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Frequency of Testing for Dyslipidemia: An Evidence-Based Analysis

Health Quality Ontario

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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. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—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.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About the *Ontario Health Technology Assessment Series*

To conduct its comprehensive analyses, Evidence Development and Standards and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

In addition, Evidence Development and Standards 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 add an important dimension to the review.

The Ontario Health Technology Advisory Committee uses a unique decision determinants framework when making recommendations to the Health Quality Ontario Board. The framework takes into account clinical benefits, value for money, societal and ethical considerations, and the economic feasibility of the health care intervention in Ontario. Draft Ontario Health Technology Advisory Committee recommendations and evidence-based reviews are posted for 21 days on the Health Quality Ontario website, giving individuals and organizations an opportunity to provide comments prior to publication. For more information, please visit: http://www.hqontario.ca/evidence/evidence-process/evidence-review-process/professional-and-public-engagement-and-consultation.

Disclaimer

This report was prepared by Health Quality Ontario or one of its research partners for the Ontario Health Technology Advisory Committee and was developed from analysis, interpretation, and comparison of scientific research. It also incorporates, when available, Ontario data and information provided by experts and applicants to Health Quality Ontario. It is possible that relevant scientific findings may have been reported since the completion of the review. This report is current to the date of the literature review specified in the methods section, if available. This analysis 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

Abstract

Background

Dyslipidemias include high levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides and low levels of high-density lipoprotein (HDL) cholesterol. Dyslipidemia is a risk factor for cardiovascular disease, which is a major contributor to mortality in Canada. Approximately 23% of the 2009/11 Canadian Health Measures Survey (CHMS) participants had a high level of LDL cholesterol, with prevalence increasing with age, and approximately 15% had a total cholesterol to HDL ratio above the threshold.

Objectives

To evaluate the frequency of lipid testing in adults not diagnosed with dyslipidemia and in adults on treatment for dyslipidemia.

Research Methods

A systematic review of the literature set out to identify randomized controlled trials (RCTs), systematic reviews, health technology assessments (HTAs), and observational studies published between January 1, 2000, and November 29, 2012, that evaluated the frequency of testing for dyslipidemia in the 2 populations.

Results

Two observational studies assessed the frequency of lipid testing, 1 in individuals not on lipid-lowering medications and 1 in treated individuals. Both studies were based on previously collected data intended for a different objective and, therefore, no conclusions could be reached about the frequency of testing at intervals other than the ones used in the original studies. Given this limitation and generalizability issues, the quality of evidence was considered very low.

No evidence for the frequency of lipid testing was identified in the 2 HTAs included.

Canadian and international guidelines recommend testing for dyslipidemia in individuals at an increased risk for cardiovascular disease. The frequency of testing recommended is based on expert consensus.

Conclusions

Conclusions on the frequency of lipid testing could not be made based on the 2 observational studies. Current guidelines recommend lipid testing in adults with increased cardiovascular risk, with the frequency of testing based on individual cardiovascular risk.

Plain Language Summary

An abnormal lipid level is a risk factor for cardiovascular disease and mortality. About 23% of participants in a Canadian survey were found to have high levels of low-density lipoprotein (LDL) cholesterol.

The objective of this report is to evaluate the frequency of testing for lipid levels in adults not diagnosed with high lipid levels and in adults being treated for high lipid levels. A literature search for studies that evaluated the frequency of lipid testing in these groups identified very low quality evidence for our research question. As a result, no conclusions could be reached based on the studies found.

Current guidelines recommend testing in undiagnosed individuals with an increased cardiovascular risk.

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List of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CHD	Coronary heart disease
CHMS	Canadian Health Measures Survey
CVD	Cardiovascular disease
FRS	Framingham Risk Score
HDL	High-density lipoprotein
HTA	Health Technology Assessment
LDL	Low-density lipoprotein
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
OHTAC	Ontario Health Technology Advisory Committee
RCT	Randomized controlled trial
S/N	Signal-to-noise ratio

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

To evaluate the frequency of lipid testing in adults not diagnosed with dyslipidemia and in adults being treated for dyslipidemia.

