Management of anticoagulation in patients with heparin-induced thrombocytopenia requiring cardiac surgery with cardiopulmonary bypass: Guidance from the ISTH SSC on Perioperative and Critical Care Haemostasis and Thrombosis

Allyson M. Pishko[1]*, Corinne Frere[2]*, Cheryl L. Maier[3], Jerrold H. Levy[4] and Jean M. Connors[5]

[1]Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[2]Department of Hematology, Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris; Sorbonne Université, INSERM UMR_S 1166, Paris, France

[3]Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia, USA

[4]Department of Anesthesiology, Critical Care and Surgery, Duke University School of Medicine, Durham, NC, USA

[5] Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

* *These authors contributed equally to the work*

Correspondence to:

Jean M Connors

Dana Farber Cancer Institute

44 Binney Street

Boston, MA 02215

jconnors@bwh.harvard.edu

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Authors: 10

Text: 4983

Tables/figures: 5

ABSTRACT

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse drug reaction characterized by thrombocytopenia and a high risk of thrombosis. Patients with HIT and need for cardiac surgery with cardiopulmonary bypass (CPB) represent a challenging group, as systemic anticoagulation with unfractionated heparin (UFH) is the primary treatment choice. Evidence to guide intraoperative anticoagulation in patients with HIT undergoing cardiac surgery remains limited to observational studies and case reports. We conducted a systematic review evaluating intraoperative anticoagulation strategies for patients with a history of HIT that required cardiac surgery with CPB. Eligible studies included randomized trials, observational studies and case series with ≥3 patients, as well as key case reports deemed informative. Data were extracted and summarized regarding anticoagulation strategy, efficacy, thrombotic and bleeding outcomes, and mortality. Guidance statements were generated through consensus of the writing group, using standardized terminology to reflect the strength of the recommendation and certainty of evidence. Of 1732 screened articles, 31 studies were included. Strategies evaluated included use of (1) direct thrombin inhibitors (bivalirudin or argatroban); (2) UFH after preoperative or intraoperative therapeutic plasma exchange (TPE), with or without intravenous immunoglobulin (IVIG); (3) UFH in combination with a potent antiplatelet agent (e.g., iloprost, tirofiban, cangrelor); and (4) Heparin re-exposure in patients with negative functional assays. Of these, bivalirudin has the strongest supportive data and appears effective; still, its association with increased bleeding and transfusion requirements and practical limitations, including lack of a reversal agent, limit use. Evidence for argatroban is limited and associated with a high bleeding risk. TPE with or without IVIG reduces anti-PF4/heparin antibody titers and has allowed for safe intraoperative UFH use, although protocols are heterogeneous. Use of potent antiplatelet agents in the setting of UFH re-exposure show promise but carry risks of bleeding and hypotension. Thus, alternative strategies of using UFH in combination with TPE or potent antiplatelet agents may be considered on a case-by-case basis. For patients with negative functional assays, available evidence suggests that limiting UFH re-exposure to the intraoperative period

carries a very low risk of HIT recurrence, provided postoperative monitoring is performed. .

These guidance statements provide a framework for multidisciplinary decision-making in a complex clinical scenario.

1. Introduction

Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction to heparin, mediated in most cases by immunoglobulin G (IgG) antibodies that target platelet factor 4 (PF4)/heparin complexes [1]. These antigen-antibody complexes activate platelets, resulting in thrombocytopenia and a hypercoagulable state, which in turn promotes both venous and arterial thrombosis. In patients with acute HIT, heparin should be discontinued immediately and replaced with a non-heparin anticoagulant to prevent thrombotic complications[1].

Patients undergoing cardiopulmonary bypass (CPB) require systemic anticoagulation during surgery to prevent clotting in the CPB circuit and thromboembolism. Due to its rapid onset of action, long history of use, established effectiveness, ease of monitoring with the point-of-care activated clotting time (ACT) assay, and reversibility with protamine, unfractionated heparin (UFH) is highly preferred in this setting. Although bivalirudin is used as an alternative anticoagulant for CPB, there are many limitations, as there is no reversal agent, its metabolism and excretion are variable due to changes in temperature and renal perfusion, and can result in thrombosis in low-flow areas of the heart and venous reservoir of the CPB circuit [2,3].

Although a history of HIT is not an absolute contraindication to cardiac surgery, some patients undergoing CPB may require alternative anticoagulation strategies. Selecting the best option for intraoperative anticoagulation is challenging; the risk of thrombosis with heparin re-exposure varies based on whether HIT is acute, remote, or somewhere in between. The management of patients with HIT, including those undergoing cardiac surgery, has been previously addressed in guidelines published by the American College of Chest Physicians (ACCP) in 2012 [4] and the American Society of Hematology (ASH) in 2018 [5]; however, variability in institutional practices for patients undergoing CPB still exists [6].

In this document, we summarize the limited available evidence and provide guidance for intraoperative anticoagulation in patients with a history of HIT undergoing CBP.

2. Methodology

A comprehensive literature search was performed using the following keywords: {("heparin-induced thrombocytopenia" [tiab] OR "HIT" [tiab]) AND ("cardiac surgical procedures" [Mesh] OR "cardiac surgery"[tiab] OR "heart surgery" [tiab] OR "coronary artery bypass"[tiab] OR "valve replacement"[tiab] OR “heart transplant” [tiab])} iin MEDLINE, EMBASE, and the

Cochrane Central Register of Controlled Trials from database inception to May 30, 2025. The search was restricted to English articles and human studies. The reference lists of all included studies were screened for additional relevant studies. Covidence (Veritas Health Innovation, Melbourne, Australia) was used to remove duplicates and manage citations across databases. Three members of the writing group (A.M.P., J.H.L., and C.F.) screened all records independently to identify potentially eligible references based on the titles and abstracts. Studies had to include patients with a history of laboratory-confirmed HIT who received any of the following interventions for cardiovascular surgery with CBP:

1. Direct thrombin inhibitor
2. Therapeutic plasma exchange and intra-operative UFH
3. Potent antiplatelet agent and intra-operative UFH
4. Intra-operative UFH re-exposure alone (in patients with negative functional assays)

Studies were excluded if they did not report any of the critical outcomes: mortality, bleeding, thrombotic events. Randomized controlled trials (RCTs), observational studies, and case series of at least 3 patients were included. Exceptional case reports that were identified by the data extractors as having key insights into the risks of UFH re-exposure or other strategies were included and reported separately. Abstracts, editorials and press releases were excluded. Two panelists (A.M.P. and C.F.) extracted, analyzed, and summarized the data in evidence tables. Guidance statements were generated after reviewing the available evidence and discussion between co-authors.

All co-authors submitted a declaration of competing interest. Conflicts of interest of all co-authors were reviewed prior to discussion of the guidance statement. If any significant financial conflict of interests existed, the co-author was recused from discussion of the guidance statement.

Consistent with previous ISTH guidance documents, the wording “we recommend” indicates a strong guidance statement with good consensus among panelists, which clinicians should consider adopting into practice in most cases. The wording “we suggest” reflects a weak guidance statement, characterized by moderate consensus among the panelists and the lack of high-quality evidence, which clinicians may or may not adopt.

3. Results

Of the 1732 articles identified, 1564 were excluded as not meeting eligibility criteria based on title and abstract review. Of the 168 manuscripts that underwent full text review, 30 met eligibility criteria for inclusion (Supplemental Figure 1). No randomized controlled studies and

only one retrospective observational study [7] compared management strategies of the interventions of interest in the target population. Four studies reported on direct thrombin use [7–10], 5 studies reported use of TPE with or without IVIG [11–15], and 10 studies reported potent antiplatelet [16–25]. Seven studies reported on UFH re-exposure alone in patients with history of HIT[26–32]. Four case reports were included that were deemed by data extractors to have key insights into risks of UFH re-exposure or other strategies[33–36].

4. Evaluating patients with a history of HIT who require cardiac surgery

Patients with a history of HIT who require cardiac surgery with CPB should first undergo a thorough review of their medical history, as overdiagnosis or misdiagnosis of HIT is common [37]. Meticulous review is necessary to definitively confirm or rule out HIT, and should include the duration of heparin exposure, the timing and percent fall in platelet count, whether a thrombotic complication occurred, and the results of confirmatory laboratory tests that led to the diagnosis of HIT. Notably, HIT diagnosis can be particularly challenging in medical-surgical ICU patients because thrombocytopenia is common and results from multiple factors, including comorbid conditions (e.g., sepsis, consumption coagulopathy, and multiorgan system failure) and treatments and procedures (e.g., other drug-induced thrombocytopenia, intra-aortic balloon pump, and extracorporeal membrane oxygenation)[38]. Although the 4Ts score is the most validated clinical scoring system for determining the pretest probability of HIT[39], it performs poorly in medical-surgical ICU patients [40]. More specific scores have been developed but have not yet been sufficiently validated for clinical use [41,42].

