

## Original Article

# TEG<sup>®</sup> 6s—Guided Algorithm for Optimizing Patient Blood Management in Cardiovascular Surgery: Systematic Literature Review and Expert Opinion



Courtney Maxey-Jones, MD<sup>\*</sup>, Troy G. Seelhammer, MD<sup>†</sup>,  
 Francisco A. Arabia, MD<sup>‡</sup>, Brian Cho, MD<sup>§</sup>,  
 Bradford Cardonell, MD<sup>||</sup>, Daniel Smith, MD<sup>¶</sup>,  
 Vincenzo Leo, PhD<sup>\*\*</sup>, Joao Dias, PhD<sup>\*\*</sup>,  
 Linda Shore-Lesserson, MD<sup>††</sup>, Jan Hartmann, MD<sup>\*\*1</sup>

<sup>\*</sup>CNY Medical Services, PLLC, Baldwinsville, NY

<sup>†</sup>Mayo Clinic, Rochester, MN

<sup>‡</sup>Banner Health, Phoenix, AZ

<sup>§</sup>Johns Hopkins University, Baltimore, MD

<sup>||</sup>University of Missouri Columbia, Columbia, MO

<sup>¶</sup>Spectrum Healthcare Partners, Portland, ME

<sup>\*\*</sup>Haemonetics Corporation, Boston, MA

<sup>††</sup>Northwell, New Hyde Park, NY; and Anesthesiology, North Shore University Hospital, Manhasset, NY

**Objectives:** To propose a comprehensive TEG 6s—based intraoperative and/or immediately postoperative treatment algorithm for bleeding patients undergoing cardiac surgery. To achieve this, TEG-based treatment algorithms in cardiac surgery were evaluated through a literature review and structured expert opinion.

**Design:** Systematic literature review.

**Setting:** Cardiac surgery.

**Participants:** Adult patients undergoing cardiac surgery with intraoperative and/or immediately postoperative bleeding.

**Interventions:** TEG-guided transfusion algorithm.

**Measurements and Main Results:** A literature search was conducted for original studies reporting TEG-based treatment algorithms in cardiac surgery settings. Of 304 identified manuscripts, fourteen met all inclusion criteria, with two further articles identified through authors' suggestions. There is limited evidence describing the use of TEG 6s assays in cardiac surgery with only one study reporting a dedicated algorithm using the TEG 6s device at a non-US center. Two additional studies assessed TEG 6s assays. The remaining manuscripts reported algorithms based on the TEG 5000 device. Following the author's review of the available data, and feedback from expert opinion, a simple transfusion algorithm was proposed as an initial framework for developing a TEG 6s—based protocol with consideration for the 2021 Society of Thoracic Surgery/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology/Society for the Advancement of Patient Blood Management Patient Blood Management Guidelines.

**Conclusions:** A new algorithm for cardiac surgery based on TEG 6s assays has been proposed based on the available evidence and expert opinion for research alignment and clinical validation.

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**Key Words:** thromboelastography; TEG 6s; transfusion; cardiac surgery; hemostasis; PBM; patient blood management

<sup>1</sup>Address correspondence to Jan Hartmann, MD, Chief Medical Officer, Haemonetics Corp, Boston, MA 02110.  
 E-mail address: [jan.hartmann@haemonetics.com](mailto:jan.hartmann@haemonetics.com) (J. Hartmann).

CARDIAC SURGERY IS ASSOCIATED with large blood loss and transfusion requirements, particularly in procedures requiring cardiopulmonary bypass (CPB). Real-world data suggest that approximately 50% of patients undergoing cardiac surgery require perioperative blood product transfusion.<sup>1</sup> In the United States, blood transfusions administered during cardiac surgery represent up to 10% to 15% of all blood products used nationwide.<sup>2,3</sup> Allogeneic blood product transfusions can be associated with increased adverse outcomes such as an elevated risk of infections, respiratory complications, acute kidney injury as well as increased risk of mortality.<sup>4,5</sup> Many guidelines, including Practice Guidelines for Perioperative Blood Management by the American Society of Anesthesiologists Task Force on Perioperative Blood Management,<sup>6</sup> recommend the application of transfusion algorithms incorporating predefined intervention triggers based on point-of-care (POC) coagulation monitoring assays to guide hemostatic intervention in bleeding patients and to improve the management of perioperative coagulopathic bleeding.<sup>6–8</sup> However, despite these ongoing efforts, blood transfusion rates in cardiac surgery have seen only modest decline over the past decade, with high-risk patients representing a particularly vulnerable population.<sup>9</sup> Furthermore, there is still a significant variability in patient transfusion practices across different institutions and adherence to the guidelines is overall poor.<sup>9</sup>

Over the past few decades, POC coagulation monitors have become more prevalent. However, these are still not widely available across every institution.<sup>9</sup> Many clinical studies and meta-analyses have demonstrated the benefits of using POC viscoelastic hemostatic assays (VHA) such as thromboelastography during cardiac surgery.<sup>10–12</sup> In particular, these studies suggest that VHA-guided algorithms may be beneficial in reducing the requirement for allogeneic transfusion of red blood cells, fresh frozen plasma, and platelets, as well as in reducing postoperative blood loss<sup>12</sup> and blood loss within 24 hours after surgery.<sup>13</sup> The first thromboelastography-based algorithm used to guide transfusion therapy in complex cardiac surgery was proposed in 1999 in a study by Shore-Lesserson et al.<sup>14</sup> The study demonstrated a reduction in transfusion requirements with better hemostasis control in patients using the TEG 5000 device (Haemonetics Corp., Boston, MA). Since then, the TEG 5000 system has played an important role in clinical practice, with many institutional algorithms proposed for use in cardiac surgery developed using this technology.<sup>15–18</sup> Based on these studies, the 2021 Society of Thoracic Surgery/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology/Society for the Advancement of Patient Blood Management Patient Blood Management Guidelines now include a Class I recommendation to use goal-directed transfusion algorithms that incorporate point of care testing, specifically referring to viscoelastic devices.<sup>19</sup> Similarly, the 2024 European Association for Cardio-Thoracic Surgery/European Association of Cardiothoracic and Vascular Anaesthesia and Intensive Care Guidelines on patient blood management in adult cardiac surgery in

collaboration with EBCP also gives a Class I recommendation for an interdisciplinary algorithm/protocol for transfusion, anticoagulation, and thrombosis and a further Class I recommendation that a viscoelastic POC test be performed at least daily alongside laboratory blood tests.<sup>20</sup>

