J Extra Corpor Technol. 2018;50:5–18
The Journal of ExtraCorporeal Technology

Original Articles

STS/SCA/AmSECT Clinical Practice Guidelines: Anticoagulation during Cardiopulmonary Bypass

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Abstract: Despite more than a half century of "safe" cardiopulmonary bypass (CPB), the evidence base surrounding the conduct of anticoagulation for CPB has not been organized into a succinct guideline. For this and other reasons, there is enormous practice variability relating to the use and dosing of heparin, monitoring heparin anticoagulation, reversal of anticoagulation, and the use of alternative anticoagulants. To address this and other gaps, the Society of Thoracic Surgeons (STS), the Society of Cardiovascular Anesthesiologists (SCA), and the American Society of Extracorporeal Technology (AmSECT) developed an Evidence Based Workgroup. This was a group of interdisciplinary professionals gathered together to summarize the evidence and create practice recommendations for various aspects of CPB. To date, anticoagulation practices in CPB have not been standardized in accordance with the evidence base. This clinical practice guideline was written with the intent to fill the evidence gap and to establish best practices in anticoagulation for CPB using the available evidence. To identify relevant evidence a systematic review was outlined and literature searches were conducted in PubMed® using standardized MeSH terms from the National Library of Medicine list of search terms. Search dates were inclusive of January 2000 to December 2015. The search yielded 833 abstracts which were reviewed by two independent reviewers. Once accepted into the full manuscript review stage, two members of the writing group evaluated each of 286 full papers for inclusion eligibility into the guideline document. Ninety-six manuscripts were included in the final review. In addition, 17 manuscripts published prior to 2000 were included to provide method, context, or additional supporting evidence for the recommendations as these papers were considered sentinel publications. Members of the writing group wrote and developed recommendations based on review of the articles obtained and achieved more than two thirds agreement on each recommendation. The quality of information for a given recommendation allowed assessment of the level of evidence as recommended by the AHA/ACCF Task Force on Practice Guidelines. Recommendations were written in the three following areas 1) Heparin dosing and monitoring for initiation and maintenance of CPB, 2) Heparin contraindications and heparin alternatives, 3) Reversal of anticoagulation during cardiac operations. It is hoped that this guideline will serve as a resource and will stimulate investigators to conduct more research and expand upon the evidence base on the topic of anticoagulation for CPB. **Keywords:** cardiopulmonary bypass, heparin, heparin alternatives, protamine, anticoagulation reversal, bivalirudin. *J Extra Corpor Technol. 2018;50:5–18*

Received for publication September 8, 2017; accepted November 2, 2017.
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The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

INTRODUCTION

The development of cardiopulmonary bypass (CPB) in the 1960s so successfully enabled open heart surgery that rigorous evidence based clinical trials did not play a part in the initial phases of development (1). After World War II, clinicians were faced with more and more treatment

choices to the point that uncertainty existed about the "best" options. Indeed Archie Cochrane recognized the need for a more rigorous approach to give clinicians answers to key questions about patient treatments. Cochrane's efforts eventually led to the formation of the Cochrane Collaboration, as a repository of evidence based summaries to answer important clinical questions (2). As a result, the modern era expects, and indeed requires, evidence to support surgeons' interventions, preferably in the form of randomized controlled trials (RCTs). Over the last 60-plus years since the introduction of clinical CPB as the foundation for performance of cardiac operations, surgeon investigators developed a safe, efficient, and reproducible method of performing highly complex cardiac procedures using CPB. Many advances in CPB are the result of evidence-based RCT's. Others derive from prospective cohort studies and still others, from anecdotal practice or consensus.

Recognizing this large scope of practice and the varied nature of the evidence base to support the use of CPB, the Evidence Based Workforce of the Society of Thoracic Surgeons (STS) undertook a project to develop a series of practice guidelines that reflect the evidence base for the use of CPB in the current era. This effort included a collaboration with the Society of Cardiovascular Anesthesiologists (SCA) and with the American Society of Extracorporeal Technology (AmSECT) to summarize available evidence in various areas of CPB. A critically important part of CPB is the use of anticoagulation. To date, there are no evidence-based practice guidelines that define the optimal management of anticoagulation during the conduct of CPB. As a result, practice in this area is highly variable and not standardized in accordance with the evidence base to date. Thus, The STS recognized this deficit and undertook a collaboration with the SCA and the AmSECT to address the evidence gap regarding the use of anticoagulation during CPB. This article reviews relevant published information about the use of anticoagulation for the conduct of CPB and provides a synthesis of the available evidence to create a clinical practice guideline. This guideline represents the initial evidence based approach to the use of anticoagulation in CPB and is the only available comprehensive guideline of its kind. It is the hope of the authors that this guideline will stimulate investigators to amplify and elaborate upon the evidence available on this topic.

Search Methods

To identify relevant evidence a systematic review was outlined and literature searches were conducted in PubMed® using standardized MeSH terms from the National Library of Medicine list of search terms and were inclusive of dates January 2000 up to December 2015. The following terms comprised the standard baseline search terms for topics and were connected with the logical OR connector:

- Extracorporeal circulation (MeSH number E04.292 includes ECMO, left heart bypass, hemofiltration, hemoperfusion & cardiopulmonary bypass).
- Cardiovascular surgical procedures (MeSH number E04.100 includes OPCAB, CABG, myocardial revascularization, all valve operations, and all other operations on the heart).
- Pharmacologic actions of anti-coagulant drugs (MeSH number D27.505 includes molecular mechanisms, physiologic effects, and therapeutic use of drugs).
- Anticoagulation reversal (MeSH number D12.776 includes protamine sulfate and other protamines and nuclear proteins).

