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SUPPLEMENTARY MATERIAL **OPEN ACCESS**

Thrombocytopenia in Continuous Kidney Replacement Therapy (CKRT): A Systematic Literature Review and Assessment of its Clinical Relevance

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PRISMA 2009 Checklist

Section/topic	#	Checklist Item	Reported on Page #
TITLE			-
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			-
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			-
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			-
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (*e.g.*, Web address), and, if available, provide registration information including registration number.	30
Eligibility criteria	6	Specify study characteristics (*e.g.*, PICOS, length of follow-up) and report characteristics (*e.g.*, years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-5
Information sources	7	Describe all information sources (*e.g.*, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3-5

Section/topic	#	Checklist Item	Reported on Page #
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	31-34
Study selection	9	State the process for selecting studies (*i.e.*, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-5
Data collection process	10	Describe method of data extraction from reports (*e.g.*, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3-5
Data items	11	List and define all variables for which data were sought (*e.g.*, PICOS, funding sources) and any assumptions and simplifications made.	3-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3-5
Summary measures	13	State the principal summary measures (*e.g.*, risk ratio, difference in means).	5-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (*e.g.*, I^2) for each meta-analysis.	10-29
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (*e.g.*, publication bias, selective reporting within studies).	6-10
Additional analyses	16	Describe methods of additional analyses (*e.g.*, sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/a
RESULTS			-
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (*e.g.*, study size, PICOS, follow-up period) and provide the citations.	10-26
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-26
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-26
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-10
Additional analysis	23	Give results of additional analyses, if done (*e.g.*, sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/a
DISCUSSION			-
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (*e.g.*, healthcare providers, users, and policy makers).	26-29
Limitations	25	Discuss limitations at study and outcome level (*e.g.*, risk of bias), and at review-level (*e.g.*, incomplete retrieval of identified research, reporting bias).	29
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	29
FUNDING			-
Funding	27	Describe sources of funding for the systematic review and other support (*e.g.*, supply of data); role of funders for the systematic review.	N/a

Note: *From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: **www.prisma-statement.org**.

Supplemental Table 1. Search criteria used for Embase and PubMed databases.

Step	Procedure
1	Set up a search with at least two of the following database search engines: a. EMBASE b. PUBMED
2	Perform a comprehensive literature search specific to the FME product using defined search criteria in **EMBASE.** Search # Criteria 1 (random$ or rct).tw 2 exp randomized controlled trials/ 3 exp random allocation 4 exp double blind[Method] 5 exp single blind method/ 6 Randomized controlled trial.pt 7 Clinical trial.pt 8 (clin$ adj trial$).tw 9 (clin$ or double$ or trebl$ or tripl$) adj(blind$ or mask$)).tw. 10 Exp PLACEBOS/ 11 Exp Research Design/ 12 Exp Prospective Studies/ 13 Exp Comparative Study/ 14 Exp*random allocation/mt 15 1-14 16 Exp kidney failure acute, acute kidney injury/ 17 16 and thrombocytopenia 18 17 and dialyzer or membrane OR device OR mechanism 19 18 and Fresenius Medical Care OR FMC OR FME OR FMCNA OR Fresenius OR Baxter OR NxStage 20 19 and continuous renal replacement therapy OR continuous kidney replacement therapy OR CRRT OR CKRT 21 17 and clotting OR clogging, OR filter life OR circuit life OR bleeding OR adverse event 22 17 and epidemiology OR management OR mitigation 23 17 and risk factors, anticoagulation OR anticoagulant, OR drug interaction 24 15-23 25 Limit 24 to the English language. 26 Limit 25 to adults 27 Limit 26 to Case reports or case series publications. 28 Limit 27 to (addresses or bibliography or comment or dictionary or directory or editorial or festschrift or guideline or interview or lectures or legal case or letter or meta-analysis or news or periodical index or practice guideline or review literature or review of reported cases or review, academic or review, multicase or review, tutorial)
3	Perform a comprehensive literature search specific to the product using defined search criteria in **PubMed**: Search # Criteria 1 Search first for random with multiple endings or randomized controlled trials, then look for text words tag. 2 Search for subject heading “randomized controlled trials” and also broader subject headings, and narrow down under those found. 3 Search for “random allocation” and broader subject headings, and narrow down under those found. 4 Search for “Double-blind” with Method tag and broader subject headings, and narrow down under those found. 5 Search for the subject heading “single-blind method” and also broader subject headings, and narrow down under those found. 6 Search “randomized clinical trial” under publication type. 7 Search “clinical trial” under publication type. 8 Search for words “clin” with any alternate ending and words that are close to “trial” with any alternative endings, then any tags of text words. 9 Search first for words “clin” or “double” or “trebl” or “tripl” with any alternative endings, then search words “blind” or “mask” with any alternative endings that are close to each other, and finally search for text words tag. 10 Search for subject headings “placebos” and also broader subject headings, and narrow down under those found. 11 Search for subject headings “research design” and also broader subject headings, and narrow down under those found. 12 Search for subject headings “prospective studies” and also broader subject headings, and narrow down under those found. 13 Search for subject headings “comparative study” and also broader subject headings, and narrow down under those found. 14 Search for subject headings “random allocation,” which is the major focus of the article, and also broader subject headings, and narrow down under those found, also using the mesh (medical) term. 15 Search for current subject headings or saved search #s 1-14 17 Search for subject headings “kidney failure acute”, “acute kidney injury”, and also broader subject headings, and narrow down under those found. 18 Search for 17 and Fresenius Medical Care OR FMC OR FME OR FMCNA OR Fresenius OR Baxter OR NxStage 19 Search for 17 and continuous renal replacement therapy OR continuous kidney replacement therapy OR CRRT OR CKRT. 20 Search for 17 and clotting OR clogging, OR filter life OR circuit life OR bleeding OR adverse event. 21 Search for 17 and epidemiology OR management OR mitigation. 22 Search for 17 and risk factors, anticoagulation OR anticoagulant, OR drug interaction. 23 15-22 24 Limit 23 to the English language 25 Limit 24 to adults 26 Limit 25 to Case reports or case series publications. 27 Limit saved search 26 to addresses or bibliography or comment or dictionary or directory or editorial or festschrift or guideline or interview or lectures or legal case or letter or meta-analysis or news or periodical index or practice guideline or review literature or review of reported cases or review, academic or review, multicase or review, tutorial.