The latest generation platform—the TEG 6s device—was introduced to the European market in 2014 and to the United States in 2016. The TEG 6s system has increased portability and enhanced usability compared with the TEG 5000 device, enabling clinicians to receive real-time results and adjust patient treatment as required. The device is also designed to be easier to use than the TEG 5000, with enhanced ease of operation achieved through fully automatic cartridge-based assays. These assays require a reduced quantity of blood and can be operated with less extensive training than its predecessor.<sup>21,22</sup> The TEG 6s runs four assays simultaneously in a single “citratd multichannel” cartridge:

1. Citrated kaolin (CK) assay in which the contact activation coagulation pathway is activated using kaolin;
2. Citrated kaolin with heparinase, allowing identification and assessment of the effects of heparin and heparinoids on coagulation;
3. Citrated RapidTEG (CRT) in which the addition of tissue factor to kaolin accelerates clotting, and
4. Citrated functional fibrinogen (CFF) in which the fibrin/fibrinogen contribution to clot strength is measured by glycoprotein IIb/IIIa inhibitor elimination of the platelet component.<sup>22</sup>

Together, these assays provide an overview of the coagulation status and relative contributions of coagulation factors, platelets and fibrin to the clot. The reference ranges for these assays, on the TEG 5000, TEG 6s citrated multichannel (CM) cartridge, and the recently cleared Global Hemostasis-HN (heparin neutralization) cartridge, are shown in [Table 1](#). Adopting the newer TEG 6s technology requires that centers design and validate updated treatment algorithms; however, the extent to which this shift has occurred is unclear.

Therefore, we aimed to develop a comprehensive TEG 6s-based treatment algorithm that can be used as a starting point to guide intraoperative and/or immediate postoperative hemostatic intervention in cardiac surgery patients. To achieve this, expert opinion was gathered during an advisory board session and subsequently analyzed alongside a systematic literature review to identify evidence for using TEG 5000 and TEG 6s treatment algorithms.

## Methods

### Expert Opinion

The use of TEG in cardiac surgery formed the basis of a virtual advisory board to review the available evidence, understand the differences between the TEG 5000 and TEG 6s

Table 1  
Overview of Different TEG Analyzers and Cartridges

|                                                                            | TEG 5000                                                                                                                                                                                                                                                                                                                                                | TEG 6s with Citrated Multichannel (CM) cartridge                                                                                                                                                                                                                          | TEG 6s with Global Hemostasis-HN (heparin neutralization) cartridge                                                                                                                                                                                                      |
|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Technical description                                                      | Mechanical measure of coagulability using a rotating cup with a static pin                                                                                                                                                                                                                                                                              | Uses resonance frequency to measure whole blood viscoelasticity                                                                                                                                                                                                           | Uses resonance frequency to measure whole blood viscoelasticity                                                                                                                                                                                                          |
| FDA cleared channels, parameters and references ranges for citrated blood* | Kaolin reagent<br>R (min): 5–10<br>K (min): 1–3<br>$\alpha$ -angle (deg): 53–72<br>MA (mm): 50–70<br>Heparinase cups and pins<br><i>Sold separately, no official reference ranges</i><br>RapidTEG reagent<br>R (sec): 22–44<br>K (sec): 34–138<br>$\alpha$ -angle (deg): 64–80<br>MA (mm): 52–71<br>Functional fibrinogen reagent<br>MA (mm): 11.5–31.6 | Citrated kaolin<br>R (min): 4.6–9.1<br>K (min): 0.8–2.1<br>$\alpha$ -angle (deg): 63–78<br>MA (mm): 52–69<br>Citrated Kaolin with heparinase<br>R-value (min): 4.3–8.3<br><br>Citrated RapidTEG<br>MA (mm): 52–70<br><br>Citrated functional fibrinogen<br>MA (mm): 15–32 | Citrated kaolin<br>R (min): 4.6–9.1<br>MA (mm): 52–69<br><br>Citrated Kaolin with heparinase<br>R-value (min): 4.3–8.3<br>LY30 (%): 0–3.2<br>Citrated RapidTEG with heparinase<br>MA (mm): 53–69<br><br>Citrated functional fibrinogen with heparinase<br>MA (mm): 15–34 |

\*Note that the TEG 5000 can run non-citrated blood, however the TEG 6s cannot. All results used for the algorithm are therefore based on citrated blood samples.

Abbreviations: MA, clot strength (Maximum Amplitude); R, reaction time.

devices, and gather insights from experts in the field to establish a TEG 6s–based algorithm for hemostatic management of bleeding patients undergoing cardiac surgery. Seven experts (cardiac anesthesiologists, anesthesiologists, critical care physicians, and cardiothoracic surgeons) participated in the discussions, and their input was instrumental in developing the algorithm.

### Systematic Literature Review—Search Strategy

A systematic literature review was performed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) guidelines.<sup>23</sup> A PubMed and EMBASE literature search was carried out for original studies published from January 2009 to June 2024, reporting the use of TEG 5000– and TEG 6s–based intraoperative and/or immediately postoperative treatment algorithms in cardiac surgery settings. The search terms that were used to capture relevant publications included: *thromboelastography, TEG, TEG6S/TEG 6s, TEG5000/TEG 5000 and cardiac surgery, heart surgery, cardiothoracic surgery, cardiopulmonary bypass/CPB, valve replacement, aortic surgery, coronary artery bypass graft/CABG, and left ventricular assist device/LVAD*. Full search strings that were used to capture relevant publications are provided in [Supplementary Table 1](#).

### Study Selection and Inclusion Criteria

Study eligibility criteria were defined using the Population, Intervention, Comparator, and Outcomes (PICO) framework and the inclusion/exclusion criteria applied are described in [Supplementary Table 2](#). Articles were screened to capture

original research articles, including retrospective and prospective observational studies and randomized controlled trials (RCTs) using TEG assays to assess coagulation status and guide hemostatic therapy. One independent researcher (B.V.), conducted the screening, and all articles were checked by a second researcher (S.G.). All authors reviewed the final screening list for final approval. Additionally, authors were asked for any further suggestions for inclusion based on their clinical experience.

