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Beta-2 microglobulin clearance in high-flux dialysis and convective dialysis modalities: a meta-analysis of published studies

Maria-Eleni Roumelioti[1], Gregory Trietley[2,3], Thomas D. Nolin[2,3], Yue-Harn Ng[1], Zhi Xu[1], Ahmed Alaini[1], Rocio Figueroa[1], Mark L. Unruh[1] and Christos P. Argyropoulos[1]

[1]Nephrology Division, Department of Medicine, University of New Mexico, Albuquerque, NM, USA, [2]Department of Pharmacy and Therapeutics, Renal-Electrolyte Division, University of Pittsburgh Schools of Pharmacy and Medicine, Pittsburgh, PA, USA and [3]Department of Medicine, University of Pittsburgh Schools of Pharmacy and Medicine, Pittsburgh, PA, USA

Correspondence and offprint requests to: Christos P. Argyropoulos; E-mail: CArgyropoulos@salud.unm.edu

ABSTRACT

Background. Recent meta-analyses suggest that higher removal of beta-2 microglobulin (β_2M) with either high-flux (HFD) dialysis or hemodiafiltration (HDF) may be associated with decreased total and cardiovascular mortality in dialysis patients. However, there are limited data about the performance of high flux dialyzers and/or convective therapies in removing β_2M.

Methods. This is a random effects meta-analysis and meta-regression of data extracted from randomized controlled trials and observational studies in hemodialysis, hemofiltration and HDF regarding the efficiency of high flux dialyzers to remove β_2M. Studies were searched using ProQuest in SCOPUS, EMBASE and MEDLINE.

Results. We included 69 studies from 1 January 2001 to 12 June 2017 on 1879 patients with 6771 available measurements. Average β_2M clearance was 48.75 mL/min [95% confidence interval (CI) 42.50–55.21] for conventional HF dialysis, and 87.06 mL/min (95% CI 75.08–99.03) for convective therapies (hemofiltration and HDF) with substantial heterogeneity among studies [P (Q) $\leq$ 0.001]. In multivariable meta-regression analyses, we found significantly higher β_2M clearance for polyarylethersulfone dialyzers when used for HFD and polysulfone membranes in convective therapies. However, the mass of β_2M removed into the dialysate did not depend on membrane material. Adjusted dialysate-side (−22.279, 95% CI −9.8 to −34.757, P < 0.001) β_2M clearances were significantly lower than whole blood clearances, suggesting that adsorption contributes substantially to β_2M removal. Higher Kuf, blood flow and substitution fluid rates but not dialysate flow rates were associated with statistically significant and clinically meaningful elevation in β_2M clearance from the body independent of the dialysis modality.

Conclusions. Membrane composition and characteristics, modality (convective versus diffusive), blood flow rates and substitution fluid rates in HDF play a significant role in the efficient removal of β_2M from the body in both diffusive and convective dialysis.

Keywords: beta-2 microglobulin, clearance, hemodiafiltration, hemofiltration, high-flux hemodialysis

INTRODUCTION

The accumulation of middle molecular weight solutes, such as beta-2 microglobulin (β_2M), is toxic to various body tissues and has been associated with adverse cardiovascular and infectious outcomes among patients with end-stage renal disease (ESRD) [1, 2]. β_2M precipitates and forms fibrillary structures and amyloid deposits in bones, periarticular tissues [3], vessel walls and internal organs, especially the heart [4–7]. Dialysis-related amyloidosis and other disorders associated with abnormal β_2M accumulation and function [8] are clinically silent, develop early in the development and progression of chronic kidney disease (CKD) and may even imply a potential causal link with the highly prevalent cardiovascular disease (CVD) in ESRD patients [9, 10].

Several meta-analyses of randomized controlled trials (RCTs) in conventional dialysis suggest that high-flux dialyzers, which more efficiently remove β_2M than their low-flux (LF) counterparts, are associated with improved cardiovascular outcomes [11, 12]. Convective therapies, including hemodiafiltration (HDF) and hemofiltration, achieve even higher middle molecule clearances relative to HF dialysis. These therapies may improve the chronic retention of β_2M over time noted with

thrice-weekly HFD [5, 11, 13]. In these modalities, clearance is a function of the total volume of solution utilized (both dialysate flow rate and replacement solution). A recent individual patient-level meta-analysis of published RCTs suggests that the higher clearance from the body achieved by these therapies may result in clinically and statistically significant improvement in total and cardiovascular mortality relative to conventional HFD [14, 15]. Nevertheless, the quality of the evidence and the putative effects of convective dialysis have been called into question by large collaborative aggregate level meta-analyses by the Cochrane Group [16, 17] and others [18, 19].

The interpretation of these contradicting analyses of data outcomes is complicated by the limited evidence synthesis of the performance and the determinants of β_2M clearance by high flux dialyzers when the latter are used in conventional or convective forms of renal replacement therapies. The aforementioned meta-analyses have reported only on a limited number of studies that examined dialyzer clearance or β_2M mass removal, focusing instead on reduction ratios as the sole measure of dialyzer performance. None of the aforementioned studies has attempted to analyze the impact of different dialysis configurations (e.g. membrane material, surface area, substitution fluid rate) on multiple measures of β_2M body removal. This literature gap limits our ability to better understand the performance of these therapies, and how best to modify treatment parameters to optimize clearance of middle molecules, thus moving beyond urea-centric approaches that have been widely used in modern dialysis. To do so, we conducted a meta-analysis of data about the performance of HFD and/or convective dialysis therapies to remove β_2M. We included studies published between 2001 and 2017, covering the period in which the landmark RCTs in HFD [13, 20] and HDF [21–23] were published.

MATERIALS AND METHODS

This is a meta-analysis of data collected in RCTs and observational studies in hemodialysis (HD) about the performance (ability) of HFD and convective therapies (HDF or hemofiltration, HF) to remove β_2M from the body. The focus of this meta-analysis was on studies that could provide determinations of β_2M 'clearance from the body' as the primary outcome measure of dialysis procedure performance.

Search strategy

The overarching search strategy for this meta-analysis was to include studies that had employed formal methods to characterize dialytic performance. Our initial focus was on studies published from 1 January 2001 to 31 December 2013. The date range was determined to capture performance of dialyzers that were likely used in the main outcomes trials in HFD and HDF. Subsequently, we extended the search for articles up to 12 June 2017. The search was based on free text and MeSH terms (see Text Query in Supplementary data). Articles were searched by using ProQuest in two databases (EMBASE and MEDLINE) for the initial query and only in MEDLINE from 1 January 2014 and onwards as we did not have access to ProQuest after that date. We used the SCOPUS database to compile a list of citations from, as well as citations to, the articles considered relevant after abstract and full text review of the initial search. Articles in this citation analysis were also subjected to abstract and full text review as detailed below.

Inclusion and exclusion criteria for abstract review

Eligible studies reported *in vivo* measurements of β_2M clearance from the body (primary outcome of this meta-analysis). Second, we examined β_2M reduction ratio and/or β_2M mass removal from the body in human subjects receiving HFD, HDF or hemofiltration among the studies reporting β_2M clearance measurements. Studies performed before 2001, *in vitro* studies, review studies and meta-analyses were excluded along with studies not involving extracorporeal circuits (e.g. peritoneal dialysis), mathematical simulations without experimental data, and studies on extracorporeal circuits perfused in a closed loop manner with non-blood fluid (crystalloid or colloid) or *ex vivo* blood.

Process

Two reviewers (M.-E.R. and G.T.) independently screened potentially relevant titles and abstracts to ensure that the identified studies met the inclusion criteria and none of the exclusion criteria. Then the abstract review was adjudicated by C.P.A. All adjudicated papers were selected for full text review by M.-E.R. and C.P.A. to ensure they met the full text inclusion criteria for the meta-analysis. Full text review for papers written in Chinese was performed by Y.-H.N. and Z.X. Abstract and full text criteria are provided in the Supplementary data. Citation analysis was carried out by M.-E.R. and C.P.A. using the same abstract and full text criteria as the initial search.

Data extraction

We did not restrict articles by language. Data for the articles in English were extracted from tables and figures by M.-E.R. and C.P.A. Information from non-English publications was extracted from the abstract and the tables in the text. Data for the articles in Chinese were extracted from tables and figures by Y.-H.N. and Z.X. All data were inserted into standardized data collection forms and imported into an Excel spreadsheet.

Measurements extracted included: (i) kinetic parameters [type of therapy, flow pump parameters, membrane surface area (MSA), dialyzer material, dialysis session duration, ultrafiltration volumes, session frequency] and (ii) β_2M body clearance measurements, mass removal and reduction ratios. Volumes infused and ultra-filtered were converted from L to mL/min to account for the confounding role of dialysis session duration on convective clearance. For studies for which we had individual patient-level data (i.e. HEMO), we aggregated measurements to distinct groups defined by the type of dialyzer used, prior to analysis. Dialyzer specifications (Kuf: ultrafiltration coefficient, MSA) were downloaded from the manufacturer's brochures and if those were not available (e.g. discontinued products), from dialysis textbooks and articles in the literature.

Quality assessment

Quality metrics of the included studies were assessed independently by two reviewers (C.P.A. and M.-E.R.) using the

Effective Public Health Project Quality Assessment Tool for Quantitative Studies (EPHPP) (see Table S1) [24]. This tool was developed by the Effective Public Health Project, Canada and was chosen because it covers any quantitative study design. The latter was a particularly desirable feature for our project, which included RCTs, non-randomized controlled and uncontrolled studies. This quality assessment tool is comprised of the following components: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity and analyses. Each section is rated as strong, moderate or weak by each reviewer. At the end, a global rating for the meta-analysis is provided.

