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TEM International	**1.**			**General comments and limitations of the study:** This manuscript clearly demonstrates the advantages of VETs compared to SLTs. However, an important limitation of this study is that cost-effectiveness analysis is based on several unproven or even inapplicable assumptions. Here, cost-effectiveness calculation is based on device and test costs for the three different devices (ROTEM, TEG, and Sonoclot), the assumed number of tests performed per case, and the assumed clinical effectiveness. Since two out of three factors (number of tests performed and clinical effectiveness) have been assumed to be equal for all three devices (which is unfounded as discussed later), the cost-effective analysis is based on test costs (which are not calculated adequately), solely. Therefore, the term "cost-effectiveness analysis" is misleading here because the differences in "cost-effectiveness" reported in this study is in fact just a cost analysis for the three different devices. The most important factor for cost-effectiveness – clinical effectiveness – was assumed to be equal for all three devices despite the published evidence for clinical	We do not agree with the first part of the comment, regarding this study not being a true cost-effectiveness study. If we had only been comparing the 3 VE devices, then indeed our study could have been described better as a cost-minimization study. However, the main goal of the study was to compare SLT against VE testing. Since we have clearly included the effectiveness of VE testing in preventing blood transfusions compared to SLT, our study is a true cost-effectiveness study. We applied explicit inclusion criteria for the review. As specified in the protocol, where RCTs were available lower levels of evidence were not included. This was the case for cardiac surgery and resulted in the inclusion of 11 RCTs: 6 of TEG, 4 of ROTEM and one of ROTEG. Detailed analysis found no evidence of a difference between devices. The assumption that the effectiveness of ROTEM and TEG is similar is therefore reasonable. There were no RCTs on Sonoclot but analysis of lower lever evidence did

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				effectiveness is obviously different for the three devices: at least five ROTEM studies demonstrating a significant improvement in outcome [1-9] (need for massive transfusion, surgical re-exploration, thrombosis, acute lung injury, acute renal failure, multiple organ failure, nosocomial infection/sepsis, composite adverse events) including three studies showing a significant reduction in six-month or in-hospital mortality, respectively (one RCT in cardiac surgery [7] and two retrospective analysis in trauma [3,8]), two TEG studies (before-and-after studies) reporting improved outcome or reduced mortality [10-11], no data on the clinical effectiveness of Sonoclot at all. Furthermore, there are six ROTEM studies reporting cost-savings in cardiac surgery and in overall hospital costs [5-7,12-15] (including one RCT [7]) and only one TEG study is reporting cost-savings in cardiac surgery which were not specified in the publication [16]. The main limitation of the systematic review of the literature in this manuscript is that at least 18 meaningful publications dealing with ROTEM/TEG-guided bleeding	not find evidence of a difference between Sonoclot and TEG. The assumption of equal effectiveness to TEG and ROTEM was therefore the best assumption that could be made based on limited data. We have acknowledged the limitation of this assumption in the report. The studies that you have listed as being excluded from the review were excluded because they did not meet the review inclusion criteria (see response to comments 19 and 20). Weber was included in the clinical effectiveness review but should also have been included in the review of cost-effectiveness studies. However, this would not have altered the results of the economic model as the cost data in this study is German and so not transferable to a UK setting. The studies by Görlinger (2011), Hanke (2012), and Esler (2013) indeed present the difference in costs of blood products between a ROTEM and a non-ROTEM group and hence should have been listed under the cost-minimization studies.

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				management in cardiovascular surgery and trauma (see comments below) considered in other recently published systematic reviews [1,9] of the literature and European guidelines [14,34] have not been included in the systematic review of the authors. This is questionable and reduces the value of the manuscript regarding their conclusions on the clinical effectiveness of the three VET devices. This explains that the authors assumed that the clinical effectiveness of the devices is similar (due to a supposed lack of data showing difference) and that calculation of cost-effectiveness is reduced to calculation of device and test costs, finally. However, the authors clearly point out the uncertainties and limitations of their study in section 5.3. So, the thoughtful reader will be able to make his own decision based on the provided data.	The study by Spalding (2007) is already in the cost-effectiveness review. Görlinger (2011) is a review paper, and Kozek- (2013) is a guideline paper, with neither of them presenting new evidence. Finally, the paper by Speiss (1995) does mention some cost estimates in the discussion of the paper but no comprehensive results are presented.
	2.			**Specific comments:**	
	3.	**19**	**Scientific summary, Results**	**4. What is the cost-effectiveness of VE devices during or after cardiac surgery?:** "In the absence of data on the	We disagree. This is supported by the data included in our review, see response above (comment 1).

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				clinical effectiveness of Sonoclot, we assumed that the TEG- and ROTEM-based estimates used in the model would also be applicable to Sonoclot. Thus, given that all three devices were assumed to be equally effective, the same health effect outcomes were obtained for all three VE devices." **Comment:** As discussed above, this assumption is not in line with the published data.	
	4.	**22**	**Plain English Summary**	Here, the authors point out the following advantages of "viscoelastic" methods. However, these advantages are not applicable for all three devices in equal measure: • VETs are performed near the patient **Comment:** TEG is limited by high sensitivity against shock and agitation artefacts; therefore, mobile us in the OR and ICU is not feasible. • VETs have a shorter turn-around time compared to SLTs **Comment:** The turn-around time of TEG is significantly	The comment about turnaround time is comparing all VE devices against SLTs not against each other and so is correct. The comment regarding which assays should be modelled is discussed in more detail below (comments 11 and 12). Inter- and intra-individual variability of test results was not in the scope of this assessment.