Results of the initial HIT diagnostic laboratory testing should also be reviewed. Commercially available HIT immunoassays are highly sensitive and can detect circulating anti-PF4/heparin antibodies, regardless of whether they have the ability to activate platelets. These screening assays have a low specificity, and positivity may reflect the presence of non-pathogenic anti-PF4/heparin antibodies, which are particularly prevalent following cardiac surgery, appearing in nearly 50% of patients[43,44]. It is important to consider the degree of positivity of ELISA based assays based on optical density (OD) as the likelihood of HIT increases with a higher OD[45]. Similarly, rapid turnaround immunoassays have a low threshold for positivity, with increasing likelihood based on degree of positive results in U/mL [46]. Functional tests, including the serotonin release assay (SRA) and the washed-platelet heparin-induced platelet activation (HIPA) assay, detect antibodies that activate platelets in a heparin-dependent manner and are thus highly specific confirmatory tests for HIT.

If a history of HIT is confirmed, the next step is to order laboratory testing as soon as possible to guide the management strategy for CPB. Tests should include platelet count, either ELISA or rapid immunoassay, and a functional assay (ideally SRA or HIPA). HIT typically follows a

predictable course with the platelet count recovering first, followed by a negative functional assay, and then loss of detectable antibody. In most patients, platelet count recovery occurs within 10 days of heparin cessation and use of an alternative anticoagulant, although it may take weeks in a minority of individuals. Functional assays and immunoassays become negative at a median of 50 (95% CI, 32–64) and 85 (95% CI, 64-124) days, respectively [47]. The risk of UFH re-exposure for CPB differs depending on whether the functional assay has become negative or not [5].

In patients with a documented history of HIT who require emergent cardiac surgery with CPB and for whom confirmatory laboratory test results are unavailable prior to surgery, the management strategy should be based on the time elapsed since the diagnosis of HIT and the last exposure to heparin. The time to seroreversion after an episode of HIT ranges from 40 to 100 days, with significant variability between individuals [47]. Nevertheless, while the likelihood of clinically significant HIT antibodies being present in a patient diagnosed with HIT five years ago is negligible, they are likely to persist in a patient diagnosed a month ago.

Guidance statements:

-In patients with a history of HIT who require cardiac surgery with CPB, we recommend meticulous review of the clinical history and laboratory testing that led to the HIT diagnosis to definitively confirm or rule out HIT.

- In patients with a documented history of HIT, we recommend ordering laboratory testing as soon as possible, including platelet count, immunoassay and functional assay, to determine the current status of HIT, which will guide the cardiopulmonary bypass management strategy.

- In patients with a documented history of HIT who require emergent cardiac surgery with CPB and for whom HIT laboratory test results are unavailable before surgery, we suggest considering the natural history of anti-PF4/heparin antibodies seroreversion (*i.e.*, 40 to 100 days) to aid in determining the type of anticoagulant to use.

4. Management strategy for patients with positive HIT immunoassay and positive HIT functional assay

In patients who have platelet-activating anti-PF4/heparin antibodies, as evidenced by a positive functional assay, heparin re-exposure confers an immediate risk of severe thrombotic complications (44%) and thrombosis-related death (33%) [48]. These patients with positive results on both the screening and functional assays have what is often termed “acute HIT.” The ACC and ASH guidelines recommend postponing surgery until a patient with acute HIT has a negative functional assay, if feasible, at which time standard high-dose UFH can be used for anticoagulation during CPB [4,5]. If cardiac surgery cannot be delayed, three alternatives to

UFH anticoagulation during CPB have been evaluated: 1) intraoperative anticoagulation with a direct thrombin inhibitor (DTI), 2) intraoperative anticoagulation with heparin following preoperative and/or intraoperative therapeutic plasma exchange (TPE), and 3) intraoperative anticoagulation with heparin in combination with a potent antiplatelet agent [5]. We evaluated each of these strategies in patients with a history of HIT. Limited data were reported for patients specifically with positive functional assays, and thus the data presented includes patients who have negative or unknown functional assays.

Intraoperative anticoagulation with direct thrombin inhibitors

Two DTIs, bivalirudin and argatroban, were evaluated in patients with HIT or history of HIT undergoing cardiovascular surgery with CPB (see **Table 1**). Bivalirudin, a synthetic, bivalent, polypeptide DTI, reversibly binds to the active site and exosite-1 of thrombin, inhibiting both free and clot-bound thrombin. Its onset of action is 2–4 minutes and its half-life is 25 minutes in patients with normal renal function; it is prolonged in patients with renal impairment. Bivalirudin clearance is primarily mediated by proteolytic cleavage by plasma proteases (80%). Renal clearance also plays a role. Dose adjustments are required for renal impairment but not hepatic impairment. Argatroban, a synthetic univalent DTI, reversibly binds to the active catalytic site of thrombin, inhibiting both free and clot-bound thrombin. Its onset of action is 30 minutes, and its half-life is 30–50 minutes. Argatroban is primarily metabolized in the liver and can thus be used in patients with renal failure. Dose adjustments are necessary for patients with hepatic impairment. Neither bivalirudin nor argatroban have a specific reversal agent.

The open-label, multicenter CHOOSE-ON study enrolled 49 patients with confirmed or suspected HIT and/or anti-PF4/H antibodies undergoing cardiac surgery with CPB for CABG and/or valve replacement [10]. Forty-two (85.7%) patients were diagnosed with HIT shortly before their operation (35 having positive serologic assays and 7 with positive functional assays). Six (12.2%) patients were classified as having a “history of HIT” without documented anti-PF4/H antibodies or thrombocytopenia at time of surgery. In 3 (6.1%) patients, HIT test results were not available. Patients with severe renal failure (CrCl <30 mL/min or were dependent on dialysis), as well as those with a ventricular ejection fraction of less than 0.30 or those requiring surgery on more than one heart valve were excluded. The primary outcome of in-hospital procedural success (defined as an absence of death, myocardial infarction, stroke, or repeat revascularization) at 7 days, 30 days, and 12 weeks was achieved in 46 (94%), 42 (86%), and 40 (82%) patients, respectively. At day 30, 2 patients (4.1%) had major hemorrhage or required surgical re-exploration, and 1 patient (2.1%) had a stroke; the authors did not comment on whether the stroke was thought to be due to HIT.

In a retrospective study of patients with HIT antibodies (functional assay results not reported) requiring left ventricular assist device (LVAD) implantation, 21 patients received bivalirudin and were compared to 36 non-HIT patients who received UFH [8]. The primary outcome of need surgical re-exploration within 7 days post-operatively due to persistent hemorrhage or cardiac tamponade after surgery occurred in four (19%) patients in the bivalirudin group and six (16.7%) patients in the heparin group. Delayed chest closure, stroke, intracranial bleeding, re-thoracotomy after seven days, and mortality within one year were similar in both groups.

In a retrospective study of patients with a history of HIT who underwent CPB, primarily for CABG and/or valve surgery, 13 patients with a diagnosis of HIT within three months of CPB received a DTI during CPB, and 59 patients with a diagnosis of HIT within three years of CPB received heparin with protamine reversal [7]. The rates of 30-day mortality, thrombosis, and hemorrhage were similar in both groups.

Overall, available data suggests that intraoperative anticoagulation with bivalirudin appears to be an effective alternative to UFH with protamine reversal. There may be an increased risk of bleeding and increased need for blood products. As no reversal agent is available and bivalirudin does not prevent clot formation in stagnant blood at clinical concentrations, surgical and perfusion practices must be adapted[10]. Blood must be recirculated through any closed shunts of the bypass machine every 15–20 minutes. Separating cardiotomy suction from the venous reservoir or processing stagnant blood pools through the cell saver may be necessary. In addition, maintaining normothermia is necessary to ensure that metabolization of bivalirudin is not slowed, since hypothermia reduces the proteolysis of bivalirudin.

Experience with the use of argatroban for intraoperative anticoagulation during cardiac surgery in patients with positive HIT immunoassays is very limited. In the largest case series to date, six out of seven patients who received argatroban during CPB for LVAD implantation had successful implantation[9]. However, four patients experienced bleeding complications requiring re-exploration after surgery. One patient developed a massive intraventricular thrombus and multiorgan failure due to uncontrollable coagulopathy, leading to death on postoperative day two.

Although argatroban has FDA and EMA approval for use as prophylaxis and treatment of HIT, available data suggest off-label use of bivalirudin, which is approved only for PCI, as the preferred heparin alternative for intraoperative anticoagulation during CPB[5].

