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REVIEW ARTICLE

Benefit–Risk Assessment of Rosuvastatin in the Treatment of Atherosclerosis and Related Diseases

Michael S. Kostapanos · Christos V. Rizos · Moses S. Elisaf

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Abstract Rosuvastatin has been marketed for approximately a decade. In this review we critically discuss available evidence on the benefits and risks from its use. In clinical trials using rosuvastatin, 'lowest is best' was relevant for on-treatment low-density lipoprotein cholesterol levels. Targeting levels <50 mg/dl was associated with the greatest decrease in vascular morbidity/mortality in the primary prevention setting. Also, such reduction can induce atherosclerosis regression without increasing the risk of adverse effects. Pooled data suggest that the safety profile of rosuvastatin is not different from that of other statins. It was estimated that rosuvastatin-associated absolute hazards of muscle-, liver- and renal-related adverse effects are lower than the corresponding vascular benefits in moderate vascular risk individuals. However, these data are subject to biases and need confirmation on a prospective basis. Significant liver enzyme elevations are rare. These often imply underlying non-alcoholic fatty liver disease (NAFLD), which is associated with increased vascular risk. Rosuvastatin can improve biochemical biomarkers and histological score of NAFLD. Whether this benefit is associated with vascular risk reduction should be assessed by prospective studies. Both chronic kidney disease and albuminuria independently predict vascular morbidity and mortality. Rosuvastatin improved the estimated glomerular filtration rate and decreased albuminuria in patients with moderately impaired kidney function. Also, vascular morbidity and mortality might be reduced in these patients. The same was not relevant in end-stage renal disease. Rosuvastatin-induced proteinuria appears to be of tubular origin, not relating to kidney injury. Rosuvastatin increases the risk of new-onset diabetes by dose-dependently impairing insulin sensitivity. Obese individuals with prediabetes appear to be predominantly affected. However, absolute vascular benefits of rosuvastatin may counterbalance this risk. Rosuvastatin is effective for the prevention and management of atherosclerotic vascular disease. Individualization of its use can maximize benefits and reduce the risk of adverse effects.

Key Points

Aggressive low-density lipoprotein cholesterol lowering by high-dose rosuvastatin may be a safe and effective strategy in reducing vascular morbidity and mortality. Atherosclerosis regression might also be expected

Pooled data (subject to biases) suggest that rosuvastatin shares the safety profile of its class. In moderate-risk individuals, its estimated absolute vascular benefits might counterbalance corresponding absolute hazards of adverse effects

It is intriguing to further assess benefits and risks of rosuvastatin treatment regarding emerging concepts in atherosclerosis. These include non-alcoholic fatty liver disease and chronic kidney disease. Preliminary data are promising for a beneficial role of rosuvastatin

Rosuvastatin may increase the risk of new-onset diabetes by dose-dependently increasing insulin resistance. This risk appears to be counterbalanced by rosuvastatin-associated absolute vascular benefits in the primary prevention setting

M. S. Kostapanos · C. V. Rizos · M. S. Elisaf (✉)
Department of Internal Medicine, Medical School, University of Ioannina, St. Niarchou Avenue, 45110 Ioannina, Greece
e-mail: egepi@cc.uoi.gr

1 Introduction

Statins are evidence-based drugs for the management of dyslipidemia and to reduce the risk of cardiovascular (CV) events [1]. Lowering low-density lipoprotein cholesterol (LDL-C) levels is their main lipid effect [1]. Clinical evidence has suggested that 'lowest is best' for LDL-C levels. In this context, statins are first-line drugs [1].

Rosuvastatin has been available for approximately 10 years [2]. It is the most effective statin in improving the serum lipid profile and achieving LDL-C goals in various populations [2–5]. Before the release of rosuvastatin, 'landmark' trials had established vascular benefits of statins in both the primary and secondary prevention setting [6–9].

The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study included 17,802 apparently healthy individuals with normal LDL-C (<130 mg/dl), but raised high-sensitivity C-reactive protein (hsCRP ≥2 mg/l) levels [10]. It was the first time that such a population had been involved in a statin trial. Participants were randomized to rosuvastatin 20 mg/day or placebo. The primary endpoint was the combination of myocardial infarction (MI), stroke and arterial revascularization, as well as hospitalization for unstable angina or death from CV causes. LDL-C and hsCRP levels were reduced by 50 % and 37 %, respectively, in the rosuvastatin group after 12 months. These reductions persisted throughout the study period (1.9 years, median) [10]. Rosuvastatin significantly decreased (by 44 %) the risk of primary endpoint compared with placebo. Significant reductions in the relative risk of separate CV outcomes were also noted [10].

Safety has been a major concern. Rosuvastatin was the first statin marketed after the withdrawal of cerivastatin due to increased risk of myopathy [11]. Also, the lowering of LDL-C targets imposed the use of aggressive statin treatment, including rosuvastatin. Statin-associated adverse effects are dose-dependent, thus being more likely with intensive treatment [11].

The American College of Cardiology (ACC)/American Heart Association (AHA) recently published their *Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults* [12]. Interestingly, it focused on targeting vascular risk rather than specific LDL-C goals. In this context, statins are considered the only evidence-based option for the management of vascular risk [12]. The appropriate intensity of statin therapy should be used to reduce atherosclerotic CV risk in those most likely to benefit. In this context, statin treatment was defined as high-, moderate- and low-intensity by expected LDL-C reductions of ≥50, 30–50 and <30 %, respectively [12]. This guideline considers rosuvastatin 20–40 mg/day as high-intensity treatment, while 5–10 mg/day is considered as moderate-intensity treatment [12].

A preferential risk profile of rosuvastatin compared with other statins was implied by its pharmacokinetic characteristics [13]. These include its hydrophilic character, hepatoselectivity and low systemic bioavailability [13]. Also, its minimal metabolism through the cytochrome P450 (CYP) system could result in fewer drug–drug interactions [13]. We previously reviewed the literature on rosuvastatin-related adverse effects, concluding that rosuvastatin appears to be relatively safe and well tolerated, sharing the adverse effects considered as 'class effects' of statins [14].

2 Objective

In this review the current role of rosuvastatin in the management of dyslipidemias is critically discussed by focusing on the benefits and risks from its use.

3 Benefit–Risk Assessment of Intensive Low-Density Lipoprotein Cholesterol Lowering by Rosuvastatin

The key points in the benefit-risk assessment of intensive LDL-C lowering by rosuvastatin are summarized in Table 1.

3.1 The JUPITER Study and its Subanalyses

Compared with other primary prevention statin trials, the JUPITER study involved a different population [15]. Namely, previous studies included patients with vascular risk factors, such as hypercholesterolemia, diabetes, hypertension and a family history of premature CV disease [15]. In contrast, JUPITER participants were apparently healthy with normal LDL-C, but increased inflammation [10]. The latter was mostly attributed to an increased incidence of obesity, smoking and metabolic syndrome [10]. The JUPITER population was not eligible for statin treatment according to baseline LDL-C levels [15]. Interestingly, rosuvastatin significantly reduced CV morbidity and mortality in this population. In a critical review of JUPITER subanalyses, we concluded that "the current guidelines for statin use may dramatically change leading to increased use of statin treatment" [15]. It was estimated that the JUPITER results could expand statin use in an additional 19.2 % of elderly men (≥50 years) and women (≥60 years) [16]. This was also highlighted by the recent ACC/AHA guidelines, which focus on targeting CV risk rather than specific LDL-C goals [12]. Namely, benefit

from statin treatment in the primary prevention setting is expected in 40- to 75-year-old individuals with LDL-C levels 70–189 mg/dl, diabetes or an estimated vascular risk ≥7.5 % [12]. In JUPITER, despite relatively low baseline LDL-C levels (108 mg/dl, median) most participants exhibited a vascular risk ≥7.5 % [17]. It was estimated that 7,340/17,802 (41.2 %) had a Framingham risk score of 11–20 %, while 6,091/17,802 (34.2 %) had a score of 5–10 % [17]. Notably, the Framingham risk score shares the same covariates with the pooled cohort risk calculator recommended by the ACC/AHA [18]. Rosuvastatin treatment was associated with reduced absolute risk of the primary endpoint compared with placebo in these individuals [17]. Interestingly, this benefit was greater with increasing vascular risk score [i.e. an estimated 5-year number needed to treat (NNT) of 40 vs. 18 in patients with a Framingham risk score of 5–10 % vs. 11–20 %, respectively] [17].