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				longer compared to ROTEM analysis since reference range for R time in kaolin activated test is 3.8-9.8 min [17] compared to 137-246 s in INTEM and 42-74 s in EXTEM test [18] and early variables for clot firmness (A5 = Amplitude of clot firmness 5 min after CT and A10 = Amplitude of clot firmness 10 min after CT) [19-23] are not available for TEG. Therefore, TEG users have to wait for MA for decision-making which takes about 15-25 min after R time. Overall, turn-around time for TEG is about 21-31 min compared to 6-11 min using ROTEM. This allows for earlier decision-making and a shorter time-to-treat in ROTEM- vs. TEG-guided bleeding management. • VETs provide additional information on the clotting process and allow for targeted administration of specific blood products and avoidance of risks associated with unnecessary transfusion **Comment:** The diagnostic performance of the panel of specific reagents used in thromboelastometry is higher compared to tests activated by kaolin, solely. [24] Thereby, inappropriate transfusion of platelets and FFP can be	

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				avoided [23-25]. Several studies demonstrated the importance of FIBTEM (see page 27, Table 2: Summary of ROTEM Delta assays) or functional fibrinogen (see page 30, Table 3: Summary of TEG assays) for bleeding management in cardiac surgery [26-30], trauma [10,31-34] and postpartum hemorrhage [35-37]. However, functional fibrinogen has not been included in cost analysis for TEG in cardiac surgery (Table 27, page 110; Table 28, page 111) and trauma (table 36, page 123). Here, it is inconsistent assuming on the one hand the same clinical effectiveness for TEG and ROTEM (which might be given using the whole panel of TEG tests: kaolin TEG, heparinase TEG, rapid TEG, and functional fibrinogen) but one the other hand not including the costs for functional fibrinogen in the cost-effectiveness analysis for TEG. However, FIBTEM has been shown to be even more effective than functional fibrinogen to discriminate between fibrinogen deficiency and thrombocytopenia [38-39]. **Additional comment:** Inter- and intra-individual variability of test results is significantly lower in ROTEM compared to TEG [40].	

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	5.	**22**	**Plain English Summary**	"We did not find any studies on the clinical effectiveness of Sonoclot or in the **effectiveness in trauma patients**." **Comment:** Data regarding the clinical effectiveness of ROTEM-guided bleeding management in trauma and burn patients have been published by Schöchl et al. 2010 [3], Nienaber et al. 2011 [4], Schaden et al. 2012 [41], and Lendemans et al. 2013 [8].	These were not RCTs and so did not fulfil our inclusion criteria. See more detailed response below (comment 19).
	6.	**95**	**4.2.1**	"Most complications are a consequence of RBC transfusion, although some were modelled as a consequence of any transfusion." **Comment:** This assumption is not true. In particular, fresh frozen plasma transfusion is associated with transfusion-associated circulatory overload (TACO), acute lung injury (ALI), multiple organ failure, transfusion-related immunomodulation (TRIM), nosocomial infections and sepsis in trauma and cardiac surgery [42-53]. In cardiac surgery, the impact of fresh frozen plasma transfusion on mortality is even higher compared to red blood cell transfusion. Therefore, the avoidance mortality is even higher than red blood cell and platelet transfusion [50-51].	We agree with the commentator that complications of blood transfusions can be related to all type of blood products, though some complications only occur with one type of product. So ideally, the model would have been set-up in such a way that these relationships are properly reflected. However, most patients receiving any transfusion receive RBC, and no data was available to deal with probabilities of complications for RBC, platelet or FFP only, or any combination of these. The studies included in the review do not indicate which percentage of patients receive what type of combination of blood products.

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				Therefore, avoidance or reduction of fresh frozen plasma transfusion has to be considered in clinical effectiveness and cost-effectiveness analysis, too [25]. Here, several studies demonstrated a significant reduction in the incidence of multiple organ failure, thrombosis and/or composite adverse events (acute renal failure, sepsis, and thrombosis) in patients with ROTEM-guided bleeding management and avoidance/significant reduction of fresh frozen plasma transfusion [4-7].	So overall, we chose to model RBC transfusion as it was reported in all but one of the studies reported in the systematic review (unlike the percentage of patients with any transfusion). This was in line with the approach taken in the previous cost-effectiveness study in this area, the Scottish HTA report. In addition, we had reliable data from a large cohort study in a UK setting on which to base the mortality calculations related to RBC transfusion (Murphy, 2007). This decision was supported by the fact that the RR for mortality in transfused versus non-transfused patients obtained when we used data from Murphy was almost identical to the pooled estimate obtained from studies that reported short term mortality included in the clinical effectiveness review.
	7.	**95f**	**4.2.1**	"Complications related to surgery and/or transfusion, included in the model were: renal dysfunction, myocardial infarction, stroke, thrombosis, excessive bleeding requiring re-operation, wound complications and septicaemia." **Comment:** Weber et al. [7] demonstrated a significant reduction in composite adverse events (acute renal failure,	These outcomes are considered in the model and the Weber study is included in the clinical effectiveness review. If possible during the peer review stage, we will include these data in the appendices and will add the 6 month mortality and adverse events to the results section. This will not affect any of the

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				sepsis, and thrombosis; 8 vs. 38%; P<0.001) as well as six-month mortality (4 vs. 20%; P = 0.013) in the ROTEM-group compared to the SLT-group in his RCT in complex cardiac surgery.	conclusions of the review or input to the model.
	8.	**96**	**4.2.1**	"It should be noted that, as in Davies et al. 2006, bacterial contamination is the only transfusion-transmitted infection that was assumed to occur during the hospitalisation period." **Comment:** Again, this assumption is not true. Transfusion-related immunomodulation (TRIM) and subsequent nosocomial infection/sepsis is increased from 6 to 18% in patients transfused with fresh frozen plasma compared to patients not transfused with fresh frozen plasma [43]. Accordingly, the incidence of sepsis could be reduced from 14 to 2% in the ROTEM-group in the RCT published by Weber et al. [7].	We agree with the commentator that sepsis is also a relevant complication of transfusion. However, we listed sepsis under the surgery and/or transfusion related complications rather than as a transfusion-transmitted infection. For the latter group, we followed the definition as it is also used in the SHOT-reports.
	9.	**108**	**4.3.1.7**	"Data on units of blood transfused (see Table 26) were obtained from Shore-Lesserson et al. 1999. … The mean number of units of RBC transfused for patients in the VE group was slightly higher than in the SLTs group, whereas	We selected the Shore-Lesserson study to calculate mean units of blood transfused as this study was conducted in a general surgical population and provided data on the mean

