Lipids in Primary Prevention:

A Calculated Risk

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"Seek simplicity, and mistrust it."
Alfred North Whitehead

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Definitions and Abbreviations

ACR	Albumin creatinine ratio
AR	Absolute risk
ARI	Absolute risk increase
ARR	Absolute risk reduction
CDA	Canadian Diabetes Association
CHD	Coronary heart disease
CCS	Canadian Cardiovascular Society
CIMT	Carotid intima media thickness. The change in thickness of the intima and media of the carotid artery. This outcome has often been used as a surrogate for cardiovascular events although the validity is now being questioned.
CK	Creatine kinase
CVD	Cardiovascular disease
FRS	Framingham risk score
HDL	High density cholesterol
HR	Hazard ratio
hsCRP	High sensitivity C-reactive protein
LDL	Low density cholesterol
MI	Myocardial infarction
NNT	Number needed to treat
PAD	Peripheral arterial disease
RR	Relative risk
RRI	Relative risk increase
RRR	Relative risk reduction
TC	Total cholesterol
TIA	Transient ischemic attack
TRIGL	Triglycerides
ULN	Upper limit of normal

Acronyms of selected studies

JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
PROSPER	PROspective Study of Pravastatin in the Elderly at Risk

SUMMARY STATEMENTS

Question 1: How have the Framingham risk scores changed and what are the consequences? Page 13

- Before 2009, the Framingham risk scores recommended in the Canadian guideline referred to the 10-year risk of a patient experiencing a **non-fatal MI** or **CHD death**.
- The Framingham risk scores now recommended in the Canadian guideline refer to risk of developing many more manifestations of cardiovascular disease such as angina, MI, TIA, stroke, revascularization, or peripheral artery disease.
- The result of changing from CHD to CVD is that many more people have moved into the intermediate and high risk categories.
- The risk categories have not changed i.e., low risk is <10%, intermediate risk is 10% to 19%, high risk is ≥ 20%.
    - The Canadian guideline states that the categories "are completely arbitrary and have been chosen by consensus rather than by scientific evidence. Accordingly, clinical judgement is essential."
- The recent guidelines recommend that among patients 30-59 years of age without diabetes, the risk should be adjusted (percent risk doubled) when family history of premature CVD is positive (i.e., first-degree relative < 55 years for men and < 65 years of age for women).
    - One content expert suggests taking into consideration the risk factor burden in the first degree relative (i.e. smoking, metabolic syndrome, sedentary lifestyle) when deciding to modify a patient's risk based on family history.

Question 2: What are the secondary tests and alternate targets in assessing and decreasing risk of developing CVD? Page 12

- According to the 2012 Canadian guideline
    - The alternate targets are apo B and non-HDL which are considered to have high predictive value for CV risk.
    - New **optional** secondary testing is also suggested for patients found to be at intermediate risk but without significant dyslipidemia. Tests included are lipoprotein (a), hsCRP, hemoglobin A1c, and albumin to creatinine ratio (ACR).
        - However, the guidelines do not recommend multiple tests in an individual patient.
    - Clinicians should minimize the number of additional tests and use only those most appropriate based on the individual's risk profile and local availability and expertise. When using more than 1 secondary test the estimated increase in risk is **not** incremental.
- A summary of systematic reviews conducted for the US Preventive Services Task Force concluded that current evidence does not support the **routine** use of several novel risk factors for further risk stratification of intermediate-risk patients.

Question 3: What is the evidence for LDL targets in primary prevention? Page 21

- For intermediate and high risk patients, the LDL targets are ≤ 2 mmol/L or ≥ 50% decrease in LDL.
- The Canadian guideline comments that targets for treatment are
  - Somewhat arbitrary because none of the intervention studies have aimed for specific lipid targets, and
  - Extrapolated from individual trial data and meta-analyses.
- Other guidelines state that treatment for lipid lowering "should **aim towards** these targets rather than consider them definitive" or "would not recommend the use of target levels of cholesterol for people at high risk of CVD".
- One content expert suggests that, for consistency with secondary prevention, efforts should be made to strive to achieve the targets in primary prevention.

Question 4: What is the evidence for using ezetimibe in combination with statins? Page 23

- Ezetimibe lowers LDL which in turn increases the proportion of patients reaching target lipid levels. However, there is currently no conclusive evidence that it reduces cardiovascular events or mortality, either alone or with statins.
  - One pending trial, IMPROVE-IT, is comparing simvastatin monotherapy to a simvastatin/ezetimibe combination for the prevention of cardiovascular events. Primary completion of data collection is expected by June 2013.
- ENHANCE is the only RCT that compared a high dose of statin (simvastatin 80 mg) alone to the same dose plus ezetimibe 10 mg in patients with familial hypercholesterolemia. After two years there was **no significant difference** in changes in the thickness of carotid media between the two treatments.
- One study, SHARP, found a benefit from simvastatin plus ezetimibe in reduction of coronary events in patients with chronic kidney disease. However this was compared to **placebo**, not statin alone.
- The Canadian guideline states "No studies to date have demonstrated a decrease in CVD event rate with the addition of lipid modulating drugs to statin therapy".

Question 5: What is the evidence for lipid lowering for primary prevention in select populations? Page 26

Women

- Statins might provide some benefit in reducing CVD events in women. However there are limitations in published evidence.
- Because women may have a lower baseline risk of CVD than men at comparable ages, their absolute benefit may be lower and the NNTs will be higher.

Elderly

- The Framingham Risk Score calculations are based on studies that included subjects between 30 and 74 years old. If used in patients over 74 years old, results should be interpreted with caution.
  - The Canadian guideline states "Though clinical studies are currently under way to address this group, at this point clinical judgment is required in consultation with the patient to determine the value of pharmacotherapy."
- In the elderly (≥ 65 years old) there is no conclusive evidence of a statistically significant decrease in mortality in primary prevention.
- There is uncertainty in the evidence for efficacy of statins **in primary prevention** of CVD events in the elderly.
- The elderly are reported to be more prone to adverse effects. In primary prevention, consider a trial of discontinuation of statin therapy if there is concern about myalgias, cognitive impairment, or drug interactions from polypharmacy.

Statin use in severe frailty

- This consensus approach is intended to apply to patients who are **≥ 7 on the Clinical Frailty Scale**. It is also applicable to most older adults living in long term care facilities, who are typically severely frail, e.g. completely dependent for personal care.
- We found no studies reporting the effect of lipid lowering in the **severe frail** elderly in primary or secondary prevention. Therefore we examined studies in the **non-frail** elderly to determine if they reported outcomes that were meaningful and could be applied to the **frail** elderly.
- Meaningful outcomes for the frail elderly might be different from other patients. Prolonging life might not be a goal of therapy so mortality might not be a meaningful outcome. Symptomatic non-fatal MI and non-fatal stroke leading to disability are more likely to be meaningful outcomes since they affect quality of life.
- Primary Prevention: It is unlikely that statins provide benefit in applicable outcomes and so there is no reason to prescribe or continue statins for primary prevention.
- Secondary prevention: Statin treatment in severe frailty is probably not necessary, although there may be extenuating individualized circumstances that shift the risk/benefit ratio.
- Heart failure: There is evidence that statins are ineffective in improving clinical outcomes in the elderly and there is no reason to start or continue them for this indication.
- Statin dosing: If statins are to be used, use lower doses.

Question 6: How clinically significant are the adverse effects of statins? Page 42

- **Myopathy** is one of the main adverse effects that limits compliance with statin therapy.
- In real world clinical pratice myalgias can affect up to 29% of persons prescribed statins.
- Several options are reported for managing the symptoms of myopathy; however most are not supported by high levels of evidence.
  - Switch to a statin with hydrophilic (rosuvastatin, pravastatin) rather than lipophilic characteristics or lower potency (fluvastatin) which may result in a lower risk of myopathy.
  - Non-daily doses of statin. Atorvastatin and rosuvastatin have long half-lives and may be suited to alternate day, or up to once weekly dosing.
- Significant **liver** pathology attributable to statins is rare.
- Statins may increase the risk of developing **diabetes** by about 9% (OR 1.09, 95% CI 1.02 to 1.17; NNH 255, 95% CI 150 to 852 for 4 years)
  - Intensive doses are more likely than moderate doses to increase risk of developing diabetes.
- Some patients on statins may complain of **memory loss** or **cognitive impairment**.

Introduction

- This topic is an update of our 2005 session on Statins and Cardiovascular disease with a focus on **primary prevention**. Since then there have been several developments such as
  - New risk assessment tools e.g. Framingham Risk Score (FRS) for cardiovascular disease (CVD)
  - New optional tests for further risk assessment e.g. hsCRP, A1c, ACR
  - Lower LDL targets
  - Alternate targets for treatment of dyslipidemia e.g. non-HDL cholesterol
  - Outcome studies for potent statins which decrease LDL to a greater extent than previous agents e.g. rosuvastatin
  - Studies which show no benefit from lipid lowering
  - Lack of evidence for using LDL-lowering drugs (e.g. ezetimibe) in combination with statins
- The overall effect of changes is to recommend more aggressive therapy for more people, particularly those without existing CVD (primary prevention), which has led to some controversy.
- One objective of this topic is to discuss the extent to which these changes increase the number of people on treatment and the **absolute** benefits and harms that patients may experience.
  - We are addressing lipid lowering only in **primary** prevention. The benefit in secondary prevention is well established in the populations that have been studied.
- In preparing this topic we have reviewed
  - Primary publications
  - Review articles and meta-analyses
  - Cochrane reviews
  - Guidelines from Canada and other countries (Australia, Europe, United States, New Zealand, United Kingdom).

- **We will use a case-based approach and address the following questions:**
  1. How have the Framingham risk scores changed and what are the consequences?
  2. What are the recommendations for secondary tests and alternate targets in assessing and decreasing risk of developing CVD?
  3. What is the evidence for LDL targets in primary prevention?
  4. What is the evidence for using ezetimibe in combination with statins?
  5. What is the evidence for lipid lowering in select populations (women, elderly, frail elderly)?
- We have also included information on adverse effects of statins and appendices which highlight statin characteristics and costs, as well as evidence tables of relevant clinical trials.

Canadian Guidelines

- The 2012 Canadian Cardiovascular Society (CCS) Dyslipidemia Guideline Update [1] has the following **new** features:
  - Introduction of the concept of Cardiovascular Age determination
  - Recommending more frequent monitoring of patients with FRS > 5% and < 10%
  - Using either apo B or non-HDL-C as alternate lipid targets
  - Recommendation for secondary testing in selected patients
  - Addition of chronic kidney disease definitions and treatment
  - Lower age for treatment in diabetes
  - More implicit recommendations for health behavior change
  - New recommendation about statin adverse effects and a statin intolerance approach
  - Use of GRADE recommendations and process for categorizing evidence.
- There is reduced prominence for hsCRP. It is now an optional secondary test whereas in 2009, it was a factor to consider along with LDL and TC/HDL ratio in determining who should be treated in the moderate risk group.
- There is a recommendation for patients whose plasma lipid profile should be screened (italics indicate changes from 2009 guidelines)
  - Men ≥ 40 years old, and women ≥ 50 years old or postmenopausal
  - All patients, regardless of age with any of the following conditions
    - Diabetes
    - Arterial hypertension
    - Current cigarette smoking
    - Obesity (*metabolic syndrome, pre-diabetes, polycystic ovarian syndrome, BMI > 27*)
    - Family history *of premature CVD* in first-degree relative *(< 55 years in men and < 65 in women)*
    - Inflammatory diseases
    - Moderate renal function impairment (eGFR ≤60ml/min/1.73 m^2) or urinary albumin:creatinine ratio ≥ 3 mg/mmol (micro-albuminuria)
    - Evidence of atherosclerosis
    - HIV infection
    - Clinical manifestations of hyperlipidemias (xanthomas, xanthelasmas, premature arcus cornealis)
    - Erectile dysfunction
    - Family history of hyperlipidemia
    - *Chronic obstructive pulmonary disease*
    - *Abdominal aneurysm*
- The Canadian guideline states that people of South Asian and First Nation's ancestry have increased risk and consideration should be given to screening at an earlier age. [1]

- High risk is defined as those subjects who have
  - Adjusted Framingham Risk Score of ≥ 20% (adjusted indicates adjustment for family history)
  - Clinical coronary, cerebrovascular, or peripheral vascular disease
  - Diabetes >15 years duration and age ≥30 years or microvascular complications
  - Diabetes and age ≥40 years
  - Abdominal aortic aneurysm
  - Chronic kidney disease (eGFR ≤ 45 or ACR ≥ 30, or eGFR ≤ 60 and ACR ≥ 3)
  - High risk hypertension (hypertension + 3 risk factors)
- The guidelines suggest that **all patients** be encouraged to adopt **healthy lifestyle interventions**.[1]
- Table 1 lists treatment target recommendations for various levels of risk.

