Negative outcome studies in end-stage renal disease: how dark are the storm clouds?

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ESRD—the epidemiological challenge

The end-stage renal disease (ESRD) population treated by dialysis has grown remorselessly over the last five decades, in all continents. This growth is already a major burden to the healthcare economies of wealthy countries, and is thus a challenge for policy makers, health care providers and financial planners [1]. Fortunately, recent data (just published in NDT) suggest a stabilization/decline in the incidence of ESRD in some developed countries, possibly related to the successful implementation of renoprotective strategies in pre-dialysis chronic kidney disease (CKD) [2,3].

Dialysis patients have an impressive and worrying mortality, comparable to or worse than that seen in many cancers, e.g. 20–25% annualized mortality in some systems [4]. Around 50% of this increased mortality is due to cardiovascular (CV) disease. This is explicable, as at the start of dialysis, up to 80% of subjects already have at least subclinical CV disease.

Despite significant progress in many branches of medicine over the last decades—for example, significant reductions in myocardial infarction and stroke rates in the general population [5,6]—mortality rates for dialysis patients remain practically unchanged [4,7] over the same time period. This is first explained by more liberal criteria for inclusion in renal replacement therapy (RRT) programmes, with more elderly, diabetic and CV-diseased patients treated by dialysis in recent years. Second, CV disease in ESRD is often underinvestigated and undertreated, compared to CV disease in non-renal cohorts [8]. Third, therapeutic interventions in dialysis patients aimed at reducing CV morbidity and mortality may be either ‘too little, too late’ or inadequate, as most traditional and uraemia-specific [9] risk factors start to exert their deleterious effects long before initiation of RRT.

Hard scientific data on life-prolonging therapy in chronic dialysis patients have been peculiarly and worryingly scarce for many years, with the result that it has been necessary to try to extrapolate from studies in the general population—from which of course patients with any significant degree of renal impairment, and clearly all dialysis patients, have by design been excluded. Applying treatment strategies verified in the non-renal populations to CKD patients is a highly debatable approach for several reasons, such as a particular, unique, CV risk profile, currently referred to as ‘reverse epidemiology’ [10].

Eventually, and in the last few years, results from properly conducted prospective, randomized controlled trials (RCTs) become available. It is no secret that the rather surprising general trend of these efforts has been ‘negative’—with few real exceptions. This has now germinated a pessimistic mood in the renal community—renal nihilism or ‘renalism’ [8]! We will analyse briefly the most significant results of recent RCTs of therapeutic interventions aimed at reducing mortality in ESRD (and to some extent, also in pre-dialysis CKD).

Dialysis dose and mortality

The dose of dialysis delivered and the size of molecules removed became early tempting targets with the aim of reducing morbidity and mortality. The National Cooperative Dialysis Study, the first randomized trial on dialysis dose and morbidity [11], demonstrated the beneficial effect of an increased dialysis dose on morbidity, but at dialysis doses well below the current standards and in patients with substantially fewer co-morbidities than those found in current haemodialysis (HD) populations. Subsequent observational studies have suggested that the use of high-flux dialysis membranes, with an improved clearance of middle-sized molecules, is associated with improved outcomes. Therefore, the HEMO study was the first randomized clinical trial designed to determine whether increasing the dose of dialysis or using a high-flux dialyzer membrane improves survival or morbidity among patients undergoing HD, and the results were disappointingly negative [12]. Eligible
patients were randomly assigned in a 1:1 ratio with a 2 × 2 factorial design, to either a standard-dose (equilibrated kT/V 1.05) or a high-dose goal (ekT/V 1.45) and to dialysis with either a low-flux or a high-flux dialyzer. After adjustment for baseline factors, the high-dose group had a risk of death that was only 4% lower than that of the standard-dose group, and the high-flux group had a risk of death that was 8% lower than that of the low-flux group—i.e. a non-significant difference. The only significant interactions were between the dose intervention and gender (women in the high-dose group had a 19% lower risk of death than the standard group) and between the flux intervention and dialysis vintage (patients in the high-flux group with more than 3.7 years on dialysis had a 32% decreased risk of death compared to the low-flux group) [12]. The reason for this possible gender effect is not clear. Also supported by several observational reports [13,14], high-flux dialysis/online haemodiafiltration might be the method of choice in (some groups of) dialysis patients, particularly the malnourished, low-albumin individuals, as shown by the recently completed MPO trial [15].

