

**EFFICACY AND SAFETY OF LOW MOLECULAR WEIGHT HEPARIN
COMPARED TO UNFRACTIONATED HEPARIN FOR CHRONIC
OUTPATIENT HEMODIALYSIS IN END STAGE RENAL DISEASE:
SYSTEMATIC REVIEW AND META-ANALYSIS.**

**DINESH KEERTY, MD
THE WRIGHT CENTER FOR GRADUATE MEDICAL EDUCATION
SCRANTON, PA
USA**

BACKGROUND

- Chronic kidney disease (CKD) was prevalent in 25.8 million adults in the United States in 2004
- Further, CKD prevalence will increase by 5 million every decade in the United States
- This alarming increase in CKD prevalence had been due to an associated increase in the prevalence of hypertension, type 2 diabetes mellitus and obesity in the United States
- CKD, obesity, hypertension and diabetes in unison are estimated to cost the American health care system a sum of \$110 billion annually

OBJECTIVES

- Evaluate the efficacy of LMWH compared to UFH in patients with ESRD receiving outpatient, chronic, intermittent hemodialysis.
- Evaluate the safety of LMWH compared to UFH in patients with ESRD receiving outpatient, chronic, intermittent hemodialysis

LOW MOLECULAR WEIGHT HEPARIN

- Low molecular weight heparins (LMWH) are widely used heparin derivatives with a mean molecular weight of less than 8000 Daltons
- They are much more beneficial to unfractionated heparin (UFH) because of lower incidence of heparin induced thrombocytopenia and have been widely used in prevention and treatment of thromboembolic episodes
- Commonly used LMW heparins are Enoxaparin, Dalteparin, Bemiparin, Certoparin, Nadroparin, Parnaparin, Reviparin and Tinzaparin
- LMWH acts by accentuating the effects of antithrombin III (a blood protein that acts by lysing clots) and is an inhibitor of factor 10, an enzyme that acts as a pro-coagulant
- Hence, by this dual mechanism, LMWH acts better than UFH in lysing clots

WHY IT IS IMPORTANT TO DO THIS REVIEW

- Observational studies showed that LMWH was associated with greater bleeding risk compared to UH in patients with renal disease
- RCTs had either excluded patients with renal disease or through inadequately powered sub-group analysis, had shown correlation between anti-coagulation efficacy of LMWH and renal clearance suggesting that patients with renal disease may indeed have increased bleeding risk
- A systematic review and meta-analysis on the same topic was conducted by Lim et al. in 2004 where they had abstracted data from 17 trials.
 - They concluded that LMW H was as effective and safe as conventional heparin in patients with ESRD receiving regular hemodialysis
 - However, as the authors had reported, risk of bias was high for the studies included in this meta-analysis and they were small population studies.



- We have focused our comparison to LMWH and UFH only.
- Our review will be clinically useful because 95% centers use only these 2 drugs
- We have focused our review to only those LMWH that are currently approved by the Food and Drug Administration (FDA).
- Our review will be clinically relevant for US dialysis centers.
- We have only included studies that had an explicit random allocation.
- We excluded controlled clinical trials that did not have an explicit random allocation.

TYPES OF PARTICIPANTS

Only ESRD patients receiving chronic, intermittent, out-patient hemodialysis

- **Chronic:** Only included patients receiving chronic dialysis for ESRD.
- **Intermittent:** Patients' receiving continuous dialysis and continuous venovenous hemofiltration were not included
- **Outpatient:** we are excluding patients receiving home dialysis and hospitalized
- **Hemodialysis**

The diagnosis of ESRD should have been physician (primary care physician or a nephrologist) made. All adult patients aged > 18 years, all races, both males and females were included in the review. We excluded patients with hyper-coagulable states and those receiving anti-coagulant or anti-platelet drugs.

TYPES OF INTERVENTIONS

- Included all studies that have used any analogue of low molecular weight heparin that is approved for use in the United States by the FDA
 - Included Dalteparin, Enoxaparin, and Tinzaparin.
- Studies were not considered ineligible based on route of administration, dose, duration of intervention, or frequency of administration.
- Exclude studies where LMW heparin was administered to patients not for the indication of anti-coagulation for hemodialysis but for therapy of another condition such as deep vein thrombosis, pulmonary embolism etc.
- We also excluded articles that have used LMW heparin as lock solution.
- Excluded all other comparison interventions such as citrate, other analogues of LMWH, direct thrombin inhibitors (example: argotroban), vitamin K antagonists (warfarin), anti-platelets (aspirin, clopidogrel) and any other anti-coagulant with any other mechanism of action.

PRIMARY OUTCOMES

For meta-analysis we only included studies that had our outcomes of interest.

