Toward Optimized Practice

PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE RISK IN PRIMARY CARE

Clinical Practice Guideline | February 2015

OBJECTIVE

Alberta primary care clinicians and their teams offer primary and secondary prevention for cardiovascular disease (CVD) focused on CVD risk estimation and lipid management.

TARGET POPULATION

Men aged 40-75

Women aged 50-75 (optional start at age 40 for simplicity)

EXCLUSIONS

Men and women of any age with previously diagnosed familial hypercholesterolemia

RECOMMENDATIONS

- ✓ Screen for CVD risk beginning at age 40 for men and 50 for women.

> **PRACTICE POINT**
>
> *Always use a risk calculator with every lipid measurement to assess CVD risk.*

- X Fasting for lipid tests is NOT required.
- ✓ Calculate a baseline CVD risk using the principles of shared, informed decision-making.
- ✓ Advise patients a statin can be expected to lower that risk by 25-35%.

> **PRACTICE POINT**
>
> *Starting and keeping a patient on any type of statin will have the greatest benefit.*

- X DO NOT target specific lipid levels.
- X DO NOT repeat lipid level testing for a patient on a statin.
- ✓ Recommend lifestyle changes for all patients.
- ✓ Consider acetylsalicylic acid (ASA) only after statin therapy in high-risk individuals with a low risk of bleeding.

For detailed recommendations see the Screening and Management sections and the Lipid Algorithm in Appendix A.

SCREENING

- ✓ Screen patients without cardiovascular disease (primary prevention).
    - Perform global CVD risk estimation with every lipid test.

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- ✓ Consider screening at earlier age for patients who have known traditional cardiovascular risk factor(s) including, but not limited to, hypertension, family history of premature CVD, diabetes, and smoking.
- ✓ Repeat screening for patients not on lipid lowering therapy.
    - Lipid testing is part of a global CVD risk estimation performed no more than every five years.
- ✓ Repeat screening sooner if other CV risk factors develop in the interim.

> **PRACTICE POINT**
>
> *Patients do not need to fast prior to lipid testing.*
> *Non-fasting lipid levels can be used to calculate global cardiovascular risk.*

Risk Estimation

- ✓ Use any CVD risk calculator, e.g., Framingham, every time lipid testing is performed.
- ✓ Perform lipid testing and risk estimation for men between age 40 and 75, and women age 50 to 75 (optional start both at age 40 if simplicity preferred).
    - Estimate risk at earlier age if indicated by other risk factors.
    - Use the same approach to estimate risk for patients with diabetes mellitus.
- ✓ Use a CVD risk calculator that includes chronic kidney disease (CKD) in its estimation of risk (e.g., QRISK-2) for patients with CKD.
- X DO NOT estimate risk on patients:
    - With pre-existing CVD (they are classified high-risk)
    - Less than 40 years of age without identified risk and those over 75 years of age
    - On lipid therapy

      Note: If risk calculation is performed for patients on lipid therapy, pre-treatment lipid levels should be used and risk adjusted for known benefit of statin/ASA therapy.
- X DO NOT use biomarkers as part of the risk assessment until further research is available.

Management

Interventions

- ✓ Discuss lifestyle interventions with all patients (including but not limited to smoking cessation, exercise and for Mediterranean diet refer to: https://myhealth.alberta.ca/health/healthy-living/pages/conditions.aspx?hwid=aa98646&aa98646-sec).
- ✓ Discuss the risks and benefits of moderate or high intensity statins with primary prevention patients based on an individual's risk of CVD.

- For patients with a 10-year CVD risk of <10% re-test lipids in five years with risk estimation.
- For patients with a 10-year risk of 10-19% discuss and offer statins (preferably moderate intensity).
- For patients with a 10-year CVD risk of ≥ 20% discuss and strongly encourage statins (preferably high intensity).

✓ Discuss the risks and benefits in order to strongly encourage high intensity statin therapy with secondary prevention patients.

✓ Offer low intensity statin therapy for patients that are elderly (based on frailty as much as age) or those patients with renal impairment.

✓ Provide the patient with Reducing Your Risk of Heart Attack and Stroke – an information pamphlet summarizing key messages they need to know.

X DO NOT routinely test lipids, estimate CVD risk, and prescribe statins for primary prevention in patents > age 75.

- Consider offering statins if life expectancy and overall health is good.
- Discuss the risks and benefits of moderate potency statins for secondary prevention.

✓ DO NOT discontinue or reduce a patient's statin just because the patient has aged beyond 75.

X DO NOT consider pravastatin as a first-line intervention for patients aged ≥65 until the uncertainty of cancer in this sub-group related to this drug is resolved.

✓ Offer patients intolerant of a specific statin regimen a lower intensity regimen with the same or a different statin, and/or a short drug holiday followed by a re-challenge to help clarify if statins are related to the intolerance.

- Any statin intensity is preferred to non-statin lipid-lowering therapy.
- Consider prescribing alternate daily dosing if the patient is not tolerating daily dosing.

X DO NOT use retrial in severe reactions like rhabdomyolysis.