### Data Extraction and Synthesis

Transfusion recommendations from the published algorithms were extracted using a standardized Excel spreadsheet form by one independent researcher (B.V.); and a second researcher (S.G.) provided a data check. A summary of recommendations for TEG-based intraoperative and/or immediately postoperative monitoring of hemostasis and transfusion of blood products/administration of pharmacological treatments in cardiac surgical patients was presented in a table format.

Following the authors' review of the available data and expert opinion, a practical algorithm based on the TEG 6s coagulation assays was developed. Given the lack of validated data from RCTs, the predefined TEG assay intervention triggers for the algorithm were suggested following a hierarchical decision process as follows: published data with TEG 6s device were prioritized; if not available, TEG 5000 assay parameters were used if the measured parameter was available on the new TEG 6s device; and finally, more recent articles were prioritized over older studies, as these were expected to better reflect the current clinical practice and the more modern testing environment. If the published data were insufficient

or inconclusive, expert opinion was incorporated to ensure the algorithm was comprehensive and clinically relevant.

## Results

Overall, our literature search yielded 223 unique articles from PubMed and 81 unique articles from Embase databases. An initial title and abstract screen against *a priori* determined inclusion/exclusion criteria excluded 176 publications, with 28 undergoing a full-text review. Of these, 14 publications presented TEG-based treatment algorithms meeting the inclusion criteria, alongside two additional articles identified through author suggestions. The characteristics of all 16 included studies are summarized in Table 2. Only three identified studies included data on TEG 6s device use in cardiac surgery, none of which were from US centers.

Only one of the included articles reported a dedicated algorithm utilizing the TEG 6s device. Rigal et al. (2019) described a protocol for the ongoing IMOTEC study (NCT02972684) to assess the cost-effectiveness of VHA-guided management of patients with ongoing bleeding during cardiac surgery with CPB.<sup>25</sup> This ongoing multicenter study is designed to leverage the latest version of TEG (TEG 6s) or ROTEM devices (ROTEM Sigma) with TEG- and ROTEM-guided algorithms based on previously published protocols utilizing the older device models. The IMOTEC study is based in France and uses the CE marked TEG 6s analyzer.<sup>25</sup> A study by Magunia et al. (2020), although not describing a whole treatment algorithm, identified a TEG 6s maximum amplitude of citrated functional fibrinogen assay (CFF-MA) cut-off value to identify hypofibrinogenemia (i.e., fibrinogen plasma level below 150 mg/dL) and to guide fibrinogen concentrate substitution in adult patients undergoing cardiac surgery.<sup>24</sup> Finally, Wong et al. (2020), described a TEG 5000–based management algorithm for cardiac surgery and also analyzed the TEG 5000 and TEG 6s parameters interchangeability in paired arterial blood samples from patients undergoing cardiac surgery at the same center.<sup>26</sup> The authors of this report conclude that using the TEG 6s with their current TEG 5000–based management algorithm for cardiac surgery would result in a change in treatment recommendation in at least 10% of their cardiac surgical patients.<sup>26</sup>

The remaining 11 studies reported algorithms based on TEG 5000 measurements. Transfusion thresholds and recommendations from the published algorithms are summarized in Table 3.

### *Intraoperative and/or Immediately Postoperative TEG-Based Algorithm for Cardiac Surgery*

We have reviewed multiple published transfusion algorithms and summarized recommendations that are widely accepted and easy to apply in the suggested hemostatic management algorithm as presented in Fig 1. The presented algorithm is derived from the previously described available published literature while incorporating a set of suggestions that integrates expert opinion of the authors and can be modified according to the clinical needs or institutional limitations.

Threshold algorithm values may differ across different practices, and the attending healthcare professionals should always make the final decision for treatment considering the full clinical picture. The proposed algorithm is for cases of active or suspected coagulopathy, such as when excessive microvascular bleeding occurs. The algorithm evaluates residual heparin effects, fibrinolysis, coagulation factor deficiencies and platelet and fibrinogen deficiencies using the TEG 6s assays. The most critical issue should be treated first to stabilize the patient or prevent further deterioration. Furthermore, the authors suggest using a unit-based algorithm due to its simplicity, ease of understanding and a higher likelihood of adherence than weight-based transfusion protocols.

**Heparin reversal:** Most published algorithms recommend additional protamine administration if the R time is at least twice as long as R with heparinase (R-hep), indicating residual heparin in the blood. This cut-off value is historically based on studies using TEG 5000 assays, and since R time is the most user-dependent parameter, greater variability in this parameter was expected. However, as the TEG 6s device is less user-dependent,<sup>26</sup> a suggested 1.25-fold difference between R and R-hep to trigger additional protamine administration<sup>36</sup> as recommended by the Society of Cardiovascular Anesthesiologists Clinical Practice Improvement Advisory<sup>9</sup> seems appropriate.

**Coagulation factor deficiency:** Elevated R time implies deficiency in clotting factors and clinicians should consider repleting coagulation factors with either prothrombin complex concentrate (PCC) or with plasma depending on institutional and regional practice. The cut-off values for intervention were taken from the values in the newest published algorithm,<sup>30</sup> as per our prioritization matrix described in the methods. The following recommended PCC dosing was arrived at by expert opinion and is based upon using the 4-factor non-activated PCC formulations. R times between 10 and 12 minutes suggest a mild coagulation factor deficiency/dysfunction and may be treated with either 2 U plasma or 12 to 15 U/kg PCC. R time of 13 to 15 minutes suggests a moderate coagulopathy and may be treated with either 3 U plasma or 15 to 20 U/kg PCC. R time longer than 15 minutes suggests severe factor deficiency and recommended treatment is 4 U plasma or 20 to 25 U/kg PCC. These doses allow for the use of an entire vial of the closest matching dose where appropriate.

**Deficiency in platelet contribution to clot strength:** Decreased CRT-MA, in the presence of normal CFF-MA, serves as an indicator of low platelet count or platelet dysfunction; therefore, in this instance clinicians should consider platelet transfusion. The intervention trigger values were derived from Lanigan et al.,<sup>30</sup> as per our prioritization matrix described in the methods. Based on this and expert opinion, our algorithm includes: MA between 48 and 50 mm suggests mild platelet dysfunction warranting consideration of desmopressin administration; MA between 43 and 47 mm indicates moderate platelet dysfunction, recommending transfusion of 1 U platelets along with desmopressin; and MA less than or equal to 42 mm indicates severe platelet dysfunction with recommended transfusion of 2 units of platelets along with desmopressin.

