

How Much Protamine is Enough? Current Evidence and Controversies: A Narrative Review

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ABSTRACT

Protamine sulfate remains the standard agent for reversing unfractionated heparin following cardiopulmonary bypass (CPB). Conventional reversal is typically based on a fixed protamine-to-heparin ratio of 1 mg per 100 IU of heparin. However, increasing evidence indicates that this empirical approach may not accurately reflect residual circulating heparin levels at the end of CPB and may result in either inadequate reversal or protamine overdose. Excess protamine administration has been associated with platelet dysfunction, impaired thrombin generation, coagulopathy, and increased postoperative bleeding. This narrative review summarizes current evidence on individualized protamine dosing and discusses major controversies and future directions in precision anticoagulation reversal. A literature search was conducted in PubMed/MEDLINE, Embase, and the Cochrane Library for English-language studies published between 2021 and 2026, with earlier landmark studies included when relevant. Priority was given to randomized controlled trials, pharmacokinetic–pharmacodynamic studies, systematic reviews, and meta-analyses. Current evidence consistently demonstrates that individualized protamine dosing reduces total protamine exposure compared with conventional fixed-ratio protocols while maintaining effective heparin neutralization. Heparin concentration-guided strategies and low-dose protamine protocols have achieved comparable reversal outcomes without increasing postoperative bleeding or transfusion requirements. Pharmacokinetic–pharmacodynamic modeling suggests that a protamine-to-heparin ratio of approximately 0.625:1 may be adequate for most patients, substantially lower than traditional recommendations. Meta-analytic evidence further indicates improved coagulation-related outcomes and fewer bleeding complications with concentration-guided management, although definitive benefits regarding mortality, re-exploration for bleeding, and thrombotic events remain uncertain. Individualized protamine dosing represents a promising approach to optimizing anticoagulation reversal after CPB. Nevertheless, further large, multicenter randomized trials evaluating patient-centered outcomes are required before individualized dosing strategies can be recommended as the universal standard of care.

INTRODUCTION

Systemic anticoagulation during cardiopulmonary bypass (CPB) is essential to prevent thrombus formation within the extracorporeal circuit, which could otherwise result in catastrophic thromboembolic complications and compromise patient safety. Unfractionated heparin has remained the standard anticoagulant for cardiac surgery for more than six decades, primarily because of its rapid onset of action, well-characterized pharmacodynamic profile,

predictable efficacy, and complete reversibility with protamine sulfate. The fundamental principle underlying heparin administration during CPB is the potentiation of antithrombin III, which subsequently inactivates coagulation factors, including thrombin and factor Xa, thereby producing a robust anticoagulant state necessary for the safe conduct of extracorporeal circulation. Despite significant advances in surgical techniques, perfusion technology, and perioperative monitoring, reliance on unfractionated heparin as the primary anticoagulant has persisted, reflecting its favorable risk–benefit profile and the absence of a superior alternative that matches its combination of efficacy, reversibility, and cost-effectiveness (Miles et al., 2021; Wahba et al., 2025).

Following separation from CPB, restoration of physiological hemostasis requires complete and timely neutralization of circulating heparin to prevent excessive postoperative bleeding and associated complications. Protamine sulfate, a highly basic polypeptide derived from salmon sperm, remains the primary clinically approved agent for heparin reversal, functioning through the formation of stable ionic complexes with negatively charged heparin molecules. The stoichiometric interaction between protamine and heparin is well established, with each milligram of protamine capable of neutralizing approximately 100 IU of heparin under ideal conditions (Crivellari et al., 2024; Green, 2020; Sharga et al., 2022; Sokolowska et al., 2016). However, the clinical application of this pharmacological principle has been complicated by substantial interpatient variability in heparin pharmacokinetics, the dynamic nature of heparin metabolism during CPB, and the limitations of traditional monitoring techniques. Consequently, determining the appropriate protamine dose for each patient remains a persistent clinical challenge that has attracted considerable research attention over the past decade (Boer et al., 2018; Mondal et al., 2024).

The conventional approach to protamine administration after CPB has been remarkably consistent across institutions worldwide, relying on a fixed ratio of 1 mg of protamine for every 100 IU of heparin administered as the initial bolus before bypass. This empirical strategy, which originated from early clinical observations and experimental studies, is appealing because of its simplicity, cost-effectiveness, and ease of implementation in the operating room. The assumption underlying this approach is that the entire administered heparin dose remains biologically active at the conclusion of the surgical procedure and therefore requires complete stoichiometric neutralization (Green, 2020; Sharga et al., 2022). However, this assumption fails to account for the complex pharmacokinetic behavior of heparin during CPB, including redistribution into extravascular compartments, endothelial binding, uptake by the reticuloendothelial system, enzymatic degradation, and renal elimination, all of which contribute to a progressive decline in circulating heparin concentration throughout the duration of bypass (Gkiouliava et al., 2024; Jain et al., 2025; Wahba et al., 2025).

Recent evidence has increasingly challenged the validity of the fixed-ratio paradigm, demonstrating that circulating heparin concentrations at the end of CPB are often substantially lower than the initial administered dose. A growing body of literature indicates that conventional dosing protocols frequently administer protamine in excess of what is physiologically required for complete heparin neutralization, potentially exposing patients to the adverse effects of protamine overdose without additional clinical benefit. Pharmacokinetic studies have revealed that heparin clearance during CPB follows a complex multicompartmental model influenced by numerous factors, including patient age, body

composition, renal function, inflammatory status, antithrombin levels, hemodilution, hypothermia, and bypass duration. As a result, patients receiving identical heparin doses may exhibit markedly different residual heparin concentrations at the time of reversal, rendering a universal protamine-to-heparin ratio inappropriate for many individuals (Gkiouliava et al., 2024; Lanoiselée et al., 2026; Miles et al., 2021; Raner et al., 2024).

The clinical consequences of both inadequate and excessive protamine administration are substantial and have been well documented in the cardiac surgery literature. Residual heparin activity resulting from insufficient protamine dosing has been consistently associated with increased postoperative bleeding, higher transfusion requirements, prolonged intensive care unit stays, and an elevated likelihood of surgical re-exploration for hemorrhage. Conversely, protamine overdose is increasingly recognized as a contributor to perioperative coagulopathy, with excess protamine exerting its own anticoagulant effects through multiple mechanisms, including inhibition of thrombin generation, impairment of platelet aggregation and adhesion, interference with fibrin polymerization, and disruption of the intrinsic coagulation cascade (Boral et al., 2016). This paradoxical anticoagulant effect of protamine excess creates a clinical scenario in which the agent intended to restore hemostasis may instead perpetuate bleeding, thereby complicating postoperative management and potentially worsening patient outcomes (Boer et al., 2018; Jain et al., 2025; Mondal et al., 2024).