Clinical Need and Target Population

Description of Condition

Dyslipidemias include high levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. (1;2) High-density lipoprotein (HDL) and LDL are the main components of total cholesterol. While LDL has an atherogenic effect, higher levels of HDL have been shown to predict atherosclerosis regression. (3) Measuring the level of total cholesterol alone may therefore be misleading especially in individuals with either abnormally high or low HDL levels. (1)

The likelihood of lipid abnormalities depends on age, sex, and the presence of other cardiovascular risk factors. (4) Dyslipidemia is a risk factor for cardiovascular disease, which is a major contributor to mortality in Canada. (3)

Statins remain the main treatment for high LDL cholesterol. (5) A review of the literature on the effectiveness of statins compared with placebo in primary prevention of coronary heart disease concluded that statins significantly reduced the risk of major coronary events (combined fatal and non-fatal coronary events) in people without a previous history of cardiovascular disease. (5)

Canadian Prevalence

Table 1 summarizes the prevalence of lipid abnormalities in Canadian adults based on the Canadian Health Measures Survey (CHMS) conducted between 2009 and 2011. (6) High levels of LDL cholesterol and of total cholesterol were observed in 23% and 39% of the survey participants, respectively, with prevalence increasing with age up to 59 years of age. (6) The prevalence of low HDL did not seem to change with age. (6) The prevalence of total cholesterol to HDL ratio above the threshold was observed in approximately 15% of Canadians. (6) Triglyceride levels equal to or above the threshold of 1.7 mmol/L were observed in 25% of CHMS 2007/09 respondents aged 20 to 79 years old, 17% of 20- to 39-year-olds, 28% of 40- to 59-year-olds, and 34% of 60- to 79-your olds. (7)

Table 1: Prevalence of Lipid Disorders in the General Population[a,b] in Canada

TC Above Limit,[c] %	LDL Above Limit,[d] %	HDL Below Limit,[e] %	TC to HDL Ratio Above Limit,[f] %
Overall[g]: 39	Overall[g]: 23	Overall[g]: 26	Overall[g]: 15
20–39 years: 19	20–39 years: 12	20–39 years: 27	20–39 years: 12
40–59 years: 57	40–59 years: 40	40–59 years: 27	40–59 years: 23
60–79 years: 44	60–79 years: 26	60–79 years: 22	60–79 years: 15

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol.
[a]Excludes individuals living on Indian Reserves or Crown lands, residents of institutions, full-time members of Canadian Forces, and residents of remote regions.
[b]Age range 6–79 years. Data on individuals < 20 years not included in this table.
[c]Total cholesterol: ≥ 5.2 mmol/L (≥ 20 years)
[d]LDL ≥ 3.4 mmol/L.
[e]HDL: ≤ 1.0 mmol/L for men; ≤ 1.3 mmol/L for women.
[f]TC to HDL ratio: < 5.
[g]Overall prevalence includes individuals aged 6–79 years.
Source: Canadian Health Measures Survey, 2009–2011[a] (6)

Table 2 shows the prevalence of high levels of LDL in men 20 to 35 years old and in women 20 to 45 years old stratified according to the presence and numbers of risk factors based on the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2006. (8) An increased prevalence of high LDL was observed with an increase in the number of risk factors.

Table 2: Prevalence of High LDL Cholesterol Stratified According to Risk Factors

Definition of High LDL in mmol/L	LDL Above Limit, %		
	Overall (N = 2,587)	Men 20–35 years (N = 1,041)	Women 20–45 years (N = 1,546)
	None: 6.7	None: 10.1	None: 4.6
LDL: ≥ 4.1 (≤ 1 risk factor [a])	1 risk factor: 12.5	1 risk factor: 13.9	1 risk factor: 11.6
LDL: ≥ 3.4 (≥ 2 risk factors [a])	≥ 2 risk factors: 25.9	≥ 2: 27.5	≥ 2: 24.9
LDL ≥ 2.6 (CHD[b])	CHD: 65.1	CHD: 55.1	CHD: 68

Abbreviations: BMI, body mass index; CHD, coronary heart disease; LDL, low-density lipoprotein.
[a]Risk factors: cigarette smoking; hypertension, family history of premature coronary heart disease (angina or myocardial infarction) in 1st degree relative < 50 years old; obesity (BMI ≥ 30).
[b]CHD definition: history of angina or myocardial infarction. Self-reported stroke or diabetes (fasting glucose ≥ 126 mg/dL) classified as CHD equivalent.
Source: National Health and Nutrition Examination Survey (NHANES) 1999–2006 (8)

Ontario Context

Laboratory testing for plasma lipid levels is available in Ontario.