Intraoperative anticoagulation with heparin following preoperative and/or intraoperative therapeutic plasma exchange

Pre-operative and/or intraoperative TPE with or without intravenous immunoglobulin (IVIG) has been described in patients with acute HIT to remove anti-PF4/heparin antibodies from the circulation and enable intraoperative UFH re-exposure. Five case series [14–18] evaluated the efficacy and safety of preoperative and/or intraoperative TPE, with or without intravenous immunoglobulin (IVIG) (**Table 2**). Protocols for TPE varied widely across studies. The number of preoperative TPE sessions ranged from one to nine. Both albumin and plasma (or a combination of both) were used as replacement fluids during TPE, with considerable variation between studies. In most cases, the volume of plasma exchanged was 1-1.3 times the plasma volume. Use of repeated laboratory testing and target serologic endpoints varied (i.e. negative immunoassay, negative functional assay, and/or threshold).

One case series of TPE prior to CPB included eleven patients, nine with newly diagnosed HIT within two weeks of cardiac surgery and 2 with history of HIT and positive PF4/heparin ELISA within 2 months of surgery[11]. None of the patients had a positive functional assay (heparin-induced platelet aggregation assay). A single TPE session before re-exposure to heparin during CPB reduced anti-PF4/heparin antibody titers by 50%-84%. There was no HIT recurrence. One patient developed ischemic foot syndrome, likely due to the use of an intra-aortic balloon pump in the setting of cardiogenic shock.

In the largest case series (n = 24), which included patients with positive HIT immunoassays (HIT functional assay not reported) who underwent one TPE session prior to re-exposure to heparin during CPB, TPE significantly reduced anti-PF4/heparin antibody titers (median OD decreased from 1.99 to 0.34)[13]. There were three non-HIT-related deaths. Thromboembolic events occurred in three patients within seven days of surgery; two of these events (one stroke, one DVT) were considered HIT-related due to concomitant declines in platelet count.

Another case series described 3 patients who received polyvalent IVIG before or after TPE to prevent anti-PF4/heparin antibody–induced platelet activation, and no patient who received both TPE and IVIG experienced a thromboembolic event[14].

When TPE is used prior to cardiac surgery, residual levels of anti-PF4/heparin antibodies may persist. Ideally, a negative functional assay (e.g., SRA or HIPA) would be achieved prior to CPB[49], however, in many institutions the turnaround time to obtain functional assay results can be days, in which case a negative or at least decreasing immunoassay level may suffice. While many institutions have TPE protocols available for patients with immunoassay and functional assay positive HIT, there is wide heterogeneity in approach and outcomes have not been published [6].

No published studies report the use of IVIG as monotherapy in patients with positive functional assays undergoing cardiac surgery. The use of IgG is more robust for cases of “auto-immune”

HIT and similar polyaninon-PF4 prothrombotic conditions such as vaccine-induced immune thrombotic thrombocytopenia (VITT) [50,51]. Mechanistically, IVIG blocks Fcγ receptor-mediated platelet activation, which is central to the pathogenesis of these prothrombotic disorders. It is plausible that IVIG would also block heparin-PF4 antibody complexes, but the evidence is more limited, and when used in conjunction with TPE less able to discern effect.

Intraoperative anticoagulation with heparin in combination with a potent antiplatelet agent

Limited data exists on the efficacy and safety of intraoperative re-exposure to UFH in combination with a potent antiplatelet agent for patients with acute HIT. Antiplatelet agents used in this setting include prostacyclin receptor agonists (epoprostenol sodium and iloprost), GP IIb/IIIa antagonists (tirofiban, abciximab), and the P2Y12 receptor antagonist cangrelor (**Table 3)**.[16–25]

Six case series have documented the use of prostacyclin receptor agonists to facilitate intraoperative re-exposure to heparin during cardiac surgery in patients with positive HIT immunoassays[16–20,24]. In a retrospective series of 110 cases of acute HIT (ELISA immunoassay and HIPA positive) and 118 controls without HIT, the 30-day postoperative mortality rate (8.2% vs. 8.5%) and postoperative thrombosis rate (5.1% vs. 5.4%) were similar in the iloprost and control groups[20]. However, prostacyclin analogues have a very short half-life (six minutes for epoprostenol and 30 minutes for iloprost) and require individualized dose titration because their antiaggregant effect varies among individuals. Additionally, they have an affinity for other prostanoid receptors and have been associated with severe hypotension and an increased need for vasopressors in most reports[20] .

The use of the GP IIb/IIIa antagonist tirofiban to facilitate re-exposure to heparin during CPB in patients with positive HIT immunoassays with and without positive HIT functional assays has been evaluated in one retrospective cohort study [21] and one case series of patients with renal failure [25]. Koster et al. reported on their one-year experience using heparin in combination with tirofiban during continuous renal replacement therapy (CRRT) in 47 patients with HIT, including 35 patients with both positive immunoassay and functional assays[25]. There were no HIT-related deaths or postoperative thrombotic complications; two patients died of myocardial failure. In a series of ten patients with positive immunoassays and functional assays and impaired renal function, none experienced thromboembolic events or major bleeding[25].

Lee et al. reported on six patients with HIT who underwent LVAD implantation with heparin in combination with the GP IIb/IIIa antagonist abciximab, including four (67%) patients with acute HIT[22].None of the patients experienced thromboembolic events. One patient (17%) required mediastinal re-exploration due to bleeding and temporary external right ventricular VAD placement. Although rare, profound and severe thrombocytopenia can occur rapidly within hours after a dose of abciximab in some patients, making use in patients undergoing CPB concerning[52].

The P2Y12 receptor antagonist cangrelor has been proposed for facilitating intraoperative re-exposure to UFH during cardiac surgery in patients with positive HIT functional assays and positive HIT immunoassays. In one series of ten patients [23] including three patients with acute HIT, cangrelor was administered before heparin and throughout CPB. None of the three patients with acute HIT experienced a postoperative thrombotic event. One patient with intracardiac tumor, for whom life support was withdrawn, died. Another patient developed bleeding that required packed red blood cell transfusions on postoperative days 4 and 6. Notably, in one case report in a patient with HIT (positive PF4/H antibodies and functional tested) treated with cangrelor and heparin for CPB a patient developed massive iliofemoral venous thrombosis and continued thrombocytopenia on postoperative day 1, thought likely due to HIT exacerbation[36].

Comparison of strategies

A recent systematic review and meta-analysis compared the efficacy of TPE versus intravenous cangrelor before heparin re-exposure in patients with a history of HIT (positive antibody or functional testing or clinical criteria such as high 4T score) undergoing CPB. The pooled perioperative thromboembolism avoidance rate was 91.0% (95% CI, 82.6%-96.9%) with TPE and 83.0% (95% CI, 61.2%-97.6%) with cangrelor [53].

Of all of these strategies, bivalirudin use is supported by the most evidence, although available data suggest the risk of thrombotic events and major bleeding may be similar across treatment options. However, no studies directly compare treatment options in patients with positive functional assays.

In the absence of comparative studies or robust data in patients with acute HIT (i.e. positive functional assay results), a specific intra-operative anticoagulant strategy could not be recommended by the panel. Some panelists noted that for higher risk cardiovascular surgeries, such as cardiac transplant, surgical teams at their institution will not use bivalirudin due to concern for adverse bleeding and thrombotic events. Institutions with ready access to experienced apheresis teams and HIT laboratory tests may opt for TPE with intra-operative

heparin re-exposure. *Figure 1* outlines considerations in selection of management strategy for patients with positive functional assays who require urgent CV surgery with CPB.

Guidance statements:

-In patients with positive HIT functional assays who require elective CPB, we recommend postponing surgery until the patient has a negative HIT functional assay

-In patients with positive HIT functional assays who require emergent cardiac surgery, we recommend defining the anticoagulation protocol based on a thorough evaluation of the patient, including clinical status, renal and liver function, and risk of bleeding. The protocol should be established within the framework of a multidisciplinary team (surgeon, anesthesiologist, hemostasis specialist and perfusionist). The team's experience, available drugs and locally available testing modalities should be taken into account.

-In patients with positive HIT functional assays who require emergent cardiac surgery, we suggest a case-by-case consideration of the following alternatives to heparin for intraoperative anticoagulation during CPB:

- ✓ Intraoperative anticoagulation with bivalirudin (requires adaptation of surgical and perfusion practices) with close monitoring.
- ✓ Intraoperative anticoagulation with heparin after preoperative and/or intraoperative therapeutic plasma exchange with or without IVIG followed by reversal with protamine and close monitoring.
- ✓ Anticoagulation with heparin in combination with a potent antiplatelet agent (tirofiban, cangrelor), followed by reversal with protamine and with close monitoring.