Table 1 Summary of 2012 CCS treatment target guidelines[1]

Risk level	Initiate therapy if	Primary target LDL	Alternate target
High (FRS ≥ 20%)	Consider treatment in all Lifestyle plus pharmacotherapy *Strong, High*	≤ 2 mmol/L or ≥ 50% decrease in LDL *Strong, High*	Apo B ≤ 0.8 g/L Non-HDL ≤ 2.6 mmol/L *Strong, High*
Intermediate (FRS 10-19%)	LDL ≥ 3.5 mmol/L Consider drug therapy if LDL ≥ 3.5 after a trial of lifestyle modification *Strong, Moderate* For LDL < 3.5 consider if - Apo B ≥ 1.2 g/L or - Non-HDL ≥ 4.3 mmol/L *Strong, Moderate*	≤ 2 mmol/L or ≥ 50% decrease in LDL *Strong, Moderate*	Apo B ≤ 0.8 mg/L Non-HDL ≤ 2.6 mmol/L *Strong, Moderate*
Low[a] (FRS < 10%)	LDL ≥ 5.0 mmol/L Familial hypercholesterolemia *Strong, Moderate*	≥ 50% reduction in LDL *Strong, Moderate*	

CCS, Canadian Cardiovascular Society; FRS, Framingham risk score;
Strong = strong recommendation
High = high level of evidence, Moderate = moderate level of evidence
a For those in the 6-9% group, consider yearly calculation of FRS and discussion about risk-benefit ratio of pharmacotherapy at lower levels of LDL

Alternate targets and secondary testing

- The 2012 Canadian guideline[1] indicates that other indicators for therapy and **alternate targets** are apo B and non-HDL and states
  - They are considered to have high predictive value for CV risk.
  - Apo B may not be a funded laboratory test.
  - Non-HDL is easily calculated (TC minus HDL) and incurs no additional cost.
- The Emerging Risk Factors Collaboration[76] conducted a study which aimed to determine whether additional lipid-related markers improved CV risk prediction. The study concluded:
  - None of the following measures were superior to total cholesterol and HDL when they replaced traditional cholesterol measurements in risk prediction scores:
    - Total cholesterol: HDL ratio
    - Non–HDL
    - Linear combination of apolipoprotein B and A-I
    - Apolipoprotein B:A-I ratio.
  - **Replacement** of total cholesterol and HDL with apolipoprotein B and A-I significantly worsened risk discrimination.
  - The value of **adding** information on emerging lipid related markers to risk scores, already containing total cholesterol, HDL, and other conventional risk factors resulted in **slight** potential for improvement in CVD prediction.
  - None of the additional markers significantly improved reclassification of participants beyond what is currently used to inform treatment decisions.
  - The authors conclude the clinical benefits of using any of these biomarkers remains to be established.
- The 2012 Canadian Guideline suggests **optional** secondary testing for patients found to be at intermediate risk but without significant dyslipidemia.[1] Included are
  - Biomarkers - lipoprotein(a), hsCRP, hemoglobin A1c and albumin to creatinine ratio (ACR)
  - Imaging – exercise stress test, carotid imaging, ankle-brachial index and coronary artery calcium
  - However, the guidelines do not recommend multiple tests in an individual patient.
    - Clinicians should minimize the number of additional tests and only use those most appropriate based on the individual's risk profile and local availability and expertise. When using more than 1 secondary test the estimated increase in risk is **not** incremental.
- According to a recent summary of systematic reviews conducted for the U.S. Preventive Services Task Force,[77]current evidence does not support the routine use of several novel risk factors for further risk stratification of intermediate-risk patients.
  - Included in the review were lipoprotein(a), hsCRP, fasting blood glucose, coronary artery calcium, homocysteine level, leucocyte count, periodontal disease, ankle-brachial index and carotid intima-media thickness.

Case Step 1 Patient characteristics

John Hayward consults you about a painful shoulder, the result of some overzealous yard work over the weekend. He attends your office infrequently and you wonder if you should take advantage of this visit to screen for cardiovascular disease.

Age	51
Height	178 cm
Weight	92 kg
BMI	29
Cigarettes	Lifelong non-smoker
BP	140/90 not taking antihypertensives

The 2012 Guidelines recommend a screening lipid profile on men ≥ 40 years old and those with a BMI > 27.[1]

Results of a lipid profile are:

TC	6.1 mmol/L
HDL	1.0 mmol/L
LDL	3.2 mmol/L
TRIGL	2.6 mmol/L

His HbA1c is 5.4%

He has no kidney dysfunction and no family history of premature CVD.

Estimating Cardiovascular Risk

- When you get the results of his lipid profile you want to estimate his risk of having a cardiovascular event. There are several options, for example
  - The 2012 Canadian Guideline recommends that initial risk assessment be completed using the FRS to estimate the 10-year risk of developing total CVD [1,2] using risk score tables or an online calculator www.circl.ubc.ca/cardiorisk-calculator.html
  - Other online calculators are at
    - http://www.ccsguidelineprograms.ca/index.php?option=com_content&view=article&id=98&Itemid=68
      - Offers smart phone apps for download and useful tools for communicating risk to patients.
    - http://cvrisk.mvm.ed.ac.uk/calculator/calc.asp
      - This site is convenient because it includes both FRS CVD and CHD risk calculators, along with others developed in the UK. It also has tools for communicating risk to patients based on a meta-analysis of 22 statin trials.[3]
    - http://www.framinghamheartstudy.org/risk/index.html
      - Includes risk calculators for various CVD conditions such as CHD, stroke, MI, and PAD.

- http://www.cvdcheck.org.au/
  - Australian calculator which estimates 5-year CV risk
- http://www.chiprehab.com/
  - Designed for patient use and suggested in 2012 Canadian guideline to calculate CV age particularly in younger patients where 10-year FRS may underestimate long-term risk.

- Previous versions of risk calculators considered hard outcomes such as non-fatal MI and CHD death. The outcomes have now been expanded to include many more manifestations of CVD (coronary death, MI, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, TIA, PAD, revascularization, and heart failure.)

- Although the new risk assessment tool includes all CVD, the cut points for categories of **10-year risk** remain the same at the following Framingham Risk Scores[1]
  - High risk ≥ 20%
  - Intermediate risk 10-19%
  - Low risk < 10%

    - The Canadian guideline states that the categories "are completely arbitrary and have been chosen by consensus rather than by scientific evidence. Accordingly, clinical judgement is essential."

- Not all risk assessment models use the same categories. For instance the 2012 Australian model uses categories based on **5-year risk**. [4]
  - High risk > 15%
  - Moderate risk 10-15%
  - Low risk < 10%

- The result of including extra outcomes in calculating risk is that more patients will be included in the moderate and high risk categories and therefore eligible for interventions including lipid-modifying therapies and additional screening tests. A recent US study[5] estimated
  - 63% of men and 74% of women will increase at least one risk category.
  - The low risk population drops from 52% to 16%.
  - The high-risk population increases from 4% to 20%.
  - Of subjects changing risk categories, 30% will now fail to meet their new lipid goals.
  - In patients reclassified to a higher risk category and not meeting the new lipid goals approximately 80% are not currently on lipid lowering therapy.

- A Canadian study on the effect of the change in the FRS calculator also reported increases in the number of patients moving from the low and moderate risk categories to high risk leading to a 2.3-fold increase in the need for lipid-lowering treatment.[65]

- There are limitations to the risk assessment calculators:
  - Most do not calculate risk for patients >75 years old and may not be accurate in patients younger than 30 or older than 65. [6]
  - They do not predict risk well for all ethnic groups such as Japanese-American men, native-American women, or Hispanic men. [6]
  - Different calculators give different estimates of cardiovascular risk and predict different outcomes.[6]
  - We did not find articles validating the CVD calculators for Canadians. One cannot assume that a calculator developed in one country or population applies to another unless it is validated.
  - According to the guidelines[1], there are no randomized trials showing optimal outcomes based on FRS for guiding therapy. In addition, no risk equation is perfect.
- LDL has **not** been found to **improve** prediction of CVD when included in Framingham risk scores,[2] which is why it does not appear in any of the risk calculators.

Case Step 2 Calculating Risk

Being a curious person you want to see if there is any difference in the risk estimates from the different calculators. Here are the estimates of 10-year risk you calculate

Framingham paper-based version	15.6%
Edinburgh online version of Framingham CVD risk	16.8%

You note that in the Framingham paper-based version points assigned are based on categories of the risk factors. For example a patient with a total cholesterol of 5.3 will get the same number of points as a patient with a total cholesterol of 6.2. Also, a patient with TC of 6.2 can be assigned 2 or 3 points.

You decide to see how much difference there is between the paper-based version and the online version at the extremes of the risk factor categories used to calculate risk for your patient.

Age	TC	HDL	SBP	Paper-based risk score	Online risk score
50	5.3	1.1	140	15.6%	13%
54	6.1	0.9	149	15.6%	24%

You realize the online calculators in which you enter exact numbers for risk factors base their estimates on the actual Framingham equations and decide this provides a more individualized estimate of risk.

In accordance with the Canadian guideline you advise him of the importance of following a healthy lifestyle including proper diet, weight loss, and regular physical activity.

Decision-making for patients at intermediate risk

- Mr Hayward is at intermediate risk of having a CV event within the next 10 years.
- For people at intermediate risk the 2012 guideline recommends[1]
  - **Starting** treatment if LDL is ≥ 3.5 mmol/L. (Strong recommendation, Moderate evidence)
  - **Considering** treatment if LDL < 3.5 mmol/L if the **optional** test of Apo B is ≥ 1.2 g/L or non-HDL ≥ 4.3 mmol/L (Strong recommendation, Moderate evidence)
  - In both cases, the guideline emphasizes the need for health behavior modification.
- According to the 2012 guidelines Mr Hayward is not a candidate for pharmacotherapy based on his LDL (3.2 mmol/L) but might be based on his non-HDL (5.1 mmol/L).
  - You are uncertain about starting statin therapy based on his non-HDL cholesterol since this is considered an alternate target and the clinical benefit from its use remains to be established.[76]
  - The 2012 guidelines suggest that in intermediate risk patients with LDL < 3.5 mmol/L, if apo B or non-HDL levels are above suggested targets, these patients may be at increased risk and **considered** for pharmacotherapy.
  - However the guideline also states that "Pervasive pharmacologic therapy for intermediate risk patients with LDL <3.5 mmol/L is not routinely recommended because of the smaller estimated absolute benefit of therapy."
- The Australian Guideline states the benefits of lipid-lowering therapy depend on initial levels of risk: **absolute** reductions in risk are **highest** in people at the **highest** baseline risk irrespective of initial lipid levels.
  - The decision to treat people at **moderate** levels of risk with lipid-lowering pharmacotherapy is more complex and can be determined by responsiveness to lifestyle interventions, taking into consideration other risk factors not included in the Framingham risk equations.[4]
- Before deciding to start a statin you would like to have some idea of the **absolute** benefit he might expect.

Relative and Absolute Benefits of Statins

- While you are confident in recommending statins for lipid lowering in people with existing CVD (secondary prevention) you are less certain about the benefits in primary prevention.
- **Table 2** shows results of recent meta-analyses[7-10] of **primary** prevention studies indicating that statins lead to a **relative risk reduction** of about
  - 10% in death (range from no benefit to 27%)
  - 20% in stroke (range 6% to 35%)
  - 30% in coronary events including MI (range 19% to 50%)

Table 2 Results of primary prevention meta-analyses

Study	Measure	Death	Stroke	MI /Coronary events
Cochrane[10]	RR	0.84 (0.73–0.96)	0.78 (0.65–0.94)	0.72 (0.65–0.79)
Tonelli[7]	RR	0.90 (0.84–0.97)	0.83 (0.74–0.93)	0.63 (0.50–0.79)
Brugts[8]	OR	0.88 (0.81–0.96)	0.81 (0.71–0.93)	0.70 (0.61–0.81)
Ray[9]	RR	0.91 (0.83–1.01)	Not reported	Not reported

- The meta-analysis by Ray et al[9] resulted in non-statistically significant benefit in death which might be because the authors obtained additional detail allowing exclusion of 3695 secondary prevention patients. [87] Therefore all patients in the analysis were primary prevention.
- In general LDL reductions ranged between 23% and 32% in the trials included in the meta-analyses and LDL levels achieved were **not below** 2 mmol/L.
- A Cochrane review found a 30% relative risk reduction in fatal and non-fatal CVD events
  - RR 0.70 (95% CI: 0.61 to 0.79).[10]
- The authors of meta-analyses point out that the **absolute** benefit in people at less than 20% risk is likely to be small with large numbers needed to treat (NNTs). A Canadian meta-analysis[7] calculated the following NNTs:

	NNT	95% CI
Death from any cause	239	149 to 796
Myocardial infarction	216	160 to 381
Stroke	291	190 to 707

(Median duration 2 years, range 0.5 to 5.3 years)

- A recent meta-analysis of 22 statin trials (n=134 537) categorized patients into various categories based on their 5-year risks of developing CVD. The authors then calculated the effect of lowering LDL by 1 mmol/L on the **5-year** risk of developing CVD.[3]
  - A 20% to 25% **relative** risk reduction of CVD events was associated with a 1 mmol/L decrease in LDL regardless of baseline risk.
  - The meta-analysis should be considered a **post-hoc observational** study of many RCTs. Patients in the analysis were no longer randomized and other factors besides lowering of LDL may have influenced the results. [11] Moreover, the trials were not designed to study this outcome. Therefore results should be interpreted with caution.
- The UK[12] and Australian Guidelines[4] state "There are no clinical trials in primary prevention that have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events."
- It would help to have some idea of the **absolute** benefit Mr Hayward might obtain from taking a statin.
- **Table 3** provides estimates of the benefits of statins based on the Cochrane review.[10]

- There are limitations to the use of any of the risk score calculations and estimates of the effectiveness of statins.
  - Clinical studies are done under ideal conditions and with carefully selected patients. Benefits in actual practice may not be as great and adverse events may be more common.
  - In low to intermediate risk patients, the Framingham risk score may overestimate the true risk of a cardiovascular event, while in high risk patients it may underestimate the true risk.[13]

Because of these limitations, the estimates provided in **Table 3** are the "best case" scenario.

