Hemodiafiltration versus Hemodialysis in End-Stage Kidney Disease: A Systematic Review and Meta-Analysis

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Rationale & Objective: The use of hemodiafiltration (HDF) as a kidney replacement therapy (KRT) in patients with end-stage kidney disease (ESKD) has sparked a debate regarding its advantages over conventional hemodialysis (HD). The present study aims to shed light on this controversy by comparing mortality rates and cause-specific deaths between ESKD patients receiving HDF and those undergoing HD.

Study Design: Systematic review and meta-analysis of randomized controlled trials (RCTs). The search was conducted using PubMed, EMBASE, and Cochrane Central on July 1, 2023.

Setting & Participants: Adult patients with ESKD on regular KRT.

Exposure: Studies with participants undergoing HDF.

Outcomes: Primary outcomes were all-cause mortality, cardiovascular (CV) mortality, deaths related to infections, and kidney transplant. We also evaluated the endpoints for deaths related to malignancy, myocardial infarction, stroke, arrhythmias, and sudden death.

Analytical Approach: We included RCTs evaluating HDF versus HD. Crossover trials and studies with overlapping populations were excluded. Two authors independently extracted the data following predefined search criteria and quality assessment. The risk of bias was assessed with Cochrane's RoB2 tool.

Results: We included 5 RCTs with 4,143 patients, of which 2,078 (50.1%) underwent HDF, whereas 2,065 (49.8%) were receiving HD. Overall, HDF was associated with a lower risk of all-cause mortality (risk ratio [RR], 0.81; 95% confidence interval [CI], 0.73-0.91; $P < 0.001$; $I^2 = 7\%$) and a lower risk of CV-related deaths (RR, 0.75; 95% CI, 0.61-0.92; $P = 0.007$; $I^2 = 0\%$). The incidence of infection-related deaths was also significantly different between therapies (RR, 0.69; 95% CI, 0.50-0.95; $P = 0.02$; $I^2 = 26\%$).

Limitations: In individual studies, the HDF groups achieved varying levels of convection volume.

Conclusions: Compared with those undergoing HD, patients receiving HDF experienced a reduction in all-cause mortality, CV mortality, and infection-related mortality. These results provide compelling evidence supporting the use of HDF as a beneficial intervention in ESKD patients undergoing KRT.

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Chronic kidney disease (CKD) has emerged as a significant and rapidly growing comorbid condition, exerting substantial pressure on global health care systems.[1] Over the past 3 decades, the incidence of CKD has witnessed an alarming increase of nearly 30%.[2] In 2017 alone, its complications led to the deaths of over 1.2 million individuals worldwide, surpassing the mortality rates of certain types of cancer.[3] Notably, patients with end-stage kidney disease (ESKD) face an even greater mortality risk, experiencing a substantial reduction in life expectancy with the commencement of kidney replacement treatment (KRT).[4]

For several years, hemodialysis (HD) has served as the primary modality for blood purification and ultrafiltration in patients diagnosed with ESKD. Nevertheless, the efficacy of hemodiafiltration (HDF), a KRT that leverages convective principles to remove molecules, has yielded inconclusive findings regarding its impact on pertinent outcomes for individuals with kidney failure, as suggested by prior evidence.[5-7]

A previously conducted randomized controlled trial (RCT) provided initial evidence of reduced overall mortality in patients treated with HDF.[8] However, the replication of this finding remained elusive until the recent publication of the CONVINCE trial in 2023.[9] In light of this significant development, the primary objective of our meta-analysis was to evaluate the impact of HDF compared with HD on key outcomes, including all-cause mortality, cardiovascular (CV) mortality, and kidney transplant rates. By synthesizing the available evidence, we aim to provide a more precise assessment of the effectiveness of HDF as a treatment modality for ESKD.

METHODS

Search Strategy

We conducted a systematic search of the literature using PubMed, EMBASE, and Cochrane Central Register of Controlled Trials up to July 01, 2023. The following search terms were used: "hemodialysis," "hemodiafiltration," and "end-stage kidney disease." The complete electronic search strategy is provided in the Supplementary Appendix. Additionally, we manually searched the references of all included studies to identify any additional relevant studies.

Two authors independently extracted the data based on predefined search criteria and quality assessment guidelines. Any discrepancies were resolved through discussion and consensus. To ensure transparency, this study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023438362.

