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The Final Thesis

Viscoelastic Hemostasis Testing to Guide Transfusion Decisions in Liver Transplantation

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SUMMARY

Implementing the World Health Organization's 2021 "patient blood management" (1) encouraged research about the value of viscoelastic tests in the diagnosis and treatment of coagulopathies during liver transplantation. This thesis aims to review evidence and challenges regarding the predictive value and effect of viscoelastic tests on patient outcomes and blood product requirements when guiding transfusion decisions in liver transplantation, compared to standard care under conventional coagulation tests. The determination and implementation of transfusion thresholds will be discussed. PubMed search included literature from January 2017 to January 2024.

Viscoelastic test-based transfusion strategies increase rates of transfusion-free liver transplantation. They reduce platelet concentrate and fresh frozen plasma requirements, without increasing perioperative complications. Prothrombin complex concentrate and/or fibrinogen concentrate use for factor replacement increase. Likewise, the total fibrinogen administration is higher, without augmenting thrombotic complications. Evidence is ambiguous about whether fibrinogen concentrate or cryoprecipitate is preferable for fibrinogen substitution. The implication on cryoprecipitate requirement remains to be investigated. Intraoperative bleeding volume and red blood cell requirement are indistinguishable between transfusion strategies. Recombinant factor 7a is not recommended.

Transfusion-related acute lung injury and costs may be reduced through viscoelastic testing. Long-term mortality, graft dysfunction, reoperations, bleeding and length of stay are comparable. Short-term mortality and acute kidney injury are strongly variable among studies.

Viscoelastic tests' predictive value lies within the risk assessment for massive transfusion events.
A major problem for research and formulation of transfusion algorithms comprises the lacking validation of viscoelastic thresholds and further methodological challenges, limiting study comparability and quality of evidence.

KEYWORDS

Adult orthotopic liver transplantation, Viscoelastic testing, VET, Rotational thromboelastometry, ROTEM, Thromboelastography, TEG, Hemostatic monitoring, VET-guided transfusion, Blood transfusion, Patient blood management

ABBREVIATIONS

LT – Liver transplantation, OLT – Orthotopic Liver transplantation, LT – Liver transplantation, ROTEM – Rotational Thromboelastometry, TEG – Thromboelastography, VET – Viscoelastic test(-ing), CCT – Conventional coagulation test, PLT – Platelet, RCT – Randomized Controlled Trial, FC – Fibrinogen Concentrate, PCC – Prothrombin Complex Concentrate, pRBC – packed Red Blood Cells, WHO – World Health Organization, MT – Massive transfusions, TRALI – transfusion-related acute lung injury, TACO – transfusion-associated circulatory overload, ESLD – End-Stage Liver Disease, vWF – von Willebrand Factor

1. INTRODUCTION

Blood transfusions have been associated with an increased mortality, morbidity and complication rate in transplantation surgery, such as hemolytic reactions, reduced graft function, renal injury or sepsis. (2–4) The administration of prophylactic transfusions ergo is no longer broadly recommended, although in reality it is still practiced. (3,5–7) A study by Massicotte et al. (8) about transfusion outcomes in liver transplantation revealed 4.2 times higher one-year survival rates in non-transfused patients than those receiving four or more pRBCs. Another study (9) established the adverse effect of prophylactic FFP transfusions in fuelling splanchnic and portal hypertension, provoking more bleeding and transfusions with an ultimate 20% decrease in 1-year survival. Similarly, platelet concentrate was also associated with anaphylactic, hemolytic reactions. (4) Overtransfusing in LT is associated with increasing thromboembolic complications, too. (10) The reduction of blood transfusion hence is connected with a reduction of risks and complications. (11) This risk association was one of the reasons for the WHO to introduce the new concept of “patient blood management” (1) in 2021 in their article “the urgent need to implement patient blood management” with a three-pillar approach: (I) Improved detection and management of anemia, (II) Minimization of blood loss and optimization of coagulopathy and (III) Measures to leverage and optimize the patient-

specific physiological tolerance to anemia. The concept aims to reduce transfusion-associated risks and complications, reduce transfusion dependency, improve patient outcomes and the utilization of health care resources. (1)

The body is dependent on the liver's function to produce and degrade factors involved in primary hemostasis, secondary hemostasis and the (anti-) fibrinolytic system. The inability of the liver to maintain this hemostatic regulatory function in end-stage liver disease makes it difficult to maintain a stable hemostatic environment. In the past it was assumed that the decreased synthetic liver function causes all patients with severe liver disease to be "auto-anticoagulated" (12), thereby prone to bleeding. This assumption is today outdated, because it did not consider the parallel decrease in anticoagulant and fibrinolytic factors, as well as platelets' ability to outbalance decreased number with increased activity. (12) Modern literature adapted the notion of "rebalanced hemostasis" (13). It is rather accurate to say that the "resiliency" (13) of the hemostatic system is lower in these patients. Liver transplantation is a complex surgery that can provoke severe perioperative bleeding or thrombosis and requires monitoring and intervention plans.

Blood transfusion algorithms in all surgical disciplines up until now are oriented towards established lab parameters such as prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count (PLT), international normalized ratio (INR), plasma fibrinogen and hemoglobin (Hb). (14) They will be referred to as traditional or conventional coagulation tests (CCTs) in this text. Conventional hemostatic lab tests give a snapshot of hemostasis at a specific point in time. This can be considered a weakness in patient groups with complex hemostatic derangements or frequent changes as in ESLD and liver transplantation. The duration from sampling till receiving CCT results takes between 30 and 60 minutes. (15) What's more is the lack of specificity regarding the quality of formed clots and fibrinolysis. (16) PT or INR ignore any other than the extrinsic coagulation pathway, which has led to evidence that they are not valuable in assessing the overall preoperative bleeding risk. (17) Just to name another example, platelet count does not take into account elevated vWF levels in cirrhosis. (2,4) Elevated vWF facilitates platelet aggregation in thrombocytopenia to maintain primary hemostasis. (18) There is an assay called viscoelastic test (VET) that may offer a solution to these problems.

Vicoelastic testing machines can simulate clotting and lysis in a whole blood sample ex vivo. The graphic output makes the entire process of clot formation and lysis easily comprehensible (see Annex 1). (5) VET's strength is that it acknowledges the complexity of the hemostatic

system including compensatory mechanisms, which means it “reflects the interaction of plasma, blood cells, platelets” (19). Yoon et al. explain that “studies have demonstrated improved correlation of VETs with in vivo clotting function and bleeding compared to CCTs in ESLD“ (20).

The disadvantages for CCTs in predicting bleeding risk make them a weaker basis for transfusion decisions, keeping in mind that every transfusion increases mortality. Therefore, science has researched the efficacy of alternative hemostasis assessment tools to make transfusion decisions. A trial (21) has indicated decreased mortality under VET-guided transfusion algorithms when compared to CCT-guided transfusion groups. Even though VET itself is not a brand new technology, CCT-based transfusion has remained the standard care for liver transplantation in most hospitals. (19)

The Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (22) states that PT/INR is not adequate in mirroring the complex rebalanced hemostatic state of cirrhotic patients. The core idea behind VET-guided transfusion in LT is that it flexibly assesses hemostasis in a patient group with frequent and complex hemostatic changes. This is feasible through the short machining time of 10 min until the earliest results appear. (10)

The two most described viscoelastic test technologies nowadays are Rotational thromboelastometry (ROTEM) and Thromboelastography (TEG). VET technology was first described in 1948 by Dr. Hellmut Hartert. (23) Only in 1985 it was first used to guide transfusions in the setting of liver transplantation. (13) Up until now it was most relevant to emergency and intensive care medicine, major surgeries and obstetrics. (24) With the implementation of “patient blood management” (1) research around the application of VET in liver transplantation has received more attention.

The primary goal of this thesis is to review current **evidence and challenges** of using **viscoelastic hemostasis tests** to **guide transfusion decisions** for **blood products** in **adult orthotopic liver transplantation,** to **prevent or treat bleeding** within the **perioperative** period.

The four main subgoals are firstly to identify how VET alters the **transfusion requirements** for the listed transfusion products (packed red blood cells, platelet product, fresh frozen plasma, prothrombin complex concentrate, cryoprecipitate, fibrinogen concentrate, recombinant factor VIIa), secondly to gather evidence about VET-guided transfusion on specific **outcomes** of this surgery, thirdly to identify the **predictive value** of VET in liver transplantation, and lastly to

present and discuss the construction of **evidence-based VET-guided transfusion algorithms** and their implementation. The use of the presented blood products will be set in the context of the **physiological peculiarities** of liver transplantation surgery**.** Annexes 2-4 contain overviews of the basic interpretation of TEG and ROTEM parameters and component assays.

2. LITERATURE SELECTION CRITERIA

A literature search algorithm was applied to PubMed for materials in English language not older than 5 years from the time of the first search, i.e. not older than January 2017. The literature search was later repeated to add new articles published till January 2024. All articles are related to adult/adolescent orthotopic liver transplantation. Studies with patients under 12 years of age were excluded.

The search algorithm was formulated to select literature according to the research goal (resembling the PICO model). The advanced search builder used boolean connectors, truncations, MeSH search and keyword search (see Annex 5). Handpicked articles were included when they were found to give significant contribution to the work. Those are articles that gave answers to specific questions, frequently quoted articles and original sources. Annex 6 contains a flow chart summarizing the literature selection process.

For the data extraction, the literature was sorted according to the study design and relevant research objective.

3. PREDICTIVE VALUE OF VISCOELASTIC TESTS IN LIVER TRANSPLANTATION

3.1 Preoperative predictive value of viscoelastic tests regarding red blood cell requirement and risk for massive transfusion events

A prospective study from Somani et al. (7) including 150 cirrhotic patients undergoing invasive procedures assessed CCTs' and TEG's ability to predict post-procedural bleeding risk, requiring any intervention. Interestingly, in bleeding patients with abnormal CTTs (INR/aPTT/PLT count), TEG R (and MA) values were normal in 61% (and 75%) of patients. (7) This might be explained by VETs' ability to assess hemostatic compensation. (7) For clinical practice this firstly indicates that abnormal CCTs might not predict bleeding risk well and secondly that transfusion decisions might have been made differently.

The only significant relevance of VET parameters as predictive values lies within the prediction of bleeding and pRBC requirements. Single VET parameters can not be used as stand-alone mortality predictors. Studies attempting to associate preoperative VET values with postoperative mortality have failed to prove the pathophysiological connection. This is most likely related to the fact that mortality is influenced by many perioperative factors. Results from such studies could be used as part of a multivariable, predictive risk model, but there was no study identified that tried to construct such a model.

Rashidi et al. (25) discussed an interesting thought about VETs' lacking role in predicting survival. Rashidi et al. (25) believe that a variable predicting long-term survival after LT needs to be able to reflect the liver's synthetic ability. Rashidi et al. (25) see the theoretical advantage of VET in acute, decompensated patients, but it logically does not pose any value in compensated patients. Therefore, VETs' application or strength lies within the prediction of bleeding and guidance of transfusions in acute situations, but cannot predict long-term survival. (25)

Being able to preoperatively identify a patient at risk of requiring (many) intraoperative transfusions, would help in the procedural planning. Quite a few studies (26–30) investigated VETs' ability to predict massive transfusion events. Fewer studies (30) tried to predict if intraoperative transfusions will be needed at all.

3.1.1. Prediction of general intraoperative need for packed red blood cells

A multicentre retrospective study by Viguera et al. (30) compared the ability of preoperative baseline Hb vs. MCF_{EXTEM} (ROTEM) to predict the general requirement for intraoperative pRBC in 591 LTs (if pRBCs will be needed yes or no, unrelated to quantity; applied transfusion algorithm see Annex 7). Whereas preoperative Hb ≤10 g/dl was sensitive at 93% and specific at 47% to predict RBC transfusion, MCF_{EXTEM} ≤45mm did not significantly show this ability. (30)

3.1.2. Prediction of intraoperative massive transfusion events

Massive transfusions (MT) are usually defined as the need for 10 or more pRBC units within 24 hours. (29) MT events are associated with high mortality. (29) According to Lawson et al. (29) TEG has already proven to predict massive transfusions in trauma medicine. A single VET parameter alone cannot sufficiently predict MT. However, the results of studies associating

VET values with massive transfusion events, as presented below, can be used as part of a risk model, like the one by Pustavoitau et al. (26,27)

Lawson et al. (29) prospectively investigating preoperative TEG vs. CCTs (INR, PLT count, Hb) ability to evaluate MT event risk and found that MA <47mm had a sensitivity of 90% and specificity of 72% to predict such occurrence (≥10 pRBC units). INR was second placed in predictive value here. (29) The LTs in this study were CCT-guided. (29) The significance of this study result is limited, due to a small study population and the question of pathophysiological causality. (29) Thakrar and Mallet (28) also proved a significant association with a mean hepTEG MA of 42mm in patients receiving MT. Thakrar and Mallet (28) explain this association between MA and massive transfusion events by the fact that MA represents both platelet and fibrinogen contribution to clot formation. In Viguera et al. (30) MCF_{EXTEM} was not meaningful in predicting MT events (defined ≥6 pRBCs; ROTEM MCF corresponds to TEG MA, but TEG and ROTEM numerical values cannot be compared directly, which will be explained further below).

3.1.3. Multivariable predictive models for massive transfusion events in liver transplantation

There are a few researchers that tried to build models to predict MT, but without incorporating VET e.g. McCluskey et al. (31) risk index, Cywinski et al. (32), Massicotte et al. (33). However, none of them are applicable to a broad population, because they used institution-specific transfusion strategies, different definitions of MT, included other operations besides LT or had an insufficient cohort size. (15,26)

Pustavoitau et al. (26) are one of few to build a complex, multivariable MT risk model specifically for LT that also incorporates VET. Their motivation was to customize blood ordering schedules based on risk rates, which they also tested clinically. (26,27) In short terms, they first identified variables with significant MT association using univariate regression and then applied Akaike information criterion to select variables for the ultimate model. (26) They ultimately chose the following seven significant factors for their model (26): MELD score, cirrhosis stage, preoperative hemoglobin concentration, platelet concentration, TEG R interval, TEG alpha angle and lastly whether or not concomitant kidney transplant was performed. These variables are incorporated into a formula that calculates the probability of an individual to experience MT in LT (see Annex 8). (26) A probability of ≥0.25 identifies patients at higher risk. (26) The model demonstrated good calibration (Hosmer-Lemeshow goodness-of-fit test $P = .45$) and good discrimination (*c* statistic: 0.835; 95% confidence interval, 0.781–

0.888). (26) The model's sensitivity and specificity are 86.7% and 69.9%, positive predictive value 54.7% and negative predictive value 92.6%. (26)

In a follow-up study (27) they tried to validate the same predictive model, containing some alterations. Blood ordering according to their model's predictions, would have saved crossmatching of 358 RBC units and the thawing of 358 FFP units for every 100 LTs with a blood order schedule that allocated either 15 or 6 unit containers. (27) A major limitation of this study is its retrospective nature and single-centre execution. (27) Whether their model is truly applicable to any other institution, as the authors claim, needs to be established.

4. VISCOELASTIC TESTS INFLUENCE ON TRANSFUSION REQUIREMENTS AND DIFFERENT OUTCOMES

4.1. Influence of viscoelastic test-guided transfusion strategies on transfusion requirements under consideration of procedural physiological peculiarities

Returning to the study from Somani et al. (7) in which TEG values were normal in the presence of abnormal CCT values, it could be hypothesized that VET-based transfusion thresholds lead to altered transfusion requirements. The extracted statistical results and corresponding transfusion thresholds of all presented studies can be found in Annexes 7, 9 and 10.

4.1.1. The pre-anhepatic surgical phase and use of fresh frozen plasma, fibrinogen concentrate and prothrombin complex concentrate

Within the first stage of liver transplantation, the pre-anhepatic stage, high blood loss can be expected from the surgically induced trauma under portal hypertension. (18) The losses in the pre-anhepatic phase lead to a "functional decline in blood coagulation factors and platelet" (14). CCT values will immediately change in response. However, since they only evaluate parts of hemostasis it would be misleading to already presume severe coagulopathy. (14) VET graphs will change only much later when rebalancing mechanisms reach their limit. On VET the clot initiation time, quantified as R in TEG (or CT in ROTEM) would prolong, just as the clot strength MA (or MCF) would decrease. (14,34) In the past physicians may have transfused fresh frozen plasma more aggressively based on CCTs to compensate for coagulation factor decline and thinking to prevent bleeding (14), when it was not necessary according to the newest evidence.

A prospective RCT from Bonnet et al. (35) comparing transfusion requirements for FFP based on PT vs. ROTEM CT showed a decrease in transfused patient proportion (patients receiving FFP yes or no) in the latter group (15% vs. 46.3%), which they explained with PT not assessing all factors contributing to clot firmness. The median transfusion amount in patients that needed it was not statistically significantly reduced between CCT and VET groups in this particular study (3 vs. 4 units, $P = 0.448$; no mean reported). (35) Vice versa Smart et al. (36) prospectively did not show a significant difference in transfused patient proportion, but significantly reduced units of FFP (Median 4 units *vs.* 6.5 units, p = 0.015). A meta-analysis by Tangcheewinsirikul et al. (37) about periprocedural bleeding in cirrhotic patients also showed lower rates of FFP transfusion need in VET groups (28.1% and 60.5% of patients, six RCTs). The mean of transfused FFP units (four RCTs) was decreased in VET too (3.60 units; 95% CI 1.74–5.47; I 2 = 95% vs. 4.12 units; 95% CI 2.60–5.63; I 2 = 94%). (37) Summarizing the results from six out of eight studies that reported the patient proportion transfused with FFP, all authors (4,35,38–41) described a reduction. Seven out of the eight articles reported the amount of transfused FFPs in units, in which six (4,36,38,39,41,42) showed a decrease in the amount. Looking at systemic reviews (with meta-analyses) four out of six drew conclusions about patient proportions transfused with FFP. All four of them (37,43–45) found that fewer patients received FFP under VET transfusion guidance. Five analyses (21,37,43–45) reported transfused FFP amounts as an outcome and all of them proved a decrease in the VET groups, except for Hartmann et al. (21), which reported indifference between groups.
Aceto et al. (45) explain the higher FFP transfusions (amount and patients) under CCT with long turnaround times that may lead anaesthesiologists to make transfusion decisions solely on their clinical judgment instead of waiting for the CCT results.