Table 3 Absolute benefits that may be achieved from taking in statin according to differing levels of baseline risk

No Statin treatment		Statin Treatment		
Calculated 10-year risk of having a CVD event e.g. from FRS[a]	**Probability of remaining event free**	**Estimated 10-year risk of having a CVD event[b]**	**Probability of remaining event free**	**NNT for 10 years**
5%	95%	3.5%	96.5%	67
10%	90%	7%	93%	33
15%	85%	10.5%	89.5%	22
20%	80%	14%	86%	17
25%	75%	17.5%	82.5%	13
30%	70%	21%	79%	11

a Framingham Risk Score
b Calculations based on 30% reduction in CVD events from taking statin[10]

- After discussing the possible benefits of taking a statin, (in his case taking a statin for 10 years will increase his chance of **not** having a CVD event from 85% to 90%) you review the benefits of lifestyle modification[1,14,15] and emphasize the importance of proper diet, weight loss, and regular physical activity.
- **CASE DECISION POINT:** He decides to try lifestyle modification and not to take a statin. You ask him to return for follow-up in three months.

Lifestyle Modification

Weight loss is associated with a modest reduction of LDL.[16]

- For every kg of weight loss, total cholesterol, LDL, and triglycerides are reduced by 0.05, 0.02, and 0.015 mmol/L respectively. If weight loss is maintained HDL increases by 0.007 mmol/L per kg loss.
- For example, if Mr Hayward loses 10 kg his LDL will drop by 0.2 mmol/L.

Exercise reduced the risk for acute MI by 14% in the case–control INTERHEART Odds ratio 0·86 (95% CI 0·76–0·97) [17]

- Similarly, a meta-analysis of 33 studies found that 150 min /week of moderate-intensity activity resulted in a 14% lower risk for CHD compared with a sedentary lifestyle. Increasing to 300 min/week resulted in a 20% lower risk.[18]
- Higher levels of physical activity were found to proportionally increase total life expectancy in an analysis of the Framingham cohort. [19]
  - Moderate and high activity increased longevity by more than 1.3 and 3.5 years respectively and increased years free of CV disease by more than 1.1 and 3.2 years longer compared with low activity.
  - Low levels of physical activity were defined as <30 minutes per day, moderate (30-33 minutes), and high >33 minutes.

Daily fruits and vegetables and moderate alcohol consumption are also protective factors.[17]

"At present, tobacco avoidance, maintenance of optimum weight, a prudent diet, and regular exercise should remain the **foundations** for prevention of cardiovascular disease in apparently healthy individuals with average risk factors." [15]

"In view of the potentially large public-health and economic implications of widespread use of statins in apparently healthy individuals with average risk levels, confirmation of the long-term results of major lowering of LDL cholesterol is needed before potent statins are used widely in average-risk healthy people." [15]

Effect of Family History on Calculating CVD Risk

Case Step 3 Reassessing risk based on family history

Mr Hayward returns 3 months later. He is doing well and has lost 3 kg, is walking about 30 minutes per day, and has increased his intake of fruit and vegetables.

However, he tells you his older brother (54 years old) is in hospital recovering from a heart attack. His brother had no cardiovascular risk factors. The hospital staff told Mr Hayward he may be at increased risk of also having a heart attack. He asks for your opinion.

His lipid profile has changed

	Baseline (mmol/L)	3 months lifestyle (mmol/L)
TC	6.1	5.9
HDL	1.0	1.1
LDL	3.2	3.1
TRIGL	2.6	2.5

His FRS based on his new lipid levels is slightly lower (10 year risk = 13%). However adjusting by 1.5 to 2 times because of his family history puts him in the high risk category (20% to 26%).

- The 2012 guidelines[1] recommend that among patients 30-59 years of age without diabetes, the risk should be adjusted (percent risk doubled) when family history of premature CVD is positive (i.e., first-degree relative < 55 years for men and < 65 years of age for women).
  - Our content expert suggests taking into consideration the risk factor burden in the first degree relative (i.e. smoking, metabolic syndrome, sedentary lifestyle) when deciding to modify a patient's risk based on family history.
- **CASE DECISION POINT:** According to the Canadian guideline criteria, Mr Hayward now has a **positive family history**.
- The UK Guideline recommends increasing calculated risk by 1.5 if there is a history of male first-degree relative under 55 years with CHD or a history of first-degree female relative under 65 years. If more than one first-degree relative has CHD history, estimated risk should be increased by a factor of up to 2.[12]
- Other studies have shown approximate doubling of risks with parental or family history of CVD [20] regardless of the relative's age with risk increasing by up to 6 times if more than 1 first degree relative has a history of premature CVD (defined as <50 [17] or <55[21]).
  - In some studies the association between family history and CVD is statistically significant in men but not women.[20-22]
- Because of his family history, Mr Hayward's 10-year risk estimate of having a CVD event might increase to between 20% and 26% (1.5 to 2 times). Taking a statin might now increase his chance of **not** having a CVD event from about
  - 80% to 86% (if his risk estimate is 20%)
  - 75% to 83% (if his risk estimate is 26%)

- You discuss these benefits and the possible adverse effects of statin therapy (see page 42 for adverse effects). He is very concerned about his brother's condition and decides that he would like to start taking medication to lower his CVD risk.
- **CASE DECISION POINT:** After checking his thyroid function, fasting blood glucose, liver function (ALT) and CK (all normal) you start him on a moderate dose of a statin.

Case Step 4 Lipid target

After 3 months of therapy you check his lipids again with the following results.

	Baseline (mmol/L)	3 months lifestyle (mmol/L)	3 months on statin (mmol/L)
TC	6.1	5.9	5.2
HDL	1.0	1.1	1.1
LDL	3.2	3.1	2.3
TRIGL	2.6	2.5	2.5

Should you try to lower his LDL further?

LDL Targets

- The 2012 guidelines cite 4 primary prevention studies to support initiating therapy at LDL ≥ 3.5 mmol/L in intermediate risk.[29,30,32,33]
- The guidelines[1] also recommend lowering his LDL to ≤ 2 mmol/L or by ≥ 50% which would be 1.6 mmol/L and comment that the targets for treatment are
  - Somewhat arbitrary because none of the intervention studies have aimed for specific lipid targets, and
  - Extrapolated from individual trial data and meta-analyses.
- To support the LDL target, the 2012 guideline cites 5 studies of intensive LDL lowering that have "confirmed that lowering LDL to a mean of 2.0 mmol/L or less is associated with the lowest risk of recurrent CVD events in **secondary** prevention patient populations."[PROVE IT, AtoZ, IDEAL, TNT, SEARCH 23-27]
- All these studies were in **secondary prevention populations,** two of which were in acute coronary syndrome.[23,24] Of these 5 studies:
  - Three showed no statistically significant difference in the primary outcomes from intensive LDL lowering.[24,25,27]
  - Two did not achieve LDL levels in the intensively treated groups ≤ 2.0 mmol/L[25,27]
  - One study did achieve an LDL level of 2.0 mmol/L and showed benefit in reducing CV outcomes when LDL was reduced to 2.0 mmol/L compared to 2.6 mmol/L with atorvastatin 80 mg compared to atorvastatin 10 mg daily.[26]
    - However there were more adverse events and discontinuations with the higher dose (Table 4).

- Of note, the groups were not randomized to different LDL targets. They were randomized to receive either atorvastatin 10 mg or 80 mg, so this study is **not** a treat to target study.

Table 4 Efficacy and safety outcomes of TNT[26]

Efficacy outcomes	Event Rate		ARR	RRR	NNT for 4.9 yrs	
	Atorv 10 mg n=5006	Atorv 80 mg n=4995			NNT	95% CI
Primary outcome – CHD death, non-fatal MI, stroke, resuscitation after cardiac arrest	10.9%	8.7%	2.2%	21%	44	29 to 92
Safety outcomes	**Atorv 10 mg**	**Atorv 80 mg**	**ARI**	**RRI**	**NNH**	**95% CI**
Adverse outcomes	5.8%	8.1%	2.4%	41%	42	30 to 74
Discontinuation from adverse events	5.3%	7.2%	1.9%	36%	53	35 to 105

ARR, absolute risk reduction; ARI, absolute risk increase; RRR, relative risk reduction; RRI, relative risk increase; NNT, number needed to treat; NNH, number needed to harm; CI, confidence intervals: atorv, atorvastatin

- In support of the recommendation to decrease LDL by at least 50%, the guideline cites a 1995 study which analyzed data from 11 studies (n=1851). These studies used quantitative coronary angiography to measure change in the diameter of coronary arteries in relation to absolute LDL levels achieved and percent reduction in LDL.[28]
  - Mean duration of the studies was 2.6 years with a range of 1 to 4 years.
  - There was strong correlation between percent change in the diameter of coronary arteries and the percent change in LDL ($r=0.74$ $p<0.0005$) but not the absolute LDL level achieved ($r=0.36$, $p=0.086$).
  - The paper states that a graph demonstrates that a 44% reduction of LDL should arrest progression of atherosclerosis. However the graph is mislabeled and it is impossible to make such a conclusion based on it.
- MEGA, a Japanese trial of pravastatin 10 to 20 mg plus diet vs. diet alone achieved a 30% reduction in CHD and stroke that was associated with only an approximate 20% reduction in LDL to 3.3 mmol/L.[34]
- The Australian guideline[4] on management of CVD risk states
  - "Targets for lipid-lowering therapy have been developed by extrapolation from the apparent benefits indicated by major trials of lipid lowering, therefore treatment for lipid lowering should **aim towards** these targets rather than consider them definitive."
- The UK Guideline[12] states
  - "There are **no clinical trials** in primary prevention that have evaluated the relative and absolute benefits of cholesterol lowering to different total and LDL cholesterol targets in relation to clinical events.

- In addition, the clinical effectiveness of higher intensity statins and of combining statins with other lipid lowering drugs has yet to be demonstrated for primary prevention.
- Due to lack of evidence, this guideline would **not recommend** the use of target levels of cholesterol for people at high risk of CVD."

- **Academic detailing comments about LDL targets in primary prevention**
  - We agree with the guideline comment that the targets for treatment are somewhat arbitrary because none of the intervention studies have aimed for specific lipid targets and targets are extrapolated from individual trial data and meta-analyses.
  - Our content expert suggests that, for consistency with secondary prevention, efforts should be made to strive to achieve the targets in intermediate to high risk primary prevention patients.

Case Step 5 Managing side effects

CASE DECISION POINT Even though you are unsure about the evidence to support a recommendation to lower Mr Hayward's LDL to ≤2.0 mmol/L you decide to increase his dose of statin.

However Mr Hayward returns in two weeks complaining of generalized muscle soreness keeping him from his exercise routine. His liver enzymes and CK are normal but you suspect the high dose statin is causing his myalgias.

You discontinue the statin until his symptoms subside and put him back on his original lower dose. (See page 44 for other strategies to manage myopathic symptoms.)

You now wonder if you should add ezetimibe to try to reach his LDL target of ≤2.0. mmol/L.

Combination Therapy with Ezetimibe

- Ezetimibe (Ezetrol) has a different mechanism of action than statins. It blocks the intestinal absorption of dietary and biliary cholesterol and related plant sterols, without affecting the uptake of triglycerides or fat-soluble vitamins. It can be administered alone or in combination with a statin. Ezetimibe is officially indicated as an adjunct to lifestyle changes, including diet, when the response to diet and other non-pharmacological measures alone has been inadequate.

- Ezetimibe has extensive evidence for lowering LDL which in turn, increases the proportion of patients reaching target lipid levels; however there is currently **no conclusive evidence** that it reduces cardiovascular events or mortality either alone or with statins. (See Appendix 3)

- The 2012 CCS guidelines[1] state that "no studies to date have demonstrated a decrease in CVD event rate with the addition of lipid-modulating drugs to statin therapy."

- ENHANCE [35] is the only RCT that compared a high dose of statin (simvastatin 80 mg) alone to the same dose plus ezetimibe 10 mg and was conducted in patients with familial hypercholesterolemia. After two years there was **no significant difference** in changes in the

thickness of carotid media between the two treatments despite ezetimibe/simvastatin lowering LDL to a greater extent (5.0 vs 3.7 mmol/L).

- There have been two published trials investigating the effect of ezetimibe in combination with simvastatin on clinical events in patients with aortic stenosis (the SEAS trial [36]) and chronic kidney disease (SHARP[37]).
  - Both studies compared the simvastatin/ezetimibe combination to **placebo**.
  - SEAS[36] (patients with aortic stenosis) showed **no** statistically significant **reduction** in the primary composite endpoint, although there was a significant reduction in CABG surgeries in the treatment arm.
  - SHARP[37] (patients with chronic kidney disease, n=9270, 4.9 years) showed a **significant reduction** in a composite of adverse coronary events with the use of simvastatin/ezetimibe (Table 5).
    - There was **no benefit** in overall **mortality**.
      - Placebo 24.1% vs Sim+Eze 24.6%

Table 5 Results of primary outcome of SHARP [37]

Efficacy outcomes	Event Rate		ARR	RRR	NNT for 4.9 yrs	
	Placebo n=4620	Sim+Eze n=4650			NNT	95% CI
Primary outcome – cardiac death, non-fatal MI, stroke, revascularization	13.4%	11.3%	2.1%	16%	48	29 to 134

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat; CI, confidence intervals: sim+eze, simvastatin 20 mg+ezetimibe 10 mg

  - It is **not possible** to determine whether the addition of ezetimibe in these trials conferred more benefit than would have been seen with the use of simvastatin alone.

Negative studies of ezetimibe are summarized in Appendix 2 along with other negative studies.

- One pending trial, IMPROVE-IT, is comparing simvastatin monotherapy to a simvastatin/ezetimibe combination for the prevention of cardiovascular events. Primary completion of data collection is expected by June 2013.