Statistical analysis

Most of the studies included, reported on multiple 'configurations', i.e. combinations of dialysis operational parameters (e.g. pump flow rates, infusion volume, dialyzers) in the same patient groups. For this meta-analysis, a multi-level random effects model was adopted to account for clustering of measurements within the same configurations and within the same study. Despite the computational complexity, this approach is conceptually similar to using a paired *t*-test for the analysis of matched sample data. One subtle feature of this approach is that it enforces a form of averaging of multiple measurements from the same study. For studies reporting instantaneous clearance values, this implies that our object of analysis is the average of the instantaneous clearances. This quantity may not be much different from the average clearance computed via other means (e.g. pooled dialysate samples or pre-post β_2M measurements), even though the individual measurements averaged may be far from it, e.g. due to loss of dialyzer performance over time. We opted for this approach, because we feel that the clinically relevant quantity is the capacity of the dialyzer to remove β_2M over the entire course of the treatment (average clearance) rather than at any given point in time.

This modeling was conducted separately for studies of convective and diffusive therapies reporting β_2M clearance and together for studies of convective and diffusive therapies reporting β_2M mass removal. Clearance values, reduction ratios and mass removal of β_2M were summarized and heterogeneity was assessed graphically by the use of forest plots. Meta-regression models were utilized to statistically assess heterogeneity. For these models, the same multi-level structure was used as the one that was used to generate the forest plots. Univariate meta-regressions, assessing each variable in isolation, were followed by multivariable meta-regressions adjusting for more than one study characteristics. Variables were selected by univariate meta-regression analyses at the level of $P = 0.05$ if $>70\%$ of the studies were available for these analyses. The Restricted Maximum Likelihood (REML) approach was used to derive unbiased point estimates of dialysis relevant parameters (themselves treated as fixed effects) but at the expense of wider confidence intervals (CIs) for these models. Analysis of variance (ANOVA) was used to assess the global statistical significance of study characteristics with more than two levels (e.g. type of dialysis procedure) by comparing models that adjusted for these characteristics versus the models that did not. ANOVA tests were carried out in models fitted with conventional Maximum Likelihood approach, since these tests cannot be applied to compare models with different fixed effects specifications when REML is used. Operational parameters of clinical interest (e.g. substitution volume flows or year of the study) were forced into the models even if not significant in univariate models. Secular trends in the performance of the dialyzers over time were assessed by including the year of the publication as a covariate in the models. In these analyses, 2001 was taken as Year 0 and the secular trend was defined as a linear change in the outcome (e.g. clearance) with each subsequent year. Outcomes explored with meta-regression models were β_2M clearance, β_2M mass removal and the pre-dialysis and post-dialysis β_2M reduction ratio. All analyses were performed in R statistical software (version 3.1.1) with the package metaphor [25].

RESULTS

Study search results

Electronic searches from 1 January 2001 to 12 June 2017 identified 638 potentially relevant reports. Of these, 481 were excluded after title and abstract review. After adjudication, 150 articles were selected for full text review and 53 relevant articles were identified (52 were published before 2014). Out of these, 47 articles reported aggregate (group data) and 5 studies reported patient-level data. In addition, the HEMO study (one of the studies identified in the initial search) provided data about 984 patients with 3967 measurements in non-reused dialyzers (most dialyzers were reused in HEMO). These measurements were taken from the HEMO analytic data files distributed by the National Institutes for Digestive Diabetes and Kidney Diseases (NIDDK), made available to our group through a data use agreement. Citation analysis of these 53 papers in SCOPUS identified 673 potentially relevant studies; we screened out 622 papers based on abstract review and selected 109 for full text review. Full text review uncovered 34 papers that had been identified during the initial search and 16 papers with relevant clearance data. A summary flow diagram is shown in Figure 1. The overall final study population for this meta-analysis consisted of 69 studies of 1879 patients with 6771 available measurements.

Study characteristics

Table 1 presents the characteristics of the patients that participated in the included studies, such as number of patients, age, gender, time on chronic dialysis therapy and their pre-dialysis weight. The same table details characteristics of the included studies, which fell into two main categories: comparisons of different types of dialyzers (46 on HFD) and comparisons of different types of convective dialysis therapies [31 studies on post-dilution HDF (post-HDF), 6 on pre-dilution HDF (pre-HDF), 15 on mid-dilution HDF (mid-HDF), 5 on mixed HDF (mixed-HDF), 2 studies on pre-dilution hemofiltration (pre-HF) and 2 studies on post-dilution hemofiltration (post-HF)]. These studies used a wide variety of dialyzer membrane material, e.g. cellulose acetate (CA, $n = 4$), polysulfone (PS, $n = 146$), polymethylmethacrylate (PMMA, $n = 2$),

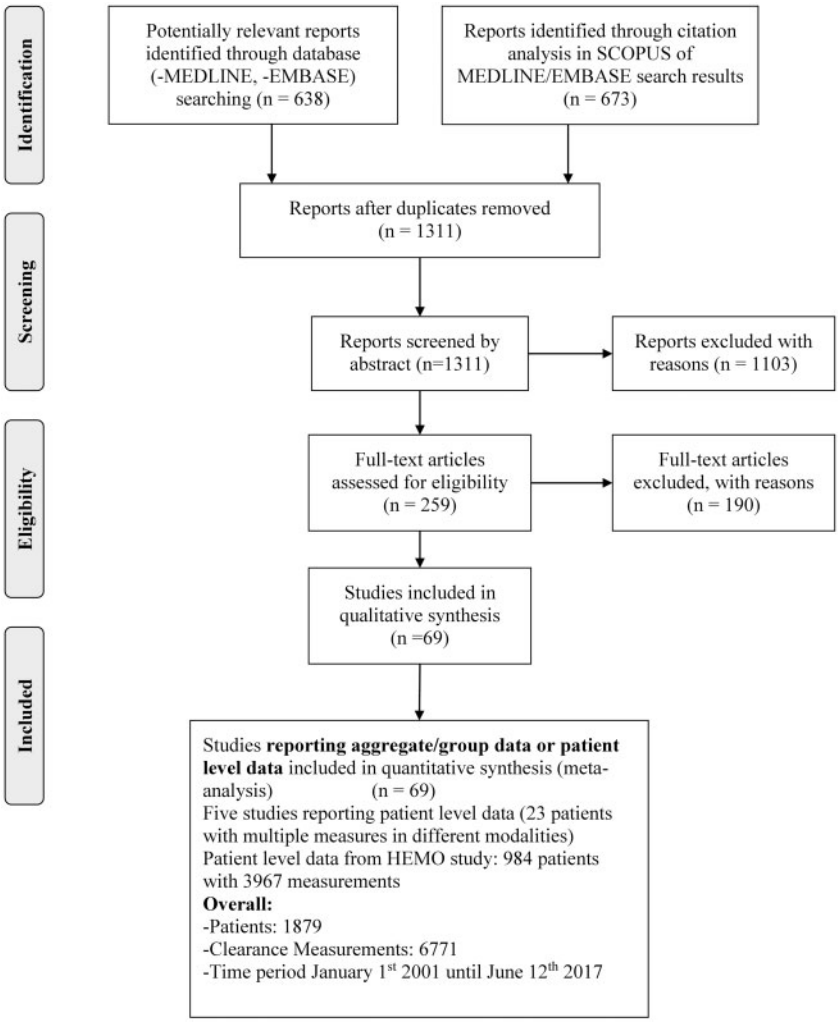

FIGURE 1: Flow diagram of the literature search.

polyacrylnitrile (PAN, $n = 2$) and polyarylethersulfone (PAES, $n = 97$). All included studies enrolled patients under chronic dialysis regimens. Participant numbers were highly variable and ranged from 5 to 52. Only one study (HEMO [20]) had 984 participants. Clearances (mL/min), reduction ratios of β_2M and/or β_2M mass removal (mg or g/session) were measured and reported either in the blood side (serum or plasma) or in the dialysate side at a single time point during the dialysis session (instantaneous) or as average over the course of the treatment. A wide variety of methods were used for the calculation of clearance. The formulas and the numerical aspects of these approaches are summarized in the Supplementary data. Other study characteristics such as blood and dialysate flow rate, treatment duration, substitution fluid rate and MSA are reported as average and standard errors in Table 1.

Study quality

Quality of the included studies varied widely based on each of the five components of the EPHPP (Table S1). For our meta-analysis, the global rating was characterized to be of moderate quality for most of the included studies [93], strong for 20 and weak for 16 studies. Both reviewers discussed the ratings and there was no discrepancy between them with respect to the components' ratings and the final global scoring and rating. This high inter-rate agreement was in line with a previous evaluation of the EPHPP [94]. Main determinants of moderate quality were selection bias, study design and blinding procedures (methodologic heterogeneity), whereas data collection, study confounders and withdrawals/dropouts provided strong quality to the included studies.