Technology/Technique

Total cholesterol, HDL cholesterol, and triglyceride levels are measured in plasma. LDL cholesterol can be calculated using Friedwald's formula based on the plasma levels of total cholesterol, HDL, and triglyceride if the triglyceride level is below or equal to 4.5 mmol/L. (1)

Regulatory Status

Health Canada has approved different test reagents and kits to measure lipid levels. (9)

Evidence-Based Analysis

Research Question

What is the appropriate frequency of testing for dyslipidemia? This evidence-based analysis focuses on adults who have not been diagnosed with dyslipidemia and adults being treated for dyslipidemia.

Research Methods

Literature Search

Search Strategy

A literature search was performed on November 29, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2000, until November 29, 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 publications
- published between January 1, 2000, and November 29, 2012
- randomized controlled trials (RCTs), systematic reviews, meta-analyses, health technology assessments (HTAs), and longitudinal observational studies
- that evaluate the frequency of lipid testing in individuals on lipid-lowering therapies or not

Exclusion Criteria

- cross-sectional studies
- longitudinal studies that follow the subjects' lipid levels over time but where the use of lipid-lowering interventions were not clearly reported
- studies with fewer than 20 patients

Outcomes of Interest

- frequency of testing for dyslipidemia

Expert Panel

In August 2012, an Expert Advisory Panel on Appropriate Use of Lipid Measurements was convened. 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 Measurements was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate use of lipid

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.

Statistical Analysis

The results of the eligible studies are presented as shown in the publications. Dichotomous variables were presented as absolute numbers and percentages, and continuous variables as mean or median; the measure of spread was reported as provided in the publications.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the GRADE Working Group criteria. (10) 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. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: large magnitude of effect, dose response gradient, and accounting for all residual confounding factors. (10) For more detailed information, please refer to the latest series of GRADE articles. (10)

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 Evidence-Based Analysis

The database search yielded 2,363 citations published between January 1, 2000, and November 29, 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. Figure 1 shows the breakdown of when and for what reason citations were excluded in the analysis.

Four studies (2 observational studies and 2 HTAs) met the inclusion criteria.

