7 Whole Blood Assay: Thromboelastometry – Bleeding Management Algorithms

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Pathophysiology of Perioperative Hemostasis

In contrast to hereditary bleeding disorders, pathophysiology of posttraumatic or perioperatively acquired bleeding is most often multifactorial [1–5]. For example, trauma-induced coagulopathy (TIC), disseminated intravascular coagulation (DIC), and coagulopathy in liver cirrhosis are different pathophysiological entities requiring different treatment strategies [2, 5–11]. Notably, patients can be at risk of bleeding and thrombosis at the same time [12, 13].

One common issue in perioperative bleeding is that bleeding, coagulopathy, and transfusion are independent risk factors for poor outcomes and can build up each other in a vicious circle [14]. Furthermore, preexisting issues such as anemia, coagulopathy, drug effects, genetic factors, trauma, inflammation, and surgical bleeding can aggravate the vicious circle of perioperative bleeding. Other amplification factors can be shock, hypoperfusion, acidosis, hypothermia, hemodilution, inappropriate transfusion, transfusion-associated adverse events, nosocomial infection, and sepsis [15]. Finally, this can result in single or multiple organ failure.

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The best way to avoid this vicious circle is to identify the specific hemostatic deficits, to stop bleeding as soon as possible, and to avoid any inappropriate or unnecessary blood transfusion. This was addressed in the "STOP the Bleeding Campaign" initiated by the authors of the updated European trauma guidelines in 2013 [16]. Here the acronym "*STOP*" comprises the following elements: *Search* for patients at risk of coagulopathic bleeding; *Treat* bleeding and coagulopathy as soon as they develop; *Observe* the response to interventions; *Prevent* secondary bleeding and coagulopathy. However, overtreatment should be avoided to prevent thrombotic or thromboembolic events in the postoperative phase [17–19]. Here, a "therapeutic window" concept may address this issue most appropriate [20, 21]. Due to the multifactorial pathophysiology of perioperative bleeding, a systematic diagnostic approach is needed to identify the underlying hemostatic disorder and to guide hemostatic therapy in a specific and timely manner. This approach is addressed in the terms "precision medicine," "personalized medicine," "goal-directed therapy," "targeted therapy," and "theranostic approach" [2, 6–8, 10, 11, 21–26].

Thromboelastometry-Guided Hemostatic Therapy

Development of Thromboelastometry-Guided Algorithms

Pathophysiology of posttraumatic and perioperative bleeding is complex and cannot always be addressed adequately by hemostatic resuscitation (1:1:1 concept) only [7, 27, 28]. In order to guide hemostatic therapy in bleeding patients, algorithms have been developed as a link between ROTEM™ diagnostics and hemostatic therapy ("theranostic approach") [6, 11, 20, 23, 29–33]. Due to the increasing number of publications and data available – the number of ROTEM™ publications nearly doubled in the last 3 years since the first edition of this textbook in 2016 – these algorithms changed

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from experience-based algorithms to evidence-based algorithms. Furthermore, these algorithms have been validated in big cohort studies and randomized controlled trials (RCTs) showing that the implementation of these algorithms is able to reduce transfusion requirements, complication rates, patient's morbidity and mortality, and health care costs, in particular in cardiovascular surgery [10, 17, 18, 34–46]. Several cohort studies reported similar results in liver transplantation, trauma, and postpartum hemorrhage (PPH), but only four RCTs have been published in the setting of trauma, burns, and pediatric orthopedic surgery [10, 11, 29, 37, 44, 47–62]. The RETIC trial randomized patients with TIC to a group treated with fresh frozen plasma (FFP) or to a group treated with coagulation factor concentrates guided by ROTEM™ [62]. The study had to be stopped early since the FFP group failed after two rounds of FFP (2 × 15 mL/kg body weight) in 52% to stop bleeding and to correct coagulopathy. In contrast, the ROTEM™-guided administration of coagulation factor concentrates failed only in 4%. Furthermore, massive transfusion (12% vs. 30%, $P = 0.042$) and days on hemofiltration (11 vs. 27 days; $P = 0.038$) could be reduced significantly in the ROTEM™-guided group. In addition, there was a strong trend to reduce the incidence of multiple organ failure (50% vs. 66%; $P = 0.15$) and venous thrombosis (8% vs. 18%; $P = 0.22$) in the ROTEM™-guided group. Further RCTs have just been finalized or are still running [63–66].

Evidence-based ROTEM™-guided algorithms for bleeding management in severe trauma/major surgery, obstetric/postpartum hemorrhage, and cardiovascular surgery are presented in Fig. 7.1a–c and characteristic thromboelastometric traces in Fig. 7.2a–j.

Since the ROTEM™ parameter A5 is not yet FDA-approved (as of December 2019), ROTEM™-algorithms for the USA actually have to use A10, whereas A5 is used as clot firmness parameter in the rest of the world in order to speed up decision-making. Due to the good correlation and fixed bias between A5, A10, and MCF, ROTEM™ MCF, A10, and A5 algorithms can be converted to each other easily. The difference between A10 and A5 for FIBTEM is usually 1 mm and for EXTEM, APTEM, INTEM, and HEPTEM 8–10 mm [67–70]. The bias between early clot values (A5 and A10) and MCF is displayed in Table 7.1.

Clinical Assessment

Hemostatic interventions should be performed only in patients with diffuse bleeding and if blood transfusion is considered. Severity of trauma (ISS ≥25), clinical bleeding scores (e.g., TASH score ≥15), hemodynamic instability (e.g., hemorrhagic shock), hypothermia (core temperature <35 °C), and results of blood gas analysis (e.g., pH <7.2, BE <–6 mmol/L, Hb <10 g/dL, Ca_i^{++} <1 mmol/L) should be considered, too, since they may be associated with an increased risk of hyperfibrinolysis, hypofibrinogenemia, and decreased thrombin generation [30, 71, 72]. Accordingly, decision-making for hemostatic interventions should not be based on ROTEM™ results solely, in the absence of clinically relevant bleeding.

Furthermore, the concept behind an *evidence-based ROTEM™-guided bleeding management algorithm* is to administer the *right hemostastic drug/intervention*, in the *right dose*, at the right time, and in the *right sequence*. Accordingly, *vertical algorithms* with a clear sequence of diagnostic steps and interventions (Fig. 7.1a–c) should be preferred to horizontal algorithms which don't provide a ranking of pathologic ROTEM™ results [20]. Due to the low positive and high negative predictive value of ROTEM™ results for bleeding, ROTEM™ algorithms have to be understood as *"not-to do" algorithms*, which means:

- *Avoid inappropriate blood transfusion/hemostatic interventions* (high negative predictive value of 16–23%) [73].
- *Don't treat numbers (pathologic results) in the absence of clinically relevant bleeding* (low positive predictive value of 90–97%) [73].

Management of Fibrinolysis

Hyperfibrinolysis (≥18% within 60 min after CT) as well as fibrinolysis shutdown (≤2% within 60 min after CT) is associated with increased mortality in severe trauma due to bleeding on the one hand or multiple organ failure on the other hand [74]. Therefore, exogenous inhibition of the fibrinolysis system in severely injured patients requires careful selection, as it may have an adverse effect on survival, in particular if tranexamic acid is given later than 3 hours after injury [74–79]. In contrast to trauma and postpartum hemorrhage, even 50% fibrinolysis during liver transplantation is not associated with increased mortality but may be associated with an increased incidence of thrombotic events [76]. Therefore, it is still under discussion, whether antifibrinolytic drugs should be given prophylactically to every bleeding patients or not. The answer of this question seems to be dependent on the clinical setting, timing, application (bolus and/or continuous infusion), and dosing.