β_2M dialyzer clearance in diffusive, high flux dialysis

This meta-analysis also included 49 studies on HF dialysis, which evaluated 147 configurations of dialyzers and operational characteristics of treatment (e.g. blood or dialysate blood flows). Average (over the course of treatment) β_2M clearance was 48.75 mL/min (95% CI 42.50–55.21) with substantial heterogeneity among studies [P (Q) $\leq$ 0.001] (Figure 2). Instantaneous β_2M clearance was 52.09 mL/min (95% CI 41.39–62.78) with substantial heterogeneity among studies [P (Q) $<$ 0.001] (Figure S1). There were no differences between instantaneous and average (over the course of the treatment) β_2M clearances in univariate meta-regressions (difference of 1.88 mL/min, 95% CI −6.58 to 10.34, P = 0.66). Therefore, we combined

Table 1. Characteristics of the studies analyzed

First Author	Year	N	N meas	Female	Age	Vintage	PreWt	Modality	Material	MSA	QB	QD	Qinf	Duration
Leto [26]	2001	15	30	40.0%	45.7 (—)	156.3 (—)	(—)	HFD	CA/PS	1.3 (0.1)	250.0 (0.0)	600.0 (0.0)	(—)	240.0 (0.0)
Xu [27]	2001	10	10	40.0%	70.2 (5.6)	71.2 (37.0)	63.9 (10.6)	HFD	PS	1.8 (0.5)	(—)	(—)	(—)	300.0 (0.0)
Yamada [28]	2001	28	28	39.0%	58.1 (16.4)	64.0 (47.0)	49.0 (8.0)	HFD	PS	1.42 (0.0)	188.0 (18.0)	500.0 (0.0)	(—)	237.0 (18.0)
Stiller [29]	2002	15	15	73.0%	54.3 (10.2)	134.0 (100.6)	(—)	HFD	PAES/PS	1.24 (0.1)	(—)	(—)	(—)	240.0 (0.0)
Eknoyan [20]	2002	984	3967	59.0%	58.6 (13.7)	63.1 (59.2)	71.8 (1.5)	HFD	PMMA/CA/PS/ PAN/PAES	1.8 (0.2)	372.4 (8.8)	671.8 (10.1)	(—)	204.5 (2.7)
Ding [30]	2002	12	36	33.0%	49.7 (11.3)	83.5 (76.7)	(—)	pre-HDF/post-HDF	PS	1.3 (0.0)	250.0 (0.0)	616.7 (2.9)	92.5 (3.0)	282.5 (29.6)
Klingel [31]	2002	22	22	0.0%	61.4 (—)	(—)	74.6 (0.0)	HFD	PS	1.3 (0.0)	250.0 (0.0)	500.0 (0.0)	(—)	228.8 (0.0)
Mann [32]	2003	5	5	0.0%	(—)	(—)	(—)	HFD	PS	1.6 (0.05)	(—)	(—)	(—)	240.0 (0.0)
Mandolfo [33]	2003	8	16	0.0%	61.4 (—)	(—)	68 (8.6)	HFD/post-HDF	PS	1.8 (0.0)	350.0 (0.0)	550.0 (0.0)	30.0 (0.0)	240.0 (0.0)
Pedrini [34]	2003	20	20	35.0%	63.0 (17.0)	116.4 (86.4)	60.3 (12.6)	post-HDF/mixed-HDF	PS	2.1 (0.0)	403.0 (55.9)	580.2 (36.6)	219.6 (36.6)	227.0 (17.7)
Ward [35]	2003	12	24	41.6%	53.0 (13.0)	63.0 (18.3)	(—)	HFD	PS	1.8 (0.0)	410.0 (1.9)	700.0 (0.0)	(—)	228.0 (11.7)
Bammens [36]	2004	14	70	28.6%	66.6 (3.1)	24.8 (10.0)	62.10 (1.94)	HFD/pre-HDF/post-HDF	PS	1.8 (0.0)	323.9 (116.3)	500.0 (0.0)	87.0 (0.0)	230.0 (0.0)
Yamashita [37]	2004	5	5	80.0%	(—)	(—)	(—)	post-HF	PS	1.8 (0.0)	(—)	(—)	84.2 (18.8)	120.0 (0.0)
Emiliani [38]	2004	10	10	20.0%	66.0 (18.0)	80.0 (36.0)	66.2 (7.5)	mid-HDF	PAES	2.6 (0.0)	312.0 (18.0)	500.0 (0.0.0)	43.6 (7.2)	240.0 (10.0)
Leypoldt [39]	2004	22	88	37.5%	61.0 (18.0)	(—)	80.3 (19.4)	HFD	PS	1.77 (0.0)	338.0 (49.6)	540.0 (60.0)	(—)	178.5 (19.0)
Lucchi [40]	2004	10	20	40.0%	61.1 (8.9)	51.8 (35.9)	(—)	HFD/post-HDF	PS	1.6 (0.0)	300.0 (0.0)	625.0 (0.0)	20.9 (0.0)	240.0 (0.0)
Pisitkun [41]	2004	9	18	22%	48.0 (6.1)	51.4 (42.0)	55.2 (8.3)	HFD/mid-HDF	PS	2.7 (0.9)	475.0 (36.4)	800.0 (0.0)	59.9 (9.7)	240.0 (0.0)
Tonelli [42]	2004	5	15	0.0%	(—)	(—)	(—)	HFD	PS	1.8 (0.0)	300.0 (0.0)	500.0 (0.0)	(—)	240.0 (0.0)
Santoro [43]	2005	20	40	0.0%	(—)	(—)	(—)	HFD/mid-HDF	PAES	1.90 (0.0)	363.0 (39.2)	(—)	58.0 (11.9)	(—)
Brendolan [44]	2005	3	24	0.0%	(—)	(—)	(—)	HFD/post-HDF	PS	2.2 (0.4)	333.3 (12.0)	500.0 (0.0)	16.6 (1.9)	226.1 (14.5)
Padrini [45]	2005	11	22	36.4%	66.8 (11.9)	80.9 (66.9)	64.1 (9.2)	post-HF/pre-HF	PAES	2.1 (0.0)	327.8 (22.3)	(—)	186 (40.1)	240 (6)
Petras [46]	2005	6	36	0.0%	56.0 (16.0)	86.0 (50.0)	(—)	HFD/post-HDF/Pre-HF	PAES	2.1 (0.0)	350.0 (0.0)	500.0 (0.0)	95.0 (0.0)	240.0 (0.0)
Krieter [47]	2005a	5	5	60.0%	52.0 (22)	(—)	68.5 (27.5)	mid-HDF	PAES	1.9 (0.0)	400.0 (0.0)	800.0 (0.0)	200.0 (0.0)	205.0 (15.0)
Krieter [48]	2005b	10	40	30.0%	57.3 (13.7)	99.6 (92.4)	66.3 (10.4)	mid-HDF/post-HDF	PAES/PS	1.9 (0.1)	400.0 (0.0)	550.0 (0.0)	148.3 (2.9)	240 (23.4)
Evenepoel [49]	2006	20	20	25.0%	68.8 (10.9)	19.3 (31.5)	59.9 (7.9)	HFD	PS	1.8 (0.0)	322.7 (21.6)	500.0 (0.0)	(—)	230.0 (0.0)
Mandolfo [50]	2006	12	18	66.7%	69.0 (9.0)	117.6 (69.6)	65.2 (8.1)	HFD/post-HDF	PS	1.8 (0.0)	350.0 (0.0)	700.0 (0.0)	50.0 (0.0)	240.0 (0.0)
Nakashima [51]	2006	12	24	0.0%	49.1 (12.1)	127.2 (73.2)	66.8 (12.7)	HFD	PS	2.10 (0.0)	200.0 (0.0)	500.0 (0.0)	(—)	240.0 (0.0)
Panich [52]	2006	10	20	50.0%	58.2 (14.7)	(—)	54.2 (3.8)	HFD/post-HDF	PS	1.8 (0.0)	425.3 (12.6)	(—)	61.6 (0.6)	240.0 (0.0)
Pedrini [53]	2006	12	72	25.0%	64.2 (6.6)	45.0 (38.0)	64.9 (11.2)	mixed-HDF	PS	2.1 (0.0)	422.0 (37.9)	609.0 (27.9)	178.0 (20.9)	218.0 (25.9)
Potier [54]	2007	6	18	0.0%	(—)	(—)	(—)	post-HDF/pre-HDF/mid-HDF	PAES	1.90 (0.0)	360.0 (0.0)	500.0 (0.0)	175.0 (0.0)	(—)
Feliciani [55]	2007	10	30	20.0%	64.7 (8.0)	54.7 (57.7)	73.25 (12.5)	mixed-HDF/mid-HDF	PAES/PS	1.85 (0.1)	385.5 (18.3)	609.0 (20.7)	167.5 (14.1)	231.5 (16.8)
Krieter [56]	2007	8	32	62.5%	62.1 (13.8)	76.0 (55.3)	68.5 (7.1)	HFD	PS/PAES	1.7 (0.1)	300.0 (0.0)	500.0 (0.0)	(—)	236.0 (10.5)
Santoro [57]	2007	8	16	50.0%	56.6 (23.6)	(—)	(—)	mid-HDF	PAES	1.9 (0.0)	306.5 (10.3)	(—)	100.0 (0.0)	231.0 (10.3)
Tiranathanagul [58]	2007	12	48	33.0%	54.2 (13.6)	42.0 (32.3)	62.85 (9.4)	post-HDF/mid-HDF	PS	2.7 (0.9)	416.7 (24.1)	800.0 (0.0)	113.0 (6.0)	240.0 (0.0)
Abe [59]	2008	15	45	40%	65.5 (13.2)	72.9 (63.8)	(—)	HFD	PMMA/CA/PS	1.5 (0.1)	200.0 (0.0)	500.0 (0.0)	(—)	240.0 (0.0)
Eloot [60]	2008	9	27	55.5%	71.0 (10.0)	19.0 (12.0)	79.0 (11.5)	HFD	PS	1.8 (0.0)	260.0 (0.0)	260.0 (0.0)	(—)	360.0 (0.0)
Mandolfo [61]	2008	8	16	37.5%	72.2 (4.8)	62.0 (24.0)	61.7 (11)	HFD/mid-HDF	PAES	1.9 (0.0)	251.5 (32.4)	700.0 (0.0)	56.0 (4.8)	240.0 (0.0)
Spalding [62]	2008	12	12	50.0%	65.3 (12.9)	(—)	(—)	HFD/post-HDF	(—)	(—)	358.4 (84.4)	800.0 (0.0)	37.5 (12.6)	197.4 (55.3)
Krieter [63]	2008a	8	40	25.0%	64.0 (16.0)	70.0 (74.0)	74.2 (10.7)	HFD/post-HDF	PAES/PS	1.7 (0.1)	300.0 (0.0)	460.0 (0.0)	40.0 (0.0)	240.0 (0.0)
Ouseph [64]	2008a	12	48	25.0%	57.0 (4.0)	52.0 (17.0)	81.3 (4.35)	HFD	PS/PAES	1.65 (0.1)	382.0 (4.8)	800.0 (0.0)	(—)	219.0 (5.3)
Ouseph [64]	2008b	12	60	41.6%	46.0 (3.0)	48.0 (8.0)	84.2 (6.75)	HFD	PS/PAES	1.90 (0.2)	404.0 (1.0)	800.0 (0.0)	(—)	240.0 (0.0)
Krieter [65]	2008b	8	48	37.5%	63.0 (14.0)	77.5 (38.9)	76.5 (11.15)	HFD	PAES/PS	1.7 (0.1)	300.0 (0.0)	500.0 (0.0)	(—)	240.0 (0.0)
Joyeux [66]	2008	20	40	35.0%	58.0 (20.9)	46.0 (46.1)	71.5 (10.2)	HFD/post-HDF	PAES	2.10 (0.0)	310.5 (33.3)	(—)	31.8 (5.2)	235.5 (14.6)
Lee [67]	2009	8	16	50.0%	68.7 (19.1)	50.3 (53.1)	(—)	HFD	PAES	1.1 (0.0)	325.0 (24.6)	500.0 (0.0)	(—)	255.0 (14.8)
Meert [68]	2009	14	42	50.0%	63.5 (17.0)	30.2 (36.0)	(—)	pre-HDF/pre-HF/post-HDF	PAES	1.8 (0.2)	312.3 (15.6)	384.7 (5.0)	185.7 (20.7)	249.3 (13.0)
Pedrini [69]	2009	15	90	20.0%	67.3 (8.7)	44.1 (20.8)	76.9 (13.8)	mid-HDF	PAES	2.1 (0.2)	378.5 (27.4)	599.5 (6.5)	167.5 (9.7)	223.0 (21.4)
Susantitaphong [70]	2009	12	36	66.6%	59.5 (13.5)	81.6 (52.8)	57.5 (11.6)	Pre-HDF/mid-HDF/post-HDF	PAES	2.2 (0.1)	440.3 (19.9)	554.2 (10.4)	245.9 (2.1)	240.0 (0.0)
Troidle [71]	2009	8	8	0.0%	45.0 (7.0)	(—)	(—)	HFD	PS	1.8 (0.0)	400.0 (0.0)	600.0 (0.0)	(—)	480.0 (0.0)
Wang [72]	2009	18	54	27.8%	46.9 (9.6)	52.5 (—)	(—)	HFD	PS	1.5 (0.0)	250.0 (0.0)	500.0 (0.0)	(—)	240.0 (0.0)
Bhimani [73]	2010	12	144	75.0%	60.0 (4.0)	81.0 (19.0)	(—)	HFD	PS/PAES	1.7 (0.2)	400.0 (1.8)	550.0 (0.0)	(—)	(—)

