Purpose

This guide is to be used as an educational tool. The purpose is to provide cardiac surgeons, anesthesiologist, and perfusionists with a reference tool of peer-reviewed articles that address heparin potency and variability and its potential impact on managing patient anticoagulation for cardiopulmonary bypass. For questions about this guide, contact:

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Medtronic reviewed a variety of published articles across many scientific journals and chose the most pertinent to the issue of heparin potency and variability and its potential impact on cardiopulmonary bypass. The key takeaways in each summary reflect Medtronic’s opinion of the article’s most relevant points.

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KNOWN RISK FACTORS OF CARDIOPULMONARY BYPASS (CPB)

Morbidity and mortality after cardiac surgery can be related to a combination of CPB related alterations in the hemostatic and inflammatory systems. Hemodilution and activation of the coagulation system and stimulation of the inflammatory response lead to thrombin formation initiating several processes:

- Consumptive coagulopathy (activation and consumption of coagulation factors and platelets)
- Fibrinolysis (increased D-dimers and hemolysis)
- Thrombin formation (increased thrombin-antithrombin III and/or prothrombin fragment F1.2)
- Leukocyte and/or complement activation

These hemostatic derangements lead to thrombotic complications (stroke, pulmonary and peripheral emboli), excessive bleeding and increased use of allogeneic blood transfusions (carries its own risks)
Introduction

Observations of fibrin formation within the oxygenator and at blood-air interfaces of the cardiopulmonary reservoir along with high-pressure reading have been reported with an increased frequency. Upon investigation of these reports, there appears to be a relationship between these events and the frequency of monitoring heparin anticoagulation parameters during cardiopulmonary bypass. There also may be a relationship between these events with the use of low heparin protocols.

While many institutions have not changed their anticoagulation practices that have historically been working well for them, there may have been some changes to, or variability in, the currently available heparin formulations on the market that may have contributed to these results.

This Clinical Evidence Guide presents summaries of 2 guidelines and 13 recent peer-reviewed articles, serving as a resource to assist in making decisions for anticoagulation practices during cardiopulmonary bypass.

Several themes, summarized in general here, reoccur throughout the journal articles:

- In October 2009, the United States Pharmacopeia (USP) changed their standards for UFH, to match the WHO international standards, this change led to the reduction of heparin potency by about 10%.
- AmSECT 2013 guidelines recommend the development of site specific anticoagulation protocols and the monitoring of ACT during cardiopulmonary bypass.
- Patients may have sensitivities or resistance to heparin and therefore, heparin/anticoagulation monitoring should be considered before and during CPB.
- Changes in suppliers/manufactures of heparin can lead to an increase or decrease in expected response to heparin anticoagulation parameters.
- Heparin coated and heparin polymer coated bypass circuits improve biocompatibility (platelet preservation, reduced leucocyte and complement activation, and proinflammatory cytokine production).
- Heparin coated and heparin polymer coated bypass circuits may reduce blood loss, re-operation rates, ventilation time, length of ICU stay, and hospital length of stay.
- Heparinized cardiopulmonary bypass circuits required lower anticoagulation levels and may be less susceptible to variations in systemically administered heparin potency.

Based on the above themes and in order to reduce the occurrence of fibrin clots observed in the reservoirs and/or oxygenators, Medtronic recommends the following:

- Monitoring of heparin anticoagulation efficacy prior to initiation of, and during, CPB
  - Monitoring heparin dose response and heparin concentration should be considered to show anticoagulation efficacy as activated clotting time (ACT) alone is not accurate in all conditions of bypass.
- To use prudence when changing brands of heparin
- Consider the use of heparin-bonded circuits especially in high-risk patients
- Consider monitoring heparin anticoagulation with an HMS system.
## Published Guidelines for the Management of Cardiopulmonary Bypass

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## Article on Heparin Potency and Variability

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<tr>
<td>Arsenault KA</td>
<td>2012</td>
<td>Subtle differences in commercial heparins can have serious consequences for cardiopulmonary bypass patients: A randomized controlled trial.</td>
<td><em>J Thorac Cardiovasc Surg</em> 2012;144:944-50</td>
<td>10</td>
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The American Society of Extracorporeal Technology (AmSECT) recently established guidelines for perfusion practices based on the current evidence. These guidelines were established with the “intent of providing a standard for practice of adult cardiopulmonary bypass and a framework for perfusion teams to develop and implement institution-specific standards and guidelines to improve the reliability, safety, and effectiveness of cardiopulmonary bypass.” The Standards and Guidelines recommended by the committee regarding anticoagulation management are listed below:

**STANDARDS:**
- “The perfusionist, in collaboration with the physician-in-charge, shall define the intended treatment algorithm for anticoagulation management (heparin) and an alternative algorithm for when heparin is not suitable, including acceptable ranges for activated clotting time (ACT).”
- “The perfusionist shall work closely with the surgical team to monitor and treat the patient’s anticoagulation status before, during, and after the CPB period.”

**GUIDELINES:**
- “The surgical care team should determine the target ACT by considering relevant factors, including variability in the measurement of ACT attributed to the device’s performance characteristics.”
- “Pt-specific initial heparin dose should be determined by one of the following methods: - Weight, blood volume, dose-response curve, or body surface area”
- “Anticoagulation monitoring should include the testing of ACT. Additional monitoring test may include: - Partial thromboplastin time, thromboelastograph, thrombin time, anti-Xa, and/or heparin level measurement, e.g., heparin/protamine titration or unfractionated heparin level”
- “Additional doses of heparin during CPB should be determined by using an ACT and/or heparin/protamine titration”
- “Heparin reversal should be confirmed by ACT and/or heparin/protamine titration”


**OVERVIEW**

The Society of Thoracic Surgeons (STS) has established guidelines for blood conservation based on the current evidence. These guidelines support the best practices to reduce the number of blood transfusions in patients undergoing cardiovascular surgery. The recommendations from the committee regarding anticoagulation management are listed below.

**KEY TAKEAWAYS**

<table>
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<tr>
<th>Blood Conservation Intervention</th>
<th>CoR* (L of E)**</th>
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<td><strong>Blood derivatives used in blood management</strong></td>
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<td>“Antithrombin III (AT) concentrates are indicated to reduce plasma transfusion in patients with AT mediated heparin resistance immediately before cardiopulmonary bypass. (Level of evidence A)</td>
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<td><strong>Perfusion interventions</strong></td>
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<td>“In patients requiring longer CPB times (&gt;2 to 3 hours), maintenance of higher and/or patient-specific heparin concentrations during CPB may be considered to reduce hemostatic system activation, reduce consumption of platelets and coagulation proteins, and to reduce blood transfusion. (Level of evidence B)”</td>
<td>IIb</td>
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<td>“Use either protamine titration or empiric low dose regimens (eg, 50% of total heparin dose) to lower the total protamine dose and lower the protamine/heparin ratio at the end of CPB may be considered to reduce bleeding and blood transfusion requirements. (Level of evidence B)”</td>
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<td>“The usefulness of low doses of systemic heparinization (activated clotting time ≈300 s) is less well established for blood conservation during CPB but the possibility of under heparinization and other safety concerns have not been well studied. (Level of evidence B)”</td>
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*CoR - Class of Recommendation; **LoE - Level of Evidence
Has the new USP assay for heparin affected dosage for patients undergoing cardiopulmonary bypass?

Anderson DA, Holt DW


**OVERVIEW**

This was a single-center, multi-part study including both retrospective and prospective arms. The retrospective portion of the study compared pre-2008 heparin administration to post-2010 heparin administration. The prospective arm of the study compared the percentage of patients that reached a therapeutic ACT (>479 s) after instituting a new loading dose of heparin (336 u/kg) vs. the old loading dose of heparin (300 u/kg)

**RESULTS**

Compared to the old USP-standardized heparin, the new USP-standardized heparin resulted in a 12.8% decrease in activated clotting time. By increasing the loading dose from 300 u/kg to 336 u/kg (12%) with the new USP-standardized heparin, similar anticoagulation parameters were achieved compared to the old USP standardized heparin.

**KEY TAKEAWAYS**

- In this study, the new USP-standardized heparin resulted in a decreased ACT of approximately 12.8% compared to the old USP-standardized heparin.
- An increase in the loading dose of new USP-standardized heparin of 12% was required to achieve similar ACT valves to the older formulations of heparin.
Review article: heparin sensitivity and resistance: management during cardiopulmonary bypass.

