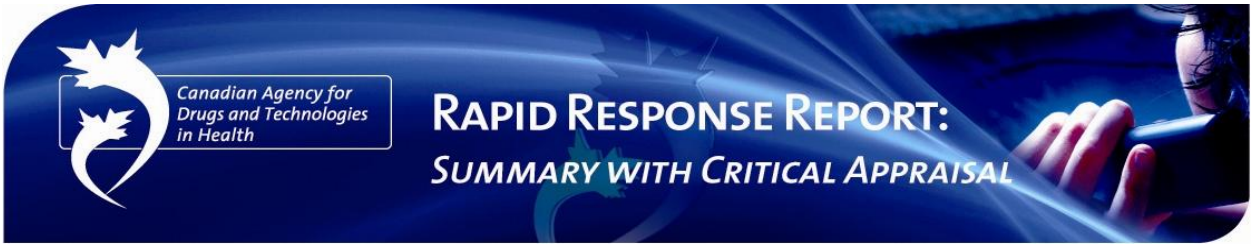

TITLE: Point of Care Cholesterol Testing for Coronary Heart Disease: A Review of the Clinical Effectiveness and Guidelines

DATE: 24 May 2011

CONTEXT AND POLICY ISSUES

Point of Care (POC) testing is diagnostic testing that is performed in a non-laboratory setting by appropriately-trained personnel at or near the site of patient care.[1] Compared with conventional laboratory testing, advantages of POC testing are small blood samples, short turnaround times, no specimen transport and no requirement for repeat clinic visits to obtain results.[1,2] The technology facilitates immediate, informed clinical decision making and direct discussion of the result with the patient.[3] Potential disadvantages of POC testing are capital costs, sample quality, infection control, record keeping and that it may not be suitable for all testing.[1,4]

Cholesterol testing to identify individuals at risk of coronary heart disease (CHD) is increasingly being conducted at the POC.[3] Dyslipidemia is a well established, modifiable risk factor for CHD,[5,6] which is the second leading cause of death in Canada.[7] Most POC devices are hand held meters with compact desktop analyzers that are capable of measuring individual or multiple analytes on whole blood, plasma or serum collected from a fingerprick (capillary) or venous blood sample.[3] Examples of commercially available POC cholesterol analyzers are the Cholestech LDX® system (Cholestech Corporation, Hayward, CA) and the CardioChek® PA System (Polymer Technology Systems, Indianapolis, IN).[8] Depending on the test cassette (Cholestech LDX® System) or test strip (CardioChek® PA System) selected, the devices are capable of measuring a full lipid panel [i.e., total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and calculated low density lipoprotein cholesterol (LDL-C)], ratios of analytes or individual analytes (e.g., glucose).[8] The Cholestech LDX® System is also capable of measuring liver function (ALT, AST), high-sensitivity C-reactive protein (hs-CRP) and can perform a CHD risk assessment calculation based on the Framingham 10-year risk score for CHD.[9]

Numerous clinical practice guidelines are available for the detection, evaluation and treatment of dyslipidemia in adults. Perhaps the most recognized are the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III guidelines,[5] which were last updated in 2004.[10] The NCEP ATP III guidelines recommend routine measurement of a fasting lipid profile (TC,

HDL-C, LDL-C and TG) in all adults aged 20 and older at least once every five years.[5] The Canadian Cardiovascular Society (CCS)[6] recommends that a screening with fasting lipid profile be obtained in all men ≥40 years of age and women ≥50 years of age or postmenopausal. It follows that POC cholesterol testing has the potential for widespread screening applications, especially for individuals living in remote areas or in institutionalized or confined settings who may have difficulty accessing conventional laboratory testing.

The purpose of this report is to review the evidence for the clinical effectiveness of POC testing compared to conventional laboratory testing for cholesterol and to identify evidence-based guidelines regarding the use of cholesterol testing to identify individuals at risk of CHD. This information will be used to inform decision makers considering the purchase of a POC device for cholesterol testing to identify inmates at a federal institution who are at risk for CHD.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of POC testing versus laboratory testing for cholesterol testing to identify individuals at risk of CHD?

2. What are the evidence-based guidelines regarding cholesterol testing to identify individuals at risk of CHD?

KEY MESSAGE

POC cholesterol testing may be suited for screening purposes as there is insufficient evidence to support that it can replace laboratory testing for diagnosis of CHD or that it has comparable clinical effectiveness. Evidence-based recommendations for cholesterol testing are outlined in select guidelines which are assessed for quality and limitations in this report.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. For the first question, no methodological filters were applied to limit retrieval by study type. For the second question, methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and April 25, 2011.

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, randomized controlled trials (RCTs) are presented first. These are followed by non-randomized studies and evidence-based guidelines.

Domains identified in the Appraisal of Guidelines Research and Evaluation (AGREE) instrument[11] were used to evaluate the quality of the guidelines identified from the literature search. The domains of scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence were assessed. Only North American guidelines for cholesterol testing were included in this report.