Continued

Table 1. Continued

First Author	Year	N	N meas	Female	Age	Vintage	PreWt	Modality	Material	MSA	QB	QD	Qinf	Duration
Gasco [74]	2010	16	263	50.0%	52.7 (—)	(—)	(—)	post-HDF	PS	1.8 (0.0)	323.0 (0.0)	800.0 (0.0)	(—)	242.0 (0.0)
Kohn [75]	2010	5	38	60.0%	(—)	142.0 (60.9)	86.0 (29.0)	HFD	PAES	(—)	425.0 (75.0)	200.0 (0.0)	(—)	174.0 (15.0)
Krieter [76]	2010	8	64	12.5%	63.0 (12.0)	81.8 (144.0)	70.8 (17.5)	HFD/post-HDF	PAES	1.9 (0.0)	378.0 (31.1)	500.0 (0.0)	47.0 (6.0)	229.0 (20.7)
Park [77]	2010	52	52	52.0%	54.0 (12.4)	112.7 (188.6)	(—)	HFD	PS	1.3 (0.0)	237.0 (23.0)	500.0 (0.0)	(—)	240.0 (12.0)
Basile [78]	2011	11	22	18.2%	54.1 (17.8)	78.0 (60.2)	69.1 (9.9)	HFD	PS	1.8 (0.0)	270.0 (0.0)	270.0 (0.0)	(—)	469.1 (2.7)
Ficheux [79]	2011	18	54	0.0%	79.7 (1.7)	(—)	66.1 (2.3)	HFD	PS	2.2 (0.1)	318.0 (2.0)	500.0 (9.8)	(—)	222.0 (2.9)
Pedrini [80]	2011	15	60	33.3%	67.2 (8.3)	(—)	73.1 (14.0)	post-HDF/mid-HDF	PS/PAES	2.3 (0.1)	374.0 (34.0)	580.0 (39.7)	147.5 (11.1)	224.0 (18.5)
Panichi [81, 82]	2012	30	180	33.3%	55.9 (14.0)	58.0 (59.0)	(—)	post-HDF	PAES	2.1 (0.0)	313.5 (32.7)	600.0 (0.0)	78.1 (0.0)	235.0 (13.8)
Susantitaphong [83]	2012	12	48	66.6%	57.8 (14.8)	43.2 (42.0)	55.5 (11.1)	mid-HDF/mixed-HDF	PAES	2.2 (0.0)	425.0 (24.5)	600.0 (0.0)	200.0 (0.0)	240.0 (0.0)
Tessitore [84]	2012	26	26	53.9%	63.0 (12.0)	(—)	(—)	HFD	PP	0.7 (0.0)	297.0 (32.0)	500.0 (0.0)	(—)	230.0 (13.0)
von Albertini [85]	2013	12	35	0.0%	(—)	(—)	(—)	HFD/post-HDF	PAES/PS	1.8 (0.0)	417.1 (0.0)	667.4 (0.0)	30.7 (0.0)	206.3 (22.5)
Heaf [86]	2013	12	96	30.0%	63.1 (11.7)	78.0 (52.8)	79.2 (17.8)	HFD	PAES	2.0 (0.0)	276.0 (38.7)	500.0 (0.0)	(—)	240.0 (0.0)
Melo [87]	2014	14	28	50.0%	48.9 (14.4)	(—)	76.35 (19.63)	HFD/post-HDF	PS	2.0 (0.0)	375.0 (8.2)	760.0 (0.0)	40.0 (0.0)	115.7 (16.8)
Pedrini [88]	2014	16	32	18.8%	(—)	(—)	77.60 (10.78)	post-HDF	PAES/PS	2.20 (0.10)	388.0 (25.9)	574.5 (39.0)	121.0 (11.9)	226.5 (13.7)
Cornelis [89]	2014	13	52	23.1%	53.6 (20.4)	49.0 (29.0)	(—)	HFD/post-HDF	PS	1.8 (0.0)	286.0 (4.8)	573.7 (13.1)	30.1 (1.4)	366.3 (3.9)
Potier [90]	2016	6	24	66.7%	65.4 (25.5)	68.6 (43.7)	73.9 (2.1)	HFD/post-HDF/ mixed-HDF/pre-HDF	PS	2.3 (0.0)	339.4 (3.4)	600.0 (0.0)	122.1 (5.1)	240.0 (0.0)
Gayrard [91]	2017	12	48	50.0%	73.0 (12.0)	(—)	71.0 (1.9)	HFD/post-HDF	PS	1.8 (0.0)	366.3 (5.1)	602.3 (1.0)	51.8 (1.1)	233.6 (2.9)
Kirsch [92]	2017	39	59	28.2%	60.5 (13.6)	63.1 (43.8)	80.2 (18.4)	post-HDF/HFD	PS	1.9 (0.1)	368.1 (12.8)	(—)	27.5 (1.4)	252.4 (11.8)

N, number; N meas, number of measurements; Vintage, time on chronic intermittent dialysis in months; PreWt, pre-dialysis weight in kilograms; MSA, membrane surface area (in square meters); QB, blood flow rate (mL/min); QD, dialysis fluid flow rate (mL/min); Duration, the dialysis session (in min). For each parameter the table summarizes the mean and the SD over all arms in each study or a (—) if the relevant parameter could not be extracted from the paper.

