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Surrogates in chronic disease: misleading substitutes

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INTRODUCTION

Cheaper and easier to measure, surrogate end points are often used as substitutes for clinical outcomes when evaluating response to interventions in clinical trials, and they are used either when it is difficult to collect data based on clinical outcomes or when the sponsor needs clinical trials to be completed quickly and at low cost.

The key criterion for the validity of a surrogate end point is the possibility of predicting the effect of the treatment on the clinical outcome by the effect of the treatment on the surrogate. Surrogate end points are expected to predict clinical benefit or harm on the basis of biological plausibility, epidemiological data (changes in the putative surrogate are correlated with changes in clinical outcomes), and clinical trials showing that changes in clinical outcomes are fully accounted for by the effect of the intervention on the surrogate end point[1].

In chronic kidney disease, blood pressure levels are used as a surrogate end point for kidney disease progression or cardiovascular events; calcium, phosphorus and parathyroid hormone levels as surrogates for renal bone disease (fractures, bone pain) or mortality; haemoglobin as a surrogate for quality of life, cardiovascular events or all-cause mortality; and dose of dialysis as a surrogate for all-cause mortality. Nephrological care is largely driven by surrogates.

However, several studies have challenged the assumption that reliance on surrogate end points can predict the effect of treatment on clinical outcomes. In the non-nephrological area, there are antiarrhytmic drugs such as encainide and flecainide that were used in patients with asymptomatic or mildly symptomatic ventricular arrhythmia after myocardial infarction and which were proven to increase mortality compared with placebo[2]; drugs such as niacin which improve HDL cholesterol but do not decrease cardiovascular events[3]; drugs such as torcetrapib which improved cholesterol profiles but resulted in an increased risk of morbidity and mortality[4]; antihypertensive drugs such as ß blockers which reduce blood pressure level but do not decrease the risk of stroke[5], and oral hypoglycaemic drugs which decrease HbA1c level but increase cardiovascular risk[6].

In the nephrological area, there is anaemia therapy with epoetin which increases serum haemoglobin levels but which was shown to be associated with increased risk of cardiovascular events[7,8]; drugs such as statins which improve cholesterol profiles in dialysis patients but do not reduce cardiovascular morbidity and mortality[9-11]; and dose of dialysis (using different metrics such as Kt/V or URR) which quantifies the removal of small molecular weight uraemic toxins but which has not been shown to reduce mortality[12]. However, a critical question remains: are these studies examples of exceptions or just data challenging the value of surrogate end points?

SURROGATES: IMPERFECT SUBSTITUTES

Low density lipoprotein (LDL) cholesterol, blood pressure and glycaemic levels are among the surrogate end points that are believed to be in the causal pathway for the disease process. Strong associations between their levels and clinical outcomes, observed in epidemiological studies, as well as across a wide range of interventions, make them important surrogate end points. However, even the validity of LDL cholesterol as a surrogate end point has been challenged by studies with drugs such as torcetrapib which improved cholesterol profiles but resulted in an increased risk of morbidity and mortality[4].

In fact, no surrogate end point is a perfect substitute for a clinical outcome. But surprisingly, some surrogate end points frequently used in clinical practice in nephrology, such as calcium and parathyroid hormone levels, are simply based on weak epidemiological associations, as no relevant clinical trial using clinical outcomes has ever targeted any of these putative surrogates as the intervention. Additionally, other putative surrogate end points such as "effective duration of haemodialysis session", "prescribed time of haemodialysis per week" or "number of haemodialysis sessions per week", are merely based on personal beliefs, as there is neither epidemiological nor interventional evidence to support their surrogacy. Therefore, they should not be used as surrogate end points, as overinterpretation of data based on putative surrogate end points can lead to misinterpretation of the evidence.

There are several reasons for failure of surrogate endpoints[13]: (A) The surrogate is not in the causal pathway of the disease process; (B) Of several causal pathways of disease, the intervention affects only the pathway mediated through the surrogate; (C) The surrogate is not in the pathway of the intervention's effect or is insensitive to its effect; (D) The intervention has mechanisms of action independent of the disease process.

