Int Urol Nephrol (2015) 47:805–813
DOI 10.1007/s11255-015-0937-9

NEPHROLOGY - REVIEW

Should we use statins in all patients with chronic kidney disease without dialysis therapy? The current state of knowledge

Jacek Rysz · Anna Gluba-Brzózka · Maciej Banach · Andrzej Więcek

Received: 13 January 2015 / Accepted: 19 February 2015 / Published online: 11 March 2015

Abstract
Purpose The aim of this article was to present the most important matters associated with dyslipidemia treatment in CKD patients. Moreover, the most important recommendations of the current (2013) KDIGO clinical practice guideline for lipid management in chronic kidney disease are presented.
Methods Authors looked through the most recent large clinical trials and meta-analyses and presented their results. We searched using the electronic databases [MEDLINE, EMBASE, Scopus, DARE]. Additionally, abstracts from national and international cardiovascular meetings were studied.
Results Analysis results suggest that statins exert beneficial effects on kidney since they considerably reduce 24 h urinary protein excretion and are associated with a rise in GFR. Beneficial effects of statins may be influenced by kidney disease stage, doses of medicine and treatment duration. Data suggest that statins are effective and safe for secondary prevention of CV events in individuals with mild CKD. Patients treated with statins had decreased frequency of major atherosclerotic events compared with placebo, reduced risk of CV mortality and deaths from all causes.
Conclusions Meta-analyses results suggest that statins are associated with lipid lowering, cardiovascular and anti-proteinuric benefits in CKD patients. However, their effects on overall and cardiovascular mortality are much less obvious. Bearing in mind the advantageous effects and low risk of adverse effects, it seems that mild renal impairment should not exclude these patients from receiving a statin. However, because CKD patients in stages III–V are underrepresented in clinical trials, administration of statins to these patients who have not yet had a vascular event remains controversial.

Keywords Chronic kidney disease · Dyslipidemia · Statins · Recommendations · Guidelines

J. Rysz · A. Gluba-Brzózka (✉)
Department of Nephrology, Hypertension and Family Medicine, WAM University Hospital of Lodz, Zeromskiego 113, 90-549 Lodz, Poland
e-mail: aniagluba@yahoo.pl

J. Rysz
e-mail: jacek.rysz@umed.lodz.pl

J. Rysz · A. Gluba-Brzózka · M. Banach
Healthy Aging Research Center, Medical University of Lodz, Lodz, Poland

M. Banach
Department of Hypertension, Medical University of Lodz, Lodz, Poland

A. Więcek
Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland

Introduction

The prevalence of chronic kidney disease (CKD) is rising rapidly, and more and more people require renal replacement treatment [1]. Moreover, cardiovascular (CV) mortality accounts for the largest portion of fatalities in this group of patients [2]. The frequency of CV events is increased even in patients with a mild to moderate degree of kidney function, without other CV risk factors [3]. Apart from traditional risk factors, in CKD patients, increased oxidative stress, inflammation, proteinuria, electrolyte imbalances and endothelial dysfunction significantly increase CV risk [4, 5]. According to studies, dyslipidemia

(increased concentrations of total cholesterol (TCh), triglycerides and low-density lipoprotein cholesterol [LDL-C], and decreased high-density lipoprotein cholesterol [HDL-C] level) as well as hypertension is implicated in the increased CV risk in CKD patients [6]. Moreover, dyslipidemia accompanied by the formation of toxic lipid intermediates is also a major risk factor for the progression and amplification of nephropathy [7–9]. Thus, it seems that optimal management of dyslipidemia should be associated with CV and renal benefits in patients with kidney disease. According to the results of clinical trials, there is a strong, independent correlation between the reduction in LDL-C concentration and the risk of overall and CV mortality in both the general population and people with CV disease [1, 10, 11]. This matter is much more complicated in CKD patients. Not only is the number of studies including this group of patients limited, but also their results are conflicting. Apart from dyslipidemia, albuminuria has been recognized as an independent risk factor for CV morbidity and mortality [12, 13]. According to studies, therapy with HMG-CoA reductase inhibitors (statins) may also influence this pathologic state. Several clinical trials have revealed that statins are commonly used for the primary and secondary prevention of atherosclerosis and CVD [14–16]. Statins, apart from improving the lipid profile, may exert a renoprotective effect associated with pleiotropic actions including anti-inflammatory activity, influence on endothelial function, monocyte recruitment, matrix accumulation, mesangial cell proliferation and renal hemodynamics [4, 17–20]. Moreover, statins reduce abnormal permeability to plasma proteins [21], attenuate angiogenesis induced by tumor necrosis factor-α in vitro and reverse myocardial expression of inflammatory and growth factors [22]. Animal studies have demonstrated that use of statins in the case of rat glomerulonephritis not only prevented macrophage glomerular infiltration but also inhibited mesangial cell proliferation and mesangial matrix development [14, 23]. Thus, some researchers have suggested that statin administration may be beneficial for CKD patients due to its positive influence on kidney perfusion as a result of improved endothelial and cardiac function and ameliorated protein trafficking in the glomerulus and proximal tubular epithelium [14, 24].