Table 2  
Summary of the Identified Studies

| Citation                                                 | Study Type                        | Population Size | Type of Surgery                                             | TEG Model           | TEG Assays      | Time of TEG Analysis                                                                                                                      |
|----------------------------------------------------------|-----------------------------------|-----------------|-------------------------------------------------------------|---------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Studies reporting algorithms with TEG 6s device</b>   |                                   |                 |                                                             |                     |                 |                                                                                                                                           |
| Magunia H, et al. (2020) <sup>24</sup>                   | Retrospective observational study | 423 patients    | Cardiac surgery with CPB                                    | TEG 6s              | Citrated kaolin | Not reported                                                                                                                              |
| Rigal JC, et al. (2019) <sup>25</sup>                    | Prospective pragmatic RCT         | NA              | Protocol for the RCT                                        | TEG 6s              | Citrated kaolin | Abnormal bleeding, > 10 min post-protamine or >30 min after ICU admission                                                                 |
| Wong Q, et al. (2020) <sup>26</sup>                      | Prospective RCT                   | 99 patients     | 243 matched blood samples                                   | TEG 5000 vs TEG 6s  | Kaolin, FF      | Before anesthesia and 9 min post-protamine                                                                                                |
| <b>Studies reporting algorithms with TEG 5000 device</b> |                                   |                 |                                                             |                     |                 |                                                                                                                                           |
| Agarwal S, et al. (2015) <sup>15</sup>                   | Prospective RCT                   | 249 patients    | CABG                                                        | TEG 5000            | Kaolin, FF      | 10 min post-protamine                                                                                                                     |
| Ak K, et al. (2009) <sup>27</sup>                        | Prospective RCT                   | 224 patients    | CABG                                                        | TEG 5000            | Kaolin          | Before anesthesia (baseline); after start of CPB; 15 mins after administration of protamine; on admission to ICU); 6 h and 24 h after CPB |
| Aksun M, et al. (2021) <sup>16</sup>                     | Single center prospective RCT     | 200 patients    | CABG                                                        | Not reported        | Kaolin          | After CPB and a t least once in ICU (within 3 h)                                                                                          |
| Aoki K, et al. (2012) <sup>28</sup>                      |                                   | 100 patients    | Cardiac surgery with CPB                                    | TEG 5000            | Kaolin          | 20 min post-protamine                                                                                                                     |
| Fleming K, et al. (2017) <sup>17</sup>                   | Retrospective observational study | 681 patients    | Complex cardiac surgery                                     | TEG 5000            | Kaolin          | 10 min post-protamine                                                                                                                     |
| Lanigan M, et al. (2022) <sup>29</sup>                   | Retrospective observational study | 68 patients     | LVAD placement, heart transplant                            | TEG 5000            | Kaolin          | Post-protamine                                                                                                                            |
| Lanigan M, et al. (2024) <sup>30</sup>                   | Prospective observational study   | 184 patients    | CABG, aortic and/or valve replacement, repair surgery       | TEG 5000            | Kaolin          | Post-protamine                                                                                                                            |
| Ranucci M, et al. (2009) <sup>31</sup>                   | Retrospective observational study | 7988 patients   | Cardiac surgery                                             | TEG 5000            | Not reported    | Post-CPB/in ICU in case of microvascular bleeding                                                                                         |
| Raphael J, et al. (2019) <sup>9</sup>                    | Guidelines/Recommendations        | Not applicable  | Cardiovascular surgery with expected significant blood loss | TEG 5000            | Not reported    | During rewarming phase of bypass, in the presence of excessive microvascular bleeding                                                     |
| Redfern RE, et al. (2019) <sup>32</sup>                  | Retrospective observational study | 677 patients    | CABG, valve repair/replacement, aortic arch/root repair     | TEG 5000            | Kaolin          | Post-protamine                                                                                                                            |
| Redfern RE, et al. (2020) <sup>33</sup>                  | Retrospective observational study | 1098 patients   | CABG                                                        | TEG 5000            | Kaolin          | Post-protamine                                                                                                                            |
| Welsh KJ, et al. (2014) <sup>34</sup>                    | Protocol review                   | Not applicable  | Not applicable                                              | TEG (not specified) | Not reported    | At the rewarming just before discontinuation of CPB and 10 min post-protamine                                                             |
| Westbrook A, et al. (2009) <sup>35</sup>                 | Prospective RCT                   | 69 patients     | Cardiac surgery                                             | TEG 5000            | Kaolin          | Before CPB, during rewarming, and 15 min post-protamine                                                                                   |

Abbreviations: CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; FF, functional fibrinogen; ICU, intensive care unit; LVAD, left ventricular assist device; RCT, randomized controlled trial; TEG, thromboelastography with TEG analyzer.

