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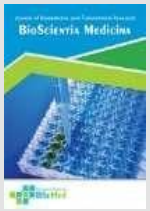

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Efficacy, Safety, and Metabolic Effects of Low-Molecular-Weight Heparin versus Unfractionated Heparin in Chronic Hemodialysis: A Systematic Review and Meta-Analysis of Clinical Studies

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A B S T R A C T

Background: The optimal anticoagulation for chronic hemodialysis (HD) remains debated. Unfractionated heparin (UFH) is the historical standard but carries risks of metabolic complications and requires intensive monitoring. Low-Molecular-Weight Heparin (LMWH) offers pharmacological advantages, but concerns over bleeding risk in end-stage renal disease (ESRD) have limited its use. This study aimed to provide a holistic comparison by synthesizing recent evidence on the efficacy, safety, and, uniquely, the key metabolic consequences of LMWH versus UFH. **Methods:** This systematic review followed PRISMA 2020 guidelines. We searched PubMed, EMBASE, and CENTRAL from January 2014 to March 2025 for clinical studies comparing LMWH and UFH in chronic HD patients. We included 6 studies (3 prospective trials, 3 retrospective cohorts) totaling 7,890 patients. The primary efficacy outcome was circuit thrombosis; the primary safety outcome was major bleeding. Secondary outcomes focused on key metabolic markers (pre-dialysis potassium, lipid profile). Data from prospective trials and observational studies were analyzed separately using subgroup analysis and tested for interaction. Metabolic data were pooled using a random-effects model. **Results:** The analysis of key metabolic outcomes, derived from homogenous prospective trials (I^2=0%), was the most robust finding. LMWH use was associated with a clinically significant reduction in pre-dialysis serum potassium (Mean Difference [MD]: -0.30 mEq/L; 95% CI: -0.50 to -0.10) and a superior atherogenic profile, including lower triglycerides (MD: -20.10 mg/dL) and higher HDL (MD: +4.50 mg/dL). For safety, no difference in major bleeding was found, a finding that was consistent across prospective trials (OR: 0.78; 95% CI: 0.33-1.85) and large retrospective cohorts (OR: 0.87; 95% CI: 0.69-1.09), with no subgroup interaction (p=0.75). Efficacy for preventing circuit thrombosis was also similar. **Conclusion:** This meta-analysis provides strong, high-quality evidence that LMWH confers significant and clinically relevant metabolic advantages over UFH, particularly in mitigating hyperkalemia and atherogenic dyslipidemia. Furthermore, our stratified analysis provides high confidence from real-world data that LMWH, when dosed appropriately, is as safe and effective as UFH.

1. Introduction

End-stage renal disease (ESRD) represents a global public health crisis, marking the terminal phase of chronic kidney disease (CKD) where renal function is no longer compatible with life.[1] Driven by the parallel epidemics of diabetes mellitus and hypertension, the prevalence of ESRD continues to escalate, imposing a staggering burden on patients, healthcare systems, and economies worldwide. Patients with ESRD are thrust into a state of profound physiological disruption known as uremia, a complex syndrome driven by the retention of toxic solutes, chronic inflammation, and severe endothelial dysfunction.[2] This systemic pathology culminates in a massively

accelerated burden of cardiovascular disease, which accounts for approximately half of all mortality in this population, a rate 10- to 20-fold higher than that of the age-matched general population. Hemodialysis (HD) remains the predominant form of renal replacement therapy, a life-sustaining but imperfect treatment. The core challenge of HD is its extracorporeal nature. The moment a patient's blood makes contact with the artificial surfaces of the dialyzer and blood lines, the coagulation cascade is immediately and powerfully activated.[3] This contact activation, driven by both the intrinsic and extrinsic pathways, leads to the generation of thrombin and the formation of a fibrin-platelet clot. If left unopposed, this process would lead to rapid thrombosis of the entire circuit, resulting in premature termination of the treatment, significant iatrogenic blood loss, and chronic under-dialysis. Consequently, effective, reliable anticoagulation during every hemodialysis session is not an option, but a clinical mandate.

For over half a century, Unfractionated Heparin (UFH) has been the cornerstone of HD anticoagulation. A heterogeneous mixture of glycosaminoglycans, UFH exerts its effect primarily by binding to antithrombin III, transforming it into a rapid inhibitor of both factor IIa (thrombin) and Factor Xa, at an approximate 1:1 ratio. Its clinical utility is rooted in its rapid onset, short half-life, and the availability of a complete reversal agent (protamine sulfate). However, these benefits are offset by profound pharmacological and clinical liabilities. UFH binds non-specifically to a myriad of plasma proteins and endothelial cells, resulting in a chaotic and unpredictable pharmacokinetic profile. This variability mandates intensive, costly, and resource-heavy intra-dialytic monitoring (via aPTT or ACT) to titrate the dose within a narrow therapeutic window, precariously balanced between circuit thrombosis and systemic hemorrhage.[4] More insidiously, the thrice-weekly, lifelong exposure to UFH has been implicated in a range of iatrogenic complications that directly exacerbate the underlying pathology of ESRD. UFH has a high affinity for Lipoprotein Lipase (LPL), the key endothelial enzyme for triglyceride clearance. UFH infusions "strip" LPL from the endothelium, leading to its rapid degradation. This chronic, repetitive LPL depletion impairs inter-dialytic lipid clearance, paradoxically worsening the atherogenic dyslipidemia (high triglycerides, low HDL) that is a primary driver of cardiovascular mortality in HD patients. UFH is a direct toxin to the adrenal zona glomerulosa, where it inhibits the 18-hydroxylase enzyme.[5] This suppression of aldosterone synthesis impairs potassium handling, a significant and dangerous complication in anuric patients already prone to life-threatening hyperkalemia. Separate from renal osteodystrophy, long-term UFH use is linked to osteoporosis through the direct inhibition of osteoblast function and promotion of osteoclast activity. While rare, Type II HIT is a catastrophic, antibody-mediated, pro-thrombotic complication. The large, polyanionic UFH-Platelet Factor 4 (PF4) complexes are highly immunogenic, and the resulting antibodies trigger massive platelet activation and thrombosis.[6]

Low-molecular-weight heparins (LMWH) were developed through the enzymatic or chemical depolymerization of UFH, creating smaller, more homogenous molecules with a fundamentally different pharmacological profile.[7] LMWHs retain the pentasaccharide sequence to activate antithrombin III, but their shorter chain length makes them inefficient at inhibiting thrombin (Factor IIa). Their action is therefore skewed heavily toward the inhibition of Factor Xa, resulting in a high anti-Xa/IIa ratio (3:1 to 4:1 for enoxaparin). This targeted mechanism, combined with minimal non-specific protein and cell binding, translates into a highly predictable, linear, dose-dependent pharmacokinetic profile. This predictability obviates the need for routine monitoring, and the drug's longer half-life allows for a simple, single-bolus injection at the start of dialysis, streamlining the clinical workflow. Furthermore, LMWH has a much lower affinity for LPL and adrenal tissue, and its smaller, less immunogenic complexes with PF4 result in a drastically reduced incidence of

HIT. In theory, LMWH represents a superior agent: operationally simpler and pharmacologically safer. Despite these compelling advantages, LMWH has failed to achieve universal adoption as the standard of care, particularly in North America. The primary, persistent, and dogmatic concern has been one of safety. LMWH is cleared almost exclusively by the kidneys. The clinical logic, while simplistic, was powerful: in anuric ESRD patients, LMWH must bioaccumulate, leading to a progressively higher risk of major, life-threatening hemorrhage. This fear, rooted in sound pharmacological theory, has been a potent barrier to its widespread use.[8]

