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Timing of start of dialysis in diabetes mellitus patients: a systematic literature review*

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ORIGINAL ARTICLE

ABSTRACT

Background. Diabetes mellitus is a frequent cause of the need for renal replacement therapy (RRT). Historically, RRT was started earlier in patients with diabetes, in an attempt to prevent complications of uraemia and diabetes. We did a systematic review to find support for this earlier start of dialysis in patients with versus without diabetes.

Methods. The MEDLINE, EMBASE and CENTRAL databases were searched for articles about the timing of dialysis initiation in (subgroups of) patients with diabetes and CKD Stage 5.

Results. A total of 340 papers were screened and 11 papers were selected to be reviewed. Only three studies showed data of at least one subgroup of patients with diabetes. Two observational studies concluded that start of dialysis with a higher estimated glomerular filtration rate (eGFR) is beneficial with regard to survival, one did not find a difference and six observational studies concluded that start of dialysis with a lower eGFR is associated with better survival in patients with diabetes. The effect of timing of initiation of dialysis did not differ between patients with versus without diabetes. Lastly, one randomized controlled trial (two papers) reported that there was no difference in survival between start at higher versus lower eGFR overall and a P-value for the interaction with diabetes of P = 0.63, indicating no difference between patients with versus without diabetes with regard to the timing of start of dialysis and subsequent mortality on dialysis.

Conclusions. There is no difference between early (eGFR) and late (lower eGFR) start of RRT with regard to mortality in patients with versus without diabetes. RRT should thus be initiated based on the same criteria in all patients, irrespective of the presence or absence of diabetes.

Keywords: chronic kidney disease, diabetes mellitus, start of dialysis, survival

INTRODUCTION

Diabetes mellitus (DM) is a major contributing factor to the increasing number of patients with chronic kidney disease (CKD) [1]. Over the last decade, an increase in the number of patients (starting) renal replacement therapy (RRT) has been noted, in combination with an overall trend of starting dialysis earlier, and thus with higher estimated glomerular filtration rates (eGFRs) [2–5]. An explanation for this trend quite often mentioned in the literature is that physicians, perhaps in the absence of clear guidelines, prefer to start RRT when patients are still in relatively good condition, in an attempt to slow the progression of harm. Some authors claim that economic incentives might also be at play. However, evidence that this concept, coined 'healthy start', is beneficial with respect to survival and/or quality of life on RRT is lacking so far [6–9].

In the early history of dialysis therapy, patients with DM were excluded from this treatment due to a shortage of dialysis capacity. The underlying rationale was that the few dialysis beds that were available had to be reserved for those patients who could benefit most from the treatment. Patients with diabetes had such a grim prognosis that offering RRT to them was considered a waste. RRT has now become available for patients with diabetes, but the belief that they have a different prognosis than patients without diabetes has prevailed to this day, as is reflected in the observation that patients with diabetes start RRT even earlier than patients without diabetes [10].

In a recent survey among 443 nephrologists, 60% of nephrologists indicated they would start RRT earlier in patients with versus without diabetes [11], even though it is unclear whether there is sufficient evidence to support this inclination [12, 13].

Therefore, the aim of our study is to systematically review the available evidence with regard to the timing (early at higher eGFR versus later at lower eGFR) of the start of RRT in patients

with diabetes and CKD Stage 5 and, accordingly, whether the timing of and criteria for the start of RRT should be different in patients with versus without diabetes.

METHODS

Data source and search strategy

The MEDLINE, EMBASE and CENTRAL databases were searched for English-language articles with search terms as described in Supplementary data, Table S1. Additional articles were found by manually screening references of relevant articles and reviews on the same topic [14].

Study selection

Articles that met any of the following criteria were included: every study with start of dialysis as exposure that (i) provided outcome data in patients with diabetes and advanced CKD specifically, (ii) reported outcome data of an interaction analysis for DM or (iii) had at least 30% of patients with diabetes in the study population. Patients with diabetes and CKD Stage 5 were included, irrespective of whether their primary kidney disease was diabetic nephropathy or whether they had CKD due to another cause with DM as comorbidity. There were no predefined specific levels of kidney function at which RRT was initiated that were deemed early or late start of dialysis. The definitions of early and late start as used in a study were considered early or late start for that particular study. RRT encompassed all forms of haemodialysis and peritoneal dialysis. Editorials, case reports, reviews, letters and studies performed in children (age <18 years) or animals were excluded after screening for relevant references.

Quality assessment

Study quality was assessed by the Newcastle-Ottawa scale for observational studies, which provides a quality score per study based on three items: study participants (0–4 points), adjustment for confounding (0–2 points) and exposure/outcome of interest ascertainment (0–3 points). A study that meets all the criteria for these three dimensions would score a maximum of 9 points [15]. The randomized controlled trials (RCTs) were assessed for risk of bias using the Cochrane Risk of Bias assessment tool, which helps identify biases that could arise during random sequence generation, concealment of treatment allocation, blinding, incomplete outcome data, selective outcome reporting or other sources of bias [16]. Ultimately, RCTs are qualified as having a low, unclear or high risk of bias based on the level of bias risk and the validity of the results.