Table 3  
Summary of Transfusion Recommendations From the Published Algorithms

| Citation                                                 | Protamine                                                                   | FFP                                                                                             | Cryoprecipitate/Fibrinogen Concentrate             | Platelets                                                                                                                              | Antifibrinolytics                                          | Additional Notes                                                                                                   |
|----------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>Studies reporting algorithms with TEG 6s device</b>   |                                                                             |                                                                                                 |                                                    |                                                                                                                                        |                                                            |                                                                                                                    |
| Magunia H, et al. (2020) <sup>24</sup>                   |                                                                             |                                                                                                 | FF-MA <19.9 mm fibrinogen 50 mg/kg                 |                                                                                                                                        |                                                            |                                                                                                                    |
| Rigal JC, et al. (2019) <sup>25</sup>                    | R > 2 × R-hep: 30 U/kg                                                      | R > 10 min AND R-hep > 10 min: 10–15 mL/kg FFP or 12.5 U/kg PCC if volume expansion not needed  | FF-MA <17 mm AND MA >47 mm: fibrinogen 20–50 mg/kg | MA <48 mm AND FF-MA >16 mm: 1 PLT pool                                                                                                 | LY30 >3%:<br>TxA 1–2 g                                     |                                                                                                                    |
| Wong Q, et al. (2020) <sup>26</sup>                      | hTEG looks “more normal” than TEG - additional Protamine 50 mg              | R 11–14 min: 7 mL/kg (1 U/35 kg)<br>R > 14 min: 15 mL/kg (2 U/35 kg)                            |                                                    | MA <40 mm: PLT 2 U<br>MA 40–50 mm: PLT 1 U<br>Suspect vWF consider DDAVP 0.3 µg/kg                                                     |                                                            |                                                                                                                    |
| <b>Studies reporting algorithms with TEG 5000 device</b> |                                                                             |                                                                                                 |                                                    |                                                                                                                                        |                                                            |                                                                                                                    |
| Agarwal S, et al. (2015) <sup>15</sup>                   | R > 2 × R-hep: 50 mg                                                        | R 10–14 min: 8 mL/kg (~2 U)<br>R > 14 min: 16 mL/kg (~4 U)                                      | FLEV <1 g/L; Cryo 10 U equal to MA-FF ~ 2.6 mm     | MA 25–40 mm: 1 PLT pool (or if ADP inhibition > 60%) MA <25 mm, 2 PLT pools (or if ADP inhibition > 70%)                               |                                                            |                                                                                                                    |
| Ak K, et al. (2009) <sup>27</sup>                        | R > 2 × R-hep: 25 mg                                                        | R 14–24 min: 1 U<br>R 21–28 min: 2 U R ≥ 28 min: 4 U                                            |                                                    | MA 40–48 mm: 1 PLT pool<br>MA <40 mm: 2 PLT pools                                                                                      | LY30 >7.5%: TxA                                            |                                                                                                                    |
| Aksun M, et al. (2021) <sup>16</sup>                     |                                                                             | R 7–10 min: 1 U or 4 mL/kg<br>R 11–14 min: 2 U or 8 mL/kg<br>R > 14 min: 4 U or 16 mL/kg        | α <45: Cryo 0.06 U/kg                              | MA 49–54 mm: DDAVP 0.3 µg/kg<br>MA 41–48 mm: 5 U PLT<br>MA <40 mm: 10 U PLT                                                            | LY30 >7.5%, CI <3 antifibrinolytic selection               |                                                                                                                    |
| Aoki K, et al. (2012) <sup>28</sup>                      | R > 2 × R-hep: 50 mg                                                        |                                                                                                 |                                                    | MA < 35 mm AND PLT count < 70k: 1 PLT pool                                                                                             |                                                            |                                                                                                                    |
| Fleming K, et al. (2017) <sup>17</sup>                   | R > 0.5 min longer than R-hep: 50 mg<br>R > 1 min longer than R-hep: 100 mg | R 11–14 min: 2 U<br>R > 14 min: 4 U                                                             | α <45: Cryo 0.06 U/kg                              | MA 46–54 mm: DDAVP 0.3 µg/kg<br>MA 41–45 mm: 1 U plateletpheresis<br>MA ≤40 mm: 2 U platelet pheresis                                  |                                                            | Algorithm not followed strictly, and surgeons' judgment also used to direct therapy                                |
| Lanigan M, et al. (2022) <sup>29</sup>                   |                                                                             | R 10–12 min: 2 U<br>R 13–15 min: 3 U<br>R > 15 min: 4 U                                         | K > 3 min: Cryo 1 U<br>α <53: Cryo 1 U             | MA 48–50 mm: DDAVP 0.3 µg/kg<br>MA <47 mm: 1 U PLT<br>MA <42 mm: 2 U PLT                                                               |                                                            |                                                                                                                    |
| Lanigan M, et al. (2024) <sup>30</sup>                   |                                                                             | R 10–12 min: 2 U<br>R 13–15 min: 3 U<br>R > 15 min: 4 U                                         | K > 3 min: Cryo 1 U<br>α <53: Cryo 1 U             | MA 48–50 mm: DDAVP 0.3 µg/kg<br>MA <47 mm: 1 U PLT<br>MA <42 mm: 2 U PLT                                                               |                                                            | Same algorithm as in Lanigan et al, 2022                                                                           |
| Ranucci M, et al. (2009) <sup>31</sup>                   | R > 1.5 × R-hep (dose not stated)                                           | R > 12 s (dose not stated)                                                                      |                                                    |                                                                                                                                        | LY30 >10%: TxA                                             |                                                                                                                    |
| Raphael J, et al. (2019) <sup>9</sup>                    | R > 1.25 × R-hep                                                            | R > 12 min FFP 10–15 mL/kg OR PCC                                                               | MA <40 mm AND FF <8 mm Cryo or fibrinogen          | MA <40 mm AND FF > 8 mm: platelets ± DDAVP 0.3 µg/kg                                                                                   | LY30 > 7.5% aminocaproic acid OR TxA                       |                                                                                                                    |
| Redfern RE, et al. (2019) <sup>32</sup>                  |                                                                             | R 11–14 min: 2 U<br>R > 14 min: 4 U                                                             | α <45: Cryo 0.06 U/kg                              | MA 46–54 mm: DDAVP 0.3 µg/kg<br>MA 41–45 mm: 1 U platelet pheresis<br>MA ≤40 mm: 2 U platelet pheresis                                 |                                                            |                                                                                                                    |
| Redfern RE, et al. (2020) <sup>33</sup>                  |                                                                             | R 11–14 min: 2 U<br>R > 14 min: 4 U                                                             | α <45: Cryo 0.06 U/kg                              | MA 46–54 mm: DDAVP 0.3 µg/kg<br>MA 41–45 mm: 1 U platelet pheresis<br>MA ≤40 mm: 2 U platelet pheresis                                 |                                                            | Same algorithm as in Redfern et al., 2019                                                                          |
| Welsh KJ, et al. (2014) <sup>34</sup>                    |                                                                             | R 10–15 min: 1–2 U<br>R 15–20 min: 2–4 U<br>R > 20 min: 6 U<br>α 20–45 AND normal MA: 1–2 U FFP |                                                    | MA 35–45 mm AND EPL <15 AND LY30 <8%: 1–2 U single donor apheresis<br>MA <35 mm AND EPL <15 AND LY30 <8%: 2–3 U single donor apheresis | (EPL >15% OR LY30 >8%) AND (MA <50 mm or CI <1.0): TxA 1 g | Bleeding not responding to treatment: (EPL <15% or LY30 <8%) and (MA <70 mm or CI <3.0) consider rFVIIa (15 µg/kg) |
| Westbrook A, et al. (2009) <sup>35</sup>                 | R > 3 min longer than R-hep: 50 mg                                          | R 11–14 min: 1 U<br>R 14–20 min: 2 U<br>R > 20 min: 4 U                                         | K > 3 min: Cryo 5 U or α <45: Cryo 5 U             | MA ≤41 mm: PLT 5 U                                                                                                                     | LY30 >15%: consider starting TxA                           |                                                                                                                    |