These broad search terms allowed specific topics to be added to the search with the logical "AND" connector and publication types and group to be excluded (see Appendix). This search methodology provided a broad list of generated references specific for the search topic. The searches yielded 833 abstracts. Abstracts were reviewed by two independent reviewers for acceptance into the paper review stage. Abstracts with at least one acceptance were sent to full manuscript review. A total of 286 full papers were reviewed by at least two members of the writing group for inclusion eligibility in the Guideline. In order to be included, a paper had to report data on each of the following: 1) anticoagulant used for cardiopulmonary bypass and 2) the monitoring techniques used to measure that anticoagulation. After passing mandatory inclusion criteria, it was preferable that included papers have a prospective study design, and also report on the frequency of anticoagulation monitoring, bleeding outcomes, and transfusion outcomes. Ninety six manuscripts were included in the final review. In addition seventeen manuscripts published prior to 2000, that were referenced within a manuscript, and considered to be sentinel papers, were included to provide method, context, or additional supporting evidence for the recommendations.

Individual members of the writing group read the retrieved references for their assigned topics and formulated recommendations based on assessment of the relevant literature. Only English language articles contributed to the final recommendations. For almost all topics reviewed, only evidence relating to adult patients entered into the final recommendations, primarily because of limited availability of high quality evidence relating to pediatric patients having cardiac procedures. Evidence tables were constructed in order to ensure that selected studies conformed to minimum requirements in terms of study design and reporting of outcomes. A representative evidence table evaluating the Anticoagulation studies is shown in Supplemental Table 1 (online only). Study appraisals of randomized controlled trials

and meta-analyses are shown in Supplemental Table 2 (online only), and the Newcastle-Ottawa appraisal for nonrandomized studies is depicted in Supplemental Table 3 (online only).

Duties of the Writing Group

Members of the writing group wrote and developed recommendations based on review of the articles obtained using the search technique described above. The quality of information for a given recommendation allowed assessment of the level of evidence as recommended by the AHA/ACCF Task Force on Practice Guidelines (http://www.americanheart.org/downloadable/heart/12604770597301209Methodology_Manual_for_ACC_AHA_Writing_Committees.pdf). Appendix 1 contains a summary of recommendations put forth in this guideline as a result of the evidence base.

HEPARIN DOSING FOR INITIATION AND MAINTENANCE OF CPB

Class I Recommendation

A functional whole blood test of anticoagulation, in the form of a clotting time, should be measured and should demonstrate adequate anticoagulation before initiation of, and at regular intervals during cardiopulmonary bypass. (Level of Evidence C)

Class IIa Recommendations

- Bolus administration of unfractionated heparin based upon weight is reasonable for achieving adequate anticoagulation, but individual response to heparin is heterogeneous and requires a therapeutic functional test of clot inhibition before initiation of CPB, independent of the bolus dose used. (Level of Evidence C)
- It is reasonable to use Activated Clotting Time (ACT) tests that produce "maximally activated" clotting times since these tests mitigate ACT variability, are less susceptible to hypothermia, and correlate more closely with Factor Xa activity compared to tests that employ a single activator. (Level of Evidence B)
- It is reasonable to maintain activated clotting time above 480 seconds during CPB. However this minimum threshold value is an approximation and may vary based upon the bias of the instrument being used. For instruments using 'maximal activation' of whole blood or microcuvette technology, values above 400 seconds are frequently considered therapeutic. (Level of Evidence C)

Class IIb Recommendations

- Use of a heparin dose-response formula may identify reduced sensitivity to heparin, but has not been shown to be more useful than weight-based heparin dosing, in determining the heparin dose required to achieve an adequate ACT *for initiation of CPB*. (Level of Evidence B)
- Use of heparin concentration monitoring in addition to ACT might be considered, *for the maintenance of CPB,* as this strategy has been associated with a significant reduction in thrombin generation, fibrinolysis, and neutrophil activation. However, its effects on postoperative bleeding and blood transfusion are inconsistent. (Level of Evidence B)
- During CPB, routine administration of unfractionated heparin at fixed intervals, with ACT monitoring, might be considered and offers a safe alternative to heparin concentration monitoring. (Level of Evidence C)

Activated Clotting Time (ACT) is considered the gold standard in monitoring anticoagulation for CPB. The establishment of a safe or optimal range for ACT dates back to data published in the 1970s when Bull et al. (3) showed no development of clot in the oxygenator or circuit when ACT was maintained above 300 seconds. However, Young et al. (4) challenged this threshold when they demonstrated fibrin formation in the circuits of rhesus monkeys maintained on CPB with a minimum ACT value of 300 seconds, and they recommended that this threshold value be increased to 400 seconds by showing it was safe in five pediatric patients on CPB. In order to maintain a margin of safety above 400 seconds, the minimum acceptable ACT value of approximately 480 seconds became a "standard of care," that was used in multiple future studies and in clinical practice, but was based on limited evidence. Despite this widely accepted level of anticoagulation, there is no clear consensus on the accurate calculation of this initial dose of unfractionated heparin. Options for calculating the initial heparin bolus include a fixed, weight-based dose (e.g. 300 IU/kg), or use of point-of-care tests that measure the whole blood sensitivity to heparin using an associated dose-response.

In addition to the heterogeneity of heparin formulations themselves, individual responsiveness to heparin is variable. The pharmacodynamics of unfractionated heparin are highly dependent on the level and function of plasma antithrombin III (ATIII). In patients with preoperative hypercoagulability or reduced ATIII responsiveness, increased levels of circulating heparin are necessary to achieve a therapeutic ACT value before CPB (5). Na and coauthors reported significant variations to heparin responsiveness in an observational study of patients with known, stabilized infectious endocarditis. Garvin et al. (6) also reported observed variations in heparin response in patients having CPB. In a retrospective institutional database review of 3,880 patients, these authors found wide variation in the heparin bolus dose required to obtain a target ACT. The initial unfractionated heparin bolus dose

did not correlate well with the first post-heparin ACT ($r^2 = .03$).

