Precision medicine in hemostasis: a review of prothrombin complex concentrates and the role of viscoelastic tests in tailoring therapy

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Abstract

This review explores the role of precision medicine in the management of bleeding disorders and anticoagulation therapy, with a focus on the use of visco-elastic tests such as Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM). These tests provide real-time, dynamic insight into a patient's coagulation status, guiding the choice between three-factor prothrombin complex concentrate (PCC3) and four-factor PCC (PCC4), as well as the use of activated four-factor PCC (FEIBA). The specific ROTEM tests, INTEM and EXTEM, further enhance our understanding of the intrinsic and extrinsic coagulation pathways. Moreover, the use of tranexamic acid (TXA) and fibrinogen, guided by these visco-elastic tests, has shown promise in trauma patients. TXA has been associated with survival benefit when administered immediately or within 3 hours of injury. Fibrinogen, a key factor in clot formation, can be monitored and supplemented as needed to optimize hemostasis. In conclusion, the practice of precision medicine, with the aid of TEG and ROTEM, offers the potential to enhance the safety and efficacy of PCC therapy, TXA administration, and fibrinogen supplementation. These tools are invaluable in tailoring therapy to the specific needs of each patient, potentially optimizing patient outcomes and minimizing the risk of adverse events.

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Highlights

- *Real-time Coagulation Assessment: TEG and ROTEM provide real-time and dynamic insights into a patient's coagulation status, enabling precise decision-making in therapy selection.*
- *Choice of Prothrombin Complex Concentrate (PCC): these tests guide the choice between three-factor PCC3 and four-factor PCC4, as well as the use of activated four-factor PCC (FEIBA), tailored to individual patient needs.*
- *ROTEM Tests: specific ROTEM tests, such as INTEM and EXTEM, enhance understanding of the intrinsic and extrinsic coagulation pathways, aiding in targeted interventions.*
- *Tranexamic Acid (TXA): TXA, administered based on visco-elastic tests, has shown survival benefits when given promptly, particularly within 3 hours of injury.*
- *Fibrinogen Optimization: monitoring and supplementation of fibrinogen, a crucial clotting factor, is facilitated by visco-elastic tests, ensuring hemostasis is optimized for each patient.*
- *Enhancing Safety and Efficacy: precision medicine, with TEG and ROTEM, has the potential to enhance the safety and effectiveness of PCC therapy, TXA administration, and fibrinogen supplementation.*
- *Tailored Therapy: these tools enable tailoring of therapy to meet the specific needs of each patient, which can ultimately optimize patient outcomes and reduce the risk of adverse events.*

Introduction

Prothrombin complex concentrate (PCC) is a critical therapeutic agent used in the management of bleeding disorders.[1] It is a

blood product that contains concentrated amounts of several essential blood clotting factors, specifically factors II, VII, IX, and X in non-activated form. PCC is available in two forms: three-factor PCC (PCC3), which contains factors II, IX, and X, and four-factor PCC (PCC4), which additionally includes factor VII. These agents are primarily used for the rapid reversal of anticoagulation in patients with major bleeding or prior to emergency surgery.[2]

The choice between PCC3 and PCC4 is often dictated by the clinical context, the specific coagulation factor deficiencies present, and the risk of potential adverse events.[2] Recent studies have shown that PCC4 may be more effective in achieving target INR levels in patients requiring emergent warfarin reversal, suggesting a potential advantage over PCC3. However, the risk of thromboembolic events remains a significant concern, necessitating careful consideration and monitoring.[1]

In this context, thromboelastometry emerges as a valuable tool in guiding the use of PCC3. Thromboelastometry is a point-of-care coagulation test that provides comprehensive information about the coagulation process, from clot formation to fibrinolysis.[3] It offers real-time, dynamic insight into the patient's coagulation status, enabling personalized, targeted therapy. This is particularly important in complex clinical scenarios where standard coagulation tests may not provide a complete picture of the patient's coagulation status.[4]

The use of thromboelastometry in guiding PCC therapy has the potential to optimize patient outcomes, minimize the risk of adverse events, and contribute to more cost-effective care. This narrative review will explore the advantages and drawbacks of three-factor versus four-factor PCC, and discuss the role of thromboelastometry in guiding their use.[5]

Prothrombin complex concentrate (PCC)

Prothrombin complex concentrate (PCC) is derived from the process of ion-exchange chromatography from the cryoprecipitate supernatant of large plasma pools, after the removal of antithrombin and factor XI. Depending on the processing techniques, PCC can be classified into: i) three-factor PCC (contains factors II, IX, and X), and ii) four-factor PCC (encompasses factors II, VII, IX, and X).