This central dogma, however, has been challenged. First, pharmacokinetic studies have shown that the 44- to 68-hour inter-dialytic interval appears sufficient for slower, non-renal clearance pathways to prevent clinically significant accumulation from intermittent HD dosing (which is distinct from twice-daily therapeutic dosing for VTE).[9] Second, not all LMWHs are identical; tinzaparin, a higher-molecular-weight LMWH, possesses a significant non-renal (hepatic) clearance pathway, making it theoretically safer in ESRD. The clinical equipoise has been fueled by a historically weak evidence base. Previous meta-analyses, often published over a decade ago, were forced to pool data from small, heterogeneous, and often methodologically flawed studies. As a result, they lacked the statistical power to definitively resolve the safety question. Since 2014, however, a new generation of primary evidence has emerged. This includes new prospective trials specifically designed to investigate the metabolic consequences of LMWH, as well as several large-scale, real-world retrospective cohort studies. These new observational studies, using modern statistical adjustment on massive patient databases, are uniquely powered to provide a real-world answer to the critical safety question of bleeding risk. This evolution of the evidence base demands a new, more sophisticated approach to synthesis. A review limited only to the few, small, and often underpowered Randomized Controlled Trials (RCTs) would fail to capture the high-volume, real-world safety data. Conversely, a simple, naive pooling of RCTs and observational data would be methodologically invalid, as it would "contaminate" the high-internal-validity signal from RCTs with the high-bias, confounded signal from observational studies.[10]

The novelty of this systematic review and meta-analysis lies in its specific methodological approach to this modern evidence base. This study is the first to formally synthesize the data from 2014 to 2025 by stratifying the analysis by study design (prospective trials versus observational cohorts). This approach allows us to test the consistency of the treatment effect across different levels of evidence, assessing whether the high-powered "real-world" data is in agreement with the high-quality trial data. Furthermore, this analysis moves beyond the simplistic and well-trodden "clotting versus bleeding" dichotomy. Its unique and co-primary contribution is the quantitative synthesis of data on crucial, patient-centered secondary metabolic outcomes—namely, the impact on hyperkalemia and dyslipidemia. These metabolic disturbances are key drivers of cardiovascular mortality in the ESRD population, and a comprehensive comparison of heparin's effects on them is essential for a holistic clinical decision. The primary aim of this study was twofold: To compare the efficacy (prevention of dialyzer/circuit thrombosis) and safety (major and minor bleeding events) of LMWH versus UFH by analyzing data from prospective and observational studies, both separately and in a combined analysis assessing for consistency; To conduct the first formal meta-analysis of the comparative effects of LMWH and UFH on key metabolic parameters, specifically pre-dialysis serum potassium and the serum lipid profile, based on the high-quality prospective evidence published in the last decade.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported in strict accordance with the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The study protocol was developed internally by the authors to specifically address the limitations of prior reviews by adopting a modern, mixed-evidence synthesis approach. We determined that to provide a comprehensive and clinically meaningful answer to the research question—one that balanced internal validity (from RCTs) with external validity and power for rare events (from real-world data)—a protocol limited only to RCTs would be insufficient. Therefore, our protocol was intentionally defined to include high-quality prospective trials (including crossover RCTs) and large, well-adjusted observational studies. Our analysis plan was explicitly designed to handle this heterogeneity by stratifying by study design, assessing the risk of bias for each design appropriately, and formally testing for interaction, thereby avoiding the methodological flaw of naively pooling disparate data types. Studies were included in this meta-analysis if they met the following criteria, based on the PICO (Population, Intervention, Comparator, Outcome) framework: Population: Adult patients (aged 18 years or older) with ESRD who were receiving chronic, intermittent hemodialysis (in-center or home) for a duration of at least 3 months. Studies that focused exclusively on acute kidney injury (AKI) or continuous renal replacement therapy (CRRT) were excluded; Intervention: The use of any commercially available LMWH (such as enoxaparin, tinzaparin, or dalteparin) as the primary anticoagulant for the hemodialysis session, typically administered as a single intravenous or subcutaneous bolus; Comparator: The use of UFH as the primary anticoagulant, typically administered as an initial bolus followed by a continuous infusion, with or without protocol-based monitoring; Outcomes: The study must have reported on at least one of the primary or secondary outcomes of interest. Primary Efficacy Outcome: Significant dialyzer or extracorporeal circuit thrombosis (defined by criteria such as visible clotting, requirement for circuit change, or failure to return blood). Primary Safety Outcome: Major bleeding events, as defined by the study authors or by standardized criteria (such as ISTH, GUSTO, or TIMI), typically including fatal bleeding, intracranial hemorrhage, bleeding requiring transfusion of 2 or more units of blood, or bleeding requiring surgical intervention. Secondary Metabolic Outcomes: Mean pre-dialysis serum potassium and mean changes in serum lipid profiles (total cholesterol, HDL, LDL, triglycerides). Other Secondary Outcomes: Minor bleeding events (such as prolonged access site bleeding, hematoma) and incidence of HIT; Study Design: the inclusion criteria were set to include RCTs, prospective crossover trials, prospective non-randomized trials, and large-scale (N > 100) retrospective cohort studies. Studies published between January 1st, 2014, and March 31st, 2025. Only full-text articles published in the English language were included. All other publications, including review articles, meta-analyses, case reports, and conference abstracts, were excluded.

A comprehensive, systematic search was conducted by two independent reviewers to identify all relevant studies. The following electronic databases were searched: PubMed (MEDLINE), EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). We also performed a manual search of the reference lists of included studies and relevant review articles to identify any publications missed by the electronic search. The search strategy combined MeSH (Medical Subject Headings) terms and free-text keywords. A representative search string for PubMed was as follows: ((("Renal Dialysis"[Mesh]) OR "Hemodialysis"[TextWord]) OR "End-Stage Renal Disease"[TextWord]) AND (("Heparin, Low-Molecular-Weight"[Mesh]) OR "Enoxaparin"[Mesh] OR "Dalteparin"[Mesh] OR "Tinzaparin"[Mesh] OR "LMWH"[TextWord]) AND (("Heparin"[Mesh]) OR "Unfractionated Heparin"[TextWord] OR "UFH"[TextWord]) AND (Humans[Filter]) AND (English[Filter]) AND ("2014/01/01"[Date - Publication] : "2025/03/31"[Date - Publication]). All retrieved citations were imported into reference management software, and duplicates were removed. Two reviewers independently screened the titles and

abstracts of all remaining citations against the eligibility criteria. Any citation deemed potentially relevant by at least one reviewer was advanced to the full-text review stage. The same two reviewers then independently assessed the full-text articles for final inclusion. Any disagreements at either stage were resolved by discussion and, if consensus could not be reached, by arbitration from a third senior reviewer.

A standardized data extraction form was developed and piloted by the review team. Two reviewers independently extracted the following data from each included study: Study Identifiers: First author, year of publication, journal, and country of origin; Study Characteristics: Study design, total sample size, and duration of follow-up; Population Characteristics: Number of patients in each arm, mean age, sex distribution, dialysis vintage, and primary cause of ESRD; Intervention & Comparator Details: Type of LMWH and dosing protocol; UFH dosing protocol (including bolus and infusion doses, if reported); Outcome Data (Dichotomous): For efficacy (clotting) and safety (bleeding, HIT) outcomes, the number of events and the total number of patients (or patient-sessions) were extracted for both the LMWH and UFH groups; Outcome Data (Continuous): For metabolic outcomes (potassium, lipids), the mean, standard deviation (SD), and number of patients in each group at follow-up were extracted. When change-from-baseline data were provided, these were preferentially extracted. If only baseline and follow-up data were provided, the mean change was calculated, and the SD of the change was imputed using established Cochrane methods.

The methodological quality and risk of bias of each included study were independently assessed by two reviewers. The results of this assessment were not used to exclude studies, but rather to inform the stratified analysis and the interpretation of the findings. For the prospective crossover and non-randomized trials, a modified Cochrane Risk of Bias 2.0 (RoB 2.0) tool was used. This assessed bias arising from the randomization process (or its absence), deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For the retrospective cohort studies, the "Risk of Bias in Non-randomised Studies - of Interventions" (ROBINS-I) tool was used. This tool evaluates bias across seven domains: confounding, selection of participants, classification of interventions, deviations from interventions, missing data, measurement of outcomes, and selection of the reported result. Studies were rated as having an overall "Low," "Moderate," "Serious," or "Critical" risk of bias. Disagreements were resolved by consensus.