In order to enable quick decision-making, early thromboelastometric variables of clot firmness in EXTEM (A5 and A10) can be used to identify patients at risk for fibrinolysis. An EXTEM A5 threshold of ≤35 mm (EXTEM A10 ≤45 mm) detects more than 90% of patients which will develop hyperfibrinolysis, finally [80]. Notably, FIBTEM is more sensitive to fibrinolysis compared to EXTEM and kaolin-TEG [81, 82]. A flat-line in FIBTEM characterized

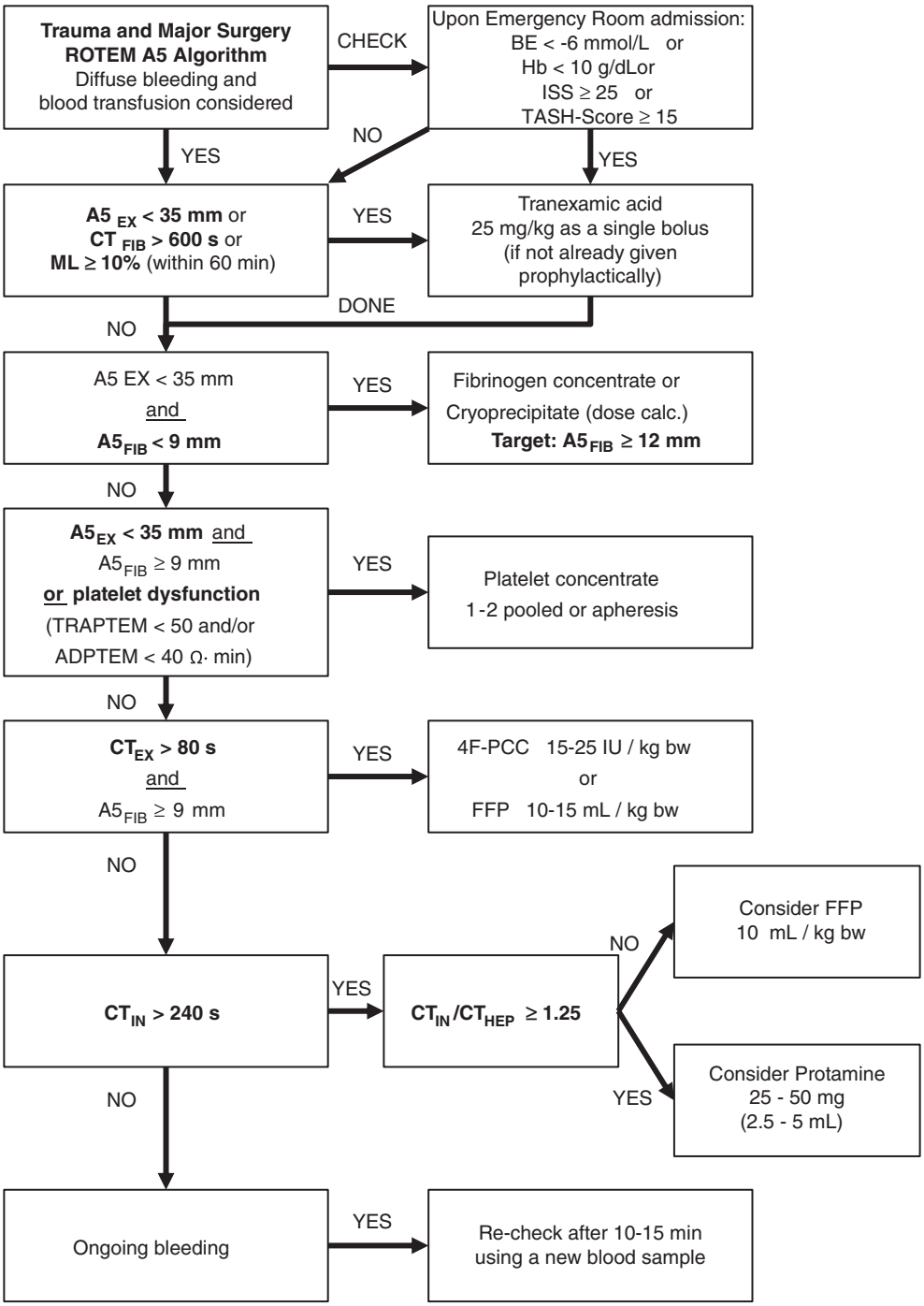
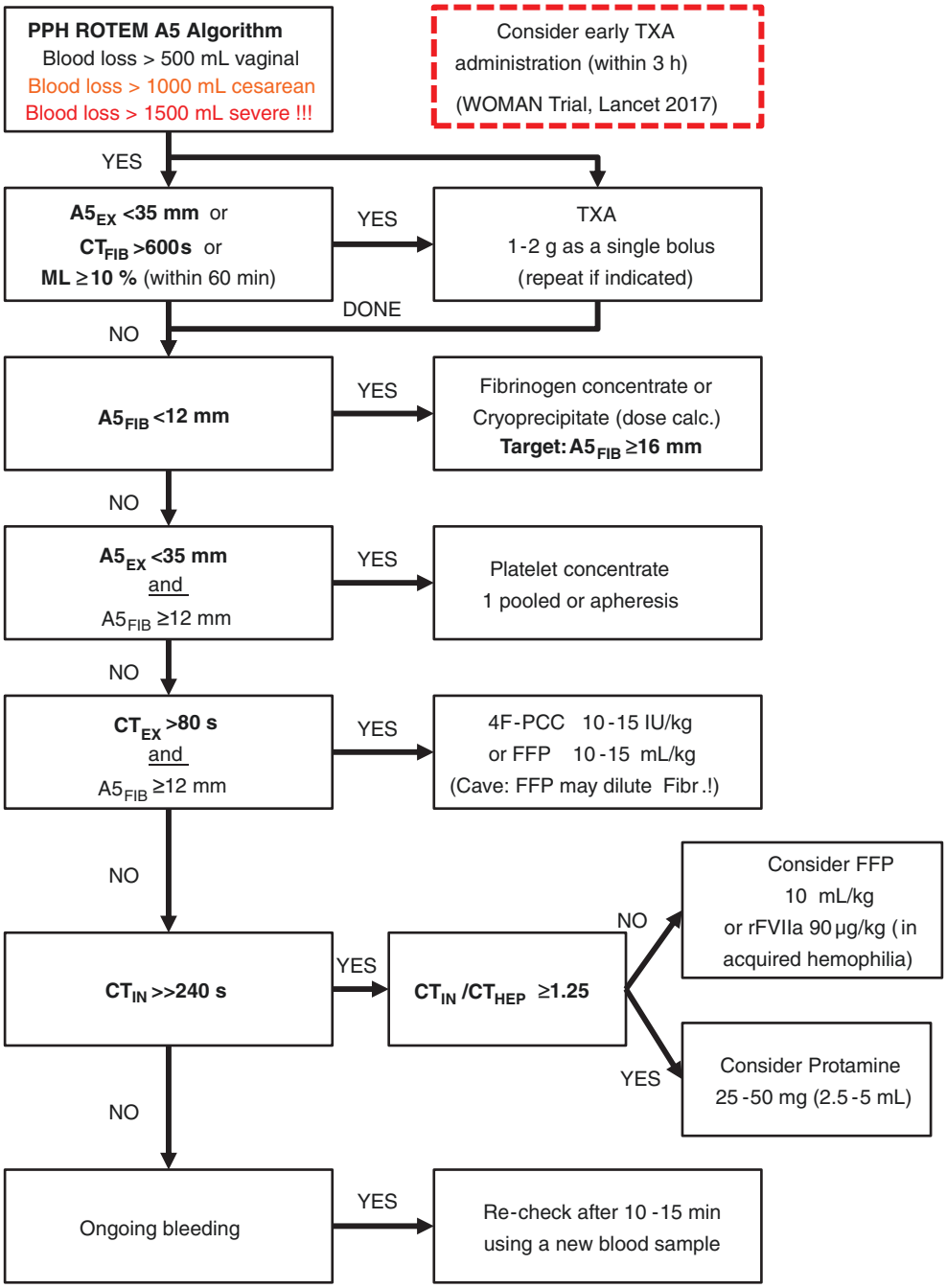