Study Selection and Eligibility Criteria

We included studies that met the following eligibility criteria: (1) RCTs, (2) comparing postdilution online HDF with HD, (3) conducted in patients with ESKD, and (4) reporting at least 1 of the clinical outcomes of interest. We excluded studies that met any of the following criteria: (1) had overlapping patient populations, (2) were nonrandomized studies, or (3) employed a crossover design.

The primary outcomes of interest included the following: (1) all-cause mortality, (2) CV mortality, (3) infection-related deaths, and (4) transplantation. Additionally, we considered the following secondary outcomes of interest: (1) fatal myocardial infarction, (2) fatal stroke, (3) fatal arrhythmias, (4) malignancy-related deaths, and (5) sudden death.

We also conducted a subgroup analysis based on the sum of the results from an individual pooled analysis study from the 4 prior RCTs combined with the subgroup findings reported from the CONVINCE study.[7,9]

Quality Assessment

We used the Cochrane Collaboration's tool RoB-2 for assessing the risk of bias in randomized trials for quality assessment of individual randomized studies.[10] Each trial was evaluated for risk of bias in 5 domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and reporting results biases. Risk of bias judgments was categorized as "high," "low," or "some concerns." The risk of bias was adjudicated independently by 2 investigators (MG and FT), with any disagreements resolved through discussion and analysis by a third author (NS).

Two authors (MG and NS) independently evaluated the results using the Grading and Recommendations Assessment, Development and Evaluation (GRADE) system, considering the domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias.[11]

Statistical Analysis

This systematic review and meta-analysis was conducted in accordance with the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions version 6.3, 2022, and followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[12,13]

To assess the outcomes of interest, we analyzed the risk measures along with their corresponding confidence intervals (CIs). Statistical analysis was performed using Review Manager 5.4 (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).[14]

To compare treatment effects for categorical endpoints, we used risk ratio (RR) with corresponding 95% CIs, considering a P value less than 0.05 as statistically significant in the analysis performed. Hazard ratios were used for the subgroup analyses, as reported in individual studies. We adopted the Mantel–Haenszel test for all binary endpoints. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. Significance for heterogeneity was set at I^2 values over 50%. For outcomes with low heterogeneity ($I^2 \leq 50\%$), considering all included studies were RCTs with a similar distribution of patients among each group, a fixed-effect model was used.

To assess the robustness of the results, a sensitivity analysis was conducted. This involved systematically removing each study from the analysis and recalculating the results to evaluate their influence on the overall findings. Additionally, we performed an analysis excluding studies with a higher potential for bias to assess the consistency of the results.

RESULTS

Study Selection and Baseline Characteristics

The initial search yielded 1,593 records (Fig 1). After removing duplicate records and screening for eligibility, a total of 8 studies underwent a thorough review. Ultimately, 5 studies met the inclusion criteria, involving a total of 4,134 patients.[8,9,15-17] Additionally, for the purpose of performing subgroup analysis on the primary outcome of all-cause mortality, we included data from a previous study that reported individual patient data from the 4 later RCTs included in this meta-analysis.[7]

A total of 4,134 patients with ESKD were included in this meta-analysis, with 2,078 (50.1%) undergoing HDF and 2,065 (49.8%) receiving HD. The study characteristics are presented in Table S1. The mean convection volume in the HDF groups ranged from 17.2 to 23.9 L per session. Four of the studies used high-flux hemodialysis as the control group. The duration of the sessions ranged from 3.77 to 4 hours in the HDF group and 3.81 to 4 hours in the patients receiving HD. All studies used ultrapure fluids for both treatments. The median follow-up ranged from 19 to 36 months.

Pooled Analysis

The pooled analysis of the data showed that patients who received HDF had a significantly lower incidence of all-cause mortality compared with those undergoing HD (RR, 0.81; 95% CI, 0.73-0.91; $P < 0.001$; $I^2 = 7\%$; Fig 2). Similarly, the HDF group demonstrated a lower incidence of CV mortality (7% vs 9.7% in the HD group) (RR, 0.75; 95% CI, 0.61-0.92; $P = 0.007$; $I^2 = 0\%$; Fig 3). We also found a significant reduction in infection-related mortality in patients receiving HDF (RR, 0.69; 95% CI, 0.50-0.95; $P = 0.02$; I2 = 26%; Fig 4). Although the HDF group exhibited a slightly higher percentage of kidney transplants (12.9% vs 11%), this

