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# Does chronic kidney disease impact on cardiovascular complications and mortality in the elderly?

# Czy przewlekła choroba nerek wpływa na występowanie chorób układu sercowo-naczyniowego i zgony z ich powodu u osób w wieku podeszłym?

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S u m m a r y

Chronic kidney disease (CKD) is highly prevalent among elderly patients and the risk of CKD increases with age. Reduced glomerular filtration rate (GFR) is well-recognized risk factor for development of atherosclerotic cardiovascular (CVS) disease. It is also an independent predictor of increased all-cause and CVS death. Albuminuria, another parameter of kidney damage, is even better prognostic factor for adverse outcome. Excessive risk of CVS complications in patients with CKD translates into relatively lower risk of end-stage renal disease in elderly people as compared to the younger age groups – much more patients in an advanced age with CKD die before reaching the more advanced stages of CKD and need of dialysis or kidney transplantation. Although many therapeutic strategies applied to limit the burden of CVS disease and mortality in the general population were not tested in CKD, it seems appropriate to assume than many of them are also effective in patients with CKD. These include: aspirin, statins, angiotensin-converting enzyme inhibitors, beta- blocking agents and revascularization procedures. Elderly patients with CKD deserve special attention and care to limit their excessive CVS mortality.

Key words: chronic kidney disease, cardiovascular disease, cardiovascular mortality, glomerular filtration rate, albuminuria

S t r e s z c z e n i e

Przewlekła choroba nerek (PChN) dotyczy znacznego odsetka pacjentów w wieku podeszłym, a ryzyko jej rozwoju rośnie wraz z wiekiem. Obniżona wartość współczynnika przesączania kłębuszkowego jest istotnym czynnikiem ryzyka rozwoju chorób układu sercowo-naczyniowego w tej grupie pacjentów oraz niezależnym czynnikiem predykcyjnym zgonu. Podobną rolę pełni inny wskaźnik uszkodzenia nerek, albuminuria. Ogromne ryzyko powikłań sercowo-naczyniowych i zgonu powoduje, że – pomimo dużej częstości występowania PChN w starszym wieku – zmniejsza się względne ryzyko rozwoju schyłkowej niewydolności nerek (wymagającej leczenia dializami lub przeszczepienia nerki) w tej grupie wiekowej. Większość pacjentów umiera bowiem zanim PChN rozwinie się do najbardziej zaawansowanego, schyłkowego stadium. Wiele spośród uznanych metod leczenia chorób układu krążenia, stosowanych w populacji ogólnej, nie zostało poddanych formalnej ocenie u pacjentów z PChN; niemniej jednak można przyjąć, że wiele z nich cechuje podobna skuteczność także u chorych z upośledzoną czynnością nerek. Dotyczy to zarówno leczenia farmakologicznego (m.in. aspiryny, statyn, inhibitorów enzymu konwertującego angiotensynę), jak i procedur rewaskularyzacyjnych. Pacjenci w podeszłym wieku ze współistniejącą PChN wymagają szczególnej uwagi i opieki medycznej, aby zmniejszyć ryzyko powikłań sercowo-naczyniowych.

Słowa kluczowe: przewlekła choroba nerek, choroby układu sercowo-naczyniowego, zgony sercowo-naczyniowe, współczynnik przesączania kłębuszkowego, albuminuria

## INTRODUCTION

Chronic kidney disease (CKD) is recognized as one of the contemporary epidemics – it may affect up to 10-15% of the general population and increases together with increasing age (1, 2). It has been reported that in population aged 65 years and older the prevalence of CKD may reach 40% or even more, especially in particular risk groups, such as diabetics (3-5). The true dimension of this epidemic is not known – the knowledge is estimated based on imprecise criteria. For example, in many epidemiological studies one of the key criteria of diagnosis, i.e. chronicity (duration of at least

3 months) has not been confirmed and CKD was diagnosed based just on single serum creatinine measurement and eGFR calculaction (6, 7). Secondly, applied to diagnose CKD, namely formulas used to calculate glomerular filtration rate were not well validated versus reference methods, especially in some risk groups (including elderly) and patients with borderline GFR abnormalities (i.e. close to 60 mL/min.) (8, 9). These flaws forced the renal community to search for new, more precise tools that might be used for the GFR calculation in certain populations, including elderly; the most important new formula, CKD-EPI has been repeatedly validated recently in older people and appeared to be more precise than MDRD formula, although this notion is not universally confirmed (10, 11).

