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SUDDEN DEATH IN END STAGE RENAL DISEASE: COMPARING HEMODIALYSIS VERSUS PERITONEAL DIALYSIS

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Author Comments:	Date 11 October 2016 Dear Editor in chief, I am submitting the following manuscript for consideration in Clinical and Experimental Nephrology: "SUDDEN DEATH IN END STAGE RENAL DISEASE: COMPARING HEMODIALYSIS VERSUS PERITONEAL DIALYSIS" My co-authors have all contributed to this manuscript and approve of this submission. The results presented in this paper have not been published previously in whole or part, except in abstract form. I have communicated with all of my co-authors and obtained their full disclosures. A disclosure statement is also included within my manuscript before the reference section. My co-authors and I declare no conflicts of interest. Individual contributions of authors: Simonetta Genovesi: study design, interpretation of results, writing of the manuscript Silvio Volmer Bertoli,, Antonio Vincenti: interpretation of results, writing of the manuscript Luca Porcu, Valter Torri: statistical analysis Maria Carmen Luise , Hilary Riva , Elisa Nava , Gina Contaldo , Andrea Stella , Claudio Pozzi , Patrizia Ondei , Claudio Minoretti , Maurizio Gallieni , Giuseppe Pontoriero , Ferruccio Conte: data collection Sincerely, Dr. Simonetta Genovesi Dipartimento di Medicina e Chirurgia, Università di Milano-Bicocca Via Cadore 48, 20900, Monza (MB), Italy tel: +39 039 2332426 Fax: +390392332376 Email: simonetta.genovesi@unimib.it
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SUDDEN DEATH IN END STAGE RENAL DISEASE: COMPARING HEMODIALYSIS VERSUS PERITONEAL DIALYSIS

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Abstract

Background: Hemodialysis (HD) population show a high incidence of sudden death (SD), but few data are available on this issue in peritoneal dialysis (PD) patients. Aim of the study was to evaluate total and sudden mortality in a cohort of dialysis patients, comparing HD versus PD.

Methods: Clinical data of 2072 dialysis patients were retrospectively collected. The Hazard Ratio of total (HR) and sudden ($HR_{cpRisk)}$ mortality were estimated by Cox, and Fine and Gray regression models.

Results: HD patients had a greater number of comorbidities (p=0.02). Deaths were 626/1823 in HD and 62/249 in PD. PD patients had a lower risk of death than HD patients at the start of dialysis (HR 0.13, 95%CI 0.05-0.33, p-value<0.001), however the advantage decreased with time ($HR_{[linear\ interaction\ with\ time]}$ 1.33, 95%CI 1.20-1.46, p-value<0.001). Mortality predictors were left ventricular ejection fraction<35% (p-value <0.001), older age (p-value<0.001), ischemic heart disease (p-value=0.01), diabetes mellitus (p-value=0.01), previous stroke (p-value=0.02) and atrial fibrillation (p-value=0.02). The HR for comorbidities was higher in PD patients and the interaction for dialysis modality was significant for ischemic heart disease and atrial fibrillation (p-value=0.01 and 0.03, respectively). SD were 84:71 in HD and 13 in PD (12.1% and 22.8% of all causes of death, respectively). A no significant risk of SD among PD compared to HD patients was detected (HR_{cpRisk} 1.21, 95%CI 0.66-2.22, p-value=0.53). SD predictors were older age (p-value=0.03), ischemic heart disease (p-value=0.02) and left ventricular ejection fraction<35% (p-value=0.04), without interactions for treatment.

Conclusions: HD patients showed a greater presence of comorbidities and reduced survival compared to PD patients, however, the incidence of SD does not differ in the two populations.

Key words: hemodialysis, mortality, peritoneal dialysis, regression models, sudden death

Introduction

Cardiovascular disease is the leading cause of death in dialysis patients and sudden death (SD) represents a significant proportion of overall mortality in both hemodialysis (HD) and peritoneal dialysis (PD) patients. Sudden death accounts for about 37.0% of all causes of death in patients with end stage renal disease (ESRD) and for 65.0% of cardiovascular deaths. The rate of cardiac arrest is 7.3% in HD and 6.0% in PD patients [1]. There is evidence showing that left ventricular ejection fraction (LVEF) is the best predictor of total and sudden mortality in patients with cardiac disease, but without ESRD [2-4]. Less clear are the factors associated with SD in patients undergoing dialysis. It was shown that the high incidence of SD in HD patients could be partly explained by the rapid changes of plasma electrolytes related to the intermittent nature of this dialysis technique [5, 6]. However, in PD patients factors that can cause SD, despite continuous treatment, are not yet clear and few studies were carried out on this topic. Moreover, there are no data comparing the incidence of SD in HD patients with those undergoing PD.

In the last few years several studies comparing the risk of total mortality in HD patients and patients on PD were performed. Almost all these studies showed a better survival during the first period from the start of dialysis in PD than in HD patients, but it is unclear whether the dialysis modality is associated with greater long-term survival [7-12].

The purpose of the present study is to assess, in a population of ESRD patients, the relationship between the different dialysis modality (HD versus PD) and overall and sudden mortality and to identify predictors of outcomes for each dialysis modality.

Methods

In this Italian multicenter retrospective study all dialysis patients (undergoing HD or PD) referred to 7 dialysis centers of Lombardy, alive on the 1st of January 2010 or starting dialysis between the 1st

January 2010 and the 31th of January 2013 (recruitment time), were enrolled and their clinical charts were revised. Patients were considered eligible for the study only if an echocardiogram with a measured value of left ventricular ejection fraction was available, either obtained within 6 months before recruitment if alive, or 6 months before death if deceased. Information on the presence of the following comorbidities was collected: ischemic cardiac disease, diabetes mellitus, previous stroke and atrial fibrillation. Death causes were derived from medical records. The presence of an implanted cardioverter defibrillator (ICD) was also considered. Sudden death was defined as spontaneous death preceded by a sudden loss of consciousness within 1 h after onset of acute symptoms, even in the presence of pre-existing heart disease, but with unexpected timing and mode. Nephrologists or relatives were interviewed to confirm all cases of SD. Procedures were performed according to the Helsinki declaration for ethics treatment of human subjects.