instantaneous and average β_2M clearances together for meta-regression analyses. First, we explored the sources of heterogeneity through 'univariate' meta-regressions examining only one study characteristic. Kuf (and Kuf scaled to MSA), clearance calculation formula, MSA, indexing clearance to the plasma (rather than blood) volume compartment, blood pump flow rate and dialysis membrane material were statistically significant predictors of variation in β_2M clearance by diffusive, HF dialysis in these analyses (Table S2). Interestingly, there was no evidence of a secular trend of improving dialytic clearance over the last 17 years. Subsequently, we carried out 'multivariable' meta-regression to simultaneously adjust for multiple study characteristics. In these analyses shown in Table 2, we forced the type of measurement (instantaneous versus average) and the secular trend into the models. We found a significantly higher β_2M clearance for PAES dialyzers (higher by 12.25 mL/min, 95% CI 5.472–19.028, $P < 0.0001$) relative to PS dialyzers. A significantly higher β_2M clearance was found for higher blood flow rates in HF dialysis, i.e. an increase of 0.091 mL/min per 1 mL/min blood flow rate, 95% CI 0.024–0.159, $P = 0.007$). Adjusted dialysate side clearances were significantly lower than blood clearances (by 22.279 mL/min, 95% CI 9.8–34.757, $P < 0.001$). Other significant predictors were Kuf of the dialyzer (scaled to the MSA), while the MSA was of borderline significance ($P = 0.057$). In these multivariable analyses, there was no evidence for improving dialyzer performance over calendar time ($P = 0.854$). Similarly, there was no statistically significant difference in sensitivity analysis that compared the HEMO measurements against all the other measurements, or when we ran the multivariate regression, excluding the HEMO study (data not shown).

β_2M clearance in convective dialysis therapies

This meta-analysis included 63 papers on HDF and 5 hemofiltration studies that examined 132 unique configurations of dialyzers, infusion volumes and patient cohorts. Average β_2M clearance (over the course of treatment) was 8706 mL/min (95% CI 75.08–99.03) with substantial heterogeneity among studies [P (Q) $\leq$ 0.001] (Figure 3). Instantaneous β_2M clearance was 125.26 mL/min (95% CI 103.92–146.59) with substantial heterogeneity among studies [P (Q) $\leq$ 0.001] (Figure S2). Kuf, blood pump flow rate, blood (versus plasma) compartment clearance, the side of the clearance (blood versus dialysate) were significant predictors in 'univariate' meta-regressions (Table S3). MSA, membrane material and substitution fluid infusion rates were not significant predictors in these univariate analyses. In 'multivariable' meta-regression analyses (Table 3) we found a significantly higher β_2M clearance from the body when this calculation was indexed to whole blood versus plasma, while dialysate side body clearance was substantially lower than plasma by −41.523 mL/min (95% CI −54.525 to −28.52, $P < 0.0001$). Higher blood flow (0.188 mL/min per 1 mL/min blood flow, 95% CI 0.046–0.330, $P = 0.01$), membrane material (PS higher than PAES or PMMA) and certain forms of modality (e.g. pre-dilution HDF versus pre-dilution hemofiltration) but not substitution fluid infusion rates were significantly associated with higher β_2M clearances. ANOVA tests suggested that both membrane material ($P = 0.0033$) and

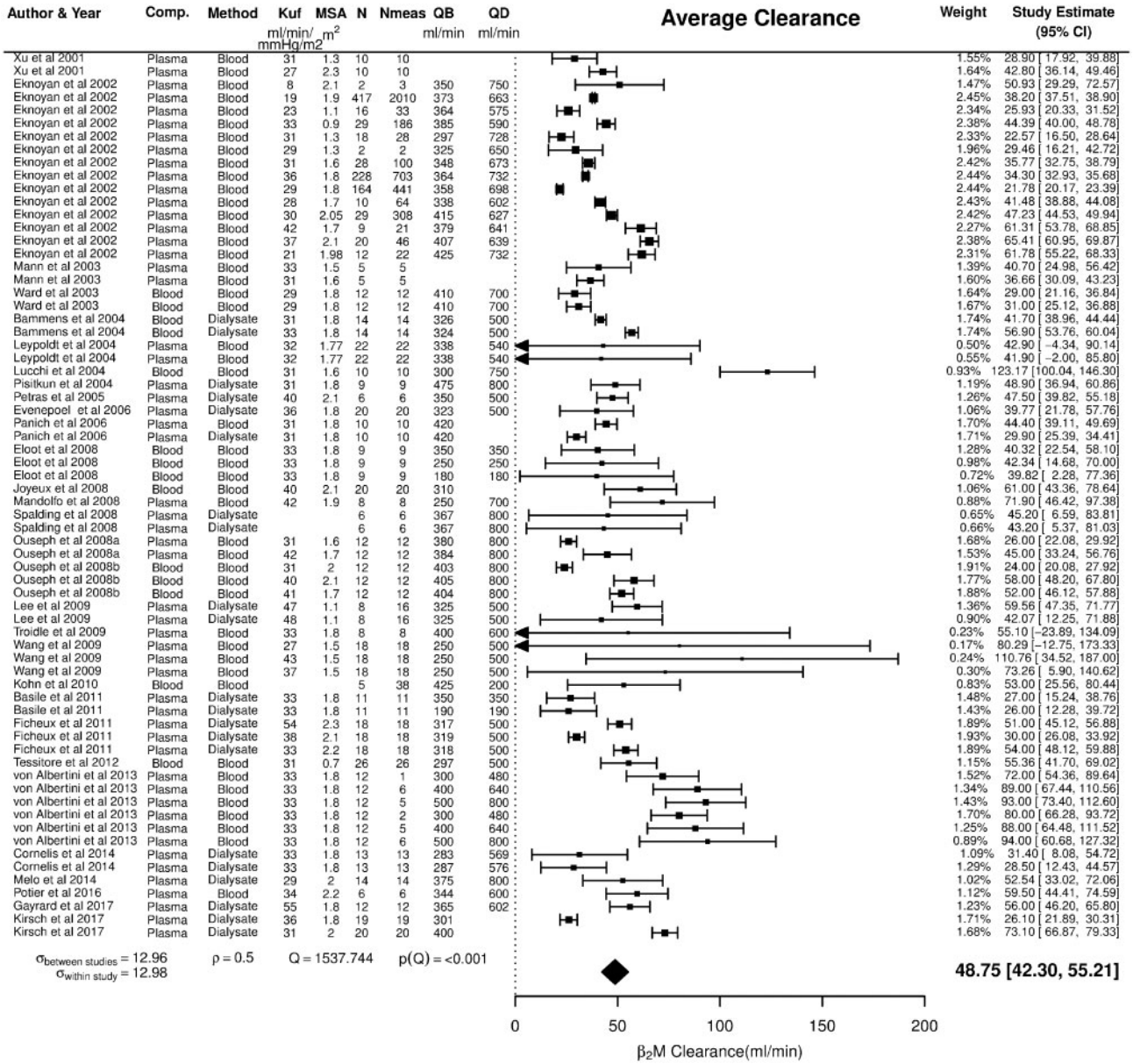

FIGURE 2: Forest plot of average (over the course of the treatment) β_2M dialyzer clearance in HFD. Comp, compartment; Kuf, ultrafiltration coefficient of the dialyzer; *n*, number; N meas, number of measurements; QB, blood flow rate (mL/min); QD, dialysate flow rate (mL/min).

any convective modality (P = 0.0013) were significant predictors of dialytic body clearance of β_2M.

In our dataset, there were 73 distinct configurations in post-HDF, which allowed us to better clarify the effects of different parameters upon dialytic clearance. Significant predictors of dialytic clearance in post-HDF were the substitution fluid infusion rate: increase by 0.297 mL/min for each mL/min increase in infusion rate (95% CI 0.200–0.394, P < 0.001) and Kuf: increase 1.346 mL/min for each mL/min/mmHg/m^2 (95% CI 0.271–2.420, P = 0.014), while dialysis with a PAES dialyzer was associated with reduced clearance by −18.480 mL/min (95% CI −34.86 to −2.101, P = 0.027). Dialysis with a membrane with a higher surface area was associated with a numerically higher β_2M clearance of 37.040 mL/min/m^2 (95% CI −1.487 to 75.566); this association was of borderline statistical significance (P = 0.06). Interestingly, higher blood pump flow rates were not associated with enhanced dialytic clearance in post-HDF (0.042 mL/min for each mL/min increase in blood pump flow rates, 95% CI −0.045 to 0.128, P = 0.345), while other factors (side of clearance, blood versus plasma compartment calculations, instantaneous versus average clearance and secular trends) were numerically like the patterns noted in Table 3 (data not shown).

β_2M reduction ratios are higher in convective versus diffusive dialysis therapies

For this meta-analysis, we identified a total of 140 configurations (with covariate information) that reported reduction ratios of β_2M in either HFD (*n* = 81) and convective dialysis therapies (*n* = 59) for multivariable adjustments. In univariate

Table 2. Metaregression of β_2M clearance for high flux dialysis

Variable	Effect size (mL/min)	CI	P (Wald)
Blood pump flow (per mL/min)	0.091	(0.024 to 0.159)	0.007
Kuf (scaled to MSA)	0.803	(0.373 to 1.232)	<0.001
MSA (per m^2)	10.923	(−0.327 to 22.173)	0.057
Dialysis membrane (relative to PS)			
PAES	12.25	(5.472 to 19.028)	<0.001
CA	5.025	(−7.01 to 17.061)	0.413
PAN	3.571	(−10.378 to 17.519)	0.616
PMMA	9.15	(−2.501 to 20.8)	0.124
Compartment			
Blood (versus plasma)	8.876	(−3.999 to 21.75)	0.177
Clearance side			
Dialysate (versus blood)	−22.279	(−34.757 to −9.8)	<0.001
Type of measurement			
Instantaneous (versus average)	6.589	(−3.422 to 16.6)	0.197
Secular trend[a]	0.178	(−1.716 to 2.072)	0.854

Kuf, ultrafiltration coefficient of a dialyzer.