-If heparin is used for anticoagulation during cardiac surgery (after preoperative and/or intraoperative TPE or in combination with a potent antiplatelet agent) in patients with positive HIT functional assays, we recommend scrupulously avoiding heparin before and after surgery; if pre- or post-operative anticoagulation is indicated, a non-heparin anticoagulant should be prescribed.

-In patients with positive HIT functional assays who are re-exposed to heparin during cardiac surgery, we recommend monitoring the postoperative platelet count throughout, from immediately post-surgery through the typical HIT onset timeline (five to ten days) after re-exposure to heparin.

5. Management strategy for patients with negative HIT functional assays and negative or positive HIT immunoassays

The safety of intraoperative re-exposure to heparin followed by protamine reversal during cardiac surgery with or without CPB in patients with negative or unknown HIT functional assays has been evaluated in four case series [26–29], and three retrospective cohort studies[30–32] **(Table 4)**. Overall, the available evidence suggests that the risk of HIT recurrence in these patients is very low if UFH re-exposure is strictly limited to the intraoperative setting.

In a series of three patients with remote HIT who received intraoperative UFH during CPB for CABG, none developed recurrent HIT or thrombotic events[26].The functional assay (HIPA) was negative for all three patients before surgery and remained negative after surgery. In another series of ten patients with remote HIT undergoing CBP, the immunoassay remained negative ten days after re-exposure to heparin. There were no cases of recurrent HIT or thrombotic events[27].

In a series of twelve patients with negative HIT functional assays who underwent CPB, including six patients with remote HIT who received intraoperative UFH during CPB, no thrombotic events or deaths occurred [28]. One of the six patients experienced bleeding and tamponade, which required re-exploration.

Warkentin and Sheppard reported a case series including 9 patients who received intraoperative heparin during CPB [30]. Immediately prior to heparin re-exposure, HIT immunoassays were positive in 55.6% (n=5) and negative in 44.4%(n=4). All patients had negative functional assays prior to heparin re-exposure. Re-exposure to heparin in previously immunoassays negative patients resulted in immunoassay seroconversion in 75% (3/4) patients. SRA seroconversion occurred in 55.6% (5/9) patients. Four of the 5 (80%) patients who had a SRA reconversion were judged not to have recurrent HIT as they did not develop thrombosis or recurrent platelet count fall. One patient in whom both the HIT immunoassay and HIT functional assay were negative prior to surgery developed a fall in platelet count on post-operative day 7 as well as deep vein thrombosis. The patient was deemed to have recurrent HIT and treated with therapeutic fondaparinux and IVIG.

Selleng et al. reported on three patients with negative HIT functional assay and positive HIT immunoassays who received intraoperative heparin without treatments during an orthotopic heart transplant (OHT) [29]. In one patient's anti-PF4/heparin antibodies increased on postoperative day seven, though the functional assay remained negative. No recurrent HIT or thrombotic events occurred.

Overall, available data suggest that re-exposure to heparin during cardiac surgery, provided it is strictly limited to the intraoperative setting, is associated with a very low risk of recurrent HIT. The risk of major bleeding with non-heparin anticoagulants during cardiac surgery may exceed

the risk of recurrence of HIT with brief heparin re-exposure. However, direct comparisons of treatment options are lacking.

To prevent the risk of recurrent HIT, heparin use should be limited to the intraoperative setting and avoided before and after surgery. Although the risk of recurrent HIT is low, it is not zero. Therefore, postoperative platelet count monitoring throughout the timeline of typical HIT onset (five to ten days) after UFH re-exposure is warranted.

Guidance statements:

-In patients with negative HIT functional assays and positive or negative HIT immunoassays who require cardiac surgery, we suggest using intraoperative anticoagulation with heparin, followed by reversal with protamine.

-In patients with negative HIT functional assays and positive or negative HIT immunoassays who receive intraoperative heparin followed by reversal with protamine during cardiac surgery, whether to avoid exposure to heparin pre and postoperatively is unclear. From a conservative standpoint, we suggest avoiding heparin before and after surgery; if pre- or post-operative anticoagulation is indicated, a non-heparin anticoagulant may be preferred.

- In patients with negative HIT functional assays and positive or negative HIT immunoassays who are re-exposed to heparin during cardiac surgery, we recommend monitoring the postoperative platelet count throughout the typical HIT onset timeline (five to ten days) after re-exposure to heparin.

6. Considerations for low resource settings

In low resource settings, HIT confirmatory laboratory testing with functional assays may not be readily available or available at all given logistical and financial requirement for shipping frozen samples under strict conditions. Clinical history (*e.g,* 4Ts score) and immunoassays may be used for diagnosis and planning for CPB. Time from HIT diagnosis may aid in risk-stratification in patients with a history of HIT as well as immunoassay trajectory. The panel recognizes that many countries lack access to DTI and thus would need to employ a heparin-based strategy for cardiac surgery.

7. Considerations for children

HIT is extremely rare in children and thus this review focused on adult populations for systematic review. Data on HIT in children was limited to case reports, with most describing use of bivalirudin [33–35].

8. Conclusions

Patients with a history of HIT who require cardiac surgery with CPB present unique management challenges. Although the current evidence is limited to non-randomized studies and case series, our review highlights several potential strategies for patient management. Bivalirudin remains the most studied non-heparin anticoagulant but requires careful perioperative adaptation. Re-exposure to UFH, either following TPE or in combination with potent antiplatelet agents, may be feasible in select patients. Importantly, for patients with negative functional assays, intraoperative UFH re-exposure with protamine reversal is associated with a low risk of HIT recurrence and may be preferable given the bleeding risks of non-heparin alternatives.

TPE has emerged as an important option to enable safe heparin re-exposure in patients with persistent HIT antibodies, particularly in urgent surgical settings where delaying surgery is not possible. While protocols vary, even a single TPE session appears to substantially reduce anti-PF4/heparin antibody titers, and the addition of IVIG may provide further protection against postoperative antibody-mediated platelet activation. The major limitations of TPE are the lack of standardized regimens, resource intensity, and the persistence of residual antibody titers in some patients. Nonetheless, in experienced centers, TPE offers a practical strategy to reduce perioperative thrombotic risk and allow the use of heparin, which remains the most effective and reversible anticoagulant for CPB. Multidisciplinary evaluation, careful review of the patient's HIT history and close postoperative platelet monitoring remain essential to ensure safe outcomes.

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A.M.P., J.H.L., J.M.C and C.F. drafted the manuscript. All authors provided intellectual input, critically reviewed, and agreed to the guidance recommendations. All authors read and approved the final document.

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Figure 1. Selecting a strategy for anticoagulation in patients with a history of HIT requiring CPB surgery. Adapted from Pishko et al[54].

Table 1. Studies reporting the intraoperative use of direct thrombin inhibitors during cardiac surgery in patients with a history of heparin-induced thrombocytopenia (HIT).

Author, year	Study design	Non-heparin anticoagulant and dose	Gender, age, race	HIT diagnosis	Immunoassay and Functional assay at time of surgery, % (n)	Preoperative Platelet Count	Cardiac surgery indications	Death	Thrombotic events and/or major bleeding; other complications
Hillebrand 2015 [9]	Retrospective case series (n=7)	Argatroban to reach a target aPTT of 50–60 s in one patient, increased to 70–80 s	6 males, mean age 51.2 ± 18.1 years	ELISA+, HIPA+	Immunoassay Positive: 100% (7) Functional assay positive: 85% (6)	Not reported	VAD under ECLS	3 deaths on POD 2 (n=2) and POD 17	Four patients needed re-exploration due to postoperative bleeding complications. One developed progressive intracardiac thrombosis under ECLS
Koster, 2007 [10]	Prospective open-label, multicenter CHOOSE-ON study (n=49)	Bivalirudin bolus of 1 mg/kg followed by a continuous infusion of 2.5 mg/kg/h	57.1% of male, 57.1% of patients >65 years	Patients with acute HIT ELISA + (n=35) Functional assay + (n=7) Patients with remote HIT ELISA + (n=3) Functional assay + (n=1)	Immunoassay Positive: 87.8% (43) Functional assay positive: 16.3% (8)	Not reported	On-pump surgery CABG (44.9%), CABG + valve (26.5%), CABG + other (4.1%), valve (18.4%), valve + other (2%), other (4.1%)	At POD7: 2% At POD30: 6.1%	At POD7: 1 stroke (2%) 1 revascularization (2%) At POD30: 1 stroke (2%) 1 revascularization (2%) 2 bleeding requiring re-exploration (4%) Intraoperative blood loss: 575 ± 524 mL (50-1900) 24-h blood loss: 936 ± 525 mL (600-2745)
Ljajikj, 2017 [8]	Retrospective cohort (n = 21 patients with HIT antibodies who received bivalirudin and 36 patients	Bivalirudin group: bivalirudin bolus of 0.25-0.5 mg/kg and a continuous bivalirudin infusion of	Bivalirudin group: 76.2% of men, 51.0 ± 12.7 years Heparin group: 80.6% of men, 52.5 ± 13.0 years	Intermediate or high 4T score and IgG-specific chemoillumiescence assay positive (IgG PF4-H)	Immunoassay positive 100% (21) Functional assays not reported	Not reported	LVAD on ECSL	Thirty-day mortality Bivalirudin group: 9.5% Heparin group: 11.1%	Stroke Bivalirudin group: 9.5% Heparin group: 11.1% Re-thoracotomy <7 days due to persistent haemorrhage or cardiac tamponade postoperatively Bivalirudin group: 19%