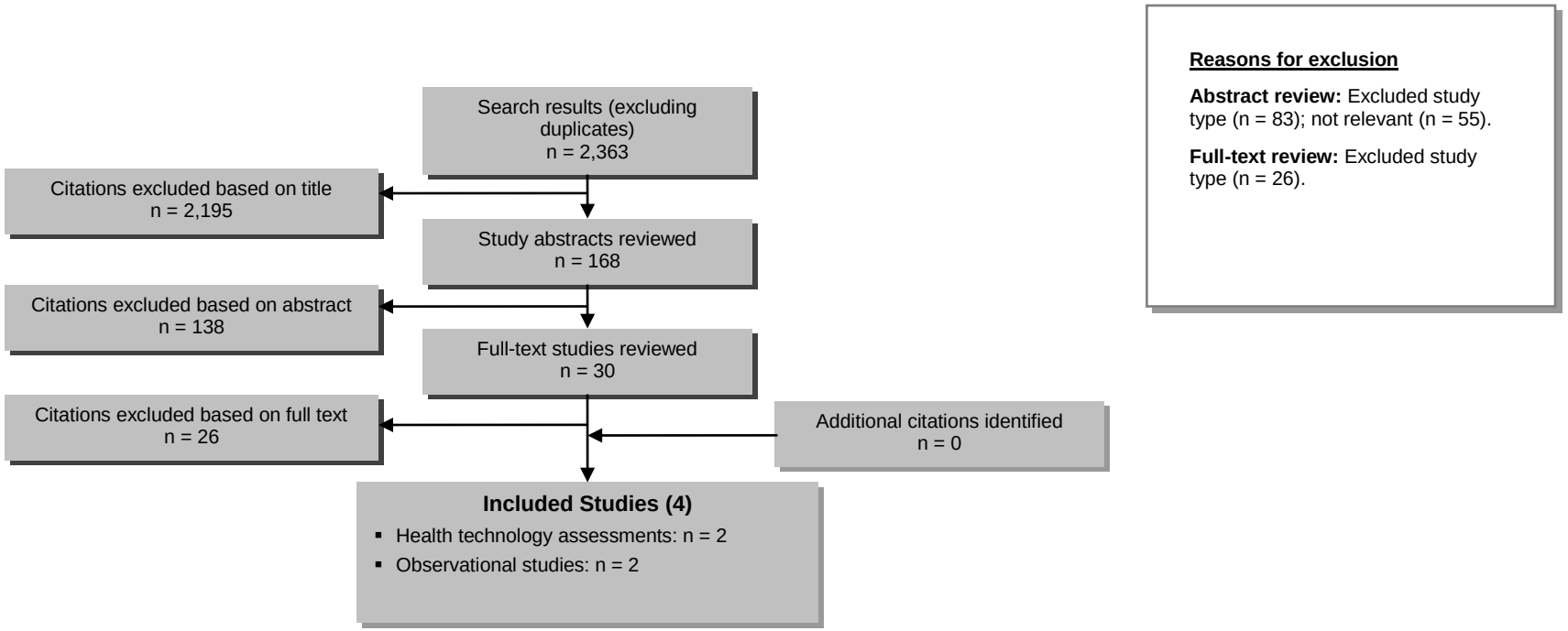

Figure 1: Citation Flow Chart

For each included study, the study design was identified. The design is summarized below in Table 3, which is a modified version of a hierarchy of study design by Goodman. (11)

Table 3: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCT Studies	
Systematic review of RCTs	
Large RCT	
Small RCT	
Health Technology Assessments	**2**
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	
Non-RCT with contemporaneous controls	2
Systematic review of non-RCTs with historical controls	
Non-RCT with historical controls	
Database, registry, or cross-sectional study	
Case series	
Retrospective review, modelling	
Studies presented at an international conference	
Expert opinion	
Total	**4**

Abbreviation: RCT, randomized controlled trial.

Health Technology Assessments

Two HTAs that evaluated the screening strategies for lipid disorders were identified. According to the Agency for Healthcare Research and Quality (AHRQ), (4) the decision to test lipid levels in people not diagnosed with dyslipidemia should take into account the likelihood of finding an abnormal lipid level and the risk of coronary heart disease, among other factors. The National Institute for Health and Clinical Excellence (NICE) (12) recommends testing in people aged 40 to 74 years who are expected to be at high risk for cardiovascular disease. No evidence on the frequency of lipid testing was identified in the HTAs. (4;12) Their main conclusions are summarized in Table 4.

The Health Technology Assessment Programme in the UK is undertaking an HTA that will evaluate the optimal strategies for monitoring lipid levels in individuals with cardiovascular disease or at risk of cardiovascular disease. (13) Some of the objectives will be to assess the value of different lipid measures in detecting changes in lipid status and to estimate the impact of different lipid measurements and intervals for assessing cardiovascular risk and monitoring lipid levels. (13) The latter will be based on a secondary analysis of individual patient data from observational studies, RCTs, databases, and an economic analysis. (13)

Table 4: Health Technology Assessments on Lipid Testing

Study, Year	Frequency of Testing		Population Groups to be Considered for Testing
	No treatment	Treatment with statins	
AHRQ, 2001 (4) Primary Prevention	No evidence found	Not evaluated	Strong evidence: Men (≤ 70 yrs) with moderate to high CHD risk[a] Less strong evidence, based both on evidence from statin trials and likelihood of abnormal lipid levels Postmenopausal women with CHD risk Men and women > 70 years with CHD risk
NICE, 2008 (12) Primary and Secondary Prevention	Not reported	*Primary prevention* Repeat lipid test is unnecessary once statin treatment started Use of clinical judgement to decide whether to repeat lipid test *Secondary prevention* Not reported	Cardiovascular risk assessment including assessment of lipid levels *Primary Prevention* Men and women 40–74 years old who are likely to be at high risk People should be prioritized based on CVD risk *Secondary Prevention* Individuals with established CVD Based on the results of an economic model

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; CHD, coronary heart disease; CVD, cardiovascular disease; NICE, National Institute for Health and Clinical Excellence.