FFP can be criticised for its high risk for transfusion complications e.g. transfusion-associated circulatory overload (10), because a large volume is required for a clinically significant effect. (18) The high added volume again may interfere with thrombin generation, because of citrate overload and hypothermia. (46) Because of these limitations a new transfusion approach in LT is trying to replace FFP with targeted administration of the factor concentrate four-factor PCC and/or fibrinogen concentrate. (24,39,18) Fibrinogen concentrate purely contains fibrinogen. Modern four-factor prothrombin complex concentrate contains factors II, VII, IX, X (and protein C/S) with a higher factor concentration than FFPs. (18) It is administered if coagulation initiation is prolonged on VET (CT or R) in a bleeding patient without hypofibrinogenemia (3), so classically in persistent bleeding after fibrinogen correction. (18)

VET implementation in several studies was associated with increased transfusion of PCC (and FC). Four out of eight studies reported the effect of VET guidance on PCC transfusion amounts. Half of them (39,40) showed an increase with VET groups and the other half (41,42) showed no group difference. Four out of eight studies investigated the transfused patient proportion as an outcome, in which three (4,39,40) again showed an increase and only one (41) indifference. PCC amount increases were always accompanied by fibrinogen concentrate increases. (39,40) An interesting finding by Zamper et al. (39) showed that factor substitution with FC and PCC decreased requirements for FFP and that this overall did not negatively affect adverse outcomes.

Only the meta-analyses by Aceto et al. (45) and systematic review by Yoon et al. (20) reported the VET-guidance effect on PCC amount, which was found to be increased. Both analyses (45) did not investigate the patient proportion.

Regarding the safety of increasing PCC and FC, Yoon et al. (20) could neither report a higher incidence of thromboembolic events related to FC or PCC, nor that they do not. Therefore the authors (20) wrote that PCC and FC can be considered in patients with volume overload or hyponatremia.

Because of the risks associated with FFPs several authors (10,42) only recommend FFP in case of clinically relevant bleeding in LT that cannot be managed by prothrombin complex concentrate and/or fibrinogen concentrate.

4.1.2. The use of recombinant factor 7a

Another coagulation factor substitute is recombinant factor 7a (rFVIIa). Because it is a purely procoagulant product, unlike PCC which also contains anticoagulant factors, it bears a higher risk to provoke thromboembolisms. (18) It seems that the use of rFVIIa is no longer significantly relevant in LT (17) and is therefore not recommended by EJA guidelines. (3) It can be considered as reserve therapy in treatment-resistant hemorrhage. (41) Administration could also be considered to prevent intraoperative blood transfusion in Jehovah's witnesses, because it is a synthetic product. (47) This might be an explanation for why none of the included studies reported the use of rFVIIa as an outcome.

4.1.3. The anhepatic phase, hyper-fibrinolysis and use of tranexamic acid, fibrinogen concentrate and cryoprecipitate

As soon as the hepatic vasculature is clamped to remove the sick organ, which marks the beginning of the anhepatic stage, the major concern becomes the absence of coagulation factor

synthesis and clearance of activated fibrinolytic factors, e.g. tissue plasminogen activator that was released by endothelium. (12,18) This state can lead to hyperfibrinolysis and severe bleeding (18), which can be seen as LI30 and LI60 (ROTEM)/LY30 and LY60 (TEG) decrease. (14) In case of hyperfibrinolysis it would be appropriate to administer anti-fibrinolytics i.e. tranexamic acid. (14) As this thesis focuses on blood products, the use of hemostatic medication will not be discussed in greater detail.

ROTEM and VET have component assays that allow the assessment of fibrinogen content in a clot without the influence of physiological „platelet-mediated clot retraction“ (18) (FIBTEM in ROTEM, Functional fibrinogen assay in TEG). (24) Fibrinogen concentration measured via VET proved to be more valuable than plasma fibrinogen concentration in predicting bleeding and thromboembolic events. (48,49) Fibrinogen can be replaced by FFP, fibrinogen concentrate or cryoprecipitate. Cryoprecipitate does not purely contain fibrinogen, but also Factor XIII, Factor VIII and vWF. (18,50) The total fibrinogen content is variable, so the clinical effect may be variable. (18,50) Administering cryoprecipitate to correct hypofibrinogenemia bears the risk of thromboembolic complications, because of overadministration of prothrombic factors. (46) However, fibrinogen concentrate also bears this risk, if administered incorrectly. There are very few studies (50) comparing the occurrence of thromboembolic events between FC and Cryoprecipitate use. In a retrospective study by Kim et al. (50) that used ROTEM to correct hypofibrinogenemia in LT either with cryoprecipitate or FC, researchers did not notice a significant difference in the incidence of major thromboembolic events between the groups (16 [14.7%] vs. 14 [14.4%], p = 1.000). Nevertheless, the overall evidence on this specific question is not high enough to speak for or against fibrinogen concentrate vs. cryoprecipitate to correct hypofibrinogenemia in LT. Some researchers (50) believe that the additional factors in cryoprecipitate may have a beneficial effect on massive bleeding events.

Different studies investigating the effect of VET algorithms on cryoprecipitate transfusion requirements found widely variable results. Five out of eight studies reported the amount of cryoprecipitate units transfused. Two studies (41,42) showed a decrease between VET and CCT-guided cohorts, two an increase (36,40) and the last study (39) no difference. Regarding the patient proportion needing cryoprecipitate, four studies reported this outcome, in which two (36,40) saw an increase and two (39,41) no difference. This mixed picture allows no identification of a clear tendency. Equally the results from systematic reviews (with meta-analyses) were widely inconsistent. In both outcome categories, the transfusion amount and

transfused patient proportion, different authors (21,37,43–45) showed either increase, decrease or indifference, allowing no clear conclusion.

Scarlatescu et al. (41) compared two matched cohorts of LT patients before and after the implementation of a VET-guided transfusion algorithm. Both the patient proportion (36 vs. 17 patients, $p = 0.03$) and median amount of cryoprecipitate units were significantly lower in the VET group. (41) At the same time the transfused patient proportion (18 vs. 54 patients, $p < 0.001$) and units of FC were higher in the VET group. (41) Six studies in total reported the transfused FC amount in their cohorts. Four of these studies (38–41) reported a clear increase in FC use. Two (35,42) did not notice any difference. The number of patients that required FC at all was measured by four studies (4,35,39,41) and all of them found an increase in VET groups.

From the systematic reviews (with meta-analyses) only two (20,45) analysed the FC amount and no one analysed the patient proportion. All other authors reported exclusively about cryoprecipitate usage for fibrinogen replacement. Aceto et al. (45) and Yoon et al. (20) both detected an increase in transfused FC units. Aceto et al. (45) meta-analysis further established that FC use is associated with less cryoprecipitate requirement, as it was the case in Scarlatescu et al. (41).

Parallel to this decrease in cryoprecipitate, there was a median reduction of FFP units in Scarlatescu et al. (41). The researchers were interested in the total fibrinogen amount both groups received and found that significantly more was given after VET establishment. (41) Despite this increase in total fibrinogen there were no higher thrombotic complications in the VET groups. (41)

4.1.4. The late anhepatic phase, neohepatic phase and use of platelet concentrate

The reperfusion phase of the transplanted donor liver is characterized by a „heparin-like effect“ (18), which means that the ischemic donor liver endothelium releases heparinoids. The donor liver might also still contain heparin from the organ harvesting. (18)

Some patients may additionally experience an accelerated release of t-PA from the graft endothelium. (18) In combination with low antifibrinolytic factors like Pai-1 and alpha 2 antiplasmin a state of hyperfibrinolysis may worsen bleeding. (14) This hyperfibrinolytic state will fade when the new organ starts to clear and produce factors. (18)

After graft reperfusion platelets may be increasingly consumed by the new liver, leading to thrombocytopenia. (51) „Entrapment of platelets in a donor’s liver sinusoids can be profound

enough to create a 50% gradient in platelet counts between arterial and venous circulation“ (18). Delayed production of anticoagulants in combination with early production of procoagulant factors plus platelet activation from thrombocytopenia make hypercoagulability in the post-perfusion and postoperative phase possible. (18,51) Paradoxically it is possible that bleeding and thrombosis concomitantly occur in these patients. (12,52)

Platelet transfusions in liver transplantation are generally only indicated in case of acute bleeding with thrombocytopenia. (18) CCTs can measure platelet amount, but they can not measure the compensatory function of platelets. (2) ROTEM does not have a specific assay just to assess platelet contribution to clot strength, but it can be assessed by measuring fibrin clot strength at $A10_{FIBTEM}$ and substracting it from $A10_{EXTEM}$. (53) Platelet transfusion during LT is associated with reduced 1-year survival. (42) Prophylactic administration of platelet concentrates is not recommended. (3) Interestingly prophylactic platelet transfusion does not even improve clot firmness (54), which is why there is insufficient evidence that these transfusions effectively reduce bleeding risk. (3) Katsanoulas et al. (42) found that adequate clot firmness could be ensured primarily with fibrinogen concentrate, reducing the need for platelets in their study. This again emphasizes the new strategy for targeted fibrinogen administration as previously mentioned in the context of FFP reduction.

All eight studies reported the transfusion amount of platelet concentrate in CCT and VET-guided groups. The majority (35,36,39–41) did not see a difference between the groups. Only three studies (4,38,42) saw a decrease in this outcome. As for the number of patients requiring platelet transfusions, four out of the six studies (36,39–41) reporting this outcome did not see a difference. The two remaining studies (4,38) reported a decrease.

As for the systematic reviews (with meta-analyses) four (21,37,43,44) authors concluded a decrease in the transfused platelet amounts. Another author (45) showed indifference and the last one (20) did not report this outcome. Four out of six studies analyzed the transfused patient proportions. Three of them (37,43,44) reported decreased patient proportions and one study (45) found indifference. This uniform tendency within the systematic analyses speaks for a VET-induced decrease in the overall need for platelet concentrate in LT.

Tangcheewinsirikul et al. (37) found decreased utilization of platelet and FFP transfusions, most interestingly, without increasing postprocedural bleeding complications. They therefore concluded that FFP and platelet transfusion could be “harmlessly avoided” (37).

4.1.5. Bleeding and use of packed red blood cell transfusions

Overall procedural bleeding volume was reported inconsistently (two from eight studies (36,41), two from six systematic reviews with/without meta-analyses (43,44)). Results were either significantly reduced (36,44) or at least not different (41,43) between groups. In a prospective study by Smart et al. (36) the ROTEM group had two litres of intraoperative blood loss vs. three litres in the control (p = 0.04). Kovalic et al. (44) meta-analysis of intra-operative blood loss in litres during LT found it to be significantly less in VET group, too (pooled MD −1.46; 95% CI −2.49 to −0.44; *P* = 0.005).

VETs are generally not used to guide transfusion decisions for packed red blood cell concentrate, because pRBCs are transfused to correct hemoglobin. The patient number requiring pRBCs in response to bleeding events was however frequently documented as an indirect parameter to assess the efficacy of experimental VET transfusion strategies. To be precise, six out of eight studies reported this outcome. Zamper et al. (39), Schumacher et al. (4) and Leon-Justel et al. (38) found a statistically significant decrease through VET, whereas the other three (36,40,41) found no difference. In those patients requiring pRBC transfusion half of the studies (4,38,39,42) found a decreased amount in VET groups, while the other half (35,36,40,41) reported no difference. The reasoning for one or another outcome was different among authors, revealing differences or similarities between VET and CCT transfusion strategies. Aceto et al. (45) showed a reduction in pRBC amounts and the number of patients receiving at least one unit of pRBC. They explain this directly with the concomitant reduction of FFPs through VET, because of a lower haemodilution effect by FFPs. (45) Scarlatescu et al. (41) before and after study had no significant differences, neither in intraoperative bleeding, nor in pRBC transfusions (patients or units). They explained this with quicker intervention time through VET in case of bleeding. (41) Tangcheewinsirikul et al. (37) did not see a periprocedural difference between VET and CCT either. Not in pRBC transfused patient proportion and not in the amount. (37) Their explanation for this is that pRBC transfusions in both groups are generally very restrictively applied with a threshold of Hb<7-9g/dl. (37)
Kovalic et al. (44) meta-analyses had the same finding as Tangcheewinsirikul et al. (37). Hartmann et al. (21) only reported the transfused pRBC amount and likewise did not notice a difference.
Leon-Justel et al. (38) specifically measured the occurrence of massive transfusion events (>10 pRBC units). MT events could be reduced from 13% of patients in the CCT-guided group to

only 2% of patients in the VET group. (38) Other than that, only Schumacher et al. (4) reported this specific outcome, but without a true statistical significance.

4.1.6. Viscoelastic tests impact on total blood product units and total need for any transfusion

Up until now, the impact of VET transfusion strategies on individual blood products was highlighted. Now the question remains, if the overall total of blood product amount and patients requiring any blood product decrease too or if VET only has an influence on specific products' usage.

There is evidence that due to the new conception of rebalanced hemostasis under VET guidance more liver transplantations can be done without transfusions at all, such as in a prospective study by Leon-Justel et al. (38) in which fully blood product-free transplantations increased from 5% in the CCT guided group to 24% in the VET group. Most studies (20,35,41) did find an overall decrease in the patient number that received any blood product. Yoon et al. systematic review correctly points out that the „magnitude of this effect" (20) strongly varied in every study, because every study used different transfusion algorithms.

Scarlatescu et al. (41) and Bonnet et al. (35) both attribute the frequently seen reduction of total blood products primarily to the decrease in FFP. PT, which can be used to guide FFP transfusion in CCT groups, considers only procoagulant factors (35) and "is usually prolonged in patients with chronic liver disease, while VET reflect better the hemostatic balance of chronic liver disease" (41).

According to Scarlatescu et al. (41), the VET-associated overall decrease in blood product amount was not accompanied by increased bleeding complications.

4.2. Influence of viscoelastic test-guided transfusion on periprocedural complications and mortality

4.2.1. Perioperative transfusion-related adverse events, postoperative bleeding and other postoperative complications

Periprocedural complications and outcomes were inconsistently reported in the sense that studies selected different clinical complications, defined the same complications differently or followed up the same outcome at different points in time, which makes it difficult to synthesize information. Both systematic reviews of Hartmann et al. (21) and Wei and Child (43) did not

calculate a meta-analysis for this reason. Yoon et al. (20) also declare a low quality of evidence about postoperative complications, because no studies reported postoperative complications as primary outcome. Therefore the presented study results below have to be seen critically. The complications that were most consistently reported were acute kidney injury, TRALI, bleeding and thrombosis. Hence, these are the outcomes that will be presented below.

One RCT by Bonnet et al. (35) and one before-after study by Scarlatescu et al. (41) saw no difference in acute kidney injury in VET groups, whereas Leon-Justel et al. (38) did see less acute kidney injury, as did Yoon et al. (20) systematic review. Interestingly, none of the studies that reported postoperative bleeding and thrombosis as outcome (21,35,38,41), saw a difference between VET and CCT-guided groups, i.e. neither decreasing them, but also not increasing them. The occurrence of TRALI was indifferent in the before-after study (41) and the prospective study (38), but Tangcheewinsirikul et al. (37) (30.2% of VET group, RR 0.25; 95% CI 0.11–0.56; $p = 0.001$) and Hartmann et al. (21) did calculate less TRALI in their meta-analyses (12.2% of VET group vs. 48.9%, $p < 0.001$). Tangcheewinsirikul et al. (37) convincingly explains the lower TRALI rates with the overall lower transfusion rates.

4.2.2. Short and long-term survival and mortality

The follow-up time points regarding mortality and survival were quite variable. All investigated studies and all systematic reviews that assessed mortality (20,21,35–38,40,41,44,45) however agreed that mortality at any point of time from 30 days or later (at 60 days, 90 days, 1 year, 3 years) was not significantly different between VET and CCT groups. Results were variable concerning short-term survival and mortality at 7 days or in-hospital, but there was no study that found a significantly more negative outcome in the VET group.

4.2.3. Length of intensive care and hospital stay

Only Scarlatescu et al. (41) reported a statistically significant reduction of ICU length of stay in the VET patient group (6 days vs 5 days, $p=0.003$).

With one exception all systematic reviews (with meta-analysis) (20,21,37,43,45) confirmed that there was no difference in ICU or hospital length of stay. It has to be mentioned that the length of stay may not purely depend on patient factors, but also on standard operating procedures e.g. mandatory surveillance intervals.

Those studies that determined an overall reduction of blood products (39,36,40,4), did not show a difference in hospital or ICU stay, except for Scarlatescu et al. (41).

4.2.4. Graft dysfunction and reoperation

Within the four studies that reported graft dysfunction and reoperation, e.g. revision surgery or retransplantation, three (35,40,41) did not notice an increase or decrease between VET and CCT transfused patients. Only Leon-Justel et al. (38) prospective study found a statistically significant decrease in the VET group for re-transplantation (10% vs. 2%, $p = 0.033$) and reoperation, specifically because of bleeding (13.0% vs. 5%, $p = 0.048$).

None of the meta-analyses presented a calculation of these outcomes.

4.2.5. Cost analysis

Only one study was identified that explicitly gave cost results. Smart et al. (36) summated the total cost of blood products and viscoelastic testing, in which ROTEM could lead. $113,142.89 *vs.* $127,814.77 were spent in 34 vs. 34 LTs. (36) The absolute transfusion amount for every product was lower in VET, except for cryoprecipitate. (36) Generally fewer patients received FFP in this study and more patients received cryoprecipitate. (36)

Yoon et al. (20) systematic review found two studies that reported cost analyses (no exact numbers reported). Even though viscoelastic testing costs more, the reduced transfusion product cost is low enough to cause an overall total cost reduction. (20)

5. FORMULATION OF VISCOELASTIC TEST-GUIDED TRANSFUSION ALGORITHMS: PRINCIPLES, CONSIDERATIONS AND DIFFICULTIES IN THEIR CONSTRUCTION AND PRACTICAL IMPLEMENTATION. EVIDENCE-BASED TRANSFUSION THRESHOLDS AND ALGORITHMS.