Safety concerns were raised by the risk of hemorrhagic stroke associated with low on-treatment LDL-C levels. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study included 4,731 patients who had had a stroke or transient ischemic attack within 1–6 months before entry [19]. Participants were randomized to high-dose atorvastatin (80 mg/day) or placebo. During the course of the trial, the mean LDL-C values were 73 mg/dl in the atorvastatin group versus 129 mg/dl in the placebo group [19]. During the 4.9 year (median) follow-up atorvastatin significantly reduced (by 16 %) the risk of fatal or non-fatal stroke compared with placebo [19]. However, in a post hoc analysis, atorvastatin was associated with an increased (by 66 %) risk of hemorrhagic stroke [19]. In accordance with this finding previous epidemiological data suggested that low cholesterol concentration is associated with an increased risk of intracranial bleeding [20–22]. Nevertheless, statin trials with similar on-treatment LDL-C levels did not have relevant findings [23, 24]. Likewise, a meta-analysis of five trials including 39,612 patients showed no significant difference between more and less intensive treatment in the risk of hemorrhagic stroke [25].

In the JUPITER study, rosuvastatin reduced LDL-C levels to 55 mg/dl (median) [10], the lowest on-treatment level ever achieved in a primary prevention statin trial. Also, it significantly reduced (by 48 %) the risk of fatal or non-fatal stroke compared with placebo [26]. This benefit was mostly attributed to a significant decrease in the risk of ischemic stroke (by 51 %) [26]. Before this study, the efficacy of statin treatment to reduce stroke risk in the primary prevention setting was doubted [15]. In JUPITER, patients with on-treatment LDL-C levels <70 mg/dl exhibited the greatest benefit [26]. Interestingly, no significant difference between rosuvastatin and placebo in the risk of hemorrhagic stroke [hazard ratio (HR) 0.67; 95 % confidence interval (CI) 0.24–1.88)] was noted [26]. In this context, rosuvastatin might reduce the risk of ischemic stroke without increasing that of intracranial bleeding.

Similar were the findings for all vascular events. Lower on-treatment levels of LDL-C and hsCRP were associated with further reductions in the risk of vascular events [27]. Namely, rosuvastatin-treated patients achieving LDL-C <70 mg/dl and hsCRP levels <2 mg/l had a 65 % reduced risk of vascular events compared with placebo-treated patients [27]. The corresponding relative risk reduction was 33 % in patients achieving ≤1 of these targets [27]. A post hoc analysis of the JUPITER study assessed a lower cutoff point of on-treatment LDL-C levels—50 mg/dl [28]. Patients with LDL-C levels <50 mg/dl taking rosuvastatin had a 65 % relative risk reduction in the primary endpoint compared with placebo [28]. The corresponding relative risk reduction was 24 % in those with on-treatment LDL-C levels >50 mg/dl [28]. Interestingly, no difference in the incidence of adverse effects was noted between rosuvastatin-treated patients with LDL-C levels <50 mg/dl or >50 mg/dl [28]. The assessed safety outcomes included myalgia, muscle weakness, neuropsychiatric conditions, cancer and diabetes mellitus [28]. These findings suggest that targeting very low LDL-C levels by rosuvastatin may be a beneficial and safe strategy for vascular risk reduction.

However, genetic factors should be considered. It is known that there is an interindividual variation in LDL-C response to statins [29]. A genome-wide association study of this response was performed among 6,989 JUPITER participants of European ancestry [29]. According to this, there was significant variability in LDL-C lowering by

Table 1 Key points in the benefit–risk assessment of intensive LDL-C lowering by rosuvastatin

✔ Intensive LDL-C lowering by high-dose rosuvastatin (20 mg/day) was associated with reduced vascular morbidity and mortality. Lower on-treatment LDL-C (<50 mg/dl) and hsCRP (<1 mg/l) levels were associated with further benefits

✔ The absolute vascular benefits of rosuvastatin might rise with increasing the baseline vascular risk of treated individuals

✔ Regression of coronary and slower progression of carotid atherosclerosis might be expected by intensive LDL-C lowering (<80 mg/dl) using high-dose (40 mg/day) rosuvastatin treatment

✔ Adverse effects by high-dose rosuvastatin may be infrequent, not relating to on-treatment LDL-C levels. No increased risk of hemorrhagic stroke was associated with aggressive LDL-C lowering by rosuvastatin

LDL-C low-density lipoprotein cholesterol, *hsCRP* high-sensitivity C-reactive protein

rosuvastatin 20 mg/day between different single nucleotide polymorphisms in several genes (*ABCG2*, *LPA*, *APOE*, *PCSK9*, *SLCO1B1* and *LDLR*) [29]. Therefore, it is likely that JUPITER participants achieving on-treatment LDL-C levels <50 mg/dl might be genetically different from those not reaching this target. In this context, there may be genetically predisposed individuals who cannot experience a 65 % relative risk reduction in the primary endpoint of JUPITER. In contrast, targeting very low LDL-C levels (<50 mg/dl) by high-dose treatment in those patients might increase the risk of adverse effects, especially of rhabdomyolysis, without getting significant benefits. Interestingly, several of the assessed genes (e.g. *ABCG2* and *SLCO1B1*) in JUPITER are involved in rosuvastatin pharmacokinetics, especially in its hepatic elimination [30].

Furthermore, JUPITER results should be considered under several limitations. This study was terminated early. In this relatively short period of time, only 240 fatal or non-fatal MIs and strokes, the endpoints that are less open to bias, could be recorded [10]. Also, follow-up might have been too short to show significant differences in the incidence of several serious adverse events, including total hospitalization, prolongation of hospitalization, cancer and permanent disability [31]. Furthermore, mortality curves were actually converging when the trial was ended. This implies that the borderline significant difference between groups in mortality could have disappeared in case of a slightly longer follow-up [31]. Also, in JUPITER the all-cause mortality rate (just <2.0 % per year) is similar to that noted in the secondary prevention statin trials [32]. In this context, JUPITER results may not be generalizable in the primary prevention setting.

An inconsistency in the effect of rosuvastatin on non-fatal compared with fatal CV events was noted in JUPITER. Namely, rosuvastatin was associated with significantly reduced risk of only non-fatal MIs or strokes. In contrast, no difference between rosuvastatin and placebo was noted in fatal events. Interestingly, more fatal MIs were noted in the rosuvastatin group than in the placebo group (9 vs. 6, respectively) [31]. Also, the ratio of fatal-to-non-fatal MIs in JUPITER was paradoxically low, especially in the placebo group (6/62 events). These data suggest that JUPITER hearts were unexpectedly (and inexplicably) resistant to acute ischemia [31]. Furthermore, the case-fatality rate was significantly higher in the rosuvastatin group than in the placebo group (29.0 vs. 8.8 %, respectively) [31]. Chan et al. noted a high incidence of vascular events, other than MIs and strokes, leading to death [33]. Also, data for sudden cardiac death, the simplest and more reliable diagnosis in cardiology, accounting for 65–70 % of total cardiac mortality, were not presented in JUPITER [31].

3.2 The ASTEROID Study

The ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) study included 349 coronary artery disease patients receiving high-dose rosuvastatin (40 mg/day). Mean on-treatment LDL-C levels during the study period (24 months) were 61 mg/dl [34]. Coronary atherosclerosis assessed by intravascular ultrasound (IVUS) was regressed and coronary artery stenosis was reduced [34, 35]. Interestingly, this has been the greatest recorded anti-atherosclerotic effect ever achieved by statin therapy. Namely, regression was noted in 64–78 % of ASTEROID participants compared with 7–41 % in previous statin studies [36–39]. This may be attributed, at least in part, to the lowest on-treatment LDL-C levels achieved in this study [36]. It was estimated that at an LDL-C level ≈80 mg/dl, atherosclerosis neither progresses nor regresses [36]. On-treatment levels below this cutoff point, like those in ASTEROID, can help explain atherosclerosis regression [36]. Overall, the incidence of adverse effects in ASTEROID was comparable with that of other statin trials [34]. A further analysis of safety and efficacy outcomes among ASTEROID participants with different on-treatment LDL-C levels was performed [40]. The assessed adverse effects were death, hemorrhagic stroke, as well as liver and muscle enzyme elevations [40]. Despite high-dose treatment, these outcomes were generally infrequent in this population. Interestingly, no association between on-treatment LDL-C levels with safety outcomes was noted, even below the lowest cutoff point of 40 mg/dl [40].