Statistical analysis

Study endpoints were:

a. Overall Survival defined as the time from the start of dialysis to the time of death from any cause
b. Cause of death
c. Cause-specific Survival defined as the time from the start of dialysis to the time of SD or other cause.

Survival data of patients starting dialysis before the 1st January 2010 and alive on the 1st of January 2010 were left-truncated [13]. In other terms these patients were not considered at risk of death during the interval time between the beginning of dialysis and 1st of January 2010 (i.e. truncation period). Overall Survival distribution was estimated by the product-limit method. A linear time by treatment interaction term was introduced in a Cox regression model to demonstrate formally the curvature over time of the relative hazard function. The average hazard of death per unit time (i.e. each year following dialysis start) was estimated. A fixed-effects meta-regression was fitted to the point and standard error estimate of the average hazard of death per unit time. A meta-regression forest plot was

used to summarize meta-regression results. The Cox regression model was used to evaluate predictors of Overall Survival and to test their interaction with treatment.

In order to estimate the statistical association between the two cohorts of patients (i.e. HD and PD patients) and the specific cause of death (i.e. sudden death) and to identify patient characteristics statistically associated to the specific cause of death, a survival analysis in the presence of competing risks was performed. The Fine and Gray regression model was used to estimate the cause-specific hazard ratio (HR_{cpRisk}).

In the multivariable Cox and Fine and Gray regression models ICD implantation was considered a time-varying treatment.

Survival status was updated on the 31st of January 2014. Median follow-up and its interquartile range (IQ range) were estimated with the reverse Kaplan–Meier method [14]. The *C* completeness index [15] was used in order to quantify the completeness of follow-up at the update of survival status.

Baseline covariate distributions were summarized using descriptive statistics (median and range for continuous variables, and absolute and percentage frequencies for categorical variables). The logistic regression model was used to detect imbalances between baseline covariate distributions.

Statistical analysis was performed using Stata software, version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

(see supplementary material for extended statistical analysis)

Results

Table 1 shows the characteristics of the study population: 249/2072 (12.0%) patients were on PD. There were no significant differences in the prevalence of comorbidities considered, except for atrial fibrillation, which was more prevalent in HD patients (Odds Ratio, OR 1.46 95%CI 1.05-2.02, P=0.024). Hemodialysis patients had a greater number of comorbidities than those on PD (OR 1.18, 95%CI 1.02-1.37, p=0.025). Fifty-two patients (2.5%) received an ICD for primary or secondary SD

prevention, and 10 of them (19.2%) were PD patients. The median duration of follow-up was 1.76 years (IQ range 0.79-3.35 years) in HD patients and 1.94 years (IQ range 0.84-3.34 years) in those on PD (*C* completeness index 98% of the potential time of follow-up in HD patients and 99% in PD patients). The observed deaths were 688: 626/1823 (34.3%) in HD patients and 62/249 (24.9%) in PD patients. One hundred and fifty/626 (24.0%) patients on HD, and 22/62 (35.5%) PD patients died from cardiovascular causes. (Table 2)

Total mortality

The median survival was 3.16 (95%CI 2.82-3.60) years in HD patients and 5.33 (95%CI 4.05 to 6.04) years in patients on PD. Considering only patients alive at 6 months after starting dialysis [early mortality, 13.4% (95%CI 11.3-15.8%) in HD and 4.5% (95%CI 2.2-9.2%) in PD], the prognosis was still better in PD patients [3.88 (95%CI 3.55 to 4.36) versus 5.33 (95%CI 4.59-6.92) years]. Figure 1 shows the survival curves of the two populations: at the start of dialysis the survival of PD patients was higher than that of HD patients (Hazard Ratio, $HR_{[at\ dialysis\ start]}$ 0.41, 95%CI 0.29-0.60, P-value <0.001); however, this advantage tended to decrease with time ($HR_{[linear\ interaction\ with\ time]}$ 1.21, 95%CI 1.11-1.31, P-value<0.001). (Figure 2, panel a). Because the likelihood-ratio test was not significant ($\chi 2$=3.64; df=1; P-value=0.06), the quadratic term was removed from the regression model. The restricted mean at 8 years showed a weaker advantage in comparison to median survival [3.87 (95%CI 3.65-4.08) years in HD patients and 4.81 (95%CI 4.27-5.36) years in PD patients; P-value <0.001].

The analysis relative to the influence of each comorbidity on total mortality in the two cohorts of patients is shown in Table 3. In both populations, factors associated with an increased risk of mortality were older age, LVEF<35% and the presence of ischemic heart disease, diabetes mellitus, previous strokes and atrial fibrillation. The HR for individual comorbidity was higher in patients on PD, and the interaction test for dialysis treatment (HD versus PD) was significant for ischemic heart disease (P-value<0.001), diabetes mellitus (P-value=0.02) and atrial fibrillation (P-value=0.01).

Multivariable analysis confirmed that PD patients had a lower risk of death than HD patients (HR 0.13, 95%CI 0.05-0.33, P-value<0.001) at the start of dialysis, and that the difference was significantly reduced with increasing time ($HR_{[linear\ interaction\ with\ time]}$ 1.33, 95%CI 1.20-1.46, P-value <0.001). The independent association between risk of death and older age, ischemic heart disease, LVEF<35%, diabetes mellitus, previous stroke and atrial fibrillation was also confirmed. An interaction effect between dialysis modality and comorbidities was still present for ischemic heart disease (P-value=0.01) and atrial fibrillation (P-value=0.02). (Table 4)

Sudden death

During follow-up 84 SD occurred. Sudden death, excluding unknown causes, accounted for 22.8% (13/57) of causes of death in PD patients and 12.1% (71/588) in those on HD. There was no significant difference in the incidence of SD among patients on HD compared to PD patients, although the latter showed an increased risk of 23.0% (HR_{cpRisk} 1.23, 95%CI 0.68-2.23, P-value=0.49) (Figure 3). The time from starting dialysis treatment did not significantly affect the HR_{cpRisk} and the incidence of SD in either group ($P\text{-value}_{[linear\ interaction\ with\ time]}$=0.19) (Figure 2, panel b).