The route and timing of the initial administration of unfractionated heparin directly impacts the ability to obtain a therapeutic ACT. A small randomized trial done by Grima and colleagues found that intermittent doses of unfractionated heparin administered before CPB (100 IU/kg $\times$ 3 doses) maintained adequate levels of anticoagulation during CPB better than a single bolus dose of 300 IU/kg (7). Intermittent pre-CPB heparin treatment resulted in lower mean decreases in factor VIII, fibrinogen, ATIII, and platelet count than if a large bolus dose were administered. In a prospective non-randomized trial performed by Neema et al. (8), six of the 100 patients that received 300 IU/kg of unfractionated heparin prior to CPB had a resultant post-heparin ACT $<$ 350 seconds. Other pathological disturbances such as thrombocytosis may limit the effectiveness of weight-based heparin bolus administration.

Due to the heterogeneity of the pharmacodynamic response to unfractionated heparin, the utilization of ex-vivo heparin dose-response technologies was studied as a more accurate prediction of initial heparin dosing. While ex-vivo heparin dose-response technologies may identify patients who have a reduced sensitivity to conventional doses of heparin, these tests have limited ability to calculate correctly an optimal initial unfractionated heparin bolus dose. The aforementioned observational study by Garvin et al demonstrated poor correlation of the calculated in vitro heparin dose response curve compared with the actual patient heparin dose-response, resulting in a failure to reach therapeutic ACT values in nearly 17% of patients (6).

During CPB, an overestimation of heparin concentration may occur when using the ACT assay alone. Falsely elevated ACT values may be observed under conditions of hypothermia, reduced hemoglobin concentration, hypofibrinogenemia, and pharmacologic agents that are not associated with a concomitant increase in heparin concentration (9). In a controlled, non-randomized study of 42 patients, Machin et al. (10) demonstrated prolongation of ACT values during hypothermic CPB when compared to normothermic CPB. Leyvi et al. (11) reported similar ACT prolongation under conditions of both hypothermia and hemodilution using multiple ACT technologies while plasma anti-factor Xa heparin level activity remained constant. Maintaining ACT values during CPB without heparin concentration monitoring may result in lower doses of heparin. These known sensitivity limitations in ACT monitoring may result in subclinical plasma coagulation occurring during CPB.

Whole blood heparin concentration assays are statistically more closely correlated with plasma anti-Xa levels than the ACT (12). Clinically heparin concentration tests are performed alongside a functional test of clotting, such as an ACT, since a therapeutic functional confirmation of anticoagulation provides important safety data. In a randomized controlled trial of 200 patients, Koster et al. found that adhering to a heparin concentration maintenance protocol led to a significant reduction in thrombin generation, fibrinolysis, and neutrophil activation, when compared to ACT monitoring alone (480 seconds) (13). Despotis et al. (14) randomized patients to ACT-based (using 5,000 unit unfractionated heparin doses to maintain ACT values $>$480 seconds) versus heparin concentration-based management (with minimum ACT $>$ 480 seconds), and reported a higher heparin total dose in patients in the heparin concentration group (612 $\pm$ 147 vs. 462 $\pm$ 114 U/kg, $p < .0001$). Patients in the heparin concentration group also had lower protamine to heparin ratios, and required significantly fewer blood product transfusions (platelets, plasma, and cryoprecipitate) than the ACT-based control group. Another randomized trial of 31 patients scheduled for re-operative surgery resulted in significant reductions in perioperative blood loss and blood product usage when maintaining higher patient-specific heparin dosing during CPB (15). Another study found reduced platelet activation and evidence of reduced thrombin generation with heparin concentration monitoring compared to routine ACT monitoring (16). Together, these studies suggest that whole blood heparin concentration monitoring results in larger doses of unfractionated heparin during CPB and improved hemostatic suppression compared to ACT monitoring alone. However, these results did not translate into improved clinical outcomes and have not been wholly reproducible in the literature. A retrospective analysis in 686 patients favored ACT-based monitoring compared with heparin concentration monitoring because of less postoperative bleeding and transfusion requirements associated with ACT-based monitoring (17).

Traditionally, the gold standard for the measuring the anticoagulant effects of heparin is inhibition of factor Xa (anti-Xa) activity. Factor Xa is a major target for unfractionated heparin and can be readily measured in plasma using laboratory assays. The various studies that seek to validate a new measure of heparin's activity, or a clotting time assay, use anti-Xa activity as the gold standard comparison. However, plasma assays for anti-Xa activity are not ideally suited for point-of-care testing. Anti-Xa measurement serves as a validating test for novel point-of-care assays that reflect anti-Xa activity. Hansen et al. (18) studied a whole blood modified ACT test and found it to be highly correlated to laboratory anti-Xa measurement. Helstern et al. (19) reported another one-step clotting assay that correlates well with anti-Xa tests and is not influenced by hemodilution, but clinical studies are lacking.

Routine re-dosing of unfractionated heparin at fixed intervals during CPB, despite a therapeutic ACT, is commonly

used when heparin concentration assays are not available, to simulate the practice of "higher heparin dosing." This practice prescribes additional fixed doses of unfractionated heparin at specific time points, even though ACT may be above target. In a prospective trial of 100 patients presenting for cardiac surgery, 1/3 of the initial heparin bolus was administered at the 90-minute point of CPB, with repeat doses every 60 minutes thereafter (8). This strategy maintained adequate anticoagulation during the entire period of hypothermic CPB; bleeding parameters were not reported.

Despite the reported benefits of higher heparin dosing, other studies seemingly contradict these results. In a small prospective trial of 21 patients, Gravlee et al. (20) concluded that subclinical plasma coagulation occurs during CPB despite heparin concentrations greater than 4.1 IU/mL. Further, postoperative mediastinal chest tube drainage correlates with increased heparin concentration, especially if heparin rebound is not carefully monitored. A subsequent, prospective study of 63 patients by Gravlee et al. (21) showed that subjects who received an unfractionated heparin bolus of 400 IU/kg and had heparin concentration maintained >4 IU/mL did not differ in mediastinal drainage or transfusion products from a control group of patients receiving a bolus dose of 200 IU/kg plus additional heparin for ACT values <400 seconds. A prospective trial in 31 patients undergoing cardiac surgery revealed that all patients had a residual circulating heparin level after protamine administration (mean .18 IU/mL), detected by a chromogenic anti-Xa assay. This residual heparin concentration did not correlate with ACT or whole blood heparin concentration nor did it correlate with postoperative mediastinal tube drainage volume (22). While the studies supporting higher unfractionated heparin doses are greater in size and number, the impact of using higher doses of heparin on postoperative bleeding appears to be unclear, especially if residual effects of heparin are not detected or treated.