Abbreviations: α, angle; ADP, adenosine diphosphate; CABG, coronary artery bypass grafting; CI, coagulation index; CPB, cardiopulmonary bypass; Cryo, cryoprecipitate; DDAVP, desmopressin; EPL, estimated percent lysis; FF, functional fibrinogen; FFP, fresh frozen plasma; FLEV, functional fibrinogen level; hep, heparin; ICU, intensive care unit; K, kinetic time; LVAD, left ventricular assist device; LY30, lysis at 30 minutes; MA, maximum amplitude; MAFF, maximum amplitude functional fibrinogen; PCC, prothrombin complex concentrate; PLM, platelet mapping; PLT, platelets; R, reaction time; RCT, randomized controlled trial; rFVIIa, recombinant factor VIIa; TEG, thromboelastography with TEG analyzer; TxA, tranexamic acid.

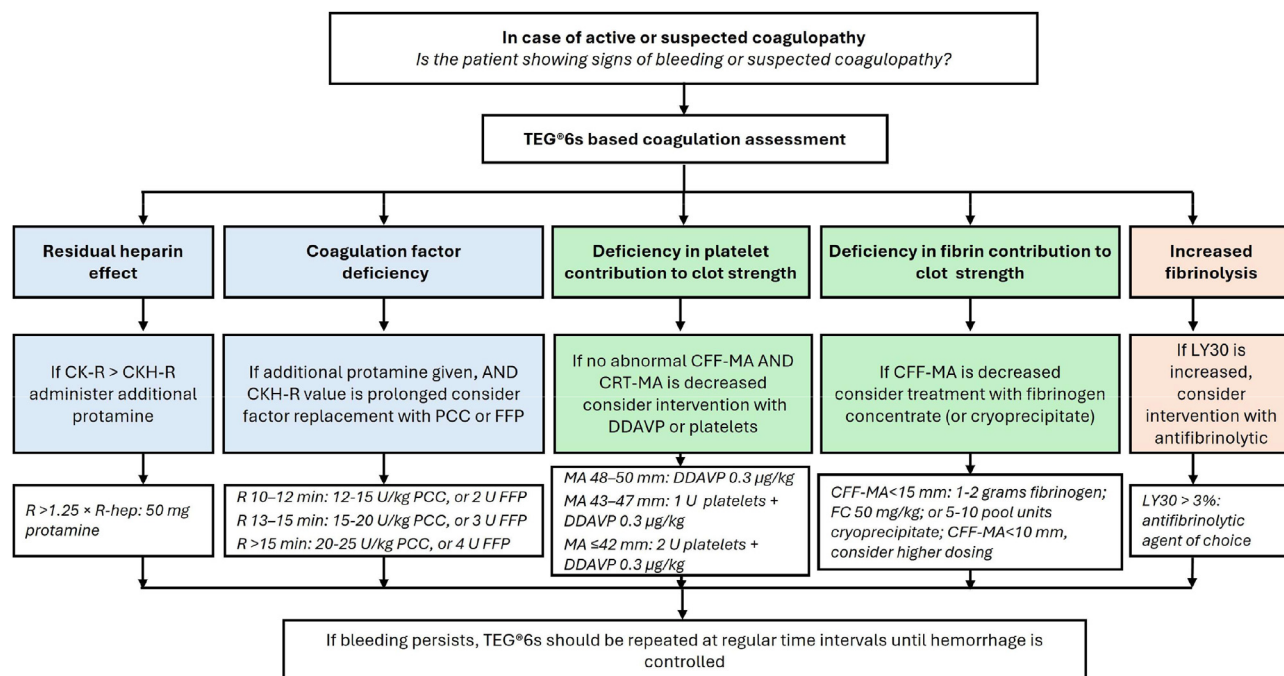


Fig 1. Proposed TEG 6s treatment algorithm for intraoperative and/or immediately postoperative targeted transfusion in cardiac surgery in the presence of significant bleeding. DDAVP, desmopressin; FC, fibrinogen concentrate; FF, functional fibrinogen; FFP, fresh frozen plasma; hep, heparin; LY30, lysis at 30 minutes; MA, maximum amplitude; R, reaction time; PCC, 4-factor prothrombin complex concentrate

**Deficiency in fibrinogen contribution to clot strength.** The contribution of fibrinogen to clot formation can be analyzed by TEG 6s specialized CFF assay. The suggested cut-off value of CFF-MA <15 mm to identify hypofibrinogenemia (Clauss fibrinogen levels <1.5 g/L) is based on the normal reference range from the TEG 6s validation study.<sup>22</sup> In case of evidence of hypofibrinogenemia, supplementation with 1 to 2 g of fibrinogen or the equivalent “dose” in cryoprecipitate is recommended. Dosage is dependent on the degree of fibrinogen deficiency/dysfunction measured by the CFF-MA. If the CFF-MA is <10 mm, higher dosing may be considered.

**Hyperfibrinolysis.** LY30 offers a rapid measure of fibrinolysis by measuring clot lysis at 30 minutes after maximum clot strength. The normal upper value of LY30 of 7.5% used historically in most published algorithms is an older value based on the TEG 5000 device reference range. In contrast, the TEG 6s LY30 reference range is narrower with an upper limit of 2.6%. Additionally, several studies in different settings, particularly in bleeding trauma patients, have previously concluded that LY30 >3% defines clinically relevant hyperfibrinolysis predicting the need for massive transfusion. Therefore, this threshold value represents an indication for the treatment of fibrinolysis.<sup>37,38</sup> Based on these arguments, we suggest that LY30 >3% is appropriate for guiding antifibrinolytic therapy in patients after cardiac surgery. Of note, based on the 2021 Society of Thoracic Surgery/Society of Cardiovascular Anesthesiologists/American Society of Extracorporeal Technology/Society for the Advancement of Patient Blood Management Guidelines,<sup>19</sup> most centers are using antifibrinolytic therapy as a prophylactic and standard part of care for cardiac surgery,

making the LY30 both the last variable to result on the TEG 6s but also the least likely to potentially alter care.