X DO NOT use non-statin lipid lowering drugs in primary prevention as a first-line monotherapy or in combination with statins.

✓ Consider and discuss ezetimibe in secondary prevention with patients as an add-on therapy to statins.

- Maximize statin therapy first (to high intensity) due to the higher relative benefit.

LIPID LEVELS AND FOLLOW-UP

X DO NOT use cholesterol targets for reducing CVD.

X DO NOT monitor/repeat lipid levels after a patient begins statin therapy.

✓ Reinforce patient adherence to statins.

X DO NOT routinely test for baseline CK or alanine transaminase (ALT) in healthy individuals prior to starting statin therapy.

✓ Reserve routine monitoring of CK and ALT for symptomatic patients or those at higher risk of adverse events.

ASA IN PRIMARY PREVENTION

X DO NOT prescribe ASA for patients without previous CVD and an estimated 10-year CVD risk <20%.

✓ Offer ASA for primary prevention in patients with a 10-year CVD risk ≥ 20% and bleeding risk is considered low.

✓ Consider ASA for primary CVD prevention after statin therapy has been discussed.

✓ Inform patients offered ASA of the potential benefits and harms of ASA use.

BACKGROUND

INTRODUCTION

The purpose of this guideline is to provide a simplified approach to primary prevention of cardiovascular disease (CVD) risk, concentrating on CVD risk estimation and lipid management for primary care clinicians and their teams. All recommendations are based on the best evidence available. These recommendations should be considered with other factors when making decisions about therapy including, but are not limited to, patient preference, comorbidities, potential adverse effects, drug interactions, and cost. Patient preference and shared, informed, decision making should guide all patient care decisions.

There is considerable controversy regarding the management of dyslipidemia, and whether or not using cholesterol targets is evidence-based. Because best available evidence was used to develop these recommendations and the focus is on use in primary care, there are differences from other Canadian guidelines on the same topic, and more aligned with the 2013 American guideline.[1-3] Clinicians are encouraged to discuss their approach to CVD risk management with their patients, allowing the patient to decide what is best for him/herself.

Genetic hypercholesterolemia should be considered in patients with markedly elevated lipids despite appropriate lifestyle changes (e.g., low density lipoprotein (LDL) >5mmol/L). This guideline does not apply to patients meeting the diagnostic criteria for familial hypercholesterolemia (which includes LDL level, physical findings, and family/personal history of CVD).[4] In addition, treating hypertension is important when managing CVD risk, however, blood pressure management is beyond the scope of this guideline.

SCREENING/TESTING

WHAT IS SCREENING?

In this guideline context, screening refers to lipid testing accompanied by an overall CVD risk assessment. Using only one risk factor (such as lipids) to target therapy will not identify many patients at higher risk. Without a risk assessment tool (e.g., the Framingham risk calculator) clinicians and patients will estimate risk less accurately resulting in starting treatment when it is not warranted or failing to start treatment for individuals at higher risk. Therefore, it is recommended that a CVD risk assessment with a risk calculator be performed with every lipid measurement.

WHEN TO START SCREENING?

Mass population-based screening and interventions (including annual physicals or periodic health assessments) for cardiac risk factors in patients without CVD do not appear to reduce CVD or all-cause mortality.[5] However, this evidence is limited; many studies pre-date statin therapy and/or use lifestyle counseling as the only intervention.

CVD is most strongly associated with advancing age and traditional CVD risk factors.[5] Patients with one CVD risk factor are more likely to have another CVD risk factor.[5] Additional evidence is needed to determine which ethnicities and non-cardiac chronic medical conditions (such as chronic autoimmune inflammatory conditions like rheumatoid arthritis) are truly independently associated with elevated CVD risk.

With respect to age of increasing CVD risk, starting screening for men at age 40 and women at age 50 is suggested as a prudent approach. Although there is debate regarding screening all patients at age 40, most women would not typically be at CVD risk at this age and the recommendation to screen would then not follow the best available evidence. Screening may be considered at earlier ages for patients with known risk factors like hypertension or diabetes.

HOW OFTEN SHOULD REPEAT LIPID LEVELS/CVD SCREENING BE CONDUCTED FOR PATIENTS NOT ON THERAPY?

For patients not on lipid lowering therapy, there is substantial short-term variability and minimal long-term change in lipid levels.[5] Frequent lipid testing is likely to reflect the short-term variability and is unlikely to meaningfully alter global CV risk assessment.[5] Because lipid levels change minimally over the long term and constitute only one variable in determining global CVD risk assessment, the same lipid profile remains relevant for many years.[5] There is no need to frequently repeat the lipid profile to update risk estimation in untreated patients. Therefore, for those not on statin therapy, screening (repeat lipid levels and risk assessment) is not required more often than every five years. Because lipid levels change minimally over the long term and constitute only one variable in determining global CVD risk assessment, it is possible to use the initial lipid profile for future CVD risk estimation and therefore no need to periodically repeat the lipid profile over time in order to update risk estimation in untreated patients.[5] Regardless, for those not on statin therapy, screening (repeat lipid levels and risk assessment) is not required more often than every five years.