5.1. Determination of transfusion thresholds

With the progressing implementation of „patient blood management“ (10) physicians are moving away from prophylactic transfusions, because of the adverse outcomes. A danger when making transfusion decisions, both in CCT or VET-guided situations, is trying to correct numerical values without seeing them in the clinical context. (10,23,41) Transfusing in any case should be done primarily in situations of clinically relevant bleeding. (10)

Reference values to determine normal ranges of laboratory parameters are usually determined through sampling in a healthy reference population. (14,23,41) However, in ESLD population a value outside of the healthy population range does not automatically indicate coagulopathy, because of rebalancing. (10,14) The reference values from a healthy population as provided by

the TEG/ROTEM manufacturers (see Annexes 11 and 12) are thus not meant to be transfusion triggers. Achieving healthy population reference values in non-bleeding ESLD/LT patients would lead to over-transfusion and lower health outcomes. (41)

In general, those laboratory parameters can be used as transfusion thresholds that prove themselves as reliable bleeding predictors. (15,48) The determination of concrete VET transfusion triggers firstly requires observational cohort studies specific to LT that are statistically assessed with receiver operating characteristics (ROC) curve analysis or multivariate regression analysis of different variables e.g. different VET parameters and outcomes e.g. transfusion requirements, mortality. (10) It is important to calculate sensitivity and specificity in risk-benefit analysis for these VET thresholds (risk-benefit of intervening vs. not intervening), because only then they are applicable in an algorithm. (48) Görlinger et al. recommend to use a „high negative predictive value of viscoelastic testing (90%–97%)“ (10) when choosing thresholds. VET thresholds should also be chosen with high specificity, so that a VET not indicating coagulopathy well rules out a coagulopathy, even if CCTs are abnormal. (10) Görlinger et al. use the word “Not-to-do (restrictive) POC” (10) algorithms, in which transfusions are only applied when necessary and less likely to cause complications.

Practical validation, according to Görlinger et al., takes place in “setting-specific interventional trials” (10) with a prospective design, in which a threshold is tested for its effect on outcomes. In the optimal case, that threshold would reduce transfusion requirements without reducing patient outcomes or even improving them. All transfusion thresholds in comparison with study outcomes from the previous chapter can be found in Annexes 7, 9 and 10.

As discussed in the last chapter, science is suggesting that VET-guided transfusion safely decreases blood product requirements. Now research needs to establish meaningful thresholds.

5.2. Lacking standardization of viscoelastic test transfusion thresholds in research

One difficulty surrounding this research is that there is no uniform VET-guided transfusion algorithm for LT in research or clinics (see Annex 7). This variability of used algorithms comprises a problem for the comparability and significance of study results. (15) When looking precisely into the transfusion algorithms it is not only the VET parameters and numerical thresholds that vary, but also the blood products and dosages. This might be connected to the availability of certain products in different institutions, but the problem for research persists. (15) Rarely (4,42) numerical transfusion thresholds were not reported at all.

The meta-analysis by Aceto et al. pointed out that they ”could not quantify the effect” (45) of specific VET thresholds on the outcomes because of this inconsistency. Tangcheewinsirikul et al. (37) meta-analysis faced the same difficulty, but they attempted a meta-regression analysis of different thresholds’ effects.

It is important to mention that this review does not have the competency to say which VET-guided transfusion strategy is the best or better than others in any outcome. This review can summarize and discuss the results of studies that put VET-guided transfusion algorithms to proof. In the long run, it needs more RCTs and meta-analyses with consistent transfusion strategies to validate predictive values, which is required to formulate standardized algorithms for a broad mass. (17)

5.3. Current European and international guidelines on viscoelastic test-guided transfusion strategies in liver transplantation

In the latest 2023 guidelines for management of severe peri-operative bleeding the European Journal of Anaesthesiology (EJA) (3) newly incorporated evidence about VET in liver transplant. In the previous 2017 guidelines (55) VET was recommended primarily in the context of cardiac and obstetrical surgery. VET guidance for fibrinogen replacement is strongly recommended, but has low-quality of evidence (1C). (3) Recombinant factor 7a is not recommended for routine use (1C). (3) Low dosage PCC in bleeding without hypofibrinogenemia has a weak recommendation and low quality of evidence. (3) There are no recommendations listed for VET guidance of pRBC, cryoprecipitate, FFP or PC in liver transplantation. (3) The predictive value of preoperative VET on blood loss and intraoperative transfusion requirement has low evidence. (3)

The 2020 Society of Critical Care Medicine (SCCM) guidelines (56) on the management of adults with acute and acute-on-chronic liver failure in the intensive care unit strongly recommend the use of VET over INR, platelet count and fibrinogen value, but with moderate evidence quality.

The 2022 congress of the International Liver Transplantation Society (ILTS) (57) strongly recommends intraoperative viscoelastic testing, but the quality of evidence regarding short-term postoperative outcomes is low.

The 2021 practice update of the American Gastroenterological Association (AGA) (58) acknowledged the advantages of VET technology in assessing hemostasis in cirrhotic patients, but because of the limited evidence did not make a recommendation for perioperative bleeding management over CCT.

5.4. Technical limitations of viscoelastic testing technologies

There are a few factors whose influence on hemostasis cannot be assessed by the ROTEM/TEG machine. For example, the effect of elevated vWF in cirrhosis cannot be measured, because vWF is not activated under "no flow-conditions" (59). VETs generally do consider the anti-coagulant effect, but with the exception of protein C. (15) Lastly, the influence of tissue factor is not considered by VET either. (23)
Coagulability also depends on factors unrelated to the blood itself like the size of the injured vessel, blood flow characteristics, local vessel wall biology and membrane-bound pro- and anticoagulation factors. (23) This is another reason why VETs too need to be interpreted together with the clinical picture, just like CCTs. (23)
VET will also not detect in vivo coagulopathy caused by hypothermia. (45)
Even if VET cannot assess all hemostatic components, it is still a step forward in comprehending hemostasis as a whole, better than a single CCT.

Regarding the utilization of VET machines staff needs to be trained, to correctly interpret VET graphs and parameters. (60) Depending on the procedural standardization and the user, VET results may differ inter- or even intra-laboratory, although this can happen with CCTs too. (60) Staff training ensures the correct exertion of transfusion algorithms in practice. (60,61)

5.5. No interchangeability of rotational thromboelastometry and thromboelastography values

Both ROTEM and TEG visualize results in the same manner, which implies that the numerical results are the same with just different terminologies. Different studies have found that the results from ROTEM and TEG component assays cannot be directly compared to each other. (62,63) The differences are probably arising from procedural differences between the machines

e.g. different reagents or moving elements. (23) Reference values and algorithms should be formulated specifically for one or another VET system and not be used for the wrong machine. In the following chapters, VET thresholds will be presented. As the majority of researchers used ROTEM technology, only ROTEM-adjusted thresholds will be presented. Cut-off values from the one study using TEG can still be viewed in Annex 13.

5.6. Timing and sequencing of sampling and transfusions

Two authors (18,10) promote blood sampling for VET at particular, critical points of surgery. It is generally recommended to establish a baseline sample before the surgical cut. (10) Görlinger et al. (10) recommend first intraoperative sampling during the pre-anhepatic phase at 60 minutes, if not earlier due to bleeding complications, next at 5-10 min and 30-45 min after vena cava clamping and again two samples in the re-perfusion phase. Most studies in clinical reality took a baseline measurement and one sample per surgical phase (see Annex 7).

Remembering the physiological peculiarities of ESLD patients Görlinger et al. believe that transfusions need to be applied in a meaningful sequence: „Treat first what kills first!“ (10). This incorporates to treat (hyper-)fibrinolysis in bleeding with tranexamic acid, before turning to the management of clot firmness with fibrinogen concentrate. (10) The shape of this transfusion algorithm could be described as vertical, because it gives a step-by-step sequence of actions and prioritizes interventions in a hierarchical order. Nevertheless, almost all transfusion algorithms in the presented studies were arranged in a horizontal manner and without instructions on the sequence of actions. This gave clinicians more freedom in choosing their treatment approach.

Görlinger et al. (10) recommend to repeat VET 10-15 min after any hemostatic intervention, but the effect should most importantly be seen in clinical success. Considering laboratories' normal turnover time this monitoring frequency would not even be possible with CCTs.

5.7. Presentation of evidence-based viscoelastic test transfusion thresholds and algorithms

A tabular summary of all evidence-based transfusion thresholds and algorithms can be found in Annex 13. Dötsch et al. (48) are excluded from this chapter, because their thresholds are not

risk-benefit adjusted. Their thresholds are mathematically the optimal cut-off value, but they are not applicable to reality.

The article „The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management“ by Görlinger et al. is unique, because they used liver transplant-specific trigger values from cohort studies, RCTs and meta-analyses to synthesize an „evidence-based A5 transfusion algorithm“ (10). Their algorithm has been used by numerous studies comparing outcomes of VET and CCT-guided transfusion e.g. Katsanoulas et al. (42), Bonnet et al. (35), Scarlatescu et al. (41), Nascimento et al. (40). It is also the transfusion algorithm used during liver transplantation in the Vilnius University Hospital Santaros Klinikos. The clinic currently employs ROTEM primarily for complicated liver transplantation cases, but not regularly for all patients. (Expert opinion Strainys, Tomas; personal communication on 24.11.2023)

Görlinger et al. (10) algorithm starts with the assumption that decompensated patients with increased fibrinolysis in the pre-anhepatic phase are at highest mortality risk. Good predictors for fibrinolysis are a low clot firmness $A5_{EXTEM} < 25$ mm and a $CT_{FIBTEM} > 600$ s. (10) In these patients or those with $LI60_{EXTEM} < 85\%$ in the pre-anhepatic phase or $LI30_{EXTEM} < 50\%$ in the anhepatic phase tranexamic acid should be used. (10) Following hyperfibrinolysis, fibrinogen can be substituted, if $A5_{FIBTEM}$ sinks to < 8 mm in combination with $A5_{EXTEM} < 25$mm. (10)

FIBTEM was found to be the most sensitive assay for fibrinolysis and fibrinogen administration. (42) FIBTEM assay purely assesses fibrinogen contribution to clot strength, without the effect of platelets. (18,24) Three authors (42,45,64) found that FIBTEM-guided fibrinogen administration to correct clot strength reduced the requirements for packed red blood cells, fresh frozen plasma and platelet concentrate. All evidence-based algorithms evaluated FIBTEM and EXTEM results together to differentiate if fibrinogen or platelets contribute more to clot strength. Put differently: This explains if decreased clot strength is solely caused by hypofibrinogenemia and/or thrombocytopenia. (10) The exact cut-offs for FIBTEM and EXTEM varied among studies. FIBTEM MCF/A5/A10 were all found by different studies (10,65) to correlate well with plasma fibrinogen and therefore all could be used to guide fibrinogen transfusion.
According to Blasi et al. “the cut-off value that best predicted the transfusion threshold for fibrinogen was […] $A10_{FIBTEM} = 8$ mm“ (66). Caballero et al. (67) randomized, blinded, multicentre trial specifically determined, if $A10_{FIBTEM} = 8$ or $A10_{FIBTEM} = 11$ is the best target

to guide fibrinogen replacement. Surprisingly a higher $A10_{FIBTEM}$ target did not cause more adverse outcomes (patient proportions requiring RBCs, thrombosis or reoperation), but it also did not show benefit. (67) The authors explained this indifference with similarly low plasma fibrinogen concentrations in both study groups. (67) Görlinger et al. found similar values predictive (10): "With a cut-off value of 25 mm for $A5_{EXTEM}$ (35 mm for $A10_{EXTEM}$ and 45 mm for MCF_{EXTEM}) and a cut-off value of 8 mm for $A5_{FIB}$ (9 mm for $A10_{FIB}$ and 10 mm for MCF_{FIB}), lower levels of clot firmness seem to be adequate in liver transplantation".
Viguera et al. (30) strongly promote the use of MCF_{EXTEM} instead of $A5_{EXTEM}$ or $A10_{EXTEM}$ with a cut-off of 45mm for fibrinogen replacement. Blasi et al. (64) investigated the association between MCF_{FIBTEM}, plasma fibrinogen and transfusion requirements. According to Blasi et al. (64) MCF_{FIBTEM} values over 10 mm compose no benefits, which makes correction of MCF_{FIBTEM} >10mm unnecessary.
Correct fibrinogen administration is essential to prevent thromboembolic complications. Görlinger et al. (10) suggested a formula based on ROTEM to calculate optimal fibrinogen requirements (see Annex 13).

Platelet transfusion is only indicated when EXTEM is low in the presence of adequate fibrinogen levels as explained earlier. According to Blasi et al. (66) $A10_{EXTEM}$ well predicts the maximum clot firmness, which is why $A10_{EXTEM}$ can confidently be used as transfusion thresholds without waiting for MCF_{EXTEM} results. The predictable threshold for thrombocytopenia was reported at $A10_{EXTEM}$ = 35 mm. (66) Görlinger et al. (10) recommend using $A5_{EXTEM}$ <25mm here, because the $A5_{EXTEM}$ result is even earlier available.

In persistent bleeding due to coagulation factor deficiency administration of FFP or PCC may be considered. Görlinger et al. (10) analysed that CT_{EXTEM} of >75 s is superior to INR in predicting bleeding during LTs from coagulation factor deficiency. Their evidence-based CT_{EXTEM} threshold reduced FFPs, PCCs and transfusion-associated thrombosis. (10) Because of the risks associated with FFP it is used as last resort, which is why FFP administration comes last in the Görlinger et al. algorithm. (10) Other than $CT_{EXTEM,}$ Fayed et al. (65) identified CFT_{EXTEM}, CT_{INTEM} and MCF_{FIBTEM} as independent predictors for FFP transfusion. The best cut-off value to administer FFP was MCF_{FIBTEM} <9.5. (65) If MCF_{FIBTEM} dropped to <8.5mm cryoprecipitate could also be considered. (65) Not all algorithms (64,65,67) equally incorporated cryoprecipitate or PCC, which could be related to the availability of a centre, but no author gave an explicit reason on this question. The same thing goes for the use of Protamine

to counteract endogenous heparinization/heparin-like effect, which only Görlinger et al. (10) used.

6. CONCLUSIONS

Viscoelastic testing methods have major advantages in diagnosing coagulopathies in a patient population with frequent and complex changes. There are few technical limitations compared to conventional coagulation tests.

Viscoelastic test-based transfusion strategies achieve a reduction in the total amount and patient proportion requiring fresh frozen plasma and platelet concentrate, without increasing bleeding and perioperative complications.

The need for fresh frozen plasma can be reduced by replacing coagulation factors with prothrombin complex concentrate and/or fibrinogen concentrate instead. Consequently, prothrombin complex concentrate transfusion amounts and patient proportions have increased under viscoelastic test-guided strategies.

The total amount of transfused fibrinogen tends to be increased in viscoelastic test-guided groups, driven by the increase in fibrinogen concentrate. This increase is not associated with higher thrombotic complication rates. There is no clear consensus on whether viscoelastic test-based strategies alter the requirement for cryoprecipitate (amount and patient proportion). Current evidence does not show a clear preference for whether hypofibrinogenemia should be corrected through fibrinogen concentrate or cryoprecipitate, with respect to adverse outcomes. Adequate clot firmness can be maintained primarily with fibrinogen concentrate (and prothrombin complex concentrate), which might lead to reduced platelet and plasma requirements. No study reported a higher incidence of thrombotic events with increased prothrombin complex concentrate and fibrinogen concentrate usage.

Recombinant factor 7a is not frequently applied during liver transplantation. Recent guidelines have not recommended its use, except for very specific indications.

Results investigating the overall intraoperative bleeding volume and packed red blood cell requirement (amount and patient proportion) do not show a clear alteration between viscoelastic and conventional transfusion guidance. The same thing goes for the occurrence of massive red blood cell transfusion events.

All in all viscoelastic test-guided transfusion strategies reduce the general need for any blood product during orthotopic liver transplantation.

Long-term mortality is not altered between conventional coagulation test-transfusion groups and viscoelastic test groups. Study results show variable sequels regarding short-term mortality and survival, although no study has found a worse outcome. No difference among groups was determined in the length of intensive care or hospital stay. The overall reduction in transfusion volumes achieves decreased blood product costs.
Adverse outcomes like graft dysfunction, reoperation rates, bleeding and thrombosis are not different between transfusion strategies. Only the occurrence of transfusion-related acute lung injury seems to be reduced. No concordant result was found regarding the rate of acute kidney injuries.

Despite viscoelastic tests' promising results in transfusion guidance, their predictive value is strongly limited. Viscoelastic tests' predictive value primarily lies within the risk evaluation for massive transfusion events during liver transplantation. Preoperative viscoelastic measurements have significantly added value to multivariable predictive models**.**

Viscoelastic test-based transfusion thresholds need to be chosen with high sensitivity, specificity, negative predictive value and positive predictive value, in order to balance the risks and benefits of transfusions. A major problem for research comprises the lack of validation of viscoelastic test-based transfusion thresholds that hinder the construction of a broadly applicable algorithm. Studies comparing outcomes between viscoelastic test-guided liver transplants and standard care used different transfusion thresholds, which limits their comparability and quality of evidence.

Reducing blood product requirements through viscoelastic testing is in the interest of the „patient blood management" (1) concept and hospitals' resource-efficient planning. Therefore, some major anaesthesiology and internal medicine guidelines have called out the need for more research in this field.

7. SUGGESTIONS AND RECOMMENDATIONS

The clinical evidence of viscoelastic test-based transfusion strategies needs to be proven in large sample, multi-centre, randomized controlled trials.

Determining exercisable transfusion thresholds requires risk-benefit analysis. It is an indispensable tool to ensure sufficient sensitivity and specificity of a threshold in clinical practice.

A standard of reporting outcomes among studies should be established. For instance, survival should be followed up at specific points in time. Studies should use the same definition of transfusion-related complications e.g. for massive transfusion events. Similarly, transfusion thresholds as well as transfused units and blood products, should be reported in detail, to ensure that the effect of viscoelastic testing could be quantified with high evidence quality.