## Discussion

The use of the TEG 5000 device in guiding hemostatic management in cardiac surgery is very well established and the ability of TEG-based algorithms to reduce transfusion of blood products and/or improve patient outcomes has been demonstrated in multiple studies.<sup>10–12</sup> The newer-generation TEG 6s device introduced to the market in 2016 is designed to be easier to use and requires a reduced quantity of blood for testing, as compared with the predecessor device. Developing a TEG 6s–specific algorithm for cardiac surgery is important in order to standardize clinical research to allow data integration into evidence-based guidelines and to ensure further consistency in clinical practice. However, our literature search revealed limited evidence describing the use of TEG 6s–based treatment algorithms in cardiac surgery, and therefore the algorithm proposed requires further research for confirmation and validation.

Due in part to the unfortunately circumscribed available evidence detailing TEG 6s–based management approaches, clinicians may continue to rely on TEG 5000 algorithms for hemostatic guidance based on observed correlations between TEG 6s and TEG 5000 data.<sup>22,39,40</sup> As an illustrative example, the IMOTEC study protocol<sup>25</sup> reports that the study will utilize TEG 6s–guided management of patients with ongoing bleeding during cardiac surgery with CPB. However, it is important to note that the thresholds in the reported algorithm are based on previously proposed algorithms for TEG 5000.

Without studies using TEG 6s assays we expanded our literature search to include published algorithms using the TEG 5000 device and summarized the available recommendations. We have limited our search to the last 15 years to capture the evidence from the “modern era” of hemostatic management marked by the implementation of patient blood management and the introduction of pharmacologic agents that can replace coagulation factors (PCC) and fibrinogen (fibrinogen concentrate). Based on the available data, we proposed a simple transfusion algorithm to manage bleeding in patients undergoing cardiac surgery. This algorithm can serve as a starting point for discussions aimed at building a TEG 6s–based protocol.

It is also important to note that many previously published algorithms rely on historical reference cut-off values. While these were successfully demonstrated at the institutions that published them, they may not necessarily be the optimal cut-off values in terms of patient and clinical outcomes. Systematic research addressing these questions is lacking, limiting the generalizability of the algorithms across different institutions. With the advancement of technology and more available data from RCTs, some of these historical trigger values can be adapted to align with the newest research. For instance, we suggested adjusting the cut-off values to trigger additional protamine administration or to identify hyperfibrinolysis. Nevertheless, new specific treatment algorithms for cardiac surgical patients based on TEG 6s assays will require development and validation.

In the case of the CFF-MA cut-off to identify hypofibrinogenemia and guide fibrinogen substitution, we suggested a 15 mm trigger in our algorithm based on the normal reference range from the TEG 6s validation study.<sup>22</sup> In contrast, the most recent analysis of a large set of blood samples from cardiac surgical patients by Magunia et al. suggests the cut-off value of CFF-MA <20 mm to guide fibrinogen substitution.<sup>24</sup> These two values represent the extremes of a range of possible cut-offs: the lower value optimizes for high specificity with relatively low sensitivity. In comparison, the higher cut-off value optimizes for sensitivity at the expense of reduced specificity. Given the goal of rational blood product use, we prioritized specificity in our recommendations. In cases of apparent or suspected coagulopathy with CFF-MA values at the lower end of the normal reference range, fibrinogen replacement could reasonably be considered.

### *TEG 6s Versus TEG 5000 Values Correlation*

Some publications have demonstrated that the TEG 6s measured parameters closely correlate with those obtained from its predecessor.<sup>22,39,40</sup> In a technical validation study, TEG 6s and TEG 5000 results were compared using blood samples from healthy volunteers and patients undergoing coronary revascularization, and this study confirmed that reference ranges were comparable between the two TEG systems.<sup>22</sup> Other studies reported high correlation coefficients when comparing citrated TEG assay parameter values between TEG 5000 and TEG 6s devices in critically ill patients in the ICU<sup>39</sup> and in trauma patients.<sup>40</sup> However, some studies are reporting a lesser

correlation between the two devices. In a small study involving 10 patients undergoing liver transplant, TEG 5000 non-citrated and citrated samples compared with TEG 6s found acceptable agreement when results were within the normal reference ranges; however, with increasing coagulopathy, agreement was poorer.<sup>41</sup> The study by Wong et al. compared 243 paired arterial blood samples in 99 patients undergoing cardiac surgery using TEG 5000 (non-citrated) and TEG 6s (citrated) assays after induction of anesthesia (prior to heparin administration) and following protamine administration at the end of the cardiac bypass.<sup>26</sup> The study suggested that the two devices are discordant with differences between two devices becoming more marked at more abnormal values. Overall, to date the preponderance of evidence from several high-quality, systematic, prospective, and controlled clinical studies suggests that TEG 6s data correlate well with TEG 5000 for individual assay values, with particularly high correlation seen within the expected reference ranges of the parameters tested and acceptable bias at the relevant clinical decision points.<sup>22,40,42,43</sup> Additional studies to explore the effect of TEG 6s–guided treatment on patient clinical endpoints would further provide evidence on potential advantages of the device for patient management in cardiac surgery or other clinical settings.

### *Emerging Applications of the TEG 6s Device in Cardiac Surgery*

The original standard citrated multichannel TEG 6s cartridge does not neutralize heparin in the CRT or the CFF channel, thus limiting its ability to diagnose hemostasis defects in patients who are receiving heparin. Patients on cardiopulmonary bypass or mechanical circulatory assist devices represent a specific population for whom hemostasis monitoring is crucial. The novel heparin neutralization (HN) cartridge does incorporate heparinase into the RapidTEG and functional fibrinogen assays. This allows the cartridge to enhance the information available to support clinical decision-making in patients with heparin in circulation. The FDA has recently cleared the HN cartridge, thus extending the TEG 6s testing capabilities to fully heparinized patients. Normal reference ranges for the cartridge have been established, and the reproducibility of assays has been demonstrated.<sup>44</sup> The technical validity of the cartridge was further demonstrated by a positive correlation between the citrated functional fibrinogen with heparinase and Clauss fibrinogen assay (Pearson correlation coefficient of 0.74), and between citrated kaolin with heparinase and citrated RapidTEG with heparinase MA values.<sup>44</sup> The first clinical validation of the HN cartridge in a multicenter cohort of patients with expected intraoperative exposure to unfractionated heparin (cardiovascular surgery, cardiovascular interventional procedures, and liver transplantation) was performed and recently presented at the American Society of Anaesthesiologists Congress 2024.<sup>43</sup> The HN cartridge was only recently cleared by the Food and Drug Administration, and therefore no published clinical data are available regarding this cartridge for consideration. However, the parameters are substantially equivalent to the predicate parameters,

suggesting that the algorithm should still be applicable. In the authors' opinion, the new HN cartridge has the potential to provide early and accurate hemostasis assessment for patients with heparin in circulation, helping to identify bleeding issues during surgery and improve the speed of clinical decision-making.