Case Step 6 Combination therapy

CASE DECISION POINT

Because of the lack of clinical outcome studies and the uncertainty about an LDL target of ≤2 mmol/L, you decide not to add ezetimibe to his regular dose of statin even though his LDL is not ≤2 mmol/L.

You further encourage him to continue with his positive lifestyle changes.

Choice of Statin and Monitoring

- The choice of statin and monitoring depend on whether you decide to treat to a specific LDL target.

Option 1: Treat to target

- If you decide to treat to target and lower LDL by 50% or to ≤ 2mmol/L you will probably need to prescribe a high potency statin such as atorvastatin or rosuvastatin (see Appendix 5). You will also need to monitor LDL levels to determine if the target is being reached.
    - The Canadian Guideline[1] recommends obtaining a fasting lipoprotein profile before starting drug therapy for dyslipidemia. Patients should refrain from alcohol for 24 h to 48 h.
    - The lipoprotein profile should include TC, HDL, and TRIGL. The LDL is derived from the Friedewald formula and is considered accurate for TRIGL levels of less than 5 mmol/L.
    - Also obtain baseline fasting glucose and TSH to identify diabetes or hypothyroidism and baseline ALT, CK, and creatinine.
    - The 2012 Guideline states "Baseline transaminases (ALT), creatinine, and creatine kinase are useful to monitor potential side effects associated with therapy. There is however no indication for routine repeat measures of ALT and creatine kinase in patients using statin therapy unless symptoms develop."
        - Our content expert suggests checking the lipoprotein profile and liver function (ALT) at 6 to 8 weeks and then semi-annually.
        - Note: it is not necessary to check AST and ALT. ALT is sufficient.

Option 2: Don't treat to target

- You may decide **not to treat to a specific target** because most outcome benefit is seen at the initial dose of statin therapy and 2/3 of the lipid-lowering effect of a statin is realized at the starting dose. Thereafter, doubling the dose will lower LDL by only a further 4% to 7%. [38] For example if a dose of atorvastatin 20 mg lowered LDL by 40%, doubling the dose might lower LDL to about 47%.
    - In this case you may wish to follow UK recommendations,[12] an approach similar to that suggested by a Canadian family physician.[38]
        - "When the decision has been made to prescribe a statin, it is recommended that therapy should usually be initiated with a low cost drug." (See appendix 5 for costs.)
        - "Once a person has been started on a statin for primary prevention, repeat lipid measurement is unnecessary. Clinical judgement and patient preference should guide the review of drug therapy and whether to review the lipid profile."
- The decision on which approach to take may also be influenced by patient preferences.
- Whichever approach is adopted it is important to emphasize the need for a healthy lifestyle – physical activity, tobacco avoidance, normal body weight, and prudent diet.

Lipid Lowering in Women in Primary Prevention

- It is not well established whether the protective effect of statins is equal for women and men. [39]

- Evidence for the efficacy of statins in the **primary** prevention of CVD in women is limited for the following reasons:
  - Major RCTs have not enrolled high percentages of women.
  - Earlier RCTs were focused on hard coronary outcomes rather than broader definitions of cardiovascular outcomes.
    - A meta-analysis published in 2004 [40] suggested that although the summary estimate suggests a reduction in CHD events, the small number of events limits the ability to make a firm conclusion about the true magnitude of benefit.
    - Data indicate that women's risks for stroke and heart failure through middle and older age typically exceeds their risk for CHD, in contrast to the pattern observed in men, for whom CHD risk increases earlier.[41]

- Two recently conducted RCTs have enrolled larger numbers of women in primary prevention.
  - **JUPITER** [33] included 6801 women over the age of 60 with normal LDL and elevated hsCRP; however the study has been criticized for methodological problems and reporting inconsistencies (see Appendix 1 for details of JUPITER).
    - Primary outcome: combined outcome of MI, stroke, hospitalization for unstable angina, arterial revascularization or cardiovascular death.
      - There was benefit in the primary outcome though the NNT was high (Table 6). Hospitalizations for unstable angina and arterial revascularization were the only two components of the primary outcome with statistically significant benefit.
    - LDL: In women levels dropped from 2.8 to 1.4 mmol/L (51%). In men levels dropped 49%.
    - For the complete trial, 89,890 patients were screened and 17,802 met the inclusion criteria for randomization which may limit its applicability to most women in primary prevention.
  - The Japanese trial, **MEGA**[34] included 5356 postmenopausal women with elevated cholesterol (TC 5.7 to 7.0 mmol/L) aged 40 to 70 years and lasted 5.3 years.
    - Intervention: pravastatin 10 mg or 20 mg per day plus diet vs diet alone
    - Primary outcome: fatal and nonfatal MI, cardiac and sudden death, coronary revascularization procedure, and angina
    - LDL: In women levels dropped from 4.1 to 3.3 mmol/L (19%). In men levels dropped 18%.
    - The primary outcome and total cardiovascular events were **not statistically significant.**
      - Primary outcome hazard ratio 0.74 (95% CI 0.45 to 1.23)
      - Total CV events hazard ratio 0.71 (95% CI 0.50 to 1.01) [42]

- Table 6 and Table 7 show the primary outcomes for men and women in JUPITER and MEGA. Note the larger NNT for women.

Table 6 Primary outcome of JUPITER for men and women[43]

Sex	Event Rate		ARR	RRR	NNT for 1.9 yrs	
	Placebo	Rosuv 20 mg			NNT	95% CI
Women	2.1%	1.1%	0.9%	45%	107	65 to 296
Men	3.3%	1.9%	1.4%	43%	72	50 to 125

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat; CI, confidence intervals; rosuv, rosuvastatin

Primary outcome = MI, stroke, CV death, hospitalization for UA, arterial revascularization

Table 7 Primary outcome of MEGA for men and women[42]

Sex	Event Rate		ARR	RRR	NNT for 5.3 yrs	
	Diet	Diet + Prav			NNT	95% CI
Women	1.3%	1.0%	0.3%	26%	*295*[a]	NS
Men	3.9%	2.5%	1.4%	36%	71	36 to 8148

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat; CI, confidence intervals; prav, pravastatin

a NNT presented for demonstration purposes. NNT should not normally be presented for non-significant results

Primary outcome = MI, cardiac and sudden death, angina, coronary revascularization

- The most recent meta-analysis of the efficacy of statins in women for primary prevention included JUPITER, MEGA and AFCAPS.[43] It looked at data from trials that contained only primary prevention subjects and described outcomes as total CVD events (Table 8)
  - For **total CVD** events there was **benefit** RR 0.63: 95% CI 0.49 to 0.82 p<0.001
  - There was **no** statistically significant **benefit** found in total **mortality**.
  - Because of the published criticisms of JUPITER[15,44] (see Appendix 1) we conducted an analysis of CVD outcomes with data from only MEGA and AFCAPS. For total CVD events, the decrease in total CVD events was **not statistically significant** (RR 0.72, 95% CI 0.51 to 1.01).

Table 8 Characteristics of studies included in meta-analysis of women[43]

Study	N	Duration	CVD outcomes included
JUPITER[43]	6801	1.9 years	MI, unstable angina, CV death, revascularization, stroke
MEGA[42]	5356	5.3 years	MI, angina, cardiac & sudden death, revascularization, stroke
AFCAPS[30]	997	5.2 years	MI, unstable angina, sudden cardiac death, revascularization

- The Canadian, [1] Australian,[4] and UK Guidelines [12] do not provide any therapeutic differentiation for their treatment recommendations between women and men.
- In 2011, the American Heart Association published an update of effectiveness-based guidelines for the prevention of CV disease in women.[41]
  - These guidelines offer a unique classification of CVD risk in women and define a new concept of "ideal cardiovascular health" which includes
    - The absence of clinical CVD
    - The presence of all ideal levels of cholesterol, BP and fasting blood sugar, and
    - Adherence to healthy behaviours.
- Evidence from a meta-analysis supports the benefit of statins in women in **secondary** prevention but absolute risk reduction in women was **constantly lower** than that in men leading to higher number needed to treat.[39]

- **Academic detailing comments about primary prevention in women**
  - Statins might provide some benefit in preventing CVD events in women. However there are limitations in the evidence (few women in studies, few events, few studies, inconsistent results).
  - The lower baseline risk for CVD in women compared to men is acknowledged in the point system in the FRS.
  - Because women may have a lower baseline risk of CVD than men, their absolute benefit may be lower and the NNTs will be higher as observed in JUPITER and MEGA.
  - Clinicians will need to discuss the benefits and possible adverse events of statin treatment.

Lipid Lowering in the Elderly in Primary Prevention

- Theoretically, the elderly (≥ 65 years) and very elderly (≥ 80 years) should experience greater absolute benefit from lipid lowering therapy because age is the greatest determinant of baseline risk which will therefore increase with increasing age.
- However, there are a number of uncertainties when considering the need for **primary** prevention of CVD in the elderly and the very elderly.
  - The Framingham Risk Score calculations are not designed for use in patients over 74 years old. http://www.framinghamheartstudy.org/risk/gencardio.html# [45,46] However, some risk calculators including the one in the Canadian guideline have a category of 75+ years.
    - The 2012 guidelines acknowledge this limitation and suggest that clinical judgement is required in consultation with the patient to determine the value of pharmacotherapy in those older than 75 years of age.[1]

- The power of the classic risk factors (age, sex, SBP, total cholesterol and HDL, diabetes, smoking and ECG-based left ventricular hypertrophy) to accurately predict risk of cardiovascular disease seems to diminish with advancing age. [47]
- Epidemiological studies show a weaker relationship between cholesterol levels and CV morbidity and mortality in the elderly and very elderly.[48,49]
  - Some studies show a positive relationship with total cholesterol and CVD while others do not.[49]
  - In the very elderly there is evidence that increased morbidity and mortality is associated with lower cholesterol levels.[50] This may be because people with high cholesterol have already died or serious illness leads to lower cholesterol levels.
- RCTs have included few primary prevention patients over 65 years old.

- **PROSPER** [51] was the only RCT that addressed lipid lowering treatment specifically in the elderly (pravastatin 40 mg vs placebo; n=5804; mean 3.2 years)
  - Age: inclusion 70 to 82 years, mean 75 years.
  - 56% of subjects were **primary** prevention
  - LDL in pravastatin group: 3.8 mmol/L → 2.5 mmol/L (34% reduction)
  - In the **overall** population (primary and secondary prevention groups combined) pravastatin showed benefit in the primary combined outcome of CHD death, non-fatal MI, and stroke (Table 9).

Table 9 Primary outcome in combined primary and secondary prevention groups of PROSPER [51]

Efficacy outcome in primary and secondary prevention population	Event Rate		ARR	RRR	NNT for 3.2 yrs	
	Placebo n=2913	Pravastatin n=2891			NNT	95% CI
Primary outcome: composite of non-fatal MI, stroke, CHD death	16.2%	14.1%	2.1%	13%	47	25 to 358

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat.

- Sub-group analysis showed there was **no statistically significant benefit** in the primary outcome of CHD death, non-fatal MI, or stroke in the **primary prevention** group
  - Event rate placebo 12.1% vs pravastatin 11.4% (not significant)
  - Hazard ratio 0.94 (95% CI 0.77 to 1.15).
  - The lack of statistically significant difference raises the possibility of lack of benefit from statins in **primary** prevention even though the test for heterogeneity between primary and secondary prevention was negative.
- There was **no** statistically significant **reduction** overall **mortality** from pravastatin therapy in the **combined** primary and secondary groups.

- A meta-analysis of **secondary** prevention studies in the elderly obtained data from PROSPER that showed a statistically significant 18% **decrease** in all-cause mortality from pravastatin therapy in the **secondary** prevention group. [52]

- Since the **overall** results of PROSPER showed **no benefit** in mortality, this implies a possible **increase** in mortality in the **primary** prevention group from pravastatin therapy. [53]

- **JUPITER** is a primary prevention study in which investigators performed an **exploratory secondary** analysis of the elderly population (N= 5695) included in the trial.[82]
  - Publications have pointed out **methodological limitations** of JUPITER (see Appendix 1) and so results of this exploratory analysis should be interpreted with caution.
  - A **benefit** was reported in the primary outcome from rosuvastatin 20 mg in patients 70 to 97 years old (median age 74, interquartile range 72 to 78), but the NNTs over 2 years were high, and the confidence intervals wide.