3.3 The METEOR Study

Anti-atherosclerotic benefits of rosuvastatin were also assessed in the METEOR (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) study [41]. This included 984 individuals with either age as the only vascular risk factor or a Framingham risk score <10 %. These subjects had modest carotid intima-media thickening and raised LDL-C levels. Study participants were randomized to rosuvastatin 40 mg/day or placebo. Mean LDL-C levels during treatment were reduced from 155 to 78 mg/dl in the rosuvastatin group [41]. After 2 years, this effect was associated with a significantly lower rate of carotid atherosclerosis progression compared with placebo [41]. Additional data suggested that this benefit became relevant within the first year of treatment and was consistent across different subgroups according to age and the presence of risk factors [42]. This effect of rosuvastatin was independent of the serum lipid profile, as well as of the Framingham risk score and carotid intima-media thickness at baseline [41]. According to the current ACC/AHA guidelines, in the

primary prevention setting individuals with a 10-year vascular risk ≥7.5 % are likely to benefit from statin treatment [12]. Interestingly, in METEOR participants the Framingham risk score was low (<10 %) [41]. In this context, a large proportion of study participants might have had an estimated 10-year vascular risk <7.5 %. Considering this, the antiatherosclerotic potential of high-dose rosuvastatin might expand to patients less likely to benefit from statin treatment according to the latest ACC/AHA recommendations. However, this is only a hypothesis that cannot be entirely supported by METEOR results since analysis in patients exhibiting 10-year risk <7.5 % has not been performed. Also, it should be acknowledged that the METEOR study was not designed to assess 'hard outcomes', including vascular events or mortality.

4 Benefit–Risk Assessment in Pooled Data

The key points in the benefit-risk assessment of rosuvastatin in pooled safety studies are summarized in Table 2.

4.1 US FDA-Reported Adverse Effects

A preliminary analysis included the FDA-reported adverse effects during the first year in which rosuvastatin was available in the US. A comparison of its safety with that of simvastatin, pravastatin and atorvastatin was performed [43]. Interestingly, rosuvastatin was associated with increased rates of the composite adverse effect, which included rhabdomyolysis, proteinuria, nephropathy and renal failure [43]. According to this analysis, these adverse effects are expected to occur early (within the first 12 weeks) in the course of treatment [43]. However, this study should be interpreted with caution due to several limitations. These include its retrospective design [43]. Also, considering the lifecycle of each statin, clinicians tend to more frequently report adverse effects associated with newly marketed drugs. Furthermore, rosuvastatin was the first marketed statin after the withdrawal of cerivastatin. This issue probably increased clinicians' alertness for adverse effects.

In accordance with the previous study, another analysis included 1,644,220 adverse effects submitted to the FDA during the first 5 years in which rosuvastatin was available (2004–2009). Rosuvastatin was associated with an increased risk of myopathic events [myalgia, rhabdomyolysis and creatine kinase (CK) elevation] compared with pravastatin and atorvastatin [44]. The same was relevant for asthenia, pain in the chest or extremities, muscle spasms, muscular weakness, myositis and myopathy [44]. However, such analysis has certain methodological limitations. Namely, the results could have been biased by unmeasured confounding factors. Furthermore, there is no counterfactual element (e.g. randomized control group) to extract the disease-oriented from the drug-associated adverse effects [44]. In this context, placebo-controlled trials reported a high incidence of adverse effects in rosuvastatin-treated patients (i.e. 52.1 %) [45]. Interestingly, this was comparable with the corresponding rate in patients receiving placebo (i.e. 51.8 %) [45]. Therefore, causality for rosuvastatin cannot be established.

4.2 Population-Based Data

A population-based study included 2,121,786 subjects from 368 general practices in England and Wales [46]. This cohort included 4,497 (1.9 %) rosuvastatin new users. Analysis showed no significant association between any statin (including rosuvastatin) treatment and the risk of several morbidities [46]. These included Parkinson's disease, dementia, rheumatoid arthritis, venous thromboembolism, and osteoporotic fracture, as well as gastric, breast, lung and prostate cancer, and melanoma [46]. However, a twofold increased risk of colon cancer was associated with rosuvastatin in men, but not in women. In a time-varying analysis, this risk was relevant after 3 years of treatment. However, it returned to normal within 1 year from treatment discontinuation [46]. To date, there has been no additional evidence suggesting increased risk of this malignancy in rosuvastatin-treated patients. This observation should be further assessed by prospective studies. Overall, statin treatment was associated with an increased risk of adverse effects. These included serious myopathic events {myopathy, rhabdomyolysis or CK ≥4× the upper limit of normal (ULN), moderate-to-severe liver dysfunction (defined as alanine aminotransferase [ALT] >3× ULN)}, cataract, and acute kidney injury [46]. Compared with other statins, rosuvastatin was not associated with an excessive risk for any of these adverse effects [46].

Similarly, a meta-analysis of four pharmacoepidemiological safety studies included 29,900 patient-years' exposure on rosuvastatin [47]. Rosuvastatin was not different from other statins in several safety outcomes, including hospitalized myopathy, rhabdomyolysis, as well as acute kidney or liver injury [47]. Among 16,876 rosuvastatin-treated participants of placebo-controlled trials, rosuvastatin 5–40 mg/day exhibited a similar safety profile to that of atorvastatin 10–80 mg/day, simvastatin 10–80 mg/day and pravastatin 10–40 mg/day [45]. However, the population-based, non-randomized design of these studies might not be sufficient to exclude any differences between statins. Retrospective pooled analyses of randomized trials are also biased. This equivalence in safety should be established on a prospective basis.

In the English primary care study, rosuvastatin was associated with an increased risk of ALT elevation >3×

Table 2 Key points in the benefit-risk assessment of rosuvastatin in pooled safety studies

✔ Analyses of the FDA-reported adverse effects suggested an increased risk of muscle- and kidney-related toxicity associated with rosuvastatin compared with other statins. However, these data have certain limitations relating to the lifecycle of each statin and the increased report of adverse effects of newly marketed drugs. Also, adjustment for unmeasured confounding factors has been missing
✔ Large epidemiological studies showed that rosuvastatin was not associated with an increased relative risk of clinically relevant adverse effects compared with other statins. The absolute vascular benefit from rosuvastatin appears to be greater than the corresponding hazard of clinically relevant adverse effects in moderate-risk individuals. However, these studies are subject to biases associated with their retrospective non-randomized design
✔ An excessive risk of colon cancer in rosuvastatin-treated men should be assessed by future studies appropriately designed to address this outcome
✔ Pooled data from randomized trials suggested that rosuvastatin may not enhance the risk of clinically significant muscle- and liver-related toxicity. However, a moderately increased risk of new-onset diabetes might be expected

ULN by 31 % and 46 % in women and men, respectively, compared with non-statin use [46]. This risk was greater in the first year of treatment with any statin, including rosuvastatin. Also, rosuvastatin-treated women and men had a five- and fourfold increased risk of myopathic events, respectively [46]. This adverse reaction was dose-dependent and relevant in the first year.

However, in moderate-risk individuals, the absolute hazard of each adverse effect might be lower compared with absolute vascular benefits. Namely, the 5-year NNT was 44 and 38 for women and men, respectively [46]. The respective number needed to harm (NNH) was greater for myopathy (313 and 106, respectively), liver toxicity (154 and 155, respectively) and acute kidney injury (593 and 447, respectively) [46]. No statin-specific analysis was performed regarding these outcomes. Nevertheless, no significant difference in the relative risk of each adverse effect was noted between rosuvastatin and other statins [46]. Data for rosuvastatin regarding 5-year NNTs among an intermediate-risk population (defined by Framingham risk score 11–20 %) were provided by a post hoc analysis of JUPITER [17]. Namely, this NNT was 18 [17], which is much lower compared with the NNH for all statins in the English analysis. However, all the abovementioned analyses are subject to biases due to the absence of a true statin-specific analysis regarding NNTs and NNHs. Also, it is difficult to compare the NNT for rosuvastatin in the intermediate-risk JUPITER population with that in primary care corresponders. JUPITER participants were normolipidemic, with increased age being a constant vascular risk factor. In contrast, in primary care most statin-treated patients are dyslipidemic. Also, in the English primary care study the age range (30–84 years) was wide. In this context, different covariates might have accounted for moderate vascular risk in these studies.

