

# Should the Hematocrit Be Normalized in Dialysis and in Pre-ESRD Patients?

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## Introduction

Just over a decade ago, a new therapeutic agent was introduced that could effectively treat the anemia associated with chronic renal failure. This treatment, called recombinant human erythropoietin (epoetin), was rapidly shown to be successful in 90–95% of patients treated. It could increase the hematocrit (or hemoglobin – see below) to whatever level the physician desired, and yet the early treatment studies elected to aim for partial rather than full correction of the anemia. This practice has largely persisted, with few nephrologists currently aiming for normalization of hematocrit in their patients. The first question we have to ask ourselves is why this is the case.

Indeed, the appropriate target hematocrit for dialysis patients has arguably been one of the most controversial and debated issues in nephrological practice throughout the last decade [1, 2]. Attempts to provide guidelines for nephrologists have suggested a hematocrit of 33–36% (hemoglobin 11–12 g/dl) in the NKF-DOQI Guidelines [3], and a hemoglobin of >11 g/dl (with no upper limit specified) in the European Best Practice Guidelines [4]. And yet most of us involved in the creation of such guidelines would have to confess that these target levels are somewhat arbitrary, based on the limited amount of scientific evidence available in the literature.

What is clear is that the normal (and physiological) levels of hematocrit present in healthy non-uremic individuals are not a common finding in renal patients, even with the 'technology' available to achieve this.

## Why Do We Aim for Subnormal Hematocrit Levels?

There are several possible reasons for this. The first is a historical one in that the first two pivotal studies conducted on either side of the Atlantic aimed for subnormal correction of the anemia [5, 6]. Second, there has been some concern that full correction of anemia in renal failure patients may expose such individuals to an increased risk of developing adverse events, such as hypertension and vascular access thrombosis, or even (in the early studies) hypertensive encephalopathy or seizures. Third, the largest study ever set up to investigate this issue (the US Normal Hematocrit Study) failed to live up to the expectation that dialysis patients randomized to a normal hematocrit would have a better outcome than those aiming for a conventional (subnormal) hematocrit [7]. Fourthly, in the current climate of evidence-based medicine, the purist nephrologist might argue that there is no direct evidence that targeting a normal hematocrit in patients receiving epoetin results in a significant improvement in morbidity and mortality compared with partial correction of the anemia. Finally, there is an economic issue. At the present time, epoetin therapy remains a fairly costly treatment; many units have large numbers of patients on epoetin, and the treatment is long-term, i.e. usually until the patient dies or receives a renal transplant. As will be described later, the cost of fully correcting anemia in dialysis patients is considerably greater than aiming for partial correction.

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## Hematocrit or Hemoglobin?

Before discussing the allocated topic, it is perhaps worth spending a moment or two reflecting on the choice of hematocrit or hemoglobin as a measure of anemia. For good reasons, the European Best Practice Guidelines have recommended the hemoglobin concentration to monitor anemia [4]. Measurement of hematocrit is extremely variable, dependent on the method used, and dependent on the age of the sample when analyzed. The microhematocrit method can yield different results from measurement of hematocrit by commercially-available automated blood count analyzers, and one automated analyzer may give a different result from another. Furthermore, there is no international standard for hematocrit measurement as there is for measurement of hemoglobin, and indeed most hematology laboratories perform daily quality control on their automated blood count analyzers using a known standard. Most units outside the USA use hemoglobin concentration, including their Canadian neighbors, and it is to be hoped that Americans will soon take heed of these facts and do likewise. Unfortunately, this has clearly not happened for the current meeting debate which still has 'hematocrit' in the title. To promote the trend, however, I shall use the term 'hemoglobin' to describe the degree of anemia throughout the remainder of this article.

### Should Hemoglobin Be Normalized in Dialysis and in Pre-ESRD Patients?

This is the question to be addressed in the current debate. The first issue is whether this question is equally appropriate for dialysis and for predialysis patients. There are certainly factors which are different in these two patient populations, and these are sufficiently diverse to suggest that this topic should be discussed separately.

### Normalization of Hemoglobin in Dialysis Patients

There are clearly arguments for and against this motion based on the current literature available. My remit is to discuss factors which would argue *against* normalizing hemoglobin in this patient population. The first point to make is that one has to consider each patient as an individual rather than as one of a population. Thus, it may not be appropriate to target the same hemoglobin for every dialysis patient in the same unit. To illustrate this point, I

would like to present 2 completely contrasting fictitious cases which have been deliberately selected to include factors which may influence the choice of target hemoglobin.

*Case 1* is a 26-year-old man who recently reached end-stage renal failure from chronic glomerulonephritis. He has been on automated peritoneal dialysis for 3 months, and his hemoglobin at the time of starting dialysis was 9.2 g/dl, having been 11 g/dl 4 months earlier. He was started on epoetin therapy, and his hemoglobin was gradually increasing. He had borderline hypertension, easily controlled by a long-acting calcium antagonist, but he was otherwise very well with no other co-morbid conditions. He works as a builder, and until recently was captain of the local rugby team. Unfortunately, his level of fitness had deteriorated to an extent that he could no longer compete at the level required of him. He had undergone a number of cardiac investigations as part of a workup for renal transplantation; he had a normal exercise treadmill test with no signs of myocardial ischemia, and a normal echocardiogram with an ejection fraction of 56% and no evidence of left ventricular hypertrophy. What should his target hemoglobin on epoetin be?