Outcome	**NNT**	**95% CIs**
Primary outcome *(non-fatal MI, non-fatal stroke, hospitalization for UA, revascularization, CV death)*	62	39 to 148
Myocardial infarction	211	106 to 32,924
Revascularization or hospitalization for UA	102	62 to 292
Stroke	161	86 to 1192
Overall mortality	Not statistically significant	

- The 2012 CTT meta-analysis[3] analyzed the decrease in major vascular events per 1 mmol/L lowering of LDL in three age categories: < 60 years, 61 to 70 years, and >70 years.
  - Patients up to age 70 showed benefit in all levels of baseline risk.
  - In patients >70 years old there was **no statistically significant benefit** in those with 5-year baseline risk of <10% which would be more representative of the primary prevention population.
    - However the number of events was small and the confidence intervals were wide indicating the lack of research in this primary prevention age group and the uncertainty of results.
- Statins have not been found efficacious in decreasing decline in cognition[46,12]and in some cases have been reported to cause memory and cognitive impairment (see section on adverse effects page 42.)
- Age has been reported to be a risk factor for statin-induced adverse effects. [55,56,

Interpretation and application to practice

- Review articles in primary prevention state that
  - Insufficient evidence is available to guide evidence-based approaches to cholesterol lowering for primary prevention of CVD after age 75.[46,54]
  - "The optimal cholesterol level for people aged 80 or above is not known, neither is it known whether lipid lowering drugs should be used in this age group."[50]
- A consideration when deciding to prescribe therapy for the elderly in **primary** prevention is if their expected lifespan is likely to be long enough for the benefit of statins if any, to be realized. Most primary prevention studies took 3 to 4 years to achieve a 1% absolute risk reduction in their primary outcomes[29,30,34] and it has been suggested that statins should be considered for primary prevention for elderly patients with a life expectancy of 5 years.[66]
- When treating for primary prevention, consideration should be given to the decreased life expectancy, increased co-morbidities, risk of polypharmacy, and increased risk of adverse reactions in the geriatric population. In addition, cost implications play an increasingly important role as this demographic continues to increase. [57]
- Guidelines and reviews tend to recommend treatment of the elderly at high risk but have some reservations about treating the very elderly.
  - "There is not sufficient data to recommend anything regarding initiation or continuation of lipid-lowering treatment for the population 80+, with known CVD, and it is even possible that statins may increase all-cause mortality in this group of elderly individuals without CVD."[50]
- A 2009 primary prevention review article states [46]
  - It may be reasonable to consider statin treatment to achieve an LDL level of < 2.6 mmol/L in persons 75 to 80 years old who are in excellent health.
  - In those ≥ 80 years old, the decision to treat cholesterol should be individualized and made in close consultation with the patient.
  - Most elderly patients should achieve an LDL level <2.6 mmol/L on moderate dose of statins and high dose therapy should be reserved for those at highest risk and used with caution with advancing age.
  - Avoid lipid lowering drugs other than statins because of lack of demonstrable safety and safety concerns in the elderly.
  - Undertake lipid management within the context of controlling other risk factors such as hypertension, smoking and other prophylactic measures such as aspirin, which have been shown to benefit older adults.
- The NICE UK Guideline[12] states
  - People aged 75 or older should be considered at increased risk of CVD, particularly people who smoke or have raised blood pressure. They are likely to benefit from statin treatment.
  - Assessment and treatment should be guided by the benefits and risks of treatment, informed preference and comorbidities that may make treatment inappropriate.

- The New Zealand Guideline [58] on stopping medications in older people recommends
  - The decision to stop a statin is based on an assessment of individual benefits and risks. For example, stopping may be justified in a person at relatively low risk of a cardiovascular event, who is also poorly compliant or experiencing troublesome adverse effects. In most cases statins can be stopped without the need for tapering.
  - Statins should **not** be stopped in patients with a history of cardiovascular events including acute coronary syndrome, myocardial infarction, and stroke.
- The European Cardiovascular Society [58] guideline states
  - In some age categories in the elderly, the vast majority, especially of men, will have estimated CV risks exceeding the 15–30% level, based on age (and gender) only, even when other CV risk factor levels are relatively low.
    - This could lead to excessive usage of drugs in the elderly and should be evaluated carefully by the clinician.
  - Statin therapy may be considered in elderly subjects free of CVD, particularly in the presence of at least one other CV risk factor besides age. Class 2b recommendation

- **Academic Detailing Comments**
  - The Framingham Risk Score calculations are based on studies that included subjects between 30 and 74 years old. If used in patients over 74 years old, results should be interpreted with caution.
  - In the elderly >70 years old, there is no conclusive evidence of statistically significant decrease in **mortality** in **primary** prevention.
  - There is uncertainty in the evidence for efficacy of statins in **primary** prevention of CVD events in the elderly because the main study involving the elderly did not show a benefit in the primary prevention sub-group.
  - The elderly are reported to be more prone to adverse effects.

Statin Use in Severe Frailty

- This is an evidence-informed consensus developed in collaboration with PATH, the Palliative and Therapeutic Harmonization Program. *www.pathclinic.ca*

Recommendations

These recommendations consider the significant impact and decreased life expectancy of **severe frailty**.

Primary Prevention: It is unlikely that statins provide benefit in applicable outcomes and so there is no reason to prescribe or continue statins for primary prevention.

Secondary Prevention: With severe frailty there is

- Uncertainty about whether statin trial outcomes are clinically meaningful
- Uncertainty about whether statins confer benefit in clinically meaningful outcomes
- Uncertainty about the magnitude of any benefit conferred partly because of the decreased life expectancy in severe frailty
- Increased potential for adverse events.

Therefore, statin treatment in severe frailty is probably not necessary, although there may be extenuating individualized circumstances that shift the risk/benefit ratio.

Heart failure: There is no reason to start or continue statins for heart failure.

Ezetimibe: There is no reason to start or continue ezetimibe for primary or secondary prevention.

Combination therapy with statins: There is no reason to start or continue other lipid lowering drugs in conjunction with statins.

Adverse events: Consider a trial of discontinuation of statin therapy if there is concern about myalgias, cognitive impairment, or drug interactions from polypharmacy.

Statin dosing: If statins are to be used, use lower doses.

- This consensus approach is intended for patients who are **≥ 7 on the Clinical Frailty Scale (CFS)** (See Appendix 6 for Frailty Scale). It is also applicable to most older adults living in long term care facilities, who are typically severely frail, e.g. completely dependent for personal care.
- The average life expectancy in Nova Scotia long term care facilities is 2.5 years.[78]

Guiding Principles of Pharmacotherapy in the Frail elderly

- Guideline-driven care contributes to polypharmacy in the elderly; however, **what is good for the disease may not be good for the patient.**[79]
  - An analysis of the applicability of clinical practice guidelines to elderly patients with comorbidities showed that only a handful adequately addressed issues related to the care of elderly patients. The authors suggest there is a pressing need to improve the evidence base that guides the care of people of advanced age and with multiple concurrent chronic diseases. [80]
- For many, the goal of therapy with frailty is to maintain or improve quality of life rather than prolong life. Maintenance or improvement of quality of life can mean
  - Optimizing function, mobility, and cognition
  - Minimizing **symptomatic** non-fatal MI and the **disabling** effects of stroke
  - Minimizing polypharmacy, adverse events, and unnecessary investigations including lab tests.
- Patients with severe frailty have more functional limitations and are less likely to benefit from therapies designed to prevent further disability.[91]
- The following questions can help guide decisions for therapy in the frail elderly [83,85]
  - Is the person's life expectancy long enough to achieve benefit?
  - Are trial outcomes clinically meaningful for the frail elderly?
  - Are there clinically significant adverse effects or drug interactions?
  - Does the medication match the goals of care?

Evidence in the frail elderly

- We found **no studies** that reported the effect of lipid lowering in the **severe frail** elderly in primary or secondary prevention. Therefore we examined studies in the **non-frail** elderly to determine if they reported outcomes that were meaningful and could be applied to the **frail elderly**.

Relevant outcomes in the frail elderly

- When examining outcomes in statin studies in the **non-frail elderly,** we need to consider whether they will be applicable to the frail. Points to consider include:
  - Mortality: There are competing causes for mortality in the frail elderly; therefore we cannot assume that a mortality benefit shown in non-frail populations applies to frail populations. In addition, the goals of therapy may not be to prolong life in the frail.
  - CHD events: For the frail elderly the important outcome is **symptomatic** non-fatal MI (e.g., leading to morbidity such as angina or heart failure.) In some statin studies, the primary composite outcome and the outcome of CHD events include those with **asymptomatic** heart disease such as silent MIs. Preventing asymptomatic heart disease might not prevent morbidity for the frail. Therefore, the outcome of CHD events, as reported in studies of the non-frail, **might not** be applicable to the frail.

- Stroke: For the frail elderly, the important outcome is **non-fatal stroke leading to disability**. However, sometimes the outcome of non-fatal stroke includes mild strokes and TIAs and the number of strokes leading to disability is not reported separately. Therefore, the outcome of non-fatal stroke as reported in studies of the non-frail **might not** be applicable to the frail.

Evidence in Primary Prevention in the non-frail elderly

- **PROSPER** is the only RCT which studied the effect of a statin (pravastatin 40 mg) exclusively in the elderly (ages 70-82).[51]
  - **There was no statistically significant benefit (NS)** in the primary composite or individual secondary outcomes in the primary prevention group.

	Event rate		Statistical
Outcome	**Placebo**	**Pravastatin**	**Significance**
Primary composite outcome *(CHD death, non-fatal MI, fatal or non-fatal stroke)*	12.1%	11.4%	NS
Individual secondary outcomes			
Fatal and non-fatal MI	8.8%	7.9%	NS
Fatal and non-fatal stroke	3.7%	3.8%	NS
TIA	2.3%	1.9%	NS

  - The lack of statistical significant difference raises the possibility of lack of benefit from statins in primary prevention even though the test for heterogeneity between primary and secondary prevention groups was negative.

- **JUPITER** is a primary prevention study in which investigators performed a **secondary** analysis of the elderly population included in the trial. The study compared rosuvastatin 20 mg to placebo in patients **70 to 97 years old** (median age 74, interquartile range 72 to 78).[82]
  - They report a **benefit** in the primary outcome and its individual components, but the NNTs over **2 years** were high.
    - We do not know how many MIs and strokes were symptomatic.

Outcome	**NNT**	**95% CIs**
Primary outcome *(non-fatal MI, non-fatal stroke, hospitalization for UA, revascularization, CV death)*	62	39 to 148
Myocardial infarction	211	106 to 32,924
Revascularization or hospitalization for UA	102	62 to 292
Stroke	161	86 to 1192

- Publications have pointed out methodological limitations of JUPITER (see Appendix 1 for detailed critique).
  - JUPITER was stopped early, which likely exaggerates the magnitude of benefit. As shown above the absolute benefit was small and NNTs high.
  - The trial included a select patient population with normal LDL and elevated hsCRP. Of the 90,000 patients screened, 72,000 did not meet inclusion criteria and were not enrolled in the trial.

- The study populations in PROSPER[51] and JUPITER[82] were **non-frail** elderly.

Evidence in Secondary prevention in the non-frail elderly

- Secondary prevention was defined as the presence of coronary artery disease in most studies. Although PROSPER[51] and HPS[31] included those with vascular disease such as peripheral vascular disease, the majority had CHD (71% in PROSPER and 87% in HPS). Any benefit demonstrated in these trials may therefore be most applicable to patients with CHD.
- In the PROSPER[51] trial, **for secondary prevention**, there was **benefit** in the primary composite outcome and the combined outcome of CHD death and non-fatal MI (Table 10). However, the outcome of non-fatal MI included definite and **suspect** events.

Table 10 Outcomes in secondary prevention group of PROSPER[51]

Efficacy outcome in secondary prevention population	Event Rate		ARR	RRR	NNT for 3.2 yrs	
	Placebo n=1259	Pravastatin n=1306			NNT	95% CI
Primary outcome: composite of non-fatal MI, stroke, CHD death	21.7%	17.4%	4.3%	20%	23	14 to 81
CHD death and non-fatal MI (includes definite and *suspect* events)	16.8%	12.7%	4.1%	24%	25	15 to 77

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat, calculated on raw numbers.

- **Time to benefit:** For secondary prevention, it took approximately 3 years to achieve a 4% ARR in CHD and non-fatal MI. As mentioned above, this outcome included those with definite and **suspect** events. Therefore, we question if this outcome is clinically relevant to frail older adults.
- There was **no benefit** in the combined outcomes of **fatal and non-fatal stroke** or **TIAs** (Table 11).

- A recent meta-analysis of **secondary** prevention studies in the **non-frail** elderly (9 studies, 19,569 patients, age range 65 to 82) found benefit from statins in reducing all cause mortality and in preventing non-fatal MI and stroke in a population of patients with CHD.[52] The authors calculated the following NNTs **over 5 years:**
  - Stroke NNT = 58 (95% CI 27 to 177)
    - Stroke was not defined and includes fatal and non-fatal stroke.
    - The outcome of non-fatal stroke includes disabling and non-disabling strokes.
    - The NNT to prevent one disabling stroke is therefore uncertain and cannot be calculated from the data provided.

      For instance, in the largest study included in the meta-analysis, only 43% of strokes in the overall study population (not just the elderly population) were severe enough to be disabling.[31]
  - Non-fatal MI NNT = 38 (95% CI 16 to 118)
    - Non-fatal MI includes symptomatic and asymptomatic (silent) events. Therefore, the ability of statins to prevent **symptomatic** MIs cannot be calculated from the data provided.
  - There was benefit in mortality but our content experts do not consider this to be an important outcome, as frailty poses too many competing risks for mortality.
  - With the exception of PROSPER[51], the meta-analysis included younger elderly patients, with mean age of < 70 years, which limits the relevance of the results when applied to frailty.

Heart Failure

- We found two studies in **heart failure** patients whose mean age was 68 (GISSI-HF)[70] and 73 (CORONA).[69] In both studies there was **no significant benefit** from rosuvastatin 10 mg despite LDL lowering of 27% and 45% respectively.
  - **GISSI-HF** (n=4574, mean age 68, duration 3.9 years, rosuvastatin 10 mg vs placebo)[70]
    - The authors of GISSI-HF describe their study subjects as being frail. It is unlikely they had severe frailty (i.e., CFS 7).
    - 40% of patients had heart failure of ischemic origin
    - 44% were ≥ 70 years old
    - NYHA class II 62%; NYHA class III 35%
    - There was **no significant benefit** in
      - Co-primary outcomes of mortality and hospitalization for CVD (rosuvastatin 57%, placebo 56%) or the
      - Secondary outcomes of fatal and non-fatal MI (rosuvastatin 2.7%, placebo 3.1%) and fatal and non-fatal stroke (rosuvastatin 3.6%, placebo 2.9%)

- **CORONA** (n=5011, mean age 73, duration 2.7 years, rosuvastatin 10 mg vs placebo)[69]
  - Subjects in CORONA were older and a greater percentage of patients were NYHA class III than in GISSI-HF, so it is possible they too were frail.
  - 41% were ≥ 70 years old
  - NYHA class II 37%; NYHA class III 61%
  - There was **no significant benefit** in the primary outcome of CV mortality, non-fatal MI and non-fatal stroke (rosuvastatin 27.5%, placebo 29.3%).