Data extraction and analysis

After the selected titles were reviewed, two reviewers (H.N. and D.B.) independently read the abstracts to select the relevant articles for full-text review. After this full-text review, the data in the full-text articles that met the inclusion criteria were extracted, tabulated and analysed. Discrepancies between the two reviewers were solved by asking a third author (W.v.B.) to review the problematic articles and reach consensus.

RESULTS

Search results

Three hundred and forty potentially relevant articles were retrieved by the search. Five more articles were added that were found through reference screening. Based on title and abstract, 296 articles were excluded due to search overlap or because the population or the exposure of the study did not meet our inclusion/exclusion criteria. A flow diagram of the article selection process is depicted in Figure 1. Of the 49 studies selected for full-text examination, 38 were excluded because after full-text review it became apparent that these studies did not deal with the timing of dialysis start ($n = 26$) or had the wrong population (percentage of patients with diabetes <30%) ($n = 12$). Finally, 11 studies were reviewed in detail and included in this review. The characteristics of these studies can be found in Table 1.

Characteristics of selected studies

Eleven studies were reviewed, among which four were prospective [7, 22, 24, 19] and seven were retrospective cohort studies [6, 20, 17, 18, 21, 23, 25]; two of the four prospective articles reported on the same RCT (IDEAL) [7, 24] but with different outcomes of interest. The oldest study was published in 1999 [26] and the most recent in 2014 [21]. The smallest study included 100 patients [17] and the largest included 896 546 patients [20]. DM was present in from 34% [7] to 100% [17] of the patients in the studies. Only one study was performed exclusively in diabetics [17], one observational study reported separate results for patients with versus without diabetes [20] and one study reported the outcome of an interaction analysis[7]; the remaining eight studies did not report specific results for DM patients but did have at least 30% of patients with diabetes in the study population. Two studies included only haemodialysis patients [23, 25], three studies only peritoneal dialysis patients [19, 17, 21] and the rest included both. All but one study used Cox proportional hazards regression to calculate hazard ratios (HRs) for mortality. The cost-effectiveness investigation by Harris *et al.* [24] in the IDEAL study was the one study that by its nature did not use Cox regression. Based on quality assessment scores, the quality of most studies was low to moderate. A detailed overview of the characteristics of the 11 studies is displayed in Table 1 and Supplementary data, Table S2.

Study outcomes

Mortality. Tang *et al.* [19] and Coronel *et al.* [17] were the only studies observing higher all-cause mortality in the late starters. Tang *et al.* observed that those patients who chose to wait and thus did not start with PD when advised had higher mortality rates compared with the elective starters. This result remained present and did not change materially after adjustment for age, sex and eGFR [$HR_{Crude} = 3.12$ (95% CI 1.34–9.88), $P = 0.01$ versus $HR_{Adj} = 3.01$ (95% CI 1.32–9.40), $P = 0.01$].

Coronel *et al.* [17] included exclusively patients with DM and found that of the patients who started dialysis with an eGFR >7.7 mL/min/1.73 m^2 at 3 years, 61% survived, whereas