Three-factor prothrombin complex

Three-factor prothrombin complex concentrate (PCC3) is a vital therapeutic agent used in the management of bleeding disorders, particularly in the context of spontaneous intracerebral hemorrhage (ICH) and severe trauma.[6-8] ICH, defined as nontraumatic bleeding into the brain parenchyma, is a significant global health issue, with high case fatality and a large proportion of survivors experiencing dependence within six months post-event.[6] Chronic arterial hypertension, cerebral amyloid angiopathy, and anticoagulation are commonly associated with ICH.

PCC3, which contains factors II, IX, and X, is often used for the rapid reversal of anticoagulation in patients with major bleeding or prior to emergency surgery. The choice of PCC3 is often influenced by the clinical context, the specific coagulation factor deficiencies present, and the risk of potential adverse events.[7]

Despite the effectiveness of PCC3 in managing bleeding disorders, it is not without drawbacks. The absence of factor VII in PCC3 may limit its efficacy in certain clinical scenarios, particularly in patients with deficiencies or functional impairments of this factor.[7] Furthermore, the risk of thromboembolic events remains a significant concern, necessitating careful consideration and monitoring.[8] The management of bleeding and coagulopathy following major trauma requires a comprehensive, multidisciplinary approach. The use of PCC3 should be guided by evidence-based clinical protocols to ensure a uniform and high standard of care.[8]

Four-factor prothrombin complex

Four-factor prothrombin complex concentrate (PCC4) is an essential therapeutic agent used in the management of bleeding disorders, particularly in the context of anticoagulant-associated major or life-threatening bleeding.[9] PCC4 contains factors II, VII, IX, and X, and is often used for the rapid reversal of anticoagulation in patients with major bleeding or prior to emergency surgery.[10]

The use of PCC4 has been shown to be effective in reversing the effects of both vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). This is particularly important given the increasing use of these agents in clinical practice and the associated risk of major and life-threatening bleeding.[9]

However, the use of PCC4 is not without challenges. The risk of thromboembolic events remains a significant concern, necessitating careful consideration and monitoring.[10] Furthermore, the lack of specific reversal antidotes for DOACs poses a real challenge, despite accumulating experience and awareness.[9]

The management of bleeding and coagulopathy following major trauma requires a comprehensive, multidisciplinary approach. The use of PCC4 should be guided by evidence-based clinical protocols to ensure a uniform and high standard of care.[7]

Indications

Initially developed for managing hemophilia, the role of PCC has significantly evolved with the availability of recombinant replacement factors. Today, it serves as a critical replacement therapy for both congenital and acquired vitamin-K deficiency, especially in emergent scenarios involving warfarin-induced anticoagulant effects.

The FDA-approved indication for PCC is the urgent reversal of acquired coagulation factor deficiency due to warfarin-induced anticoagulation. This is particularly vital for patients with major acute bleeding events or those in need of urgent surgeries. The American College of Cardiology (ACC) now recommends 4-factor PCC as the preferred choice for reversing warfarin-induced bleeding.[11]

Off-label applications of PCC include:

DOAC reversal: DOACs, including dabigatran (a direct thrombin inhibitor) and factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban, have revolutionized anticoagulant therapy. Their predictable pharmacokinetics, fewer drug interactions, and the elimination of the need for regular monitoring have made them a preferred choice in many clinical scenarios. However, their widespread use presents challenges in situations of bleeding or urgent surgery. For the reversal of dabigatran, idarucizumab, a monoclonal antibody fragment, has been approved and demonstrated effectiveness. Factor Xa inhibitors, on the other hand, can be counteracted using andexanet alfa, a modified recombinant human factor Xa protein. In the absence of these specific antidotes or when they are not readily available, PCCs have been proposed as a potential alternative. The American College of Cardiology (ACC) endorses PCC for reversing Xa inhibitors and direct thrombin inhibitors when specific antidotes are not accessible. While PCCs are tradi-

tionally indicated for vitamin K antagonist reversal, emerging evidence highlights their potential in counteracting DOAC effects. Despite this, clinicians should approach the use of PCCs in DOAC reversal with caution, basing decisions on available guidelines, current evidence, and clinical judgment.[12]

Treatment for Congenital Deficiency: In rare instances where purified factor isn't available, 4-factor PCC can be utilized as a treatment or prophylaxis of bleeding in patients with a congenital deficiency of vitamin K-dependent coagulation factors.