CKD is traditionally considered a potent risk factor for development and acceleration of cardiovascular (CVS) disease. In this paper we would like to discuss the impact of CKD on several aspects of cardiovascular health in the elderly and the issue of competing risks between development of end-stage renal disease (ESRD) and CVS complications and death.

## IMPACT OF CKD ON CARDIOVASCULAR COMPLICATIONS AND DEATH

Review of the literature indicates that almost all possible manifestations of CVS disease are associated with progressing CKD. These include: atherosclerotic peripheral artery disease (PAD), coronary artery disease (CAD), chronic congestive heart failure (CHF), stroke, dysrrhythmias, cognitive function impairment, and others.

In a large observational study assessing the risk factors of stroke that included 23,405 patients in a mean age of 64.9 ± 9.6 years 2,586 subjects with eGFR below 60 mL/min./1.73 m$^2$ were identified. These patients were older (71.1 ± 9.3 vs 64.1 ± 9.4 years) and significantly more frequently suffered from stroke or TIA (18.6 vs 8.3%), CAD (24.9 vs 11.6%), diabetes (33 vs 19%), arterial hypertension (79.7 vs 54.8%) and left ventricular hypertrophy (6.7 vs 6.1%) as compared with subjects with GFR above 60 mL/min./1.73 m$^2$ (all differences with $p < 0.001$) (12). The Reduction of Atherothrombosis for Continued Health (REACH) registry which included 51,208 patients with high risk for development of atherothrombotic event (patients with CAD, PAD, cerebrovascular disease, diabetes, hypertension, etc.) revealed that CKD significantly increases risk of CVS death, myocardial infarction and limb amputation; the risk increases by factor two or more in subjects with GFR < 30 mL/min./1.73 m$^2$ as compared to those with normal kidney function (13).

Recently the long-term follow-up results of the milestone trial in hypertension (ALLHAT; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial) were published with respect to kidney function. The authors found that during 8.8-year follow-up period the risk of all-cause and cardiovascular mortality, congestive heart failure, stroke or composite cardiovascular end-point was only marginally affected by moderately impaired kidney function (i.e. MDRD-eGFR between 60 to 90 ml/min./1.73 m$^2$), but hazard ratio for all above events was 50 to 100% higher for subjects with eGFR below 60. This was the case for the whole study population and patients with diabetes. In terms of treatment, all three strategies applied in this trial (chlorthalidone, amlodypine and lisinoril) led to similar results and none of them appeared superior to another in terms of prevention of death, CVS events nor development end-stage renal disease (ESRD) (14).

Many data from elderly population come from the US Veteran Affair health system. In the group of 5.787 veterans with PAD falling GFR was associated with increasing prevalence of diabetes, hypertension, coronary artery disease and congestive hear failure (all differences with p value of less than 0.001 between patients with eGFR ≥ 60, 30-60 and < 60 mL/min./1.73 m$^2$). Peripheral artery disease also increased with decrease in GFR and patients with most advanced CKD and PAD manifested in almost 50% with a very severe course (gangrene) as compared to those with eGFR ≥ 60 (35%). Risk of death in patients with PAD and eGFR < 30 mL/min./1.73 m$^2$ was almost three times higher as compared to those with PAD and eGFR exceeding 60 mL/min./1.73 m$^2$ (15).

CKD was an independent predictor of death or unplanned hospital admission in patients with CHF included to the CHARM trial (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity). In the group of patients with a mean age of 65.3 years the hazard ratio of the predefined endpoint was not increased in patients with eGFR between 60 and 90 ml/min./1.73 m$^2$ vs. those with eGFR above 90 mL/min./1.73 m$^2$; however fall in GFR into the range of 45 and 60 mL/min./1.73 m$^2$ increased the HR by 50%; it almost doubled (HR 1.86, $p < 0.001$) in subjects with eGFR below 45 mL/min./1.73 m$^2$ (16). eGFR reduced below 50 mL/min./1.73 m$^2$ was also the most powerful, independent predictor of mortality in the group of 266 patients aged ≥ 70 years with systolic congestive heart failure; interestingly 'old-fashioned' formula for GFR calculation (Cockcroft-Gault) predicted the risk better than the modern one (MDRD) (17). These results were confirmed in another study, demonstrating that the Cockcroft-Gault formula best predicts the risk of death associated with decreasing GFR in patients with congestive heart failure as compared to both MDRD and CKD-EPI (18). Since multiple other studies indicated better performance of CKD-EPI formula on cardiovascular risk prediction, it clearly indicates that the optimal formula for GFR estimation is yet to be found (19-21).