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ANNEXES (1-13)

Annex 1:

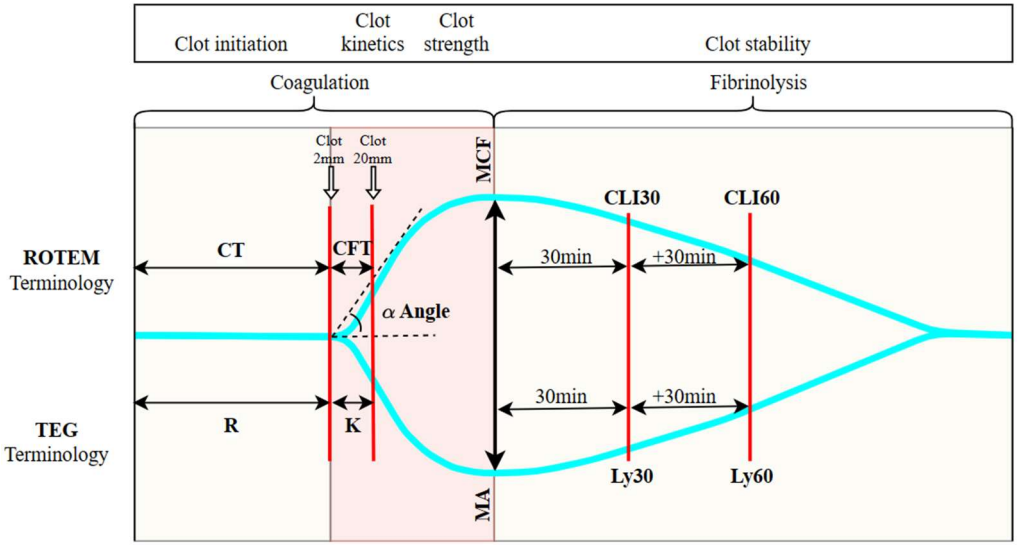

Figure I. Viscoelastic tests graphic output (for TEG and ROTEM) Abbreviations: TEG=Thromboelastography, ROTEM=Rotational thromboelastometry, CFT= Clot formation time, CT=Clotting time, R=Reaction time, K=K time, MA=Maximum amplitude, MCF=Maximum clot firmness, CLI30=Clot lysis index at 30 min after maximum clot firmness, CLI60=Clot lysis index at 60 min after maximum clot firmness, Ly30=Clot lysis at 30 min after maximum amplitude, Ly60=Clot lysis at 60 min after maximum amplitude; *Sources*: (5,14,68)

Annex 2:

Table 1. Overview of ROTEM and TEG Parameters and Meaning

Clot measurement	**ROTEM**	**TEG**	**Process**
Clotting initiation	Clotting time (CT)	Reaction time (R)	Time from VET initiation till first measurable clot formation (2mm)
Clot kinetics	Clot formation time (CFT); alpha angle	K time (K); alpha angle	Speed to reach a certain clot strength (20mm); Rapidity of fibrin synthesis
Clot strength	Maximum clot firmness (MCF)	Maximum amplitude (MA)	Ultimate strength of clot
Clot stability	Clot lysis index at 30 min after MCF (CLI30) Clot lysis index at 60 min after MCF (CLI60)	Clot lysis at 30 min after MA (Ly30) Clot lysis at 60 min after MA (Ly60)	Clot degradation process

Sources: (5,68)

Annex 3:

Table 2. ROTEM Component Assays, characteristics and their interpretation

ROTEM (ROTEM delta) Component assay	Corresponding CCT (in theory)	Measurement	Pathologies that can be detected/cause alterations	Activator/reagents to provoke clotting	Basic interpretation
NATEM	-	Whole blood	Unspecific	None	Unspecific
INTEM	aPTT	Intrinsic pathway	Decreased PLT, Decreased fibrinogen	Phospholipids, Ellagic acid (natural phenol able to activate factor XII)	Evaluate the effect of heparin and protamine
EXTEM	PT, INR	Extrinsic pathway	Decreased PLT, Decreased fibrinogen	Tissue factor	CT_{EXTEM} increase =delay in initiation of coagulation cascade because of thrombin formation. deficiency $MCF_{EXTEM}/A10_{EXTEM}$ reduction = platelet and/or fibrinogen deficiency
APTEM	-	Fibrinolysis (compared to EXTEM)	Decreased PLT, Hyperfibrinolysis	Tissue factor, Aprotinin (bovine enzyme inhibiting plasmin)	APTEM compared to EXTEM parameters. Better clot formation in APTEM indicates an in vitro effect of anti-fibrinolytic drugs.
FIBTEM	Plasma fibrinogen	Clot strength without the contribution of PLTs	Decreased fibrinogen	Cytochalasin D (inhibits PLT aggregation) and tissue factor	Differentiate between hypofibrinogenemia or platelet deficiency. $MCF_{FIBTEM}/A10_{FIBTEM}$ reduction= hypofibrinogenemia
HEPTEM	-	Eliminates heparin effect (compared to INTEM)	Effect of heparin	Phospholipids, ellagic acid, heparinase	Effect of heparin
ROTEM platelet mapping with subtypes	-	Impedance aggregometry to analyse platelet aggregation	Decreased PLT, Platelet dysfunction, Effect of anti-platelet drugs	ARATEM with arachidonic acid TRAPTEM with glycoprotein IIbIIIa receptor blockers. ADPTEM with adenosine diphosphate receptor blocker	Amplitude at 6 min ($A6_{ARATEM}$) = How well PLTs aggregate after activation Maximum slope ($MS_{TRAPTEM}$) =How quick platelets aggregate Area under curve (AUC_{ADPTEM}) = overall platelet aggregation

Abbreviations*:* ROTEM=Rotational thromboelastometry, PLT=Platelets, CCT=Conventional Coagulation Test**;** *Sources*: (62,69–71)

Annex 4:

Table 3. TEG Component Assays, characteristics and their interpretation

TEG (TEG 6s) Component assay	Corresponding CCT (in theory)	Measurement	Pathologies that can be detected/cause alterations	Activator/reagents to provoke clotting	Basic interpretation
CK (citrated kaolin)	aPTT	Intrinsic Pathway	Decreased PLT, Decreased fibrinogen	Kaolin	Risk of bleeding and thrombosis
CKH (citrated kaolin & heparinase)	-	Eliminates heparin effect (r-time CKH vs. r-time K-TEG)	Effect of heparin	Kaolin, Heparinase	Evaluate presence/effect of heparin
Citrated Rapid TEG (CRT or rTEG)	N/A	Intrinsic and extrinsic pathway	Unspecific	Kaolin, Tissue Factor	Speeds up entire coagulation process
CFF (citrated functional fibrinogen)	Plasma Fibrinogen	Clot strength without the contribution of platelets	Decreased fibrinogen	Kaolin, Tissue Factor, Abciximab	Differentiate between hypofibrinogenemia or platelet deficiency MA_{CFF} reduction= hypofibrinogenemia
TEG Platelet mapping with subtypes	-	Platelet aggregation	Decreased PLT, Platelet dysfunction, Effect of anti-platelet drugs	"A" subtype with reptilase and factor XIIIa "Thrombin" subtype with reptilase, factor XIIIa, Kaolin "AA" subtype with reptilase, factor XIIIa and arachidonic acid "ADP" subtype with reptilase, factor XIIIa, ADP	A = determines fibrinogen contribution to MA Thrombin = determines PLT contribution to MA AA = determines aspirin effect relative to "A" and "thrombin" ADP= assess P2Y12 inhibitors effect relative to "A" and "thrombin"

Abbreviations: TEG=Thromboelastography, CCT=Conventional Coagulation Test, PLT=Platelet*; Sources:* (14,72)

Annex 5:

Table 4. Literature search algorithm (complex search builder)

((("liver transplantation"[MeSH Terms] OR ("liver transplantation*"[Text Word] OR "liver transplant*"[Text Word])) **NOT** ("child"[MeSH Terms:noexp] OR "infant"[MeSH Terms:noexp] OR "infant, newborn"[MeSH Terms] OR "child, preschool"[MeSH Terms])) **AND** ("thrombelastography"[MeSH Terms] OR ("rotem"[Text Word] OR "viscoelastic test*"[Text Word] OR "viscoelastic testing*"[Text Word] OR "teg"[Text Word] OR "viscoelastic"[Text Word] OR "viscoelastic haemostatic assay*"[Text Word] OR "viscoelastic haemostatic"[Text Word] OR "viscoelastic assay"[Text Word] OR "thromboelastography"[Text Word] OR "thromboelastometry"[Text Word] OR "global hemostatic assays*"[Text Word] OR "viscoelastic coagulation tests"[Text Word] OR "viscoelastic coagulation testing"[Text Word] OR "rotational thromboelastometry"[Text Word] OR "viscoelastic guided"[Text Word] OR "viscoelastic haemostatic assay guided"[Text Word] OR "viscoelasticity"[Text Word])) **AND** ("blood transfusion"[MeSH Terms] OR ("blood transfusion"[MeSH Terms] OR "blood component transfusion"[MeSH Terms]) OR "plasma"[MeSH Terms] OR ((("transfusion"[Text Word] OR "blood transfusion"[Text Word] OR "transfusion strategy"[Text Word] OR "transfusion guideline"[Text Word] OR "blood product"[Text Word] OR "blood product administration"[Text Word] OR "transfusion product"[Text Word] OR "blood product administration"[Text Word] OR "transfusion program*"[Text Word] OR "platelet product"[Text Word] OR "blood component transfusion"[Text Word] OR "fresh frozen plasma"[Text Word] OR "ffp"[Text Word] OR "prothrombin complex concentrate"[Text Word] OR "pcc"[Text Word] OR "cryoprecipitate"[Text Word] OR "fibrinogen"[Text Word] OR "packed red blood cells"[Text Word] OR "platelet"[Text Word] OR "platelet concentrate"[Text Word] OR "fibrinogen concentrate"[Text Word] OR "recombinant factor viia"[Text Word]) **AND** ("procedures and techniques utilization"[MeSH Terms] OR "algorithms"[MeSH Terms])) OR "hemorrhage/prevention and control"[MeSH Terms] OR "hemorrhage/therapy"[MeSH Terms] OR "outcome and process assessment, health care"[MeSH Terms] OR "bleeding risk"[Text Word] OR "massive hemorrhage"[Text Word] OR "hemorrhage"[Text Word] OR "prevent bleeding*"[Text Word] OR "prevent bleeding complications*"[Text Word] OR "treat bleeding"[Text Word] OR "reduce blood transfusion"[Text Word] OR "reduce blood transfusion requirements"[Text Word] OR "mortality"[Text Word] OR "reduce mortality"[Text Word] OR "increase mortality"[Text Word] OR "transfusion amount"[Text Word] OR "amount of transfusion"[Text Word]) OR "graft survival"[Text Word] OR "transfusion reactions"[Text Word] OR "major bleeding complications"[Text Word] OR "transfusion algorithm"[Text Word])) **AND** (2017:2024[pdat])

Annex 6:

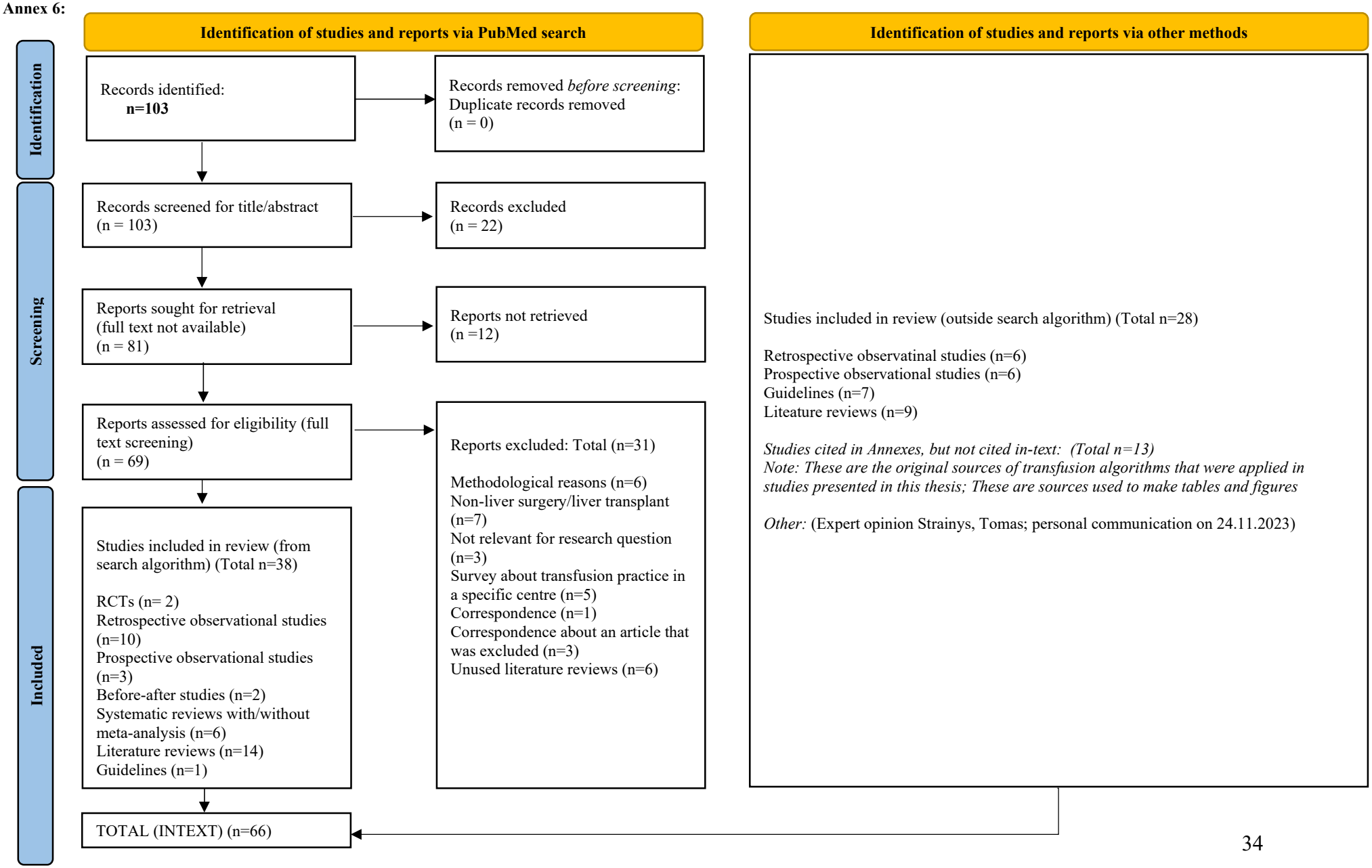

Figure II. Literature selection (flow diagram). Template source: (73)

Annex 7:

Table 5. Characteristics of included studies and transfusion practices

Author (Year) (Citation number)	**Study design (Country)**	**Procedure**	**VET**	**Transfusion thresholds in VET-guided group,** ***Source of studies thresholds (if reported)***	**Transfusion thresholds in SCT-guided group,** ***Source (if reported)***	**Time points of VET**
Leon-Justel et al. (2015) **(38)**	Prospective single-center cohort study (Spain)	OLT	ROTEM	$A10_{EXTEM}$ >40mm AND %Lysis >15% — TXA (1 g IV bolus) CT_{EXTEM} >120s AND MCF_{FIBTEM} >8mm — PC MCF_{FIBTEM} <4mm — FC CT_{EXTEM} >120s AND MCF_{FIBTEM} <6mm AND MCF_{EXTEM} <35mm — FFP CT_{EXTEM} >120s AND MCF_{FIBTEM} <6mm AND MCF_{EXTEM} >35mm — FFP + PC CT_{EXTEM} >120s AND MCF_{FIBTEM} >6mm AND MCF_{EXTEM} <32mm — FFP + PC + FC CT_{EXTEM} >120s AND MCF_{FIBTEM} >6mm AND MCF_{EXTEM} >32mm — FFP + FC Hb <7 g/dL — pRBC *Source*: Developed in their centre. Based on (73)	Platelet count <70 × 10^9/L — PC Plasma Fibrinogen <1 g/L — FC INR >1.6 — FFP Hb <7 g/dL — pRBC	Baseline, At end of hepatectomy, 20 min after vascular clamping, 20 min after revascularization
Bonnet et al. (2019) **(35)**	Prospective single center randomized controlled study (France)	OLT	ROTEM	EXTEM Hyperfibrinolysis or max lysis>15% OR APTEM decrease >15% in CT/CFT or increase >15% MCF compared with EXTEM — TXA (1g bolus, then 3g daily) $A10_{EXTEM}$ <35 mm or MCF <40 mm AND $A10_{FIBTEM}$ or MCF >8 mm — PC (1U) $A10_{FIBTEM}$ ≤8 mm — Fibrinogen (3g) CT_{EXTEM} >110 seconds — FFP (2U) *Source:* (74), (66)	Positive fibrin degradation products — TXA (1g bolus, then 3g daily) Platelets <$50x10^9$ l^{-1} at baseline/anhepatic phase/hemorrhage OR Platelets <$30x10^9$ l^{-1} at declamping/end of surgery & NO hemorrhage — PC (1U) Fibrinogen ≤1.0 g/L — Fibrinogen (3g) PT <40% at baseline/ anhepatic phase/hemorrhage OR PT <30% at de-clamping/end of surgery and NO hemorrhage — FFP (2U)	Intraprocedural baseline, Anhepatic phase, 30 min after revascularization, At the end of surgery
Smart et al. (2017)	Prospective cohort with	OLT	ROTEM	$MCF_{IN.EX}$ < 50 mm — PC (1-2 U) CT_{EXTEM} > 90s — FFP (4 U)	PLT count 25k- 50 k/uL — PC (1U) PLT count <25k/uL — PC (2U)	Baseline, Anhepatic phase,

(36)	historical controls (CCT group) (USA)			MCF_{FIB} < 10	Cryo (1-2 U)	Plasma Fibrinogen <150mg/dL	Cryo (1U)	Neo-hepatic phase, Before transfer to ICU
				ACT > 20% baseline OR CT_{IN}-CT_{HEP} >20%	IV Protamine (25-50mg increments)	INR >1.8	FFP (2U)	
				ML IN.E > x 15%	Aminocaproic acid (2g IV)			
Nascimento et al. (2020) **(40)**	Prospective and retrospective data, single-center study (Brazil)	OLT	ROTEM	EXTEM A10 <40mm or MCF<45mm, with FIBTEM normal	PC (1U per every 7–10kg OR 1 apheresis OR 1 buffy coat)	Platelet count <50.000/mm^3	PC (1U per every 7–10kg OR 1 apheresis OR 1 buffy coat)	After arterial puncture and before skin incision, At the beginning of anastomosis of the vena cava in the anhepatic phase, At the beginning of anastomosis of the bile ducts in the neohepatic phase, Directly before any intervention, 10 minutes after each intervention.
				EXTEM CT >80–100s (Bleeding due to decreased coagulation factors)	PCC (25–40 IU/kg) and/or FFP (15–20 ml/kg)	PT > 1.5 X normal; INR>1.5.	PCC (25–40 IU/kg) and/or FFP (15–20 ml/kg)	
				INTEM CT >240s and $HEPTEM_{CT}$/$INTEM_{CT}$≥0.8 (Bleeding due to decreased plasma factors)	FFP: (15-20ml/kg)	aPTT>1.5 X normal (Bleeding due to decreased plasma factors)	FFP: (15-20ml/kg)	
				EXTEM A10<40mm or MCF<45mm, FIBTEM MCF<9mm Calculation with ROTEM: Fibrinogen (g)=MCF ΔFIBTEM (mm)×weight (kg)/140	Fibrinogen concentrate (25–60mg/kg or 2–4g)	Plasma Fibrinogen <1.5–2.0g/L	FC (Fibrinogen (g)=ΔFibrinogen (g/L)×weght (kg)/140)	
				EXTEM A10 <40mm or MCF<45mm, FIBTEM MCF <9mm Calculation with ROTEM: Fibrinogen (g)=MCF ΔFIBTEM (mm)×weight (kg)/140	Cryo (1 unit/5–10kg)	Plasma Fibrinogen <1.5–2.0g/L	Cryo (1 unit/5–10kg)	
				INTEM CT >240seconds and $HEPTEM_{CT}$ / $INTEM_{CT}$<0.8	Protamine (50–100mg)	N/A, because only ROTEM can assess Heparin's effect on coagulation	Protamine	
				for hyperfibrinolysis, when EXTEM maximal lysis in 60 minutes>15% and APTEM maximal lysis in 60 minutes<15%.	EACA (50mg/kg)	N/A	EACA	
				Source: Algorithm adapted from (55,75,76)				
Fayed et al. (2015) **(65)**	prospective observational study, anaesthesiologists blinded	OLT (LDLT)	ROTEM	MCF_{EXTEM} <25mm	Platelets, FFP and cryoprecipitate	N/A, because all procedures ROTEM-guided (study aim: preoperative ROTEM as predictor for intraoperative transfusion requirements)		Presurgical, Pre-anhepatic phase, Anhepatic, After reperfusion, End of surgery, In clinical evidence of bleeding.
				$CLI_{30\ EXTEM}$ <50%	TXA			
				MCF_{EXTEM} <45mm AND MCF_{FIBTEM} >8mm	PC			
				MCF_{EXTEM} <45mm AND MCF_{FIBTEM} <8mm	Cryo			
				CT_{EXTEM} >80s	FFP			
Zamper et al. (2018) **(39)**	Retrospective single-center cohort study (Brazil),	OLT	ROTEM	If at beginning of anaesthesia $A5_{EXTEM}$ <15mm	Prophylactic TXA (30mg/kg)	Hb <7 g/d	pRBC	Preoperative, 15 min after arterial reperfusion, 6h after the end of surgery.
				A5 EXTEM <25mm AND A10 FIBTEM<10mm	FC	N/A	"Synthetic factor concentrates were	

