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Creatine Kinase Measurements for Patients on Statins: A Rapid Review

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Conflict of Interest Statement

All reports prepared by the Division of Evidence Development and Standards at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards at Health Quality Ontario in consultation with experts, end-users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies included in the systematic review are retrieved and a maximum of two outcomes are graded. If no well-conducted systematic reviews are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

Disclaimer

This rapid review is the work of the Division of Evidence Development and Standards at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current to the date of the literature search specified in the Research Methods section, as appropriate. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

About Health Quality Ontario

Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. Health Quality Ontario works with clinical experts, scientific collaborators, and field evaluation partners to develop and publish research that evaluates the effectiveness and cost-effectiveness of health technologies and services in Ontario.

Based on the research conducted by Health Quality Ontario and its partners, the Ontario Health Technology Advisory Committee (OHTAC)—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy makers.

Rapid reviews, evidence-based analyses and their corresponding OHTAC recommendations, and other associated reports are published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, Health Quality Ontario and/or its research partners reviews the available scientific literature, making every effort to consider all relevant national and international research; collaborates with partners across relevant government branches; consults with clinical and other external experts and developers of new health technologies; and solicits any necessary supplemental information.

In addition, Health Quality Ontario collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario can add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
CK	Creatine kinase
HQO	Health Quality Ontario
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
ULN	Upper limit of normal

Background

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit our website at www.hqontario.ca.

Objective of Analysis

The objective of this analysis was to determine the clinical utility of creatine kinase (CK) measurements in patients who are on statin therapy; in particular, to determine which patients should have their CK levels measured and how frequently this should be done.

Clinical Need and Target Population

Serum cholesterol levels are directly related to mortality from coronary artery disease. For every 1 mmol/L reduction in serum low density lipoprotein cholesterol achieved by statin therapy, the relative risks of cardiovascular events and mortality are reduced (by 21% and 12%, respectively). (1)

The withdrawal of cerivastatin by the United States Food and Drug Administration in 2001 due to reports of rhabdomyolysis (muscle aches, soreness, or weakness associated with markedly elevated CK, generally greater than 10 times the upper limit of normal [ULN]) led to concerns about the safety of statins. (2) Kashani et al (3) reviewed the risk of rhabdomyolysis for all 6 currently available statins compared to a control group and found no increased risk associated with statin use (0.2% and 0.1%, respectively; relative risk, 1.09; 95% confidence interval, 0.65–1.83). Since it is rare that patients treated with *currently available* statins exhibit a severe myopathy such as rhabdomyolysis, it is unclear whether CK levels should be routinely measured in patients on statin therapy, and if so, how frequently.

Rapid Review

Research Question

What is the clinical utility of CK measurements in patients who are on statin therapy? In particular, which patients should have their CK levels measured, and how frequently?

Research Methods

Literature Search

Search Strategy

A rapid review literature search was performed on July 28, 2012, using OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Wiley Cochrane, and Centre for Reviews and Dissemination database, for studies published from January 1, 2008, to July 28, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language full-text reports
- published between January 1, 2008, and July 28, 2012
- health technology assessments, systematic reviews, and meta-analyses
- enrolled adult patients on statin therapy

Exclusion Criteria

- randomized controlled trials, observational studies, case reports, editorials

Outcomes of Interest

- adverse events
- CK measurement/monitoring schedules

Expert Panel

In August 2012, an Expert Advisory Panel on Appropriate Use of Lipid and Creatine Kinase Measurements was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, and representation from the community laboratories.

The role of the Expert Advisory Panel on Appropriate Use of Lipid and Creatine Kinase Measurements was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate use of lipids and creatine kinase measurements within the Ontario health care setting. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of the systematic reviews. (4)

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (5) The overall quality was determined to be very low, low, moderate, or high using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality, whereas observational studies are low quality. (5) Five additional factors—risk of bias, inconsistency, indirectness, imprecision and publication bias—were then taken into account. Limitations or serious limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 factors were considered which may raise the quality of evidence: large magnitude of effect, dose response gradient, and accounting for all residual confounding. (5) For more detailed information, please refer to the latest series of GRADE articles. (5)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	Very confident that the true effect lies close to the estimate of the effect
Moderate	Moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect
Very Low	Very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Literature Search

The database search yielded 42 citations published between January 1, 2008, and July 28, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

No studies were identified that examined the clinical utility of CK measurement/monitoring schedules for patients on statin therapy.