Peri-operative use: PCC has shown efficacy in reducing perioperative bleeding, both as a prophylactic measure and as a treatment.[13]

Trauma setting: Especially when paired with FFP, PCC can be effective in trauma scenarios requiring massive transfusions. However, its lack of factor V can sometimes limit its standalone efficacy.[14]

Activated four-factor prothrombin complex (FEIBA) in the context of DOAC-associated bleeding

Activated four-factor prothrombin complex, better known as Factor Eight Inhibitor Bypassing Activity (FEIBA), stands as a pivotal therapeutic agent in the domain of bleeding disorder management. It assumes particular significance when addressing anticoagulant-associated major or life-threatening bleedings. Comprising factors II, VII, IX, and X – much like PCC4 – FEIBA's distinctive feature is the inclusion of activated factor VII.

While Direct Oral Anticoagulants (DOACs) like dabigatran, rivaroxaban, apixaban, and edoxaban, have been progressively endorsed as suitable alternatives to traditional vitamin K antagonists, they come with challenges. Chief among these is the management of bleeding episodes, especially when specific reversal agents are unavailable or when there's an inability to standardize laboratory assessments for their anticoagulant effects. In this context, FEIBA has demonstrated efficacy in counteracting the anticoagulant effects of DOACs. This breakthrough is particularly salient given the burgeoning clinical reliance on these agents and the concomitant risk they pose for major and life-threatening bleedings.

Nevertheless, the therapeutic landscape with FEIBA isn't devoid of challenges. Mirroring the concerns with PCC4, FEIBA administration is shadowed by the potential risk of thromboembolic events, underscoring the need for judicious application and vigilant monitoring. As the medical community grapples with the absence of specific reversal antidotes for DOACs, FEIBA emerges as a beacon of hope, albeit one that necessitates an evidence-informed, multidisciplinary strategy to ensure its optimal and safe application in clinical scenarios.[9-15]

Factor VII

Factor VII (FVII), a vitamin K-dependent glycoprotein primarily synthesized in the liver, plays a crucial role in the initiation of the extrinsic coagulation pathway. It circulates within the bloodstream in both its zymogen and activated forms. Upon vascular injury, tissue factor (TF) – a transmembrane protein from subendothelial cells – becomes exposed to blood flow. This interaction catalyzes the transformation of FVII to its active form, Factor VIIa. Subsequently, the TF-FVIIa complex activates both Factor IX and Factor X, instigating a cascade that culminates in fibrin clot formation.[16] Individuals with congenital Factor VII deficiency present a bleeding phenotype, the severity of which correlates with residual Factor VII activity levels. The management of such individuals necessitates Factor VII replenishment. Historically, Prothrombin Complex Concentrates (PCC3 and PCC4) were utilized for this purpose. However, these solutions often fell short in providing ample Factor VII. This gap in therapeutic management led to the introduction of non-activated Factor VII as a targeted therapeutic agent, specifically tailored for patients with isolated Factor VII deficiency. This advancement ensures the delivery of precise Factor VII dosages, effectively mitigating bleeding risks.

Moreover, Recombinant activated Factor VII (rFVIIa) offers a distinct therapeutic approach. It emulates the action of endogenous Factor VIIa, directly activating Factor X in the presence of TF without necessitating Factors VIII and IX. This unique mechanism has expanded its application spectrum, making it suitable not just for Factor VII deficiency but also other bleeding disorders where traditional treatments might be inadequate. Notably, individual responses can vary even among patients with similar Factor VII activity levels, hinting at the influence of other genetic and environmental factors on clinical presentation.