Author, year	Study design	Non-heparin anticoagulant and dose	Gender, age, race	HIT diagnosis	Immunoassay and Functional assay at time of surgery, % (n)	Preoperative Platelet Count	Cardiac surgery indications	Death	Thrombotic events and/or major bleeding; other complications
	without HIT antibodies who received heparin	0.25-0.5 mg/kg Heparin group: heparin bolus of 10 000 IU						One-year mortality Bivalirudin group: 33.7% Heparin group: 42.4%	Heparin group: 16.7% Intracranial bleeding Bivalirudin group: 4.8% Heparin group: 8.3%
Carlson, 2020 [7]	Retrospective cohort study (n=59 *patients treated with heparin*, n=13 *patients treated with a DTI*)	*Patients treated with a DTI*: 10 patients received bivalirudin, 3 patients received Argatroban (dose not reported)	*Patients treated with heparin*: 67.8% of male, median age 69 years (63-74) *Patients treated with a DTI:* 61.5% of male, median age 65 years (49-70)	Prior diagnosis of acute HIT within 3 years of CPB in the heparin treated group and within 3 months in the DTI-treated group ELISA + at the time of surgery	Immunoassay positive (OD >1.0): 100% (13) of bivalirudin patients 86.4%(51) Functional Assay not reported	Not reported	On-pump surgery *Patients treated with heparin*: CABG (20.3%), Valve surgery (20.3%), Combined CABG + valve (20.3%), HT (13.6%), other (25.4%), *Patients treated with a DTI*: CABG (30.8%), Valve surgery (23.1%), Combined CABG + valve (15.4%), HT (0%), others (30.8%),	At POD30 *Patients treated with heparin*:8.5% *Patients treated with a DTI*: 0%	*Patients treated with heparin:* Thrombotic events: 25.4% Significant bleeding: 50.8% *Patients treated with a DTI:* Thrombotic events: 7.7% (OR 0.33; 95%CI 0.03–3.18 compared to heparin) Significant bleeding: 7.7% (OR 0.10; 95%CI 0.01–0.82 compared to heparin)

Abbreviations: 4Ts, 4 T score; ARR, aortic root replacement with homologous graft and coronary reimplantation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting ; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet aggregation; HIT, heparin-induced thrombocytopenia; IVC, inferior vena cava; IVIG, intravenous immunoglobulin; LA, left atrium; LAA, left atrial appendage LVAD, left ventricular assist device; OD, optical density; OHT, orthotopic heart transplant; MVR, mitral valve replacement; PF4, platelet factor-4; PFO, patent foramen ovale; PTE, pulmonary thromboendoarterectomy; PVR, pulmonic valve replacement; SAVR, surgical aortic valve replacement; SRA, serotonin release assay; TAVR, transcatheter aortic valve replacement; TVR, tricuspid valve replacement.

Table 2. Studies reporting preoperative and/or intraoperative therapeutic plasma exchange (TPE) before intraoperative re-exposure to heparin during cardiac surgery in patients with a history of heparin-induced thrombocytopenia (HIT).

Author, year	Study design	TPE	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery or prior to TPE initiation, (n)	Preoperative Platelet Count	CBP indications	Death	Other outcomes (thrombotic events, major bleeding, blood loss, seroconversion)
Welsby, 2010 [11]	Case series (n=11)	1 preoperative TPE (immediately prior to heparinization), 1.3 × plasma volume (FFP)	Number of males not reported mean age 48.4 years	ELISA +, SRA or HIPA not performed Median preoperative OD 0.8 (0.7–2.2)	HIT diagnosis within 2 weeks of surgery (n=9) History of HIT within 2 months of procedure and positive PF4/H ELISA (n=2)	Not reported	BiVAD (n=1), OHT (n=6), replace LVAD (n=1), CABG + AVR+ MVR (n=1), AVR (n=1), explant LVAD (n=1)	3 died from non-HIT-related causes	1 patient developed an ischemic foot
Ramu, 2018 [12]	case series (n=4)	5 preoperative TPE sessions (3-7 days before surgery)	Male, 31 years	4Ts = 7, ELISA+ (OD 0.73), SRA-	Immunoassay positive, SRA negative	174	BiVAD	No	POD1: bleeding requiring rexploration Post TPE ELISA -
		7 preoperative TPE sessions	Male, 29 years	4Ts = 5, ELISA+ (OD 2.46), SRA+	Immunoassay positive_, SRA positive	Not reported	LVAD	No	No postoperative thrombotic events No postoperative major bleeding
		1 preoperative TPE session (day of surgery) and 1 intraoperative TPE session	Female, 24 years	4Ts = 6, ELISA+ (OD 2.72), SRA not performed	Immunoassay positive, SRA not performed	104	OHT	No	No postoperative thrombotic events No postoperative major bleeding
		4 preoperative TPE sessions	Male, 50 years	4Ts = 4, ELISA+ (OD 1.44), SRA+	Immunoassay positive, SRA positive	Thrombocytopenia (platelet count not reported)	MVR and AVR		No postoperative thrombotic events No postoperative major bleeding Post TPE ELISA -

Author, year	**Study design**	**TPE**	**Gender, age, race**	**Initial HIT diagnosis**	**Immunoassay and Functional assay at time of surgery or prior to TPE initiation, (n)**	**Preoperative Platelet Count**	**CBP indications**	**Death**	**Other outcomes (thrombotic events, major bleeding, blood loss, seroconversion)**
Moreno-Duarte, 2020 [13]	Case series (n=24)	1 TPE session (immediately prior to heparinization), 1.0 L plasma exchange volume	79% of males, mean age 55.2 ± 9.44 years	12 (50%)-positive PF4/H ELISA performed at reporting institution SRA not performed	Confirmed ELISA positive (12) SRA not reported	Median 160	LVAD (n=13), HT (n=6), others (n=5)	3 non-HIT- related deaths (hemorrhagic stroke, pneumonia/pulmonary failure, sepsis)	3 thromboembolic events (including 2 considered HIT related, i.e., 1 stroke and 1 DVT) OD median change from pre- to post-surgery is 1.57 (-2.01-0.01) in 11 patients
Sandoval, 2020 [14]	Case series (n=3)	2 preoperative TPE sessions (9 and 10 days before surgery) + 2 IVIG sessions	Male, 24 years	ELISA+ (OD 0.60)	Immunoassay positive, SRA not reported	<100	OHT	None	No postoperative thrombotic events Significant perioperative bleeding ELISA—
		4 preoperative TPE sessions (8, 9, 15, and 16 days before surgery) + 4 IVIG sessions	Male, 51 years	ELISA+ (OD 2.0)	Immunoassay positive SRA not reported	<150	OHT		No postoperative thrombotic events No postoperative bleeding ELISA—
		2 preoperative TPE sessions (12 and 13 days before surgery) + 5 IVIG sessions	Male, 59 years	ELISA+ (OD 0.80)	Immunoassay positive SRA not reported	200	OHT		No postoperative thrombotic events No postoperative bleeding ELISA— after 1 additional IVIG session
Naqvi, 2022 [15]	Case series (n=4)	2 preoperative TPE sessions	Male, 69 years	ELISA+	Immunoassay positive SRA not reported	Not reported	LVAD	No	No postoperative thrombotic events No postoperative major bleeding

