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Safety Concerns of Statins Allayed After Long Experience with the Most Potent Agents

A report from recent peer-reviewed publications
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Very large databases appear to rule out any relationship between the degree to which statins reduce LDL-C and the risk of the idiosyncratic adverse events that have been associated with this class of drug. The overall safety of statins, which are a mainstay of cardiovascular (CV) risk management, is well recognized, but a note of caution has long been signalled by the unpredictable instances of adverse events related to muscles, liver and kidney function. All statins have been associated with these events but differences between statins, if any, appear to be very modest, and no single characteristic, including relative LDL-C-lowering effect, has been shown to predict risk. In clinical practice, the only major difference between statins is lipid-lowering efficacy, and while this predicts protection against CV events, the preponderance of data indicates that it does not predict risk of adverse events. This is important information, particularly when more aggressive lowering of LDL-C is needed to reach evidence-based treatment goals.

Statins are among the most widely prescribed therapies of any kind. Their high degree of efficacy for reducing the risk of cardiovascular (CV) events has been documented in a series of multinational and landmark trials that underlie the evidence-based guidelines for preventing myocardial infarction (MI), stroke and other life-threatening complications of atherosclerosis. Statins are well tolerated and have an acceptable safety profile, but serious and unpredictable damage to the muscles, liver, and kidney has been documented. New data confirm that these uncommon risks are unlikely to be statin-specific.

The most significant of recent studies drew on the power of almost 200,000 person-years of follow-up. Published in *Pharmacoepidemiol Drug Saf* (García Rodríguez et al. 2010;19:1218-24), the study employed databases from Canada (Saskatchewan Health Database), the US (Ingenix Research Database), The Netherlands (PHARMO Database) and the UK (General Practice Research Database). The objective was to enhance estimates of rosuvastatin safety relative to other statins, but it also provided an opportunity to evaluate whether there is an association between the relative potency of statins and the risk of myopathy, rhabdomyolysis, acute renal failure or acute liver failure. Rosuvastatin, which achieves the greatest per-milligram reduction in LDL-C, was compared to all other statins.

Statin Efficacy and Risk Unrelated

Calculated per 10,000 patient-years, the incidences of acute renal failure were 4.14 (95% CI, 2.39-7.15) for rosuvastatin vs. 4.36 (95% CI, 3.15-6.06) for all other statins. The incidences of acute liver injury were 0.33 (95% CI, 0.05-2.37) vs.1.13 (95% CI, 0.60-2.13), respectively. The incidence rates of myopathy were 0.91 (95% CI, 0.29-2.86) vs. 0.42 (95% CI, 0.15-1.18), respectively. The incidence rates of rhabdomyolysis were 0.82 (95% CI, 0.26-2.59) vs. 0.14 (95% CI, 0.05-0.37), respectively. The overlapping confidence intervals, which were substantial for most comparisons, excluded a statistical difference for any relative incidence rate.

These results, which "are comparable to previous pharmacoepidemiological findings and randomized

controlled trials," suggest that more effective statins have a safety profile similar to other marketed statins, according to the lead author of the study, Dr. Luis A. García Rodríguez, Spanish Centre for Pharmacoepidemiological Research (CEIFE), Madrid, Spain. He emphasized that large databases are essential to accrue sufficient statistical power "to quantify rare drug-related outcomes, such as those associated with statin use." He indicated that the large and diverse populations included in the four sets of data overwhelm the likelihood for confounders that would alter the basic conclusions.

Equally reassuring within this relative comparison, the more effective statin was associated with a statistically lower rate of all-cause mortality. The incidence of mortality in the pooled data was 6.66 (95% CI, 5.67-7.83) for rosuvastatin and 13.31 (95% CI, 12.61-14.05) for all other statins.

This mortality advantage is likely to stem simply from a greater lipid-lowering effect translating into a lower risk of life-threatening CV events. The absence of overlap of the confidence interval for mortality, confirming a significant advantage, is consistent with statin trials which have repeatedly demonstrated the same relationship between greater LDL-C reductions and fewer CV events.