Effects of statins on lipid profile

Dyslipidemia frequently occurs in CKD patients. Usually CKD patients have lowered HDL-C levels, elevated LDL-C concentrations and elevated level of triglycerides [25]. Moreover, in CKD increased hepatic very low density lipoprotein (VLDL) secretion and impaired clearance of VLDL and its remnants from serum may also be present, which result in hypertriglyceridemia and enhanced HDL catabolism [26]. Analysis of NHANES III data revealed that low glomerular filtration rate was accompanied by decreased apolipoprotein A-I (ApoA-I) and increased apolipoprotein B (ApoB) serum concentrations [27, 28]. Higher concentrations of remnant intermediate (IDL), very low density lipoproteins (VLDL) and oxidized low-density lipoproteins (oxLDL) are another components of atherogenic lipid profile in CKD [27]. In hemodialysis patients, hypertriglyceridemia, decreased HDL concentration and total and LDL cholesterol usually within normal limits are frequently observed [27, 29, 30].

Among mechanisms associated with unfavorable lipid profile, there are: decreased activities of hepatic lipase (HL) peripheral lipoprotein lipase (LPL), lecithin-cholesterol acetyltransferase (LCAT), which is involved in cholesterol esterification and HDL maturation [31, 32], as well as elevated serum concentration of apolipoprotein C-III (ApoC-III), which is a direct inhibitor of LPL [27, 33], activity of cholesterol ester transfer protein (CETP) and acyl CoA: cholesterol acyltransferase (ACAT) [27, 34]. Moreover, levels of lipids in CKD patients may also be influenced by the presence of inflammatory state and decreased albumin concentration in patients with renal failure [35].

However, in some patients normal or even reduced level of LDL cholesterol, elevated small low-density lipoprotein particles, higher lipoprotein remnants, decreased high-density lipoprotein (HDL) concentrations, high triglyceride concentrations and increased ApoB concentrations are observed [1, 36, 37]. Although the mechanisms responsible for lipid abnormalities in CKD are complex, proteinuria seems to be the key factor [26, 38]. According to studies, LDL-C can bind to specific receptors in mesangial cells, stimulate cell hypertrophy and aggravate glomerulosclerosis [26, 39]. In CKD, due to the presence of a pro-inflammatory state and oxidative stress, LDL can undergo enzymatic oxidation and in this form promotes macrophage scavenging and foam cell formation, further propagating tissue injury [26, 40, 41]. Results of experimental studies confirmed that lipid abnormalities may contribute to the progression of kidney disease [38]. According to studies, in pre-dialysis CKD patients, statins reduce TCh, LDL-C and triglyceride levels depending on the duration of the treatment [42–44]. A study by Di Lullo et al. [45] demonstrated that fluvastatin, which is safe and well tolerated in CKD patients, not only improves the lipid profile but also may contribute to nephroprotection. In CKD patients, plasma lipids as well as remnant-like particle cholesterol were also positively influenced by rosuvastatin [46]. The results of meta-analysis of 16 trials comprising 3594 subjects demonstrated a greater benefit of statin therapy in CKD patients excluding those on dialysis treated for at least 3 months [26].

Total cholesterol

The meta-analysis of 26 randomized controlled trials or subsets of randomized controlled trials in pre-dialysis CKD populations revealed that statins significantly lowered concentrations of TCh; however, the extent of influence depended on the type of statin and baseline cholesterol concentration. CKD stage had no impact on statins' lipid-lowering effects [1]. According this meta-analysis, atorvastatin and cerivastatin were most efficient in the reduction in TCh and their cholesterol-lowering effect increased proportionally with the rise in baseline cholesterol concentrations [1]. Statin therapy was highly effective in the lowering of TCh in pre-dialysis patients especially in the long-term treatment compared with the short-term one (56.3 vs. 66.8) [4]. Also, the meta-analysis of 16 trials revealed that long-term statin treatment was associated with more advantageous effect of statins on TC than short-time therapy ($p > 0.28$) [26].

LDL cholesterol

A meta-analysis by Strippoli et al. [1] revealed that the concentration of LDL-C was significantly lower in patients treated with statins than in those obtaining placebo. As in case of TCh, the effect of statin depended on the type of statin. Another meta-analysis also demonstrated that statins were highly effective in the lowering of LDL-C in pre-dialysis patients especially in the case of long-term therapy when compared with short-term treatment (53 vs. 56.1 mg/dL) [4]. Also, in the meta-analysis by Nikolic et al. [26], the comparison of statins effect on LDL-C in case of short-time versus longtime treatment showed an advantage (but not significant) of long-term statin treatment ($p > 0.41$).

HDL cholesterol

The meta-analysis of 26 randomized controlled trials demonstrated that statins had no significant effect on the concentration of HDL-C in comparison with placebo in CKD patients [1]. Also, the meta-analysis of 16 trials revealed that long-term statin treatment was associated with greater beneficial effects of statins on HDL-C than short-time therapy ($p > 0.24$) [24].

Triglycerides

In the meta-analysis by Strippoli et al. [1], statins significantly lowered triglyceride concentrations with statins in pre-dialysis patients in comparison with placebo. In the meta-analysis by Nikolic et al. [4], statin therapy was found to significantly lower triglyceride levels in pre-dialysis patients especially in the case of long-term treatment in comparison with short-term therapy (22.5 vs. 24.1). Another meta-analysis of randomized controlled trials, comparing the effect of statins on TG in relation to therapy duration (short-time vs. longtime), demonstrated an advantage of long-term statin treatment ($p > 0.47$) [26].