*Case 2* is a frail 74-year-old lady with diabetic nephropathy who has been on unit-based hemodialysis for 13 years. She was heavily transfusion-dependent when she started dialysis, but this ceased when she commenced epoetin therapy in 1992. She did, however, also suffer from active sero-negative rheumatoid arthritis over the years, and this had resulted in some resistance to her epoetin, with hemoglobin levels ranging from 7.2 to 9.9 g/dl over the last 8 years. She had suffered two myocardial infarctions in 1994 and 1997, and this had left her with a moderately severe ischemic cardiomyopathy, causing NYHA Grade III heart failure. She had two previous failed vascular access episodes, with a thrombosis of her left radial fistula in 1996, and a thrombosed left brachial fistula in 1999. She was currently dialyzing satisfactorily via a right brachial PTFE graft. Because of her arthritis, she was largely wheelchair-bound and often breathless at rest due to her heart failure. Of late, she was becoming somewhat forgetful and intermittently confused, although she did have a supportive and caring husband. A CT scan of her brain showed changes of diffuse atherosclerotic cerebrovascular disease, but with no discrete lesion. Her family ask you what level of hemoglobin you are aiming for. What do you answer?

In brief, Case 1 is a fit young man with no significant co-morbidity who has a physically demanding job and an active lifestyle, whereas Case 2 is a frail elderly lady with

multiple other medical problems, including significant cardiac disease and a limited life expectancy. In real life, one has to select a target hemoglobin for each patient, but should this be the same for both patients or should it be individualized? Having a unit policy on target hemoglobin, or devising clinical guidelines on this issue, tends to consider a total population, whereas this population is made up of many different individuals who may have very different characteristics or clinical features. With reference to the 2 cases described above, one could offer an argument for normalizing hemoglobin in the first patient, whereas the scientific evidence [7] suggests a note of caution in doing the same for Case 2.

Before discussing the disadvantages of normalizing hemoglobin, let us consider in turn some of the factors which may influence the choice of target hemoglobin in an individual patient (table 1).

#### *Age*

There are no studies specifically looking at the choice of target hemoglobin in the elderly versus the younger population. We do know that elderly patients benefit from epoetin therapy both with regard to their exercise capacity [8] and cardiac function [9]. There are, however, two reasons why the nephrologist uses epoetin therapy: firstly for a fairly rapid improvement in anemic symptoms, exercise capacity, and quality-of-life, and secondly to improve cardiac function along with (hopefully) long-term survival. Whilst the first of these criteria is applicable to patients of all ages, the potential impact of the latter phenomenon is clearly much greater in younger patients than in the frail elderly patient whose life expectancy is less than two years. More aggressive anemia management may therefore be more appropriate in the younger patient.

#### *Gender*

Again, few studies have differentiated between males and females in terms of target hemoglobin. Interestingly, the Scandinavian Multicentre Study [10, 11] did aim for a higher target hemoglobin in male patients (14.5–16.0 g/dl) compared to females (12.5–14.0 g/dl), but there was no gender difference in either the US Normal Hematocrit Trial [7] or the Canadian Multicentre Study [12]. In healthy individuals, there is a higher physiological hemoglobin in males compared to females, although this becomes less marked when the latter become postmenopausal. Some might argue that this physiological difference between males and females should be maintained in renal failure patients; others might suggest that most female dialysis patients are post-menopausal, either due

**Table 1.** Factors affecting choice of target hemoglobin in an individual patient

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Age
Gender
Occupation
Level of physical activity
Length of time with chronic renal failure/renal anemia
Starting hemoglobin/length of time on epoetin
Co-morbid conditions
Dialysis modality

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to age or to biological factors causing premature menopause in uremic patients. If one were to select a target hemoglobin for a fit and healthy male hemodialysis patient aged 25 years versus a fit and healthy female dialysis patient aged 25 years who is still menstruating, then there may be some rationale in selecting a slightly lower target hemoglobin concentration for the latter patient. Much of this discussion is, however, speculative with little in the way of scientific data to support it.

#### *Occupation*

If a young patient is in full-time employment, and particularly if the job involves fairly strenuous physical activity, then there may be a rationale for maximizing exercise capacity in these patients. There is indeed evidence that physical capacity and maximum oxygen consumption is greater in dialysis patients with a hemoglobin concentration of around 14 g/dl compared with one around 10 g/dl [8]. This is true for both young and old patients.

#### *Level of Physical Activity*

For the same reasons as indicated in the previous section, a patient with a fairly active lifestyle involving much physical activity (including sport) would benefit from a higher rather than a lower hemoglobin.

#### *Length of Time with Chronic Renal Failure/Renal Anemia*

It is well known that physiological homeostatic mechanisms, such as altered diphosphoglycerate levels (causing a shift in the oxygen dissociation curve), come into play during chronic anemia. It is these compensatory mechanisms that allow a patient with homozygous sickle cell disease to function fairly well with a hemoglobin concentration of around 5–6 g/dl between blood transfusions. The length of time a patient has suffered from renal anemia, and indeed the severity of this condition, may influence

the potency and reversibility of these compensatory mechanisms. Thus, if a patient has been exposed to a hemoglobin of between 6 and 8 g/dl for several years, homeostatic mechanisms may have become so established that to bring the hemoglobin concentration up to 14 g/dl in the space of a few months might be deleterious. It may in fact result in 'relative' polycythemia for such patients, and this may also explain why severely anemic patients previously developed hypertensive encephalopathy or seizures even with a suboptimal hemoglobin. Conversely, if a patient has been exposed to anemia for a short time (as illustrated in Case 1) then they may be better equipped to deal with a normal physiological hemoglobin level.

#### *Starting Hemoglobin/Length of Time on Epoetin*

For the same reasons as outlined in the previous section, both the starting hemoglobin concentration and the length of time the patient has been on epoetin therapy, may influence how well the patient can cope with normalization of hemoglobin. Thus, if the anemia has been mild and the patient has been on epoetin for several years, then the further increment in increasing their hemoglobin to normal might be achieved relatively easily. Conversely, if the hemoglobin has been increased fairly rapidly from around 7 g/dl up to 11 g/dl with epoetin, then a further increase to 14 g/dl might be more hazardous.