Primary outcomes:

- Extracorporeal circuit thrombosis during dialysis session
 - Extracorporeal circuit thrombosis during the dialysis sessions because the primary reason for heparin administration is to prevent circuit thrombosis during dialysis.
- Graft or fistula thrombosis
 - Time point of outcome determination that we would have considered will be 7 days after study commenced and patients received the interventions.

SECONDARY OUTCOMES

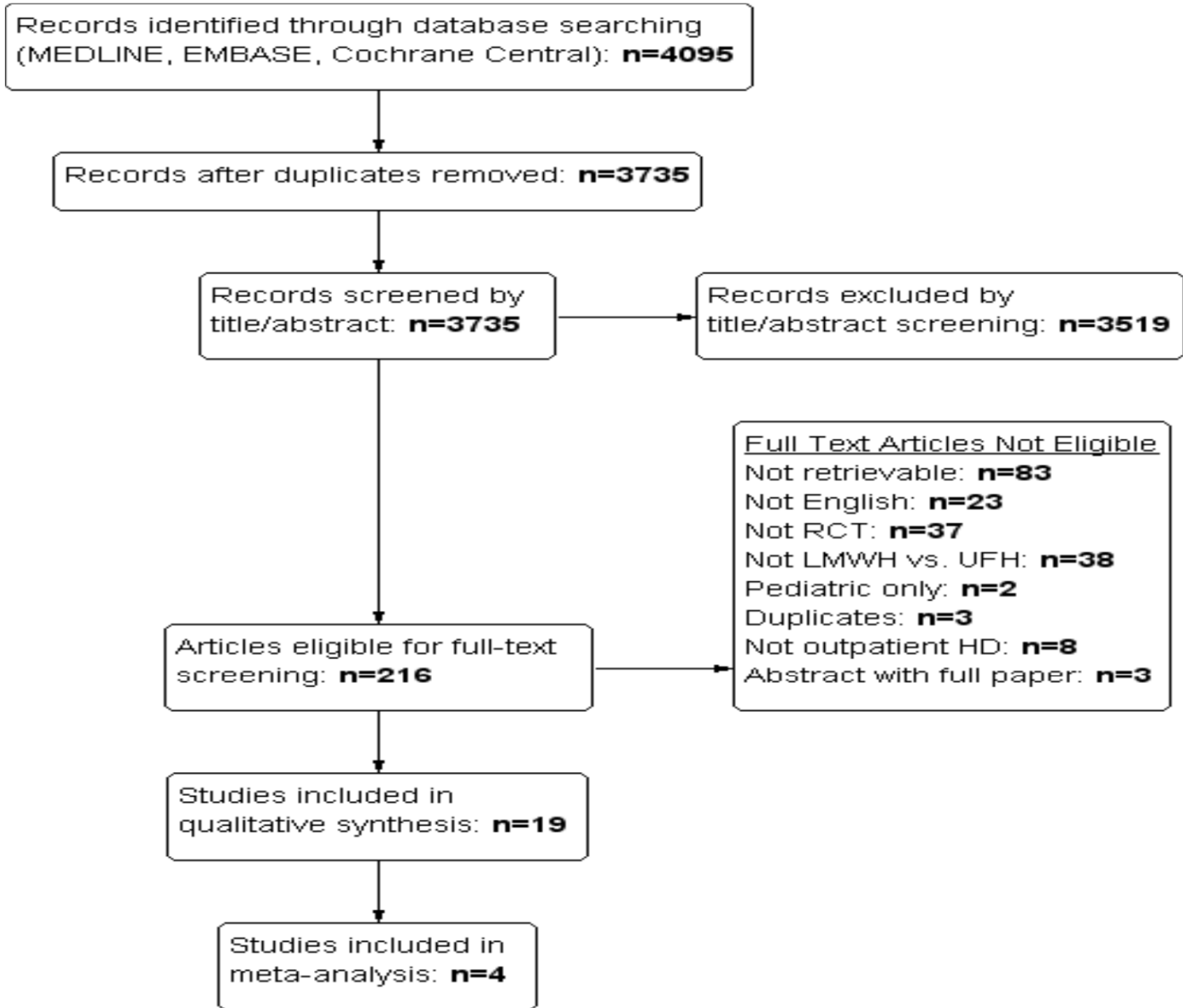
- Bleeding complications (i.e. intra-cranial hemorrhage, hemorrhagic stroke or any clinically recorded bleeding)
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Vascular compression time