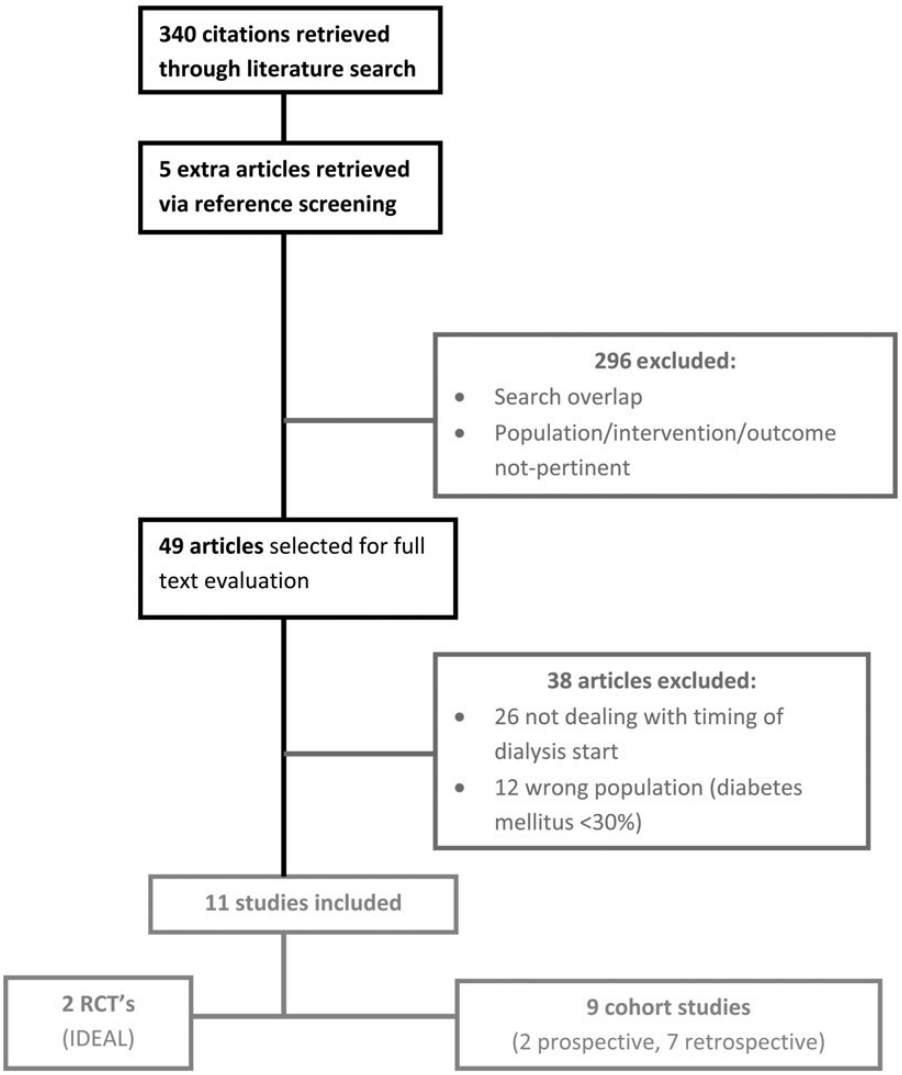

FIGURE 1: PRISMA flow chart for paper selection.

of the patients who started later (i.e. eGFR ≤7.7 mL/min/1.73 m^2), 39% were still alive after 3 years (no effect measure reported).

Of the remaining seven observational studies, six found that a late start is associated with a lower mortality risk. Kazmi *et al.* [6] demonstrated that after extensive adjustment, each 1 mL/min/1.73 m^2 higher eGFR at the start of dialysis was associated with an increased mortality risk [HR = 1.034 (95% CI 1.032–1.036)]. Furthermore, repeating this analysis in a subset of low-risk patients (n = 90 540) without diabetes, heart failure or atherosclerotic heart disease did not substantially change the results [HR = 1.031 (95% CI 1.026–1.036)]. Lassalle *et al.* [18] also demonstrated that after extensive adjustment, a higher eGFR at the start of dialysis is associated with increased risk of dying on dialysis [HR = 1.09 (95% CI 1.05–1.14)]. Again, the difference between crude and adjusted HR was small. Wright *et al.* [20] had the largest cohort (n = 896 546) in which the association between the timing of dialysis start and mortality on dialysis was investigated. Also, this observational study reported separate results for patients with versus without diabetes. Overall, patients who started dialysis with higher eGFRs experienced a higher risk of mortality on dialysis. Patients with an eGFR >15 mL/min/1.73 m^2 had an HR of 1.44 (95% CI 1.42–1.45, P < 0.001) for mortality on dialysis compared with patients with an eGFR between 5 and 10 mL/min/1.73 m^2 at the start of dialysis. Patients with an eGFR ≤5 mL/min/1.73 m^2 had an HR of 0.88 (95% CI 0.87–0.88, P < 0.001) for dying on dialysis compared with the same reference group. Stratification for diabetes showed that patients with versus without diabetes in the early and late start groups have similar hazards of mortality [i.e. $HR_{\leq 5mL/min}$ = 0.89 (95% CI 0.88–0.90) in patients with diabetes and $HR_{\leq 5mL/min}$ = 0.88 (95% CI 0.87–0.89) in those without diabetes; $HR_{>15mL/min}$ = 1.43 (95% CI 1.41–1.45) in patients with diabetes and $HR_{>15mL/min}$ = 1.45 (95% CI 1.44–1.47) in those without diabetes].

Beddhu *et al.* [22] also investigated the timing of the start of dialysis and mortality, but in incident haemodialysis and peritoneal dialysis patients. They modelled renal function at the start of dialysis continuously rather than dividing patients in to categories of early and late start. They found that a higher eGFR (MDRD) at baseline of 5 mL/min was associated with a 14% increased risk of dying on dialysis [HR = 1.14 (95% CI 1.06–1.22)]. Hwang *et al.* [25] aimed to answer the same

