REVIEW ARTICLE

Can we prolong life of patients with advanced chronic kidney disease: what is the clinical evidence?

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KEY WORDS

anemia, chronic kidney disease, dyslipidemia, hypertension, mineral and bone disorders

ABSTRACT

The risk of death in patients with advanced chronic kidney disease (CKD) is markedly higher than in the population without CKD, even in patients suffering from advanced cardiovascular disease. Among several clinical features of CKD, the following are considered the most important areas of therapeutic intervention: hypertension, lipid abnormalities, mineral and bone disorders of CKD (previously known as renal osteodystrophy), renal anemia, and uremic toxicity. However, numerous treatment strategies, which are applied based on the understanding of underlying pathologies, did not result in significantly improved prognosis. These strategies include lowering of blood pressure, use of statins, control of hyperphosphatemia and hyperparathyroidism, erythropoesis-stimulating agents, use of better and more biocompatible dialysis membranes, and higher dialysis dose. In this critical review, we discuss the most important, large clinical trials, in which the above therapies failed to show desirable results and to reduce mortality in patients with advanced CKD.

Introduction Unacceptably high mortality among patients with advanced chronic kidney disease (CKD), including end-stage renal disease (ESRD), prompted the nephrology community to search for therapeutic strategies with the aim to change the prognosis in patients with this clinical entity. Based on the understanding of pathomechanisms of CKD, the following areas of therapeutic intervention were addressed: renal anemia, bone-mineral disorders of CKD, hypertension, endothelial dysfunction, oxidative stress, and hyperlipidemia. In addition, in patients with ESRD treated with dialysis, several attempts have also been made to improve survival by increasing the efficacy of dialysis (i.e., higher dialysis dose). Some features of chronic uremia, such as anemia, hyperphosphatemia, abnormalities of bone-mineral metabolism, and high levels of certain uremic toxins, have been shown to worsen the prognosis of patients with advanced CKD in several observational clinical studies. In the case of other pathologies (dyslipidemia, hypertension), such clear association could not be demonstrated. A number of observational trials have shown a paradoxical survival benefit in patients with CKD and hypercholesterolemia, hypertension, or moderate obesity when compared with patients without these abnormalities (this phenomenon is frequently called "reverse epidemiology" of cardiovascular disease in CKD). Nevertheless, intuitively and by analogy to the general population, it has been postulated that intervention in these areas should also improve the outcome of CKD patients. The aim of this review is to briefly discuss the current experience with evidence-based treatment strategies in CKD that, unfortunately, had little or no effect on patient prognosis.

Hypertension Unquestionably, hypertension is one of the most common comorbidities in patients with CKD. In advanced stages of the disease, it is present in more than 80% of the patients, reaching up to 90% in those treated with dialysis. Despite the fact that there is no clear association between blood pressure (BP) values and mortality in ESRD patients, it is believed that lowering of BP should be beneficial also in this patient group. Two meta-analyses published recently on this topic highlighted the ambiguous results of controlling hypertension in dialysis

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patients. Five studies (3 of which were randomized, prospective, and double-blind) were included into the meta-analysis by Agarwal and Sinha.[1] Altogether, these studies included 1202 patients who received antihypertensive drugs, but in 2 of these studies, patients were not really hypertensive (they suffered from dilative cardiomyopathy or left ventricular hypertrophy), so the trials were more focused on pleiotropic effects rather than on BP lowering. When looking exclusively at hypertensive patients, the overall benefits from BP-lowering drugs could be demonstrated (51% reduction of the risk of cardiovascular events), while such a positive effect could not be shown for all patients. The trials included into this meta-analysis were highly heterogeneous and the highest survival benefit was associated with the use of carvedilol in patients with congestive cardiomyopathy, who were not hypertensive.