[a]Secular trend includes a slope to adjust for a linear trend of increasing clearance in studies published in more recent years relative to HEMO (2001). Inclusion of these variables decreased the apparent degree of heterogeneity by more than half (Q statistic of unadjusted model 4694.5603 versus 1947.1515 for the fully adjusted model), but significant heterogeneity did remain (P-value of QE statistic <0.001). Results based on 123 distinct configurations of dialyzer and dialysis procedure operational parameters. See text for other abbreviations.

analysis, convective dialysis (taken as a group) afforded greater β_2M reduction ratios by 14.300% (95% CI 10.756–17.845%, $P < 0.0001$) relative to HF dialysis (estimate of 59.169%, 95% CI 55.484–62.854%). In multivariable meta-regression analyses (Table 4), higher membrane Kuf was a significant predictor of higher β_2M reduction ratio in both diffusive and convective dialysis. In HFD, β_2M reduction ratios were significantly higher for PAES (8.367%, 95% CI 2.913–13.822%, $P = 0.003$) compared with PS dialyzers. There was a strong secular trend in the reduction ratio afforded by HF dialysis, i.e. an increase of 1.443% per year since 2001 (95% CI 0.363–2.523, $P = 0.009$). There were no differences by membrane material or type of modality in convective therapies, yet higher substitution flow rates were associated with higher β_2M reduction ratios.

β_2M mass removal is higher in convective versus diffusive dialysis therapies

For this meta-analysis, we identified 60 configurations reporting mass removal data (mg/session) of β_2M. β_2M mass removal (mg/session) was 151.66 mg/session (95% CI 126.98–176.34, $P < 0.001$) with substantial heterogeneity among studies [P (Q) < 0.001] (Figure 4). Kuf and type of modality were significant predictors of higher dialytic mass removal of β_2M (data not shown) in univariate metaregression analyses. In multivariable meta-regressions (Table 5), Kuf and convective (relative to HF dialysis) were associated with higher removal of β_2M into the dialysate ($P < 0.001$ in ANOVA). Removal of β_2M was numerically higher with pure filtration therapies rather than HDF. However, when we restricted the analyses to convective techniques ($n = 31$), there was no statistically significant difference among the different techniques in terms of their ability to remove β_2M from the body ($P = 0.892$). Furthermore, there was no evidence for heterogeneity in this analysis (residual heterogeneity, $P = 0.08$). More extensive analysis of the role of the substitution volume on β_2M mass removal by post-HDF was limited by the small number of configurations ($n = 12$) that reported dialytic mass removal of β_2M.

DISCUSSION

This meta-analysis, combining 69 studies and including 1879 patients with 6771 clearance measurements, shows that membrane composition, modality (convective versus diffusive), blood flow rates and substitution fluid infusion rates independent of the dialysis modality are significant determinants of HF dialyzer performance in removing β_2M. Our analysis is timely, as it provides quantitative information to aid the interpretation of a number of meta-analyses and secondary analyses of HD [11, 12, 14]. The significance of this work lies in our analysis of nearly 8-fold higher number of studies than previous reports by the Cochrane Group [16, 17] and others [18, 19]. Furthermore, our access to the primary study records of the HEMO trial allowed us to assess dialyzer performance using patient-level information from non-reused membranes thus overcoming a major limitation of a previous report [18].

One of the main and novel results of this study was that membrane material proved to be an important determinant of β_2M clearance. Higher β_2M clearances were noted with dialyzers made from PAES in respect to PS when applied in HF dialysis, the opposite of when applied in HDF. This is probably related to the chemical composition of the membranes as well as the 3D structure of the membranes and the different pressure profiles in these two modalities. The influence of membrane material on β_2M clearance of HF dialysis was first reported 30 years ago [95]. Of relevance to our report, this early investigation showed that some dialysis membranes, such as cellulose acetate dialyzers, appear to induce β_2M production during dialysis, whereas others, such as PS, do not. In the same study volume-controlled dialysis with HF membranes (PS 0.65 m^2 and PS 1.25 m^2) lowered β_2M; clearance values, however, were significantly higher when these dialyzers were used in a HDF procedure. In another study [96] among patients receiving conventional HD using CA membranes, β_2M levels increased 25.4% after HD, whereas in patients receiving HF HD using PS membrane, β_2M levels decreased significantly (43.0%) after HD. Our results are also in accordance to a prospective,

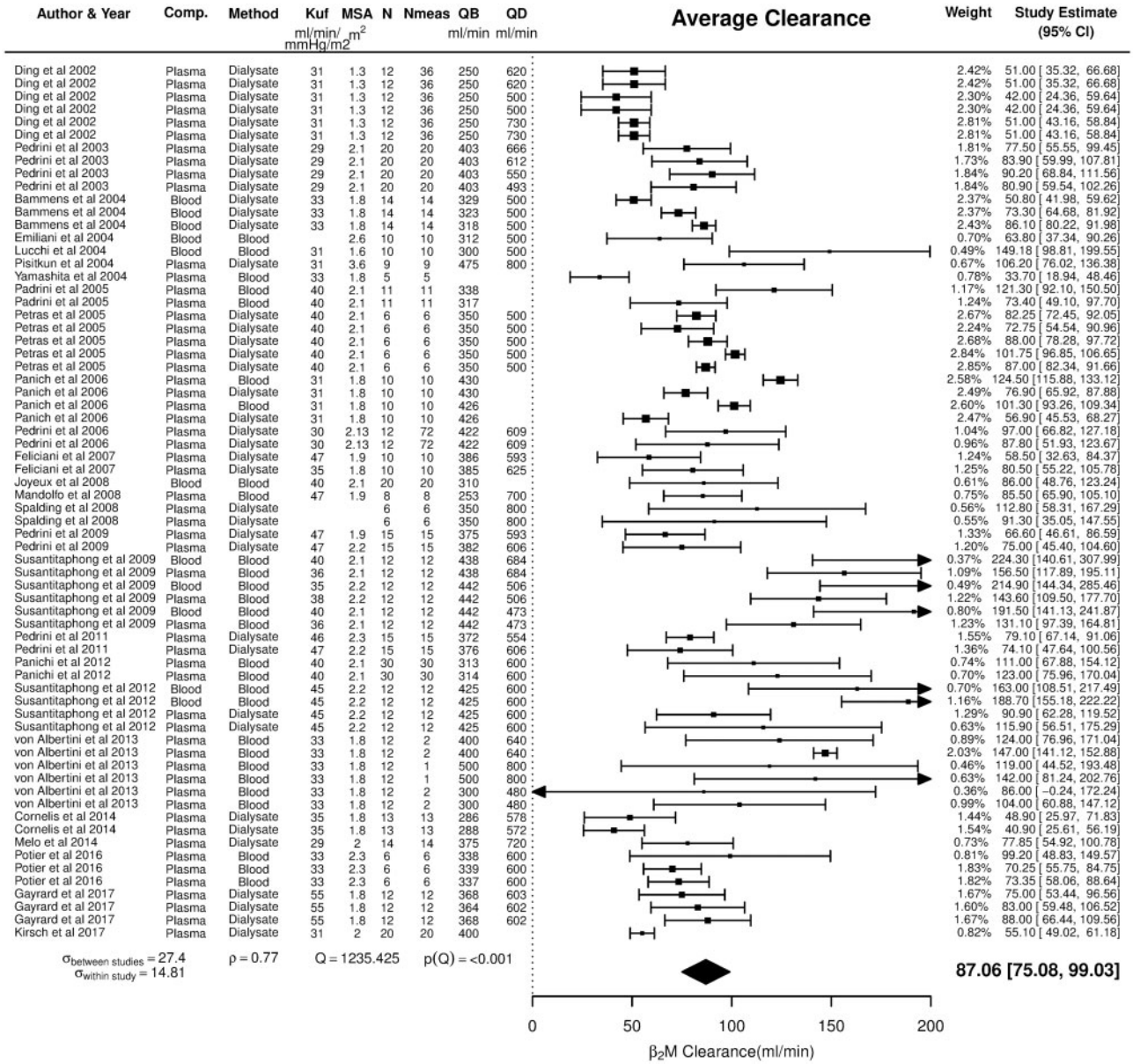

FIGURE 3: Forest plot of average (over the course of treatment) β2M dialyzer clearance in convective dialysis (HF/HDF). Comp, compartment; Kuf, ultrafiltration coefficient of the dialyzer; *n*, number; N meas, number of measurements; QB, blood flow rate (mL/min); QD, dialysate flow rate (mL/min).

randomized, crossover study showing that the clearance of β_2M was higher with PAES than PS [97]. Interestingly enough, β_2M clearance during HDF was related to membrane material but in the inverse direction than in HF dialysis. We hypothesize that this is due to differential adsorption of β_2M on membranes under the different transmembrane pressure (TMP) profiles of dialysis and HDF. Application of the higher TMP during HDF may result in a disproportionate increase in β_2M adsorption in PS relative to PAES, so that the difference in clearance between the two membranes seen in HF is nearly reversed. An alternative explanation invokes a more efficient convection in membranes without adsorption versus those with more adsorption e.g. as a result of membrane clogging. Regardless of the explanation, this observation should be corroborated in future prospective, head to head comparisons given the substantial heterogeneity of methodologies for the measurement of β_2M clearance employed by the different studies.