CKD impacts also on survival in patients with acute worsening of CHF. Mortality of elderly patients (aged mean 69 ± 13 years) discharged from the hospital after an episode of acute CHF exacerbation was more than doubled if they simultaneously suffered from CKD with eGFR < 60 mL/min./1.73 m$^2$, as compared to those

with eGFR above this value. Interestingly, in multivariate analysis low GFR was better prognostic factor than plasma brain natriuretic peptide level, left ventricle ejection fraction below 40% or diabetes mellitus in predicting an adverse outcome (22).

Chronic kidney disease defined as proteinuria and/or eGFR< 60 ml/min./1.73m$^2$ is also a strong pretictor of stroke. In the Japanese stroke registry almost 35% of patients suffered from CKD; survival, neurologic deterioration and functional outcome after stroke were much worse among CKD patients, although the risk was related entirely to the presence of proteinuria, but not to reduced GFR (23). In another registry report CKD almost doubled the risk of stroke independent from other classical risk factors both in people younger and older that 75 years old (24).

Increasing prevalence of CVS morbidity and atherosclerosis advancement with decreasing GFR translates also into the worsening of cognitive function. It has been estimated that cognitive function decreases by 11% for each 10 mL/min./1.73 m$^2$ loss and correlates with cerebrovascular disease. This is important to remember about negative trends in cognition developing with GFR deterioration. Elderly patients with CKD and other comorbidities face several challenges from healthcare system. We prescribe them multiple drugs, recommend troublesome dietary restrictions, expect decisions on future treatment options (such as choice of dialysis mode, transplantation, etc.). This burden may clearly exceed the patient's potential to cope with and it seems obvious that cognitive impairment may be an important reason of non-compliance and lower-than-expected treatment results (12). According to the latest report cognitive impairment is critically dependent on the level of albuminuria rather than low GFR; decreased GFR leads to increased prevalence of cognitive impairment only in patients with low grade albuminuria (25). Since CKD is mostly associated with vascular (and microvascular) disease, cognitive impairment in the course of this disease is mostly attributable to vascular mechanisms (26).

CKD may also predispose to arrhythmias, including the most prevalent one – atrial fibrillation (AF). In a prospective study of 118 patients in the mean age of 63 years with sinus rhythm at baseline a risk of new-onset AF was assessed over the 4.5 year observation period. Patients were evaluated monthly or bi-monthly using ECG with or without Holter monitoring. There were 57 new cases of AF per year; the risk of new onset AF was doubled in patients with GFR between 30 and 60, tripled in patients with CKD stage 4 (GFR 15 – 50 ml/min./1.73 m$^2$) and was 6 times more frequent in those with GFR below 15, as compared to those with preserved GFR. CKD patients were older, more frequently diabetic, with higher values of systolic and diastolic blood pressure, larger left atrium dimension and left ventricular mass index. Nevertheless, after adjustment to all these variables (as well as tobacco smoking) CKD still remained an independent predictor of AF (27).