For peritoneal-dialysis (PD) patients, small-solute clearance targets have often been established on the basis of the unproven assumption that peritoneal and renal clearances are equivalent and therefore additive. The ADEMEX [16] trial was the first prospective, randomized, controlled, interventional trial to examine the effects of increased peritoneal small-solute clearances (goal: to achieve a peritoneal creatinine clearance of 60 L/week) compared to standard dialysis prescriptions on survival for patients undergoing PD. Despite differences in small-solute clearances, patients’ survival was similar for the control and intervention groups, even after stratification for several factors.

In summary, the available evidence does not support a net beneficial effect on patients’ survival of increasing the dialysis dose (PD and HD). The most plausible explanations for these negative results are probably related to the following issues: (i) undefined non-dialyzable toxins may have a significant clinical impact; (ii) the peculiar kinetics of removable toxins add no benefit for ‘intensive’ dialysis regimens and (iii) several observational studies which suggest that daily 2–3 h HD has a favourable impact on certain clinical parameters [17]. The frequent haemodialysis network (FHN) is currently testing the latter hypothesis, comparing standard thrice-weekly HD with in-centre daily dialysis and home nocturnal dialysis, respectively [18]; however, even positive results will hardly impact on daily clinical practice, as frequent dialysis is very difficult to implement for more than a small minority of patients.

**Targeting CV risk factors—the ‘disappointing statin issue’**

Primary and secondary prevention trials in the general population have documented substantial CV benefits from lipid-lowering strategies, particularly with the use of statins. In nephrology, current evidence has relied on one or two studies, and these are firmly negative. The 4D Study [19] randomized almost 1300 subjects to either atorvastatin (20 mg/day) or placebo. The primary end point (a composite of death from cardiac causes non-fatal myocardial infarction and stroke) was similar with atorvastatin or placebo in the two groups, despite the pronounced and sustained LDL cholesterol—lowering activity of atorvastatin. Moreover, more cases of fatal stroke occurred in the atorvastatin group than in the placebo group. The study investigators proposed some explanations for these results: (i) a different pathogenesis of vascular events in uremic diabetic patients; (ii) the presence of additional pathogenetic pathways different from the traditional CV risk factors and (iii) structural abnormalities that can no longer be reversed [19].

Clearly, more outcome studies on statin therapy in predialysis and dialysis CKD patients are now very urgently needed. The ongoing SHARP-2 and AURORA studies in these populations should give us some usable answers; SHARP-2 will be by far the largest outcome study in any CKD setting, with 6000 pre-dialysis and 3000 dialysis patients now enrolled to simvastatin and ezetimibe versus placebo. Until then, of note, in renal-transplantation patients (an imperfect ‘model’ of CKD), according to the ALERT study, fluvastatin had no impact on the composite CV end point of cardiac death, non-fatal myocardial infarction or coronary intervention procedure [20].

**Hypertension therapy in ESRD**

Unlike the non-renal population, in ESRD, hypertension is not necessarily a CV risk factor. In contrast, rather low BP (suggesting low cardiac output) is associated with a worse outcome [21]. Observational studies suggest that pre-dialysis systolic BP values in the range of 140–160 mmHg may be the most advantageous for survival, but this has yet to be prospectively confirmed [22]. Surprisingly, only two RCTs are available to date on antihypertensive therapy in uraemic patients [23,24]. One study [23] examined the effect of fosinopril (plus conventional therapy) on combined fatal and non-fatal CV events, again with negative results. After adjustments for risk factors, only very modest trends were observed, suggesting a lower CV risk with the angiotensin-converting enzyme inhibitor. A small controlled Japanese study demonstrated a positive effect of candesartan (versus no therapy) on cardiovascular events and mortality [24]. However, as is so frequently the case in studies of CKD cohorts, these investigations were clearly underpowered (numbers, duration) to permit a reliable conclusion.

Interestingly, this total lack of usable evidence on BP in dialysis has not stopped people from advocating BP targets in dialysis cohorts.