Notwithstanding the effects of membrane material on β_2M reduction ratio, it should be noted that recovery of β_2M into the dialysate, was not affected by membrane material. This is consistent with a landmark prospective RCT [97], showing that the higher β_2M clearance of PAES did not translate into more efficient mass removal of β_2M. In that study, it was postulated that the higher mass removal of β_2M by PAES arises from transmembrane transport augmented by adsorption within the membrane matrix. Membrane adsorption was experimentally demonstrated >20 years ago [98, 99] and the propensity of different membranes to differentially adsorb low molecular weight proteins was recently characterized with proteomic techniques [100]. Our analysis recapitulates previous findings that despite

Table 3. Metaregression of β_2M clearance for convective therapies (HF/HDF)

Variable	Effect size (per mL/min)	CI	P (Wald)
Kuf (scaled to MSA)	1.691	(0.609 to 2.773)	0.002
MSA (per m^2)	−1.336	(−19.017 to 16.346)	0.882
Compartment			
Blood (versus plasma)	49.868	(34.794 to 64.942)	<0.001
Clearance side			
Dialysate (versus blood)	−41.523	(−54.525 to −28.52)	<0.001
Blood pump flow (per mL/min)	0.188	(0.046 to 0.33)	0.01
Dialysis membrane			
PAES	−23.524	(−40.635 to −6.412)	0.007
PMMA	−22.421	(−41.627 to −3.215)	0.022
Type of measurement			
Instantaneous (versus average)	4.719	(−7.401 to 16.84)	0.445
Substitution fluid rate (per mL/min)	0.046	(−0.045 to 0.137)	0.321
Modality (relative to pre-hemofiltration)			
post-hemofiltration	42.719	(−1.957 to 87.395)	0.061
post-HDF	−7.764	(−27.834 to 12.306)	0.448
mid-HDF	5.614	(−16.493 to 27.721)	0.619
mixed-HDF	−12.972	(−36.947 to 11.002)	0.289
pre-HDF	−25.464	(−45.137 to −5.792)	0.011
Secular trend[a]	−0.925	(−3.31 to 1.46)	0.447

Kuf, ultrafiltration coefficient of a dialyzer.

[a]Secular trend includes a slope to adjust for a linear trend of increasing clearance in studies published in more recent years relative to HEMO (2001). Inclusion of these variables decreased the apparent degree of heterogeneity by >70% (Q statistic of unadjusted model 2361.8089 versus 675.8222 for the fully adjusted model), but significant heterogeneity did remain (P-value of QE statistic <0.001). Results are based on 127 distinct configurations of dialyzer and dialysis procedure operational parameters. See text for the abbreviations.

Table 4. Metaregression of β_2M reduction ratios for high flux dialysis and convective therapies

	HF dialysis			Convective therapies		
	Effect size (per mL/min)	CI	P (Wald)	Effect size (per mL/min)	CI	P (Wald)
Blood pump flow (per mL/min)	−0.01	(−0.051 to 0.03)	0.619	−0.017	(−0.051 to 0.018)	0.344
Kuf (scaled to MSA)	0.388	(0.073 to 0.703)	0.016	0.326	(0.046 to 0.606)	0.023
MSA	7.44	(−1.987 to 16.867)	0.122	5.068	(−2.155 to 12.291)	0.169
Membrane material (ref: PS)						
PAES	8.367	(2.913 to 13.822)	0.003	−0.836	(−4.792 to 3.121)	0.679
PMMA	12.403	(4.737 to 20.07)	0.002	−2.491	(−9.733 to 4.751)	0.5
CA	0.262	(−9.675 to 10.199)	0.959	—	—	—
PAN	3.525	(−6.677 to 13.727)	0.498	—	—	—
Correction of post dialysis β_2M value						
Corrected for hemoconcentration	−2.04	(−11.171 to 7.091)	0.661	−4.29	(−12.542 to 3.962)	0.308
Secular trend	1.443	(0.363 to 2.523)	0.009	0.438	(−0.198 to 1.075)	0.177
Substitution fluid rate (per mL/min)				0.077	(0.001 to 0.152)	0.047
Modality (relative to pre-hemofiltration)						
post-hemofiltration	—	—	—	15.931	(−6.334 to 38.195)	0.161
post-HDF	—	—	—	19.583	(−0.727 to 39.893)	0.059
mid-HDF	—	—	—	16.235	(−2.687 to 35.156)	0.093
mixed-HDF	—	—	—	14.587	(−4.303 to 33.477)	0.13
pre-HDF	—	—	—	6.891	(−9.21 to 22.992)	0.402

Kuf, ultrafiltration coefficient of a dialyzer.

the higher clearance, β_2M removal in the dialysate is not higher with any of the currently available membranes. This suggests that adsorption to the membrane, rather than convective or diffusive elimination of β_2M in the dialysate, underlines the differences between dialyzers of different membrane material. The *a priori* plausibility of differential adsorption of β_2M in membranes according to the dialysis mode is high. There are reports using proteomic techniques that demonstrate differential absorption of β_2M in PS versus triacetate membranes [93], PS versus PMMA membranes [101] or even the same PS when exposed to the different pressure profiles associated with HF versus low flux dialysis [102]. An interesting report also showed a change of contribution of the different forms of clearance when the same dialyzer used in post- versus pre-HDF mode (adsorption is lower in post) [45]. Hence, the available data do point to differential adsorption patterns by material, permeability and even mode of HDF. The only credible way to test our hypothesis that PAES and PS adsorb β_2M differently under HF dialysis and HDF is by properly designed head to head comparisons using standardized collection methods, blood

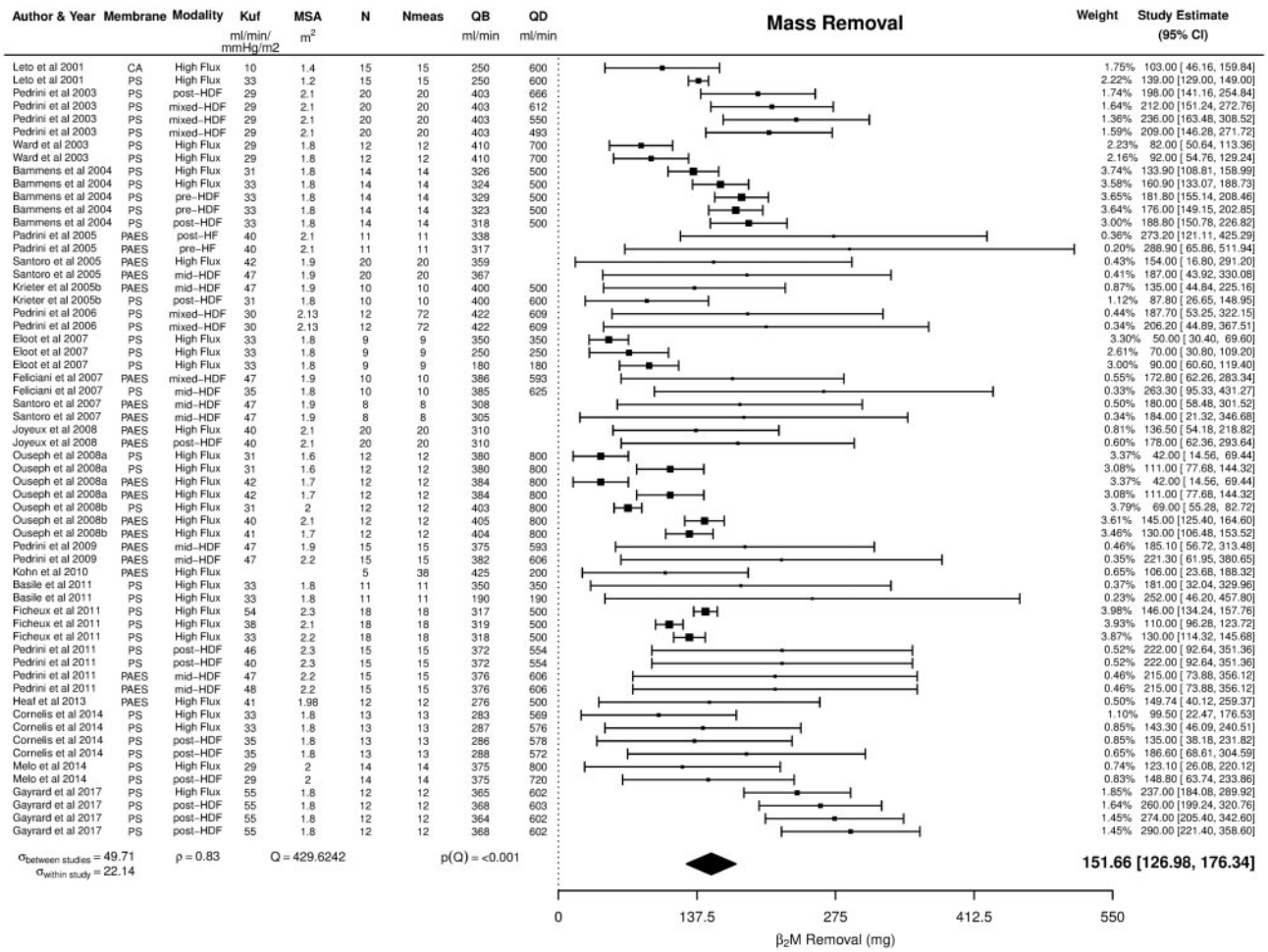

FIGURE 4: Forest plot of β_2M mass removal (mg/session) in diffusive HFD and convective (HDF/HF) dialysis. Comp, compartment; Kuf, ultrafiltration coefficient of the dialyzer; *n*, number; N meas, number of measurements; QB, blood flow rate (mL/min); QD, dialysate flow rate (mL/min).