SUMMARY OF FINDINGS

The literature search identified one RCT[12], six non-randomized studies[13-18] and six evidence-based guidelines.[6,19-23] No health technology assessments, systematic reviews or meta-analyses were identified. Additional information of potential interest is included in Appendix 1

Randomized controlled trials

One large, multicentre, cluster RCT was identified that compared the clinical effectiveness of POC testing and conventional laboratory pathology testing in patients with established chronic conditions when used in general practices in Australia. Bubner et al., 2009[12] randomized 4968 patients with type 1 or 2 diabetes, hyperlipidemia, or who were receiving anticoagulant therapy to blood and urine testing by POC devices (intervention group; n=3010 in 30 practices) or by usual laboratory testing (n=1958 in 23 practices) over a 17 month period. Three different POC devices were used to test for a variety of parameters, one of which is relevant to this report—the Cholestech LDX® System, which was used to measure blood lipid levels (TC, HDL-C and TG). The primary outcome was the proportion of patients with results in the target range (i.e., TC < 4.0 mmol/L, HDL-C > 1.0 mmol/L) and TG < 2.0 mmol/L). Secondary outcomes were the proportion of tests with results in the target range and the change in the test results from baseline. Results were compared using non-inferiority analysis. The non-inferiority margin for the difference in percentage (intervention - control) was determined *apriori* to be -7% by an expert clinical group. Practice characteristics and geographic location (i.e., urban, rural and remote) were similar across the study groups. At baseline, patient characteristics were similar between groups with a total of 3819 (77%) of all patients had hyperlipidemia. Analysis of the proportion of patients whose lipid test results were in the target range showed that POC testing was non-inferior to laboratory testing for TC and TG, but not HDL-C. Differences between POC testing and laboratory testing were: 17.0% (90% CI: 13.0%; 21.1%); p<0.001 for TC, 2.0% (90% CI: -2.0%; 6.1%); p<0.001 for TG and -9.2% (90% CI: -14.2%; -4.3%); p=0.77 for HDL-C. Similarly, the analysis of the proportion of tests with results in the normal range and the proportion of patients with an improvement in their test results from baseline showed that POC testing was non-inferior to laboratory testing for TC and TG, but not for HDL-C. The study may have been limited by not measuring the actual time spent in the therapeutic range, as this could have produced a different result. As well, the study did not report LDL-C levels which are generally what treatment decisions are based upon.[5,6] It was concluded that the results provide evidence that POC testing is non-inferior (i.e., no worse than by a pre-specified small amount) than conventional laboratory pathology testing.

Non-randomized studies

Six non-randomized studies[13-18] were identified that compared POC testing and conventional laboratory testing for the determination of lipid profiles. Details of the studies are provided in Appendix 2. Five studies[13-15,17,18] evaluated the correlation or degree of agreement of TC, HDL-C and TG levels resulting from POC and laboratory testing of blood samples obtained from the same individuals. In the remaining study,[16] investigators conducted a validation of a POC device by comparing the results of TC and TG levels with those obtained by laboratory testing of the same blood samples. Four studies[13-15,18] investigated the Cholestech LDX® System whereas the other two studies, originating from Italy, investigated the MultiCare device[16] and the CR3000 system.[17] None of the studies measured clinical outcomes; however, one study[14] investigated the agreement of POC and laboratory testing on identifying individuals at risk of cardiovascular disease (CVD) using four different CVD risk calculators and another study[15] reported the

agreement between the methods of identifying abnormal results. All studies, with the exception of one that included patients with CVD or hypertension,[13] evaluated POC cholesterol testing for screening or the primary prevention of CVD in asymptomatic individuals. There was no follow-up testing in any of the studies to confirm a CVD diagnoses or any clinical outcomes.

Degree of agreement between POC and laboratory cholesterol testing

Overall, the degree of agreement between POC and laboratory cholesterol testing measured as a correlation coefficient (r) or by kappa statistics was high. Statistically significant correlations between POC and laboratory testing for TC ranged from r=0.91 to 0.98, for TG from r=0.93 to 0.98, and for HDL-C from r=0.77 to 0.92. [13,15,17] Two studies reported the degree of correlation for calculated LDL-C levels which ranged from r=0.86 to 0.88.[13,15] Similar results were also demonstrated by kappa statistics in one study which reported significant agreement between POC and laboratory testing for TC (κ=0.67), TG (κ=0.86) and HDL-C (κ=0.73).[18] A κ>0.75 was considered to be excellent agreement.[18] One study[13] reported statistically significant absolute differences between POC and laboratory testing for TG and HDL-C. POC testing overestimated TG levels by 0.25 mmol/L and underestimated HDL-C levels by 0.11 mmol/L; both p<0.001, although the differences were unlikely to be of clinical significance. Another study[14] found that although there was good overall agreement of POC and laboratory testing across the range of concentrations tested, concentration-dependent biases with POC testing may occur at lower concentrations (e.g., for HDL-C< 1.0 mmol/L, POC testing underestimated levels by 0.2 mmol/L; p<0.0001). Three studies[13-15] compared POC testing of blood samples obtained by fingerprick with laboratory testing of venous blood samples, which would best approximate actual practice. The remaining studies utilized the same venous blood sample which was tested by the two methods. Only two studies[15,18] incorporated the transport of samples to a distant laboratory for testing in their design, which also more closely approximates actual practice as factors such as prolonged transit time, temperature variations, and storage conditions can potentially impact on the results. One study[16] tested the practicability of POC testing by comparing the results of patient self-measurement of TC or TG from capillary blood with those obtained by a professional operator. There were no statistically significant differences in the results. In general, all studies concluded that POC testing is an accurate and useful alternative to laboratory testing for CHD screening purposes based on cholesterol levels.