Table 1. Characteristics and risk of bias of the included studies

Study	Publication year, time frame, location	Study design, *n*, % DM modality, % HD, methods, outcomes	Inclusion and exclusion criteria	Patient characteristics	Intervention (*n*) and comparator (*n*) duration	Outcome(s)	Results	Quality of evidence	Newcastle-Ottawa score (Cochrane risk of bias for the RCTs)	Notes
Cooper *et al.* [7]	2010 2000–08 Australia/ New Zealand	RCT (IDEAL study) *n* = 828 34% DM 44% HD Cox regression mortality	Patients were eligible for inclusion in the study if they had progressive chronic kidney disease (patients with a failing kidney transplant were eligible) and an eGFR between 10.0 and 15.0 mL/min/1.73 m^2 Exclusion: <18 years of age, eGFR <10.0 mL/min/1.73 m^2, planned living donation within 12 months, cancer that was likely to affect mortality	Age: 60.3 years Gender: 65% male DM (as PRD): 34% eGFR at start: 9.9 mL/min/1.73 m^2	Late start of dialysis group ($eGFR_{CG}$ 5–7 mL) (*n* = 424) Early start of dialysis group ($eGFR_{CG}$ 10–14 mL)(*n* = 404) FU until November 2009	Mortality	HR 1.04 (95% CI 0.83–1.30), P = 0.75. P for interaction for early or late start of dialysis with diabetes = 0.63.	High	Selection bias: low, performance bias: unclear, detection bias: low, attrition bias: low, reporting bias: low, other bias: unclear	RCT with proper subgroup analysis for interaction in diabetics
Coronel *et al.* [17]	2009 1982–2004 Europe	Retrospective cohort study *n* = 100 100% DM 0% HD KM and Cox regression Mortality	They had begun PD as the first RRT, remained on the therapy for >2 months and had sufficient parameters to measure the GFR by MDRD-7 [13], a currently validated method used to measure the GFR in diabetic CKD patients	Age: 53 years Gender: 65% male DM = 100% DM1 = 54% PD = 100% Median eGFR at start: 7.7 mL/min/1.73 m^2	$eGFR_{MDRD-7}$ ≤7.7 mL/min/1.73 m^2 (*n* = 56) $eGFR_{MDRD-7}$ >7.7 mL/min/1.73 m^2 (*n* = 44) 60 months FU	Mortality (on PD in diabetics, in DM1 and in DM2)	1/KM higher actuarial mortality in eGFR >7.7 mL group, P < 0.007 1/KM: similar mortality in eGFR >7.7 mL group with DM 1, P = 0.2 1/KM higher actuarial mortality in eGFR >7.7 mL in DM2 group. P = 0.045 1.5 ± 1.2 admission/ year P = NS	Low	5	No (adjusted) effect measures provided. Limited population size and only PD patients
Kazmi *et al.* [6]	2005 North America 1996–99	Retrospective cohort study *n* = 302 287 48% DM 90% HD Cox regression Mortality	In principle, all North American patients that start dialysis. The extent to which the ESRD Medical Evidence Form covers these patients is not mentioned. Patients with missing GFR values, acquired HIV virus, or cancer	Age: 62 years Gender: 53% male DM (PRD): 46% DM (comorbid): 48% eGFR at start: 8.4 mL/min/1.73 m^2	$eGFR_{MDRD}$ 5–7.5 mL (*n* = 99 940), 7.6–10 mL (*n* = 74 656), >10 mL at start of dialysis (*n* = 76 046) $eGFR_{MDRD}$ <5 mL (*n* = 51 645) at start of dialysis Until 31 December 2000	Mortality/ mortality on dialysis in (i) whole population (fully adjusted), (ii) in a low-risk population of patients without DM, HF, atherosclerosis (fully adjusted),	(i) HR = 1.03 (95% CI 1.03–1.04), P < 0.05 (ii) HR = 1.03 (95% CI 1.03–1.04), P < 0.05 (iii) HR = 1.03 (95% CI 1.03–1.03), P < 0.05	Moderate	8	Observational study that extensively adjusts for potential confounders. Despite this fact there might be a risk of selection bias and (residual) confounding (by indication)

Continued

Table 1. Continued

Study	Publication year, time frame, location	Study design, *n*, % DM modality, % HD, methods, outcomes	Inclusion and exclusion criteria	Patient characteristics	Intervention (*n*) and comparator (*n*) duration	Outcome(s)	Results	Quality of evidence	Newcastle-Ottawa score (Cochrane risk of bias for the RCTs)	Notes
			were excluded from this analysis			(iii)an older population (fully adjusted)				
Lassalle *et al.* [18]	2010 Europe 2002–06	Retrospective cohort study *n* = 11 685 35.8% DM 57.1% HD Cox regression Mortality	The REIN Registry includes all ESRD patients on RRT, either dialysis or transplantation, treated in France. Patients with acute kidney failure are excluded, that is, those who recover all or some renal function within 45 days or who die before 45 days and are diagnosed with acute kidney failure by experts	Age: 67 years Gender: 62% male DM (PRD): 21.2% DM (comorbid): 35.8% eGFR at start: 8.8 mL/min/1.73 m^2	$eGFR_{MDRD}$ 5–10 mL/min (*n* = 6683), 10–15 mL (*n* = 2517), 15–20 mL/min (*n* = 633), >20 mL/min at start of dialysis (*n* = 265) $eGFR_{MDRD}$ ≤5 mL (*n* = 1587) 21.9 months	Mortality/ mortality on dialysis (+ KM)	HR = 1.09 (95% CI 1.05–1.14), P < 0.05). Mortality decreased strongly with increasing MDRD eGFR (log-rank P < 0.0001). Two-year mortality decreased from 79 to 46% for the lowest versus the highest eGFR levels	Low	8	Observational study that extensively adjusts for potential confounders. Despite this fact, there might be a risk of selection bias and (residual) confounding (by indication)
Tang *et al.* [19]	2007 2002–04 Asia	Prospective cohort study *n* = 233 42% DM 0% HD Cox regression Mortality	All patients with chronic renal failure and their close relatives were invited	Age: 58 years Gender: 52% Male DM2: 42% - eGFR at start in elective starters: 9.21 mL/min - eGFR at start in initial refusers: 8.89 mL/min	Initial refusers (*n* = 82) Elective starters (*n* = 151) 1 year (5 years for outcome 'need for blood transfusion')	(i) all-cause mortality, crude HR) (ii) all-cause mortality on dialysis (adjusted for MD, age, sex, eGFR) (iii) Cardiovascular mortality	(i) HR = 3.12 (95% CI 1.34–9.88), P = 0.011 (ii) HR = 3.01 (95% CI 1.32–9.40), P = 0.01 (iii) 2.6 versus 9.8% in initial refusers, P = 0.014	Very low	5	The two groups compared in this study might suffer from confounding since the choice to electively start dialysis or initially refuse might be in relation to factors that influence mortality. These factors are almost certainly not adjusted for
Wright *et al.* [20]	2010 North America 1995–2006	Retrospective cohort study *n* = 896 546 56% DM 92.8% HD Cox regression Mortality	Incident dialysis patients age >18 years Renal transplantation or renal function recover. Outliers in BMI, weight or height	Age: 64.7 years Gender: 53.1% DM (PRD): 46.7% DM (comorbid): 56.2% HD: 92.8% Serum	DM—Dialysis started at $eGFR_{MDRD}$ ≤5 mL/min *n* = 34 053 Non-DM—Dialysis started at $eGFR_{MDRD}$ ≤5 mL/min *n* = 79 457	Mortality/ mortality at 60 months	DM ≤5 mL/min HR = 0.89 (95% CI 0.88–0.90) Non-DM ≤5 mL HR = 0.88 (95% CI 0.87–0.89) DM >15 mL/min HR = 1.43 (95% CI 1.41–1.45) Non-DM >15 mL	Moderate–high	8	Observational study that extensively adjusts for potential confounders and provides adjusted separate outcome for diabetics versus non-diabetics. Despite this fact, there might be a risk of