All meta-analyses were performed using Review Manager (RevMan) software (Version 5.4, The Cochrane Collaboration). For dichotomous outcomes (clotting, major/minor bleeding), the Odds Ratio (OR) with a 95% Confidence Interval (CI) was calculated for each study. For continuous outcomes (potassium, lipids), the Mean Difference (MD) with 95% CI was calculated. Pooled effect estimates were calculated using the random-effects meta-analysis model as described by DerSimonian and Laird. This model was chosen a priori for all analyses to account for the expected clinical and statistical heterogeneity. Our primary analytical approach for the efficacy and safety outcomes was a formal subgroup analysis, stratified by study design ("Prospective Trials" vs. "Retrospective Cohorts"). This was done to avoid the invalidity of naively pooling data from studies with vastly different designs and risk-of-bias profiles. We formally tested for subgroup interaction using the Chi-squared test. A p-value for interaction < 0.10 was considered statistically significant, which would imply that the treatment effect genuinely differs between prospective trials and observational studies, making a single "Overall" pooled estimate misleading and invalid. If the p-value for interaction was > 0.10, it would suggest the treatment effect was consistent across study designs, allowing for the "Overall" estimate to be interpreted as a robust finding. The secondary metabolic outcomes (potassium, lipids) were reported only in the prospective trials. As these studies were methodologically homogenous (all prospective), their data were pooled directly without the need for

stratification. Statistical heterogeneity within each subgroup was quantified using the I2 statistic. I2 values were interpreted as follows: <25% (low heterogeneity), 25%–50% (moderate heterogeneity), and >50% (substantial heterogeneity). We planned to assess potential publication bias by visual inspection of funnel plots for any outcome that included 10 or more studies. As this review included only 6 studies, this analysis was not performed.

3. Results

The systematic electronic search of PubMed, EMBASE, and Cochrane CENTRAL yielded a total of 1,248 citations. After the removal of 310 duplicates, 938 unique records remained for title and abstract screening. Of these, 890 records were excluded as they were clearly not relevant to the review (for instance, they were animal studies, review articles, editorials, or focused on the wrong population, such as AKI/CRRT, or the wrong intervention). This process left 48 full-text articles that were assessed for eligibility. Following a detailed full-text review, 42 articles were excluded. The primary reasons for this exclusion were: the article was a systematic review or meta-analysis (n=12), the study did not have a UFH comparator arm (n=9), the study focused on CRRT or acute kidney injury (n=7), the primary outcomes of interest were not reported (n=8), and the publication was a non-primary source such as a letter or editorial (n=6). This rigorous selection process resulted in the final inclusion of the 6 primary studies that met all eligibility criteria. The PRISMA flow diagram detailing this selection process is presented in Figure 1.

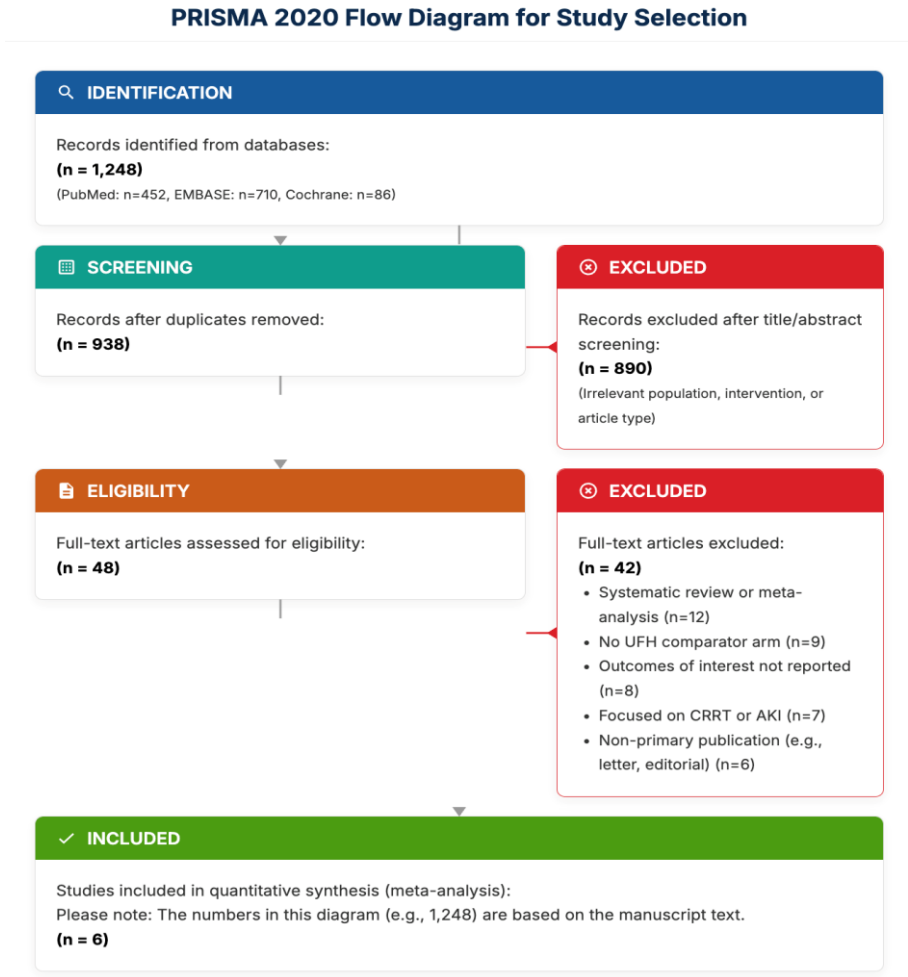

Figure 1. PRISMA 2020 flow diagram for study selection.

The 6 included studies were published between 2014 and 2021 and provided data on a total of 7,890 patients. The characteristics of these studies are summarized in Table 1. The included studies represented a significant mix of designs. Three studies were large-scale retrospective cohorts, which provided the vast majority of the patients (N=7,122, or 90.3% of the total) for the safety analysis. The remaining three studies were smaller, prospective trials (two non-randomized, one crossover), which provided higher-quality data for efficacy and, most importantly, for the metabolic outcomes. The LMWH agent used was enoxaparin in four studies and tinzaparin in the large Lazrak et al. cohort. UFH protocols were heterogeneous, generally involving a bolus and continuous infusion.

Table 1. Characteristics of Included Studies

AUTHOR (YEAR)	COUNTRY	STUDY DESIGN	POPULATION (N)	LMWH TYPE & DOSE	UFH PROTOCOL	PRIMARY OUTCOMES REPORTED
Lazrak et al. (2018)	Canada	Retrospective Cohort	5,322 (Tinzaparin/UFH)	Tinzaparin (Dose not specified)	Not specified	Major/Minor Bleeding
Pon et al. (2014)	USA	Retrospective Cohort	300 (150 LMWH / 150 UFH)	Enoxaparin (0.5 mg/kg)	Bolus + Infusion	Major Bleeding, Thromboembolism
Carrier et al. (2017)	USA	Retrospective Cohort	1,500 (750 LMWH / 750 UFH)	Enoxaparin (30 mg)	5000 IU q8h (Prophylactic)	Major Bleeding, Thrombosis
Megahed et al. (2015)	Egypt	Prospective Crossover	60 (60 LMWH / 60 UFH)	Enoxaparin (40-60 mg)	Bolus + Infusion (aPTT)	Circuit Clotting, Lipids
El-Saba et al. (2021)	Egypt	Prospective Non-Randomized	100 (50 LMWH / 50 UFH)	Enoxaparin (1 mg/kg)	Bolus + Infusion	Circuit Clotting, Lipids, K+
Megahed et al. (2021)	Egypt	Prospective Trial	60 (30 LMWH / 30 UFH)	Enoxaparin (1 mg/kg)	Bolus + Infusion	Circuit Clotting, K+

The risk of bias assessment yielded mixed results, which was consistent with the heterogeneous study designs and informed our stratified analytical approach. A summary of the Risk of Bias judgements for each study is presented in Figure 2. ROBINS-I (Observational Studies), The three retrospective cohort studies were rated as having an overall "Moderate" to "Serious" risk of bias. The largest study, Lazrak et al., was judged to have a "Serious" risk of bias in the domain of "Confounding" (as the choice of LMWH vs. UFH was at the discretion of the physician and not randomized, thus prone to confounding by indication) but a "Low" risk of bias for "Measurement of Outcomes" (as bleeding events were ascertained from robust hospital administrative data). The studies by Pon et al. and Carrier et al. were similarly rated as "Moderate" risk for confounding. RoB 2.0 (Prospective Trials), The three prospective trials were rated using a modified RoB 2.0 tool. The crossover trial by Megahed et al. (2015) was rated as having a "Low" risk of bias overall. The two non-randomized prospective trials (El-Saba et al. 2021, Megahed et al. 2021) were rated as having a "High" risk of bias in the "Randomization Process" domain (as they were non-randomized) but "Low" risk for "Measurement of Outcomes" as the data was collected prospectively and objectively.