Stroke

- Disabling **stroke** that worsens function is considered an important outcome in the frail elderly. The outcome of stroke from PROSPER,[51] JUPITER[82] and the Afilalo meta-analysis[52] is summarized separately in Table 11. Interpretation of this data is limited by the fact that the stroke outcome includes disabling and non-disabling strokes.
- Note that after 3.2 years there was no benefit in stroke reduction in PROSPER for both primary and secondary prevention. [51]
- The secondary prevention meta-analysis in the elderly demonstrated a stroke benefit of less than 2% ARR over 5 years resulting in an NNT of 58 and wide confidence intervals (27 to 177).[52]
- After 2 years, JUPITER did show benefit in stroke for primary prevention, but this was very small with a large NNT and wide confidence intervals, NNT 161 (86 to 1192).[82]

Dosing of statins

- Doses of statins depend on potency which refers to the LDL lowering effect per milligram of drug taken. Atorvastatin and rosuvastatin are considered high potency and require lower doses to achieve the same LDL lowering as lower potency statins.
- Statin doses used in PROSPER[51] and trials included in the Afilalo meta-analysis[52] were as follows:
  - Atorvastatin 10 mg Rosuvastatin 10 mg
  - Simvastatin 10 to 40 mg Pravastatin 40 mg Fluvastatin 80 mg
- High doses of statins are associated with increased adverse effects[56] and uncertain benefit, especially when the standard of disabling outcomes is considered.
- If statins are to be used, we suggest doses no higher than above, and possibly lower.

Table 11 Stroke outcomes in statin studies in the elderly

Primary Prevention: Efficacy outcomes	Event Rate		ARR or ARI	RRR or RRI		
	Placebo	Statin			NNT	95% CI
PROSPER[51] **mean age 75 years, Pravastatin 40 mg daily**					**NNT for 3.2 yrs**	
Fatal or non fatal stroke	**N=1654** 3.8%	**N=1585** 3.9%	***ARI*** 0.1%	***RRI*** 2.7%	NS	NS
Transient Ischemic Attack	2.3%	1.9%	0.4%	18%	NS	NS
JUPITER[82] **(Secondary analysis of age 70 -97, median 74 IQR 72-78 yrs)**					**NNT for 2 yrs**	
Stroke (percent based on raw number of events)	**N=2817** 1.4%	N=**2878** 0.8%	0.6%	45%	161	86 -1192

Secondary Prevention: Efficacy outcomes	Event Rate		ARR	RRR		
	Placebo	Treatment			NNT	95% CI
Afilalo (Meta-analysis of elderly subgroups)[52] **age range 65 to 82**					**NNT for 5 yrs**	
Stroke (disabling and ***non-disabling***)	**N=8698** 7.0%	**N=8723** 5.3%	1.8%		NNT = 58	27 to 177
PROSPER[51] **(mean age 75 years, Pravastatin 40 mg daily)**					**NNT for 3.2 yrs**	
Fatal and non fatal stroke	**N=1259** 5.5%	**N = 1306** 5.7%	***ARI*** ***0***.2%	***RRI*** 3.4%	NS	NS
TIA	5.1%	3.6%	1.5%	29%	NS	NS

ARR, absolute risk reduction; RRR, relative risk reduction; ARI, absolute risk increase; RRI, relative risk increase; TIA, Transient Ischemic Attack; IQR, interquartile range NS = not statistically significant, i.e., p> 0.05 and numbers needed to treat (NNTs) not calculated on these results

Ezetimibe, combination therapy and adverse effects

- Ezetimibe has extensive evidence for lowering LDL; however there is currently **no conclusive evidence** that it reduces cardiovascular events or mortality either alone or with statins in any population.
- The 2012 CCS Guidelines state, "No studies to date have demonstrated a decrease in CVD event rate with the addition of lipid modulating drugs to statin therapy".[1]
- Two adverse events that may impair quality of life are myalgias and cognitive impairment.
  - Myopathy
    - **RCT** evidence reports incidence rates of 1.5-5%, which is comparable to placebo. Clinical trials use differing definitions for myopathy and tend to exclude individuals with previous intolerance or who experience adverse effects during run-in periods.[56]

- **Clinical** experience suggests that muscle adverse effects are relatively common, reported as 29% in the general population. [59]
- Myalgias typically develop within the first 6 months but may occur at any time during treatment. Symptoms typically resolve within 2 months of stopping statins.[56]
- Advanced age, frailty, severe renal or liver disease are considered risk factors for myopathy.[56]

o Cognitive impairment: Due to case reports of memory loss, the FDA issued a warning that statins have been associated with memory loss and confusion. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm Aggression and irritability have also been reported. It may be difficult to tell if a statin is causing or aggravating such symptoms when individuals have dementia.

Interpretation of evidence

- Clinical trials are not available to provide direction on whether statins provide benefit in outcomes that are meaningful to **the frail elderly** in either primary or secondary populations.
- **Symptomatic non-fatal MI and non-fatal disabling stroke** are considered meaningful outcomes in the frail elderly since they can lead to further disability; however, the degree of disability is not consistently reported in studies of the non-frail elderly.
- We reviewed the clinical trials enrolling **non-frail elderly** patients (the most relevant trial, PROSPER[51], included patients up to age 82) to consider whether the results could be extrapolated to the **frail elderly**.
  - We concluded that extrapolation from these trials is not a valid approach to guide prescribing in the **frail elderly** because the patient populations are too different; trials enrolled relatively healthy participants without the number of competing causes for morbidity and mortality typical of the frail elderly population.
    - Of all the trials, the one that is the closest to representing the older elderly population, albeit without frailty, is the PROSPER[51] trial and in primary prevention it reported no statistically significant benefit in the outcomes of CHD death and non-fatal MI, fatal and non-fatal stroke, and TIAs.
    - The more recent primary prevention trial that included the elderly (JUPITER[82]) is even less applicable to the frail elderly since it included a very select population with normal LDL and high hsCRP. JUPITER had other methodological issues that limit generalizability. Any benefit shown was associated with small absolute benefit and high NNTs.
- In the **non-frail elderly** population for **primary prevention,** there is evidence that statins provide little[82] to no[51] benefit in meaningful outcomes.
- In **non-frail elderly** for **secondary prevention**, the NNTs for statins over 5 years to prevent both symptomatic and asymptomatic outcomes[52] may be appropriate in the non-frail. However since the severely frail elderly have (1) shortened life expectancy; (2) many competing risks for morbidity and mortality, and (3) increased risk for adverse effects from medication, the benefit of statins is uncertain. In addition, there is uncertainty about the NNT to treat if the focus is on clinically meaningful outcomes.

Suggested approach for statin therapy in the frail elderly

- In the absence of evidence in the frail elderly, and recognizing the limitations of applying evidence from studies of the non-frail elderly, and in consultation with local experts, we suggest the following approach:
  - Primary prevention: It is unlikely that statins provide benefit in applicable outcomes and so there is no reason to prescribe or continue statins for primary prevention.
  - Secondary Prevention: With severe frailty there is
    - Uncertainty about whether statin trial outcomes are clinically meaningful
    - Uncertainty about whether statins confer benefit in clinically meaningful outcomes
    - Uncertainty about the magnitude of any benefit conferred partly because of the decreased life expectancy in severe frailty
    - Increased potential for adverse events

    Therefore, statin treatment in severe frailty is probably not necessary, although there may be extenuating individualized circumstances that shift the risk/benefit ratio.
  - Heart failure: There is evidence that statins are ineffective in improving clinical outcomes in the elderly and there is no reason to start or continue them for this indication.
  - Ezetimibe: There is currently no conclusive evidence that ezetimibe reduces cardiovascular events or mortality either alone or with statins in any population. There is no reason to start or continue ezetimibe for primary or secondary prevention.
  - Combination therapy with statins: There is no evidence of added benefit in clinical outcomes for combination therapies for either primary or secondary prevention in any population. These added medications can be stopped.
- Adverse effects: Advancing age is reported to be a risk factor for adverse effects of statins, which may alter the benefit to harm ratio.
  - Consider a trial of discontinuation of statin therapy if there is concern about myalgias, cognitive impairment, or drug interactions from polypharmacy.
- Statin dosing: If statins are to be used, we suggest doses no higher than the following, and possibly lower.
  - Atorvastatin 10 mg Rosuvastatin 10 mg
  - Simvastatin 10 to 40 mg Pravastatin 40 mg Fluvastatin 80 mg
- When prescribing, consider the life expectancy, evidence for meaningful outcomes, and possible adverse effects when making decisions about whether to initiate or continue statin therapy in severely frail patients.

Adverse Effects of Statins

Myopathy

- Myopathy is recognized as one of the main adverse effects that limits compliance with statin therapy. The precise mechanisms underlying statin myopathy are incompletely understood.
- Statin-related myopathy comprises myalgias (muscle pain, weakness, stiffness, and cramps), myositis, and rhabdomyolysis; different groups and studies use different definitions.
- RCT evidence suggests statin myopathy incidence is about 1.5% to 5.0% which is comparable to placebo.[55]
- However, in real world clinical practice myalgias can affect **up to 29%** of persons prescribed statins, whereas rhabdomyolysis is rare and dose dependent.[55,59,60]
- The PRIMO[60] study of patients receiving high dose statins reported that
  - 10.5% of patients reported myalgias. Of those 10.5%
    - More than 80% of patients reporting myalgia had not experienced similar symptoms before beginning statin treatment.
    - 25% had generalized symptoms
    - 25% reported tendon-associated pain
    - 4% had symptoms that warranted confinement to bed or cessation of employment,
    - 38% had symptoms that prevented moderate exertion during daily activity
- The USAGE internet survey study,[59] found that **29%** of respondents reported muscle-related side effects while taking a statin:
  - 25% were among current users and 60% among former users (P <0.05).
  - The primary reason for discontinuing a statin was adverse effects (62%).
- Myalgia commonly develops within the first 6 months of starting statin therapy but may occur after several years. Symptoms typically resolve within 2 months of discontinuing the statin. [56]
- Health Canada warns the regular use of 80 mg of **simvastatin** may lead to increased risk of myopathy/rhabdomyolysis, particularly during the first year of treatment.
- The recommended simvastatin dosage is 5 to 40 mg/day. Full details are at http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/zocor_hpc-cps-eng.php
- Muscle biopsies show myopathic changes in some patients on statins and are not consistently related to symptoms or creatine kinase elevations. [55]

Table 12 Risk factors for myopathy [55,56,67]

Patient-related	Statin-related
• Advanced age (age >80) • Female sex • Small body frame and frailty • Hypothyroidism • Alcoholism • Grapefruit juice consumption • Excessive physical activity • Severe renal disease • Major surgery • History of myopathy with lipid-lowering therapy (self or family members) • History of creatine kinase elevation • Multisystem disease (particularly liver, kidney, or both) • Genetic polymorphisms of CYP isozymes • Use of illicit drugs (cocaine, amphetamines)	• High-dose statin therapy • Statin properties that may increase the risk of myopathy: • Lipophilicity, high bioavailability, limited protein binding (Pravastatin is 50% protein bound, other statins are 90-98% bound.) • Drug interactions*, i.e., Medications metabolized through cytochrome P450 (3A4 or 2C9) system. Some important examples are: - Fibrates - Cyclosporine - Azole antifungals - Macrolide antibiotics - HIV protease inhibitors - Nefazodone - Amiodarone - Verapamil - Nicotinic acid - Digoxin - Fusidic acid Rosuvastatin and pravastatin are reported to have fewer drug interactions. ***Please consult pharmacist or drug interaction resources for a full list of interactions, statin-specific interactions, and the relative severity of interactions.**

Assessment of CK elevation and statin-related myopathy

- If CK ≤ upper limit of normal (ULN) and **without symptoms** of muscle pain or weakness , no further CK testing is required unless symptoms occur, the dose of the statin is increased, or there is a switch to a different statin.
- If CK elevations ≤ 5 times ULN **without symptoms** the statin can be continued with reassessment in 6-12 weeks or sooner if symptoms appear.
- In addition to searching for other causes of CK elevation and myopathy (Table 12), the following outlines a general approach to assessment and management. Refer to CCS on-line resources for greater details.
  http://www.ccsguidelineprograms.ca/images/stories/Dyslipidemia_Program/2012/statin_intolerance_canadian_working_group_consensus.ppt%20read-only.pdf[68]
  - If the patient has symptoms without CK elevations, **the statin should be stopped** and restarted when asymptomatic. Reassess CK and symptoms in 6-12 weeks or sooner if symptoms reappear.
  - If the patient has CK elevations (> 5 times ULN), with or without symptoms, **the statin should be stopped** and restarted when asymptomatic and when CK levels return to normal.
  - The same statin can be restarted if the episode was mild. Alternatively, a lower dose or different statin can be tried. Monitoring enzymes and symptoms in 3-6 weeks is recommended or sooner if symptoms recur.
  - If the episode was **moderate to severe** (CK > 10 times ULN), the patient should be assessed for rhabdomyolysis and consultation with a specialist is recommended before re-starting the statin.