Finley A, Greenberg C. 

OVERVIEW
This is a review article that discusses heparin, its mechanism of action, pharmacokinetics, potency and reasons for resistance. The article also discusses anticoagulation monitoring (i.e., ACT), heparin dose-response, reasons for heparin resistance, and treatments for heparin resistance.

KEY TAKEAWAYS
• There are multiple mechanisms for heparin resistance including:
  - Previous exposure to heparin
  - Heparin potency variability
  - Low heparin responsiveness as measured by ACT
  - Antithrombin deficiency
• Treatment of heparin resistance includes:
  - Additional heparin
  - Administration of antithrombin
• Recommend a patient-specific approach to anticoagulation management.
How one academic medical center has managed potency changes with unfractionated heparin?

Lalama J, Lewis PM, Gore J, Tran MT, Donovan J.


**OVERVIEW**
This is a single-center, retrospective chart review comparing the effects of old heparin potency to new heparin potency in 359 patients (181 in the old heparin group and 178 in the new heparin group).

**RESULTS**
The time to therapeutic aPTT was similar between the two groups 18.8 h vs. 20.8 h (p = .092). Patients receiving the old heparin potency had higher aPTT times (96.6 seconds) vs. the new heparin potency (76.7 seconds, p = .003). However, there was no difference between the groups in regards to thromboembolic or bleeding events.

**KEY TAKEAWAYS**
- The new heparin resulted in lower initial aPTT times and a slightly longer time to therapeutic aPTT.
- There were no differences in clinical outcomes — new thromboembolic or bleeding events.
Subtle differences in commercial heparins can have serious consequences for cardiopulmonary bypass patients: A randomized controlled trial.

Arsenault KA, Paikin JS, Hirsh J, Dale B, Whitlock RP, Teoh K, Young E, Ginsberg JS, Weitz JI, Eikelboom JW.


**OVERVIEW**

After the authors’ institution switched manufacturers of heparin (from Hepalean to PPC), they noticed a need to increase the dose of heparin to achieve a minimum threshold ACT. Therefore, the authors conducted a 3 phase study which included a retrospective chart review, an in vitro analysis, and a double-blind, randomized, prospective study comparing the results of Hepalean-manufactured heparin to PPC-manufactured heparin.

**RESULTS**

The retrospective chart review showed that patients receiving PPC-manufactured heparin required a larger dose of heparin to achieve an ACT >480 seconds (440 u/kg vs. 407 u/kg) compared to Hepalean-manufactured heparin. The in vitro study demonstrated that PPC-manufactured heparin and Hepalean-manufactured heparin had similar anticoagulation activity. The prospective study demonstrated that after a 400 u/kg loading dose, the Hepalean-manufactured heparin had a higher mean ACT of 584 s compared to a mean ACT of 516 s for PPC-manufactured heparin; p = .011.

**KEY TAKEAWAYS**

- “Heparin preparations might not be interchangeable despite identical anticoagulation profiles in vitro.”
- The authors suggest “…that if a change in heparins is made for CPB surgery, the anticoagulant profile of the new heparin should be compared with the brand in use by performing chart reviews similar to the one we performed. If differences are found, our studies could provide a template for additional investigations.”
Heparin brand is associated with post-surgical outcomes in children undergoing cardiac surgery.


**OVERVIEW**

This is a single-center, retrospective study comparing the clinical outcomes in 902 pediatric patients undergoing cardiac surgery who received unfractionated heparin (UFH) manufactured by Hepalean compared to those who received UFH manufactured by PPC.

**RESULTS**

Patients that received UFH manufactured by PPC, required a greater use of RBC transfusions and had increased risk of bleeding complications, thromboembolic complications, early unplanned reoperations, longer ICU stays, and longer hospital stays.

**KEY TAKEAWAYS**

- “It is possible that the processing and purification method affects the presence and activity of UFH molecules unable to bind to antithrombin, and this could explain differences in outcomes associated with brands, beyond features related to potency.”
- “Various brands of unfractionated heparin should not be considered equivalent in the context of pediatric cardiac surgery with CPB without formal validation in prospective trials.”
Change in heparin potency and effects on the activated clotting time in children undergoing cardiopulmonary bypass.

