimics. We discuss the functional difference between various gene targeting approaches, and propose the hemostatic system to represent an ideal model for assessment of the efficacy and safety of such therapeutic components, ushering in a novel therapeutic era with broad applicability.

Keywords

Dabigatranetexilat (Pradaxa), Apixaban (Eliquis), Rivaroxaban (Xarelto), Edoxaban (Lixiana)

List of Abbreviations

aPTT, activated partial thromboplastin time; ASO, antisense oligonucleotide; ceRNA, competing endogenous RNA; circRNA, circular RNA; DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; FGA, fibrinogen alpha; FGB, fibrinogen beta; FGG-alpha, fibrinogen gamma, alpha isoform; FII, factor 2; FIX, factor 9; FV, factor 5; FVIIa, factor 7 activated; FVIII, factor 8; FX, factor 10; FXI, factor 11; FXII, factor 2; miRNA, MicroRNA; RBP, RNA binding protein; RISC, RNA induced silencing complex ; SNP, single nucleotide polymorphism; TF, tissue factor; UTR, untranslated regions; VKA, vitamin K antagonists; VSMC, smooth muscle of vascular walls, ; VT, venous thrombosis; VTE, venous thromboembolism; VTE, venous thromboembolism; VWF, Von Willebrand factor

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1. Introduction

Cardiovascular disorders including myocardial infarction, ischemic stroke and venous thromboembolism (VTE) are the leading global cause of mortality with over 17 million deaths annually (Lozano, et al., 2012). The incidence of VTE increases markedly with age, starting in the late 40s, with a dramatic increase occurring at 60 years of age (Silverstein, et al., 1998). Around 30% of patients experience a recurrence within 10 years, underscoring a high demand for therapeutic intervention to treat and prevent VTE (Connors, 2017).

Therapeutic targeting of blood coagulation is an inherently difficult task as it interferes with the delicate balance of pro- and anticoagulant activities. Anticoagulants are employed in millions of thrombophilic patients worldwide each year to limit the otherwise essential function of blood clotting (Wendelboe & Raskob, 2016). However this intervention inevitably leads to an elevated risk of undesired bleeding. While some bleeding events are clinically mild and less critical, others can be life threatening, such as intracranial or abdominal bleeding.

Here we provide insights into the distinctiveness of the hemostatic system and illustrate the challenges and opportunities associated with therapeutic targeting. In addition, we present an interdisciplinary contribution to the exciting discussion about next-generation anticoagulants from the area of RNA biology, and how this might foster the implementation of miRNA therapeutics in other disciplines as well.

2. The hemostatic system

Hemostasis is accomplished through a network of processes that include platelets, coagulation, anticoagulant and fibrinolytic pathways, which all support the dynamic equilibrium that provides proper blood flow. Such processes have evolved to maintain the blood in a fluid state under physiologic conditions and to stop bleeding after vascular injury (Borissoff, Spronk, & ten Cate,

2011). Disruption of this well-regulated balance leads to pathologic conditions, such as thrombosis or bleeding.

The response to vascular injury culminates in the formation of a platelet plug, the generation of a fibrin clot, the deposition of white cells in the area of tissue injury, and ultimately the initiation of wound repair. During initiation of blood coagulation, tissue factor (TF), the main trigger of coagulation, is exposed at the site of the vascular lesion (Figure 1). The activation of the TF (extrinsic) pathway results in the formation of a catalytic complex with factor VIIa leading to subsequent activation of factors IX and X. The so-called prothrombinase complex, consisting of activated factors X and V promotes a downstream enzymatic cleavage of prothrombin, which yields small amounts of thrombin. Thrombin is pleiotropic; it acts as a central coagulation enzyme that converts fibrinogen into fibrin but also has a critical role in the activation of platelets and factor XIII to induce fibrin polymerization, a fundamental process in the formation of a stable clot or thrombus. In addition, thrombin plays a crucial part in the amplification and propagation of coagulation by supporting positive-feedback activation of the upstream factors V, VIII and XI. Together with factor VIIIa, factor IXa forms the so-called tenase complex which triggers a burst of additional thrombin that is essential for the formation of sufficient fibrin and the sealing of the vascular defect.

In contrast to the extrinsic pathway, which is essential for protection against bleeding, the contact activation (intrinsic) pathway primarily serves to amplify blood coagulation (Grover & Mackman, 2019) (Figure 1). The exposure of plasma prekallikrein, high-molecular weight kininogen, and factors XI and XII to negatively charged molecules including platelet-derived polyphosphate (Muller, et al., 2009) and collagen (van der Meijden, et al., 2009), results in the conversion of prekallikrein to kallikrein, which activates factor XII. Activated factor XII in turn activates factor XI, and promotes the conversion of additional prekallikrein to kallikrein (see above) which reciprocally amplifies the cascade (Gailani & Broze, 1991; Naito & Fujikawa,

1991). This sequence ultimately leads to the activation of factor IX resulting in proteolytic activation of factor X, culminating in the convergence of both coagulation pathways.

3. Current anticoagulants and their limitations

The treatment and prevention of VTE is under a period of rapid change. The introduction of direct oral anticoagulants (DOACs), which specifically target blood coagulation factors Xa (Rivaroxaban, Apixaban, Edoxaban) or IIa (Dabigatran), has changed the management of VTE (Wu & Matijevic-Aleksic, 2005). They are replacing traditional anticoagulants, such as vitamin k antagonists (VKA), which more broadly impair the biosynthesis of factors II, VII, IX and X (Figure 1). DOACs have several advantages; this includes predictable pharmacokinetics, a wider therapeutic window, rapid onset and offset of action, a shorter plasma half-life, fewer food–drug and drug–drug interactions, fixed dosing with - in most cases - no need for laboratory monitoring or dietary discretion, and improved patient satisfaction (Barkun, et al., 2019; Cha, et al., 2017; Y. H. Chan, et al., 2019; Inoue, et al., 2019; Jansson, et al., 2020; Kjerpeseth, et al., 2019). Large clinical trials have demonstrated the superiority of DOAC over VKA in terms of efficacy and safety of VTE treatment (Agnelli, et al., 2013; Bauersachs, et al., 2010; Buller, et al., 2013; Schulman, et al., 2014). An improved benefit/risk profile has also been documented for nonvitamin K anticoagulants regarding the prevention of embolic events and bleeding in atrial fibrillation (Connolly, et al., 2009; Giugliano, et al., 2013; Granger, et al., 2011; M. R. Patel, et al., 2011), and selective Xa inhibition improves the cardiovascular outcome (risk reduction of death from myocardial infarction, or stroke) in patients with recent acute or stable coronary syndrome (Eikelboom, et al., 2017; Mega, et al., 2012).

Nevertheless, despite these improvements, bleeding is still the most frequently reported side effect of DOACs (Eikelboom, et al., 2017; Lanas, et al., 2015; Lanas-Gimeno & Lanas, 2017; B. K. Martinez, Sood, Bunz, & Coleman, 2018; Mega, et al., 2012; van Montfoort & Meijers, 2013; Villines, et al., 2019). Further, selected sub-groups of patients do not show a significant benefit of DOAC with regard to VTE recurrence and bleeding risk (Agnelli, et al., 2015; Prins, et al., 2014; Schulman, et al., 2015). Accumulating studies also report that dabigatran is associated with esophagitis and gastric ulceration, suggesting that the drug may directly injure the gastrointestinal mucosa (Cangemi, et al., 2017; Lanas, 2019; Sostres, et al., 2019). Additionally, satisfying therapeutic options are still lacking for a growing population with co-morbidities who exhibit an increased risk of bleeding under DOACs (Burnett, et al., 2016; Martin & Key, 2016). Apixaban and rivaroxaban are contraindicated in patients with severe renal impairment or advanced liver disease (Abraham, et al., 2015; Alexander, et al., 2019; Andersson, Svanstrom, Lund, Pasternak, & Melbye, 2018; Beyer-Westendorf, et al., 2019; Camm, et al., 2019; Fralick, et al., 2020; S. Y. Lin, et al., 2020; Nissan, et al., 2019; Sakuma, et al., 2019). In patients with mechanical heart valves the use of dabigatran is associated with increased rates of thromboembolic and bleeding complications compared to warfarin, thus showing no benefit and an excess risk (Eikelboom, et al., 2013). As uptake and metabolization of DOACs are P-Glycoprotein- and Cytochrome 3A4-dependent, co-medication with Cytochrome 3A4 and P-Glycoprotein inhibitors (which includes a substantial number of standard pharmaceuticals) can significantly alter DOAC concentrations and increase bleeding risk (Gong & Kim, 2013). Finally DOACs appear to be associated with an increased risk in patients with antiphospholipid syndrome (Pengo, et al., 2018) limiting their use in this critical population with a significant risk of thromboembolic events.

4. Contact system as novel target for anticoagulation therapy

The DOAC targets, factor IIa and Xa, are located downstream in the common pathway (Figure 1) and play essential roles in physiological hemostasis. Targeting either one disrupts both intrinsic and extrinsic coagulation pathways, preventing the positive feedback activation of factors XI, VIII and V by factor IIa generation. Consequently, DOACs have a strong impact on the clotting process, and result in an increased bleeding risk (Gale, 2011). Owing mainly to this concern, their clinical application is still restricted and therapeutic monitoring requirement is controversial (Lesko, 2016; Shoeb & Fang, 2013).

In the search for new and safer anticoagulant therapies, bleeding side-effects may be avoided with the selective targeting of coagulation factors that play more important roles in pathological thrombosis than for physiological hemostasis (Plow, Wang, & Simon, 2018; Sikka & Bindra, 2010). Specific targeting the contact pathway may represent such a strategy. It is hoped that this approach may overcome functional obstacles in the quest for the 'ideal anticoagulant', that of treating or preventing thrombosis without affecting hemostasis. A key question in following up this approach is which of these factors is likely to be the more reliable target in the challenging endeavor of inhibiting blood clotting while maintaining hemostasis?

While physiological hemostasis depends primarily on the TF-factor pathway, the intrinsic pathway is not considered to be essential for hemostasis in vivo, even though its components appear to be involved in the pathogenesis of thrombosis (Doggen, Rosendaal, & Meijers, 2006; Meijers, Tekelenburg, Bouma, Bertina, & Rosendaal, 2000; Minnema, et al., 2000; Wheeler & Gailani, 2016). Epidemiologic data suggest that individuals with congenital factor XI deficiency while largely being protected against venous and arterial thrombosis (Rosen, Gailani, & Castellino, 2002; Salomon, Steinberg, Koren-Morag, Tanne, & Seligsohn, 2008; Salomon, et al., 2011; Tucker, et al., 2009), generally do not exhibit spontaneous bleeding (Duga & Salomon, 2013; James, Salomon, Mikovic, & Peyvandi, 2014). Additionally bleeding associated with

severe deficiency, injury or surgery tends to be relatively mild, often not requiring treatment (Duga & Salomon, 2013; He, Chen, & He, 2012; James, et al., 2014; Preis, et al., 2017; Salomon, et al., 2008; Salomon, et al., 2011). A wide range of factor XI plasma levels has been found in the healthy population (Van Hylckama Vlieg, Callas, Cushman, Bertina, & Rosendaal, 2003) and elevated plasma levels of factor XI have been associated with increased risk of VTE and ischemic stroke (Folsom, et al., 2015; Meijers, et al., 2000; Salomon, et al., 2008; Siegerink, Rosendaal, & Algra, 2014; Yang, Flanders, Kim, & Rodgers, 2006). Conversely, lower factor XI levels have been associated with reduced risks of (recurrent) venous thrombosis and ischemic stroke, without evidence for an associated risk of major bleeding (Georgi, et al., 2019; Kyrle, Eischer, Šinkovec, & Eichinger, 2019).

Studies of patients with factor XII deficiency are limited. However, while factor XII deficiency does not cause abnormal bleeding (Kenne, et al., 2015), patients do not appear to be protected against thrombotic events (Key, 2014). In animal models both factor XI and XII inhibition results in protection from arterial and venous thrombosis without altering bleeding (Cai, et al., 2015; Larsson, et al., 2014; Matafonov, et al., 2014; Renne, et al., 2005; Rosen, et al., 2002; van Montfoort, et al., 2014; X. Wang, et al., 2005). These observations suggest that plasma factor XI level is a significant factor in thrombosis. Yet, therapeutic targeting of factor XI may also become relevant to interfere with vascular dysfunction, arterial hypertension (Kossmann, et al., 2017), and thrombus formation in atherosclerotic lesions (van Montfoort, et al., 2014), or during cardiopulmonary bypass (Pireaux, et al., 2019).

5. Shortcomings of current classes of anticoagulant therapeutics

While numerous approaches targeting intrinsic coagulation factors (XII, XI and IX) are currently under preclinical study (Al-Horani, 2020; Al-Horani & Afosah, 2018; Rai, Balters, & Agrawal,

2019; Weitz & Fredenburgh, 2017), only therapies utilizing small molecule inhibitors, antibodies and antisense oligonucleotides (ASO) targeting factors XII and XI have reached early phase human trials (DeLoughery, Olson, Puy, McCarty, & Shatzel, 2019). Here the use of an ASO to specifically reduce factor XI was the first of only two studies to complete phase II trials (Büller, et al., 2015; Weitz, et al., 2020). ASOs are relatively short, chemically modified single-stranded nucleic acid sequences that selectively pair to specific regions of mRNA resulting in endonucleolytic cleavage and degradation (Cosmi, 2016; DeVos & Miller, 2013; Heestermans & van Vlijmen, 2017; Kole, Krainer, & Altman, 2012) (Table 1). Currently over 60 ASO therapies are in, or have completed phase I/II trials (S. Zhu, Rooney, & Michlewski, 2020), with a substantial number of anti-thrombotic ASO therapeutics currently under development (Table 2). In animal studies, factor XI ASO can safely prevent thrombus formation without bleeding complications (J. R. Crosby, et al., 2013; van Montfoort, et al., 2014; Yau, et al., 2014; Younis, et al., 2012; H. Zhang, et al., 2010). A phase II study in surgical patients indicated that a specific factor XI ASO effectively protects patients against venous thrombosis with a relatively limited risk of bleeding (Büller, et al., 2015). However, this proof-of-concept trial was too small to assess the effect on other thrombotic end points**.** Additionally, changes in platelet counts in nonhuman primates treated with ASOs have been observed (Henry, et al., 2017), which has been attributed to peripheral clearance (Narayanan, et al., 2018) and could potentially impact hemostasis.

RNA therapeutics offer the promise of uniquely targeting virtually any gene of interest involved in a particular disease with greater specificity, high potency, and decreased toxicity (Drosopoulos & Linardopoulos, 2013; Perwitasari, Bakre, Tompkins, & Tripp, 2013; Quemener, et al., 2020; S. Zhu, et al., 2020). The ASO-messenger(m)RNA heteroduplex silences gene expression by a variety of mechanisms including triggering RNase H activity resulting in mRNA degradation, steric blocking of ribosomal activity resulting in translational arrest, interfering with mRNA maturation by inhibiting splicing, destabilizing pre-mRNA in the nucleus or inhibiting 5'cap formation (J. H. Chan, Lim, & Wong, 2006; Crooke, 2000) (Table 1). While RNA therapeutic

approaches have been applied to the development of new drugs and clinical trials currently being carried out (Tiemann & Rossi, 2009; Titze-de-Almeida, David, & Titze-de-Almeida, 2017), there are still concerns and challenges to be overcome. These include, but are not limited to, off-target effects (Snove & Holen, 2004; Yu, Jian, Yu, & Tu, 2019), triggering innate immune responses, efficacy and delivery into the target cell (X. Zhao, Pan, Holt, Lewis, & Lu, 2009). Recently, a new class of RNA therapeutic has attracted considerable attention, that of miRNA targeting.

6. miRNA targeting as novel class of therapeutic

MicroRNAs (miRNAs) are a class of short (17 to 25 bp), endogenous noncoding RNAs, that post-transcriptionally down-regulate target gene expression (Bartel, 2009; K. Chen & Rajewsky, 2007; Friedman, Farh, Burge, & Bartel, 2009). miRNAs are transcribed as primary transcripts, then processed in the nucleus by the microprocessor complex consisting of Drosha and DGCR8 to produce a pre-miRNA (S. Li & Patel, 2016). After further processing by Dicer (Krol, Loedige, & Filipowicz, 2010) the mature miRNA duplex is exported into the cytoplasm and incorporated into the RISC (Meister, 2013; Wilson & Doudna, 2013). This complex is guided by miRNA base pairing to a target gene mRNA resulting in translational inhibition and/or transcript degradation via one of several possible mechanisms (Fabian, Sonenberg, & Filipowicz, 2010; Oliveto, Mancino, Manfrini, & Biffo, 2017). In general miRNAs target mRNAs via the 3' untranslated regions (3'UTR), while to a lesser extent, miRNAs can also carry out their inhibitory function by binding to the coding region or the 5’UTR of target mRNAs (Bartel, 2009).

Over 2600 human miRNAs have been identified (Kozomara, Birgaoanu, & Griffiths-Jones, 2019), regulating the majority of all human genes (Friedman, et al., 2009). Thus almost every biological process is modulated through miRNAs (Saliminejad, Khorram Khorshid, Soleymani

Fard, & Ghaffari, 2019). Although miRNAs generally fine-tune gene expression (Mukherji, et al., 2011), they may also function as master regulators depending on the cellular environment (Lui, Jin, & Stevenson, 2015). Multiple miRNAs can cooperatively silence a single gene to gain regulatory specificity, with the targeting of particular network hub genes enabling the regulation of entire pathways (X. Li, et al., 2012). Additionally a single miRNA can target multiple genes (Bartel, 2009), allowing broad regulation of molecular networks (Megiorni, Cialfi, Dominici, Quattrucci, & Pizzuti, 2011). Perturbations of miRNA expression are observed in most disorders, with some of them even causally contributing to the development and progression of disease (Paul, et al., 2018; Saliminejad, et al., 2019). This underscores the extensive involvement of miRNAs in a variety of biological functions.

6.1 miRNA and therapy

The clear role of miRNAs in human disease has made them attractive targets for novel therapeutic intervention (Bajan & Hutvagner, 2020; Rupaimoole & Slack, 2017). miRNA-based therapeutics are actively being investigated and developed for clinical applications (Bonneau, Neveu, Kostantin, Tsongalis, & De Guire, 2019), with several currently the subject of clinical trials (Bajan & Hutvagner, 2020; Rupaimoole & Slack, 2017; Saliminejad, et al., 2019). Advances in RNA chemical modifications to improve stability, efficiency, target specificity and in vivo delivery while lowering toxicity have made miRNA-based therapeutics feasible (Egli & Manoharan, 2019; D. Lu & Thum, 2019). Several animal studies suggest that modified RNA-based oligonucleotides are specific, stable and non-toxic when delivered intravenously (Elmen, et al., 2008; Lanford, et al., 2010). Onset and duration of action are largely determined by the backbone chemistry of RNA-based oligonucleotides, with phosphorothioate-modified single-stranded ASOs exhibiting rapid transfer from blood into tissues (minutes to hours) and long half-lives and prolonged activity (2-4 weeks) (Geary, Norris, Yu, & Bennett, 2015).

Depending on the desired outcome several different approaches to miRNA-based therapy may be taken. In situations where a miRNA is down-regulated in disease, the restoration of miRNA function can be achieved through the use of miRNA mimics or pre-miRNA. This involves RNA oligonucleotides, which match the corresponding miRNA sequence and can restore or increase miRNA function (Rupaimoole & Slack, 2017; van Rooij & Kauppinen, 2014). As an example, a miRNA mimic targeting miR-29, Remlarsen, is currently under Phase 2 trial in the prevention of fibrous scar tissue formation (Gallant-Behm, et al., 2019).

