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ORIGINAL ARTICLE

# Association between implementation of novel therapies and improved survival in patients starting haemodialysis: the Swedish Renal Registry 2006–15

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## ABSTRACT

**Background.** The recent years have witnessed significant therapeutic advances for patients on haemodialysis (HD). We evaluated temporal changes in treatments practices and survival rates among incident HD patients.

**Methods.** This was an observational study of patients initiating HD in Sweden in 2006–15. Trends of HD-related practices, medications and routine laboratory biomarkers were evaluated. The incidence of death and major cardiovascular events (MACEs) across calendar years were compared against the age- and sex-matched general population. Via Cox regression, we explored whether adjustment for implementation of therapeutic advances modified observed survival and MACE risks.

**Results.** Among 6612 patients, age and sex were similar, but the burden of comorbidities increased over time. The proportion of patients receiving treatment by haemodiafiltration, ≥3 sessions/week, lower ultrafiltration rate and working fistulas increased progressively, as did use of non-calcium phosphate binders, cinacalcet and vitamin D3. The standardized 1-year mortality decreased from 13.2% in 2006–07 to 11.1% in 2014–15. The risk of death decreased by 6% [hazard ratio (HR) = 0.94, 95% confidence interval (CI) 0.90–0.99] every 2 years, and the risk of MACE by 4% (HR = 0.96, 95% CI 0.92–1.00). Adjustment for changes in treatment characteristics abrogated these associations (HR = 1.00, 95% CI 0.92–1.09 for death and 1.00, 0.94–1.06 for MACE). Compared with the general population, the risk of death declined from 6 times higher in 2006–07 [standardized incidence rate ratio (sIRR) = 6.0, 95% CI 5.3–6.9] to 5.6 higher in 2014–15 (sIRR = 5.57, 95% CI 4.8–6.4).

**Conclusions.** Gradual implementation of therapeutic advances over the last decade was associated with a parallel reduction in short-term risk of death and MACE among HD patients.

**Keywords:** death, haemodialysis, survival, trend, trialSwedish Research council (2019-01059), The Heart and Lung Foundation, the Stig and Gunborg Westman foundation, Grants for strategic research and CIMED (Karolinska University hospital), Stockholm City Council (ALF), and Baxter Healthcare (to Karolinska Institutet)

## INTRODUCTION

People with chronic kidney disease (CKD) undergoing maintenance haemodialysis (HD) have a dramatically reduced life expectancy and increased risk of death [1, 2], especially attributed to cardiovascular diseases (CVDs) [3]. The recent years have witnessed the introduction of multiple therapeutic improvements in the management of these patients, such as the use of high-flux dialysers and convective therapies [4]; the endorsement of programmes to improve vascular access such as the Fistula First initiative [5]; the use of more frequent sessions or longer sessions including nocturnal HD with lower ultrafiltration (UF) rates [6]; improved medication practices, such as calcium (Ca)-free phosphate (PO4) binders [7] and calcimimetics [8]; and the setting of appropriate anaemia treatment targets based on evidence-based ascertainments provided by clinical trials [9–11].

Although admittedly, such new treatments in isolation have shown limited or at times no efficacy in improving hard clinical

## KEY LEARNING POINTS

**What is already known about this subject?**

- there have been substantial changes in both haemodialysis (HD) and cardiovascular treatment during the last decade; and
- survival and cardiovascular mortality have improved in patients treated with HD.

**What this study adds?**

- between 2006–07 and 2014–15, the proportion of patients treated with haemodiafiltration, at least three HD sessions/week, non-calcium phosphate binders, cinacalcet and vitamin D3, and who had a working fistula increased;
- in incident HD patients, all-cause mortality and major cardiovascular event rate decreased by 6 and 4%, respectively, every 2 years, and mortality also improved in comparison with the general population; and
- adjustment for treatment practice changes annulled the statistically significant associations with both mortality and cardiovascular events.

**What impact this will have on practice or policy?**

- our results indicate that we can improve outcomes by promoting the implementation of new therapeutic advances and by efforts making these advances available for the entire dialysis population.

outcomes in pivotal clinical trials [12–15], the accumulated changes in treatment strategies may nevertheless have had a positive impact on patient survival. However, this has not been comprehensively evaluated, as it requires detailed serial registrations of patients, treatments and outcomes in large representative populations, and the need to consider not only the possible effects of implementation of therapies over time, but also the changes in patient characteristics and comorbidities as well as the parallel temporal changes in mortality in the population at large.

The objective of this study was to describe the gradual implementation of therapeutic advances and the time-related changes in all-cause mortality and major cardiovascular events (MACEs) in a contemporary nationwide register of incident HD patients. We contrasted these changes against the overall health improvements of the general population and further evaluated apparent associations between the implementation of new treatments and the changes in short (1 year) and long-term (2 years) outcomes.

## MATERIALS AND METHODS

### Study population

This observational cohort study is based on the Swedish Renal Registry (SRR), which is a nationwide register of patients with CKD referred to nephrologists in Sweden [16]. SRR has registered initiation of kidney replacement therapies and changes between treatment modalities since 1991. Since 2002, the SRR also collects yearly information about clinical parameters, laboratory measures and treatment outcomes of all patients undergoing dialysis treatment in the country. The national coverage of HD clinics is 100% and it has been estimated that >95% of the HD patients are included in this follow-up [16].