Among HD patients who died suddenly, 58/71 (81.7%) had an LVEF>35%, while among PD patients who suffered a SD those with preserved LVEF were 7/13 (53.8%; P-value=0.03). Twenty-two/48 (45.8%) HD patients, in whom the timing of death with respect to the HD session could be established, died during the first inter-dialytic interval and 18/48 (37.5%) during the last long inter-dialytic interval of the week.

The analysis of the influence of each comorbidity on SD risk in the two cohorts of patients is shown in Table 5. Variables associated with a higher incidence of SD in HD patients were older age, presence of LVEF<35%, ischemic heart disease and diabetes mellitus, while in patients on PD, reduced LVEF, previous strokes and, slightly, ischemic heart disease were associated with SD. The interaction test for dialysis treatment (HD versus PD) was not significant for any of the comorbidities considered.

Multivariable analysis showed that factors significantly associated with SD were older age, presence of LVEF<35%, ischemic heart disease and, slightly, diabetes mellitus. The difference in SD incidence was not significantly influenced by dialysis modality (HR_{cpRisk} 1.21, 95%CI 0.66-2.22, P-value=0.53) (Table 6).

Discussion

This study shows that, in an ESRD population, survival is higher in PD than in HD patients. Sudden death incidence, however, is not different in the two cohorts of patients and sudden death, when considering all causes of death, is relatively more frequent in PD than in HD patients.

In the literature, data on mortality risk comparing PD with HD are not univocal [11, 12, 16-19]. It is likely that patients reaching ESRD due to acute renal failure or having worse clinical conditions are preferentially placed on HD. The frailty of these patients may increase early mortality after starting renal replacement therapy [20], however in our study the survival of PD patients still remains higher compared to HD patients, even after eliminating early mortality from the analysis. Nevertheless, this advantage decreases over time from starting dialysis therapy. Moreover, in PD patients, the presence of each comorbidity determines an increase in the risk of death for any cause from 2 to 3 times compared to HD patients, and this finding is particularly evident for ischemic heart disease and atrial fibrillation. This result confirms what had already been observed by other authors [19, 21]. In ESRD patients, the presence of diabetes mellitus and poor glycemic control are often associated with several clinical complications and with an increase of mortality, particularly in PD patients [22-24]. In addition, in the tissues of PD patients, diabetic or not, there is a great deposition of Advanced Glycation End products that predispose to the metabolic syndrome [25], a condition associated with an increased risk of cardiovascular mortality in this population [26]. Several studies demonstrated that in PD patients accelerated atherosclerosis processes are actively present and suggest that

atherosclerosis risk is even higher in PD than in HD patients [27-29].

An increased risk of death in HD patients with atrial fibrillation has been described [30], while there are no data on atrial fibrillation and mortality in PD patients. The HD session may trigger episodes of atrial fibrillation, particularly of the paroxysmal type [31, 32]. It is possible that, in our study population, PD patients had more frequently forms of permanent atrial fibrillation and that this may partly justify the higher risk of death associated with the arrhythmia compared to HD patients. Non-paroxysmal atrial fibrillation, in fact, is usually associated with the presence of cardiac disease and with a highly significant increase in thromboembolism and death [33]. Moreover, HD patients meet their nephrologist three times a week, while PD patients perform clinical checks only monthly. This could create a less effective clinical monitoring of cardiovascular disease in the latter population.

In our population, the incidence of sudden death was independent of dialysis modality and even slightly higher in subjects undergoing PD. Data also show that among all causes of death, sudden death was about twice as frequent in PD as in HD patients. The reported sudden death incidence is 49/1,000 patients per year in the HD population and 36/1,000 patient per year in the population on PD (1). The factors that lead PD patients to die suddenly could somewhat differ from those that induce sudden death in HD patients. A previous study linked sudden death in PD patients with reduced LVEF and elevated plasma levels of pro-BNP and troponin T, suggesting an important role of heart failure and ischemic heart disease as factors associated with increased sudden mortality [34]. In our population, among patients who suffered sudden death, prevalence of subjects with LVEF<35% was higher in PD compared to HD patients. This finding suggests that the presence of severe cardiac disease could play an important role in determining sudden death in the PD population, while in HD patients factors most closely related to dialysis modality may be relevant. In an Australian population a daily variation in the pattern of cardiac deaths was observed in HD patients receiving three dialysis sessions per week, but not in PD patients [35]. Sudden death occurs more frequently during the long interdialytic interval or after the first HD session of the week [5, 6], and in 50 HD patients having an

implanted cardiac monitor, the risk of sudden death and significant arrhythmias was greatest during the long interdialytic interval [36]. Moreover, HD sessions themselves can cause cardiac arrest and lower concentrations of potassium and calcium in the dialysate are associated with a higher incidence of cardiac intradialytic arrest [37, 38]. In agreement with these data, we observed that the majority of sudden deaths of our HD patients occurred just before or just after the first HD session of the week. All this evidence partly justifies the high sudden death incidence in HD patients, even in those with preserved LVEF, but less clear is why sudden mortality is also high in PD patients. The effects of intradialytic modifications of the electrolytes on the cardiac action potential have been widely investigated in HD patients [39-41], while very few studies have been done regarding possible electrolyte disturbances in PD patients and their potential arrhythmogenic effects. However, both HD and PD populations show an alteration of potassium handling, even if the electrolyte plasma fluctuations differ in relation to different dialysis modalities. Some authors have shown an excess of mortality in PD patients associated with serum potassium disturbances. Torlen et al. described that PD patients are more likely to have serum potassium <4 mEq/L compared to HD patients and that there is a U-shaped relationship between time-averaged serum potassium and PD patients mortality [42]. Recently it was reported that both time-averaged serum potassium and its fluctuation contribute to the high death risk in PD patients [43]. These studies allow us to hypothesize that electrolyte abnormalities could increase the risk of death also in this population.

Our study has some limitations being a retrospective study. A treatment selection bias was present, because the nephrologist was free to choose the dialysis modality for each patient. Moreover, data on plasma concentrations of electrolytes in the two study populations are lacking. However, our data show that sudden death is an important clinical problem even in the PD population and not only in HD patients and strongly suggest the need to undertake studies with the aim of understanding the mechanisms behind this type of death in patients undergoing PD.

Ethical statement and Informed consent

As a retrospective study of de-identified data, the study is not subject to ethical committee approval according to Italian regulation. All patients, when they were referred to the dialysis center at the beginning of renal replacement therapy, signed a consent for the potential uses of their data. anonymously.