Identification of individuals at risk of CVD

Two studies[14,15] compared POC and laboratory cholesterol testing for identifying individuals at risk of CVD. Jain et al., 2011[14] investigated the degree of agreement between the two methods (measured by kappa statistics) on categorizing patients at risk of CVD based on lipid values using four different web-based risk calculators (i.e., JBS2, QRISK2, ETHRISK and Framingham). There was excellent agreement on the calculated CVD risk using all four risk calculators: JBS2 (κ=0.86), QRISK2 (κ=0.92), ETHRISK (κ=0.94) and Framingham (κ=0.88). Similarly, Parikh et al., 2009[15] found that the categorical agreement of abnormal lipid results was high between POC and laboratory testing: TC (κ=0.75), TG (κ=0.78), LDL-C (κ=0.69) and HDL-C (κ=0.40). For both studies, a result of κ>0.75 was considered excellent, 0.4 to 0.75 fair to good and <0.4 poor agreement. The study populations in both studies were individuals attending CVD screening programs, therefore, it is not known if these results are generalizable to patients with known CVD or undergoing treatment for dyslipidemia.

Guidelines and recommendations

Six North American guidelines[6,19-23] were identified that specifically described evidence-based processes for developing recommendations regarding cholesterol testing. The guideline recommendations are summarized in Table 1.

The 2010 Preventive Services for Adults Health Care Guidelines[20] from the US Institute for Clinical Systems Improvement (ICIS) list lipid screening as a Level I preventative service that providers and care systems must assess the need for and offer to each patient. The scope and target population (i.e., asymptomatic adults seeking healthcare who would benefit from preventive services) are clearly identified. The objective of the guidelines is to increase the rate of patients on time with Level I preventative services. The lipid management portion of the guideline was developed by a working group with representatives from various specialties (e.g., internal medicine, family medicine, nursing, pharmacy and health education) who are identified in the guideline. It does not appear that patient's views and preferences were sought during development or that the guideline was piloted among target users. The guideline development process was based upon a literature search to identify clinical trials, meta-analyses, systematic reviews, regulatory statements and other professional guidelines. It is stated in the guideline that the evidence and conclusions were graded according to the ICSI's Evidence Grading System; however, the results were not provided. It was not explicitly stated that a systematic review was conducted, nor were selection criteria for the evidence described. The guideline was reviewed by medical groups who are members of ICSI and feedback was incorporated in the revision of the guideline. A revision process was described that ensures guidelines are updated every 12 to 24 months. The recommendations are clearly presented; however, those pertaining to lipid screening are grouped with other Level I preventative services such as screening for alcohol abuse, cancer, hypertension and influenza, etc., so it is not readily apparent that the guidelines also incorporate lipid screening. A small number of application tools are provided which are largely counseling messages and a list of resources available from various organizations. In contrast to the other guidelines, the ICSI guideline contains a comprehensive section on strategies and measurement specifications to use in assessing the impact of the guideline. There is also a section on implementation that highlights organizational infrastructure and system changes required to support implementation of the guideline. The extent of editorial independence is unclear; however, working group members were required to fully disclose potential conflicts of interest.

The 2009 CCS guidelines[6] for the diagnosis and treatment of dyslipidemia are an update of the previous 2006 version.[24] In the 2009 version, the major principles of screening and risk stratification are retained, with the main differences from the previous version being a change in the development process, inclusion of additional stakeholder groups, and incorporation of new data in the strategies and recommendations pertaining to primary and secondary prevention of CVD and treatment targets.[6] Although the overall objectives, scope and purpose of the guidelines are not specifically described, it is implied that the guidelines are targeted to all adults who are candidates for lipid screening. Specific clinical questions are not described, but the guidelines are broad in that they cover recommendations on screening, CVD risk assessment, targets of therapy and overall treatment. There are 18 stakeholder groups identified as contributing to the guidelines, spanning a wide range of disciplines (e.g., cardiac rehabilitation, obesity network, diabetes, tobacco control and public health). The guidelines appear to have been developed with rigour as an updated systematic review was conducted, key words were listed, and selection criteria stated. Specific criteria for grading recommendations (i.e., Class I, II or III) and the level of evidence (Level A, B or C) were clearly described in the guideline.[6] Both

efficacy and safety of lipid-lowering therapies were considered. Although a specific procedure for updating the guidelines was not stated, the importance of incorporating new data into guidelines to promote a current and uniform standard of care was discussed. It was not clear if the guidelines were reviewed externally; however, with the large number of stakeholders involved it is assumed that many clinical experts would have contributed. It does not appear that there was patient input into the development of the guidelines and no patient advocacy groups are listed amongst the stakeholders. The recommendations are clear and unambiguous and the key recommendations are included in a succinct one page summary. In terms of application tools, the Framingham 10-year CHD risk calculator is included as supplementary information. There is no discussion of potential organizational barriers or cost implications of applying the recommendations or key review criteria for monitoring and/or audit purposes. It is stated that the 2009 guidelines were developed by volunteer experts in lipid disorders and CVD with full and open disclosure of their relationships with the pharmaceutical industry. There was no direct financial support or involvement from industry in the guideline writing process. Overall, the guidelines are current and comprehensive as they address screening, assessment, therapies and treatment targets to mitigate the risk of CVD.

The 2009 Screening and Management of Lipids Guideline for Clinical Care[22] prepared by the Lipid Therapy Guideline Team at the University of Michigan is intended for adults 20 to 75 years of age without familial or severe dyslipidemias. The scope, purpose and target patient population are clearly stated; however, the clinical questions answered by the guideline are not described. The objectives of the guidelines are to outline strategies for lipid screening, identify patients who would benefit from treatment and to recommend appropriate treatment regimens. Stakeholder involvement and the guideline development process are not clearly described. A list of team members is provided with representation from general medicine, medical education, pharmacy, family medicine and cardiology. A literature search was conducted and the search strategy including key words used was provided; however, it was unclear if a systematic review was conducted. Conclusions were based on evidence from prospective RCTs and if unavailable, observational studies were considered. The level of evidence according to study design (A, B, C or D) was graded as was the strength of the recommendation (I, II or III) as defined in the guideline.[22] Key recommendations are clearly identified and presented in a one page summary as well as in greater detail in the text of the guideline. It was not mentioned if the guideline was reviewed externally prior to finalization or if a formal process is in place for future updates. No application tools or discussion of implementation issues was provided. Editorial independence was not mentioned although a list of disclosures of team members' relationships with the pharmaceutical industry was provided.