Effects of statins on renal condition

An analysis of six randomized controlled trials and 311 patients suggested that statins exert a beneficial effect on the kidney since they considerably reduced 24 h urinary protein excretion (g/24 h) in pre-dialysis patients compared with placebo. However, in this meta-analysis, statins had no influence on creatinine clearance [1]. In another analysis, beneficial effects of statin were observed in patients with overt proteinuria (protein excretion >300 mg/day) but not with microalbuminuria or normoalbuminuria [47]. In the analysis of LIVALO Effectiveness and Safety (LIVES) substudy including 958 patients with hypercholesterolemia and eGFR of <60 ml/min/1.73 m^2 treated with pitavastatin for 104 weeks, a substantial improvement in eGFR (increase by 5.4 ml/min/1.73 m^2, $p < 0.001$) was demonstrated [48]. Also, Sandhu et al. [49] demonstrated the slowdown in glomerular filtration rate (GFR) worsening and reduction in albuminuria and proteinuria in patients with CKD and CAD.

In prospective, open-label study including 91 patients with CKD (stages 1–3) treated with ACE inhibitors, the administration of rosuvastatin in the dose 2.5–10 mg/day resulted in significant reduction in urinary albumin/creatinine ratio (308 ± 38 mg/g Cr at baseline vs. 195 ± 25 mg/g Cr after 24 weeks of treatment; $p < 0.0001$) and serum cystatin C concentration (1.08 ± 0.04 mg/L at baseline vs. 1.03 ± 0.04 mg/L after 24 weeks of treatment; $p < 0.0001$) [50]. Decline of the urinary protein excretion associated with atorvastatin treatment was observed in the study of 56 patients who were treated simultaneously with ACE inhibitors or ARBs (from 2.2 ± 0.1 g/24 h to 1.2 ± 1.0 g/24 h; $p < 0.01$) [38] and in 20 patients with glomerulonephritis and proteinuria >0.3 g/24 h (22 % reduction; from 1.80 g/24 h to 1.42 g/24 h; $p = 0.005$) [51].

A decrease in albuminuria and proteinuria following statin therapy was also observed by Douglas et al. [52]. In their study, statin effects depended on baseline levels. A reduction by 2 % was seen in patients with excretion < 30 mg/day (95 % CI −32 to 35 %), by 48 % in those with excretion of 30–300 mg/day (95 % CI −71 to −25 %) and by 47 % in those with excretion >300 mg/day (95 % CI −67 to −26 %). Although in the meta-analysis of Nikolic et al. [4] a change in urinary albumin was not observed (0.003 g/24 h, $p = 0.95$), it supported the hypothesis that statins exert renoprotective effects since they influenced

urinary protein with the effect persisting in the case of short-term therapy (≤ 12 months) and serum creatinine but only in the case of long-term therapy (3 years) [4]. Moreover, statin therapy was associated with modest maintenance of GFR, with a significant increase between 1 and 3 years [4]. According to studies, renal effects of statins relate to the hampering of vascular calcification in CKD subjects [53, 54] as well as to the inhibition of renal cell proliferation, anti-fibrotic and antioxidant effects [54], and the reduction in neutrophil and macrophage infiltration [53], up-regulation of endothelial nitric oxide (NO) synthase [55] and down-regulation of inflammatory cytokines [54]. A meta-analysis of studies including 6452 subjects with CKD treated with either statins or placebo demonstrated a substantial rise in GFR after statin administration (increase by 0.29 ml/min/1.73 m^2, $p = 0.04$), with the most pronounced GFR improvement after 1–3 years of treatment (0.50 ml/min/1.73 m^2; $p < 0.0001$) [4]. Fassett et al. [56] reported a change in serum creatinine (and thus eGFR) without altering its clearance following atorvastatin therapy. However, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial did not show any impact of statins on renal function since they observed similar decrease in GFR between rosuvastatin and placebo group during 12 months of follow-up [57]. Similar results were obtained in a post hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study where the occurrence of ESRD and the decline in eGFR during the 6 years of follow-up in patients treated with pravastatin in dose 40 mg/day and those receiving usual care were comparable [58]. Similarly, Study of Heart and Renal Protection (SHARP) enrolling 9270 patients with CKD revealed no protection from reaching ESRD (RR 0.97, 95 % CI 0.89–1.05; p = NS), and no difference in the occurrence of ESRD or death (RR 0.97, 95 % CI 0.90–1.04; p = NS) or doubling of baseline creatinine (RR 0.93, 95 % CI 0.86–1.01; $p = 0.09$) [59].

According to studies, the beneficial effects of statins may be influenced by kidney disease stage (effect diminishes with the renal impairment progression), doses of medicine (usually too low) and duration of treatment [56]. The results of the meta-analysis of Nikolic et al. [4] suggest that statin treatment duration seems to be important in the achievement of renoprotective effects (the longer the therapy, the better the results).