Three additional trials were added to the 5 studies already discussed in the paper by Agarwal and Sinha,[1] which was the basis for another meta-analysis (including the total of 1679 patients), published recently in *The Lancet* by Heerspink et al.[2] In this meta-analysis, it has been found that an active treatment with BP-lowering agent resulted in systolic BP reduction by 4.5 mmHg and diastolic BP reduction by 2.3 mmHg as compared with controls (again, in only 3 studies hypertension was the sine-qua-non inclusion criterion; in the remaining 5, the populations were mixed, i.e., normo- and hypertensive, exclusively normotensive, or BP values were not provided). Heerspink et al.[2] did not analyze the data separately for patients with or without hypertension. In the whole group, BP-lowering treatment was associated with the reduction in the risk of cardiovascular event by 29% (P = 0.009), all-cause mortality by 20% (P = 0.014), and cardiovascular mortality by 29% (P = 0.044).[2] However, as in the first meta-analysis, most of the observed benefit was due to the effect of carvedilol in patients with congestive heart failure who were not hypertensive.

The meta-analysis of Heerspink et al.,[2] as well as another analysis focusing on the treatment of patients with early stages of CKD with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), have been recently discussed by Gross et al.[3] According to the authors, the publications analyzed so far brought a frustrating message, namely, that effectiveness in BP lowering could not be translated into survival benefit, not only in patients with the most advanced stages of CKD but also in those with incipient disease.

Many studies demonstrated that treatment with ACE inhibitors or ARBs or both was associated with the lowering of: BP, albuminuria or proteinuria, and glomerular filtration rate (GFR) loss; and also with delayed doubling of serum creatinine or the onset of ESRD. However, it had no effect on survival or on the rate of the development of cardiovascular complications. To summarize it somewhat sarcastically, BP-lowering treatment did not change mortality rate, but patients died having lower BP and healthier kidneys. Gross et al.[3] emphasized the need for large primary studies to verify the actual usefulness of antihypertensive strategies in renal patients.

Lipid-lowering therapies Advanced and complex abnormalities of lipid profile (elevated total and low-density lipoprotein cholesterol, triglycerides, lipoprotein(a), decreased high-density lipoprotein cholesterol) are common among patients with CKD, especially among those who have proteinuria and advanced stages of the disease.[4] This directly translates into increased risk of cardiovascular events, although a clear association between lipid disturbances and mortality cannot be demonstrated in patients with ESRD, as already mentioned above.

The effect of lipid-lowering therapy on cardiovascular episodes and survival in advanced CKD still generates large controversy in nephrology. It has been repeatedly addressed in a few recently completed clinical studies. It started with the post-hoc analyses of trials in subjects receiving pravastatin (usually after excluding patients with CKD) in the cardiovascular setting, which demonstrated that subjects with mild renal insufficiency and those with normal kidney function derived a similar benefit from lipid-lowering therapies in terms of cardiovascular risk reduction. A positive effect was also observed in terms of slowing the progression of CKD. The concept of changing clinical outcome of patients with ESRD with lipid-lowering drugs has been tested in large, prospective, randomized trials, i.e., 4D (Die Deutsche Diabetes Dialyse Study) and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events). Lipid-lowering intervention with atorvastatin in 4D and rosuvastatin in AURORA did not decrease mortality and morbidity, despite a potent effect on lipid profile or (as in the AURORA trial) chronic inflammation measured using serum C-reactive protein.[5,6]

In an interesting editorial published recently in the *Polish Archives of Internal Medicine*, Piecha et al.[4] referred to the expected and possibly more convincing results from SHARP (Study of Heart and Renal Protection). Only some results of this study have been published to date, but more details were provided during the latest American Society of Nephrology congress (November 2010). SHARP analyzed the effect of the combined lipid-lowering therapy (simvastatin with ezetimibe) on cardiovascular event rate and CKD progression in more than 9000 patients with ESRD or with advanced CKD not yet on dialysis. It demonstrated quite convincingly that such combined therapy was effective in decreasing the risk of cardiovascular events but had no impact on the rate of CKD progression or the incidence of ESRD (at least in such an advanced stage of CKD;

baseline estimated GFR of 27 ±13 ml/min). Although considered the largest trial in CKD to date, according to the authors, it was underpowered to detect a difference in mortality.[7]