[a]The published clinical trials available at the time of the review predominantly included middle-aged men (≤ 70 years) of European descent. (4)

Observational Studies

Two observational studies evaluated the frequency of testing for high lipid levels, 1 in individuals not being treated for dyslipidemia (14) and 1 in individuals treated for dyslipidemia. (15)

Takahashi et al (14) examined the lipid levels measured during annual checkups over 3 years of 15,810 adults not taking lipid-lowering medications. (14) The study estimated the true change in lipid levels (signal) and the short-term variation of the change in lipid level (noise) so as to estimate the optimal re-screening interval, defined as signal-to-noise (S/N) ratio greater than 1 (Table 5). (14) The authors concluded that the optimal re-screening interval in their study population of relatively stable patients not taking lipid-lowering agents should be greater than 3 years (Table 6). (14) However, the authors also point out that other factors, such as changes in patient lifestyle and drug treatment as well as other cardiovascular risk factors, should be considered when deciding on this optimal interval. (14) The generalizability of the study results may be compromised by the fact that only relatively stable individuals from 1 institution in Japan were included, and the large number of withdrawals from the study.

Glasziou et al (15) estimated the frequency of false positives and true positives of long-term changes in total cholesterol based on the data collected for a statin clinical trial (Table 5). The authors found that it took at least 3 years for the number of true positives to exceed the number of false positives (Table 6) and that testing in people who reached the target level every 3 to 5 years may be sufficient. (15) Some of the limitations raised by the authors include that the results were based on data from a trial using a single statin, with a lack of dose variation, and the fact that the patients' adherence to treatment in the trial can

be expected to be better than that in clinical practice. (15) Almost 20% of the patients included in the statin group withdrew from the study. (15) These factors may affect the generalization of the findings.

In addition to the generalizability issues in both studies, the original data collected were not designed to test the frequency of lipid testing, and so the importance of testing at time intervals outside of those predefined in the original studies cannot be assessed. The importance of accounting for the presence of other cardiovascular risk factors when deciding on the frequency of testing, as pointed out by Takahashi et al, (14) was not taken into consideration by Glasziou et al (2008) (15).

Table 5: Design and Characteristics of Observational Studies

Study	Study Design and Analysis	Study Population	Outcomes
Takahashi et al (2010) (14) N = 15,810 Japan Follow-up: 3 years	Secondary analysis based on data collected longitudinally Withdrawals dealt with in 2 ways: • Last value carried forward method • Exclusion	Adults (> 20 years) not using lipid-lowering medication at baseline, undergoing annual checkup	**S/N[a] ratio of change over time for each lipid measure** TC, LDL, HDL, and TC-HDL and LDL-HDL ratios
Glasziou et al (2008) (15) N = 9,014 Multinational Follow-up: 5 years	Secondary analysis using data from a long-term statin RCT Withdrawals dealt with in 3 different ways: • Last value carried forward method • Exclusion • Imputation	Adult patients included in a statin RCT Baseline total cholesterol 4.0–7.0 mmol/l, triglycerides < 5 mmol/L	**True positives[b] -** TC level exceeds the threshold **False positives[b] -** TC level does not exceed the threshold

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; RCT, randomized controlled trial; S/N, signal-to-noise; TC, total cholesterol.
[a]Noise: short-term within-person variation* of the average change in cholesterol level. Signal: true long-term change in cholesterol levels.
[b]True and false positives were determined based on the mean change in cholesterol level at the different time intervals and the true within-person variability.

The quality of the evidence based on the GRADE Working Group criteria was considered very low (Appendix 2).

