Simplified Lipid Guidelines: Evidence Review of 12 Key Clinical Questions

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CHAPTER 1: SCREENING FOR CARDIOVASCULAR RISK

When should screening for cardiovascular risk begin? Who should be screened and how often should patients be screened for risk?

We then identified four sub-questions:

a. Does screening reduce cardiovascular or all-cause mortality?
b. Who should we screen and when should we start screening
c. How often should we repeat lipid levels in those not on lipid-lowering agents?
d. Are fasting lipid measurements required, or will non-fasting lipids suffice?

Question 1a: Does screening reduce cardiovascular or all-cause mortality?

Introduction and Methods

In Canada, primary care health professionals commonly perform adult periodic health exams.[1] During these visits, cardiovascular (CV) risk factors (including age, smoking status, blood pressure, diabetes, and lipid levels) are often assessed and entered into a CV risk calculator to predict the likelihood of future cardiovascular disease (CVD).[2] Decisions regarding treatment of dyslipidemia for patients without CVD are based primarily on global CV risk assessments or individual lipid results.[3-6]

It is unknown whether population based screening and assessing patients' CV risk is effective in decreasing CV mortality and overall mortality. If mass CV screening is effective in reducing future cardiovascular events (CVE) or mortality, best evidence should help clarify who should be screened, when screening should commence and optimal intervals for repeat screening.

Evidence search:

National and international guidelines on CV risk assessment and screening and management of dyslipidemia for the prevention of primary prevention of CVD were reviewed. These guidelines include the:

- 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult;[3]
- 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Assessment of Cardiovascular Risk[4] and 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults;[5]
- European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemias;[6]

- National Institute for Health and Care Excellence (NICE) Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (draft).[7]

To determine whether mass screening for CV risk factors through adult periodic health exams (which often includes checking lipid levels) impacts future clinical outcomes, we tracked citations from a systematic review in our archived manuscript repository.[8] We found the same review published fully as a Cochrane review,[9] and other systematic reviews that examined the effectiveness of population based periodic health exams or 'health checks' in general practice clinics[10] and multiple risk factor interventions for the primary prevention of CVD.[11]

Primary papers from these systematic reviews were reviewed when necessary with an emphasis on papers that included: Cholesterol/lipid assessments, papers published post 1980, and that examined clinical (not surrogate) outcomes.

In addition, to look for recent applicable papers, we updated the search strategy performed in the highest quality systematic review.[8] (Appendix 1) Titles of the 284 articles were reviewed, with one study identified as potentially relevant and therefore retrieved. This study however did not report clinical outcomes and was not further reviewed.[12] Finally, we contacted the authors of a large randomized control trial (RCT) examining health checks (including cholesterol levels) in Denmark to determine when their long term mortality results would be published.[13]

Results

Systematic reviews of periodic health exams / health checks on cardiovascular and overall mortality

Two systematic reviews (involving three publications) examined population based screening of asymptomatic patients with periodic health exams or 'health checks' and CV outcomes or overall mortality.[8-10] One methodologically low quality systematic review limited its analysis to interventions from 'general practice based health checks' and focused on surrogate markers.[10] This meta-analysis reported an increase in CV mortality in the screened groups, but due to its low quality, will not be presented in detail.

One high quality review was published both in a condensed form[8] and as a full Cochrane Review.[9] This review examined the effectiveness of health checks performed by physicians, nurses or screening clinics on CV and overall mortality. Health checks were defined as screening for more than one disease or risk factor in more than one organ system and could involve screening and lifestyle intervention. Patients were a general representative of asymptomatic, middle aged patients, and were recruited from the community, workplace or general practice lists, and randomized to health checks or no health checks.

Health checks focused on CV risk reduction, as all studies except one included blood pressure measurement, 11 studies including cholesterol testing (in three studies it was unclear whether cholesterol was tested) and 10 included a clinical or family history.[8] Five

studies also included cancer screening including chest x-rays, mammograms, fecal occult blood testing (FOBT), sigmoidoscopy, or pap tests. A total of 14 trials involving 182,880 patients reported on clinical outcomes. After a median of nine years of follow up (range 4-22 years), health checks were not found to reduce CV risk (RR 1.03, 95%CI 0.91 to 1.17) or overall mortality (RR 0.99, 95%CI 0.95 to 1.03).[8,9]

Limitations of this systematic review included: Nine studies were published over 35 years ago and before the advent of statins, and may not be reflective on current populations or the treatment of hyperlipidemia; many studies appeared to only offer lifestyle intervention; and some controls may have received health checks.

Systematic review of randomized controlled studies examining risk factor modification for the primary prevention of cardiovascular disease

Another systematic review specifically examined the effectiveness of screening and subsequent risk factor modification for the primary prevention of CVD.[11] This review included studies of adults >35 years old with or without specific CV risk factors risk factors (i.e. diabetes, hypertension, hyperlipidemia, obesity) recruited from general populations, occupational groups, or general practitioners' offices. Studies were at least six months long, and patients were randomized to usual care or health promotion activity including counselling or educational interventions, +/- pharmacological treatments, to alter more than one CV risk factor (diet, blood pressure, smoking, total blood cholesterol, or physical activity). The primary outcome was all-cause mortality, fatal coronary heart disease (CHD), and fatal stroke events.

Overall, 14 trials of 139,256 participants reported on clinical endpoints. Only one study was also included in the aforementioned high quality systematic review of health checks.[14] The mean age of the patients was 50 years and median follow up was one year (range six months to 12 years). CV mortality and all-cause mortality was again unchanged in patients who received CV risk factor screening and modification with odds ratios (OR) of 0.99 (95%CI 0.92 to 1.07) and 1.00 (95%CI 0.96 to 1.05) respectively.[11]

Two sub-group analyses demonstrated reductions in fatal and non-fatal CV disease and overall mortality. These two analysis enrolled patients only if they had diabetes or hypertension, or examined patients given hypertensive **or** cholesterol agents. In both these analysis, the same studies were commonly included.[11]

Limitations of this systematic review included: Some studies recruited only patients with known CV risk factors and therefore not truly screening general asymptomatic population; many studies took place before the advent of statins; and many only employed non-pharmacological interventions.

One of the largest studies in the systematic review is likely the most representative of clinical practice.[15] In this study, about 30,000 Swedish men (47-55 years old) were randomized to CV risk screening, which included a personal and family history, an exam (including height, weight, and blood pressure) and serum cholesterol measurement and

ECG recording, or no CV risk screening. Those screened and found to have hypertension or hyperlipidemia were treated with anti-hypertensive agents (commonly Beta-blockers and/or diuretics) and cholesterol reducing agents (clofibrate and nicotinic acid). Smokers were provided cessation counseling. After a mean follow up of 11.8 years, there was no difference in CHD, stroke or mortality between the two groups (statistics not reported).[15]

Finally, a large RCT published since the systematic reviews examined whether screening 30-60 year olds for CV risk factors with subsequent lifestyle interventions (diet, exercise, and smoking cessation) affected ischemic heart disease, stroke or mortality rates.[16] After 10 years of follow up, they found there was no difference in the rates of ischemic heart disease (Hazard Ratio (HR) 1.03, 95%CI 0.94 to 1.13), stroke (HR 0.98, 95%CI 0.87 to 1.11), or overall mortality (HR 1.00, 95%CI 0.91 to 1.09) in the screened group [(n=11,629) compared to the control group (n=47,987)]. This trial is also limited by the fact that only lifestyle interventions were employed.

Bottom Line
Mass population based screening and interventions for cardiac risk factors in patients without CVD do not appear to reduce CV or all-cause mortality. This evidence is limited by many studies only employing lifestyle treatment for cardiovascular risk factors and pre-dating the advent of statin therapy.

Question 1b: Who should we screen and when should we start screening?

Introduction
Despite the lack of mortality benefit, periodic health exams with CV risk assessments and interventions are commonly performed,[1] are expected by patients,[17] and believed necessary by many physicians.[18] The lack of benefit could possibly be explained by screening populations at low risk of future CVD, and in whom any intervention will not be shown to be effective. Therefore, in order to get a better understanding of who may benefit from CV risk screening and modification, cohort or epidemiological data should be used to explore age and sex related incidence of CVD, the attributable risk of cardiac risk factors, and whether certain individuals warrant earlier or different screening than the general population.

Methods
Again, national and international guidelines on CV risk assessment and screening and management of dyslipidemia for the prevention of primary prevention of CVD were reviewed.[3,4,6,7] Relevant papers cited in these references were reviewed and citation tracking was performed. We also searched PubMed and Medline for cohort/epidemiological data demonstrating the true age and sex specific probability of developing CVD, specifically related to Canada or North America. We found a comprehensive review of the current epidemiology of CVD in the United States,[19] and subsequently reviewed relevant citations from this review.

The incidence of CVD rises with age and comparable incidence rates occur about 10 years later in women compared to men.[19] For males between 35-44 years of age, the annual incidence of CVE is 3/1000. This rate increases from 10.2/1000 person years (PY) for 45-54 year olds to 21.4/1000 PYs in 55-64 year olds. In women, the incidence of CVD rates increases from 4.2/1000 PYs for 45-54 year olds to 8.9/1000 PYs for 55-64 year olds.[19]

Two of the aforementioned guidelines recommend screening begin at age 40 for men and 50 for women.[3,6] Other guidelines recommend commencing CV screening in both men and women at 40 years of age,[4,19] with one guideline also recommending assessing traditional CV risk factors (including cholesterol) in patients at 20 years of age (Table 1).[4]

Table 1: General Screening Recommendations from National / International Guidelines on Cardiovascular Risk Assessment

Guideline	General Screening Recommendations	Screening Tool Used	Screening Frequency
CCVS 2012[3]	Men >40 years Women >50 years or post menopausal	Framingham	Annually if 10 year FRS >5% Q 3-5 years if FRS <5%
AHA 2013[4]	All patients 40-79 years	Pooled Cohort equations	4-6 years
	All patients 20-79 years*	Pooled Cohort equations	4-6 years
NICE 2014[7]	All patients 40-74 years	QRISK2 UKPDS for diabetic patients	Not formally stated: suggest 'ongoing basis' or 'mandated q 5 years' and 'annual risk assessments not useful'
ECS 2012[6]	Men >40 years Women >50 or post menopausal	SCORE	Response to therapy assessed at 6-8 weeks from initiation or dose increases for statins. Standard practice for subsequent follow-up monitoring is 6-12 months, but such monitoring intervals are arbitrary.

* = assess traditional risk factors (including cholesterol levels)

<u>Special populations to screen</u>

Patients with identified CV risk factors:

Most CV risk is still attributed to traditional CV risk factors including age and gender, hypertension, smoking, diabetes, hyperlipidemia, and also obesity, lack of physical activity, and poor diet.[20,21] Patients who have one CV risk factor are likely to have another CV risk factor further increasing their CV risk.[20] For these reasons, patients who have been identified with a CV risk factor should be screened for other CV risk factors to assess the individual's global CV risk.

Ethnicity:

Persons of different ethnicities have been identified as having differing rates of CVD. While a complete review of different CV risk of all ethnicities is beyond the scope of this document, the increased risk of African Americans warrants mention.

Compared with whites, African Americans have a 1.8 times greater rate of fatal stroke, a 1.5 times greater rate of death attributable to heart disease.[19] This increased risk may reflect

the fact that African Americans have the highest prevalence rate of hypertension in the world,[19] with over 44% of adult African American women being diagnosed with hypertension.[22]
In Canada, patients of First Nation or South Asian descent may be at increased CV risk.[3] Whether this elevated risk reflects true ethnic/genetic differences or confounding by other CV risks factors needs to be better delineated before strong recommendations can be made.

Other chronic medical conditions:
Some guidelines[3,6,7] recommend CV risk assessments and screening lipid measurements in all patients, irrespective of age, with:

- Chronic autoimmune inflammatory conditions[3,6,7] including: Rheumatoid arthritis, systemic lupus erythematosis, psoriatic arthritis, or ankylosing spondylitis;
- Other conditions including: Inflammatory bowel disease,[3] chronic obstructive lung disease,[3,6] HIV infection,[3,6] chronic kidney disease (CKD),[3,6] and erectile dysfunction.[3]

The evidence associating some medical conditions (CKD)[23] or treatments (protease inhibitors for HIV)[24] with CVD appears robust. However, associations between other medical conditions and CVD is inconsistent[25,26] and potentially misleading due to small cohort or case control studies with a small number of CVEs.[25,27] Ultimately large prospective cohort studies are needed to better understand which chronic medical conditions truly elevate one's CV risk and whether the risk is related to the disease, medications,[28] or other potential confounders.

Bottom Line
CVD is most associated with advancing age and traditional CV risk factors. Although it may be simpler to start CV risk assessments in all patients over the age of 40 years, best evidence supports starting screening men at 40 years and women at 50 years. Patients with one CV risk factor are more likely to have another CV risk factor. More evidence is needed to determine which non-cardiac chronic medical conditions or treatments are truly independently associated with elevated CVD risk.

Suggested Recommendation(s)
For the primary prevention of CVD, it is reasonable to perform lipid screening and global CV risk assessment in:

- All men over 40 years of age and women over the age of 50 years,
- Patients who have a known traditional CV risk factor including: Hypertension, diabetes, smoker, physical inactivity, and obesity.

Question 1c: How often should we repeat lipid levels in those not on lipid-lowering agents?

Introduction and Methods
Patients often have their lipids re-checked during their annual periodic health exam. Recommendations pertaining to repeat lipid testing frequency were found in the

aforementioned guidelines.[3,4,6,7] We also searched for evidence specifically addressing changes in cholesterol levels over time through citation tracking from a key paper in our manuscript repository.[29]

Results

Guidelines differed in their recommendations as to the frequency to which lipid testing should be repeated. One guideline recommended repeating lipid levels to assess response to therapy at 6-8 weeks,[6] while another recommended annual re-testing if the 10-year Framingham risk score is >5%.[3] Other guidelines recommend repeating every to 4-6 years,[4] while another does not provide statements as to when to repeat lipid levels, but states that annual risk assessments are 'not useful' (Table 1).[7]

Within the same person, serum lipid measurements are variable. This variability is due to both the collection and laboratory analysis process and the within patient biological variability of cholesterol.[30,31] A five year study of 9,000 CHD patients randomized to a statin or placebo, assessed the short term variability and long term trends in cholesterol levels.[29] Short term variability was determined by repeat cholesterol levels performed four weeks apart, prior to any intervention. Long term variability was determined by serial cholesterol measurements (every six months for the first year and annually thereafter for five years) after six months of treatment with pravastatin 40 mg or placebo.

The calculated coefficient of variation of within person cholesterol levels was 7% and the 95%CI of a single cholesterol level was +/- 0.80 mmol/L.

In this study, long term cholesterol levels did not change substantially over the five years. In the placebo arm, mean cholesterol levels rose by 1.4% (from 5.65 to 5.73 mmol/L) or about 0.3% per year. Combining the within-person variation with the minimal long-term change in cholesterol levels, it appears to take around four years for the long-term variation to exceed the average short term variation in cholesterol levels.[29] The authors conclude that in order to measure true changes in lipids and not just the short term variability, repeat lipid testing should occur no more frequently than every 3-5 years.[29]

Another study performed repeat CV risk assessments on two cohorts of middle-aged men and women. One cohort followed 13,757 patients from Tokyo (mean age 47.8 years and 47.5% men) for three years, while the other followed 3,855 Framingham patients (mean age 45.7 years and 41.2% men) for 19 years. The study's objective was to determine the proportion of individuals, based on initial 10-year CV risk assessment (classified as <5%, 5-10%, 10-15%, or 15-20%) that with repeated risk assessments over time would be re-classified into the high CV risk category (10-year risk >20%).[32]

In the Tokyo cohort, patients initially classified in the <5% and 5-10% risk categories had a three year risk of re-classification to high risk of 0.05% and 0.7% respectively. In the American cohort, patients initially classified in the <5% and 5-10% risk categories had an eight year risk of re-classification to the high risk category of 0.5% and 9.1% respectively.[32] Even after 19 years of follow up, the risk of re-classification of a patient with an initial risk assessment of <5% was only 6.8%.[32]

It therefore appears reasonable that for middle aged individuals with an initial 10-year CV risk assessment of <10% and in whom do not develop other CV risk factors, repeating initial lipid testing and CV risk assessment could be lengthened to eight years. For simplicity we propose that 10 years is a reasonable interval for repeat lipid testing in these low risk patients.

What 10 year CV risk are most middle-aged Canadians at?
When risk calculations are performed on relatively healthy middle-aged patients, the majority will have a 10-year CVD risk of <10%. From above mentioned cohorts of Tokyo and American patients, 84.6% and 73.7% of patients respectively had an initial CV risk of <10%. Similarly, 61.7% of 3,015 middle aged Canadians (mean age 56.3 years and 58.8% men) assessed in Canadian primary care offices had a calculated 10-year risk of <10%.[33] It therefore appears that many middle-aged Canadians would be categorized as low risk and could have their initial cholesterol levels repeated in 10 years.

Bottom Line
For patients not on lipid lowering therapy, there is substantial short-term variability and minimal long-term changes in lipid levels. Frequent lipid testing is likely only measuring the short-term variability and is unlikely to truly alter global CV risk assessment.

Suggested Recommendation(s)
- In patients without lipid lowering therapy or changes in other cardiovascular risk factors, we recommend repeating lipid levels and global CV risk assessments at least every five years (Moderate Quality Evidence),
- In low risk patients without lipid lowering therapy in the absence of or changes in other CV risk factors, and with an initial 10-year CV risk assessment of <10% we recommend repeating lipid levels and global CV risk assessment every 10 years (Moderate Quality Evidence),
- It could be argued that as lipid levels change minimally over the long term, the initial lipid results could be used for ongoing (future) CV risk assessments.

Question 1d: Are fasting lipid measurements required, or will non-fasting lipids suffice?

Introduction and Methods
Fasting lipids levels have been recommended as it was thought fasting levels better reflect future CV risk.[34] Restricting patients to fasting before laboratory testing may contribute to testing non-adherence, unnecessary fluctuations in laboratory demand and wait times, and even potential hypoglycemia in diabetic patients.[35] As a result, whether non-fasting lipids can reliably estimate fasting lipids levels and future CVD risk has recently been explored. We performed citation tracking from key manuscripts in our repository along with a PubMed search.