Mineral-bone disorders of chronic kidney disease

Abnormalities of calcium-phosphate metabolism in CKD directly translates into increased mortality.[8] Mineral-bone disorders affect patient outcome in several different ways: parathyroid hormone (PTH) is considered a uremic toxin; excess of phosphate stimulates valve mineralization and vascular calcification that leads to increased arterial stiffness and cardiovascular mortality; a low calcitriol level is associated, among many other effects, with dysregulation of the immune system and excessive activation of renin-angiotensin-aldosterone axis, etc.[9,10] Last but not least, patients with abnormal bone turnover (previously known as renal osteodystrophy) are also exposed to substantially higher risk of fractures, which may result in increased mortality.

Renal community has made numerous efforts to normalize dysregulation of calcium-phosphate metabolism in CKD by means of phosphate binders, active forms of vitamin D (alphacalcidol, calcitriol), vitamin D analogues (paricalcitol), and a new class of drugs suppressing PTH secretion – calcimimetics. All these strategies appeared to be extremely successful in terms of correcting laboratory tests: phosphate binders lowered serum phosphate levels, while vitamin D derivatives and calcimimetics enabled to achieve sufficient control of elevated PTH.[11-13] What is even more interesting, some of them were able to substantially lower the rate of vascular (coronary, aortic) calcification, as demonstrated for the novel, nonabsorbable phosphate binder – sevelamer.[14,15]

Unfortunately, while studies convincingly show the effectiveness of several drugs in the correction of biochemical parameters and improvement of computed tomography scan results, no study to date has been able to show similar effectiveness in the improvement of clinical outcomes. In the Kidney Disease Improving Global Outcomes (KDIGO) document[16] reviewed recently by Matuszkiewicz-Rowińska,[17] a group of experts emphasized the lack of well-designed prospective clinical trials showing any benefit in terms of patient outcome (hard clinical endpoints) that might be associated with these drugs. Currently, we are awaiting the results of the ongoing EVOLVE study (Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events), which is designed to show the effect of a calcimimetic drug, cinacalcet, on survival and cardiovascular morbidity in 3800 patients on dialysis.[18]

Correction of anemia

Probably the largest and the most painful disappointment in contemporary nephrology has been the failure of the concept that correction of renal anemia significantly improves the prognosis of patients with ESRD. Undoubtedly, a decrease in hemoglobin (Hb) and hematocrit in CKD directly translates into increased morbidity and mortality. It seemed well justified that treatment of anemia of renal disorders (mostly by correction of iron deficiency and using erythropoietin-stimulating agents [ESA]) would reverse or at least attenuate the risk. However, which target levels of Hb should be considered appropriate for renal patients is still a matter of debate (the levels above 10 to 15 g/dl have been considered appropriate over the last decades). Indeed, many short-term observational clinical studies demonstrated that ESA improved several hemodynamic parameters, decreased or reversed left ventricular hypertrophy, as well as improved physical performance and quality of life in patients with ESRD and earlier stages of CKD.[19-23]

Unfortunately, the tantalizing myth surrounding the effectiveness of ESA has been destroyed by a series of prospective randomized clinical trials. First, it has been shown that correction of renal anemia to the high-normal target of Hb (13–15 mg/dl) has no clinical superiority over the correction to low-normal values (11–13 mg/dl) both in dialyzed and nondialyzed patients, in terms of lowering all-cause or cardiovascular mortality or reduction of cardiovascular events.[24-28] Studies conducted in subjects with earlier (predialysis) stages of CKD have also demonstrated that treatment with ESA had virtually no effect on the rate of GFR loss and, quite unexpectedly, on the quality of life.[25,26]