				creatinine: 7.2 (3.5) mg/dL	DM—dialysis started at eGFR >15 mL/min $n = 52\,989$ Non-DM—dialysis started at eGFR >15 mL/min $n = 46\,242$ Reference—dialysis started at eGFR >5–10 150 months		HR = 1.45 (95% CI 1.44–1.47)			selection bias and (residual) confounding (by indication)
Jain *et al.* [21]	2014 North America 2001–09	Retrospective cohort study $n = 8047$ 42.9% DM 0% HD Cox regression Mortality	All incident PD patients (age ≥18 years at dialysis therapy initiation) who had a recorded value for serum creatinine at dialysis therapy initiation and who received PD as their first form of RRT between 1 January 2001 and 31 December 2009	Age: 60.9 years Male: 57.3% DM (PRD): 36.2% DM (comorbid): 42.9%	Mid-start of dialysis at eGFR 7.5–10.5 ($n = 2670$) and early start at eGFR >10.5 mL/min/1.73 m^2 ($n = 2994$) Late start of dialysis at eGFR <7.5 mL/min/1.73 m^2 ($n = 2383$) 2.2 years (2.3, 2.2 and 1.9 years in the early, mid and late start groups, respectively)	Mortality/ mortality at5 years	HR = 1.16 (95% CI 0.82–1.63) for early versus late HR = 0.99 (95% CI 0.70–1.39) for mid versus late	Moderate	8	Observational study in incident PD patients that extensively adjusts for potential confounders. Despite this fact, bias and residual confounding might still play a role
Beddhu *et al.* [22]	2003 North America 1996–97	Prospective cohort study $n = 2920$ 42% DM 53% HD Cox regression Mortality	Incident chronic HD and PD patients who initiated dialysis therapy in 1996 and early 1997. Patients with previous RRT, duplicate entries, missing USRDS identification numbers or missing follow-up data and patients < 18 years of age, missing data for age, sex, race height, weight, blood urea nitrogen, serum creatinine, serum albumin, haematocrit, and serum bicarbonate were excluded	Age: 59 years Male: 53% Ethnicity White: 64% Black: 28% DM (PRD): 42% HD: 53% $eGFR_{MDRD}$: 8.2 ± 3.9 mL/min Haematocrit: 30.8 ± 5.4 BUN: 87 ± 31 Bicarbonate: 22.0 ± 4.6 BMI: 26.3 ± 5.8	5 mL/min increase in $eGFR_{MDRD}$ at start of dialysis ($n = 2920$) 5585 patient-years of follow-up	Mortality/ mortality	$HR_{adj} = 1.14$ (95% CI 1.06–1.22) for every 5 mL/min increase in eGFR at start of dialysis	Low	8	A random sample in a prospective US dialysis population that adjusts for confounders using propensity scores. However, propensity scores cannot control different sources of bias