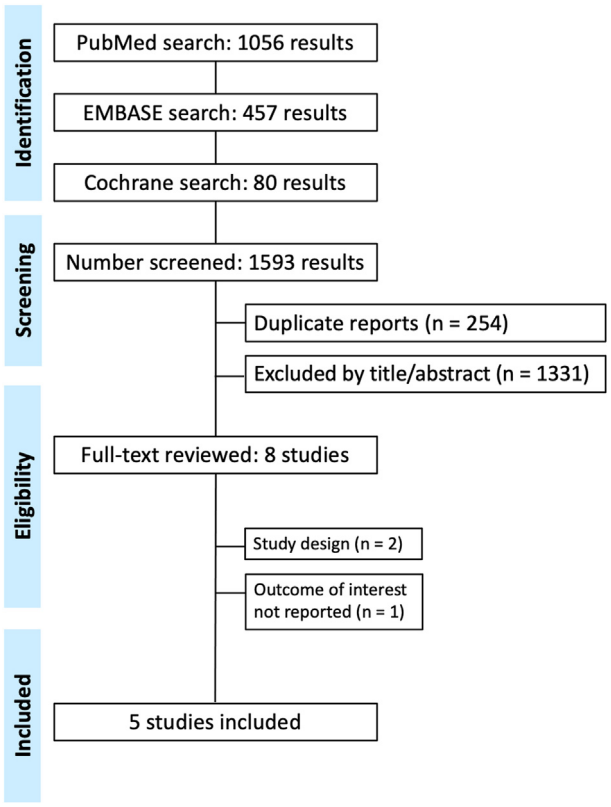

Figure 1. PRISMA flow diagram summarizing the systematic search and review process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

difference did not reach statistical significance (RR, 1.14; 95% CI, 0.97-1.34; P = 0.11; I^2 = 0%; Fig 5).

Among the 3 studies reporting individual cardiovascular events resulting in death, there was no significant difference in the incidence of fatal myocardial infarction between the HDF and HD groups (RR, 1.16; 95% CI, 0.99-1.36; P = 0.07; I^2 = 0%; Fig 6).[8,9,16] Additionally, no significant differences in the incidence of fatal stroke and fatal arrhythmias were noted between the 2 treatment modalities (P = 0.10 and 0.50, respectively).

The mortality rates associated with malignancy did not exhibit any significant variation across the different treatment modalities (P = 0.31) (as shown in Fig S1). Moreover, there were no discernible differences in sudden death between the groups (RR, 0.95; 95% CI, 0.64-1.42; P = 0.81; I^2 = 0%; Fig S2).

Subgroup Analysis

We assessed the outcome of all-cause mortality for elderly patients (over 65 years old), women, patients with prior cardiovascular disease (CVD) and diabetes, as well as patients with arteriovenous (AV) fistulas or other forms of vascular access for KRT.

Among elderly patients, HDF demonstrated a significant reduction in all-cause mortality (RR, 0.77; 95% CI, 0.64-0.91; P = 0.003; I^2 = 35%; Fig S3). Additionally, a reduction in mortality was observed in patients with AV fistulas, as well as those with different forms of vascular access (P = 0.04 and 0.03, respectively). However, no significant difference in all-cause mortality was found in female patients (P = 0.05). Similar mortality rates were observed in patients with prior CVD and diabetes (P = 0.21 and 0.06, respectively).

We also performed an analysis on the outcome of mortality removing the 2 studies with a high risk of bias, resulting in a significant reduction in mortality when we assessed this analysis (RR, 0.86; 95% CI 0.75-0.99; P = 0.03; I^2 = 0%; Fig S4).

Sensitivity Analyses

Leave-one-out sensitivity analyses confirmed the consistency of the findings after sequentially removing each study and recalculating results. The RR remained statistically significant, ranging from 0.76 to 0.85 for the outcome of all-cause mortality, from 0.73 to 0.78 for the outcome of CV mortality, and 0.63 to 0.77 for infection-related deaths when each study was systematically withdrawn from the analysis.

Quality Assessment

The individual appraisal of each RCT included in the meta-analysis is summarized in the Supplementary Material. The studies included were found to have a risk of bias classified as either "some concerns" or "high."