Table 6: Results of Observational Studies

Study	Baseline Characteristics	Losses to Follow-up Withdrawals	S/N or True to False Positives Ratio
Takahashi et al (2010) (14) N = 15,810 Japan Follow-up: 3 years	Mean (SD) age: 49.3 (12.2) years Male (%): 8,362 (52.9%) Mean (SD) BMI: 22.5 (3.2) kg/m^2 Mean (SD) TCl: 5.3 (0.9) mmol/L	Individuals with < 3 years of follow-up: 22,666/38,476 (58.9%) Started lipid-lowering medication: 758 (4.8%)	S/N ratio TC: Year 1: 0.3 Year 3: 0.8 S/N ratio LDL Year 1: 0.4 Year 3: 0.99 S/N ratio HDL Year 1: 0.2 Year 3: 0.7 S/N ratio TC/HDL Year 1: 0.5 Year 3: 1.6 S/N ratio LDL/HDL Year 1: 0.4 Year 3: 1.5
Glasziou et al (2008) (15) N = 9,014 Multinational Follow-up: 5 years	Median age: 62 years Male, n (%): 7,481 (83%) Mean (SD) TC: 5.65 (0.82) mmol/L	Losses to follow-up: 1 (0.2%) Withdrawals: Stopped medication (statin group): 6% (year 1), 9% (year3), 19% (end of study) Deaths: 226 (5%)	False positive:true positive ratio of TC at different intervals: Starting at 4.5 mmol/L: Year 1: 16 Year 3: 1.6 Year 5: 1 Starting at 4.0 mmol/L Year 1: > 1000 Year 3: 10 Year 5: 3

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; S/N, signal-to-noise; TC, total cholesterol.

Conclusions

The quality of the evidence was considered very low given the methodological and the generalizability issues in the 2 observational studies identified in the literature. Two HTAs published in or before 2008 did not identify any evidence on the frequency of lipid testing. Therefore, conclusions on the frequency of lipid testing could not be made based on the 2 observational studies.

The 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia in adults (16) provide recommendations on the frequency of lipid testing in people not diagnosed with dyslipidemia. Testing for dyslipidemia is recommended in groups that are expected to have increased cardiovascular risk and the frequency of testing depends on the person's cardiovascular risk profile. (16)

Existing Guidelines for Technology

Table 7 summarizes the recommendations on testing for lipid disorders from Canadian, American, and European guidelines. The Canadian guidelines identify individuals not diagnosed with dyslipidemia and with an increased risk for cardiovascular events as the population who should be tested for lipid disorders. (16) The proposed frequency of testing in these individuals is based on expert consensus and depends on the risk of cardiovascular events based on the 10-year Framingham Risk Score modified according to the presence of family history of premature cardiovascular disease. (16) Additional details in Table 7.

Table 7: Summary of Guideline Recommendations

	Canadian Cardiovascular Guidelines (2012) (16)	US Preventive Services Task Force (2008) (2)	European Society of Cardiology / European Atherosclerosis Society (2010) (1)
Who to test among people *not* diagnosed with dyslipidemias	• Men ≥ 40 years • Women ≥ 50 years or postmenopausal *Ethnic groups at increased risk (South Asians or First Nations) may be tested earlier* **All patients with the** following conditions, regardless of age: • Current cigarette smoking • Diabetes • Arterial hypertension • Family history of premature CVD • Family history of hyperlipidemia • Erectile dysfunction • Chronic kidney disease • Inflammatory disease • HIV infection • Chronic obstructive pulmonary disease • Clinical evidence of atherosclerosis or abdominal aneurysm • Clinical manifestation of hyperlipidemia • Obesity (BMI > 27 kg/m^2) Based on literature on increased cardiovascular risk in the groups listed above	Primary Prevention Strongly recommended for: • Men ≥ 35 years • Women ≥ 45 years if at increased risk for CHD[a] Recommended • Men 20–35 years if at increased risk for CHD[a] • Women 20–45 years if at increased risk for CHD[a] Based on the finding that the groups listed above benefit substantially from statin treatment	To be considered in the following populations: • Men ≥ 40 years • Women ≥ 50 years or postmenopausal Recommended in people with the following conditions: • Diabetes type 2 • Established CVD • Hypertension • Smoking • BMI ≥ 30 kg/m^2 or waist circumference > 94 cm for men and 90 cm for women • Family history of premature CVD • Chronic inflammatory disease • Chronic kidney disease • Family history of familial dyslipidemia Based on expert consensus and/or small studies or registries

	Canadian Cardiovascular Guidelines (2012) (16)	US Preventive Services Task Force (2008) (2)	European Society of Cardiology / European Atherosclerosis Society (2010) (1)
Frequency of testing of people not diagnosed with dyslipidemias	If FRS < 5%: Every 3–5 years If FRS ≥ 5%: Annually Based on Expert Consensus	Overall: Every 5 years If level is close to goal or longer intervals: more frequent If low risk and repeatedly normal results**:** less frequent Based on Expert Opinion	Not reported
Frequency of testing **Individuals receiving <u>treatment for dyslipidemias</u>**	Not reported	Not reported	• **Until target level is reached:** 8 ± 4 weeks after starting or adjusting treatment • **Once target is reached:** Annually unless there are adherence problems **<u>Evidence Base</u>** Limited evidence/expert opinion

Abbreviations: BMI, Body Mass Index; CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein.