Continued

Table 1. Continued

Study	Publication year, time frame, location	Study design, *n*, % DM modality, % HD, methods, outcomes	Inclusion and exclusion criteria	Patient characteristics	Intervention (*n*) and comparator (*n*) duration	Outcome(s)	Results	Quality of evidence	Newcastle-Ottawa score (Cochrane risk of bias for the RCTs)	Notes
Clark *et al.* [23]	2011 North America 2001–07	Retrospective cohort study *n* = 25 910 36% DM 100% HD Cox regression Mortality	All adult (≥18 years) patients with a recorded serum creatinine value who started with HD as their first form of RRT	Age: early group: 67.5 years (14.0), late group: 63.7 years (15.2) Male: early: 67%, late: 56.4% DM (PRD): early: 40.6%, late: 33.9% DM (comorbid): early: 52.7%, late: 43.4%	Early initiation of dialysis with $eGFR_{MDRD}$ <10.5 mL/min/1.73 m^2 (*n* = 8441) Late start of dialysis with $eGFR_{MDRD}$ ≤10.5 mL/min/1.73 m^2 (*n* = 17 469) 2.3 years of follow-up	Mortality/ mortality	HR_{Adj} = 1.18 (1.13–1.23) for early initiation of dialysis compared with late initiation of dialysis	Moderate	8	Retrospective cohort study in Canadian registry data with substantial adjustment for confounding, although never sufficient to be absolutely sure benefits of late start are not a reflection of other factors
Harris *et al.* [24]	2011 2002–08 Australia/ New Zealand	RCT (IDEAL study) *n* = 642 34% DM 43% HD Cost-effectiveness and quality of life analysis Difference in quality of life and cost-effectiveness	Patients were eligible for inclusion in the study if they had progressive chronic kidney disease (patients with a failing kidney transplant were eligible) and an eGFR between 10.0 and 15.0 mL/min/1.73 m^2 Patients could not be included in the study if they were <18 years of age, had an eGFR <10.0 mL/min, had plans to receive a kidney transplant from a live donor within the next 12 months, had a recently diagnosed cancer that was likely to affect mortality or were unable to provide written informed consent	Age: early starters: 60.0 ± 13.2 years, late starters: 60.5 ± 12.1 years Male: early: 64%, late: 64%. DM (PRD): early: 33.2%, late: 34.6% DM (comorbid): early: 42%, late: 43.6%	Late start of dialysis group ($eGFR_{CG}$ 5–7 mL/min) (*n* = 335) Early start of dialysis group ($eGFR_{CG}$ between 10–14 mL/min) (*n* = 307) Time to dialysis: early: 1.90 months, late: 7.30 months 4.15 years of follow-up	Quality of life QALY Total cost of treatment	Difference in quality of life between early and late start: 0.00 (−0.03–0.03) QALY: early: 1.97 (1.81–2.14), late: 2.07 (1.92–2.21) Difference in QALY (adjusted for baseline quality of life): −0.09 (−0.12–0.31) Early start group: $215 354 ($114 777–$311 713) versus Late start group: $202 124 ($114 636–$288 704)	High	Selection bias: low, performance bias: unclear, detection bias: low, attrition bias: low, reporting bias: low, other bias: unclear	Randomized trial comparing early versus late with respect to costs on dialysis. There is an absence of quality of life and mortality advantage for early start of dialysis, whereas it costs more and patients are dialyzed for a longer period of time

Hwang *et al.* [25]	2010 Asia 2001–04	Retrospective cohort study $n = 23\,551$ 42.9% DM 100% HD Cox regression Mortality	Incident HD patients between July 2001 and December 2004 Patients with age <20 years, PD as primary treatment, incomplete ID digits, eGFR >15 mL/min/1.73 m^2 at start of dialysis or mortality <3 months (90 days)	Age: 61.5 ± 14.0 years Male: 47.7% DM (PRD): 42.9% $eGFR_{MDRD}$: 4.7 (3.6–6.1) mL/min	Reference = 1st quintile [eGFR <3.29 mL/min) ($n = 4669$) 2nd quintile (eGFR (MDRD) 3.29–4.27 mL/min] ($n = 4749$), 3rd quintile (eGFR 4.28–5.20 mL/min) ($n = 4727$) 4th quintile (eGFR 5.21–6.51 mL/min) ($n = 4708$) 5th quintile (eGFR ≥6.52 mL/min) ($n = 4698$) Follow-up: 22 291 patient-years in 23 551 patients	Mortality/ mortality	$HR_{AdjQ2\ versus\ Q1}$: 1.18 (95% CI 1.01–1.37) $HR_{AdjQ3\ versus\ Q1}$: 1.21 (95% CI 1.04–1.41) $HR_{AdjQ4\ versus\ Q1}$: 1.66 (95% CI 1.43–1.93) $HR_{AdjQ5\ versus\ Q1}$: 2.44 (95% CI 2.11–2.81)	Moderate	8	Large observational study in incident Taiwanese HD patients with adjustment for confounding

HD, haemodialysis; PD, peritoneal dialysis; PRD, primary disease; QALY, quality-adjusted life-year; USRDS, US Renal Data System.

question in 23 551 Taiwanese incident haemodialysis patients. Based on quintiles of renal function at the start of haemodialysis, patients were divided into five groups, with the fifth quintile representing the earliest start. They demonstrated that there was a dose–response relationship between the level of eGFR at the start of dialysis and risk of mortality on dialysis. Results were adjusted for potential confounders and the first quintile served as reference [Q2: $HR_{Adj} = 1.18$ (95% CI 1.01–1.37), Q3: $HR_{Adj} = 1.21$ (95% CI 1.04–1.41), Q4: $HR_{Adj} = 1.66$ (95% CI 1.43–1.93) and Q5: $HR_{Adj} = 2.44$ (95% CI 2.11–2.81)]. A more recent cohort study in incident haemodialysis patients by Clark *et al.* [23] found that 8441 patients in the CORR cohort who started dialysis early [eGFR (MDRD) >10.5 mL/min] had an 18% greater risk of dying on dialysis [HR = 1.18 (95% CI 1.13–1.23)] compared with late start of dialysis [eGFR (MDRD) ≤10.5 mL/min] in 17 469 incident haemodialysis patients.