Fig. 7.1 (**a–c**) (**a**) Evidence-based ROTEM™ A5 bleeding management algorithm for severe trauma and major surgery. (**b**) Evidence-based ROTEM™ A5 bleeding management algorithm for obstetric/postpartum hemorrhage. (**c**) Evidence-based ROTEM™ A5 bleeding management algorithm for cardiovascular surgery. $A5_{EX}$, amplitude of clot firmness 5 min after CT in EXTEM; $A5_{FIB}$, amplitude of clot firmness 5 min after CT in FIBTEM; ACT, activated clotting time; BE, base excess; bw, body weight in kg; CT_{EX}, coagulation time in EXTEM; CT_{FIB}, coagulation time in FIBTEM (CT_{FIB} >600 s reflects a flat-line in FIBTEM); CT_{HEP}, coagulation time in HEPTEM; CT_{IN}, coagulation time in INTEM; FFP, fresh frozen plasma; Hb, hemoglobin concentration; ISS, injury severity score; IU, international units; ML, maximum lysis (within 1 hour run time); 4F-PCC, four-factor prothrombin complex concentrate; TASH score, trauma-associated severe hemorrhage score (Courtesy of Klaus Görlinger, Essen, Germany)



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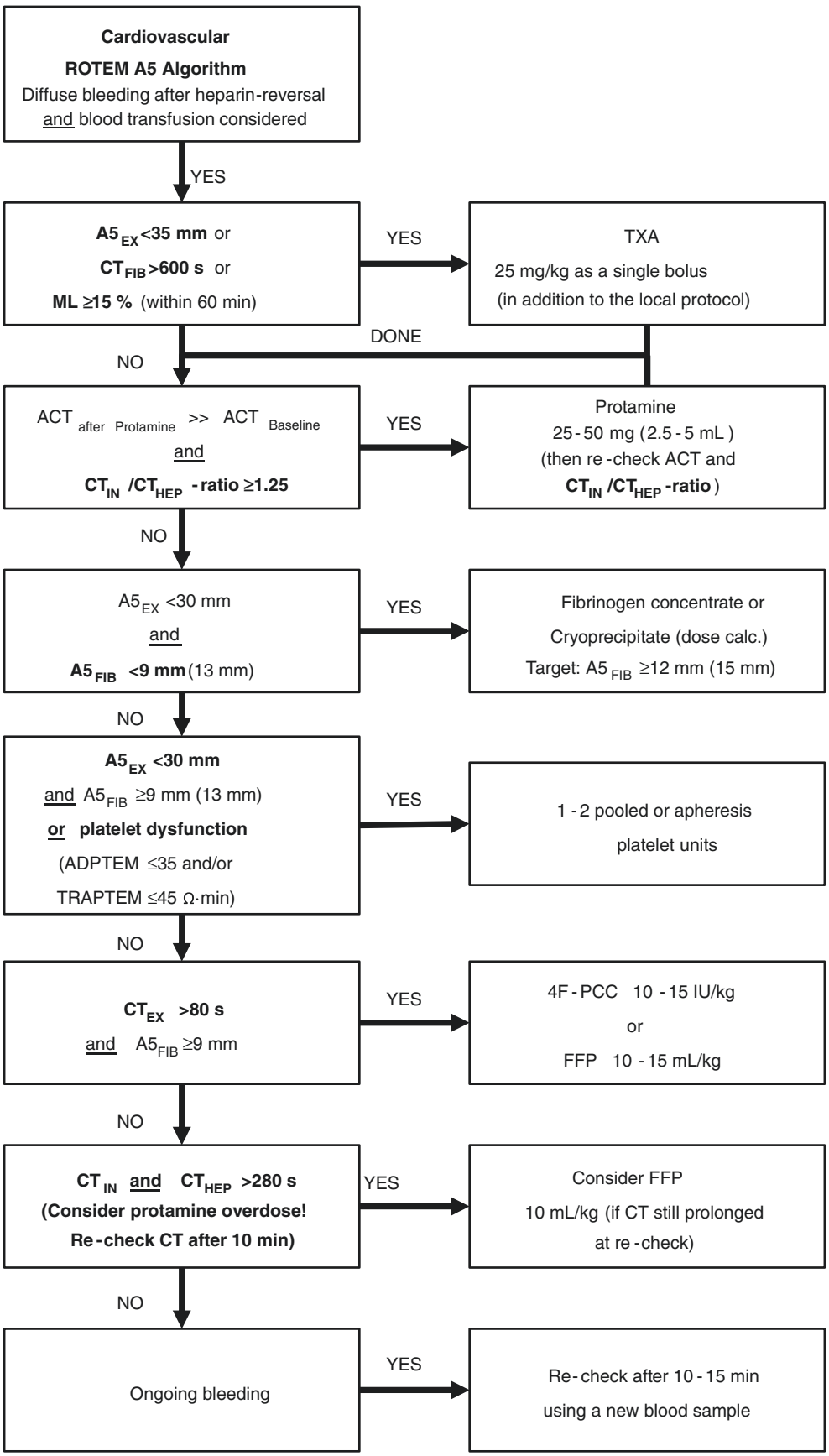


Fig. 7.1 (continued)

by a FIBTEM CT >600 s seems to be associated with hyperfibrinolysis, too. Furthermore, colloid infusion (HES > gelatin > albumin) results in reduced resistance of polymerized fibrin to plasmin degradation [83]. In contrast, high factor XIII levels attenuate tissue plasminogen activator-induced hyperfibrinolysis in human whole blood [84].

Management of Clot Firmness

TIC is functionally characterized by a reduced clot firmness in EXTEM with an A5 <35 mm (A10 <45 mm) and predicts the need for massive transfusion [2, 7, 85–87]. Reduced clot firmness can be based on hypofibrinogenemia, fibrin polym-