This study included all incident HD patients registered between 1 January 2006 and 31 December 2015. This period was chosen because national collection of data by the Swedish drug prescription register (which is nationwide register of dispensed medications) started in 2005, and because this was the most recent dataset at the time of analysis with all individuals having a minimum of 2 years of follow-up (hence follow-up ended in 2018). We excluded patients with missing information on age or sex ($n = 30$), with a pre-emptive kidney transplant ($n = 873$) or with <3 months on chronic dialysis ($n = 701$) at the time of registration (Supplementary data, Figure S1), leaving 6612 incident cases for analysis. All patients were informed about their participation in the registry and were able to opt-out. The National Board of Health and Welfare approved the merging of data from these registries, and the regional ethics committee in Stockholm approved the study protocol.

The yearly registration consists of data from an arbitrary mid-week dialysis session between September 15 and October 15. Patient demographics, clinical characteristics and selected routine laboratory values were registered in the SRR protocol by the participating clinics. Comorbidity history was registered by pre-defined forms in SRR and enriched with information from the National Patient Registry, which contains a complete collection of all diagnoses issued since inception of the International Classification of Diseases 10th revision system in 1997 (Supplementary data, Table S1). Information on concomitant medication use was collected in the SRR protocol and enriched with information from the Swedish Drug Dispensation Registry [17], with contains complete collection of all prescribed drugs dispensed at Swedish pharmacies. Information on HD treatment characteristics [such as dialysis duration, ≥3 HD sessions per week, fistula/graft, standard $K_t/V$ and use of haemofiltration (HF) or haemodiafiltration (HDF)] came directly from the SRR protocol as entered by the participating clinics.

### Outcome definitions

The study outcomes were all-cause mortality and MACEs (composite of cardiovascular mortality, myocardial infarction, hospitalization for heart failure and stroke) within 1 or 2 years from incident dialysis (Supplementary data, Table S2). Vital status was obtained from the Swedish Population register, which has complete national coverage and essentially no loss to follow-up, or otherwise ended on 1 January 2018. All patients thus had 2 years of follow-up.

### Statistical analysis

The 10-year study period was divided into 2-year blocks and individual-level data were used for analysis. The rationale for using 2-year blocks was the need for adequate numbers of study outcomes in order to provide adequate precision and narrow confidence intervals (CIs) when comparing standardized incidence rates (SIRs) between time periods and allow adjustments for multiple baseline characteristics and treatments. Continuous variables are displayed as mean ± standard deviation (SD) and categorical variables as proportions. Differences over time were tested by Jonckheere–Terpstra trend test for categorical variables and with linear-by-linear trend test for continuous data.

SIRs of study outcomes after 1 and 2 years were calculated using logistic regression models to account for the effect of differences in patient characteristics throughout the observation period. Stepwise adjustment for explanatory variables included (i) crude; (ii) age and sex; and (iii) baseline comorbidities [hypertension, diabetes, CVD, stroke, atrial fibrillation, chronic obstructive pulmonary disease (COPD), rheumatoid disease and cancer]. Covariates were selected based on biological plausibility as confounders.

Time-to-event was graphically displayed by Kaplan–Meier curves. To assess the effect of time on outcome, a similar standardization analysis was performed with the simplifying assumption of a constant hazard ratio (HR) for moving one 2-year time block forward, facilitating the computation of CIs for the trend. Cox-regression models (for 1- and 2-year events) were fitted. Stepwise adjustments were performed as (i) crude; (ii) age and sex; (iii) baseline comorbidities; and (iv) medical treatments and dialysis treatment characteristics.

In order to account for mortality changes in the underlying background population, standardazied incidence rate ratios (sIRR) were also calculated, using an age-, sex- and calendar-matched general population from Statistics Sweden (www.scb.se). Analyses were performed using R (https://www.r-project.org) and Stata version 15.0 (StataCorp, College Station, TX, USA).

## RESULTS

### Changing clinical characteristics

A total of 6612 patients (Supplementary data, Figure S1) initiated HD in Sweden between 2006 and 2015. During this 10-year time period, there were no changes in the mean age (65 ± 15 years), and about one-third of patients were women (33%). Whereas body mass index, parathyroid hormone and the proportion of some comorbidities (cerebrovascular disease including stroke, atrial fibrillation and history of cancer) increased, there was a statistically significant decreasing trend for mean diastolic blood pressure, serum haemoglobin, PO4 and albumin during the investigated period (Table 1).

### Changing treatments and medications

Between 2006 and 2015, there was a marked increase in the proportion of patients undergoing HF and HDF, from 5% to 30%. As convective therapies became more prevalent, the proportion of patients with a high convection volume (>23 L) decreased, from 56% to 48%. There was a gradual increase in the proportion of patients with three or more HD sessions per week (from 53% to 62%), and, correspondingly, the mean UF rate also decreased over time, from median 4.6 to 3.8 mL/body weight (BW)/h. The proportion of patients with a working fistula increased from 41% to 48% (Table 2 and Figure 1). The use of beta-blockers and statins remained stable over the period. While the use of angiotensin-converting enzyme inhibitor (ACEi)/angiotensin-receptor blocker (ARB) (from 60% to 52%) and diuretics (from 82% to 77%) tended to decrease, the use of Ca channel blockers (CCB) (from 64% to 72%) and other antihypertensive drugs (from 16% to 25%) increased. The use of medications related to mineral bone disorders changed substantially; Ca-free PO4 binders (from 41% to 58%), cinacalcet (from 2% to 5%) and vitamin D3 (from 64% to 70%) increased, while the use of Ca-containing supplements markedly decreased (from 63% to 47%) (Table 2 and Figure 1).