One study of over 30,000 Danish patients estimated that maximal changes between non fasting and fasting lipids was: -0.2 mmol/L (low-density lipoprotein (LDL) and total cholesterol (TC)), -0.1 mmol/L (high-density lipoprotein (HDL)), and +0.3 mmol/L for triglycerides (TG).[36] Another Canadian study of over 200,000 patients found that non-fasting changed TC and HDL by <2%, LDL by ~10%, and TG by ~20%.[37] These small differences between fasting and non-fasting levels lipid levels are less than the within person variability[29] and the suggested minimal clinically important differences in LDL and TC of 1 mmol/L.[36]

Although TG are most susceptible to non-fasting patients, commonly used CV risk calculators do not use TG to predict CV risk.[38] In addition, a recent large compilation of prospective cohort studies involving 302,430 patients and 2.7 million person years of follow up failed to demonstrate an association between TG levels and CVE.[39] This study also demonstrated that non-fasting HDL and LDL levels correlate at least as well with future CV risk as fasting levels.[39]

Bottom Line
Due to the minimal differences between fasting and non-fasting lipid parameters, and that non-fasting HDL and LDL levels correlate with future CVE, patients should not be required to fast for their lipid testing. Removing this restriction should improve test adherence and limit unnecessary variations in laboratory demand and potential patient harm.

Suggested Recommendation(s)
Non-fasting or fasting lipid levels can be used to calculate global CV risk (Moderate Quality Evidence).

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Appendix 1: Updated Literature Search: Health Checks and Mortality outcomes performed April 17, 2014

1. Physical examination/ and ((annual or GP or periodic or yearly or routine).ti. or ((primary adj2 (care or healthcare)) or primary health$ or general practitioner? or general practice or family doctor? or family practice? or family physician?).ti,ab.)
2. (health check$ or healthcheck$ or annual physical? or annual medical or medical check$ or primary care check$ or wellness check$ well care or wellcare or well woman or well visit?).ti.
3. ((annual or periodic or regular or routine or yearly) and (check$ or check-up? or health$ exam$ or health evaluation? or medical exam$ or physical? exam$ or wellness check$ or GP visit? or physician? visit? or doctor? visit? or office visit?)).ti.
4. ((annual or yearly) adj2 (medical? or physical?)).ti.
5. ((annual or yearly) and visit?).ti.
6. (preventive? and (care check$ or checkup? or check-up? or visit? or exam$ or family doctor? or GP or family physician? or general practitioner?)).ti.
7. or/1-6
8. 7 not (cannibis or alcohol$ or abuse or narcotics or addiction?).ti.
9. Physical examination/
10. (check-up? or checkup?).ti,ab.
11. (annual medical or yearly medical or annual physical).ab.
12. ((annual or periodic or (primary adj2 (care or healthcare)) or primary health$ or general practitioner? or general practice or GP or family doctor? or family practice? or family physician? or regular or routine or yearly) adj3 (healthcheck? or health$ exam$ or health evaluation? or medical exam$ or office visit? or GP visit? or physical? exam$ or wellness check$)).ab.
13. ((annual or yearly) adj3 (physician? visit? or doctor? visit? or office visit?)).ab.
14. "well care".ti,ab.
15. (prevent$ and (screen$ or visit?)).ti. or (prevent$ adj3 (screen$ or visit?)).ab.
16. or/9-15
17. Mass screening/
18. Multiphasic screening/
19. ((community$ or program? or multiphasic or multi-phasic or (primary adj2 care) or "office visit?" or GP or general practice or care or healthcare or routine or annual) adj2 screening).ab.
20. screening.ti.
21. or/17-20
22. Primary prevention/
23. exp Preventive Health Services/
24. Health promotion/ or Healthy People Programs/
25. (prevention or preventive or preventative).ti.
26. Risk assessment/
27. or/22-26
28. Risk factors/
29. or/22-26,28
30. exp Primary health care/ or Family practice/ or Physicians, family/
31. ((family or general) adj (doctor? or practice? or practitioner? or physician$)).ti.
32. (primary adj2 (care or health care or healthcare or medical care or patient care)).ti.
33. Community Health services/ or Community mental Health Services/ or Community Pharmacy Services/ or Mobile Health units/ or Community Health Centers/ or Community health nursing/
34. community$.ti.
35. or/30-34
36. exp Aged/
37. (exp Cardiovascular Diseases/ or exp Digestive System Diseases/ or exp Endocrine System Diseases/ or exp Musculoskeletal Diseases/ or exp Lung Diseases, Obstructive/) and (pc or di).fs.
38. disease?.hw. and (pc or di).fs.
39. (diabet$ or cardio$ or heart or disease or copd).ti.

40. or/37-39
41. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
42. exp animals/ not humans.sh.
43. "comment on".cm. or systematic review.ti. or literature review.ti. or editorial.pt. or letter.pt. or meta-analysis.pt. or news.pt. or review.pt.
44. 41 not (or/42-43)
45. 17 and (or/26,28)
46. intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab.
47. (collaborativ$ or collaboration? or tailored or personali?ed).ti,ab.
48. (exp hospitals/ or exp Hospitalization/ or exp Patients/ or exp Nurses/ or exp Nursing/) and (study.ti. or evaluation studies as topic/)
49. demonstration project?.ti,ab.
50. (pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab.
51. (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.
52. trial.ti. or ((study adj3 aim?) or "our study").ab.
53. (before adj10 (after or during)).ti,ab.
54. ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw.
55. ("time series" adj2 interrupt$).ti,ab,hw.
56. (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab.
57. pilot.ti.
58. Pilot projects/
59. (clinical trial or multicenter study).pt.
60. (multicentre or multicenter or multi-centre or multi-center).ti.
61. random$.ti,ab. or controlled.ti.
62. (control adj3 (area or cohort? or compar? or condition or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt.
63. "comment on".cm. or systematic review.ti. or literature review.ti. or editorial.pt. or letter.pt. or meta-analysis.pt. or news.pt. or review.pt.
64. exp animals/ not humans.sh.
65. *experimental design/ or *pilot study/ or quasi experimental study/
66. ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab.
67. ("time series" adj2 interrupt$).ti,ab.
68. (animal/ or animal.hw.) not ((animal/ or animal?.kw,hw.) and (human/ or human?.hw,kw.))
69. (book or letter).pt.
70. (or/46-53,56-57,60-62,65-67) not (or/68-69)
71. (or/46-62) not (or/63-64)
72. 16 and 35
73. 16 and (or/21,27,40)
74. 7 and 71
75. 7 and 44
76. 16 and 35 and 44
77. 16 and 35 and 71
78. (or/17-18) and (or/26,28)
79. 74 not 75
80. 16 and (or/21,27,40) and 44

81. (or/17-18) and (or/26,28) and 44
82. or/75-76,80-81
83. (or/74,77,79) not 82
84. (2011$ or "2012" or 201012$).ed.
85. 82 and 84
86. 83 and 84
87. limit 82 to yr="2011-current"
88. limit 83 to yr="2011-Current"
89. 85 or 87
90. 86 or 88
91. 82 or 83
92. limit 91 to yr="2012 -Current"
93. 92 not 90

CHAPTER 2: BIOMARKERS

Do we have evidence to support the use of biomarkers in risk assessment or monitoring?

We identified four sub-questions:

a. Are risk factors-biomarkers associated with risk of cardiovascular events?
b. Do risk factors-biomarkers added to conventional risk prediction models contribute meaningfully to risk prediction?
c. Are changes in risk factors-biomarkers, through medical/lifestyle interventions, associated with improved clinical outcome? Will a certain risk factor-biomarker be useful to monitor as a surrogate of clinical effect?
d. Does high-level evidence (from randomized controlled trials) verify that changes or targeting of risk factors-biomarkers improves outcomes?

Question 2a. Are biomarkers associated with risk of cardiovascular events?

Introduction and Methods

It has been estimated that there are over 300 risk factors associated with cardiovascular disease (CVD) risk.[1] We focused our evaluation on risk factors-biomarkers that have a substantial body of evidence. Therefore we examined meta-analyses of risk factors or biomarkers. We included only articles examining risk factors-biomarkers in primary prevention (those without a history of CVD). We also did not look at specific populations (examples include HIV positive patients, those of certain ethnicity, etc.). We did not examine diabetics alone but did include them if they were part of primary prevention study. Figure 1 provides a summary of our search. The results are not meta-analyzed but reported in qualitatively.

Biomarkers are often felt to be serological markers only. Risk factors include a somewhat broader group and arise from any radiological, serological or clinical finding (from coronary artery calcium (CAC) to waist circumference). For the purposes of this and all questions, risk factors and biomarkers will be grouped together and abbreviated as RFB (risk factor or biomarker).

Results

Table 1 (Excel supplement) provides a list of RFB reporting association with cardiovascular (CV) risk examined in meta-analyses.[2-10] Combined cohorts are grouped by RFB. There are 139 unique meta-analyses of RFB identified by our search and from two overview systematic reviews of meta-analyses. This included 68 specific risk factors. The largest number of meta-analyses for single specific risk factor was 11 (for total cholesterol (TC)). Many were also variations in a risk factor. For example, blood pressure was examined seven ways as daytime blood pressure, nighttime blood pressure, night-to-day blood pressure ratio, non-dipping blood pressure, masked blood hypertension, white coat hypertension, and blood pressure difference between arms.

Of the 139 meta-analyses, 121 (87%) found statistically significantly association of a RFB and CVD. RFB that were not statistically significant in at least one meta-analysis were: White coat hypertension (not significant in 1 of 1 meta-analysis); insulin fasting (1 of 4); insulin post-glucose load (2 of 2); glucose fasting (1 of 2); adiponectin (1 of 1); von Willebrand factor (1 of 2); TSH (6 of 7); testosterone (1 of 2); triglycerides (TG) (2 of 7); retinal arterial caliber (1 of 1); and retinal venular caliber (1 of 1). Even if all these were excluded, 57 of the 68 (84%) RFB were statistically significant in each meta-analyses in which the RFB was investigating. Eighty-six (71%) of the 121 statistically significant results had associations of ≤15% (for reduced CVD) or ≥25% (for increased CVD), indicating a possible clinically important association.

Limitations

1. Different Analyses: We have to be cautious of over-interpreting differences between meta-analyses. Some use dichotomous comparisons between quartiles, highest to lowest or extremes vs normal. These will give larger associations. If incremental increases over a long range are used, the associations maybe smaller. For example, using a dichotomous outcome for "glucose, post load", the association was 1.58 (1.19 to 2.10) while examining "glucose, post load" per 1 Standard Deviation increment yielded an association of only 1.03 (1.02 to 1.04). False differences may also occur with the use of different statistics (Cox regression vs random effects relative risks) and different outcomes (myocardial infarction (MI) vs all CVD).
2. Heterogeneity: Individual studies within the meta-analyses frequently had different results. Within the 58 from our sample that provided heterogeneity statistics, 28 (48%) had heterogeneity (by i-stat) ≥50%. When it was reported in other studies as a dichotomous outcome, it was positive 43% of the time. The remaining meta-analyses were unclear as the authors of one overview systematic review[3] assumed heterogeneity was negative if not reported.
3. Selective Reporting: Of 56 meta-analyses in one overview systematic review, 29 (52%) had an excess of statistically significant studies (test of actual vs predicted statistically significant). This would suggest selective publication of positive studies.
4. Excess Statistical Significance of Individual Studies: In one overview systematic review of 919 studies (in 56 meta-analyses), 472 (51%) showed nominal (barely) statistically significant results. The expected number of nominal statistical significance was 317. This suggests that there is either selective reporting of outcomes, adjustment of results or both.
5. Small Samples: Of the 127 meta-analyses that provided the total number of events used in the analysis, 27 (21%) had samples <1,000.
6. Small Sample Effects from Individual Studies: Small studies are generally at higher risk of bias, particularly in exaggerating the effect size. This can be examined by comparing how often the effect size of a meta-analysis is unpredictably larger than the effect size of the largest study included in the meta-analysis. In one overview systematic review,[2] 13 of 56 meta-analyses had evidence that small studies within the meta-analyses were causing an inflation of the association.

Summary of Limitations

Many of the results may not be reliable: Either not statistically significant or not meaningfully different. In one overview systematic review,[2] only 23% of meta-analyses were at low risk of bias.

Discussion

There is no doubt that there are many RFB associated with CVD. This supports the concept that the pathogenesis of CVD is multi-factorial and complicated. This should dissuade us from being too enthusiastic about identifying a single factor that will add meaningfully to our ability to predict CVD. In fact, some have suggested that relative risks beyond 1.5 should cause skepticism not enthusiasm.[11] Given that the data is frequently at high risk of bias and many of the findings appear to be exaggerated, we need to be very cautious regarding any our eagerness for adoption of any biomarkers. Even if we find a marker that strongly and reliably predicts CVD, we need to consider whether it adds meaningfully to established risk assessment tools (like Framingham) and whether modification of that marker improves outcomes. For example, both homocystiene and Vitamin D maybe associated with a 38% and 83% increase in the risk of CVD, respectively. However, studies targeting these risk factors fail to show any reduction in CVD.[12,13]

Limitations of Our Review

Our search was not comprehensive and there are undoubtedly more meta-analyses of RFB. However, this would not meaningful change the conclusion that there are a lot of physiological factors that have demonstrated association with cardiovascular outcomes.

Bottom Line

There are many RFB that are statistically significantly associated with CVD (Low to Moderate Level Evidence). Interpretation of the research is challenged by multiple limitations. For any to have utility, that need to demonstrate they add meaningfully to established risk assessment tools (like Framingham).

Question 2b: Do biomarkers added to conventional risk prediction models contribute meaningfully to risk prediction?

Introduction

There are a large number of new RFB that have been examined in multiple studies and show statistically significant association with CVD. However, there are large numbers of predictive tools, like Framingham, available that use six or seven different risk factor combinations to estimate the risk of having CVD in the next five to 10 years (see section on Risk Calculators). Given that we have reasonable tools to assess risk, the remaining question is, "What do novel RFB add to existing risk assessment tools or to risk stratification?"

Traditionally, the value of new RFB added to established risk assessment tools was assessed with the receiver-operator-characteristics (ROC) curve. The statistic in measuring the predictive performance within the ROC is the area-under-the-curve (AUC) or C-

statistic.[14-17] The increase in the AUC due to the addition of the new RFB is known as the Incremental Improvement in the AUC or the IAUC. In recent years, it has been suggested that the AUC or IAUC are inadequate. In particular, it may be too conservative and could fail to capture the number of patients reclassified or shifted considerably to lower or higher risks. Therefore, a number of other measures have been put forward.[14-17] Reclassification tables provide a descriptive presentation of the number/percent of the population reclassified by the addition of the new RFB to the existing assessment tools. The Net Reclassification Improvement measures the people reclassified in to risk categories correctly (in having or not having CVD) by the addition of the new RFB. The Net Reclassification Improvement can be modified to examine the number of patients moving up or down in risk without categories. The Integrated Discrimination Improvement (IDI) assesses the difference in the projected probabilities for events and non-events of the models. For further information on the new measures, readers are directed to citations 14-17.

Many limitations of these new measures remain. What is a meaningful change for any of these measures is still unknown.[14] Additionally, despite enthusiasm for new measures that can hopefully identify the potential utility for new RFB, a number of issues exist.[18,19] For example, the reporting of net reclassification index is often incorrect or incomplete[18] and interpretation can be misleading.[19] Additionally, it should be noted that reclassification reporting might be deceptive itself.[20] Risk categories are arbitrarily assigned cut-offs. Shifting from 19% estimated risk to 21% estimated risk would move a patient from moderate or intermediate risk to high risk. However, this is only a 2% change in risk and well within the boundaries of the confidence limits of the estimate.[21,22] Additionally, the benefits of statins in reducing CVD, derived from the risk estimate, would move from 4.75% to 5.25%, a meaningless difference. For other examples, see the review of C-reactive Protein (CRP) by McCormack.[20]

Methods

We searched for systematic reviews and meta-analyses reporting the incremental value of novel RFB added to Framingham or other established risk assessment models. Two systematic reviews of quality of the research on biomarkers and utility of biomarkers were completed in 2009. We therefore focused on these and augmented with all biomarker meta-analyses from 2009 onward. These were augmented with single cohort studies examining multiple biomarkers from the same time frame. We required, at a minimum, reporting of AUC (or C-statistic) before and after the introduction of the new/additional RFB.

Results

Two overview systematic reviews were identified.[23,24] Tzoulaki et al[23] examined the quality of 79 cohort studies of modifications to the Framingham risk equation. Studies were identified if they referenced the Framingham equation published in Circulation 1998. Amount of improvement in AUC with a new RFB correlated with poorer baseline AUC. AUC change of 0.05 or more were seen only when baseline AUC ≤0.72. Framingham was calculated or used sub-optimally in 62% of the studies and mean/median follow-up was <8 years in 56% of studies. Only 46% provided a ROC (AUC) analysis and only 9% performed a

reclassification analysis. Improved prediction with at least one RFB was claimed in 80% of studies. The improvement in AUC was higher when Framingham was sub-optimally done and when the methods of statistical analysis were not adequately described.[23]

Helfand and colleagues[24] reviewed the evidence for the use of CRP, CAC score, lipoprotein(a), homocysteine, leukocyte count, fasting blood glucose, periodontal disease, ankle–brachial index, and carotid intima–media thickness (CIMT).

For CRP, the evidence quality was rated as having "some" limitations but the overall strength of evidence and applicability to intermediate risk patients was "good." However, reclassification numbers are unreliable. Examining patients with a 15-20% estimated risk, adding CRP would reclassify 0-5% of women to high risk and an unknown number of men. Note, this is from only three studies and the definition of intermediate risk (15-20%) is not consistent with the common used standard of 10-20%. Using CRP to guide therapy is also unclear due to a lack of evidence. All remaining RFB were felt to have poor evidence, inconsistent results and/or provide no meaningful prediction.[24]

We identified five other meta-analyses with 22 RFB.[9,25-28] RFB include TG, apolipoprotein B, apolipoprotein A-I, apolipoprotein B and A-I, lipoprotein(a), lipoprotein-associated phospholipase A_2 activity, lipoprotein-associated phospholipase A_2 mass, A1c, fasting glucose, random glucose, post-load glucose, BMI, waist circumference, waist-to-hip ratio, BMI plus waist circumference, BMI plus waist-to-hip ratio, CIMT, CRP, fibrinogen, CRP plus fibrinogen, leukocyte count, and albumin. Full details are provided in Supplement Table 2. Change in AUC was reported for all 22 risk factors and ranged from -0.0001 to 0.0040 (for CRP and fibrinogen combined), with 12 being statistically significant. The largest statistically significant change in AUC with a single RFB was with CRP (0.0039) and the next closest as leukocyte count (0.0036). Net reclassification improvement was reported for 17 RFB and was not statistically significant in any. The integrated discrimination improvement (IDI) statistic was reported for nine RFB. The seven statistically significant results ranged from 0.0005 to 0.0013 in IDI value. For the best result (0.0013 with A1c), this means the ability to differentiate the cases (those having events) from the controls (those not having events) improved by 1.7% with the addition of A1c to standard risk assessment tools.

The Emerging Risk Factors Collaboration[25-28] propose estimating risk with traditional risk factors (such as Framingham) and then only further examining RFB in those at intermediate risk (10-20% chance of CVD over 10 years). They then calculated the Number Needed to Treat (NNT) (test) to prevent one CVD through the use of that RFB. This was performed for five of the 21 risk factors they examined. The best NNT was 440 over 10 years for CRP and 490 for fibrinogen. Among the lipoprotein markers tested, the 10-year NNT ranged from 801 to 4,541.