Conflict of interest: The authors have declared that no conflict of interest exists.

References

1. United States Renal Data System. 2015 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2015.

2. Bigger JT Jr, Fleiss JL, Kleiger R, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation. 1984;69:250-8.

3. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005;112:3738-44.

4. Solomon SD, Zelenkofske S, McMurray JJ, et al; Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med. 2005;352:2581-8.

5. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in haemodialysis patients. Kidney Int. 1999;55:1553-9.

6. Genovesi S, Valsecchi MG, Rossi E, et al. Sudden death and associated factors in a historical cohort of chronic haemodialysis patients. Nephrol Dial Transplant. 2009;24:2529-36.

7. Fenton SS, Schaubel DE, Desmeules M, et al. Haemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. Am J Kidney Dis. 1997;30:334-42.

8. McDonald SP, Marshall MR, Johnson DW, et al. Relationship between dialysis modality and mortality. J Am Soc Nephrol. 2009;20:155-63.

9. Heaf JG, Løkkegaard H, Madsen M. Initial survival advantage of peritoneal dialysis relative to haemodialysis. Nephrol Dial Transplant. 2002;17:112-7.

10. Liem YS, Wong JB, Hunink MG, et al. Comparison of haemodialysis and peritoneal dialysis survival in The Netherlands. Kidney Int. 2007;71:153-8.

11. Kumar VA, Sidell MA, Jones JP, et al. Survival of propensity matched incident peritoneal and hemodialysis patients in a United States health care system. Kidney Int. 2014;86:1016-22.

12. Lukowsky LR, Mehrotra R, Kheifets L, et al. Comparing mortality of peritoneal and hemodialysis patients in the first 2 years of dialysis therapy: a marginal structural model analysis. Clin J Am Soc Nephrol. 2013;8:619-28.

13. Cleves M, Gutierrez RG, Gould W, et al. An Introduction to Survival Analysis Using Stata, Stata Press, Texas, US, 2010

14. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials. 1996;17:343–6.
15. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet. 2002;359:1309-10.
16. Jaar BG, Coresh J, Plantinga LC, et al. Comparing the risk for death with peritoneal dialysis and haemodialysis in a national cohort of patients with chronic kidney disease. Ann Intern Med. 2005;143:174-83.
17. Mehrotra R, Chiu YW, Kalantar-Zadeh K, et al. Similar outcomes with haemodialysis and peritoneal dialysis in patients with end-stage renal disease. Arch Intern Med. 2011;171:110-8.
18. Waldum-Grevbo B, Leivestad T, Reisæter AV, et al. Impact of initial dialysis modality on mortality: a propensity-matched study. BMC Nephrol. 2015;16:179.
19. Yang F, Khin LW, Lau T, et al. Haemodialysis versus Peritoneal Dialysis: A Comparison of Survival Outcomes in South-East Asian Patients with End-Stage Renal Disease. PLoS One. 2015;doi: 10.1371/journal.pone.0140195.
20. Murphy SW, Foley RN, Barrett BJ, et al. Comparative mortality of haemodialysis and peritoneal dialysis in Canada. Kidney Int. 2000;57:1720-6.
21. Weinhandl ED, Foley RN, Gilbertson DT, et al. Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients. J Am Soc Nephrol. 2010;21:499-506.
22. Park JI, Bae E, Kim YL, et al. Glycemic Control and Mortality in Diabetic Patients Undergoing Dialysis Focusing on the Effects of Age and Dialysis Type: A Prospective Cohort Study in Korea. PLoS One. 2015;doi: 10.1371/journal.pone.0136085.
23. Duong U, Mehrotra R, Molnar MZ, et al. Glycemic control and survival in peritoneal dialysis patients with diabetes mellitus. Clin J Am Soc Nephrol. 2011;6:1041-8.
24. Yi C, Guo Q, Lin J, et al. Clinical Outcomes of Remote Peritoneal Dialysis Patients: A Retrospective Cohort Study from a Single Center in China. Blood Purif. 2016;41:100-7.
25. McIntyre NJ, Chesterton LJ, John SG, et al. Tissue-advanced glycation end product concentration in dialysis patients. Clin J Am Soc Nephrol. 2010;5:51-5.
26. Li PK, Kwan BC, Ko GT, et al. Treatment of metabolic syndrome in peritoneal dialysis patients. Perit Dial Int. 2009;29:S149-S152.
27. Ozdemir FN, Güz G, Sezer S, et al. Atherosclerosis risk is higher in continuous ambulatory peritoneal dialysis patients than in haemodialysis patients. Artif Organs. 2001;25:448-52.
28. Harmankaya O, Akalin N, Akay H, et al. Comparison of risk factors for cardiovascular disease in haemodialysis and peritoneal dialysis patients. Clinics. 2015;70:601-5.

29. Wang IK, Liang WM, Lin CL, et al. Impact of dialysis modality on the survival of patients with end-stage renal disease and prior stroke. Int Urol Nephrol. 2016;48:139-47.
30. Genovesi S, Vincenti A, Rossi E, et al. Atrial fibrillation and morbidity and mortality in a cohort of long -term hemodialysis patients. Am J Kidney Dis. 2008;2:255-62.
31. Vincenti A, Passini E, Fabbrini P, et al. Recurrent intradialytic paroxysmal atrial fibrillation: hypotheses on onset mechanisms based on clinical data and computational analysis. Europace. 2014;16:396–404.
32. Buiten MS, de Bie MK, Rotmans JI, et al. The dialysis procedure as a trigger for atrial fibrillation: new insights in the development of atrial fibrillation in dialysis patients. Heart. 2014;100:685–90.
33. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. European Heart Journal. 2016;37:1591–602
34. Wang AY, Lam CW, Chan IH, et al. Sudden cardiac death in end-stage renal disease patients: a 5-year prospective analysis. Hypertension. 2010;56:210-6.
35. Krishnasamy R, Badve SV, Hawley CM, et al. Daily variation in death in patients treated by long-term dialysis: comparison of in-center haemodialysis to peritoneal and home haemodialysis. Am J Kidney Dis. 2013;61:96-103.
36. Wong MC, Kalman JM, Pedagogos E, et al. Temporal distribution of arrhythmic events in chronic kidney disease: Highest incidence in the long interdialytic period. Heart Rhythm. 2015;12:2047-55.
37. Pun PH, Lehrich RW, Honeycutt EF, et al. Modifiable risk factors associated with sudden cardiac arrest within haemodialysis clinics. Kidney Int. 2011;79:218-27.
38. Pun PH, Horton JR, Middleton JP. Dialysate calcium concentration and the risk of sudden cardiac arrest in haemodialysis patients. Clin J Am Soc Nephrol. 2013;8:797-803.
39. Severi S, Grandi E, Pes C, et al. Calcium and potassium changes during haemodialysis alter ventricular repolarization duration: in vivo and in silico analysis. Nephrol Dial Transplant. 2008;23:1378-86.
40. Näppi SE, Virtanen VK, Saha HH, et al. QTc dispersion increases during haemodialysis with low-calcium dialysate. Kidney Int. 2000;57:2117-22.
41. Genovesi S, Dossi C, Viganò MR, et al. Electrolyte concentration during haemodialysis and QT interval prolongation in uraemic patients. Europace. 2008;10:771-7.
42. Torlén K, Kalantar-Zadeh K, Molnar MZ, et al. Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. Clin J Am Soc Nephrol. 2012;7:1272-84.
43. Li SH, Xie JT, Long HB, et al. Time-averaged serum potassium levels and its fluctuation associate