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				the units of FFP and platelets were lower. This might suggest that VE testing leads to some substitution of one blood product by another." **Comment:** The reduction in transfusion requirements for RBC and FFP were considerable higher in the ROTEM studies in cardiac surgery published by Görlinger et al. 2011 [5], Weber et al. 2012 [7], and Esler et al. 2013 [15]. This again, clearly demonstrates that the author's assumption that the clinical effectiveness of all three devices is the same is incorrect. Accordingly, using the results of the Shore-Lesserson study for the ROTEM studies, too, results in an underestimation of the clinical effectiveness and cost-effectiveness of the ROTEM device.	volume of blood transfused. Goerlinger and Esler were not RCTs and so were not eligible for inclusion in our review. The Weber study was restricted to complex cardiothoracic surgery patients who had experienced a bleeding event and so was not considered to be representative of general cardiac surgery patients. Further, this review only reported data as median volumes of blood transfused. While this may be an appropriate measure to present it does not allow us to perform the necessary calculations to obtain units of blood per transfused patients.
	10.	**111**	**Table 28**	**Comment:** Here, the assumption that a basic test for ROTEM in cardiac surgery has to be defined as a combination of the INTEM, EXTEM, FIBTEM and HEPTEM assays is inapplicable. Looking at the published ROTEM algorithms for cardiac surgery [5-7,13,54] the authors would easily recognize that EXTEM and FIBTEM are the basic tests and HEPTEM and INTEM are only used after weaning from	We modelled the assays used in the trials. Although this may not be reflective of actual clinical practice, we cannot assume that the same effectiveness would be achieved when using fewer or different assays. We will perform some additional sensitivity analyses to show how the results of the cost-effectiveness model would have changed if we had modelled

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				CPB and heparin-reversal with protamine in order to detect or exclude a residual heparin effect or even a protamine overdose. Therefore, the test cost calculation is not appropriate. Assuming three analysis per patient (which is only necessary in patients with ongoing bleeding) this would result in overall 3 EXTEM, 3 FIBTEM, 1 INTEM and 1 HEPTEM test per cardiac patient with bleeding. In order to provide the same diagnostic performance with the TEG (which was assumed by the authors), here 3 rapid TEG tests, 3 functional fibrinogen tests, 1 kaolin TEG and 1 heparinase TEG have to be included in the TEG test cost analysis per cardiac patient. This would result in the following **test costs per cardiac patient** (costs for one rapid TEG (£ 11.25) see page 123, table 36, and costs for one functional fibrinogen test (£8.33) see page 302, Protocol Table 5 Comparison of costs of TEG and ROTEM based on 2008 costs): **ROTEM:** 3 x £1.13 + 3 x £2.22 + 1 x £1.13 + 1 x £2.43 + 8 x £3.15 = **£38.81** (excl. equipment costs) **TEG:** 3 x £11.25 + 3 x £8.33 + 2 x £2.72 + 1 x £8.75 + 7 x	different basic tests.

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				£5.45 = **£111.08** (excl. equipment costs) Viz, TEG test costs per cardiac patient are **2.9fold** higher compared to ROTEM if a similar test combination is used. Based on the minimal assumption that only kaolin TEG and heparinase TEG are used three times in cardiac surgical patients, INTEM and HEPTEM would be the corresponding ROTEM test combination. Here, test cost for both devices have to be calculated as follows: **ROTEM**: 3 x £1.13 + 3 x £2.43 + 6 x £3.15 = **£29.58** (excl. equipment costs) **TEG**: 6 x £2.72 + 3 x £5.45 + 3 x £8.75 = **£58.92** (excl. equipment costs) In this constellation again, TEG test costs per cardiac patient are **2fold** higher compared to ROTEM.	
	11.	**123**	**Table 36**	**Comment:** Here, the assumption a basic test for ROTEM in trauma patients has to be defined as a combination of the INTEM, EXTEM and FIBTEM assays is inapplicable. Looking at the published ROTEM algorithms for trauma patients	See response above (comment 11).

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				[13,25] the authors would easily recognize that EXTEM and FIBTEM are the basic tests and HEPTEM and INTEM are only used if a heparin effect has to be considered [55]. Therefore, the test cost calculation is not appropriate. Assuming five analysis per patient (which is only necessary in patients with ongoing bleeding) this would result in overall 5 EXTEM, 5 FIBTEM, 1 INTEM and 1 HEPTEM test per trauma patient with ongoing bleeding. In order to provide the same diagnostic performance with the TEG (which was assumed by the authors), here 5 rapid TEG tests, 5 functional fibrinogen tests, 1 kaolin TEG and 1 heparinase TEG have to be included in the TEG test cost analysis per trauma patient. This would result in the following test costs per cardiac patient (costs for one rapid TEG (£ 11.25) see page 123, table 36, and costs for one functional fibrinogen test (£8.33) see page 302, Protocol Table 5 Comparison of costs of TEG and ROTEM based on 2008 costs): **ROTEM:** 5 x £1.13 + 5 x £2.22 + 1 x £1.13 + 1 x £2.43 + 12 x £3.15 = **£58.11** (excl. equipment costs)	

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				TEG: 5 x £11.25 + 5 x £8.33 + 2 x £2.72 + 1 x £8.75 + 9 x £5.45 = **£161,14** (excl. equipment costs) Viz, TEG test costs per trauma patient are **2.8fold** higher compared to ROTEM if a similar test combination is used. Based on the minimal assumption that only rapid TEG is used five times in trauma patients, EXTEM would be the corresponding ROTEM test. Here, test cost for both devices have to be calculated as follows: **ROTEM**: 5 x £1.22 + 5 x £3.15 = **£21.58** (excl. equipment costs) **TEG**: 5 x £11.25 + 5 x £5.45 = **£83.50** (excl. equipment costs) In this constellation TEG test costs per trauma patient are even **3.9fold** higher compared to ROTEM.	
	12.	**128f**	**Table 37**	**Comment:** As discussed above and below, 30% of the assumptions made in this model are unproven, questionable or even inapplicable.	Regarding the mismatch between the costs of a 4 channel TEG device in table 27 (£ 20,000) and in the table on page 302 (£ 26,000), the number in Table 27 is based on 2013 prices provided by