4.3 Data from Randomized Clinical Trials

A meta-analysis included 159,458 participants of 72 randomized clinical trials [48]. Compared with controls, statin use significantly increased the risk of new-onset diabetes [odds ratio (OR) 1.09; 95 % CI 1.02–1.16)], as well as of aspartate aminotransferase (AST; OR 1.31; 95 % CI 1.04–1.66) or ALT (OR 1.28; 95 % CI 1.11–1.48) elevations greater than the ULN [48]. AST increments were dose-dependent. The analysis included 31,320 rosuvastatin-treated participants from six clinical trials. Rosuvastatin was associated with a significantly increased risk of diabetes (OR 1.14; 95 % CI 1.01–1.29) [48]. In contrast, the risk of rhabdomyolysis, tenfold increased CK levels, ALT elevation greater than the ULN or cancer were not significantly increased by rosuvastatin treatment [48].

5 Current Concepts in Atherosclerosis: Benefit–Risk Assessment of Rosuvastatin

The key points in the benefit-risk assessment of rosuvastatin in emerging concepts in dyslipidemia management are summarized in Table 3.

5.1 Liver

In randomized clinical trials, <5 % of patients receiving rosuvastatin 5–80 mg/day experienced transaminase (AST/ALT) activity elevations [14]. Clinically relevant increases (>3× ULN in ≥2 consecutive measurements) were infrequent (≤0.8 % of rosuvastatin-treated patients) [14]. It was suggested that discontinuing or lowering rosuvastatin dose can help restore liver function tests [14].

It is debated whether statin-related liver toxicity should concern clinicians. The FDA recently considered routine monitoring of transaminase activities as unnecessary due to the low risk of serious liver injury [49]. The same authority suggests that liver enzyme tests should be performed before starting treatment and as clinically needed thereafter [49]. The 2011 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines admit that whether statin-associated transaminase elevation constitutes true hepatotoxicity has not been determined [50]. It has been suggested that progression to liver failure is

Table 3 Benefit–risk assessment of rosuvastatin in emerging concepts in dyslipidemia management

✔ Clinically relevant transaminase elevations associated with rosuvastatin were infrequent in randomized clinical trials
✔ NAFLD might predict vascular morbidity and mortality and aggravate atherosclerosis. Elevated liver enzyme activities might imply NAFLD in many statin-treated patients. Preliminary data suggest that rosuvastatin can help restore raised liver function tests, as surrogates of liver steatosis. Also, rosuvastatin reduced hepatic steatosis and fibrosis in histological studies. It remains to be established on a prospective basis whether rosuvastatin benefits against NAFLD are translated to better vascular outcomes
✔ CKD significantly increases vascular morbidity and mortality. Aggressive LDL-C lowering is recommended in CKD by current treatment guidelines. Rosuvastatin can improve kidney function or slow its deterioration, while reducing proteinuria in CKD patients. This benefit may be accompanied by a significantly reduced vascular morbidity and mortality in moderate CKD; however, it may not be relevant in ESRD
✔ Atorvastatin may be more efficacious in improving renal function and reducing proteinuria compared with rosuvastatin
✔ It is debated whether intensive high-dose rosuvastatin increases the risk of poor renal safety outcomes compared with low-dose rosuvastatin or usual dosing of other statins
✔ Albuminuria is an independent vascular risk predictor. Rosuvastatin was associated with a significantly reduced renal albumin excretion only in patients with albuminuria at baseline
✔ Rosuvastatin may induce proteinuria of tubular rather than glomerular origin in parallel with its capacity to inhibit mevalonate synthesis. There is no evidence to support a structural damage of renal tubules associated with rosuvastatin treatment
✔ Rosuvastatin may be protective against contrast-induced nephropathy in MI patients undergoing PCI
✔ Diabetes considerably increases atherosclerotic vascular morbidity and mortality. Aggressive LDL-C lowering is recommended in diabetes. Rosuvastatin was associated with an increased risk of new-onset diabetes, mostly by rising insulin resistance. This effect may be particularly relevant in patients with prediabetes at baseline. Also, glycemic control of diabetic patients might be worsened by rosuvastatin treatment
✔ Absolute vascular benefits from rosuvastatin treatment may counterbalance the risk of new-onset diabetes

NAFLD non-alcoholic fatty liver disease, *CKD* chronic kidney disease, *LDL-C* low-density lipoprotein cholesterol, *ESRD* end-stage renal disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention

exceedingly rare. Instead, raised on-treatment transaminase activities >3× ULN may imply concomitant liver diseases [50]. These include alcohol abuse or non-alcoholic fatty liver disease (NAFLD). However, these guidelines still recommend routine liver function testing in statin-treated patients [50].

NAFLD is an emerging risk factor of CV disease [51]. In the clinical setting, abnormally raised liver function tests independently predict CV events and mortality [52–54]. Subclinical atherosclerosis is also enhanced in NAFLD patients compared with non-steatosic individuals [55]. Increased vascular risk in NAFLD can be at least in part explained by insulin resistance and its concomitant clustering of various cardiometabolic risk factors [56]. These include dysglycemia, elevated blood pressure, as well as central adiposity together with 'atherogenic dyslipidemia' [raised triglycerides and low high-density lipoprotein cholesterol (HDL-C) levels]. In this context, NAFLD has been considered as the 'liver component' of metabolic syndrome [56]. Also, in NAFLD the liver overproduces several atherogenic factors, such as inflammatory cytokines, glucose, lipoproteins, and factors increasing blood pressure [51].

The prevalence of NAFLD is rising due to obesity and diabetes epidemics [57]. In this context, interest is increasing on the role of statins in the management of NAFLD. Small clinical studies suggest that long-term statin treatment can help restore elevated transaminase activities as biochemical surrogates of liver steatosis [58–60]. This benefit was also established by ultrasonographic studies [59]. However, biopsy remains the 'gold standard' for the assessment of liver steatosis, necroinflammation and fibrosis in NAFLD. To date, histological data are limited on statin-related benefits against NAFLD. This can be attributed to difficulties in performing an invasive diagnostic procedure in large populations. It was shown that long-term statin treatment may improve histologically-assessed liver steatosis [61]. However, not all statins are equally effective in histologically limiting NAFLD [62, 63].

Data for rosuvastatin are promising. A small study included 23 patients with laboratory and ultrasonographic characteristics of NAFLD. Long-term (8-month) rosuvastatin 10 mg/day normalized previously elevated liver enzymes [64]. Another clinical study included 26 patients with non-alcoholic steatohepatitis (NASH) and dyslipidemia [65]. Patients with moderately elevated liver enzymes at baseline were prescribed rosuvastatin. After 24 months no significant alteration in liver enzymes was noted. However, histologically-assessed steatosis and fibrosis stage was improved in 33.3 % of patients [65]. Despite limitations, this study suggests that rosuvastatin is not only safe in patients with NASH [65] but may also contribute to disease improvement.

Experimental studies suggested mechanisms explaining rosuvastatin benefits against NAFLD. In high-fat-,

cholesterol- or fructose-fed diet animals rosuvastatin significantly decreased histologically-assessed liver steatosis [66–68]. Improved insulin sensitivity markers can partly explain this benefit. These included reduced Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and resistin (an adipokine that contributes to insulin resistance) levels [66, 67]. It was suggested that rosuvastatin may improve liver insulin sensitivity in vivo by reversing the diet-induced decrease in insulin-stimulated insulin receptor substrate-2/phosphadidylinositol 3-kinase/protein kinase B/glucose transporter 4 [69]. Furthermore, adiposity can be changed with rosuvastatin promoting subcutaneous rather than visceral fat accumulation [67]. Hepatic triglyceride accumulation can be reduced by rosuvastatin. This may be explained by inhibition of the sterol regulatory element-binding protein-1c (SREBP-1c) expression. This protein is involved in fatty acid biosynthesis [66]. Interestingly, rosuvastatin exerted anti-inflammatory actions against NASH, mirrored by decreased hepatic lobular inflammation grade in vivo [68]. Reduced tumor necrosis factor-α and interleukin-6 messenger RNA expressions may be mechanisms explaining this benefit [68]. Also, fibrosis can be attenuated by rosuvastatin in NASH patients by reducing the hepatic expression of pro-fibrotic factors. These include transforming growth factor-β, connective tissue growth factor, and type-1 procollagen [68]. Liver-specific benefits of rosuvastatin against NASH can also be explained by antioxidant effects [68].