Where inhibition of miRNA activity is desired several strategies are available. Antagomirs are chemically modified synthetic antisense RNA oligonucleotides complementary to the target miRNA. An antagomir binds to and sequesters the endogenous target miRNA preventing it from binding the mRNA targets (Rupaimoole & Slack, 2017). One of the first miRNA therapies to be developed is Miravirsen, an antagomir against miR-122, which plays an important role in the replication cycle of the hepatitis C virus (Kaluzna, 2014). In human trials Miravirsen resulted in a decrease in viral RNA levels with no cytotoxicity (Janssen, et al., 2013; Ottosen, et al., 2015).

Although the use of such technology is widely developed for in vitro models, due to the ubiquitous nature of miRNA binding, application in vivo is hampered by undesired off-target effects (Y. Chen, Zhao, Tan, Zhang, & Fu, 2015; Messina, et al., 2016; Singh, Narang, & Mahato, 2011). Several approaches may assist in preventing off-target effects while maintaining the benefits of miRNA target diversity. The functional synergy of several miRNA mimics targeting a single gene, with each individually at sub-effective doses, allows for an increase in effect size and a reduction in side effects (Nourse, Braun, Lackner, Hüttelmaier, & Danckwardt, 2018). For miRNA inhibition a more precise alternative to inhibit miRNA function involves the use of an ASO designed to specifically bind an individual miRNA site within a target mRNA (termed target site blockers, or masks) preventing miRNAs from gaining access to the site (Louloupi & Orom, 2018; Z. Wang, 2011). This does not affect the expression of other genes thereby reducing potential

off-target effects. Initial in vivo studies with miRNA targeting ASOs required relatively high (80 mg per kg) doses (Krützfeldt, et al., 2005), increasing the risk of off-target effects. The development of more efficient in vivo delivery systems that confer higher stability has reduced this (to the single-digit mg per kg range) (Forterre, Komuro, Aminova, & Harada, 2020). Although miRNA expression tends to exhibit tissue and cell type specificity (Nowakowski, et al., 2018; Sood, Krek, Zavolan, Macino, & Rajewsky, 2006), miRNA modulation in a target tissue may be accompanied by on-target side effects involving normal miRNA expression in non-target tissues, potentially leading to toxicity. To alleviate this miRNA delivery vehicles enabling tissue-specific targeting have been developed. Conjugates under investigation include antibodies (Cuellar, et al., 2015; Song, et al., 2005) and aptamers (McNamara, et al., 2006; J. Zhou & Rossi, 2017), while an alternative approach involves the production of targeted exosomes (Ohno, et al., 2013).

6.2 Comparison of miRNA to current therapeutic approaches

Protein expression (and hence the downstream functional consequences) depends not only on the rate of transcription, but on other regulatory mechanisms, including mRNA processing, stability, transport and translational regulation. These post-transcriptional mechanisms are principally mediated by the binding of RNA-binding proteins (RBPs), long non-coding RNAs (lncRNAs) and miRNAs to regulatory elements in the 3'UTRs of mRNAs (Figure 3). The emerging picture is that of complex and multifaceted layers of 3’UTR-mediated regulation, including competition and cooperativity of these regulatory components, to adjust protein synthesis in a spatiotemporal manner (Jens & Rajewsky, 2015; Tay, Rinn, & Pandolfi, 2014). Of note such mechanisms also tune the hemostatic system, for example in an acute event of blood loss to stockpile blood coagulation factors (Danckwardt, et al., 2011).

As opposed to ASO silencing, and in many cases siRNAs, which exhibit perfect complementary to their targets, and inevitably result in degradation of the target mRNA (Figure 3 right, and Table 1) (Haley & Zamore, 2004; J. Martinez & Tuschl, 2004; Schwarz, et al., 2006), the partial base-pairing of miRNAs prevents the cleavage activity of RISC, with silencing predominately resulting from translational repression, and in some cases deadenylation, decapping and finally mRNA degradation (Fabian & Sonenberg, 2012; Huntzinger & Izaurralde, 2011) (Figure 3 left). Although the proportion of mRNA target degradation is reported to occur to a highly variable extent (Jonas & Izaurralde, 2015), a number of targets are almost exclusively repressed at the level of translation (Selbach, et al., 2008). How much each process contributes to down-regulation depends on characteristics, such as seed-flanking nucleotides, of the individual miRNA–mRNA pair (Grimson, et al., 2007; Nielsen, et al., 2007; Selbach, et al., 2008). Significantly, translational repression appears to be particularly relevant for secretory proteins (such as components of the hemostatic system) as miRNA translational repression is stronger for mRNAs produced at the endoplasmic-reticulum compared to free cytosolic ribosomes (Selbach, et al., 2008). Thus, miRNA-mediated therapeutic targeting without degradation of such target mRNAs preserves cell intrinsic regulatory mechanisms executed by 3'UTRs and their 'interacting partners' such as RBPs, miRNAs and/or other layers of control, such as ceRNA, circRNA miRNA sponges (Figure 3). Finally miRNA sites in proximity to RBP sites are often subject to mechanisms of physiological control (Danckwardt, Hentze, & Kulozik, 2008; Jens & Rajewsky, 2015; Y. C. Lu, et al., 2014; Tay, et al., 2014), which may play important regulatory roles to control the delicate balance of hemostatic system in response to environmental cues (Danckwardt, et al., 2011).

In the context of thrombosis and hemostasis, the versatility of miRNA-based approaches enables many therapeutic possibilities. miRNA mimics may be employed to silence pro-coagulant genes to treat thrombosis or alternatively, anticoagulant genes to treat bleeding.

Conversely, antagomirs or target blockers may be used to relieve silencing of procoagulant genes to treat bleeding, or anticoagulant genes to treat thrombosis.

miRNA therapeutics are at an early stage of development and require time to reach the maturity point needed to reach the bedside (Beierlein, McNamee, & Ledley, 2017). One of the biggest challenges in the maturation of miRNA-based therapeutics is the identification of key miRNA candidates and targets. There is currently a relatively small number of experimentally validated miRNA:mRNA interactions (Lee, Kim, Muth, & Witwer, 2015) and here knowledge of the miRNA targetome in the hemostatic system is potentially a major trove for future targeted therapeutics (Nourse, et al., 2018), not only for the development of safe anticoagulants but also for developing treatments for coagulopathies.

6.3 Evidence for a functional role of miRNAs in the hemostatic system

Several lines of evidence implicate significant functional roles for miRNAs in the regulation of the hemostatic system. Firstly, a growing number of studies show essential contributions of miRNAs to the regulation of hemostatic (De Los Reyes-Garcia, et al., 2019; Jankowska, Sauna, & Atreya, 2020; Teruel-Montoya, Rosendaal, & Martinez, 2015) and thrombotic (Arroyo, et al., 2018; Hembrom, Srivastava, Garg, & Kumar, 2020; Jankowska, Sauna, et al., 2020; Morelli, Braekkan, & Hansen, 2020) functions (Table 3). Secondly, miRNAs have been demonstrated to directly regulate multiple hemostatic factors through interactions with the 3'UTR. This include key genes of the hemostatic system, including the fibrinogens FGA (Z. Chen, et al., 2010; Nourse, et al., 2018), FGB (Fort, et al., 2010) and FGG-alpha (Nourse, et al., 2018); the coagulation factors VII (Nourse, et al., 2018), VIII (Jankowska, Chattopadhyay, Sauna, & Atreya, 2020; Jankowska, McGill, et al., 2020; Nourse, et al., 2018; Sarachana, et al., 2015)], XI (Nourse, et al., 2018); TF (S. Li, Chen, et al., 2014; S. Li, Ren, et al., 2014; Sahu, et al., 2017; Teruel, et al., 2011;

Witkowski, et al., 2016; X. Zhang, et al., 2011); prekallikrein (Nourse, et al., 2018); TFPI (Ali, et al., 2016; Arroyo, et al., 2017); antithrombin (SERPINC1) (Nourse, et al., 2018); protein c (Nourse, et al., 2018); protein z (Nourse, et al., 2018); protein z-dependent protease inhibitor (SERPINA10) (Nourse, et al., 2018); heparin cofactor 2 (SERPIND1) (Nourse, et al., 2018); VWF (L. Liu, et al., 2018); ADAMTS13 (L. Zhao, Hua, Li, Sun, & Wu, 2015); PAI-1 (SERPINE1) (Luo, et al., 2016; Marchand, Proust, Morange, Lompre, & Tregouet, 2012; Patel, Tahara, Malik, & Kalra, 2011); plasminogen (Nourse, et al., 2018) and the plasminogen activator PLAT (S. Li, et al., 2017). Additionally, miRNAs can impact hemostatic factors indirectly, for example fibrinogen via interleukin-6-mediated signaling (Brock, et al., 2011), factor IX by repressing nonsense-mediated mRNA decay (G. Wang, Chai, & Yang, 2016), PAI-1 via SMAD2 signaling (Liao, et al., 2014) and CXCL12 to reduce inflammatory response and thrombosis altering the expression of multiple factors including TF, PAI-1 and VWF (S. Sun, Chai, Zhang, & Lu, 2020).

A third line of evidence implicating miRNAs in the hemostatic system comes from the important roles miRNAs may play in the development of bleeding disorders and thrombosis. Blood miRNA levels are associated with many hemostatic diseases, suggesting not only an etiologic role, but their potential use as prognostic or diagnostic tools (J. Wang, Chen, & Sen, 2016). These include hemophilia A (Sarachana, et al., 2015), aberrant coagulation in sepsis (H. J. Wang, et al., 2014), venous thrombosis (Rodriguez-Rius, Lopez, Martinez-Perez, Souto, & Soria, 2020; X. Wang, et al., 2016; X. Wang, et al., 2019; Xiang, et al., 2019), venous thrombo-embolism (Hembrom, et al., 2020; Jiang, et al., 2017), arterial thrombosis (J. Lin, et al., 2016), acute pulmonary embolism (Guo, et al., 2014; Kessler, et al., 2016; Liu, Kang, & Liu, 2018; Q. Wang, et al., 2018; Xiao, et al., 2011; X. Zhou, et al., 2016), trauma-induced coagulopathy (L. J. Chen, Yang, Cheng, Xue, & Chen, 2017), coronary artery disease (Fichtlscherer, et al., 2010; Fujii, Sugiura, Dohi, & Ohte, 2016; X. Sun, Zhang, et al., 2012), atherosclerosis (Feinberg & Moore, 2016; Hosin, Prasad, Viiri, Davies, & Shalhoub, 2014; Menghini, Stohr, & Federici, 2014), stenosis (Dolz, et al., 2017; Jansen, et al., 2017), acute heart failure (Ovchinnikova, et al., 2016),

congestive heart failure (Fukushima, Nakanishi, Nonogi, Goto, & Iwai, 2011; Tijsen, et al., 2010), ischemic stroke (Sorensen, Nygaard, & Christensen, 2016; Y. Wang, Ma, Kan, & Zhang, 2017) and systemic lupus erythematosus (SLE) (J. Q. Chen, et al., 2017; Kim, Jung, Jeon, Kim, & Suh, 2016; Perez-Sanchez, et al., 2016).

Cellular alterations in miRNAs are also associated with disease. In SLE and antiphospholipid syndrome patient monocytes miRNAs that target TF are down-regulated (Teruel, et al., 2011), while in patient neutrophils miRNAs linked to thrombosis and early atherosclerosis are expressed at lower levels (Perez-Sanchez, et al., 2016). Dysregulation of miRNA results in dysfunctional endothelial progenitor cells potentially trigger deep vein thrombosis (DVT) (Du, et al., 2019; Kong, et al., 2016; W. D. Li & Li, 2016; W. Wang, et al., 2019). On the other hand, polymorphisms affecting miRNA binding of hemostatic genes are associated with disease. Deletion of the miR-759 binding site of FGA is associated with the susceptibility to chronic thromboembolic pulmonary hypertension (Z. Chen, et al., 2010). SNPs in the 3′UTR of the F2, F8 and F11 genes are associated with increased plasma activity of the gene-products (Rosset, Vieira, Salzano, & Bandinelli, 2016; Sabater-Lleal, et al., 2012; Sennblad, et al., 2017; Voetsch & Loscalzo, 2004; Vossen, et al., 2017).

The importance of miRNAs in hemostasis is further highlighted by their role in platelet biology (De Los Reyes-Garcia, et al., 2019). Here miRNAs modulate the expression of target mRNAs important for hemostatic and thrombotic function (Dahiya, et al., 2015; Edelstein, et al., 2013; Elgheznawy, et al., 2015; Rowley, et al., 2016; Sunderland, et al., 2017). For example, miRNA levels are altered in platelets from patients with essential thrombocythemia and this is associated with elevated platelet counts and an increased risk of thromboembolic events (Tran, et al., 2020). Additionally in patient atherosclerotic plaques altered miRNA expression is observed (Raitoharju, et al., 2011).

Finally, miRNA treatment has been demonstrated to result in therapeutic response in thrombosis and hemostasis. In murine models of venous thrombosis, over-expression of miRNAs contributes to thrombus resolution (W. Wang, et al., 2019), reduces thrombogenesis (Sahu, et al., 2017), enhances endothelial progenitor cell migration and tubulogenic activity (Meng, et al., 2015) and significantly enhanced angiogenesis and thrombosis recanalization (L. L. Sun, et al., 2019). Antagomir inhibition has been shown to block miR-19b-3p-mediated silencing of SERPINC1 (antithrombin), resulting in an up-regulation of expression and increase in antithrombin activity, illustrating the in-principal druggability of the hemostatic system in a miRNA directed manner (Nourse, et al., 2018). Altogether multiple lines of evidence suggest a critical functional role of miRNA in the hemostatic system.

6.4 Factor XI is under significant miRNA control

Dysregulated miRNA-mediated control of factor XI expression can increase thrombotic risk. The F11 3'UTR SNP rs4253430 is associated with plasma factor XI levels and clotting time in idiopathic thrombophilia patients (Sabater-Lleal, et al., 2012; Sennblad, et al., 2017), and with increased factor XI activity and risk of VTE (Vossen, et al., 2017). This SNP disrupts a binding site for miR-544a preventing the miRNA from silencing factor XI expression and resulting in increased plasma factor XI activity (Vossen, et al., 2017).

The 3'UTR of the F11 mRNA is functionally targeted by miR-181a-5p (Salloum-Asfar, et al., 2014; Sennblad, et al., 2017). In healthy human liver samples a wider range of expression of F11 mRNA as compared with plasma levels was observed and the tissue levels were found to be inversely and significantly related to miR-181a-5p levels (Salloum-Asfar, et al., 2014). This suggests post-translational regulation may act to control plasma factor XI activity (Salloum-Asfar, et al., 2014). Another miR-181 family member, miR-181b-5p, also targets the 3'UTR of F11

mRNA (Nourse, et al., 2018) and members of this family are involved in several aspects of hemostasis including vascular inflammation and thrombogenicity (J. Lin, et al., 2016; X. Sun, Icli, et al., 2012; Witkowski, et al., 2020) and platelet activation (Dahiya & Atreya, 2020).

Other miRNAs demonstrated to functionally target the F11 3'UTR include miR-145, miR-103a-3p, miR-1255a, miR-148b-3p, miR-151a-3p, miR-15b-5p, miR-24-3p, miR-30a-3p, miR-30d-3p and miR-96-5p (Nourse, et al., 2018), with many of them exhibiting associations with vascular disease (L. J. Chen, et al., 2017; Cordes, et al., 2009; Elia, et al., 2009; Hergenreider, et al., 2012; Starikova, et al., 2015; J. Wang, et al., 2020; X. Wang, et al., 2019).

Finally, and most surprisingly in a recent endeavor to identify and characterize the hemostatic miRNA targetome (see further below) the largest quantity of functional miRNAs appear to target factor XI (Table 3).

The numerous roles played in hemostasis and thrombosis by miRNAs suggest the targeting of factor XI may be part of a network regulating coagulation, potentially offering new avenues for therapeutic targeting.

7. Factor XI miRNA as a novel anticoagulant therapy targeting avenue

In the search for novel and rationale therapeutic targets we recently performed a large-scale determination of functional miRNAs targeting the hemostatic system (Nourse, et al., 2018). Based on this study, and in conjunction with data presented above, we find factor XI to be the coagulation factor targeted by the largest number of miRNAs, while factor XII does not appear to be regulated by miRNAs (Table 3). Biologically, this finding is remarkable. It suggests that factor XI expression is under tight control via 3'UTR mediated regulation to ensure modest levels of factor XI protein while factor XII is not. This is in line with tighter regulation reflected by the leptokurtic distribution (i.e. narrower range) and lower percent coefficient variation (%CV) of

factor XI plasma levels as compared to factor XII in our cohort (Figure 2A), which is consistent with earlier observations (Q. Chen, et al., 2015). The biological importance is corroborated by the functional consequences in patients where elevated factor XI levels predispose to thrombosis, while patients with FXI deficiency are protected from VTE and ischemic stroke (see above). Further support for the regulatory importance of the F11 gene 3'UTR comes from the observation that while the 3'UTR of F12 is relatively short (~150 nucleotides), that of F11 spans over ~1000 nucleotides, and as described previously F11 3'UTR SNPs are associated with plasma FXI activity and risk of venous thrombosis. Additionally, the F11 3'UTR is under control of alternative polyadenylation, which is consistent with increased regulation of gene expression and is associated with several diseases (Nourse, Spada, & Danckwardt, 2020). In addition to the high number of miRNAs, using RNA affinity pull-downs coupled to mass spectrometry, we identify here that the F11 3'UTR also binds numerous RNA binding proteins (RBPs) in close proximity to, and sometimes even in the direct target region of miRNAs (Figure 3B-C).

With regards to the important question as to which of the two components of the upstream intrinsic pathway (factor XI or factor XII) is likely to be a more reliable therapeutic target, our data suggests that the specific miRNA mediated control of factor XI may be a hitherto unrecognized rationale for the therapeutic targeting of factor XI. Additionally it may provide a novel avenue for this targeting.

It is important to realize that by mimicking the endogenous function of miRNAs to limit excessive expression, therapeutic miRNA delivery may possibly reflect a more physiological state in limiting factor XI levels to treat and prevent VTE while retaining sufficient hemostasis for the prevention of bleeding. Although miRNA targeting to silence factor XI could potentially have off-target effects, the functional synergy of several targeting miRNAs (at individually sub-functional levels) in a therapeutic cocktail may allow for an increase in effect size and a reduction in side effects (Nourse, et al., 2018). Finally and most importantly, as highlighted above (and see Table

1) miRNA-mediated targeting may also preserve cell intrinsic regulatory mechanisms, such as modulated ‘occlusion’ of miRNA binding sites by RNA binding proteins (RBPs) (Danckwardt, et al., 2008; Jens & Rajewsky, 2015; Y. C. Lu, et al., 2014), regulation through other noncoding RNAs or interaction with competing endogenous (ce)RNAs (i.e. miRNA sponges, circRNA) as well as other regulatory mechanisms (Tay, et al., 2014), ensuring the normal physiological fine tuning of the availability of the factor is maintained (Danckwardt, et al., 2011) (Figure 3, Table 1). Thus even in the presence of the miRNA therapeutic, RBP-mediated regulation (and other posttranscriptional gene regulatory mechanisms) may be in place to evade (therapeutic) miRNA-mediated silencing, for example in order to stockpile blood clotting factors in an acute event of blood loss (Danckwardt, et al., 2011).

Finally, although we have previously demonstrated the in-principle druggability of the hemostatic system in a miRNA-directed manner using intravenously administered LNA oligonucleotides (Nourse, et al., 2018), future therapies would ideally require a more convenient oral delivery route. This may be accomplished through novel delivery vehicles that allow oral miRNA uptake, for example milk exosomes (Manca, et al., 2018).

We thus believe that despite the impressive ‘juggernaut’ of anticoagulants, there are untapped therapeutic options that can help meet unmet medical needs. miRNA-based therapeutics, currently emerging as attractive therapies in many other disciplines (F. Wang, Zuroske, & Watts, 2020), may represent an avenue for correction of deregulated hemostasis and associated processes in the future. Given the plethora of miRNA-based therapeutic possibilities, such as miRNA mimicking, silencing, target specific miRNA target site blockers, knowledge of the miRNA targetome in the hemostatic system is potentially a major trove for future targeted therapeutics, not only for the development of safe anticoagulants but also for developing treatments for coagulopathies. In aid of these endeavors the first comprehensive hemostatic miRNA targetome is provided as a repository accompanying our recent paper (Nourse, et al., 2018).