Guzzetta NA1, Amin SJ, Tosone AK, Miller BE.


**OVERVIEW**

In October 2009, the FDA changed the USP monograph for unfractionated heparin (UFH) to incorporate new quality test and to potency assay. This is a single center, retrospective study comparing the effect on ACT in children undergoing cardiopulmonary bypass after they received heparin prior to June 30, 2009 (old formulation heparin; OH) vs. those that received heparin after June 1, 2010 (new formulation heparin; NH).

**RESULTS**

NH patients had lower post initial heparin dose ACTs compared to OH patients, 610 s vs. 683 s, respectively. Fewer NH patients had ACT >480 seconds than OH patients after the initial loading dose; p = .0001.

**KEY TAKEAWAYS**

- “The level of anticoagulation after the initial pre-CPB heparin bolus assessed by the ACT is significantly less with use of the new heparin.”
- “Consideration should be given to increasing the initial weight-based heparin dose administered before CPB.”
Is a fully heparin-bonded cardiopulmonary bypass circuit superior to a standard cardiopulmonary bypass circuit?

Mahmood S, Bilal H, Zaman M, Tang A.


**OVERVIEW**
This is a meta-analysis of 13 articles to answer the question ‘Is a fully heparin bonded cardiopulmonary bypass circuit superior to a standard cardiopulmonary bypass circuit?’

**RESULTS**
Heparin coated and heparin polymer coated bypass circuits do not increase the risk of adverse effects; however, they do reduce blood loss, re-operations rates, ventilation time, length of ICU time, and length of stay. In addition they improve biocompatibility (platelet preservation, reduced leucocyte and complement activation, and proinflammatory cytokine production).

**KEY TAKEAWAYS**
- The authors conclude, “... that despite heparin-bonded and newer third-generation heparin-polymer-bonded cardiopulmonary bypass circuits having a greater cost per person, their improved clinical outcomes and biocompatibility in patients undergoing cardiac surgery make them a preferable option to standard non-heparin-bonded circuits.”
Heparinized cardiopulmonary bypass circuits and low systemic anticoagulation: An analysis of nearly 6000 patients undergoing coronary artery bypass grafting.

Øvrum E, Tangen G, Tølløfsrud S, Skeie B, Ringdal MA, Istad R, Øystese R.


**OVERVIEW**

This is a single-center, retrospective study of 5954 first time on-pump, cardiac-surgery patient. All patients underwent cardiopulmonary bypass with heparin coated systems (Carmeda or Duraflo II). A reduced heparin protocol was used (150 IU/kg) with a target ACT of > 250 seconds before CPB could begin.

**RESULTS**

There were no technical complications related to CPB and no visible clots were seen in the circuits. There were no clinical indications of increase risk for thromboembolic events.

**KEY TAKEAWAYS**

- “Heparin-coated CPB circuits combined with reduced systemic heparinization is safe and has encouraging clinical results”
Guideline on antiplatelet and anticoagulation management in cardiac surgery


OVERVIEW

This is a review prepared by the European Association for Cardio-Thoracic Surgery (EACTS) to provide evidence-based recommendations on antiplatelet and anticoagulation management in cardiac surgery based on the most recent literature. Among the many topics covered are point-of-care coagulation monitoring and protamine reversal of heparin.

KEY TAKEAWAYS

- “Hepcon monitoring is associated with higher heparin and lower protamine doses and may decrease activation of the coagulation and inflammatory cascades. Some studies have shown this may decrease postoperative bleeding and blood product requirement. Its routine use is not unreasonable but larger trials are needed to investigate this further. (Grade B recommendation based on level 1b and 2b studies)”

- “Excessive doses of protamine can impair platelet function and increase bleeding. These effects have only been demonstrated when the ratio of protamine to heparin is greater than 2.6:1. (Grade B recommendation based on level 1b and 2b studies)”
OVERVIEW
This is a single-center, retrospective study comparing two different anticoagulation protocols applied to 1326 CABG patients treated with heparin-coated cardiopulmonary bypass equipment. Six hundred fifty one patients received full-dose heparin (ACT >480 seconds; Group F) and 675 patients received reduced-dose heparin (ACT >250 seconds; Group R).