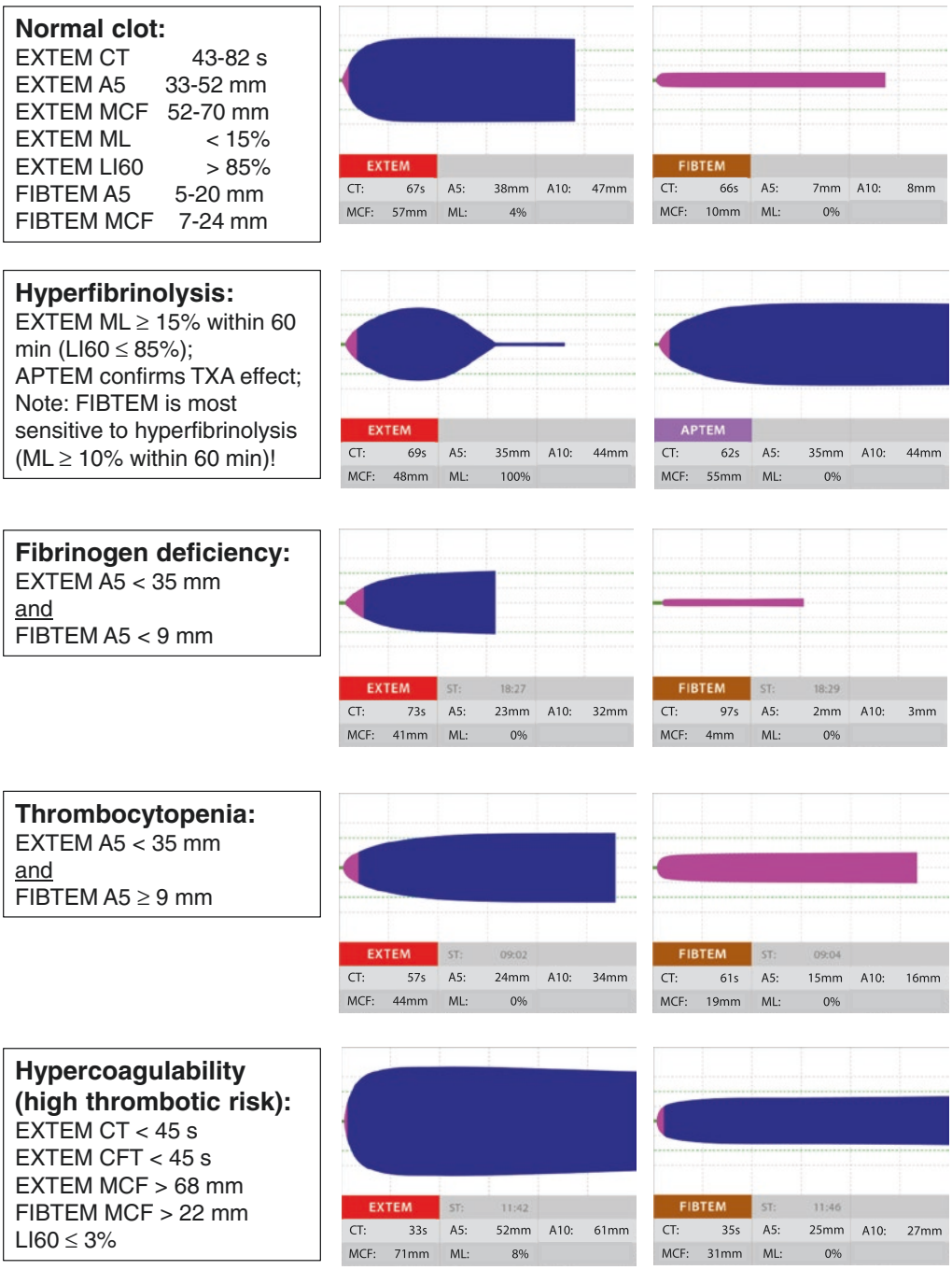
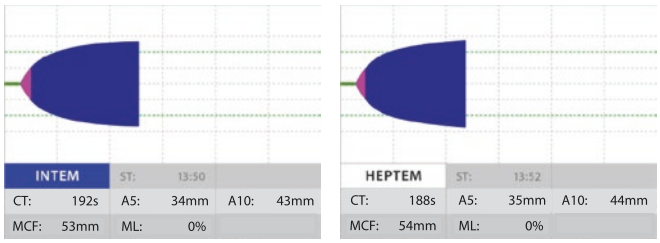
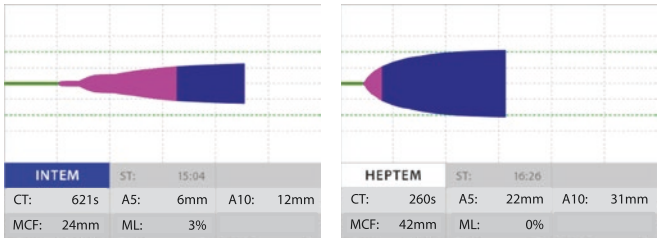


Fig. 7.2 (**a–j**) Characteristic thromboelastometry traces. The diagnostic performance is increased by test combinations, e.g., EXTEM and FIBTEM, EXTEM and APTEM, or INTEM and HEPTEM. 4F-PCC, four factor prothrombin complex concentrate; A10, amplitude of clot firmness 10 min after CT; CFT, clot formation time; CPB, cardiopulmonary bypass; CT, coagulation time; LI60, lysis index 60 min after CT; MCF, maximum clot firmness; ML maximum lysis during runtime; OLT, orthotopic liver transplantation; TXA, tranexamic acid (or other antifibrinolytic drug) (Courtesy of Klaus Görlinger, Essen, Germany)

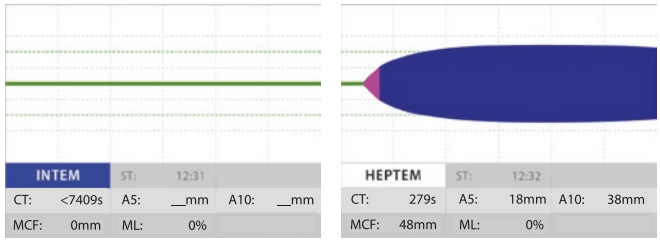
Normal clot (adequate heparin - reversal with protamine after CPB):
INTEM CT 122-208 s
INTEM A5 33-52 mm
INTEM MCF 51-72 mm
INTEM/HEPTEM CT-ratio 0.9-1.1



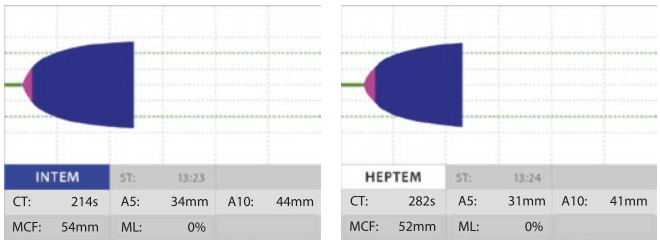
Heparin, low dose (e.g., endogenous heparin-like effect during OLT, sepsis or severe shock):
INTEM/HEPTEM CT-ratio 1.1-2.5 (significant ≥ 1.25)



Heparin, high dose (e.g., during CPB):
INTEM flat-line (CT > 1200s)
and
HEPTEM CT < 280 s



Protamine overdose (after heparin-reversal):
HEPTEM CT prolonged and
INTEM/HEPTEM CT-ratio < 1.1



Deficiency of vitamin K-dependent factors (warfarin or cirrhosis):
EXTEM CT > 80 s
(here, EXTEM CT decreased to 70 s after 4F-PCC administration; right graph)

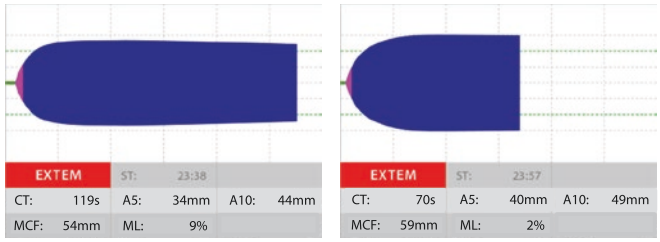


Fig. 7.2 (continued)

erization disorders (e.g., due to colloids or factor XIII deficiency), thrombocytopenia, and severe thrombocytopathy (reduced platelet aggregation due to inactivation of platelets' ADP and thrombin (PAR-1) receptors) [88–92].

FIBTEM A5 (A10) can be used for rapid and correct discrimination between hypofibrinogenemia and thrombocytopenia [50, 69, 70, 93, 94]. A FIBTEM A5 <8 mm (A10 <9 mm) is associated with an increased risk of massive bleeding in severe trauma and major surgery and can be used as a trigger value for fibrinogen substitution in these settings [2, 7, 51, 94, 95]. Here, the targeted FIBTEM A5 value is usually ≥12 mm (A10 ≥13 mm). However, some patients may even need a higher FIBTEM A5 trigger value of 12 mm (with a targeted value of 16 mm) – in particular in patients with severe bleeding due to obstetric hemorrhage/PPH, unstable pelvic fractures, traumatic brain injury (TBI), or

Table 7.1 Bias between early clot firmness values (A5 and A10) and maximum clot firmness (MCF) for all assays as obtained from Bland-Altman analyses. Data are presented in number of ROTEM™ analyses (*N*), mean differences (bias; ΔMCF-A5 and ΔMCF-A10 in mm), and Spearman's correlation coefficient rho (*r*) from linear regression analyses. The good correlation and fixed bias allows for easy conversion between ROTEM™ MCF-, A10- and A5-based algorithms [67–70]

Assay	*N*	Δ MCF-A5	*r*	Δ MCF-A10	*r*
INTEM, HEPTEM	3654	19 mm	0.94	10 mm	0.96
EXTEM, APTEM	7226	19 mm	0.94	10 mm	0.96
FIBTEM	3287	2–4 mm	0.95	1–3 mm	0.96

Courtesy of Klaus Görlinger, Essen, Germany

major aortic surgery [38, 96, 97]. The required fibrinogen dose can be calculated based on the targeted increase in FIBTEM A5 (A10):

$$\text{Fibrinogen dose}\left(\text{g}\right) = \text{targeted increase in FIBTEM A5 (or A10)}\left(\text{mm}\right) \times \text{body weight}\left(\text{kg}\right)/160\left(\text{mm}\bullet\text{kg}\bullet\text{g}^{-1}\right)$$

Here, the correction factor (140–160 mm·kg·g^{-1}) depends on the actual plasma volume [22, 29, 30, 38]. In case of high plasma volume (e.g., in pregnancy), hemodilution (in particular with colloids), transfusion-associated circulatory overload (TACO), factor XIII deficiency or in severe bleeding, the achieved increase in FIBTEM A5 (A10) may be lower than the calculated increase. Fibrinogen substitution can be done by fibrinogen concentrate administration or cryoprecipitate transfusion, dependent on the local approval and availability. As a rule of thumb, 10 units cryoprecipitate contain about 2 g fibrinogen. Table 7.2 provides a quick overview about the fibrinogen concentrate or cryoprecipitate dose needed to achieve the targeted increase in FIBTEM A5 (A10) [21, 29, 30].