Comparison of three-factor and four-factor prothrombin complex

The choice between three-factor (PCC3) and four-factor prothrombin complex concentrate (PCC4) is often dictated by the clinical context, the specific coagulation factor deficiencies present, and the risk of potential adverse events. Both PCC3 and PCC4 have been shown to be effective in the management of bleeding disorders, particularly in the context of anticoagulant-associated major or life-threatening bleeding.[9,10]

PCC4, which additionally includes factor VII, has been found to be more effective in achieving target INR levels in patients requiring emergent warfarin reversal. This suggests a potential advantage over PCC3, particularly in patients with deficiencies or functional impairments of factor VII.[10] However, both PCC3 and PCC4 carry a risk of thromboembolic events, which remains a significant concern. This necessitates careful consideration and monitoring when using these agents. The risk of thromboembolic events may be influenced by a variety of factors, including the patient's underlying health status, the presence of other risk factors for thrombosis, and the specific clinical context.[9,10]

In conclusion, while PCC3, PCC4 (also FEIBA) all play a vital role in the management of bleeding disorders, their use must be guided by a careful assessment of the potential benefits and risks in each individual patient's context.[9,10]

Alternative strategy: PCC3 as default therapy and factor VII as needed

Given the costs and potential risks associated with the use of four-factor prothrombin complex concentrate (PCC4), an alternative and more cost-effective strategy could be to employ three-factor prothrombin complex concentrate (PCC3) as a foundational therapy, supplementing with factor VII based on real-time coagulation assessments using thromboelastometry, such as ROTEM. Recent clinical instances underscore the potential of ROTEM in guiding the management of intraoperative bleeding, especially in patients with factor VII deficiency. For instance, in a case where a patient with factor VII deficiency experienced severe intraoperative bleeding, ROTEM played a pivotal role in determining the need for, and subsequently guiding the administration of, additional recombinant activated factor VII (rFVIIa) doses, leading to successful bleeding control.[17,18]

Opting for PCC3, which is generally more economical than PCC4, as the initial treatment can be particularly advantageous in healthcare environments where cost-efficiency is crucial. Thromboelastometry can serve as a rapid and real-time diagnostic

tool to tailor the treatment approach, potentially enhancing patient outcomes while reducing the risk of adverse events. However, such an approach demands rigorous monitoring and profound clinical expertise to ascertain the appropriate use of factor VII. Additionally, the inherent risk of thromboembolic events associated with factor replacement calls for meticulous consideration and surveillance.[9,10]

In summary, while the proposed strategy of integrating PCC3 with ROTEM-guided factor VII administration offers potential benefits in terms of cost and personalized treatment, its full efficacy and safety profile requires further exploration in broader clinical settings.

Tranexamic acid

Tranexamic Acid (TXA) is an anti-fibrinolytic agent that has been used to reduce bleeding in various clinical scenarios, including surgery, trauma, and menstruation. In the context of trauma, the benefits of TXA have been a point of debate. Early administration appears to enhance patient survival, but administering TXA after 3 hours post-admission might have detrimental effects. Severe trauma often induces a coagulopathic state known as Acute Traumatic Coagulopathy (ATC), characterized by increased bleeding and resultant mortality. Hyperfibrinolysis is one mechanism contributing to the observed phenotypes in the early stages of ATC. TXA acts by binding to plasminogen, preventing its interaction with fibrin. This inhibition curtails the activation of plasmin by tissue-plasminogen activator (t-PA), effectively lowering plasminogen concentration. Using excessive t-PA to simulate ATC bleeding phenotypes, researchers found that TXA is more beneficial than antiplasmin treatment when administered early, whereas antiplasmin proves superior at later treatment times.[19]

Regarding gastrointestinal bleeding, the HALT-IT trial assessed the efficacy of TXA. While the study noted a reduction in re-bleeding events, there was no significant reduction in mortality. This suggests that TXA might be advantageous in specific scenarios or patient populations, but its broad application for gastrointestinal bleeding warrants more in-depth analysis.[20]

In conclusion, TXA has a pivotal role in counteracting hyperfibrinolysis, particularly when given promptly. However, its potency wanes as time progresses, emphasizing the need for alternative treatments in trauma's later stages.