Effects of statins on the occurrence of CV events

Although reports from large clinical trials concerning the treatment of CKD patients with statins are sparse, available data suggest that statins are effective and safe for secondary prevention of CV events in individuals with mild CKD [14, 60]. According to the meta-analysis by Strippoli et al. [1], statin administration was associated with a considerable reduction in the risk of non-fatal CV events [by 20 %, relative risk (RR) 0.78, 0.73–0.84] in comparison with placebo. Another meta-analysis revealed that statins influence CV outcomes especially in pre-dialysis patients [61]. Also, in a meta-analysis by Upadhyay et al. [62], lipid-lowering therapy reduced the risk of CV events. Another meta-analysis performed by Barylski et al. [14] demonstrated that statin therapy resulted in a 45 % reduction in CV events ($p = 0.0001$) and 34 % reduction in stroke ($p = 0.004$) in pre-dialysis CKD patients. The authors concluded that statins should be indicated in CV prevention particularly in patients with non-dialysis-dependent CKD. *Post hoc* analysis of the Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) study, demonstrated that in comparison with usual care, atorvastatin reduced the RR of the first CV event by 28 % in patients with CKD [63]. In a meta-analysis of 26 randomized controlled trials including 25,017 pre-dialysis patients with CKD, statins reduced the risk of CV events (RR 0.80; 95 % CI 0.70–0.90) [64]. Another confirmation of the beneficial effect of statins in patients with a GFR from 30 to 60 ml/min/1.73 m^2, with type 2 diabetes and without previous history of CVD, was provided by a post hoc analysis of the Collaborative Atorvastatin Diabetes Study (CARDS) study, in which atorvastatin 10 mg/day significantly reduced new CV events after a median follow-up period of 3.9 years [65]. Reduction in CV event incidence in participants with CKD receiving pravastatin (hazard ratio HR 0.72; 95 % CI 0.55–0.95; $p = 0.02$) was also observed in a post hoc analysis of the Cholesterol And Recurrent Events (CARE) trial [66]. In this analysis, statin administration was associated with reduced adjusted HR for major coronary events (HR 0.72; 95 % CI 0.59–0.88; $p = 0.001$) and coronary revascularization (HR 0.65; 95 % CI 0.50–0.83; $p = 0.001$) [66]. The recent SHARP study revealed that patients randomized to a combination of ezetimibe/simvastatin (10/20 mg) experienced a 17 % decrease in major atherosclerotic events compared with the placebo group (RR 0.83; 95 % CI 0.74–0.94; $p = 0.0021$) after a median follow-up of 4.9 years [59].

Effect of statins on patients' mortality

A meta-analysis of 44 trials including 23,665 patients revealed no significant reduction in the risk of all-cause mortality associated with the use of statins in CKD patients. However, nearly 20 % reduction in this risk was observed in pre-dialysis patients (21 trials, 18 781 patients; RR 0.81, 0.74–0.89) [1]. Moreover, similar risk reduction was seen in the case of CV mortality in CKD

patients treated with statins (RR 0.81, 0.73–0.90) irrespective of the type of statin. A meta-analysis of 11 randomized trials including 21,295 CKD non-dialysis and dialysis-dependent patients revealed that the use of statins was associated with 34 % reduction in deaths from all causes ($p < 0.0001$) and 31 % reduction in deaths from cardiac causes ($p = 0.0012$) [14]. In another meta-analysis of 26 randomized controlled trials performed by Navaneethan et al. [64], statins reduced the risk of all-cause mortality (RR 0.81; 95 % CI 0.74–0.89). Also JUPITER trial revealed that administration of rosuvastatin (20 mg daily) was associated with a 44 % reduction in all-cause mortality in participants with moderate CKD [57]. However, post hoc analysis of the Collaborative Atorvastatin Diabetes Study (CARDS) study did not confirm the beneficial effect of atorvastatin 10 mg/day in patients with a GFR from 30 to 60 ml/min/1.73 m^2, with type 2 diabetes and without previous history of CVD on total mortality (HR 0.81; 95 % CI 0.61–1.08; $p = 0.14$) [66]. Also, in the Prevention of Renal and Vascular End-stage Disease Intervention Trial (PREVEND IT), pravastatin treatment of 864 microalbuminuric patients did not result in a significant reduction in CV mortality or hospitalization for CV morbidity (HR 0.87; 95 % CI 0.49–1.57; $p = 0.649$) [67].

Adverse effects of statins

In the analysis of 26 trials and 6726 patients, no significant increase in liver function parameters or risk of rhabdomyolysis (raised creatinine phosphokinase concentrations) was observed in CKD patients receiving statins in comparison with placebo. Heterogeneity of statin effects in the meta-analysis of Strippoli et al. [1] was mostly associated with statin type, baseline cholesterol concentrations, and age as well as allocation concealment. According to some studies, the presence of CKD increases the risk of statin intolerance [68, 69].