If clot firmness in EXTEM is reduced (A5 <35 mm or A10 <45 mm), but FIBTEM clot firmness is above the trigger value (A5 ≥8 mm or A10 ≥9 mm), platelet transfusion has to be considered in severe bleeding. Notably, ROTEM™ analysis has been shown to be superior to platelet count in predicting bleeding in patients with severe thrombocytopenia [98, 99]. The expected increase in EXTEM A5 (A10) per transfused pooled or apheresis platelets is 5–10 mm in adult patients [100–102]. Therefore, the number of transfused platelets can be calculated based on the targeted increase in EXTEM A5 (A10). At least one pooled or one apheresis platelet unit is needed per targeted increase of 10 mm. In case of very low EXTEM A5 (<15 mm or A10 <25 mm), a combined administration of fibrinogen and platelets should be considered.

Notably, standard viscoelastic assays are not sensitive to the effects of antiplatelet drugs such as COX-inhibitors (e.g., aspirin) and ADP-receptor antagonists (e.g., clopidogrel, prasugrel, and ticagrelor) since high amounts of thrombin are generated in the test system which overcomes the effects of antiplatelet drugs. Therefore, platelet function analysis should be performed in patients with suspected platelet dysfunction [15, 103]. In the ROTEM™ system, this is realized by the ROTEM™ *platelet* module, which provides two channels of whole blood impedance aggregometry in addition to the four viscoelastic channels of the ROTEM™ *delta* device. Characteristic ROTEM™ *platelet* traces are displayed in Fig. 7.3a–f. Besides detection of the effects of antiplatelet drugs and other drugs with antiplatelet effects (e.g., analgetics, antidepressants, antibiotics, cardiovascular drugs and protamine), whole blood impedance aggregometry has been shown to detect early direct effects of trauma and sepsis on platelet function which is associated with increased mortality [21, 95, 104–111]. However, actually it is not yet clear whether early trauma- or sepsis-induced platelet dysfunction should be treated with platelet transfusion or not [112, 113]. In liver transplantation, platelet transfusion is associated with increased mortality, independent from the platelet count prior to transfusion [85, 87, 114, 115]. Therefore, decision-making for platelet transfusion should be done carefully and alternatives (e.g., desmopressin, tranexamic acid, fibrinogen concentrate, or cryoprecipitate) may be considered [38, 97, 116–119].

Table 7.2 FIBTEM-guided fibrinogen substitution. Here, fibrinogen dose calculation is based on the targeted increase in FIBTEM A5 (A10) in mm [22, 29, 30, 89]. In case of severe bleeding, high plasma volume (e.g., in pregnancy, significant hemodilution or TACO) and/or factor XIII deficiency, the achieved increase in FIBTEM A5 (A10) may be lower than the calculated increase

Targeted increase in FIBTEM A5 (A10) (mm)	Fibrinogen dose (mg/kg bw)	Fibrinogen concentrate (mL/kg bw)	Cryoprecipitate (mL/kg bw)
2	12.5	0.6 [1 g per 80 kg]	1 [5 U per 80 kg]
4	25	1.2 [2 g per 80 kg]	2 [10 U per 80 kg]
6	37.5	1.9 [3 g per 80 kg]	3 [15 U per 80 kg]
8	50	2.5 [4 g per 80 kg]	4 [20 U per 80 kg]
10	62.5	3.1 [5 g per 80 kg]	5 [25 U per 80 kg]
12	75	3.8 [6 g per 80 kg]	6 [30 U per 80 kg]

Courtesy of Klaus Görlinger, Essen, Germany
TACO transfusion-associated circulatory overload

Management of Coagulation Time (Thrombin Generation)

Coagulation times (CT) can be prolonged due to a deficiency of enzymatic coagulation factors, a low plasma fibrinogen concentration, or the presence of an anticoagulant, e.g., war-