	Before-after study (Retrospective analysis of prospectively recorded data)			<table><tr><td></td><td>(Dosage: ΔFIBTEM (mm) x weight in kg/140) OR Cryo (1 U/7kg of weight)</td></tr><tr><td>A5 EXTEM <25mm AND A10 FIBTEM>10mm</td><td>Platelet apheresis</td></tr><tr><td>CT_{EXTEM} >80s</td><td>PCC (15 U/kg)</td></tr><tr><td>CT_{INTEM} >240s → HEPTEM: If CT_{HEPTEM} < CT_{INTEM}</td><td>Protamin</td></tr><tr><td>CT_{INTEM} >240s → HEPTEM: If CT_{HEPTEM} ≥ CT_{INTEM}</td><td>FFP (2-4 U)</td></tr><tr><td>If after reperfusion $CLI_{30\ EXTEM}$ <50%</td><td>TXA (15mg/kg)</td></tr></table> *Source:* "POC-VET algorithm adapted from those used in cardiovascular surgeries, designed in conjunction with hematologists and experts in the area" (39)	<table><tr><td></td><td>available, but we did not have institutional authorization for using them in an off-label setting, so the patients in the control phase did not receive these concentrates." (39)</td></tr><tr><td>N/A</td><td>"Antifibrinolytics were used prophylactically in all cases" (39)with exception of specific listed comorbidities</td></tr></table>	
Katsanoulas et al. (2021) **(42)**	Retrospective cohort study without randomization (Greece)	OLT	ROTEM	<table><tr><td>Group 2 Transfusion strategy</td><td>Based on ROTEM values adjusted for cirrhosis, not reported</td></tr><tr><td>Group 3 Transfusion strategy</td><td>A5 liver algorithm</td></tr></table> *Source* Group 3 algorithm from (10)	<table><tr><td>Group 1 Transfusion strategy</td><td>CCT based, not reported</td></tr></table>	N/A	
Schumacher et al. (2019) (4)	Retrospective single-center cohort study (Germany)	OLT	ROTEM	Applied standard reference intervals by the manufacturer for therapeutic decisions (see Annex 12), Anaesthesiologists were "free to initiate measures of their choice at any time." (4) <table><tr><td>Not reported</td><td>PC</td></tr><tr><td>Not reported</td><td>PCC</td></tr><tr><td>Not reported</td><td>FC</td></tr><tr><td>Not reported</td><td>antithrombin concentrate</td></tr><tr><td>Not reported</td><td>Factor XIII concentrate</td></tr><tr><td>Not reported</td><td>Antithrombin concentrate</td></tr><tr><td>Not reported</td><td>FFP</td></tr><tr><td>Not reported</td><td>pRBC</td></tr><tr><td>Not reported</td><td>Apoprotinin or TXA</td></tr></table>	Same products available, thresholds not reported		Baseline at beginning of surgery, At beginning anhepatic stage, After reperfusion.
Blasi et al. (2017) **(64)**	*Post hoc* analysis of randomized, multicenter, double-blind study (Spain)	OLT	ROTEM	<table><tr><td>>15% lysis at 60 min</td><td>TXA (IV Bolus 500mg)</td></tr></table>	<table><tr><td>Hb <80 g/l</td><td>pRBC</td></tr><tr><td>Platelet count <50.000/mm^3</td><td>PC</td></tr><tr><td>Persistent bleeding without correction through pRBC and PC</td><td>FFP (2U/30min)</td></tr><tr><td>Plasma fibrinogen <1g/l</td><td>FC (1g)</td></tr></table>		Baseline before anesthesia induction, At end of hepatectomy, In anhepatic phase, After reperfusion of graft, At end of surgery.

<table>
<tr>
<td>Scarlatescu et al. (2022)

(41)</td>
<td>A propensity score-matched, before-after study (Romania)</td>
<td>OLT</td>
<td>ROTEM</td>
<td>Preoperative:
<table><tr><td>A10_{EXTEM} <25mm OR CT_{FIBTEM} >600s AND no previous thrombotic events</td><td>TXA (10-15mg/kg bolus in 15 min)</td></tr></table>
Intraoperative:
<table><tr><td>Lysis60_{EXTEM} <85% preanhepatic OR Lysis30 _{EXTEM} <50% anhepatic or after reperfusion</td><td>TXA (10-15mg/kg bolus in 15 min)</td></tr><tr><td>A10_{EXTEM}<25mm and A10_{FIBTEM}<8mm</td><td>FC OR Cryo
(Target: A10_{FIBTEM} ≥10mm, to increase A10_{FIBTEM} by 4mm use 25mg/kg Fibrinogen or 2ml/kg Cryo)</td></tr><tr><td>A10_{EXTEM} <25mm and A10_{FIBTEM} >8mm</td><td>PC (6-10U or 1 apharesis)</td></tr><tr><td>CT_{EXTEM} >80s and A10_{FIBTEM}>8mm</td><td>PCC (10-25 IU/kg) OR
FFP (10-15ml/kg)</td></tr><tr><td>CT_{INTEM} >280s and CT_{HEPTEM} >280s</td><td>FFP</td></tr><tr><td>CT_{INTEM} >280s and CT_{HEPTEM}<CT_{INTEM}</td><td>Protamine</td></tr><tr><td>Hb < 7 g/dl</td><td>pRBC</td></tr><tr><td>If ongoing diffuse bleeding, pH>7.2, no hyperfibrinolysis, A10_{FIBTEM}>15mm, A10_{EXTEM} >45mm. CT_{EXTEM}<80s. CT_{HEPTEM} approximately equals CT_{INTEM}</td><td>Rescue therapy with rVIIa</td></tr></table>
Source: (77)</td>
<td><table><tr><td>Platelet count < 50 G/l</td><td>PC</td></tr><tr><td>INR > 2</td><td>FFP or PCC</td></tr><tr><td>Plasma fibrinogen < 150 mg/dl</td><td>FC or Cryo</td></tr><tr><td>Hb < 7 g/dl</td><td>pRBC</td></tr></table></td>
<td>Baseline,
At 10 min after graft reperfusion,
At end of the procedure,
After 10-15min after any intervention.</td>
</tr>
<tr>
<td>Trautman et al. (2017)

(34)</td>
<td>Retrospective cohort study (USA)</td>
<td>OLT</td>
<td>TEG</td>
<td>Not applicable

Measured TEG parameters and norms:
<table><tr><td>r time</td><td>normal, 4.0–10.0 min</td></tr><tr><td>k time</td><td>normal, 1.0–3.0 min</td></tr><tr><td>r time plus k time</td><td>r+k time; normal, 5.0–13.0 minutes</td></tr><tr><td>α angle</td><td>normal, 58.0–78.0 degrees</td></tr><tr><td>MA</td><td>normal, 50.0–74.0 mm</td></tr></table></td>
<td>Not reported</td>
<td>Repeated measurements during first 24h after post-transplant
ICU admission</td>
</tr>
<tr>
<td>Kamel et al. (2018)

(49)</td>
<td>Prospective observational study (South Africa)</td>
<td>OLT (LDLT)</td>
<td>ROTEM</td>
<td>Not reported

Sources: (77,78)</td>
<td>N/A</td>
<td>Preoperatively,
During anhepatic phase,
Post reperfusion,
Postoperative days 1, 3, 7</td>
</tr>
<tr>
<td>Caballero et al. (2022)</td>
<td>Randomized, blinded,</td>
<td>OLT</td>
<td>ROTEM</td>
<td>Mixed VET and CCT approach:
Study aims to compare two A10_{FIBTEM} targets for FC transfusion</td>
<td>Mixed VET and CCT approach</td>
<td>Baseline,
10 minutes after portal clamp,</td>
</tr>
</table>

<table>
<tr><td>(67)</td><td>multicentre trial (Spain)</td><td></td><td></td><td><table><tr><td>Intervention target
A10_{FIBTEM}=11 mm VS.
Standard target
A10_{FIBTEM}=8 mm</td><td>FC</td></tr><tr><td>Hb target >80 g/L</td><td>pRBC</td></tr><tr><td>Platelet count <30 000/mm3</td><td>PC</td></tr><tr><td>>15% lysis at 60 minutes</td><td>TXA (IV bolus 500mg)</td></tr></table>
In case of massive bleeding (>150 mL/min):<table><tr><td>A10_{EXTEM} <15 mm OR
CT_{FIBTEM} of >300 s</td><td>pRBC (4U) + TXA (1g) + FC (2g) + Platelet apheresis (1U) + FFP (15mL/kg)</td></tr></table></td><td></td><td>10 minutes after reperfusion of the liver graft,
End of procedure.</td></tr>
<tr><td>Viguera et al. (2021)

(30)</td><td>Retrospective cohort study (Spain)</td><td>OLT</td><td>ROTEM</td><td><table><tr><td>Hb <8 g/dl</td><td>pRBC</td></tr><tr><td>MCF_{EXTEM} <45mm with hypofibrinogenemia</td><td>FC</td></tr><tr><td>MCF_{EXTEM} <45mm without hypofibrinogenemia</td><td>PC</td></tr><tr><td>Prolonged CT AND low MCF_{EXTEM} (value not reported)</td><td>FFP</td></tr><tr><td>CL₃₀/CL₆₀ > 15 %, signifying that clot amplitude was < 85 % lower than MCF</td><td>TXA (10mg x kg IV in 30min)</td></tr></table></td><td>N/A</td><td>Baseline</td></tr>
<tr><td>Dötsch et al. (2017)

(48)</td><td>Retrospective, single-centre, observational study (Germany)</td><td>OLT</td><td>ROTEM</td><td>Postoperative ROTEM coagulation management:<table><tr><td>MCF_{FIBTEM} ≤9 mm
MCF_{FIBTEM} ≤6 mm</td><td>FC (2g)
FC(4g)</td></tr><tr><td>MCF_{FIBTEM} was ≥9 mm AND MCF_{EXTEM} was ≤40 mm</td><td>PC (1 apheresis or pooled unit)</td></tr><tr><td>CT_{EXTEM} was >80 s
CT_{EXTEM} >100 s</td><td>PCC (25 U kg^{-1}, in 20min)
PCC (40 U kg^{-1})</td></tr><tr><td>If hyperfibrinolysis and bleeding</td><td>TXA (25 mg kg^{-1})</td></tr><tr><td>Hb <7 g/dL</td><td>pRBC</td></tr><tr><td>Factor XIII activity <70% and all ROTEM values within target range</td><td>Factor XIII concentrate (1250-2500 U)</td></tr><tr><td>CT_{INTEM} was >240 s, in persistent bleeding after unsuccessful correction</td><td>FFP (10 ml kg^{-1})</td></tr></table></td><td>N/A</td><td>At ICU admission</td></tr>
</table>

Abbreviations: CCT=Conventional Coagulation Test, PC=Platelet concentrate**,** FC=Fibrinogen concentrate**,** pRBC=packed Red Blood Cells**,** FFP= Fresh Frozen Plasma**,** TXA= Tranexamic acid, Cryo=Cryoprecipitate, PCC=Prothrombin Complex Concentrate, U= Unit, OLT=orthotopic liver transplantation, LDLT=living donor liver transplantation, N/A=not applicable or not reported, TX= Transplantation, TEG=Thromboelastography, ROTEM=Rotational thromboelastometry, CFT= Clot formation time, CT=Clotting time, R=Reaction time, K= K time, MA=Maximum amplitude, MCF=Maximum clot firmness, CLI30= Clot lysis index at 30 min after maximum clot firmness, CLI60= Clot lysis index at 60 min after maximum clot firmness, Ly30=Clot lysis at 30 min after maximum amplitude, Ly60=Clot lysis at 60 min after maximum amplitude

Annex 8:

Table 6. Studies investigating predictive value of VET and determined predictive threshold

Authors (Year) (Citation number)	**Study design**	**Procedure**	**VET type**	**Study aim**	**Results (related to VETs predictive value)**
Pustavoitau et al. (2017) **(26)**	Retrospective cohort study	OLT N=203	TEG	1.Construction of a multivariable predictive model, including TEG parameters, for occurrence of MT event (> 10 U pRBCs)	<u>1.Model to predict probability of experiencing MT (contains multivariate prediction factors):</u> $Odds = Exp\left(-1.236 - 0.409 * Hgb - \begin{cases} 0.053, if\ plts \le 50 \\ 0.073, if\ plts > 50 \end{cases} * Plt + 0.459 * teg_r + 0.057 * teg_{angle} + 0.034 * meld_{raw} + 0.667 * slk + 0.133 * cirr_{stage} \right)$ Source: (26) $Probability = \frac{odds}{odds + 1}$ Source: (26) Models statistical validation: - Hosmer-Lemeshow χ^2 statistic (model calibration): 7.87 (p =0.45) - ROC analysis*: c* statistic: 0.835 (95% CI, 0.781–0.888), i.e. good discrimination - Probability cutoff = 0.25 (risk for MT>0.25) →At this cutoff, model sensitivity: 86.7% (95% CI, 74.9–93.7), specificity: 69.9% (95% CI, 61.6–77.1), positive predictive value: 54.7% (95% CI, 44.2–64.8), negative predictive value:92.6% (95% CI, 85.5–96.5). - In theory: Median 4 patients (IQR 3–5) per 100 LTs would have been harmfully misclassified (=predicted not to require MT, when they did require) - In study cohort: 6 of 8 misclassified patients received median of 14 U (IQR 12–27) pRBCs - In study cohort: Patients who were correctly predicted to require MT received Median 19.5 U (IQR 14–27) pRBCs <u>2.Saving of blood products:</u> Difference between number of Prbc/FFP U typed and crossed and actual pRBCs/FFP transfused (ordering in 15- or 6-unit containers): would save 338 U pRBCs and 338 units of FFP for every 100 LTs
				2.Potential impact of the model on blood bank resources	

Pustavoitau et al. (2020) **(27)**	Retrospective, single-centre cohort study	OLT n=403	TEG	1.Determination multivariable predictive parameters, including TEG parameters, for occurrence of MT event (> 10 U pRBCs) (Included Pustavoitau et al. 2017 cohort + 200 new patients) 2.Clinical validation of the altered 2020 Pustavoitau et al. multivariable predictive model for MT	1.Final 2020 multivariate prediction model for MT events included: Hb concentration, PLT concentration, TEG R interval, need for retransplantation, simultaneous liver and kidney transplantation Altered models statistical validation: - Hosmer-Lemeshow $\chi 2$ (model calibration): 7.87 ($P = .45$) in the previous (2017) cohort, 6.61 ($P = .58$) in the new (2020) cohort, 7.10 ($P = .53$) in the combined cohort - ROC analysis: *c* statistic 0.69 (95% CI, 0.60-0.78), i.e. good discrimination - Probability cutoff value = 0.25 (risk for MT>0.25) 2.Saving of blood products: Difference between number of pRBC/FFP U typed & crossed and actual pRBCs/FFP transfused (ordering in 15- or 6-unit containers): would save crossmatching of 358 U pRBCs and thawing of 358 U FFP for every 100 LTs
Thakrar and Mallet (2017) **(28)**	Retrospective study	OLT n=246	TEG	Relationship between baseline platelet count, clauss fibrinogen, TEG maximum amplitude (MA) with intraoperative blood product requirements and occurrence of MT event	Parameters with statistically significant difference between MT patient group and no-MT group: baseline hepMA (hep MA in MT group 35.28 ± 9.49 vs No MT group 47.85 ± 11.93, P ≤ 0.001). (and baseline Hb, platelet count, clauss fibrinogen) Determined MT predictive TEG cut-off value: - Mean hepMA = 42mm associated with MT (> 1200 mL returned; in n=114 i.e. 46.3%) vs. - Mean hepMA = 47mm in those withOUT MT (< 1200 mL returned; in n=132, i.e. 53.7%)
Lawson et al. (2017) **(29)**	Prospective study	OLT n=28	TEG	Relationship between pre-operative R-time, alpha angle, MA, LY30 with pRBC, FFP, Cryo, PC units in first 24 hours after surgery AND occurrence of MT events (≥10 pRBC U/24hr)	Parameters with statistically significant differences between MT patient group and no-MT group: low MA (MT group 37mm (14–41) vs No-MT group 56mm (44–64), p<0.001), low alpha angle (MT group 36° (3–43) vs No-MT group 52° (40°–57°), p=0.014) *No* significant differences in: R-time (MT group 11min (7–13) vs No-MT group 10min (8–12), p=0.763), LY30 (MT group 0.0% (0.0–2.1) vs No-MT group 0.1 (0.0–0.9), p=0.945) Determined MT predictive TEG cut-off value and statistical validation 1: - MA < 47mm (Optimal inflection point determined by Youden index) - Sensitivity to predict MT 90%, Specificity 72% , PPV 64%, NPV 03% - MA highest AUC (0.861), [Second INR (0.803), Third alpha angle (0.764)] - In patients with MA < 47mm, 67% underwent MT - MA < 47mm excluded patients not requiring MT in 93% of patients - MA the only variable with strong correlation to every blood product (pRBC/FFP/Cryo/PC) (p<0.001) - MA < 47mm missed only 1 patient who required MT, but did not receive it Determined MT predictive TEG cut-off value and statistical validation 2: - Alpha angle <41° (Optimal inflection point determined by Youden index) - Sensitivity to predict MT 81%, Specificity 59%, PPV 72%, NPV 70% - AUC alpha angle (0.764) - Angle strong correlation only to Cryo (p<0.002)