Table 5. Metaregression of β_2M removal for high flux dialysis and convective therapies

	Effect size (mg/session)	CI	P (Wald)
Blood flow (per mL/min)	−0.157	(−0.398 to 0.084)	0.202
Kuf scaled to MSA	2.229	(0.316 to 4.142)	0.022
MSA (per m^2)	−0.206	(−66.052 to 65.64)	0.995
Membrane material (relative to polysulfone)			
PAES	−1.874	(−34.069 to 30.321)	0.909
CA	22.983	(−61.608 to 107.573)	0.594
Modality (relative to HF dialysis)			
mid-HDF	56.138	(−1.787 to 114.063)	0.057
mixed-HDF	97.522	(41.638 to 153.405)	<0.001
post-HDF	54.714	(22.879 to 86.549)	<0.001
post-hemofiltration	151.036	(−17.467 to 319.538)	0.079
pre-HDF	41.564	(1.7 to 81.427)	0.041
pre-hemofiltration	163.451	(−71.28 to 398.182)	0.172
Secular trend[a]	1.783	(−2.718 to 6.283)	0.438

Kuf, ultrafiltration coefficient of a dialyzer.
[a]Secular trend includes a slope to adjust for a linear trend of increasing clearance in studies published in more recent years relative to HEMO (2001). See text for other abbreviations.

and dialysate clearances and possibly proteomic techniques. An interesting direction for future innovations in dialyzer development that builds on this hypothesis would explore the properties of different membranes to optimize clearance for convective versus diffusive forms of dialysis. There have been reports in the literature about dialyzers (some of them already in the market) that are specifically targeted for convective therapies [103, 104], while safety considerations about albumin loss suggest

that not all HF dialyzers may be used in high-volume convective therapies [105]. Such considerations should be taken into account during the design of follow-up studies in convective therapies.

Our results suggest that dialyzers introduced in the last 15 years do not have substantially larger β_2M clearance than those used during the landmark HEMO study in the late 1990s and early 2000s when used for conventional (diffusive) dialysis. Nevertheless, large secular trends consistent with improving dialyzer performance were observed when reduction ratios, rather than measured clearance or mass removal, were analyzed. Collectively, our analysis suggests not only that the basic mechanisms of middle molecule elimination by HF dialyzers has remained unchanged over the years, but the quantitative aspects of middle molecule centric HF dialysis have largely remained unchanged since HEMO was published. We should point out that these assessments do not apply to the emerging class of middle cut-off dialyzers, which not only have substantially higher middle molecule clearance than high flux membranes, but may even narrow the gap between high flux dialysis and HDF [92].

Despite the apparent lack of improvements in dialyzer performance, higher clearance (by up to 44%) may be attained by using the same dialyzers in convective therapies (HF or HDF). This was also noted when alternative, simple measures of middle molecule elimination, i.e. the reduction ratios, were utilized to compare diffusive and convective forms of dialysis. There are two mechanisms by which higher (pump) blood flow rates may increase β_2M clearance in convective therapies: directly by increasing the amount of β_2M available for diffusive clearance and indirectly by allowing higher rates of substitution fluid to be used, boosting the convective clearance. The latter mechanism is underscored by our finding that higher fluid substitution rates were significantly associated with higher β_2M clearances in post-HDF therapies. This finding is supported by early studies on online HDF [106, 107] comparing the reduction ratios and the clearances of β_2M, BUN, creatinine and phosphorus between HD and online HDF with 40–120 mL/min substitution fluid. The maximum benefit was achieved in HDF 100 (i.e. with 24 L substitution volume per 4-h treatment) versus classical HD. Another study of 2293 incident patients treated by post-dilution online HDF determined the convection volume threshold and range associated with survival advantage [108]. The relative adjusted survival rate was found to increase at about 55 L/week of convection volume and to stay increased up to about 75 L/week. The same paper found a nearly linear decrease in pre-dialysis β_2M concentration by 0.6 mg/L for every 10 L/week of additional convection volume as the latter increased from 40 to 75 L/week. However, this mode can only be achieved with a permanent effective blood flow rate of at least 300 mL/min, since less than a third of this value can be accepted as the flow rate of the substitution fluid to avoid too high a TMP causing damage to the membrane. In the modern era, technical developments such as the adoption of variable ultrafiltration rates adapted to the level of the TMP during the treatment can be applied to achieve such high convection rates [109].

In fact there was a direct linear relationship between blood pump and dialysate flow rates in all the studies we analyzed, so that higher blood flow rates were associated with higher substitution fluid flow rates. The net result is that patients whose access could support high blood pump flow rates were the ones who received higher substitution fluid rate (>100 mL/min) and experienced the largest dialytic β_2M removal. This pattern may be clinically significant, since a recent meta-analysis [14] of the large online HDF trials [21–23] and *post hoc* analyses published by the investigator teams in the last 5 years suggest an overall and cardiovascular survival advantage for these high-fluid rates. Treatment center policies about blood flow, treatment time, filter size and even hemoglobin level can be used in conjunction with the aforementioned technical innovations to achieve high convection volumes despite non-modifiable factors such as dialysis access that limit the achievement of higher blood and substitution fluid flow rates [109]. A surprising finding of our analysis was the lack of a meaningful effect of higher dialysate flow rates on improving diffusive or convective middle molecule clearance. This observation, which seems to go against classical teachings, is however fully in line with recent experiments about contemporary dialyzers for both small [110–112] and middle molecule clearance [113]. Design innovations such as spacer yarns in the fiber bundle, fiber undulations and changes in fiber-packing density have reduced the dependence of clearance on dialysate flow rates because of improved flow distribution in the dialyzer. Theoretical analysis based on the Weryński [114] and Michaels [115] equations relating diffusive clearance, sieving coefficient, Membrane Transfer Area Coefficient, blood and dialysate flow rates suggests that for dialyzers used in modern HF dialysis (sieving coefficient $S = 0.65$) and HDF ($S = 0.75$), increasing the dialysate flow by 60% from 500 to 800 mL/min will have a very small effect (∼0.4 mL/min) on middle molecule body clearance.

Some limitations of this meta-analysis need to be acknowledged. First, the studies included differed in study design, methodologically (methods used for the calculation of clearance, dialysis modalities) and operationally (different dialyzers, different blood and dialysate flow rates, etc.). In particular, different approaches to calculate clearance will systematically overestimate (e.g. whole blood versus plasma) or underestimate (e.g. dialysate versus plasma) the dialytic clearance. We attempted to account for these systematic differences in our analyses through statistical modeling. However, residual confounding cannot be excluded. Such confounding may particularly apply to the apparent lack of an improvement of convective dialyzer performance with time, during a period in which many manufacturers released dialyzers with higher sieving coefficients for β_2M and thus greater capacity for convective clearance. These dialyzers may also be more likely to remove β_2M through adsorption in the inner layers of the dialyzer, so that studies relying on dialysate side measurements may have missed this finding. It should be noted that despite the lack of a statistically significant effect, the magnitude of the temporal trend for all dialyzer performance measures considered, is in the direction of more efficient removal with time. As further studies become available, our finding may notwithstand the passage of time. Second, most of the included studies recruited chronic HD patients on a thrice-weekly 4-h treatment schedule. Third, the apparent lack of an effect of higher dialysate flows

may not apply to short, frequent, slow flow dialysis for membranes that do not exhibit enhanced dialytic removal at higher flows in conventional thrice-weekly dialysis [116]. Fourth, the limited sample size, selection of sampling points in the source data and analytical methodology of mixed models may have limited our ability to detect a statistically significant difference between instantaneous and average dialyzer clearances. Finally, this work is limited to adult patients and cannot be generalized to the pediatric dialysis population.

CONCLUSIONS

Dialysis prescription parameters (e.g. blood and dialysate flow rates in HD and infusion volume in HDF), as well as membrane material (HD), are major determinants of β_2M clearance from the body in renal replacement therapies. Future prospective studies should standardize methodology for these measurements and investigate a wide variety of dialysis configurations to directly account for variability within and between patients and dialysis units. Such experimental studies are better suited than our statistical analyses to highlight clinically important differences related to the differential effects of β_2M body removal seen with membranes of different material to inform their use in clinical HD and HDF.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

AUTHORS' CONTRIBUTIONS

The study was conceived and data were analyzed by the corresponding author. Data were generated by M.-E.R., G.T., Y.-H.N., Z.X., A.A. and R.F. Significant intellectual content was contributed by T.D.N. and M.L.U. All authors contributed to the interpretation of the data, drafting and revision of the manuscript. All authors have approved the final version of the article that was uploaded to the journal website.

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CONFLICT OF INTEREST STATEMENT

None declared.

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