The limitations of activated clotting time (ACT), the most widely used monitoring tool for assessing anticoagulation during CPB and confirming adequate reversal, have further motivated the search for alternative approaches to protamine dosing. Although ACT is rapid, inexpensive, and widely available in the operating room, it is influenced by numerous variables independent of heparin concentration, including hypothermia, hemodilution, thrombocytopenia, platelet dysfunction, anemia, and coagulation factor deficiencies. Consequently, ACT may not accurately reflect residual heparin activity after protamine administration, and normalization of ACT does not reliably confirm complete heparin neutralization. Recent investigations have demonstrated substantial discordance between ACT values and direct measures of heparin activity, such as anti-factor Xa assays, with some patients showing normalized ACT despite measurable residual anticoagulation, whereas others exhibit prolonged ACT in the absence of significant heparin activity. This dissociation between ACT and true heparin concentration has raised important questions regarding the appropriateness of ACT-guided reversal protocols (Lanoiselée et al., 2026).

In response to the recognized limitations of conventional fixed-ratio dosing and ACT-guided management, individualized protamine dosing strategies have emerged as a promising alternative that aims to tailor reversal therapy according to each patient's actual anticoagulation status rather than empirical calculations. These individualized approaches encompass a range of techniques, including direct heparin concentration measurement, automated protamine titration systems such as the Hepcon HMS Plus, pharmacokinetic–pharmacodynamic modeling, anti-factor Xa activity monitoring, and viscoelastic hemostatic testing (Martinez et al., 2015; Meesters et al., 2017; Taylor & Maldonado, 2016). The fundamental principle underlying these strategies is that protamine requirements should be determined by the amount of biologically active heparin remaining in circulation at the end of CPB, which can be measured directly or estimated using mathematical models incorporating patient-specific and procedural variables. Contemporary evidence from randomized controlled trials, systematic

reviews, and meta-analyses has consistently demonstrated that individualized approaches significantly reduce total protamine exposure while maintaining effective heparin neutralization and comparable hemostatic outcomes to conventional strategies (Gkiouliava et al., 2024; Jain et al., 2025; Miles et al., 2021; Raner et al., 2024).

Despite the growing body of evidence supporting individualized protamine dosing, important controversies and unresolved questions remain that limit its widespread adoption as the standard of care. The optimal protamine-to-heparin ratio for complete and safe reversal has not been definitively established, with recent pharmacokinetic–pharmacodynamic modeling suggesting that ratios substantially lower than the traditional 1:1 ratio may be adequate for most patients. The relative merits of different monitoring modalities, including ACT, anti-factor Xa activity, heparin concentration measurement, and viscoelastic testing, remain subjects of ongoing debate, with each approach offering distinct advantages and limitations. Furthermore, the clinical significance of residual heparin activity versus protamine excess in contributing to postoperative bleeding has not been fully elucidated, and the balance between these competing risks remains uncertain. The cost-effectiveness and practical feasibility of individualized monitoring systems in diverse healthcare settings, particularly in low- and middle-income countries, represent additional barriers to implementation that require careful consideration (Jain et al., 2025; Lanoiselée et al., 2026; Raner et al., 2024).

The 2024 EACTS/EACTAIC/EBCP Guidelines on cardiopulmonary bypass in adult cardiac surgery have acknowledged the potential benefits of individualized anticoagulation management; however, they have stopped short of recommending individualized protamine dosing as the universal standard of care. This cautious stance reflects the heterogeneity among published studies in terms of patient populations, surgical procedures, monitoring techniques, and outcome definitions, as well as the limited statistical power of most investigations to detect differences in clinically significant endpoints, such as mortality, thrombotic events, and re-exploration for bleeding (Lee et al., 2015; Pathirana & Jackson, 2018; Sedgwick, 2015). The available evidence, although promising, is derived predominantly from single-center studies that focus on pharmacological and coagulation-related endpoints rather than patient-centered outcomes that are most meaningful to patients and clinicians. Consequently, uncertainty remains regarding whether the improvements in pharmacological precision achieved through individualized dosing translate into clinically meaningful improvements in patient outcomes that justify the additional complexity and cost associated with these strategies (Jain et al., 2025; Wahba et al., 2025).

The present narrative review aims to summarize and critically evaluate current evidence on individualized protamine dosing after cardiopulmonary bypass, with particular emphasis on the physiological rationale, recent clinical evidence, major controversies, and future directions in precision anticoagulation reversal. By synthesizing findings from randomized controlled trials, pharmacokinetic–pharmacodynamic studies, systematic reviews, and meta-analyses, this review seeks to provide clinicians with a comprehensive understanding of current protamine management practices and identify knowledge gaps that warrant further investigation. The review addresses key questions, including whether individualized dosing strategies can safely reduce protamine exposure, what the optimal monitoring modality and protamine-to-heparin ratio may be, and whether current evidence is sufficient to support a paradigm shift from conventional to individualized reversal protocols. Ultimately, the goal is to inform evidence-

based clinical decision-making and guide future research toward improving outcomes for cardiac surgical patients through precision anticoagulation management (Boer et al., 2018; Gkiouliava et al., 2024; Jain et al., 2025; Lanoiselée et al., 2026; Miles et al., 2021; Mondal et al., 2024; Raner et al., 2024; Wahba et al., 2025).

METHOD

This study was conducted as a narrative literature review to summarize and critically evaluate contemporary evidence on individualized protamine dosing for heparin reversal after cardiopulmonary bypass (CPB). A comprehensive literature search was performed using PubMed/MEDLINE, Embase, and the Cochrane Library for English-language articles published between January 2021 and January 2026, with earlier landmark studies and clinical practice guidelines included when relevant. The search strategy combined MeSH terms and free-text keywords, including protamine, heparin reversal, cardiopulmonary bypass, individualized protamine dosing, protamine-to-heparin ratio, heparin concentration monitoring, anti-factor Xa, viscoelastic hemostatic testing, and pharmacokinetic-pharmacodynamic modeling. Priority was given to randomized controlled trials, prospective cohort studies, systematic reviews, meta-analyses, and clinical practice guidelines involving adult cardiac surgery patients. Studies focusing exclusively on pediatric populations, animal models, or in vitro experiments were excluded.