Over the years, the use of surrogate end points has been critical to the regulation of medicinal products (including drugs, biologics and devices). However, although it is already known that no surrogate end point is a perfect substitute for a clinical outcome, regulatory authorities continue to approve medicinal products based on the effect on surrogate end points, even when similar products are already available on the market. Although regulators are now frequently requesting postmarketing surveillance studies when approvals are based on putative surrogate end points, a critical question remains: why do they approve new medicinal products of uncertain value when similar products are already available on the market?

FLAWED OR NONVALIDATED SURROGATE END POINTS: ASSOCIATED FACTORS

Haemoglobin levels in patients with chronic kidney disease have been considered as a surrogate end point, based on the association between higher haemoglobin levels and favourable clinical outcomes observed in epidemiological studies. However, several randomised trials have shown that anaemia therapy with epoetin increases serum haemoglobin levels, but may be associated with increased risk of cardiovascular events and no effect on mortality[7,8,14]. Thus, the available evidence does not support the use of serum haemoglobin levels as a surrogate end point for cardiovascular morbidity or mortality, and therefore the effect of epoetin on this flawed surrogate has given false hopes to patients, clinicians, haemodialysis providers and regulators.

Graded associations between uraemia and cardiovascular disease and mortality suggest that interventions which increase dialysis dose may improve clinical outcomes. This suggestion led clinicians to use dialysis dose as a surrogate end point for morbidity and mortality. But has this surrogate been validated?

The influence of dialysis dose on patients' morbidity has been evaluated by the National Cooperative Dialysis Study (NCDS)[15,16], a small randomised trial published in the early eighties. The NCDS included 151 patients undergoing haemodialysis, with a thrice-weekly treatment schedule, followed for a period of 22 months, and evaluated the effect of two mean concentrations of blood urea nitrogen, designated as TAC_{urea} (TAC_{urea} about 50 and about 100 mg/dL). The primary end points were not prespecified.

Up to four reasons for patient withdrawal were allowed: withdrawal for medical reasons, death, transplantation and "other". A patient was considered removed for medical reasons if any medical diagnosis thought to be related to uraemia was included on the exit form. Data from hospitalisations attributed to uraemia were taken from the treatment log. Withdrawal for medical reasons and hospitalisations attributed to uraemia were designated as patient failure (PF), and were considered as end points. The number of patients withdrawn for medical reasons from the high TAC_{urea} groups (31 patients) was significantly greater than those withdrawn from the low TAC_{urea} groups (7 patients). The NCDS was reanalysed four years later using a mechanistic analysis[15], which defined the dose of dialysis as Kt/V. This was the study which gave rise to the concept of Kt/V. The mechanistic analysis showed that morbidity was a discontinuous function of Kt/V and that the risk of PF increased below a single-pool Kt/V of 0.9. However, the interpretation of this study's results have been hampered by methodological problems, such as the small sample size, the low number of events and the absence of pre-defined primary end points in a study with an open label design.

While the dose of dialysis (using different metrics such as Kt/V or URR) has been considered a surrogate end point based on the association between Kt/V or URR and all-cause mortality observed in epidemiological studies, a higher dose of dialysis has not shown to reduce mortality in randomised trials[12]. The HEMO study[12], the only relevant randomised trial that evaluated the effect of the dose of dialysis on mortality, enrolled 1846 patients undergoing thrice-weekly dialysis. Patients were randomly assigned to a standard or high dose of dialysis. The standard-dose goal was an equilibrated Kt/V of 1.05. The high-dose goal was an equilibrated Kt/V of 1.45. Achieved equilibrated Kt/V in standard-dose and in high-dose groups were, respectively, 1.16 and 1.53. After adjustment for baseline factors, the high-dose group had a risk of death that was not statistically different (95 percent confidence interval, –10 to 16; P=0.53) from the standard-dose group.

Therefore, there is a need for well-designed clinical trials evaluating the relationship between the dose of dialysis and patients' morbidity and mortality before dose of dialysis can be validated as a surrogate end point. Whether an achieved equilibrated Kt/V below 1.2 is associated with increased mortality is a hypothesis that has never been tested in relevant clinical trials, and therefore, needs to be evaluated. However, with current environment and prescription patterns, it is unlikely the dose of dialysis will have a significant impact on patients' morbidity or mortality.