While current Canadian guidelines recommend a lipid level <2 mmol/L or at least a 50% reduction from baseline in patients with established coronary heart disease (CHD) (Genest et al. *Can J Cardiol* 2009;25:567-79), there is no level yet identified at which further reductions have not provided further CV protection.

Strong Consistency for Efficacy and Risk

The recent findings from this comparison are remarkably similar to one of the largest studies previously conducted to address the same question. In that study (McAfee et al. *Pharmacoepidemiol Drug Saf* 2006;15:444-53), rosuvastatin was again employed as the index comparator, which allows the best opportunity to explore the relationship between lipid-lowering efficacy and risk of adverse effects. For LDL-C reductions, rosuvastatin 5 mg is equivalent to approximately atorvastatin 20 mg, simvastatin 40 mg and 80 mg of either pravastatin or lovastatin. In this US study, adverse events in 11,249 rosuvastatin initiators were compared to adverse events in 37,282 patients who initiated another statin. There were up to 18 months of follow-up.

The denominator used to compare adverse events in this study was the incidence rates of any given event over 1000 patient-years of exposure. For renal dysfunction, these rates were 1.18 (95% CI, 0.61-2.06) for rosuvastatin vs.1.26 (95% CI, 0.91-1.71) for all other statins. For hepatic dysfunction, the rates were 0.2 (95% CI, 0.02-0.71) vs. 0.24 (95% CI, 0.1-0.47), respectively. For myopathy, the relative rates were 0.2 (95% CI, 0.02-1.71) vs. 0.0 (95% CI 0.0-0.09). For rhabdomyolysis, the rates were 0.1 (95% CI, 0.0-0.55) vs. 0.06 (95% CI, 0.01-0.22) (Table 1). The lead author of the report, Dr. Andrew T. McAfee, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, called the incidence of rhabdomyolysis "reassuringly low" on the statins overall. Although he acknowledged the potential for bias in retrospective analyses, he observed that confounders large enough to alter the conclusions in a study of this size were not only unlikely but "difficult to imagine."

SLCO1B1 Gene May Underlie Renal Risk

In the past, numerous studies comparing statins have attempted to evaluate whether there are any differences in regard to either benefit or risk that are independent of lipid-lowering, but no differences between marketed agents have been convincing. An exception is cerivastatin, which was withdrawn from the market in 2001 because of high rates of rhabdomyolysis. Some differences in rates of myopathy

Table 1. **Incidence Rates of Study Outcomes**

Outcome events	Rosuvastatin initiators (n=11,249)		Other statin initiators (n=37,282)	
	n	IR (95% CI)*	n	IR (95% CI)*
Rhabdomyolysis	1	0.10 (0.00, 0.55)	2	0.06 (0.01, 0.22)
Myopathy	2	0.20 (0.02, 0.71)	0	0.00 (0.00, 0.09)
Renal dysfunction	12	1.18 (0.61, 2.06)	42	1.26 (0.91, 1.71)
Hepatic dysfunction	2	0.20 (0.02, 0.71)	8	0.24 (0.10, 0.47)
In-hospital death	8	0.78 (0.34, 1.54)	44	1.32 (0.96, 1.77)

*Incidence rate per 1000 person-years and 95% confidence interval.

Adapted from McAfee et al. *Pharmacoepidemiol Drug Saf* 2006;15:444-53.

in non-comparative studies now appear to be more likely explained by variability in the SLCO1B1 gene (Maggo SD, Kennedy MA, Clark DW. *Drug Saf* 2011;34:1-19), which influences statin metabolism, than by fundamental differences between statin drugs. For example, two recently presented but as yet unpublished studies suggested that relative benefits of statins may differ in patients with chronic kidney disease [CKD], but this is uncorroborated by numerous other sets of data. Again, the problem is the ability of small studies to generate accurate data about the relative risk of rare events.