## COMPETING RISKS BETWEEN CVS COMPLICATIONS AND END-STAGE RENAL DISEASE (ESRD)

CKD, if untreated or unresponsive to treatment, ultimately progresses and may end up with ESRD (which means a need for dialysis or kidney transplantation). One could expect that the risk of developing ESRD is also increasing with age and is extremely high among the elderly. Recent analyses from the Veteran Affairs healthcare database provide however opposite results. When compared with patients with preserved GFR aged between 18 and 44 years, the risk of death among subjects aged between 75 and 84 years with normal kidney function is 4.55 higher; in opposite, the risk of ESRD in elderly patients is 10-50% lower as compared to the 18-44 years old group. Even more interestingly, risk of death in subjects aged 75-84 years with GFR between 15 and 29 mL/min./1.73 m$^2$ exceeds more than three times the respective risk in young patients with such a low GFR value. The risk for development of ESRD is almost 80% lower in the older vs. younger age group (28). As it has been calculated in another study, the hazard ratio (HR) for development of ESRD decreases by 36% for each five years of age, whereas HR all-cause mortality increases by 60% per each five years in patients with baseline eGFR < 60 mL/min./1.73 m$^2$. In cited analysis of the Cardiovascular Health Study 768 deaths (61%) were observed among 1278 elderly subjects with decreased baseline renal function over the mean observation period of 8.9 years (44% of deaths were CVS in nature). It has been calculated in this study that older adults with CKD are thirteen-fold more likely to die from any cause and six-fold – to die due to CVS disease, than to develop ESRD (29). Recent study from Canada, comprising the data of more than 1.8 million people found that prevalence of CKD sharply increases with age and among people aged 65-74 years 19.6% have eGFR < 60 ml/min./1.73 m$^2$, whereas in octogenarians this percentage increases to 61%. Risk of death among people aged more than 85 years with eGFR within the range of 15 and 29 ml/min./1.73 m$^2$ was 11-fold higher as compared to those aged between 18 and 44 years within the same GFR range. Adjusted rate of advanced kidney failure and end-stage renal disease was however several fold higher among younger patients (30). Recently published data from the Alberta Kidney Disease Network indicate that the adjusted risk of death among patients with CKD (eGFR between 15 and 60 ml/min./1.73 m$^2$) is comparable with those after myocardial infarction without diabetes and CKD and with those with diabetes and eGFR more than 60 ml/min./1.73 m$^2$ (in all cases, 30-40% higher as compared to subjects without history of infarction, CKD or diabetes). The risk of death in people with diabetes and CKD was 90% higher versus the reference group (31). These data indicate that there is the competing risk between CVS complications and mortality, and ESRD: younger patients with less comorbidity and lower expected mortality are able to live long enough (even with moderately advanced renal disease)

to reach the degree of ESRD. In case of elderly patients their age – and comorbidity – related risk of death, very high already at baseline and further worsened by the presence of CKD, leads to excess death long before the development of ESRD. Some additional explanations are also possible: first – the nature and natural history of CKD in older people may be different and the disease may be less progressive as compared to younger subjects; second – lower GFR and presence of albuminuria or proteinuria may not necessary be the manifestations of clinically important kidney disease, but rather the surrogate markers of generalized atherosclerosis, multiple organ function impairment and worsened general status (28, 32). Although elderly people are the fastest growing group among incident dialysis patients and in absolute numbers constitute the large part of subjects treated with the renal replacement therapy, the relative risk of reaching ESRD is relatively low in this age group (33).

## REDUCED GFR OR ALBUMINURIA – WHICH IS MORE IMPORTANT IN RISK PREDICTION?

As we mentioned at the beginning of this paper, the value of GFR (especially when estimated using anthropometric formulas) has been recently questioned. Increasing evidence suggests that even remarkably decreased eGFR may not predict adverse outcome without presence of proteinuria (albuminuria) and vice versa – relatively preserved glomerular filtration with albuminuria has much stronger negative prognostic significance.

In 5,010 patients with heart failure included into the Valsartan in Heart Failure Trial (Val-HeFT) trial the risk of all-cause death and first morbid event were higher among those with preserved GFR and positive dipstick proteinuria as compared to those with GFR < 60 mL/min./1.73 m$^2$ and lack of protein in a dipstick test (the prognosis was worse in proteinuric subjects with low GFR) (34). Nord-Trøndelag Health Study (HUNT) revealed an additive effect of albuminuria (urine albumin-to-creatinine ratio) and GFR on prognosis: Prognosis of patients with eGFR between 45 and 60 and between 15 and 45 did not differ among patients with normal albumin excretion; relative risk of death sharply increased however along with decreasing GFR in those who excreted albumin in high – normal range or manifested with microalbuminuria. As can be concluded from this study, the risk of CVS complications does not increase with decreasing GFR from normal value until 60 mL/min./1.73 m$^2$, whereas such a plateau does not exist in case of albuminuria: "the steepest in crease of risk could be observed when urinary albumin rises from 0 to 10 mg/g of creatinine, i.e. well below the lowest value defined as microalbuminuria" (35). An analysis of the Cardiovascular Health study results (patients in a mean age of 78 ± 5 years) showed an increasing risk of death with increasing quintiles of urinary albumin; however proportion of patients with GFR > 90, 60-90 and below 60 mL/min./1.73 m$^2$ was roughly similar within the groups with increasing albuminuria despite significantly worsening prognosis (36). Lack of increase in cardiovascular and all-cause mortality with fall in GFR from normal to 75 mL/min./1.73 m$^2$ was also confirmed in a large meta-analysis that included 21 studies in which both GFR and albuminuria were measured; there was however the continuous risk increase with rising albuminuria (staring from the lowest urinary albumin excretion, without any threshold value) (37). These and other data may suggest that low grade albuminuria (below the threshold of microalbuminuria) as well as microalbuminuria may be considered as markers of early and subtle kidney damage, but – more likely – they seem to reflect systemic CVS damage (for example serve as surrogates of generalized endothelial dysfunction).