The belief in the benefits associated with the correction of anemia was so strong over the last 2 decades that a possible trial that would test the effectiveness of ESA vs. placebo was considered unethical. This view has been changed by the TREAT study (Trial to Reduce Cardiovascular Events With Aranesp Therapy), in which patients with advanced CKD and diabetes who were not yet treated by dialysis were randomized to active treatment with darbepoetin α (target Hb of approximately 13 g/dl) or placebo, with the possibility of "rescue" treatment with darbepoetin if Hb in the placebo arm would fall below 9 mg/dl (with return to placebo immediately after correction of Hb above this threshold). The announcement of the results at the American Society of Nephrology annual meeting in 2009 was possibly one of the most exciting moments in nephrology over the last decade. The study (published a few days after the first announcement) clearly demonstrated no benefit from the treatment of anemia with ESA and from reaching the target Hb in the group of predialysis and dialysis patients with diabetic nephropathy in terms of lowering overall and cardiovascular mortality, cardiovascular event rate or the rate of GFR loss. On the contrary, darbepoetin α tended to increase the risk of death in patients with a history of cancer.[29]

This and other prospective trials paved the way for substantial changes in the anemia treatment guidelines, which substantially lowered the suggested target Hb levels to be achieved with ESA

therapy, from the previously suggested levels of 13 to 15 g/dl to the currently indicated levels of 11 to 12 g/dl. There is a possibility that target levels for Hb will be even lower in the upcoming KDIGO recommendations on the treatment of renal anemia.

Dialysis mode and adequacy Healthy kidneys work continuously 168 hours a week; an ESRD patient is exposed to conventional dialysis treatment for 12 hours a week on average (and the most sophisticated dialysis membrane is much worse than the kidney, even if not perfectly healthy). Not surprisingly, the efforts of many researchers focused on dialysis adequacy (dialysis dose; efficient removal of dialysis toxins) as a "magic bullet" that might significantly improve prognosis. This suggestion came from a number of observational studies and was later tested in prospective trials. Unfortunately, the concept of improved survival in patients reaching higher clearances of toxins during dialysis, or dialyzed using modern, more biocompatible dialysis membranes, failed to pass this test. In such studies as HEMO (Hemodialysis), MPO (Membrane Permeability Outcome), or ADEMEX (Adequacy of Dialysis in Mexico), performed in patients on hemodialysis or peritoneal dialysis, increased dialysis dose or improved quality of dialysis membrane was not sufficient to improve patient survival (although some survival benefit could be observed in the MPO study in patients with diabetes and those with low serum albumin, but not for the whole study group).[30-32]

Apart from dialysis adequacy, also none of particular modes of dialysis showed any benefit over other available options. Although many authors reported several clinical benefits associated with peritoneal dialysis, it could not yet be demonstrated in prospective clinical trials.[33] At best, observational, cohort trials showed noninferiority of peritoneal dialysis vs. hemodialysis. Studies that focused on the improvement of purity, quality, or biocompatibility of peritoneal dialysis fluids also failed to show any clinical benefit in patients treated with "better" fluids. The same applies to the so called convective methods of extracorporeal blood purification: multiple short-term, small-sample-size studies suggested better clinical outcome associated with hemofiltration/hemodiafiltration as compared with standard hemodialysis, but these data are still unconvincing and do not show survival benefit.[34]

Many centers that use long dialysis regimens (6–8 hours per session 3 times a week) or daily/nocturnal dialysis (6 times a week during the day or overnight, at home or at the dialysis unit) repeatedly report impressive results achieved in their patients, including excellent BP control, lack of hyperphosphatemia, near-normal or normal Hb without ESA or on low ESA doses, and long-term survival. Unfortunately, this approach was not adequately tested in prospective clinical trials, except for 2 small, short-term studies (Frequent Hemodialysis Network Daily and Nocturnal Trials) awaiting publication or published very recently. In addition, many authors indicated that daily or home hemodialysis is usually applied in younger patients with better vascular access and fewer comorbidities, which has a substantial effect on the results that are achieved.