"Given the focus on more aggressive statin therapy, there has developed an appropriately enhanced concern about adverse events associated with this class," Dr. McAfee observed. However, although statins do appear to increase myopathy, there is no prospective level-1 evidence or retrospective evidence from datasets large enough to minimize risk of bias that there are any substantial differences between them. One of the reassuring aspects of the large retrospective databases is that they "complement randomized clinical trials and spontaneous reporting systems through their effective ability to study large heterogeneous groups of people for an extended period of time."

Renal safety is particularly important, because CKD is a well recognized risk factor for the CV events which statins are administered to reduce. Despite the relatively rare reports of acute kidney failure (~1 event per 1000 patient-years), statins have been shown repeatedly to be highly effective in reducing CV risk even in patients who have CKD at baseline. A substudy of the secondary prevention study CARE (Cholesterol and Recurrent Events) evaluated the relative benefit of pravastatin in reducing CV risk in patients with CKD. The 28% reduction (P=0.001) in the risk of a composite end point of major coronary events on pravastatin relative to placebo was similar to that achieved in individuals without CKD (Tonelli et al. *Ann Intern Med* 2003;138:98-104).

JUPITER Substudy in CKD Patients

In a more recently published substudy of the primary prevention trial JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), the statin again was highly effective in patients with CKD (Ridker et al. *J Am Coll Cardiol* 2010;55:1266-73). In JUPITER, patients with elevated high-sensitivity C-reactive protein (hsCRP) levels but unremarkable LDL-C levels (patients were required to have LDL-C <3.4 mmol/L at entry) were randomized to rosuvastatin or placebo. The study proved that individuals with at least one risk factor and elevated hsCRP, an inflammatory biomarker, benefit from lipid lowering. The substudy demonstrated that those patients with moderate CKD (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) benefited just as much as those without overt CKD (eGFR ≥60 mL/min/1.73 m^2).

When compared after a median follow-up of 1.9 years, there was 45% reduction (P=0.002) in the primary end point of MI, stroke, hospitalization for unstable angina, arterial revascularization, or CV death on rosuvastatin relative to placebo in patients with CKD vs. 43% reduction in those without CKD (P<0.001). In addition there was a 44% reduction (P=0.005) in all-cause mortality in the moderate

Table 2. **JUPITER Substudy: Patient Outcomes According to Baseline eGFR**

	eGFR <60 mL/min/1.73 m^2						eGFR ≥60 mL/min/1.73 m^2					
	Randomized rosuvastatin		Randomized placebo				Randomized rosuvastatin		Randomized placebo			
	n	Rate*	n	Rate*	HR (95% CI)	*P* value	n	Rate*	n	Rate*	HR (95% CI)	*P* value
Primary end point	40	1.08	71	1.95	0.55 (0.38–0.82)	0.002	102	0.69	180	1.21	0.57 (0.45–0.72)	<0.001
MI	8	0.21	20	0.54	0.40 (0.17–0.90)	0.02	23	0.15	48	0.32	0.48 (0.29–0.79)	0.003
Stroke	10	0.27	14	0.38	0.71 (0.31–1.59)	0.40	23	0.15	50	0.33	0.46 (0.28–0.76)	0.002
Arterial revascularization	19	0.51	39	1.07	0.48 (0.28–0.83)	0.006	52	0.35	92	0.62	0.57 (0.40–0.80)	0.001
MI, stroke, or confirmed CV death	24	0.64	40	1.09	0.59 (0.36–0.99)	0.04	59	0.40	117	0.78	0.50 (0.37–0.69)	<0.001
VTE	6	0.16	17	0.46	0.34 (0.14–0.88)	0.02	28	0.19	43	0.29	0.65 (0.41–1.05)	0.08
All-cause mortality	34	0.85	61	1.53	0.56 (0.37–0.85)	0.005	164	1.04	186	1.17	0.88 (0.72–1.09)	0.25
Primary end point plus any death	64	1.72	114	3.13	0.55 (0.41–0.75)	0.0001	231	1.56	327	2.20	0.71 (0.60–0.84)	<0.001
Primary end point plus VTE plus any death	69	1.86	127	3.51	0.53 (0.40–0.71)	<0.0001	251	1.69	356	2.41	0.70 (0.60–0.83)	<0.001

*Rates are per 100 person-years. VTE=venous thromboembolism

Adapted from Ridker et al. *JACC* 2010;55:1266-73.