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				General: Assumption 1-4 (see comments above and below). Assumption 6: "Only those extra items that were available (and comparable) for the three devices, were included in the acquisition costs. After-care and training costs were also included." (see comments on page **110**, table **27**) **Comment:** This statement is not correct. TEG tools equivalent to the optional ROTEM Connectivity Kit or the Database Commander Software are not included in the TEG device costs. The TEG device does even not include a **computer/laptop** which is necessary to use the device ("Computer required for TEG system operation to be obtained from your IT or purchasing departments or through an external source." Source: TEG® 5000 Hemostasis Analyzer System Folder, Haemonetics Cooperation, 2008-2010). Therefore, the cost of a computer/laptop and a **printer** has to be added to the device costs of the TEG. Furthermore, there is a significant **mismatch** between the **costs of a 4 channel TEG device** in **table 27 (£ 20,000)** and in the table on **page 302 (£**	the manufacturer. Page 302 is the protocol for the assessment which showed a table with costs based on 2008 prices. This was only a preliminary figure and the value in Table 27 is the correct one. If after discussion at the DAC there are shown to be errors in the costings, we will make adjustments to the model to address these.

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				26,000). Notably, **costs for quality controls** (QCs) are not considered in the cost analysis. However, this might be important because the ROTEM device requires only a QC once a week (due to an internal electronic QC; FDA approved), whereas the TEG device requires a QC once a day. This results in a about **seven times higher cost for QCs** in the TEG device compared to the ROTEM device which has to be considered for the cost calculation per year. Cardiac: Assumption 16 and 17 (see comments on page **111**, table **28**). Trauma: Assumption 28 and 29 (see comments on page **123**, table **36**).	
	13.	**138**	**4.5.5**	"As with the cardiac surgery model, the CEACs for ROTEM, TEG and Sonoclot were very close together, which would be expected as the only difference between the three strategies assumed in the model was a difference in technology cost." **Comment:** Here again, a questionable/unfounded assumption about similar clinical effectiveness of the three	See earlier response (comment no. 1)

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				devices and an inadequate calculation of technology cost have been made (see comments above).	
	14.	**146**	**5.1.2**	"There were no data on the clinical effectiveness of Sonoclot; we therefore assumed that the TEG- and ROTEM-based estimates used in the model would also be applicable to Sonoclot; thus the same health effect estimates were used for all three VE devices." **Comment:** see general comments and limitations of the study and comments above.	See earlier response (comment no. 1)
	15.	**150**	**5.2.2**	"We might reasonably assume, given that mortality is low between one month and one year, that this would also be the case if we had made similar changes to one year mortality." **Comment:** Again, this assumption is not in line with the published literature. Several studies have shown that blood transfusion – in particular fresh frozen plasma transfusion – is associated with long-term mortality [50,56-57]. Accordingly, Weber et al. [7] clearly demonstrated in their RCT that one-month mortality only represented 60% of the	The highlighted comment relates to a comment on the sensitivity analysis that we made in the discussion. We meant to describe here that as the model results are insensitive to changes in the 1 month mortality, they are likely to be even less sensitive to changes in the 1-11 month mortality, as that is lower than the 1 month mortality. Thus, taken in the context of the rest of the paragraph in which it is included we think this statement is reasonable.

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				six-month mortality in complex cardiac surgery. Therefore, the assumption that mortality between one month and one year is low is inapplicable.	
	16.	**151**	**5.2.2**	"There were no data on the clinical effectiveness of any of the VE devices in trauma patients. We therefore assumed equivalent clinical effectiveness to the cardiac surgery population." **Comment:** see comments above.	See response above (comment 1).
	17.	**155**	**5.3.1**	"The ROTEM FIBTEM assay and the TEG functional fibrinogen assay use a reagent specific for the fibrin polymerisation process, which decline more rapidly than fibrinogen levels as measured in the laboratory." **Comment:** As already mentioned above, ROTEM FIBTEM and TEG functional fibrinogen are important assays for early detection of hypofibrinogenaemia and the discrimination between low fibrinogen and thrombocytopenia in cardiac surgery [26-30], trauma [31-34], and postpartum hemorrhage [35-37]. Without these tests the diagnostic performance of VETs is significantly reduced	See response above (comments 11 and 12).

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				which may result in inappropriate platelet transfusion [23-25]. Therefore, TEG functional fibrinogen assay has to be included in the cost calculation for TEG testing in cardiac surgery and trauma. Otherwise, a significant lower clinical effectiveness has to be assumed for TEG-guided bleeding management [23-25].	
	18.	**143f**	**5.**	**Comments on the discussion section and missing references** **General comment:** A systematic review of the literature has already been performed recently for the updated European Trauma Guidelines [34] and the ESA Guidelines of the management of severe perioperative bleeding [14]. A systematic review of the literature on the clinical effectiveness of TEG- or ROTEM-driven transfusion protocols in cardiac surgery has been published by Görlinger et al.[1] in 2013. Furthermore, a systematic review of the literature on thromboelastometry for guiding bleeding management of the critically ill patient (severe trauma, cardiac and aortic surgery, liver transplantation, and postpartum hemorrhage) has just been published	We have reviewed the documents which are claimed to be systematic reviews: 34 and 14 are general guidelines for trauma patients and severe postoperative bleeding, only a small number of recommendations relate to VE devices with no clear details on included studies. We therefore do not consider these to be SRs. We do not have a full text copy of the Gorlinger review but its abstract does not suggest that it is a systematic review. We were not able to access this article online for further evaluation and there was insufficient time before the DAC meeting to order a full text copy. Our report was submitted before the publication of the article in Minerva Anesthesiologica and so we were not aware of this review at the time the report was submitted. We have also been unable to obtain

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				online in Minerva Anesthesiologica (2014 Feb 11) [9]. Another systematic review of the literature on the utility of thromboelastography and/or thromboelastometry in adults with sepsis has been published online in Critical Care (2014 Feb 10) [58]. Finally, another systematic review of the literature on the effect of thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®) on diagnosis of coagulopathy, transfusion guidance and mortality in trauma is just under review in Critical Care. At least 18 meaningful publications dealing with ROTEM/TEG-guided bleeding management in cardiovascular surgery and trauma (see comments below) considered in other recently published systematic reviews [1,9] of the literature and European guidelines [14,34] have not been included in the systematic review of the authors. This is unreproducible and reduces the value of the manuscript regarding their conclusions on the clinical effectiveness of the three VET devices. This explains that the authors assumed that the clinical effectiveness of the devices is similar (due to a supposed lack of data showing difference) and that calculation of cost-effectiveness is reduced to	a copy of this review online. None of the publications listed met inclusion criteria for our review – see response to comments 19 and 20