DISCUSSION

This systematic review and meta-analysis, including 5 RCTs with a total of 4,143 patients with ESKD, compared

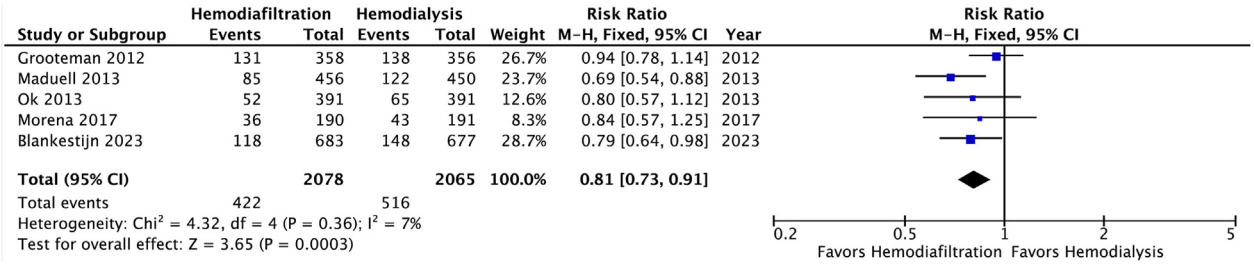

Figure 2. All-cause mortality in patients receiving HDF versus HD. HD, hemodialysis; HDF, hemodiafiltration.

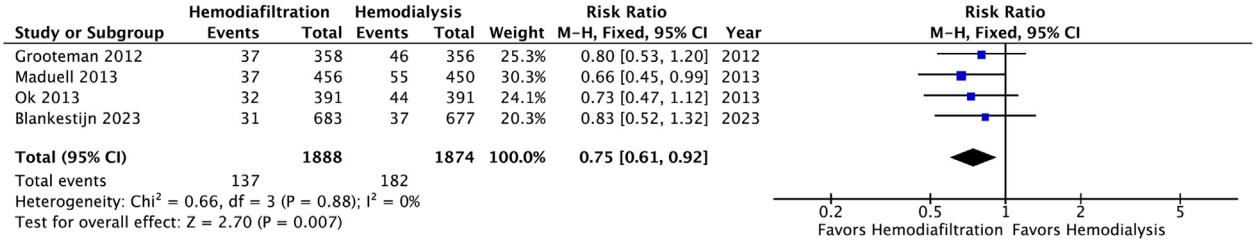

Figure 3. Cardiovascular mortality in patients receiving HDF versus HD. HD, hemodialysis; HDF, hemodiafiltration.

the effectiveness of HDF versus HD as a KRT. The main findings from the pooled analyses showed that HDF significantly reduced the risk of all-cause mortality by nearly 20% compared with the HD group (20% vs 25%, respectively). Additionally, HDF was effective in reducing the risk of CV-related deaths by 25% and infection-related mortality by 31%. The studies included in the analysis did not differ significantly regarding blood flow rates, therapy duration, and the use of ultrapure dialysis fluids between groups. However, there were significant variations in the reported convection volume. These findings were robust and consistent across sensitivity analyses, with minimal heterogeneity between studies. A subgroup analysis from the individual studies also corroborated the reduction in mortality in elderly patients and in patients with AV fistulas or other forms of vascular access.

Our study presents compelling evidence that HDF is beneficial for patients with ESKD. We included a larger number of patients than previous pooled analyses, and we reported a reduction in clinically relevant outcomes for patients with kidney failure requiring KRT. A previous study with patient-level data from the 4 prior RCTs included in this study had already showed a 14% reduction in all-cause mortality and a 23% reduction in CV mortality for HDF patients.[7] The present meta-analysis has reinforced this discovery, using aggregated data from the CONVINCE trial, with a larger patient population, resulting in more accurate findings and providing stronger evidence for the use of HDF in patients with kidney failure. We observed a greater reduction in the risk of all-cause mortality in the HDF group compared with prior meta-analysis, with a more precise CI. It is worth noting that the HDF group showed a decrease in mortality across the subgroup analysis of patients with or without AV fistulas. This finding is particularly important because the blood flow delivered during HDF sessions is a critical factor for its efficacy, addressing concerns raised in previous studies.[18] Altogether, we found a reduction in overall mortality in elderly patients as well, a growing population worldwide that requires greater medical attention and may be more susceptible for complications related to KRT.

Prior individual studies have demonstrated that patients who undergo HDF exhibit a reduction in mortality rates.[19-22] However, these results had been subject to criticism regarding potential confounding bias in non-randomized studies. Notably, the ESHOL trial exhibited randomization bias, with uneven distribution in age, Charlson comorbidity index, and vascular access among the assigned patients in the HDF group. More recently, the CONVINCE trial addressed these concerns by implementing well-balanced randomization and reported promising results, reducing all-cause mortality by 23% in patients who achieved a high convective volume in the HDF group.