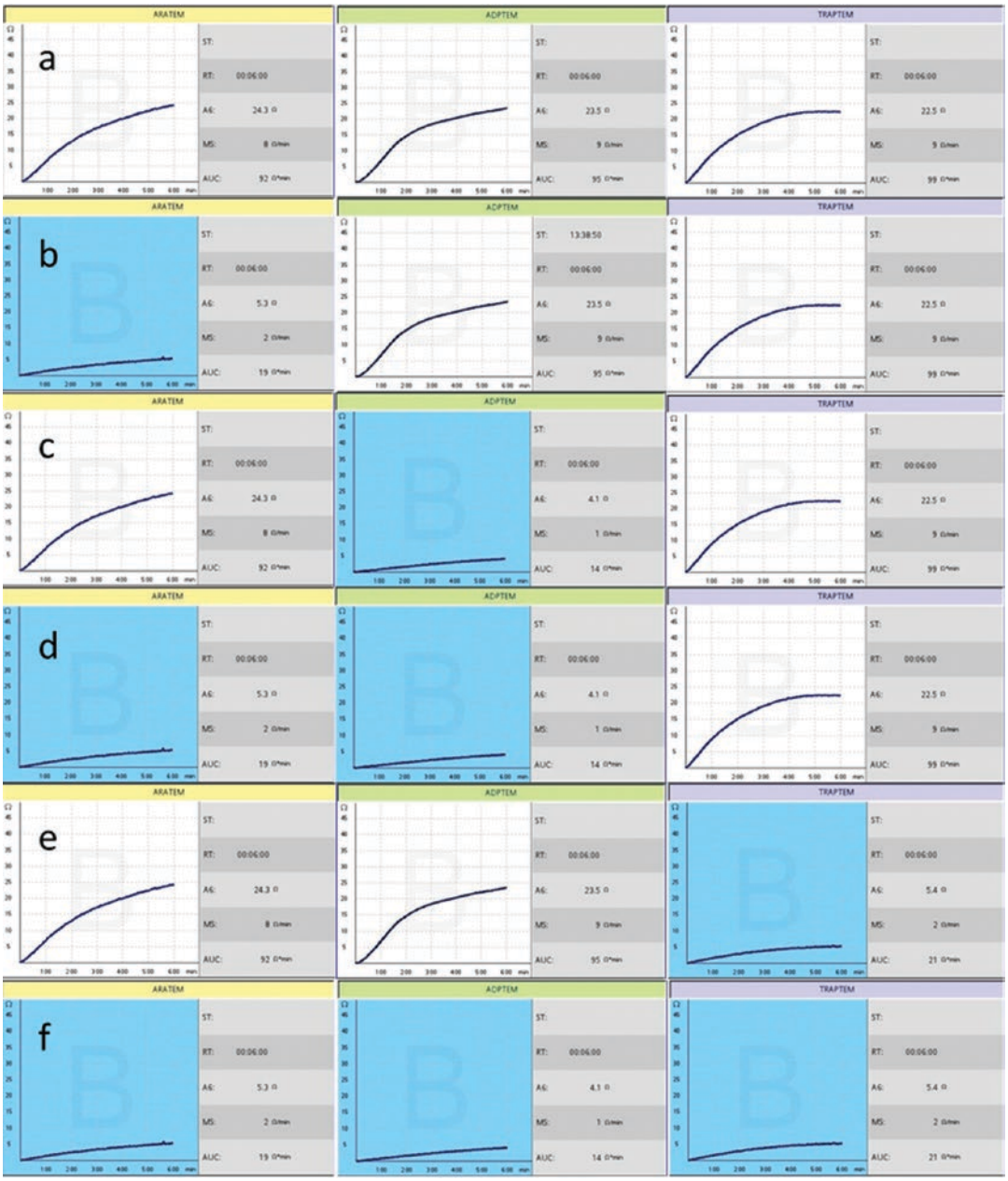


Fig. 7.3 (**a–f**) Characteristic whole blood impedance aggregometry traces (ROTEM® *platelet*) achieved by activation with arachidonic acid (ARATEM; left column), ADP (ADPTEM; middle column), and TRAP-6 (TRAPTEM; right column). (**a**) Normal platelet function; (**b**) Selective inhibition of the arachidonic acid pathway (e.g., by aspirin); (**c**) selective inhibition of the ADP-receptor pathway (e.g., by clopidogrel or prasugrel); (**d**) inhibition of the arachidonic acid and ADP-receptor pathway (e.g., dual antiplatelet therapy with aspirin and clopidogrel); (**e**) selective inhibition of the thrombin-receptor pathway (e.g., by vorapaxar); (**f**) general platelet dysfunction due to triple antiplatelet therapy, GPIIbIIIa-receptor antagonists (e.g., abciximab, eptifibatide, or tirofiban), platelet receptor destruction (e.g., due to cardiopulmonary bypass, severe trauma, or sepsis), or severe thrombocytopenia (Courtesy of Klaus Görlinger, Essen, Germany)

farin, heparin, direct thrombin inhibitors (e.g., hirudin, argatroban, or bivalirudin), or direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, or edoxaban (Fig. 7.4a) [34, 120–133]. Notably, a protamine overdose can prolong CT, too (Fig. 7.4b) [134–136].

Usually a CT prolongation in EXTEM indicates a deficiency of coagulation factor from the extrinsic or common pathway (factors VII, X, V, II, and I). A deficiency of vitamin K-dependent coagulation factors (factors X, IX, VII, and II) can be based on a therapy with vitamin K-antagonists (warfarin), liver cirrhosis, or hemodilution/consumption during sever bleeding. Since the vitamin K-dependent inhibitors proteins C and S in these situations are low, too, the coagulation system can be re-balanced at a low unstable

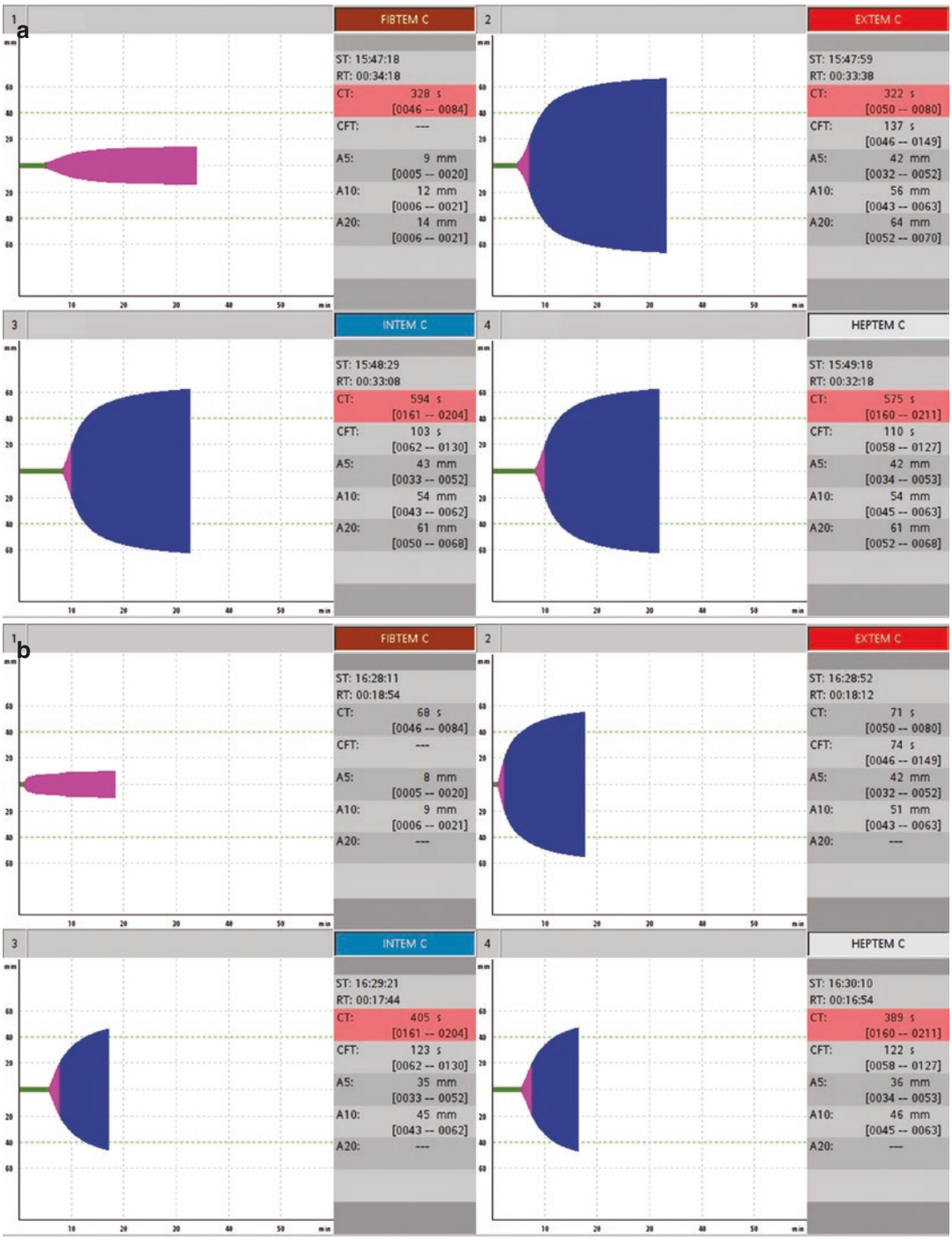


Fig. 7.4 (**a–c**) Characteristic ROTEM™ patterns for (**a**) *direct thrombin inhibitors* (argatroban, bivalirudin or dabigatran; dabigatran concentration (ng/mL) = 1.59 × EXTEM CT - 64; e.g., an EXTEM CT of 322 s corresponds to a dabigatran concentration of 448 ng/mL [124]), characterized by a prolonged CT in extrinsic and intrinsic ROTEM™ assays, (**b**) *protamine overdose* within 15–20 min after excess protamine administration (here 0.5 IU/mL), characterized by prolonged CT in INTEM and HEPTEM and an INTEM/HEPTEM CT-ratio <1.1) and (**c**) *acquired hemophilia A* characterized by short CT in EXTEM and FIBTEM and marked prolongation of CT in INTEM and HEPTEM; rare disease occurring most often during or after pregnancy, in patients with malignancies and in older patients (Courtesy of Klaus Görlinger, Essen, Germany)

