The issue of studying the effect of interventions in renal replacement therapy—to what extent may we be deceived by selection and competing risk?

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Abstract
Patients with chronic kidney disease (CKD) who live up to renal replacement therapy (RRT) are a selected group of patients with a high mortality risk. The aim of this paper is to contribute an epidemiological explanation as to why therapeutic interventions—targeting specific causes of death—of which the effectiveness has been shown in the general population may not have a similar impact in a highly selected population like RRT patients. In this perspective, selection processes over the course of renal disease progression as well as the potential ‘dilution’ of an effect in the presence of highly increased mortality from other causes need attention. We suggest that the results from well-conducted high-quality studies in incident RRT patients without or with only very limited in- and exclusion criteria are likely the ones best qualified to be extrapolated to other RRT populations.

Keywords: competing risk; methods; renal replacement therapy; selection; survivor bias

Introduction
Patients with chronic kidney disease (CKD) who live up to renal replacement therapy (RRT) are the vulnerable survivors of a huge group of individuals with renal disease. Such patients have outlived their even more vulnerable counterparts who died sometimes long before ever reaching end-stage renal failure. Nevertheless, the age- and gender-standardized mortality rates in these survivors who have reached RRT are eight times as high as those in the general population [1].

The aim of this paper is to contribute an epidemiological explanation as to why therapeutic interventions—targeting specific causes of death—of which the effectiveness has been shown in the general population, may not have a similar impact in a highly selected population like RRT patients. To this end, it makes an attempt to quantify in numerical terms the patient ‘selection’ that takes place during the different stages of renal function decline when many people stay alive without the significant progression to renal failure, a substantial number die and only a limited number reach RRT. Such patient selection during progression of renal failure may be further aggravated during the course of RRT, inducing survivor bias in studies where investigators make use of existing (prevalent) RRT patients. Finally, this paper describes the potential effect of competing risk in the RRT population itself, where death from other causes may compete with specific causes of death.

Patient selection during the progression of renal failure

Many patients with CKD die before reaching RRT. In the UK Prospective Diabetes Study (UKPDS), Adler and colleagues showed that in each stage of nephropathy, the annual transition rates to death are higher than those to the next stage of renal failure [2]. Also, in a systematic review on CKD and mortality risk, Tonelli et al. clearly demonstrated an exponential relationship between the severity of renal dysfunction and the risk of all-cause mortality. During a median follow-up of 4.9 years, the predicted risk of death increased from 12% at an eGFR of 80 mL/min to 25% when eGFR was 40 mL/min [3]. Further extrapolation to an eGFR level of 20 mL/min suggested a predicted mortality risk of ~40%.

More recently, other studies provided information on death as compared with reaching RRT. In a study performed in a clinical database of almost 28 000 patients insured with the US Kaiser Permanente health plan, outcome
was determined in patients in different stages of CKD. Patients in stages 2, 3 and 4 were followed up for an average period of 50, 51 and 38 months. Figure 1 shows that, whereas in CKD stage 2, 20% of patients had died, and 1% had started RRT at the end of the observation period; in stage 3, this was the case for 24% and 1%, and in stage 4 for 46% and 20%, respectively [4]. So, in absolute terms, the risk of death becomes higher with declining renal function. However, in those alive over the different stages of renal function decline, the relative chances of death and RRT are changing in favour of RRT.

In the previous paragraphs, we outlined that RRT patients are the survivors of a group of individuals with a very high mortality risk. The left part of Figure 2 shows this process of increasing selection during the progression of renal failure before the start of RRT. An example of a recent study that provided results that may, in part, have been a consequence of this progressive selection process was published by the Swedish nationwide coronary care unit registry SWEDHEART [8]. These investigators studied whether patients with non-ST-elevation myocardial infarction derive a similar benefit from an early invasive therapy at different levels of renal function (in categories from ≥90 to <15 mL/min/1.73 m²). They found that while fewer patients were treated invasively with declining renal function, the risk of death becomes more frequent with declining renal function, in those staying alive over the course of disease progression, the relative chances of death and RRT are changing in favour of RRT.

Fig. 1. Patient outcome in CKD stages 2–4 after an average observation period of 50, 51 and 38 months in patients insured with the US Kaiser Permanente health plan [4]. Whereas death as an outcome becomes more frequent with declining renal function, in those staying alive over the course of disease progression, the relative chances of death and RRT are changing in favour of RRT.

Fig. 2. The process of increasing selection during the progression of renal failure as a result of death as a competing event for reaching RRT (left part of the figure). On RRT, further selection takes place inducing survivor bias in studies using prevalent patients (right part of figure). The right part of the figure also shows that on RRT, death from other causes is competing with death from a specific cause. For this reason, the effects of studies on therapeutic interventions targeted at cause-specific mortality may be ‘diluted’ as a result of the huge overall mortality risk in RRT.
function, the survival advantage (36% lower mortality at 1 year) declined with lower renal function and even converted to a tendency towards harm in patients with an eGFR <15 mL/min/1.73 m² (hazard ratio 1.61, 95% confidence interval 0.84–3.09). As this was an observational study, confounding by indication (worse results of an intervention in patients who received it, because they were worse off before treatment, than those who did not receive it) may be one of the explanations for the findings. The authors, however, speculated that the lack of survival advantage in patients with more advanced renal insufficiency may be due to more advanced atherosclerosis that is not easily treated with revascularization, and also that in these patients, atherosclerosis is in part caused by other mechanisms that have also been outlined in other papers [9,10]. Such unusual clinical characteristics — the ‘deviations from normal’ — for example caused by a potential lower vulnerability to traditional risk factors than those who died or by a different genetic make-up that allows better adaptation to an increasingly disadvantageous uraemic milieu, may constitute the basis for a ‘survival of the fittest’.