**Homocysteine—a missed target**

High serum total homocysteine (tHcy) is an established risk factor for cardiovascular disease in the general population [25]. In ESRD, mean Hcy levels are commonly elevated and the role of Hcy as an indicator of enhanced CV risk has been confirmed by some prospective studies [26]. Randomized trials have demonstrated that various folate forms and route of administration are effective in reducing hyperhomocysteinaemia in ESRD [27,28]. In the only outcome of RCTs to date, Wrone et al. [29] randomly assigned 510 dialysis patients to 1 mg, 5 mg or 15 mg of folic acid daily, with a median follow-up of 2 years; this showed that
disappointingly, despite effective decreases of serum Hcy levels, there was no difference among the treatment arms in total survival or CV events with different folic acid regimens. According to expert commentary [30], beneficial effects of Hcy-lowering therapy cannot be excluded so far, as there was no real placebo arm in Wrone’s study, and no dose of vitamin supplements affected a normal plasma-Hcy level. Currently, two studies designed to examine the role of combined therapy with folic acid, vitamins B12 and B6 in advanced CKD and in renal transplantation patients, respectively, are underway. We are not optimistic—despite maximal effort, it is rarely if ever possible to normalize tHcy levels in ESRD patients, and there is a potential confounder of a separate beneficial effect of folate therapy on endothelial dysfunction (not related to tHcy reduction) [31]. Finally, it is important to note that Hcy might be just a marker and not the cause of enhanced CV risk (see [32]). This might be one of the reasons why lowering Hcy levels appears to be ineffective in reducing CV risk.

Influencing mineral-metabolism parameters

Correction of mineral-metabolism disorders is crucial for survival in ESRD. Block and colleagues [33], analysing a sample of >40 000 HD patients, found significant associations between survival and normal phosphate, calcium and parathormone levels. Disorders of mineral metabolism accounted for 17.5% of population attributable risk, much more than the risk conferred by inefficient dialysis (5%) or anaemia (11%). Furthermore, in the real world of clinical practice, the goal of normalizing all mineral-metabolism parameters is achieved in a minority of patients; in a recent survey in Spanish dialysis centres, just roughly 11% of patients reached all guideline targets [34]. A similar pessimistic view emerged from the analysis of data in the Dialysis and Outcome Practice Pattern Survey (DOPPS) population [35].

Hyperphosphataemia and a raised calcium–phosphate product are clearly deleterious for ESRD patients. Areal calcification, arterial stiffness and bone and other organ pathology can ensue. High doses of vitamin D and calcium-containing phosphate binders (CCPBs) may play a negative role if misused [36]. Non-CCPBs such as sevelamer (or possibly lanthanum carbonate, magnesium, iron) may lessen vascular calcifications [37]. However, the effect of non-CCPBs on outcome is a subject to debate; a very recent study assessing all-cause mortality in 127 patients new to HD demonstrated a better survival with sevelamer compared to conventional calcium-based phosphate-lowering therapy [38]. In contrast, data from the DCOR study (to be published soon) showed no benefit of sevelamer over calcium-containing phosphate binding therapy on the outcome, through the entire study population during the 3 years of follow-up. There was a survival advantage with sevelamer in elderly patients, this effect being apparent later during therapy. Outcome studies concerning the other major non-CCPB—lanthanum carbonate—are disappointingly lacking. Calcimimetic agents like cinacalcet, used for treating secondary hyperparathyroidism in ESRD, have been associated with significant improvements in biochemical parameters that observational studies demonstrated to be associated with increased mortality, CV risk and osteitis fibrosa, but patient-based benefits have not yet been demonstrated in trials. This we hope will change with the EVOLVE study, which is currently recruiting 3800 patients with a follow-up period of 4–5 years, using hard end-point trial parameters. For patients with secondary hyperparathyroidism, the benefits of calcimimetics over standard therapy remain uncertain, until results from further RCTs become available [39].

The anaemia story in CKD—a lost opportunity

Untreated anaemia is clearly a negative prognostic factor in ESRD. Partial correction of anaemia is improving both echocardiographic parameters and quality of life in ESRD [40]. However, normalization of haemoglobin (Hb) in prospective trials in both prevalent and incident dialysis patients did not significantly improve the ventricular geometry or decrease the risk of death [41–43]. This whole area has become very controversial lately and has been addressed in many other articles and journals.