8. Conclusion

RNA-based therapeutics have attracted considerable attention in the past decade because of their potential to treat numerous diseases, including cardiovascular disorders (D. Lu & Thum, 2019). Compared to conventional small therapeutic molecules, ASOs, siRNAs and miRNAs offer the advantage that they are highly effective and can act on “non-druggable” targets (e.g. proteins that lack an enzymatic function or whose conformation is not accessible to traditional drug molecules) as they can be designed to affect virtually any gene of interest (Daka & Peer, 2012). Innovative next-generation sequencing technologies provide platforms to assess the role of non-coding RNAs in the control of the hemostatic system and their utility as potential treatment targets (Nourse, et al., 2018).

Aligning with the more recent discovery of novel therapeutic targets in the hemostatic system (Büller, et al., 2015) factor XI appears to represent a potentially interesting target for miRNA-based approaches. Future studies are urgently needed to test this therapeutic principle in a clinical setting. This is particularly applicable in hemostaseology where monitoring of therapeutic effects remains a daily routine and thus assessment of the efficacy and safety of such therapeutic components could be simply implemented ushering in a novel therapeutic era with broad applicability.

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Contribution

All authors contributed to the research and edited the manuscript; J.N. performed the data analysis; J.N. and S.D. wrote the manuscript.

Disclosure of Conflicts of Interest

The authors declare no competing financial interests.

References

Abraham, N. S., Singh, S., Alexander, G. C., Heien, H., Haas, L. R., Crown, W., & Shah, N. D. (2015). Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. *Bmj, 350*, h1857.

Agnelli, G., Buller, H. R., Cohen, A., Curto, M., Gallus, A. S., Johnson, M., Masiukiewicz, U., Pak, R., Thompson, J., Raskob, G. E., & Weitz, J. I. (2013). Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med, 369*, 799-808.

Agnelli, G., Buller, H. R., Cohen, A., Gallus, A. S., Lee, T. C., Pak, R., Raskob, G. E., Weitz, J. I., & Yamabe, T. (2015). Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost, 13*, 2187-2191.

Al-Horani, R. A. (2020). Factor XI(a) inhibitors for thrombosis: an updated patent review (2016-present). *Expert Opin Ther Pat, 30*, 39-55.

Al-Horani, R. A., & Afosah, D. K. (2018). Recent advances in the discovery and development of factor XI/XIa inhibitors. *Med Res Rev, 38*, 1974-2023.

Alexander, K. P., Brouwer, M. A., Mulder, H., Vinereanu, D., Lopes, R. D., Proietti, M., Al-Khatib, S. M., Hijazi, Z., Halvorsen, S., Hylek, E. M., Verheugt, F. W. A., Alexander, J. H., Wallentin, L., & Granger, C. B. (2019). Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: Insights from the ARISTOTLE trial. *Am Heart J, 208*, 123-131.

Ali, H. O., Arroyo, A. B., Gonzalez-Conejero, R., Stavik, B., Iversen, N., Sandset, P. M., Martinez, C., & Skretting, G. (2016). The role of microRNA-27a/b and microRNA-494 in estrogen-mediated downregulation of tissue factor pathway inhibitor alpha. *J Thromb Haemost, 14*, 1226-1237.

Andersson, N. W., Svanstrom, H., Lund, M., Pasternak, B., & Melbye, M. (2018). Comparative effectiveness and safety of apixaban, dabigatran, and rivaroxaban in patients with non-valvular atrial fibrillation. *Int J Cardiol, 268*, 113-119.

Arroyo, A. B., de Los Reyes-Garcia, A. M., Teruel-Montoya, R., Vicente, V., Gonzalez-Conejero, R., & Martinez, C. (2018). microRNAs in the haemostatic system: More than witnesses of thromboembolic diseases? *Thromb Res, 166*, 1-9.

Arroyo, A. B., Salloum-Asfar, S., Perez-Sanchez, C., Teruel-Montoya, R., Navarro, S., Garcia-Barbera, N., Luengo-Gil, G., Roldan, V., Hansen, J. B., Lopez-Pedrera, C., Vicente, V., Gonzalez-Conejero, R., & Martinez, C. (2017). Regulation of TFPIalpha expression by miR-27a/b-3p in human endothelial cells under normal conditions and in response to androgens. *Sci Rep, 7*, 43500.

Bajan, S., & Hutvagner, G. (2020). RNA-Based Therapeutics: From Antisense Oligonucleotides to miRNAs. *Cells, 9*.

Barkun, A. N., Almadi, M., Kuipers, E. J., Laine, L., Sung, J., Tse, F., Leontiadis, G. I., Abraham, N. S., Calvet, X., Chan, F. K. L., Douketis, J., Enns, R., Gralnek, I. M., Jairath, V., Jensen, D., Lau, J., Lip, G. Y. H., Loffroy, R., Maluf-Filho, F., Meltzer, A. C., Reddy, N., Saltzman, J. R., Marshall, J. K., & Bardou, M. (2019). Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group. *Ann Intern Med, 171*, 805-822.

Bartel, D. P. (2009). MicroRNAs: target recognition and regulatory functions. *Cell, 136*, 215-233.

Bauersachs, R., Berkowitz, S. D., Brenner, B., Buller, H. R., Decousus, H., Gallus, A. S., Lensing, A. W., Misselwitz, F., Prins, M. H., Raskob, G. E., Segers, A., Verhamme, P., Wells, P., Agnelli, G., Bounameaux, H., Cohen, A., Davidson, B. L., Piovella, F., & Schellong, S. (2010). Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med, 363*, 2499-2510.

Beierlein, J. M., McNamee, L. M., & Ledley, F. D. (2017). As Technologies for Nucleotide Therapeutics Mature, Products Emerge. *Mol Ther Nucleic Acids, 9*, 379-386.

Beyer-Westendorf, J., Camm, A. J., Fox, K. A. A., Le Heuzey, J. Y., Haas, S., Turpie, A. G. G., Virdone, S., & Kakkar, A. K. (2019). International longitudinal registry of patients with atrial fibrillation and treated with rivaroxaban: RIVaroxaban Evaluation in Real life setting (RIVER). *Thromb J, 17*, 7.

Bonneau, E., Neveu, B., Kostantin, E., Tsongalis, G. J., & De Guire, V. (2019). How close are miRNAs from clinical practice? A perspective on the diagnostic and therapeutic market. *Ejifcc, 30*, 114-127.

Borissoff, J. I., Spronk, H. M., & ten Cate, H. (2011). The hemostatic system as a modulator of atherosclerosis. *N Engl J Med, 364*, 1746-1760.

Brock, M., Trenkmann, M., Gay, R. E., Gay, S., Speich, R., & Huber, L. C. (2011). MicroRNA-18a enhances the interleukin-6-mediated production of the acute-phase proteins fibrinogen and haptoglobin in human hepatocytes. *J Biol Chem, 286*, 40142-40150.

Büller, H. R., Bethune, C., Bhanot, S., Gailani, D., Monia, B. P., Raskob, G. E., Segers, A., Verhamme, P., & Weitz, J. I. (2015). Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med, 372*, 232-240.

Buller, H. R., Decousus, H., Grosso, M. A., Mercuri, M., Middeldorp, S., Prins, M. H., Raskob, G. E., Schellong, S. M., Schwocho, L., Segers, A., Shi, M., Verhamme, P., & Wells, P. (2013). Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med, 369*, 1406-1415.

Burnett, A. E., Mahan, C. E., Vazquez, S. R., Oertel, L. B., Garcia, D. A., & Ansell, J. (2016). Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis, 41*, 206-232.

Cai, T. Q., Wu, W., Shin, M. K., Xu, Y., Jochnowitz, N., Zhou, Y., Hoos, L., Bentley, R., Strapps, W., Thankappan, A., Metzger, J. M., Ogletree, M. L., Tadin-Strapps, M., Seiffert, D. A., & Chen, Z. (2015). Factor XII full and partial null in rat confers robust antithrombotic efficacy with no bleeding. *Blood Coagul Fibrinolysis, 26*, 893-902.

Camm, A. J., Amarenco, P., Haas, S., Hess, S., Kirchhof, P., Lambelet, M., Bach, M., & Turpie, A. G. G. (2019). Real-world vs. randomized trial outcomes in similar populations of rivaroxaban-treated patients with non-valvular atrial fibrillation in ROCKET AF and XANTUS. *Europace, 21*, 421-427.

Cangemi, D. J., Krill, T., Weideman, R., Cipher, D. J., Spechler, S. J., & Feagins, L. A. (2017). A Comparison of the Rate of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin. *Am J Gastroenterol, 112*, 734-739.

Cha, M. J., Choi, E. K., Han, K. D., Lee, S. R., Lim, W. H., Oh, S., & Lip, G. Y. H. (2017). Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asian Patients With Atrial Fibrillation. *Stroke, 48*, 3040-3048.

Chan, J. H., Lim, S., & Wong, W. S. (2006). Antisense oligonucleotides: from design to therapeutic application. *Clin Exp Pharmacol Physiol, 33*, 533-540.

Chan, Y. H., Lee, H. F., See, L. C., Tu, H. T., Chao, T. F., Yeh, Y. H., Wu, L. S., Kuo, C. T., Chang, S. H., & Lip, G. Y. H. (2019). Effectiveness and Safety of Four Direct Oral Anticoagulants in Asian Patients With Nonvalvular Atrial Fibrillation. *Chest, 156*, 529-543.

Chen, J. Q., Papp, G., Poliska, S., Szabo, K., Tarr, T., Balint, B. L., Szodoray, P., & Zeher, M. (2017). MicroRNA expression profiles identify disease-specific alterations in systemic lupus erythematosus and primary Sjogren's syndrome. *PLoS One, 12*, e0174585.

Chen, K., & Rajewsky, N. (2007). The evolution of gene regulation by transcription factors and microRNAs. *Nat Rev Genet, 8*, 93-103.

Chen, L. J., Yang, L., Cheng, X., Xue, Y. K., & Chen, L. B. (2017). Overexpression of miR-24 Is Involved in the Formation of Hypocoagulation State after Severe Trauma by Inhibiting the Synthesis of Coagulation Factor X. *Dis Markers, 2017*, 3649693.

Chen, Q., Shou, W., Wu, W., Guo, Y., Zhang, Y., Huang, C., & Cui, W. (2015). Biological and analytical variations of 16 parameters related to coagulation screening tests and the activity of coagulation factors. *Semin Thromb Hemost, 41*, 336-341.

Chen, Y., Zhao, H., Tan, Z., Zhang, C., & Fu, X. (2015). Bottleneck limitations for microRNA-based therapeutics from bench to the bedside. *Pharmazie, 70*, 147-154.

Chen, Z., Nakajima, T., Tanabe, N., Hinohara, K., Sakao, S., Kasahara, Y., Tatsumi, K., Inoue, Y., & Kimura, A. (2010). Susceptibility to chronic thromboembolic pulmonary hypertension may be conferred by miR-759 via its targeted interaction with polymorphic fibrinogen alpha gene. *Hum Genet, 128*, 443-452.

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P. A., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B. S., Darius, H., Diener, H. C., Joyner, C. D., & Wallentin, L. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med, 361*, 1139-1151.

Connors, J. M. (2017). Thrombophilia Testing and Venous Thrombosis. *N Engl J Med, 377*, 1177-1187.

Cordes, K. R., Sheehy, N. T., White, M. P., Berry, E. C., Morton, S. U., Muth, A. N., Lee, T. H., Miano, J. M., Ivey, K. N., & Srivastava, D. (2009). miR-145 and miR-143 regulate smooth muscle cell fate and plasticity. *Nature, 460*, 705-710.

Cosmi, B. (2016). An update on the pharmaceutical management of thrombosis. *Expert Opin Pharmacother, 17*, 2149-2164.

Crooke, S. T. (2000). Progress in antisense technology: the end of the beginning. *Methods Enzymol, 313*, 3-45.

Crosby, J., Gao, D., Zhao, C., Bhattacharjee, G., May, C., Zhang, H., Robert MacLeod, R., & Monia, B. P. (2009). Systematic Evaluation of Coagulation Factors as Targets for Anti-Thrombotic Therapy Using Antisense Technology. *Blood, 114*, 4181.

Crosby, J. R., Marzec, U., Revenko, A. S., Zhao, C., Gao, D., Matafonov, A., Gailani, D., MacLeod, A. R., Tucker, E. I., Gruber, A., Hanson, S. R., & Monia, B. P. (2013). Antithrombotic effect of antisense factor XI oligonucleotide treatment in primates. *Arterioscler Thromb Vasc Biol, 33*, 1670-1678.

Cuellar, T. L., Barnes, D., Nelson, C., Tanguay, J., Yu, S. F., Wen, X., Scales, S. J., Gesch, J., Davis, D., van Brabant Smith, A., Leake, D., Vandlen, R., & Siebel, C. W. (2015). Systematic evaluation of antibody-mediated siRNA delivery using an industrial platform of THIOMAB-siRNA conjugates. *Nucleic Acids Res, 43*, 1189-1203.

Dahiya, N., & Atreya, C. D. (2020). MiR-181a Reduces Platelet Activation via the Inhibition of Endogenous RAP1B. *Microrna, 9*, 240-246.

Dahiya, N., Sarachana, T., Vu, L., Becker, K. G., Wood, W. H., 3rd, Zhang, Y., & Atreya, C. D. (2015). Platelet MicroRNAs: An Overview. *Transfus Med Rev, 29*, 215-219.

Daka, A., & Peer, D. (2012). RNAi-based nanomedicines for targeted personalized therapy. *Adv Drug Deliv Rev, 64*, 1508-1521.

Danckwardt, S., Gantzert, A. S., Macher-Goeppinger, S., Probst, H. C., Gentzel, M., Wilm, M., Grone, H. J., Schirmacher, P., Hentze, M. W., & Kulozik, A. E. (2011). p38 MAPK controls prothrombin expression by regulated RNA 3' end processing. *Mol Cell, 41*, 298-310.

Danckwardt, S., Hentze, M. W., & Kulozik, A. E. (2008). 3' end mRNA processing: molecular mechanisms and implications for health and disease. *Embo j, 27*, 482-498.

de Freitas, R. C. C., Bortolin, R. H., Lopes, M. B., Tamborlin, L., Meneguello, L., Silbiger, V. N., Hirata, R. D. C., Hirata, M. H., Luchessi, A. D., & Luchessi, A. D. (2017). Modulation of miR-26a-5p and miR-15b-5p Exosomal Expression Associated with Clopidogrel-Induced Hepatotoxicity in HepG2 Cells. *Front Pharmacol, 8*, 906.

De Los Reyes-Garcia, A. M., Arroyo, A. B., Teruel-Montoya, R., Vicente, V., Lozano, M. L., Gonzalez-Conejero, R., & Martinez, C. (2019). MicroRNAs as potential regulators of platelet function and bleeding diatheses. *Platelets, 30*, 803-808.

DeLoughery, E. P., Olson, S. R., Puy, C., McCarty, O. J. T., & Shatzel, J. J. (2019). The Safety and Efficacy of Novel Agents Targeting Factors XI and XII in Early Phase Human Trials. *Semin Thromb Hemost, 45*, 502-508.

DeVos, S. L., & Miller, T. M. (2013). Antisense oligonucleotides: treating neurodegeneration at the level of RNA. *Neurotherapeutics, 10*, 486-497.

Doggen, C. J., Rosendaal, F. R., & Meijers, J. C. (2006). Levels of intrinsic coagulation factors and the risk of myocardial infarction among men: Opposite and synergistic effects of factors XI and XII. *Blood, 108*, 4045-4051.

Dolz, S., Gorriz, D., Tembl, J. I., Sanchez, D., Fortea, G., Parkhutik, V., & Lago, A. (2017). Circulating MicroRNAs as Novel Biomarkers of Stenosis Progression in Asymptomatic Carotid Stenosis. *Stroke, 48*, 10-16.

Dong, Y. M., Liu, X. X., Wei, G. Q., Da, Y. N., Cha, L., & Ma, C. S. (2015). Prediction of long-term outcome after acute myocardial infarction using circulating miR-145. *Scand J Clin Lab Invest, 75*, 85-91.

Drosopoulos, K., & Linardopoulos, S. (2013). Integration of RNAi and small molecule screens to identify targets for drug development. *Methods Mol Biol, 986*, 97-104.

Du, X., Hong, L., Sun, L., Sang, H., Qian, A., Li, W., Zhuang, H., Liang, H., Song, D., Li, C., Wang, W., & Li, X. (2019). miR-21 induces endothelial progenitor cells proliferation and angiogenesis via targeting FASLG and is a potential prognostic marker in deep venous thrombosis. *J Transl Med, 17*, 270.

Duga, S., & Salomon, O. (2013). Congenital factor XI deficiency: an update. *Semin Thromb Hemost, 39*, 621-631.

Edelstein, L. C., McKenzie, S. E., Shaw, C., Holinstat, M. A., Kunapuli, S. P., & Bray, P. F. (2013). MicroRNAs in platelet production and activation. *J Thromb Haemost, 11 Suppl 1*, 340-350.

Edwardson, M. A., Zhong, X., Fiandaca, M. S., Federoff, H. J., Cheema, A. K., & Dromerick, A. W. (2018). Plasma microRNA markers of upper limb recovery following human stroke. *Sci Rep, 8*, 12558.

Egli, M., & Manoharan, M. (2019). Re-Engineering RNA Molecules into Therapeutic Agents. *Acc Chem Res, 52*, 1036-1047.

Eikelboom, J. W., Connolly, S. J., Bosch, J., Dagenais, G. R., Hart, R. G., Shestakovska, O., Diaz, R., Alings, M., Lonn, E. M., Anand, S. S., Widimsky, P., Hori, M., Avezum, A., Piegas, L. S., Branch, K. R. H., Probstfield, J., Bhatt, D. L., Zhu, J., Liang, Y., Maggioni, A. P., Lopez-Jaramillo, P., O'Donnell, M., Kakkar, A. K., Fox, K. A. A., Parkhomenko, A. N., Ertl, G., Störk, S., Keltai, M., Ryden, L., Pogosova, N., Dans, A. L., Lanas, F., Commerford, P. J., Torp-Pedersen, C., Guzik, T. J., Verhamme, P. B., Vinereanu, D., Kim, J. H., Tonkin, A. M., Lewis, B. S., Felix, C., Yusoff, K., Steg, P. G., Metsarinne, K. P., Cook Bruns, N., Misselwitz, F., Chen, E., Leong, D., & Yusuf, S. (2017). Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med, 377*, 1319-1330.

Eikelboom, J. W., Connolly, S. J., Brueckmann, M., Granger, C. B., Kappetein, A. P., Mack, M. J., Blatchford, J., Devenny, K., Friedman, J., Guiver, K., Harper, R., Khder, Y., Lobmeyer, M. T., Maas, H., Voigt, J. U., Simoons, M. L., & Van de Werf, F. (2013). Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med, 369*, 1206-1214.

Elgheznawy, A., Shi, L., Hu, J., Wittig, I., Laban, H., Pircher, J., Mann, A., Provost, P., Randriamboavonjy, V., & Fleming, I. (2015). Dicer cleavage by calpain determines platelet microRNA levels and function in diabetes. *Circ Res, 117*, 157-165.

Elia, L., Quintavalle, M., Zhang, J., Contu, R., Cossu, L., Latronico, M. V., Peterson, K. L., Indolfi, C., Catalucci, D., Chen, J., Courtneidge, S. A., & Condorelli, G. (2009). The knockout of miR-143 and -145 alters smooth muscle cell maintenance and vascular homeostasis in mice: correlates with human disease. *Cell Death Differ, 16*, 1590-1598.