Documented therapeutic anticoagulation of patients having CPB is necessary and is routinely performed using an ACT. However, ACT devices vary considerably in their measurement platforms, activators, sample volumes, and sensitivities to external elements such as hemodilution, hypothermia, and concomitant drug therapies (23,24). It appears that arterial versus venous blood sampling and a wait period up to 15 minutes do not significantly impact the ACT result (25,26). Currently there are many instruments and platforms available that purport to measure ACT values. To rationally utilize an ACT device for patients undergoing CPB, it is important to understand how the testing platform works, the therapeutic target that corresponds to an historical ACT of 480 seconds, and how well the results correlate with anti-Xa activity. In an early study of heparin monitoring and ACT threshold values, it was noted that the two most commonly used ACT devices correlated with each other, yet there was significant bias with one of the instruments (27). Another observational study showed that many ACT tests correlated poorly with heparin level as assessed by anti-Xa plasma activity (28). Patteril et al. (29) demonstrated that after switching their cohort population to a newer ACT device, the new instrument yielded a lower mean ACT value compared with temporal controls (557 vs. 618 seconds, $p < .05$) and a higher dose of unfractionated heparin was needed to achieve a minimum ACT of 480 seconds. A certain level of validation has been performed for other ACT instruments as well (30).

Tests that use a maximal degree of activation of the blood sample by using multiple or more potent activators produce shorter clotting times relative to the standard ACT with a single activator (31). The tests that utilize a maximally activated sample also report less variability in clotting times, and are less susceptible to prolongation by hypothermia and artifacts (32). The maximal activation removes the variability induced by hemodilution of clotting factors. Maximal activation is also accomplished in the microcuvette ACT technology due to the small sample volume and minimization of sample dilution. A plasma supplemented-ACT accomplishes a similar result. This test has been shown to mitigate the ACT variability to more closely mirror anti-Xa levels, however it is cumbersome and difficult to perform at the point of care (19).

The viscoelastic tests have been modified for point-of-care measurement of the ACT and in a small ex vivo analysis in CPB patients, the two tests performed similarly to standard ACT tests with respect to heparinization and hemodilution (30,33). Another observational study in 50 CPB patients demonstrated that a viscoelastic measurement of ACT activity mirrored the activity of both standard ACT tests and anti-Xa levels (34). It remains uncertain what the threshold minimum safe values are for the viscoelastic clotting times in CPB and how they correspond with the historical 480 seconds target. Further clinical and outcome studies are warranted before switching patient management to a viscoelastic ACT test.

HEPARIN CONTRAINDICATIONS & HEPARIN ALTERNATIVES

Class IIa Recommendations

- Clinical scoring estimates that use a fall in platelet count greater than 50% and/or a thrombotic event between 5 and 14 days following a heparin exposure can be used to determine whether a heparin-platelet antibody test should be performed to diagnose heparin-induced thrombocytopenia (HIT) (Level of Evidence B)

- Serum tests that include functional testing with serotonin release assay (SRA) or heparin-induced platelet activation (HIPA) can be beneficial in identifying patients with HIT who have a history of thrombocytopenia, and elevated clinical HIT risk scores, when PF4/heparin antibody testing is inconclusive (weakly positive) for HIT. (Level of Evidence C)
- In patients who are seropositive for heparin-platelet antibodies or have a recent history of HIT, it is reasonable to delay elective cardiac operations requiring CPB until a patient's functional test and/or antigenic (antibody) assay are negative, with the expectation that heparin anticoagulation for CPB is likely to be safe and effective. (Level of Evidence C)
- In patients with a diagnosis of HIT and in need of an urgent operation requiring CPB, anticoagulation with bivalirudin is a reasonable option. (Level of Evidence B).

Class IIb Recommendation

- In patients with significant renal dysfunction who are seropositive for HIT and require urgent operation requiring CPB, use of plasmapheresis, argatroban, or heparin with antiplatelet agents (such as tirofiban, ilioprost) may be considered, understanding that there are increased risks of bleeding with these interventions. (Level of Evidence C).

The chief contraindications to the use of heparin for cardiopulmonary bypass are a history of heparin-induced thrombocytopenia (HIT) and known hypersensitivity to heparin. Whereas HIT is characterized by the development of IgG antibodies recognizing platelet factor 4 (PF4)-heparin complexes (35,36), hypersensitivity reactions to heparin can be Type I, II or IV (37,38). HIT with or without thrombosis occurs in patients who form PF4-heparin immune complexes capable of activating platelets (39,40). The presence of these anti-PF4/heparin antibodies forms the basis for the clinical antigenic (ELISA) assay for HIT (39). Although the presence of PF4-heparin complexes following heparin exposure can be quite high (>30% in surgical patients), the incidence of HIT is much lower (1–2%) (41–45). Patients who test positive (antigen assay) for anti-PF4-heparin antibodies preoperatively appear to have a higher overall risk for complications and increased mortality following cardiac surgery (46–48). Given the 60–90 days amnestic period for HIT antibodies, postponing elective cardiac surgery in patients with elevated PF4-heparin antibodies could potentially mitigate this avoidable risk (49–52). Platelet count monitoring is currently recommended for patients with heparin exposure prior to cardiac surgery (e.g. cardiac catheterization or DVT prophylaxis) to determine whether further testing is indicated (45).

Detection of PF4-heparin antibodies that activate platelets and trigger serotonin release requires a highly specific and sensitive functional test for HIT (53). Functional testing with serotonin release assay (SRA) or heparin-induced platelet activation (HIPA) detect only those IgG antibodies capable of activating platelets (45). Thrombocytopenia and/or thrombosis are much more likely when platelet activation occurs. Specific tests of platelet serotonin release can be particularly helpful when low-levels of positivity are detected using HIT antibody (antigen) assays, which are sensitive, but not specific to platelet activation (39,53).