#### *Co-Morbid Conditions*

Conditions that may influence the choice of target hemoglobin might include cardiac disease, cerebrovascular disease, and other arteriopathic conditions, diabetes mellitus, chronic obstructive pulmonary disease, and precarious or precious vascular access (particularly if there has been a previous thrombosis). As will be discussed in more detail below, patients with known ischemic heart disease or cardiac failure may be no better (or even worse off) with normalization of their hemoglobin compared to partial correction of anemia [7]. Although this study may have its limitations [13], one cannot ignore the findings of this large randomized controlled trial, one of the major conclusions of which was that patients with cardiac disease should not have their hemoglobin normalized until any further data become available.

There have been studies of epoetin therapy in diabetic patients, although no useful information has appeared on what the optimal target hemoglobin is in such patients. In view of the known microvascular disease occurring in diabetics, however, there is a rheological argument for running such patients with a slightly lower hemoglobin

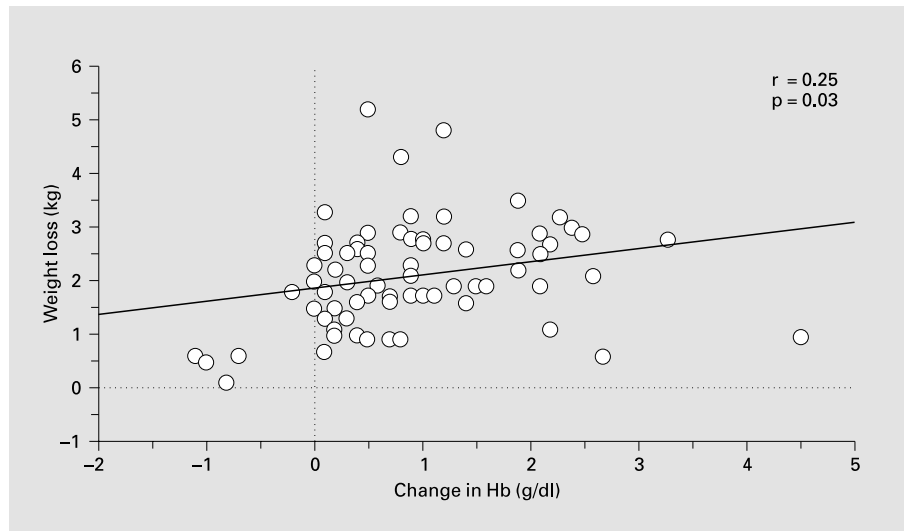
to reduce whole blood viscosity and improve red cell fluidity.

Nonuremic patients with chronic obstructive pulmonary disease often develop a secondary polycythemia to compensate for chronic hypoxia. Such patients often feel less breathless with a higher hemoglobin, and there is no reason why the same rationale should not be applied to renal failure patients. There is indeed a peritoneal dialysis patient in our unit who has chronic bronchiolitis due to rejection in his heart-lung transplant, and who feels symptomatically less breathless at a hemoglobin of 14 g/dl than when it is reduced to 12 g/dl.

Finally, there is some evidence from controlled studies that a higher hemoglobin concentration may exacerbate the risk of a vascular access thrombosis [7, 14]. The incidence of access thrombosis was higher in the initial Canadian Multicentre Study [14] in the group of patients randomized to a hemoglobin of 11.5–13.0 g/dl (7 of 38 patients) compared with those randomized to the lower hemoglobin group (9.5–11.0 g/dl; 4 of 40 patients). Similarly in the US Normal Hematocrit Trial there was an excess of vascular access thrombosis in the patients assigned to the normal hematocrit group compared to those remaining on the lower (conventional) hematocrit (39 vs. 29%;  $p = 0.001$ ) [7]. The implication of these data may seem somewhat obvious, but patients with a history of vascular access complications, or those with a poor quality access, or those in whom limited sites remain for further vascular access, should probably not aim for complete correction of anemia unless there are compelling reasons to do so.

#### *Dialysis Modality*

As already discussed, there may be a case for targeting a different hemoglobin concentration in a pre-dialysis compared to a dialysis patient. This will be discussed further later on. The other issue to consider is whether the same target hemoglobin concentration should be used in hemodialysis compared with peritoneal dialysis patients. There is one important point in this respect, which is that the hemoglobin concentration in peritoneal dialysis patients is generally much more stable than in hemodialysis patients. Data shown below indicate that the hemoglobin concentration can increase by 1–3 g/dl across a dialysis session, depending on how much fluid is removed (fig. 1). Thus there might be less concern in maintaining a peritoneal dialysis patient with a hemoglobin of 14 g/dl compared with a hemodialysis patient whose predialysis hemoglobin was 14 g/dl and whose post-dialysis hemoglobin was 17 g/dl.



**Fig. 1.** Change in hemoglobin concentration across dialysis (post-dialysis minus pre-dialysis sample) in relation to weight loss in a cohort of hemodialysis patients.