The retrieved evidence was synthesized narratively and organized according to key themes, including the physiological basis of individualized protamine dosing, clinical evidence from major studies and meta-analyses, current controversies, and future directions for precision anticoagulation management. Data analysis involved critical appraisal of each included study with emphasis on protamine exposure, heparin neutralization efficacy, coagulation outcomes, bleeding complications, and transfusion requirements. The narrative synthesis approach enabled integration of evidence from diverse study designs and facilitated interpretation of findings not suitable for quantitative pooling, while maintaining a critical perspective by evaluating both supporting evidence and remaining uncertainties regarding optimal monitoring modalities, protamine-to-heparin ratios, and effects on major clinical outcomes.

RESULT AND DISCUSSION

Conventional Protamine Dosing

Historical Background of Conventional Protamine Administration

Protamine sulfate has been the standard heparin reversal agent since CPB's early development, forming stable ionic complexes with heparin molecules to neutralize its anticoagulant activity. Despite major advances in monitoring and perfusion technology, the fundamental principle of protamine administration has remained largely unchanged for decades, with most centers still using empiric dosing based on heparin amount administered rather than actual circulating concentration at CPB's end (Boer et al., 2018; Miles et al., 2021).

The persistence of conventional dosing is mainly attributable to its simplicity, low cost, and ease of implementation. Historically, clinicians assumed complete neutralization required protamine in direct proportion to the total heparin dose—forming the basis for the widely adopted 1 mg per 100 IU ratio. However, increasing understanding of heparin pharmacokinetics has challenged this paradigm, particularly because substantial heparin

metabolism and clearance occur during prolonged CPB procedures (Gkiouliava et al., 2024; Jain et al., 2025).

Standard Fixed-Ratio Protamine Dosing

Conventional protamine dosing is generally based on a fixed heparin-protamine ratio. After an initial heparin dose of approximately 300-400 IU/kg to achieve adequate anticoagulation for CPB, protamine is administered after separation from bypass at a ratio of 1 mg for every 100 IU of the total heparin dose given. This approach assumes that all administered heparin remains biologically active at the end of surgery and therefore requires complete stoichiometric neutralization.

In routine practice, the conventional protocol often results in administration of 250-400 mg of protamine, depending on patient size and total heparin exposure. Some institutions have adopted simplified fixed-dose regimens, such as a standard dose of 250 mg protamine regardless of the total heparin dose. These simplified approaches are intended to reduce dosing complexity and limit excessive protamine administration while still maintaining adequate reversal. Recent randomized evidence has shown that fixed-dose protocols may achieve comparable ACT normalization and postoperative bleeding outcomes while using substantially lower total protamine doses than traditional 1:1 ratio-based strategies (Jain et al., 2025).

Physiological Basis and Limitations of Fixed-Ratio Dosing

The conventional dosing strategy is based on the theoretical stoichiometric interaction between heparin and protamine. However, this model does not adequately account for the dynamic pharmacokinetic behavior of heparin during CPB. Heparin undergoes metabolism through endothelial uptake, macrophage-mediated degradation, plasma protein binding, and renal elimination. Consequently, the circulating heparin concentration progressively declines throughout the procedure, and the actual amount of heparin present at the end of CPB may be considerably lower than the initial administered dose (Raner et al., 2024).

Interindividual variability further complicates this relationship. Factors such as age, body mass index, antithrombin concentration, renal function, inflammatory activation, hemodilution, hypothermia, and CPB duration influence both heparin pharmacokinetics and pharmacodynamics. Patients receiving identical heparin doses may therefore show markedly different residual heparin concentrations at the end of surgery. Conventional dosing strategies do not account for this variability and may consequently expose patients either to residual anticoagulation or to excessive protamine administration (Gkiouliava et al., 2024; Raner et al., 2024).

Activated Clotting Time-Guided Reversal

Activated clotting time (ACT) remains the most widely used method for assessing anticoagulation during CPB and for confirming adequacy of heparin reversal after protamine administration. After protamine infusion, ACT is typically measured and compared with baseline pre-heparin values, and restoration of ACT toward baseline is generally interpreted as successful reversal. Because ACT testing is rapid, inexpensive, and readily available in the operating room, it continues to serve as the cornerstone of conventional anticoagulation management (Gkiouliava et al., 2024). However, ACT has recognized limitations as a surrogate marker of residual heparin activity, a point discussed further below (Boer et al., 2018).

Clinical Consequences of Conventional Protamine Dosing

Conventional protamine dosing carries dual risks: overdosing may paradoxically impair hemostasis through anticoagulant effects, while underdosing may leave residual heparin activity or cause heparin rebound, both contributing to postoperative bleeding and increased transfusion requirements (Boer et al., 2018; Mondal et al., 2024). Recent evidence has challenged the routine 1:1 protocol—a 2024 meta-analysis of 3,810 patients showed concentration-guided management reduced protamine exposure and improved coagulation outcomes, while a 2025 RCT found that a fixed 250-mg regimen achieved equivalent ACT normalization and bleeding outcomes with significantly lower protamine administration (Jain et al., 2025; Raner et al., 2024).

Although conventional dosing remains widely practiced due to its simplicity, it is limited by substantial pharmacokinetic assumptions and inability to account for patient-specific variability. These limitations have prompted increasing interest in individualized strategies based on direct heparin concentration measurement, protamine titration systems, and precision anticoagulation management (Raner et al., 2024).

RATIONALE FOR INDIVIDUALIZED PROTAMINE DOSING

Limitations of Empirical Protamine Administration

Individualized protamine dosing is justified by the recognition that conventional fixed-ratio dosing fails to account for the complex pharmacokinetics of heparin during CPB—including redistribution, endothelial uptake, protein binding, hepatic metabolism, and renal elimination—meaning circulating heparin at reversal often differs substantially from the initial dose, creating risks of both underdosing and overdosing (Gkiouliava et al., 2024; Miles et al., 2021). Recent evidence confirms that conventional strategies frequently administer excess protamine; a randomized trial demonstrated that individualized heparin-protamine titration significantly reduced protamine requirements compared with ACT-guided management while maintaining adequate reversal, indicating that empiric dosing routinely exposes patients to unnecessary protamine excess (Gkiouliava et al., 2024).