Recommendations

Current European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) 2011 guidelines indicate that CKD patients should be treated as individuals at very high CV risk and thus they should have all risk factors adequately managed [60, 70]. According to the aforementioned guidelines, statins use should be considered in CKD patients due to their ability to retard kidney function loss and to protect against the development of dialysis-dependent ESRD (IIa/C level of recommendation/evidence) [60, 70]. The use of statins in patients with moderate to severe CKD should be considered in order to achieve LDL-C 570 mg/dL (1.8 mmol/L) (IIa/C level of recommendation/evidence) [60, 70]. In the global recommendations for the management of dyslipidemia issued by the International Atherosclerosis Society (IAS), there appears a suggestion that in CKD patients the optimal range of LDL-C should be <100 mg/dL (2.6 mmol/L) [60, 71]. Also the recent 2012 update of the Canadian CV Society guidelines recommends the use of statins in CKD patients in order to lower lipid levels and as a prevention of CV disease [72]. According to current KDIGO Clinical Practice Guideline for Lipid Management in CKD [73] treatment escalation to achieve specific LDL-C targets by increasing the dose of statin and/or combination therapy is no longer recommended for CKD populations because of medication-related toxicity and also due to the fact that higher CAD risk and not elevated LDL-C is now the primary indication to initiate or adjust lipid-lowering therapy in this group of patients. The guidelines are as follows:

- in adults aged ≥50 years with eGFR <60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), the treatment with a statin or statin/ezetimibe combination is recommended (1A)*
- in adults aged ≥50 years with CKD and eGFR ≥60 ml/min/1.73 m^2 (GFR categories G1-G2), treatment with a statin is recommended (1B)**
- in adults aged 18–49 years with CKD but not treated with chronic dialysis or kidney transplantation, statin treatment in people with one or more of the following (2A)***:
    - known coronary disease (myocardial infarction or coronary revascularization)
    - diabetes mellitus
    - prior ischemic stroke
    - estimated 10-year incidence of coronary death or non-fatal myocardial infarction >10 % is suggested [73].

Nomenclature and description for rating guideline recommendations

* 1A—Grade: 'We recommend'; Quality of evidence: High; Meaning: We are confident that the true effect lies close to that of the estimate of the effect.
**1B—Grade: 'We recommend'; Quality of evidence: Moderate; Meaning: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
***2A—Grade: 'We suggest'; Quality of evidence: High; Meaning: We are confident that the true effect lies close to that of the estimate of the effect [73].

Table 1 Recommended doses of statins in CKD adults (prepared on the basis of KDIGO recommendations [73]

Type of statin	G1–G2 (≥90—60–89 ml/min/1.73 m^2)	G3a–G5 (45–59—<15 ml/min/1.73 m^2)	Clinical trial
Lovastatin	General population	Not studied	–
Fluvastatin	General population	80	ALERT
Atorvastatin	General population	20	4D
Rosuvastatin	General population	10	AURORA
Simvastatin/Ezetimibe	General population	20/10	SHARP
Pravastatin	General population	40	–
Simvastatin	General population	40	–
Pitavastatin	General population	2	–

Since CKD patients are at high risk of medication-related adverse events, due to decreased renal excretion, frequent polypharmacy and high prevalence of comorbidity in this population and also because of potential toxicity of higher doses of drugs, lower doses of statins are recommended for patients with advanced stages of CKD. KDIGO Work Group suggests that prescription of statins in people with eGFR <60 ml/min/1.73 m^2 should be based on beneficial regimens and doses described in appropriate large randomized trials (ALERT, 4D, AURORA, SHARP) [Table 1]. Dose reduction should be considered especially in patients with severe kidney dysfunction receiving very aggressive treatment. Patients with eGFR ≥60 ml/min/1.73 m^2 and no history of kidney transplantation may be treated with any statin doses approved for the general population. Work Group recommends also that fibrates should not be used concomitantly with statins in patients with CKD due to higher risk of adverse events when statins and fibrates are used in combination in this group of patients. Moreover, they suggest that statin treatment gives more beneficial clinical effects, and thus this type of drugs should be prescribed instead of fibrates [73].

In 2013, treatment guideline concerning serum cholesterol management for both primary and secondary atherosclerotic cardiovascular disease (ASCVD) prevention was also published by the American College of Cardiology/American Heart Association (ACC/AHA) [74, 75]. According to these guidelines, there are four categories of adults who benefit from statins therapy: individuals with clinical ASCVD who are administered statins as a secondary prevention, individuals with primary elevations of LDL-C ≥190 mg/dL taking statins as a primary prevention, 40- to 75-year-old individuals with diabetes and LDL-C 70–189 mg/dL using statins as a primary prevention and finally 40- to 75-year-old individuals without diabetes, with LDL-C 70–189 mg/dL and with estimated 10-year ASCVD risk ≥ 7.5 % treated with statins as a primary prevention [74]. The 2013 ACC/AHA guideline increased the number of people in USA who are recommended statin therapy [76]. According to these recommendations, statins should be used for as much as for 92.0 % of participants with CKD, while only 8.0 % of participants with CKD do not meet the criteria for statins [74, 75]. The recommendations are defined on the basis of large study results which demonstrated that:

- in adults with CHD/CVD and CKD (excluding hemodialysis patients), fixed high-intensity statin treatment (80 mg of atorvastatin) resulting in LDL-C level of 79 mg/dl reduced CHD/CVD events more than lower dose of statin [77–79]
- in adults ≥40 years of age with CKD (but not hemodialysis patients), 10 mg of ezetimibe co-administered with simvastatin lowered LDL-C by 37 mg/dl, reduced risk of CVD events by 22 %, modestly increased the risk of muscle symptoms requiring discontinuation of treatment and did not increase the risk of elevated hepatic transaminases, cancer, hemorrhagic stroke or non-cardiovascular mortality [80] in comparison with placebo [74].