**Why Should Hemoglobin Not Be Normalized in Dialysis Patients?**

At a simplistic level, one would instinctively like to normalize hemoglobin in all dialysis patients. The reasons why this is not happening in routine clinical practice have already been discussed, but there are also some fairly compelling scientific arguments to support this practice (table 2). These will be discussed in turn:

*No Compelling Evidence That a Higher Hemoglobin Is Significantly Better*

There are several studies systematically examining the effect of normalizing hemoglobin in dialysis patients with respect to various outcomes. Some of these are small in number [8, 15], although there are also three large multi-center studies in the USA [7], Scandinavia [10, 11], and Canada [12]. The initial report of normalizing hematocrit in 13 hemodialysis patients by Eschbach et al. [15] suggested that there were modest improvements in quality-of-life, exercise capacity, and a further reduction in left ventricular hypertrophy. There was, however, no control group in this study. Two more recent studies by McMahon et al. [8, 16] on the same cohort of hemodialysis patients have shown modest improvements in exercise capacity, quality-of-life, maximum oxygen consumption, and cardiac parameters at a hemoglobin of 14 g/dl compared to 10 g/dl, but with an enormous additional cost as discussed in the next section. The US Normal Hematocrit Trial [7] set out with a hypothesis that normalizing hemoglobin in high-risk cardiac patients on regular hemodialy-

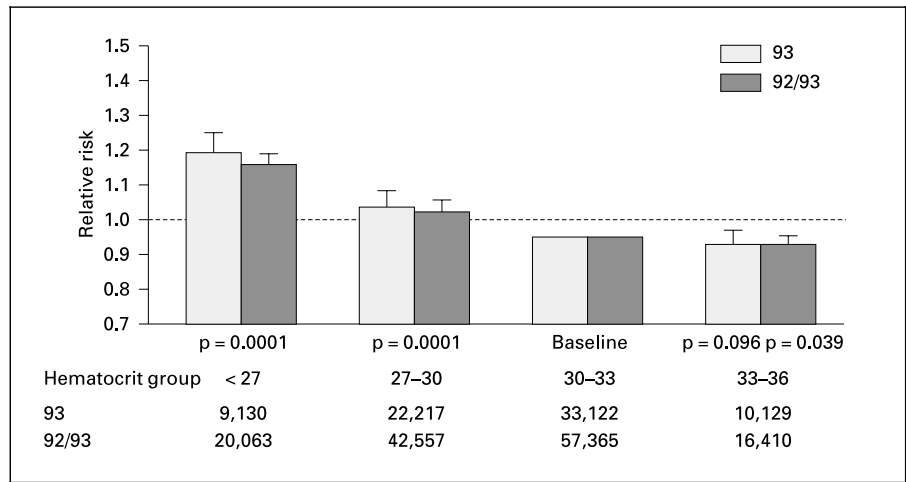
**Table 2.** Arguments for not normalizing hemoglobin in dialysis patients

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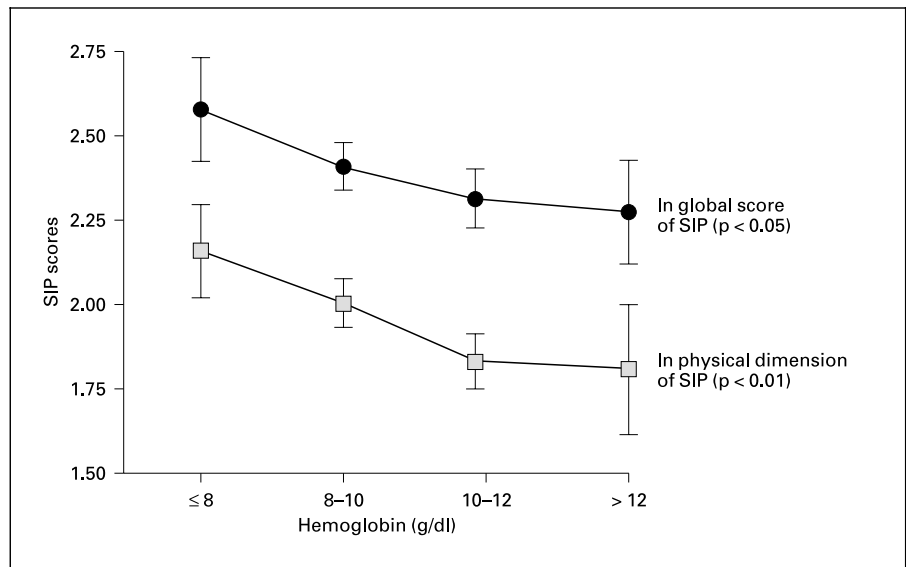
No compelling evidence that a higher hemoglobin is significantly better
Normalization of hemoglobin greatly increases epoetin dose requirements and cost
Requirements for IV iron supplementation greater
Normalization of hemoglobin increases the risk of vascular access thrombosis
Normalization of hemoglobin results in less efficient dialysis
Normalization of hemoglobin increases the risk of dialyzer clotting
Hemoglobin concentration increases significantly across dialysis
Hemoglobin fluctuates significantly in dialysis patients on epoetin

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sis would improve outcome in terms of the two primary endpoints (death and first non-fatal myocardial infarction). Although the follow-up was intended to be 3 years, the study was aborted prematurely after 29 months, at which time there was no benefit shown for the higher hemoglobin (and indeed it was at the brink of showing a worse outcome). The Data Monitoring Group made it clear that even if the study were to continue to its natural end it could not show a positive benefit. At best, there would be no difference between the two groups, and at worst, the normalized hemoglobin group could end up with a worse outcome. This must be the strongest piece of evidence yet for not introducing a global normalization of hemoglobin policy across all dialysis units. The Scandinavian [10, 11] and Canadian [12] Multicentre Studies also