Viguera et al. (2021) **(30)**	Retrospective study	OLT n=591	ROTEM	Relationship between baseline haemoglobin and MCF_{EXTEM} with intraoperative pRBC requirements AND occurrence of MT event (≥ 6 pRBC U) AND influence on mortality	Parameters with statistically significant difference between pRBC requiring patients and no-pRBC requiring patients: Baseline MCF_{EXTEM} (and baseline Hb) <u>Determined pRBC requirement predictive ROTEM cut-off value and statistical validation</u> - MCF_{EXTEM} (Transfused patients Mean 51mm (SD 11) vs. non-transfused patients Mean 55mm (SD 9),p = 0.001) - MCF_{EXTEM} ≤45mm (threshold applied in their transfusion strategy for transfusing FC (or Cryo) and/or PC): MCF_{EXTEM} ≤45mm alone no predictive value for RBC transfusion, but predictive probability of MCF + Hb improved (AUC 0.827, 95 % CI 0.791−0.863, p < 0.001) Parameters with statistically significant differences between MT patient group and no-MT group: MCF_{EXTEM} (and Hb ≤ 10 g/dL) <u>Determined MT predictive ROTEM cut-off value and statistical validation</u> - In patients with Hb ≤ 10 g/dL the addition of MCF_{EXTEM} ≤45mm did not increase the predictive probability (AUC 0.675 (95 % CI 0.615−0.736, p < 0.001) - BUT in patients with Hb > 10 g/dL the addition of MCF_{EXTEM} ≤45mm had slight influence on predictive probability (Mean pRBC amount 8 U (6–11) vs 7(6–8))

Abbreviations: MT=massive transfusion, AUC=Area under curve, SD=Standard deviation, IQR=Interquartile range, U=Unit, CCT=Conventional Coagulation Test, PC=Platelet concentrate**,** FC=Fibrinogen concentrate**,** pRBC=packed Red Blood Cells**,** FFP= Fresh Frozen Plasma**,** TXA= Tranexamic acid, Cryo=Cryoprecipitate, PCC=Prothrombin Complex Concentrate, U= Unit, OLT=orthotopic liver transplantation, LDLT=living donor liver transplantation, N/A=not applicable or not reported, TX= Transplantation, TEG=Thromboelastography, ROTEM=Rotational thromboelastometry, CFT= Clot formation time, CT=Clotting time, R=Reaction time, K= K time, MA=Maximum amplitude, MCF=Maximum clot firmness, CLI30= Clot lysis index at 30 min after maximum clot firmness, CLI60= Clot lysis index at 60 min after maximum clot firmness, Ly30=Clot lysis at 30 min after maximum amplitude, Ly60=Clot lysis at 60 min after maximum amplitude

Annex 9:
Table 7. Study outcomes

Author (Year) (Citation number)	**Cohort sizes (n=CCT-guided OLTs vs. n= VET-guided OLTs)**	**Transfusion requirements in VET-guided groups (vs. CCT- guided)** Product amount in U (unless specified differently) Patient proportion requiring product in absolute number (and percentage)	**Perioperative complications**	**Length of hospital /ICU stay**	**Mortality/Survival**	**Other outcomes**
Leon-Justel et al. (2015) **(38)**	n=100 vs n=100	Unadjusted analysis: FFP amount: Decrease (Median 2 vs. 0 U, p < .001) FFP patient proportion: Decrease (not reported) FC amount in g/patient: Increase (CCT 0.48 ± 1.28 vs. VET 1.13 ± 1.44, p=0.001) FC patient proportion: - pRBC amount: Decrease (Median 5 vs. 3 U, p < .001) pRBC patient proportion: Decrease (not reported) PC amount: Decrease (Median 1 vs. 0 U, p < .001)	Unadjusted analysis (in % of patients): Respiratory complications: Indifferent (9% CCT vs 16% VET, p=0.134) Graft complications: Indifferent (40% CCT vs	N/A	Unadjusted analysis: No difference in 1-year survival (81% in CCT group vs 79% in VET, P=0.663)	N/A

PC patient proportion	Decrease (not reported)
TXA (1g IV bolus) amount TXA patient proportion	- Indifferent (CCT 1 vs. VET 4, p=0.369)
Incidence of MT	Decrease 13% vs. 2% (p = 0.005)
Incidence of Transfusion avoidance (any product)	Increase (CCT 5% vs. VET 24%, p < 0.001)

Adjusted analysis (multivariate logistic regression)

FFP amount	Decrease (OR 18.188, CI 8.289–39.907, p< 0.001)
pRBC amount	Decrease (OR 7.799, CI 2.440–24.927, p=0.001)
PC amount	Decrease (OR 4.032, CI 2.045–7.952, p< 0.001)

	37 VET, p=0.663)
Postoperative hemorrhage	Indifferent (14% CCT vs 6% VET, p=0.059)
Bacterial infection	Indifferent (38% CCT vs 43 VET, p=0.471)
Fungal infection	Indifferent (2% CCT vs 2% VET, p=1.000)
Postreperfusion syndrome	Indifferent (2% CCT vs 1% VET, p=1.000)
Portal Thrombosis	Indifferent (4% CCT vs 1% VET, p=0.369)
Delayed graft function	Indifferent (8% CCT vs 5% VET, p=0.390)
Biliary complications	Indifferent (21% CCT vs 16% VET, p=0.363)
Biliary fistula	Indifferent (7% CCT vs 3% VET, p=0.331)
Biliary stenosis	Indifferent (5% CCT vs 3% VET, p=0.721)
Arterial hypertension	Indifferent (3% CCT vs 0% VET, p=0.246)

			Thrombopenia	Indifferent (4% CCT vs 2% VET, p=0.683)			
			Ascites	Indifferent (18% CCT vs 20% VET, p=0.718)			
			Abdominal wall haematoma	Indifferent (3% CCT vs 0% VET, p=0.246)			
			Hemodynamic instability	Decreased (29% CCT vs 16% VET, p = .028)			
			Pancytopenia	Decreased (12% CCT vs 3% VET, p=0.029)			
			AKI	Decreased (17% CCT vs 2% VET, p<0.001)			
			Reoperation for bleeding	Decreased (13% CCT vs 5% VET, p=0.048)			
			Reoperation for other reasons	Indifferent			
			Retransplantation	Decreased (10% CCT vs 2% VET, p=0.033)			
			Neurological complications	Increased (145 CCT vs 27% VET, p=0.023)			
			Viral infections	Increased (7% CCT vs 20% VET, p=0.007)			

<table>
<tr>
<td>Bonnet et al. (2019)

(35)</td>
<td>n=41 vs. n=40</td>
<td>Unadjusted analysis:
<table>
<tr><td>Total amount of any transfusion (RBC, Plasma or Platelets)</td><td>Decreased (Median VET 3 [2 to 4] U vs. CCT 7 [4 to 10] U, P = 0.005)</td></tr>
<tr><td>Total proportion of patients receiving any transfusion (RBC, FFP or PC)</td><td>Indifferent</td></tr>
<tr><td>FFP amount

FFP patient proportion</td><td>Indifferent (Median VET 3 [2 to 6] U vs. Median CCT 4 [2 to 7] U, P = 0.448),
Decreased (VET 15% vs. CCT 46.3%, P = 0.002)</td></tr>
<tr><td>FC amount
FC patient proportion</td><td>Indifferent
Increased (VET 72.5% vs. CCT 29.3%, P < 0.001)</td></tr>
<tr><td>pRBC amount

pRBC patient proportion</td><td>Indifferent (Median VET 3 [2 to 5] u vs. Median CCT 4 [2 to 6] U, P = 0.330)
-</td></tr>
<tr><td>PC amount

PC patient proportion</td><td>Indifferent (Median VET 1 [1 to 2] U vs. Median CCT 1 [1 to 2] U, P = 0.910)
-</td></tr>
<tr><td>TXA amount
TXA patient proportion</td><td>-
Decreased (VET 27.5% vs. CCT 58.5%, P = 0.005)</td></tr>
<tr><td>Total number of units transfused postoperatively (RBC, Plasma or Platelets)</td><td>Indifferent</td></tr>
</table>
Adjusted Multivariable Regression:
<table>
<tr><td>Total amount of any intraoperative transfusion (RBC, Plasma or Platelets)</td><td>Decreased (beta coefficient -2.87, p= 0.046)</td></tr>
</table></td>
<td>Unadjusted analysis:
<table>
<tr><td>Hemorrhage or revision surgery at 24 and 48 h</td><td>Indifferent</td></tr>
<tr><td>Graft dysfunction (until 7d postop)</td><td>Indifferent</td></tr>
<tr><td>Arterial or portal vein thrombosis</td><td>Indifferent</td></tr>
<tr><td>Sepsis measured up until 1 and 3 months post-op</td><td>Indifferent</td></tr>
<tr><td>AKI measured up until 1 and 3 months post-op</td><td>Indifferent</td></tr>
<tr><td>ICU readmission measured up until 1 and 3 months post-op</td><td>Indifferent</td></tr>
<tr><td>Thrombosis up until 3m postop</td><td>Indifferent</td></tr>
</table></td>
<td>N/A</td>
<td>Unadjusted analysis:
No difference in 30- and 90-day mortality</td>
<td>N/A</td>
</tr>
<tr>
<td>Nascimento et al. (2020)

(40)</td>
<td>n=71 vs. n=82</td>
<td>Unadjusted analysis:
<table>
<tr><td>FFP amount
FFP patient proportion</td><td>Indifferent
Decreased (CCT 46.5% vs. VET 30.5%; P= 0.047)</td></tr>
<tr><td>FC amount in g

FC patient proportion</td><td>Increased (VEZ 0.8 ± 1.8g vs. CCT 0.2 ± 0.9 g; P=0.004)
-</td></tr>
<tr><td>Cryo amount

Cryo patient proportion</td><td>Increased (VET 7.6 ± 10.5 U vs. CCT 1.2 ± 3.2 U; P<0.001)
-</td></tr>
<tr><td>Cryo and/or FC patient proportion</td><td>Increased (VET 54.9% vs. CCT 19.7%; P<0.001)</td></tr>
<tr><td>PCC amount in IU</td><td>Increase (VET 1.4 ± 2.3 vs. CCT 0.2 ± 0.7 IU; P=0.002)</td></tr>
</table></td>
<td>Unadjusted analysis:
<table>
<tr><td>Need for hemodialysis</td><td>Indifferent</td></tr>
<tr><td>Tracheal extubation within 6 h</td><td>Indifferent</td></tr>
<tr><td>Unplanned reoperation within the first 24 h</td><td>Indifferent</td></tr>
<tr><td>Graft rejection</td><td>Indifferent</td></tr>
</table></td>
<td>Unadjusted analysis:

No difference in length of hospital or ICU stay</td>
<td>Unadjusted analyses:

No difference in 1-year survival</td>
<td>N/A</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td><table>
<tr><td>PCC patient proportion</td><td>Increased (VET 32.9% vs. CCT 9.9%; P=0.008)</td></tr>
<tr><td>pRBC amount
pRBC patient proportion</td><td>Indifferent
Indifferent</td></tr>
<tr><td>PC amount
PC patient proportion</td><td>Indifferent
Indifferent</td></tr>
<tr><td>Anti-fibrinolytics amount
Anti-fibrinolytics patient proportion</td><td>-
Decreased (CCT 85.9% vs. VET 47.6%; P<0.001).</td></tr>
<tr><td>EACA amount
EACA patient proportion</td><td>-
Decreased (VET 39 patients i.e. 47.6% vs CCT 61 patients i.e. 85.9%, p<0.001)</td></tr>
</table></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Zamper et al. (2018)

(39)</td><td>Unmatched cohort
Before VET implementation n= 183

After n= 54</td><td>Unadjusted analysis (results from unmatched cohort):
Data presented as (mean ± SD) or (absolute umber/total (percentage))<table>
<tr><td>Total amount of any transfusion (pRBC, platelets, FFP or Cryo)
Total proportion of patients receiving any transfusion (pRBC, platelets, FFP or Cryo)</td><td>-

Decreased (After 19 of 54 patients (35.2%) vs Before 103 of 183 (56.3%), p= 0.006)</td></tr>
<tr><td>FFP amount

FFP patient proportion

(Mean ± SD)</td><td>Decreased (After 0.2 ± 0.8 U vs. Before 2.1 ± 4.2 U, p= 0.001)
Decreased (After 3 / 53 (5.7%) vs. Before 50 / 183 (27.3%), p < 0.001)</td></tr>
<tr><td>FC amount in g

FC patient proportion</td><td>Increased (After 1.4 ± 2.3 g vs Before 0.0 ± 0.0 g, p<0.001)
Increased (After 18/54 (33.3%) vs Before 0/183 (0.0%), p<0.001)</td></tr>
<tr><td>Cryo amount
Cryo patient proportion</td><td>Indifferent
Indifferent</td></tr>
<tr><td>PCC amount in IU

PCC patient proportion</td><td>Increased (After 222.2 ± 711.5 IU vs Before 0.0 ±0.0 IU, p<0.001)
Increased (After 6/54 (11.1%) vs Before 0/183 (0.0%), p<0.001)</td></tr>
<tr><td>pRBC amount

pRBC patient proportion</td><td>Decreased (After 0.7 ± 1.3 U vs Before 1.7 ± 2.7 U, p=0.007)
Decreased (After 16 / 53 (30.2%) vs. Before 96 / 183 (52.5%), p=0.004)</td></tr>
<tr><td>PC amount
PC patient proportion</td><td>Indifferent
Indifferent</td></tr>
<tr><td>Anti-fibrinolytics amount</td><td>-</td></tr>
</table></td><td>Unadjusted analysis (results from unmatched cohort):<table>
<tr><td>Any procedure-related complications</td><td>Indifferent</td></tr>
<tr><td>Upper GI hemorrhage</td><td>Indifferent</td></tr>
<tr><td>Arterial thrombosis</td><td>Indifferent</td></tr>
<tr><td>Duration of postoperative ventilation</td><td>Indifferent</td></tr>
</table>
Adjusted analyses with propensity score matching:<table>
<tr><td>Any procedure-related complications</td><td>Indifferent</td></tr>
<tr><td>Upper GI hemorrhage</td><td>Indifferent</td></tr>
<tr><td>Arterial thrombosis</td><td>Indifferent</td></tr>
<tr><td>Duration of postoperative ventilation</td><td>Indifferent</td></tr>
</table></td><td>Unadjusted analyses (results from unmatched cohort):<table>
<tr><td>Hospital LOS (Mean ± SD, in d)</td><td>Increased (After 12.1 ± 8.9 vs. 17.2 ± 15.4, p= 0.022)</td></tr>
<tr><td>ICU LOS (Mean ± SD, in d)</td><td>Indifferent (After 3.2 ± 4.0 vs. Before 4.2 ± 6.6 0.290)</td></tr>
</table></td><td>Unadjusted analysis:

No difference in in-hospital mortality

Adjusted analyses with propensity score matching:

No difference in in-hospital mortality</td><td>N/A</td></tr>
</table>

		Anti-fibrinolytics patient proportion: Decreased (After 8/54 (14.8%) vs before 77 / 182 (42.3%), p< 0.001) Adjusted analyses with propensity score matching (Adjusted by age, Child, MELD, presence of HCC and pre-transplantation hemoglobin): Data presented as (mean ± SD) or (absolute umber/total (percentage)) Total proportion of patients receiving any transfusion (pRBC, platelets, FFP or Cryo): Decreased (After 37.0% vs Before 58.4%; OR, 0.42; 95% CI, 0.20–0.87; p = 0.019). pRBC amount: Decreased (After 0.6 ± 1.0 U vs Before 1.7 ± 2.7 U, p=0.008) pRBC patient proportion: Decreased (After 30.2% vs Before 52.5%; OR, 0.21; 95% CI, 0.08–0.56; p = 0.002) FFP amount: Decreased (After 0.2 ± 0.9 U vs Before 2.2 ± 4.5U, P=0.004) FFP patient proportion: Decreased (After 5.7% vs Before 27.3%; OR, 0.11; 95% CI, 0.03–0.43; p = 0.002). Cryo amount: Indifferent (After 0.5 ± 2.3 U vs before 0.4 ± 1.9 U, p=0.938) Cryo patient proportion: Indifferent (After 3 / 46 (6.5%) vs before 5 / 89 (5.6%), p=0.833) PC amount: Indifferent (After 0.0 ± 0.0 U vs before 0.1 ± 0.6 U, p=0.474) PC patient proportion: Indifferent (After 10 / 46 (21.7%) vs Before 16 / 89 U (18.0%), p=0.599) FC amount in g: Increased (After 1.4 ± 2.4 g vs Before 0.0 ± 0.0 g, p < 0.001) FC patient proportion: Increased (After 16 / 46 (34.8%) vs before 0 / 89 (0.0%), p < 0.001) PCC amount in IU: Increased (After 195.6 ± 645.3 IU vs. before 0.0 ± 0.0 IU, p=0.005) PCC patient proportion: Increased (After 5 / 46 (10.9%) vs before 0 / 89 (0.0%), p=0.001) Anti-fibrinolytic patient proportion: Decreased (After 7 / 46 (15.2%) vs 36 / 88 (40.9%), p< 0.001)		Adjusted analyses with propensity score matching: Hospital LOS: Indifferent ICU LOS: Indifferent		
Smart et al. (2017) **(36)**	n=34 vs n=34	Unadjusted analysis: Total amount of blood products: Indifferent (VET Median 14.5 U *vs.* CCT 17 U, p = 0.11). pRBC amount: Indifferent (VET Median 4 (2-8) U vs CCT 5 (4-12) U, p=0.1352)	N/A	Unadjusted analysis: No difference in median ICU LOS	Unadjusted analysis: No difference in 30-day or 60-day mortality	Unadjusted analysis: Intraoperative: Decreased (VET