[a]Diabetes, previous history of CHD or non-coronary atherosclerosis, family history of cardiovascular disease < 50 yrs in male relatives or < 60 yrs in female relatives, smoking, hypertension, obesity (BMI ≥ 30)

Acknowledgements

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Cardiac Lipid Expert Advisory Panel

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

Appendices

Appendix 1: Literature Search Strategies

Search date: November 29, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Cochrane Library; CRD

Database: Ovid MEDLINE(R) 1946 to November Week 3 2012, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 27, 2012, Embase 1980 to 2012 Week 47
Search Strategy:

#	Searches	Results
1	exp Dyslipidemias/ use mesz	60165
2	exp Lipids/ use mesz	875117
3	*Dyslipidemia/ use emez	6318
4	exp *Hyperlipidemia/ use emez	40897
5	*Abnormally High Substrate Concentration in Blood/ use emez	133
6	exp *Hyperlipoproteinemia/ use emez	4220
7	(hyperlipemia? or hyper-lipemia? or hyperlipaemia? or hyper-lipaemia? or lipemia? or lipaemia? or hyperlipidemia? or hyper-lipidemia? or hyperlipidaemia? or hyper-lipidaemia? or lipidemia? or lipidaemia? or dyslipidemia? or dyslipidaemia? or dyslipoproteinemia? or dyslipoproteinaemia?).ti,ab.	87681
8	(hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesteremia? or hyper-cholesteremia? or hypercholesterolemia? or hyper-cholesterolemia? or hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesterinaemia? or hyper-cholesterinaemia? or hypercholesterinemia? or hyper-cholesterinemia? or cholesteremia? or cholesterinemia? or cholesterolemia?).ti,ab.	50983
9	(((high* or elevat* or raise*) adj5 cholesterol*) or high- cholesterol* or highcholesterol*).ti,ab.	95602
10	lipid disorder?.ti.	734
11	or/1-10	1060090
12	exp Mass Screening/ use mesz	93966
13	mass screening/ use emez	46521
14	rescreening/ use emez	95
15	screen*.ti.	232496
16	(re-screen* or rescreen*).ti,ab.	2219
17	((optimal or appropriate* or reasses* or re-assess* or frequen*) adj3 (interval* or screen*)).ti,ab.	19425
18	((interval* or optimal) adj3 monitor*).ti,ab.	3175
19	*Time Factors/ use mesz	1087
20	Unnecessary Procedures/ use mesz	2895
21	unnecessary procedure/ use emez	1636
22	or/12-21	332543

23	11 and 22	6747
24	limit 23 to english language	5898
25	Animals/ use mesz	5093266
26	animal/ use emez	1802180
27	or/25-26	6895446
28	24 not 27	5432
29	limit 28 to yr="2000 -Current"	3057
30	remove duplicates from 29	2374