Do Patients Need to Fast to Have Their Cholesterol Checked?

Minimal differences exist between fasting and non-fasting high density lipoprotein (HDL), LDL, and total cholesterol.[5] The differences that occur are less than the "within person variability" from repeat lipid testing.[5] Tests of non-fasting HDL and non-HDL levels correlate with future CVD events.[5] Although triglycerides are most susceptible to change without fasting, triglycerides contribute minimally to total cholesterol levels and triglyceride levels are not consistently associated with CVD.[5] Removing the fasting restriction should improve test uptake adherence and reduce potential patient harm (e.g., hypoglycemia in diabetic patients).[5] However, physicians should be aware that some labs in Alberta may not offer "non-fasting lipid profile" as an option at this time (but most do).

Risk Assessments

Why Estimate Risks?

Overall risk, not lipid level, is the best predictor of benefit from statins.[6] Estimating risk without a risk assessment tool (like Framingham) is challenging; both patients and clinicians frequently err in their estimation.[7] An over-reliance on lipids and lack of appreciated risk may contribute to why many high risk patients go without treatment.[7] Additionally, estimation of risk promotes shared-informed decision-making, allowing a discussion with patients about their baseline risk and, as a result, the potential absolute benefit of taking a statin. Low potency statins reduce baseline estimated CVD risk by about 25% and at high potency by about 35%.[5] As an example, a patient with 20% 10-year risk of CVD, would have his/her risk reduced by 5% with low potency (25% of 20) or 7% with high potency (35% of 20).

Risk calculators are not without limitations. For example, in paired comparisons risk calculators disagree about risk level (high, moderate, or low) approximately 33% of the time.[8] That said, risk calculation is the most reliable way to estimate patients' CVD risk and potential benefit from a statin/ASA.[7] Although Framingham could over-estimate risk somewhat, it presents risks of combined CVD outcomes and some research validates its use in the Canadian population.[5] To account for the issues associated with risk overestimation using Framingham, the traditional risk cut-offs of 10% and 20% are used instead of the US guideline cut-off of 7.5% (using a different calculator).[2]

See Table 1 for examples of calculators. The list is not meant to be all encompassing or to encourage use of one over another.

CVD Risk Calculator	Description
The University of Edinburgh Cardiovascular Risk Calculator: http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp	Three different databases to compare calculated risk, different display options (some will show statin risk reduction)
Best Science Medicine: http://chd.bestsciencemedicine.com/calc2.html#basic	Three different databases to compare risks, including Framingham and QRISK2, shows potential benefit of different therapies
QRISK2-2014: http://www.qrisk.org/	Includes chronic kidney disease in risk estimation

Table 1: Examples of Cardiovascular Risk Calculators

Diabetes and Chronic Kidney Disease

Patients with diabetes or chronic kidney disease (CKD) are at increased risk of CVD, although the risk is not equivalent to the risk in patients with coronary heart disease (see Appendix B). The Framingham calculator can include diabetes in its calculation of risk. For patients with CKD, a risk calculator that includes CKD in the risk equation is recommended (e.g., QRISK2).

Some clinicians may choose to prescribe statins to all patients with diabetes or chronic kidney disease. In most cases, and individual's risk may be above 10%. However, without risk estimation it will be difficult to allow patients to make an informed choice given they are unaware of their absolute risk and the potential benefits of statin therapy.

Biomarkers

A number of risk factors and biomarkers are significantly associated with CVD. For simplicity, these will be collectively referred to as "biomarkers." Interpreting the research is challenged by multiple limitations. For any biomarker to have utility in risk estimation it should add meaningfully to established risk assessment tools (e.g., Framingham).

Presently only one biomarker (coronary artery calcium) appears to offer a potentially meaningful improvement in all measures of performance when added to Framingham Risk Scores.[5] However, this biomarker requires further validation, safety assessment, and cost- effective analyses.[5] Commonly promoted biomarkers (like lipoproteins and CRP) have a substantial body of evidence demonstrating that they do not add meaningfully to risk prediction.[5] There is currently no high level evidence to support testing and monitoring of any biomarker in the management of CVD risk.

When is Risk Estimation Unnecessary?

Secondary Prevention

For patients with known CVD (such as a history of myocardial infarction or stroke), risk assessment is not appropriate. These patients have risks greater than 20% and are good candidates for statins, particularly at high dose/intensity.[9-11] Patients with previous CVD should be prescribed and strongly encouraged to take the highest approved dose/intensity statin they can tolerate.[5]

YOUNGER AND OLDER AGES

For primary prevention (those without previous CVD), risk assessment tools like Framingham and ASSIGN include patients age 35 to 75 while ASCVD includes patients up to 79. The evidence suggests screening (testing lipids and risk assessment) should likely begin at age 40 for men and age 50 for women (or earlier if risks are identified). However, it may be reasonable to start screening (testing lipids and risk assessment) women early for simplification, thus an age 40 start for all. Acknowledging reduced screening intervals, the increase testing and risk assessment would be no more than two more episodes. However, either approach (starting women at 40 or 50) would be reasonable. Given the uncertainty surrounding primary prevention treatment of the elderly and limits in risk assessment after age 75, risk assessment should stop at age 75.