Elmen, J., Lindow, M., Schutz, S., Lawrence, M., Petri, A., Obad, S., Lindholm, M., Hedtjarn, M., Hansen, H. F., Berger, U., Gullans, S., Kearney, P., Sarnow, P., Straarup, E. M., & Kauppinen, S. (2008). LNA-mediated microRNA silencing in non-human primates. *Nature, 452*, 896-899.

Fabian, M. R., & Sonenberg, N. (2012). The mechanics of miRNA-mediated gene silencing: a look under the hood of miRISC. *Nat Struct Mol Biol, 19*, 586-593.

Fabian, M. R., Sonenberg, N., & Filipowicz, W. (2010). Regulation of mRNA translation and stability by microRNAs. *Annu Rev Biochem, 79*, 351-379.

Faccini, J., Ruidavets, J. B., Cordelier, P., Martins, F., Maoret, J. J., Bongard, V., Ferrieres, J., Roncalli, J., Elbaz, M., & Vindis, C. (2017). Circulating miR-155, miR-145 and let-7c as diagnostic biomarkers of the coronary artery disease. *Sci Rep, 7*, 42916.

Feinberg, M. W., & Moore, K. J. (2016). MicroRNA Regulation of Atherosclerosis. *Circ Res, 118*, 703-720.

Fichtlscherer, S., De Rosa, S., Fox, H., Schwietz, T., Fischer, A., Liebetrau, C., Weber, M., Hamm, C. W., Roxe, T., Muller-Ardogan, M., Bonauer, A., Zeiher, A. M., & Dimmeler, S. (2010). Circulating microRNAs in patients with coronary artery disease. *Circ Res, 107*, 677-684.

Folsom, A. R., Tang, W., Roetker, N. S., Heckbert, S. R., Cushman, M., & Pankow, J. S. (2015). Prospective study of circulating factor XI and incident venous thromboembolism: The Longitudinal Investigation of Thromboembolism Etiology (LITE). *Am J Hematol, 90*, 1047-1051.

Fort, A., Borel, C., Migliavacca, E., Antonarakis, S. E., Fish, R. J., & Neerman-Arbez, M. (2010). Regulation of fibrinogen production by microRNAs. *Blood, 116*, 2608-2615.

Forterre, A., Komuro, H., Aminova, S., & Harada, M. (2020). A Comprehensive Review of Cancer MicroRNA Therapeutic Delivery Strategies. *Cancers (Basel), 12*.

Fralick, M., Colacci, M., Schneeweiss, S., Huybrechts, K. F., Lin, K. J., & Gagne, J. J. (2020). Effectiveness and Safety of Apixaban Compared With Rivaroxaban for Patients With Atrial Fibrillation in Routine Practice: A Cohort Study. *Ann Intern Med, 172*, 463-473.

Friedman, R. C., Farh, K. K., Burge, C. B., & Bartel, D. P. (2009). Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res, 19*, 92-105.

Fujii, S., Sugiura, T., Dohi, Y., & Ohte, N. (2016). MicroRNA in atherothromobosis: is it useful as a disease marker? *Thromb J, 14*, 21.

Fukushima, Y., Nakanishi, M., Nonogi, H., Goto, Y., & Iwai, N. (2011). Assessment of plasma miRNAs in congestive heart failure. *Circ J, 75*, 336-340.

Gailani, D., & Broze, G. J., Jr. (1991). Factor XI activation in a revised model of blood coagulation. *Science, 253*, 909-912.

Gale, A. J. (2011). Continuing education course #2: current understanding of hemostasis. *Toxicol Pathol, 39*, 273-280.

Gallant-Behm, C. L., Piper, J., Lynch, J. M., Seto, A. G., Hong, S. J., Mustoe, T. A., Maari, C., Pestano, L. A., Dalby, C. M., Jackson, A. L., Rubin, P., & Marshall, W. S. (2019). A MicroRNA-29 Mimic (Remlarsen) Represses Extracellular Matrix Expression and Fibroplasia in the Skin. *J Invest Dermatol, 139*, 1073-1081.

Gao, H., Guddeti, R. R., Matsuzawa, Y., Liu, L. P., Su, L. X., Guo, D., Nie, S. P., Du, J., & Zhang, M. (2015). Plasma Levels of microRNA-145 Are Associated with Severity of Coronary Artery Disease. *PLoS One, 10*, e0123477.

Geary, R. S., Norris, D., Yu, R., & Bennett, C. F. (2015). Pharmacokinetics, biodistribution and cell uptake of antisense oligonucleotides. *Adv Drug Deliv Rev, 87*, 46-51.

Georgi, B., Mielke, J., Chaffin, M., Khera, A. V., Gelis, L., Mundl, H., van Giezen, J. J. J., Ellinor, P., Kathiresan, S., Ziegelbauer, K., & Freitag, D. F. (2019). Leveraging Human Genetics to Estimate Clinical Risk Reductions Achievable by Inhibiting Factor XI. *Stroke, 50*, 3004-3012.

Giugliano, R. P., Ruff, C. T., Braunwald, E., Murphy, S. A., Wiviott, S. D., Halperin, J. L., Waldo, A. L., Ezekowitz, M. D., Weitz, J. I., Špinar, J., Ruzyllo, W., Ruda, M., Koretsune, Y., Betcher, J., Shi, M., Grip, L. T., Patel, S. P., Patel, I., Hanyok, J. J., Mercuri, M., & Antman, E. M. (2013). Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med, 369*, 2093-2104.

Gong, I. Y., & Kim, R. B. (2013). Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. *Can J Cardiol, 29*, S24-33.

Granger, C. B., Alexander, J. H., McMurray, J. J., Lopes, R. D., Hylek, E. M., Hanna, M., Al-Khalidi, H. R., Ansell, J., Atar, D., Avezum, A., Bahit, M. C., Diaz, R., Easton, J. D., Ezekowitz, J. A., Flaker, G., Garcia, D., Geraldes, M., Gersh, B. J., Golitsyn, S., Goto, S., Hermosillo, A. G., Hohnloser, S. H., Horowitz, J., Mohan, P., Jansky, P., Lewis, B. S., Lopez-Sendon, J. L., Pais, P., Parkhomenko, A., Verheugt, F. W., Zhu, J., & Wallentin, L. (2011). Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med, 365*, 981-992.

Grimson, A., Farh, K. K., Johnston, W. K., Garrett-Engele, P., Lim, L. P., & Bartel, D. P. (2007). MicroRNA targeting specificity in mammals: determinants beyond seed pairing. *Mol Cell, 27*, 91-105.

Grover, S. P., & Mackman, N. (2019). Intrinsic Pathway of Coagulation and Thrombosis. *Arterioscler Thromb Vasc Biol, 39*, 331-338.

Guo, L., Yang, Y., Liu, J., Wang, L., Li, J., Wang, Y., Liu, Y., Gu, S., Gan, H., Cai, J., Yuan, J. X., Wang, J., & Wang, C. (2014). Differentially expressed plasma microRNAs and the potential regulatory function of Let-7b in chronic thromboembolic pulmonary hypertension. *PLoS One, 9*, e101055.

Haley, B., & Zamore, P. D. (2004). Kinetic analysis of the RNAi enzyme complex. *Nat Struct Mol Biol, 11*, 599-606.

Hartmann, P., Zhou, Z., Natarelli, L., Wei, Y., Nazari-Jahantigh, M., Zhu, M., Grommes, J., Steffens, S., Weber, C., & Schober, A. (2016). Endothelial Dicer promotes atherosclerosis and vascular inflammation by miRNA-103-mediated suppression of KLF4. *Nat Commun, 7*, 10521.

He, R., Chen, D., & He, S. (2012). Factor XI: hemostasis, thrombosis, and antithrombosis. *Thromb Res, 129*, 541-550.

Heestermans, M., & van Vlijmen, B. J. M. (2017). Oligonucleotides targeting coagulation factor mRNAs: use in thrombosis and hemophilia research and therapy. *Thromb J, 15*, 7.

Hembrom, A. A., Srivastava, S., Garg, I., & Kumar, B. (2020). MicroRNAs in venous thrombo-embolism. *Clin Chim Acta, 504*, 66-72.

Henry, S. P., Narayanan, P., Shen, L., Bhanot, S., Younis, H. S., & Burel, S. A. (2017). Assessment of the Effects of 2'-Methoxyethyl Antisense Oligonucleotides on Platelet Count in Cynomolgus Nonhuman Primates. *Nucleic Acid Ther, 27*, 197-208.

Hergenreider, E., Heydt, S., Treguer, K., Boettger, T., Horrevoets, A. J., Zeiher, A. M., Scheffer, M. P., Frangakis, A. S., Yin, X., Mayr, M., Braun, T., Urbich, C., Boon, R. A., & Dimmeler, S. (2012). Atheroprotective communication between endothelial cells and smooth muscle cells through miRNAs. *Nat Cell Biol, 14*, 249-256.

Hosin, A. A., Prasad, A., Viiri, L. E., Davies, A. H., & Shalhoub, J. (2014). MicroRNAs in atherosclerosis. *J Vasc Res, 51*, 338-349.

Huntzinger, E., & Izaurralde, E. (2011). Gene silencing by microRNAs: contributions of translational repression and mRNA decay. *Nat Rev Genet, 12*, 99-110.

Inoue, H., Uchiyama, S., Atarashi, H., Okumura, K., Koretsune, Y., Yasaka, M., Yamashita, T., Taniguchi, A., & Fukaya, T. (2019). Effectiveness and safety of long-term dabigatran among patients with non-valvular atrial fibrillation in clinical practice: J-dabigatran surveillance. *J Cardiol, 73*, 507-514.

James, P., Salomon, O., Mikovic, D., & Peyvandi, F. (2014). Rare bleeding disorders - bleeding assessment tools, laboratory aspects and phenotype and therapy of FXI deficiency. *Haemophilia, 20 Suppl 4*, 71-75.

Jankowska, K. I., Chattopadhyay, M., Sauna, Z. E., & Atreya, C. D. (2020). A Foundational Study for Normal F8-Containing Mouse Models for the miRNA Regulation of Hemophilia A: Identification and Analysis of Mouse miRNAs that Downregulate the Murine F8 Gene. *Int J Mol Sci, 21*.

Jankowska, K. I., McGill, J., Pezeshkpoor, B., Oldenburg, J., Atreya, C. D., & Sauna, Z. E. (2020). Clinical manifestation of hemophilia A in the absence of mutations in the F8 gene that encodes FVIII: role of microRNAs. *Transfusion, 60*, 401-413.

Jankowska, K. I., Sauna, Z. E., & Atreya, C. D. (2020). Role of microRNAs in Hemophilia and Thrombosis in Humans. *Int J Mol Sci, 21*.

Jansen, F., Schafer, L., Wang, H., Schmitz, T., Flender, A., Schueler, R., Hammerstingl, C., Nickenig, G., Sinning, J. M., & Werner, N. (2017). Kinetics of Circulating MicroRNAs in Response to Cardiac Stress in Patients With Coronary Artery Disease. *J Am Heart Assoc, 6*.

Janssen, H. L., Reesink, H. W., Lawitz, E. J., Zeuzem, S., Rodriguez-Torres, M., Patel, K., van der Meer, A. J., Patick, A. K., Chen, A., Zhou, Y., Persson, R., King, B. D., Kauppinen, S., Levin, A. A., & Hodges, M. R. (2013). Treatment of HCV infection by targeting microRNA. *N Engl J Med, 368*, 1685-1694.

Jansson, M., Sjalander, S., Sjogren, V., Renlund, H., Norrving, B., & Sjalander, A. (2020). Direct comparisons of effectiveness and safety of treatment with Apixaban, Dabigatran and Rivaroxaban in atrial fibrillation. *Thromb Res, 185*, 135-141.

Jens, M., & Rajewsky, N. (2015). Competition between target sites of regulators shapes post-transcriptional gene regulation. *Nat Rev Genet, 16*, 113-126.

Jia, L., Hao, F., Wang, W., & Qu, Y. (2015). Circulating miR-145 is associated with plasma high-sensitivity C-reactive protein in acute ischemic stroke patients. *Cell Biochem Funct, 33*, 314-319.

Jiang, Z., Ma, J., Wang, Q., Wu, F., Ping, J., & Ming, L. (2017). Circulating microRNA expression and their target genes in deep vein thrombosis: A systematic review and bioinformatics analysis. *Medicine (Baltimore), 96*, e9330.

Jonas, S., & Izaurralde, E. (2015). Towards a molecular understanding of microRNA-mediated gene silencing. *Nat Rev Genet, 16*, 421-433.

Kaluzna, E. M. (2014). MicroRNA-155 and microRNA-196b: promising biomarkers in hepatitis C virus infection? *Rev Med Virol, 24*, 169-185.

Kenne, E., Nickel, K. F., Long, A. T., Fuchs, T. A., Stavrou, E. X., Stahl, F. R., & Renne, T. (2015). Factor XII: a novel target for safe prevention of thrombosis and inflammation. *J Intern Med, 278*, 571-585.

Kessler, T., Erdmann, J., Vilne, B., Bruse, P., Kurowski, V., Diemert, P., Schunkert, H., & Sager, H. B. (2016). Serum microRNA-1233 is a specific biomarker for diagnosing acute pulmonary embolism. *J Transl Med, 14*, 120.

Key, N. S. (2014). Epidemiologic and clinical data linking factors XI and XII to thrombosis. *Hematology Am Soc Hematol Educ Program, 2014*, 66-70.

Kim, B. S., Jung, J. Y., Jeon, J. Y., Kim, H. A., & Suh, C. H. (2016). Circulating hsa-miR-30e-5p, hsa-miR-92a-3p, and hsa-miR-223-3p may be novel biomarkers in systemic lupus erythematosus. *Hla, 88*, 187-193.

Kjerpeseth, L. J., Selmer, R., Ariansen, I., Karlstad, O., Ellekjaer, H., & Skovlund, E. (2019). Comparative effectiveness of warfarin, dabigatran, rivaroxaban and apixaban in non-valvular atrial fibrillation: A nationwide pharmacoepidemiological study. *PLoS One, 14*, e0221500.

Kole, R., Krainer, A. R., & Altman, S. (2012). RNA therapeutics: beyond RNA interference and antisense oligonucleotides. *Nat Rev Drug Discov, 11*, 125-140.

Kong, L., Hu, N., Du, X., Wang, W., Chen, H., Li, W., Wei, S., Zhuang, H., Li, X., & Li, C. (2016). Upregulation of miR-483-3p contributes to endothelial progenitor cells dysfunction in deep vein thrombosis patients via SRF. *J Transl Med, 14*, 23.

Kossmann, S., Lagrange, J., Jäckel, S., Jurk, K., Ehlken, M., Schönfelder, T., Weihert, Y., Knorr, M., Brandt, M., Xia, N., Li, H., Daiber, A., Oelze, M., Reinhardt, C., Lackner, K., Gruber, A., Monia, B., Karbach, S. H., Walter, U., Ruggeri, Z. M., Renné, T., Ruf, W., Münzel, T., & Wenzel, P. (2017).

Platelet-localized FXI promotes a vascular coagulation-inflammatory circuit in arterial hypertension. *Sci Transl Med, 9*.

Kozomara, A., Birgaoanu, M., & Griffiths-Jones, S. (2019). miRBase: from microRNA sequences to function. *Nucleic Acids Res, 47*, D155-d162.

Krol, J., Loedige, I., & Filipowicz, W. (2010). The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet, 11*, 597-610.

Krützfeldt, J., Rajewsky, N., Braich, R., Rajeev, K. G., Tuschl, T., Manoharan, M., & Stoffel, M. (2005). Silencing of microRNAs in vivo with 'antagomirs'. *Nature, 438*, 685-689.

Kyrle, P. A., Eischer, L., Šinkovec, H., & Eichinger, S. (2019). Factor XI and recurrent venous thrombosis: an observational cohort study. *J Thromb Haemost, 17*, 782-786.

Lanas, A. (2019). International Consensus Guidelines for Nonvariceal Gastrointestinal Bleeding: A Step Forward. *Ann Intern Med, 171*, 853-854.

Lanas, A., Carrera-Lasfuentes, P., Arguedas, Y., Garcia, S., Bujanda, L., Calvet, X., Ponce, J., Perez-Aisa, A., Castro, M., Munoz, M., Sostres, C., & Garcia-Rodriguez, L. A. (2015). Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol, 13*, 906-912.e902.

Lanas-Gimeno, A., & Lanas, A. (2017). Risk of gastrointestinal bleeding during anticoagulant treatment. *Expert Opin Drug Saf, 16*, 673-685.

Lanford, R. E., Hildebrandt-Eriksen, E. S., Petri, A., Persson, R., Lindow, M., Munk, M. E., Kauppinen, S., & Orum, H. (2010). Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. *Science, 327*, 198-201.

Larsson, M., Rayzman, V., Nolte, M. W., Nickel, K. F., Björkqvist, J., Jämsä, A., Hardy, M. P., Fries, M., Schmidbauer, S., Hedenqvist, P., Broomé, M., Pragst, I., Dickneite, G., Wilson, M. J., Nash, A. D., Panousis, C., & Renné, T. (2014). A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. *Sci Transl Med, 6*, 222ra217.

Lee, Y. J., Kim, V., Muth, D. C., & Witwer, K. W. (2015). Validated MicroRNA Target Databases: An Evaluation. *Drug Dev Res, 76*, 389-396.

Lesko, L. J. (2016). Anticoagulants: What is new and what is the standard? *Clin Pharmacol Ther, 100*, 126-128.

Li, S., Chen, H., Ren, J., Geng, Q., Song, J., Lee, C., Cao, C., Zhang, J., & Xu, N. (2014). MicroRNA-223 inhibits tissue factor expression in vascular endothelial cells. *Atherosclerosis, 237*, 514-520.

Li, S., & Patel, D. J. (2016). Drosha and Dicer: Slicers cut from the same cloth. *Cell Res, 26*, 511-512.

Li, S., Ren, J., Xu, N., Zhang, J., Geng, Q., Cao, C., Lee, C., Song, J., Li, J., & Chen, H. (2014). MicroRNA-19b functions as potential anti-thrombotic protector in patients with unstable angina by targeting tissue factor. *J Mol Cell Cardiol, 75*, 49-57.

Li, S., Zhang, R., Yuan, Y., Yi, S., Chen, Q., Gong, L., Liu, J., Ding, F., Cao, Z., & Gu, X. (2017). MiR-340 Regulates Fibrinolysis and Axon Regrowth Following Sciatic Nerve Injury. *Mol Neurobiol, 54*, 4379-4389.

Li, W. D., & Li, X. Q. (2016). Endothelial progenitor cells accelerate the resolution of deep vein thrombosis. *Vascul Pharmacol, 83*, 10-16.

Li, X., & Cao, G. (2015). [Potential role of microRNA-181b on atherosclerosis]. *Zhonghua Xin Xue Guan Bing Za Zhi, 43*, 516-520.

Li, X., Jiang, W., Li, W., Lian, B., Wang, S., Liao, M., Chen, X., Wang, Y., Lv, Y., Wang, S., & Yang, L. (2012). Dissection of human MiRNA regulatory influence to subpathway. *Brief Bioinform, 13*, 175-186.

Liao, Y. C., Wang, Y. S., Guo, Y. C., Lin, W. L., Chang, M. H., & Juo, S. H. (2014). Let-7g improves multiple endothelial functions through targeting transforming growth factor-beta and SIRT-1 signaling. *J Am Coll Cardiol, 63*, 1685-1694.

Lin, J., He, S., Sun, X., Franck, G., Deng, Y., Yang, D., Haemmig, S., Wara, A. K., Icli, B., Li, D., & Feinberg, M. W. (2016). MicroRNA-181b inhibits thrombin-mediated endothelial activation and arterial thrombosis by targeting caspase recruitment domain family member 10. *Faseb j, 30*, 3216-3226.

Lin, S. Y., Kuo, C. H., Yeh, S. J., Tsai, L. K., Liu, Y. B., Huang, C. F., Tang, S. C., & Jeng, J. S. (2020). Real-World Rivaroxaban and Apixaban Levels in Asian Patients With Atrial Fibrillation. *Clin Pharmacol Ther, 107*, 278-286.