Both KDIGO Lipid Management guideline and the 2013 ACC/AHA guideline recommend general statin treatment for individuals >50 years of age with CKD. According to the 2013 ACC/AHA guideline, there is limited evidence supporting the initiation of statin therapy in primary prevention for persons over 80 years due to higher risk of statin-related adverse events and drug–drug interactions [75, 81, 82].

Conclusions

Results of most of the meta-analyses suggest that statins are associated with lipid lowering, CV and anti-proteinuric benefits in CKD patients [1]. Lipid-lowering effects of statins seem to depend on the duration of the treatment (the longer the more effective) in CKD patients excluding those on dialysis [26]. However, their effects on overall and CV mortality are much less obvious. The

discrepancies of meta-analysis results might be due to the inclusion of different studies using various inclusion and exclusion criteria. Bearing in mind the advantageous effects and low risk of adverse effects, it seems that mild renal impairment should not exclude these patients from receiving a statin. However, because CKD patients in stages III–V are underrepresented in clinical trials, administration of statins to these patients who have not yet had a vascular event remains controversial [72]. On the other hand, lack of statins administration in this group of patients but not drug efficiency may pose a problem. There is a need for large controlled trials which will help to draw final conclusions concerning the use of statins in this group of patients [83].

Conflict of interest None.

References

1. Strippoli GFM, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A, Craig JC (2008) Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomized controlled trials. BMJ 336(7645):645–651
2. Foley RN, Collins AJ (2007) End-stage renal disease in the United States: an update from the United States renal data system. J Am Soc Nephrol 18:2644–2648
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351:1296–1305
4. Nikolic D, Banach M, Nikfar S, Salari P, Mikhailidis DP, Toth PT, Abdollahi M, Ray KK, Pencina MJ, Malyszko J, Rysz J, Rizzo M, Lipid and Blood Pressure Meta-Analysis Collaboration Group (2013) A meta-analysis of the role of statins on renal outcomes in patients with chronic kidney disease. Is the duration of therapy important? Int J Cardiol 168:5437–5447
5. Uhlig K, Levey AS, Sarnak MJ (2003) Traditional cardiac risk factors in individuals with chronic kidney disease. Semin Dial 16:118–127
6. Jungers P, Massy ZA, Khoa TN, Fumeron C, Labrunie M, Lacour B et al (1997) Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. Nephrol Dial Transpl 12:2597–2602
7. Mallamaci F, Zoccali C, Tripei G et al (2002) CREED Investigators Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. Kidney Int 61:609–614
8. Schaeffner ES, Kurth T, Curhan GC et al (2003) Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol 14:2084–2091
9. Gluba A, Rysz J, Banach M (2010) Statins in patients with chronic kidney disease: why, who and when? Expert Opin Pharmacother 11:2665–2674
10. Rossouw JE, Lewis B, Rifkind BM (1990) The value of lowering cholesterol after myocardial infarction. N Engl J Med 323:1112–1119
11. Law MR, Wald NJ, Thompson SG (1994) By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ 308:367–372
12. Douglas K, O'Malley PG, Jackson JL (2006) Meta-analysis: the effect of statins on albuminuria. Ann Intern Med 145:117–124
13. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ et al (2002) Urinary albumin excretion predicts cardiovascular and non-cardiovascular mortality in general population. Circulation 106:1777–1782
14. Barylski M, Nikfar S, Mikhailidis DP, Lipid and Blood Pressure Meta-Analysis Collaboration Group (2013) Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy—a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacol Res 72:35–44
15. Randomized trial of cholesterol lowering in (1994) 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383–1389
16. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels (1998) The long-term intervention with pravastatin in ischaemic disease (LIPID) study group. N Engl J Med 339:1349–1357
17. Ridker PM, Cannon CP, Morrow D, Braunwald E (2005) Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 (PROVE IT-TIMI 22) investigators: C-reactive protein levels and outcomes after statin therapy. N Engl J Med 352:20–28
18. Tonelli M, Isles C, Curhan GC et al (2004) Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 110:1557–1563
19. Epstein M, Campese VM (2005) Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on renal function. Am J Kidney Dis 45:2–14
20. Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC, For the Cholesterol and Recurrent Events (CARE) Trial Investigators (2003) Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. J Am Soc Nephrol 14:1605–1613
21. O'Driscoll G, Green D, Taylor RR (1997) Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. Circulation 95:1126–1131
22. Zhu XY, Daghini E, Chade A, Napoli C, Ritman EL, Lerman A et al (2007) Simvastatin prevents coronary microvascular remodelling in renovascular hypertensive pigs. J Am Soc Nephrol 18:1209–1217
23. Yoshimura A, Nemoto T, Sugenoya Y, Inui K, Watanabe S, Inoue Y et al (1999) Effect of simvastatin on proliferative nephritis and cell-cycle protein expression. Kidney Int Suppl 71: S84–S87
24. Tonelli M (2008) Statins for slowing kidney disease progression: an as yet unproven indication. Am J Kid Dis 52:391–394
25. Franczyk-Skora B, Gluba A, Banach M et al (2012) Prevention of sudden cardiac death in patients with chronic kidney disease. BMC Nephrol 13:162
26. Nikolic D, Nikfar S, Salari P, Rizzo M, Ray KK, Pencina MJ, Mikhailidis DP, Toth PP, Nicholls SJ, Rysz J, Abdollahi M (2013) Banach M; lipid and blood pressure meta-analysis collaboration group. Effects of statins on lipid profile in chronic kidney disease patients: a meta-analysis of randomized controlled trials. Curr Med Res Opin 29(5):435–451
27. Kujawa-Szewieczek A, Piecha G, Więcek A (2014) Hyperlipidemia as a risk factor for progression of CKD in Nondiabetics. In: Covic A et al (eds) Dyslipidemias in kidney disease. Springer Science + Business Media, New York
28. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J (2004) The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. Ann Intern Med 140:9–17
29. Cheung AK, Wu LL, Kablitz C, Leypoldt JK (1993) Atherogenic lipids and lipoproteins in hemodialysis patients. Am J Kidney Dis 22:271–276