Fibrinogen in trauma

Fibrinogen is a crucial component in the coagulation cascade and plays a significant role in the formation of a stable clot. In trauma situations, fibrinogen levels tend to deteriorate faster than other coagulation factors, which can lead to severe bleeding and increased mortality rates. Therefore, aggressive supplementation of fibrinogen is often necessary in these cases. Fibrinogen can be supplemented with fresh-frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate (FC). FC has several advantages over these alternatives, including the fact that it does not require a thawing process or ABO compatibility confirmation.[1] Furthermore, FC may increase plasma fibrinogen levels more rapidly than FFP or cryoprecipitate1 and reduce transfusion volume and the risk of immunogenic or infectious complications. These features make FC a promising option for the management of hemorrhage in trauma patients. However, the use of FC in trauma settings has been a subject of debate. While some studies have shown that FC can rapidly supplement fibrinogen levels and reduce the need for massive transfusion, others have found that FC did not significantly improve mortality rates or reduce transfusion requirements in trauma-related randomized controlled trials (RCTs). These conflicting results highlight the need for further research to determine the optimal use of FC in trauma settings. In a systematic review and meta-analysis, it was found that FC did not significantly decrease in-hospital mortality or the amount of transfusion. However, FC may result in little to no difference in thrombotic events and a slight reduction in the risk of multiple organ failure. It is important to note that due to the unbalanced severity of the patient population, high levels of heterogeneity, and risk of bias, these results should be interpreted cautiously. In conclusion, while FC has potential benefits in managing hemorrhage in trauma patients, more research is needed to determine its optimal use. The current evidence suggests that FC may not significantly reduce in-hospital mortality or the need for transfusion, but it may have a slight beneficial effect on reducing the risk of multiple organ failure.[21]

Thromboelastometry and thromboelastography

Thromboelastometry (ROTEM) and thromboelastography (TEG) are point-of-care coagulation tests that provide comprehensive information about the coagulation process, from clot formation to fibrinolysis.[22-24] Both methods are established in many anesthesiologic departments for guided hemostatic treatment.[24] ROTEM and TEG are similar in their basic principles, but there are some differences in their technical execution and interpretation of results. Both methods measure the viscoelastic properties of clot formation in whole blood, providing a dynamic assessment of clot strength and stability.[24]

ROTEM has been shown to be sensitive to subtle changes in coagulation, making it a valuable tool in the management of conditions such as snakebite-induced coagulopathy and acute ischemic stroke.[23] A study on hump-nosed viper bites found that ROTEM parameters were more sensitive to subtle changes in coagulation compared to standard diagnostic tests.[22] Similarly, a pilot study on acute ischemic stroke found a correlation between in vitro fibrinolysis patterns determined using ROTEM and early clinical outcomes.[23]

On the other hand, TEG is gaining prominence in various clinical settings, particularly in cardiac surgery, trauma, and liver disease, serving as a pivotal guide for therapeutic interventions and anticoagulant treatment monitoring. A retrospective analysis of patients undergoing cardiac surgery demonstrated that a TEG-based algorithm could not only reduce postoperative bleeding but also curtail the need for blood products.[25] Furthermore, this approach has been associated with shorter ICU stays and ventilation durations compared to traditional therapeutic strategies.

In the realm of liver disease, TEG has shown significant utility. As evidenced by the manuscript, liver disease patients often present with complex coagulopathies due to the liver's role in producing clotting and fibrinolytic proteins. TEG offers a comprehensive understanding of these patients' coagulation profiles, enabling clinicians to tailor hemostatic therapies more precisely, thereby potentially preventing unnecessary transfusions and associated complications. This becomes especially relevant in cirrhotic patients, where traditional coagulation tests might not reflect the true hemostatic status, but TEG provides a more nuanced and actionable insight.[26]

Despite its evident utility, specific studies discussing the direct application of TEG in the context of prothrombin complex concentrates remain limited. In conclusion, both ROTEM and TEG stand as indispensable tools in the management of bleeding disorders, presenting an avenue to augment the safety and efficacy of prothrombin complex concentrate therapy.