It is important to investigate the underlying mechanisms that account for these observed benefits and determine whether there is a synergistic effect of hemodynamics and middle molecule removal in producing these outcomes as well as the ideal convective dose for achieving them.[23-26] For example, it is plausible that the reduction in CV deaths might be related to an improved hemodynamic stability during HDF, with less intradialytic hypotension.[27] Even though all the studies reported the use of ultrapure dialysates in both groups, an important quality factor that may be related to infectious events, we hypothesize that the greater removal of endotoxins and cytokines through convective methods is a relevant mechanism to reduce the mortality rates related to infections, although other clinically relevant factors are intertwined for this outcome (age, vascular access, nutritional status, and immunosuppression).[28-30]

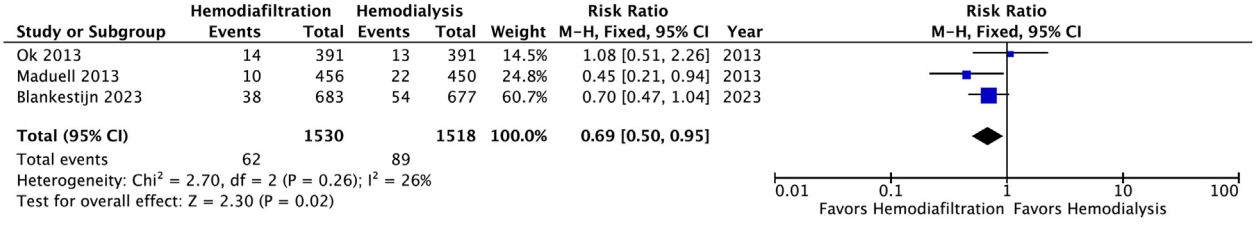

Figure 4. Infection-related deaths in patients receiving HDF versus HD. HD, hemodialysis; HDF, hemodiafiltration.

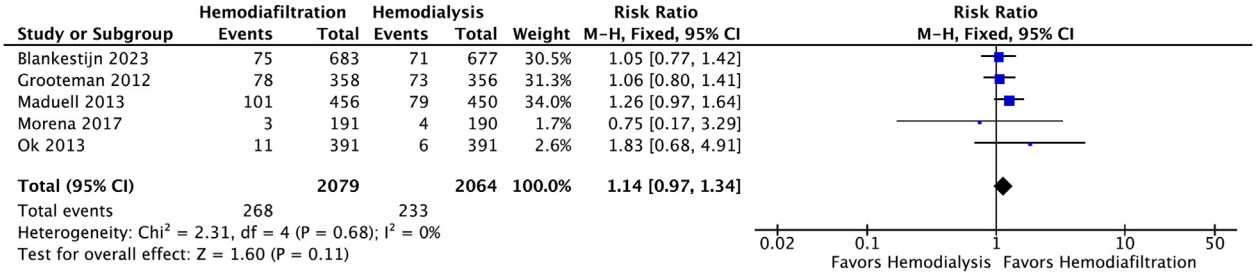

Figure 5. Kidney transplant rates in patients receiving HDF versus HD. HD, hemodialysis; HDF, hemodiafiltration.

It is remarkable that a single intervention can reduce mortality risk in patients with advanced CKD, as they face multiple pathophysiological mechanisms that increase their risk compared with individuals with other chronic diseases. The present meta-analysis adds to the growing body of evidence suggesting that HDF may be the optimal strategy for ESKD patients, given its efficacy in reducing overall death rates, including cardiovascular mortality and infection-related deaths, in this ever-growing population that puts high pressure on health care systems. A cost-effectiveness analysis of this intervention is being assessed with an ongoing RCT.[31]

This study has certain limitations. Most importantly, there was a variation in the convective volume achieved in individual studies, ranging from 17.2 to 23.9 L per session. Although we cannot exclude the possibility that a nonstandardized intervention regarding the target convection volume would have led to different results in the individual studies accessed in this meta-analysis, we had a low heterogeneity in the findings in the pooled results for our study. We believe that future studies should address the "ideal" convective dose to obtain relevant clinical outcomes in this population. The included studies had a "high" or "some concerns" of bias because of the unblinded nature of both the intervention and control groups. It is also important to note that most of the studies were conducted in European centers which may limit the generalization of the findings to other ethnic groups. Finally, the absence of patient-level data precluded the analysis of individual and composite