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				calculation of test costs, finally.	
	19.	**143**	**5.1.1**	"There were no apparent differences in clinical outcomes (re-operation, surgical cause of bleed on re-operation and mortality) between patients managed using VE testing and those managed using SLTs." **Comment (Cardiac surgery):** Massive transfusion rate (1.26 vs. 2.5%; P = 0.0057), incidence of surgical re-operation (2.24 vs. 4.19%; P = 0.0007), and the incidence of composite thrombotic/thromboembolic adverse events (1.77 vs. 3.19%; P = 0.01115) were significantly reduced by in the ROTEM-group of the before-and-after study in 3,865 cardiac surgical patients published by Görlinger et al.[5] in 2011. Hanke et al.[6] reported in 2012 a significant reduction of composite bleeding and thrombotic/thromboembolic incidence (0 vs. 80%; P = 0.048) in the ROTEM group of a pilot study in patients with acute type A aortic dissection. Again, composite adverse events (acute renal failure, sepsis, thrombosis; 8 vs. 38%; P < 0.001) and six-month mortality (4 vs. 20%; P = 0.013) were significant reduced in the ROTEM-group of the RCT published by Weber et al.[7] in	Almost all of the suggested publications were identified by our searches. They did not meet inclusion criteria as they were not RCTs. See response to comment 1. Further, none of the studies reported here provided direct comparisons between ROTEM and TEG and so would not help address the question of the relative effectiveness of these devices.

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				2012. (see also comments on trauma patients below) The following publications dealing with ROTEM/TEG-guided bleeding management in cardiovascular surgery are missing in the systematic review of the literature in this manuscript (see [1,9,14]): • Anderson et al.[59] Transfus Med. 2006: retrospective cohort study (before-and-after introduction of a ROTEM-guided algorithm) • Fassl et al.[60] J Cardiothroac Vasc Anesth. 2013: retrospective data analysis (ROTEM-guided algorithm vs. conventional treatment) • Hvas et al.[61] J Cardiothorac Vasc Anesth. 2012: prospective study group vs. historical control group (before-and-after implementation of ROTEM-guided therapy) 1. Rahe-Meyer et al. [61] Br J Anaesth. 2009: pilot study with two prospective groups vs. a historic control group (FIBTEM-guided	

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				fibrinogen substitution in aortic value and ascending aortic surgery) • Rahe-Meyer et al.[62] J Thorac Cardiovasc Surg. 2009: pilot study with a prospective group vs. historic control group (FIBTEM-guided fibrinogen substitution in thoracoabdominal aortic aneurysma surgery) • Hanke et al.[6] Transfus Med Hemother. 2012: pilot study with a prospective group vs. matched control group (ROTEM-guided therapy in patients undergoing aortic arch replacement due to acute type A aortic dissection) • Rahe-Meyer et al.[63] Anesthesiology 2013: RCT (FIBTEM-guided fibrinogen substitution in aortic replacement surgery; total avoidance of any allogeneic blood transfusion in 45 vs. 0%; P < 0.001) • Romlin et al.[64] Anesth Analg 2011: prospective study group vs. matched control group (before-	

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				and-after implementation of ROTEM-guided therapy in pediatric cardiac surgery) • Görlinger et al.[5] Anesthesiology 2011: retrospective cohort study in 3,865 cardiac surgical patients (before-and-after implementation of ROTEM-guided therapy) • Esler et al.[15] HAA 2013: prospective study group vs. historic control group (before-and-after implementation of ROTEM-guided therapy in cardiac surgery in Brisbane, Australia; overall reduction in allogeneic blood transfusion requirement by 39.2% and blood product cost-savings of $ 928,998 (48.3%) within one year) • Smith et al.[54] J Cardiothorac Vasc Anesth. 2013: Case report describing the ROTEM-algorithm used in Esler et al.[15] 2013. Since at least ten important papers dealing with ROTEM-guided bleeding management in cardiovascular surgery considered in other recently published systematic reviews	

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				of the literature[1,9,14] are not included in the systematic review of the authors of this manuscript it is not surprisingly that the authors did not report on clear differences in clinical effectiveness between the three VET devices. However, this is not due to an absence of published data but due non-inclusion of these studies into the systematic review. Since most of these studies have been published in well recognized peer-reviewed journal (e.g., BJA and Anesthesiology) this is surprisingly.	
	20.	**144**	**5.1.1**	"With the exception of one small, non-randomised controlled trial (ref. 65: Messenger et al. 2011) all studies conducted in trauma patients or women with PPH included in our systematic review were prediction studies." **Comment (Trauma):** The following publications focusing on clinical effectiveness of TEG/ROTEM-guided therapy in trauma patients are missing in the systematic review of the literature: • Schöchl et al.[3] Crit Care. 2010: retrospective cohort study (therapeutic); observed mortality vs.	All but two of the publications listed were identified by our searches. None of the publications met the inclusion criteria for our review. The main reason for this was the lack of a concurrent control group. As explained in the discussion section (p.157) "We did not include studies of VE devices with a historical control group in our review, as it is not possible to attribute any observed differences between groups in these studies solely to the introduction of the VE device." Specific reasons for exclusion were as follows: Schochl (3): Case series, no control group

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				predicted TRISS mortality • Schöchl et al.[65] Crit Care. 2011: matched-pair analysis (therapeutic); observed transfusion requirements and mortality vs. matched patients from the German Trauma Registry DGU • Nienaber et al.[4] Injury 2011: matched-pair analysis (therapeutic); observed RBC transfusion requirements, incidence of multiple organ failure and mortality vs. matched patients from the German Trauma Registry DGU • Schaden et al.[41] Br J Anaesth. 2013: RCT in burn patients (therapeutic) • Lendemans et al. DKOU 2013 8: retrospective cohort study (before-and-after implementation of a ROTEM-guided algorithm) analysed by the German Trauma Registry DGU (therapeutic) • Johansson et al.[10] Transfusion 2013: retrospective cohort study (before-and-after implementation of	Schochl (65): no VE testing device NIenaber: no VE testing device Schaden (41): patients undergoing surgical excision of burn wounds; not trauma Lendemans: no concurrent control group Johansson (10): no concurrent control group Tapia (11): no concurrent control group. Liver transplantation was not included in the scope of this assessment.