### Changes in death and MACE rates

Between 2006 and 2015, there was a drop in 1-year (from 16% to 13%) and 2-year (from 30% to 25%) mortality and 2-year MACE incidence (from 29% to 24%) (Table 3). The improvements in mortality occurred mainly during the first 6 years, while MACE incidence decreased over the entire follow-up period. We also observed a reduction in the 2-year CVD death rate from 14% to 10%. During the same period, there was no apparent change in the 1-year incidence of MACE.

After adjusting for changes in age, sex and comorbidities over time, the 1-year SIR of death decreased from 13.2% in 2006–07 to 11.1% in 2014–15, corresponding to a 16% reduction in overall mortality (Table 3 and 4). The improvements in both mortality and MACE were more pronounced when modelling the adjusted SIR over 2 years; mortality improved markedly, from 25.5% to 20.3% (a reduction by 20%), whereas MACE incidence fell from 24.9% to 21.0% (a 15% reduction) (Figure 2). Sensitivity analyses including all incident patients starting HD (adding those with <3 months on dialysis) showed even stronger trends for both 1- and 2-year outcomes (Supplementary data, Table S3).

The multivariable effect of moving a 2-year time block forward on the 1-year outcomes, showed that mortality improved by 6% (HR = 0.94, 95% CI 0.90–0.99) and MACE risk improved by 4% (HR = 0.96, 95% CI 0.92–1.00) after adjusting for changes in age, sex and baseline comorbidity (Figure 3). The

**Table 1. Baseline characteristics for incident chronic HD patients (>3 months on dialysis) in Sweden between 2006 and 2015**

| Time period | 2006–07 | 2008–09 | 2010–11 | 2012–13 | 2014–15 | P for trend |
|---|---|---|---|---|---|---|
| *n* | 1372 | 1299 | 1323 | 1240 | 1378 | |
| Age, years | 65 (15) | 65 (15) | 64 (16) | 65 (15) | 65 (15) | 0.2 |
| Women, % | 34 | 36 | 33 | 32 | 33 | 0.4 |
| BMI, kg/m$^2$ | 25.7 (5.1) | 26.2 (5.9) | 26.6 (5.7) | 26.9 (5.9) | 27.1 (6.1) | <0.001 |
| Systolic blood pressure, mmHg | 145 (26) | 143 (26) | 142 (24) | 144 (23) | 144 (24) | 0.2 |
| Diastolic blood pressure, mmHg | 77 (15) | 75 (15) | 74 (14) | 74 (15) | 73 (14) | <0.001 |
| Laboratory values | | | | | | |
| Ca, mmol/L | 2.4 (0.3) | 2.4 (0.2) | 2.4 (0.2) | 2.4 (0.2) | 2.4 (0.3) | 0.1 |
| PO4, mmol/L | 1.6 (1.4–2.0) | 1.6 (1.3–1.9) | 1.6 (1.3–1.9) | 1.6 (1.3–1.9) | 1.5 (1.3–1.9) | <0.001 |
| PTH, pmol/L | 16.0 (8.0–31.0) | 18.8 (9.4–32.0) | 21.1 (11.6–35.1) | 20.0 (11.0–34.0) | 21.0 (11.0–36.1) | <0.001 |
| Albumin, g/L | 35.0 (32.0–39.0) | 35.0 (31.0–38.0) | 35.0 (31.0–38.0) | 34.0 (31.0–38.0) | 34.0 (31.0–37.0) | <0.001 |
| CRP, mg/L | 7.5 (3.0–16.0) | 7.0 (3.0–16.0) | 6.0 (3.0–15.0) | 5.1 (3.0–15.0) | 5.0 (2.9–13.6) | 0.01 |
| Ferritin, pmol/L | 384.0 (227.0–650.0) | 388.0 (210.0–610.0) | 440.0 (243.0–680.0) | 360.0 (204.0–639.0) | 407.0 (213.0–661.5) | 0.68 |
| Haemoglobin, g/L | 117 (14) | 115 (14) | 113 (14) | 114 (14) | 112 (14) | <0.001 |
| Comorbidities, % | | | | | | |
| Hypertension | 92 | 91 | 92 | 93 | 92 | 0.4 |
| Diabetes mellitus | 39 | 35 | 38 | 39 | 40 | 0.06 |
| CVD | 40 | 41 | 39 | 43 | 41 | 0.4 |
| Congestive heart failure | 17 | 18 | 17 | 19 | 19 | 0.2 |
| Myocardial infarction | 13 | 14 | 14 | 16 | 14 | 0.4 |
| Peripheral vascular disease | 13 | 13 | 14 | 14 | 13 | 0.9 |
| Cerebrovascular disease | 13 | 13 | 12 | 16 | 15 | 0.01 |
| Stroke | 10 | 10 | 9 | 12 | 12 | 0.02 |
| Atrial fibrillation | 7 | 9 | 8 | 11 | 11 | 0.001 |
| COPD | 6 | 5 | 6 | 6 | 7 | 0.4 |
| Rheumatoid disease | 4 | 3 | 5 | 3 | 4 | 0.4 |
| Cancer (within 3 years) | 10 | 9 | 9 | 12 | 13 | 0.01 |

Numbers are % or mean (SD) or median (interquartile range), as appropriate. P-values were tested with Jonckheere–Terpstra trend test for categorical variables and with linear-by-linear trend test for continuous data. PTH, parathyroid hormone; CRP, C-reactive protein.