HIT is a clinicopathologic diagnosis (54). The spectrum ranges from formation of anti-PF4/heparin antibodies to increasing degrees of thrombocytopenia due to platelet activation and in its most severe form diffuse deposition of platelet-related thrombi into microcirculation and extreme depletion of circulating platelets. In a single-center observational study of 1,722 patients undergoing cardiac surgery, HIT was suspected in 63 (3.6%) and confirmed in 24 (1.4%) (55). Validated clinical scoring systems can guide initial decision-making and laboratory testing (39,55–59). These scoring methods take into consideration the characteristic temporal relationship of the onset of thrombocytopenia (± thrombotic event) to heparin exposure (5–14 days) (60), the percent decrease in platelet count (>30–50%) and absolute level of platelets (20–100,000/μL), in addition to duration of CPB, and other potential contributory causes of thrombocytopenia (57,59). The negative predictive value (for HIT) for those with a low clinical scores is 98% (range 97–100%) (58,59). As such, additional serological testing and delays in heparin anticoagulation and/or complications associated with heparin alternatives in these patients can be avoided.

The positive predictive value (PPV) of the anti-heparin-PF4 (ELISA) assay for HIT is very low (2–15%) (61,62). As such, this assay should be limited to those with higher pre-test probabilities (for HIT) found in those with intermediate (PPV of 10–20%) or high (PPV of 40–80%) clinical scores. This usually occurs when the fall in platelet count exceeds 50%, and/or a thrombotic event occurs between postoperative days 5 and 14. Those with low antibody titers (OD < .4) would be candidates for heparin anticoagulation without further intervention given the high sensitivity (90–98%) of this clinical assay (45,53). Postoperatively, close monitoring of platelet counts are recommended and screening for HIT antibodies considered if clinical scores indicate further serological testing is warranted.

Patients with mild elevations in anti-heparin-PF4 titers (OD .4–1.0) should have further serologic testing using a functional assay especially if their clinical scores are in the intermediate or high ranges (39). The high sensitivity (90–98%) and specificity (80–97%) of the functional assays

(SRA/HIPA) make them the gold standard for diagnosing HIT (63). Negative SRA/HIPA frequently occurs in patients with elevated antibody titers using the clinical antigen (ELISA) assays due to the presence of heparin-PF4 antibodies that do not activate platelets or cause thrombocytopenia and/or thrombosis (35). Patients with high clinical scores and high antibody titers (>OD 1.0) are candidates for heparin alternatives when urgent operations preclude the use a functional (SRA/HIPA) assay.

True hypersensitivity to heparin is rare, yet can occur in those allergic to heparin or their sources of heparin (e.g. porcine or bovine sources of heparin) (37,38,64–66). Patients with a clinical suspicion for hypersensitivity to heparin should undergo testing to confirm the diagnosis as soon as possible given the often urgent need for heparin anticoagulation in a variety of clinical settings (37).

The decision to utilize an alternative anticoagulant during CPB is based on the urgency of the cardiac procedure and the presence of heparin antibodies capable of activating platelets. The American College of Chest Physicians recommends delaying non-urgent cardiac procedures until heparin antibodies are no longer detectable (45). The single most cumbersome aspect of heparin alternatives is inability to rapidly reverse anticoagulation after weaning from CPB. For nearly all heparin alternatives there is no reversal agent equivalent to protamine. Other negative side effects include prolonged operative times and the risk of increased blood loss and transfusion. Although several agents have been used as alternates to heparin (47,54), there is only sufficient data on bivalirudin to make recommendations in this clinical setting.

Bivalirudin: Bivalirudin, a recombinant direct thrombin inhibitor, is not currently approved by the Food and Drug Administration for use during CPB (albeit approved for this use outside of the United States). Bivalirudin effectively inhibits the coagulation cascade and has a short 25 minutes half-life in patients with normal renal function. Monitoring of anticoagulation with bivalirudin is more challenging than with heparin. The ecarin clotting time (ECT) correlates strongly (R^2 = .91) with therapeutic bivalirudin concentrations but is not commonly available as a point-of-care test (67). In a comparative analysis study of 10 patients undergoing cardiopulmonary bypass, three different methods of the ACT test were compared to the ECT (68). While not as accurate as the ECT, the more commonly available celite ACT was found to have an acceptable correlation to ECT determined bivalirudin concentration (R^2 = .93).

Bivalirudin has the broadest experience in patients undergoing cardiac surgery (with and without CPB) and in those with HIT and thrombosis (HITT) requiring CPB (69). This includes procedures requiring deep hypothermic circulatory arrest (70). Controlled trials suggest that bivalirudin provides adequate anticoagulation in all patients (71,72). In these trials secondary end points including mortality, 24-hour blood loss, overall incidence of transfusions, and duration of surgery were similar in bivalirudin-treated patients and in patients having CPB with heparin anticoagulation and protamine reversal. Several studies (EVOLUTION-ON, CHOOSE-ON) propose a reliable therapeutic protocol for bivalirudin (71,72). Bivalirudin dosing in the CHOOSE-ON and EVOLUTION-ON trial included a loading dose of 1.0 mg/kg, infusion of 2.5 mg/kg/h and pump prime of 50mg. The adequacy of anticoagulation was monitored using 2.5 times the baseline activated clotting time (ACT). In many centers, target ACT levels were achieved with lower loading dose and infusion rates.