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				a packages and TEG-based algorithm)(therapeutic) • Tapia et al.[11] J Trauma Acute Care Surg. 2013: retrospective cohort study (before-and-after changing from a TEG-based algorithm to a ratio (1:1:1)-based algorithm) (therapeutic) Here, ROTEM-guided therapy showed improved survival rates (33.7 vs. 24.4%; P = 0.032) compared to predicted TRISS mortality in trauma patients published by Schöchl et al.[3] 2010. The incidence of multiple organ failure was significantly reduced (16.7 vs. 61.1%; P = 0.015) in ROTEM-guided trauma patients in the study published by Nienaber et al.[4] 2011. Johansson et al.[10] reported in 2013 a reduction in hemorrhagic trauma deaths after implementation of transfusion packages and early TEG-directed hemastatic resuscitation. Tapia et al.[11] reported in 2013 an increase in mortality (54.1 vs. 33.3; P = 0.04) in patients with penetrating trauma receiving 10 units or more RBC after changing the transfusion management from an individualized TEG-driven protocol to a ratio (1:1:1)-driven massive transfusion protocol. In-hospital mortality (20.9 vs.	

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				38.3%; P = 0.012) and incidence of multiple organ failure (36.3 vs. 66.7%; P = 0.00012) were significantly reduced in the before-and-after study (ROTEM) in trauma patients published by Lendemans et al.[8] in 2013. Since only one abstract (Messenger et al. Anesth Analg. 2011) out of at least eight publications looking at outcome in trauma patients with ROTEM/TEG-guided bleeding management are included in this systematic review, it is not surprisingly that the authors did not find convincing data on clinical effectiveness. This means that 88% of the available literature dealing with outcome in VET-driven bleeding management in trauma has not been considered in this analysis of clinical efficacy (compared to other systematic analyses of the literature published recently [1,34]). **Additional comment:** Publications dealing with cost-savings in liver transplantation have not been considered in the systematic review at all. This might be an additional limitation in describing difference in clinical effectiveness	

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				of the three VET devices (see also [9,14]).	
	21.	**146**	**5.1.1**	"We are not aware of any previous systematic reviews assessing the effectiveness of VE devices for the management of patients with trauma-induced coagulopathy or PPH. " **Comment:** see general comment on the discussion section and missing references, above. The following systematic reviews of the literature and guidelines dealing with this topic have been published recently (and one additional systematic review is under revision in Critcal Care): • Görlinger et al.[1] Curr Opin Anaesthesiol. 2013: Transfusion protocols in cardiac surgery • Haas et al.[9] Minerva Anaesthesiol. 2014: Thromboelastometry for guiding bleeding management of the mritically ill patient • Müller et al.[58] Crit Care. 2014: TEG or ROTEM in	See response above (comment 18)

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				adults with sepsis • Spahn et al. Crit Care.[34] 2013: Updated European Trauma Guidelines • Kozek-Langenecker et al.[14] Eur J Anaesthesiol. 2013; ESA Guidelines on the management of severe perioperative bleeding Besides the missing references for the systematic review of the literature (see comments above), the lack of awareness to the recently published systematic reviews and guidelines may limit the value of the conclusions of the authors regarding the differences in clinical effectiveness between the three VET devices. Of course, this has a direct impact on the conclusions on cost-effectiveness, too.	
	22.	**150**	**5.2.2**	**Comment:** It is difficult to understand that there is such a big number of missing reference (at least 18) and lack of awareness to other systematic reviews of the literature and current guidelines despite this high quality systematic review. Furthermore several assumptions made I this model are unproven, questionable or even inapplicable	See response to previous comments (comments 18, 19, 20 and 6).

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				(e.g., the assumption that mortality between one month and one year is low and that only RBC transfusion increases morbidity and mortality; see comments above).	
	23.	**151**	**5.2.2**	"We decided which assays and number of tests to model based on the combination of assays and numbers of tests used in the trials so that the costs included in the model correspond to the source of the effectiveness data." **Comment:** As discussed above, the selection of test for cost calculation is not in line with published algorithms for ROTEM-guided bleeding management in cardiac surgery [5-7,13,54] and trauma [13,25] as depicted in the comments on page 111-128f. Test cost calculation based on the use of comparable tests for both, the ROTEM and TEG device (EXTEM – rapid TEG; FIBTEM – functional fibrinogen; INTEM – kaolin TEG; HEPTEM – heparinase TEG), leads to completely different results in test cost calculation and subsequent cost-effectivness analysis (see calculations in the comments on page 111, table 28 and page 123, table 36). Similar diagnostic performance between both VET devices can only be assumed if similar test panels are used.	See response to earlier comments (comments 10 and 11).

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				Here, the importance of FIBTEM and functional fibrinogen have been pointed out by several ROTEM and TEG users for bleeding management in cardiac surgery, liver transplantation, trauma, and postpartum hemorrhage [10,23-37]. However, this quite expensive TEG test (£8.33) is not included in any test cost calculation, here.	
	24.	**151**	**5.2.2**	"A major limitation of both models was the lack of data on the effectiveness of the Sonoclot device. None of the RCTs included in our review assessed this device. As the only difference in the models was the costs of the devices, and Sonoclot was the cheapest device, Sonoclot was the most likely to be cost-effective. However, this should be interpreted with extreme caution due to the lack of evidence." **Comment:** I agree that characterizing the Sonoclot device as the "most cost-effective" device as to be interpreted with extreme caution since it is based on the assumption of similar clinical effectiveness, solely, which is not supported by any data. In principle, cost-effectiveness cannot be certified without any proof of clinical	No response needed

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				effectiveness. Here we are just talking about the cheapest device without any proof of clinical effectiveness. Therefore, the characterization of the Sonoclot device as the "most cost-effective" device might lead to misinterpretation in readers who do not read the paper carefully.	
	25.	**152**	**5.2.2**	"There were no data on the clinical effectiveness of any of the VE devices in trauma patients." **Comment:** This statement is inapplicable and an important limitation of this study (see **comments on page 143-146** and the **updated European Trauma Guidelines** published in 2013 [34]).	See response to earlier comments (comment 20).
	26.	**153**	**5.2.2**	**"**EVPI" **Comment:** The abbreviation EVPI (Expected Value of Perfect Information) is neither explained in the list of abbreviations (page 12) nor at any other part of the manuscript. I assume that not all clinicians are familiar with this term and therefore, the term EVPI should be added to	EVPI will be added to the list of abbreviations. It was defined in full the first time that it was used (p.127).