30. Rapoport J, Aviram M, Chaimovitz C, Brook JG (1978) Defective high-density lipoprotein composition in patients on chronic hemodialysis. A possible mechanism for accelerated atherosclerosis. N Engl J Med 299:1326–1329
31. Guarnieri GF, Moracchiello M, Campanacci L, Ursini F, Ferri L, Valente M et al (1978) Lecithin-cholesterol acyltransferase (LCAT) activity in chronic uremia. Kidney Int Suppl 13:26–30
32. McLeod R, Reeve CE, Frohlich J (1984) Plasma lipoproteins and lecithin: cholesterol acyltransferase distribution in patients on dialysis. Kidney Int 25:683–688
33. Hirano T, Sakaue T, Misaki A, Murayama S, Takahashi T, Okada K et al (2003) Very low-density lipoprotein-apoprotein CI is increased in diabetic nephropathy: comparison with apoprotein CIII. Kidney Int 63:2171–2177
34. Vaziri ND (2006) Dyslipidemia of chronic renal failure: the nature, mechanisms, and potential consequences. Am J Physiol Renal Physiol 290:262–272
35. Chmielewski M, Carrero JJ, Nordfors L, Lindholm B, Stenvinkel P (2008) Lipid disorders in chronic kidney disease: reverse epidemiology and therapeutic approach. J Nephrol 21:635–644
36. Lin J, Hu FB, Rimm EB, Rifai N, Curhan GC (2006) The association of serum lipids and inflammatory biomarkers with renal function in men with type II diabetes mellitus. Kidney Int 69:336–342
37. Wheeler DC, Bernard DB (1994) Lipid abnormalities in the nephrotic syndrome: causes, consequences, and treatment. Am J Kidney Dis 23:331–346
38. Bianchi S, Bigazzi R, Caiazza A, Campese VM (2003) A controlled prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. Am J Kidney Dis 41:565–570
39. Takemura T, Yoshioka K, Aya N et al (1993) Apolipoproteins and lipoprotein-receptors in glomeruli in human kidney diseases. Kidney Int 43:918–927
40. Keane WF, O'Donnell MP, Kasiske BL, Kim Y (1993) Oxidative modification of low density lipoproteins by mesangial cells. J Am Soc Nephrol 4:187–194
41. Coritsidis G, Rifici V, Gupta S et al (1991) Preferential binding of oxidized LDL to rat glomeruli in vivo and cultured mesangial cells in vitro. Kidney Int 39:858–866
42. Shurraw S, Tonelli M (2006) Statins for treatment of dyslipidemia in chronic kidney disease. Perit Dial Int 26:523–539
43. Nitta K (2012) Clinical assessment and management of dyslipidemia in patients with chronic kidney disease. Clin Exp Nephrol 16:522–529
44. Banach M, Hering D, Narkiewicz K, Mysliwiec M, Rysz J, Malyszko J (2012) Lipids, blood pressure, kidney—what was new in 2012? Int J Pharmacol 8:659–678
45. Di Lullo L, Addesse R, Comegna C et al (2005) Effects of fluvastatin treatment on lipid profile, C-reactive protein trend, and renal function in dyslipidemic patients with chronic renal failure. Adv Ther 22:601–612
46. Sawara Y, Takei T, Uchida K et al (2008) Effects of lipid-lowering therapy with rosuvastatin on atherosclerotic burden in patients with chronic kidney disease. Inter Med 47:1505–1510
47. DouglasK O', Malley PG, Jackson JL (2006) Meta-analysis: the effect of statins on albuminuria. Ann Intern Med 145:117–124
48. Kimura K, Shimano H, Yokote K, Urashima M, Teramoto T (2010) Effects of pitavastatin (LIVALO tablet) on the estimated glomerular filtration rate (eGFR) in hypercholesterolemic patients with chronic kidney disease. Sub-analysis of the LIVALO Effectiveness and Safety (LIVES) study. J Atheroscler Thromb 17:601–609
49. Sandhu S, Wiebe N, Fried LF, Tonelli M (2006) Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol 17:2006–2016
50. Abe M, Maruyama N, Yoshida Y, Ito M, Okada K, Soma M (2011) Efficacy analysis of the lipid-lowering and renoprotective effects of rosuvastatin in patients with chronic kidney disease. Endocr J 58:663–674
51. Ozsoy RC, Koopman MG, Kastelein JJ, Arisz L (2005) The acute effect of atorvastatin on proteinuria in patients with chronic glomerulonephritis. Clin Nephrol 63:245–249
52. Douglas K, O'Malley PG, Jackson JL (2006) Meta-analysis: the effect of statins on albuminuria. Ann Intern Me 145(2): 117–124
53. O'Donnell MP, Kasiske BL, Kim Y et al (1993) Lovastatin retards the progression of established glomerular disease in obese Zucker rats. Am J Kidney Dis 22:83–89
54. Campese VM, Nadim MK, Epstein M (2005) Are 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors renoprotective? J Am Soc Nephrol 16:S11–S17
55. Joyce M, Kelly C, Winter D et al (2001) Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, attenuates renal injury in an experimental model of ischemia–reperfusion. J Surg Res 101:79–84
56. Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Coombes JS (2010) Effect of atorvastatin on kidney function in chronic kidney disease: a randomized double-blind placebo—controlled trial. Atherosclerosis 213:218–224
57. Ridker PM, MacFadyen J, Cressman M, Glynn RJ (2010) Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. J Am Coll Cardiol 55:1266–1273
58. Rahman M, Baimbridge C, Davis BR, Barzilay J, Basile JN, Henriquez MA et al (2008) Progression of kidney disease in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin versus usual care: a report from the antihypertensive and lipid-lowering treatment to prevent Heart Attack Trial (ALLHAT). Am J Kidney Dis 52:412–424
59. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C et al (2011) The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet 377:2181–2192
60. Banach M, Lipid and Blood Pressure Meta-Analysis Collaboration Group (2013) Statins in patients with chronic kidney disease—an attempt at recommendations. Curr Med Res Opin 29(11):1419–1422
61. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF (2012) Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 157(4):263–275
62. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM (2012) Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 157(4):251–262
63. Koren MJ, Davidson MH, Wilson DJ, Fayyad RS, Zuckerman A, Reed DP (2009) Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. Am J Kid Dis 53:741–750
64. Navaneethan SD, Pansini F, Perkovic V, Manno C, Pellegrini F, Johnson DW, et al. (2009) HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev 2:CD007784
65. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ et al (2009) Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the collaborative atorvastatin diabetes study (CARDS). Am J Kid Dis 54:810–819