The final observational study was conducted by Jain *et al.* [21] and did not detect a survival benefit or disadvantage of starting dialysis early or late. They used the same CORR cohort to study this association, but now in incident peritoneal dialysis patients, and demonstrated that neither an early start of dialysis ($n = 2994$) [eGFR (MDRD) >10.5 mL/min; HR = 1.08 (95% CI 0.96–1.23)] nor a mid-start of dialysis ($n = 2670$) [eGFR (MDRD) 7.5–10.5; HR = 0.96 (95% CI 0.86–1.09)] led to an increased mortality risk compared with 2383 patients who started late [eGFR (MDRD) <7.5 mL/min].

Finally, the IDEAL study, of which we reviewed two articles, gave an answer to the question of whether early or late start of dialysis leads to better or worse survival, quality of life and cost-effectiveness. Cooper *et al.* [7] investigated survival, and their results show that there is no difference in survival between patients initiating dialysis early versus late [HR = 1.01 (95% CI 0.83–1.30), P = 0.92]. Furthermore, they found no interaction with diabetes, implying that for patients with diabetes there is no benefit of starting dialysis early or late (P for interaction = 0.63).

Quality of life and costs. Harris *et al.* [24] investigated quality of life on dialysis in the IDEAL population. The patients who started dialysis early had a similar quality of life on dialysis as patients who started late [mean difference −0.00 (95% CI −0.03–0.03)]. Harris *et al.* [24] also performed a cost-effectiveness study and investigated the effect of early or late start of dialysis on quality of life on dialysis in the IDEAL study population. They demonstrated that on average the early start group has more total costs than the late start group, i.e. $215 354 (95% CI $114 777–$311 713) versus $202 124 (95% CI $114 636–$288 704). This is also true for dialysis-related costs [$117 163 (95% CI $54 844–$168 307) versus $96 763 (95% CI $45 012–$155 662)] in the early and late start of dialysis groups, respectively.

DISCUSSION

Our systematic review, including 11 studies for a total of 581 445 patients with diabetes in which a comparison between early and late start was made, found conflicting results with

regard to the benefit of early or late start of dialysis in patients with diabetes and advanced CKD. Six observational studies reported better survival in the patients who started dialysis with a lower eGFR. One observational study reported no difference in mortality between patients who started early or late. Lastly, two observational studies reported a benefit for early start of dialysis with respect to survival. Only one of these nine observational studies reported separate results for patients with diabetes and did not demonstrate a difference in outcome between patients with and without diabetes [20]. The only RCT reported separate results for diabetes patients in an interaction analysis. The IDEAL investigators found no difference between early and late start of dialysis and subsequent mortality on dialysis and found no interaction between diabetes and early start of dialysis with respect to their primary outcome. Overall, there seems to be no evidence supporting that patients with versus without diabetes should start dialysis earlier or based on different criteria.

The IDEAL study is a large RCT that included patients with an eGFR of 10–15 mL/min, comparing start at eGFR of ∼10 versus ∼5–7 mL/min/1.73 m^2. The authors concluded that there was no difference between the late and early start group in terms of mortality. Based on an interaction analysis, the conclusions of the study are not different for patients with versus without diabetes. However, a substantial number of patients who were allocated to the late start group (5–7 mL/min/1.73 m^2) in fact started before their eGFR declined below 7 mL/min because of uraemic symptoms. As a consequence, the question answered in real practice changed, and IDEAL provided evidence that not eGFR, but rather the presence of uraemic symptoms should be taken into account in the decision to start dialysis [13]. However, in patients with diabetes it might be cumbersome to make a distinction between true uraemic symptoms and symptoms secondary to diabetes. As a consequence, some of the patients with diabetes and advanced CKD might be initiated on dialysis earlier than needed with respect to kidney function, in an attempt to relieve disturbing symptoms that are in fact attributable to diabetes. Nevertheless, compelling evidence supporting the presumed benefits of an early start of dialysis is lacking.

Delaying the start of dialysis in patients who need it might be deleterious, as demonstrated by Tang *et al.* [19]. These authors compared mortality between patients who chose to start dialysis —the elective starters—with that of patients who preferred to wait, the initial refusers, finding a higher mortality in the initial refusers. Nevertheless, it still might be that these initial refusers are considerably different, e.g. in terms of compliance, health literacy or social background, from the elective starters and that these differences affected their survival probabilities. On the other hand, start of dialysis also carries some additional risk for the patient. There is the potential for haemodynamic instability and cardiac hypoperfusion during a haemodialysis session [27, 28] and the risk of anticoagulation. There is also, over the longer term, the problem of the untimely wear of the vascular access and the potential for accelerated decline of residual renal function [29]. In peritoneal dialysis, there is the risk of peritonitis and wear-off of the peritoneal membrane [30]. Besides these medical arguments, dialysis also disrupts quality of life for most patients. As a consequence, the potential benefits of starting dialysis earlier should be balanced by the potential drawbacks.