Author, year	Study design	TPE	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery or prior to TPE initiation, (n)	Preoperative Platelet Count	CBP indications	Death	Other outcomes (thrombotic events, major bleeding, blood loss, seroconversion)
									Post-TPE ELISA-
		3 preoperative TPE sessions	Male, 30 years	ELISA+	Immunoassay positive SRA not reported	Not reported	LVAD	No	No postoperative thrombotic events POD1: large hemothorax with 3 L of blood in the left pleural space while on bivalirudin drip Post-TPE ELISA-
		3 preoperative TPE sessions	Female, 51 years	ELISA+	Immunoassay positive SRA not reported	Not reported	LVAD	Yes	No postoperative thrombotic events Devere hypotension requiring high-dose vasopressors Post-TPE ELISA-
		3 preoperative TPE sessions	Female, 22 years	ELISA+	Immunoassay positive SRA not reported	Not reported	LVAD	No	No postoperative thrombotic events Postoperatively, pericardial hematoma with tamponade requiring return to the operating room for clot evacuation and placement of a temporary RVAD POD8: subarachnoid hemorrhage Post-TPE ELISA-

Abbreviations: 4Ts, 4 T score; AVR, aortic valve replacement; BiVAD, biventricular assist device; CABG, coronary artery bypass grafting ; ELISA, enzyme-linked

immunosorbent assay; FFP, fresh frozen plasma; HIPA, heparin-induced platelet aggregation; HIT, heparin-induced thrombocytopenia; IVIG, intravenous immunoglobulin; LVAD, left ventricular assist device; MVR, mitral valve replacement; OD, optical density; OHT, orthotopic heart transplant; PF4, platelet factor-4; PTE, pulmonary thromboendoarterectomy; RVAD, right ventricular assist device; TPE, therapeutic plasma exchange.

Table 3. Studies reporting intraoperative re-exposure to heparin in combination with antiplatelet agents during cardiac surgery in patients with a history of heparin-induced thrombocytopenia (HIT).

Author, year	Study design	Antiplatelet agent and dose	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count (G/L)	Cardiac surgery indication	Death	Other outcomes (thrombotic events, major bleeding, blood loss)
Aouifi, 2001 [16]	Retrospective case series (n=10, including 6 patients receiving heparin + epoprostenol sodium during CPB)	Epoprostenol infusion started at 5 ng/kg/min and increased to 30 ng/kg/min over a period of 30 min	Male, 71 years	HIPA +	Not documented	90	Double CABG	None	No postoperative thrombotic event No postoperative major bleeding All 6 patients discharged from ICU at POD 3
			Male, 58 years		Not documented	116	AVR		
			Female,84 years		Not documented	103	AVR		
			Male, 73 years		Not documented	104	Redo MVR		
			Male, 74 years		Not documented	101	Mitral valvuloplasty		
			Female,67 years		Not documented	61	Triple CABG		
Mertzlufft, 2000 [17]	Retrospective case series (n=3)	Epoprostenol infusion (titrated to antiplatelet effect monitored by the hemoSTATUS II platelet function assay)	Male, 75 years	Prior diagnosis of acute HIT 2 years ago (ELISA +, HIPA +)	ELISA +, HIPA +	Not reported	Perforation of a thoracoabdominal aortic aneurysm	None	No postoperative thrombotic event
			Male, 55 years	Prior diagnosis of acute HIT 1 year ago (ELISA +, HIPA +)	ELISA -, HIPA -	Not reported	OTH		No postoperative thrombotic event

Author, year	Study design	Antiplatelet agent and dose	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count (G/L)	Cardiac surgery indication	Death	Other outcomes (thrombotic events, major bleeding, blood loss)
			Male, 56 years	Prior diagnosis of acute HIT 11 months ago (4Ts = 4, ELISA +, HIPA +)	ELISA -, HIPA -	Not reported	TVR		No postoperative thrombotic event
Kraenzler 1988 [18]	Retrospective case series (n=3)	Iloprost infusion started at 3 ng/kg/min and increased progressively to inhibit HIPA	Male, 50 years	HIPA + (2 weeks before surgery)	Platelet aggregation studies + Her platelets no longer aggregated in the presence of heparin when the dose of Iloprost reached 6 ng/kg/min	170	MVR	None	No postoperative thrombotic event No postoperative major bleeding
			Male, 69 years	HIPA +	Platelet aggregation studies + His platelets no longer aggregated in the presence of heparin when the dose of Iloprost reached 24 ng/kg/min	75	Left ventricular aneurysectomy, implantation of an automatic implantable cardiac defibrillator		No postoperative thrombotic event No postoperative major bleeding
			Female, 63 years	HIPA +	Platelet aggregation studies + Her platelets no longer aggregated in the	125	Myocardial revascularization		No postoperative thrombotic event No postoperative major bleeding

Author, year	Study design	Antiplatelet agent and dose	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count (G/L)	Cardiac surgery indication	Death	Other outcomes (thrombotic events, major bleeding, blood loss)
					presence of heparin when the dose of Iloprost reached 12 ng/kg/min				
Antoniou, 2002 [19]	Retrospective cohort study (n=22)	Iloprost infusion (6-12 ng/kg/min; infusion dosage titrated to inhibition of HIPA preoperatively and intraoperatively)	73% of males, mean age, 66.43 years (range, 53-76)	ELISA +, HIPA +	ELISA +: 100% (22) HIPA +: 100% (22)	Mean: 150	12 CABG, 4 AVR, 3 t AVR with CABG and 3 MVR and CABG	None	No postoperative thrombotic event 3 patients required postoperative reexploration for bleeding, but in all 3 patients a surgical cause for the hemorrhage was detected
Palatianos, 2004 [24]	Retrospective, case-control (n=10 cases and 10 controls)	Cases: iloprost infusion started at 3 ng/kg/min and increased to progressively (doubled) every 5 minutes up to the dose corresponding to the concentration of iloprost, which in vitro inhibited HIPA	Cases: 90% of males, mean age 61.1 ± 7.2 years, Controls: 90% of males, mean age 62.7 ± 8.4 years,	ELISA +, HIPA +	Cases ELISA +: 100% (10) HIPAG +: 100% (10)	Cases: mean 151.6 ± 63.012 Controls: mean 212.7 ± 52.637	Cases: 7 CABG, 3 MVR Controls: 7 CABG, 1 MVR, 1 CABG and MV repair, 1 CABG and MVR	None	No postoperative thrombotic event No postoperative bleeding requiring exploration
Palatianos 2015[20]	Retrospective, case-control (n=110 cases and 118 controls (HIT negative)	Cases: Iloprost infusion, mean dose 7.63 ng/kg/min (range, 3–24 ng/kg/min)	Cases: 78.2% of males, median age 68 years (47-84), Controls, 87.3% of males,	ELISA + at initial screening	Cases ELISA+: 100% (110) HIPAG+: 100% (110)	Cases: mean 153.5 ± 28.5 Controls: mean 190.1 ± 79.3	Cases: CABG (67.3%), cardiac valve replacement (44.5%), AAA ±AVR (10.9%) Controls:	30-day-mortality similar in both groups (8.2% in the iloprost-	Incidence of thrombotic events similar in both groups (5.1% in the iloprost-treated group *versus* 5.4% in the control group). Incidence of re-exploration owing to

Author, year	Study design	Antiplatelet agent and dose	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count (G/L)	Cardiac surgery indication	Death	Other outcomes (thrombotic events, major bleeding, blood loss)
			median age 66 years -28-87)				CABG (69.5%), cardiac valve replacement (36.4%), AAA ±AVR (18.6%)	treated group *versus* 8.5% in the control group	excessive bleeding similar in both groups (8.2% in the iloprost-treated group *versus* 6.8% in the control group).
Koster, 2001a [25]	Retrospective case series of patients with HIT and impaired renal function (n=10)	Tirofiban bolus of 10 µg/kg followed by infusion of 0.15 µg/kg /min	Male, 65 years	ELISA +, or HIPA + or both	ELISA+ and HIPA+: 30% (3) Not documented: 70% (7)	Not reported	Re-MVR	None	No postoperative thrombotic event No postoperative major bleeding
			Male, 32 years				Re-MVR		
			Female, 28 years				AVR + CABG		
			Male, 73 years				ARR		
			Female, 75 years				Re-CABG		
			Male, 45 years				CABG		
			Male, 47 years				AVR + MVR		
			Male, 54 years				MVR +TVR		
			Female, 43 years				CABG		
			Female, 25 years				PTE		
Koster, 2001b [21]	Retrospective cohort study (n=47)	Tirofiban bolus of 10 µg/kg	Not reported		HIPA +: 74.5% (n=)	Not reported	Urgent surgery in 37 patients	2patients died because of	No postoperative thrombotic event