with 5-year survival of peritoneal dialysis patients: two-center based study. Sci Rep. 2015;doi: 10.1038/srep15743.

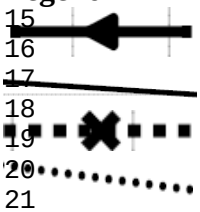
Figure Legends

Figure 1. Survival curves of patients on hemodialysis (HD) and peritoneal dialysis (PD)

Figure 2. Annual mortality rates of patients on HD and PD

First row: annual estimates for patients on HD. Second row: annual estimates for patients on PD

Legend



Point and standard error estimates for patients on HD

Fixed-effects meta-regression model fitted to the annual estimates for patients on HD

Point and standard error estimates for patients on PD

Fixed-effects meta-regression model fitted to the annual estimates for patients on PD

Figure 3. Cumulative incidence of sudden death and of death due to other causes of patients on hemodialysis (HD) and peritoneal dialysis (PD)

Table 1. Characteristics of the study population

		Patients		Statistical association	
		HD	**PD**	**Odds Ratio[§] (95%CI)**	**P-value**
Age (years) at dialysis start					
	N	1823	249		
	Median	68.6	67.5	1.05 (0.96-1.15)°	0.25
	Range	12.9-94.4	23.2-87.1		
Gender					
Female	N (%)	681 (37.4)	95 (38.2)	1	0.81
Male	N (%)	1142 (62.6)	154 (61.8)	1.03 (0.79-1.36)	
Left ventricular ejection fraction					
< 35%	N (%)	89 (4.9)	19 (7.6)	1	0.07
≥ 35%	N (%)	1734 (95.1)	230 (92.4)	1.61 (0.96-2.69)	
Ischemic heart disease					
No	N (%)	1182 (64.8)	167 (67.1)	1	0.49
Yes	N (%)	641 (35.2)	82 (32.9)	1.10 (0.83-1.46)	
Diabetes mellitus					
No	N (%)	1325 (72.7)	189 (75.9)	1	0.28
Yes	N (%)	498 (27.3)	60 (24.1)	1.18 (0.87-1.61)	
Previous ischemic stroke					
No	N (%)	1585 (86.9)	222 (89.2)	1	0.33
Yes	N (%)	238 (13.1)	27 (10.8)	1.23 (0.81-1.88)	
Atrial fibrillation					
No	N (%)	1334 (73.2)	199 (79.9)	1	0.02
Yes	N (%)	489 (26.8)	50 (20.1)	1.46 (1.05-2.02)	
N° of comorbidities					
0	N (%)	638 (35.0)	116 (46.6)		
1	N (%)	652 (35.8)	64 (25.7)	1.18 (1.02-1.37)	0.02[†]
2	N (%)	400 (22.0)	53 (21.3)		
3	N (%)	118 (6.5)	15 (6.0)		
4	N (%)	15 (0.8)	1 (0.4)		

§ Probability modelled is the probability to be assigned to the HD cohort
° A 10-unit increase in age was considered
† Test for trend
HD: hemodialysis; PD: peritoneal dialysis

Table 2. Follow-up and events

			Patients	
			HD	**PD**
Sample size		N	1823	249
Number of deaths		N (%)	626 (34.3)	62 (24.9)
Accrual period			1st of January 2010 to 31th of January 2013	
Closing date			31st of January 2014	
Length of follow-up (years)		Median	1.76	1.94
		IQ range	0.79-3.35	0.84-3.34
Completeness of follow-up (*C* index)			98%	99%
Causes of death	Cachexia	N (%)*	153 (26.0)	18 (31.6)
	Sepsis	N (%)*	134 (22.8)	11 (19.3)
	Sudden death	N (%)*	71 (12.1)	13 (22.8)
	Neoplasia	N (%)*	66 (11.2)	3 (5.3)
	Heart Failure	N (%)*	40 (6.8)	8 (14.0)
	Stroke	N (%)*	39 (6.6)	1 (1.8)
	Vascular Disease	N (%)*	48 (8.2)	1 (1.8)
	Haemorrhage	N (%)*	18 (3.1)	0
	Chronic Pulmonary Disease	N (%)*	13 (2.2)	1 (1.8)
	Dementia	N (%)*	4 (0.7)	0
	Liver cirrhosis	N (%)*	2 (0.3)	1 (1.8)
	Unknown	*N (%)*	*38 (6.1)*	*5 (8.1)*

HD: hemodialysis; PD: peritoneal dialysis

* percentage was calculated by excluding unknown causes

Table 3. Univariate Cox analysis results on death risk for any cause in the two cohorts