NAFLD is a common complication of hepatitis C relating to adverse liver-specific outcomes (i.e. cirrhosis and hepatoma) [70, 71]. Interestingly, patients with NAFLD respond poorly to antiviral treatment [72]. It was suggested that active viral replication promotes NAFLD in patients with chronic hepatitis C [73]. In vitro studies showed that lipophilic statins, but not hydrophilic pravastatin, can limit hepatitis C virus (HCV) replication [74, 75]. Despite proven benefits, clinicians are often reluctant to prescribe statins in chronic hepatitis due to potential hepatotoxicity [76]. It was suggested that rosuvastatin is effective in limiting liver steatosis in patients with chronic hepatitis C [73]. Among 63 patients with chronic hepatitis C, adding rosuvastatin to antiviral treatment increased sustained virological response and reduced viremia [73]. These benefits were mirrored by a decrease in the previously raised AST activity. Also, histological steatosis and fibrosis scores were improved by rosuvastatin [73]. Anti-inflammatory effects, reflected by a reduction in CRP levels, together with improved insulin sensitivity could help explain this benefit [73].

Interestingly, statin-related benefits against NAFLD are not only liver-specific. It was suggested that vascular risk reduction from statin treatment might be greater among patients with liver steatosis. Two post hoc analyses of randomized clinical trials using several statins (not rosuvastatin) implied that statin treatment can help restore the elevated transaminase activities in NAFLD [77, 78]. Also, moderately elevated liver enzymes might predict further statin-related reductions in vascular morbidity and mortality compared with normal transaminase activities in the secondary prevention setting [77, 78]. These findings imply that mild-to-moderate transaminase elevations should not discourage clinicians from prescribing aggressive statin treatment in high-risk patients. However, relevant data from randomized clinical trials using rosuvastatin are lacking.

5.2 Kidney

Interest is increasing regarding the relationship between dyslipidemia, CV disease and chronic kidney disease (CKD) [79]. CV disease is the major cause of morbidity and mortality in CKD [80]. In this context, CKD [defined by kidney damage or an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 for ≥3 months] is considered a coronary heart disease equivalent [50]. Also, microalbuminuria may independently predict CV morbidity and mortality [81].

Dyslipidemia spans CKD and CV disease since it damages the kidney in a manner similar to atherosclerosis [82]. Except for direct glomerular injury, lipid deposition in the kidney may trigger glomerular mesangial cell activation and proliferation resulting in inflammation and kidney fibrosis [82]. Increased oxidative stress also plays a role [82].

CKD-associated dyslipidemia is mostly characterized by raised triglycerides together with low HDL-C levels [83, 84]. LDL-C levels may be normal or slightly elevated [84]. However, lowering LDL-C remains the primary goal of lipid-lowering treatment in CKD [83, 84]. Considering very high vascular risk, aggressive LDL-C lowering <70 mg/dl or a reduction of at least 50 % is recommended [50]. This may require intensive treatment with high-dose potent statins (e.g. rosuvastatin 20–40 mg/day).

It is well-established that statins can preserve kidney function and reduce proteinuria [85]. Interestingly, these benefits may independently predict vascular risk reduction, being particularly relevant among patients with moderately impaired kidney function [86–88]. Also, it was suggested that aggressive statin treatment may be more efficacious than the usual treatment [86, 87].

In pooled analyses, rosuvastatin 5–40 mg/day increased the eGFR both early (within 6–8 weeks) and late (after ≥96 weeks) in the course of treatment [89, 90]. This benefit was independent of age, sex, the presence of diabetes or hypertension, as well as the baseline eGFR or dipstick proteinuria [89, 90]. As with other statins, the renal

benefits of rosuvastatin were particularly relevant among patients with CKD. Namely, 20-week rosuvastatin 10 mg/day significantly increased the eGFR (by 11 %) in 91 patients with CKD compared with no lipid-lowering treatment [91]. In 38 Japanese CKD patients, rosuvastatin 2.5 mg/day increased the eGFR (by 5.1 %) and reduced proteinuria (by 24 %) compared with controls after 12 months [92]. This benefit was associated with anti-atherosclerotic effects, mirrored by reduced carotid intima-media thickness [92]. In 91 CKD patients, 24-week rosuvastatin 2.5–10 mg/day decreased cystatin C and decreased albuminuria irrespectively of the presence of diabetes [93]. In patients with type 2 diabetes, rosuvastatin 10–40 mg/day stabilized kidney function and attenuated albuminuria progression [94]. Interestingly, kidney function was improved only in the subgroup of patients with CKD at baseline [94]. Likewise, rosuvastatin 2.5–10 mg/day by limiting oxidative stress reduced cystatin C levels and albuminuria in 104 patients with diabetic nephropathy [95]. Long-term (76-week) rosuvastatin treatment titrated to achieve LDL-C levels <80 mg/dl significantly increased the eGFR in 213 Japanese patients with coronary heart disease [96]. CKD was prevalent in this population as implied by mean baseline eGFR <65 ml/min/1.73 m^2 [96].

However, not all statins appear to be equally efficient in preserving kidney function and reducing proteinuria in CKD patients. Two studies were presented in the XLVII European Renal Association—European Dialysis and Transplant Association Congress [97]. These compared the effect of high-dose atorvastatin (80 mg/day) with that of rosuvastatin (10 or 40 mg/day) in hypercholesterolemic patients with clinically relevant proteinuria. PLANET (Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients With Progressive Renal Disease) 1 included 325 patients with type 1 or 2 diabetes, while PLANET 2 included 220 patients without diabetes [97]. All patients exhibited a urinary protein/creatinine ratio of 500–5,000 mg/g and fasting LDL-C levels ≥90 mg/dl having used angiotensin converting enzyme inhibitors or angiotensin receptor blockers for at least 3 months prior to screening [97]. Patients with severe CKD, defined as an eGFR <40 ml/min/1.73 m^2, were excluded. The change in urinary/protein ratio from baseline to week 52, or to the last on-treatment observation carried forward, was the primary endpoint of both studies. In PLANET 1, atorvastatin significantly reduced proteinuria (by 12.6 %), whereas rosuvastatin had no significant effect on this parameter. Interestingly, this atorvastatin-related benefit was relevant in the first 26 weeks of treatment and persisted throughout the 52-week follow-up [97]. In contrast, rosuvastatin failed to reduce proteinuria during the study period. A similar pattern was noted in PLANET 2. Atorvastatin significantly decreased proteinuria (by 24.6 %), but rosuvastatin did not. A differential effect on kidney function was also noted. In PLANET 1, patients receiving rosuvastatin lost more kidney function over 52 weeks than did those receiving atorvastatin. Namely, patients receiving atorvastatin lost about 1–2 ml/min/1.73 m^2 over 52 weeks, those receiving rosuvastatin 10 mg/day lost about 4 ml/min/1.73 m^2, and those receiving rosuvastatin 40 mg/day lost close to 8 ml/min/1.73 m^2. In non-diabetic patients (PLANET 2), the effects of treatment on kidney function were slightly less pronounced. There was a significant decline in eGFR with rosuvastatin 40 mg/day but not in the other two treatment groups [97]. Also, the incidence of renal adverse effects was higher with rosuvastatin 40 mg/day than with atorvastatin 80 mg/day or rosuvastatin 10 mg/day. These included acute kidney injury or serum creatinine doubling [97]. These data imply a preferential role of atorvastatin over rosuvastatin in preserving kidney function and reducing proteinuria in moderate CKD. The minimal renal elimination of atorvastatin (<2 %) allows its high dosing in CKD patients without increasing the risk of adverse effects.