DATABASES

We searched 3 databases namely

1. Pubmed
2. Embase
3. Cochrane central.

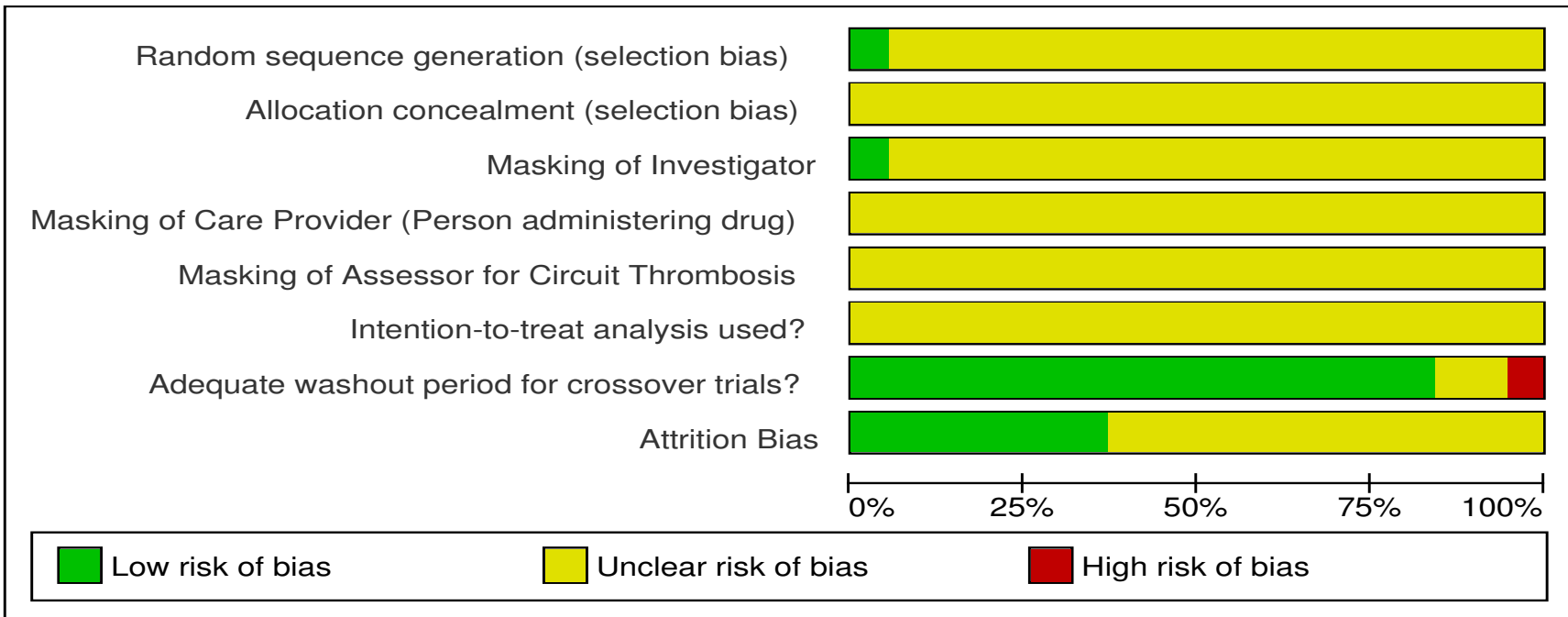
PROGRESSION OF STUDY SELECTION



BIAS

- Risk of bias was assessed by two independent reviewers. When there was a discrepancy, it was resolved by consensus. The studies were evaluated for the following criteria:
 - Allocation:
 - Sequence generation: Adequate vs. Inadequate
 - Concealment: Adequate vs. Inadequate
 - Masking of investigators and participants
 - Masking of outcome assessment and care provider
 - Loss to follow-up (attrition) and intention to treat analysis
- All components were assessed before deciding the study quality.
- We did not follow any scoring system to assess quality of the included studies but determined quality based on the subjective assessment of the reviewers from the subheadings discussed above.

RISK OF BIAS GRAPH: REVIEW AUTHORS' JUDGMENTS ABOUT EACH RISK OF BIAS ITEM PRESENTED AS PERCENTAGES ACROSS ALL INCLUDED STUDIES