All other observational studies reported higher mortality in the patients that started at a higher eGFR. However, these observational studies are prone to bias. First, it has been demonstrated in other studies that patients with more comorbidity have a higher eGFR at the start of dialysis. This can be due to the effect of muscle mass wasting on creatinine generation and thus eGFR, but also to the presence of fluid overload, causing dilution of serum creatinine and thus higher eGFR. Second, there might be indication bias, as patients who do poorly are started on dialysis in an attempt to reverse their negative course. These two forms of bias were partly dealt with by multivariate adjustment for potential confounders, but residual confounding may well exist. Third, most of these observational studies include only patients who actually started dialysis. Patients who started late can have a survival-of-the-fittest bias, as less fit patients might have died before they actually had the opportunity to start dialysis and are thus dropped from the analysis.

Another important source of bias in these observational studies, however, is lead time bias. In studying the effect on mortality, for patients who start early, one starts counting earlier compared with for patients who start late. Consequently, finding no survival benefit after start of dialysis for patients who start early thus means that the early starters live, on average, the same amount of time after the start of dialysis, but because they start at an earlier time, they also die at an earlier time. On top of this loss in survival time, patients who initiate dialysis early lose valuable dialysis-free time compared with patients who start late and are, by default, dialysis free for a longer amount of time. It may be difficult to estimate the magnitude of this lead time, i.e. the calendar time between early and late start, but a number of studies have been able to estimate this time frame. First, Korevaar *et al.* [31], in 2001, estimated the amount of lead time based on a review of the literature and found that after correction for a lead time of 4–8 months, early start was associated with worse survival. Second, in 2002, Traynor *et al.* [32] were able to estimate lead time in their own patients by going back to patient records and estimated, by interpolation, the date of eGFR = 20 mL/min/1.73 m^2 in 235 patients using known dates on which eGFR was above and below 20 mL/min/1.73 m^2. This enabled them to calculate the lead time bias in those 235 patients, which was 8 months. Third, the IDEAL study, published in 2010, obviously had no lead time bias, because of the randomization, but the difference in time to start for early versus late start was 6 months. Most observational studies reported on in this review did not take lead time into account, most likely thereby underestimating the negative effect of early start of dialysis on survival.

Interestingly, from the 11 studies that are reviewed here, the 2 articles that found that early start was beneficial with respect to survival and the one finding no difference included exclusively peritoneal dialysis patients [19, 17]. It can be speculated that peritoneal dialysis is a more gentle treatment than haemodialysis [27] and therefore the potential benefits of starting

dialysis earlier might more easily balance out eventual drawbacks of the treatment. The IDEAL trial, however, did not find a difference in the impact of late versus early start of dialysis according to renal replacement modality [21]. Further research to explore these observed differences is warranted.

Our review has some strengths and limitations. A major limitation is that we were unable to find a large number of (high quality) studies that specifically investigated the associations between early and late start of dialysis with mortality on dialysis in patients with versus without diabetes. We therefore opted to include studies that investigated our research question in a population containing a large enough subgroup of diabetes patients. This might hamper the generalizability of our results to the true diabetic CKD population, since the conclusions of these studies that also included variable numbers of patients without diabetes might not be representative for patients with diabetes and advanced CKD. However, we feel our final conclusion is valid, as it is supported by an RCT reporting an interaction analysis with diabetes [7].

The heterogeneity among the studies was quite high, with differences in sample size, size of the subgroup of patients with diabetes and initial dialysis modality. This prevented us from pooling data together and performing cumulative meta-analyses. Lastly, although we performed a systematic search, the possibility of publication bias still remains present.

Our study also has some strengths: as mentioned, we performed a systematic search according to a strict methodology. All article selection and data extraction were reviewed independently by two reviewers and a third who resolved potential disputes about the content among the first two reviewers. A notable strength of this review is that it includes two articles on an RCT controlled trial of which one reports the outcomes of an interaction analysis with the group of diabetics. Also, one observational study reports separate results for diabetics compared with non-diabetics.

In conclusion, whereas observational studies with regard to timing of dialysis initiation mostly find that an earlier start is associated with poor survival on dialysis, it is clear that they deal with a number of methodological issues that hamper the comparability of the early and late start group. The only RCT comparing early and late start of dialysis with respect to mortality, quality of life and cost-effectiveness on dialysis concludes that there is no difference in survival between early and late start and that diabetic status does not alter this relationship. What this latter trial demonstrates above everything is that the decision to start dialysis is indeed very complex and relies on a plethora of factors that can sometimes be hard to evaluate, especially in patients with diabetes. This conclusion supports recent recommendations by the ERBP group and by the Canadian Society of Nephrology [33].

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

None of the authors reports a conflict of interest with regard to issues dealt with in this systematic review. The declarations of interest of interest of the different authors can be found online at http://www.european-renal-best-practice.org.

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