Author, year	Study design	Antiplatelet agent and dose	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count (G/L)	Cardiac surgery indication	Death	Other outcomes (thrombotic events, major bleeding, blood loss)
		followed by infusion of 0.15 µg/kg /min			Not documented: 25.5 % (12)		Elective surgery in 10 patients	multiorgan failure as a result of myocardial failure	No postoperative major bleeding requiring reexploration Mean blood loss of 410 ± 180 mL
Lee, 2018 [22]	Retrospective case series (n=6)	Abciximab loading dose of 0.25 mg/kg followed by infusion of 0.125 ug/kg/min	Female, 29 years	4Ts = 4, ELISA+ (OD 2.0), SRA not performed	ELISA + (OD 1.755)	Not reported	LVAD 2 weeks later	No	No postoperative thrombotic event No postoperative major bleeding
			Male, 69 years	4Ts = 6, ELISA+ (OD 0.73), SRA SRA not performed	Not documented (ELISA+ 8 days ago)	Not reported	LVAD, AVR, MVR	No	No postoperative thrombotic event No postoperative major bleeding
			Male, 41 years	4Ts = 3, ELISA+ (OD 2.54), SRA +	Not documented (ELISA+ and SRA+ 8 days ago)	Not reported	LVAD, MVR, LAA ligation	No	No postoperative thrombotic event No postoperative major bleeding
			Female, 63 years	4Ts = 4, ELISA+ (OD 1.94), SRA +	Not documented (ELISA+ and SRA+ 16 days ago)	Not reported	LVAD, PFO closure, LA thrombectomy, Mitral prosthesis, thrombectomy, LAA ligation	No	No postoperative thrombotic event Postoperative major bleeding requiring chest reexploration and temporary right VAD support.
			Female, 69 years	4Ts = 4, ELISA+ (OD 0.5), SRA -	Not documented (ELISA+ and SRA+ 2 days ago)	Not reported	LVAD	No	No postoperative thrombotic event No postoperative major bleeding
			Male, 43 years	4Ts = 4, ELISA+ (OD 2.19), SRA -	Not documented (ELISA+ and SRA+ 3 days ago)	Not reported	LVAD, MVR, PFO closure, LAA ligation	No	No postoperative thrombotic event No postoperative major bleeding
Gernhofer, 2020 [23]	Retrospective case series (n=10)	Cangrelor, loading dose of 30 µg/kg followed by	Male, 20 years, hispanic	4Ts=5, ELISA+ (OD 1.19), SRA -	4Ts=5, ELISA+ (OD 1.19), SRA -	114	PTE	No	No postoperative thrombotic event No postoperative major bleeding

Author, year	Study design	Antiplatelet agent and dose	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count (G/L)	Cardiac surgery indication	Death	Other outcomes (thrombotic events, major bleeding, blood loss)
		infusion of 4 g/kg/min	Male, 47 years, White	4Ts = 4, ELISA+ (OD 3.26), SRA -	4Ts = 4, ELISA+ (OD 3.26), SRA -	40	HM3 LVAD	No	No postoperative No postoperative thrombotic event No postoperative major bleeding
			Female, 64 years, Other	4Ts = 4, ELISA+ (OD 0.85), SRA -	4Ts = 4, ELISA+ (OD 0.85), SRA -	268	SAVR	No	No postoperative thrombotic event No postoperative major bleeding
			Male, 21 years, Hispanic	4Ts = 4, ELISA+ (OD 1.13), SRA not performed	4Ts = 4, ELISA+ (OD 1.13), SRA not performed	187	PTE	No	No postoperative thrombotic event No postoperative major bleeding
			Male, 50 years, Asian	Acute HIT in 2014 ELISA- (OD 0.2)	Acute HIT in 2014 ELISA- (OD 0.2)	171	PTE	No	No postoperative thrombotic event No postoperative major bleeding
			Male, 53 years, Black	4Ts = 4, ELISA+ (OD 2.41), SRA +	4Ts = 4, ELISA+ (OD 2.41), SRA +	71	HVAD	No	No postoperative thrombotic event No postoperative major bleeding
			Male, 54 years, Black	Acute HIT > 6 months ago: 4Ts = 4, ELISA+ (OD 2.41), SRA +	Acute HIT > 6 months ago: 4Ts = 4, ELISA+ (OD 2.41), SRA +	301	LVAD explantation, OHT	No	Right IJ and basilic veins thrombosis on POD 11 with suspected catheter-associated thrombosis
			Male, 32 years, White	4Ts = 7, ELISA+ (OD 3.32), SRA +	4Ts = 7, ELISA+ (OD 3.32), SRA +	79	PTE, IVC thrombus removal	No	Bleeding requiring PRBC transfusion on POD4 and POD6
			Male, 39 years, White	4Ts = 7, ELISA+ (OD 3.23), SRA +	4Ts = 7, ELISA+ (OD 3.23), SRA +	40	PTE, intracardiac mass removal, TVR, PVR	Death from intracardiac mass at POD 1	Coagulopathy

Author, year	Study design	Antiplatelet agent and dose	Gender, age, race	Initial HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count (G/L)	Cardiac surgery indication	Death	Other outcomes (thrombotic events, major bleeding, blood loss)
			Male, 47 years, White	Prior diagnosis of acute HIT > 3 months ago: 4Ts = 6, ELISA+ (OD 2.20) SRA + Before surgery: ELISA+ (OD 1.94), SRA -		191	PTE	No	No postoperative thrombotic event No postoperative major bleeding

Abbreviations: 4Ts, 4 T score; AAA, ascending aortic aneurysm ; ARR, aortic root replacement with homologous graft and coronary reimplantation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting ; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet aggregation; HIT, heparin-induced thrombocytopenia; HT, heart transplantation; IVC, inferior vena cava; IVIG, intravenous immunoglobulin; LA, left atrium; LAA, left atrial appendage LVAD, left ventricular assist device; OD, optical density; OHT, orthotopic heart transplant; MVR, mitral valve replacement; PF4, platelet factor-4; PFO, patent foramen ovale; PTE, pulmonary thromboendoarterectomy; PVR, pulmonic valve replacement; SAVR, surgical aortic valve replacement; SRA, serotonin release assay; TAVR, transcatheter aortic valve replacement; TVR, tricuspid valve replacement.

Table 4. Studies reporting intraoperative re-exposure to heparin during cardiopulmonary bypass in patients with a history of heparin-induced thrombocytopenia (HIT) with negative functional assays and positive or negative immunoassays

Author, year	Study design	Gender, age, race	HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count	Cardiac surgery indications	Anticoagulant during CPB	Death	Other outcomes (thrombotic events, major bleeding, blood loss, seroconversion)
Olinger, 1984 [26]	Case series (n=3)	Female, 49 years	Previous history of HIT with HIPA+ 2 years ago	Immunoassay not reported Functional assay negative (HIPA)	>200k/uL	CABG	Heparin	No	None reported Postoperative HIPA negative
		Female, 74 years	Previous history of HIT with HIPA+ 7 weeks ago	Immunoassay not reported Functional assay negative (HIPA)	>200k/uL	Coronary revascularization	Heparin	No	None reported Postoperative HIPA negative (3 days after heparin re-exposure)
		Female, 63 years	Previous history of HIT with HIPA+ 8 weeks ago	Immunoassay not reported Functional assay negative (HIPA)	>200k/uL	5-vessel CABG	Heparin	No	None reported Postoperative HIPA negative-
Pötzsch, 2000[27]	Case series (n=10)	Not reported	Previous history of HIT with HIPA+	Immunoassay negative Functional assay not reported	Not reported	CPB	Heparin	No	None reported Excellent recovery No seroconversion at POD10
Nutall, 2003[28]	Case series (n=12, including 6 patients with remote HIT)	Male, 74 years	Previous clinical diagnosis of HIT	Immunoassay negative	Not reported	Redo 3-vessel CABG	Porcine heparin	No	No postoperative thrombotic event No postoperative major bleeding
		Female, 33 years	Previous clinical diagnosis of HIT	Immunoassay negative	Not reported	MVR	Porcine heparin	No	No postoperative thrombotic event No postoperative major bleeding
		Female, 68 years	Previous clinical diagnosis of HIT	Immunoassay negative	Not reported	AVR	Porcine heparin	No	No postoperative thrombotic event