(Table 1) contd.....

Step	Procedure
4	Perform a comprehensive literature search specific to the product using defined search criteria in **Google Scholar**: Search # Criteria 1 Search for subject headings "kidney failure acute", "acute kidney injury", and also broader subject headings, and narrow down under those found. 2 Search for 1 and Fresenius Medical Care OR FMC OR FME OR FMCNA OR Fresenius OR Baxter OR NxStage 3 Search for 1 and continuous renal replacement therapy OR continuous kidney replacement therapy OR CRRT OR CKRT. 4 Search for 1 and clotting OR clogging, OR filter life OR circuit life OR bleeding OR adverse event. 5 Search for 1 and epidemiology OR management OR mitigation. 6 Search for 1 and risk factors, anticoagulation OR anticoagulant, OR drug interaction. 7 Search for 1-6 8 Limit 7 to the English language 9 Limit 8 to adults 10 Limit 9 to Case reports or case series publications. 11 Limit saved search 10 to addresses or bibliography or comment or dictionary or directory or editorial or festschrift or guideline or interview or lectures or legal case or letter or meta-analysis or news or periodical index or practice guideline or review literature or review of reported cases or review, academic or review, multicase or review, tutorial.

Supplemental Table 2. Drugs associated with thrombocytopenia according to vigibase.