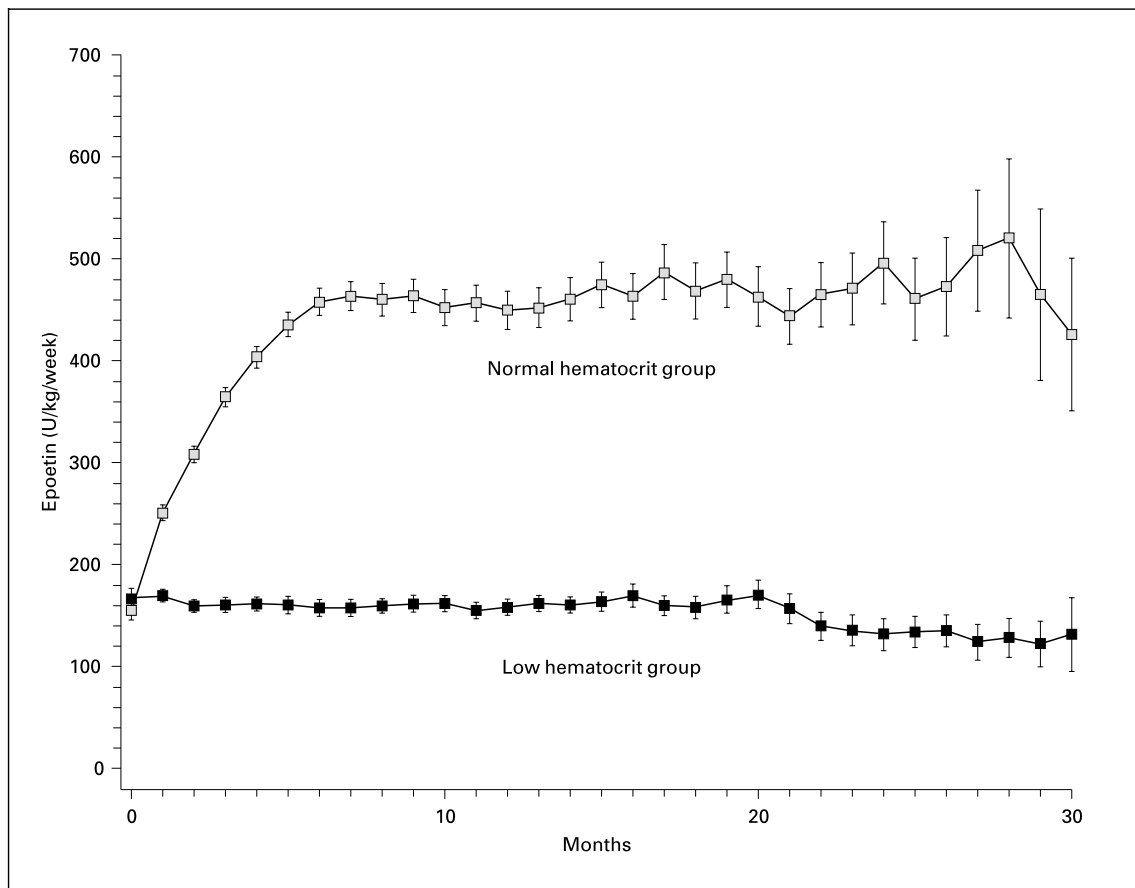
**Fig. 2.** Relative mortality risk in relation to hematocrit in a US observational study conducted in 1992 and 1993 in 75,283 hemodialysis patients. p values are calculated versus a hematocrit of 30–33%. Data from Ma et al. [18].



**Fig. 3.** Relationship between hemoglobin and Sickness Impact Profile score as a measure of quality-of-life in 1,013 dialysis patients. Data from Moreno et al. [20].

did not live up to full expectations. In the Scandinavian Study, while there was no excess mortality seen in the normalized hemoglobin group, the cardiac benefits were less marked than many had expected [10]. This was also true in the Canadian Multicentre Study which examined specifically the changes in left ventricular mass and cavity volume in hemodialysis patients randomized to either a normal hemoglobin group or a subnormal hemoglobin group. Although both groups showed some reduction in left ventricular mass, there was no reduction in left ventricular cavity volume in patients with left ventricular dilatation, even when the hemoglobin was normalized. The major benefit seen was in the patients with a normal left ventricular cavity volume at baseline, in whom full correction of anemia prevented this worsening [12]. In

summary, although there have been some improvements in quality-of-life [17], exercise capacity [8] and cardiac parameters [10, 12] with normalization of hemoglobin, many of these are less marked than would have been anticipated 5 years ago. There are also no controlled studies to suggest that increasing the hemoglobin to normal with epoetin therapy in dialysis patients *improves* long-term morbidity and mortality. There are, however, some epidemiological data showing correlations between the degree of anemia and mortality [18], length of hospitalizations [19], and quality-of-life [20]. Although not specifically related to epoetin therapy, the data do suggest that dialysis patients with more profound anemia have an increased mortality rate, longer duration of hospital admission, and lower quality-of-life scores. If one examines



**Fig. 4.** Mean monthly epoetin doses in the US Normal Hematocrit Trial of 1,233 hemodialysis patients. There was a significant difference in the mean doses between the two groups from 1 month onwards ( $p < 0.001$ ). Error bars indicate 95% confidence intervals of the mean.

these data closely, however, it can be seen that the effect is beginning to plateau at around a hematocrit of 30–33%, with a marginal additional benefit in the higher hematocrit groups (fig. 2, 3).

#### *Normalization of Hemoglobin Greatly Increases Epoetin Dose Requirements and Cost*

All of the studies examining normalization of hemoglobin have shown quite considerable increases in epoetin dose requirements attempting to drive the patients' hemoglobin concentrations into the normal range. The first study by Eschbach et al [15] showed a 69% increase in epoetin dose, and the largest study of its kind (the US Normal Hematocrit Trial) showed that patients required a threefold increase in mean epoetin dose to achieve a normal hematocrit (fig. 4) [7]. Moreno et al. [17] found that normalization of hemoglobin required a 51% in-

crease in epoetin dose requirements, while the latest study to be published, by McMahon et al. [16], showed an 80% increase in epoetin dose requirements in the patients targeting a normal hemoglobin. With the current fairly high costs of epoetin therapy, it is difficult to justify this extra expenditure for what may be a limited benefit. Using this 80% increase in epoetin dose requirements, the health economist would be able to calculate that for every 5 patients treated for normalization of hemoglobin, he can treat 9 patients aiming for partial correction of anemia. If the cost of epoetin were to reduce, then this argument may be less strong, but there is no sign of this at the present time.