Two single studies of multiple biomarkers are also included as adjunctive content.[29,30] Melander and colleagues[29] followed 5,067 patients who had 418 CVD events over a median 12.8 years of follow-up. The change in AUC for the five biomarkers tested (CRP, Cystatin C, midregional proadrenomedullin (MR-proADM), midregional proatrial natriuretic peptide

(MR-proANP), and N-BNP) was statistically significant for two (Cystatin C and MR-proADM) but the value was less than 0.005 for each. Additionally, none of the net reclassification and IDI statistics were statistically significant. The change of AUC, net reclassification improvement or IDI did not improve meaningfully when RFB were combined together.[29] Yeboah and colleagues[30] followed 1,330 intermediate risk (10-year CVD risk) patients who had 123 CVD events over a median 7.6 years of follow-up. The six risk factors were examined Ankle Brachial Index, Brachial Flow Mediated Dilation (FMD), CAC, CIMT, Family History, and High-Sensitivity CRP. Compared to Framingham alone, the addition of any risk factor did not meaningfully change the AUC (≤0.011) except CAC and that was 0.097. The net reclassification improvement with the addition of CAC was 0.466 while the next closest was ankle brachial index of 0.068. CAC correctly reclassified 10.6% of these intermediate risk patients up (to high risk) and 36% down (to lower risk), approximately 10 times better than any other risk factor.[30]

Limitations

Many of the modeling studies that examined the NNT of using new biomarkers (via risk reclassification) assume the treatment is black or white at a 20% cut-off. For example, those with less than 20% would not be offered treatment and those with greater than 20% risk would all get treatment. It also assumes that those offered treatment (statin) would take the treatment for 10 years with compliance similar to clinical trials; an assumption not likely given poor compliance in actual practice. There is also an assumption that you would only test intermediate-risk patients. This would mean that you would order lipids, calculate risk and then if intermediate (about 15%) you would send them back to get another biomarker done. These models also don't look at testing high-risk patients and the possible benefit reclassification down to check that not over-treating. They also don't look at testing it in low risk.

Discussion

The benefits of adding any RFB to the established risk equation like Framingham are tiny and without clinical utility. Despite enthusiastic effort to find statistics that will better delineate the advantages of new biomarkers, the changes with additional RFB remain minimal. It should be noted that past research, if anything, would have exaggerated the utility of these RFB. Therefore, the small changes reviewed here are the "best" we are likely to see. The only RFB that appears to offer potential is CAC; unfortunately, more work is required to determine the risk of CT scans to assess CAC and if it is cost effective.[29]

Regarding CRP, should be stated that even if an NNT of 440 over 10 years was seen as potentially reasonable, it would require patients going for a second blood test, recall, and then discussion of the risks and benefits. All this is based on an arbitrary cut-point (20%). By modifying the approach from a strict treat vs no-treat based on a 20% cut-off, to a discussion with patients at an intermediate threshold, the issue becomes moot. This testing has the additional burden of abnormal results that may require further investigation (such as a very high CRP). These issues have not been explored.

As others have noted,[14,19] improving a prediction model that is already quite good is difficult. It should be remembered, the factors contributing to CVD are numerous and the

interactions are complex. A model that perfectly assesses who will and will not have CVD event in a given time frame will likely not be possible in the foreseeable future, if ever. This may be a case where "the enemy of good is perfect." Perhaps instead of focusing on how to optimize risk prediction, we should focus on how to best use the tools we have.

Bottom Line
Presently only one RFB (CAC) appears to offer a potentially meaningful improvement in all measures of performance when added to Framingham Risk Scores (Moderate Level Evidence). However, this risk factor requires further confirmation, safety assessment and cost effective analyses. Commonly promoted RFB (like lipoproteins and CRP) have a substantial body of evidence showing they do not add meaningfully to risk prediction (Moderate Level Evidence).

Questions 2c and 2d. Are changes in biomarkers, through medical/lifestyle interventions, associated with improved clinical outcome? Will a certain biomarker be useful to monitor as a surrogate of clinical effect? Does high-level evidence (from randomized controlled trials) verify that changes or targeting of biomarkers improves outcomes?

Introduction
More than simple risk prediction and assessment, RFB may serve useful if their modification might be linked to benefits in CVD reduction. These then become surrogate markers that can be "improved" with interventions and those improvements manifest as clinical benefits. This approach has served as the foundation of most of our treatment strategies. Examples include blood pressure reduction which generally correspond quite well to benefits, at least when blood pressures are greater than 160 systolic.

A key approach to the management of CVD risk is founded on the management of lipids. It has given birth to statin medications, ezetimibe, fibrates, niacin, resins, trapibs (cholesteryl ester transfer protein inhibitors), PCSK9 inhibitors (e.g. evolocumab), and multiple new, upcoming medicines. Medications have numerous different lipid mechanisms including lowering LDL, increasing HDL, lowering TG, and lowering non-HDL cholesterol. Unfortunately, the evidence has not supported the linkage between lipid modification and improved clinical outcomes. Only statin medications have reliable shown reductions in CVD. Although the Cholesterol Treatment Trialists have published patient-level meta-analyses drawing association between LDL reduction and statin benefit,[31] there is no certainty that the reduction in CVD results from the reduction in LDL. Other medications reduce LDL without change in CVD. As addressed elsewhere in the document, while there is strong evidence that statins reduce the risk of CVD, the mechanism by which these medicines reduce CVD remains less clear. Therefore, following LDL level as a measure of the effectiveness of treatment is without clear justification.

Other failed cases of RFB being used as surrogate markers for CVD prevention include:

1. Improvement in HDL: Multiple studies with multiple interventions have failed to show a benefit in CVD;[32-35]

2. CIMT: Reductions in or stabilization of CIMT has not been shown to be associated with reduction in CVD;[36]
3. Homocysteine: Reduction of homocysteine with B vitamins does not improve clinical outcomes;[12]
4. Vitamin D: Improvement in Vitamin D does not improve outcomes;[13]
5. CRP: Although reduced by statins, CRP is also reduced by other medications that have been associated with no improvement in outcomes or worsening of outcomes.[20]

These are just a sample of examples demonstrating that linkages between changes in surrogate markers and CVD reduction are not consistent and frequently lack high-level data. It is clear that only randomized controlled trials (RCTs) can tell use if targeting surrogate markers (RFB) will consistently result in improved outcomes. Further, we need surrogate marker targets or changes included as part of the randomization to verify if the benefits seen in the trials arose from use of particular surrogate marker management strategies.

Methods
We looked for RCTs in which one of the randomized arms focused on modifying surrogate marker to a certain level of change or target with clinical endpoints as the primary outcome. Ideally, these trials would use simplified or standardized therapy of proven benefit (i.e. like a fixed moderate dose statin) as a comparator arm.

Results
No trials are identified.

Discussion
As mentioned in the introduction, there is evidence that some RFB change with interventions (like B vitamins changing homocysteine[12]) but many do not change CVD outcomes. Even in those cases where changes in surrogate occur with improved CVD outcomes (like statins reducing LDL and CVD outcomes), these linkages are associations and it is not clear that the reduction in LDL is the mechanism of action. Multiple medications reduce LDL (torcetrapib and to a lesser extent fibrates) but do not improve outcomes. This challenge is also true for lipoproteins (like apolipoprotein B and A-I). While statins have been documented to improve lipoprotein levels, other drugs without clinical benefits improve lipoprotein levels.[37,38] This suggests that simply improving lipoprotein is not the mechanism of clinical benefit. Until we have randomized clinical trials with interventions directed at specific surrogate marker targets compared with standardized treatments of proven therapies, uncertainty around targeting surrogates will remain.

Bottom Line
There is presently no high level evidence to support testing and monitoring of any RFB in the management of CVD risk. (This may not include glucose or hemoglobin A1c in diabetic patients, which was not specifically examined in this review.)

Suggested Recommendation(s)

Until new evidence is available, we should not use any additional RFB for screening, reclassification or monitoring (Moderate Level Evidence).

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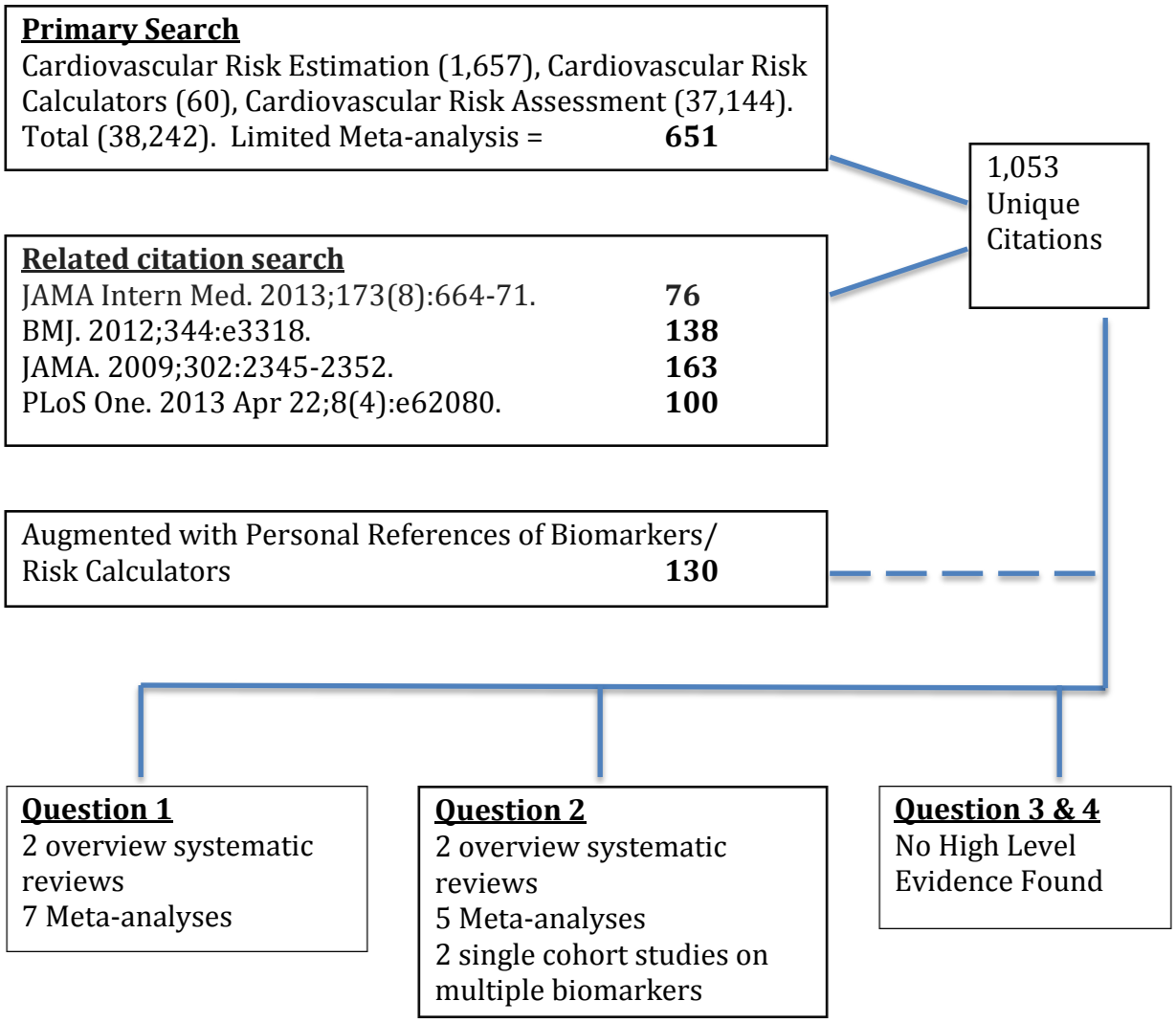
Figure 1: Biomarker Search (Search Date May 5-11, 2014)



CHAPTER 3: RISK CALCULATORS

According to evidence, ease of use and principles of shared, informed, decision making, which risk calculator(s) should be recommended?

NOTE: Please see "Comparison of CVD risk calculators" from the journal "Current Opinion in Lipidology" by the authors G Michael Allan, Scott Garrison, and James McCormack.[1]

An additional note, the bottom line, and the recommendations are available below.

Addendum for Lipid Pathway
Grover and colleagues looked at how accurately 1998 Canadian guidelines risk assessment tools predicted risk.[2] They used LRC (Lipid Research Clinics) Prevalence Study to determine the discrimination ability of Canadian guidelines. LRC Prevalence Study data is derived from 10 North American clinics. Ideally, the guidelines would be validated on Canadian data but only one of the 10 North America clinics in LRC was in Canada. The multi-variant risk tool (a Framingham derived model) had an area-under-the-curve (AUC) of 0.83 and was superior to a risk counting strategy and a number of other tools. Although positive, this is not the most update version in Canadian guidelines or Framingham and it was validated on a population that was only approximately 10% Canadian.

Bottom Line
Calculators vary based on the database from which they're derived, the choice of clinical endpoints, the length of the risk interval upon which the estimate is based, inclusion of additional risk factors and the way the information is presented.

Studies comparing risk calculators suggest that the risk estimates from calculators can vary considerably, many comparative studies have a high risk of bias and that no calculator is clearly superior to all others in all populations (Moderate Level Evidence).

When possible, clinicians should select a calculators derived from, or calibrated for, the population that they see (Moderate Level Evidence). Ideally, calculators should give absolute risks, provide a graphic representation for patients and an estimate of the benefit of key interventions, to enhance the shared decision making process between clinician and patient. From very limited data, Framingham models may be reasonable for Canadian populations (Low Level Evidence).

Suggested Recommendation(s)
We should generate one calculator based on the Framingham model with a few different graphic tools to enhance discussion and provide automatic calculation of the benefits of statins. These should have 10-year absolute risks for consistency in North America. We should also recommend some Framingham-derived calculators as secondary options.

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CHAPTER 4: LIPID LOWERING THERAPY

Which lipid lowering drugs decrease the risk of cardiovascular disease (myocardial infarction, stroke), by how much and what are the harms?

Introduction and Methods

There are six main classes of lipid lowering therapies: Statins, fibrates, bile acid resins, niacin, ezetimibe, and CETP inhibitors. We sought to determine which ones have any effect on cardiovascular (CV) outcomes and mortality, the magnitude of the effect, and the drugs main adverse effects.

Since two recent, major guidelines completed systematic reviews of the literature to answer these questions, we utilized their results.[1,2] The studies referenced in these guidelines were then reviewed. We sought information on the use of the drugs in both primary and secondary prevention.

The NICE guidelines also meta-analyzed the data. It should be noted that non-randomized controlled trial (RCT) data was included, and that intention-to-treat was not followed, which could exaggerate the size of the treatment effects.

Results

The degree of cholesterol lowering and the effects on cardiovascular disease (CVD) and mortality for all drug classes discussed are outlined in Table 1.

The US guidelines state "nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD."[1] They refer to both the AIM-HIGH[3] and ACCORD[4] trials as two major studies that have shown no additional benefit of a non-statin drug (niacin and fenofibrate, respectively) when added to a statin on patient outcomes. These and the remaining studies reviewed by the US guidelines to make their evidence statements [the Coronary Drug Project (CDP), the HDL Atherosclerosis Treatment Study (HATS), the Lipid Research Clinics project (LRC), the Fenofibrate Intervention and Event Lowering in Diabetes trial (FIELD), the Veterans Affairs High-density Lipoprotetin Cholesterol Intervention Trial (VA-HIT), Helsinki Heart Study, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) and Study of Heart and Renal Protection (SHARP)] will be reviewed under their corresponding drug.[5-12] Results of the meta-analyses by NICE are also highlighted.

Niacin

In AIM-HIGH, 3,414 patients with CVD were randomized to simvastatin + placebo or simvastatin + niacin for three years.[3] The trial was stopped early for futility as no difference was found in the primary outcome of coronary heart disease (CHD) death, nonfatal myocardial infarction (MI), ischemic stroke, acute coronary syndrome (ACS), or revascularization. Although the full results are not published yet, the more recent HPS2-THRIVE study found no difference in the composite outcome of CHD death, nonfatal MI,

stroke, or revascularization in 25,673 patients with a history of CVD when extended release niacin and laropiprant were added to simvastatin.[13,14]

The lipid-treatment arms of the placebo-controlled Coronary Drug Project (CDP) randomized secondary prevention patients to niacin, clofibrate, or placebo. After 74 months of follow-up, there was no difference in mortality between either drug and placebo.[5] Niacin decreased the risk of nonfatal MI (10.2% vs 13.8%, p<0.005) but also increased the rate of atrial fibrillation (4.7% vs 2.8%, p<0.01) and other arrhythmias (32.7% vs 28.2%, p<0.01). Clofibrate did not decrease the risk of nonfatal MI, but increased the risk of PE/thrombophlebitis (5.8% vs 3.7%, p<0.005) and other arrhythmias (33.3% vs 28.2%, p<0.005). This trial from the 1970s had few patients on modern "standard" CV risk modifiers, like ace-inhibitors or beta-blockers. Additionally, adherence was a large problem in this study, with 14% of participants taking less than 20% of their medications.

Fifteen year follow-up data of the CDP, which included 8.8 years of follow-up off drugs, demonstrate a reduction in mortality (52% vs 58.5% placebo, p=0.0004) and CHD death (36.5% vs 41.3%, p<0.01) with niacin, but not with clofibrate.[15] However, these results should be interpreted with caution as this cohort data is at risk of numerous confounders.

HATS was a smaller, secondary prevention study of 160 patients.[6] Although quoted as reducing events by 90%, the study was underpowered to find differences across its four arms of simvastatin-niacin, simvastatin-niacin-vitamins, vitamins alone, or placebo (primary outcome: Coronary death, non-fatal MI, stroke, revascularization; occurred in nine patients on placebo, one on simvastatin-niacin, six on simvastatin-niacin-vitamins, and nine on vitamins alone).

Niacin increased the risk of gastrointestinal (GI) symptoms (RR 1.5, 95%CI 1.29 to 1.78), flushing (RR 21.55, 95%CI 18 to 25.79), itching (RR 7.89, 95%CI 6.73 to 9.25), and new onset diabetes in impaired fasting glucose (HR 1.34, 95%CI 1 to 1.8), compared to placebo. Niacin also increased alanine transaminase (ALT)>3x ULN (RR 2.37, 95%CI 1.94 to 2.9), myopathy (RR 4.08, 95%CI 2.86 to 5.81), and rhabdomyolysis (RR 4.38, 95%CI 2.63 to 7.31) when combined with a statin compared to statin alone.[2]

<u>Fibrates</u>

In ACCORD, there was no difference when fenofibrate was added to simvastatin in the primary outcome of nonfatal MI or stroke or CV death in 5,518 "high-risk" patients with diabetes.[4] There was also no difference in any secondary outcome, including the individual components of the composite outcome. However, a subgroup analysis found that patients with elevated TG and low HDL did benefit from the addition of fenofibrate on the primary outcome (12.4% vs 17.3%, P for interaction with others=0.06). However, this secondary analysis must be considered hypothesis generating only.