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				the list of abbreviations.	
	27.	**154**	**5.3.1**	"Our systematic review included one small (n=50) controlled clinical trial which compared the effectiveness of an 'institutional massive transfusion protocol' (details not reported) to a TEG-guided protocol (details not reported) for the management of trauma patients (Messenger 2011)." **Comment:** As already mentioned above (see comments on page **144**) at least seven publications reporting on outcome in ROTEM-guided bleeding management in trauma have not been recognized and/or included in the systematic review of the literature. However, I completely agree "that further investigation of the clinical utility of VE devices in trauma patients and women with PPH is warranted."	See earlier responses (comment 20)
	28.	**157**	**5.3.2**	"The influence of RBC transfusion on longer term mortality (beyond in hospital mortality) in trauma patients is also	See earlier response to comments (comment 6).

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				unclear." **Comment:** There is increasing evidence that not only RBC transfusion but also FFP and platelet transfusion is associated with increased short-term and long-term morbidity and mortality (see comments on page 95ff). This should be considered in future models.	
	29.	**158**	**6.1**	"The available data did not support an improvement in clinical outcomes (re-operation, surgical cause of bleed on re-operation and mortality), or length of hospital stay, for patients managed using VE testing compared with those managed using SLTs." **Comment:** This might be changing after including the data from the 18 studies missing in the systematic review performed, here (see comments above).	See earlier response to comments; these studies did not meet our inclusion criteria (comments 19 and 20).
	30.	**158**	**6.1**	"The per-patient cost-saving was slightly smaller for ROTEM (£43) than for TEG (£79) and Sonoclot (£132). This finding was entirely dependent on material costs which were slightly higher for ROTEM."	See earlier response to comments (comments 10 and 11).

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				Comment: see comments on page 111-128f and 151.	
	31.	**158**	**6.1**	"There was no evidence on the clinical effectiveness of VE testing, using any device, in trauma patients." **Comment:** see comments on page 144 and 154.	See earlier response to comments (comment 20).
	32.	**159**	**6.2**	"No studies providing data on the clinical effectiveness of Sonoclot were identified in any of the populations considered by this assessment (patients undergoing cardiac surgery, trauma patients and women with PPH). Therefore, if the adoption of Sonoclot were to be considered, trials of this device would have high priority." **Comment:** I completely agree. However, I assume that the motivation of the manufacturer of Sonoclot to initiate any studies providing evidence for clinical effectiveness of the device will even be lower after this diagnostic assessment report since the authors already attested this device the highest "cost-effectiveness". Therefore, further studies cannot improve the rating of this device regarding "cost-effectiveness" but may disprove the assumption of the authors that Sonoclot shows similar clinical effectiveness	No response needed

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				compared to ROTEM and TEG.	
	33.	**159**	**6.2**	"Clinical trials are urgently required in these populations (trauma and PPH), in order to assess the effectiveness of VE testing compared with management based on SLTs." And "Future trials should include longer term follow-up, beyond the initial hospital episode, with a view to informing improved cost-effectiveness modelling." **Comment:** I completely agree, and further RCTs are already planned or even running.	No response needed.
	34.	**161**	**7**	**Additional references cited in the comments:**	Moved to separate document to save space.
NHS Professional	**35.**	**111** **123**	**Table 28** **Table 36**	The comparison of the cost of ROTEM and TEG tests has assumed that four ROTEM tests would be undertaken at each time point in cardiac surgery but only two TEG tests, and that three ROTEM tests would be undertaken at each time point in trauma patients but only one TEG test. This is not a valid comparison and leads to the false conclusion that testing with ROTEM is more expensive than is actually the case.	We have modelled the test combinations that were evaluated in the studies included in the clinical effectiveness review. We appreciate that these may not be reflective of clinical practice but we did not feel that we could assume that the estimates of effectiveness would apply to different assay combinations. See response to comments 10 and 11 for a more detailed

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				The manufacturer of the ROTEM analyser has promoted the concept of it often being useful to obtain more detailed information about haemostasis by using additional tests rather than simply looking at the shape of the curve produced by a single test. However, a single ROTEM test will provide every bit as much information as a single TEG test. We have many years experience of the use of both ROTEM and TEG analysers. Most ROTEM users will not routinely perform four different ROTEM tests on each blood sample (except perhaps in research studies). There are equivalent tests for the ROTEM and TEG analysers that provide the user with the same information on the abnormalities of haemostasis. The equivalent tests are: 1. ROTEM Intem test with one cup & pin and TEG Kaolin vial with plain cup & pin 2. ROTEM Extem test with one cup & pin and TEG Rapid TEG with plain cup & pin	response.