This selection process continues during the course of RRT as is shown in the right part of Figure 2. If used within the context of (flaws in) study design, this selection is usually referred to as survivor bias. Survivor bias is a specific form of selection bias, also known as prevalence-incidence bias. It is defined as a bias that occurs when we try to estimate the risk of a disease or death on the basis of data collected at a given time point in survivors rather than on data gathered in a group of incident cases [11,12]. This bias is particularly relevant in cross-sectional studies but may also occur in case-control and cohort studies using existing (prevalent) patients. To avoid survivor bias, studies in RRT patients will need to make use of new (incident) RRT patients. An example of this is given in Figure 3 which depicts the consecutive patients in a hypothetical renal centre with five dialysis stations. Patients are starting dialysis, and when they die, they are being replaced by new dialysis patients. Let us suppose that the nephrologist in charge would like to perform a study in his centre. He may argue that it is easier for him to perform the study in prevalent patients, because in this way, he will sooner reach the number of patients needed to answer the study question. Figure 3 shows that at any time of prevalent patient sampling for the study, there will be an over-representation of patients (three out of five patients) who have been on dialysis for a longer period of time. Because also these dialysis survivors constitute a ‘selected’ group of patients, they may have other clinical characteristics compared with patients starting dialysis. In summary, selection — whether or not within the context of study design where it is referred to as survivor bias — is a process that results in individuals that may not be representative and therefore cannot be easily compared with less selected groups like the general population or the RRT patients in general.

Survivor bias — and selection for that matter — may distort the relative risk in either direction [11], and as a result, a risk factor like a therapeutic intervention that is known to reduce the risk of death in the general population may not affect or even increase risk in RRT patients and vice versa. Therefore, studies in the ‘selected group’ of RRT patients may provide results that are contradictory to results from studies in less selected populations like the general population. Likewise, studies in prevalent RRT patients may provide results conflicting with those performed in incident RRT patients.

**Death from ‘other causes’ as a competing risk for death from specific causes in RRT**

The authors of the same paper on this SWEDEHEART registry also put forward that patients with advanced renal insufficiency may have comorbidities that increase their risk of death, both cardiac and non-cardiac, and that this increased risk of death may be unaffected by treatment choices [8]. As outlined earlier, the risk of death increases with the decline of renal function [3] to reach ~45% at 5-year follow-up in RRT patients [13]. In the latter group, mortality from different causes, that is cardiovascular and non-cardiovascular (including infection- and malignancy-related death), is on average eight times as high as in the general population [1]. This increased competing risk of death from other causes is illustrated in the right part of Fig. 3. An example of survivor bias in a study in existing (prevalent) dialysis patients. Patients who die are being replaced by new ones. When these patients are measured in a cross-sectional study or included in a cohort study at any of the time points (t1, t2 or t3), the patients who live longest — the survivors — (three out of five patients) will be over-represented. Circles denote start of RRT, daggers denote death and t denotes time of sampling patients.
Selection and competing risk in RRT intervention studies

Figure 2. Any effect of an intervention targeting a specific cause of death may therefore be ‘diluted’ by the tremendously increased mortality risk from other causes. Only a considerable reduction of death from those other causes would make a beneficial effect of such an intervention visible. Therefore, as a comment to the paper by Szummer et al., Szczech wondered whether or not it is reasonable to conclude that revascularization indeed offers no benefit in the presence of an importantly increased risk of, for example, sudden cardiac or infection-related death [14]. In other words, the benefit of revascularization remains possible in those who remain infection-free or do not die suddenly.

The consequences of studying selected patient populations

In this paper, we have discussed potential epidemiological explanations as to why findings on the effectiveness of interventions in RRT patients may sometimes deviate from findings on the effectiveness of the same interventions in the general population. Both selection and competing risk from other causes of death than the specific one under investigation — resulting in the ‘dilution’ of an effect — may contribute to these dissimilar results.

In general, randomized controlled trials are criticized for their sometimes low generalizability to other patient populations, as they tend to be conducted in selected patient populations [15,16]. This may particularly be the case for studies performed within the RRT population because of the unusual risk profile of these patients.

Conclusions

For nephrologists to understand why ‘negative studies’ in RRT patients are negative, they may consider epidemiological explanations in addition to any clinical explanations. With regard to epidemiological explanations, selection processes over the course of renal disease progression as well as the potential dilution of any effect in the presence of highly increased mortality from other causes need attention. With respect to clinical explanations, a better understanding is needed of biological mechanisms both in increased cardiovascular and non-cardiovascular mortality, and of the related potential change in the relative importance of risk factors throughout the spectrum of disease progression. For this, we need observational studies including patients progressing from early stages of renal disease to advanced renal failure.

As far as the investigation of treatment or other risk factors is concerned, we suggest that the results from well-conducted high-quality studies in incident RRT patients without or with only very limited in- and exclusion criteria are likely the ones best qualified to be extrapolated to other RRT populations.

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