Liu, L., Pan, J., Wang, H., Ma, Z., Yin, J., Yuan, F., Yuan, Q., Zhou, L., Liu, X., Zhang, Y., Bao, Z., Yang, H., & Ling, J. (2018). von Willebrand factor rescued by miR-24 inhibition facilitates the proliferation and migration of osteosarcoma cells in vitro. *Biosci Rep, 38*.

Liu, T., Kang, J., & Liu, F. (2018). Plasma Levels of microRNA-221 (miR-221) are Increased in Patients with Acute Pulmonary Embolism. *Med Sci Monit, 24*, 8621-8626.

Long, G., Wang, F., Duan, Q., Yang, S., Chen, F., Gong, W., Yang, X., Wang, Y., Chen, C., & Wang, D. W. (2012). Circulating miR-30a, miR-195 and let-7b associated with acute myocardial infarction. *PLoS One, 7*, e50926.

Long, G., Wang, F., Li, H., Yin, Z., Sandip, C., Lou, Y., Wang, Y., Chen, C., & Wang, D. W. (2013). Circulating miR-30a, miR-126 and let-7b as biomarker for ischemic stroke in humans. *BMC Neurol, 13*, 178.

Louloupi, A., & Orom, U. A. V. (2018). Inhibiting Pri-miRNA Processing with Target Site Blockers. *Methods Mol Biol, 1823*, 63-68.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., Abraham, J., Adair, T., Aggarwal, R., Ahn, S. Y., Alvarado, M., Anderson, H. R., Anderson, L. M., Andrews, K. G., Atkinson, C., Baddour, L. M., Barker-Collo, S., Bartels, D. H., Bell, M. L., Benjamin, E. J., Bennett, D., Bhalla, K., Bikbov, B., Bin Abdulhak, A., Birbeck, G., Blyth, F., Bolliger, I., Boufous, S., Bucello, C., Burch, M., Burney, P., Carapetis, J., Chen, H., Chou, D., Chugh, S. S., Coffeng, L. E., Colan, S. D., Colquhoun, S., Colson, K. E., Condon, J., Connor, M. D., Cooper, L. T., Corriere, M., Cortinovis, M., de Vaccaro, K. C., Couser, W., Cowie, B. C., Criqui, M. H., Cross, M., Dabhadkar, K. C., Dahodwala, N., De Leo, D., Degenhardt, L., Delossantos, A., Denenberg, J., Des Jarlais, D. C., Dharmaratne, S. D., Dorsey, E. R., Driscoll, T., Duber, H., Ebel, B., Erwin, P. J., Espindola, P., Ezzati, M., Feigin, V., Flaxman, A. D., Forouzanfar, M. H., Fowkes, F. G., Franklin, R., Fransen, M., Freeman, M. K., Gabriel, S. E., Gakidou, E., Gaspari, F., Gillum, R. F., Gonzalez-Medina, D., Halasa, Y. A., Haring, D., Harrison, J. E., Havmoeller, R., Hay, R. J., Hoen, B., Hotez, P. J., Hoy, D., Jacobsen, K. H., James, S. L., Jasrasaria, R., Jayaraman, S., Johns, N., Karthikeyan, G., Kassebaum, N., Keren, A., Khoo, J. P., Knowlton, L. M., Kobusingye, O., Koranteng, A., Krishnamurthi, R., Lipnick, M., Lipshultz, S. E., Ohno, S. L., Mabweijano, J., MacIntyre, M. F., Mallinger, L., March, L., Marks, G. B., Marks, R., Matsumori, A., Matzopoulos, R., Mayosi, B. M., McAnulty, J. H., McDermott, M. M., McGrath, J., Mensah, G. A., Merriman, T. R., Michaud, C., Miller, M., Miller, T. R., Mock, C., Mocumbi, A. O., Mokdad, A. A., Moran, A., Mulholland, K., Nair, M. N., Naldi, L., Narayan, K. M., Nasseri, K., Norman, P., O'Donnell, M., Omer, S. B., Ortblad, K., Osborne, R., Ozgediz, D., Pahari, B., Pandian, J. D., Rivero, A. P., Padilla, R. P., Perez-Ruiz, F., Perico, N., Phillips, D., Pierce, K., Pope, C. A., 3rd, Porrini, E., Pourmalek, F., Raju, M., Ranganathan, D., Rehm, J. T., Rein, D. B., Remuzzi, G., Rivara, F. P., Roberts, T., De Leon, F. R., Rosenfeld, L. C., Rushton, L., Sacco, R. L., Salomon, J. A., Sampson, U., Sanman, E., Schwebel, D. C., Segui-Gomez, M., Shepard, D. S., Singh, D., Singleton, J., Sliwa, K., Smith, E., Steer, A., Taylor, J. A., Thomas, B., Tleyjeh, I. M., Towbin, J. A., Truelsen, T., Undurraga, E. A., Venketasubramanian, N., Vijayakumar, L., Vos, T., Wagner, G. R., Wang, M., Wang, W., Watt, K., Weinstock, M. A., Weintraub, R., Wilkinson, J. D., Woolf, A. D., Wulf, S., Yeh, P. H., Yip, P., Zabetian, A., Zheng, Z. J., Lopez, A. D., Murray, C. J., AlMazroa, M. A., & Memish, Z. A. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*, 2095-2128.

Lu, D., & Thum, T. (2019). RNA-based diagnostic and therapeutic strategies for cardiovascular disease. *Nat Rev Cardiol, 16*, 661-674.

Lu, Y. C., Chang, S. H., Hafner, M., Li, X., Tuschl, T., Elemento, O., & Hla, T. (2014). ELAVL1 modulates transcriptome-wide miRNA binding in murine macrophages. *Cell Rep, 9*, 2330-2343.

Lui, P. Y., Jin, D. Y., & Stevenson, N. J. (2015). MicroRNA: master controllers of intracellular signaling pathways. *Cell Mol Life Sci, 72*, 3531-3542.

Luo, M., Li, R., Ren, M., Chen, N., Deng, X., Tan, X., Li, Y., Zeng, M., Yang, Y., Wan, Q., & Wu, J. (2016). Hyperglycaemia-induced reciprocal changes in miR-30c and PAI-1 expression in platelets. *Sci Rep, 6*, 36687.

Maitrias, P., Metzinger-Le Meuth, V., Massy, Z. A., M'Baya-Moutoula, E., Reix, T., Caus, T., & Metzinger, L. (2015). MicroRNA deregulation in symptomatic carotid plaque. *J Vasc Surg, 62*, 1245-1250.e1241.

Manca, S., Upadhyaya, B., Mutai, E., Desaulniers, A. T., Cederberg, R. A., White, B. R., & Zempleni, J. (2018). Milk exosomes are bioavailable and distinct microRNA cargos have unique tissue distribution patterns. *Sci Rep, 8*, 11321.

Marchand, A., Proust, C., Morange, P. E., Lompre, A. M., & Tregouet, D. A. (2012). miR-421 and miR-30c inhibit SERPINE 1 gene expression in human endothelial cells. *PLoS One, 7*, e44532.

Martin, K., & Key, N. S. (2016). How I treat patients with inherited bleeding disorders who need anticoagulant therapy. *Blood, 128*, 178-184.

Martinez, B. K., Sood, N. A., Bunz, T. J., & Coleman, C. I. (2018). Effectiveness and Safety of Apixaban, Dabigatran, and Rivaroxaban Versus Warfarin in Frail Patients With Nonvalvular Atrial Fibrillation. *J Am Heart Assoc, 7*.

Martinez, J., & Tuschl, T. (2004). RISC is a 5' phosphomonoester-producing RNA endonuclease. *Genes Dev, 18*, 975-980.

Matafonov, A., Leung, P. Y., Gailani, A. E., Grach, S. L., Puy, C., Cheng, Q., Sun, M. F., McCarty, O. J., Tucker, E. I., Kataoka, H., Renné, T., Morrissey, J. H., Gruber, A., & Gailani, D. (2014). Factor XII inhibition reduces thrombus formation in a primate thrombosis model. *Blood, 123*, 1739-1746.

McNamara, J. O., 2nd, Andrechek, E. R., Wang, Y., Viles, K. D., Rempel, R. E., Gilboa, E., Sullenger, B. A., & Giangrande, P. H. (2006). Cell type-specific delivery of siRNAs with aptamer-siRNA chimeras. *Nat Biotechnol, 24*, 1005-1015.

Meder, B., Keller, A., Vogel, B., Haas, J., Sedaghat-Hamedani, F., Kayvanpour, E., Just, S., Borries, A., Rudloff, J., Leidinger, P., Meese, E., Katus, H. A., & Rottbauer, W. (2011). MicroRNA signatures in total peripheral blood as novel biomarkers for acute myocardial infarction. *Basic Res Cardiol, 106*, 13-23.

Mega, J. L., Braunwald, E., Wiviott, S. D., Bassand, J. P., Bhatt, D. L., Bode, C., Burton, P., Cohen, M., Cook-Bruns, N., Fox, K. A., Goto, S., Murphy, S. A., Plotnikov, A. N., Schneider, D., Sun, X., Verheugt, F. W., & Gibson, C. M. (2012). Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med, 366*, 9-19.

Megiorni, F., Cialfi, S., Dominici, C., Quattrucci, S., & Pizzuti, A. (2011). Synergistic post-transcriptional regulation of the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) by miR-101 and miR-494 specific binding. *PLoS One, 6*, e26601.

Meijers, J. C., Tekelenburg, W. L., Bouma, B. N., Bertina, R. M., & Rosendaal, F. R. (2000). High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med, 342*, 696-701.

Meister, G. (2013). Argonaute proteins: functional insights and emerging roles. *Nat Rev Genet, 14*, 447-459.

Meng, Q., Wang, W., Yu, X., Li, W., Kong, L., Qian, A., Li, C., & Li, X. (2015). Upregulation of MicroRNA-126 Contributes to Endothelial Progenitor Cell Function in Deep Vein Thrombosis via Its Target PIK3R2. *J Cell Biochem, 116*, 1613-1623.

Menghini, R., Stohr, R., & Federici, M. (2014). MicroRNAs in vascular aging and atherosclerosis. *Ageing Res Rev, 17*, 68-78.

Messina, A., Langlet, F., Chachlaki, K., Roa, J., Rasika, S., Jouy, N., Gallet, S., Gaytan, F., Parkash, J., Tena-Sempere, M., Giacobini, P., & Prevot, V. (2016). A microRNA switch regulates the rise in hypothalamic GnRH production before puberty. *Nat Neurosci, 19*, 835-844.

Minnema, M. C., Peters, R. J., de Winter, R., Lubbers, Y. P., Barzegar, S., Bauer, K. A., Rosenberg, R. D., Hack, C. E., & ten Cate, H. (2000). Activation of clotting factors XI and IX in patients with acute myocardial infarction. *Arterioscler Thromb Vasc Biol, 20*, 2489-2493.

Monia , B., Zhang, H., Zhao, C., Siwkowski, A., Freier, S., & Witchell, D. (2007). ISIS 401025, a Second Generation Antisense Oligonucleotide Targeting Prothrombin, Inhibits Plasma Prothrombin Level and Promotes Anticoagulation in Mice. *Circulation, 116*, 716.

Morelli, V. M., Braekkan, S. K., & Hansen, J. B. (2020). Role of microRNAs in Venous Thromboembolism. *Int J Mol Sci, 21*.

Mukherji, S., Ebert, M. S., Zheng, G. X., Tsang, J. S., Sharp, P. A., & van Oudenaarden, A. (2011). MicroRNAs can generate thresholds in target gene expression. *Nat Genet, 43*, 854-859.

Muller, F., Mutch, N. J., Schenk, W. A., Smith, S. A., Esterl, L., Spronk, H. M., Schmidbauer, S., Gahl, W. A., Morrissey, J. H., & Renne, T. (2009). Platelet polyphosphates are proinflammatory and procoagulant mediators in vivo. *Cell, 139*, 1143-1156.

Naito, K., & Fujikawa, K. (1991). Activation of human blood coagulation factor XI independent of factor XII. Factor XI is activated by thrombin and factor XIa in the presence of negatively charged surfaces. *J Biol Chem, 266*, 7353-7358.

Narayanan, P., Shen, L., Curtis, B. R., Bourdon, M. A., Nolan, J. P., Gupta, S., Hoffmaster, C., Zhou, F., Christian, B., Schaubhut, J. L., Greenlee, S., Burel, S. A., Witztum, J. L., Engelhardt, J. A., & Henry, S. P. (2018). Investigation into the Mechanism(s) That Leads to Platelet Decreases in Cynomolgus Monkeys During Administration of ISIS 104838, a 2'-MOE-Modified Antisense Oligonucleotide. *Toxicol Sci, 164*, 613-626.

Nielsen, C. B., Shomron, N., Sandberg, R., Hornstein, E., Kitzman, J., & Burge, C. B. (2007). Determinants of targeting by endogenous and exogenous microRNAs and siRNAs. *Rna, 13*, 1894-1910.

Nissan, R., Spectre, G., Hershkovitz, A., Green, H., Shimony, S., Cooper, L., Nakav, S., Shochat, T., Grossman, A., & Fuchs, S. (2019). Apixaban Levels in Octogenarian Patients with Non-valvular Atrial Fibrillation. *Drugs Aging, 36*, 165-177.

Nourse, J., Braun, J., Lackner, K., Hüttelmaier, S., & Danckwardt, S. (2018). Large-scale identification of functional microRNA targeting reveals cooperative regulation of the hemostatic system. *J Thromb Haemost, 16*, 2233-2245.

Nourse, J., Spada, S., & Danckwardt, S. (2020). Emerging Roles of RNA 3'-end Cleavage and Polyadenylation in Pathogenesis, Diagnosis and Therapy of Human Disorders. *Biomolecules, 10*.

Nowakowski, T. J., Rani, N., Golkaram, M., Zhou, H. R., Alvarado, B., Huch, K., West, J. A., Leyrat, A., Pollen, A. A., Kriegstein, A. R., Petzold, L. R., & Kosik, K. S. (2018). Regulation of cell-type-specific transcriptomes by microRNA networks during human brain development. *Nat Neurosci, 21*, 1784-1792.

Ohno, S., Takanashi, M., Sudo, K., Ueda, S., Ishikawa, A., Matsuyama, N., Fujita, K., Mizutani, T., Ohgi, T., Ochiya, T., Gotoh, N., & Kuroda, M. (2013). Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells. *Mol Ther, 21*, 185-191.

Oliveto, S., Mancino, M., Manfrini, N., & Biffo, S. (2017). Role of microRNAs in translation regulation and cancer. *World J Biol Chem, 8*, 45-56.

Ottosen, S., Parsley, T. B., Yang, L., Zeh, K., van Doorn, L. J., van der Veer, E., Raney, A. K., Hodges, M. R., & Patick, A. K. (2015). In vitro antiviral activity and preclinical and clinical resistance profile of

miravirsen, a novel anti-hepatitis C virus therapeutic targeting the human factor miR-122. *Antimicrob Agents Chemother, 59*, 599-608.

Ovchinnikova, E. S., Schmitter, D., Vegter, E. L., Ter Maaten, J. M., Valente, M. A., Liu, L. C., van der Harst, P., Pinto, Y. M., de Boer, R. A., Meyer, S., Teerlink, J. R., O'Connor, C. M., Metra, M., Davison, B. A., Bloomfield, D. M., Cotter, G., Cleland, J. G., Mebazaa, A., Laribi, S., Givertz, M. M., Ponikowski, P., van der Meer, P., van Veldhuisen, D. J., Voors, A. A., & Berezikov, E. (2016). Signature of circulating microRNAs in patients with acute heart failure. *Eur J Heart Fail, 18*, 414-423.

Patel, M. R., Mahaffey, K. W., Garg, J., Pan, G., Singer, D. E., Hacke, W., Breithardt, G., Halperin, J. L., Hankey, G. J., Piccini, J. P., Becker, R. C., Nessel, C. C., Paolini, J. F., Berkowitz, S. D., Fox, K. A., & Califf, R. M. (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med, 365*, 883-891.

Patel, N., Tahara, S. M., Malik, P., & Kalra, V. K. (2011). Involvement of miR-30c and miR-301a in immediate induction of plasminogen activator inhibitor-1 by placental growth factor in human pulmonary endothelial cells. *Biochem J, 434*, 473-482.

Paul, P., Chakraborty, A., Sarkar, D., Langthasa, M., Rahman, M., Bari, M., Singha, R. S., Malakar, A. K., & Chakraborty, S. (2018). Interplay between miRNAs and human diseases. *J Cell Physiol, 233*, 2007-2018.

Pawlowska, Z., Chabielska, E., Kobylanska, A., Maciaszek, A., Swiatkowska, M., Buczko, W., Stec, W. J., & Cierniewski, C. S. (2001). Regulation of PAI-1 concentration in platelets by systemic administration of antisense oligonucleotides to rats. *Thromb Haemost, 85*, 1086-1089.

Pawlowska, Z., Pluskota, E., Chabielska, E., Buczko, W., Okruszek, A., Stec, W. J., & Cierniewski, C. S. (1998). Phosphorothioate oligodeoxyribonucleotides antisense to PAI-1 mRNA increase fibrinolysis and modify experimental thrombosis in rats. *Thromb Haemost, 79*, 348-353.

Pengo, V., Denas, G., Zoppellaro, G., Jose, S. P., Hoxha, A., Ruffatti, A., Andreoli, L., Tincani, A., Cenci, C., Prisco, D., Fierro, T., Gresele, P., Cafolla, A., De Micheli, V., Ghirarduzzi, A., Tosetto, A., Falanga, A., Martinelli, I., Testa, S., Barcellona, D., Gerosa, M., & Banzato, A. (2018). Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood, 132*, 1365-1371.

Perez-Sanchez, C., Aguirre, M. A., Ruiz-Limon, P., Barbarroja, N., Jimenez-Gomez, Y., de la Rosa, I. A., Rodriguez-Ariza, A., Collantes-Estevez, E., Segui, P., Velasco, F., Cuadrado, M. J., Teruel, R., Gonzalez-Conejero, R., Martinez, C., & Lopez-Pedrera, C. (2016). 'Atherothrombosis-associated microRNAs in Antiphospholipid syndrome and Systemic Lupus Erythematosus patients'. *Sci Rep, 6*, 31375.

Perwitasari, O., Bakre, A., Tompkins, S. M., & Tripp, R. A. (2013). siRNA Genome Screening Approaches to Therapeutic Drug Repositioning. *Pharmaceuticals (Basel), 6*, 124-160.

Pireaux, V., Tassignon, J., Demoulin, S., Derochette, S., Borenstein, N., Ente, A., Fiette, L., Douxfils, J., Lancellotti, P., Guyaux, M., & Godfroid, E. (2019). Anticoagulation With an Inhibitor of Factors XIa and XIIa During Cardiopulmonary Bypass. *J Am Coll Cardiol, 74*, 2178-2189.

Plow, E. F., Wang, Y., & Simon, D. I. (2018). The search for new antithrombotic mechanisms and therapies that may spare hemostasis. *Blood, 131*, 1899-1902.

Preis, M., Hirsch, J., Kotler, A., Zoabi, A., Stein, N., Rennert, G., & Saliba, W. (2017). Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood, 129*, 1210-1215.

Prins, M. H., Lensing, A. W., Brighton, T. A., Lyons, R. M., Rehm, J., Trajanovic, M., Davidson, B. L., Beyer-Westendorf, J., Pap, A. F., Berkowitz, S. D., Cohen, A. T., Kovacs, M. J., Wells, P. S., & Prandoni, P. (2014). Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol, 1*, e37-46.

Quemener, A. M., Bachelot, L., Forestier, A., Donnou-Fournet, E., Gilot, D., & Galibert, M. D. (2020). The powerful world of antisense oligonucleotides: From bench to bedside. *Wiley Interdiscip Rev RNA*, e1594.