CKD patients on rosuvastatin relative to placebo vs. 12% reduction in those without CKD (*P*=0.25) (Table 2). There was no evidence that rosuvastatin had any adverse effect on renal function as measured with eGFR.

"As anticipated, absolute rates of vascular disease were higher among those with moderate CKD. Thus, absolute risk reductions associated with rosuvastatin were higher and the NNTs [numbers needed to treat] were lower in those with eGFR levels below 60 mL/min/1.73 m^2 when compared to those with higher eGFR levels," reported the lead author Dr. Paul Ridker, Brigham and Women's Hospital.

Like JUPITER, the CARDS (Collaborative Atorvastatin Diabetes Study) was also terminated early because the overwhelming benefit from lipid lowering made further allocation of patients into the placebo group unethical (Colhoun et al. *Lancet* 2004;364:685-96). In CARDS, patients with type 2 diabetes but no heart disease and a baseline LDL-C <4.15 mmol/L were randomized to atorvastatin 10 mg or placebo. Again, despite the increased risk of renal impairment in diabetic patients, the statin was found to be safe, while the risk of CV events was reduced by 37% (*P*=0.001). The 27% reduction in mortality approached statistical significance (*P*=0.059).

When the first statin was introduced in 1987, it provided the opportunity to understand the pathophysiology of atherosclerosis in new detail because of the unprecedented ability of this class of drug to decrease LDL-C. The goals of LDL-C lowering have been consistently dropping in a long series of large, multinational trials that progressively and consistently demonstrated greater CV risk reductions with lower LDL-C. First demonstrated in individuals who already had CV disease and then in patients with risk factors only, the studies supported an overall hypothesis that "lower is better" for LDL-C in the presence of CV risk.

This hypothesis remains unchallenged. As of yet, no degree of LDL lowering has been found unsafe, and greater reductions generally produce larger risk reductions independent of the starting or ending LDL-C level. Although there are several theories that the clinical benefits of statins are pleiotropic, so that protection from atherosclerosis not only includes less build-up of atherosclerotic plaque but also antithrombotic activity, the antithrombotic effects may still be fundamentally linked to cholesterol lowering. For example, the anti-inflammatory activity linked to statins may still be derived from lipid lowering. Overall, there is no compelling evidence that there is any important difference between these agents other than their relative lipid-lowering effect.

Perhaps equally important, there is also no compelling evidence of any difference between these agents for tolerability or risk of adverse events despite the numerous trials that have addressed this question. These findings are helpful because they permit clinicians to concentrate on meeting the evidence-based cholesterol targets with adequate doses of the statin which offers the best opportunity to achieve treatment goals.

Summary

With almost 25 years of clinical experience, the only significant difference between statins for their relative ability to lower the risk of CV events appears to stem from their relative efficacy in reducing LDL-C and raising HDL-C. Conversely, uncommon adverse events associated with statins do not appear to be related to lipid lowering. Rather, these events have been largely unpredictable and idiosyncratic, although a dose response for myopathy risk has been observed. In at least some cases, they may be related to genetic susceptibility. The relative efficacy of statins cannot be divorced from their LDL-C-lowering effect, so benefits in subgroups, such as those with CKD, diabetes or other comorbidities, are dependent on efficacy in lowering LDL-C. These findings are useful for clinicians concerned about employing aggressive regimens needed to reach evidence-based targets. As a class, statins are remarkably effective and well tolerated, making LDL-C reductions the key distinction between agents. □

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