The 2008 Cardiovascular Disease - Primary Prevention Guidelines[19] by the British Columbia (BC) Guidelines and Protocol Advisory Committee provide a summary of strategies for the assessment and mitigation of risk factors for CHD. The objectives of the guidelines are to reduce the risk of clinical CHD by providing a summary of various strategies and to integrate these strategies with other existing guidelines. The scope, target population, objectives and purpose of the guideline are clearly described; however, no specific clinical questions were provided. The BC guideline primarily summarizes recommendations from other evidence-based guidelines such as the NCEP ATP III guidelines[5] and the 2006 CCS dyslipidemia guidelines.[24] The guidelines were developed by the BC Guidelines and Protocols Advisory Committee and identified stakeholders are the BC Medical Association and the BC Ministry of Health Services. It does not appear that patient's views and preferences were sought during development of the guideline or that it was piloted among target users. A systematic review of the peer-reviewed literature was conducted and relevant guidelines from other jurisdictions were considered.

Pharmacologic recommendations are based on large RCT evidence (wherever possible) and lifestyle recommendations on large, prospective, cohort trials. Criteria for selecting evidence or the methods used for formulating recommendations were not described, nor where recommendations graded as to level of evidence or strength of the recommendation. It was stated that the evidence for optimal frequency of lipid testing is lacking and therefore, recommendations in this area were based on expert opinion. Recommendations are organized into those pertaining to lifestyle management and CHD risk control. Various tools to assist with categorization of a patient's risk of CHD (e.g., smoking cessation assessment, Framingham 10-year CHD risk calculator, etc.) are provided as appendices. It is not clear if the guideline was externally reviewed or if there is a process in place to facilitate guideline updates. Overall, the recommendations are clearly presented; however, they are numerous and there is no distinction as to which are the key recommendations. There is no discussion of potential organizational barriers or cost implications of applying the recommendations or key review criteria for monitoring and/or audit purposes. No details on editorial independence were provided. Overall, the BC guideline recommendations are based on those of other well known guidelines and the distinguishing feature of this guideline is the appended tools are clearly presented in a user-friendly manner to assist with identification of an individual's risk of CHD.

The 2008 US Preventive Services Task Force (USPSTF) Screening for Lipid Disorders in Adults Recommendation Statement[23] provides guidance for lipid measurement to identify asymptomatic men and women aged 20 and older who are eligible for preventive therapy. The purpose, scope, target population and the rationale for the recommendation statement are clearly stated. Although an objective was not stated per se, the mandate of the USPSTF is to make accurate, up-to-date and relevant recommendations about preventative services in primary care. Clinical questions were not stated in the recommendation statement and it is not clear if patients' views and preferences were sought during the development process. While stakeholders were not specifically mentioned, a list of USPSTF members was provided which includes representation from most medical specialties. The guideline development process was not specifically described; however, presumably similar methods and processes were followed as with all USPSTF recommendation statements. It was noted that the USPSTF reviewed the literature on the accuracy of screening tests, the efficacy of treatment and the harms of screening and treatment for dyslipidemia. The USPSTF bases its recommendations on systematic evidence reviews, which are conducted by members of the Evidence Based Practice Center (EPC) in association with the Agency for Healthcare Research and Quality (AHRQ). The quality of the overall evidence was graded on a 3-point scale (good, fair, or poor). The key recommendations for lipid screening are clearly identifiable and are graded (A, B, C, D or I) according to the strength of the evidence and magnitude of net benefit (i.e., benefits minus harms) as defined by the USPSTF.[23] The recommendations differ from those of other guidelines in that TG are not included in the initial tests used to routinely screen for dyslipidemia because of insufficient evidence. The preferred screening tests are TC and HDL-C (and LDL-C calculated from these measures). No tools for application, discussion of potential organizational barriers or cost implications of applying the recommendations, or key review criteria for monitoring and/or audit purposes are provided. No details on editorial independence or potential conflicts of interest were provided; however, the USPSTF is mandated to ensure transparency, accountability and integrity of the process and recommendations. The USPSTF was the only organization to comment on the harms of detection and early treatment of lipid disorders. It was stated that there is good evidence that the harms from screening and treatment are small and include possible labeling of an individual as having high cholesterol which may result in psychological sequel and the potential adverse effects associated with lipid-lowering therapy (e.g., rhabdomyolysis).