**Table 2. Medications and dialysis treatment characteristics for incident HD patients (>3 months on dialysis) in Sweden between 2006 and 2015**

| Time period | 2006–07 | 2008–09 | 2010–11 | 2012–13 | 2014–15 | P for trend* |
|---|---|---|---|---|---|---|
| *n* | 1372 | 1299 | 1323 | 1240 | 1378 | |
| Dialysis treatment characteristics | | | | | | |
| HDF/HF, % | 5 | 10 | 15 | 23 | 30 | <0.001 |
| Infusion volume, L | 25 (19–30) | 24 (19–30) | 22 (17–27) | 21 (17–25) | 22 (18–26) | <0.001 |
| Infusion volume >23 L, % | 56 | 61 | 43 | 37 | 48 | <0.001 |
| UF rate, mL/BW/h | 4.6 (1.4–7.5) | 4.4 (1.3–7.3) | 4.8 (1.4–7.3) | 4.2 (1.2–6.8) | 3.8 (0.5–6.9) | <0.001 |
| Three or more sessions/week, % | 53 | 59 | 64 | 63 | 62 | <0.001 |
| Standard $K_t/V$ | 2.2 (0.7) | 2.2 (0.5) | 2.2 (0.5) | 2.3 (0.5) | 2.3 (0.5) | 0.2 |
| Vascular access | | | | | | |
| Fistula, % | 41 | 43 | 47 | 48 | 48 | 0.02 |
| Catheter, % | 53 | 53 | 48 | 47 | 47 | – |
| Graft, % | 6 | 4 | 6 | 5 | 5 | – |
| Medication use (%) | | | | | | |
| ACEi/ARBs | 59 | 58 | 60 | 54 | 52 | <0.001 |
| Beta-blockers | 70 | 69 | 70 | 71 | 72 | 0.5 |
| CCB | 64 | 64 | 70 | 72 | 68 | <0.001 |
| Other antihypertensive drugs | 16 | 19 | 22 | 25 | 25 | <0.001 |
| Diuretics | 81 | 78 | 82 | 80 | 77 | 0.03 |
| Statins | 46 | 46 | 49 | 49 | 49 | 0.2 |
| Erythropoietin/darbepoetin | – | 81.4 | 81.7 | 80.0 | 80.2 | <0.001 |
| ESA dose/week | – | 4000 (40–8000) | 4000 (40–8000) | 3000 (40–8000) | 2000 (40–8000) | <0.001 |
| ESA dose/kg/week | – | 51 (0.6–116) | 51 (0.5–114) | 34 (0.5–97) | 28 (0.5–92) | <0.001 |
| Iron (oral/IV) | – | 66 | 68 | 64 | 62 | <0.001 |
| Non-Ca PO4 binders | 41 | 45 | 52 | 56 | 58 | <0.001 |
| Ca supplements | 63 | 59 | 54 | 49 | 47 | <0.001 |
| Vitamin D3 supplements | 64 | 67 | 68 | 70 | 68 | 0.02 |
| Cinacalcet | 2 | 4 | 5 | 5 | 4 | 0.001 |

Numbers are % or mean (SD) or median (interquartile range), as appropriate. *P-values were tested with Jonckheere–Terpstra trend test for categorical variables and with linear-by-linear trend test for continuous data. IV, intravenous.