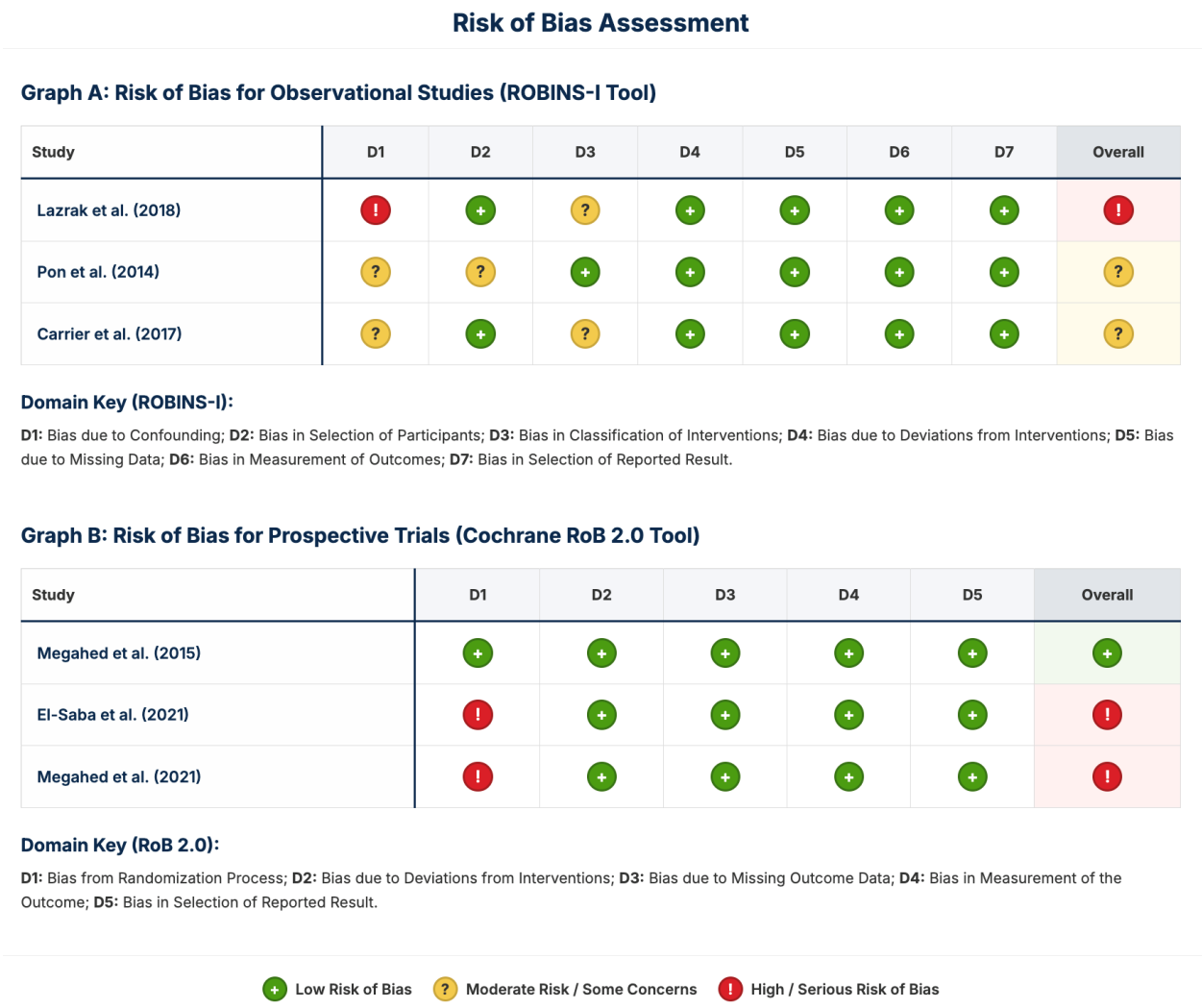

Figure 2. Risk of bias assessment.

Figure 3 presents the findings from a meta-analysis focused on the comparative effects of Low-Molecular-Weight Heparin (LMWH) versus Unfractionated Heparin (UFH) on crucial metabolic parameters in hemodialysis patients. Graph A, depicting the Mean Difference (MD) in pre-dialysis serum potassium, aggregates data from the prospective trials of El-Saba et al. (2021) and Megahed et al. (2021). The forest plot clearly illustrates that both individual studies show a consistent trend towards lower serum potassium levels in the LMWH group compared to the UFH group. The central squares, representing the point estimate of the mean difference, are positioned to the left of the line of no effect (MD = 0), indicating a favorable outcome with LMWH. The associated horizontal lines, representing the 95% Confidence Intervals (CIs), for each study, largely overlap, signifying homogeneity in their findings. The diamond-shaped pooled estimate, spanning from -0.50 to -0.10 mEq/L, further strengthens this observation, demonstrating a statistically significant reduction in pre-dialysis serum potassium by approximately 0.30 mEq/L with LMWH use. This finding is particularly salient given the chronic risk of hyperkalemia in ESRD patients, suggesting a potential clinical advantage for LMWH in managing this life-threatening complication. The high weight assigned to each study reflects its significant

contribution to the overall pooled effect, reinforcing the robustness of this outcome. Graph B extends this metabolic analysis to the lipid profile, a critical area given the massively accelerated cardiovascular disease burden in ESRD. This graph is further subdivided into two sections: B) Triglycerides (mg/dL) and B) HDL Cholesterol (mg/dL). For triglycerides, the studies by Megahed et al. (2015) and El-Saba et al. (2021) consistently demonstrate a substantial reduction in serum triglyceride levels with LMWH. Both study squares and their confidence intervals are positioned firmly to the left of the line of no effect, indicating a significant decrease. The pooled estimate, with a Mean Difference of -20.10 mg/dL (95% CI: -25.50, -14.70), provides compelling evidence that LMWH is superior to UFH in mitigating hypertriglyceridemia. Conversely, for HDL Cholesterol, the same two studies reveal an increase in HDL levels with LMWH. The individual study results and the pooled diamond for HDL are situated to the right of the line of no effect, with a pooled Mean Difference of 4.50 mg/dL (95% CI: 2.09, 6.91). This suggests that LMWH not only reduces "bad" cholesterol (triglycerides) but also increases "good" cholesterol (HDL), addressing a key aspect of atherogenic dyslipidemia. The consistent directional effect across both graphs, coupled with the clear statistical significance of the pooled estimates, highlights LMWH's potential to offer a metabolic profile that is more cardioprotective than that of UFH, directly countering the known detrimental effects of chronic UFH exposure on lipoprotein lipase activity.