The 2006 Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guideline for the Management of Dyslipidemia[21] was developed for primary care providers working within a broad range of clinical settings within VA or the DoD. The scope, purpose and target population for the guideline are clearly described. The objective of the guideline is to appropriately target individuals for lipid profile screening. The guideline was developed by a working group comprised of health care professionals from medicine, nursing, pharmacy and other disciplines; however, the specific affiliations of the members were not listed. It does not appear that patient's views and preferences were sought during development or that the guideline was piloted among target users. Guideline development was done according to an internal working process intended to produce evidence-based action recommendations. Research questions were formulated by the working group and a literature review was conducted. It was not clear if a systematic literature review was conducted; however, inclusion criteria for selecting articles were listed. Only evidence from RCTs was included and the quality of each trial was rated along with the overall quality of the evidence and the net effect of the intervention. The final grade assigned to each recommendation was based on the quality of evidence (I, II or III), overall quality (good, fair, poor) and the net benefit of the intervention (A, B, C, D, or I) as defined in the guideline.[21] Where existing literature was ambiguous, conflicting or lacking, recommendations were based on the clinical experience of the working group. The guidelines were reviewed internally by medical experts working in the VA/DoD healthcare systems and it was stated that the guidelines were to be updated every two years. Recommendations are clearly presented in the text as well as according to an algorithm format. Each recommendation is also presented along with the source of the evidence, the rating of the quality of the evidence, overall quality and overall grade for the recommendation. Tools included as appendices are the Framingham 10-year CHD risk calculator, nutrition information, exercise and drug therapy information and a summary of supporting studies for pharmacologic therapy for primary and secondary prevention of CHD. Implementation of the guidelines, cost or key review criteria for monitoring or audit purposes were not discussed. Similarly, editorial independence or potential conflicts of interest were not mentioned; however, presumably the guideline was developed internally by staff of VA and the DoD.

Table 1: Guidelines and Recommendations on Cholesterol Testing to Identify Individuals at Risk of CHD

Title, Group, Year of Guideline Publication	Recommendations Identified in the Guideline
Preventative Services for Adults, Institute for Clinical Systems Improvement (ICSI), 2010[20]	A fasting cholesterol fractionation (TC, calculated LDL-C, HDL-C and TG) must be done for men over age 34 years and women over age 44 years every five years. • If patient is not fasting and probability of a return visit is low, consider checking TC and HDL-C. If available, also consider measuring direct LDL-C • Based on risk assessment, patients and providers should discuss the issues surrounding lipid screening with men between the ages of 20 and 34 years and women between the ages of 20 and 44 years. A specific example would be the need to screen those men ages 20-34 years and women ages 20-44 years with first degree relatives with TC > 300 mg/dL or history of premature CHD. • Individuals with TC < 200 mg/dL, LDL-C < 130 mg/dL, TG < 200 mg/dL, and HDL-C $\geq$ 40 mg/dL have a desirable cholesterol level and should be advised to repeat cholesterol testing in five years.

Table 1: Guidelines and Recommendations on Cholesterol Testing to Identify Individuals at Risk of CHD	
Title, Group, Year of Guideline Publication	**Recommendations Identified in the Guideline**
	• Individuals with TC ≥ 200 mg/dL, LDL-C ≥ 130 mg/dL, TG ≥ 200 mg/dL, and HDL-C < 40 mg/dL may be at higher risk of vascular disease, and should follow treatment recommendations as outlined in the ICSI Lipid Management in Adults guideline. Patients whose screening recommendations would be different include those who: • have histories of CHD, CVD, PVD, DM, metabolic syndrome or who are being case managed for dyslipidemia. Their disease management will involve a more aggressive approach to lipid monitoring; • have health status or life expectancy that would not be affected by knowledge of their lipid status (e.g., those with comorbid conditions such as terminal cancer); and • are in circumstances where cholesterol levels may not represent their usual levels. These situations include acute illness, hospitalization, unintended weight loss, pregnancy or lactation within the previous three months. Screening should be delayed under these circumstances.

Canadian Cardiovascular Society (CCS)/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult, CCS, 2009[6]	A screening of the fasting lipid profile should be performed in:
	• Men ≥40 years of age, and women ≥50 years of age or postmenopausal [IC]
	• All patients with the following conditions, regardless of age:
	  • Diabetes
	  • Hypertension
	  • Current cigarette smoking
	  • Obesity (Obesity Canada guidelines)
	  • Family history of premature CAD (<60 years in first-degree relatives)
	  • Inflammatory diseases (systemic lupus erythematosis, rheumatoid arthritis, psoriasis) although data are lacking
	  • Chronic renal diseases (eGFR <60 mL/min/1.73 m^2)
	  • Evidence of atherosclerosis
	  • HIV infection treated with highly active antiretroviral therapy
	  • Clinical manifestations of hyperlipidemias (xanthomas, xanthelasmas, premature arcus cornealis)
	  • Erectile dysfunction
	• Children with a family history of hypercholesterolemia or chylomicronemia

Screening and Management of Lipids Guideline for Clinical Care, University of Michigan Lipid Therapy	For primary prevention: • Screen men age 35 and older and age 20 to 35 if at increased risk for CHD. Screen women only if at increased risk for CHD. [IC] Repeat screening in 5 years in patients with normal lipids. [IID] Screening with fasting lipid profile is advised. If screened