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				2. ROTEM Heptem test with one cup & pin and TEG Heparinase cup & pin 3. ROTEM Fibtem test with one cup & pin and TEG Functional fibrinogen assay with plain cup & pin A comparison of the cost of using the two analysers should compare the same number of tests and the equivalent tests for each analyser.	
	36.	**19** **20** **130** **137**	**4** **5** **4.5.1** **4.5.4**	As a result of the above issue with the comparison of costs of ROTEM and TEG tests, the figures for the comparative costs of testing with the two analysers given elsewhere in the document are misleading	See response above (comment 35).
Royal College of Nursing	**37.**			This is to inform you that there are no comments to submit on behalf of the Royal College of Nursing to inform on the Diagnostic Assessment Report for the above technology.	No response needed.
Roche Diagnostics	**38.**	**34**	**2.3**	This section is a good description of platelet function testing (PFT). It may be beneficial to mention the reasons	No response needed

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				for performing PFT tests in patients undergoing cardiac surgery and receiving antiplatelet medication: platelet function testing using Multiplate has been shown to predict bleeding in patients on dual anti-platelet therapy undergoing CABG ((Ranucci et al., 2011) or PCI (Sibbing et al., 2010). Recent guidelines support to use platelet function testing in order to decide on the preoperative waiting period for patients on dual antiplatelet therapy undergoing cardiac and non-cardiac surgery (IIa recommendation in Ferraris et al., 2012). References: Ferraris, V. A., Saha, S. P., Oestreich, J. H., Song, H. K., Rosengart, T., Reece, T. B., et al. (2012). 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. [Practice Guideline]. The Annals of thoracic surgery, 94(5), 1761-1781. Ranucci, M., Baryshnikova, E., Soro, G., Ballotta, A., Benedetti, D. D., Conti, D., et al. (2011). Multiple electrode whole-blood aggregometry and bleeding in cardiac surgery patients receiving thienopyridines. Ann Thorac Surg, 91(1),	

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				123-129. Sibbing, D., Schulz, S., Braun, S., Morath, T., Stegherr, J., Mehilli, J., et al. (2010). Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. J Thromb Haemost, 8(2), 250-256	
	39.	**36**	**2.5**	The description of the current care pathway in 2.5.1 (p. 36) highlights the need to balance the risk of bleeding during surgery with the risk of adverse events when delaying surgery for patients taking anticoagulant or antiplatelet medications (clopidogrel, warfarin, and aspirin). Recent guidelines (Ferraris et al., 2012) supporting the use of preoperative platelet function testing for patients on dual antiplatelet therapy undergoing cardiac and non-cardiac surgery could be cited here.	No response needed
Haemonetics	**40.**	**33**	**2.2 Intervention technologies**	MRTG (Maximum Rate of Thrombin Generation), TMRTG (Time for Maximum Rate of Thrombin Generation) and total Thrombus Generated (TG) TEG parameters that are obtained from the TEG velocity curves (V-Curves) are	Thank you this will be corrected.

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				missing	
	41.	**33**	**2.2 Intervention technologies**	In the "Lysis at fixed time" it should be read in the TEG column "Lysis in 30, 60 minutes (LY30, LY60)" and not "Clot lysis (CL)30, CL45, CL60"	Thank you this will be corrected.
	42.	**33**	**2.2 Intervention technologies**	In the initial clot/fibrin formation line in the TEG column it should be read R or ACT instead of just R	Thank you this will be corrected.
	43.	**33**	**2.2 Intervention technologies**	In the "time to lysis" row it should be read in the TEG column "Clot Lysis Time (CLT) (2mm drop from MA)" instead of "Time to lysis (TTL) (2mm drop from MA)"	Thank you this will be corrected.
	44.	**34**	**2.3 Platelet function tests**	The TEG Platelet Mapping(PLM) test has been used in prospective studies to predict increased blood loss and transfusion requirement in cardiac surgery patients by identifying the differential platelet inhibition rates in response to dual anti-platelet therapy with clopidogrel and	No response needed

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				aspirin.1,2,3 Furthermore, a TEG PLM guided strategy reduced the waiting period of clopidogrel-treated patients by nearly 50% without increased bleeding, transfusion rates or adverse cardiac events.3 Current guidelines recommend discontinuing clopidogrel and other antiplatelet drugs five days prior to surgery in order to avoid excessive perioperative bleeding.4 However, there is a variable response to these drugs (approximately 30% of patients do not respond to clopidogrel) as well as a variable recovery of platelet function following cessation of therapy. This suggests that an objective measurement of the antiplatelet effect of clopidogrel before surgery may obviate the need for the recommended waiting period in a substantial number of patients.5-7 Considering this evidence, the Society of Thoracic Surgeons recommends (Class IIa) using platelet function testing to assist in the timing of surgery.4 1. Kwak, YL et al. J Am Coll Cardiol. (2010) Dec 7;56(24):1994-2002 2. Preisman, S et al. European Journal of Cardio-thoracic Surgery 37 (2010) 1367—1374	

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				3. Mahla E et al., Circ Cardiovasc Interv (2012);5:261-269 4. Ferraris et al, Society of Thoracic Surgeons. Ann Thorac Surg (2012);94:1761-81 5. Price et al. Am J Cardiol (2006);98:681-684 6. Price et al. Am J Cardiol 2008;102:790-795 7. Price et al. J Am Coll Cardiol 2012;59:2338-2343	
	45.	**144**	**5.1.1 Clinical effectiveness**	It might be worth the reference the statement "These studies either reported the predictive accuracy of different VE device parameters and/or SLTs with a reference standard consisting of clinical outcome or measure of transfusion requirements.": • Cotton et al. J Trauma. (2011);71: 407–417) • Van et al. J Trauma. (2009);66:1509–1517. • Cotton et al. J Trauma Acute Care Surg. (2012);72(6):1470-5; discussion 1475-7.	We don't think this needs a reference as the section reports all included studies.
	46.	**144**	**5.1.1 Clinical effectiveness**	Furthermore, a hypercoagulable status identified by TEG in trauma patients is predictive of pulmonary embolism (PE) and deep venous thrombosis (DVT) • Van et al. J Trauma. (2009);66:1509–1517.	We will consider adding these references.

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				• Cotton et al. J Trauma Acute Care Surg. (2012);72(6):1470-5; discussion 1475-7	
	47.	**155**	**5.3.1 Clinical effectiveness**	It should be used the reference Kashuk et al Transfusion. (2012) Jan;52(1):23-33. for the discussed rTEG results instead of the reference 64 (Moore E. A prospective, randomized comparison of rapid thrombelastography (r-TEG) and conventional coagulation testing for guiding the diagnosis and hemostatic resuscitation of trauma patients at risk for post-injury coagulopathy (NCT 01536496) [Trial protocol: COMIRB No.: 10-0477]. Denver, US: Denver Health and Hospital Authority 2012/11/26. 48p.)	Thank you this will be corrected.