The FIELD study randomized 9,795 patients with diabetes to fenofibrate or placebo.[8] After five years, there was no difference in the rate of nonfatal MI and CHD death, but the rate of nonfatal MI decreased from 4% to 3% (p=0.01) with fenofibrate. Fenofibrate increased the risk of pancreatitis (0.8% vs 0.5%, p=0.031) and PE (1% vs 0.7%, p=0.022).

Two gemfibrozil studies are available, both in men with CVD. The first, VA-HIT, was a secondary prevention study in 2,531 men with CHD and low HDL.[9] After 5.1 years, gemfibrozil reduced the risk of non-fatal MI or CHD death (21.7% vs 17.3%, p=0.006) compared to placebo. Gemfibrozil also increased the risk of dyspepsia (40% vs 34%, p=0.002).

The second study, The Helsinki Heart Study, randomized 4,081 men and also found a reduction in the risk of the combined endpoint of fatal or nonfatal MI and CV death (2.7% vs 4.1%, p<0.02).[10] However, over 80% of the events were nonfatal MI. GI adverse effects were experienced in 11.3% of patients on gemfibrozil and 7% placebo. There was also an increase in the risk of basal cell carcinoma (2.4% vs 0%, p=0.032), but this could be due to a lower than expected rate of the condition among the placebo group.

NICE included nine RCTs of fibrates, both primary and secondary prevention.[2] Fibrates were found to have no effect on all-cause mortality, CV death, sudden cardiac death, stroke, or hospitalizations. Fibrates were found to prevent non-fatal MIs (RR 0.82, 95%CI 0.74 to 0.91) in five trials, but not when compared in combination with a statin vs a fibrate alone (RR 0.93, 95%CI 0.76 to 1.13). Fibrates also increase the risk of ALT >3x ULN (RR 0.58, 95%CI 0.34 to 0.98). The rate of cancer was not reported.

Resins

The 1984 LRC trial of 3,806 men without CVD found cholestyramine reduced the risk of CHD death or nonfatal MI from 9.8% to 8.1%, z=1.92 (statistically significant) compared to placebo after 7.4 years.[7] There was no difference in all-cause mortality. The study had strict entrance criteria (such as no diabetes mellitus (DM), hypothyroid, or obesity, and LDL ≥4.9 mmol/L). As such, over 480,000 men were screened. Data on the number of drop-outs were not provided, and compliance appeared difficult (e.g. of the six packets/day men were expected to take, the mean dose was 3.8/day). At one year, 68% of men on the resin had a GI adverse effect compared to 43% on placebo.

NICE included two RCTs, LRC and the other with mixed primary and secondary prevention, both compared to placebo.[2] There was no statistical difference between groups with respect to all-cause death, MI, hospitalizations, GI adverse effects, or sudden cardiac death. There was a difference in CHD death based on one small trial of 1,100 men in combined primary and secondary prevention (1.6% vs 5.4%, p≤0.02), with no difference in death among women. It should be noted that this study is misquoted in NICE with the numbers of deaths reversed in each group.

Ezetimibe

Two trials have investigated adding ezetimibe to a statin, however both were compared to statin plus placebo.[11,12] It is therefore impossible to determine if any benefits seen were a result adding ezetimibe or use of the statin itself. One RCT of 208 patients over 14 months comparing ezetimibe + statin to niacin/laropiprant + statin found more benefit on CIMT with niacin, as well as on the secondary outcome of major CVE (5% vs 1%, p=0.04).[16]

There are no published RCTs comparing ezetimibe alone to statin or ezetimibe + statin to statin alone on CVD outcomes. The IMPROVE-IT trial is attempting to address this issue, but keeps getting extended as there has been no difference in outcomes between ezetimibe and placebo.

CETP inhibitors

Despite strong HDL raising and LDL lowering properties, torcetrapib and dalcetrapib have not been shown to reduce CVD outcomes. In fact, torcetrapib was associated with increased mortality (1.2% vs 0.8% p=0.006) and increased CVD by 1.2% while a major study of dalcetrapib investigating its effects on CVD was stopped early for futility.[17,18]

Statins

The majority of the evidence for statins is discussed in chapter 5, "Does evidence support decreasing LDL, TG, TC or TC:HDL, increasing HDL or attaining specific lipid targets to decrease CVD?" and adverse effects are discussed in chapter 7, "How should patients on statins be monitored for safety and efficacy?"

NICE included 34 RCTs of statins in both primary and secondary prevention.[2] Statins were found to reduce the risk of all-cause mortality (7.1% vs 8.2%; RR 0.87, 95%CI 0.84 to 0.91), CV death (4.6% vs 5.6%; RR 0.82, 95%CI 0.78 to 0.86), nonfatal MI (3.5% vs 5.1%; RR 0.69, 95%CI 0.65 to 0.73), and stroke (2.7% vs 3.4%; RR 0.78, 95%CI 0.73 to 0.83). Statins increased the risk of liver adverse effects (0.66% vs 0.35%; RR 1.9, 95%CI 1.56 to 2.32) and new onset DM (4.7% vs 4.3%; RR 1.09, 95%CI 1.03 to 1.17). There were no statistically significant differences between statins and placebo for myalgias or rhabdomyolysis.

Specific to primary prevention, a meta-analysis of 29 randomized, placebo-controlled trials of statins (n=80,711, median age 58, mean 10-year risk=6%) found statins decrease the risk of all-cause mortality (RR 0.90, 95%CI 0.84 to 0.97, I^2=2% in 19 trials, n=78,321) without increasing the risk of serious adverse effects (RR 1.01, 95%CI 0.96 to 1.07, I^2=8%).[19] Other primary prevention meta-analyses have found similar reductions on mortality (~10%) and CVD (~25%).[20-24]

Discussion

Statins are the only lipid lowering therapies that have been shown to decrease mortality. The evidence for the benefits of statin are quite consistent and the risk of harms minimal. Although statins can increase the risk of liver adverse effects, the absolute increase is small (Number Needed to Harm (NNH)=323, decreases to 244 for high intensity statin vs placebo), as is the NNH for new onset DM (250).

Resins may lower CHD death or nonfatal MI based on two older, smaller studies at high risk of bias with no effects on all-cause death or other CVD outcomes. Other medications have been shown to reduce the risk of nonfatal MI (niacin, fibrate) when given alone, but did not reduce other outcomes and did not reduce outcomes when added to a statin. None of the non-statin agents have anywhere near the same quantity and quality of consistent evidence of benefit as statins. Additionally, tolerability of non-statins can be problematic. Although generally well tolerated, ezetimibe has not been shown to reduce the risk of any CV

outcome. Other agents, like the CETP inhibitors, have shown either no benefit to negative effects on patient outcomes.

Limitations

Studies were identified from only two sources. While it is possible that other relevant studies or meta-analyses may have been missed, the methodology of the systematic review by the US guidelines was quite robust. The methodology used by the NICE guidelines was not as detailed and the use of non-intention to treat numbers could exaggerate treatment effects.

Bottom Line

Statins should be used for managing CV risk due to their consistent effects on lowering all-cause mortality and other CVD outcomes (by about 25%) (High Level Evidence). No other lipid medication has the same level of consistency, quantity and quality of data of effects on patient outcomes in both primary and secondary prevention. When given alone, fibrates, and perhaps niacin, may reduce the risk of non-fatal MI but no other CVD event or overall mortality and have increased adverse effects (Moderate Level Evidence). They offer no advantage when added to statins (High Level Evidence). Resins may reduce the risk of non-fatal MI or CHD death based on two small studies at high risk of bias (Moderate Level Evidence). Ezetimibe has no effect on patient outcomes.

Suggested Recommendation(s)

We should recommend statins as the only lipid lowering medications that consistently reduce CV morbidity and mortality. Other medications (resins, niacin, fibrates, ezetimibe) do not have the same level of consistent benefits, if any at all, and are not as well tolerated.

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Table 1. Relative effects of lipid lowering therapies on cholesterol levels and patient outcomes.

Drug	# RCTs	n	LDL	HDL	TG	All-cause Mortality (RR)	CVD (RR)	Major Limitations
Add niacin to statin	2	29,087	-6%	+14%	-23%	ø	ø	Tolerability a problem
Niacin alone	1	3908	-5 to -25%	+15 to 35%	-20 to 35%	ø	-26%	Older study, multiple outcomes, noncompliance an issue
Resins	2	4906	-15 to -30%	+3 to 5%	ø	ø	-19%	No benefit in women in one study, and didn't report results of combined men+women.
Add ezetimibe to statin	3	29287	-24%	+2%	-12%	ø	-6%	Only 1 study (IMPROVE-IT) compared to statin alone. Outcomes worse when compared to niacin+statin
Ezetimibe alone	ø		-20%	+Min	-Min	ø	ø	No data
Add fibrate to statin	1	5518	ø	+2%	-14%	ø	ø	Only benefit seen in subgroup analysis of high TG and low HDL
Fibrate alone	3	16,407	0 to -10%	+6 to +10%	-31 to -43%	ø	-18 to -37% (nonfatal MI)	No benefits on CVD outcomes besides non-fatal MI
CETP inhibitors	2	30,938	-25%	+72%	-9%	0 to +50%	0 to +20%	
Statins	34	>120,000	-15 to -53%	Min	Min	-13%	-18% to -44%	

CHAPTER 5: LIPID TARGETS

In adult patients, should we attain specific lipid targets (eg. LDL, non-HDL) to decrease the risk of cardiovascular disease (myocardial infarction, stroke) in either primary or secondary prevention?

Introduction and Methods

Clinical practice guidelines typically recommend achieving certain cholesterol targets (e.g. low density lipoprotein (LDL) <2mmol/L in high-risk individuals) to lower the risk of cardiovascular disease (CVD).[1] However, controversy exists on whether adequate evidence supports this approach. The most recent US guidelines largely abandoned this method in favour of recommending HMG-CoA reductase inhibitors (statins) without specific lipid targets.[2] We wanted to review the highest level evidence available to determine an evidence-based approach to lipid management.

Since the US guidelines performed a complete and thorough systematic review to answer this question, we reviewed their data without an additional, independent literature search. Other major guidelines (Canadian, C-CHANGE, NICE, European Dyslipidemia, and European Primary Prevention Guidelines) were reviewed for the evidence they use to support the use of lipid targets. Every reference utilized by the above guidelines pertaining to lipid targets was then critically appraised.

Results

The recommendations and references used by each guideline are outlined in Appendix 1.

a. US Guidelines

   The 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults divided the question on lipid targets into primary and secondary prevention. Only data from randomized controlled trials (RCTs) associated with atherosclerotic CVD outcomes or meta-analyses/systematic reviews of CVD were included in their review.[2]

   The systematic review found no data on treating to specific LDL or non-HDL (high density lipoprotein) targets in adults with or without existing CVD.[2] All studies with beneficial effects on CVD outcomes used fixed-dose statin therapy and there were no RCTs comparing different LDL targets.

   Although two primary prevention trials (AFCAPS-TEXCAPS and MEGA) allowed some titration using fixed doses, none titrated all trial participants and none compared different treatment targets.[3,4]

   In secondary prevention studies, fixed statin doses were used in the majority of trials that demonstrated decreased risk of CVD, although 37% of patients in the 4S trial had their simvastatin dose increased to achieve lower LDL levels.[5]

The guidelines also refer to the AIM-HIGH study, in which niacin was added to statin therapy to raise HDL in patients with CVD who were already at target LDL levels. While the use of niacin did increase HDL, decrease triglycerides (TG), LDL, non-HDL and apoB, the study was stopped early as no benefit on CVD outcomes was found.[6] The HPS2-THRIVE study randomizing 25,763 secondary prevention patients to niacin or placebo (in addition to a statin+/- ezetimibe) was stopped early as well as no benefit on outcomes was seen.[7]

The guidelines reviewed the following trials and found none had titrated or treated to a specific LDL target: 4D, A-Z, ACCORD, ALLIANCE, ASPEN, AURORA, CARE, CORONA, GREACE, HATS, HPS, IDEAL, LIPID, LIPS, MIRACL, MUSHASHI-AMI, PROVE-IT, SPARCL, TNT, AFCAPS, ASPEN, AURORAO, CARDS, JUPITER, MEGA.[2]

b. Canadian Guidelines

The 2012 Canadian Cardiovascular Society Dyslipidemia Guidelines recommend targeting LDL levels, with differing levels based on cardiovascular (CV) risk.[1]

i. Low Risk:

In individuals at low CV risk, treatment is recommended if LDL ≥5 mmol/L with a target reduction of ≥50% in LDL. Although they acknowledge that "no prospective randomized control trial" supports a 50% LDL reduction in primary prevention, the guidelines state that this level of LDL reduction was associated with a 40% reduction in cardiovascular events (CVE), based on the Jupiter trial. However, in JUPITER, patients were randomized to fixed dose rosuvastatin or placebo, and not specific LDL targets.[8]

The Canadian guidelines also discuss the 2012 Cholesterol Treatment Trialists (CTT) meta-analysis in low-risk individuals, but use this data to support more frequent (i.e. annual) assessment, non-pharmacologic treatment of risk factors and perhaps secondary testing.[9] It should be noted that the Canadian guidelines interpret CTT's results as being based on a Framingham risk score. However, the risks presented in the CTT analysis were calculated retrospectively, and not via Framingham. They are also 5-year risks in the CTT paper, and not 10-year risks as are used throughout the Canadian guidelines document. Therefore, these individuals are likely higher-risk than we think.

Additionally, the CTT collaborators found that the response to a statin was based on a patient's baseline CV risk, and that those at higher risk would benefit more than those at lower risk.[9] Although the relative risk reduction (RRR) of statins was similar across risk strata, the absolute reduction increased as risk increased in patients at higher CV risk, demonstrating that cardiovascular risk determines the benefit of stains, and not LDL.[9]

Additionally, CTT did not investigate whether other interactions or sub-particles could explain the benefits of "lowering LDL," such as total

cholesterol (TC):HDL ratio or apoB, which others have suggested is just one of a number of possible reasons that statins are effective.[10]

ii. Intermediate Risk:

Treatment is recommended for intermediate risk patients when LDL ≥3.5 mmol/L, with a target LDL of ≤2 mmol/L in those on treatment (or a 50% reduction in LDL). For these targets, the Canadian guidelines first refer to the 2005 CTT meta-analysis. This meta-analysis of 14 statin RCTs (n=90,056) claimed to find a 20% reduction in CVD outcomes per mmol/L LDL reduction.[11] However, the study did not adjust for exposure to statin treatment (the large number of placebo-allocated study participants who received non-study statins) or dose and, hence, it is unclear if the benefits were due to higher statin doses used versus a reduction in LDL.[12]

The benefits of LDL reduction were regardless of baseline lipid levels. However, if the main mechanism of benefit of statins is via pleiotrophoic effects, we would also see benefits of statins regardless of baseline lipid levels.[12] Therefore, rather than proving that the beneficial effects of statins are purely due to LDL-lowering, the results of the CTT support that pleiotrophic effects may be responsible for the beneficial effects on statins on CVD. Additionally, the correlation found between LDL and CVD outcomes does not imply causation, and the relationship between LDL lowering and CVD outcomes does not apply when non-statin therapies are used (see chapter 4, "Which lipid lowering drugs decrease the risk of CVD (MI, stroke), by how much and what are the harms?").

Finally, the results do not suggest that LDL should be targeted to <2 mmol/L as suggested by the Canadian guidelines.[1] The meta-analysis was not designed to determine the optimal target LDL level, nor does it provide that answer. Rather, they suggest that those at risk, even those with a baseline LDL <2, should be treated with a statin.[13] It also suggests that more intense, or higher dosed statins may provide greater benefit in those at greater CV risk. Finally, this study does not prove that it is the LDL-lowering properties of statins that are responsible for their CV benefits.

The guidelines also refer to the PROVE-IT, TNT, A to Z, IDEAL and SEARCH studies as evidence that lowering LDL to 2 mmol/L or less results in the lowest risk for secondary prevention patients. Unfortunately, none of these studies prospectively tested different LDL targets.[14-18] Rather, they tested different doses and different statins, demonstrating that the intensity of the statin matters, not the degree of LDL lowering. Additionally, it should be noted that these five studies were all in patients with a history of acute coronary syndrome (ACS)/myocardial infarction (MI), and are higher risk than the "intermediate risk" category in which they were discussed in the guidelines.

Next, the guidelines refer to a meta-analysis investigating the relationship between LDL and angiographic change on coronary atherosclerosis across 11 studies.[19] The paper found a significant relationship between percent change in LDL and percent change in diameter stenosis (-2.5% with an LDL reduction of 53%), but no significant relationship between absolute LDL concentration and percent change diameter stenosis. Unfortunately, this paper did not investigate patient outcomes (like MI, stroke) and is at high risk of bias. It is not clear how trials were selected for inclusion and no description of the studies was provided. Additionally, the meta-regression drew a line of best fit through the data points for each study's control and treatment arms. However, since each of these studies differ from one another, it would have been more appropriate to use each study population as its own control,[12] which could change the relationship between LDL and diameter stenosis. As well, the small number of studies/data points increases the risk of other confounders (i.e. other than LDL) being responsible for the results.[12] Finally, a meta-analysis of 41 trials and over 18,000 patients failed to find a relationship between carotid intima-media thickness (CIMT) regression and CHD events.[20]

The reference the guidelines use for targeting apoB and non-HDL levels as alternatives to LDL is a meta-analysis investigating CV risk assessment with apoB, non-HDL, and LDL.[21] It did not study targets for these markers. See chapter 4, "Do we have evidence to support the use of biomarkers in risk assessment or monitoring?" for more information.

iii. High Risk:

The reference for targets in high-risk individuals is the 2010 CTT meta-analysis of 26 RCTs (n=170,000). [22] Although this meta-analysis found results similar to the 2005 analysis (~25% reduction in major vascular events per 1 mmol/L LDL reduction), the same limitations apply and causation was not determined (see section bii. Intermediate Risk).

Additionally, this analysis demonstrated that high-intensity treatment prevented more major vascular events than less intensive therapy (4.5% vs 5.3%, ARR=0.8, NNT=125/year or 9.4% vs 22.3%, ARR=2.9, NNT=35 over 5.1 years). This finding held true even if the patient's baseline LDL was <2.[22]

However, in both this and another analysis, less than 50% of patients achieved an LDL <2 mmol/L.[23]

c. <u>C-CHANGE</u>

The Canadian Cardiovascular Harmonization of National Guidelines Endeavour (C-CHANGE) initiative used consensus to synchronize over 400 recommendations from eight national guidelines into 89 recommendations on the management of CV risk factors.[24] Recommendations are for lipid targets based on a patient's overall CV risk

[(high or moderate risk: LDL<2 mmol/L or 50% reduction; alternate target apoB <0.8 g/L), (low risk: if LDL ≥5mmol/L, reduce it by ≥50%; apoB <0.9 g/L)].[24]

Unfortunately, independent review of the literature was not undertaken and the recommendations were based on consensus among the original authors, typically the chairs, of the individual guidelines in question. There appears to have been no opportunity for the panel to review the recommendations to determine if the recommendations were evidence-based or unbiased to begin with.

d. <u>European Dyslipidemia Guidelines</u>
The European Society of Cardiology 2011 dyslipidemia guidelines also recommend the use of specific LDL targets.[25] Similar to the Canadian guidelines, the 2010 CTT is referenced heavily.

i. Very high risk:
In addition to the 2010 CTT meta-analysis, the IDEAL and TNT studies are also referenced to support the targets in very high-risk individuals.[15,17,22] Both of these studies compared low-dose to high-dose statins and both found significant benefit on CVD outcomes.