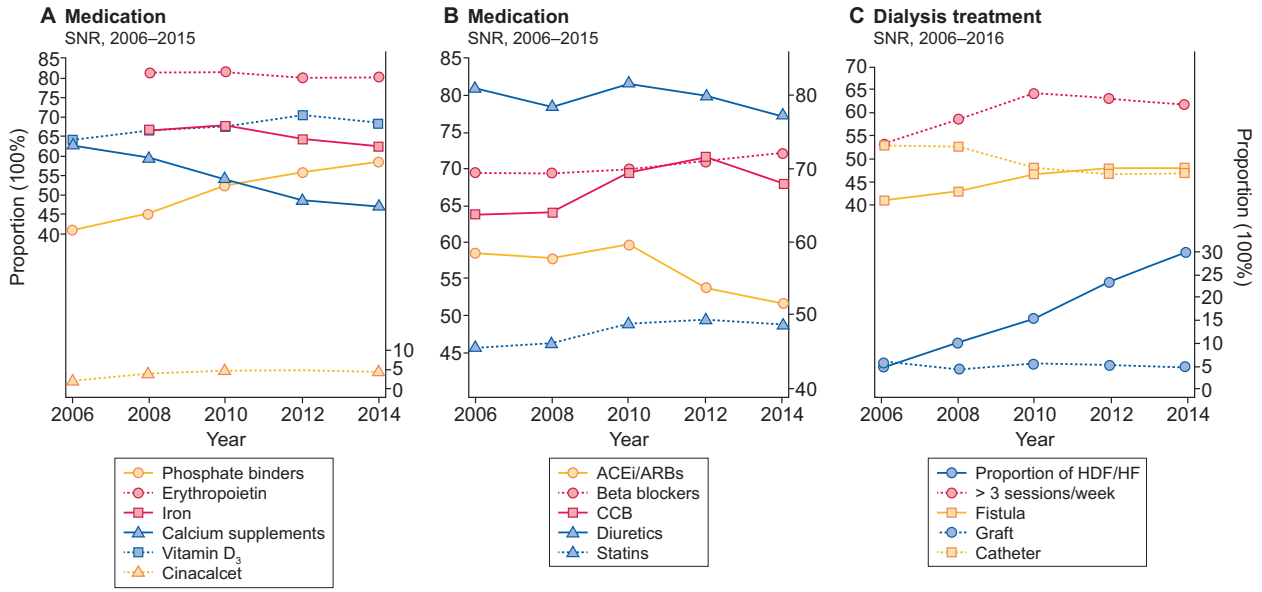


**FIGURE 1:** Changes in (**A** and **B**) medication use and (**C**) dialysis treatment characteristics in Swedish HD patients during 2006–15.

**Table 3. One- and 2-year outcomes among HD patients according to admission year**

| Time period | 2006–07 | 2008–09 | 2010–11 | 2012–13 | 2014–15 | P for trend* |
|---|---|---|---|---|---|---|
| *n* | 1372 | 1299 | 1323 | 1240 | 1378 | |
| 1-year outcomes (%) | | | | | | |
| Death | 15.9 | 15.0 | 11.1 | 15.2 | 13.4 | 0.01 |
| Percent change from 2006 to 2007 | – | *−6* | *−30* | *−4* | *−16* | |
| MACE[a] | 19.2 | 17.3 | 17.1 | 17.7 | 17.1 | 0.6 |
| Percent change from 2006 to 2007 | – | *−10* | *−11* | *−8* | *−11* | |
| Congestive heart failure | 6.6 | 6.1 | 6.1 | 6.4 | 7.4 | 0.6 |
| Myocardial infarction | 6.0 | 4.2 | 5.1 | 4.8 | 4.4 | 0.2 |
| Stroke | 3.7 | 3.9 | 4.4 | 3.7 | 3.3 | 0.7 |
| CVD | 7.2 | 6.3 | 5.4 | 6.5 | 6.2 | 0.5 |
| 2-year outcomes, % | | | | | | |
| Death | 30.3 | 26.3 | 22.1 | 26.4 | 24.7 | <0.001 |
| Percent change from 2006 to 2007 | – | *−13* | *−27* | *−13* | *−18* | |
| MACE[a] | 29.0 | 26.8 | 25.0 | 25.8 | 24.1 | 0.04 |
| Percent change from 2006 to 2007 | – | *−8* | *−14* | *−11* | *−17* | |
| Congestive heart failure | 9.3 | 8.6 | 8.6 | 8.7 | 9.7 | 0.8 |
| Myocardial infarction | 9.0 | 7.5 | 7.3 | 7.6 | 7.0 | 0.3 |
| Stroke | 6.0 | 5.8 | 6.7 | 5.8 | 4.6 | 0.2 |
| CVD death | 14.3 | 11.5 | 10.1 | 11.1 | 9.9 | 0.01 |

Numbers are presented as %.
[a]MACE, included CVD, hospitalization of re-infarction, stroke and heart failure.
*P-values were tested with Jonckheere–Terpstra trend test for categorical variables and with linear-by-linear trend test for continuous data.

adjusted 2-year mortality (HR = 0.93, 95% CI 0.90–0.96) and MACE risk (HR = 0.93, 95% CI 0.90–0.97) also demonstrated improvements by 7% every 2 years. After additional adjustments for changes in HD and medication treatment practices over time, there was no longer any apparent improvement in either 1-year mortality (HR = 1.00, 95% CI 0.92–1.09) or MACE (1.00, 95% CI 0.94–1.06) (Figure 3). Similar changes were observed when adjusting for treatment practices over time for the 2-year outcomes.

## Mortality of HD patients compared with the general population

The 1- and 2-year mortalities of the HD patients were also compared with an age-, sex- and calendar-year-matched Swedish background population. Compared with this background population, the risk of death among HD patients was 6 times higher in 2006–07 [sIRR = 6.0, 95% CI 5.3–6.9] and decreased to 5.6 times higher in 2014–15 (sIRR = 5.6, 95% CI 4.8–6.4), corresponding to a statistically significant reduction in