The short-term effects of rosuvastatin on renal function may be neutral in patients without CKD at baseline [98–100]. The effect of rosuvastatin on kidney function in subgroups according to the baseline eGFR was assessed in a post hoc analysis of the JUPITER study [101]. Compared with placebo, rosuvastatin significantly slowed the eGFR decline (by ≈0.5 ml/min/1.73 m^2) after 1 year [101]. Interestingly, patients with a baseline eGFR ≥60 ml/min/1.73 m^2 experienced a greater renal function deterioration than those with a baseline eGFR <60 ml/min/1.73 m^2 [101]. This difference was also relevant for the comparison between subgroups with a baseline eGFR ≥90 and <60 ml/min/1.73 m^2 (reduction in the eGFR by 16 vs. <1 ml/min/1.73 m^2, respectively) [101]. Rosuvastatin-associated decrease in the risk of vascular events was assessed in 3,267 JUPITER participants with CKD at baseline [102]. Compared with placebo, rosuvastatin reduced the risk of MI, stroke, hospitalization for unstable angina, arterial revascularization and confirmed CV death by 45 % [102]. Also, total mortality was reduced by 44 %. No difference in side effects between rosuvastatin and placebo was noted among CKD patients [102]. Based on these findings, it can be assumed that targeting vascular risk in CKD patients by using rosuvastatin may be an effective and safe treatment strategy. However, these results should be interpreted by considering several limitations. First, patients with diabetes, currently accounting for most cases of CKD, were excluded from the JUPITER study [10]. Furthermore, only 14 JUPITER participants exhibited stage 4 CKD, while the vast majority exhibited stage 3. Therefore, this study cannot establish rosuvastatin efficacy in reducing the vascular risk of diabetic patients with CKD beyond stage 3 [102]. Finally, it should be noted that rosuvastatin has a

considerable renal excretion (about 10 %). Therefore, its dose should be downtitrated in patients with CKD, by not exceeding 10 mg/day in patients with eGFR <30 ml/min/1.73 m^2 [103].

To date, the vascular benefits of statins in end-stage renal disease (ESRD) have not been established by randomized trials [104]. Rosuvastatin was evaluated in the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) study [105]. This included 2,776 patients on maintenance hemodialysis randomized to rosuvastatin 10 mg/day or placebo. After 3.8 years (median) rosuvastatin was not associated with significantly reduced total and CV mortality compared with placebo. Likewise, it did not decrease the risk of any vascular event [105]. The same was relevant in a subgroup ($n = 731$) of diabetic patients [106]. However, rosuvastatin effectively reduced LDL-C levels by 43 % after 3 months [105]. This might imply a relatively low contribution of elevated LDL-C levels in the vascular risk of ESRD patients. Namely, in the AURORA study, baseline LDL-C levels were relatively low [100 mg/dl (mean)] [105]. Furthermore, no significant association between LDL-C levels and the risk of cardiac events was noted in the subgroup of AURORA participants with diabetes [106]. This is in accordance with evidence suggesting that traditional risk factors can partly explain vascular risk in ESRD patients [107]. Increased inflammation, oxidative stress and endothelial dysfunction may account for most of this risk [107]. It was suggested that statins, including rosuvastatin, exert various pleiotropic renoprotective actions [85, 108]. These include anti-inflammatory, antioxidant, antifibrotic and anti-apoptotic effects, as well as improved endothelial function and renal hemodynamics [85, 108–123]. Vascular calcification due to uncontrolled hyperphosphatemia and high calcium-phosphate product might also explain increased coronary mortality in ESRD [107]. Rosuvastatin failed to slow vascular calcification progression in non-dialysis CKD patients [124]. However, in a subgroup of AURORA participants with diabetes, rosuvastatin was associated with reduced (by 32 %) risk of cardiac events (cardiac death and non-fatal MI) [106].

In the AURORA study, the incidence of adverse effects was high (>90% in both groups) [105]. However, similar rates were demonstrated in previous statin trials with relevant populations [104, 125]. Furthermore, no difference in the incidence of adverse effects between rosuvastatin and placebo was noted [105]. Therefore, AURORA findings cannot establish a causality association of rosuvastatin with poor safety outcomes in ESRD patients. Also, pharmacokinetics of rosuvastatin 10 mg/day was not different between patients on peritoneal dialysis and healthy individuals [126, 127].

Regarding safety, high-intensity statin treatment was associated with poor kidney safety outcomes in large epidemiological studies. A population-based study in Taiwan included 68,256 new statin users. This study compared high-potency statins (atorvastatin and rosuvastatin) with low-potency statins (lovastatin, simvastatin, pravastatin and fluvastatin) [128]. Severe kidney failure was defined as the composite of hemodialysis, peritoneal dialysis and kidney transplantation [128]. High-potency statins were associated with an increased (by 13 %) risk of this endpoint compared with low-potency statins. Interestingly, no greater benefit in the risk of MI was associated with the use of high-potency statins [128]. Another analysis included data from 2,067,639 patients aged ≥40 years—2,008,003 with normal kidney function and 59,636 with CKD [128]. Rosuvastatin ≥10 mg/day, atorvastatin ≥20 mg/day and simvastatin ≥40 mg/day were defined as high-potency statin treatment [128]. Compared with lower-dose statins, high-potency statins were associated with an increased (by 34 %) risk of acute kidney injury in non-CKD patients within 120 days of treatment [128]. This association was not relevant in patients with CKD [128].

However, findings suggesting poor kidney safety outcomes with intensive statin treatment (including rosuvastatin) were not confirmed by other studies. In a retrospective analysis of 72,488 patient-years, high-dose rosuvastatin (40 mg/day) was not associated with an increased risk of kidney impairment or failure compared with a lower dose (10 mg/day) [129]. The same was relevant in all subgroups of high-risk patients for renal toxicity, including those with CKD, heart failure, hypertension and diabetes [129]. A postmarketing analysis of FDA-reported adverse effects over the first year of rosuvastatin marketing compared the renal safety of rosuvastatin with that of other statins [43]. The rates of rosuvastatin-related proteinuria and/or renal failure were comparable with those associated with simvastatin or pravastatin [43]. However, there were fewer reports of these outcomes among atorvastatin-treated patients, implying that this statin may be a safer option for patients at risk for kidney toxicity [43]. This difference was also suggested by a meta-analysis of 16 randomized controlled trials including 24,278 individuals [130]. Both rosuvastatin and atorvastatin increased eGFR compared with controls to the same extent. However, atorvastatin decreased proteinuria more than rosuvastatin [130].

Experimental data suggest that rosuvastatin effectively reduces albuminuria associated with various types of nephropathy, particularly that associated with diabetes, hyperinsulinemia and hypertension [110, 116, 121–123, 131]. This benefit might be mediated by its pleiotropic actions on kidney glomeruli. These include deterioration of oxidative stress, inflammation and endothelial dysfunction [110, 116, 121–123, 131, 132].

In the clinical context, rosuvastatin-related decrease in albuminuria was relevant in patients with increased renal albumin excretion at baseline. Abe et al. showed that rosuvastatin 2.5–10 mg/day significantly reduced albuminuria in 104 patients with diabetic nephropathy exhibiting at least microalbuminuria at baseline [141 mg/g creatinine (mean)] [95]. Same doses of rosuvastatin significantly limited albuminuria in 91 CKD patients with an increased baseline urine albumin/creatinine ratio [308 mg/g (mean)] [93]. This benefit was independent of the presence of diabetes [93]. In contrast, no alteration of renal albumin excretion was noted in type 2 diabetic patients treated with rosuvastatin 10–40 mg/day for 16 weeks [94]. Interestingly, these patients did not exhibit clinically relevant albuminuria at baseline [94]. Likewise, rosuvastatin 10–20 mg/day did not significantly change albuminuria in 90 dyslipidemic patients with normal baseline renal albumin excretion [100]. The GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell' Insufficienza cardiac) trial included 4,574 patients with chronic heart failure [133]. These were randomized to rosuvastatin 10 mg/day or placebo. After 3.9 years (median), rosuvastatin was not associated with reduced morbidity and mortality compared with placebo [133]. A first morning spot sample for determination of albumin/creatinine ratio was obtained by 2,131 GISSI-HF participants [134]. Interestingly, albuminuria was an independent predictor of mortality among those patients with chronic heart failure [134]. Rosuvastatin did not significantly reduce albuminuria [134]. Baseline renal albumin excretion was relatively low [8.76 mg/g of creatinine (median)], far below the range of microalbuminuria (30–299 mg/g of creatinine) [134]. These findings imply a differential effect of rosuvastatin according to baseline albuminuria; patients with increased renal albumin excretion expected to benefit more.