Although the TNT trial stated it was comparing an LDL of 1.9 to 2.6 mmol/L, the mean LDL achieved was 2 and 2.6 mmol/L in atorvastatin 80 mg and 10 mg groups, respectively.[15] No drugs were added or doses increased if participants did not achieve target levels, and dose reductions were not performed. Despite its title, TNT was simply a dose trial of 80 mg versus 10 mg of atorvastatin.

In IDEAL, dose titrations were also not performed to achieve a specific LDL target, and a number of patients from both groups took non-study statin (8.1% in the simvastatin group and 14.5% in the atorvastatin group).[17]

The guidelines also refer to a target for apoB based on a sub-study, which compared the achieved LDL and apoB levels of patients on placebo and atorvastatin in the CARDS trial. This analysis compared the mean decreases in LDL and apoB on statin therapy and did not compare patient outcomes based on an LDL-targeting or an apoB-targeting strategy.[26] The study found that an LDL of 1.8 mmol/L correlated well with an apoB of <0.8 g/L. However, when the LDL target of 2.59 was chosen, the apoB remained above "target" at 0.95 g/L. It should be noted that the CARDS study this paper was based on used fixed doses of atorvastatin and did not titrate drug therapy to achieve a desired target of LDL. This data is association data and cannot be used to prove causation. In fact, it simply shows that when statins are given, apoB is reduced.

ii. High Risk:
The targets for high-risk individuals are based on the 2010 CTT and two other meta-analysis.[22] See above for CTT discussion.

In a meta-analysis of 10 primary prevention studies (n=70,388), LDL decreased by a mean of 25.6%. The authors did not investigate or discuss relationship between LDL lowering and mortality, but did find an inverse relationship between statin use and all-cause mortality (OR=0.88, 95%CI 0.81-0.96).[27]

Another meta-analysis of 20 RCTs (n=65,261) quoted by the guidelines did not report the degree of LDL lowering. However, they found **no** association between LDL lowering and morbidity/mortality (mortality: β-coefficient -0.07, 95%CI -0.22 to 0.06, p=0.29; CVD death: β-coefficient 0.11, 95%CI -0.11 to 0.34, p=0.33).[28]

iii. Moderate Risk:
No references were provided.

e. <u>European Primary Prevention Guidelines</u>
The European primary prevention guidelines also recommend the use of specific LDL targets.[29]

i. Low-moderate risk:
These guidelines refer to two cohort studies to support their recommendations. The first (the Whitehall study) was a cohort study of plasma cholesterol levels and mortality. No therapy was used. They found lowest risk of CVD death if cholesterol <5.17 mmol/L.[30] The second study was a cohort study the MR FIT RCT looking at serum lipids and mortality. All comparisons were done against cholesterol <4.14 mmol/L. Therefore, a total cholesterol <4.14 had the lowest risk mortality.[31]

ii. High-risk:
The guidelines refer to the CTT 2010 meta-analysis as one of their main justifications for their recommendations (see above).[22] They also refer to a meta-analysis of 10 primary prevention RCTs (n=70,388) that is also referenced to in the European Dyslipidemia Guidelines.[27] This analysis found LDL decreased by 25.6% across all studies over 4.1 years. Since the baseline LDL was 3.63 mmol/L, this would equate to a final achieved LDL of 2.7 mmol/L. They did not investigate or discuss the relationship between LDL lowering and mortality, but did discuss the link between statin use and mortality (OR 0.88, 95%CI 0.81 to 0.96).

They also refer to the Mills meta-analysis of 20 RCTs (n=65,261). The degree of LDL lowering was not reported, however they found **no** association between LDL lowering and morbidity/mortality (mortality: β-coefficient

-0.07, 95%CI -0.22 to 0.06, p=0.29; CVD death: β-coefficient 0.11, 95%CI -0.11 to 0.34, p=0.33).[28]

iii. Very high risk:
Besides the CTT 2010 meta-analysis, the guidelines refer to two RCTs to support their recommendations: IDEAL and TNT.[15,17,22] Both of these studies compared high-dose to low dose statins, and found higher doses were associated with improved outcomes over lower doses. The higher dose groups did have more LDL lowering than the lower doses, but this does not mean that lower LDL levels were responsible for the improved outcomes as LDL levels were assessed after study completion and doses were not titrated to achieved different LDL targets.

The primary prevention guidelines also make a number of statements to support their position on LDL lowering:

a. "Statins decrease mortality by decreasing LDL." They base this on the CARDS and HPS (diabetes mellitus (DM) subset) RCTs of statins versus placebo in DM primary prevention. However, both studies used fixed doses of statins and did not show LDL lowering is what prevented CVD. [32,33]

b. "Statins at doses that effectively reduce LDL cholesterol by 50% also seem to halt progression or even contribute to regression of coronary atherosclerosis". This is based on the ASTEROID study.[34] This was not a RCT as all patients were given a statin in this manufacturer-sponsored study. At the end of the study, mean LDL decreased from 130.4 mg/dL to 60.8 mg/dL (53% reduction). Percent atheroma volume for the entire vessel was -0.98% (P<0.001) from baseline. Mean change in atheroma volume was -6.1 mm^3 (P<0.001). Effects on CVD events were not reported.

<u>NICE GUIDELINES</u>
The NICE guidelines recommend a 40% reduction in non-HDL, although they also recommend dose/intensity of statin based on risk.[35] This is based primarily on a meta-analysis of 58 RCTs (n=148,321) that found similar risk reductions for a variety of lipids therapies after standardizing for reduction in LDL (including fibrates, resins, niacin, statins, and dietary changes). [36] Unfortunately, it is very difficult to determine how the authors analyzed their data. Details on which studies (and drugs) were part of the analysis are lacking, and there is no analysis of the quality of the data. This meta-analysis does not seem to match with other interpretations of the effects of non-statin therapies but does appear to support that LDL matters. Examining the 28 non-statin studies referenced for their review, it is clear that many are small studies. Twenty (71%) are less than 1,000 patients. There may be other non-statin studies but it is not clear on what the other 30 studies are (although it seems at least eight are statin studies).

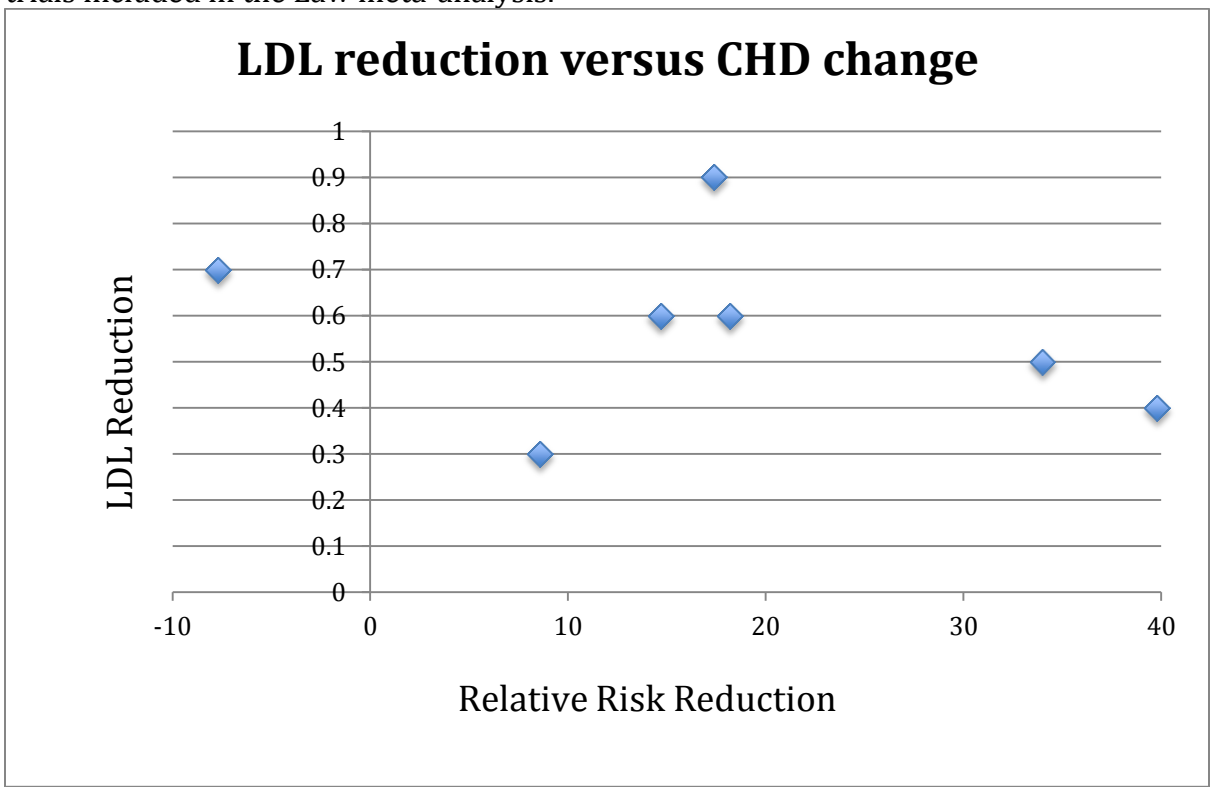
To further examine the reported relationship between LDL lowering and reduction in CHD events stated in this meta-analysis, from the studies they provide, we examined the largest

(>2,000 participants) non-statin studies with at least two years duration. Table 1 and Figure 1 outline the seven non-statin studies that met these criteria.

Table 1. LDL and CHD relative risk reductions of the largest non-statin trials included in the Law meta-analysis.

STUDY	INTERVENTION	Relative Risk Reduction in CHD	LDL Reduction
DART	Diet	8.6%	0.3
Upjohn	Resin	39.8%	0.4
Helsinki	Gemfibrozil	34.0%	0.5
WHO	Clofibrate	18.2%	0.6
CDP	Niacin	14.7%	0.6
Minnesota	Diet	-7.7%	0.7
LRC	Resin	17.4%	0.9

Figure 1. Relationship between LDL reduction and risk of CHD from the largest non-statin trials included in the Law meta-analysis.[36]



From the Figure and Table it is clear that as LDL reductions get larger RRR does not increase linearly.

The other studies referenced by NICE did not discuss lowering non-HDL or LDL with statins.[37-39]

Discussion

One of the closest sources of RCT data on lipid targets comes from the Heart Protection Study.[40] The run-in phase of this trial allocated all participants to 40 mg/d of pravastatin. The authors then performed a sub-group analysis to compare the risk of major vascular events based on the LDL-lowering "responsiveness" of each individual. No difference in outcomes was found for those with the largest response (≥48% change in LDL) and those with the least LDL-lowering response (<38%). Therefore, degree of LDL reduction does not appear to have an effect on patient outcomes.[12]

Additionally, a meta-analysis of 29 randomized, placebo-controlled trials of statins in primary prevention (n=80,711, median age 58, mean 10-year risk=6%) found statins decrease the risk of all-cause mortality (RR 0.90, 95%CI 0.84 to 0.97, I^2=2% in 19 trials, n=78,321) without increasing the risk of serious adverse effects (RR 1.01, 95%CI 0.96 to 1.07, I^2=8%).[41] Interestingly, meta-regression found the change in LDL levels from statin therapy did not significantly change the relationship between statins and all-cause mortality.[41]

Although increased statin intensity results in greater LDL reduction and improved patient outcomes, there is no reason to believe that LDL reduction is required for these better outcomes. Other drugs, such as torcetrapib, have been found to significantly improve lipid levels yet result in worse CV outcomes.[42] Note that the LDL mean change was 21.5 mg/dL with torcetrapib, which, according to CTT, should have decreased risk of morbidity and mortality by ~11%.[22] Statins decreasing mortality could be similar to ACE inhibitors in heart failure, which decrease mortality regardless of their ability to lower blood pressure.[43] We also don't monitor a surrogate marker to ensure to that ASA is working in MI prevention.

Causation occurs with each end point individually (e.g. relationship between LDL, atheroma volume, and CVD events). Current data does not prove that statins reduce LDL, and then atheroma volume, and then CVD events; rather it could be any of a number of possible biomarkers, such as non-HDL, apoB, C-reactive protein (CRP), a combination of biomarkers or an as yet unidentified biomarker that led to a reduction in events. By focusing on LDL or any other unproven markers, we are potentially being misled from the proven effect of statins on CVD events and mortality.

In 2014, the authors of the Canadian Dyslipidemia Guidelines issued a statement on the new US dyslipidemia guidelines. They stated they did not want to stop the use of LDL targets as:

> "a) both direct epidemiology and indirect evidence from clinical trials metaregression analyses suggests that lower LDL-C levels result in fewer cardiovascular events; b) coronary plaque regression based on intravascular ultrasound and angiography can be achieved at LDL-C levels or a percentage LDL-C reduction as recommended in the guidelines; c) measuring levels does

> provide some metrics around patient adherence; as well as the individual response to a given dose of statin; d) it is a paradigm that people have been comfortable with and; e) this leaves the door open for combination therapy which might still prove to be useful in subjects with aggressive atherosclerosis, or statin intolerance. In addition, this approach is similar to that put forward by the European community."[44]

As outlined above, indirect and epidemiological evidence is biased and does not prove that LDL lowering causes reductions in patient outcomes. RCTs show that statins reduce CVD outcomes. Coronary plaque regression is not an acceptable patient-oriented outcome, and rather than measuring lipids to test adherence, patients can just be asked about adherence. Change can be difficult, but utilization of statins, where indicated, reduces the risk of CVD and is an approach likely easier for patients and clinicians to implement into practice.[11] Finally, studies of combination therapy and new lipid treatments can and should be done based on patient outcomes and not surrogate markers. This is already done in other aspects of medicine, such as the use of dual antiplatelets post-ACS to prevent CVD, for which no surrogate markers are monitored or needed.[45]

Bottom Line
There is no RCT data to support the use of lipid targets in CV risk reduction. Correlation studies cannot prove that LDL lowering causes improved patient outcomes (Moderate Level Evidence). Rather, statins have been shown to reduce the risk of CVD based on level of cardiovascular risk, regardless of LDL lowering ability (High Level Evidence).

Suggested Recommendation(s)
We should not recommend use of cholesterol targets for reducing CVD. Rather, we should focus on the use of medications with known benefits in reducing CVD (i.e. statins) (High Level Evidence). Lipid levels should only be ordered when prepared to perform risk calculations.

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Appendix 1. Guideline Comparisons

Guideline	Lipid Targets Advocated?	Screening tool?	Specific lipid targets?	References provided for targets	Types data included
US ACC/AHA	No	Omnibus	N/A	N/A They discuss: AIM-HIGH ACCORD TEXCAPS/AFCAPS MEGA 4S	RCT, SR and MA only if included CVD outcomes
Canada	Yes	Modified Framingham (ref 29 and 30) for family hx	Low risk (<10% 10 year): ≥50% reduction in LDL if LDL ≥5mmol/L Intermediate risk (10-19%): LDL ≤2mmol/L or ≥50% reduction if LDL≥3.5 mmol/L (use apoB or non-HDL to determine if should tx if LDL <3.5) Alternative: apoB ≤ 0.8 g/L or non-HDL ≤ 2.6 mmol/L High risk (≥20% and	JUPITER for low risk CTT 2012 CTT 2005 Extrapolations from PROVE-IT, TNT, A to Z, IDEAL, SEARCH Ref 60 (Thompson GR, Hollyer J, Waters DD. Curr Opin Lipidol 1995;6:386-8. Ref 51 (Sniderman AD, Williams K, Contois JH, et al. Circ Cardiovasc Qual Outcomes 2011;4:337-45. Ref 50 (Sever PS, Dahlof B, Poulter NR, et	Page 158: "reviewed all RCTs and MA since 2009"

			others): LDL ≤2mmol/L or ≥50% reduction. Alternative: apoB ≤ 0.8 g/L or non-HDL ≤ 2.6 mmol/L	al. Lancet 2003;361:1149-58.) CTT 2010 Other guidelines (ATPIII and ESC 2011) Mention AIM-HIGH and ACCORD for why don't need to treat low HDL or high TG	
C-CHANGE	Yes	No specific risk calculator discussed (use "well established risk stratification or scoring model"). Discuss in more detail FRS, SCORE and Reynolds	High-risk (unsure how defined-see previous column): LDL<2 or 50% reduction, or apoB <0.8 g/L Moderate risk: as above Low risk: if LDL ≥5, reduce by 50%, apoB <0.9g/L	2009 cdn dyslipidemia guidelines	Unknown. States MA for pharmacologic interventions required for recommendations to be considered, with surrogate outcomes for health behaviors (eg lowering of blood pressure)
European dyslipidemia	Yes	SCORE/ HeartSCORE	Very high risk (SCORE ≥10% over 10 years or others): LDL<1.8 mmol/L and/or 50% reduction. OR apoB <80 mg/dL OR non-HDL <2.6	CTT 2010 IDEAL JAMA 2005 TNT NEJM2005 Non-ldl stuff: Charlton-Menys V, Betteridge DJ, Colhoun H, et al. Clin Chem 2009;55:473-80.	Unsure of search strategy

			mmol/L High risk: (SCORE <10% over 10 years): LDL<2.5 mmol/L OR apoB<100 mg/dL OR non-HDL <3.3 mmol/L Moderate risk (SCORE >1 to ≤ 5%): LDL<3 mmol/L	 CTT 2010 Brugts JJ, Yetgin T, Hoeks SE, et al. BMJ 2009;338;b237. Mills EJ, Rachlis B, Wu P, et al. JACC 2008;52:1769-81. None provided.	
European-primary prevention	Yes	SCORE	Very high risk: LDL<1.8 or ≥50% reduction or apoB<80 mg/dl High risk: LDL<2.5 or apoB <100mg/dl Low-mod (<5% at 10 yrs): LDL <3	CTT 2010 IDEAL TNT (apoB: J Intern Med 2006;259:481-92) 50% reduction: JAMA 2006;295;1556-65 (ASTEROID) CTT 2010 BMJ 2009;338:b2376. JACC 2008;52:1769-81. Mr Fit (Arch Intern Med 1992;152:1490-1500)	Search strategy not defined

			AND TC<5	Whitehall study (JAMA 1992;267:70-76. Other: "evidence that lowering LDL decreases CVD is unequivocal"- ref 2011 ESC guidelines "those with CVD highest priority for tx regardless of lipid level" Nutr Metab Cardiovasc Dis 2009;19:451-4. "statins decrease mortality by decreasing LDL" Lancet 2004;364:685-96 (CARDS) and Lancet 2003;361:2005-16 (HPS) "use highest dose statin before combo" Fundam Clin Pharmacol 2010;24:19-28.	
NICE	Yes (sort of)	Tool recommended depended on population:	For all patients started on high intensity	They do not mention a reference for their suggestion on	Randomized Controlled Trials, non-

		- Primary Prevention- QRISK2 - Type I DM- no tool rec. -Type 2 DM- UKPDS risk tool -CKD (1&2)- QRISK2 -CKD(3 or >)- no tool rec. -no tool in those with pre-existing CVD or those with familial hypercholesterolemia	statin- aim for >40% reduction in non-HDL cholesterol	non-HDL reduction. It appears as though they extrapolate data on high intensity statins achieving a 40% reduction in LDL and make a rec for same degree of reduction in non-HDL (because it is a more reliable measure). Article quoted for 40% reduction in LDL with high intensity statins is BMJ 2003;326:1423	randomized trials (case series, cohort studies) and observational studies (including prognostic studies) were included in evidence review. They also used systematic reviews. Conference abstracts were reviewed if no other full publication was available. Literature reviews, letters and editorials, foreign language publications and unpublished studies were excluded.