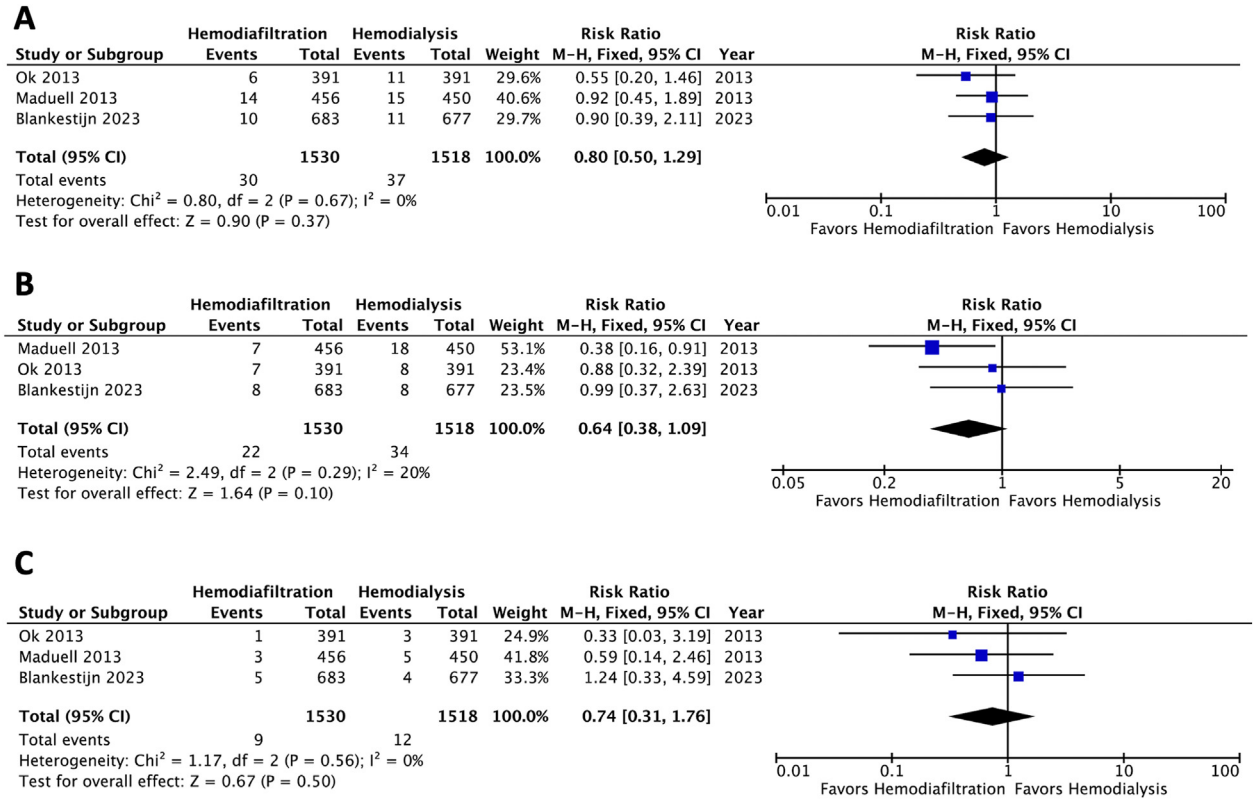

Figure 6. Fatal myocardial infarction, stroke, and arrhythmias in patients receiving HDF versus HD. HD, hemodialysis; HDF, hemodiafiltration.

outcomes for major adverse cardiovascular events and hospitalizations.

In conclusion, the present study highlights the potential benefits of HDF over HD as a KRT for patients with ESKD. Our findings show that HDF can effectively lower all-cause mortality, CV mortality, and infection-related deaths, underscoring the importance of HDF as a crucial KRT strategy to consider. These results have significant implications for the management of advanced CKD and warrant further investigation into the potential long-term benefits of HDF over HD as the preferred modality for KRT.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: There was no significant difference in the outcomes of malignancy-related deaths.

Figure S2: There was no significant difference in the incidence of sudden death between patients receiving HDF versus those receiving HD.

Figure S3: Primary asystole (fitted curve).

Figure S3: Subgroup analysis from pooled individual data and the CONVINCE trial for all-cause mortality in elderly patients (A), female patients (B), patients with prior CVD (C), patients with diabetes (D), patients with AV fistulas (E), and those with other vascular access (F).

Figure S4: Pooled analysis on the outcome of mortality removing the 2 studies with a high risk of bias.

Table S1: Risk of Bias Summary for Randomized Controlled Trials.

ARTICLE INFORMATION

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