**Table 4. SIR and 95% CI of 1- and 2-year risk of death and MACE (included CVD, hospitalization of re-infarction, stroke and heart failure)**

| | 1-year outcomes | | | 2-year outcomes | | |
|---|---|---|---|---|---|---|
| Time period<br>Death | Crude<br>SIR (%) (95% CI) | +Age, sex<br>SIR (%) (95% CI) | +Comorbidity<br>SIR (%) (95% CI) | Crude<br>SIR (%) (95% CI) | +Age, sex<br>SIR (%) (95% CI) | +Comorbidity<br>SIR (%) (95% CI) |
| 2006–07 | 15 (14.0–17.8) | 15.8 (13.9–17.7) | 13.2 (11.9–14.8) | 30.3 (27.9–32.8) | 30.0 (27.7–32.3) | 25.5 (23.9–27.5) |
| 2008–09 | 15 (13.1–17.0) | 14.6 (12.8–16.4) | 12.3 (10.9–13.8) | 26.3 (23.9–28.7) | 25.5 (23.3–27.8) | 22.6 (20.9–24.5) |
| 2010–11 | 11.1 (9.4–12.8) | 11.3 (9.6–13.0) | 9.6 (8.3–10.8) | 22.1 (19.9–24.4) | 22.6 (20.4–24.8) | 19.3 (17.6–21.0) |
| 2012–13 | 15.2 (13.2–17.2) | 15.1 (13.2–17.1) | 12.9 (11.4–14.6) | 26.4 (23.9–28.8) | 26.2 (23.9–28.6) | 21.8 (20.2–23.9) |
| 2014–15 | 13.4 (11.6–15.1) | 13.7 (11.9–15.5) | 11.1 (9.8–12.5) | 24.7 (22.4–26.9) | 24.9 (22.7–27.1) | 20.3 (18.7–22.1) |
| MACE | | | | | | |
| 2005–06 | 19.2 (17.1–21.3) | 19.3 (17.3–21.4) | 16.1 (14.5–17.7) | 29.0 (26.6–31.4) | 28.9 (26.6–31.3) | 24.9 (23.2–26.8) |
| 2007–08 | 17.3 (15.3– 19.4) | 17.0 (15.0–19.0) | 14.1 (12.7–15.7) | 26.8 (24.4–29.2) | 26.4 (24.1–28.8) | 22.7 (21.1–24.8) |
| 2009–10 | 17.1 (15.1–19.1) | 17.5 (15.5–19.6) | 14.8 (13.4–16.6) | 25.0 (22.7–27.4) | 25.6 (23.3–28.0) | 21.9 (20.3–23.8) |
| 2011–12 | 17.7 (15.5–19.8) | 17.6 (15.5–19.7) | 14.3 (12.8–15.9) | 25.8 (23.4–28.2) | 25.6 (23.3–28.0) | 20.8 (19.2–22.8) |
| 2013–14 | 17.1 (15.1–19.1) | 17.2 (15.2–19.2) | 15.0 (13.4–16.6) | 24.1 (21.8–26.4) | 24.1 (21.9–26.3) | 21.0 (19.3–22.8) |

Adjustments considered age and sex and comorbidities (hypertension, diabetes, CVD, stroke, atrial fibrillation, COPD, rheumatoid disease and cancer) within 3 years.

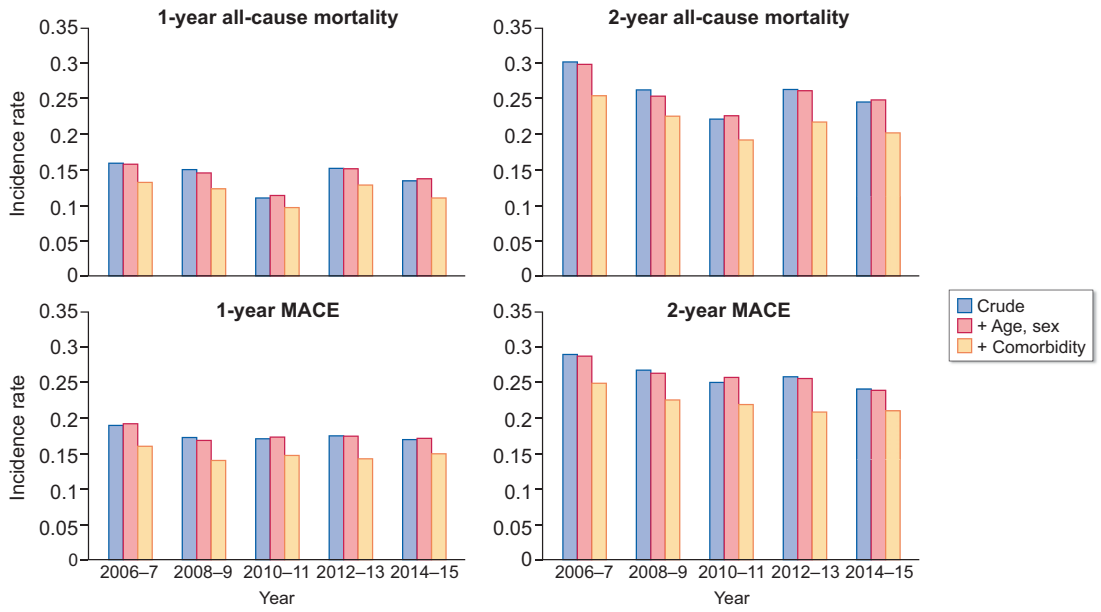


**FIGURE 2:** Standardized 1- and 2-year deaths (all-cause) and MACE in Swedish dialysis patients during 2006–15. Comorbidity included hypertension, diabetes, CVD, stroke, atrial fibrillation, COPD, rheumatoid disease and cancer within 3 years.

sIRR by 8%. A similar, and somewhat stronger trend was observed when evaluating 2-year mortality (Supplementary data, Table S4). The long-term follow-up, beyond 2 years, showed that the reductions in mortality and MACE were sustained over time, with substantially lower event rates for each more recent admission period (Figure 4).