## CAN WE DECREASE MORTALITY OF PATIENTS WITH CKD?

Treatment of cardiovascular disease in patients with CKD appears a controversial issue. Several factors may impact on the therapeutic approach in elderly patients with chronic renal failure. First, most of the general practitioners and specialists other than nephrologists and geriatricians may be afraid to use many potentially effective drugs since they expect higher rate of adverse effects. Indeed, in case of many drugs such an increased complication rate can be noticed. For example in most cases of moderately-to-severely advanced CKD aldosteron receptor antagonists (spironolactone, eplerenon) cannot be used in the treatment of congestive heart failure due to excessive risk of hyperkaliemia. This is also the case for other drugs that block renin-angiotensin-aldosteron axis. It also should be emphasized that in most of the large prospective randomized trials demonstrating the usefulness of 'cardioprotective' drugs (such as beta-blocking agents, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blocking agents or statins), even moderate-degree renal function impairment was among the key exclusion criteria. For this reason effectiveness of many potentially useful drugs is not known in CKD; some drugs may not be registered in CKD or special caution is recommended in their registration files in patients with moderately (30-60 mL/min./1.73 m$^2$) or severely impaired renal function.

'Undertreatment' of patients with CKD has been recognized several years ago as a kind of discrimination and, by the analogy to racism, called 'renalism' (discrimination in access to healthcare due to presence of renal failure). This term has been used by Chertow and colleagues to point on the markedly decreased utilization of coronary angiography and revascularization procedures among patients with CKD who fulfilled appropriate criteria for their application according to current standards (38). Once can easily predict that 'renalism' will even become worsened when paired with 'ageism' (discrimination due to advanced age). Large epidemiological trials show that using antiplatelet

treatment, statins, beta-blockers or ACEi decreases with decreasing kidney function (13). It should be acknowledged that nowadays having even advanced CKD is not a contraindication to cardiac procedures, such as coronary angiography and percutaneous interventions, although the results are still much worse as compared to subjects without CKD (for example mortality of 18.7 vs 4.4%, $p < 0.0001$ in one of the recent studies) (39). One can assume however that survival with such interventions is still better than without, although such an assumption cannot be formally tested in prospective randomized trial due to ethical issues. As in many other therapeutic approaches to patients with CKD we can only extrapolate results of trials performed in non-CKD population to patients with CKD.

The data on true effectiveness of commonly available treatment strategies in cardiovascular medicine are derived mostly from retrospective, post hoc analyses of large clinical trial databases (in most of them there were some patients with borderline serum creatinine and decreased calculated GFR). Only a few prospective randomized trials were performed specifically in patients with CKD or ESRD. Looking at this retrospective data allows to conclude that most of the strategies used for general population are also effective in patients with CKD, sometimes in the expense of slightly increased, but acceptable adverse event rate.

One of the biggest and unresolved challenges is anticoagulation treatment in the setting of CKD. In a large study analyzing the safety of vitamin K antagonist to prevent venous thromboembolism and stroke in elderly patients with atrial fibrillation CKD was associated with significantly elevated risk of bleeding complications. Up to 60% of patients had moderately or markedly decreased GFR and GFR value of less than 30 mL/min./1.73 $m^2$ doubled the risk of bleeding (patients with this level of kidney function might already experience bleeding disorders secondary to uremic toxicity) (40). On the other hand, an analysis of the Stoke Prevention in Atrial Fibrillation trial demonstrated benefits of anticoagulation using adjusted dose warfarin in patients with similar degree of kidney failure in terms of significantly reduced risk of stroke and systemic embolism, without increased risk of major bleeding (41).