#### *Requirements for IV Iron Supplementation Greater*

In addition to the need for an increased epoetin dose, there is also an increased need for iron supplementation

in patients aiming for normalization of hemoglobin. This was again most dramatically illustrated in the US Normal Hematocrit Trial in which 526 of 618 patients in the normalization of hemoglobin group received IV iron dextran compared with 464 of 615 patients in the lower hemoglobin group ( $p < 0.001$ ) [7]. This has both economic and safety considerations. Not only does the cost of targeting a normal hemoglobin increase further, but there are continuing concerns about the short- and long-term safety of IV iron [21]. Thus, patients may be exposed to a greater risk of anaphylactoid reactions, side effects from IV iron, oxidative stress, vascular endothelial damage, and bacterial infections. While the undoubted benefits of using IV iron supplementation seem fully justified at the lower levels of hemoglobin, it is not clear whether the benefit:risk ratio would be maintained in patients destined for hemoglobin normalization.

#### *Normalization of Hemoglobin Increases the Risk of Vascular Access Thrombosis*

As described earlier, two of the most scientifically robust randomized controlled trials of epoetin therapy have shown significantly increased incidences of vascular access clotting at a higher hemoglobin level [7, 14]. While it is difficult to be certain whether this is related to the hemoglobin *per se*, or to the increased epoetin dose, or to the increased IV iron requirements, it is however hard to ignore the scientific data from these two studies. Although not usually life-threatening, thrombosis of the vascular access does result in considerable morbidity and inconvenience for the patient, and the use of temporary dialysis lines while awaiting maturation of a new fistula also carries its own risk, particularly for bacterial sepsis.

#### *Normalization of Hemoglobin Results in Less Efficient Dialysis*

This is more relevant for hemodialysis patients, in whom it has been shown that higher hemoglobin levels result in less efficient clearance of various solutes. This phenomenon was first recognized in the initial epoetin study by Eschbach et al. [6] in which several patients were found to develop profound hyperkalemia. More recently, Movilli et al. [22] found an inverse relationship between hematocrit and both dialyzer clearance ( $p = 0.003$ ) and  $Kt/V$  ( $p = 0.0002$ ); the lowest  $Kt/V$  values were in the group with a hematocrit  $\geq 37\%$ . This has also recently been the subject of a study by Ronco et al. [23] in which it was shown that dialyzer efficiency was reduced in hemodialysis patients following normalization of hemoglobin with epoetin. Although it may be possible to overcome

this problem by using larger dialyzers and increasing the hours on dialysis, each of these maneuvers carries an increased cost and inconvenience for patients and health-care workers alike.

#### *Normalization of Hemoglobin Increases the Risk of Dialyzer Clotting*

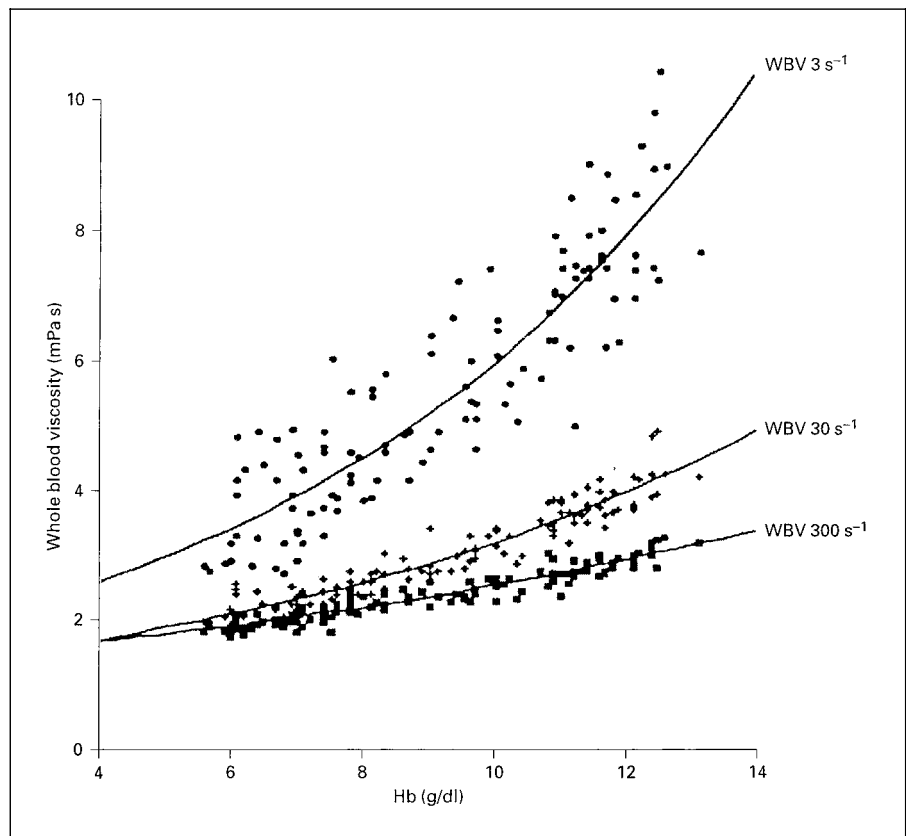
The relationship between hemoglobin and whole blood viscosity is a logarithmic one in that there is an exponential increase in whole blood viscosity for every unit increase in hemoglobin concentration (fig. 5) [24]. This increase in whole blood viscosity with normalization of hemoglobin undoubtedly increases the risk of blood clots clogging up the dialyzer. This in turn exacerbates the reduced dialyzer clearance of solute, and results in an increased requirement for heparin. The latter again carries cost and safety considerations, in that higher heparin doses may result in an increased risk of bleeding post-dialysis.