Table 1: Guidelines and Recommendations on Cholesterol Testing to Identify Individuals at Risk of CHD	
Title, Group, Year of Guideline Publication	**Recommendations Identified in the Guideline**
Guideline Team, 2009[22]	non-fasting for patient convenience, follow-up on abnormal non-fasting lipids with a fasting lipid profile. For secondary prevention: • Screen with a full lipid panel all patients with CHD, other atherosclerotic CVD, DM or Framingham 10 year risk > 20%. [IA]
Cardiovascular Disease - Primary Prevention, British Columbia Guidelines and Protocols Advisory Committee, 2008[19]	Measure lipids under the following circumstances: • Baseline full lipid profile (TG, TC, HDL, LDL) for men ≥40 years, women ≥ 50 years and postmenopausal women of any age. Reassess only if major CVD risk factors change. • Full lipid profile if patient has hypertension, DM (type 1 or 2), CKD, or abdominal obesity, even if younger than 40 years. • Full lipid profile if patient has a family history of premature CHD (onset before age 55 years for men, and before age 65 years for women), hypercholesterolemia, or signs of hyperlipidemia (e.g., tendon xanthoma). • Consider apoB for follow-up testing in high-risk patients who are undergoing treatment for hypercholesterolemia (but not for other dyslipidemias). Other lipid tests are not required if using apoB for follow-up. ApoB is a more accurate measurement of atherogenic particles than LDL. Fasting is not required for apoB measurement.
US Preventive Services Task Force (USPSTF) Screening for Lipid Disorders in Adults, UPSTF, 2008[23]	Screening Men: • The USPSTF strongly recommends screening men aged 35 and older for lipid disorders [A] • The USPSTF recommends screening men aged 20 to 35 for lipid disorders if they are at increased risk for CHD [B] Screening Women at Increased Risk: • The USPSTF strongly recommends screening women aged 45 and older for lipid disorders if they are at increased risk for CHD [A] • The USPSTF recommends screening women 20 to 45 for lipid disorders if they are at increased risk for CHD [B] Screening Young Men and All Women Not at Increased Risk: • The USPSTF makes no recommendation for or against routine screening for lipid disorders in men aged 20 to 35, or in women aged 20 and older who are not at increased risk for CHD.
VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia, Department of Veterans Affairs (VA)	Recommendations for lipid screening: • Fasting lipid profile testing should be obtained in all men age 35 and older and women age 45 years or older every 5 years. [A] • Fasting lipid profile testing should be obtained in individuals with a family history or clinical evidence of familial hyperlipidemia. [A] • Fasting lipid profile testing in young adults may be considered

Table 1: Guidelines and Recommendations on Cholesterol Testing to Identify Individuals at Risk of CHD	
Title, Group, Year of Guideline Publication	**Recommendations Identified in the Guideline**
and Department of Defense (DoD), 2006[21]	depending upon the association with other risk factors. Younger adults (men younger than age 35 and women age 45 or younger) should be screened for lipid disorders if they have one or more of the following risk factors: family history of premature CVD, hypertension (or under treatment for HTN), or smoking. [B] • A lipid profile should be obtained for individuals with abdominal obesity (waist circumference >40 inches in men and >35 inches in women) to aid in assessment of metabolic syndrome. [B] • All persons with average or below average risk for atherosclerotic events should be screened for dyslipidemia every 5 years. [I] • Elderly patients age 75 or older should be screened if they have multiple CVD risk factors, or a history of CVD and good quality of life with no other major life-limiting diseases. [I] Screening schedules: For young adults (men <age 35; women <age 45): • Every 5 years when no CVD risk factors are present • More often, if family history of premature CVD exists (definite MI or sudden death before 55 years of age in father or other male first-degree relative or before age 65 in mother or other female first-degree relative) For middle-aged adults (men >age 35; women >age 45): • Every 5 years, when no CVD risk factors are present • Annually, if CVD risk factors exist (HTN, smoking, family history of premature CVD) For elderly patients up to age 75 years: • Every 5 years when no CVD risk factors are present • More often if CVD risk factors exist For elderly patients >age 75 years: • Evaluate if patient has multiple CVD risk factors, established CVD, or a history of revascularization procedures and good quality of life with no other major life-limiting diseases.

apoB=apolipoprotein B; CAD=coronary artery disease; CHD=coronary heart disease; CKD=chronic kidney disease; CVD=cardiovascular disease; DM=diabetes mellitus; eGFR=estimated glomerular filtration rate; HDL-C=high density lipoprotein; HIV=human immunodeficiency virus; HTN=hypertension; LDL=low density lipoprotein; MI=myocardial infarction; PVD=peripheral vascular disease; TC=total cholesterol; TG=triglycerides
Note: The levels of evidence or strength of the recommendation (i.e., denoted as I, II III, A, B, C D are individually defined in each respective guideline)

Limitations

No health technology assessments, systematic reviews, or meta-analyses were identified from the literature search. Only one cluster RCT[12] that investigated the clinical effectiveness of POC

testing and conventional laboratory pathology testing for cholesterol was identified. The comparison of clinical effectiveness was based on a non-inferiority analysis of the proportion of patients with test results (TC, TG and HDL-C) in the target range. The study may have been limited by not measuring the actual length of time that patients spent in the therapeutic range, as this potentially may have produced a different result. The study found the POC method to be non-inferior to laboratory testing for TC and TG, but not for HDL-C, which may be due to the non-inferiority margin of -7% being too conservative for HDL-C. The study also did not investigate the comparison of POC and laboratory testing with regard to LDL-C levels, which are generally what intervention and treatment decisions to mitigate risk of CHD are based upon.[5,6]

The majority of evidence identified that directly compared POC and conventional laboratory testing of cholesterol levels is derived from non-randomized studies. These studies either report the degree of agreement or correlation of the testing methods in producing results from the same samples or by a comparison of validation parameters. None of the non-randomized studies included any clinical outcomes so it is not possible to evaluate the clinical effectiveness of the two testing methods based on these studies. Four of the studies[13-15,18] investigated one device (i.e., Cholestech LDX® System) whereas the other two studies,[16,17] evaluated POC devices that do not appear to be available in North America. As a result, the generalizability of these results is somewhat limited as different POC devices may perform differently. All studies, with the exception of one[13] evaluated POC cholesterol testing for the primary prevention of CHD in asymptomatic individuals. There is no information regarding the clinical effectiveness of POC testing compared with laboratory testing of cholesterol for diagnosing individuals at high risk of CHD, testing in non-compliant patients, or for monitoring response to therapy over the long-term. Lastly, there was no follow-up testing in any of the studies to confirm a CHD diagnoses, the occurrence or avoidance of cardiac events, or measurement of clinical outcomes of any kind.