		pRBC patient proportion: Indifferent (VET n=28, i.e. 82% vs CCT n=33, i.e. 97%; p=not reported, but was statistically insignificant according author) FFP amount: Decreased (VET Median 4 U vs. CCT Median 6.5 U, p = 0.02) FFP patient proportion: N/A, because one value missing Cryo amount: Increased (VET Median 2 U vs. CCT 1 U, p = 0.04). Cryo patient proportion: Increased (VET n = 25, i.e. 73% vs. CCT n = 19; i.e. 56%, p=not reported, but was statistically insignificant according author PC amount: Indifferent (VET Median 2 (1-4) U vs CCT 2 (0-4), p=0.70) PC patient proportion: Indifferent (VET n=27, i.e. 79% vs CCT n=24, i.e. 71%, p=not reported, but was statistically insignificant according author)				bloo d loss in L: 2.0 vs. CCT 3.0 L, p = 0.0375) Over all Cost: Decre ased (VET $113,142.89 vs CCT. $127,814.77)
Katsanoulas et al. (2021) **(42)**	Group 1 CCT n=46 vs Group 2 ROTEM adjusted for cirrhosis n=19 vs Group 3 ROTEM A5 algorithm n=47	Unadjusted analysis: FFP amount: Decrease in group 2 and 3 (Mean U group 1: 18.59 vs 2: 11.53 vs 3: 4, marked as statistically significant) FFP patient proportion: - FC amount in g: Indifferent (Mean in g group 1: 1.696 vs 2: 1.526 vs 3: 2.649, marked as non-statistically significant) FC patient proportion: - Cryo amount: Decrease in group 3 (Mean U group 1: 6.761 vs 2: 3.263 vs 3: 0.319, marked as statistically significant) Cryo patient proportion: - PCC amount in IU: Indifferent (Mean IU group 1: 284.1 vs 2: 236.8 vs 3: 467.4, marked as statistically insignificant) PCC patient proportion: - pRBC amount: Decrease in group 3 (Mean U group 1: 8.100 vs 2: 5.158 vs 3: 3.766, marked as statistically significant) pRBC patient proportion: - PC amount: Decrease in group 2 and 3 (Mean U group 1: 8.289 vs 2: 2.368 vs 3: 0.979, marked as statistically significant) PC patient proportion: - TXA amount in g: Increase in group 3 (Mean in g group 1: 0.717 vs 2: 0.750 vs 3: 1.202, marked as statistically significant) TXA patient proportion: -	N/A	N/A	N/A	N/A
Schumacher et al. (2019)	n=331 vs n= 82	Unadjusted analysis: FFP amount: Decreased (CCT 9.8 ± 6.9 U vs VET 8.3 ± 9.0 U, p.=0.005) FFP patient proportion: Decreased (CCT 97.9% vs VET 82.9%, p<0.001)	N/A	Unadjusted analysis: ICU LOS: Indifferen	Unadjusted analyses: No difference in ICU-related mortality	N/A

<table>
<tr>
<td>(4)</td>
<td></td>
<td>
<table>
<tr><td>FC amount in g
FC patient proportion</td><td>-
Increased (CCT 35.6% vs VET 48.8%, p=0.029)</td></tr>
<tr><td>PCC amount in IU
PCC patient proportion</td><td>-
Decreased (CCT 36.9% vs VET 23.2%, p=0.019)</td></tr>
<tr><td>pRBC amount

pRBC patient proportion</td><td>Decreased (CCT 8.2 ± 7.3 U vs VET 7.7 ± 11.0 U, p = .034)
Decreased (CCT 94.6% vs VET 87.8%, p=0.029)</td></tr>
<tr><td>PC amount
PC patient proportion</td><td>Decreased (CCT 1.2±1.5 U vs VET 0.9±1.9 U, p=0.014)
Decreased (CCT 48.9% vs 32.9%, p=0.009)</td></tr>
<tr><td>Antithrombin patient proportion</td><td>Decreased (CCT 35.3% vs VET 22.0%, p=0.021)</td></tr>
<tr><td>Anti-fibrinolytics patient proportion</td><td>Increased (CCT 22.4% vs VET 32.9%, p=0.046)</td></tr>
<tr><td>Patient proportion receiving massive transfusion of pRBC</td><td>Indifferent</td></tr>
<tr><td>Patient proportion receiving massive transfusion of FFP</td><td>Indifferent</td></tr>
<tr><td>Factor XIII patient proportion</td><td>Indifferent</td></tr>
</table>
Adjusted analysis (multivariate linear regression analysis):
<table>
<tr><td>ROTEM and pRBC amount</td><td>Multivariate correlation (P = .041; B = -2.212; 95% CI, -4.332 to -0.092)</td></tr>
<tr><td>ROTEM and FFP amount</td><td>Multivariate correlation (P = .008; B = -2.614; 95% CI, -4.545 to -0.683)</td></tr>
</table>
</td>
<td></td>
<td></td>
<td>t (mean d VET 24.7 ± 30.1 vs. CCT 24.0 ± 36.9, P = .203)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scarlatescu et al. (2022)

(41)</td>
<td>Before VET implementation n= 94

After n=94</td>
<td>
Unadjusted analysis:
<table>
<tr><td>Total amount blood products in U
Patient proportion transfused with any blood product</td><td>Decreased (Before 16.5 U (17%) vs After 8 U (12%), p<0.001)
Decreased (Before n=90 (95.7 %) vs After n=82 (87.23 %), p= 0.037)</td></tr>
<tr><td>FFP amount
FFP patient proportion</td><td>Decreased (Before 10 (9) U vs after 0 (5) U, p<0.001)
Decreased (Before n=86 (91.4 %) vs after n=40 (42.5 %), p<0.001)</td></tr>
<tr><td>pRBC amount
pRBC patient proportion</td><td>Indifferent
Indifferent</td></tr>
<tr><td>PC amount
PC patient proportion</td><td>Indifferent
Indifferent</td></tr>
</table>
</td>
<td>
Unadjusted analysis:
<table>
<tr><td>Any complications</td><td>Indifferent (Before 19 (20.2 %) vs After 21 (22.3 %), p=0.722)</td></tr>
<tr><td>Thrombotic complications</td><td>Indifferent (Before 9(9.5 %) vs After 3 (3.2 %), p=0.073)</td></tr>
<tr><td>Bleeding complications</td><td>Indifferent (Before 1 (1.06 %) vs After 4 (4.2 %), p=0.368)</td></tr>
<tr><td>Cardiovascular</td><td>Indifferent (Before 2 (2.1 %) vs After 0 (0 %), p=0.497)</td></tr>
</table>
</td>
<td>
Unadjusted analysis:
Data presented as median (IQR)
<table>
<tr><td>ICU LOS in d</td><td>Decreased (Before 6(3) vs after 5(3), p=0.003)</td></tr>
</table>
</td>
<td>
Unadjusted analysis:
<table>
<tr><td>Survival at 30 days (absolute number)</td><td>Indifferent (Before n=87 (92.5 %) vs after n= 86 (91.5 %), p= 0.788)</td></tr>
<tr><td>Survival at ICU discharge (absolute number)</td><td>Indifferent (Before n=87 (92.5 %) vs after n=</td></tr>
</table>
</td>
<td>
Unadjusted analysis:
<table>
<tr><td>Intraoperative bleeding (in ml)</td><td>Indifferent (Before 3500ml (4550ml) vs after 4500 ml (4750), p=0.41)</td></tr>
</table>
</td>
</tr>
</table>

		PCC amount PCC patient proportion: Indifferent Indifferent Cryo amount Cryo patient proportion: Decreased (Before 0 (4) U vs after 0 (0) U, p<0.001) Decreased (Before n=36 (38.3 %) vs n=17 (18 %), p=0.002) FC amount in g FC patient proportion: Increased (Before 0(0) vs After 1(2), p <0.001) Increased (before n=18 (19.1 %) vs After n=54 (57.4 %), p<0.001) Patient proportion receiving FC or cryoprecipitate: Increased (Before n=40 (42.5 %) vs after n=61 (64.8 %), p=0.002) Total amount of fibrinogen from Cryo and FC in g: Increased (Before 0 (1.8) g vs After 2(3) g, p=0.001)	complications: Neurological complications: Indifferent (Before 0 (0 %) vs After 2 (2.1 %), p=0.497) Infectious complications: Indifferent (Before 1 (1.06 %) vs After 3 (3.2 %), p=0.621) Graft dysfunction: Indifferent (Before 2 (2.1 %) vs After 3 (3.2 %), p=0.65) TRALI or TACO: Indifferent (Before 3(3.2 %) vs After 0 (0 %), p=0.246) Intra-abdominal collection/fistula: Indifferent (Before 0 (0 %) vs After 3(3.2 %), p=0.246) Renal dysfunction: Indifferent (Before 1 (1.06 %) vs After 3 (3.2 %), p=0.621)		86 (91.5 %), p= 0.788)	
Trautman et al. (2017) **(34)**	n=441	N/A	TEG associations with outcomes in multivariable analysis: Increased MA on first post-LT TEG associated with early allograft dysfunction. (Multivariable analysis: OR (95% CI) 1.42 (1.11–1.81), p=0.005) Increased MA on first post-LT TEG associated with early allograft dysfunction. (Multivariable analysis: OR (95% CI) 1.42 (1.11–1.81), p=0.005)	TEG associations with outcomes in multivariable analysis: A prolonged and/or lengthening r time, k time, and r+k time were all independently associated with increased length of hospitalization after LT	TEG associations with outcomes: No significant association between first postoperative TEG parameters and survival	N/A

				Multiplicative effects interpreted as multiplicative increase on the mean hospital LOS per the increase in parenthesis (mean across all measures) or presence of the given characteristic (sequential increases and decreases): Mean R time (Multiplicative effect (95% CI): 1.09 (1.03–1.15), p=0.002) Mean k time (Multiplicative effect (95% CI):1.13 (1.04–1.22), p=0.004) Mean R+k time (Multiplicative effect (95% CI): 1.11 (1.02–1.20), p=0.020)		
Dötsch et al. (2017) **(48)**	n=243	N/A	Outcome: Post-LT non-surgical bleeding complication yes or no <u>Parameters with predictive ability on post-LT bleeding:</u> aPTT (AUC 0.688)	N/A	N/A	N/A

			PT (AUC 0.623) CT_{EXTEM} (AUC 0.682) CFT_{INTEM} (AUC 0.615) $A10_{FIBTEM}$ (AUC 0.615) MCF_{FIBTEM} (AUC 0.611) <u>Not predictive of postoperative bleeding</u>: Fibrinogen concentration (AUC <0.6) Platelet count (AUC <0.6) Other ROTEM variables (AUC <0.6) <u>Note</u>: The calculated optimal cut-off values were not risk-benefit adjusted, which makes them unsuitable for practice and are therefore excluded from the thesis			

Abbreviations: VET= viscoelastic test, CCT=conventional coagulation test, MT=Massive Transfusions, U=Units, SD=standard deviation, CI= Confidence interval, IQR=interquartile range, TEG=Thromboelastography, ROTEM=Rotational thromboelastometry, CFT= Clot formation time, CT=Clotting time, R=Reaction time, K= K time, MA=Maximum amplitude, MCF=Maximum clot firmness, CLI30= Clot lysis index at 30 min after maximum clot firmness, CLI60= Clot lysis index at 60 min after maximum clot firmness, Ly30=Clot lysis at 30 min after maximum amplitude, Ly60=Clot lysis at 60 min after maximum amplitude

Annex 10:
Table 8. Study outcome of systematic reviews (with meta-analysis)

Author (Year), Format (Citation number)	**Procedure**	**Transfusion requirements under VET (vs. CCT-guidance)** Amounts, Patient proportion		**Perioperative complications under VET (vs. CCT-guidance)**		**Length of hospital/ICU stay under VET (vs. CCT-guidance)**	**Mortality/survival under VET (vs. CCT-guidance)**	**Other outcomes**
Tangcheewinsirikul et al. (2022), **Meta-analysis**	Various invasive procedures in cirrhotic patients (including OLT)	pRBC amount	Indifferent (Mean U VET 3.86 units; 95% CI 2.21–5.51; $I2$ = 95% vs. CCT 3.87 units; 95% CI 1.88–5.85; $I2$ = 95%)	TRAEs	Decreased (n = 194) (VET 9.2%; 95% CI 1.3– 44.3; I 2 = 76%) vs (CCT 16.5%; 95% CI 0.7–84.3; I 2 = 93%) , (Pooled RR 0.42	Indifference in Hospital LOS and ICU LOS (2 RCTs, n = 134) In-hospital LOS (MD 0.69 days; 95%	Indifference short and long-term mortality (seven RCTs, n=421) Mortality rates at the longest follow-ups in VET (30.7%; 95% CI 13.5– 55.5; I 2 = 86%) and SCT groups (26.9%; 95% CI	-

(37)		pRBC patient proportion	Indifferent (VET 53.8%; 95% CI 21.1–78.5, *I*2 = 89% vs. CCT 50.4%; 95% CI 27.2–73.4; *I*2 = 86%; four RCTs; *n* = 297)		(95% CI 0.27–0.65; p < 0.001; I 2 = 0%)	CI 5.99 to 4.61; I 2 = 35%) ICU stay (MD 1.12 days; 95% CI 2.69 to 4.94; I 2 = 49%)	11.2–51.7; I 2 = 87%) were not significantly different (RR 1.04; 95% CI 0.74–1.45; I 2 = 16%). 30-day mortality rate (four RCTs; n = 273) VET group (14.3%; 95% CI 3.2–46.2; I 2 = 85%) vs CCT (12.0%; 95% CI 3.8–32.1; I 2 = 74%)	
		PC amount	Decreased (mean transfused PC U (four RCTs; n = 265) [7, 8, 19, 21] in VET group (1.28 units; 95% CI 0.51–2.06; I 2 = 95%) was significantly lower than that in SCT group (2.34 units; 95% CI 1.40–3.27; I 2 = 95%). The pooled MD of transfused platelets was 1.06 units lower in VET group (95% CI 2.01 to 0.12; p = 0.03; I 2 = 92%; PC patient proportion Decreased (six RCTs (n = 393) Under VET 66% reduction of PC (RR 0.34; 95% CI 0.16–0.73; p = 0.006; I 2 = 79%)	TACO	Indifferent (occurred in 15.6% of (n = 96), (RR 0.48; 95% CI 0.18–1.30)."		
		FFP amount	Decreased mean FFP U (four RCTs; *n* = 265), decreased in VET (3.60 U; 95% CI 1.74–5.47; *I*2 = 95% vs CCT 4.12 U; 95% CI 2.60–5.63; *I*2 = 94%); pooled MD of transfused FFP was 1.39 U lower in VET (95% CI −2.18 to	TRALI	Reduced (occurred in 30.2%of n=96), (RR 0.25; 95% CI 0.11–0.56; p = 0.001)		

		FFP patient proportion	−0.60; p<0.001; $I2$ = 49 %) Decreased (28.1% and 60.5% of patients, six RCTs (n = 393), pooled rate of FFP transfusion was 48% significantly lower in VET group (RR 0.52; 95% CI 0.35–0.77; p = 0.001; $I2$ = 56 %9				
		Cryo amount Cryo patient proportion	Decreased (two RCTs; n = 124) VET (mean 9.80 units; 95% CI 5.10–14.51; I 2 = 67%) vs CCT (mean 17.65 units; 95% CI 15.75–19.55; I 2 = 0%). Pooled MD of transfused cryoprecipitate was 7.13 units lower in VET group (95% CI 14.20 to 0.07; p = 0.048; I 2 = 71%) Indifferent two RCTs; n = 134) in VET group (57.8%; 95% CI 42.7–71.5; I 2 = 29%) vs CCT (84.9%; 95% CI 3.0–99.9; I 2 = 92%)				
Hartmann et al. (2022), **Meta-analysis** **(21)**	Cirrhotic patients undergoing invasive procedures (including OLT)	Total blood product amount	Decreased (n ¼ 2; relative risk [95% CI] ¼ 0.24 [0.15–0.38]; p <0.001), 2 studies	Bleeding rate	Indifferent	Meta-analysis could not be performed, because outcomes reported inconsistently	Decreased at 7 days (relative risk [95% CI] ¼ 0.52 [0.30–0.91]; p ¼ 0.02), 3 studies Indifference at any of the later time points, 3 studies	-
		pRBC amount	Indifferent (n ¼ 2; relative risk [95% CI] ¼	Long-term mortality	Indifferent			
				7-day mortality	Decreased (relative risk [95% CI] ¼ 0.52 [0.30–0.91]; p ¼ 0.02).			