Interindividual Variability in Heparin Pharmacokinetics

One of the strongest arguments supporting individualized protamine administration is the marked variability in heparin pharmacokinetics among cardiac surgical patients. The anticoagulant response to heparin is influenced by multiple patient-specific factors, including age, body composition, renal function, hepatic function, inflammatory status, and antithrombin concentration. Patients receiving identical heparin doses may therefore show substantially different plasma heparin concentrations throughout CPB and at the time of reversal (Lanoiselée et al., 2026).

In addition to patient-related factors, procedural characteristics also influence heparin clearance. Duration of CPB, degree of hemodilution, hypothermia, ultrafiltration, and transfusion practices can all alter heparin pharmacodynamics. Longer bypass times are particularly important because progressive heparin elimination occurs throughout the procedure. Calculating protamine requirements only from the initial heparin dose may therefore substantially overestimate the amount of heparin that remains active at the end of surgery. This variability forms the biological basis for concentration-guided and titration-based reversal strategies (Lanoiselée et al., 2026).

Avoiding Protamine Overdose and Protamine-Induced Coagulopathy

A major motivation for individualized dosing is the recognition that excess protamine paradoxically impairs hemostasis—inhibiting platelet aggregation, thrombin generation, clot formation, and fibrin polymerization—thereby producing an anticoagulant state despite complete heparin neutralization (Boer et al., 2018; Lanoiselée et al., 2026). Clinical observations consistently link excessive protamine to increased postoperative bleeding, chest tube drainage, and transfusion requirements, shifting the goal of coagulation management from complete reversal toward identifying the minimal effective dose that restores physiological hemostasis (Boer et al., 2018; Lanoiselée et al., 2026). Additionally, protamine causes dose-dependent adverse effects including hypotension, pulmonary vasoconstriction, right ventricular dysfunction, complement activation, and anaphylactoid reactions, making minimization of unnecessary exposure beneficial for both coagulation and hemodynamic stability (Boer et al., 2018).

Inadequacy of ACT-Based Reversal Assessment

Another important rationale for individualized dosing is the limited accuracy of ACT as a surrogate marker of residual heparin activity. ACT remains the most commonly used monitoring tool during cardiac surgery because it is inexpensive and readily available. As detailed in the controversies section below, ACT is influenced by multiple factors independent of heparin concentration and cannot reliably distinguish residual heparin activity from protamine-induced coagulopathy, which is a key limitation that has driven interest in direct heparin concentration monitoring and protamine titration systems (Gkiouliava et al., 2024; Lanoiselée et al., 2026).

Emergence of Heparin Concentration-Guided Reversal

Advances in point-of-care coagulation monitoring have facilitated the development of individualized heparin-protamine management systems. Devices such as the Hepcon HMS Plus allow direct measurement of circulating heparin concentration and calculation of patient-specific protamine requirements. Unlike conventional ACT-guided protocols, these systems estimate the actual amount of heparin requiring neutralization and determine the minimum protamine dose needed for effective reversal (Gkiouliava et al., 2024).

In a randomized controlled study, individualized heparin monitoring significantly reduced protamine requirements in both coronary and non-coronary cardiac surgery without increasing postoperative bleeding or transfusion requirements. The investigators concluded that heparin concentration-guided management allows more precise reversal while avoiding unnecessary protamine exposure. These findings provide important clinical support for individualized dosing and reinforce the concept that conventional dosing may overestimate true protamine requirements (Gkiouliava et al., 2024).

Toward Precision Anticoagulation Management

The movement toward individualized protamine dosing reflects a broader transition from empirical protocols to precision medicine in perioperative cardiovascular care. Contemporary blood conservation programs increasingly emphasize patient-specific coagulation management, reduction of unnecessary transfusion, minimization of bleeding complications, and optimization of resource utilization. Within this framework, individualized protamine dosing is an important component of precision anticoagulation management because it seeks

to tailor therapy according to measured biological parameters rather than predetermined dosing formulas (Gkiouliava et al., 2024; Lanoiselée et al., 2026).

Recent pharmacokinetic-pharmacodynamic modeling studies have further strengthened this paradigm by demonstrating that the minimal effective protamine-to-heparin ratio may be substantially lower than traditional recommendations. These findings suggest that future anticoagulation management may increasingly incorporate mathematical modeling, anti-factor Xa monitoring, viscoelastic testing, and real-time heparin concentration assessment to guide reversal therapy. Individualized protamine dosing has therefore emerged as a promising strategy for improving hemostatic outcomes while minimizing the risks associated with both residual heparin activity and protamine excess (Gkiouliava et al., 2024; Lanoiselée et al., 2026).

Heparin Dose-Response Curve (HDR)

The heparin dose-response (HDR) curve describes the relationship between heparin dose and ACT changes, used to estimate initial heparin requirements and guide CPB dosing. Generated from baseline ACT and responses to known heparin concentrations, it reflects individual heparin sensitivity—steep slope indicates high sensitivity, flat slope suggests resistance. Systems like Hepcon HMS Plus incorporate HDR with heparin concentration measurements, though predictive accuracy is debated (Garvin et al., 2010).

HDR highlights interpatient variability in heparin responsiveness due to factors including antithrombin levels, hemodilution, hypothermia, and renal function. Protamine dosing based solely on total heparin dose may not reflect active heparin remaining post-CPB, as ACT cannot reliably distinguish residual heparin from coagulopathy or protamine excess (Lanoiselée et al., 2026). However, HDR has limitations—ACT-based analysis is influenced by temperature, hemodilution, thrombocytopenia, and factor deficiencies. HDR is best used as one component of individualized management, combined with direct heparin concentration, anti-Xa monitoring, and/or viscoelastic testing (Garvin et al., 2010; Lanoiselée et al., 2026).

Current Evidence

Evolution of Evidence Supporting Individualized Protamine Dosing

Interest in individualized protamine dosing has increased substantially over the last decade, driven by growing recognition that conventional fixed-ratio reversal may not accurately reflect residual circulating heparin after CPB. Recent investigations have focused on whether patient-specific heparin monitoring, pharmacokinetic modeling, and concentration-guided titration can improve reversal while minimizing excessive protamine exposure. The current body of evidence includes randomized controlled trials, prospective cohort studies, pharmacokinetic-pharmacodynamic analyses, and systematic reviews. Together, these studies suggest that individualized approaches consistently reduce protamine administration without compromising reversal; however, their effect on major clinical outcomes remains an area of ongoing investigation (Gkiouliava et al., 2024; Jain et al., 2025; Lanoiselée et al., 2026).