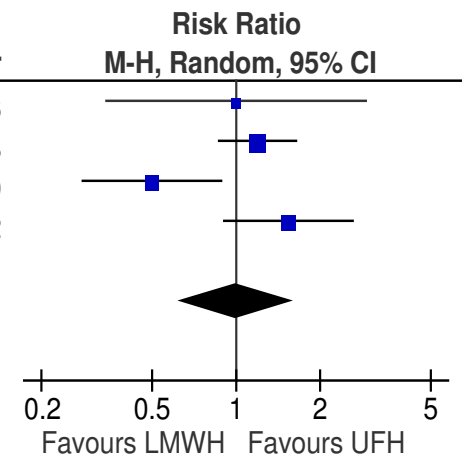


RESULTS

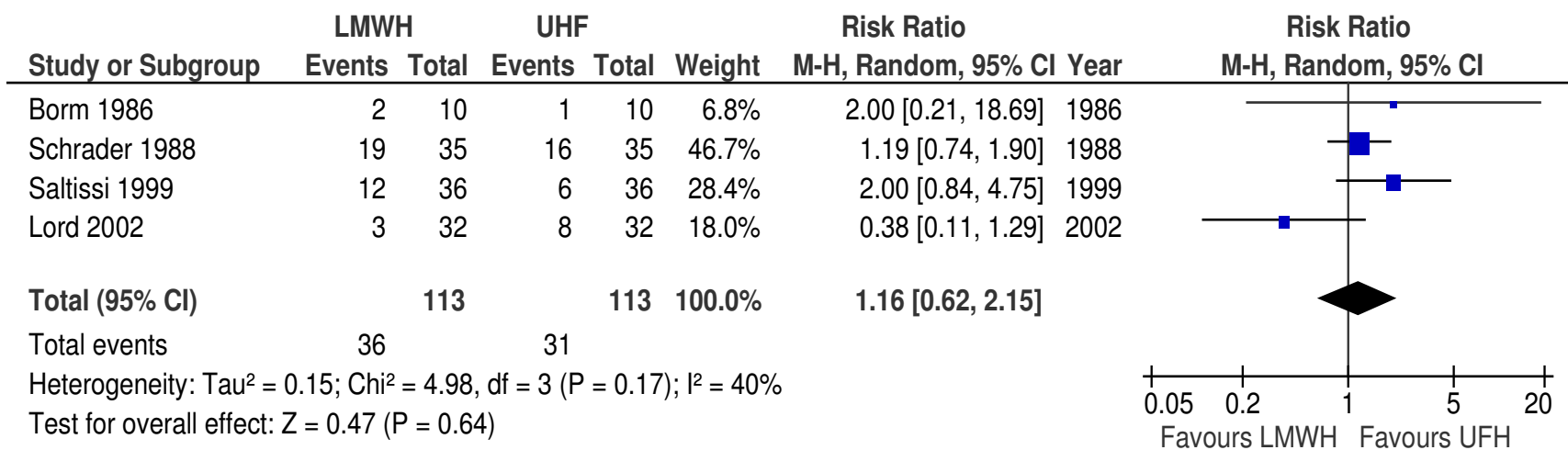
- Nineteen studies were included for systematic review and 4 were included for meta-analysis.
- There were no significant differences between LMWH and UFH for
 - Extracorporeal circuit thrombosis [risk ratio: 1 (95% C.I: 0.62 - 1.62)]
 - Bleeding complications [risk ratio: 1.16 (95% C.I: 0.62 - 2.15)].

LMWH VERSUS UFH EXTRACORPRORAL CIRCUIT THROMBOSIS (PER HD SESSION).

Study or Subgroup	LMWH		UFH		Weight	Risk Ratio		Year	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI		M-H, Random, 95% CI	
Borm 1986	4	10	4	10	13.5%	1.00	[0.34, 2.93]	1986		
Schrader 1988	80	5045	69	5197	34.0%	1.19	[0.87, 1.64]	1988		
Saltissi 1999	17	1111	35	1141	25.6%	0.50	[0.28, 0.89]	1999		
Lord 2002	32	378	21	382	26.9%	1.54	[0.90, 2.62]	2002		
Total (95% CI)		6544		6730	100.0%	1.00	[0.62, 1.62]			
Total events	133		129							
Heterogeneity: Tau ² = 0.15; Chi ² = 9.08, df = 3 (P = 0.03); I ² = 67%										
Test for overall effect: Z = 0.00 (P = 1.00)										



LMWH VERSUS UFH BLEEDING COMPLICATIONS (PER PERSON)



IMPLICATIONS OF THE STUDY

- From our review findings and that from Lim et al.
 - We may infer that it may be safe to use the three FDA approved LMWH in ESRD patients, without known hypercoagulable states other than the ESRD that they suffer, receiving regular intermittent hemodialysis.
- Since most studies included for the review were of poor quality, better RCTs with larger sample size, better randomization protocol and reporting should be conducted.
- In effect we are using drugs on American people based on trials conducted elsewhere.
- Hence more such studies should be conducted in the United States.
- In essence, generalizability of the trial findings needs testing.

CO-AUTHORS

*Ghanshyam Palamaner Subash Shantha MD^{1,2} ,
Linda Thomas-Hemak MD¹,
Jermiah Eagan MD, FASN³ ,
Manoj Das MD¹,
Qi Shi MD¹,
Louis Crevecoeur MD¹,
Amit Kakde MD^{1,4}*

1. The Wright Center for Graduate Medical Education, Scranton, PA, USA
2. John Hopkins University and Bloomberg School of Public Health, Baltimore, MD, USA
3. Northeast Nephrology Associates, Scranton, PA, USA
4. Lakeland Regional Medical Center, Lakeland, FL, USA

QUESTIONS?



THANK YOU