Variable	Category	HD			PD		
		HR	95%CI	P-value	HR	95%CI	P-value
Age (years) at dialysis start	-	1.69 °	1.56-1.83	<0.001	1.67 °	1.29-2.15	<0.001
	Test for interaction	Z: - 0.66; P-value: 0.51					
Gender	Female	1		0.40	1		0.50
	Male	0.93	0.79-1.10		1.75	0.99-3.07	
	Test for interaction	Z: -2.02; P-value: 0.04					
Left ventricular ejection fraction	<35%	1		<0.001	1		0.01
	≥35%	0.46	0.35-0.60		0.36	0.19-0.68	
	Test for interaction	Z: 0.40; P-value: 0.69					
Ischemic heart disease	No	1		0.01	1		<0.001
	Yes	1.28	1.09-1.50		3.37	2.02-5.61	
	Test for interaction	Z: -3.50; P-value: <0.001					
Diabetes mellitus	No	1		0.01	1		<0.001
	Yes	1.29	1.09-1.54		2.70	1.61-4.54	
	Test for interaction	Z: -2.35; P-value: 0.02					
Previous ischemic stroke	No	1		<0.001	1		0.01
	Yes	1.47	1.20-1.80		2.58	1.34-4.98	
	Test for interaction	Z: -1.71; P-value: 0.09					
Atrial fibrillation	No	1		<0.001	1		<0.001
	Yes	1.49	1.26-1.76		4.20	2.44-7.24	
	Test for interaction	Z: -2.66; P-value: 0.01					

° A 10-unit increase in age was considered

HD: hemodialysis; PD: peritoneal dialysis

Table 4. Multivariate Cox analysis results on death risk for any cause

Characteristics	Category		HR	95%CI	P-value
Treatment					
Type of dialysis	HD		1		<0.001
	PD *		0.13	0.05-0.33	
	HD		1		<0.001
	PD †		1.33	1.20-1.46	
ICD implantation °	No		1		0.59
	Yes		0.88	0.57-1.38	
Covariates					
Age (years) at dialysis start §	-		1.66	1.53-1.80	<0.001
Left ventricular ejection fraction	HD	<35%	1		<0.001
		≥35%	0.52	0.39-0.70	
	PD	<35%	1		
		≥35%	0.66	0.32-1.33	
	Test for interaction		Z: 0.61; P-value: 0.54		
Ischemic heart disease	HD	No	1		0.01
		Yes	1.04	0.88-1.23	
	PD	No	1		
		Yes	2.39	1.35-4.23	
	Test for interaction		Z: 2.73; P-value: 0.01		
Diabetes mellitus	HD	No	1		0.01
		Yes	1.24	1.04-1.48	
	PD	No	1		
		Yes	1.66	0.96-2.84	
	Test for interaction		Z: 1.00; P-value: 0.32		
Previous ischemic stroke	HD	No	1		0.02
		Yes	1.24	1.01-1.52	
	PD	No	1		
		Yes	1.98	1.04-3.78	
	Test for interaction		Z: 1.36; P-value: 0.17		
Atrial fibrillation	HD	No	1		0.02
		Yes	1.09	0.92-1.29	
	PD	No	1		
		Yes	2.06	1.21-3.53	
	Test for interaction		Z: 2.23; P-value: 0.03		

Legend

* HR at dialysis start; † linear type of dialysis-by-time interaction; ° Time-varying treatment; § a 10-unit increase in age was considered

Table 5. Univariate Fine and Gray analysis results on death risk for sudden deaths and not sudden deaths in the two cohorts

Variable	Category	Sudden death						Other causes					
		HD			PD			HD			PD		
		HR	95%CI	P-value	HR	95%CI	P-value	HR	95%CI	P-value	HR	95%CI	P-value
Age (years) at dialysis start	-	1.22 °	1.05-1.42	0.01	1.45 °	0.92-2.31	0.11	1.65 °	1.51-1.79	<0.001	1.61 °	1.25-2.08	<0.001
	Test for interaction	Z: -0.78; P-value: 0.43						Z: -0.73; P-value: 0.47					
Gender	Female	1		0.90	1		0.10	1		0.35	1		0.27
	Male	1.03	0.63-1.67		3.43	0.80-14.62		0.92	0.77-1.09		1.39	0.78-2.48	
	Test for interaction	Z: -1.51; P-value: 0.13						Z: -1.18; P-value: 0.24					
Left ventricular ejection fraction	<35%	1		0.01	1		0.02	1		<0.001	1		0.23
	≥35%	0.33	0.17-0.63		0.29	0.10-0.84		0.57	0.42-0.77		0.59	0.25-1.40	
	Test for interaction	Z: 0.34; P-value: 0.73						Z: -0.02; P-value: 0.99					
Ischemic heart disease	No	1		<0.001	1		0.05	1		0.17	1		<0.001
	Yes	2.35	1.47-3.77		2.96	0.99-8.85		1.13	0.95-1.34		2.89	1.65-5.06	
	Test for interaction	Z: -0.40; P-value: 0.69						Z: -3.08; P-value: 0.01					
Diabetes mellitus	No	1		0.01	1		0.65	1		0.220	1		<0.001
	Yes	2.06	1.28-3.31		1.31	0.41-4.18		1.12	0.93-1.36		2.89	1.64-5.10	
	Test for interaction	Z: 0.77; P-value: 0.44						Z: -2.76; P-value: 0.01					
Previous ischemic stroke	No	1		0.310	1		0.02	1		0.01	1		0.14
	Yes	1.37	0.75-2.49		4.85	1.24-18.89		1.44	1.16-1.79		1.67	0.84-3.30	
	Test for interaction	Z: -1.73; P-value: 0.08						Z: -0.57; P-value: 0.57					
Atrial fibrillation	No	1		0.563	1		0.07	1		<0.001	1		<0.001
	Yes	1.16	0.70-1.91		2.72	0.93-7.97		1.50	1.25-1.79		3.17	1.75-5.73	
	Test for interaction	Z: -1.41; P-value: 0.16						Z: -1.81; P-value: 0.07					

° A 10-unit increase in age was considered

HD: hemodialysis; PD: peritoneal dialysis

Table 6. Multivariate Fine and Gray analysis results on death risk for sudden deaths