Evidence from the PRODOSE Adaptive Randomized Controlled Trial

The PRODOSE Adaptive Randomized Controlled Trial by Miles et al. (2021) was one of the earliest major trials, randomizing 228 cardiac surgery patients to either pharmacokinetic model-guided dosing or conventional 1:1 ratio. The study demonstrated that individualized pharmacokinetic modeling significantly reduced total protamine exposure compared with conventional dosing, without increasing postoperative bleeding or impairing coagulation

parameters. Although differences in major clinical outcomes were modest, the trial provided early evidence that substantial protamine reductions could be achieved without compromising safety, challenging the assumption that complete heparin neutralization requires a fixed 1:1 ratio. The PRODOSE trial was particularly important for introducing the concept that protamine dosing should be based on residual heparin activity rather than initial heparin dose—a principle that became the foundation for many contemporary individualized anticoagulation management strategies (Miles et al., 2021).

Evidence from Individualized Heparin-Protamine Titration

The 2024 Gkiouliava randomized trial enrolled 132 patients undergoing elective cardiac surgery with MiECC, comparing individualized heparin-protamine titration (IHPT) using Hepcon HMS Plus with conventional ACT-guided management (0.75:1 ratio). Individualized monitoring significantly reduced protamine requirements—in CABG procedures from 163±61 mg to 118±24 mg, and in non-CABG from 197±45 mg to 151±46 mg ($p<0.001$). Despite substantial protamine reduction, no significant differences were observed in postoperative bleeding, transfusion requirements, mechanical ventilation duration, morbidity, or hospital length of stay. These findings strongly support individualized heparin concentration-guided management, demonstrating that lower protamine doses achieve equivalent hemostatic outcomes while reinforcing that conventional dosing may routinely administer excessive protamine without additional clinical benefit (Gkiouliava et al., 2024).

Evidence from Contemporary Randomized Controlled Trials

The most recent randomized evidence comes from the 2025 Jain double-blinded trial comparing fixed 250-mg protamine with conventional 1:1 ratio-based dosing in 125 adult cardiac surgery patients. The investigators found no significant differences in post-protamine ACT or 24-hour chest tube output between groups. However, patients receiving the fixed-dose strategy received substantially less protamine—reducing exposure by more than two 50-mg vials per patient—while achieving equivalent reversal. This trial directly challenged continued use of traditional 1:1 dosing and provided high-quality evidence that protamine requirements may be substantially lower than previously assumed. The study has become one of the most influential contemporary trials supporting reassessment of conventional dosing and suggesting lower-dose strategies may be sufficient in selected patients (Jain et al., 2025).

Evidence from Pharmacokinetic-Pharmacodynamic Modeling

A major advancement came from the 2026 Lanoiselée PK-PD study involving 68 adults undergoing CPB, which developed a population model linking protamine administration, anti-Xa activity, and ACT to determine the minimum effective protamine dose. Model-based simulations predicted that a protamine-to-heparin ratio of approximately 0.625:1 would achieve complete reversal in 95% of patients. Although ACT and anti-Xa were positively associated, ACT values varied widely at low anti-Xa concentrations, highlighting ACT's limitations as the sole marker of residual heparin activity. These findings suggest conventional 1:1 ratios exceed minimum requirements for many patients, contributing to unnecessary protamine exposure. This study provides a strong mechanistic argument for individualized dosing by estimating protamine requirements from measured anticoagulant activity rather than empirical assumptions, offering a scientific foundation for future precision-based dosing algorithms (Lanoiselée et al., 2026).

Evidence from Systematic Reviews and Meta-Analyses

The highest-level evidence comes from the 2024 Raner meta-analysis of 26 studies involving 3,810 patients, comparing blood concentration-guided anticoagulation with conventional weight-based dosing. The meta-analysis demonstrated that individualized heparin-protamine management was associated with significantly lower protamine exposure while maintaining effective reversal, along with improved platelet preservation and reduced bleeding-related complications. Although heterogeneity limited definitive conclusions about mortality and major morbidity, the overall evidence favored concentration-guided management. This meta-analysis provides the strongest aggregate evidence to date supporting individualized anticoagulation management, highlighting consistency across multiple clinical settings and patient populations (Raner et al., 2024).

Overall Synthesis of Current Evidence

Individualized protamine dosing consistently reduces protamine exposure versus conventional approaches—confirmed across RCTs, pharmacokinetic studies, and meta-analyses—without increasing bleeding, transfusion, or inadequate reversal (Miles et al., 2021; Gkiouliava et al., 2024; Raner et al., 2024; Jain et al., 2025; Lanoiselée et al., 2026). However, uncertainty remains regarding mortality, thrombotic complications, re-exploration, and long-term recovery, as most studies focused on pharmacological rather than patient-centered endpoints. While evidence supports the safety and physiological rationale, further multicenter trials are needed before individualized dosing replaces conventional practice as the standard of care (Miles et al., 2021; Gkiouliava et al., 2024; Raner et al., 2024; Jain et al., 2025; Lanoiselée et al., 2026).

Tabel Evidence

Table 1. Summary of Current Evidence on Individualized Protamine Dosing After Cardiopulmonary Bypass

Study	Design	Population	Intervention	Comparator	Primary Outcomes	Key Findings	Clinical Implications
Raner et al., 2024 ^{4^}	Systematic Review and Meta-analysis (26 studies)	3,810 adult patients undergoing cardiac surgery with CPB	Blood concentration-guided heparin/protamine management	Conventional weight-based dosing	Bleeding outcomes, transfusion requirements, platelet preservation, protamine exposure	Individualized anticoagulation management was associated with lower protamine-to-heparin ratios, improved platelet preservation, and reduced bleeding-related complications. No increase in thrombotic events was observed.	Supports the use of heparin concentration-guided management to optimize hemostasis while reducing unnecessary protamine administration.