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Dyslipidemias] explode all trees	4517
#2	MeSH descriptor: [Lipids] explode all trees	30386
#3	(hyperlipemia? or hyper-lipemia? or hyperlipaemia? or hyper-lipaemia? or lipemia? or lipaemia? or hyperlipidemia? or hyper-lipidemia? or hyperlipidaemia? or hyper-lipidaemia? or lipidemia? or lipidaemia? or dyslipidemia? or dyslipidaemia? or dyslipoproteinemia? or dyslipoproteinaemia?):ti,ab,kw (Word variations have been searched)	1616
#4	(hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesteremia? or hyper-cholesteremia? or hypercholesterolemia? or hyper-cholesterolemia? or hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesterinaemia? or hyper-cholesterinaemia? or hypercholesterinemia? or hyper-cholesterinemia? or cholesteremia? or cholesterinemia? or cholesterolemia?):ti,ab,kw (Word variations have been searched)	5
#5	(((high* or elevat* or raise*) near/5 cholesterol*) or high- cholesterol* or highcholesterol*):ti,ab,kw (Word variations have been searched)	8754
#6	lipid disorder?:ti,ab,kw (Word variations have been searched)	399
#7	#1 or #2 or #3 or #4 or#5 or #6	31496
#8	MeSH descriptor: [Mass Screening] explode all trees	4249
#9	screen*:ti	5233
#10	(re-screen* or rescreen*):ti,ab,kw (Word variations have been searched)	81
#11	((optimal or appropriate* or reasses* or re-assess* or frequen*) near/3 (interval* or screen*)):ti,ab,kw (Word variations have been searched)	569
#12	((interval* or optimal) near/3 monitor*):ti,ab,kw (Word variations have been searched)	140
#13	MeSH descriptor: [Unnecessary Procedures] explode all trees	80
#14	#8 or #9 or #10 or #11 or #12 or #13	7355
#15	#7 and #14 from 2000 to 2012	107

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR dyslipidemias EXPLODE ALL TREES	271
2	MeSH DESCRIPTOR lipids EXPLODE ALL TREES	1021
3	((hyperlipemia? or hyper-lipemia? or hyperlipaemia? or hyper-lipaemia? or lipemia? or lipaemia? or hyperlipidemia? or hyper-lipidemia? or hyperlipidaemia? or hyper-lipidaemia? or lipidemia? or lipidaemia? or dyslipidemia? or dyslipidaemia? or dyslipoproteinemia? or dyslipoproteinaemia?)):TI	40
4	((hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesteremia? or hyper-cholesteremia? or hypercholesterolemia? or hyper-cholesterolemia? or hypercholesterolaemia? or hyper-cholesterolaemia? or hypercholesterinaemia? or hyper-cholesterinaemia? or hypercholesterinemia? or hyper-cholesterinemia? or cholesteremia? or cholesterinemia? or cholesterolemia?)):TI	65
5	((((high* or elevat* or raise*) adj5 cholesterol*) or high- cholesterol* or highcholesterol*)):TI	5
6	(lipid disorder?):TI	0
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	1171
8	MeSH DESCRIPTOR mass screening EXPLODE ALL TREES	1820
9	(screen*):TI	2002
10	((re-screen* or rescreen*)):TI	6
11	(((optimal or appropriate* or reasses* or re-assess* or frequen*) adj3 (interval* or screen*))):TI	5
12	(((interval* or optimal) adj3 monitor*)):TI	4
13	MeSH DESCRIPTOR unnecessary procedures EXPLODE ALL TREES	16
14	#8 OR #9 OR #10 OR #11 OR #12 OR #13	2392
15	#7 AND #14	49
16	(#15):TI FROM 2000 TO 2012	36

Appendix 2: GRADE Tables

Table A1: GRADE Evidence Profile for Frequency of Testing for Dyslipidemia

No. of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Frequency of lipid testing							
2 (observational)	Limitations[a]	No serious limitations	Serious limitations (−1)[b]	Serious limitations (−1)[c]	Undetected		⊕ Very Low

[a]A large number of subjects withdrew from the studies identified, which could lead to selection bias.
[b]One study included stable patients from 1 country and had a large number of withdrawals. One study used data from a trial using 1 specific drug in a patient population with treatment adherence that is expected to be higher than in clinical practice.
[c]Information that would allow for the assessment of imprecision was not provided.

Table A2: Risk of Bias Among Observational Studies Evaluating the Frequency of Testing for Dyslipidemia

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Takahashi et al, 2010 (14)	Limitations[a]	No limitations	Serious limitations[b]	Not performed	Limitations[c]
Glasziou et al, 2008 (15)	Limitations[a]	No limitations	Serious limitations[b]	Not performed	No limitations[d]

[a]The large number of withdrawals may result in selection bias.
[b]The outcome measure (frequency of testing) was estimated based on modelling of clinical data and was not designed to test the frequency of testing, not allowing conclusions to be made on time intervals outside of those used in the original data collection.
[c]Only patients with complete follow-up were included in the analysis, which resulted in excluding more than half of the original study population.
[d]Data from patients who required a change in lipid-lowering medications were included based on imputation methods, actual data not used.

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