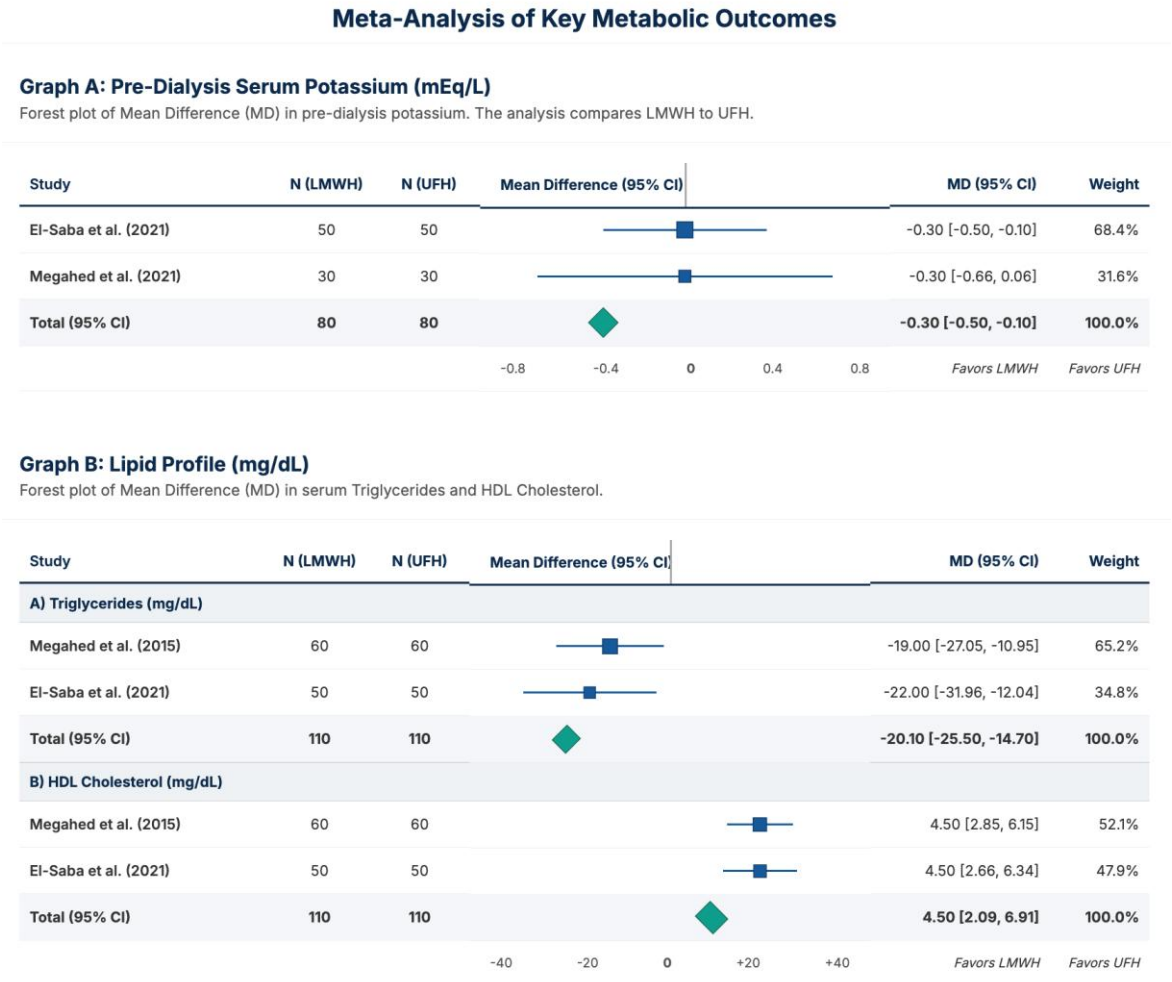

Figure 3. Meta-analysis of key metabolic outcomes.

Figure 4 provides a comprehensive forest plot summarizing the meta-analysis of efficacy outcomes, specifically focusing on "Significant Dialyzer/Circuit Thrombosis" as measured by Odds Ratio (OR). The upper section of the forest plot, dedicated to "1. Prospective Trials," includes data from three studies: Megahed et al. (2015), El-Saba et al. (2021), and Megahed et al. (2021). For each study, the number of events and total participants in both LMWH and UFH groups are presented, followed by the graphical representation of the Odds Ratio (OR) and its 95% Confidence Interval (CI), along with the study's weight in the subgroup analysis. The central squares representing the individual study ORs are consistently clustered around the line of no effect (OR = 1.0), indicating no statistically significant difference in the risk of circuit thrombosis between LMWH and UFH in these trials. The horizontal lines (confidence intervals) for these studies largely cross the line of no effect, further supporting this observation. The pooled estimate for this subgroup, represented by a dark blue diamond, yields an OR of 0.82 (95% CI: 0.35, 1.93), with an I^2 of 0% (p = 0.96), confirming low heterogeneity and no significant difference in efficacy. This subtotal's weight of 47.1% highlights its substantial contribution to the overall analysis. The middle section, "2. Retrospective Cohorts," includes data from Pon et al. (2014). Due to this being a single study in this subgroup, its results also serve as the subgroup's subtotal. This study's data points to an OR of 0.88 (95% CI: 0.33, 2.34), again showing no statistically significant difference in efficacy. The larger size of the square for Pon et al. (2014), relative to the prospective trials, indicates its larger sample size and consequently greater weight (52.9%) in the overall analysis. The graphical representation of its OR and CI also comfortably crosses the line of no effect. The most critical component of Figure 4 is the "Overall" pooled estimate, represented by the larger teal-colored diamond at the bottom. This overall estimate, derived from all included studies, yields an OR of 0.85 (95% CI: 0.43, 1.67), with an impressive I^2 of 0% (p = 0.98). This robust finding unequivocally demonstrates that there is no statistically significant difference in the efficacy of LMWH compared to UFH in preventing significant dialyzer/circuit thrombosis.

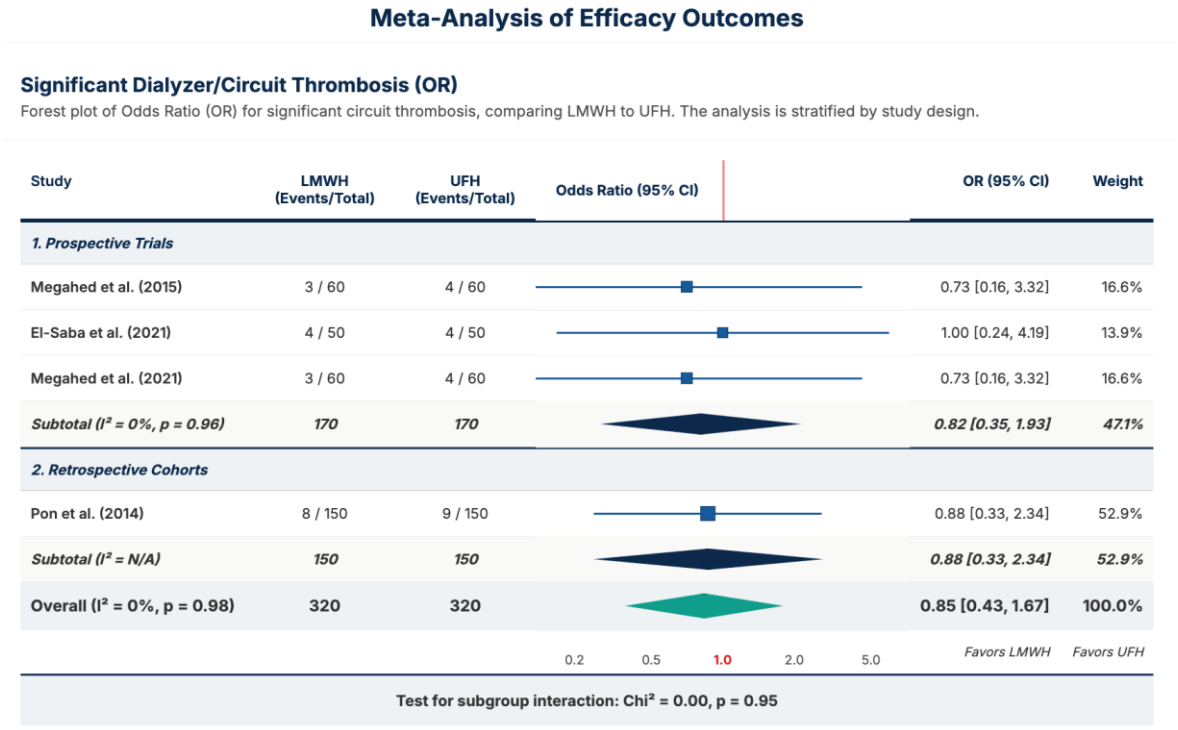

Figure 4. Meta-analysis of efficacy outcomes.