Drug	Number of Notifications (N=1787)	ROR (95% CI)
Acetylsalicylic acid	26	1. 8 (1.2-2.7)
Acyclovir	6	3. 7 (1.7-8.3)
Alemtuzumab	239	159. 5 (140.9-185.1)
Bisoprolol	6	3. 3 (1.5-7.3)
Busulfan	5	10. 1 (4.2-24.3)
Cephalexin	7	4. 2 (2.0-8.7)
Clopidogrel	17	3. 0 (1.8-4.8)
Diphtheria, hepatitis B, HIB, pertussis, polio, and tetanus vaccines	18	4. 2 (2.6-6.7)
Diphtheria, HIB, pertussis, polio, and tetanus vaccine	8	2. 8 (1.4-5.7)
Diphtheria, pertussis, polio, and tetanus vaccines	26	5. 9 (4.0-8.7)
Diphtheria, pertussis, and tetanus vaccine	47	3. 5 (2.6-4.7)
Doxorubicin	14	2. 0 (1.2-3.4)
Doxycycline	15	6. 0 (3.6-10.0)
Ethinylestradiol; etonogestrel	6	2. 7 (1.2-6.0)
Filgrastim	6	4. 8 (2.2-10.7)
Fingolimod	30	3. 7 (2.6-5.4)
Fludarabine	11	10. 1 (5.6-18.3)
Folinic acid	15	8. 1 (4.9-13.5)
Eculizumab	18	4. 7 (2.9-7.5)
Guanfacine	10	39. 4 (21.1-73.3)
Hepatitis A vaccine	43	11. 3 (8.4-15.3)
Hepatitis B vaccine	76	15. 0 (11.9-18.8)
HIB vaccine	68	16. 8 (13.2-21.4)
HPV vaccine	58	5. 8 (4.4-7.5)
Ibrutinib	27	7. 1 (4.9-10.4)
Ifosfamide	5	4. 0 (1.7-9.7)
Immunoglobulin human anti-rabies	8	83. 4 (41.5-167.5)
Influenza vaccine	70	3. 4 (2.6-4.3)
Ipilimumab	17	8. 5 (5.3-13.7)
Irinotecan	23	6. 9 (4.6-10.4)
Losartan	13	6. 7 (3.9-11.6)
Measles, mumps, and rubella vaccine	114	10. 9 (9.0-13.2)
Measles, mumps, rubella, and varicella-zoster vaccine	39	16. 1 (11.7-22.2)
Measles and rubella vaccine	10	22. 7 (12.2-42.3)
Melphalan	5	5. 9 (2.5-14.2)

(Table 2) contd.....

Drug	Number of Notifications (N=1787)	ROR (95% CI)
Meningococcal vaccine	73	8. 6 (6.8-10.8)
Nivolumab	47	10. 5 (7.8-14.0)
Ondansetron	6	3. 9 (1.7-8.6)
Oxaliplatin	35	4. 3 (3.0-5.9)
Peginterferon alfa-2a	12	2. 7 (1.5-4.7)
Peginterferon alfa-2b	5	3. 0 (1.3;7.3)
Pembrolizumab	24	9. 4 (6.3-14.1)
Pneumococcal vaccine	136	7. 4 (6.2-8.8)
Polio vaccine	38	5. 9 (4.3-8.1)
Rabies vaccine	14	16. 1 (9.5-27.2)
Ribavirin	19	2. 4 (1.5-3.7)
Rivaroxaban	33	2. 5 (1.8-3.5)
Rotavirus vaccine	54	9. 5 (7.3-12.5)
Sofosbuvir	7	3. 7 (1.8-7.8)
Sulfamethoxazole/trimethoprim	22	3. 1 (2.1-4.8)
Sunitinib	9	2. 8 (1.4-5.3)
Tacrolimus	24	4. 4 (2.9-6.5)
Temozolomide	13	9. 7 (5.6-16.8)
Teriflunomide	7	2. 2 (1.1-4.7)
Ticagrelor	6	2. 9 (1.3-6.4)
Typhoid vaccine	9	8. 3 (4.3-15.9)
Vancomycin	22	4. 2 (2.8-6.4)
Varicella zoster vaccine	45	3. 0 (2.2-4.0)
Vedolizumab	5	2. 4 (1.0-5.8)
Venetoclax	8	6. 2 (3.1-12.3)
Yellow fever vaccine	8	3. 6 (1.8-7.2)

Supplemental Table 3. Additional drugs associated with thrombocytopenia from case reports, labs, and AERS.

Abciximab	Acetaminophen	Amiodarone
Ampicillin	Carbamazepine	Eptifibatide
Ethambutol	Haloperidol	Ibuprofen
Naproxen	Phenytoin	Piperacillin
Quinidine	Quinine	Ranitidine
Rifampin	Simvastatin	Sulfisoxazole
Tirofiban	Valproic acid	-

Supplemental Table 4. Additional drugs with five or more published reports showing definite or probable evidence for a causal relationship to thrombocytopenia.

Chlorpropamide	Cimetidine	Danazol
Diclofenac	Efalizumab	Gold
Heparin	Hydrochlorothiazide	Methyldopa
Nalidixic acid	-	-

Note: Finally, in another more recent study, eight databases were examined for articles published between January 2015 and November 2018 that demonstrated definite evidence for a causal association of drugs with thrombocytopenia. The drugs found in this study that have not been previously discussed here are included in Supplemental Table 5.

Supplemental Table 5. Additional drugs with definite evidence for causal association with thrombocytopenia from eight databases.

Aceclofenac	Leucovorin	Dexamethasone
Pyrazinamide	Flucloxacillin	Quetiapine