## DISCUSSION

This study describes the development of treatment practices and outcomes in all patients starting HD in an entire country for >10 years. From 2006 to 2015, there was a gradual implementation of newer, or guideline-recommended treatments; more patients were treated with convective HD such as HDF, had more frequent HD with lower UF rates, and had more often a working fistula. A higher proportion of patients received newer drugs to manage their CKD-mineral bone disorders, while the dosages of erythropoietin-stimulating agents (ESAs) declined. In parallel, the 1- and 2-year survival improved progressively by 16 and 18%, respectively, and the rate of MACE decreased by 11 and 17%. The multivariable analyses suggested that the improvements in outcomes could, at least in part, be explained by the increasing implementation of these therapeutic advances, as the differences in mortality and MACE were almost eliminated by adjustments for the changes of these treatments. Finally, the excess death of HD patients decreased compared with the background population over time, albeit modestly.

Our observation of improved survival over time agrees with and expands previous time-trend studies from Europe and the USA [2, 18–20], and we present the novel finding of lower MACE risk over time. Our results showing improved mortality compared with the general population despite an increasing comorbidity burden also agree with two contemporary reports

from the USA and Europe assessing excess mortality in patients on kidney replacement therapy (KRT) [21, 22]. Conversely, in two slightly older studies, patients on dialysis had a worse prognosis over time and as compared with the general population [3, 18]. Both of these two older studies had data stretching as far back as the 1990s, and over the time periods investigated in those studies, access to KRT, age distribution and underlying comorbidity status changed substantially [2]. Thus, it may be difficult to entirely adjust for the profound changes in patient selection, indications for dialysis treatment, type of dialysis modality and drug therapy patterns over 30 years.

In our study, we found support for an association between the temporal changes in treatment strategies and the observed improvement in outcomes. There were no major changes in the incidence in peritoneal dialysis that would impact on the overall case-mix of the HD population. The number of kidney transplantations increased in Sweden, but the removal of healthier patients from the HD cohort would rather lead to a more conservative estimate. However, our observational approach precludes any causal inference and makes it impossible to ascertain the specific contribution of each individual treatment component on outcomes. Only an adequately designed controlled trial with random treatment assignments can estimate the effect of a specific treatment and avoid the risk of selection bias inherent to observational studies. Our findings are in line with previous cross-sectional analyses from the Dialysis Outcomes and Practice Patterns Study suggesting that differences in practice patterns explain much of the variation in survival across HD centres and countries [23], and that reaching guideline target attainment is associated with improved survival [24].

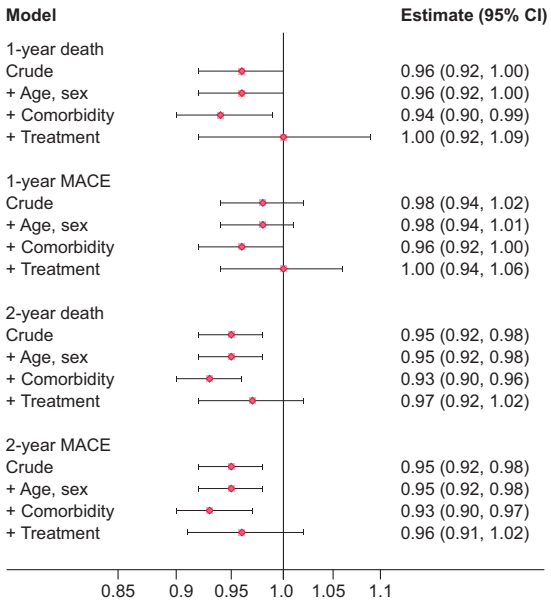


**FIGURE 3:** HRs for the association between 2 years change in time-period and outcomes (1- and 2-year) death and MACEs for incident patients on HD in Sweden during 2006–15. Time period used as continuous variable. Comorbidity included hypertension, diabetes, CVD, stroke, atrial fibrillation, COPD, rheumatoid disease and cancer within 3 years. Treatment included the use of ACE/ARBs, beta-blockers, CCB, other antihypertensive agents, diuretics, statins, PO4 binders, erythropoietin, iron, Ca supplements, vitamin D3, cinacalcet, dialysis duration, ≥3 HD sessions/week, fistula/graft, $K_t/V$ and use of HDF.

We recognize that there is still a debate regarding the effectiveness of some treatments. For instance, although several reports have indicated that HDF with a high exchange volume is superior to conventional HD, the evidence is still controversial [4, 25], and trials are on-going [26]. Furthermore, not all trials have seen better outcomes with more frequent dialysis [14], but at least one trial [27] and various observational studies [6, 28] support that more frequent dialysis regimes may have a positive effect on complications and survival. In our study, the progressive increase in HD frequency was not coupled with parallel changes in standard $K_t/V$ similar to what was seen in trials [14, 27]. Nonetheless, in line with results from the Hemodialysis study (HEMO) [13], we do not believe that any positive effect would be due to increased dialysis dose, but rather by decreasing the long interdialytic gap [29] or reducing the UF rate [30]. On the other hand, the benefit of arteriovenous fistulas over both grafts and central venous catheters is well established [5]. Practice traditions may play an important role for differences in the prevalence of fistulas between single centres [31], and differences in vascular access practices have been shown to account for as much as 30% of the mortality difference in HD patients in the USA compared with Japan [32].