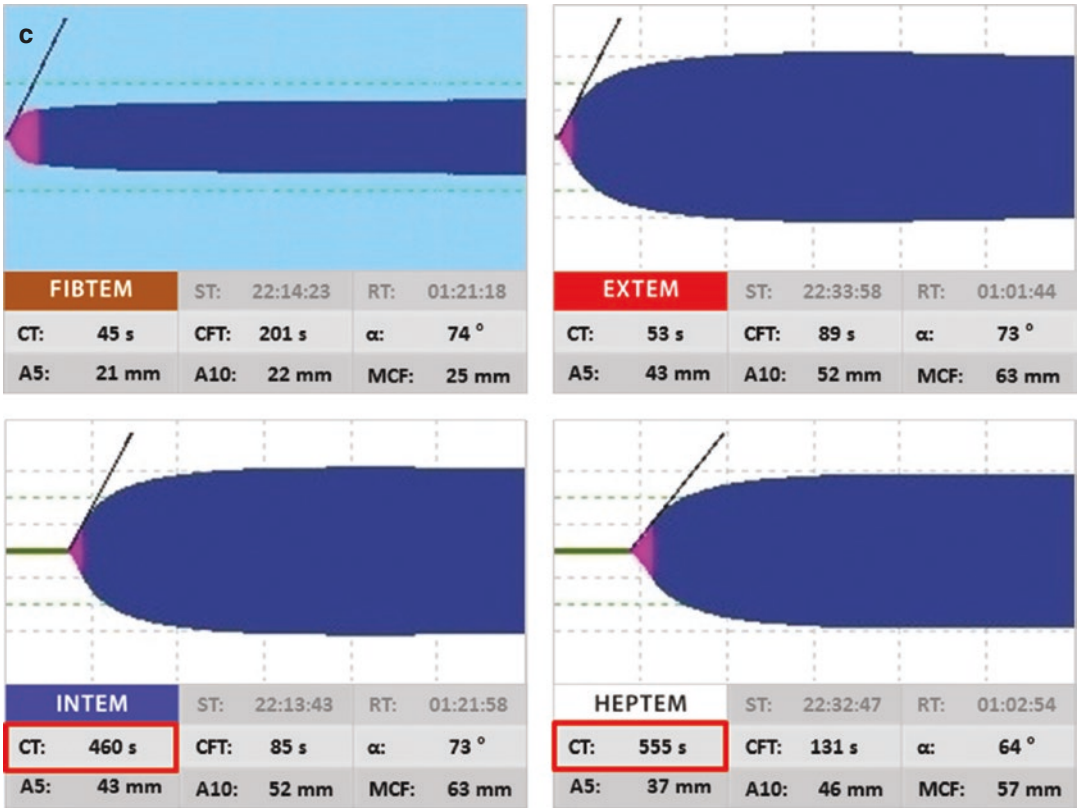


Fig. 7.4 (continued)

level – associated with a high risk of bleeding and thrombosis [12, 13]. EXTEM CT correlates well with international normalized ratio (INR) in patients treated with warfarin [120, 121]. However, the activity of the vitamin K-dependent coagulation factors usually is decreased below 30% of their normal activity if CT in EXTEM exceeds 80s [29]. Notably, a severe fibrinogen deficiency can prolong CT in EXTEM, too. Therefore, EXTEM CT can be used for guiding therapy with prothrombin concentrate complex (PCC) or FFP only in case of a normal A5 (A10) in FIBTEM [2, 6, 7, 17, 29, 31]. Accordingly, management of clot firmness precedes management of coagulation time in ROTEM™ algorithms. Usually, a dose of 15–25 units/kg body weight of PCC is sufficient to normalize EXTEM CT, to reduce INR below 1.5, and to stop coagulopathic bleeding [6, 17, 18, 29, 67, 70, 120, 121, 137, 138].

The use of three- or four-factor PCCs or FFP is dependent on the local approval and availability in the respective countries. Notably, four-factor PCCs (Beriplex™ and Octaplex™) are approved in Europe for prophylaxis and therapy of bleeding in patients with hereditary and acquired deficiencies of vitamin K-dependent factors, whereas four-factor PCC (Kcentra™) in the USA is FDA-approved for urgent reversal of vitamin-K antagonists only [139–141]. In patients with warfarin-induced bleeding complications, four-factor PCCs have been proven to be superior to FFP transfusion regarding efficacy and safety [142–145]. Even though they are not yet FDA-approved for other indications, PCCs are increasingly recommended and used as a therapeutic option in patients with severe bleeding and a proven deficit in thrombin generation (e.g., by EXTEM CT prolongation) [6, 7, 17, 29, 52, 53, 56, 61, 137, 143, 146–149]. Here, four-factor PCCs enable a rapid and calculated increase in coagulation factor activity and, at the same time, avoid the typical and serious adverse events associated with FFP transfusion, such as transfusion-related acute lung injury (TRALI), TACO and transfusion-related immunomodulation (TRIM) [139–145, 150–152]. Administered in a targeted way, the risk of thrombotic events by using four-factor PCCs seems to be low [153–155]. However, further studies are needed for final risk assessment.

Notably, direct thrombin inhibitors such as dabigatran can result in a marked increase in EXTEM, INTEM CT and ECATEM CT (Fig. 7.4a) [123, 124, 126, 127, 129]. The ecarin-based ROTEM™ assay ECATEM is specific for direct thrombin inhibitors such as hirudin, argatroban, bivalirudin, and dabigatran [127–129, 146].

Activated PCCs (factor eight inhibitor bypassing agent = FEIBA) and recombinant activated factor VII (rFVIIa) are only indicated in acquired hemophilia with inhibitors [156–159]. The typical ROTEM™ pattern of an

acquired hemophilia is shown in Fig. 7.4c. Due to the high risk of arterial thromboembolic events, the off-label administration rFVIIa should be restricted to bleeding not responding to comprehensive coagulation therapy [15, 156, 160, 161]. The implementation of thromboelastometry-guided bleeding management algorithms usually eliminates the need for rFVIIa administration as a rescue therapy [17, 18, 40, 41, 60, 61].

INTEM CT can be prolonged due to a heparin or heparin-like effect or a deficiency of coagulation factors of the intrinsic pathway and common pathway (factors XII, XI, IX, VIII, X, V, II, and I). A heparin-like effect, e.g., due to endothelial glycocalyx degradation, reperfusion of a liver graft during liver transplantation, or re-transfusion of heparin by using a cell-saver in the emergency modus, can be confirmed by the normalization of CT in HEPTEM resulting in an INTEM/HEPTEM CT-ratio ≥1.25 which corresponds to an anti-Xa activity of about 0.2 IU/mL [31, 122, 126, 162, 163]. Protamine administration can be considered – in particular in cardiovascular surgery when heparin-reversal is intended. In other settings, such as liver transplantation and hemorrhagic shock, protamine administration should considered carefully and only be done in severe bleeding because a heparin-like effect in these settings is most often self-limiting after hemodynamic stabilization [164]. Notably, protamine overdose can also prolong CT in INTEM and HEPTEM (Fig. 7.4b) and in severe cases even in EXTEM and FIBTEM. Protamine overdose results in an INTEM/HEPTEM CT-ratio <1.1 [163] and disappears most often within 15–20 min after protamine administration by binding of excess protamine to the endothelial glycocalyx. However, protamine overdose is associated with increased transfusion requirements and an increased incidence of resurgery and should therefore strictly be avoided [134, 136]. Protamine-induced platelet dysfunction might be causative, here [106]. In case of CT prolongation in INTEM and HEPTEM – not due to a protamine overdose – FFP transfusion can be considered in bleeding patients. In pregnant women and patients with malignancies, the possibility of an acquired hemophilia should not be forgotten (Fig. 7.4c) [157–159].

Clinical and ROTEM™ Reassessment

Finally, clinical bleeding has to be reassessed after running the algorithm and performing hemostatic interventions. In case of ongoing bleeding, ROTEM™ should be reassessed 10–15 minutes after the hemostatic intervention with a new blood sample and running the algorithm again.

In case of normal results in both thromboelastometry and whole blood impedance aggregometry, surgical bleeding should be considered and the patient should be re-examined surgically.