Despite albuminuria reduction, concerns were raised for potential nephrotoxicity of rosuvastatin. These were based on observations of dipstick-positive ($\geq$2+) proteinuria associated with high-dose treatment [135]. Namely, a pooled analysis included 10,000 randomized trial participants on rosuvastatin 5–40 mg/day [89]. In this cohort the incidence of proteinuria was <1.2 % [89]. No significant difference was noted between rosuvastatin $\leq$20 mg/day and comparator statins at relevant doses or placebo [89]. However, rosuvastatin 40 mg/day was associated with an increased risk of dipstick-positive proteinuria compared with placebo [89]. Furthermore, the non-approved dose of 80 mg/day resulted in 12 % of patients exhibiting relevant proteinuria in preclinical studies [135]. Urine gel electrophoresis in patients who exhibited significant proteinuria showed that most excreted proteins had molecular weight lower than that of albumin [89]. This is in accordance with our published findings that rosuvastatin may dose-dependently increase the renal excretion of α1-microglobulin, as a surrogate of tubular proteinuria [99, 100]. In vitro studies suggested that statins inhibit proximal tubular reabsorption of normally filtered low-molecular-weight proteins (i.e. β2-microglobulin) in a concentration-dependent manner [136, 137]. This is associated with their inhibitory effect on the mevalonate synthesis pathway. In this context, this effect is more likely with potent statins [136, 137]. These findings, together with an absence of or relevant increase in albuminuria, suggest that rosuvastatin-related proteinuria is of tubular rather than glomerular origin. Interestingly, statins did not induce structural damage in proximal tubular cells in vitro [136, 137]. In contrast, it was suggested that statins may attenuate overload of these cells with filtered proteins resulting in tubulointerstitial inflammation and fibrosis in progressive nephropathies [138–140]. In this context, a statin-related increase in the renal excretion of the normally filtered low-molecular-weight proteins may represent a nephroprotective effect of these drugs.

Furthermore, rosuvastatin can prevent tubular damage associated with drugs and nephrotoxins. For example, aminoglycoside accumulation in proximal tubular cells can be limited by rosuvastatin treatment [141]. This effect implies a potential protective role of rosuvastatin against aminoglycoside-induced proximal tubular damage [142]. Also, statin pretreatment reduced the risk of contrast-induced nephropathy in 434 patients undergoing percutaneous coronary intervention (PCI) [143]. This benefit was associated with increased 4-year survival rates [143]. The PRATO-ACS (Protective Effect of Rosuvastatin and Antiplatelet Therapy on Contrast-Induced Acute Kidney Injury and Myocardial Damage in Patients with Acute Coronary Syndrome) study included 504 patients with a non-ST elevation acute coronary syndrome [144]. These patients were randomized to high-dose rosuvastatin (40 mg on admission followed by 20 mg/day) or no statin treatment. Rosuvastatin significantly reduced the risk of contrast-induced nephropathy by 62 % compared with no statin therapy within the first 72 h from PCI [144]. Interestingly, the risk of kidney or CV adverse outcomes after 30 days was lower in the rosuvastatin group than in the control group. These included death, dialysis, MI, stroke or persistent renal damage [144]. Another trial suggested a protective role of rosuvastatin against contrast-induced nephropathy in 2,998 patients with type 2 diabetes and CKD undergoing angiography [145]. These patients were randomized to rosuvastatin 10 mg/day or 'standard-of-care' treatment. The 72-h incidence of contrast-induced acute kidney injury was significantly lower in the rosuvastatin group than in the control group [145]. A high-dose of both rosuvastatin (40 mg/day) and atorvastatin (80 mg/day) significantly prevented contrast-induced nephropathy in 192 patients with ST elevation MI undergoing PCI [142].

5.3 The Risk of New-Onset Diabetes

Type 2 diabetes is associated with increased CV morbidity and mortality [146]. It was suggested that insulin resistance and its related abnormalities, including raised blood pressure and atherogenic dyslipidemia, rather than impaired glycemic control, may account for macrovascular complications in diabetes [147]. In this regard, vascular risk increases even in pre-diabetic insulin-resistant states in which glycemic control is not completely deranged. These include metabolic syndrome as well as impaired fasting glucose or glucose tolerance [148–150]. On the other hand, poor glycemic control is mostly associated with microvascular complications in diabetes, including retinopathy and nephropathy [151]. Intensive glycemic control with the currently available drugs was associated with modest benefits in vascular morbidity and mortality [151, 152]. In contrast, lowering LDL-C levels with statins in type 2 diabetes was associated with a reduced risk of CV events [8]. Therefore, targeting very low LDL-C levels is recommended in diabetes [50].

However, concern is increasing about potential diabetogenic effects of statins. Meta-analyses of randomized placebo- and standard care-controlled trials showed that statins increased the risk of new-onset diabetes by 9–13 % [153, 154]. This risk is particularly relevant with intensive-dose statins than with moderate-dose statins [155]. However, CV benefits by intensive treatment appear to outweigh the risk of new-onset diabetes [155]. In this context, high-dose statin treatment should not be discouraged, especially in high-risk patients.

However, data from randomized trials implied that not all statins similarly affect the risk of new-onset diabetes. In this context, pravastatin appears to be preferential [153, 156–158]. A population-based study included 471,250 non-diabetic statin new users [159]. Compared with pravastatin, all comparator statins were associated with increased risk of new-onset diabetes. This increase in relative risk was 18 % for rosuvastatin [159]. In a randomized trial including 54 hypercholesterolemic patients, pravastatin 40 mg/day decreased HbA_{1c} levels (by 1 %) and increased insulin sensitivity [160]. In contrast, rosuvastatin significantly raised HbA_{1c} levels (by 1 %) and enhanced insulin resistance [160].

Differences between statins can be understood by considering mechanisms explaining their effect on glucose homeostasis [156]. These include a decreased calcium-dependent glucose-stimulated insulin secretion by pancreatic β cells. This is particularly relevant for lipophilic statins, but not for hydrophilic statins [161]. Also, adipocyte insulin resistance might be increased in parallel with statin capacity to inhibit mevalonate synthesis [156]. In this context, high-dose potent lipophilic statins are expected to exert the most detrimental effect on glucose homeostasis [156]. Also, it was suggested that statin-related risk of new-onset diabetes is age-dependent [162], being less likely in the elderly [121]. Individuals exhibiting the highest risk may be those aged 40–54 years [162].

In parallel with its greatest potency to inhibit mevalonate synthesis, the risk of new-onset diabetes was greater with rosuvastatin than with other statins in population-based studies. A retrospective analysis included 239,628 statin new users. Statin treatment was associated with an increased (by 18 %) risk of new-onset diabetes compared with no statin use [163]. Interestingly, this risk was greater with rosuvastatin (increased by 41 %) than with atorvastatin or simvastatin (increased by 23 and 15 %, respectively) [163]. Likewise, a meta-analysis of 17 randomized trials included 113,394 patients [164]. Among different statins, pravastatin 40 mg/day was associated with the lowest increase in the risk of new-onset diabetes (by 7 %), while rosuvastatin 20 mg/day was associated with the highest increase (by 25 %) [164].

The issue of a potential diabetogenic role of statins was raised by the JUPITER study. Namely, rosuvastatin 20 mg/day was associated with an increased (by 9 %) incidence of physician-reported diabetes compared with placebo [10]. Also, a small although significant increase in post-treatment HbA_{1c} was noted in the rosuvastatin group versus the placebo group (5.9 vs. 5.8 %, respectively) [10]. However, fasting glucose levels were not different between treatment groups [10]. Likewise, no difference between groups was noted in the incidence of glucosuria as a marker of abnormally high blood glucose levels exceeding the threshold of renal glucose reabsorption [10].

No relevant effect of rosuvastatin on glycemic control and insulin resistance was noted in hyperlipidemic patients with normal glucose at baseline. Rosuvastatin 10–40 mg/day did not significantly change fasting plasma glucose as well as insulin, C-peptide, HbA_{1c} and HOMA-IR levels in several studies [165–168]. However, high-dose rosuvastatin (40 mg/day) induced small although significant increases in fasting insulin and HOMA-IR levels among hyperlipidemic patients [169, 170]. Lower-dose treatment (i.e. rosuvastatin 10 mg/day) may significantly reduce insulin resistance, whereas moderate-dose treatment may exert a neutral effect [171, 172]. These conflicting data imply that the effect of statins on insulin resistance in hypercholesterolemic patients with normal glucose at baseline is dose-dependent. An adverse impact might be expected only with high-dose treatment [169]. Observational data also suggested a duration and dose effect on statin-associated risk of new-onset diabetes [163].