PATIENTS TAKING LIPID MEDICATION

Once patients are on lipid medications, risk assessment is inaccurate. Some medicines modify lipid levels with little or no effect on cardiovascular risk; this may cloud global risk estimation. In the case of statins, the most reliable risk estimation would be to use the untreated lipid levels for risk estimation and then reduce risk by 25 to 35% based on statin dose/potency.

MANAGEMENT

INTERVENTIONS

LIFESTYLE

Lifestyle (non-drug) interventions are considered the cornerstone of therapy and should be initiated first-line to reduce CVD and improve health. Although a full review of all lifestyle interventions is not provided, the following three lifestyle interventions should be recommended for all patients.

SMOKING CESSATION

Evidence shows that concerted smoking cessation efforts reduce mortality and other outcomes[12-14] and some studies show benefits far exceeding that seen with pharmaceutical intervention.[14]

EXERCISE

Exercise in high-risk individuals results in CVD and mortality reductions similar to or better than reductions seen in trials for most pharmaceuticals.[15-16] Consistent recommendations are for at least 150 minutes weekly (or 30-60 minutes four to seven times a week) of moderate or high intensity exercise (moderate intensity includes brisk walking).[1,17,18]

MEDITERRANEAN DIET

Three clinical trials demonstrate reduction in CVD, with a relative reduction in primary prevention similar to that seen with statins.[19-21]

STATINS

Statins are the only class of lipid lowering therapy where evidence exists for reducing all-cause mortality (relative risk reduction about 10%) and CV events (about 25%).[5] Statins are therefore

recommended as the first-line treatment for all patients when pharmaceutical intervention is warranted.

Risk estimation should stop beyond age 75 because the evidence regarding starting statin therapy for primary prevention is very limited beyond age 75; and there is no evidence for patients in their 80s.[5] The evidence for statins (moderate intensity) in secondary prevention is stronger so statins should be considered regardless of age in secondary prevention.[5] Because of the uncertainty regarding possible cancer risk associated with pravastatin use in patients aged 65 and older, another statin should be considered for patients in this age group.[5] However, there is no evidence of cancer risk for other statins used by patients 65 and older, or for pravastatin in patients under the age of 65.[5] Lastly, for elderly individuals already taking and tolerating statins, there is no need to stop statin therapy just because of the patient's advancing age.

How Should Statins be Dosed?

There is no evidence to recommend adjusting doses to achieve specific LDL targets as only fixed doses are tested in trials.[5] Patients at equivalent levels of risk will have the same benefit regardless of pretreatment LDL levels. There is evidence for secondary prevention that higher doses or higher potency statins reduce CVD more than lower doses or lower potency statins.[5] Therefore, recommended dosing should be based on *intensity* (representing both potency in the type of statin and dose) of statin therapy (see Table 2).

Intensity	Statin Options
Low Intensity	Pravastatin 10-20mg; Lovastatin 10-20mg; Simvastatin 5-10mg; Atorvastatin 5mg; Rosuvastatin 2.5mg
Moderate Intensity	Pravastatin 40-80mg; Lovastatin 40-80mg; Simvastatin 20-40mg; Atorvastatin 10-20mg; Rosuvastatin 5-10mg
High Intensity	Atorvastatin 40-80mg; Rosuvastatin 20-40mg

Table 2: Statin Dosing Ranges and Intensity
Adapted from 2013 ACC/AHA guideline[2]

The evidence suggests use of moderate or high intensity statin therapy for all patients.

The additional benefit of high intensity statin therapy, relative to low or moderate intensity, in secondary prevention is about 10% (i.e. relative risk reduction increases to 35% from 25%); this decrease is mostly due to a decrease in non-fatal myocardial infarction and stroke.[5] No trials were found comparing statin doses for primary prevention.

What Should I do if a Statin is Not Tolerated?

The incidence of adverse events, including myalgias and elevation in transaminases, will increase with increasing statin dosing. See the Follow-Up section for more information on harms from statin use. Side effects can lead to discontinuing statin therapy, and must be addressed. About 70% of patients with an adverse reaction to a statin will be able to tolerate an alternate regimen.[5] The benefit of taking any type of statin is greater than the benefit of taking a high versus low dose statin. Therefore, starting and keeping the patient on a statin is most important.