Rai, V., Balters, M. W., & Agrawal, D. K. (2019). Factors IX, XI, and XII: potential therapeutic targets for anticoagulant therapy in atherothrombosis. *Rev Cardiovasc Med, 20*, 245-253.

Raitoharju, E., Lyytikainen, L. P., Levula, M., Oksala, N., Mennander, A., Tarkka, M., Klopp, N., Illig, T., Kahonen, M., Karhunen, P. J., Laaksonen, R., & Lehtimaki, T. (2011). miR-21, miR-210, miR-34a, and miR-146a/b are up-regulated in human atherosclerotic plaques in the Tampere Vascular Study. *Atherosclerosis, 219*, 211-217.

Renne, T., Pozgajova, M., Gruner, S., Schuh, K., Pauer, H. U., Burfeind, P., Gailani, D., & Nieswandt, B. (2005). Defective thrombus formation in mice lacking coagulation factor XII. *J Exp Med, 202*, 271-281.

Revenko, A. S., Gao, D., Crosby, J. R., Bhattacharjee, G., Zhao, C., May, C., Gailani, D., Monia, B. P., & MacLeod, A. R. (2011). Selective depletion of plasma prekallikrein or coagulation factor XII inhibits thrombosis in mice without increased risk of bleeding. *Blood, 118*, 5302-5311.

Rodriguez-Rius, A., Lopez, S., Martinez-Perez, A., Souto, J. C., & Soria, J. M. (2020). Identification of a Plasma MicroRNA Profile Associated With Venous Thrombosis. *Arterioscler Thromb Vasc Biol, 40*, 1392-1399.

Rosen, E. D., Gailani, D., & Castellino, F. J. (2002). FXI is essential for thrombus formation following FeCl3-induced injury of the carotid artery in the mouse. *Thromb Haemost, 87*, 774-776.

Rosset, C., Vieira, I. A., Salzano, F. M., & Bandinelli, E. (2016). A germline variant affects putative miRNA-binding sites at the F8 3'UTR and acts as a potential haemophilia A phenotype modifier in Southern Brazilian patients. *Haemophilia, 22*, e327-329.

Rowley, J. W., Chappaz, S., Corduan, A., Chong, M. M., Campbell, R., Khoury, A., Manne, B. K., Wurtzel, J. G., Michael, J. V., Goldfinger, L. E., Mumaw, M. M., Nieman, M. T., Kile, B. T., Provost, P., & Weyrich, A. S. (2016). Dicer1-mediated miRNA processing shapes the mRNA profile and function of murine platelets. *Blood, 127*, 1743-1751.

Rupaimoole, R., & Slack, F. J. (2017). MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. *Nat Rev Drug Discov, 16*, 203-222.

Sabater-Lleal, M., Martinez-Perez, A., Buil, A., Folkersen, L., Souto, J. C., Bruzelius, M., Borrell, M., Odeberg, J., Silveira, A., Eriksson, P., Almasy, L., Hamsten, A., & Soria, J. M. (2012). A genome-wide association study identifies KNG1 as a genetic determinant of plasma factor XI Level and activated partial thromboplastin time. *Arterioscler Thromb Vasc Biol, 32*, 2008-2016.

Sahu, A., Jha, P. K., Prabhakar, A., Singh, H. D., Gupta, N., Chatterjee, T., Tyagi, T., Sharma, S., Kumari, B., Singh, S., Nair, V., Goel, S., & Ashraf, M. Z. (2017). MicroRNA-145 Impedes Thrombus Formation via Targeting Tissue Factor in Venous Thrombosis. *EBioMedicine, 26*, 175-186.

Sakuma, I., Uchiyama, S., Atarashi, H., Inoue, H., Kitazono, T., Yamashita, T., Shimizu, W., Ikeda, T., Kamouchi, M., Kaikita, K., Fukuda, K., Origasa, H., & Shimokawa, H. (2019). Clinical risk factors of stroke and major bleeding in patients with non-valvular atrial fibrillation under rivaroxaban: the EXPAND Study sub-analysis. *Heart Vessels, 34*, 1839-1851.

Sala, F., Aranda, J. F., Rotllan, N., Ramirez, C. M., Aryal, B., Elia, L., Condorelli, G., Catapano, A. L., Fernandez-Hernando, C., & Norata, G. D. (2014). MiR-143/145 deficiency attenuates the progression of atherosclerosis in Ldlr-/-mice. *Thromb Haemost, 112*, 796-802.

Saliminejad, K., Khorram Khorshid, H. R., Soleymani Fard, S., & Ghaffari, S. H. (2019). An overview of microRNAs: Biology, functions, therapeutics, and analysis methods. *J Cell Physiol, 234*, 5451-5465.

Salloum-Asfar, S., Teruel-Montoya, R., Arroyo, A. B., Garcia-Barbera, N., Chaudhry, A., Schuetz, E., Luengo-Gil, G., Vicente, V., Gonzalez-Conejero, R., & Martinez, C. (2014). Regulation of coagulation factor XI expression by microRNAs in the human liver. *PLoS One, 9*, e111713.

Salomon, O., Steinberg, D. M., Koren-Morag, N., Tanne, D., & Seligsohn, U. (2008). Reduced incidence of ischemic stroke in patients with severe factor XI deficiency. *Blood, 111*, 4113-4117.

Salomon, O., Steinberg, D. M., Zucker, M., Varon, D., Zivelin, A., & Seligsohn, U. (2011). Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis. *Thromb Haemost, 105*, 269-273.

Sarachana, T., Dahiya, N., Simhadri, V. L., Pandey, G. S., Saini, S., Guelcher, C., Guerrera, M. F., Kimchi-Sarfaty, C., Sauna, Z. E., & Atreya, C. D. (2015). Small ncRNA Expression-Profiling of Blood from Hemophilia A Patients Identifies miR-1246 as a Potential Regulator of Factor 8 Gene. *PLoS One, 10*, e0132433.

Schulman, S., Goldhaber, S. Z., Kearon, C., Kakkar, A. K., Schellong, S., Eriksson, H., Hantel, S., Feuring, M., & Kreuzer, J. (2015). Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost, 114*, 150-157.

Schulman, S., Kakkar, A. K., Goldhaber, S. Z., Schellong, S., Eriksson, H., Mismetti, P., Christiansen, A. V., Friedman, J., Le Maulf, F., Peter, N., & Kearon, C. (2014). Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation, 129*, 764-772.

Schwarz, D. S., Ding, H., Kennington, L., Moore, J. T., Schelter, J., Burchard, J., Linsley, P. S., Aronin, N., Xu, Z., & Zamore, P. D. (2006). Designing siRNA that distinguish between genes that differ by a single nucleotide. *PLoS Genet, 2*, e140.

Selbach, M., Schwanhausser, B., Thierfelder, N., Fang, Z., Khanin, R., & Rajewsky, N. (2008). Widespread changes in protein synthesis induced by microRNAs. *Nature, 455*, 58-63.

Sen, D., & Jayandharan, G. R. (2016). MicroRNA-15b Modulates Molecular Mediators of Blood Induced Arthropathy in Hemophilia Mice. *Int J Mol Sci, 17*, 492.

Sennblad, B., Basu, S., Mazur, J., Suchon, P., Martinez-Perez, A., van Hylckama Vlieg, A., Truong, V., Li, Y., Gadin, J. R., Tang, W., Grossman, V., de Haan, H. G., Handin, N., Silveira, A., Souto, J. C., Franco-Cereceda, A., Morange, P. E., Gagnon, F., Soria, J. M., Eriksson, P., Hamsten, A., Maegdefessel, L., Rosendaal, F. R., Wild, P., Folsom, A. R., Tregouet, D. A., & Sabater-Lleal, M. (2017). Genome-wide association study with additional genetic and post-transcriptional analyses reveals novel regulators of plasma factor XI levels. *Hum Mol Genet, 26*, 637-649.

Shirai, T., Revenko, A. S., Tibbitts, J., Ngo, A. T. P., Mitrugno, A., Healy, L. D., Johnson, J., Tucker, E. I., Hinds, M. T., Coussens, L. M., McCarty, O. J. T., Monia, B. P., & Gruber, A. (2019). Hepatic thrombopoietin gene silencing reduces platelet count and breast cancer progression in transgenic MMTV-PyMT mice. *Blood Adv, 3*, 3080-3091.

Shoeb, M., & Fang, M. C. (2013). Assessing bleeding risk in patients taking anticoagulants. *J Thromb Thrombolysis, 35*, 312-319.

Siegerink, B., Rosendaal, F. R., & Algra, A. (2014). Antigen levels of coagulation factor XII, coagulation factor XI and prekallikrein, and the risk of myocardial infarction and ischemic stroke in young women. *J Thromb Haemost, 12*, 606-613.

Sikka, P., & Bindra, V. K. (2010). Newer antithrombotic drugs. *Indian J Crit Care Med, 14*, 188-195.

Silverstein, M. D., Heit, J. A., Mohr, D. N., Petterson, T. M., O'Fallon, W. M., & Melton, L. J., 3rd. (1998). Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med, 158*, 585-593.

Singh, S., Narang, A. S., & Mahato, R. I. (2011). Subcellular fate and off-target effects of siRNA, shRNA, and miRNA. *Pharm Res, 28*, 2996-3015.

Snove, O., Jr., & Holen, T. (2004). Many commonly used siRNAs risk off-target activity. *Biochem Biophys Res Commun, 319*, 256-263.

Song, E., Zhu, P., Lee, S. K., Chowdhury, D., Kussman, S., Dykxhoorn, D. M., Feng, Y., Palliser, D., Weiner, D. B., Shankar, P., Marasco, W. A., & Lieberman, J. (2005). Antibody mediated in vivo delivery of small interfering RNAs via cell-surface receptors. *Nat Biotechnol, 23*, 709-717.

Sood, P., Krek, A., Zavolan, M., Macino, G., & Rajewsky, N. (2006). Cell-type-specific signatures of microRNAs on target mRNA expression. *Proc Natl Acad Sci U S A, 103*, 2746-2751.

Sorensen, S. S., Nygaard, A. B., & Christensen, T. (2016). miRNA expression profiles in cerebrospinal fluid and blood of patients with Alzheimer's disease and other types of dementia - an exploratory study. *Transl Neurodegener, 5*, 6.

Sostres, C., Marcen, B., Laredo, V., Alfaro, E., Ruiz, L., Camo, P., Carrera-Lasfuentes, P., & Lanas, A. (2019). Risk of rebleeding, vascular events and death after gastrointestinal bleeding in anticoagulant and/or antiplatelet users. *Aliment Pharmacol Ther, 50*, 919-929.

Starikova, I., Jamaly, S., Sorrentino, A., Blondal, T., Latysheva, N., Sovershaev, M., & Hansen, J. B. (2015). Differential expression of plasma miRNAs in patients with unprovoked venous thromboembolism and healthy control individuals. *Thromb Res, 136*, 566-572.

Stather, P. W., Sylvius, N., Wild, J. B., Choke, E., Sayers, R. D., & Bown, M. J. (2013). Differential microRNA expression profiles in peripheral arterial disease. *Circ Cardiovasc Genet, 6*, 490-497.

Sun, L. L., Xiao, L., Du, X. L., Hong, L., Li, C. L., Jiao, J., Li, W. D., & Li, X. Q. (2019). MiR-205 promotes endothelial progenitor cell angiogenesis and deep vein thrombosis recanalization and resolution by targeting PTEN to regulate Akt/autophagy pathway and MMP2 expression. *J Cell Mol Med, 23*, 8493-8504.

Sun, S., Chai, S., Zhang, F., & Lu, L. (2020). Overexpressed microRNA-103a-3p inhibits acute lower-extremity deep venous thrombosis via inhibition of CXCL12. *IUBMB Life, 72*, 492-504.

Sun, X., Icli, B., Wara, A. K., Belkin, N., He, S., Kobzik, L., Hunninghake, G. M., Vera, M. P., Blackwell, T. S., Baron, R. M., & Feinberg, M. W. (2012). MicroRNA-181b regulates NF-kappaB-mediated vascular inflammation. *J Clin Invest, 122*, 1973-1990.

Sun, X., Zhang, M., Sanagawa, A., Mori, C., Ito, S., Iwaki, S., Satoh, H., & Fujii, S. (2012). Circulating microRNA-126 in patients with coronary artery disease: correlation with LDL cholesterol. *Thromb J, 10*, 16.

Sunderland, N., Skroblin, P., Barwari, T., Huntley, R. P., Lu, R., Joshi, A., Lovering, R. C., & Mayr, M. (2017). MicroRNA Biomarkers and Platelet Reactivity: The Clot Thickens. *Circ Res, 120*, 418-435.

Tang, K. C., Yang, Z. P., Zeng, Q., Wang, J., Guo, F., & Zhao, Y. (2018). Effect of miR-495 on lower extremity deep vein thrombosis through the TLR4 signaling pathway by regulation of IL1R1. *Biosci Rep, 38*.

Tay, Y., Rinn, J., & Pandolfi, P. P. (2014). The multilayered complexity of ceRNA crosstalk and competition. *Nature, 505*, 344-352.

Terao, M., Fratelli, M., Kurosaki, M., Zanetti, A., Guarnaccia, V., Paroni, G., Tsykin, A., Lupi, M., Gianni, M., Goodall, G. J., & Garattini, E. (2011). Induction of miR-21 by retinoic acid in estrogen receptor-positive breast carcinoma cells: biological correlates and molecular targets. *J Biol Chem, 286*, 4027-4042.

Teruel, R., Perez-Sanchez, C., Corral, J., Herranz, M. T., Perez-Andreu, V., Saiz, E., Garcia-Barbera, N., Martinez-Martinez, I., Roldan, V., Vicente, V., Lopez-Pedrera, C., & Martinez, C. (2011). Identification of miRNAs as potential modulators of tissue factor expression in patients with systemic lupus erythematosus and antiphospholipid syndrome. *J Thromb Haemost, 9*, 1985-1992.

Teruel-Montoya, R., Rosendaal, F. R., & Martinez, C. (2015). MicroRNAs in hemostasis. *J Thromb Haemost, 13*, 170-181.

Tiemann, K., & Rossi, J. J. (2009). RNAi-based therapeutics-current status, challenges and prospects. *EMBO Mol Med, 1*, 142-151.

Tijsen, A. J., Creemers, E. E., Moerland, P. D., de Windt, L. J., van der Wal, A. C., Kok, W. E., & Pinto, Y. M. (2010). MiR423-5p as a circulating biomarker for heart failure. *Circ Res, 106*, 1035-1039.

Titze-de-Almeida, R., David, C., & Titze-de-Almeida, S. S. (2017). The Race of 10 Synthetic RNAi-Based Drugs to the Pharmaceutical Market. *Pharm Res, 34*, 1339-1363.

Tran, J. Q. D., Pedersen, O. H., Larsen, M. L., Grove, E. L., Kristensen, S. D., Hvas, A. M., & Nissen, P. H. (2020). Platelet microRNA expression and association with platelet maturity and function in patients with essential thrombocythemia. *Platelets, 31*, 365-372.

Tucker, E. I., Marzec, U. M., White, T. C., Hurst, S., Rugonyi, S., McCarty, O. J., Gailani, D., Gruber, A., & Hanson, S. R. (2009). Prevention of vascular graft occlusion and thrombus-associated thrombin generation by inhibition of factor XI. *Blood, 113*, 936-944.

van der Meijden, P. E., Munnix, I. C., Auger, J. M., Govers-Riemslag, J. W., Cosemans, J. M., Kuijpers, M. J., Spronk, H. M., Watson, S. P., Renne, T., & Heemskerk, J. W. (2009). Dual role of collagen in factor XII-dependent thrombus formation. *Blood, 114*, 881-890.

Van Hylckama Vlieg, A., Callas, P. W., Cushman, M., Bertina, R. M., & Rosendaal, F. R. (2003). Inter-relation of coagulation factors and d-dimer levels in healthy individuals. *J Thromb Haemost, 1*, 516-522.

van Montfoort, M. L., Kuijpers, M. J., Knaup, V. L., Bhanot, S., Monia, B. P., Roelofs, J. J., Heemskerk, J. W., & Meijers, J. C. (2014). Factor XI regulates pathological thrombus formation on acutely ruptured atherosclerotic plaques. *Arterioscler Thromb Vasc Biol, 34*, 1668-1673.

van Montfoort, M. L., & Meijers, J. C. (2013). Anticoagulation beyond direct thrombin and factor Xa inhibitors: indications for targeting the intrinsic pathway? *Thromb Haemost, 110*, 223-232.

van Rooij, E., & Kauppinen, S. (2014). Development of microRNA therapeutics is coming of age. *EMBO Mol Med, 6*, 851-864.

Villines, T. C., Ahmad, A., Petrini, M., Tang, W., Evans, A., Rush, T., Thompson, D., Oh, K., & Schwartzman, E. (2019). Comparative safety and effectiveness of dabigatran vs. rivaroxaban and apixaban in patients with non-valvular atrial fibrillation: a retrospective study from a large healthcare system. *Eur Heart J Cardiovasc Pharmacother, 5*, 80-90.

Voetsch, B., & Loscalzo, J. (2004). Genetic determinants of arterial thrombosis. *Arterioscler Thromb Vasc Biol, 24*, 216-229.

Vossen, C. Y., van Hylckama Vlieg, A., Teruel-Montoya, R., Salloum-Asfar, S., de Haan, H., Corral, J., Reitsma, P., Koeleman, B. P. C., & Martinez, C. (2017). Identification of coagulation gene 3'UTR variants that are potentially regulated by microRNAs. *Br J Haematol, 177*, 782-790.

Vu, T. T., Zhou, J., Leslie, B. A., Stafford, A. R., Fredenburgh, J. C., Ni, R., Qiao, S., Vaezzadeh, N., Jahnen-Dechent, W., Monia, B. P., Gross, P. L., & Weitz, J. I. (2015). Arterial thrombosis is accelerated in mice deficient in histidine-rich glycoprotein. *Blood, 125*, 2712-2719.

Wallisch, M., Olson, S. R., Crosby, J., Johnson, J., Murray, S. F., Shatzel, J. J., Tucker, E. I., McCarty, O. J. T., Hinds, M. T., Monia, B. P., & Gruber, A. (2020). Evaluation of the Antihemostatic and Antithrombotic Effects of Lowering Coagulation Factor VII Levels in a Non-human Primate. *Cell Mol Bioeng, 13*, 179-187.

Wang, F., Zuroske, T., & Watts, J. K. (2020). RNA therapeutics on the rise. *Nat Rev Drug Discov*.

Wang, G., Chai, B., & Yang, L. (2016). MiR-128 and miR-125 regulate expression of coagulation Factor IX gene with nonsense mutation by repressing nonsense-mediated mRNA decay. *Biomed Pharmacother, 80*, 331-337.

Wang, H. J., Deng, J., Wang, J. Y., Zhang, P. J., Xin, Z., Xiao, K., Feng, D., Jia, Y. H., Liu, Y. N., & Xie, L. X. (2014). Serum miR-122 levels are related to coagulation disorders in sepsis patients. *Clin Chem Lab Med, 52*, 927-933.

Wang, J., Chen, J., & Sen, S. (2016). MicroRNA as Biomarkers and Diagnostics. *J Cell Physiol, 231*, 25-30.

Wang, J., Yao, Y., Zhang, J., Tang, X., Meng, X., Wang, M., Song, L., & Yuan, J. (2020). Platelet microRNA-15b protects against high platelet reactivity in patients undergoing percutaneous coronary intervention through Bcl-2-mediated platelet apoptosis. *Ann Transl Med, 8*, 364.

Wang, Q., Ma, J., Jiang, Z., Wu, F., Ping, J., & Ming, L. (2018). Diagnostic value of circulating microRNA-27a/b in patients with acute pulmonary embolism. *Int Angiol, 37*, 19-25.

Wang, W., Zhu, X., Du, X., Xu, A., Yuan, X., Zhan, Y., Liu, M., & Wang, S. (2019). MiR-150 promotes angiogensis and proliferation of endothelial progenitor cells in deep venous thrombosis by targeting SRCIN1. *Microvasc Res, 123*, 35-41.