Management of statin-related myopathy [56]

- Several options are reported for managing the symptoms of myopathy; however most are not supported by high levels of evidence.
  - Switch to a statin with hydrophilic (rosuvastatin, pravastatin) rather than lipophilic characteristics or lower potency (fluvastatin) which may result in a lower risk of myopathy.
  - Non-daily doses of statin.
    - Atorvastatin and rosuvastatin have long half-lives and may be suited to alternate day, or up to once weekly dosing.
    - Rosuvastatin, in reduced doses or reduced frequency of dosing, has been tested in small numbers of statin intolerant patients with success.
      - Once-weekly dosing of rosuvastatin 5-20 mg was tested in 10 patients with statin intolerance. LDL was reduced by 29% (6%-62%) in the 8 patients who were able to tolerate the weekly dosing.[88]
      - A retrospective analysis of 51 patients with statin intolerance (76% due to myalgia) found that 73% tolerated alternate day dosing of rosuvastatin at a mean dose of 5.6 mg, achieving a reduction in LDL of 35%.[89]

      The reduction in cardiac events with such dosing regimens compared with daily dosing **requires study**.
  - Use of an alternative classes of lipid lowering agents including, ezetimibe, niacin or fibrates or bile acid resins.
    - Ezetimibe does not have CV outcome evidence so while it may lower LDL, it is uncertain whether CV events will be reduced.
    - The 2012 CCS guidelines[1] state that "no studies to date have demonstrated a decrease in CVD event rate with the addition of lipid-modulating drugs to statin therapy."
  - Co enzyme Q10, vitamin D supplementation
    - Evidence is contradictory or insufficient to support using supplements to alleviate statin-related myalgia. [56]
    - **Canadian Guidelines 2012** do not recommend vitamins, minerals or supplements for symptoms of myalgia perceived to be statin-associated. *(Strong Recommendation, Very Low-Quality Evidence)* [1]
- There is generally no harm in stopping statins in the non-acute situation. [56]
  - Patients should be advised to stop medications if significant symptoms occur and call the prescribing physician, as blood tests may be indicated while symptomatic.

Statin Intolerance

- Diagnosis of statin intolerance should be entertained only when
  - A patient reports symptoms associated with use of a statin (with or without abnormal laboratory findings)
  - Symptoms resolve when the statin is stopped
  - Symptoms recur with the same or a different statin[56]

- The Canadian 2012 guidelines[1] state despite concerns about a variety of other possible adverse effects, all purported statin-associated symptoms should be evaluated systematically, incorporating observation during cessation, re-initiation (same or different statin, same or lower potency, same or decreased frequency of dosing) to identify a tolerated, statin-based therapy for chronic use. *(Strong Recommendation, Very Low-Quality Evidence)*

Liver disease [56]

- Significant liver pathology attributable to statins is rare.
- The most commonly reported hepatic adverse effect is "transaminitis" (elevated liver enzyme levels in the absence of histopathological changes).
  - Incidence of elevated aminotransferase levels (> 3 times ULN) is generally not greater than 3% of treated patients.
  - It is a class effect, usually asymptomatic, reversible, dose-related, similar among all statins, and not correlated to the level of LDL reduction.
  - Most cases of "transaminitis" resolve spontaneously without the need for drug discontinuation.
    - When serious hepatotoxicity is encountered in a statin-treated patient, undiagnosed, non-statin-related liver diseases should be strongly considered in the differential diagnosis.

Monitoring Liver Enzymes [56]

- Please refer to the following website for a management approach for patients with liver disease and/or transaminitis.

  http://www.ccsguidelineprograms.ca/images/stories/Dyslipidemia_Program/2012/statin_intolerance_canadian_working_group_consensus.ppt%20read-only.pdf[68]

- Current guidelines[1] suggest that ALT should be checked within the first 3 months. Routine testing of ALT is not required thereafter.
- Patients with chronic but compensated liver disease can be treated safely with statins.
- While labeling in Canada still promotes serial testing of liver enzymes for at least up to a year and regularly thereafter, it is notable that current US statin labeling now recommends monitoring of liver transaminase values only at baseline and at the time of dose increases or when symptoms warrant.

Neurologic effects

- A potential increase in hemorrhagic stroke and impairment of memory and cognition have been reported with statins.
  - A 2012 meta analysis reports that statins reduced any stroke RR 0.76 (95% CI: 0.73 to 0.79). Subgroup analysis showed benefit in **ischemic stroke** RR 0.79 (95% CI 0.74 – 0.85) per 1.0 mmol/L LDL reduction, and a trend toward increase in **hemorrhagic stroke** RR1.15 (95%CI 0.97 – 1.38).[3]
- Some patients on statins may complain of **memory loss** or **cognitive impairment**.
  - Rojas-Fernandez et al report that cognitive impairment is a rare occurrence and suggest some approaches to management.
    - A trial discontinuation can reveal a temporal relationship.
    - Switch from lipophilic to hydrophilic statins (i.e., pravastatin and rosuvastatin) which have limited penetration across the blood brain barrier.
    - The vascular benefits and putative cognitive benefits outweigh the risk of cognitive impairment associated with statin use; therefore, the current evidence does not support changing practice with respect to statin use, given this adverse effect. [61]
    - When given in late life to people at risk of vascular disease, statins had no effect in preventing Alzheimer's disease or dementia.[62]
  - In 2012 the FDA approved new safety warnings for statins including one on cognitive impairment. The following is a message to healthcare professionals:

    "There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These reported symptoms are generally not serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks)." http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm

Renal

- The FDA reviewed data for all statins following reports of rosuvastatin-associated renal effects (proteinuria and hematuria) and concluded that while all statins have been associated with proteinuria and/or hematuria, the incidence is low and statins do not cause renal toxicity, except in the rare event of rhabdomyolysis.
- Statins may be safely used in patients with chronic kidney disease, whether or not they are receiving dialysis.
- Routine monitoring of proteinuria or renal function in statin-treated patients considered unwarranted. [56]

Diabetes

- A meta-analysis[63] found that statins were associated with a 9% increased risk for incident diabetes (OR 1.09; 95% CI 1.02 to 1.17). This was noted particularly in trials that enrolled older participants.
  - NNH = 255 (95% CI 150 to 852) for 4 years.
- **Intensive** dose statin therapy has been found to increase the risk of diabetes compared with **moderate** dose therapy.[90]
  - Risk to benefit considerations:
    - OR 1.12 (95% CI 1.04 to 1.22) for new onset diabetes
    - OR 0.84 (95%CI 0.75 to 0.94) for reduction in cardiovascular events.
    - This represents 2.0 additional cases in the intensive-dose group per 1000 patient years) and 6.5 fewer cardiovascular events per 1000 patient-years over approximately 5 years.
      - NNH 498 for new onset diabetes
      - NNT 155 for cardiovascular events.
- Findings of increased risk of diabetes have not altered current recommendations for the prevention of CVD in non-diabetic subjects as the vascular benefits markedly outweigh the small increased risk for developing diabetes.
- Canadian 2012 recommendation [1]
  - Statins should not be withheld on the basis of a potential, small risk of new-onset diabetes mellitus emerging during long-term therapy *(Strong recommendation; Very Low-Quality Evidence)*
- Health Canada's MedEffect recently announced a labeling change for statins regarding the risk of increased blood sugar levels and a small increased risk of diabetes among patients already at risk for the disease.
  - Based on the review of all available data, Health Canada concluded that the risk of diabetes appears to be mainly in patients with pre-existing risk factors for diabetes, such as high levels of glucose or triglycerides, obesity, or high blood pressure.

    For further information see: *http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/16949a-eng.php*
- In primary prevention, if a statin is suspected of precipitating diabetes, our content expert suggests emphasizing the importance of lifestyle modification.
  - If the patient has no risk factors for diabetes, consider discontinuing the statin to see if the condition resolves.
  - If the patient has risk factors for developing diabetes, their overall CV risk is likely to be high and the benefits of statin therapy probably outweigh the risks.

Cancer

- A large meta-analyses of individual patient level data found **no significant effects** on deaths due to cancer or other nonvascular causes (RR 0.97; 95% CI, 0.92-1.03;p=0.3) or on cancer incidence (RR 1.00; 95% CI, 0.96-1.04; *P* =0.9).
  - RCTs included those of more vs less intensive statin regimens (5 trials; 39,612 individuals; median follow-up 5.1 years) and of statin vs control (21 trials; 129,526 individuals; median follow-up 4.8 years). [64]

2012 Guideline practical tips for managing statin intolerance[1]

- Patients should be advised to discontinue statin therapy and contact their prescriber if worrisome symptoms develop.
- The amount of effort spent persevering with statin therapy should be directly related to the patient's level of risk.
- For patients at highest risk, all options should be exercised before alternating or withdrawing lipid-lowering therapy.
- Strong emphasis should always be placed on an aggressive nonpharmacologic approach such as diet modulation and exercise.
- For patients at lower risk who do not tolerate statin therapy, a re-evaluation of the need for lipid-lowering therapy should precede a change to alternative therapy because outcome studies are not robust.

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Appendix 1 Summary of JUPITER [33] and Limitations

- JUPITER stands for Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
- Purpose: investigate whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease the rate of first major cardiovascular events in patients with no history of CVD, LDL <3.4 mmol/L, and hsCRP >2 mg per deciliter.
- 89,980 were screened for entry, 17802 were enrolled, 38% women, median age 66 years.
- Primary outcome: composite of MI, stroke, CV death, hospitalization for UA or revascularization.
- Duration: Planned for 5 years but stopped at 1.9 years because the efficacy point had been reached but the outcome which achieved efficacy was not identified in the publication.
- LDL decreased by 50% from 2.8 to 1.4 mmol/L.
- Results:
  - There was benefit in the primary composite outcome and in overall mortality (Table 13).
  - There was benefit in the primary composite outcome in women and the elderly.
  - There was no statistically significant benefit in overall mortality in women and the elderly.

Table 13 Results of JUPITER

Efficacy outcomes	Event Rate		ARR	RRR	NNT for 1.9 yrs	
	Placebo n=8901	Rosuvastatin n=8901			NNT	95% CI
Primary outcome: composite of MI, stroke, CV death, hospitalization for UA or revascularization	2.8%	1.6%	1.2%	44%	82	61 to 127
Overall mortality	2.8%	2.2%	0.55%	20%	182	99 to 1088

ARR, absolute risk reduction; RRR, relative risk reduction; NNT, number needed to treat, calculated on raw numbers.

- JUPITER has been cited to support
  - LDL target of <2.0 mmol/L in primary prevention
  - Statins for primary prevention in the general population and in women and the elderly
  - hsCRP as an additional test for risk assessment
  - The benefit of rosuvastatin in reducing clinical outcomes
- Commentaries have raised several concerns about JUPITER which question its validity [15,44]
  - The high rate of screen failure (1 of 5 people were enrolled) limits generalizability to the entire primary prevention population.
  - The study was stopped early which can exaggerate positive findings.
  - The reduction in CV events was unexpectedly large considering the length of the study.
  - The case-fatality rate in the control group was low (8.8% of patients with an MI died). The case-fatality rate in the rosuvastatin group was 29%, implying that rosuvastatin led to more deaths from MI.

Appendix 2 Table of negative studies

Results of negative studies may not be widely known but they do provide useful information. The following table summarizes some negative studies with their implications.

Study Year	N Length	Population	Comparators	Outcome	Results LDL	Results Outcome	Comments / Implications
Women							
CASHMERE 2006	538 1 yr	Post-menopausal women with no Hx CHD	Placebo Atorvastatin 80 mg Atorvastatin 80 mg + HRT	CIMT	Not reported	No sig difference between placebo and atorvastatin	- Results were not published in the medical literature and came to light through business publications - Atorvastatin might not be effective in postmenopausal women - CIMT might not be a valid surrogate outcome - 1 year might not be long enough for benefit to be shown
Rosuvastatin							
CORONA[a 69] 2007	5011 2.7 yr	Ischemic heart failure Mean age 73	Placebo Rosuvastatin 10 mg	CVD death, non-fatal MI, non-fatal stroke	↓ 45% 3.5 → 1.9	No sig difference	- LDL reduction might not be related to clinical outcomes - Rosuvastatin might not be effective in reducing clinical outcomes - Older patients with complex co-existing conditions might not respond to statins
GISSI-HF[a 70] 2008	4574 3.9 yr	Heart failure (40% were ischemic) Mean age 68	Placebo Rosuvastatin 10 mg	Mortality Hospitalization for CVD	↓ 27% 3.2 → 2.3	No sig difference	- LDL reduction might not be related to clinical outcomes - Rosuvastatin might not be effective in reducing clinical outcomes - Older patients with complex co-existing conditions might not respond to statins - Statins might not be effective in heart failure

Study Year	N Length	Population	Comparators	Outcome	Results LDL	Results Outcome	Comments/Implications
Ezetimibe							
SEAS[36] 2008	1873 4.4 yr	Mild to moderate asymptomatic aortic stenosis No Hx of CVD (primary prevention) Mean age 68	Placebo Simvastatin 40 mg + Ezetimibe	CVD death, aortic valve replacement, CHF from aortic stenosis, MI, CHD hospitalization, stroke	↓ 54% 3.6→ 1.7	No sig difference in primary composite outcome CABG was only positive outcome	- There were no statistical corrections for the many outcomes reported - LDL reduction might not be related to clinical outcomes - Lipid lowering may be ineffective in the elderly in primary prevention (mean age 68 years, 61% of subjects were ≥ 65 years)
ENHANCE[35] 2008	720 2 years	Familial hypercholesterolemia with LDL >5.4 mmol/L	Simvastatin 80 mg+ Ezetimibe 10 mg Simvastatin 80 mg + Placebo	Change in CIMT	Simvastatin: ↓ 39% 8.2 → 5.0 Simvastatin + ezetimibe ↓ 56% 8.2 → 3.7	No sig difference	- Negative result questions value of adding ezetimibe to simvastatin
Diabetes							
ASPEN[72] 2006	2410 4 years	Type 2 diabetes with or without CVD 40 to 75 yrs old LDL ≤ 3.6 if had history of MI LDL ≤ 4.1 with no history MI	Atorvastatin 10 mg Placebo	CVD death Non-fatal MI Non-fatal stroke Revascularization Hospitalization for unstable angina	↓ 29% 2.9 → 2.1	No significant difference in any outcome in primary or secondary prevention groups	- 27% of patients in placebo group and 15% in atorvastatin group took lipid lowering therapy - Difficult to explain lack of effect of atorvastatin in primary prevention group considering the 29% decrease in LDL.
Niacin							
AIM-HIGH[73] 2011	N=3414 Stopped after mean 3 years due to lack of	≥ 45 years with CVD and LDL <4.65 mmol/L	Niacin ER 1500-2000 mg per day Vs. Placebo All patients received: Simvastatin 40-80 mg	CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary or cerebral	2 year data LDL decrease Niacin 12% (from 1.9 to 1.6 mmol/L)	Primary end point group Niacin 16.4% Placebo 16.2%, HR 1.02; 95% CI, 0.87 to 1.21; P = 0.80	- Open label run in identified patients with an acceptable side effect profile to niacin. Approx 50% of patients screened were included in study. - Addition of niacin to statin (with or without ezetimibe) provides no additional benefit and possibly harm due to