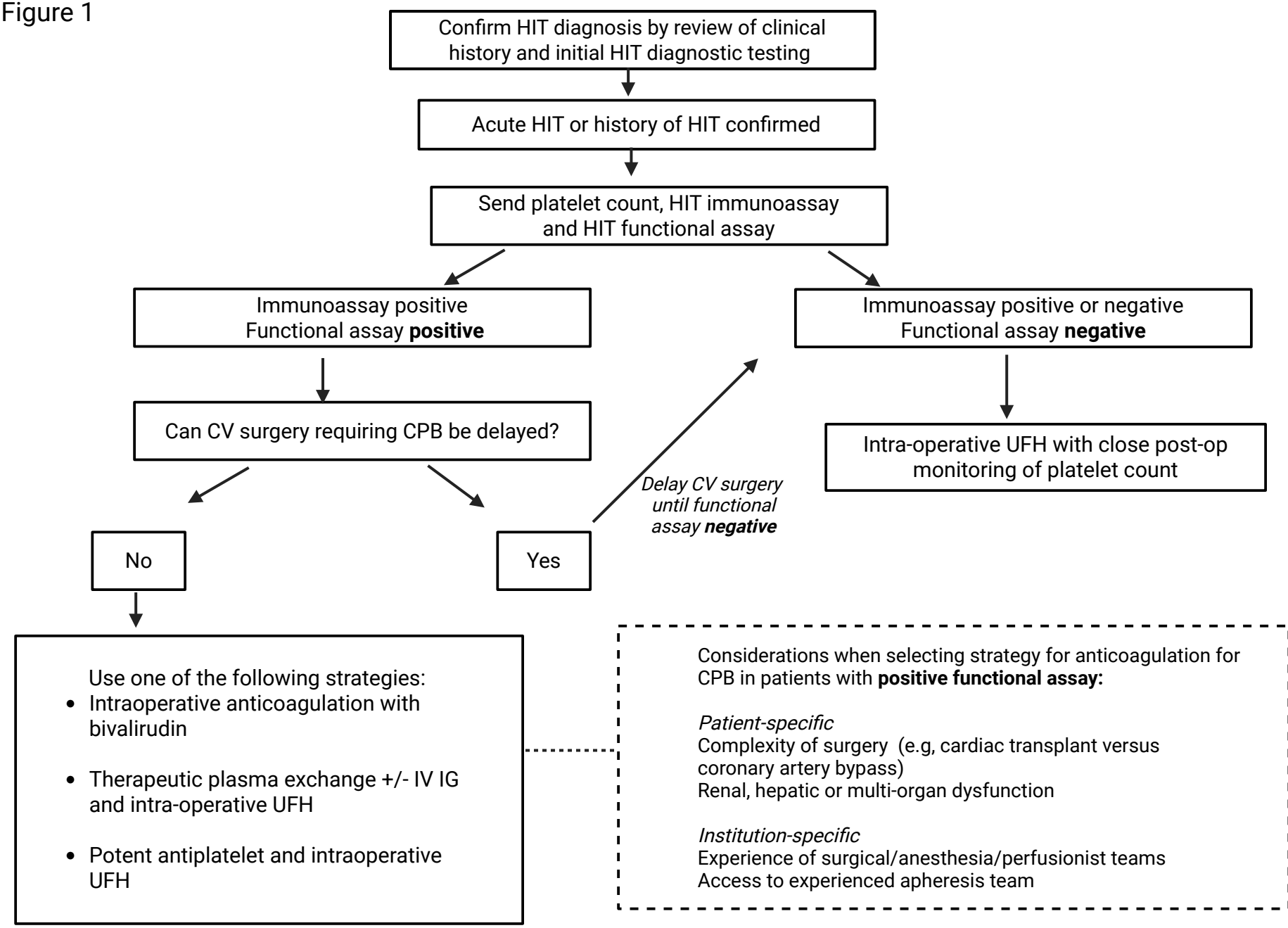
Author, year	Study design	Gender, age, race	HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count	Cardiac surgery indications	Anticoagulant during CPB	Death	Other outcomes (thrombotic events, major bleeding, blood loss, seroconversion)
									No postoperative major bleeding
		Female, 59 years	Previous clinical diagnosis of HIT	Immunoassay negative	Not reported	PTE	Porcine heparin	No	No postoperative thrombotic event Bleeding and tamponade requiring re-exploration
		Female, 75 years	Previous clinical diagnosis of HIT	Immunoassay negative	Not reported	3-vessel CABG	Porcine heparin	No	No postoperative thrombotic event No postoperative major bleeding
		Male, 74 years	Previous clinical diagnosis of HIT	Immunoassay negative	Not reported	3-vessel CABG	Heparin	No	No postoperative thrombotic event No postoperative major bleeding
Selleng, 2008[29]	Case series (n=3)	Male, 55 years	Previous diagnosis of HIT 1 week ago: ELISA+ (OD 1.1), HIPA+	Immunoassay positive (OD 1.1) Functional assay negative	Recovered	OHT	Heparin	No	No postoperative thrombotic event Major bleeding (2100 mL in 12 hours) that stopped after surgical revision Anti-PF4/heparin IgG antibodies and HIPA- until POD13
		Male, 55 years	Previous diagnosis of HIT 1 week ago: ELISA+ (OD 1.1), HIPA+	Immunoassay positive (0.627 OD) Functional assay negative	Recovered	OHT	Heparin	No	No postoperative thrombotic event No postoperative major bleeding Anti-PF4/heparin IgG antibodies increased at POD7 (OD 1.248) but HIPA -
		Male, 44 years	Previous	Immunoassay positive (OD 1.1)	Recovered	OHT	Heparin	No	No postoperative thrombotic event

Author, year	Study design	Gender, age, race	HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count	Cardiac surgery indications	Anticoagulant during CPB	Death	Other outcomes (thrombotic events, major bleeding, blood loss, seroconversion)
			diagnosis of HIT 2 weeks ago: ELISA+, HIPA+	Functional assay negative					No postoperative major bleeding
Warkentin, 2014[30]	Retrospective cohort (n=9 undergoing CPB)	7 males, 2 females, range: 48-72 years	Prior history of HIT ELISA positive 88% (8) ELISA not done 11% (1) SRA positive 66% (6), SRA not performed 34% (3)	Immunoassay Positive 55.6% (5), Negative 44.4% (4) Functional assay: Negative 100% (9)	Not reported	CPB	Heparin	No	1 of 9 (11.1%) Recurrent HIT with DVT, generalized maculopapular rash, full recovery with a therapeutic dose of fondaparinux 7.5 mg/day) 7 or 9 (78%) patients had an anti-PF4/heparin immune response 5 of 9 (55%) patients developed seroconversion to a positive SRA
Eisenberger 2023[31]	Retrospective cohort (n=7)	5 males, 2 females, Median age 51 years	HIT ELISA positive	Immunoassay positive at mean of 1 day pre-op (percentage positive at surgery not reported) Functional assay not reported	Mean 126k/uL	LVAD	Heparin	0%	No postoperative GI bleeding, No pump thrombosis, 1 patient required reoperation due to bleeding
Zucker 2010[32]	Retrospective (n-17 patients with history of HIT)		Previous exposure to heparin within the last 100 days, 50% drop in platelet count in	Immunoassay positive 82% (14)	Mean 282k/uL	Transplant 53% (9) Mechanical circulatory	Heparin (one patient received plasmapheresis prior to exposure)	11.7% (2)	Large saddle pulmonary embolism (1)

Author, year	Study design	Gender, age, race	HIT diagnosis	Immunoassay and Functional assay at time of surgery,(n)	Preoperative Platelet Count	Cardiac surgery indications	Anticoagulant during CPB	Death	Other outcomes (thrombotic events, major bleeding, blood loss, seroconversion)
			the absence of other identifiable causes of thrombocytopenia, and a positive ELISA Functional assay not performed			support device placement 47% (8)			Multiple arterial thrombosis and multi-organ failure (1) Stroke (1)

Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet aggregation; HIT, heparin-induced thrombocytopenia; ICH, intracranial hemorrhage; OD, optical density; OHT, orthotopic heart transplant; MVR, mitral valve replacement; POD, postoperative day; PTE, pulmonary thromboendoarterectomy; SRA, serotonin release assay.

Figure 1


Confirm HIT diagnosis by review of clinical history and initial HIT diagnostic testing
Acute HIT or history of HIT confirmed
Send platelet count, HIT immunoassay and HIT functional assay
Immunoassay positive
Functional assay **positive**
Immunoassay positive or negative
Functional assay **negative**
Can CV surgery requiring CPB be delayed?
Intra-operative UFH with close post-op monitoring of platelet count
*Delay CV surgery until functional assay **negative***
No
Yes
Use one of the following strategies:
• Intraoperative anticoagulation with bivalirudin
• Therapeutic plasma exchange +/- IV IG and intra-operative UFH
• Potent antiplatelet and intraoperative UFH
Considerations when selecting strategy for anticoagulation for CPB in patients with **positive functional assay:**
Patient-specific
Complexity of surgery (e.g, cardiac transplant versus coronary artery bypass)
Renal, hepatic or multi-organ dysfunction
Institution-specific
Experience of surgical/anesthesia/perfusionist teams
Access to experienced apheresis team

Supplemental Figure 1