Gkioulia et al., 2024³	Prospective Randomized Controlled Trial	132 patients undergoing elective cardiac surgery with MiECC	Individualized Heparin-Protamine Titration (IHPT) using Hepcon HMS Plus	ACT-guided management (protamine:heparin ratio 0.75:1)	Total protamine dose, postoperative bleeding, transfusion, morbidity, ICU stay	Protamine administration was significantly reduced in the IHPT group (CABG: 118 ± 24 mg vs. 163 ± 61 mg; non-CABG: 151 ± 46 mg vs. 197 ± 45 mg; p<0.001). No significant differences were found in bleeding, transfusion, or postoperative outcomes.	Demonstrates that individualized titration can safely reduce protamine exposure without compromising hemostatic efficacy.
Jain et al., 2025⁷	Double-Blinded Randomized Controlled Trial	125 adult patients undergoing CPB-assisted cardiac surgery	Fixed low-dose protamine (250 mg)	Conventional dosing (1 mg protamine per 100 IU heparin)	Post-protamine ACT, chest tube drainage, additional protamine requirements	Similar ACT normalization and 24-hour chest tube drainage were observed in both groups. The low-dose strategy significantly reduced total protamine administration.	Challenges the necessity of traditional 1:1 protamine-heparin dosing and suggests that lower-dose reversal strategies may be sufficient in selected patients.
Miles et al. (PRODOSE Trial)¹	Adaptive Randomized Controlled Trial	228 patients undergoing cardiac surgery with CPB	Pharmacokinetic model-based protamine dosing	Conventional fixed-ratio dosing	Coagulation profile, bleeding, total protamine exposure	The pharmacokinetic-guided strategy significantly reduced protamine administration without increasing bleeding complications or coagulation abnormalities.	Provides early evidence supporting individualized dosing based on estimated residual heparin activity rather than total heparin administered.
Lanoiselée et al., 2026⁸	Prospective Population Pharmacokinetic-Pharmacodynamic Study	68 adult patients undergoing CPB-assisted cardiac surgery	Anti-factor Xa-guided PK-PD protamine dosing model	Conventional protamine-heparin ratio assumptions	Minimum effective protamine dose, anti-Xa activity, ACT correlation	Model-based simulations predicted that a protamine-to-heparin ratio of approximately 0.625:1 would achieve complete	Suggests that traditional protamine doses may substantially exceed physiological requirements and

heparin neutralization in 95% of patients. Anti-Xa activity may provide a more direct assessment of residual heparin activity than ACT, while ACT values show substantial variability at low anti-Xa concentrations.

Sumber: Miles dkk. (2021); Gkiouliava dkk. (2024); Raner dkk. (2024); Jain dkk. (2025); Lanoiselée dkk. (2026).

Table 2. Comparative Summary of Major Findings Across Current Evidence

Parameter	Raner et al. 2024	Gkiouliava et al. 2024	Jain et al. 2025	PRODOSE Trial	Lanoiselée et al. 2026	Overall Evidence
Reduced protamine exposure	✓	✓	✓	✓	✓	Consistently demonstrated
Adequate heparin reversal	✓	✓	✓	✓	✓	Consistently demonstrated
Reduced postoperative bleeding	✓	No significant difference	No significant difference	No significant difference	Not evaluated	Limited evidence
Reduced transfusion requirement	Trend toward reduction	No significant difference	No significant difference	No significant difference	Not evaluated	Inconclusive
Improved platelet preservation	✓	Not assessed	Not assessed	Not assessed	Not assessed	Moderate evidence
ACT-anti-Xa discordance	Not evaluated	Not evaluated	Not evaluated	Not evaluated	✓	Emerging evidence
Reduced protamine-related toxicity risk	Potential benefit	Potential benefit	Potential benefit	Potential benefit	Strong pharmacological rationale	Promising but unproven
Mortality benefit	Not demonstrated	Not demonstrated	Not demonstrated	Not demonstrated	Not evaluated	No evidence
Re-exploration reduction	Insufficient evidence	Not demonstrated	Not demonstrated	Not demonstrated	Not evaluated	No evidence
Relative strength of evidence	High	Moderate-High	High	Moderate-High	Moderate	Overall moderate-to-high

Sumber: Diadaptasi dari Miles dkk. (2021); Gkiouliava dkk. (2024); Raner dkk. (2024); Jain dkk. (2025); Lanoiselée dkk. (2026).

Table 3. Major Current Controversies Identified by Recent Studies

Controversy	Supporting Evidence	Opposing/Unresolved Evidence
Conventional 1:1 protamine-heparin ratio may be excessive	Jain et al. (2025); Lanoiselée et al. (2026); PRODOSE Trial	Lack of large multicenter outcome trials
ACT has limitations as the sole marker of heparin reversal	Lanoiselée et al. (2026) suggested that anti-Xa activity may provide a more direct assessment of residual heparin activity than ACT.	ACT remains inexpensive, rapid, and universally available
Lower protamine doses may reduce protamine-associated coagulation impairment	Koster et al. (2014); Boer et al. (2018); Hanke et al. (2021); Jain et al. (2025)	Clinical impact on major bleeding remains uncertain
Individualized monitoring may improve coagulation-related outcomes	Raner et al. (2024) showed improved coagulation-related outcomes	Hard outcomes (mortality, re-exploration) remain inconclusive
Heparin concentration monitoring may reduce protamine exposure compared with conventional dosing	PRODOSE Trial; Gkiouliava et al. (2024); Raner et al. (2024)	Cost-effectiveness and accessibility remain barriers
Anti-Xa-guided reversal may improve assessment of residual heparin activity	Lanoiselée et al. (2026)	Limited real-time availability, cost, and lack of outcome-driven validation
TEM may help distinguish residual heparin effect from protamine-related coagulation impairment	Mittermayr et al. (2009); Meesters et al. (2015); Koster et al. (2014); Hanke et al. (2021)	TEM is not a direct quantitative assay for heparin or protamine concentration and may be influenced by CPB-related coagulopathy

Sumber: Disusun dari Boer dkk. (2018); Koster dkk. (2014); Mittermayr dkk. (2009); Meester dkk. (2015); Hanke dkk. (2021); Miles dkk. (2021); Gkiouliava dkk. (2024); Raner dkk. (2024); Jain dkk. (2025); Lanoiselée dkk. (2026).

Current Controversies In Individualized Protamine Dosing

What Is the Optimal Protamine-to-Heparin Ratio?

The optimal protamine-to-heparin (P:H) ratio for heparin reversal after CPB remains highly debated. The conventional 1:1 ratio (1 mg per 100 IU), adopted for its simplicity rather than rigorous pharmacokinetic evidence, may substantially exceed requirements for most patients. The 2026 Lanoiselée PK-PD study predicted a significantly lower ratio achieves complete reversal in most patients, suggesting routine 1:1 dosing exposes many to unnecessary protamine excess (Lanoiselée et al., 2026).

Despite this evidence, many clinicians hesitate to reduce dosing due to concerns about residual anticoagulation and bleeding. Current practice varies widely (0.5:1 to 1:1 ratios), and the absence of large multicenter outcome-driven trials prevents universal consensus on the safest and most effective ratio (Jain et al., 2025; Lanoiselée et al., 2026).