Wang, X., Cheng, Q., Xu, L., Feuerstein, G. Z., Hsu, M. Y., Smith, P. L., Seiffert, D. A., Schumacher, W. A., Ogletree, M. L., & Gailani, D. (2005). Effects of factor IX or factor XI deficiency on ferric chloride-induced carotid artery occlusion in mice. *J Thromb Haemost, 3*, 695-702.

Wang, X., Sundquist, K., Elf, J. L., Strandberg, K., Svensson, P. J., Hedelius, A., Palmer, K., Memon, A. A., Sundquist, J., & Zoller, B. (2016). Diagnostic potential of plasma microRNA signatures in patients with deep-vein thrombosis. *Thromb Haemost, 116*, 328-336.

Wang, X., Sundquist, K., Svensson, P. J., Rastkhani, H., Palmer, K., Memon, A. A., Sundquist, J., & Zoller, B. (2019). Association of recurrent venous thromboembolism and circulating microRNAs. *Clin Epigenetics, 11*, 28.

Wang, Y., Ma, Z., Kan, P., & Zhang, B. (2017). The Diagnostic Value of Serum miRNA-221-3p, miRNA-382-5p, and miRNA-4271 in Ischemic Stroke. *J Stroke Cerebrovasc Dis, 26*, 1055-1060.

Wang, Z. (2011). The principles of MiRNA-masking antisense oligonucleotides technology. *Methods Mol Biol, 676*, 43-49.

Weitz, J. I., Bauersachs, R., Becker, B., Berkowitz, S. D., Freitas, M. C. S., Lassen, M. R., Metzig, C., & Raskob, G. E. (2020). Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty: The FOXTROT Randomized Clinical Trial. *Jama, 323*, 130-139.

Weitz, J. I., & Fredenburgh, J. C. (2017). Factors XI and XII as Targets for New Anticoagulants. *Front Med (Lausanne), 4*, 19.

Wendelboe, A. M., & Raskob, G. E. (2016). Global Burden of Thrombosis: Epidemiologic Aspects. *Circ Res, 118*, 1340-1347.

Wheeler, A. P., & Gailani, D. (2016). The Intrinsic Pathway of Coagulation as a Target for Antithrombotic Therapy. *Hematol Oncol Clin North Am, 30*, 1099-1114.

Wilson, R. C., & Doudna, J. A. (2013). Molecular mechanisms of RNA interference. *Annu Rev Biophys, 42*, 217-239.

Witkowski, M., Weithauser, A., Tabaraie, T., Steffens, D., Krankel, N., Witkowski, M., Stratmann, B., Tschoepe, D., Landmesser, U., & Rauch-Kroehnert, U. (2016). Micro-RNA-126 Reduces the Blood Thrombogenicity in Diabetes Mellitus via Targeting of Tissue Factor. *Arterioscler Thromb Vasc Biol, 36*, 1263-1271.

Witkowski, M., Witkowski, M., Saffarzadeh, M., Friebel, J., Tabaraie, T., Ta Bao, L., Chakraborty, A., Dorner, A., Stratmann, B., Tschoepe, D., Winter, S. J., Krueger, A., Ruf, W., Landmesser, U., & Rauch, U. (2020). Vascular miR-181b controls tissue factor-dependent thrombogenicity and inflammation in type 2 diabetes. *Cardiovasc Diabetol, 19*, 20.

Wu, K. K., & Matijevic-Aleksic, N. (2005). Molecular aspects of thrombosis and antithrombotic drugs. *Crit Rev Clin Lab Sci, 42*, 249-277.

Xiang, Q., Zhang, H. X., Wang, Z., Liu, Z. Y., Xie, Q. F., Hu, K., Zhang, Z., Mu, G. Y., Ma, L. Y., Jiang, J., & Cui, Y. M. (2019). The predictive value of circulating microRNAs for venous thromboembolism diagnosis: A systematic review and diagnostic meta-analysis. *Thromb Res, 181*, 127-134.

Xiao, J., Jing, Z. C., Ellinor, P. T., Liang, D., Zhang, H., Liu, Y., Chen, X., Pan, L., Lyon, R., Liu, Y., Peng, L. Y., Liang, X., Sun, Y., Popescu, L. M., Condorelli, G., & Chen, Y. H. (2011). MicroRNA-134 as a potential plasma biomarker for the diagnosis of acute pulmonary embolism. *J Transl Med, 9*, 159.

Xie, X., Liu, C., Lin, W., Zhan, B., Dong, C., Song, Z., Wang, S., Qi, Y., Wang, J., & Gu, Z. (2016). Deep vein thrombosis is accurately predicted by comprehensive analysis of the levels of microRNA-96 and plasma D-dimer. *Exp Ther Med, 12*, 1896-1900.

Yamashita, D., Kondo, T., Ohue, S., Takahashi, H., Ishikawa, M., Matoba, R., Suehiro, S., Kohno, S., Harada, H., Tanaka, J., & Ohnishi, T. (2015). miR340 suppresses the stem-like cell function of glioma-initiating cells by targeting tissue plasminogen activator. *Cancer Res, 75*, 1123-1133.

Yang, D. T., Flanders, M. M., Kim, H., & Rodgers, G. M. (2006). Elevated factor XI activity levels are associated with an increased odds ratio for cerebrovascular events. *Am J Clin Pathol, 126*, 411-415.

Yau, J. W., Liao, P., Fredenburgh, J. C., Stafford, A. R., Revenko, A. S., Monia, B. P., & Weitz, J. I. (2014). Selective depletion of factor XI or factor XII with antisense oligonucleotides attenuates catheter thrombosis in rabbits. *Blood, 123*, 2102-2107.

Younis, H. S., Crosby, J., Huh, J. I., Lee, H. S., Rime, S., Monia, B., & Henry, S. P. (2012). Antisense inhibition of coagulation factor XI prolongs APTT without increased bleeding risk in cynomolgus monkeys. *Blood, 119*, 2401-2408.

Yu, A. M., Jian, C., Yu, A. H., & Tu, M. J. (2019). RNA therapy: Are we using the right molecules? *Pharmacol Ther, 196*, 91-104.

Zhang, H., Löwenberg, E. C., Crosby, J. R., MacLeod, A. R., Zhao, C., Gao, D., Black, C., Revenko, A. S., Meijers, J. C., Stroes, E. S., Levi, M., & Monia, B. P. (2010). Inhibition of the intrinsic coagulation pathway factor XI by antisense oligonucleotides: a novel antithrombotic strategy with lowered bleeding risk. *Blood, 116*, 4684-4692.

Zhang, M., Cheng, Y. J., Sara, J. D., Liu, L. J., Liu, L. P., Zhao, X., & Gao, H. (2017). Circulating MicroRNA-145 is Associated with Acute Myocardial Infarction and Heart Failure. *Chin Med J (Engl), 130*, 51-56.

Zhang, X., Yu, H., Lou, J. R., Zheng, J., Zhu, H., Popescu, N. I., Lupu, F., Lind, S. E., & Ding, W. Q. (2011). MicroRNA-19 (miR-19) regulates tissue factor expression in breast cancer cells. *J Biol Chem, 286*, 1429-1435.

Zhang, Y., Chen, M., Zhang, Y., Peng, P., Li, J., & Xin, X. (2014). miR-96 and miR-330 overexpressed and targeted AQP5 in lipopolysaccharide-induced rat lung damage of disseminated intravascular coagulation. *Blood Coagul Fibrinolysis, 25*, 731-737.

Zhang, Y., Miao, X., Zhang, Z., Wei, R., Sun, S., Liang, G., Li, H., Chu, C., Zhao, L., Zhu, X., Guo, Q., Wang, B., & Li, X. (2020). miR-374b-5p is increased in deep vein thrombosis and negatively targets IL-10. *J Mol Cell Cardiol, 144*, 97-108.

Zhang, Y., Zhang, Z., Wei, R., Miao, X., Sun, S., Liang, G., Chu, C., Zhao, L., Zhu, X., Guo, Q., Wang, B., & Li, X. (2020). IL (Interleukin)-6 Contributes to Deep Vein Thrombosis and Is Negatively Regulated by miR-338-5p. *Arterioscler Thromb Vasc Biol, 40*, 323-334.

Zhang, Z., Ran, Y., Shaw, T. S., & Peng, Y. (2016). MicroRNAs 10a and 10b Regulate the Expression of Human Platelet Glycoprotein Ibα for Normal Megakaryopoiesis. *Int J Mol Sci, 17*.

Zhao, L., Hua, C., Li, Y., Sun, Q., & Wu, W. (2015). miR-525-5p inhibits ADAMTS13 and is correlated with Ischemia/reperfusion injury-induced neuronal cell death. *Int J Clin Exp Med, 8*, 18115-18122.

Zhao, X., Pan, F., Holt, C. M., Lewis, A. L., & Lu, J. R. (2009). Controlled delivery of antisense oligonucleotides: a brief review of current strategies. *Expert Opin Drug Deliv, 6*, 673-686.

Zheng, Y., Li, Y., Liu, G., Qi, X., & Cao, X. (2018). MicroRNA-24 inhibits the proliferation and migration of endothelial cells in patients with atherosclerosis by targeting importin-alpha3 and regulating inflammatory responses. *Exp Ther Med, 15*, 338-344.

Zhou, J., & Rossi, J. (2017). Aptamers as targeted therapeutics: current potential and challenges. *Nat Rev Drug Discov, 16*, 181-202.

Zhou, J., & Zhang, J. (2014). Identification of miRNA-21 and miRNA-24 in plasma as potential early stage markers of acute cerebral infarction. *Mol Med Rep, 10*, 971-976.

Zhou, X., Wen, W., Shan, X., Qian, J., Li, H., Jiang, T., Wang, W., Cheng, W., Wang, F., Qi, L., Ding, Y., Liu, P., Zhu, W., & Chen, Y. (2016). MiR-28-3p as a potential plasma marker in diagnosis of pulmonary embolism. *Thromb Res, 138*, 91-95.

Zhou, Y., Abraham, S., Andre, P., Edelstein, L. C., Shaw, C. A., Dangelmaier, C. A., Tsygankov, A. Y., Kunapuli, S. P., Bray, P. F., & McKenzie, S. E. (2015). Anti-miR-148a regulates platelet FcgammaRIIA signaling and decreases thrombosis in vivo in mice. *Blood, 126*, 2871-2881.

Zhu, J., Yao, K., Wang, Q., Guo, J., Shi, H., Ma, L., Liu, H., Gao, W., Zou, Y., & Ge, J. (2016). Circulating miR-181a as a Potential Novel Biomarker for Diagnosis of Acute Myocardial Infarction. *Cell Physiol Biochem, 40*, 1591-1602.

Zhu, S., Rooney, S., & Michlewski, G. (2020). RNA-Targeted Therapies and High-Throughput Screening Methods. *Int J Mol Sci, 21*.

Zhu, W., Buffa, J. A., Wang, Z., Warrier, M., Schugar, R., Shih, D. M., Gupta, N., Gregory, J. C., Org, E., Fu, X., Li, L., DiDonato, J. A., Lusis, A. J., Brown, J. M., & Hazen, S. L. (2018). Flavin monooxygenase 3, the host hepatic enzyme in the metaorganismal trimethylamine N-oxide-generating pathway, modulates platelet responsiveness and thrombosis risk. *J Thromb Haemost, 16*, 1857-1872.

Zhu, X. F., Shan, Z., Ma, J. Y., Wang, M., Zhang, C. X., Liu, R. M., Wu, W. B., Shi, Y. W., Li, W., & Wang, S. M. (2015). Investigating the Role of the Posttranscriptional Gene Regulator MiR-24- 3p in the Proliferation, Migration and Apoptosis of Human Arterial Smooth Muscle Cells in Arteriosclerosis Obliterans. *Cell Physiol Biochem, 36*, 1359-1370.

Figure Legends

Figure 1. New rational therapeutic targets in the hemostatic system. The hemostatic system is tightly balanced to reduce blood loss by formation of blood clots (hemostasis), while at the same time preventing pathological clot formation (thrombosis). Deficiencies of the intrinsic pathway factors XII and XI are usually not associated with abnormal hemostasis but appear to prevent thrombus formation, qualifying them as attractive therapeutic targets. As FXI is exclusively targeted by miRNAs it provides an attractive avenue for therapeutic targeting (further details see text). miRNA-mediated control of gene expression provides an attractive avenue for therapeutic targeting of factor XI as opposed to current therapies which target the extrinsic and common pathways (such as Vitamin K antagonists, direct oral anticoagulants (DOACS) or antithrombin dependent* (low molecular weight) heparins).

Figure 2. FXI is under tight post-transcriptional control. (A) FXI plasma levels exhibit a leptokurtic distribution as compared to platokurtic distribution type of FXII (levels of FXI and FXII from patients admitted to the University Medical Center Mainz from 2012 to 2018; values were limited to patients for which both FXI and FXII assays were performed and extremes (levels ≥150% and ≤50%) have been excluded, normal distributions with standard deviations corresponding to those of FXI and FXII are shown dashed. Unpublished data). **(B)** Schematic of the in vitro pull down assay used to identify 3'UTR interacting miRNAs and RBP. Briefly baits consisting of in vitro transcribed 3'UTRs fused to copies of the bacteriophage MS2 stem-loop were immobilized by binding to amylose resin via recombinant MS2 coat protein-maltose binding (MBP-MS2BP) fusion protein. Immobilized baits were incubated with cell extracts to allow binding of 3'UTR interacting factors. Following washing protein–RNA complexes were eluted

with maltose and either RNA or proteins were purified and identified using RNA-sequencing and mass spectrometry. **(C)** Density of potential sites for miRNA and RNA-binding proteins (RBPs) across FXI 3'UTR. 125 FXI-3'UTR/miRNA interactions were identified by miTRAP/RNA-seq (Nourse, et al., 2018) and of these 41 are mapped to the FXI 3'UTR using miRWalk target site prediction. 392 FXI-3'UTR/RBP interactions identified by miTRAP/MS (unpublished data) and of these 66 could be mapped to the FXI 3'UTR using RBPDB target site prediction. Site density calculated by number of sites present in 50 nt windows over length of the FXI-3'UTR.

Figure 3. Function and consequences of therapeutic miRNA targeting versus antisense oligonucleotide (ASO) silencing. Post-transcriptional mechanisms mediated by the binding of RNA-binding proteins (RBPs), lncRNAs and miRNAs to regulatory elements in 3'UTRs of mRNAs, including competition and cooperativity of these regulatory components, to adjust protein synthesis in a spatiotemporal manner. As opposed to ASO silencing, and in many cases siRNAs, (right), which inevitably results in degradation of the target mRNA, the partial base-pairing of miRNAs (left) prevents the cleavage activity of RISC with silencing predominately resulting from translational repression, and in some cases deadenylation, decapping and finally mRNA degradation (Bartel, 2009). Thus, miRNA-mediated therapeutic targeting without degradation of such target mRNAs preserves cell intrinsic regulatory mechanisms executed by 3’UTRs and their ‘interacting partners’ such as RBPs, miRNAs and/or other layers of control, such as ceRNA, circRNA miRNA sponges. Finally miRNA sites in proximity to RBP sites are often subject to mechanisms of physiological control (Danckwardt, et al., 2008; Jens & Rajewsky, 2015; Y. C. Lu, et al., 2014; Tay, et al., 2014), which may play important regulatory roles to control the delicate balance of hemostatic system in response to environmental cues (Danckwardt, et al., 2011).

Table 1. General features of different next-generation therapeutics in the hemostatic system.

	ASO/LNA/siRNA	miRNA	Antibody/biological	Small molecule
Structure	ASO/LNA: ~12-25 nucleotide single stranded RNA siRNA: 21-23 nucleotide RNA duplex with 2 nucleotides 3'overhang	19-25 nucleotide RNA duplex with 2 nucleotides 3'overhang.	Variable	Variable
Targeting	Fully complementary to mRNA	Partially complementary to mRNA, typically targeting the 3' untranslated region of mRNA	Binds catalytic domain, can mimic catalytic activities (bispecific antibodies)	Binds catalytic domain
Mechanism of (gene) regulation	Endonucleolytic cleavage and degradation of mRNA	Translational repression (particularly prevalent for secretory proteins), endonucleolytic cleavage and degradation of mRNA (especially in case of high complementarity between miRNA and mRNA)	Gain or loss of function by blocking catalytic activity of a enzyme or by chaperoning conformational complex formations (e.g. Emicizumab)	Blocks catalytic activity of enzyme
Role, clinical application	Therapeutic agent (loss of function)	Endogenous cell intrinsic gene regulatory mechanism Diagnostic tool Biomarker Drug target and therapeutic agent (loss (mimic) and gain (antagomir) of function)	Therapeutic agent (loss and gain of function)	Therapeutic agent (loss of function)
Advantages (therapeutic)	Strong effect size Easily synthesized in commercial laboratories	Mimics physiological gene regulation Synergy with intrinsic target gene regulatory mechanisms Easily synthesized in commercial laboratories	Blocks/mimics enzymatic activity	Blocks enzymatic activity
Limitations (therapeutic)	Unspecific effect on platelet count, others? Potential off target effects May induce partial IFN response and innate immune responses Thrombocytopenia	Potential off target effects Smaller effect size	Interference with diagnostics Undesired immune reactions Provokes production of inhibiting antibodies	Variable
Therapeutic delivery	Injection	Injection Exosomes?	Injection (s.c./i.v.)	Oral/injection
Target (number)	Single	Multiple	Single (multiple, bispecific antibodies)	Single
Target	Any gene (including 'undruggable' targets)	miRNA targeted genes (including 'undruggable' targets)	Enzymes	Enzymes
Manufacturing process Development timeline	Easily synthesized Rapid	Easily synthesized Rapid	Subject to purification and post-translational modifications issues Slow	Unique chemical synthesis process for each compound Slow
Pharmaco-kinetics	Consistent	Consistent	Individual	Individual

Table 2. RNA based anti-thrombotic therapeutics

Status	Species	Type	Target	Outcome	References
Pre-clinical	Mouse	ASO	FII	Reduction of thrombosis, however deleterious effects on bleeding tendency	(J. Crosby, et al., 2009)
Pre-clinical	Mouse	ASO (ISIS 401025)	FII	Clotting times, PT and aPTT, significantly prolonged and correlated to degree of target inhibition	(Monia , et al., 2007)
Pre-clinical	Mouse	ASO	FMO3	Impacted platelet responsiveness and rate of thrombus formation	(W. Zhu, et al., 2018)
Pre-clinical	Primate	ASO	FVII	Antithrombotic effects, however significant impairment of hemostasis	(Wallisch, et al., 2020)
Pre-clinical	Mouse	ASO	FVII	Prolongation of dilute PT, however no influence on dilute aPTT	(Vu, et al., 2015)
Phase 2	Human	ASO (ISIS-FXIRx)	FXI	Reduced incidence and clot size of venous thromboembolism after surgery without increased bleeding risk	(Büller, et al., 2015)
Pre-clinical	Mouse	ASO	FXI	Safely prevented thrombus formation on acutely ruptured atherosclerotic plaques	(van Montfoort, et al., 2014)
Pre-clinical	Rabbit	ASO	FXI	Prolongation of time to catheter occlusion	(Yau, et al., 2014)
Pre-clinical	Primate	ASO	FXI	Antithrombotic effect without an increased risk of bleeding in arterial thrombosis model	(J. R. Crosby, et al., 2013)
Pre-clinical	Mouse	ASO	FXI	Reduction in thrombus formation in venous thrombosis model	(H. Zhang, et al., 2010)
Pre-clinical	Primate	ASO (ISIS 416858)	FXI	Increase in APTT with no effects on PT, platelets, or increased bleeding	(Younis, et al., 2012)
Pre-clinical	Rabbit	ASO	FXII	Prolongation of time to occlusion in a catheter thrombosis model	(Yau, et al., 2014)
Pre-clinical	Mouse	ASO	FXII	Reduction of arterial and venous thrombosis formation, without significant effect on normal hemostasis	(Revenko, et al., 2011)
Pre-clinical	Mouse	ASO	FXII	Prolongation of dilute aPTT, however no effect on the dilute PT	(Vu, et al., 2015)
Pre-clinical	Rabbit	ASO	FXII	Prolongation of time to catheter occlusion	(Yau, et al., 2014)
Pre-clinical	Rat	siRNA	FXII	Protection in arterial and venous thrombosis models	(Cai, et al., 2015)
Pre-clinical	Mouse	Antagomir	miR-148a	Reduction of thrombus formation following intravascular platelet activation via FcγRIIA	(Y. Zhou, et al., 2015)
Pre-clinical	Mouse	Mimic	miR-30c	Significant inhibition of arterial thrombosis formation	(Luo, et al., 2016)
Pre-clinical	Mouse	Mimic	miR-338-5p	Thrombus weight greatly decreased in inferior vena cava stenosis DVT model	(Y. Zhang, Zhang, et al., 2020)
Pre-clinical	Mouse	Antagomir	miR-374b-5p	Thrombus length and weight greatly decreased in inferior vena cava stenosis DVT model	(Y. Zhang, Miao, et al., 2020)