In the EVOLUTION-ON multi-center, open label trial, 101 patients were randomized to either bivalirudin or heparin with protamine reversal. Both groups were successfully anticoagulated and there were no significant differences in morbidity or mortality between groups at 7 days, 30 days or 12 weeks. Postoperative blood loss was statistically higher at 2 hours (238 vs. 160 mL; p = .0009), but not at 24 hours (793 vs. 668 mL; p = .15). Postoperative re-exploration occurred in 6.1 vs. 1.9%, but was not statistically significant (72). Anticoagulation with the direct thrombin inhibitor bivalirudin appears to provide a safe and effective alternative to heparin and protamine reversal, even though it may increase the risk of excessive bleeding. In extreme cases, a combination of modified ultrafiltration, hemodialysis and administration of recombinant factor VIIa, in addition to balanced hemostatic resuscitation with fresh frozen plasma, cryoprecipitate and platelets may be required until the anticoagulants effects of bivalirudin are reversed (70,73,74).

Other alternatives to heparin: Other strategies for anticoagulation in patients with HIT consist of reintroduction of heparin following either the removal of PF4-heparin antibodies (plasmapheresis), administration of intravenous anti-platelet therapy, or use of argatroban. The use of plasmapheresis is generally limited to those with weakly positive ELISA results requiring urgent cardiac procedures (75–77). While each approach appears to be safe and effective, there is insufficient evidence for a recommendation in the setting of CPB.

In a small case series by Welsby et al. (76), 11 patients with recent (<2 months) diagnosis of HIT received therapeutic plasma volume exchange after induction of anesthesia. All patients had a reduction in antibody titers (range of reduction: 50–84%). Of these 11 patients, two patients had positive HIT antibodies at the time of operation. One patient suffered an ischemic foot, likely related to an intra-aortic balloon pump. Three (27%) died in the post-operative period (range: 3 months to 1 year) although none

of the deaths were attributed to HIT thrombosis**.** Other case reports and smaller series are summarized in a practice guideline by the American Society for Apheresis, although recommendations regarding CPB are limited (54,75).

Iloprost (prostacyclin analogue) was used in several studies of HIT patients in order to inhibit platelet activation during cardiac surgery (78). In a large retrospective analysis of 1,518 consecutive cardiac surgery patients, Palatianos et al. (79) identified 10 patients with clinical symptoms of HIT with heparin-PF4 antibodies and compared them to 10 randomly selected controls. Patients presenting with HIT received a protocol of iloprost infusion, supplemented with norepinephrine as needed, in conjunction with heparin. The postoperative reduction in platelet count was less in the iloprost group (12.5 ± 8.7%) vs. the control (38.1 ± 15.2%) and no thrombotic complications were detected. In another small study (n = 10) by Koster et al. (80), heparin was used in conjunction with a tirofiban infusion during CPB. There was no clinical or laboratory (D-Dimer) evidence of thrombosis or excessive bleeding.

The use of argatroban has been reported in patients requiring renal replacement therapy given that renal clearance is an important means of bivalirudin excretion and inactivation, Argatroban should be limited to these exceptional circumstances, given that excessive bleeding is the norm (81–85).

Individuals who are seropositive for heparin antibodies are at increased risk of both thrombosis and bleeding (associated with heparin alternatives). Given the potentially catastrophic thrombotic complication associated with rapid-onset HIT in those with a recent history of HIT, a very high level of vigilance is recommended in patients re-exposed to heparin. These patients warrant careful surveillance, thrombo-prophylaxis and possibly other special treatments to manage the increased risk.

REVERSAL OF ANTICOAGULATION DURING CARDIAC OPERATIONS

Protamine Dosing For Heparin Reversal

Class IIa recommendation: It can be beneficial to calculate the protamine reversal dose based upon a titration to existing heparin in the blood, since this technique has been associated with reduced bleeding and blood transfusion. (Level of Evidence B)

Heparin is by far the most commonly used anticoagulant during the conduct of cardiac operations, whether done with or without CPB. The preeminent benefit of heparin as compared with other anticoagulants is the ability to reverse its effect with protamine in a safe and expeditious manner.

The goals of successful anticoagulation during CPB include limiting clotting and safely reversing the anticoagulation effect during and at the conclusion of operation, respectively. For the vast majority of operations performed using CPB, heparin is the anticoagulant used and protamine is the reversal agent. An important part of the operation is to adequately remove all of the heparin effect at the end of operation. There are at least three methods commonly used to detect residual heparin effect after protamine reversal: 1) activated clotting time (ACT) measurement, 2) point-of-care testing using protamine titration of heparinized blood samples, and 3) thromboelastography with or without heparinase. Comparisons of these three methods suggest that ACT-based measurements of residual heparin effect are the least accurate means of detecting residual heparin effect (86,87).

Methods of heparin reversal are multiple and controversy exists regarding the optimal strategy. Traditional methods administer heparin based on body weight and protamine based on the amount of heparin administered. Certain methods of protamine administration depend on titration of protamine to neutralize heparin in blood samples at the end of CPB. The literature comparisons of these methods are mixed with most reports (88–90), but not all (91,92), favoring titration methods. A meta-analysis of standard weight-based vs. titrated protamine dosing favors titrated dose protamine for heparin reversal because of less postoperative blood loss and decreased packed red blood cell transfusion (93).

Two studies suggest that viscoelastic measurements are useful indicators of adequate titrated heparin reversal (94,95). These studies found that individualized heparin-protamine titration decreased the protamine-to-heparin ratio, improved post-CPB thromboelastometric hemostatic parameters, and reduced the incidence of severe blood loss compared with an ACT-based strategy. In addition, evidence supports the use of sequential heparin/protamine titrations following CPB to further limit blood loss and to provide adequate protamine reversal (88).

Protamine Overdose

Class IIa recommendation: It is reasonable to limit the ratio of protamine/heparin to less than 2.6 mg protamine/100 Units of heparin, since total doses above this ratio inhibit platelet function, prolong ACT, and increase the risk of bleeding. (Level of Evidence C)

It is possible to overdose patients with protamine. Excess protamine inhibits platelet function and prolongs the ACT after CPB. Two studies provide convincing evidence that when the ratio of protamine to heparin (mg protamine/100 Units heparin) is above 5:1, platelet aggregation and function are impaired (96,97). In addition, Mochizuki et al. (96) demonstrated that at ratios above 2.6:1, the ACT significantly increases. The European Association of Cardiothoracic Surgery identified a ratio of 2.6:1 of protamine to heparin as risking excessive bleeding. Their

guidelines recommend limiting protamine, preferably using a titration method, after the completion of CPB (98).