The retrieval of evidence-based guidelines for cholesterol testing was limited only to North American guidelines, therefore, it is possible that guidelines from other jurisdictions may have provided additional information. The included guidelines were assessed using the AGREE instrument,[11] and for the most part, the guidelines clearly identified scope, purpose, target populations, and stakeholder involvement. Recommendations were clearly presented; however, the key recommendations were not always identified. Most guidelines were developed using rigourous processes, although in some it was unclear if a systematic review had been done and what process was followed for formulating recommendations. The methodology used to grade the level of evidence or the strength of recommendations was not always clear and not always indicated with the recommendation. Approximately half of the guidelines included application tools, whereas the rest did not. Only one guideline[20] included a section on implementation and measurement strategies to assess the impact of guideline uptake. Editorial independence was not always clearly described; however, most guidelines included conflict of interest disclosures.

The timeframe for the literature search for this report encompassed only the last five years and retrieval was limited to English language documents only. As a result, there may be literature published prior to this time or in other languages that was not included.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Based on the evidence reviewed for this report, POC cholesterol testing appears to be suited for screening purposes in asymptomatic adults. There is insufficient evidence to support that POC

cholesterol testing can replace conventional laboratory testing for diagnosis of CHD, monitoring response to therapy, or that it will result in overall comparable clinical effectiveness.

The highest level of evidence identified to support use of POC cholesterol testing was derived from one cluster RCT, [12] in which POC testing was found to be non-inferior to conventional laboratory testing for measurement of TC and TG, but not for HDL-C. As a result, this trial does not support that a full lipid panel conducted via POC testing is comparable to that obtained via laboratory testing. The majority of evidence identified in this report was derived from non-randomized studies, none of which included clinical outcomes, therefore precluding the ability to evaluate the comparable clinical effectiveness of POC and conventional laboratory testing. There is insufficient evidence to support that POC testing can replace laboratory testing for diagnostic purposes, as none of the studies included follow-up to confirm a CHD diagnosis or the avoidance or occurrence of cardiac events. There is also a lack of information on the use of POC cholesterol testing to monitor response to therapy over the long-term or to assist with screening or monitoring in non-compliant or high-risk patients.

In general, the evidence-based guidelines reviewed for this report are in agreement that there is good evidence that high levels of TC and LDL-C and low levels of HDL-C are important risk factors for CHD and that there are clear benefits to screening for dyslipidemia as early detection and intervention can substantially impact on the risk of CHD. None of the guidelines specifically included POC testing for cholesterol in their recommendations. Only one guideline[20] included a section on implementation recommendations, resources, and measurement specifications to use in assessing the impact of the guideline recommendations.

Considerations for implementation of a POC cholesterol testing service include the choice of equipment, training and on-going competence of staff, development of standard operating procedures (SOPs) for proper conduct of tests, analyzer maintenance, quality assessment, record keeping, and health and safety precautions.[2,25] The role of the conventional pathology laboratory in relation to POC testing should be clearly defined to avoid fragmentation of services, define roles and responsibilities, encourage liaison activities and to ensure that laboratory services are available for quality assurance and back-up.[2] Most importantly, the results of POC testing should be reviewed by appropriately qualified staff and treatment decisions made by qualified health care professionals with knowledge of an individual's medical history and previous results.[2,25]

POC cholesterol testing for screening of asymptomatic adults offers several potential advantages over conventional laboratory testing. These include improved patient access, immediate results and no requirement for a physician or laboratory visit, which may be important considerations for individuals with limited access to these services such as those residing in an institutionalized or confined setting.

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APPENDIX

Appendix 1: Additional information

Guideline (did not formally review the literature evidence for the recommendation)

2011 CHEP recommendations for the management of hypertension [Internet]. Markham: Hypertension Canada; 2011 [cited 2011 Apr 25].
Available from: http://hypertension.ca/chep/wp-content/uploads/2011/05/FullCHEPRecommendations_EN_2011.pdf

Appendix 2: Details of Non-Randomized Trials Comparing POC Testing and Laboratory Testing for Measurement of Lipid Parameters

Study, Year, Country	Patient Population/ Parameters Measured	Intervention and Comparator	Outcomes	Key Findings	Conclusions
Jain et al., 2011,[14] United Kingdom	South Asian subjects attending a NHS screening program in the UK (n=406); 53% male; median age 50 years (range 30-74) Parameters: TC, HDL-C, TG, LDL-C (calculated) ; finger prick and venous blood samples	POC testing with the Cholestech LDX® analyzer (POC) or hospital reference laboratory (LAB).	Agreement of POC and LAB using Bland-Altman plots; CVD risk categorization by 4 web-based calculators (JBS2, QRISK2, ETHRISK and Framingham) were compared using kappa statistics where agreement of κ>0.75 excellent, 0.4 to 0.75 fair to good and <0.4 poor	Overall agreement of POC and LAB were good although concentration-dependent biases at lower concentrations were found (e.g. for HDL-C < 1.0 mmol/L POC underestimated values by 0.2 mmol/L; p<0.0001) Excellent agreement of calculated CVD risk for JBS2 κ=0.86, QRISK2 κ=0.92, ETHRISK κ=0.94 and Framingham κ=0.88	POC testing for initial screening of CVD risk factors is appropriate. Cost-effectiveness needs to be assessed. When used appropriately POC testing can improve patient management and optimize screening services.
Parikh et al., 2009,[15] United	Subjects of mixed ethnicity (64% Caucasian)	POC testing with the Cholestech	Degree of correlation of POC and	Significant correlations between POC	POC screening is accurate and