Retrospective analysis of the Hypertension Optimal Treatment (HOT) study demonstrated that aspirin was most effective in subjects with CKD (serum creatinine $\geq$ 1.3 mg/dl). Treatment was associated with reduced risk of all major cardiovascular events, myocardial infarctions, cardiovascular and total mortality. For example, the relative risk of myocardial infarction was reduced by more than 80% in the CKD patients taking aspirin versus placebo; it should be acknowledged however that bleedings were elevated by factor 1.5. In fact the group that benefited most in the HOT study was limited to patients with eGFR of less than 45 mL/min./1.73 $m^2$, with neutral effect in subjects with eGFR > 60 mL/min./1.73 $m^2$ (42, 43). In terms of acute coronary syndromes clopidogrel as well as new drugs used in this indication, prasugrel and ticagrelor appear to be effective in patients with CKD with largely similar risk of bleeding (44-46).

Similar benefit in CKD patients as compared with 'general' population could be noticed in some statin trials. For example, in the the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, efficacy of rosuvastatin was demonstrated in patients with relatively low risk profile for development of cardiovascular events. Results in patients with eGFR < 60 mL/min./1.73 $m^2$, representing up to 20% of all JUPITER trial population were largely similar in terms of preventing cardiovascular end-points (47, 48). In another rosuvastatin study, the Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA), no benefit has been noticed in the whole study group, whereas significant reduction of study end-points was achieved in subjects with eGFR < 60 mL/min./1.73 $m^2$ (49). This is of special significance, because trials that tested statin treatment with end-stage renal disease produced very pessimistic results: no benefit or even some harm has been noticed in 4D and AURORA studies (with atorvastatin and rosuvastatin, respectively) in patients on dialysis (50, 51).

Statin (namely, simvastatin) revealed also its beneficial effect when combined with ezetimibe in the largest prospective randomized placebo-controlled trial performed to date in CKD, namely the Study of Heart and Renal Protection (SHARP). In this investigator-initiated trial 17% reduction in the major atherosclerotic events was achieved using these two drugs; although no survival benefit was noted. It is worth to mention that combining both drugs in patients with advanced renal failure was safe and did not result in significantly elevated rate of adverse events (52).

New generation beta- blocking agents are known to decrease cardiovascular mortality in high-risk patients. In a recent retrospective analysis of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials, comparing carvedilol to placebo in patients with low or very low ejection fraction it has been demonstrated that the drug decreased the risk of all-cause and cardiovascular mortality, mortality due to congestive heart failure, first hospitalization for heart failure and combined end-point of cardiovascular mortality and hospitalization for heart failure also in patients with CKD. This beneficial effect was confined however only to patients with eGFR between 45 and 60 mL/min./1.73 $m^2$, and was not observed in those with GFR lower than 45 mL/min./1.73 $m^2$ (53).

Patients with renal failure are very frequently affected with disordered circadian variations in blood pressure; many of them are considered non-dippers in 24 ambulatory blood pressure measurement. In a recently published paper authors demonstrated

significant improvement of blood pressure control and reduction in cardiovascular risk in patients with CKD who are taking their BP lowering drugs at bedtime. It seems that achieving the peak of drug effectiveness overnight best addresses pathophysiology of cardiovascular disease in this patient group (54).

## CONCLUSIONS

The above review provides an insight into the prevalence of CKD in elderly population and the risk of cardiovascular complications related to decreased renal function. Low GFR, the measure of impaired filtration, is independently associated with both CVS comorbidity and death, although the strength of such an association may differ depending on the tool used for its measurement. Albuminuria is even stronger predictor of CVS events and in many analyses it appears much more important than reduced GFR for cardiovascular outcome. Albuminuria can be considered a marker of ongoing (active) renal damage but also an indicator of systemic disease predisposing to CVS disease (for example, endothelial damage) independent from kidney function. It should be emphasized that increasing evidence suggests efficacy of many drugs used for treatment of cardiovascular disease also in patients with renal failure although most of available data come from retrospective analyses of randomized, controlled trials performed intentionally in populations unaffected with kidney disease. Despite lack of pivotal evidence we should not abandon our CKD patients and we should apply all available treatment strategies for CVS disease also in this patient group.

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received/otrzymano: 10.12.2012
accepted/zaakceptowano: 14.01.2013

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