Other interventions Small and short-term trials suggested other potential therapeutic options in advanced CKD such as vitamin E, N-acetylcysteine, or peroxisome proliferator-activated receptor γ agonists for the treatment of insulin resistance. The results of these studies are preliminary and cannot serve as the basis for any recommendation.[35]

Prospective randomized controlled trails remain the "gold standard" in the search for evidence that may be further implemented in clinical practice. It sounds quite pessimistic that the results of most trials addressing the issue of clinical outcome in nephrology are negative, namely, they show no clear "hard" endpoint benefit from certain clinical interventions. As we mentioned above, this is the case in patients with advanced CKD and ESRD. Unfortunately, the same applies to the earlier stages of CKD. In the majority of the landmark studies on nephroprotection (such as RENAAL, IRMA2, IDNT, REIN, REIN2, CHARM alternative), a clear benefit could be demonstrated in terms of lowering albuminuria or proteinuria, decreasing the rate of GFR loss, delaying the doubling of baseline serum creatinine, or reaching ESRD, but most of these studies could not prove the survival benefit (unless combined into composite outcome with the measures of "renal survival").[36]

Summary and conclusions So what is wrong with our patients? Why do they not respond to treatment? The possible answer is that renal disease, even moderately advanced, substantially changes most areas of normal homeostasis and these abnormalities cannot be sufficiently corrected with a single therapeutic intervention. Indeed, a patient with hypertension and hyperlipidemia, who lives much longer when treated with BP-lowering drug and statin, is substantially different from a patient with hypertension, hyperlipidemia, bone disease, severe anemia, fluid overload, chronic poisoning with uremic toxins, who is additionally exposed to bioincompatible extracorporeal blood purification treatment. We should thus expect that the latter will not respond to the correction of a single parameter or to the treatment with a single drug or procedure.

The future does not look promising. Since patients with CKD are getting older and suffer from numerous, more and more advanced comorbidities, one should not expect significant improvement in their outcome. The only hope may be brought by improvement in the detection and successful treatment of active renal diseases at their early stages. Renal transplantation

remains the most beneficial therapeutic option in patients with advanced CKD. Kidney transplant in patients with CKD stage 4 to 5 is the only strategy that has not disappointed us so far.

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ARTYKUŁ POGLĄDOWY

Czy można przedłużyć życie pacjentom z zaawansowaną przewlekłą chorobą nerek: co mówią badania kliniczne?

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dyslipidemia, nadciśnienie tętnicze, niedokrwistość, przewlekła choroba nerek, zaburzenia mineralno-kostne

STRESZCZENIE

Ryzyko zgonu pacjentów z zaawansowaną przewlekłą chorobą nerek (PChN) jest znacznie większe niż w populacji ogólnej, nawet w porównaniu z pacjentami cierpiącymi na choroby układu sercowo-naczyniowego. Spośród zespołów objawów typowych dla PChN za najważniejsze obszary interwencji leczniczej uznaje się: nadciśnienie tętnicze, zaburzenia lipidowe, zaburzenia mineralno-kostne w PChN (określane wcześniej mianem osteodystrofii nerkowopochodnej), niedokrwistość pochodzenia nerkowego oraz toksemię mocznicową. Wiele metod leczenia o mocnych podstawach patogenetycznych okazało się jednak nie mieć wpływu na losy leczonych pacjentów. Do tych metod zalicza się obniżanie ciśnienia tętniczego, stosowanie statyn, stosowanie leków hamujących wchłanianie fosforanów z przewodu pokarmowego oraz blokujących nadmierną syntezę i wydzielanie parathormonu, czynniki stymulujące erytropoezę, lepsze, bardziej biozgodne błony dializacyjne i zwiększanie dawki dializy. Niniejszy artykuł stanowi przegląd najważniejszych, dużych badań klinicznych, w których opisywane powyżej sposoby terapii nie przyniosły oczekiwanych rezultatów i nie wiązały się ze spadkiem śmiertelności w grupie pacjentów z zaawansowaną PChN.

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