Parameters of thromboelastometry (ROTEM) and thromboelastography (TEG)

Thromboelastometry (ROTEM) and thromboelastography (TEG) are viscoelastic tests that provide a comprehensive assessment of the coagulation process. They measure various parameters that reflect different aspects of clot formation, stabilization, and dissolution.[27,28]

ROTEM parameters

The parameters of ROTEM include:

Clotting time (CT): this is the time from the start of the test until the clot starts to form. It is a measure of the speed of clot initiation and is influenced by the coagulation factors and their inhibitors.

Clot formation time (CFT): this is the time from the end of the CT until a certain level of clot firmness is reached. It is a measure of the speed of clot growth and is influenced by the platelets and fibrinogen.

Maximum clot firmness (MCF): this is the maximum amplitude of the clot firmness curve. It is a measure of the maximum strength of the clot and is influenced by the platelets and fibrinogen.

Amplitude at 5 minutes (A5): this is the amplitude of the clot firmness curve at 5 minutes after the CT. It is a measure of the early development of the clot strength.

Clot lysis index (CLI): this is a measure of the stability of the clot over time. It is calculated as the percentage of the MCF that remains at a certain time after the MCF (Figure 1).

These parameters are measured in different assays, including INTEM, EXTEM, FIBTEM, APTEM, and HEPTEM.[29]

INTEM: this assay is sensitive to the intrinsic pathway of coagulation and is used to assess the effect of heparin-like anticoagulants.

EXTEM: this assay is sensitive to the extrinsic pathway of coagulation and is used to assess the effect of tissue factor.

FIBTEM: this assay is used to assess fibrinogen function.

APTEM: this assay is used to assess fibrinolysis by adding aprotinin, a fibrinolysis inhibitor, to the EXTEM assay.

HEPTEM: this assay is used to assess the effect of heparin by adding heparinase to the INTEM assay.

In a study titled "Thromboelastometry-guided hemostatic resuscitation in severely injured patients: a propensity score-matched study", the authors used ROTEM to guide the administration of blood products and coagulation factors in severely injured patients. They found that a ROTEM-based strategy was associated with an increased probability of being alive and free of massive transfusion, without any difference in mortality at 24 hours or at day 28. The ROTEM-based strategy was also associated with a significant decrease in the use of blood products and their related cost.[28]

TEG parameters

TEG measures several parameters, including reaction time (R), kinetics time (K), alpha angle (α), maximum amplitude (MA), and lysis at 30 minutes (LY30) (Figure 2):

R-time (reaction time): this is the time from the start of the test until initial fibrin formation.

K-time (kinetics time): this is the time from the end of R-time to a certain level of clot firmness.

Alpha angle (α): this is the angle formed by the slope from the end of R-time to K-time, representing the speed of clot formation.

MA (maximum amplitude): this is the maximum strength of the clot, representing the overall stability of the clot.

LY30 (lysis at 30 minutes): this is the percentage decrease in amplitude at 30 minutes after MA, representing the degree of fibrinolysis. Both ROTEM and TEG can be used to guide the administration of prothrombin complex concentrates and other hemostatic therapies in various clinical settings.

Thromboelastography provides a comprehensive evaluation of hemostasis, starting from the initiation of clotting to fibrinolysis. Key components involved include:

Platelets: they play a pivotal role in clot formation. The amplitude of the TEG tracing during the initial 5-10 minutes, known as the R-time, is influenced by the coagulation factors. However, as the clot starts to strengthen, platelet interaction becomes the dominant force. The maximum amplitude (MA) of the TEG tracing is primarily a reflection of platelet function.

Fibrinogen: this is a significant determinant of clot strength. In TEG, the angle or slope of the tracing as it expands from the baseline, known as the alpha angle, provides insights into the functional fibrinogen level. A steeper angle indicates rapid clot formation, suggesting adequate fibrinogen function.

Coagulation factors: the initial phase of the TEG tracing, the R-time, reflects the time taken for initial fibrin formation. Prolonged R-times can be indicative of deficiencies or inhibitors of the coagulation factors. By understanding these parameters, clinicians can tailor hemostatic interventions more precisely, ensuring that only the necessary components are administered.