Study Year	N Length	Population	Comparators	Outcome	Results		Comments / Implications
					LDL	Outcome	
	benefit shown with addition of niacin		+ezetimibe, if required to maintain LDL 1.03-2.07 mmol/L	revascularization.	Placebo+statin 5.5% (from1.9 to 1.8 mmol/L) HDL increase Niacin 25% (from 0.9 to 1.1 mmol/L) Placebo+statin 9.8% (from 0.9 to 1 mmol/L)	- Rate of ischemic stroke higher with niacin vs placebo (1.6% vs.0.9%). -no sig. Difference in secondary outcomes	ischemic stroke - Since it was studied in combination only, the study does not inform whether niacin alone would be of benefit in patients who are intolerant of other lipid lowering therapies.
HPS2-THRIVE 2013	Approx 4 years	Secondary prevention Did not preselect for low HDL	Niacin + laropiprant (anti-flushing agent) vs. statin	CHD death, nonfatal MI, stroke, coronary revascularizations		- Preliminary data reported on heart.org indicate no significant difference in primary outcome but Increased risk of nonfatal but serious side effects with niacin + liropiprant	- Results have not yet been published in peer-reviewed literature - Niacin showed no benefit compared to statin

CIMT: Carotid intima media thickness. The change in thickness of the intima and media of the carotid artery. This outcome has often been used as a surrogate for cardiovascular events.

CABG: coronary artery bypass graft

a CORONA and GISSI-HF were conducted because post-hoc analyses of RCTs, observational studies, and small studies had indicated a benefit for statins in heart failure. The negative results from two large RCTs specifically designed to determine if statins were beneficial in heart failure show the hazard of basing clinical decisions on low quality research data.

Appendix 3 Ezetimibe clinical trials

EZETIMIBE CLINICAL TRIALS				
Trial Design, Patient Population, Primary Outcome	Comparison (Daily Doses)		Results	Comments
ENHANCE[35] Kastelein JP et al 2008 *Design:* Randomized, double blind, duration: 2 years *Population:* N = 720, mean 46 years old 51% male, dx. of familial hypercholesterolemia (FH) with LDL > 5.4 mmol/L after 6 week placebo run-in. Previous statin use ~ 80%. Approx 30% current smokers. *Primary Outcome*: change in the mean carotid-artery intima–media thickness.(CIMT)	Simvastatin 80mg + Ezetimibe 10mg vs. Simvastatin 80mg + placebo		*CIMT*: No significant difference between groups Both groups had an increase in CIMT with trend favoring Simva + placebo. *LDL levels*: Simvastatin: 4.98±1.56 mmol /l Simvastatin + ezetimibe 3.65±1.36 mmol/ l	No benefit found in this higher risk, FH population questions place in therapy for ezetimibe without proven effects on hard clinical outcomes.
SANDS[74] Fleg JL et al 2008 Post-hoc subgroup analysis of a larger RCT N= 427, 36 months *Population*: SANDS study included 499 American Indian men and women ≥age 40 with type 2 diabetes, LDL-C>2.6 mmol/l , SBP>130mmHg, and no prior CV events *Primary outcome* : carotid artery intimal medial thickness (CIMT)	Standard treatment: statin vs. Intensive treatment with statin with or without addition of ezetimibe 10 mg to achieve goals. LDL treatment goals: Standard: 2.6 mmol/l Aggressive: 1.8mmol/l (Blood pressure and non- HDL goals were also managed to standard and intensive goals.)		Greater CIMT regression with intensive treatment compared to standard. In Intensive group: No difference in CIMT regression between groups that added ezetimibe to those that did not take ezetimibe.	Aggressive LDL lowering resulted in similar regression of CIMT whether from a statin alone or statin plus ezetimibe. Clinical meaningfulness of magnitude of changes in CIMT requires
VYCTOR[71] Meaney A et al 2009 Randomized, open-label comparative 1 year trial. Target level of < 2.6 mmol/l in CHD patients and < 1.8 mmol/l in diabetes *Population:* N= 90 high risk Mexican patients *Primary Outcome:* Change in intima-media thickness	Initial therapy -Pravastatin 40mg -Simvastatin 40 mg -Simvastatin 20 mg + ezetimibe 10 mg	Not at goal increased to: -Pravastatin 40 mg + ezetimibe 10 mg -Simvastatin 80 mg -Simvastatin 40 mg + ezetimibe 10 mg	All 3 arms saw a reduction in CIMT with no difference between arms	Small number of patients in each group (n=30 / group) 26 of the 90 patients discontinued the study.
ARBITER 6–HALTS[75] Taylor AJ et al 2009 RCT, open-label , terminated early due to superiority of niacin over ezetimibe *Population:* N= 363; n= 208 at early termination. Pts with CHD or CHD equivalents. 80% male, LDL at target on statins, low HDL *Primary Outcome:* Change in intima-media thickness	Open label medications added to statin: Ezetimibe 10 mg or Extended Release Niacin 500 mg per day increased to maximum tolerated dose up to 2000 mg/day.		Niacin HDL: Significant increase in niacin group by 18% CIMT: Significant regression in CIMT Reduction in major coronary events compared with ezetimibe (1% vs 5% p=0.04) Ezetimibe Reduction in LDL , HDL and triglycerides Significant increase in CIMT	CIMT regression did not correlate with LDL reduction.
SEAS[36] Rossebo AB et al 2008 R, DB trial 52 months *Population*: N= 1873 mild to moderate asymptomatic aortic stenosis *Primary Outcome*: composite of major CV events	Simvastatin 40 mg + ezetimibe 10 mg Vs. Placebo Open label statin allowed in both groups		Primary outcome occurred in 35.3% of treatment group and 38.2% of placebo (HR 0.96 95%CI 0.83-1.12) The only component of the primary outcome with a significant benefit was coronary artery bypass surgery.	Cancer more frequent in the combination treatment group. P=0.01

EZETIMIBE CLINICAL TRIALS			
Trial Design, Patient Population, Primary Outcome	Comparison (Daily Doses)	Results	Comments
SHARP[37] Baigent C et al 2011 R, DB, N= 9270 median follow-up of 4·9 years *Population*: Chronic kidney disease (3023 on dialysis and 6247 not); no known history of myocardial infarction or coronary revascularisation. 15% previous vascular disease; 23% diabetes; 63% men; mean age 62 *Primary Outcome:* First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure).	Simvastatin 20 mg plus Ezetimibe 10 mg vs. placebo (First year of study included a simvastatin 20 mg group. Patients were re randomized at one year to combination therapy or placebo) 66% compliance rate with therapy	Average LDL difference: 0·85 mmol/L *Major atherosclerotic events*: 11·3% treatment vs 13·4% placebo. RR (0·83, 95% CI 0·74–0·94; p=0·0021). -*Non-hemorrhagic stroke:* treatment 2·8% vs. placebo 3·8%; RR 0·75, 95% CI 0·60–0·94; p=0·01) *Arterial revascularization:* treatment 6·1% vs placebo 7·6%; RR 0·79, 95% CI 0·68–0·93; p=0·0036). No significant difference for non-fatal MI or death from coronary heart disease. Similar outcomes in patients on dialysis vs. not on dialysis.	Unable to determine whether the combination of simvastatin and ezetimibe confers more benefit than simvastatin alone.

Appendix 4 Statin Characteristic [55,56,84]

Generic	Daily Dose[a]		Effect on LDL		Pharmacokinetic Parameters			
All available generically	Usual Adult Daily Dose		LDL Percent Lowering		Metabolizing Liver Enzyme [g]	Renal Excretion (%)[h]	Half life (hrs)[i]	Lipophilic [j]
Atorvastatin	10–80 mg at any time		39 to 60%		CYP3A4	<2	13–16	Yes
Rosuvastatin	5–40 mg[d] at any time		52 to 63%		CYP2C9	10	19	No
Simvastatin	5–40 mg with evening meal[f]		24 to 47%		CYP3A4	13	3	Yes
Fluvastatin	20–80 mg with evening meal		19 to 35%		CYP2C9, 2C8, 3A4	<6	0.5–3	Yes
Lovastatin	20–80 mg with evening meal[b]		24 to 40%		CYP3A4	<10	3–4	Yes
Pravastatin	10–40 mg at bedtime		22 to 34%		Not known[e]	20	1.8	No

a. The lower number in the range is the usual starting dose. The higher number represents the maximum daily dose.
b. A daily dose of lovastatin 80 mg can be given at once with supper or in 2 divided doses, with breakfast and supper.
c. The usual starting dose of pravastatin is 10–20 mg daily.
d. In Asian patients and in those with severe renal impairment, the initial dose of 5 mg daily is recommended.
e. Pravastatin is not extensively metabolized by the cytochrome P450 system. Its precise metabolic pathway is not known
f. Updated simvastatin dosing accompanied a Health Canada Warning regarding simvastatin 80 mg:

   The regular use of the 80 mg dose of simvastatin has been associated with an increased risk of myopathy/rhabdomyolysis, particularly during the first year of treatment. The recommended simvastatin dosage is 5 to 40 mg/day. Patients unable to achieve their LDL-C goal with the 40 mg dose of ZOCOR® should be switched to alternative LDL-C-lowering treatments with lower risks of muscle toxicity.

   Simvastatin 80 mg dose should be restricted to patients who have been taking this dose chronically with no evidence of muscle toxicity or to patients at high risk for cardiovascular complications who do not tolerate other statins and in whom the benefits are expected to outweigh the potential risks. Concomitant use of recommended dosage of simvastatin with certain drugs and grapefruit juice increases the risk of myopathy/rhabdomyolysis. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2012/zocor_hpc-cps-eng.php
g. Statins metabolized by CYP450 3A4 have a higher potential for drug interactions.
h. Some renally excreted statins may require dose adjustment in patients with severe renal dysfunction.
i. Statins with longer half life may be suitable for longer dosing intervals in patients experiencing myopathy on daily dosing.
j. Lipophilicity may contribute to increased risks of myopathy and possibly cognitive impairment.

Appendix 5 Statin Costs for Comparable Lipid Lowering

Rows represent doses and cost of statins for comparable lipid lowering, as indicated in the 1st column

Approximate % LDL lowering	High Potency Statins		Lower Potency Statins			
	Atorvastatin*	Rosuvastatin	Simvastatin	Pravastatin	Fluvastatin	Lovastatin
22%	-	-	5 mg $0.36	10 mg $0.57	20 mg $0.96	-
25-32%	-	-	10 mg $0.71	20 mg $0.67	40 mg $1.34	20 mg $0.72
31-39%	10 mg **$0.30***	-	20 mg $0.88	40 mg $0.81	80 mg $1.62	40 mg or 80 mg 40 mg $1.32 80 mg $2.64
37-45% (Rosuvastatin 10 mg 52%)	20 mg **$0.43***	5 or 10 mg 5 mg $0.65 10 mg $0.48	40 mg $0.88	80 mg (2X 40 mg) $1.62	-	80 mg 80 mg $2.64
47-52%	40 mg **$0.46***	10 mg 10 mg $0.48	80 mg ** $0.88	-	-	-
55-60%	80 mg **$0.46***	20 mg $0.60	-	-	-	-
63%	-	40 mg $0.70	-	-	-	-

McKesson Canada Prices 2013 Costs are primarily for generic brands.

***Note: approximate atorvastatin prices starting on April 1 2013 (18% of brand).**

** no longer recommended – see footnote f. Appendix 4

Reference for equivalent doses Smith MEB, Lee NJ,Haney E, Carson S, HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin Update 5 November 2009 **http://www.rx.wa.gov/documents/statins_final_report_update5_1109.pdf**

Cost for Ezetimibe (Ezetrol) 10 mg: $1.94/ tab

Appendix 6 Clinical Frailty Scale

1. **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. **Well** – People who have no active disease symptoms but are less fit than Category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3. **Managing Well** – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. **Vulnerable** – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up," and /or being tired during the day.

5. **Mildly Frail** – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6. **Moderately Frail** – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7. **Severely Frail** – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** – Approaching the end of life. This category applies to people with a life expectancy < 6 months, who are not otherwise evidently frail.

Where dementia is present, the degree of frailty usually corresponds to the degree of dementia:

- **Mild dementia** – includes forgetting the details of a recent event, though still remembering the event itself, repeating the same question /story and social withdrawal.
- **Moderate dementia** – recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
- **Severe dementia** – they cannot do personal care without help.

1. Canadian Study on Health & Aging. Revised 2008.

2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495.