

Abstract citation ID: gfae069.075

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# Hemodiafiltration or haemodialysis for kidney failure: updated systematic review and individual participant data meta-analysis

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**Background and Aims:** A recent large European randomised controlled trial (RCT) showed a 23% reduction in all-cause mortality in favour of high dose haemodiafiltration (HDF) compared to high flux haemodialysis (HD). Several reactions critically questioned the main outcome and subgroup results and thereby its implications. Implications, however, should not be viewed based on results of one trial, but rather on the combined available evidence. Therefore, we set out to update our previous 2016 individual patient data meta-analysis (IPA-MA). An IPA-MA was chosen over an aggregated data meta-analysis as it allows more powerful and uniformly consistent analyses of subgroups and outcomes.

**Method:** The study was conducted according to PRISMA-IPD guidelines. We performed searches in MEDLINE, Embase and CENTRAL to identify RCTs in kidney failure patients with at least one year follow-up after randomisation, comparing on-line HDF with HD on mortality outcomes. Investigators were invited to share participant level data. The primary outcome was all-cause mortality. Secondary outcomes were cause-specific death (cardiovascular, only cardiac, only non-cardiac, infection-related, sudden death). We ran Cox proportional hazards models using intention to treat samples with a random effect for study, reporting hazard ratios (HR) and 95% confidence intervals (95% CI), overall and stratified by several predefined patient characteristics. Also, we ran Cox models using HDF patient data to estimate relations between achieved convective volume and mortality outcomes.

**Results:** Data from five European RCTs (i.e. ESHOL, CONTRAST, French HDF Study, Turkish HDF Study, and CONVINCENCE) were included, comprising 4153 patients. After a median follow-up of 30 months (Q1-Q3: 24-36), death from any cause occurred in 558 patients (27.2%) in the HD group and in 477 patients (23.3%) in the HDF group (HR: 0.84; 95% CI: 0.74 to 0.95). There was no evidence for a differential effect across subgroups. Cause specific analyses showed, compared to the HD, a lower risk of cardiovascular death in the HDF group (HR: 0.78; 95% CI: 0.63 to 0.96), which seemed to be driven by a lower risk for cardiac death (HR: 0.67, 95% CI: 0.50 to 0.89). The largest survival benefit was found for patients achieving a convective volume of 23 L or above, with a multivariable adjusted HR of 0.63 (95% CI: 0.50 to 0.79) for all-cause death, of 0.58 (95% CI: 0.40 to 0.85) for cardiovascular death and of 0.51 (0.28 – 0.93) for infection related death. The relation between achieved convection volume and mortality outcomes seemed gradual: the higher achieved the volume, the lower the risk compared to HD.

**Conclusion:** The combined available individual patient data from RCTs indicate that on-line HDF treatment improves survival with, at present, no clear differences across patient subgroups, when identified based on single characteristics. Our finding “the higher dose of HDF achieved, the lower the risk” seems congruent with that reported previously from observation studies.