#### *Hemoglobin Concentration Increases Significantly across Dialysis*

Depending on the amount of fluid ultrafiltered during the dialysis session, there is a variable increase in hemoglobin concentration in a predialysis compared with a postdialysis blood sample [25]. We recently studied this in our unit, systematically taking blood samples for hemoglobin measurement pre- and post-dialysis. This was correlated with the change in body weight across dialysis, and the results are shown in figure 1. Some patients have a fairly minimal increase in hemoglobin concentration, while others have an increase of up to 3–4 g/dl. Although this effect is probably short-lived due to extracellular fluid shifts postdialysis, the patient is nevertheless exposed to a higher hematocrit level for a short spell at the end of dialysis. With a target hemoglobin concentration of 11 g/dl there is a built-in 'cushion' for this, but if a patient is striving for a hemoglobin of 14 g/dl then this transient increase in hemoglobin concentration could be potentially hazardous. This phenomenon is not relevant in the peritoneal dialysis population.

#### *Hemoglobin Fluctuates Significantly in Dialysis Patients on Epoetin*

Due to a number of factors, including intercurrent illness and clinical events, patients on dialysis do not maintain a completely stable hemoglobin concentration. Even ignoring the fluid shifts across dialysis, the hemoglobin concentration can fluctuate by  $\sim 1$ –2 g/dl in patients on epoetin. A number of factors may explain this, some of



**Fig. 5.** Relationship between hemoglobin concentration and whole blood viscosity (WBV) measured at shear rates of 3, 30 and 300  $s^{-1}$  in 10 hemodialysis patients receiving epoetin over a 12-month period. Data from Macdougall et al. [24].

which are still unexplained. Thus, epoetin dose adjustments, either up or down, are frequently required in dialysis patients, and it is really impossible to keep the hemoglobin concentration within tight margins in this population. While this fluctuation in hemoglobin is probably less relevant at a target hemoglobin of around 11 g/dl, there is clearly an increased risk of serious overshoot of hemoglobin if patients are being targeted towards a normal hemoglobin. Thus, a patient who has been reasonably stable with a hemoglobin of around 14 g/dl may suddenly become more responsive to epoetin and end up with a hemoglobin of 17 g/dl. If a patient who has been maintained around 11 g/dl 'overshoots' to 14 g/dl then this may be less hazardous.

### Normalization of Hemoglobin in Pre-ESRD Patients

Although there are now many studies on the effect of epoetin in improving anemia in pre-ESRD patients, in contrast to dialysis patients there are limited scientific

data on normalization of hemoglobin in this population [26]. This makes it impossible to draw any firm conclusions either way regarding this issue. As discussed previously, however, there may be a stronger case for normalizing hemoglobin in pre-ESRD patients who have not been exposed to anemia for such a long time and who have not been rendered severely anemic. There is increasing interest in starting epoetin at an earlier stage in the development of renal failure, and indeed there is an increasing scientific rationale for doing so [27]. We are now aware that by the time the patients are started on regular dialysis treatment, they already have a high chance of having cardiac pathology, either with left ventricular hypertrophy [28], left ventricular dilatation [29], or systolic dysfunction. There is one prospective study examining the cardiovascular effects of normalizing hemoglobin with epoetin therapy in pre-ESRD patients. Hayashi et al. [26] assessed left ventricular mass, 24-hour blood pressure monitoring, and change in renal function in 9 predialysis patients after partial correction (target hematocrit 30%) and normalization (target hematocrit 40%) of their anemia. Left ventricular mass progressively

decreased from  $140.6 \pm 12.1 \text{ g/m}^2$  at baseline, to  $126.9 \pm 10.0 \text{ g/m}^2$  after partial correction of anemia at 4 months, to  $111.2 \pm 8.3 \text{ g/m}^2$  after normalization of anemia at 12 months. There was no change in the rate of progression of renal failure over the 12 months of the study.

In addition, there are currently ongoing multicenter studies of epoetin in predialysis patients in the UK, Canada and Australia, and a global study of epoetin targeting two different hemoglobin concentrations in such patients has recently been launched. This is the CREATE study (Cardiovascular Reduction Early Anemia Treatment with Epoetin Beta), the design of which was presented at a Roche Technical Forum at the European Renal Association Meeting in Nice (September 2000). In Group 1, patients are started on epoetin when their hemoglobin falls below 12.5 g/dl, and they are then treated to maintain a hemoglobin concentration between 13.0 and 15.0 g/dl. The Group 2 (control) patients will only start epoetin when their hemoglobin falls below 10.5 g/dl, and they are targeted to maintain a hemoglobin concentration between 10.5 and 11.5 g/dl. Although it may be quite some time before any data are available from this study, it is the first one to address specifically the issue of preventing renal anemia developing in the first place, and also maintaining renal failure patients with a normal hemoglobin concentration throughout the progression of their disease. Until such data are available, however, it is difficult to make any judgements either way about target hemoglobin in pre-ESRD patients. In contrast to dialysis patients, however, pre-dialysis patients do not have the problems of fluid shifts affecting the variability in hemoglobin concentration.

## Conclusions

The task I was set was to provide a counter-argument to normalization of hemoglobin in renal failure patients. The case I have mounted draws on scientific data obtained from a number of the 'normalization of hemoglobin' studies in dialysis patients. The arguments include the fact that there is no evidence that a higher hemoglobin is of significant benefit, the epoetin dose requirements are greater, the cost is significantly greater, the requirements for iron supplementation are greater, there is an increased risk of vascular access clotting, there is less efficient dialyzer clearance of solute, there is an increased risk of clotting in the dialyzer, heparin requirements may increase, there is an exponential increase in whole blood viscosity, and some hemodialysis patients may develop significant hemoglobin overshoot partly due to fluid removal across dialysis.