Pre-clinical	Mouse	Mimic	miR-495	Reduction in occurrence and development of thrombosis of femoral vein	(Tang, et al., 2018)
Pre-clinical	Mouse	Mimic	miR-103a-3p	Thrombus size decreased in IVC ligation model	(S. Sun, et al., 2020)
Pre-clinical	Mouse	Antagomir	miR-19b-3p	Significant increase of antithrombin activity	(Nourse, et al., 2018)
Pre-clinical	Rat	ASO	PAI-1	Protection against arterial thrombus formation	(Pawlowska, et al., 1998)
Pre-clinical	Rat	ASO (MPO-16R)	PAI-1	Significant delay in arterial thrombosis model occlusion time	(Pawlowska, et al., 2001)
Pre-clinical	Mouse	ASO	Prekallikrein	Reduction of arterial and venous thrombosis formation, without significant effect on normal hemostasis	(Revenko, et al., 2011)
Pre-clinical	Primate	ASO	Thrombopoietin	Sustained decline in platelet count	(Shirai, et al., 2019)

Table 3. A. Functional miRNAs targeting the hemostatic system. The first two columns are based on the hemostatic miRNA targetome identified in Nourse et. al. (Nourse, et al., 2018) by miTRAP RNA pull-downs. The first column indicates interactions validated by functional miRNA-mimic-rescue luciferase assays, while the second column indicates interactions identified by miTRAP RNA pull-down alone (Nourse, et al., 2018). The last column indicates miRNAs identified from the literature to directly target the gene 3'UTR of blood coagulation factors indicated. **B.** Identity of functionally validated FXI targeting miRNAs and their role in cardiovascular disorders (AMI, acute myocardial infarction; VTE, venous thromboembolism; PAD, peripheral artery disease; CAD, coronary artery disease; DIC, disseminated intravascular coagulation).

A

		miRNAs identified in hemostatic miRNA targetome		**Directly targeting miRNAs identified previously in literature**	
Gene	**Gene Description**	**Directly targeting**	**Potential targeting**	**Directly targeting**	**References**
F11	**Coagulation factor XI**	**10**	**126**	**4**	**(Salloum-Asfar, et al., 2014; Sennblad, et al., 2017; Vossen, et al., 2017)**
F8	Coagulation factor VIII	7	172	6	(Jankowska, Chattopadhyay, et al., 2020; Jankowska, McGill, et al., 2020; Sarachana, et al., 2015)
SERPINA10	Protein Z-Dependent Protease Inhibitor (ZPI)	7	122	0	
SERPIND1	Heparin co-factor II	6	74	0	
PROZ	Protein Z	6	57	0	
PLG	Plasminogen	5	128	0	
FGG	Fibrinogen gamma chain	4	127	0	
FGA	Fibrinogen alpha chain	2	225	2	(Z. Chen, et al., 2010; Fort, et al., 2010)
F7	Coagulation factor VII	2	103	0	
SERPINC1	Antithrombin III	2	57	0	
KLKB1	Kallikrein B1	1	48	0	
FGB	Fibrinogen beta chain	0	145	1	(Fort, et al., 2010)
PROC	Protein C	0	79	0	
PLAT	Plasminogen activator tissue type (tPA)	0	76	2	(Terao, et al., 2011; Yamashita, et al., 2015)
GP1BA	Glycoprotein Ib platelet alpha subunit	0	0	2	(Z. Zhang, Ran, Shaw, & Peng, 2016)
ADAMTS13	ADAM metallopeptidase with thrombospondin type 1 motif 13	0	0	1	(L. Zhao, et al., 2015)
F12	**Coagulation factor XII**	**0**	**0**	**0**	
F13B	Coagulation factor XIII B polypeptide	0	0	0	
F2	Coagulation factor II (thrombin)	0	0	0	
F5	Coagulation factor V	0	0	0	
HABP2	Hyaluronan binding protein 2	0	0	0	
HRG	Histidine-rich glycoprotein	0	0	0	
KNG1	Kininogen 1	0	0	0	
SERPINF2	Alpha-2-antiplasmin	0	0	0	

B

miRNA	Thrombosis/Hemostasis associations	References
miR-103a-3p	**Targets FXI**	(Nourse, et al., 2018)
miR-103a-3p	Involved in atherosclerosis and vascular inflammation by suppressi of KLF4	(Hartmann, et al., 2016)
miR-103a-3p	Biomarker for VTE	(Starikova, et al., 2015)
miR-1255a	**Targets FXI**	(Nourse, et al., 2018)
miR-1255a	Biomarker for stroke	(Edwardson, et al., 2018)
miR-145-5p	**Targets FXI**	(Sennblad, et al., 2017)
miR-145-5p	Biomarker for CAD, AMI, stroke, long-term outcome	(Dong, et al., 2015; Faccini, et al., 2017; Gao, et al., 2015; Jia, H Wang, & Qu, 2015; Maitrias, et al., 2015; Meder, et al., 2011; Sal et al., 2014; M. Zhang, et al., 2017)
miR-145-5p	Impedes thrombus formation in atherosclerosis by targeting tissue factor and influencing platelet reactivity	(de Freitas, et al., 2017; Sahu, et al., 2017)
miR-148b-3p	**Targets FXI**	(Nourse, et al., 2018)
miR-151a-3p	**Targets FXI**	(Nourse, et al., 2018)
miR-15b-5p	**Targets FXI**	(Nourse, et al., 2018)
miR-15b-5p	Involved in development of hemophilic arthropathy	(Sen & Jayandharan, 2016)
miR-15b-5p	Biomarker for PAD	(Stather, et al., 2013)
miR-15b-5p	Influences platelet reactivity and clopidogrel response	(de Freitas, et al., 2017)
miR-181a-5p	**Targets FXI**	(Salloum-Asfar, et al., 2014; Sennblad, et al., 2017)
miR-181a-5p	Biomarker for AMI and PAD	(Stather, et al., 2013; J. Zhu, et al., 2016)
miR-181b-5p	**Targets FXI**	(Nourse, et al., 2018)
miR-181b-5p	Serum levels altered in patients with atherosclerosis	(X. Li & Cao, 2015)
miR-191a-5p	**Targets FXI**	(Salloum-Asfar, et al., 2014)
miR-24-3p	**Targets FXI**	(Nourse, et al., 2018)
miR-24-3p	Biomarker for acute cerebral infarction, arteriosclerosis obliterans, atherosclerosis and severe trauma	(L. J. Chen, et al., 2017; Zheng, Li, Liu, Qi, & Cao, 2018; J. Zhou Zhang, 2014; X. F. Zhu, et al., 2015)
miR-30a-3p	**Targets FXI**	(Nourse, et al., 2018)
miR-30a-3p	Biomarker for AMI and ischemic stroke	(Long, et al., 2012; Long, et al., 2013)
miR-30d-3p	**Targets FXI**	(Nourse, et al., 2018)
miR-544a	**Targets FXI**	(Vossen, et al., 2017)
miR-96-5p	**Targets FXI**	(Nourse, et al., 2018)
miR-96-5p	Biomarker for DVT and DIC	(Xie, et al., 2016; Y. Zhang, et al., 2014)

Figures

Figure 1

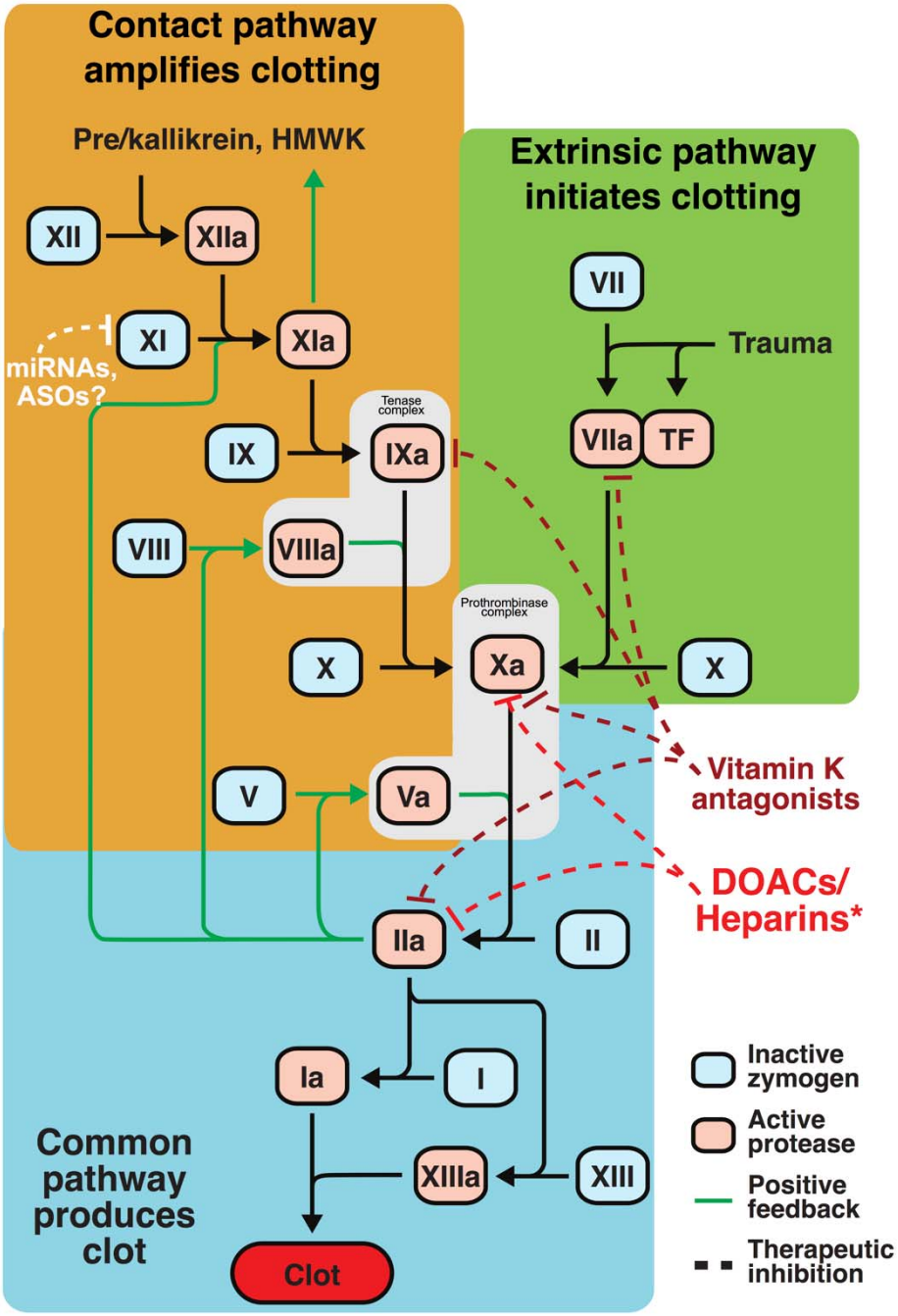


Figure 2

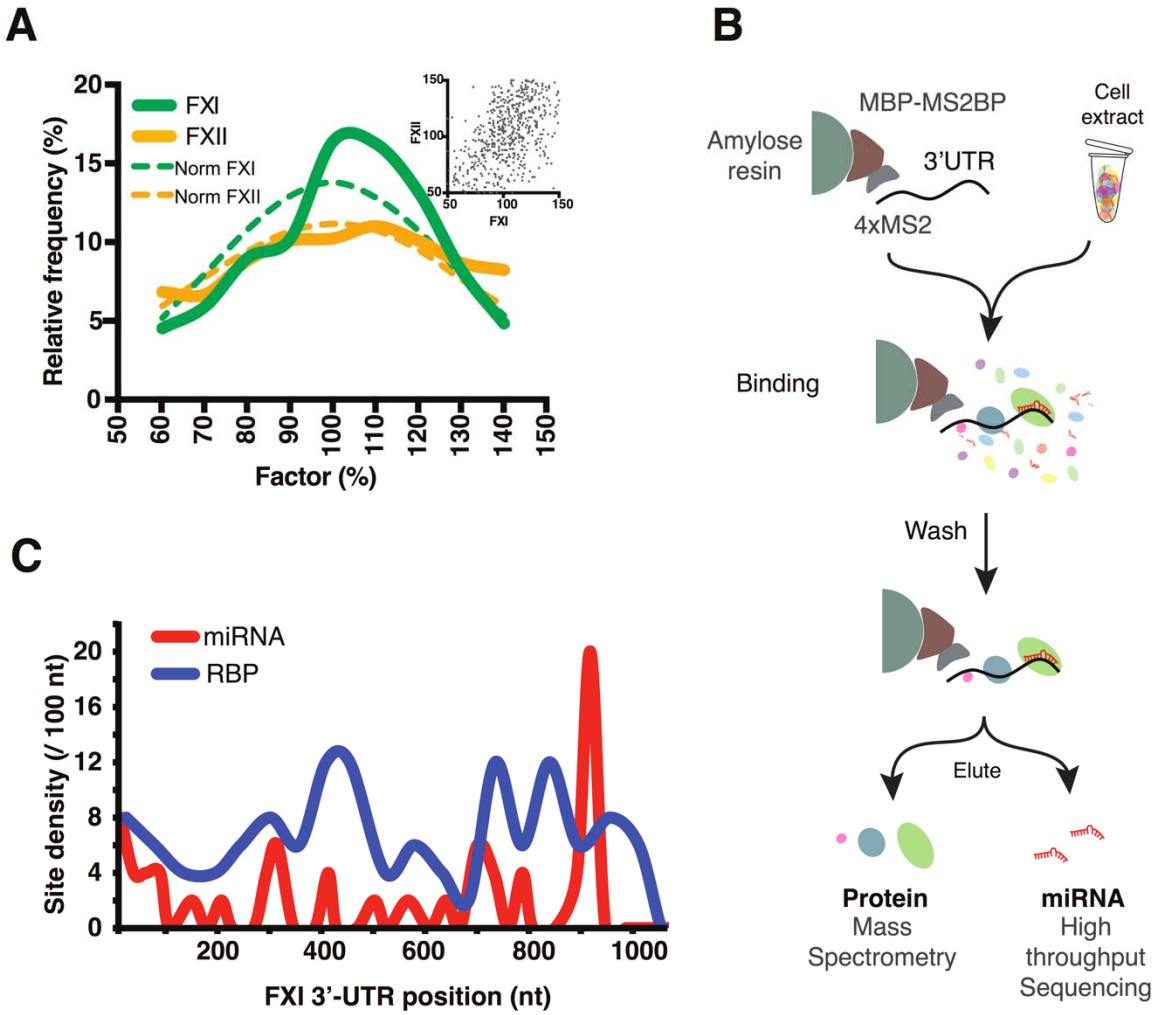
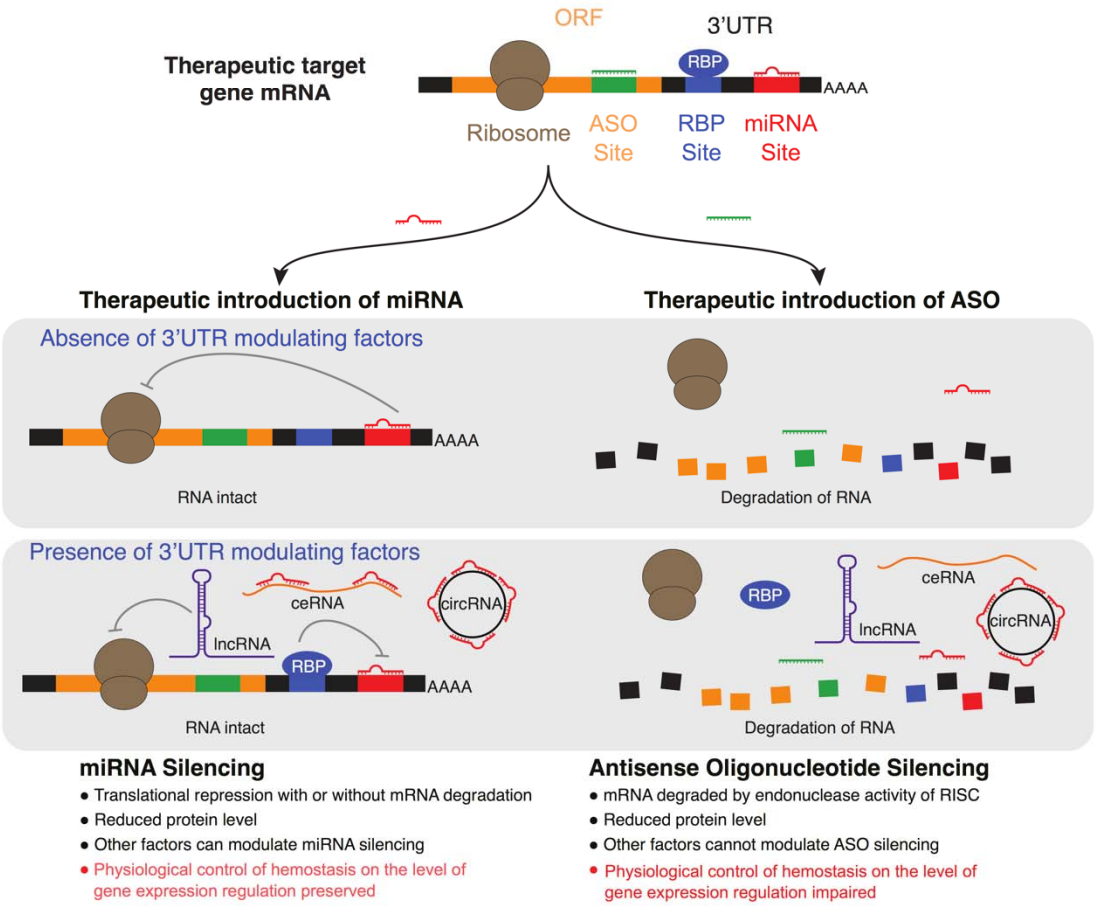

A
FXI
FXII
Norm FXI
Norm FXII
Relative frequency (%)
Factor (%)
FXII
FXI
B
MBP-MS2BP
Cell extract
Amylose resin
3'UTR
4xMS2
Binding
Wash
Elute
Protein
Mass Spectrometry
miRNA
High throughput Sequencing
C
miRNA
RBP
Site density (/ 100 nt)
FXI 3'-UTR position (nt)

Figure 3



miRNA Silencing

- Translational repression with or without mRNA degradation
- Reduced protein level
- Other factors can modulate miRNA silencing
- Physiological control of hemostasis on the level of gene expression regulation preserved

Antisense Oligonucleotide Silencing

- mRNA degraded by endonuclease activity of RISC
- Reduced protein level
- Other factors cannot modulate ASO silencing
- Physiological control of hemostasis on the level of gene expression regulation impaired