CHAPTER 6: TESTING LIPIDS POST-INTERVENTION

Is there a need to test serum lipid levels post-intervention (i.e. after starting lipid lowering therapy)?

Introduction and Methods

Many clinical practice guidelines for managing dyslipidemias recommend targeting specific lipid levels for managing cardiovascular (CV) risk.[1] Therefore, according to this practice, lipid levels need to be checked in patients on lipid lowering therapy to ensure optimal benefit from their medications.

However, as reviewed in Chapter 5, "Does evidence support decreasing LDL, TG, TC or TC:HDL, increasing HDL or attaining specific lipid targets to decrease CVD?" there is no evidence to support the practice of targeting specific lipid levels. As such, we wanted to know if there was any rationale to test serum lipid post-initiation of lipid lowering therapy.

Six major dyslipidemia guidelines (US, Canadian, C-CHANGE, European Dyslipidemia, European Primary Prevention, and NICE dyslipidemia guidelines) were reviewed for the evidence they used for their recommendations regarding monitoring lipids after starting therapy.

Results

The US dyslipidemia guidelines suggest it is reasonable to obtain a fasting lipid panel at baseline, 4-12 weeks post-initiation of a stain and every 3-12 months thereafter as clinically indicated to assess patient adherence, and state this recommendation is based on a "high level of RCT evidence."[2]

The US guidelines state high-intensity therapy will decrease low density lipoprotein (LDL) by about 50% from baseline (or to an LDL <100 mg/dL) and moderate intensity therapy will decrease LDL by about 30-50% from baseline.[2] However, the guidelines state these are not fixed targets and are only used to monitor therapy and adherence. If anticipated response is not seen, they recommend discussing adherence with the patient, and potentially screening for secondary causes (e.g. diet, drugs, biliary obstruction, nephrotic syndrome, hypothyroidism, etc.) and leaving the decision to increase statin dose to clinical judgment.

In their accompanying evidence statement, the authors state the dose of statin could be reduced in the following trials:

a. IDEAL if the LDL was <1mmol/L (39 mg/dL) (as per investigator discretion, dose reduction done in 6% of patients but unsure if this was for low LDL or adverse effects);[2,3]
b. PROVE-IT could halve dose if adverse effects occurred (dose reduction done in <2% of patients);[2,4]

c. AFCAPS if the total cholesterol was <2.6 mmol/L (100mg/dL) on two successive visits (note this is not in the AFCAPS paper) (no dose reductions performed in paper);[2,5]
d. HATS if the LDL was <1 mmol/L (40 mg/dL) (could reduce simvastatin by 10 mg/day, unsure how often this occurred);[2,6]
e. CARDS-note participants continued on study drug regardless of lipid levels.[2,7]

However, since higher-doses of statins are associated with fewer cardiovascular events (CVE) than moderate-low doses, patients could be titrated to the highest tolerated statin doses, regardless of their LDL levels (see Chapter 8, "How should statins be dosed?").

With regards to checking lipids to assess adherence, it may be preferable and more cost effective to just ask the patient about adherence, rather than subjecting them to a blood test.

The European dyslipidemia guidelines recommend testing lipids 8 (+/- 4) weeks after starting drug or after adjustments until within target range, the annually. They explain that their recommendations are based on consensus and not evidence.[8]

The NICE guidelines recommend repeating total cholesterol (TC), high density lipoprotein (HDL) and non-HDL cholesterol in patients on high-intensity statins after three months of therapy.[9] No references for this recommendation are provided.

The C-CHANGE, Canadian Dyslipidemia Guidelines and European CVD Prevention Guidelines all do not make a recommendation for testing lipids after starting therapy.[1,10-11]

Discussion

Since there is no evidence to support the achievement of specific lipid targets in patients at risk of cardiovascular disease (CVD), there is no reason to monitor serum lipids after starting a statin. There is no evidence that adding additional therapy to a statin is beneficial and hence, there is nothing to do with the information gained form performing the test. Patient adherence can be determined via discussion with the patient and dose adjustments can be made based on tolerability and level of CV risk.

Compliance with statins is often considered poor. However, a recent meta-analysis of 44 prospective studies found compliance with all secondary prevention medications is poor, with only 60% of patients adherent.[12] Good adherence was seen in 54% of patients on statins, 59% with antihypertensives, 70% with ASA, and 69% with diabetic medications.[12]

A number of factors have been associated with decreased statin adherence, including lower income,[13,14] middle age,[13] gender (women),[13,15] fewer medical visits,[16] use in primary prevention,[14] new users,[14] and less lipid testing.[13,14] However, these are usually not easily modifiable and since they are often based on cohort data, cannot prove causation. In the case of lipid testing, for example, this could be related to people who are already "compliers" agreeing to more testing or could be a reflection of better access to care.

Unfortunately, there is inadequate data on how to best improve compliance with statins. One systematic review found consistent improved adherence only with patient reinforcement and reminding, via regular phone calls (improved by 9-24%), pharmacist medication reviews (6.5%), and medication calendars (8%).[17] Additionally, a recent randomized controlled trial (RCT) found adherence improved from 74% to 89% utilizing a multifaceted approach composed of pharmacist-led medication reconciliation/tailoring, patient education, collaborative care, and voice messaging.[18] Adherence increased from 71% to 93% for patients on statins. However, surrogate marker targets did not significantly change and patient outcomes were not reported.

Bottom Line
There is no evidence for following lipid levels or adjusting medications based on levels (strength of evidence: none as no evidence).

Suggested Recommendation(s)
There is no need to repeat serum lipid levels after a patient begins lipid-lowering therapy. Adherence to statins can be improved with patient reinforcement and reminding.

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CHAPTER 7: STATIN SAFETY

How should patients on statins be monitored for safety?

Introduction and Methods

Statins as a class have been around for almost 30 years. Their clinical benefits have been exhaustively studied and are impressive. As with any medication, the benefits of statins need to be considered in the context of potential risks. As a class statins are considered generally safe medications with low rates of adverse effects (refer to Chapter 4, "Which lipid lowering drugs decrease the risk of CVD (MI, stroke), by how much and what are the harms?") but the potential for more serious side effects, particularly on muscle and liver exist. These side effects were first identified in early animal studies of lovastatin—the first statin to hit the market. Animal toxicology studies showed high dose lovastatin lead to hepatic necrosis in rabbits and skeletal muscle toxicity.[1] Pre-clinical data also showed minor elevations in alanine transaminase (ALT) that was dose related. It prompted drug manufacturers to add monitoring parameters for ALT and creatine kinase (CK) to the lovastatin monograph and when further statins hit the market, their manufacturers followed suit.[1] Despite the large number of clinical trials since performed on statins, side effects have not been the focus. Instead studies have focused on clinical benefits and the ongoing positive results have made statins one of the leading classes of medications on the market.[2] The safety of statins was highlighted with the withdrawal of cerivastatin from the market in 2001. Its rate of death related to muscle damage was shown to be much higher than the other statins and higher than pre-marketing data suggested. The need for more stringent monitoring of patients on statins was raised with the thought that serious complications were being missed.

Before making evidence based suggestions on monitoring the safety of statins we first need to know the prevalence of these side effects and the value of monitoring. We thus used this report to answer the following questions: 1) What is the rate of liver and muscle related side effects (including serious complications) with statins and does dose matter?; 2) Are there other factors that contribute to the risk?; 3) Does monitoring increase the predictive value of diagnosing and preventing serious complications?

We began our search with a review of the five Cholesterol Guidelines.[3-7] Each guideline varies somewhat in their recommendations on monitoring for safety with statins. For example, the 2012 Canadian Dyslipidemia Guidelines recommend baseline ALT and CK and to repeat only if patient is symptomatic. The 2013 ACC/AHA Cholesterol Guidelines on the other hand recommend baseline CK only in at risk patients, and baseline ALT in all. Routine monitoring of CK/ALT is suggested in symptomatic patients only. Most of the guidelines state that their recommendations are based on expert opinion or consensus statements. Two articles referenced within the guidelines were used to compile the evidence for this report.[8,9]

We also searched PubMed for additional references using the terms "hydroxymethylglutaryl coenzyme A reductase inhibitors," "statin," "safety," "adverse

effects," "liver function tests," "creatine kinase," "alanine aminotransferase," "liver disease," and "muscle disorder." From this search 66 abstracts were reviewed of which 28 full text articles were retrieved. The reference list within retrieved studies was also reviewed, providing additional studies. In total the final count of studies used in this report is 22. A systematic review by Law 2006[11] served as the basis for much of this report, in addition to details from its individual studies. Cohort data was also included where it could support data from randomized controlled trials (RCTs).

We did not examine studies on patients with confirmed liver or muscle disease, or liver transplant patients alone, unless this population was part of another study. The one exception to this was a cohort study accessed to get a better sense of the predictive value of enzyme testing. Some of the patients in this study had known liver disease.[10]

Results

Liver related side effects

A systematic review of RCTs, cohort studies, notifications to government regulatory authorities, and published case reports provide valuable information on the incidence of liver and muscle related adverse effects reported as number of cases per 100,000 person years (PYs).[11] The numbers are listed in Table 1. Liver related adverse events can be broken up into two categories: 1) Elevations in ALT (generally asymptomatic), and 2) more severe liver damage, namely liver failure. The definitions vary amongst studies, but asymptomatic ALT elevations are generally quoted as >3x the upper limit of normal (ULN). In defining liver failure some studies quote only a higher ALT elevation (ALT >10x ULN) or they use words such as "transaminitis," "hepatotoxicity," or "liver failure" without documenting the exact ALT elevation. Amongst the 13 RCTs included in the systematic review, the rate of ALT elevations (>3x ULN) was low and similar amongst statin and placebo: 300 versus 200 per 100,000 PYs.[11] Clinical trials support these low numbers with rates of ALT elevations >3x ULN quoted as <0.5%-1.5%.[8,12,13]

Rates of ALT elevations (of >3x ULN) have been shown to occur within four weeks of starting therapy, up to 80% occurring within eight weeks.[2,14] They have been shown to be reversible, asymptomatic, and similar among all statins.[2,14,15] Retrospective data shows that up to 65% of ALT elevations (>3x ULN) resolve spontaneously with subsequent testing even if statin and dose are continued unchanged.[2,15] Chart reviews in cohort studies have shown that confounding factors play a role.[2,15] See the section on confounding factors below.

Liver failure with statins has been shown to be even rarer. The review by Law (2006) quotes the rate of liver failure among patients on statins to be about 0.5 per 100,000 PYs of use, based on data from the FDA Adverse Event Report System. This is an extremely low incidence that is probably no greater than the risk of liver failure in the general population among persons not taking statins, making causality difficult.[11] According to this evidence, one would have to monitor transaminase levels in 100,000 patients each year (for an average of three years) to detect 300 patients with ALT elevations (>3x ULN) in order to identify the <1 person who may experience liver failure, assuming that statins can cause liver failure in the first place.[11]

The rarity of this event makes it difficult to detect in RCTs, which are often too small to have the power necessary to detect rare events. There is, therefore, not a great deal of RCT data on this topic. Rather, many of the RCTs comment on ALT elevations >3x ULN with less focus on liver disease or liver failure.

A retrospective cohort study of over 23,000 patients (average age: 62.4 years; average duration of statin use: -2.8 years) in a group model health organization confirmed a low rate of liver failure.[2] Medical charts of patients were reviewed to determine rate of severe ALT elevations (defined as ALT >10x ULN), potential causes and relation to statin use. Only 62 patients (0.3%) were documented with this rate of ALT elevation of which <0.1% were found to be directly related to statin therapy.[2] Concerns with this study included failing to assess all potential confounders that may have contributed to ALT elevation. For instance, the impact of alcohol, OTC medications (i.e. acetaminophen), and herbal preparations on liver function were not assessed and could in fact drop this rate even lower.

Muscle related adverse effects

Muscle related abnormalities range from mild reported myalgias (muscle ache or weakness without elevated CK), to myopathy (often reported as muscle symptoms in addition to CK levels >10x ULN), and finally to rhabdomyolysis—the most severe form of muscle disease—with severely elevated CK and additional organ damage particularly to the kidneys. Like their effect on liver, statins' rate of muscle toxicity is low and not a lot different than placebo. Myalgia (muscle pain), weakness and cramps without CK elevation remain the most common reported muscle side effects of statins, with incidence in clinical trials ranging from <1 % to 5 %.[11,13,14] RCT data within the systematic review by Law (2006) showed similar incidences of myalgia (defined as minor muscle pain, tenderness, and weakness) amongst stain and placebo with a difference that was not statistically significant.[11] Myalgia was found in 5,150 and 4,960 statin and placebo allocated patients respectively per 100,000 PYs. One may think that this incidence is low considering the number of patients who complain about muscle related symptoms in clinical practice. These incidences have to be looked at in the context of who is included in clinical trials. Patients with underlying medical conditions or even interacting medications which may predispose them to muscle related symptoms are most often excluded from clinical trials which could make these numbers appear lower. Cohort data was able to identify a number of underlying reasons apart from statin that also result in muscle related adverse effects in clinical practice.[15,16,18] See section below on confounding factors.

Myopathy in the RCTs included in the systematic review was poorly specified and likely over diagnosed but was generally defined as muscle symptoms of sufficient severity to consult a physician or stop taking pills (CK elevation not always reported).[11] Incidence was found in 97 statin allocated patients and 92 placebo allocated patients per 100,000 PYs. The difference was not found to be statistically significant but data from the included cohorts supported this estimate.[17] The cohort estimated the incidence of myopathy in persons taking statins from a UK General Practice Research Database. They found an incidence of 11 per 100,000 PYs in people taking statins other than cerivastatin.[17] RCT data within the systematic review also documented incidence rates of CK elevation >10x ULN

based on the studies that reported it.[11] On a single occasion incidence was similar between placebo and statin groups (see Table 1). Of the two trials looking at consecutive measures of CK no elevation on repeat measure was identified. Thus, it is possible given the similar incidences between statin and placebo that CK elevations may have occurred despite statin and would have resolved with time alone.

Rhabdomyolysis, the most severe form of muscle related damage from statins may occur at any time an individual is taking a statin.[11] In the RCTs included in large systematic review its definition was poorly defined with CK >10x ULN being the most consistent factor. It showed an incidence of 4.4 per 100,000 PYs in those allocated statins versus 2.8 per 100,000 PYs for those taking placebo. Although this difference did not reach statistical significance, the cohort data, also included in the systematic review found similar incidence for statin related rhabdomyolysis. Cohort data (from two studies) showed an incidence of rhabdomyolysis with statin use (omitting cerivastatin) of 3.4 per 100,000 PYs with an estimated mortality of 0.3 per 100,000 PYs.[18,19]

One cohort used data from a UK electronic medical record database of 2.5 million persons aged 20-75 years over a decade from 1990-1999 (25 million PYs).[18] They identified 25 cases of a first time diagnosis of rhabdomyolysis from any cause over the decade—an incidence of one per 1-million PYs. Upon analysis, they identified only one of the 25 cases occurred among the 52,000 persons in cohort taking lipid lowering drugs (patient was taking a statin-fibrate combination). The remaining cases were found to be secondary to things like excess alcohol ingestion, trauma, exercise, and infection. The second cohort used in the systematic review pooled data from 11 separate health maintenance organizations (HMOs) of which 252,000 individuals were studied (taking statins or fibrates). Nine cases were found in patients taking statins alone.[19]

Table 1. Incidence Rates per 100,000 Person Years for Muscle and Liver Related Adverse Effects with Statins[11]

	Elevated ALT (>3x ULN)		**Liver Failure**		**CK elevation (>10x ULN)**		**Myalgia (muscle pain, tenderness, weakness)**		**Myopathy (muscle, pain, tenderness, weakness severe enough to stop pills; CK not always specified)**		**Rhabdomyolysis (poorly defined, except for CK> 10x ULN)**	
	Statin	placebo	statin	placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo	Statin	Placebo
Incidence per 100,000 yrs	300	200	~0.5	-	83	60	5150	4960	97	92	4.4	2.8
Difference (95% CI)	100 (64-140)				23 (-4-50)		190 (-38-410)		5 (-17-27)		1.6 (-2.4-5.5)	

<u>The impact of statin dose on muscle and liver related adverse effects</u>

According to two meta-analyses comparing statin doses, adverse effects appear to be dose related.[8,20] One meta-analysis consisted of four RCTs in 27,000 patients (two trials in acute coronary syndrome (ACS) and two in stable coronary artery disease (CAD) patients), mean

age 60 years.[20] Patients followed over a mean of 3.4 years compared moderate to intensive doses of the following statins: Atorvastatin 10, 80 mg; simvastatin 20, 80 mg; pravastatin 40 mg. Intensive dose therapy (namely 80 mg of both atorvastatin and simvastatin) was associated with greater abnormalities on liver function testing (defined as ALT >3x ULN) with an OR 4.48, 95%CI 3.27 to 6.16; P<0.001; and number needed to harm (NNH) of 86 and elevations in CK (defined as CK>10xULN) with OR 9.97, 95%CI 1.28 to 77.92, p=0.028 and NNH of 1,534. The second meta-analysis of nine RCTs, including 21,765 patients, mean age range: 48.5-61.7 years, 78% male, followed over 1-5 years confirmed these numbers.[8] The majority of studies compared a lower dose statin (pravastatin 40 mg; simvastatin 20 mg, 40 mg; lovastatin 5 mg; and atorvastatin 10 mg) to high dose atorvastatin 80 mg. The relative risk for ALT elevations (defined as >2 or >3x ULN) was 3.10, 95%CI 1.72 to 5.58 and NNH=90. There was a trend toward increased CK elevations (defined as >3 or >10x ULN) with higher dose with a relative risk of 2.63, 95%CI 0.88 to 7.85, and a NNH= 1,250.[8]

Although it appears, from the above data, that dose plays a role in rates of adverse events, we need to interpret these results in the context of known statin benefit and of study limitations. Individual clinical trials in these meta-analyses report only on number of patients experiencing elevations in ALT or CK but additional information regarding the severity of the adverse effect or clinical outcome to patient was not routinely provided. We know from the previous listed data on incidence rates that these elevations are often reversible, transient and not necessarily a predictor of worsened disease. Also, definitions of these elevations vary amongst studies making it difficult to adequately combine numbers. From this data it is also not possible to reliably predict the response to particular statins and doses in specific patients, as the likelihood of adverse events and their tolerability may vary by individual differences in health status, age, metabolism of parent drug/metabolites, and use of other drugs competing for cytochrome P450 3A4 metabolism and elimination.