The abovementioned changes in treatment practices observed in our study were coupled with changes in biomarker levels. For example, in accordance with guidelines recommending stricter PO4 control [33], the mean PO4 value fell during the observation period as the use of calcimimetics, vitamin D3

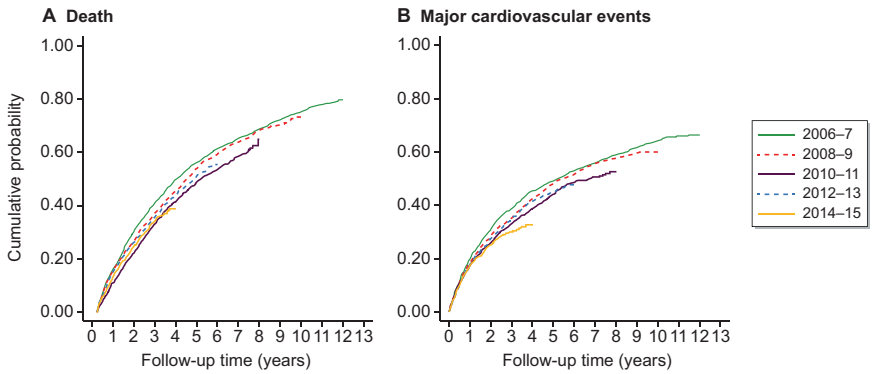


**FIGURE 4:** Long-term outcomes according to year of admission.

and Ca-free PO4 binders increased. Although we cannot infer causality here either, it is plausible that any treatment effect would be mediated through their respective biomarker change. Lower PO4 levels, as exemplified above, have previously been independently associated with lower cardiovascular event rates and improved survival [34, 35], although no single study has proved that the use of any PO4 binder (versus none) offers a clear survival benefit. Another example is the decreasing haemoglobin levels and erythropoietin dosages observed in our study, following evidence from trials suggesting better survival and lower cardiovascular event rates with a more restrained erythropoietin policy [36–38]. Some of the treatment changes we observed, such as for blood pressure medications, were likely attributed to differences in case-mix over the period. The evidence regarding the association between clinical outcomes and blood pressure treatments in HD patients is poor and conflicting [39–41], and although the use of ACEi/ARB decreased over the period, the overall use was quite high as compared with other cohorts [39].

There are strengths with this analysis, the main being the inclusion of all incident HD patients from a country with universal healthcare, no loss to follow-up, and extensive information regarding dialysis treatment characteristics, comorbid conditions and drug dispensations. This made it possible to study changes in practice patterns over a 10-year period when new dialysis treatments and guidelines were being implemented gradually in an overall relatively stable nationwide inception cohort. We also acknowledge some limitations; the definition of covariates recorded in the registry may have changed over time. Also, the use of diagnostic codes is an administrative process that does not quantify the severity of the underlying disorders. Furthermore, the definition and reporting of comorbidities in the community may have also changed over time. We do not have information on estimated glomerular filtration rate at dialysis initiation for the entire study period, but recent data in the SRR indicate that there have been no major changes over the past 5 years in when dialysis is initiated. We do not have information on ethnicity, as this is forbidden by Swedish law. Results thus only apply to Swedish practice during 2006–16, and extrapolation to other countries and periods should be made with caution. This said, improvements in survival have been observed in both Europe and the USA, and changes in practice patterns are likewise observed globally [23].

In conclusion, gradual implementation of therapeutic advances and guideline-recommended treatments in routine HD practice over the last decade in Sweden was associated with a parallel reduction in the short-term risk of death and MACE that was not explained by improved survival in the general population. While a long history of negative trials in HD patients may have generated some therapeutic nihilism, this study suggests that we are moving in the right direction. However, the risk for mortality and cardiovascular complications in this population remains unacceptably high, underlining that still much must be done for these patients.

## SUPPLEMENTARY DATA

Supplementary data are available at ndt online.


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## AUTHORS' CONTRIBUTIONS

All authors were involved in the study conception; study design was by M.E., H.X. and J.-J.C.; statistical analysis was carried out by H.X. and interpretation of data was performed by all authors; drafting the article was by M.E. and H.X., while revising it and providing intellectual content of critical importance to the work described was carried out by all authors.

## CONFLICT OF INTEREST STATEMENT

J.-J.C. acknowledges consultancy for Baxter and AstraZeneca, and grant support to Karolinska Institutet from AstraZeneca, Viforpharma and Astellas, all outside the submitted work. B.L. is employed by Baxter Healthcare. M.E. reports payment for advisory boards (Astellas, Astra Zeneca and Vifor Pharma) and payment for lectures (Astellas, Vifor Pharma) outside the submitted work. None of the other authors declares relevant financial interests that would represent a conflict of interest.

## DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on a reasonable request to the corresponding author.

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