Study, Year, Country	Patient Population/ Parameters Measured	Intervention and Comparator	Outcomes	Key Findings	Conclusions
States	randomized to a screening/educational arm of a CVD primary prevention trial (n=250); 44% male; mean age 48.0±13.5 years) Parameters: TC, HDL-C, TG, hsCRP and LDL-C (calculated); finger stick and venous blood samples	LDX® analyzer (POC) or hospital reference laboratory (LAB).	LAB by Pearson correlation coefficient and classification of patients as having abnormal lipids or hsCRP results by kappa statistics where agreement of κ>0.75 excellent, 0.4 to 0.75 fair to good and <0.4 poor	and LAB testing: TC (r=0.91), TG (r=0.93), HDL-C (r=0.77), LDL-C (r=0.88); all p<0.01. Categorical agreement of abnormal results was: TC κ=0.75, TG κ=0.78, LDL-C κ=0.69, HDL-C κ=0.40 and hsCRP κ=0.58 Sensitivity and specificity of POC to identify those with abnormal lipids or hsCRP $\geq$ 1 mg/mL all $\geq$75%	has good clinical utility to identify persons with abnormal lipids and hsCRP at the POC in a diverse patient population eligible for primary prevention of CVD.
Rapi et al., 2009,[16] Italy	Outpatients referred for diagnostic evaluation (n=636); age 22-69 years; no additional patient characteristic information provided Parameters: TC and TG; venous blood samples and a subset (n=66) of capillary blood samples for practicability testing	POC testing with the MultiCare device (POC) or central laboratory analysis (LAB)	Intra-assay imprecision, accuracy, practicability, sensitivity and specificity of POC vs. LAB Regressions of method comparisons by method of Passing and Bablock and method differences by Bland-Altman plots.	Intra-assay imprecision for TC: 4.51% (range 2.38% to 8.54%) and TG: 3.29% (range 1.06% to 7.45%). Practicability testing between professionals and non-professionals was NS. Sensitivity and specificity were 95.7% and 61.9% for TC	Characteristics of sensitivity, specificity and diagnostic accuracy make POC testing useful for obtaining an accurate stratification of a study population.

Study, Year, Country	Patient Population/ Parameters Measured	Intervention and Comparator	Outcomes	Key Findings	Conclusions
				(threshold 190 mg/dL) and 98% and 93.5% for TG (threshold 170 mg/dL).	
Sblendorio and Palmieri, 2008,[17] Italy	Unselected adults screened who previously had a lipid panel requested (n=375); no patient characteristic information provided Parameters: TC, HDL-C and TG; venous blood sampling only	POC testing with the CR3000 system (POC) or hospital clinical laboratory (LAB)	Bias between POC and LAB, Pearson coefficient correlation, differences assessed by ANOVA and linear regression analysis	Significant correlations between POC and LAB for TC (r=0.98), HDL-C (r=0.92) and TG (r=0.98). Overall mean bias was TG (0.5%), HDL-C (-1.6%) and TG (1.0%)	CR3000 lipid panel data correlate well with those from reference laboratory, is reliable and has high quality performance.
Shemesh et al., 2006,[18] Australia	Population screening of indigenous Australians living in remote areas; 76 blood samples were provided for lipid testing, no patient characteristics provided. Parameters: TC, HDL-C and TG; venous blood samples	POC testing with the Cholestech LDX® (POC) or central laboratory analysis.	Bland-Altman analysis was used to assess agreement between POC and LAB and kappa statistics used to assess chance-corrected agreement between results; κ>0.75 considered excellent agreement	Comparisons of mean difference in median results for TG, HDL-C and TG between POC and LAB were all NS. Agreement by kappa statistics was TC κ=0.67, TG κ=0.86, and HDL-C κ=0.73; all p<0.001	POC instruments provide a reliable alternative to conventional laboratory methods for screening for chronic disease factors in locations remote from urban centres.
Carey et al., 2006,[13] Ireland	Caucasian subjects with CHD or hypertension and hospital staff volunteers (n=100) at an Irish hospital; 30% male; mean age 46±13 years	POC testing with the Cholestech LDX® analyzer (POC) or hospital reference	Degree of correlation of POC and LAB by Spearman rank correlation; absolute	Significant correlations between POC and LAB testing: TC (r=0.92), TG (r=0.93), HDL-C (r=0.92) and	Results validate the Cholestech LDX® analyzer for POC lipid measurement in clinical

Study, Year, Country	Patient Population/ Parameters Measured	Intervention and Comparator	Outcomes	Key Findings	Conclusions
	Parameters: TC, HDL-C, TG and LDL-C (calculated); finger prick and venous blood samples	laboratory (LAB).	differences compared by paired t-tests	LDL-C (r=0.86); all p<0.0001 Absolute differences between POC and LAB: TC (NS), TG (POC 0.25 mmol/L higher than LAB; p<0.001) and HDL-C POC 0.11 mmol/L lower than LAB; p<0.001); unlikely to be clinically significant	practice provided by well-trained operators and supported by a hospital laboratory delivering quality assurance support.

CHD=coronary heart disease; CVD=cardiovascular disease; HDL-C=high density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; JBS=Joint British Societies; κ=kappa coefficient; LAB=laboratory; LDL-C=low density lipoprotein cholesterol; NHS=National Health Service; NS=not statistically significant; POC=point of care; r=correlation coefficient; TC=total cholesterol; TG=triglyceride