NON-STATINS

Non-statins include fibrates, niacin, ezetimibe, and bile acid binding resins. There is evidence that fibrates alone reduce non-fatal myocardial infarction but considerably less overall CVD reduction than statins and no mortality benefit.[5] Added to statins, fibrates have no benefit.[5] One old trial involving niacin suggested some benefit but studies following the introduction of statins have failed to show a benefit with niacin added to a statin.[5] Fibrates, niacin, and bile acid resins generally have a higher incidence of adverse effects compared to statins.[5]

Ezetimibe is well tolerated but has no demonstrated effect on mortality or CVD in primary prevention.[5] The IMPROVE-IT trial, in which ezetimibe 10mg was added to simvastatin 40mg compared to simvastatin 40mg alone, demonstrated a 6% relative reduction in CVD events.[22] In secondary prevention, ezetimibe may be a reasonable option after statin therapy, but the benefit of low intensity statins far exceeds the benefit of ezetimibe, and the benefit from increasing to a high intensity statin is almost double that compared with adding ezetimibe to a statin. If the relative benefits could be extrapolated to primary prevention, the absolute benefits would be only about 1% over 10 years for high-risk patients and less in moderate risk. For this reason, ezetimibe cannot be advocated in primary prevention. Lastly, it is important to note that the relative benefit from ezetimibe did not differ between high and low baseline LDL, further supporting that basing treatment decisions on LDL level is inappropriate.

FOLLOW-UP

WHAT LIPID LEVEL SHOULD I TARGET FOR MY PATIENTS?

Traditionally, clinical practice guidelines have recommended the use of lipid targets for different cardiovascular risk groups (e.g., LDL < 2mmol/L, 50% reduction in LDL etc.).[5] However, evidence is lacking for the use of particular targets to guide titration of statin therapy. RCTs showing a benefit in CVD outcomes with statin use, have compared fixed-dose statin therapy to placebo, or high-versus low-dose statin therapy.[5] No RCT data exists to show a significant benefit between particular lipid targets and CVD outcomes.[5]

WHEN SHOULD I REPEAT LIPID LEVELS AFTER STARTING A STATIN?

The lack of evidence for titrating statin therapy to particular lipid targets raises the question: do lipid levels need to be monitored after a statin is initiated? Currently, there is no evidence of benefit to repeating lipid level measurement after initiation of statin therapy.[5] While some argue that repeating lipid levels is helpful to assess patient adherence to statin therapy, there is no evidence that repeating lipid levels will increase adherence.[5] However, there is some evidence that statin adherence is improved through patient reinforcement and reminding (e.g., phone calls, pharmacist medication reviews, medication calendars).[5]

Patients on statins may (or probably will) have their risk increase as they age and/or develop new risk factors. Unfortunately ordering lipid panels on patients taking lipid modifying agents and using these new panels in CVD risk calculators will give inaccurate estimations of risk. Clinicians should use the pre-treatment lipid levels, as they generally change little over time, with new risk factors. The

overall risk can be adapted to reflect the lipid therapy by reducing the risk by the anticipated relative reduction from statin therapy (25-35% based on intensity of therapy).

Some controversy remains around lipid targets and testing on therapy. For example:

1. The Canadian Cardiovascular Society recommend targeting lipids and repeat lipid testing.[23]
2. The American College of Cardiology recommends against lipid targets but advises repeating lipids after initiating statins (justification appears to be compliance monitoring).[2]
3. US Veterans Affairs recommends against both targeting lipids and repeat lipid testing after initiating statin (as with this guideline).[24]

Until the evidence base improves, it is unlikely we will have improved clarity or agreement.

What are the Major Harms of Statins?

Harms associated with statins include muscle and liver injury, and elevation of blood glucose levels. Common adverse effects associated with statin use include myalgias, but serious adverse effects such as rhabdomyolysis and liver failure are exceedingly rare (Table 3).[5] Increases in creatine kinase (CK) and liver enzymes in asymptomatic patients can occur, and many of these enzyme elevations will return to baseline with continued statin use.[5] In fact, a trial with a sub-group analysis of patients with elevated liver test levels (assumed primarily non-alcoholic fatty liver disease) revealed that patients randomized to statins were more likely to have decreased liver test levels while the placebo group was more likely to show an increase.[25] Confounding factors, including patient comorbidities and other medications, may increase the chance of muscle and liver damage.[5]

	Elevated ALT (>3x ULN)		Liver Failure		CK Elevation (>10x ULN)		Myalgia (muscle pain, tenderness, weakness)		Myopathy (muscle pain, tenderness, weakness severe enough to stop pills; CK not always specified)		Rhabdomyolysis (poorly defined, except for CK> 10x ULN)	
	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo
Incidence per 100,000	300	200	~0.5	-	83	60	5150	4960	97	92	4.4	2.8
Difference (95% CI)	100 (64-140)				23 (-4.50)		190 (-38-410)		5 (-17-27)		1.6 92-2.4-5.5)	

Table 3: Incidence Rates per 100,000 Person Years for Muscle and Liver Related Adverse Effects with Statins.[5]

There is no RCT data to support routine monitoring of CK and alanine transaminase (ALT) in patients on statin therapy.[5] RCTs have shown that rates of elevated ALT/CK are similar between placebo and treatment groups.[5] There is cohort data showing that even if ALT is elevated at baseline, this does

not correlate with an increased likelihood of severe elevations in liver enzymes.[5] Routine monitoring of ALT/CK has the potential to do harm to patients if statins are stopped unnecessarily.