Despite all of this evidence, it does not stop me normalizing hemoglobin in select renal failure patients. The type of patient I would be more liable to maintain at a normal hemoglobin is illustrated in Case 1, whereas I would be much more nervous of attempting this in Case 2. Thus, the overriding issue with normalization of hemoglobin must be to individualize the target hemoglobin depending on the various characteristics and needs of the patient.

## Acknowledgement

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## References

- 1 Nissenson AR, Besarab A, Bolton WK: Target haematocrit during erythropoietin therapy. *Nephrol Dial Transplant* 1997;12:1813-1816.
- 2 Jacobs C: Normalization of haemoglobin: Why not? *Nephrol Dial Transplant* 1999;14(suppl 2):75-79.
- 3 NKF-DOQI Work Group: NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. *Am J Kidney Dis* 1997; 30(suppl 3):S192-S240.
- 4 European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 1999;14(suppl 5):1-50.
- 5 Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM: Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986;i:1175-1178.
- 6 Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. *N Engl J Med* 1987;316: 73-78.
- 7 Besarab A, Kline Bolton W, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339: 584-590.
- 8 McMahon LP, McKenna MJ, Sangkabutra T, Mason K, Sostaric S, Skinner SL, Burge C, Murphy B, Crankshaw D: Physical performance and associated electrolyte changes after haemoglobin normalization: A comparative study in haemodialysis patients. *Nephrol Dial Transplant* 1999;14:1182-1187.
- 9 Martinez-Vea A, Bardaji A, Garcia C, Ridao C, Richart C, Oliver JA: Long-term myocardial effects of correction of anemia with recombinant human erythropoietin in aged patients on hemodialysis. *Am J Kidney Dis* 1992;19:353-357.
- 10 Furland H, Linde T, Danielson BG: Cardiac function in patients with end-stage renal disease after normalization of hemoglobin with erythropoietin. *J Am Soc Nephrol* 1998;9: 337A.

- 11 Furuland H, Linde T, Danielson BG: Physical exercise capacity in patients with end-stage renal disease after normalization of hemoglobin with erythropoietin. *J Am Soc Nephrol* 1998;9: 337A.
- 12 Foley RN, Parfrey PS, Morgan J and the Canadian Normalization of Hemoglobin Study Group: A randomized controlled trial of complete vs partial correction of anemia in hemodialysis patients with asymptomatic concentric LV hypertrophy or LV dilatation. *J Am Soc Nephrol* 1998;9:208A.
- 13 Macdougall IC, Ritz E: The Normal Haematocrit Trial in dialysis patients with cardiac disease: Are we any the less confused about target haemoglobin? *Nephrol Dial Transplant* 1998; 13:3030–3033.
- 14 Canadian Erythropoietin Study Group: Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *BMJ* 1990; 300:573–578.
- 15 Eschbach JW, Glenny R, Robertson T, Guthrie M, Rader B, Evans R, Chandler W, Davidson R, Easterling T, Denney J, Schneider G: Normalizing the hematocrit in hemodialysis patients with EPO improves quality of life and is safe. *J Am Soc Nephrol* 1993;4:425.
- 16 McMahon LP, Mason K, Skinner SL, Burge CM, Grigg LE, Becker GJ: Effects of haemoglobin normalization on quality-of-life and cardiovascular parameters in end-stage renal failure. *Nephrol Dial Transplant* 2000;15:1425–1430.
- 17 Moreno F, Sanz-Guajardo D, Lopez-Gomez JM, Jofre R, Valderrabano F: Increasing the hematocrit has a beneficial effect on quality of life and is safe in selected hemodialysis patients. Spanish Cooperative Renal Patients Quality of Life Study Group of the Spanish Society of Nephrology. *J Am Soc Nephrol* 2000;11:335–342.
- 18 Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 1999;10:610–619.
- 19 Xia H, Ebben J, Ma JZ, Collins AJ: Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol* 1999;10:1309–1316.
- 20 Moreno F, Lopez-Gomez JM, Sanz-Guajardo D, Jofre R, Valderrabano F: Quality of life in dialysis patients: A Spanish multicentre study. *Nephrol Dial Transplant* 1996;11(suppl 2): 125–129.
- 21 Fishbane S, Maesaka JK, Mittal SK: Is there material hazard to treatment with intravenous iron? *Nephrol Dial Transplant* 1999;14:2595–2598.
- 22 Movilli E, Cancarini GC, Mombelloni S, Feller P, Ravelli M, Maiorca R: The role of hematocrit in efficiency of dialysis. *Blood Purif* 1990; 8:183–189.
- 23 Ronco C, Ghezzi PM, Metry G, Spittle M, Brendolan A, Rodighiero M, Milan M, Zanella M, Greca G, Levin N: Effect of hematocrit and blood flow distribution on solute clearance in hollow fiber hemodialyzers. *Nephron* 2000 (in press).
- 24 Macdougall IC, Davies ME, Hutton RD, Coles GA, Williams JD: Rheological studies during treatment of renal anaemia with recombinant human erythropoietin. *Br J Haematol* 1991;77: 550–558.
- 25 Vlassopoulos D, Sonikian M, Dardioti V: Hadjiconstantinou V: Target haematocrit during erythropoietin treatment in dialysis patients. Which value is true-functional haematocrit? *Nephrol Dial Transplant* 1999;14:1340–1341.
- 26 Hayashi T, Suzuki A, Shoji T, Togawa M, Okada N, Tsubakihara Y, Imai E, Hori M: Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis* 2000;35:250–256.
- 27 Macdougall IC: Higher target haemoglobin level and early anaemia treatment: Different or complementary concepts? *Nephrol Dial Transplant* 2000;15(suppl 3):3–7.
- 28 Levin A, Thompson CR, Ethier J, Carlisle E, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O: Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. *Am J Kidney Dis* 1999;34:125–134.
- 29 Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995;47:186–192.