Heparin Rebound

Class IIb recommendation: Because of the risk of heparin rebound in patients requiring high doses of heparin and with prolonged CPB times, low dose protamine infusion (25 mg/h) for up to 6 hours after the end of CPB may be considered as part of a multimodality blood conservation program. (Level of Evidence C)

Heparin rebound occurs when detectable heparin blood levels are present at some remote time after apparently adequate heparin reversal with protamine. This likely occurs because of the ability of large molecules of heparin to sequester in fat stores and plasma proteins with eventual reappearance in the blood at some time after protamine neutralization. Heparin dosing in excess of 400 IU/kg can result in heparin rebound. High heparin dosing during CPB results in higher doses of protamine required for reversal.

Randomized comparisons of high and low-dose heparin for CPB suggest that heparin rebound increases with high dose heparin (21). One study suggests that 10–15% of patients receiving usual heparin doses for CPB will have detectable heparin levels two hours after protamine reversal (99). Another study finds that detectable heparin levels, measured using both anti-Xa and viscoelastic parameters, are present immediately, two hours, and four hours after protamine administration (22).

Usual methods of monitoring heparin reversal and measuring postoperative coagulation (e.g. ACT and APTT) do not detect residual heparin levels (86,100). A randomized trial involving 300 patients showed that a continuous infusion of protamine following initial protamine reversal (25 mg/h for 6 hours) abolishes heparin rebound and results in modest, but significant, reductions in chest tube blood loss but not transfusion requirements (101).

Complications Associated with Protamine Reversal of Heparin after CPB

Class I recommendation: In patients at high risk for anaphylactic response to protamine who experience pulmonary hypertension and circulatory collapse shortly after protamine administration, discontinuation of protamine and implementation of resuscitative measures including reinstitution of CPB with adequate anticoagulation may be lifesaving. (Level of Evidence C)

As one might expect with any drug, there are side effects and complications associated with the use of protamine to reverse the effects of heparin after CPB. A unique feature of these complications associated with CPB is that they occur at a crucial time of the operative procedure. Life-threatening complications associated with protamine include anaphylaxis, pulmonary edema and pulmonary hypertension (102). Life threatening cardiovascular compromise after intravenous protamine can occur even in young infants (103). These complications are associated with operative mortality and serious organ dysfunction (104,105). It is likely that protamine complications are under- reported (102,106). A comprehensive review of the literature suggests true anaphylactic reactions to protamine are rare (less than one percent of patients having CPB), (102) and about 60% occur before CPB, likely related to other drugs used in preoperative preparation of patients (e.g. antibiotics or gelatin solution) (107). The results from this limited database of anaphylactic reactions showed that cardiac surgery proceeded without complications after cardiovascular collapse caused by pre-CPB anaphylactic or anaphylactoid reactions. Rapid institution of cardiopulmonary bypass may be lifesaving in this setting (108).

Catastrophic cardiovascular reactions to protamine are nitric oxide/cyclic guanosine monophosphate dependent and endothelium mediated. This suggests that methylene blue may be the treatment of choice in this setting but high level evidence to support this intervention is lacking (108). Evidence to date suggests that the site of protamine administration does not influence the incidence of protamine-induced pulmonary vasoconstriction, and aspirin ingestion within 1 week of surgery may decrease it (109). Additionally, acute right ventricular failure and pulmonary hypertension often precede catastrophic reactions to protamine (105,110,111). Prostacyclin and bradykinin B2 attenuate the acute pulmonary hypertension in this setting but, again, no high level evidence supports the use of these agents to reverse the early stages of a reaction to protamine (110,112). What is known is that serious protamine reactions predispose to operative mortality and discontinuation of protamine and re-institution of CPB, if serious protamine reactions occur, may be lifesaving (105,107).

Studies show that antibodies to the protamine/heparin complex occur commonly after CPB (113,114). These antibodies share a number of serologic features with HIT-derived antibodies, including platelet activation. Additionally, these protamine/heparin antibodies cross-react with protamine-containing insulin preparations (113). Development of these antibodies predisposes to adverse outcomes following cardiac procedures and may pose risks of anamnestic response upon re-exposure to protamine (113,114). For example, a meta-analysis of the surgical literature showed the risk of a protamine reaction in surgical patients to be 10–20 times higher in patients taking protamine-containing insulin compared to control patients not taking insulin preparations (109,115).

Alternate Agents Used to Reverse Heparin Anticoagulation

Reversal of heparin with protamine affects platelet aggregation and whole blood clotting (96). The overwhelming

convenience of protamine reversal of heparin makes it the drug of choice for heparin neutralization despite potential adverse effects on platelet and clotting function. There are patients who are unable to receive protamine for various reasons. For this reason, PF4 has been investigated as a heparin reversal agent in ex-vivo animal studies, and occasional case reports (116–118). PF4 is released by activated platelets and has strong attraction for heparin. Studies show that recombinant PF4 provides adequate heparin neutralization. However, pre-formed antibodies against PF4/heparin complex are important contributors to the pathophysiology of HIT. Patients previously exposed to heparin may have these pre-formed antibodies and addition of exogenous PF4 in the presence of heparin risks an anamnestic response and severe HIT and/or HITT. More clinical experience is required to validate the safety of PF4 for heparin reversal after CPB (118).

Reports document attempts at using other drugs for heparin neutralization. Methylene blue, hexadimethrine, vancomycin, and heparinase I are among drugs tested for heparin neutralization (117,119,120). None of these drugs proved equivalent to protamine in its safety profile for reversal of heparin after CPB. One of these drugs, heparinase I, was compared to protamine in a multicenter, randomized, prospective trial. Heparinase I had an inferior safety profile following reversal of heparin at the end of CPB which was a result of increased transfusion and prolonged hospital stay in the heparinase group compared to the protamine group (120).