Low potency statin use increases the risk of developing type II diabetes, by approximately one in 250 over five years.[7,26] High potency (over low potency) may increase the risk a further one in 125 over five years.[7,26] To keep this in context, approximately one patient will be diagnosed with diabetes for every two to 15 patients avoiding CVD or death

ASA IN PRIMARY PREVENTION

ASA use for primary CV prevention decreases the risk of CVD but at the expense of increased risk of bleeding, without altering all-cause or CVD mortality. The relative reduction in vascular events with ASA is approximately 12%. This is about half the benefit observed when low-dose statins are used for primary CV prevention.[5] The risk of gastrointestinal bleeds increases with ASA use by about 0.5 to 4% over 10 years, with lower risk in younger women and higher risk in older men.[5] Unfortunately, patients at increased risk of future CVD are often also at increased risk of bleeding.[5] Compared to statins, ASA has less relative benefit and higher risk of serious adverse events, and therefore ASA should be considered for primary CVD prevention only after statin therapy.

Based on the best available evidence, patients whose 10-year CVD risk is equal to or greater than 20%, may have a small net benefit derived from ASA use so it may be reasonable to consider ASA therapy for these patients. For example, in 1000 men at age 65 with a 20% chance of CVD over 10 years, ASA use would result in 64 fewer myocardial infarctions, but one additional hemorrhagic stroke, and 24 major gastrointestinal bleeds. In net terms, this equates to about 40 fewer CVD events than major bleeds.

Patients must be made aware of these potential benefits and harms, and for the majority of patients without CVD who are at relatively low risk of a future CVD, the benefits of ASA use are offset or outweighed by the potential harms.

CONCLUSION

This guideline is based on the highest quality evidence available. By removing lipid targets and associated monitoring of lipid levels, as well as other streamlining measures, the management of lipids and CVD risk has been significantly simplified. Additionally, by targeting risk clinicians can identify patients most likely to benefit while actively involving these patients in their care.

REFERENCES

1. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GB, McPherson R, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2013 Feb;29(2):151-67.
2. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S46-8.
3. Tobe SW, Stone JA, Brouweres M, Bhattacharyya O, Walker KM, Dawes M, et al. Harmonization of guidelines for the prevention and treatment of cardiovascular disease: the C-CHANGE initiative. CMAJ. 2011;183(15):E1135-50.
4. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011 Jul;32(14):1769-818.
5. Lindblad AJ, Kolber MR, Garrison S, Cotton C, Allan GM. Prvention and management of cardiovascular disease risk in primary care: evidence review of 12 key clinical questions. Supplement. Edmonton, AB: Toward Optimized Practice; 2015.
6. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581-90.
7. Allan GM, Garrison S, McCormack J. Comparison of cardiovascular disease risk calculators. Curr Opin Lipidol. 2014; 25:254-65.
8. Allan GM, Nouri F, Korownyk C, Kolber MR, Vandermeer B, McCormack J. Agreement among cardiovascular risk calculators. Circulation. 2013;127(19):1948- 56.
9. Kerr AJ, Broad J, Wells S, Riddell T, Jackson R. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease? Heart. 2009;95:125-9.
10. Wilt TJ, Bloomfield HE, MacDonald R, Nelson D, Rutks I, Ho M, et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med. 2004;164:1427-36.
11. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ. 2008;178:576-84.
12. Moreno-Palanco MA, Ibáñez-Sanz P, Ciria-de Pablo C, Pizarro-Portillo A, Rodríguez- Salvanés F, Suárez-Fernández C. Impact of comprehensive and intensive treatment of risk factors concerning cardiovascular mortality in secondary prevention: MIRVAS Study. Rev Esp Cardiol. 2011;64:179-85.
13. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142:233-9.

14. Mohiuddin SM, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. Chest. 2007;131:446-52.

15. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD001800.

16. Hambrecht R, Walther C, Möbius-Winkler S, Gielen S, Linke A, Conradi K, et al. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. Circulation. 2004;109:1371-8.

17. Eckel R, Jakicic J, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC Guideline on lifestyle management to reduce cardiovascular risk. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2960-84.

18. Hackam DG, Quinn RR, Ravani P, Rabi DM, Dasgupta K, Daskalopoulou SS, et al. The 2013 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2013;29(5):528-42.

19. de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet. 1994;343:1454-59.

20. Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet. 2002;360:1455-61.

21. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279-90.

22. Braunwald E, Califf R, Cannon C, Giugliano R, McCagg A, Pelland, C, et al. Improved reduction of outcomes: Vytorin efficacy international trial. American Heart Association, Slide Posting. http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469669.pdf Accessed Nov 29, 2014.

23. Anderson et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Nov 2016 Canadian Journal of Cardiology.32: 11 pp 1263–1282

24. Downs J, O'Malley P. Management of dyslipidemia for cardiovascular disease risk reduction: synopsis of the 2014 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. Ann Intern Med. 2015;163(4):291-7.

25. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010;376:1916-22.

26. Turgeon R, Allan GM. Statin-induced diabetes: too sweet a deal? Can Fam Physician. 2013;59:e311.

27. de Vries FM, Denig P, Pouwels KB, Postma MJ, Hak E. Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta- analysis. Drugs. 2012;72(18):2365-73.

28. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-81.

29. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011; 79(12):1341-52.

30. Mafham M, Emberson J, Landray MJ, Wen C-P, Baigent C. (2011) Estimated glomerular filtration rate and the risk of major vascular events and all-cause mortality: A meta-analysis. PLoS ONE. 6(10): e25920.

31. Baigent C, Landray M, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet.

32. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2014 May 31; 5:CF007784.

33. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013; 3: 259-305.

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Guideline Committee

The committee consisted of representatives of family medicine, internal medicine, nurse practitioners, registered nurses and pharmacy.

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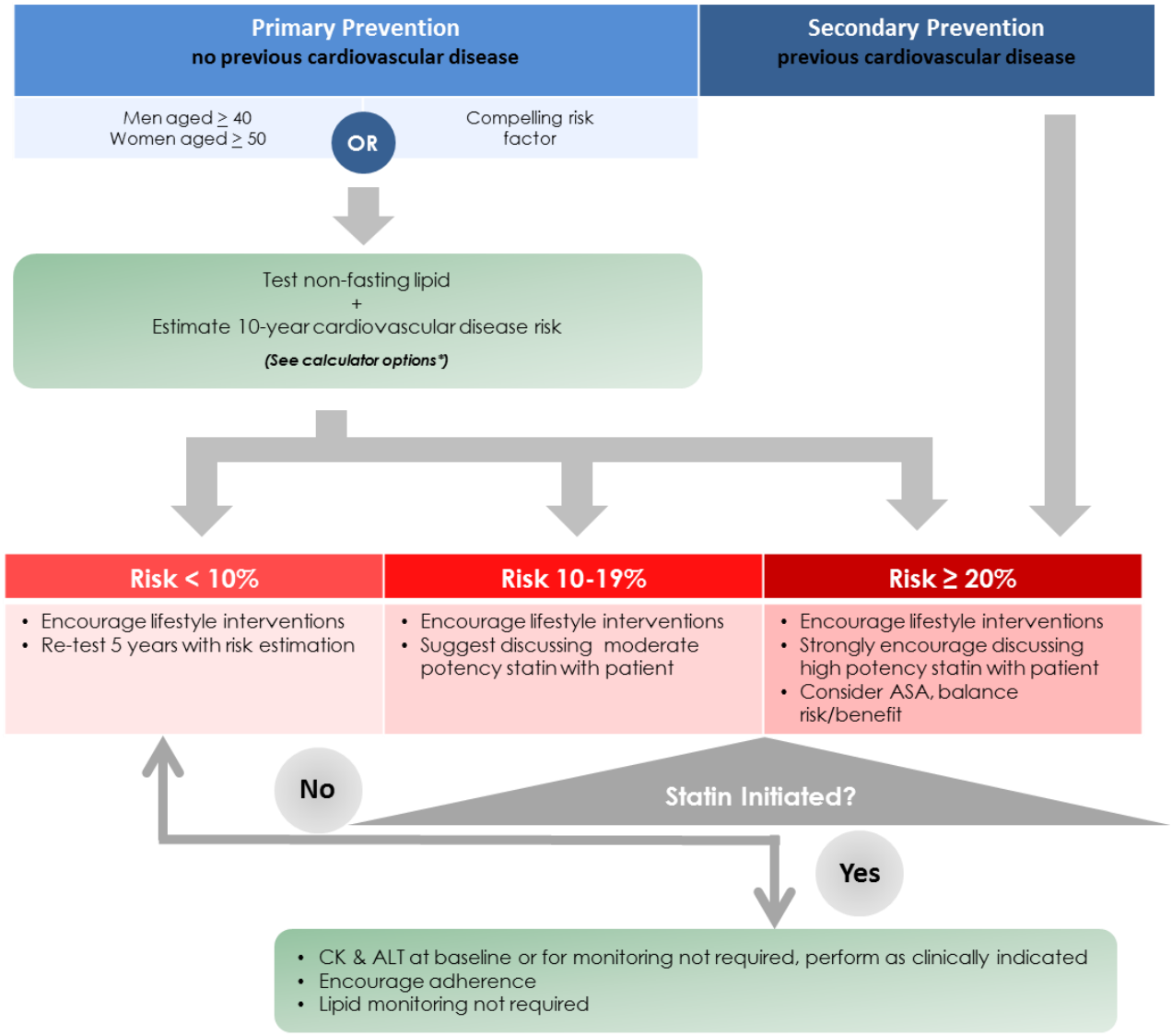
APPENDIX A

LIPID ALGORITHM

(Excludes those with familial hypercholesterolemia)



If intolerant to high or moderate potency statin, offer moderate or low potency statin, respectively.
All steps require clinical judgement and are dependent on patient preference.