<u>Confounding factors</u>

Aside from statin use, there are a number of risk factors which pre-dispose patients to muscle and liver injury, many of which have been eluded to already in this report. Drug interactions and underlying medical conditions contribute and should be considered in clinical decision making.[2,15,18] In many cases statins were ruled out as a culprit after a thorough chart review revealed another cause for adverse effect. Drug interactions are often a result of sharing a common CYP pathway (particularly CYP3A4) for metabolism. Common examples listed in studies include: Antifungals, erythromycin, azithromycin, cyclosporine, cimetidine, anti-retrovirals. Drug interactions need to be considered in assessing patient complaints of myalgia or even CK elevations and in preventing progression to rhabdomyolysis. Two cohort studies suggested that the incidence of rhabdomyolysis was higher (4.2 per 100,000 PYs) for drugs such as atorvastatin, lovastatin, and simvastatin (which are oxidized by cytochrome P450 3A4 [CYP3A4] and which is inhibited by many drugs) than for pravastatin or fluvastatin—not oxidized by CYP3A4 (incidence: 1 per 100,000 PYs).[18,19]

Comorbid conditions contributing to ALT enzyme elevations include: Gallbladder disease, infectious liver disease, passive hepatic congestion secondary to congestive heart failure,

nonalcoholic fatty liver associated with diabetes, obesity, and dyslipidemia.[2,15] For CK elevations, studies list MI, surgery, traumatic injury, excessive exercise, and undiagnosed hypothyroidism as possible confounders.[2,15] The role of alcohol also needs to be considered. Its interaction with statin treatment remains poorly studied as trials have eliminated patients with excessive alcohol intake. All of these factors need to be kept in mind when both prescribing statins and when assessing for adverse effects.

Is there a predictive value to monitoring?

In determining frequency of monitoring it would be helpful to know the predictive value of the lab tests. For instance does increased ALT predict the risk of liver failure and thus serve as an important baseline indicator of risk? The guidelines all recommend getting a baseline ALT in patients starting on statins, but this is based mainly on expert opinion. Evidence that these lab tests would prevent progression to more serious disease would be helpful in determining monitoring guidelines. Unfortunately, the evidence that CK and ALT screening and monitoring reduces progression to more serious complications is lacking. There is some cohort data that may aid in decision making (see below), but further studies are needed.

One retrospective cohort study evaluated whether patients with elevated baseline ALT/aspartate transaminase (AST) are at higher risk for hepatotoxicity from statins than those with normal baseline ALT/AST.[10] The study was made up of three cohorts (size ranged from 342 patients to 2,245 patients) from a large medical academic practice in Indianapolis who had liver biochemistry tests performed six months prior to and six months after starting statin therapy (see Table 2 of Chalasani[10]). They recorded rates of mild to moderate elevations (defined as an increase in ALT/AST up to 10x ULN for those with normal baseline levels and up to 10-fold increase in those with elevated baseline levels) and severe elevations (defined as development of bilirubin >3 mg/dL (regardless of baseline ALT/AST) or elevations in AST/ALT >10x ULN in those with normal baseline levels or >10-fold increase from baseline in those with elevated baseline enzymes). In the cohort (1437 patients) with normal baseline liver function tests (LFT) given a statin: 1.9% had mild to moderate elevation of LFTs and 0.2% had severe elevation. In the cohort (342 patients) with elevated baseline LFTs given a statin: 4.7% had mild to moderate elevation of baseline LFTs and 0.6% had severe elevation. In the cohort (2245 patients) with elevated LFTs at baseline but not given a statin: 6.4% had mild to moderate elevation of baseline LFTs and 0.4% had severe elevation.[10]

The results showed that the frequency of mild-moderate and severe elevations in liver enzymes in those with elevated baseline enzymes prescribed statins was not significantly higher than those with elevated liver enzymes not prescribed a statin. It also showed that whether your baseline enzymes were elevated or not there was not a statistically significant difference in rate of serious enzyme elevations with a statin (0.6% with elevated baseline vs 0.2 with normal baseline, p= 0.2).

The study concluded that some patients with elevated liver enzymes will experience further elevations in liver enzymes regardless of whether or not they are placed on a statin and that knowledge of baseline liver enzyme levels may not accurately predict who will

progress to severe liver complications when placed on a statin. Although the authors state that cohorts were demographically comparable, they only list age, race, cholesterol levels, and sex in Table 1. It is unknown if confounding variable were also controlled for between cohorts.

Another retrospective cohort points out the small clinical impact driven by abnormal lab results. In this study 408 statin treated patients within six primary care clinics in Israel, had their charts reviewed if they had at least one elevated enzyme level (CK, ALT, or AST) >10% above normal to evaluate the clinical impact of abnormal liver or muscle enzyme results.[16] Of the 408 patients on statins (with enzyme elevation) only 40 had further evaluation by their physician. This evaluation lead to the discontinuation of the statin in only two patients, both of which were also symptomatic at time of enzyme elevation. In other words only 0.5% of patients on a statin with enzyme level >10% of ULN (CK, ALT, or AST) had to have their statin medication stopped. This cohort raises the question of whether abnormal lab tests prompt decision making, especially in asymptomatic patients.

Screening and monitoring could be justifiable if the clinical problem was significant or if early detection would prevent progression to more serious disease without a high level of false positives. Aside from the small amount of flawed cohort data, what we do know now is that rates of ALT and CK elevations are low with statins and serious complications even rarer in the populations studied (so clinical problem not significant). We also know that confounding factors that are not always controlled for can play a significant role in abnormal lab values, even at baseline and may result in false positives. Repeat monitoring reveals numbers that return to normal and rarely progress to overt disease (hepatotoxicity or rhabdomyolysis).[2,15,16] Impaired liver function in patients with isolated, asymptomatic elevations in liver enzymes has not been proven.[16] There are no long-term prospective studies to define the natural history of the potential liver disease or muscle disease (rhabdomyolysis) in patients with asymptomatic elevations in liver chemistry tests or CK.[21] Serum ALT has diurnal variation, may vary day to day making its value as a baseline test questionable.[21]

<u>Limitations</u>

RCT data is limited and may not have the power to detect these rare events. Meta-analyses have been performed on RCT data whose primary outcomes were CV morbidity and mortality benefits of statins. Adverse effects such as ALT and CK elevations were often studied as secondary outcomes. Although the quality of meta-analyses was good, the RCTs included had limitations. For the most part, they targeted a "healthier" and younger population. This makes it difficult to generalize. The majority of patients starting statins today have more than one major diagnosis and are often on multiple medications. Unlike patients in many of these studies, some real-life patients may be at greater baseline risk for adverse effects on liver and muscle. They may, therefore, experience higher rates of these adverse effects and may benefit from more monitoring. A run-in period was used in many RCTs allowing patients who may not tolerate a statin to be excluded. This causes concern for a number of reasons, one being that it is more difficult to apply results to general population and second being that by eliminating these patients the effect size of the outcomes may be lower than expected.

Variations in definitions of muscle and liver related adverse effects among studies used in meta-analyses make it difficult to efficiently and conclusively combine outcome data. For example ALT elevations may be quoted as >2-3x ULN, >3x ULN, or >10x ULN. Myopathy may be defined as muscle symptoms plus CK elevations between 10-50 x ULN or simply as CK >10x ULN. Data on the clinical consequences (or impact to patient) of ALT/CK abnormalities is also lacking and limited to data in retrospective cohort studies.

Retrospective cohort analyses generally have been able to produce large numbers of patients to assess for adverse effects, and are generally not restricted to a certain population (i.e. "sicker" patients not necessarily excluded), but are limited by reporter bias. There is also the potential for missed events as monitoring is less strict than in an RCT.

Discussion

Despite the lack of studies, what can be concluded is that adverse effects on muscle and liver are rare in the populations studied and rarely progress to more serious problems. We, therefore question the need for both screening and routine monitoring in all statin-treated patients. Screening benefit is limited by effects of confounding variables and lack of evidence to show its predictive value in preventing serious complications. Regardless of the level of baseline lab values (normal vs elevated), cohort studies show patients on statins may progress to serious complications, questioning the specificity of baseline testing (particularly for ALT). Not to mention the cost to the healthcare system when you consider the large number of patients on statins, routine testing on all patients may lead to stopping these useful medications in patients who otherwise would be fine to continue. Until better studies are done to show a definitive role for monitoring in the prevention of more serious illness, screening and routine monitoring for all patients is questionable.

Counseling of all patients started on statins is important. In counseling patients it should be emphasized that these medications are usually well tolerated by the majority of patients who use them and that serious side effects are rare. All patients should, however, be counseled on what side effects to watch for that may be related to muscle and liver injury and encouraged to report these. In particular, patients should be counseled to report any of the following: Unexplained new or worsening muscle pain, stiffness, cramping or weakness; unusual fatigue or weakness; loss of appetite; abdominal pain; dark-coloured urine; or yellowing of skin or sclera. Monitoring of CK and/or ALT should be performed on patients who present with symptoms.

Dose seems to play a role in rate of adverse effects, although studies are limited to laboratory measurements without knowing clinical impact to patient. Clinicians should, therefore, keep this in mind when prescribing statins. Evidence does support higher doses for greater clinical benefit, especially among secondary prevention patients, however starting at low dose and increasing based on tolerability may be important especially in sicker and elderly patients or those at risk of drug interactions.

The majority of studies have not been able to comment on the impact of comorbid conditions or interacting medications as they have been excluded from studies. Healthcare

professionals need to be aware that there are risk factors that increase the potential for serious liver and muscle disease: Low body weight, advanced age, obesity, and reduced hepatic and renal function. It may, therefore, be prudent to monitor these higher risk patients more closely under the clinical judgment of the physician. The same may be the case for those taking interacting medications, if the combination cannot be avoided.

Bottom Line

Screening ALT and CK in all patients starting statins should be supported by evidence of their predictive value and this evidence is lacking especially in asymptomatic patients. That being said, some may argue the added comfort of knowing baseline values, especially when the liver is concerned. Elevations in CK and ALT have been shown in clinical trials to be as common in placebo as treatment groups, often with a confounding factor being found responsible. Therefore, routine monitoring of CK and ALT in otherwise asymptomatic patients may be doing more harm than good and is not recommended at this time. Until more studies are performed in higher risk patients using statins, regular monitoring may be appropriate and physicians should use their clinical judgment in deciding upon the frequency of monitoring.

Suggested Recommendation(s)

Baseline screening of CK is not suggested. Obtaining a baseline ALT, or not, are both acceptable and can be left to the discretion of attending physician. Routine monitoring of CK and ALT should be reserved for those patients who are symptomatic or who are at higher risk of adverse events. Frequency to be determined by clinical discretion of attending physician (Moderate Level Evidence).

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CHAPTER 8: STATIN DOSING

How should statins be dosed?

- **What is the evidence for high dose, compared to standard dose statin therapy?**
- **What is the evidence for low dose, compared to standard dose statin therapy?**

Introduction and Methods

We began by searching for systematic reviews including the terms "intensive" and "statin." This provided 82 systematic reviews, of which six appeared to compare benefits or harms resulting from different statin doses.[1-6] The two most recent systematic reviews evaluating the effect of differing statin doses on clinical outcomes were both published in 2011 (Mills and Ribeiro).[1,2] The Ribeiro review had a large focus on indirect comparisons (i.e. comparing statins across studies) which we thought less reliable and, therefore, we chose to work with Mills instead. To ensure we had all of the relevant studies published more recently than the Mills systematic review, we also searched Pubmed on April 9, 2014, using the same search algorithm as that employed in Mills for January 1, 2010, onward. The search used the MeSH term "Hydroxymethylglutaryl-CoA Reductase Inhibitors" and truncated "random*" with no restrictions other than date range. This yielded 741 articles whose titles and abstracts we reviewed. Only one of these articles was relevant to the review question (the IDEAL trial, published in 2010) and was already included in Mills. Hence the Mills review includes all relevant trials.

Results

The Mills 2011 Systematic Review (Best Evidence)

The Mills review found, after exclusions, 10 randomized controlled trials (RCTs) comparing the effect of different fixed statin doses on morbidity and mortality. Amongst the excluded trials, two were excluded because of the dosages used. In particular, one was excluded as being not intensive dosing and one was excluded as having too low a dose in the control group (lovastatin 2.5 mg). We retrieved both of these trials to supplement the Mills findings and will briefly describe them after describing the findings from Mills.

a. Population:
   Table 1 of the Mills paper shows the study characteristics of all included trials (41,760 participants enrolled for an average of 4.6 years).[1] Six of 10 trials enrolled subjects with a history of coronary heart disease (CHD), three of 10 trials enrolled subjects with acute coronary syndrome (ACS), and one of 10 trials enrolled subjects with established atherosclerosis. Roughly 64% of subjects were male, 17% were diabetic, 47% were hypertensive, and 23% were smokers. The mean baseline LDL was 2.77 mmol/L.

   Most trials had an age restriction:
   - <85 years (1 trial)
   - 65-85 years (1 trial)
   - <80 years (3 trials)

- 35-75 years (1 trial)
- 30-75 years (1 trial)
- No age restriction (3 trials)

b. Intervention:
"Intensive Statin Therapy"
In eight of 10 trials the high dose intervention was atorvastatin 80 mg. High dose in the other two trials was simvastatin 80 mg (equivalent lipid lowering to atorvastatin 40 mg) and simvastatin 40-80 mg (equivalent lipid lowering to atorvastatin 20-40 mg).

c. Comparator:
In seven of 10 trials the "standard dose statin therapy" comparator was equivalent to atorvastatin 10 mg in lipid lowering potency (this included atorvastatin 10 mg X two trials; pravastatin 40 mg X three trials; and simvastatin 20 mg X two trials). The remaining three trials compared to atorvastatin 20-40 mg, simvastatin 0-20 mg (equivalent to atorvastatin 0-10 mg), and lovastatin 5 mg (equivalent to atorvastatin 1.25 mg).

d. Outcomes:
All-cause Mortality (non-significant trend to benefit, see Figure 2 of Mills)
(10 trials; 1,791 vs 1,853 deaths) RR 0.92, 95%CI 0.83 to 1.03, p=0.14, I^2 = 38%.

Cardiovascular Disease (CVD) Deaths (non-significant trend to benefit, see Figure 3 of Mills)
(seven trials; 1,012 vs 1,086 deaths) RR 0.89, 95%CI 0.78 to 1.01, p=0.07, I^2 = 34%.

Non-Fatal Myocardial Infarction (MI) (statistically significant reduction)
(five trials; 935 vs 1,132 MIs) RR 0.82, 95%CI 0.76 to 0.90], p ≤ 0.0001, I^2 = 0%.

Composite Endpoint of Cardiovascular (CV) Deaths Plus Non-Fatal MI
(statistically significant reduction number needed to treat (NNT)=250 to prevent a death or non-fatal MI per year estimated by the Mills authors, see Figure 4 of Mills paper)
(nine trials; 1,490 vs 1,660 deaths or MIs) RR 0.90, 95%CI 0.84 to 0.96, p ≤ 0.0001, I^2 = 0%.

Composite of Fatal and Non-Fatal Stroke Excluding TIA
(statistically significant reduction)
(10 trials; 576 vs 669 strokes) RR 0.86, 95%CI 0.77 to 0.96, p = 0.006, I^2 = 0%.

e. Adverse Events:
Cancer (Not even a trend to harm)
(five trials, 826 vs 865 events) RR 0.95, 95%CI 0.87 to 1.04, p = 0.31, I^2 = 0%.

Rhabdomyolysis
(No statistically significant increase but rare events. Rhabdomyolysis could potentially be higher with higher statin doses.)
(six trials; 16 vs 7 events) RR 1.70, 95%CI 0.56 to 5.19, p = 0.34, I^2 = 20%.

The Mills meta-analysis spends much less time on the adverse effects of intensive statin dosing than it does on the potential therapeutic benefit. An older 2007 systematic review by Silva et al. includes only four trials but gives a more fulsome presentation of adverse events.[3] According to Silva "…treatment of 1,000 patients with intensive-dose rather than moderate-dose statin therapy would prevent 4 additional CV deaths, 10 MIs, and 6 strokes, and cause an additional 33 adverse events: 21 adverse events requiring drug discontinuation and 12 instances of elevated liver function test values." It is important to recognize however that a significant percentage of patients in these trials (e.g. 1/3 of PROVE-IT subjects) had already been on statins. It can be assumed that this pre-exposure would have weeded out patients who were susceptible to adverse effects of statins.

f. Mills Subgroup Analyses:
Mills performed the same analyses as in the main study after restricting to studies that recruited only patients with ACS.
   1. All-cause mortality (statistically significant reduction)
      (three trials) RR 0.75, 95%CI 0.61 to 0.91, p = 0.005, I^2 = 0%.
   2. CV deaths (statistically significant reduction)
      (three trials) RR 0.74, 95%CI 0.59 to 0.94, p = 0.013, I^2 = 0%.
      NNT = 119 estimated by authors.
   3. Non-fatal MI (nonsignificant trend to benefit)
      (three trials) RR 0.55, 95%CI 0.28 to 1.07, p = 0.08, I^2 not provided.
   4. Composite Endpoint of Coronary Heart Disease Deaths Plus Non-Fatal MI (nonsignificant trend to benefit)
      (three trials) RR 0.85, 95%CI 0.71 to 1.03, p = 0.10, I^2 = 32%.

<u>Trials not included in Mills:</u>
The Post Coronary Artery Bypass Graft Trial[7]
This trial enrolled 1,351 patients with remote coronary bypass (one to 11 years prior) and LDL 3.36 to 4.53 mmol/L into a 2X2 factorial intervention consisting of warfarin versus placebo, and lovastatin 40-80 mg vs lovastatin 2.5-5 mg (this equates to atorvastatin 10-20 mg vs atorvastatin 0.625-1.25 mg). Patients started with either 40 mg or 2.5 mg lovastatin and doubled the lovastatin dose if not reaching an LDL less than 2.20 mmol/L in the aggressive group or 3.62 mmol/L in the moderate group. The lovastatin dose was reduced if LDL fell below 1.55 mmol/L in the aggressive group or 3.36 mmol/L in the moderate group. Cholestyramine was added in the aggressive group if LDL remained above 2.46 mmol/L or if LDL remained above 4.14 mmol/L in the moderate group.