		1.09 [0.89–1.35]; p ¼ 0.41), 2 studies PC amount: Decreased 5x lower with TEG (RR 0.17 (95% [CI]: [0.030.90]; p ¼ 0.04) FFP amount: Indifferent (relative risk [95% CI] ¼ 0.34 [0.10–1.16]; p ¼ 0.09) FFP AND PC amount: Decreased (n ¼ 3; relative risk [95% CI] ¼ 0.48 [0.34–0.68]; p <0.001), 3 studies Cryo amount: Decreased (n = 1; RR [95% CI] ¼ 0.64 [0.51–0.79]; p <0.001), 1 study	Total blood product and complication: Reducing use of blood products without increasing complications Any adverse event: Indifferent (relative risk [95% CI] ¼ 0.33 [0.04–3.12]; p ¼ 0.34) (3 RCTs) TRALI: Decrease (VET n=6 [12.2%] vs n=23 patients [48.9%], p <0.001) TACO: Indifferent ARDS: Indifferent Bleeding events up to Day 5 or rebleeding after Day 5: Indifferent (2 studies)			
Aceto et al. (2023), **Systematic review with meta-analysis** **(45)**	OLT	Results from 15 observational studies pRBC amount: Decrease [mean difference: −1.40, 95% confidence interval (95% CI), −1.87 to −0.92; $P < 0.001$, $I^2 = 61\%$) pRBC patient proportion: Decreased (95% CI, OR 0.58 [0.42, 0.79, I^2 =7%] FFP amount in U: Decreased (mean U difference: −2.98, 95% CI, −4.61 to −1.35; $P =$ < 0.001; $I^2 = 98\%$) FFP patient proportion: Decreased (95% CI, OR 0.23 [0.12, 0.45, I^2 =69%]	N/A	Indifference Hospital LOS (mean difference: −1.82; 95% CI, −3.98 to 0.34; $P = 0.10$; $I^2 = 0\%$), Indifference ICU LOS (mean difference: −0.26; 95% CI, −1.02 to 0.50; $P = 0.50$; $I^2 = 64\%$)	Indifference 30-day mortality (OR: 0.79; 95% CI, 0.56 to 1.11; $P = 0.17$; $I^2 = 0\%$)	N/A

		Cryo amount: Increased (mean difference: 2.71, 95% CI, 0.84 to 4.58; P = 0.005; I^2 = 91%). PC amount: Indifference (mean difference: −0.55; 95% CI, −1.15 to 0.06; P = 0.07; I^2 = 99%) PC patient proportion: Indifferent (95% CI, OR 0.85 [0.61, 1.18, I^2 =17%] FC amount in g: Increased (mean difference of 1 (95% CI, 0.47 to 1.53; P < 0.002; I^2 = 67%)) PCC amount: Increased (mean difference: 0.61; 95% CI, 0.37 to 0.85; P < 0.001; I^2 = 0%) TXA amount in g: Decreased (mean difference: −0.41; 95% CI, −0.58 to −0.25; P < 0.001; I^2 = 0%) Results from 2 RCTs pRBC amount: Indifferent (mean difference: −0.74; 95% CI, −1.91 to 0.43; P = 0.21; I^2 = 0%) FFP amount: Indifferent (mean difference: −3.76; 95% CI, −11.50 to 3.98; P = 0.34; I^2 = 76%) PC amount: Indifferent (mean difference: 0; 95% CI, −0.33 to 0.32; P = 0.99; I^2 = 0%)			

			and mortality (RR: 0.75; 95% CI, 0.18 to 3.02; $P = 0.68$; $I^2 = 0\%$)				
Kovalic et al. (2020), **Systematic review with meta-analysis** **(44)**	Cirrhotic patients undergoing invasive procedures (including OLT)	pRBC amount pRBC patient proportion	Decrease (pooled MD −1.53 (95% CI −2.86 to −0.21; $P = 0.02$),) Decrease pooled OR 0.53 (95% CI 0.32–0.85; $P = 0.009$)	Total Bleeding events (definition: signs of overt clinical bleeding or a drop in hemoglobin of 1–2 g/dl requiring transfusion after the initial procedure and/or resuscitation) Intraoperative blood loss in L Adverse transfusion reaction	Decreased (pooled OR 0.54 (95% CI 0.31–0.94; $P = 0.03$) Decreased (pooled MD −1.46 (95% CI −2.49 to −0.44; $P = 0.005$) Only 2 studies reported, thus a meta-analysis was not performed, but appears to be decreased	N/A	Indifference overall mortality (pooled OR 0.91 (95% CI 0.63–1.30; $P = 0.60$). And mortality in hospital, 28-day, 42-day, 90-day, and 1-year mortality reported across included studies ($P = 0.16$) BUT highly inconsistent time points for reporting	Cost Meta-analysis was not performed because lack of data and differences between studies/study design countries/institutions, BUT Tendency to lower overall cost (3 studies)
		PC amount PC patient proportion	Decrease (pooled MD −0.57 (95% CI −1.06 to −0.09; $P = 0.02$), Decrease (Pooled OR 0.29 (95% CI 0.12–0.74; $P = 0.009$),				
		FFP amount FFP patient proportion	Decrease (pooled MD and −2.71 (95% CI −4.34 to −1.07; $P = 0.001$), Decrease (pooled OR 0.19 (95% CI 0.12–0.31; P < 0.00001),				
		Cryo amount Cryo patient proportion	Indifference (pooled MD 1.95 (95% CI −0.77 to 4.66; $P = 0.16$). Increased pooled OR 2.42 (95% CI 1.39–4.20; $P = 0.002$).				
Yoon et al. (2022), **Systematic review without meta-analysis** **(20)**	OLT	Total amount of any transfusion Total patient proportion receiving any transfusion	Decreased Decreased	Hemodynamic stability Acute kidney injury	Increased Reduced	No shortened LOS	N/A	<u>Transfusion ratio (results from different studies):</u> High ratio of FFP and PC (> 1 U PC and 1U FFP for each 2 U of pRBC) showed decreased transfusion of pRBC (11 vs. 19 U, p < .001), FFP (14 vs. 18 U, p = .007), and total units transfused (33 vs. 43 U, p = .006). Increase in PC
		FC amount	Increased					
		PCC amount	Increased					

		The use of VET is recommended (QOE; low-moderate | Recommendation; strong).				transfusions was observed (8 vs. 7 U, p = .002). High FFP to pRBC ratio decreased PRBC transfusion requirements (1571 vs. 2810 ml, p < .0001). FFP over pRBC volume ratio greater than .85 was associated with a reduction in PRBC use. cell salvage, transfusion triggers, improved education, and communication among physicians decreased blood product utilization by 50% (49 vs. 25 U, p < .05). PCC and FC use not associated with reductions in intraoperative transfusion <u>Transfusions and complications</u> PRBC and PC associated with higher mortality PCC and FC use not associated with increased thrombotic events A specific blood product transfusion practice is not recommended (QOE; low | Recommendation; weak). educational interventions are recommended (QOE: low | Grade of Recommendation: moderate). <u>Costs</u> transfusion and laboratory associated costs were reduced, because of lowered transfusion requirements. <u>Optimal antifibrinolytic therapy regarding immediate and short-term outcomes</u>

						EACA and TXA not associated with decreased blood product transfusion, improvements in patient or graft survival, or increases in thrombotic events. The routine use of antifibrinolytics is not recommended (QOE; low | Recommendation; weak).
Wei and Child (2020), **Systematic review without meta-analysis** **(43)**	Cirrhotic patients undergoing invasive procedures (including OLT)	Overall blood product transfusion patient proportion: Decreased (5 RCTs) FFP amount (absolute volume): 4/5 RCT, Decreased FFP transfusion: 4/5 RCT Decreased PC amount: 2/5 RCT Decreased PC patient proportion: 4/5 RCTS Decreased (no difference in LT trials) Cryo amount: 2/5 RCTs reduced (no difference in LT trials) Cryo patient proportion: 2/5 RCTs decrease (no difference in LT trials)	Bood loss and/or bleeding events: Indifferent (3 RCTs) Adverse events related to transfusions: Decrease (VET 30.6% vs CCT 74.5%, p< 0.01), (1/4 RCTs) E.g. TRALI (VET 12.2% vs CCT 48.9%) Rebleeding: No difference in the ability to control initial bleeding between VET and CCT groups (2 RCTs)	Indifference in total hospital LOS (one RCT) Decrease in ICU LOS (by mean of 2d in VET vs 3 d in CCT, p = 0.012)	Indifferent overall mortality in longest follow-up data (5 studies, reported at various time points from 6 weeks up to 3 years & small followup population size)	N/A

Abbreviations: MD=Median, RR=Relative Risk, U=Units, RCT=Random Controlled Trial, TEG=Thromboelastography, ROTEM=Rotational thromboelastometry, CFT= Clot formation time, CT=Clotting time, R=Reaction time, K= K time, MA=Maximum amplitude, MCF=Maximum clot firmness, CLI30= Clot lysis index at 30 min after maximum clot firmness, CLI60= Clot lysis index at 60 min after maximum clot firmness, Ly30=Clot lysis at 30 min after maximum amplitude, Ly60=Clot lysis at 60 min after maximum amplitude, ARDS=Acute respiratory distress syndrome, TRALI=Transfusion related acute lung injuty, TACO=Transfusion-associated circulatory overload

Annex 11:
Table 9. TEG reference values for adults by the manufacturer

TEG (TEG 6s) Component assay	Reaction time R (min)	K time (min)	Alpha angle (Degree)	MA (mm)	Ly30 (%)
CK (citrated kaolin)	4.6-9.1	0.8-2.1	63-78	52-69	0-2.6
CKH (citrated kaolin & heparinase)	4.3-8.3	0.8-1.9	64-77	52-69	N/A
Citrated Rapid TEG (CRT or rTEG)	0.3-1.1	0.8-2.7	60-78	52-70	0-2.2
CFF (citrated functional fibrinogen)	N/A	N/A	N/A	13-30	N/A

Source: (79)

Annex 12:
Table 10. ROTEM reference values for adults by the manufacturer

ROTEM (ROTEM delta) Component assay	**CT (s)**	**CFT (s)**	**Alpha angle (Degree)**	**A10 (mm)**	**MCF (mm)**	**CLI30 (%)**	**AUC (U)**	**Aggr (AU)**	**Vel (AU/min)**
EXTEM	38-79	34-159	63-83	43-65	50-72	94-100			
INTEM	100-240	30-110	70-83	44-66	50-72	94-100			
FIBTEM	N/A	N/A	N/A	7-23	9-25	N/A			
APTEM	APTEM parameters are directly compared to EXTEM parameters. Thresholds therefore identical to EXTEM.								
HEPTEM	HEPTEM parameters are directly compared to INTEM parameters. Thresholds therefore identical to INTEM.								
PLT mapping> ADPTEM							57-113	108-122	16-19
PLT mapping> ARATEM							72-125	126-140	18-21
PLT mapping> TRAPTEM							84-128	140-152	24-26

Abbreviation: AUC=Area under curve, Aggr=aggregation, Vel=velocity, AU= Area Units, ROTEM=Rotational thromboelastometry, CFT= Clot formation time, CT=Clotting time, MCF=Maximum clot firmness, CLI30= Clot lysis index at 30 min after maximum clot firmness, PLT= Platelet; *Source*: (68,71)

Annex 13:
Table 11. Evidence-based optimal cut-off values for viscoelastic test-based transfusion, i.e. Values proven as independent predictors for blood product requirement

Author (Year) (Citation number)	**pRBC & Bleeding**	**FFP**	**PC**	**FC**	**Cryo**	**Study limitations**
Fayed et al. (2015) **(65)**	**CT_{EXTEM} =62s** (Sensitivity 79.5%, Specificity 63.6%, AUC 0.76, Accuracy 76.8%, PPV 20.5%, NPV 20.5% p<0.01) **CT_{INTEM}=155s** (Sensitivity 79.5%, Specificity 54.5%, AUC 0.75, Accuracy 75.3%, PPV 45.5%, NPV 20.5%, p<0.01) **CFT_{INTEM}=205.5** (Sensitivity 71.8%, Specificity 72.7%, AUC 0.75, Accuracy 75.4%, PPV 27.3%, NPV 28.2% p<0.01) **MCF_{EXTEM} =44 mm** (Sensitivity 100%, specificity 70.5%, AUC of 0.87, Accuracy 87.4%, PPV 29.5%, NPV 0%, p<0.01) **MCF_{INTEM} =44.5mm** (Sensitivity 100%, Specificity 71.8%, AUC0.88, Accuracy	**MCF_{FIBTEM} =9,5mm** (Sensitivity 84.2%, Specificity 74.2%, AUC 0.81, Accuracy 81.6%, PPV 25.8%, NPV 15.8% p<0.01) **CT_{EXTEM} =67s** + low $A10_{FIBTEM}$ (Sensitivity 77.4%, Specificity 57.9%, AUC 0.73, Accuracy 73.2%, PPV 42.1%, NPV 22.6% p<0.01) **CFT_{EXTEM} =223s** (Sensitivity 83.9%, Specificity 78.9%, AUC 0.90, Accuracy 90.7%, PPV 21.1%, NPV 16.1%, p <0.01)	**MCF_{EXTEM} =37.5mm** (Sensitivity 73.9%, Specificity 73.3%, AUC 0.73, Accuracy 73.4%, PPV 66.7%, NPV 26.1%, p< 0.05) **MCF_{INTEM} =39.5mm** (Sensitivity 3.9%, Specificity 83.3%, AUC 0.82, Accuracy 82.3%, PPV 16.7%, NPV 26.1%, p< 0.01)	N/A	**CFT_{EXTEM} =238.5s** (Sesitivity 77.8%, Specificity 56.2%, AUC 0.74, Accuracy 74.7%, PPV 43.8%, NPV 22.2%, p<0.01) **MCF_{EXTEM} =36.5mm** (Sensitivity 90.6%, Specificity 52.8%, AUC 0.78, Accuracy 78.2%, PPV 47.2, NPV 9.4%, p <0.01) **CT_{INTEM} =178.5s** (Sensitivity 77.8%, Specificity 65.6%, AUC 0.68, Accuracy 67.5%, PPV 34.4%, NPV 22.2%,p <0.01) **CFT_{INTEM}=205.5s** (Sensitivity 77.8%, Specificity 46.9%, AUC 0.72, Accuracy 71.7%, PPV 53.1%, NPV 22.25; p<0.01) **MCF_{INTEM} =38.5mm** (Sensitivity 87.5%, Specificity 63.9%, AUC 0.80, Accuracy 80.3%, PPV 36.1%, NPV 12.5%, p <0.01	pRBC transfusion requirements affected by preoperative Hb Effect of blood loss on transfusion requirements, aggravated by volume overload and portal hypertension Unforeseen intraoperative hemostatic derangement

<table>
<tr><td></td><td>88%, PPV 28.2%, NPV 0%, p<0.01)</td><td></td><td></td><td></td><td>MCF_{FIBTEM} = 8.5mm (Sensitivity 81.3%, Specificity 83.3%, AUC 0.84, Accuracy 85.3%, PPV 16.75, NPV 18.7%, p<0.01)</td><td></td></tr>
<tr><td>Blasi et al. (2012)

(66)</td><td>-</td><td>-</td><td>A10 EXTEM well predict MCF EXTEM</td><td>A10_{FIBTEM} = 8 mm</td><td>-</td><td>-</td></tr>
<tr><td>Blasi et al. (2017)

(64)</td><td>MCF_{FIBTEM} >8mm associated with less RBC transfusion (OR [95% CI]: 2.08 [1.30-3.33], p=0.002)</td><td>N/A</td><td>N/A</td><td>MCF_{FIBTEM} >10 mm (OR [95%]: 0.42 [0.20-0.89]) unnecessary fibrinogen transfusion</td><td>N/A</td><td>Small sample size

Deviations from transfusion algorithm in clinical practice possible

Intercentre laboratory differences</td></tr>
<tr><td>Görlinger et al. (2019)

(10)</td><td>N/A</td><td>Transfusion sequence matters (follow arrow)
“Liver (TX) A5 algorithm”

If no bleeding at surgical start:
<table><tr><td>If, A5_{EXTEM} <25mm or CT_{FIBTEM} >600s AND no pre-existing thrombotic events</td><td>TXA (15-25mg/kg bw as a single bolus, can be repeated once)</td></tr></table>
If diffuse bleeding AND blood transfusion considered:
<table><tr><td>LI60_{EXTEM} <85% (preanhepatic) OR LI30_{EXTEM} <50% (anhepatic/reperfusion phase)</td><td>TXA (15-25mg/kg bw as a single bolus, can be repeated once)</td></tr><tr><td>A5_{EXTEM} <25mm AND A5_{FIBTEM}<8mm (12mm)</td><td>FC or Cryo (Target A5_{FIBTEM} ≥10mm (14mm))

Fibrinogen dose (g) = targeted increase in A5FIB (mm) × body weight (kg) / 160. With correction factor (140–160 mm kg/g) depends on the actual plasma volume.</td></tr></table></td><td>See algorithm</td><td>See algorithm</td><td>See algorithm</td><td>N/A</td></tr>
</table>

		<table><tr><td></td><td>Dose = [target FIBTEM-MCF (mm) − current FIBTEM-MCF (mm)] × weight (kg)/140 Conversion: 10 U Cryoprecipitate ≈ 2 g Fibrinogen concentrate</td></tr><tr><td>**$A5_{EXTEM}$ <25mm AND $A5_{FIBTEM}$ ≥ 8mm (12mm)**</td><td>PC (5-10 ml/kg bw or 1-2 pooled or apheresis/80kg bw)</td></tr><tr><td>**CT_{EXTEM} >75s AND $A5_{FIBTEM}$ ≥ 8mm**</td><td>PCC (10-15 IU/kg bw) OR FFP (10-15ml/kg bw). Consider AT substitution in patients with high thrombotic risk</td></tr><tr><td>**CT_{INTEM} >280s AND CT_{INTEM}/CT_{HEPTEM}-ratio ≥1.25**</td><td>Protamine (0.3-0.5 mg/kg bw; In severe bleeding 25-50mg/80kg; 2.5-5 ml/80kg)</td></tr><tr><td>**CT_{INTEM} AND CT_{HEPTEM} >280s**</td><td>FFP (10ml/kg bw; CAVE: portal hypertension may increase bleeding)</td></tr><tr><td>Ongoing bleeding</td><td>Re-check after 10-15 min using a new blood sample</td></tr></table> Time points for testing: Baseline, Re-check after 60 min or in case of bleeding during pre-anhepatic phase, 5–10 min after cava clamping (early anhepatic phase), 30–45 mm after cava clamping (late anhepatic phase), 5–10 min after reperfusion, 30–45 min after reperfusion, skin closure, Always in case of diffuse bleeding, 10–15 min after a specific hemostatic intervention.				
Tangcheewinsirikul et al. (2022) **(37)**	N/A	Negative correlation between TEG r time cut-offs and the RRs of FFP transfusion In linear regression models, using the more prolonged r time cut-off (the higher the cut-off) in TEG-guided algorithms was significantly associated with less RR of FFP transfusion (p = 0.01). **Optimal:** **r time >40 min** for FFP (RR ca -1.70; 95% CI -0.086 - -0.012, p=0.01)	Positive correlation between MA thresholds and the RRs of PC transfusion Linear regression model:	N/A	-	Variability in patient- or procedure-related bleeding risks Small sample sizes of included studies→ moderate-to-high statistical heterogeneity (therefore random-effects model applied) Variability of VET thresholds (therefore meta-regression

			shorter MA cutoff was related to the less RR of platelet transfusion (p = 0.04) Optimal: **MA <30mm (**RR ca -2.0, 95% CI [.001-0.083], p=0.04)			analysis done on effects of different thresholds)
Caballero et al. (2022) **(67)**	N/A	N/A	N/A	A10$_{FIBTEM}$ target of 11 mm not superior to standard **A10$_{FIBTEM}$ = 8mm** in reducing pRBC. 11 mm target increased plasma fibrinogen and MCF without affecting safety, BUT no clinical benefit.	N/A	Fibrinogen infusion kits were not masked in the pharmacy departments (BUT this was necessary)

Abbreviations: PPV=positive Predictive Value, NPV=Negative Predictive Value, TEG=Thromboelastography, ROTEM=Rotational thromboelastometry, CFT= Clot formation time, CT=Clotting time, R=Reaction time, K= K time, MA=Maximum amplitude, MCF=Maximum clot firmness, CLI30=Clot lysis index at 30 min after maximum clot firmness, CLI60=Clot lysis index at 60 min after maximum clot firmness, Ly30=Clot lysis at 30 min after maximum amplitude, Ly60=Clot lysis at 60 min after maximum amplitude