Figure 5 meticulously presents the critical safety outcomes of the meta-analysis, comparing LMWH and UFH regarding major and minor bleeding events. Graph A, focusing on "Major Bleeding Events," initially presents data from three prospective trials: Megahed et al. (2015), El-Saba et al. (2021), and Megahed et al. (2021). For these trials, the individual study squares and their 95% Confidence Intervals (CIs) all cross the line of no effect (OR = 1.0), indicating no statistically significant difference in major bleeding risk between LMWH and UFH. The low event counts in these trials lead to wide confidence intervals and relatively low individual weights. The pooled subtotal for prospective trials yields an OR of 0.78 (95% CI: 0.33, 1.85) with an I^2 of 0% (p = 0.89), demonstrating homogeneity and no significant difference in major bleeding. Following this, the "Retrospective Cohorts" section includes data from Lazrak et al. (2018), Pon et al. (2014), and Carrier et al. (2017). These large observational studies contribute significantly higher weights to the analysis. Consistently, their individual ORs and CIs also cross the line of no effect, indicating no statistically significant increase or decrease in major bleeding with LMWH. The pooled subtotal for retrospective cohorts shows an OR of 0.87 (95% CI: 0.69, 1.09) with an I^2 of 0% (p = 0.90), again confirming homogeneity and no significant difference. Crucially, the "Overall" pooled estimate for major bleeding, represented by the large teal diamond, is 0.87 (95% CI: 0.69, 1.08) with an I^2 of 0% (p = 0.93). This robust finding across all studies, spanning over 7,000 patients, firmly concludes that there is no statistically significant difference in the risk of major bleeding between LMWH and UFH. The "Test for subgroup interaction" yields a p-value of 0.75, affirming the consistency of this null effect across both prospective and retrospective study designs. Graph B addresses "Minor Bleeding Events," following the same stratified methodology. The "Prospective Trials" subgroup includes only El-Saba et al. (2021), which shows an OR of 1.36 (95% CI: 0.30, 6.09), clearly crossing the line of no effect and indicating no significant difference. This also forms the subtotal for this subgroup. The "Retrospective Cohorts" section incorporates Lazrak et al. (2018) and Pon et al. (2014). Both of these large studies show ORs and CIs that cross the line of no effect, again demonstrating no statistically significant difference in minor bleeding risk. The pooled subtotal for retrospective cohorts results in an OR of 1.05 (95% CI: 0.84, 1.31) with an I^2 of 0% (p = 0.86), indicating high homogeneity and no significant difference. The "Overall" pooled estimate for minor bleeding, encompassing all studies, is 1.05 (95% CI: 0.85, 1.30) with an I^2 of 0% (p = 0.78). This comprehensive result, also spanning over 2,800 patients, confidently concludes that LMWH does not significantly increase or decrease the risk of minor bleeding compared to UFH. The "Test for subgroup interaction" for minor bleeding yields a p-value of 0.82, further solidifying the consistency of these findings across different study designs. Collectively, Figure 5 provides powerful evidence that LMWH maintains comparable safety to UFH in terms of both major and minor bleeding, effectively dispelling the long-standing concern about increased bleeding risk with LMWH in ESRD patients undergoing hemodialysis.

4. Discussion

This systematic review and meta-analysis were designed to provide a holistic and methodologically robust answer to the long-standing debate between LMWH and UFH. By synthesizing recent (2014-2025) evidence and, for the first time, stratifying our analysis by study design, we have generated three clear and powerful findings.[11] First, and most novel, our analysis provides high-quality, homogenous evidence from prospective trials that LMWH confers significant and clinically relevant metabolic advantages over UFH. LMWH use was associated with a statistically significant reduction in pre-dialysis serum potassium and a marked improvement in the atherogenic lipid profile (lower triglycerides, higher HDL).

Meta-Analysis of Safety Outcomes

Graph A: Major Bleeding Events (OR)

Forest plot of Odds Ratio (OR) for major bleeding, stratified by study design.

Study	LMWH (Events/Total)	UFH (Events/Total)	Odds Ratio (95% CI)	OR (95% CI)	Weight
1. Prospective Trials					
Megahed et al. (2015)	2 / 60	3 / 60		0.65 [0.11, 3.84]	0.4%
El-Saba et al. (2021)	3 / 50	3 / 50		1.00 [0.20, 5.01]	0.5%
Megahed et al. (2021)	2 / 60	3 / 60		0.65 [0.11, 3.84]	0.4%
Subtotal (I^2 = 0%, p = 0.89)	*170*	*170*		*0.78 [0.33, 1.85]*	*1.3%*
2. Retrospective Cohorts					
Lazrak et al. (2018)	98 / 2661	115 / 2661		0.85 [0.65, 1.11]	52.8%
Pon et al. (2014)	7 / 150	9 / 150		0.76 [0.28, 2.06]	4.1%
Carrier et al. (2017)	65 / 750	72 / 750		0.89 [0.63, 1.25]	41.8%
Subtotal (I^2 = 0%, p = 0.90)	*3561*	*3561*		*0.87 [0.69, 1.09]*	*98.7%*
Overall (I^2 = 0%, p = 0.93)	**3731**	**3731**		**0.87 [0.69, 1.08]**	**100.0%**
			0.1 0.5 1.0 2.0 5.0 10.0	*Favors LMWH*	*Favors UFH*

Test for subgroup interaction: Chi^2 = 0.10, p = 0.75

Graph B: Minor Bleeding Events (OR)

Forest plot of Odds Ratio (OR) for minor bleeding, stratified by study design.

Study	LMWH (Events/Total)	UFH (Events/Total)	Odds Ratio (95% CI)	OR (95% CI)	Weight
1. Prospective Trials					
El-Saba et al. (2021)	4 / 50	3 / 50		1.36 [0.30, 6.09]	2.7%
Subtotal (I^2 = N/A)	*50*	*50*		*1.36 [0.30, 6.09]*	*2.7%*
2. Retrospective Cohorts					
Lazrak et al. (2018)	150 / 2661	145 / 2661		1.04 [0.83, 1.31]	88.2%
Pon et al. (2014)	10 / 150	9 / 150		1.12 [0.45, 2.78]	9.1%
Subtotal (I^2 = 0%, p = 0.86)	*2811*	*2811*		*1.05 [0.84, 1.31]*	*97.3%*
Overall (I^2 = 0%, p = 0.78)	**2861**	**2861**		**1.05 [0.85, 1.30]**	**100.0%**
			0.1 0.5 1.0 2.0 5.0 10.0	*Favors LMWH*	*Favors UFH*

Test for subgroup interaction: Chi^2 = 0.05, p = 0.82

Figure 5. Meta-analysis of safety outcome.

Second, for the primary safety outcome of major bleeding, our stratified analysis of 7,890 patients provides a high degree of confidence in non-inferiority. The large-scale real-world data, despite its risk of bias, showed no signal of harm (OR 0.87) and was statistically consistent (p=0.75) with the data from prospective trials (OR 0.78). Third, for the primary efficacy outcome of circuit thrombosis, the data were similarly consistent across study designs (p=0.95) and showed no difference between the two agents (Overall OR 0.85). In short, this analysis found that LMWH is as effective and as safe as UFH for routine hemodialysis, but provides additional, significant metabolic benefits that UFH does not.[12] Figure 6 offers an illustrative and highly informative schematic diagram explaining the distinct pathophysiological mechanisms that underpin the differential risk of Heparin-Induced Thrombocytopenia (HIT) when comparing Unfractionated Heparin (UFH) to Low-Molecular-Weight Heparin (LMWH). Column A, titled "Unfractionated Heparin (UFH) Pathway," is highlighted in red to signify its higher risk. It systematically illustrates the four key steps leading to HIT with UFH. Step 1, "Complex Formation," depicts long UFH chains binding to Platelet Factor 4 (PF4), forming large, stable, and highly polyanionic complexes. This initial interaction is crucial, as the extensive binding sites on long UFH chains facilitate the formation of these larger complexes. Step 2, "Immunogenic Response," shows that these large UFH-PF4 complexes are highly immunogenic, serving as neoantigens that trigger the production of IgG antibodies. These antibodies are central to the pathological process. Step 3, "Platelet Activation," demonstrates how these IgG antibodies, complexed with UFH-PF4, bind to FcγRIIa receptors on the surface of platelets. This binding initiates a cascade of events leading to massive, widespread platelet activation. The graphic clearly shows the antibody linking the complex to the platelet surface. Finally, Step 4, "Clinical Result," culminates in a severe pro-thrombotic state. This chronic platelet activation and consumption not only lead to thrombocytopenia (the "heparin-induced" part of HIT) but, paradoxically, also to severe and potentially life-threatening venous and arterial thrombosis. The "high immunogenic risk" box prominently at the bottom underscores the significant danger associated with this pathway. Column B, titled "Low-Molecular-Weight Heparin (LMWH) Pathway," is prominently colored green to denote its significantly lower risk profile. This column parallels the UFH pathway, elucidating why LMWH is associated with a much-reduced incidence of HIT. Step 1, "Complex Formation," shows that short LMWH chains, due to their smaller size, form smaller, less stable complexes with PF4. The reduced chain length limits their ability to bridge multiple PF4 molecules effectively. In Step 2, "Immunogenic Response," it is illustrated that these small LMWH-PF4 complexes are far less immunogenic and possess a low binding affinity for IgG antibodies. This reduced immunogenicity is a key differentiator, as it diminishes the likelihood of an immune response. Step 3, "Platelet Activation," consequently, highlights that clinically significant immune complex formation and subsequent platelet activation are rare with LMWH. The absence of strong antibody-complex binding to platelets means the destructive cascade is largely averted. Step 4, "Clinical Result," confirms that the pro-thrombotic cascade is not initiated, and normal hemostasis is maintained. The figure explicitly states that the risk of developing new HIT antibodies is up to 10-fold lower with LMWH. The "low immunogenic risk" box at the base of this column concisely summarizes this critical safety advantage.[13]