66. Tonelli M, Moye L, Sacks FM, Kiberd B, Curhan G (2003) Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. Ann Intern Med 138:98–104
67. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA et al (2004) Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 110:2809–2816
68. Banach M, Serban C, Sahebkar A et al (2015) Lipid and blood pressure Meta-analysis collaboration group. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. Mayo Clin Proc 90(1):24–34
69. Vrablik M, Zlatohlavek L, Stulc T et al (2014) Statin-associated myopathy: from genetic predisposition to clinical management. Physiol Res 63(suppl 3):S327–S334
70. Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), Catapano AL, Reiner Z, De Backer G, et al. (2011) ESC Committee for Practice Guidelines 2008–2010 and 2010–2012 Committees ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 217(Suppl 1):S1–44
71. An International Atherosclerosis Society (IAS) Position Paper: Global Recommendations for the Management of Dyslipidemia. Updated 25 July 2013. http://www.athero.org/IASPositionPaper.asp. Accessed 2 Aug 2013
72. Anderson TJ, Grégoire J, Hegele RA et al (2013) 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 29:151–167
73. (2013) KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Kid Int Suppl 3(3):259–305
74. Banach M, Rysz J (2010) Current problems in hypertension and nephrology. Expert Opin Pharmacother 11(16):2575–2578
75. Stone NJ, Robinson JG, Lichtenstein AH et al (2014) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129(Suppl 2):S1–S45
76. Colantonio LD, Baber U, Banach M, et al. (2014) Contrasting cholesterol management guidelines for adults with CKD. J Am Soc Nephrol. Nov 13. [Epub ahead of print]
77. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, Williams K, Neely B, Sniderman AD, Peterson ED (2014) Application of new cholesterol guidelines to a population-based sample. N Engl J Med 370:1422–1431
78. LaRosa JC, Grundy SM, Waters DD et al (2005) Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352:1425–1435
79. Shepherd J, Kastelein JJP, Bittner V et al (2008) Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. J Am Coll Cardiol 51:1448–1454
80. Shepherd J, Kastelein JP, Bittner VA et al (2008) Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. Mayo Clin Proc 83:870–879
81. Sharp Collaborative Group (2010) Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9438 patients with chronic kidney disease. Am Heart J 160(785–794):e10
82. Stone NJ, Robinson JG, Lichtenstein AH et al (2014) 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129(Suppl 2):S1–S45
83. Olyaei A, Greer E, Delos Santos R, Rueda J (2011) The efficacy and safety of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors in chronic kidney disease, dialysis, and transplant patients. Clin J Am SocNephrol 6:664–678