The TEG PlateletMapping Assay (Haemonetics Corp., Boston, MA) allows for the assessment of platelet function in patients who have received platelet-inhibiting drugs such as aspirin, clopidogrel, abciximab, tirofiban, or eptifibatide. It tests platelet inhibition along the adenosine diphosphate and arachidonic acid pathways. P2Y<sub>12</sub> inhibitors like clopidogrel inhibit the former, while drugs like aspirin inhibit the latter.<sup>45,46</sup> Clinical trials have suggested a potential role in patients undergoing cardiovascular surgery.<sup>47</sup> For example, in the TARGET-CABG trial, a strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients was associated with the same amount of bleeding observed in clopidogrel-naïve patients and about 50% shorter waiting time than recommended in the current guidelines.<sup>48</sup>

However, the adoption of the TEG PlateletMapping Assay for intraoperative testing in cardiovascular patients lags behind that of other TEG analyses. For this reason, and because preoperative decision support for the timing of surgery fell outside the scope of this algorithm, the TEG PlateletMapping Assay was not included. This is a short-coming that could be addressed in a future revision, when more and higher-quality evidence is available to guide the best use of this assay.

#### *Inherent Limitations of Viscoelastic Testing and Other Considerations*

While the principle of whole blood coagulation testing is a strength of viscoelastic testing, it comes with the need to consider related limitations (e.g., the inability to detect inherited or acquired von Willebrand disease) and potential interferences (e.g., hypothermia, acidosis, certain medications, etc.).<sup>49</sup>

Specific to this work, it is important to recognize that the cut-off values defined herein have been optimized according to the principles of patient blood management.<sup>50</sup> In patients with apparent bleeding or those suspected of coagulopathy, a focus has been placed on high specificity to avoid unnecessary blood product use. Conversely, this means that the suggested TEG 6s cut-off values should be re-evaluated for situations where high sensitivity is more important than specificity.

In trauma patients, earlier detection of a clinically not yet apparent coagulopathy may be beneficial, and it has been suggested, for example, that using the commonly published cut-off values for R-time may miss patients with procoagulant factor deficiency.<sup>51</sup> Others have suggested based on in vitro analyses using thrombin generation assays that viscoelastic parameters of clot initiation, such as R-time, may not fully represent the balance of procoagulant and anticoagulant activity.<sup>52</sup>

#### *Implications for Research and Clinical Practice*

Overall, the lack of clinical endpoint-related evidence has posed challenges in establishing standardized TEG 6s goal-directed treatment algorithms for cardiac surgery patients. Large-scale studies are needed to generate robust evidence supporting the efficacy of TEG 6s-guided algorithms in improving clinical outcomes, such as blood product consumption, and resource utilization. Furthermore, the adoption of treatment algorithms often reflects institution-specific preferences. Therefore, clinicians should critically and regularly evaluate algorithm choices and update institutional algorithms based on emerging evidence. At the same time, as the technology evolves, TEG 6s assays may offer novel applications in optimizing transfusion strategies during complex cardiac surgeries.

#### **Conclusions**

The data on TEG 6s use in cardiac surgery remains sparse, especially with regard to clinical endpoints. While awaiting additional data to inform the application of the TEG 6s use in cardiac surgery, clinicians may continue to rely on TEG 5000 algorithms to guide hemostatic therapy. Given the observed correlation of TEG 6s and TEG 5000 data, this assumption is reasonable; however, there is a need to develop and validate TEG 6s-specific treatment algorithms. Here, we proposed a simple TEG 6s-based transfusion algorithm to manage bleeding in patients undergoing cardiac surgery, which can serve as an initial framework to allow standardization of TEG 6s for future research and further clinical validation.

#### **Declaration of competing interest**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Courtney Maxey-Jones reports financial support was provided by Haemonetics Corporation. Troy G. Seelhammer reports financial support was provided by Haemonetics Corporation. Francisco A. Arabia reports financial support was provided by Haemonetics Corporation. Brian Cho reports financial support was provided by Haemonetics Corporation. Bradford Cardonell reports financial support was provided by Haemonetics Corporation. Daniel Smith reports financial support was provided by Haemonetics Corporation. Vincenzo Leo reports financial support was provided by Haemonetics Corporation. Joao Dias reports financial support was provided by Haemonetics Corporation. Linda Shore-Lesserson reports financial support was provided by Haemonetics Corporation. Jan Hartmann reports financial support was provided by Haemonetics Corporation. Courtney Maxey-Jones reports a relationship with AbioMed Inc that includes: speaking and lecture fees. Courtney Maxey-Jones reports a relationship with AtriCure Inc that includes: speaking and lecture fees. Brian Cho reports a relationship with Edwards Lifesciences Corporation that includes: consulting or advisory and speaking and lecture

fees. Bradford Cardonell reports a relationship with Haemonetics Corporation that includes: speaking and lecture fees. Linda Shore-Lesserson reports a relationship with Werfen that includes: consulting or advisory. Vincenzo Leo reports a relationship with Haemonetics Corporation that includes: employment. Joao Dias reports a relationship with Haemonetics Corporation that includes: employment. Jan Hartmann reports a relationship with Haemonetics Corporation that includes: employment. No further COI to disclose - DS If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### CRediT authorship contribution statement

**Courtney Maxey-Jones:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Troy G. Seelhammer:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Francisco A. Arabia:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Brian Cho:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Bradford Cardonell:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Daniel Smith:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Vincenzo Leo:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Joao Dias:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation. **Linda Shore-Lesserson:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jan Hartmann:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization.

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### Supplementary materials

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