Subsequently, the idea of timely correction of anaemia, long before ESRD occurs, appeared as a more promising approach. Again disappointingly, the recent publication of two RCTs in pre-dialysis CKD stage 4 patients—CREATE and CHOIR—offered negative results. Therapy with erythropoietin (EPO) did not improve the outcome in pre-dialysis patients from three continents [44] and from the USA [45]. This is in accord with the negative results from two recently published smaller trials on the impact of anaemia correction on cardiac geometry in patients not yet on dialysis [46,47]. Moreover, it is possible that the trend towards more clinical events in the high-Hb target arm in the CHOIR study be attributed to the high doses of EPO used, as this may have a deleterious vascular effect per se. CREATE and CHOIR have helped to focus attention on the need for RCTs, the need to look critically for evidence rather than accept blandishments and recommendations from conflicted parties; nevertheless, these studies have not yet sufficiently answered the key question of if there is an optimal Hb level for patients with CKD. For this purpose, large observational trials and benchmarking projects may be more suitable.

Some hope beyond dark clouds?

Remarkably, a few positive RCT studies have actually been published in the ESRD population. Cicé et al. [48] demonstrated, in a small placebo-controlled study in 114 dialysis patients with dilated cardiomyopathy, that carvedilol therapy reduces overall and CV mortality, as well as the hospital admission rate. The SPACE study [49] analysed the fate of almost 200 HD patients with pre-existing CV disease, assigned to either 800 IU vitamin E or placebo. This investigation showed a significant difference in the composite CV end point and in the myocardial infarction rate with antioxidant vitamin E therapy. However, neither CV mortality nor other component outcomes were influenced by vitamin E as antioxidant therapy. Moreover, recent data from RCTs on vitamin E therapy in the general population are invariably negative. Another antioxidant therapy—acetylcysteine (600 mg b.i.d.)—has been investigated in a
placebo-controlled RCT [50]. The difference was again significant for the primary composite end point, but not for the total and CV mortality rates of each CV component of outcome. Therefore, until larger studies in ESRD patients are available, no clear-cut conclusion on antioxidant therapy in dialysis patients can be drawn. These are intriguing data, but few, if any, clinicians have adopted these approaches and more research is urgently needed. Finally, although resulting from a retrospective cohort analysis, the data of Herzog and colleagues regarding the use of implantable cardioverter defibrillators in ESRD patients hospitalized for ventricular fibrillation/cardiac arrest should also be mentioned. Implantable defibrillators appear to reduce mid- and long-term mortality by 35–55% [51].

The multiple bullet approach—can it work for dialysis patients?

Whereas the single therapeutic approach may be misleading or disappointing, due to study design or several other factors, it is conceivable that a multi-target approach in high-risk CKD patients would have a better chance of working. The Steno-2 approach of Gaede et al. in diabetic patients was, in this sense, encouraging [52]. In a recent retrospective study of 15,000 Medicare dialysis patients, Rocco and co-workers [53] analysed clinical performance measurements (target Hb, serum albumin, use of fistula for venous access, Kt/V ≥ 1.2). Meeting multiple clinical measure targets was clearly associated with a decrease in hospitalization and mortality rates. However again in this area, we now have the results of two recently completed and reported RCT. Rakshit and co-workers [54] randomly compared CKD patients subjected to standard nephrological care to those receiving an aggressive risk factor modification strategy (targeting hypertension, dyslipidaemia, homocysteine, Hb and phosphate). Patients received atorvastatin 20–80 mg/day, folic acid 30 mg/day, alternate monthly vitamin B12 and pyridoxine, EPO and i.v. iron, ACE inhibitors or sartans, phosphate binders (including in some patients sevelamer) and aspirin. The standard and aggressively treated group did not differ in CV event rates or all-cause mortality from the more intensified treatment population. The same Australian group studied both stage 4 and 5 CKD patients, assessing surrogate end points such as atheroma burden (quantified by the intima-media thickness) and endothelial function (measured by means of brachial endothelial reactivity) in conventional- and intensive-treated patients. Unfortunately, no benefit of intensified treatment was demonstrated [55].