Variable	Category	HR_{cpRisk}	95%CI	P-value
Treatment				
Type of dialysis	HD	1		0.53
	PD	1.21	0.66-2.22	
ICD implantation °	No	1		0.68
	Yes	1.23	0.45-3.34	
Covariates				
Age (years) at dialysis start §	-	1.20 °	1.01-1.42	0.03
Left ventricular ejection fraction	<35%	1		0.04
	≥35%	0.49	0.25-0.96	
Ischemic heart disease	No	1		0.02
	Yes	1.79	1.11-2.88	
Diabetes mellitus	No	1		0.06
	Yes	1.56	0.99-2.46	
Previous ischemic stroke	No	1		0.26
	Yes	1.38	0.79-2.41	
Atrial fibrillation	No	1		0.98
	Yes	1.01	0.62-1.64	

° Time-varying treatment; § a 10-unit increase in age was considered

Figure 1

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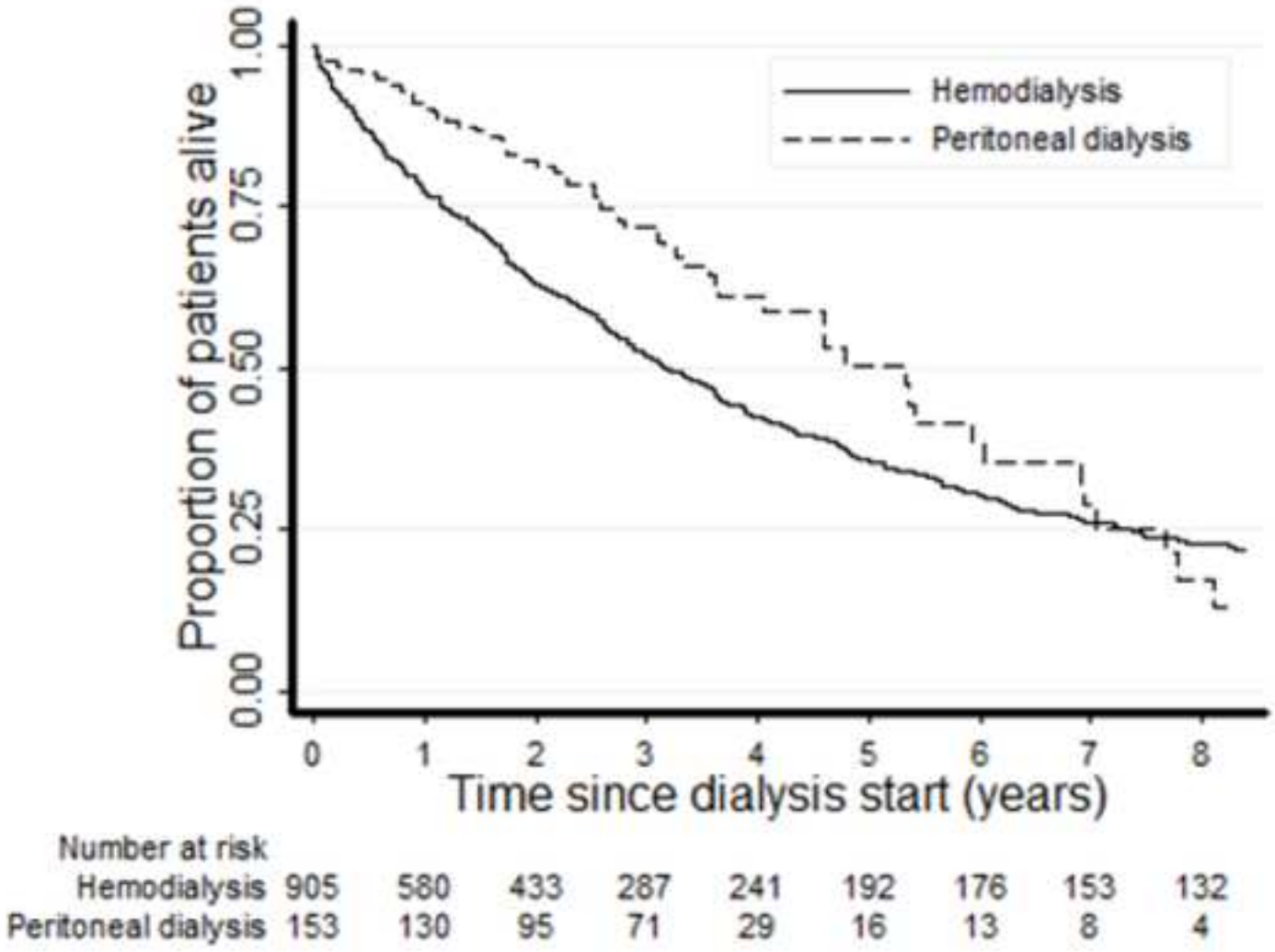

Figure 2

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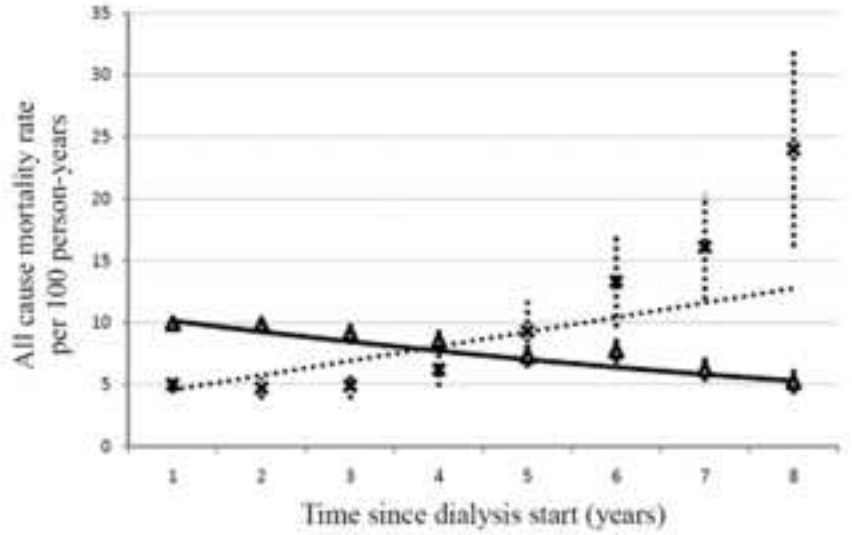
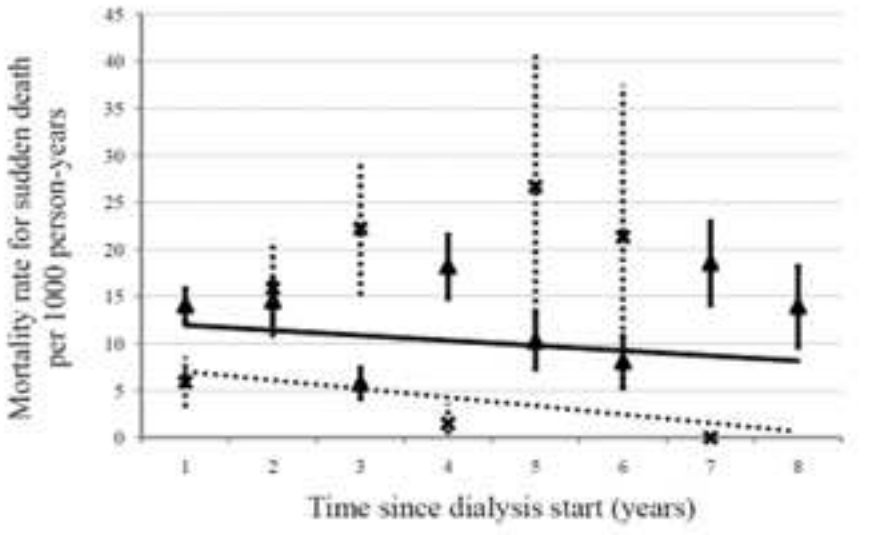
Panel a