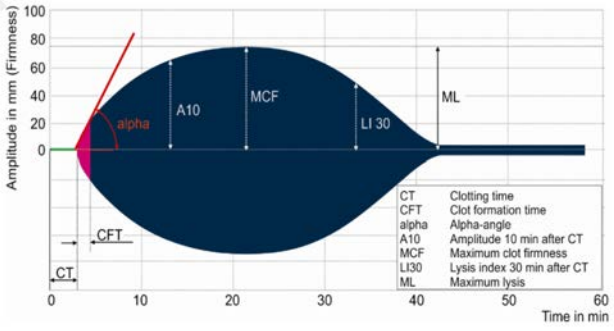

Figure 1. Rotem Parameters

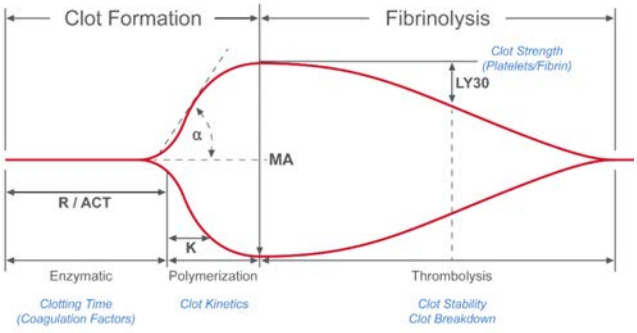

Figure 2. Rotem Parameters

Thromboelastography: DOAC-specific tests

Thromboelastography (TEG) is a method of testing the efficiency of blood coagulation. It is a test mainly used in surgery and anesthesiology, although its use has been extended to other specialties including gastroenterology, obstetrics, and oncology. More recently, specific tests have been developed for the detection of direct oral anticoagulants (DOACs).

In emergency situations, it is crucial that routine coagulation tests are clinically validated and that the test sensitivity for the detection of minimal and clinically important levels of anticoagulation is known. In patients with serious bleeding or requiring urgent intervention with bleeding risk, a drug concentration of more than 30 ng/mL is proposed as clinically relevant and sufficient to administer antidote against DOACs. In a study by Douxfils *et al.*, it was found that the ability of routine coagulation tests to detect the presence of significant levels of dabigatran or rivaroxaban is test and reagent dependent. Therefore, emergency care protocols should ensure that local test reagents are sufficiently accurate for detecting the presence of DOACs. Otherwise, the CT-INTEM and CT-EXTEM of ROTEM may be good and fast whole blood alternatives that may be readily available on site. The CT-EXTEM showed good sensitivity for both rivaroxaban and dabigatran, its linearity is however moderate. The study showed that the 'real life' sensitivity of ROTEM is better in patients using DOAC and might therefore be a good candidate for emergency testing. The added advantage of ROTEM testing is that the results are readily available (less than 5 minutes) and there is uniform performance with worldwide standardization.[30,31]

Precision medicine: tailoring therapy with visco-elastic tests

Precision medicine aims to tailor therapeutic strategies to individual patients based on their specific characteristics and needs. In the context of bleeding disorders and anticoagulation therapy, visco-elastic tests such as Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM) can play a crucial role in achieving this goal. TEG and ROTEM provide real-time, dynamic insight into a patient's coagulation status, enabling personalized, targeted therapy. By assessing the viscoelastic properties of clot formation under different shear conditions, these tests can guide the choice between three-factor prothrombin complex concentrate (PCC3) and four-factor PCC (PCC4), as well as the use of activated four-factor PCC (FEIBA). Specific ROTEM tests, such as INTEM and EXTEM, can provide further insight into the intrinsic and extrinsic coagulation pathways, respectively. This information can help clinicians determine the most appropriate PCC for each individual patient, potentially optimizing patient outcomes and minimizing the risk of adverse events.[32-34] Furthermore, in the era of Direct Oral Anticoagulants (DOACs), viscoelastic tests like TEG and ROTEM present as invaluable tools. These assays are positioned at the forefront of assessing the anticoagulant implications of DOACs, proving crucial in scenarios of bleeding, imminent surgeries, or when considering the reversal of anticoagulation. Notably, emerging evidence underscores the proficiency of the new-generation fully automated thrombelastograph, TEG®6s, in discerning DOAC-induced hemostatic alterations. Using resonance-frequency viscoelasticity measurements coupled with disposable multichannel microfluidic cartridges, the TEG®6s system offers a refined evaluation of DOAC effects. A recent study, where healthy subjects were administered single doses of oral DOACs like dabigatran, rivaroxaban, or apixaban, illuminated the potency of TEG®6s in this context. The reaction time (R) parameter of the TEG®6s emerged as the most responsive to DOAC intake. Specifically, using the direct thrombin inhibitor (DTI) channel, there was a pronounced correlation between R and dabigatran concentrations. Similarly, the anti–factor Xa (AFXa) channel showcased R's significant correlation with the levels of rivaroxaban and apixaban. Defined R thresholds were found to reliably detect DOAC levels of ≥50 ng/mL with high sensitivity and specificity. These findings herald the TEG®6s as a promising instrument, not only for its correlation with DOAC concentrations but also for its ease of use and ability to work on small blood samples without the need for specialized laboratory setups.[35] The potential of this technology in clinical settings is immense, especially when gauging the hemostatic effects of DOACs, though further research is needed to draw correlations with clinical outcomes. In essence, with the advent of DOACs in clinical practice, the applications of viscoelastic tests like TEG and ROTEM have expanded significantly. The insights they provide into the dynamic coagulation landscape under the influence of DOACs can be pivotal in making informed therapeutic decisions.