ACT Versus Anti-Factor Xa Monitoring

A major controversy concerns the most appropriate method for assessing heparin reversal adequacy. ACT remains standard due to its speed, low cost, and availability, but it is

influenced by multiple factors independent of heparin concentration—hypothermia, hemodilution, thrombocytopenia, platelet dysfunction, anemia, and factor depletion—limiting its accuracy in reflecting residual anticoagulant activity post-CPB (Lanoiselée et al., 2026).

Recent studies show considerable discordance between ACT and anti-Xa activity; the 2026 pharmacometric study found substantial variability at low anti-Xa concentrations, with some patients showing normalized ACT despite residual anti-Xa activity and others showing prolonged ACT without significant heparin activity, raising concerns about ACT as the sole reversal indicator. Although anti-Xa monitoring provides more physiologically relevant assessment, widespread adoption is limited by specialized infrastructure requirements, higher costs, and lack of immediate intraoperative results—leaving the ACT versus anti-Xa debate unresolved (Lanoiselée et al., 2026).

Role of Thromboelastometry in Assessing Residual Heparin Effect and Protamine Excess

Viscoelastic hemostatic testing (VHT), particularly thromboelastometry (TEM), provides dynamic assessment of clot initiation, propagation, strength, and fibrinolysis, serving as a valuable adjunct in individualized protamine management. Comparison between standard and heparinase-modified TEM assays helps differentiate residual heparin activity (correction after heparinase) from other coagulopathies or protamine-induced impairment (prolonged in both assays). However, TEM is a functional assessment, not a quantitative measure of heparin or protamine concentrations, and its interpretation is influenced by hypofibrinogenemia, platelet dysfunction, factor depletion, hemodilution, hypothermia, and protamine excess—requiring integration with ACT, anti-Xa, heparin concentration, fibrinogen, platelet assessment, and clinical bleeding pattern (Boer et al., 2018; Lanoiselée et al., 2026).

In patients with persistent bleeding or prolonged ACT post-protamine, TEM may help avoid unnecessary additional protamine when residual heparin is not the primary cause, while improvement after heparinase may indicate heparin rebound requiring reversal. Although TEM can identify functional consequences of protamine excess, current evidence does not support its use as a stand-alone tool for determining protamine dosage; rather, it should be considered an important component of a multimodal precision anticoagulation strategy (Boer et al., 2018; Lanoiselée et al., 2026).

Heparin Concentration-Guided Management Versus Fixed-Dose Strategies

Point-of-care systems like Hepcon HMS Plus reduce protamine exposure versus conventional dosing, but clinical benefit remains controversial (Miles et al., 2021; Gkiouliava et al., 2024; Raner et al., 2024). A 2025 RCT found lower-dose approaches achieved similar hemostatic outcomes with reduced protamine, yet differences in major outcomes—re-exploration, transfusion, mortality—were small, fueling debate over whether added complexity and cost are justified (Gkiouliava et al., 2024; Raner et al., 2024; Jain et al., 2025). Critics argue postoperative bleeding is multifactorial (platelet dysfunction, fibrinolysis, inflammation, surgical factors), so pharmacological precision may not guarantee superior outcomes, and definitive evidence remains lacking (Jain et al., 2025; Lanoiselée et al., 2026).

Protamine Overdose Versus Heparin Rebound

A central controversy in anticoagulation reversal is determining which complication poses the greater clinical threat: protamine overdose or residual heparin activity. Historically, cardiac anesthesiologists were primarily concerned with heparin rebound, a phenomenon characterized by reappearance of anticoagulant activity several hours after apparent successful

reversal. Heparin rebound has been implicated in postoperative bleeding and has traditionally justified administration of relatively generous protamine doses.

More recently, growing evidence suggests that protamine excess may be at least as clinically important as residual heparin. As detailed earlier, the anticoagulant properties of excess protamine mean that administration beyond the amount required for heparin neutralization may paradoxically increase bleeding risk. This emerging evidence has shifted attention toward minimizing protamine exposure while still maintaining adequate reversal.

The challenge lies in balancing these competing risks. Lower protamine doses may reduce protamine-induced coagulopathy but may increase the likelihood of residual anticoagulation. On the other hand, higher doses may eliminate concerns about heparin rebound while increasing exposure to protamine-related adverse effects. Current evidence is still insufficient to definitively determine the optimal balance between these opposing risks.

Clinical Relevance of Protamine-Induced Adverse Effects

Another ongoing controversy concerns the significance of protamine-related adverse reactions in contemporary cardiac surgery. Protamine administration has been associated with systemic hypotension, pulmonary hypertension, right ventricular dysfunction, complement activation, anaphylactoid reactions, and catastrophic cardiovascular collapse in susceptible individuals. Although severe reactions are relatively uncommon, their potential consequences are substantial.

Advocates of individualized dosing argue that reducing total protamine exposure may decrease the incidence of these complications. However, current studies have generally been underpowered to detect differences in rare adverse events. Whether lower-dose individualized strategies significantly reduce major protamine-related complications therefore remains uncertain, and large multicenter studies would be required to address this question definitively.

Cost-Effectiveness and Implementation Challenges

Although individualized heparin-protamine management is physiologically attractive, its economic value remains controversial. Point-of-care monitoring systems require dedicated equipment, consumables, personnel training, and ongoing maintenance. In many institutions, particularly in low- and middle-income countries, the implementation costs may represent a significant barrier to adoption.

Supporters contend that reductions in bleeding complications, blood product utilization, and re-exploration procedures could offset these costs. However, robust cost-effectiveness analyses are still limited, and the existing evidence is largely derived from single-center studies. Until large-scale economic evaluations become available, uncertainty about the financial value of individualized anticoagulation management is likely to persist.

Precision-Based Anticoagulation Reversal

The final controversy concerns the future direction of anticoagulation management after CPB. Emerging evidence suggests that precision-based strategies combining heparin concentration measurement, anti-factor Xa monitoring, viscoelastic testing, and pharmacokinetic modeling may support more individualized reversal protocols, although machine-learning approaches remain investigational and require dedicated validation before clinical implementation.

However, the transition from conventional to precision-based management will require stronger evidence showing improvements in patient-centered outcomes rather than merely

pharmacological endpoints. Future multicenter randomized trials focusing on bleeding, transfusion, re-exploration, thrombotic events, and mortality will be essential to determine whether individualized protamine dosing should become the new standard of care after cardiopulmonary bypass.