Point est. (std error)†	9.9 (0.91)	9.8 (1.11)	9.1 (1.26)	8.5 (1.42)	7.3 (1.51)	7.7 (1.67)	6.2 (1.59)	5.2 (1.62)
(per 100 person-years)	5.0 (1.54)	4.7 (1.77)	4.9 (2.08)	6.2 (2.75)	9.3 (5.23)	13.3 (7.58)	16.1 (8.91)	24.0 (16.14)

Panel b



Point est. (std error)†	14.1 (3.59)	14.5 (4.47)	5.8 (3.31)	18.2 (6.83)	10.2 (5.83)	8.1 (5.60)	18.5 (8.86)	13.9 (8.55)
(per 100 person-years)	5.9 (5.45)	15.9 (10.45)	22.2 (14.25)	1.5 (4.40)	26.7 (28.95)	21.3 (32.31)	0 (nd)	nd

Figure 3

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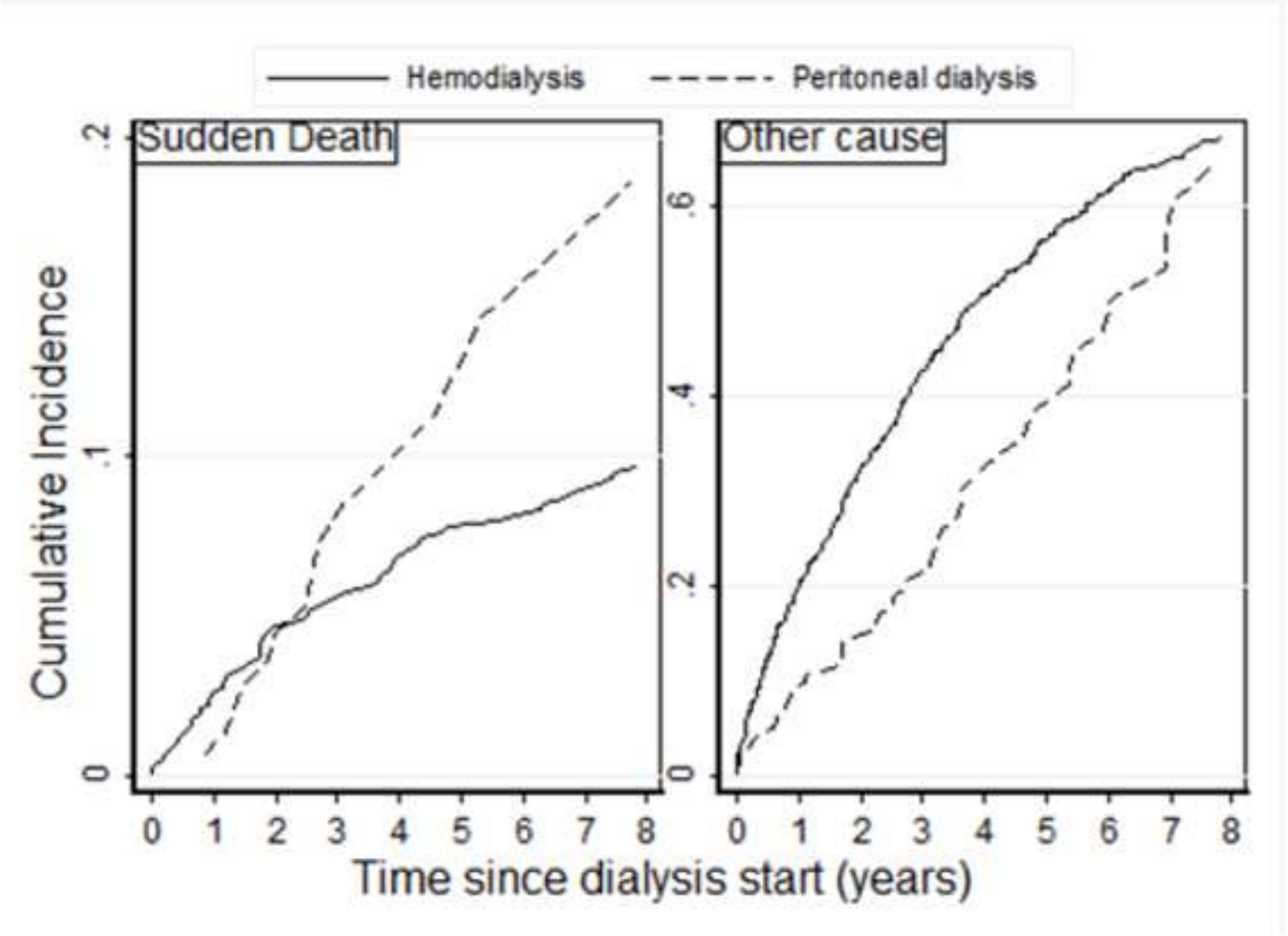

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