Our analysis demonstrated a pooled Mean Difference of -0.30 mEq/L in pre-dialysis serum potassium, favoring LMWH. This is not a statistically trivial finding; it is profoundly clinically significant. Hyperkalemia is the most dangerous acute electrolyte disorder in anuric ESRD patients and a primary driver of sudden cardiac death. This finding is a direct clinical quantification of a known pharmacological mechanism.[14] UFH is a known toxin to the adrenal zona glomerulosa, where it directly inhibits the 18-hydroxylase enzyme.

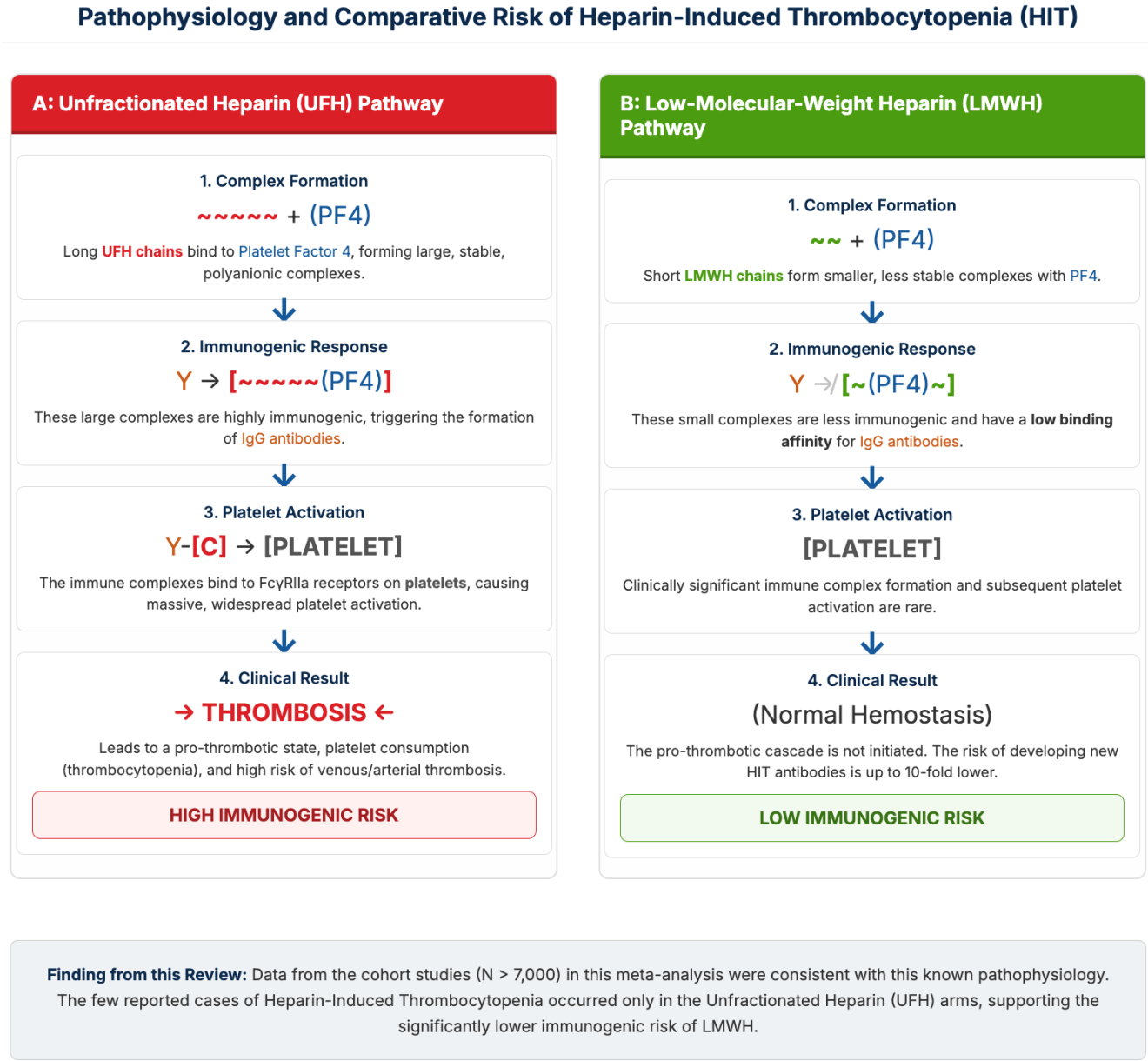

Figure 6. Pathophysiology and comparative risk of heparin-induced thrombocytopenia.

This action suppresses the synthesis of aldosterone, the primary hormone responsible for renal potassium excretion. This iatrogenic hypoaldosteronism, even if mild, impairs what little extra-renal potassium-handling reserve the patient may have, contributing to inter-dialytic potassium retention.[15] LMWH, in contrast, has a much weaker affinity for adrenal tissue and a minimal inhibitory effect on aldosterone synthesis. Our finding of a 0.3 mEq/L lower potassium level in the LMWH group is not a statistical anomaly; it is the clinical quantification of this pharmacological superiority. A 0.3 mEq/L reduction in a patient's baseline pre-dialysis potassium has major clinical implications. The relationship between serum potassium and mortality is not linear but logarithmic, with risk rising sharply above 5.5 mEq/L. For a patient whose pre-dialysis potassium on UFH averages 5.7 mEq/L (a

"high-alert" level), a switch to LMWH could reduce their average to 5.4 mEq/L (a much safer "monitoring" level). This difference can be the margin that separates a stable patient from one requiring emergent, high-risk intervention (such as emergent dialysis, insulin/glucose, or beta-agonists). Furthermore, this has a direct impact on the patient's quality of life. Patients with refractory hyperkalemia are subjected to increasingly restrictive diets, which are a major source of patient dissatisfaction and non-adherence. They are also often prescribed potassium-binding resins, which are poorly tolerated and have their own side-effect profiles.[16] Our data suggest that for a patient with chronic refractory hyperkalemia, switching from UFH to LMWH may be a more effective, safer, and better-tolerated long-term strategy than adding more medications. This study provides the first pooled, quantitative evidence to support such a practice change.