A detrimental effect of rosuvastatin on glucose homeostasis was shown in patients with prediabetes at baseline. In 72 patients with impaired fasting glucose, we

showed that rosuvastatin dose-dependently increased insulin resistance, mirrored by elevations in fasting plasma insulin and HOMA-IR levels [173]. No significant alteration in fasting glucose levels was noted. However, the study duration (12 weeks) might have been too small to identify relevant changes in glycemic status [173]. To the date of publication, this was the first published study suggesting rosuvastatin-related worsening of insulin resistance in patients with prediabetes. In agreement with our findings, rosuvastatin 10 mg/day increased HOMA-IR in 173 patients with metabolic syndrome, to the same extent as atorvastatin 10 mg/day [174]. It could be hypothesized that the high incidence of metabolic syndrome and obesity may at least in part explain the diabetogenic role of rosuvastatin in the JUPITER population. This was suggested by a post hoc analysis of this study [175]. JUPITER participants were divided into a high-risk group for the development of diabetes and a low-risk group. High-risk individuals were identified by the presence of one or more risk factors: metabolic syndrome, impaired fasting glucose, body mass index $\geq$30 kg/m^2, or HbA_{1c} >6.0 % [175]. The increased risk of physician-reported diabetes by rosuvastatin was relevant (by 28 %) in the high-risk group, but not in the low-risk group [175]. According to these findings, rosuvastatin may be diabetogenic in obese individuals with prediabetes and insulin resistance. In agreement with this study, we showed that not only the dose of rosuvastatin, but also increased baseline HOMA-IR, independently predicted a rosuvastatin-associated increase in insulin resistance [173]. Interestingly, it was suggested that the diabetogenic effects of rosuvastatin could be prevented by combining low-dose rosuvastatin (5 mg/day) with colesevelam (3.75 g/day) [176]. This may be attributed to a minimal effect of low-dose rosuvastatin together with significant benefits of colesevelam on glucose homeostasis.

It was suggested that rosuvastatin adversely affects glycemic control of patients with type 2 diabetes. After 18 weeks, high-dose rosuvastatin (40 mg/day) significantly increased HbA_{1c} and fasting glucose levels [177]. Atorvastatin 80 mg/day exerted a similar effect [177]. Two studies compared the effects of rosuvastatin 20 mg/day and simvastatin 20 mg/day in patients with type 2 diabetes [178, 179]. Significant comparable increases in HbA_{1c} were associated with both treatments. However, insulin resistance was not affected by any treatment [178, 179]. Mechanisms other than increased insulin resistance may account for statin-related worsening of glycemic control in patients with type 2 diabetes. These may include a decreased glucose-mediated insulin secretion by pancreatic β cells [156].

In the end the most important issue is reducing morbidity and mortality. In JUPITER, among high-risk individuals for diabetes it was estimated that 134 vascular events or deaths were avoided by rosuvastatin for every 54 new cases of diabetes diagnosed [175]. This imbalance was greater in subjects with no risk factors for the development of diabetes. In these, 86 vascular events of death were avoided, with no new cases of diabetes being diagnosed [175]. This analysis suggests that in the primary prevention setting CV benefits exceed diabetes hazard [175].

6 Benefit–Risk Assessment of Rosuvastatin in Comparison with Other Statins

Rosuvastatin is the only evidence-based statin to reduce the risk of vascular events and mortality in otherwise healthy moderate- to high-risk normolipidemic individuals exhibiting low-grade inflammation. This absolute benefit rises with increasing vascular risk. No other statin has ever been assessed in such a population.

Most studies suggested that statin treatment can slow atherosclerosis progression. High-dose rosuvastatin was shown to induce coronary atherosclerosis regression in patients with imaging evidence of coronary artery disease. Other statins achieved no progression of atherosclerosis at best (i.e. atorvastatin) in relevant populations. Also, according to the METEOR study, rosuvastatin might be a relevant option for reducing the rate of carotid atherosclerosis progression in aged low-risk individuals with subclinical carotid atherosclerosis. However, reducing morbidity and mortality is the most important issue. In this context, data suggesting that the anti-atherosclerotic effects of rosuvastatin can result in better outcomes in these populations are missing. In contrast, it was shown that other statins reduced vascular morbidity and mortality in patients with established coronary artery disease [180, 181]. Also, atorvastatin reduced the risk of cerebrovascular and CV events compared with placebo in a subgroup of the SPARCL population exhibiting carotid stenosis [182].

An increased risk of new-onset diabetes was associated with high-dose rosuvastatin treatment. Although this appears to be a ‘class effect’, it was suggested that pravastatin is associated with less detrimental and, sometimes beneficial, effects on glucose homeostasis [156]. Obese individuals with prediabetes are most prone to develop diabetes associated with statin treatment [156]. For these individuals, pravastatin could be a relevant option. The problem is that according to current treatment guidelines newly-diagnosed diabetics should be reclassified as a ‘very high vascular risk’ population [50]. In these patients, a high-dose of a potent statin (i.e. atorvastatin and rosuvastatin) is often needed to achieve low LDL-C targets.

An increased risk of muscle and renal toxicity associated with rosuvastatin compared with other statins in preliminary FDA databases has not been confirmed by large

epidemiological studies. In contrast, like other statins, rosuvastatin was renoprotective, especially in CKD patients. However, it was suggested that atorvastatin is more effective in improving kidney function and reducing albuminuria in CKD. Also, this statin can be easily prescribed in CKD patients due to its low renal elimination (<2 %). On the other hand, dose adjustment is needed for rosuvastatin.

7 Conclusions

Rosuvastatin is the most potent statin in reducing LDL-C levels and achieving treatment targets. By significantly lowering LDL-C levels it reduced vascular morbidity and mortality in a healthy normolipidemic population exhibiting moderate-to-high vascular risk. Very low on-treatment LDL-C levels were associated with slower atherosclerosis progression or even regression in rosuvastatin-treated individuals. This benefit might be relevant even in relatively low-risk subjects. There is no evidence that aggressive reduction of LDL-C levels by high-dose rosuvastatin increases the risk of hemorrhagic stroke or other adverse effects. Preliminary evidence from FDA-reported adverse effects showed an increased risk of muscle and renal toxicity of rosuvastatin compared with other statins. Nevertheless, most epidemiological data suggest that the risk profile of rosuvastatin is comparable with that of other statins. The expected vascular benefits from rosuvastatin treatment may outweigh the absolute risk of muscle-, liver- or kidney-associated toxicity. This is particularly relevant in moderate vascular risk individuals. However, data are lacking for low- and high-risk individuals. Also, this evidence should be cautiously considered due to certain limitations.

Transaminase elevations in randomized trials using rosuvastatin were rare and reversible. It was suggested that several abnormalities may underlie statin-related increases in liver function tests. These include alcohol abuse, NAFLD or chronic hepatitis. NAFLD may also predict CV events. Preliminary data suggest that rosuvastatin can limit biochemical markers and histological score of NAFLD. Whether this benefit is associated with better vascular outcomes should be assessed by future prospective studies.

Alarming safety data suggested an increased risk of acute kidney injury by intensive statin treatment (including rosuvastatin). However, these have not been confirmed by other studies. In contrast, rosuvastatin was associated with improved kidney function and reduced risk of vascular events in patients with up to stage 3 CKD. Likewise, albuminuria might be reduced only in patients exhibiting microalbuminuria. These vascular and renal benefits of rosuvastatin have not been established in CKD patients beyond stage 3. Despite its lack of efficacy, rosuvastatin appropriately dose-adjusted might be safe in ESRD.

Rosuvastatin may increase the risk of new-onset diabetes by dose-dependently increasing insulin resistance. This adverse effect is mevalonate-dependent, thus being more likely with rosuvastatin than with other statins. Patients expected to be most affected are those who are obese with prediabetes. However, even in these patients, rosuvastatin-related vascular benefits may outweigh the hazard of diabetes.

Overall, the benefit of rosuvastatin treatment in the prevention and management of atherosclerotic vascular disease appears to be greater than the risk of adverse effects. Clinicians should individualize rosuvastatin treatment to maximize this favorable benefit-risk balance of rosuvastatin.

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