In patients with chronic kidney disease, serum phosphorus level is a putative surrogate end point based on the association between higher phosphorus levels and increased mortality observed in epidemiological studies. However, the DCOR[17] trial, the only large randomised trial (enrolling a total of 2103 haemodialysis patients) to evaluate the impact of phosphate binders on mortality, showed no difference on all-cause mortality between patients treated with sevelamer and those treated with calcium-based binders. Importantly, there are no published trials comparing either the effect on clinical outcomes of targeting different levels of phosphorus with phosphate binders, or of treating patients with either phosphate binders or placebo. Therefore, whether lowering serum phosphorus levels has any beneficial effect is largely unknown. While there might be several explanations for the negative results of the DCOR study (such as a high rate of early discontinuation, etc.), in the absence of other large-scale clinical trials using clinically meaningful end points that have targeted phosphorus levels as the intervention, phosphorus should not be used as a surrogate end point.

Sometimes, surrogate end points and clinical outcomes are combined in a composite outcome to increase statistical power. However, in these studies surrogate end points usually include the largest number of events, while clinical outcomes include a small number of events with much smaller effects (or no-effect) of treatment. This is the case of the FHN trial, a randomised clinical trial which aimed to determine whether increasing the frequency of in-centre haemodialysis would result in beneficial changes in left ventricular mass, self-reported physical health and other intermediate outcomes among patients undergoing maintenance haemodialysis[18]. The trial had two coprimary composite outcomes that were death or change (from baseline to 12 months) in left ventricular mass, as assessed by cardiac magnetic resonance imaging, and death or change in the physical-health composite score of the

RAND 36-item health survey. The study showed that frequent haemodialysis (six times per week), as compared with conventional haemodialysis (three times per week), was associated with favourable results with respect to the composite outcomes of death or change in left ventricular mass. However, from a total of 225 patients enrolled in the study, only fourteen patients died, five patients in the frequent-haemodialysis and 9 in the conventional-haemodialysis group.

Although haemoglobin levels, dose of dialysis and calcium, phosphorus and parathyroid hormone levels are flawed or nonvalidated surrogate end points, evidence derived from studies using these putative surrogate end points is used for registration and coverage decisions of medicinal products, and is converted into guidelines, quality of care measures and performance targets. Additional putative surrogate end points such as "effective duration of haemodialysis session", "prescribed time of haemodialysis per week", or "number of haemodialysis sessions per week", are also converted into quality of care measures and performance targets. All these measures are said to be part of a Quality Measurement Programme, used for reimbursing haemodialysis providers and evaluating physicians. Therefore, physicians spend time trying to find ways of achieving the target for the surrogate, even when these interventions do not improve, or may even worsen patients' clinical outcomes[7,8].

WHERE DO WE GO FROM HERE?

Overinterpretation of studies using flawed or nonvalidated surrogate end points has turned physicians away from a patient-centred therapy based on clinical outcomes. Patients with chronic kidney disease may be asymptomatic but are treated to achieve target surrogate end points rather than improve clinical outcomes.

We need to move away from current criteria (evidence that is based on trials using surrogate end points) for registration and coverage decisions of new medicinal products when similar products are already available on the market, as well as for issuing guidelines, measuring quality, reimbursing providers or evaluating physicians. In order to assist physicians' and patients' decisions about appropriate healthcare for each clinical circumstance, we need to answer the question of how different therapies affect clinical outcomes. Knowledge based on putative surrogate end points, and especially when evidence is derived from studies based on flawed or nonvalidated surrogate end points, will not provide the right answers.

The scarcity of relevant clinical trials in nephrology has led nephrologists, dialysis providers and regulators to overestimate the value of evidence derived from studies using flawed or nonvalidated surrogate end points. Clinicians, dialysis providers and regulators seem to prefer to have an answer to every question, even when it may be the wrong answer. However, the treatment of anaemia in chronic kidney disease shows that the use of fallible correlations to support treatment decisions may be associated with unwanted (harmful) consequences.

One quote usually attributed to Sir William Osler (1849-1919), a Canadian-born British physician, states that "the higher the ignorance, the higher the dogmatism". Let's not allow our ignorance to be a source of false dogmas driving our clinical practice, the production of guidelines, the measurement of quality, the reimbursement of providers and the evaluation of physicians. The health of our patients will certainly appreciate it.

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