Thromboelastometry-Guided Bleeding Management Algorithms: Impact on Patient Outcomes

Implementation of ROTEM™-guided bleeding management algorithms reduced bleeding and transfusion requirements in several clinical settings, including cardiovascular surgery, severe trauma, liver transplantation, PPH, and major adult and pediatric surgery [10, 11, 17, 18, 20, 35–44, 49–62, 165, 166]. Görlinger, Fries, and Schöchl reported in their retrospective analysis that implementation of a ROTEM™-guided algorithm in their institutions reduced transfusion requirements for FFP, red blood cells (RBC), and platelets by 70–90%, 10–60%, and 20–70%, respectively. At the same time, the incidence of intraoperative massive transfusion (≥10 units of RBCs) could be more than halved (1% vs. 2.5%; $p < 0.001$) [29]. These results could be confirmed by several other cohort studies and RCTs [17, 18, 32, 37, 39–44, 47–62, 167, 168].

Furthermore, efficacy of viscoelastic testing can be increased by a combination with point-of-care platelet function analysis such as whole blood impedance aggregometry (e.g., ROTEM™ *platelet* or Multiplate™) [1, 17, 18, 40, 41, 60].

Besides reduction of transfusion requirements, the need for large volume (≥4 units of RBC), or massive transfusion (≥10 units of RBC), for surgical re-exploration for bleeding or for postoperative hysterectomy [17, 18, 35–37, 40, 41, 47, 48, 60], several studies could show improved patient outcomes, such as reduced incidence of pulmonary complications/postoperative ventilation time [18, 37, 47, 48], acute kidney injury/need for renal replacement therapy [18, 35, 73], thrombotic/thromboembolic events [17, 18, 35, 61, 62, 169], nosocomial infections/sepsis [18, 41], multiple organ failure (MOF) [55, 62, 168], stay at intensive care unit (ICU) [37, 39, 41, 47, 48], and mortality [18, 50, 52, 55, 61]. Notably, postoperative acute kidney injury is associated with increased short- and long-term mortality in cardiac surgery, liver transplantation, and trauma [170–174]. Furthermore, health-care costs could be reduced significantly, first by reduction of transfusion-associated costs, and second – and may be even more important – by reduction of complication-related costs, reduced ICU and hospital length of stay, and increased number of cases performed in the study period [17, 18, 29, 31, 40–42, 45, 46, 57, 61, 168, 175–181].

Therapeutic Window Concept

The algorithms presented in Fig. 7.1a–c are based on the "therapeutic window concept." This concept has been developed for guiding antiplatelet therapy in patients undergoing percutaneous coronary interventions (PCIs) in order to mini-

mize the risk of ischemia (stent thrombosis) and bleeding [20, 21, 182–184]. Accordingly, bleeding management algorithms guided by thromboelastometry and whole blood impedance aggregometry are designed to minimize the risk of both bleeding and thrombosis, by a personalized therapy according to the concept of precision medicine [2, 6–8, 10, 21–26]. Here, the right therapeutic intervention, in the right dose, at the right time, and in the right sequence is defining the framework of the therapeutic window, e.g.:

- EXTEM A5: 35–50 mm (A10: 45–60 mm)
- FIBTEM A5: 8–18 mm (A10: 9–19 mm)
- EXTEM CT: 40–80 s
- ADPTEM: 35–45 Ω x min (in patients with drug-eluting stents)

Using this concept in cardiovascular surgery, it was possible to reduce both transfusion requirements and thrombotic/thromboembolic complications, significantly [17, 18, 35, 169, 182–184].

Guidelines, Health Technology Assessments, Knowledge Translation, and Implementation

Based on the actually available evidence, the implementation of ROTEM™-guided algorithms is highly recommended (Grade 1B-1C) by the guidelines for the management of severe perioperative bleeding from the European Society of Anesthesiology (ESA), the updated European guideline for the management of bleeding and coagulopathy following major trauma, and the updated practice guidelines for perioperative blood management by the American Society of Anesthesiologists (ASA) Task Force on Perioperative Blood Management (A1-B evidence) [15, 103, 141]. Viscoelastic testing is an essential part of multimodal protocols/algorithms in patient blood management, which typically consist of a predeterminated bundles of diagnostics and interventions intended to reduce blood loss and transfusion requirements [141, 185–188]. In particular, therapeutic interventions with highly effective coagulation factor concentrates, such as fibrinogen concentrate and PCC, should be guided by thromboelastometry (Grade 1B-1C). Furthermore, it is stated that the implementation of transfusion and coagulation management algorithms (based on ROTEM™/TEG™) can reduce transfusion-associated costs in trauma, cardiac surgery, and liver transplantation (Grade C) and that targeted therapy with fibrinogen and/or PCC guided by ROTEM™/TEG™ is not associated with an increased incidence of thromboembolic events (Grade C) [103]. The importance of viscoelastic testing supported by bleeding management algorithms has been pointed out by several other national (AAGBI, American College of Surgeons, AWMF/DGU/DGAI/DIVI, AWMF/DGGG/OEGGG/SGGG/DGAI/GTH, BSH, NBA Australia, SEDAR/SEHH/SEFH/SEMICYUC/SETH/SETS, SFAR, SNG Portugal) and international guidelines (EACTS/EACTA, ISTH), too [7, 189–201].

The cost-effectiveness of ROTEM™-guided bleeding management has also been proven by several health technology assessments and pharmaco-economic analyses [45, 46, 177, 180, 202–204]. However, guidelines and health technology assessments can only change practice and improve patients' outcomes in combination with knowledge translation and implementation. Therefore, the "STOP the Bleeding Campaign" was initiated in 2013, the NHS/NBTC "Recommendation for the implementation of PBM (patient blood management)" has been published by the UK National Blood Transfusion Committee (NBTC) in 2014, the "National Patient Blood Management Implementation Strategy 2017–2021" has been published by the Australian National Blood Authority in 2017, the "PBM Implementation Guides" for health authorities and for hospitals have been published by the European Commission in April 2017, and the "National STOP the Bleed Month" has been initiated in the USA in May 2019 [16, 205–208].

Thromboelastometry as an Integral Part of a Patient Blood Management (PBM) and Patient Safety Program

PBM is the timely application of a multidisciplinary, evidence-based medical concept, which helps to optimize the patient's own blood volume, minimize blood loss, and thereby significantly reduce or even avoid allogeneic blood transfusion [209, 210]. The patient blood management concept was highlighted in 2010 by the World Health Assembly as an important concept to improve patient safety. Accordingly, all WHO member states were requested to implement this concept in a timely manner. Perioperative thromboelastometry-guided bleeding management is an essential part of PBM and patient safety [57, 167, 169, 200, 211–215]. Accordingly, all NHS hospitals in the UK have been requested by the NHS Blood and Transplant, the UK Department of Health and the UK National Blood Transfusion Committee (NBTC) to establish a PBM program, including point-of-care (POC) testing and implementation of bleeding management protocols [205]. In 2014, a German PBM network has been founded, and a prospective multicenter trial enrolling 129,719 patients has been performed to assess safety, efficiency, and cost-effectiveness of implementing a PBM program. Besides a significant relative reduction in blood transfusion by 17% ($P < 0.001$), the incidence of acute renal failure could be decreased by 30% (1.67% vs. 2.39%; $P < 0.001$) without any safety issues [216]. Notably, the

decrease in acute renal failure is of high clinical importance since postoperative acute renal failure is associated with increased short- and long-term mortality [170–174]. Accordingly, blood transfusion was reduced by 41% ($P < 0.001$), hospital acquired infections by 21% (OR, 0.79; $P < 0.001$), acute myocardial infarction and stroke by 31% (OR, 0.69; $P < 0.001$), and hospital mortality by 28% (OR, 0.72; $P < 0.001$) in a Western Australian patient blood management implementation study recruiting 605,046 patients. This was also associated with a significant reduction in hospital length of stay and cost savings (US$ 18,078,258 over 6 years) [215, 217]. A recently published meta-analysis confirmed that implementing a comprehensive PBM program addressing all three PBM pillars (e.g., viscoelastic testing in pillar two) is associated with reduced transfusion needs, lower complication and mortality rates, and thereby improving clinical outcome [218]. Thus this first meta-analysis investigating a multimodal approach should motivate all executives and health-care providers to support further PBM activities and by doing so decrease health-care costs [46, 175, 215–218].

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