FUTURE DIRECTIONS

Transition Toward Precision-Based Anticoagulation Reversal

The future of protamine administration after cardiopulmonary bypass (CPB) is increasingly moving away from empirical dosing protocols toward precision-based anticoagulation management. Traditional fixed-ratio strategies were developed in an era when real-time assessment of heparin activity was unavailable and clinical decision-making relied primarily on activated clotting time (ACT). However, advances in pharmacokinetic modeling, coagulation monitoring, and precision medicine have highlighted the substantial interindividual variability in heparin metabolism and protamine requirements. Future anticoagulation management is therefore expected to focus on individualized reversal strategies that account for patient-specific pharmacokinetic and pharmacodynamic characteristics rather than relying only on the administered heparin dose.⁸ As discussed above, recent PK-PD modeling suggests that future dosing algorithms may be built from mathematical prediction models rather than from fixed empirical ratios.⁸

Integration of Anti-Factor Xa-Guided Reversal

Incorporating anti-Xa measurement into routine management is a promising future development. Unlike ACT, anti-Xa directly reflects residual heparin concentration, and substantial discordance between the two suggests ACT inadequately assesses reversal completeness (Lanoiselée et al., 2026).

As point-of-care technology evolves, rapid anti-Xa testing may enable protamine titration based on measured heparin activity rather than indirect parameters, potentially improving reversal accuracy while minimizing residual anticoagulation and protamine-induced coagulopathy. Future multicenter studies are needed to determine whether anti-Xa-guided management improves clinical outcomes versus conventional ACT-based protocols (Lanoiselée et al., 2026).

Expansion of Point-of-Care Heparin Concentration Monitoring

Technological advances in point-of-care monitoring, such as the Hepcon HMS Plus, enable direct heparin concentration measurement and individualized protamine titration. Although current adoption is limited by cost and availability, future improvements in accuracy, portability, and affordability may enable broader implementation, transforming anticoagulation from standardized protocols into patient-specific therapeutic strategies (Gkiouliava et al., 2024; Lanoiselée et al., 2026).

Future platforms may integrate multiple parameters simultaneously—heparin concentration, anti-Xa activity, thrombin generation, platelet function, and viscoelastic clot formation—allowing clinicians to identify precise bleeding causes and deliver targeted therapy rather than relying on empiric transfusion or additional protamine (Lanoiselée et al., 2026).

Incorporation of Viscoelastic Hemostatic Testing

Viscoelastic hemostatic testing (TEG and TEM) is increasingly incorporated into perioperative management, providing dynamic assessment of clot initiation, strength, platelet

function, fibrinogen, and fibrinolysis. Unlike ACT which primarily reflects anticoagulant activity, viscoelastic testing evaluates overall hemostatic competence. Future individualized reversal protocols may combine heparin concentration monitoring with viscoelastic assessment for comprehensive coagulation evaluation post-CPB (Lanoiselée et al., 2026).

Because postoperative bleeding after cardiac surgery is multifactorial—beyond residual heparin alone—future algorithms are likely to incorporate both anticoagulant monitoring and global hemostatic assessment to guide precision-based treatment (Lanoiselée et al., 2026).

Pharmacometric and Artificial Intelligence-Based Dosing Algorithms

The emergence of advanced computational modeling represents another promising direction for individualized protamine dosing. Recent PK-PD studies have shown that mathematical models can accurately predict heparin neutralization kinetics and estimate the minimal effective protamine dose required for complete reversal. These models incorporate variables such as body weight, total heparin exposure, CPB duration, and measured anticoagulant activity to generate individualized dosing recommendations.^{8^}

Future research may explore machine-learning and artificial intelligence (AI)-assisted dosing algorithms using large perioperative datasets. However, AI-assisted protamine dosing remains investigational and requires dedicated validation before clinical implementation.^{8^}

Outcome-Oriented Randomized Clinical Trials

Despite growing evidence, most existing studies focus on pharmacological endpoints (ACT normalization, anti-Xa, protamine exposure) rather than patient-centered outcomes. Future research must shift toward evaluating postoperative bleeding, transfusion requirements, re-exploration, thrombotic complications, ICU stay, and mortality through large multicenter RCTs to determine whether individualized dosing provides clinically meaningful benefits beyond pharmacological precision (Jain et al., 2025; Lanoiselée et al., 2026).

Future trials should also investigate specific populations that may derive particular benefit, including elderly patients, those undergoing complex aortic surgery, prolonged CPB, minimally invasive procedures, and patients with preexisting coagulation abnormalities. Such studies will help define which patient groups should be prioritized for precision-based anticoagulation management (Jain et al., 2025; Lanoiselée et al., 2026).

Toward Personalized Hemostasis Management in Cardiac Surgery

Individualized protamine dosing should be viewed within personalized hemostasis management, where future strategies may integrate heparin concentration monitoring, anti-Xa measurement, viscoelastic testing, pharmacokinetic modeling, and AI-based decision support into unified precision platforms—tailoring reversal therapy to each patient's unique coagulation profile rather than administering standard doses (Jain et al., 2025; Lanoiselée et al., 2026).

As precision medicine advances, individualized protamine dosing has potential to become a key component of modern blood conservation programs. However, widespread adoption depends on robust evidence showing improved patient outcomes, cost-effectiveness, and feasibility across diverse settings. Until such evidence emerges, individualized protamine dosing remains one of the most promising yet evolving areas of perioperative cardiovascular medicine (Jain et al., 2025; Lanoiselée et al., 2026).

CONCLUSION

Individualized protamine dosing after cardiopulmonary bypass addresses the fundamental limitations of conventional fixed-ratio reversal strategies. Current evidence consistently demonstrates that individualized approaches—heparin concentration-guided management, protamine titration, anti-Xa monitoring, and pharmacokinetic modeling—significantly reduce unnecessary protamine exposure while maintaining effective heparin neutralization and comparable hemostatic outcomes, with ratios as low as 0.625:1 potentially adequate for most patients. However, uncertainties remain regarding the optimal monitoring modality, clinical significance of reduced protamine exposure, and the balance between protamine overdose and heparin rebound risks.

Large multicenter randomized controlled trials evaluating patient-centered outcomes—postoperative bleeding, transfusion, re-exploration, thrombotic complications, and mortality—are urgently needed, along with rigorous cost-effectiveness analyses to justify implementation costs, particularly in resource-limited settings. Until such evidence emerges, individualized protamine dosing remains a promising yet evolving area of perioperative cardiovascular medicine with potential to become a key component of modern blood conservation and precision medicine initiatives in cardiac surgery.

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