At this time, protamine is considered the gold standard for reversal of heparin anticoagulation. If protamine cannot be used, there are not enough data to make a recommendation regarding safety and efficacy of any of the alternative heparin reversal agents.

Anticoagulation reversal when using heparin alternatives and direct thrombin inhibitors

Class IIb recommendation: In patients requiring anticoagulation with bivalirudin who experience excessive bleeding after CPB, a combination of modified ultrafiltration, hemodialysis, and the administration of recombinant factor VIIa with blood product replacement may be considered to improve hemostasis in these extreme situations. (Level of Evidence C)

The ideal anticoagulation strategy for cardiac surgery with CPB in patients who cannot take heparin does not exist. Heparin and protamine remain the gold standard for anticoagulation therapy. A small subset of patients requires heparin alternatives for the conduct of CPB. Bivalirudin seems to offer the safest heparin alternative in this setting. This drug has a short half-life of approximately 25 minutes. Nonetheless, coagulopathy occurs in bivalirudin treated patients. There is no well-defined reversal agent for bivalirudin, and patients with coagulopathy and excessive bleeding require unusual interventions for hemorrhage control. Only anecdotal experience is available to address coagulopathy in bivalirudin-related hemorrhage (70,73). Consensus suggests that a multifaceted approach offers the best chance of successful hemorrhage control in these patients. Recombinant activated Factor VII may be an important part of hemorrhage control but other interventions including modified ultrafiltration, hemodialysis, and clotting factor replacement are also advocated (73).

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APPENDIX 1: EXECUTIVE SUMMARY OF RECOMMENDATIONS

A functional whole blood test of anticoagulation, in the form of clotting time, should be measured and should demonstrate adequate anticoagulation before initiation of and at regular intervals during cardiopulmonary bypass (CPB). (Class I, Level of Evidence C).

Bolus administration of unfractionated heparin based upon weight is reasonable for achieving adequate anticoagulation, but individual response to heparin is heterogeneous and requires a therapeutic functional test of clot inhibition before initiation of CPB, independent of the bolus dose used (Class IIa, Level of Evidence C).

It is reasonable to use activated clotting time (ACT) tests that produce "maximally activated" clotting times because these tests mitigate ACT variability, are less susceptible to hypothermia, and correlate more closely with Factor Xa activity compared with tests that employ a single activator (Class IIa, Level of Evidence B).

It is reasonable to maintain ACT above 480 seconds during CPB. However, this minimum threshold value is an approximation and may vary based upon the bias of the instrument being used. For instruments using "maximal activation" of whole blood or microcuvette technology, values above 400 seconds are frequently considered therapeutic (Class IIa, Level of Evidence C).

Use of a heparin dose-response formula may identify reduced sensitivity to heparin, but has not been shown to be more useful than weight-based heparin dosing, in determining the heparin dose required to achieve an adequate ACT *for initiation of CPB* (Class IIb, Level of Evidence B).

Use of heparin concentration monitoring in addition to ACT might be considered, *for the maintenance of* CPB, as this strategy has been associated with a significant reduction in thrombin generation, fibrinolysis, and neutrophil activation. However, its effects on postoperative bleeding and blood transfusion are inconsistent (Class IIb, Level of Evidence B).

During CPB, routine administration of heparin at fixed intervals, with ACT monitoring, might be considered and offers a safe alternative to heparin concentration monitoring (Class IIb, Level of Evidence C).

Clinical scoring estimates that use a fall in platelet count greater than 50% and/or a thrombotic event between 5 and 14 days after a heparin exposure can be used to determine whether a heparin-platelet antibody test should be performed to diagnose heparin-induced thrombocytopenia (HIT) (Class IIa, Level of Evidence B).

Serum tests that include functional testing with serotonin release assay or heparin-induced platelet activation can be beneficial in identifying patients with HIT who have a history of thrombocytopenia, and elevated clinical HIT risk scores, when platelet factor 4 (PF4)/heparin antibody testing is inconclusive (weakly positive) for HIT (Class IIa, Level of Evidence C).

In patients who are seropositive for heparin-platelet antibodies or have a recent history of HIT, it is reasonable to delay elective cardiac operations requiring CPB until a patient's functional test and/or antigenic (antibody) assay are negative, with the expectation that heparin anticoagulation for CPB is likely to be safe and effective (Class IIa, Level of Evidence C).

In patients with a diagnosis of HIT and in need of an urgent operation requiring CPB, anticoagulation with bivalirudin is a reasonable option (Class IIa, Level of Evidence B).

In patients with significant renal dysfunction who are seropositive for HIT and require urgent operation requiring CPB, use of plasmapheresis, argatroban, or heparin with antiplatelet agents (such as tirofiban and ilioprost) may be considered, understanding that there are increased risks of bleeding with these interventions (Class IIb, Level of Evidence C).

It can be beneficial to calculate the protamine-reversal dose based upon a titration to existing heparin in the blood because this technique has been associated with reduced bleeding and blood transfusion (Class IIa, Level of Evidence B).

It is reasonable to limit the ratio of protamine/heparin to less than 2.6 mg protamine/100 Units of heparin because total doses above this ratio inhibit platelet function, prolong ACT, and increase the risk of bleeding (Class IIa, Level of Evidence C).

Because of the risk of heparin rebound in patients requiring high doses of heparin and with prolonged CPB times, low-dose protamine infusion (25 mg/h) for up to 6 hours after the end of CPB may be considered as part of a multimodality blood conservation program (Class IIb, Level of Evidence C).

In patients at high risk for anaphylactic response to protamine who experience pulmonary hypertension and circulatory collapse shortly after protamine administration, discontinuation of protamine and implementation of resuscitative measures including reinstitution of CPB with adequate anticoagulation may be lifesaving (Class I, Level of Evidence C).

In patients requiring anticoagulation with bivalirudin who experience excessive bleeding after CPB, a combination of modified ultrafiltration, hemodialysis, and the administration of recombinant factor VIIa with blood product replacement may be considered to improve hemostasis in these extreme situations (Class IIb, Level of Evidence C).