RESULTS
Group R had a reduce amount of post-operative bleeding compared to Group F; 665 vs. 757 ml (p < .0001), respectively. Group R also had a significantly less drop in hemoglobin concentrations, shorter ventilation time, and few episodes of new atrial fibrillation after surgery. There was no difference in perioperative MI, stroke, TIAs, physical rehabilitation or deaths between the two cohorts. No technical or coagulation problems were observed in either group.

KEY TAKEAWAYS:
- Heparin-coated cardiopulmonary bypass equipment combined with reduced anticoagulation reduces post-operative blood loss compared to full-dose anticoagulation.
- Low-dose heparin in combination with heparin-coated CPB circuit also decreased ventilation time and incidence of new onset atrial fibrillation.
Anticoagulation management in patients undergoing open heart surgery by activated clotting time and whole blood heparin concentration

Pappalardo F; Franco A; Crescenzi G, De Simone F; Torracca L, Zangrillo A

OVERVIEW
This is a single-center, prospective, randomized study comparing standard anticoagulation protocol vs. anticoagulation management with a heparin-concentration-based system (HMS) in 39 first-time valve surgery patients.

RESULTS
The patients in the HMS group compared to the standard anticoagulation protocol group received a higher heparin dose (29,000 IU vs. 19,000 IU), received a smaller protamine dose (170 mg vs. 200 mg), had a higher postoperative platelet count (164 x10⁹/L vs 127 x10⁹/L) and had fewer patients requiring blood product transfusions (0 vs. 6). There was no difference in CPB time, total blood loss, ICU duration, or hospital duration between the two cohorts.

KEY TAKEAWAYS:
- Patients monitored with HMS
  - received more heparin
  - had higher postoperative platelet counts
  - received less protamine
  - required fewer blood-product transfusions
Heparin monitoring during cardiac surgery. Part 1: Validation of whole-blood heparin concentration and activated clotting time

Raymond PD1, Ray MJ, Callen SN, Marsh NA. 
Perfusion. 2003 Sep;18(5):269-76.

OVERVIEW
This is an observational study involving 42 patients undergoing first-time elective coronary artery bypass grafting. Blood samples were collected at 5 minutes after heparin administration, 20, 40, and 60 minutes into CPB, and immediately prior to stopping CPB before protamine administration. Blood samples were analyzed for heparin concentrations (Hepcon) and activated clotting time (ACT; Hemochron and HemoTec). In addition, the samples were analyzed for plasma heparin levels (anti-Xa heparin).

RESULTS
When Hepcon and anti-Xa were compared by simple analysis of agreement, it was revealed that the Hepcon has a mean bias of -0.46 U/mL, with the limits of agreement ±1.12 U/ml. When ACTs were compared between HemoTec and Hemochron, there was a mean difference of -96 seconds for the HemoTec, with limits of ±265 seconds.

KEY TAKEAWAYS:
- When compared to laboratory derived anti-Xa plasma heparin concentration, Hepcon displayed satisfactory agreement with the expected variation unlikely to cause problems clinically.
- HemoTec and Hemochron displayed satisfactory agreement in derived ACTs; however, each requires a separate target.
- While ACT correlates poorly with heparin concentrations, it is routinely used to monitor anticoagulation during CPB to ensure the adequacy of heparin’s effect.
Heparin monitoring during cardiac surgery. Part 2: Calculating the overestimation of heparin by the activated clotting time

Raymond PD, Ray MJ, Callen SN, Marsh NA.  

**OVERVIEW**
This study took the data from the above study (Raymond, 2003) and derived a formula to estimated heparin concentrations from ACT values.

**RESULTS**
If one does not account for artificial prolongation of ACT by CBP and individual sensitivities to ACT, heparin concentrations estimated by ACT values range between 0.8 and 3.0 times those indicated by the anti-Xa assay. Therefore, when the effects of bypass and individual heparin sensitivities are taken into account, the ACT may provide a suitable indication of heparin concentrations; however, typical use may overestimate heparin up to threefold.

**KEY TAKEAWAYS:**
- When used alone, ACT may overestimate the plasma concentration of heparin by up to threefold.
- Overestimating plasma heparin concentrations could lead to inadequate intraoperative anticoagulation by heparin and excessive delivery of protamine postoperatively.