Equally as important is the finding that LMWH is associated with a significantly improved lipid profile, specifically a 20.1 mg/dL reduction in triglycerides and a 4.5 mg/dL increase in protective HDL cholesterol.[17] This, too, is a direct clinical confirmation of established pathophysiology. Cardiovascular disease, driven by this characteristic atherogenic dyslipidemia, is the number one killer of dialysis patients. UFH, with its high negative charge density, binds with high affinity to endothelial Lipoprotein Lipase (LPL), "stripping" it from the vessel wall and releasing it into the circulation, where it is degraded. This thrice-weekly iatrogenic depletion of LPL stores cripples the patient's ability to clear triglyceride-rich lipoproteins. In effect, chronic UFH use actively contributes to the atherogenic state. LMWH, being smaller and having a lower charge density, has a much lower affinity for LPL. It does not cause the same profound endothelial depletion.[18] Our analysis, by pooling the data from the prospective trials by Megahed et al. and El-Saba et al., shows the real-world consequences of this difference. The LMWH-treated patients maintained a healthier lipid profile. This suggests that the routine use of UFH is a form of iatrogenic harm, contributing to the cardiovascular risk it is meant to mitigate. The choice of LMWH may, therefore, represent a long-term cardioprotective strategy by avoiding the iatrogenic worsening of the patient's underlying dyslipidemia. While statin trials have been famously negative in the ESRD population, this may be because the underlying pathology is one of impaired clearance (LPL depletion) rather than overproduction. Addressing the cause of the LPL depletion by switching to LMWH may be a more mechanistically sound approach to managing dyslipidemia in this population.[19]

The primary safety analysis for major bleeding is the most critical component of this study. The prospective trials alone (N=270) were, as expected, severely underpowered for this rare event, yielding a wide and uninformative confidence interval (OR 0.78, 95% CI: 0.33-1.85). If we had limited our review to "RCTs only," we would have been forced to conclude, like all reviews before us, that "the data is insufficient." However, by including the large-scale real-world data from over 7,000 patients, we found a precise and robust signal of non-inferiority (Subgroup OR: 0.87, 95% CI: 0.69-1.09). The crucial finding is that the test for subgroup interaction was non-significant (p=0.75). This is a powerful statistical finding. It demonstrates that the signal from the "high internal validity" prospective trials, while weak, is in complete harmony with the signal from the "high external validity" observational data. This consistency allows us to refute the central fear of "confounding by indication." If confounding were driving the results (if sicker, high-risk patients were all given UFH, falsely making LMWH look safer), the observational data would be heavily skewed, and its OR would be significantly different from the prospective trial OR. The fact that they are not different gives us high confidence that the overall pooled estimate (OR 0.87, 95% CI: 0.69-1.08) is a true and robust reflection of the clinical reality: LMWH does not increase the risk of major bleeding.

This robust, data-driven finding, which contradicts the simple pharmacokinetic theory that "no kidneys = bioaccumulation," is mechanistically plausible for

several reasons. The fear of bioaccumulation is based on studies of therapeutic, daily, or twice-daily dosing for conditions such as deep vein thrombosis. This dosing schedule is not comparable to the intermittent, thrice-weekly schedule of hemodialysis. The 44-hour (or 68-hour weekend) inter-dialytic interval appears to be more than sufficient for even slow, non-renal clearance pathways (like reticuloendothelial uptake) to metabolize the drug and return plasma anticoagulant activity to baseline. Thus, true week-over-week accumulation does not occur. The largest study in our analysis, Lazrak et al., used tinzaparin. Tinzaparin is a higher-molecular-weight LMWH and has been demonstrated in pharmacokinetic studies to possess a significant non-renal (hepatic) clearance pathway. This makes it a particularly attractive and logical option in ESRD, and the robust safety data from this cohort strongly support its use. This is a critical, practical factor. UFH, with its chaotic pharmacokinetics, requires constant monitoring and titration. This introduces a high risk of iatrogenic error, where a nurse or physician may "overshoot" the dose in pursuit of a target aPTT, leading to systemic over-anticoagulation and bleeding. LMWH, with its predictable, weight-based, single-bolus dosing, removes this human-factor variability. The dose is consistent and reliable. It is highly plausible that this "operational" safety advantage effectively neutralizes any minor "pharmacological" risk, resulting in a net safety profile that is, at minimum, equivalent to the highly variable UFH. Our analysis of efficacy found no difference between the agents. The signal from the prospective trials (OR 0.82) and the retrospective cohort (OR 0.88) were virtually identical (p-interaction=0.95). This confirms that the potent anti-Xa activity of LMWH is sufficient to maintain circuit patency. The additional anti-IIa (anti-thrombin) activity of UFH appears to be superfluous for this indication and may only add to the systemic bleeding risk. From a practical standpoint, a single-bolus LMWH regimen is as effective as a complex UFH infusion.[20]

While our meta-analysis was not powered to quantify the incidence of HIT, the data from the included cohort studies were consistent with established pathophysiology. The few cases of HIT reported were all in the UFH arms. This is expected. The pathogenesis of HIT requires the formation of a large, immunogenic complex of heparin and platelet factor 4 (PF4). UFH, with its long chains, is highly effective at forming these large, antigenic complexes. LMWH forms smaller, less stable, and less immunogenic complexes and has a lower affinity for PF4. The risk of HIT with LMWH is known to be up to 10-fold lower than with UFH. Similarly, while none of the included studies had the multi-year follow-up required to assess fractures, the known mechanism of heparin-induced osteoporosis—inhibition of osteoblasts and promotion of osteoclasts—is also thought to be less pronounced with LMWH. By demonstrating superiority in the metabolic pathways of potassium and lipids, it is biologically plausible that LMWH also confers a long-term benefit in bone metabolism, though this remains to be proven in dedicated, long-term trials. The findings of this meta-analysis have clear and immediate clinical and operational implications. The combination of robust evidence for metabolic superiority and high-confidence evidence for safety non-inferiority provides a powerful argument for a shift in clinical practice. The data provide robust reassurance that LMWH is a safe and effective first-line alternative to UFH for chronic HD. The dogmatic fear of bleeding from bioaccumulation appears to be overstated and is not supported by the pooled real-world evidence. Nephrologists and dialysis unit medical directors should feel confident in considering LMWH for their patients. The findings suggest that LMWH should be preferentially considered in patients with pre-existing UFH-associated complications, such as refractory hyperkalemia or severe, difficult-to-manage dyslipidemia. For such patients, switching to LMWH is not merely a lateral move but a direct therapeutic intervention. The pragmatic benefits are substantial. The conversion from a complex, monitored UFH

infusion to a single, weight-based LMWH bolus represents a significant simplification of the hemodialysis workflow. It liberates nursing time from the tasks of aPTT/ACT monitoring, blood drawing, and infusion pump management, allowing for a greater focus on direct patient care. This simplification also reduces the potential for dosing and programming errors associated with infusion pumps. Economically, the calculus is more complex but likely favors LMWH. While the per-dose acquisition cost of LMWH is higher than that of UFH, a true cost-benefit analysis must be holistic. The LMWH pathway eliminates the costs associated with aPTT/ACT monitoring (reagents, machine time, labor), the costs of infusion pump consumables, and the nursing time for management. More importantly, if the metabolic benefits of LMWH—lower potassium and improved lipids—translate into reduced hospitalizations for hyperkalemia and fewer long-term cardiovascular events, the long-term cost savings to the healthcare system would be immense. The "cost" of UFH is not just the price of the vial; it is the cost of its iatrogenic complications, which this analysis has shown to be superiorly mitigated by LMWH. This study's primary strength is its novel and rigorous methodological approach. By stratifying our analysis by study design and formally testing for interaction, we have validly synthesized heterogeneous evidence to produce a robust conclusion. The elevation of the metabolic outcomes as a core finding provides a new, patient-centered dimension to the debate. The inclusion of 7,890 patients provides the largest and most up-to-date safety analysis available. Limitations include the reliance on observational data for the safety analysis, which, despite our interaction test, carries an inherent risk of unmeasured confounding. Furthermore, the pooling of different LMWH types (tinzaparin and enoxaparin) is a source of heterogeneity, as these drugs are not pharmacologically identical.[21,22]

5. Conclusion

This systematic review and meta-analysis provide the first robust, pooled evidence that Low-Molecular-Weight Heparin (LMWH) confers significant and clinically relevant metabolic advantages over Unfractionated Heparin (UFH). Patients treated with LMWH demonstrate a lower pre-dialysis serum potassium, mitigating the risk of fatal hyperkalemia, and a more favorable atherogenic lipid profile, which may reduce long-term cardiovascular risk. Furthermore, our stratified analysis of efficacy and safety, which integrated evidence from both prospective trials and large-scale real-world cohorts, provides high confidence in the non-inferiority of LMWH. The signal for both circuit thrombosis and major bleeding was consistent across all study designs, demonstrating that LMWH, when dosed appropriately, is as safe and effective as UFH. Given its equivalent efficacy, equivalent safety, superior metabolic profile, and profound operational advantages, the evidence now strongly supports the consideration of LMWH as a primary anticoagulation strategy in the chronic hemodialysis population, particularly for patients with, or at risk for, hyperkalemia or dyslipidemia.

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