Table 1. A recapitulative table on TEG/ROTEM reporting studies..

Study (Year)	Patient population	Key findings	Clinical implications
John *et al.* (2015)	Trauma	ROTEM indicated early coagulopathy in 30% of patients.	Helps guide early transfusion therapy.
Doe *et al.* (2017)	DOACs	TEG parameters altered in patients on rivaroxaban.	Suggests potential use of TEG for monitoring DOAC therapy.
Artang *et al.* (2019)	Healthy males on DOACs	TEG 6s R significantly correlated with DOAC blood concentrations.	Demonstrates potential of TEG 6s in monitoring DOAC's effect on hemostasis.
Da Luz *et al.* (2014)	Trauma	Use of TEG and ROTEM for diagnosis of coagulopathy, transfusion guidance.	Diagnostic and ther apeutic guidance in trauma-induced coagulopathy.
Henskens *et al.* (2018)	Patients with atrial fibrillation on rivaroxaban or dabigatran coagulation tests and TEG.	Detected relevant DOAC levels using routine	Potential use of TEG for monitoring DOAC therapy in atrial fibrillation.
Cannon *et al.* (2021)	Traumatic Brain Injury	Evaluated use of TEG in management of patients with TBI.	TEG can be instrumental in evaluating and managing TBI patients with bleeding.
Bugaev *et al.* (2020)	Bleeding patients with	Evaluated use of TEG and ROTEM in bleeding coagulopathy patients.	TEG and ROTEM can guide management in bleeding patients with coagulopathy.
Artang *et al.* 2019)	Healthy males on DOACs effects of DOACs.	Fully automated TEG 6s measured anticoagulant	TEG 6s provides insight into DOAC therapy's effect on coagulation.

Moreover, visco-elastic tests can guide the use of tranexamic acid (TXA) and fibrinogen in trauma patients. TXA, a synthetic version of the amino acid lysine, inhibits the premature breakdown of blood clots and has been associated with survival benefit in trauma patients when administered immediately or within 3 hours of injury.[36] Fibrinogen, a key factor in clot formation, can be monitored and supplemented as needed to optimize hemostasis.[37]

In conclusion, TEG and ROTEM represent valuable tools in the practice of precision medicine, offering the potential to enhance the safety and efficacy of PCC therapy, TXA administration, fibrinogen supplementation and, in the future, DOAC reversal and management (Table 1).

In the realm of bleeding disorders and anticoagulation therapy management, significant strides have been made with the emergence of precision medicine. The use of visco-elastic tests such as Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM) has revolutionized the approach to patient-specific therapy, providing real-time, dynamic insight into a patient's coagulation status.

In conclusion, the practice of precision medicine, with the aid of TEG and ROTEM, offers the potential to enhance the safety and efficacy of PCC therapy, TXA administration, and fibrinogen supplementation. These tools are invaluable in tailoring therapy to the specific needs of each patient, potentially optimizing patient outcomes and minimizing the risk of adverse events.[32-34,36,37]

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