How do we deal with (negative) randomized controlled trials?

RCTs are certainly imperfect tools, but appear to be the best we can get to date. RCTs may hide several pivotal methodological flaws; first, underpowering appears to be particularly relevant in renal studies, as opposed to research in the non-renal population subjected to CV risk. This is a combination of over-‘optimistic’ assumptions about event rates and equally rosy assumptions about the therapeutic impact of any intervention. Second, large trials may detect statistically significant differences with active intervention arms, but the number-to-treat analysis may offer rather pessimistic results. Third, significant biases may occur, for instance due to the selection of ‘healthier’ patients for the trial, hiding therefore a survivor effect of a prevalent cohort. The choice of young healthy patients mixed with older very sick patients in a truly ‘randomized’ trial, though ‘correct’, is in our view a serious concern, as it is likely that there will be contemporaneous competing mortality drivers. Fourth, high trial drop-out rates (so typical of renal studies) may potentially mask deaths and account for an artificially low mortality. Finally, it is likely that randomizing patients into a RCT may generally cause a survival benefit (compared to non-study patients), due to a higher intensity of care. This is suggested for instance by the surprisingly low deaths rates in the 4D study as compared to mortality data from the major registries.

These are not reasons to abandon RCTs. They are reasons to look very critically at those already performed, and to take account of these interferences in any such trials planned in the future.

These and other culprits may be overcome by a recent initiative by QUEST-PRIMA, a pragmatic multinational European trial, assessing the effect of care by protocol versus usual care, but according to European Best Practice guidelines. A second ‘control’ group would be derived randomly from the ERA-EDTA Registry. Proposed clinical action plans include individual risk profiling, nutrition, malnutrition-inflammation, vascular access monitoring, HD performance and infection/hygienic measures (C. Wanner, personal communication). Optimal care, rather than specific pharmacologic interventions, is aimed at in this RCT, therefore facing a paradigm shift in clinical research.

What should we do next?

It is easy to succumb to therapeutic nihilism: ‘nothing further can be done for ESRD patients’; at best, something should have been done (meaning therapeutic interventions) long before the occurrence of ESRD. In fact, as we might have thought obvious from our daily practice, an individualized, careful approach to the renal patient may often work. Nevertheless, the nephrological community needs more certainty than this. For the moment, there are more clear-cut negations derived from interventional trials in uraemic patients than there are positive results. The negative trend is rapidly spreading to pre-dialysis CKD; some measures considered a decade ago as a must in nephrology are demonstrated nowadays as having no benefit (e.g. low protein diet) or are subjected to continued debate (ACE inhibitors for retarding the progression of renal disease over and above BP reduction). Currently, our therapeutic approach in renal disease is based on remarkably few hard data (derived from small trials) and more often on opinion-based recommendations and on extrapolations from data in the general population. Perhaps we are not addressing the right targets (or all of the targets) and certainly are not concentrating all the efforts on the fate of CKD patients.

Although always imperfect (by not mimicking real life), properly designed RCTs in uraemic patients (having a
sufficient statistical power) remain a mandatory goal. Furthermore, we agree with the demonstration by Garg, Green and Levin (published in this issue of NDT), that even from negative trials, important influences on theory, daily practice and future research may be filtered. Stopping unnecessary or potentially harmful therapies used before the arrival of hard data from proper trials is just as important a piece of progress in clinical practice. We think that along with the nec plus ultra of the RCT, we also need to nest the primus inter pares of clinical practice epidemiological research.

In our opinion, therapeutic interventions (single or multiple) designed to reduce CV mortality in uraemic patients have probably now reached their limits. No dramatic benefits may be expected from ongoing trials in this severely diseased population. Individualized care and the use of the (few) useful drugs proven in the positive trials is of course rational, but we must be aware that benefits are rather modest; the claims so often made for increasingly expensive pharmacological therapies are ever more seductive and enticing. For outstanding benefits in reducing CV mortality in chronic uraemia, a real breakthrough is needed: will it be the expansion of daily dialysis or new techniques like the combination of haemo- and albumin-dialysis, or portable

defusion? Unfortunately for our patients and for continuous therapies? Or the use of the artificial kidney in chronic uraemia—a puzzling and conflicting story.

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