The most recent meta-analysis of 72 randomized controlled trials (N = 159,458 patients) showed no significant increase in CK or rhabdomyolysis (muscle aches, soreness, or weakness associated with markedly elevated CK, generally greater than 10 times ULN) in patients on statins compared to a control group. (6) The criteria for CK elevation varied between studies (e.g., 5–10 times ULN, > 10 times ULN, 3–5 times ULN), but generally the most common definition was greater than 10 times ULN. Table 1 summarizes the results for each of the 6 statins that were examined.

Table 1: Summary of the Systematic Review

Drug	Rhabdomyolysis Pooled Odds Ratio (95% CI), *P* Value	CK Increase Pooled Odds Ratio (95% CI), *P* value
Atorvastatin	1.38 (0.61–3.13), *P* = 0.44 (11 RCTs, N = 26,067)	1.21 (0.19–7.92), *P* = 0.84 (6 RCTs, N not reported)
Fluvastatin	2.68 (0.68–10.55), *P* = 0.16 (4 RCTs, N = 5,181)	0.60 (0.18–2.03), *P* = 0.41 (6 RCTs, N = 5,975)
Lovastatin	1.33 (0.27–6.58), *P* = 0.73 (3 RCTs, N = 15,120)	0.85 (0.52–1.41), *P* = 0.54 (2 RCTs, N = 14,850)
Pravastatin	1.08 (0.82–1.41), *P* = 0.59 (10 RCTs, N = 40,394)	1.21 (0.96–1.54), *P* = 0.12 (7 RCTs, N = 26,407)
Rosuvastatin	0.73 (0.17–3.09), *P* = 0.67 (5 RCTs, N = 26,656)	0.52 (0.16–1.64), *P* = 0.26 (4 RCTs, N = 8,854)
Simvastatin	1.84 (0.49–6.79), *P* = 0.36 (3 RCTs, N = 25,361)	2.28 (0.92–5.69), *P* = 0.08 (2 RCTs, N = 24,980)

Abbreviations: CI, confidence interval; CK, creatine kinase; N, number of patients; RCT, randomized controlled trial.
Source: Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM. 2012;105(2):145-57. (6)

The AMSTAR measurement tool was used to assess the methodological quality of the systematic review by Alberton et al. (6) The overall score was 8 out of 11.

Conclusions

- No studies were identified that examined the clinical utility of CK measurement/monitoring schedules for patients on statin therapy.
- There was no significant increase in the occurrence of rhabdomyolysis in patients on currently available statins compared to controls (GRADE: moderate).

Acknowledgements

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Expert Advisory Panel on Appropriate Use of Lipid and Creatine Kinase Measurements

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Ms. Laurie Sweeting	Senior Program Consultant, Diagnostic Services and Planning Branch	Ministry of Health and Long-Term Care	Toronto

Appendices

Appendix 1: Literature Search Strategies

Search date: July 28, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Wiley Cochrane; Centre for Reviews and Dissemination
Limits: 2008-present; English; NOT comments, editorials, letters
Filter: meta-analyses, systematic reviews, and health technology assessments

Database: Ovid MEDLINE(R) <1946 to July Week 3 2012>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 27, 2012>, Embase <1980 to 2012 Week 30>
Search Strategy:

#	Searches	Results
1	exp Creatine Kinase/ use mesz	22603
2	((creatine adj phosphokinase) or creatinine phosphokinase or CPK or (creatine adj kinase*) or (creatinine adj kinase*) or CK-MB or (phosphotransferase adj2 phosphocreatine) or macro-creatine kinase or (creatine adj2 phosphotransferase)).ti,ab.	54449
3	Creatine Kinase/ use emez	29445
4	Creatine Kinase BB/ use emez	554
5	Creatine Kinase Isoenzyme/ use emez	804
6	Creatine Kinase MB/ use emez	6274
7	Creatine Kinase MM/ use emez	505
8	or/1-7	76682
9	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ use mesz	23501
10	(statin or statins).ti.	19164
11	(((hydroxymethylglutaryl-coa or hydroxymethylglutaryl-coenzyme a or hmg-coa) adj (reductase or inhibitor?)) or vastatin?).ti,ab.	15410
12	Atorvastatin.mp.	26312
13	(Lipitor or liptonorm).ti,ab.	321
14	Bervastatin.mp.	6
15	Cerivastatin.mp.	3995
16	(Baycol or Certa or Kazak or Lipobay or rivastatin).ti,ab.	275
17	Compactin.mp.	1848
18	mevastatin.ti,ab.	523
19	Crilvastatin.mp.	12
20	Dalvastatin.mp.	18
21	(Fluvastatin or Fluindostatin).mp.	8268
22	Glenvastatin.mp.	5
23	(Lovastatin or Mevinolin).mp.	17712
24	(mevacor or monacolin k).ti,ab.	273
25	Mevinolinic Acid.mp.	54
26	(Monacolin J or Monacolin L or Monacolin M or Monacolin N or Monacolin X).mp.	83
27	Meglutol.mp.	123
28	Pitavastatin.mp.	1732
29	(itavastatin or nisvastatin).ti,ab.	20
30	Pravastatin.mp.	18897
31	(pravacol or pravasin or lipemol or eptastatin or vasten or elisor or lipostat or bristacol or prareduct or apo-pravastatin or mevalotin or nu-pravastatin or selektine or pravachol or lin-pravastatin or liplat or vasten).ti,ab.	164
32	Rosuvastatin.mp.	8303
33	Crestor.ti,ab.	127
34	Simvastatin.mp.	31289
35	(synvinolin or Zocor).ti,ab.	285
36	exp Hydroxymethylglutaryl Coenzyme A Reductase Inhibitor/ use emez	79242
37	or/9-36	115027

38	Meta-Analysis.pt.	35060
39	exp Technology Assessment, Biomedical/ use mesz	8717
40	Biomedical Technology Assessment/ use emez	11322
41	(health technology adj2 assess*).ti,ab.	3481
42	Meta Analysis/ use emez	64707
43	Systematic Review/ use emez	51564
44	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	281910
45	or/38-44	340962
46	8 and 37 and 45	139
47	limit 46 to english language	139
48	limit 47 to yr="2008 -Current"	50
49	Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. use mesz	3012081
50	Case Report/ or Editorial/ or Letter/ use emez	4779563
51	or/49-50	5491098
52	48 not 51	46
53	remove duplicates from 52	37

Wiley Cochrane
exp Creatine Kinase/
(creatine NEXT phosphokinase) OR (creatinine phosphokinase) OR CPK OR (creatine NEXT kinase*) OR (creatinine NEXT kinase*) OR CK-MB OR (phosphotransferase NEAR/2 phosphocreatine) OR macro-creatine kinase OR (creatine NEAR/2 phosphotransferase) =ti,ab,kw

ID	Search	Hits
#1	MeSH descriptor **Creatine Kinase** explode all trees	1138
#2	(creatine NEXT phosphokinase) OR (creatinine phosphokinase) OR CPK OR (creatine NEXT kinase*) OR (creatinine NEXT kinase*) OR CK-MB OR (phosphotransferase NEAR/2 phosphocreatine) OR macro-creatine kinase OR (creatine NEAR/2 phosphotransferase):ti,ab,kw	2277
#3	(#1 OR #2), from 2008 to 2012	9

CRD

Search	Hits	
1	MeSH DESCRIPTOR Creatine Kinase EXPLODE ALL TREES	18
2	((creatine ADJ phosphokinase) OR (creatinine phosphokinase) OR CPK OR (creatine ADJ kinase*) OR (creatinine ADJ kinase*) OR CK-MB OR (phosphotransferase ADJ2 phosphocreatine) OR macro-creatine kinase OR (creatine ADJ2 phosphotransferase)):TI	2
3	#1 OR #2	18

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for Rhabdomyolysis in Patients on Statin Therapy

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Rhabdomyolysis (muscle symptoms with marked CK elevation [greater than 10 times the upper limit of normal])							
1 systematic review of RCTs	Some serious limitations (–1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: CK, creatine kinase; No., number; RCT, randomized controlled trial.

[a]Authors found that the reporting quality of studies varied: 26 studies reported how the randomization sequence was generated; 19 studies reported on how allocation to groups was concealed; 64 studies reported on loss to follow-up; 4 studies reported that the primary results were based on a per-protocol analysis rather than intent to treat; 61 studies reported on at least one specific group being blinded in the trial, typically patients and caregivers.

References

(1) Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ. 2008;178(5):576-84.

(2) Pasternak RC, Smith SC, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI Advisory on the use and safety of statins. J Am Coll Cardiol. 2002;40(3):567-72.

(3) Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation. 2006;114(25):2788-97.

(4) Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.

(5) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

(6) Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM. 2012;105(2):145-57.

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