*Risk Calculator Options:
The University of Edinburgh Cardiovascular Risk Calculator: http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp
Best Science Medicine: http://chd.bestsciencemedicine.com/calc2html#basic
QRISK2 2014: http://www.qrisk.org/ (for chronic kidney disease patients)

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Clinicians may initiate lipid testing and risk estimation before age 40 if high clinical suspicion exists (i.e., compelling risk factors such as family history, hypertension, diabetes, or smoking). Regardless, testing before 35 is not recommended for the vast majority of patients and risk estimation tools do not include patients younger than 35. Primary prevention screening beyond age 75 is generally not recommended.

Risk can be calculated using a number of risk calculators but each clinician should use the same one consistently. The Framingham calculator has been validated in a Canadian population and is likely preferred. The following calculator (based on Framingham) has been created for this guideline: http://chd.bestsciencemedicine.com/calc2html#basic

Lifestyle interventions include: smoking cessation, exercise, and the Mediterranean diet.

Exercise: ≥150 minutes in ≥4 sessions of moderate (brisk walking) to vigorous exercise/week.

Statin Dosing Ranges and Intensity:

Intensity	Statin Options
Low Intensity	Pravastatin 10-20mg; Lovastatin 10-20mg; Simvastatin 5-10mg; Atorvastatin 5mg; Rosuvastatin 2.5mg
Moderate Intensity	Pravastatin 40-80mg; Lovastatin 40-80mg; Simvastatin 20-40mg; Atorvastatin 10-20mg; Rosuvastatin 5-10mg
High Intensity	Atorvastatin 40-80mg; Rosuvastatin 20-40mg

Adapted from 2013 ACC/AHA guideline[2]

Benefits of Therapies:

Therapy		Estimating Benefit (relative risk reduction)	Example if baseline risk estimated at 20% over 10 years		
			Absolute Risk Reduction	Number Needed to Treat (NNT)	New Risk Estimate
Smoking Cessation		Recalculate without smoking	9%†	12†	11%†
Mediterranean Diet		30%	6%	17	14%
Exercise		30%	6%	17	14%
Statin Intensity	Low	25%	5%	20	15%
	Moderate	30%	6%	17	14%
	High	35%	7%	15	13%
ASA		12%	2%	50	18%

†Example used a 53 year old male smoker with total cholesterol 5, HDL 1.2 and systolic BP 128, estimated risk from Framingham (from http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp and http://chd.bestsciencemedicine.com/calc2html#basic) to attain a 20% risk over 10 years.

APPENDIX B

DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE

Some guidelines recommend that patients with diabetes age 40 to 75 be given statins rather than estimating risk and treating them based on risk.[2] This recommendation leads to the question: "should every diabetic at age 40 be encouraged to take statins regardless of their risk?" Two systematic reviews and meta-analyses examined the benefits of statins in diabetics.[6,27] Both had very similar patient characteristics, with a mean age of approximately 62 years, two thirds male, about 18% smokers, mean systolic BP about 148mmHg, mean total cholesterol about 5.5 mmol/L, and mean HDL about 1.2 mmol/L. The Cholesterol Treatment Trialists report the mean age of patients with type 2 diabetes to be 63.8 years with a standard deviation of 8.4 years.[6]

Therefore, these trials, specifically addressing type 2 diabetic patients, enrolled those aged 40 and over, but the mean age in the trials was actually much higher. As a result, the assumption that a 40-year-old diabetic without other risk factors will benefit from statin therapy may not be valid because few such patients were studied in these clinical trials. In fact, the calculated mean 10 year CVD risk of patients in these studies (using a Framingham risk calculator) was 34.8% or 38.5%.[6,27] Thus, these patients were at much higher risk than a 40 year old diabetic without other risk factors. Additionally, cohort data shows CVD risk from diabetes is not equivalent to the risk in patients with coronary heart disease.[26] Risk estimation remains the best way to identify patients for consideration of pharmacotherapy. Framingham-based risk calculators include diabetes in their calculation of risk. Therefore, instead of being started on immediate statin therapy, patients with diabetes equal to or greater than 40 years old should first undergo global risk assessment to determine the need for statin treatment.

Pooled cohort evidence suggests that patients with chronic kidney disease are at increased risk of CVD, with relative risk increases varying from 31% to 166% depending on the definition/severity of kidney disease.[28-30] The SHARP RCT including primary prevention chronic kidney disease (mean GFR 27 ml/min/1.73m2) given simvastatin and ezetimibe demonstrated a 17% reduction in CVD (Rate Ratio 0.83 (CI 0.74-0.94)).[31] In pooled RCT data (13 RCTs, 36,033 patients) of chronic kidney disease patients not on dialysis, statins reduced CVD 28% (Risk Ratio 0.72 (0.66-0.79)).[32]

As a result of this evidence, chronic kidney disease guidelines advocate treating most non-dialysis patients with statin therapy.[33] Mean data on patients in the pooled studies are not available but in SHARP the mean age was 62, 63% male, systolic blood pressure 139, total cholesterol 4.89 and HDL 1.12, giving a Framingham-based risk estimate, without CKD, >20% over 10 years. It is not clear if low risk patients will get the same advantage (those with CVD risk <10%). Therefore, it is recommended that risk assessment be conducted in these patients, preferably with a risk calculator including chronic kidney disease in the risk equation (e.g., QRISK2).