This trial was primarily looking at progression of atherosclerosis but did report on 4 year revascularization rates which were 29% lower in the group with more aggressive statin

therapy (6.5% vs 9.2%, p=0.03). Given how very low the low dose comparator was this trial doesn't appear to add anything useful.

Zou et. Al. 2003[8]
This trial (excluded from Mills because the higher dose was too low to be considered intensive therapy) randomly enrolled 197 ACS patients to open label simvastatin (either 20 mg or 10 mg) within 48 hours of admission.

Outcomes (20 mg vs 10 mg):

• MI	7 vs 12	"p<0.05"
• Re-hospitalization	24 vs 38	"p<0.05"
• Revascularization	10 vs 22	"p<0.05"
• Coronary deaths	2 vs 2	NSS
• Non-coronary deaths	0 vs 1	NSS

Discussion
Intensive versus moderate dosing
There are no primary prevention trials.

When trials involving stable CAD patients (secondary prevention) are combined with trials involving ACS patients the effect of intensive statin therapy (equating to ≅80 mg atorvastatin) versus moderate statin therapy (equating to ≅10 mg atorvastatin) on all-cause mortality and CV mortality is not statistically significant (High Quality Evidence). However the point estimates for a mortality difference are not unimportant (about a 10% relative reduction for each) and the difference does APPROACH statistical significance. Non-fatal MI (less objective) does show statistically significant benefit with an 18% relative reduction, as does a composite of CV death plus non-fatal MI (10% relative risk reduction; NNT = 250 over one year) (High Quality Evidence). Stroke, excluding TIA, also has a statistically significant reduction (14% relative reduction) in the intensive statin therapy group (High Quality Evidence).

It is possible that ACS patients receive greater benefit from intensive statin dosing than do stable CAD patients (Low Quality Evidence) and the trend to a mortality advantage when all groups are combined derives in large part from ACS patients.

Would 40 mg of atorvastatin work as well as 80 mg?
The only trial in stable CAD patients to use a lesser intensive statin dose was SEARCH, which compared simvastatin 80 mg to simvastatin 20 mg (roughly equivalent to atorvastatin 40 mg vs atorvastatin 10 mg). This was a large trial with 12,064 subjects and an average of 6.7 years of follow-up. Neither all-cause mortality, nor CV mortality were any different (RR 0.99 for both) and the composite outcome of all major cardiovascular events (CVE) was not significantly different (24.5% vs 25.7%; RR 0.94, 95%CI 0.88 to 1.01, p=0.1). This suggests that, if there is any benefit to the lower end of the "intense" statin therapy range (40-80 mg atorvastatin equivalence) over low dose therapy, it is very modest (High Quality Evidence).

The A-Z trial in ACS patients looked at simvastatin 40 mg for 30 days followed by 80 mg thereafter versus no statin for four months followed by 20 mg simvastatin thereafter. This trial found benefit on CVD mortality but being without a statin for four months out of the two year follow-up makes this difficult to interpret (Low Quality Evidence).

What about comparing lower doses with each other?
The only trial comparing low doses and looking at clinical outcomes was Zou et. al., which was not included in the Mills meta-analysis. As described, this was a small trial (N = 197) in ACS patients evaluating simvastatin 20 mg versus 10 mg but it did find a reduction in MI, revascularization, and re-hospitalization with the larger dose (Low Quality Evidence).

What about older adults?
Most of the trials included in Mills had an age exclusion as described above. This makes it difficult to know whether risk and benefit differs in the more frail oldest old (>80 years). Of the three trials which broke results down by age (greater than or less than 65 years), the only one which had no age restriction (and hence may have had some >80 year old subjects) was PROVE-IT. PROVE-IT (a trial in ACS) found no difference between intense and conventional statin doses in the over 65 age group:

- Age ≥65 years (1,230 subjects) 2-year composite CVE rate 28.1 versus 29.5
- Age ≤65 years (2,932 subjects) 2-year composite CVE rate 20.1 versus 25.0

i.e. intensive statin therapy in PROVE-IT appeared to only be better than lower doses in younger patients (Low Quality Evidence).

In contrast, the other two trials in which response is broken down by age (A-Z and SEARCH) show similar benefit in patients ≤65 and patients 65-80 years of age (both trials excluded those over 80).

When discussing whether recommendations should vary in the elderly the panel may wish to consider that peak atorvastatin drug levels (C_{max}) have been shown to be 42.5% higher in older adults (age 66-92) than in younger adults (age 19-35).[9] They may also wish to consider that renal insufficiency (which will raise statin levels) and polypharmacy are common in this age group (drugs that inhibit cytochrome P450 3A4 activity will raise statin levels, e.g. amlodipine, diltiazem, verapamil, amiodarone, colchicine). Given the adverse effects of statins are, to some extent, dose related, a lower dose recommendation in older adults might be entertained (Low Quality Evidence).

An interesting aside from the PROVE-IT trial
In the PROVE-IT trial of atorvastatin 80 mg versus pravastatin 40 mg in ACS patients, it appeared to matter whether patients had been on statin upon presentation to hospital.

- Prior Statin Therapy (1,049 subjects) 2-year composite CVD event rate 27.5 versus 28.9

- No Prior Statin (3,112 subjects) 2-year composite CVD event rate 20.6 versus 25.5

i.e. if you are already on a statin and develop ACS there is little benefit from intensive statin therapy (Moderate Quality Evidence).

A comment on current guidelines

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Athersosclerotic Cardiovascular Risk in Adults makes recommendations for either "moderate-intensity" or "high-intensity" statin therapy depending on factors such as age, LDL, presence of diabetes, and overall assessment of CV risk.[10] Choosing between moderate and high intensity dosing based on patient characteristics (i.e. balancing risk and harm) is something clinicians need to do but the decision making algorithm constructed for this guideline is an opinion-based extrapolation from the above studies. Our guideline authors will need to decide how directive they wish to be in suggesting different doses for different clinical scenarios given the lack of evidence behind such recommendations. For simplicity, providing a recommendation for the highest well tolerated statin dose and mitigating that dose downward in individuals with presumed higher drug levels or greater drug risk (e.g. the elderly or those with renal insufficiency) might be something the group wishes to consider. The relative potency of statins (pieced together from a variety of sources) and the 2013 ACC/AHA definition of "low" to "high-intensity" statin dosing is summarized below:[11-13]

Table 1. Statin Dosing Ranges and Intensity

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

Bottom Line

There are no primary prevention trials. For secondary prevention it is likely that increasing statin doses provide both greater benefit (with diminishing incremental benefit as dose increases) and greater harm (largely in the form of more adverse drug effects leading to discontinuation) (High Level Evidence). Serious side effects with statins (e.g. rhabdomyolysis) are rare and often resolve with discontinuation of the drug. The benefit of intensive dosing may be greater in patients with acute coronary syndrome and it is unknown whether frail patients over the age of 80 will have similar risk/benefit ratios.

Suggested Recommendation(s)

Statin prescribing should be equivalent in potency to 40-80 mg of atorvastatin if tolerated. Advanced age or mild-moderate renal impairment should favor the lower end of this dose range and ACS should favour the upper end. Patients who do not tolerate these doses should be placed on the highest daily (or alternate daily) dose on which they are symptom free in preference to the use of other lipid lowering therapies.

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CHAPTER 9: STATIN INTOLERANCE

How do we treat patients intolerant of statin therapy?

Introduction and Methods

Statins are the only lipid lowering therapies shown to consistently decrease mortality. However, not all patients will tolerate them. Therefore it is important to determine what to do if a patient is intolerant of statin therapy.

We reviewed six clinical practice guidelines on dyslipidemia to see if any of them performed a systematic review of the literature on this topic.[1-6] When none of them were found to have systematically reviewed the literature, PubMed was searched using the term "statin intolerance." Additionally, relevant studies were searched using the "related citations" feature of PubMed, and references of selected articles were reviewed to determine any additional literature.

Results

Figure 1 outlines our search strategy. Out of 321 papers identified, six were included.[7,11,18-21]

One systematic review of nondaily dosing of statins was found in patients with a history of statin-associated myopathy.[11] Out of the 10 studies included, with sample sizes ranging from one to 325, only one was a randomized controlled trial (RCT). This trial of 17 male veterans with a history of statin-related myalgias randomized to once weekly rosuvastatin or placebo for eight weeks. It found two placebo patients and three rosuvastatin patients experienced myalgias and had to stop treatment. When all included studies were assessed, at least 70% of patients were able to tolerate an intermittent dosing strategy. However, it is not clear if all relevant studies were included in this review.

A retrospective study of 35 patients not included in the above systematic review found that 34% of those with a history of statin intolerance could not tolerate simvastatin 2.5 mg every other day due to myalgias.[18] It is difficult to determine if this is related to the use of simvastatin itself or if the results would have been different had an alternate statin been used.

Another retrospective chart review of 1,605 statin-intolerant patients followed for 31 months found approximately 70% were able to resume a statin, 9% of whom required an alternative dosing frequency of the statin.[19]

A retrospective cohort study of 107,835 patients on statins in the US found that over half (57,292) either temporarily or permanently discontinued their statin. Of the 18,778 patients with documented adverse effects to statins, 11,124 patients temporarily or permanently discontinued their statin. Ninety-two percent of those re-challenged with a

statin were still on a statin 12 months later. However, the reasons for discontinuation are at high risk of bias due to the retrospective nature of the study.[7]

Other, small, retrospective chart reviews found many patients with statin-induced muscle toxicity were able to tolerate other statins on rechallenge.[20,21]

Limitations
All of the retrospective reviews and case series are at high risk of bias. There are a number of potential confounders including no control group, use of different drugs and dosing regimens and different patient populations. There are no studies directly comparing nondaily dosing of statins with use of lower doses of statins or use of alternative statins.

Discussion
Based mainly on retrospective chart reviews, it appears at least 70% of patients with a history of statin intolerance will be able to tolerate either a different statin, a lower dose of a statin or a reduced dosing frequency of a statin. The data is at high risk of bias. Since the main reason for intolerance in these studies is myalgias, it is difficult to determine how well patients would tolerate alternative statins or dosing regimens for other intolerances. N-of-1 trials, where a single patient is randomized to sequentially take statin or placebo to determine tolerability, is a possible method of determining if myalgias are related to statin therapy.[22] However, they are time consuming to perform and there are no formal resources in Alberta for supporting clinicians in implementation.

No other lipid lowering therapies besides statins have been shown to decrease all-cause mortality, no do any other therapies have the same level of quantity or quality of data supporting their use in reducing cardiovascular disease (CVD)(see Chapter 4, "Which lipid lowering drugs decrease the risk of CVD, by how much and what are the harms?"). Fibrates and niacin may decrease the risk of nonfatal myocardial infarction (MI) but no other CVD outcomes, and have no effect on patient outcomes when added to statin therapy. Resins may reduce the risk of non-fatal MI or coronary heart disease (CHD) death based on two small studies at high risk of bias. However, the effects of fibrates, niacin, and resins are inconsistent and tolerability and compliance remain problematic. Ezetimibe may be well tolerated, but there is currently no evidence that it has any effect on patient outcomes. As such, statins remain the first choice for reducing cardiovascular (CV) risk and all attempts should be made to find the right statin at the right dose that patients will tolerate.

Bottom Line
Many patients who are intolerant of one statin are able to tolerate different statins or lower doses/frequencies of the same statin (Low Level Evidence). Since low dose statins have been shown to reduce CVD versus placebo in RCTs, use of lower doses may be preferable to reduced dosing frequencies. However, no evidence exists comparing the effects of one strategy against another on CVD outcomes. Since statins remain the only lipid lowering treatment that consistently modifies CV risk in RCTs, their use should be thoroughly exhausted in those with statin intolerance. Even if a patient only tolerates low doses of statins, low doses are preferable to no statin use at all. There is no evidence that adding non-statin therapy will provide any benefit.

Suggested Recommendation(s)
Suggest all attempts be made to find the right statin at the right dose that a patient will tolerate. Low doses of statins are preferable to avoidance of statins, and addition of non-statin therapy will not provide any benefit on CVD outcomes.

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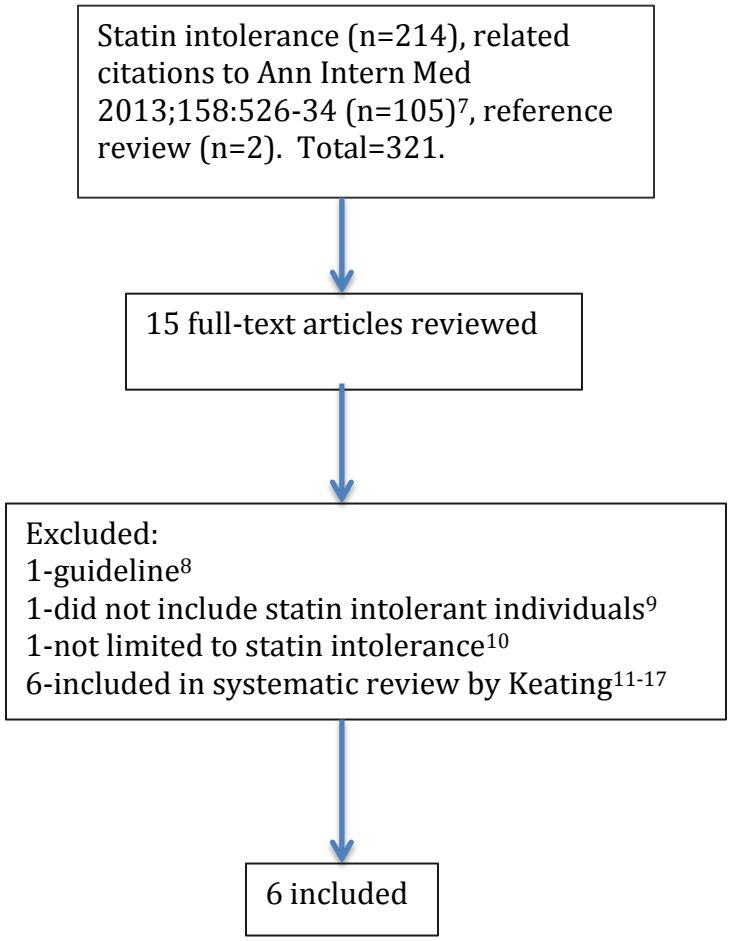
Figure 1. Search Results (search date May 25, 2014)



CHAPTER 10: PATIENT POPULATIONS

Which patient characteristics (e.g. post MI, DM, level of CV risk) warrant consideration of lipid lowering therapy?

Introduction and Methods

Various clinical practice guidelines have made recommendations about starting lipid-lowering therapy for patients with specific conditions (eg. diabetes). However, despite the presence of these conditions, an individual patients' cardiovascular risk remains the most important aspect in determining whether or not statin therapy is warranted. Other characteristics, including the presence of chronic kidney disease, rheumatoid arthritis, etc. do not add much to estimated cardiovascular risk once a risk calculation has been performed (see Chapter 3, "According to evidence, ease of use, and principles of shared, informed decision making, which risk calculator(s) should be recommended?" and Appendix. Diabetes Mellitus and Chronic Kidney Disease). We focused on the evidence for which levels of cardiovascular (CV) risk in primary prevention should be offered statins.

We only included meta-analyses of statins in primary prevention that looked at CV outcomes such as all-cause mortality, myocardial infarction (MI), or stroke. Cost effective analyses were excluded. PubMed was searched using the terms "statins and primary prevention" and limited to "meta-analysis." As discussed in Clinical Questions 4 and 5 ("Which lipid lowering drugs decrease the risk of cardiovascular disease (CVD)?" and "Does evidence support attaining specific lipid targets to decrease CVD?"), statins are effective in primary prevention. As such, we focused our review on meta-analyses that tried to determine at which level of CV risk are statins most effective. We wanted to answer two main questions: 1) Do the benefits of statins change with baseline risk? 2) What level of CV risk is a reasonable cut-off below which the benefits of statins are inconsequential?

We then took six of the largest trials within the identified meta-analysis and calculated the baseline CVD risk for the "average" patient in the trial using the mean baseline values in the placebo/control arm via the Framingham, BNF, ASSIGN, and ASCVD risk calculators.[1,2]

Results

Seventeen meta-analyses were identified, however only one provided a baseline level of CV risk.[3] This meta-analysis (29 studies, n=80,711) found the mean 10-year risk of nonfatal MI or CV death according to ATPIII criteria was 6% (range 0-18%). However, since the ATPIII method of calculating risk was used, this 6% is likely the risk of coronary heart disease (CHD) and CHD death as opposed to CV death. This is important when comparing the levels of risk across studies as CHD accounts for only ~55% of total cardiovascular disease (CVD) in women and ~65% in men.

Across 19 trials (n=78,231), statins reduced the risk of all-cause mortality by about 10% (RR 0.90, 95%CI 0.84 to 0.97, I^2=2%) for a number needed to treat (NNT) of 239 over two

years. The risk of MI (fatal, nonfatal, or unspecified) in 13 trials (n=48,023) was reduced by 37% (RR 0.63, 95%CI 0.5 to 0.79, I^2=13%) for an NNT of 216. The risk of stroke (fatal, nonfatal, or undefined) was also reduced by about 17% [14 trials (n=60,841) RR 0.83, 95%CI 0.74 to 0.93].

The level of risk of six major primary prevention trials are outlined in Table 1. The majority of trials were done in patients at moderate-high risk.

The Cholesterol Treatment Trialists meta-analysis (2012) demonstrated that statins are effective at reducing CVD regardless of baseline risk.[10] They consistently reduce risk by about 25%.[10,11] As such, it is important to determine someone's baseline risk to determine the absolute benefits of a statin for that particular patient. For example, if a patient's baseline risk of CVD is 20% over 10 years, a statin will reduce that risk to 15%. If their baseline risk is 5%, a statin will reduce their risk to about 4%.

The next question is how to determine at what level of risk it is appropriate to offer statin therapy. The risk reduction must outweigh the risk of adverse effects, and the benefits outweigh the impact on the patient for paying for and taking medications long-term. However, what a patient considers adequate benefit and acceptable risk will vary from patient to patient.

It is reasonable to consider that an absolute risk reduction of at least 2% would be an appropriate place to consider discussion of statin therapy with a patient. Therefore, if a patient's 10-year risk ≥10%, we should likely offer statin therapy and if their risk is ≥20%, statin use should be encouraged.

Bottom Line
Statins should be offered to all patients for secondary prevention, barring any contraindications, with higher doses potentially offering greater reductions in risk (High Level Evidence). For primary prevention, an individual patient's CVD risk should be calculated to determine the absolute benefit they may gain from statin therapy. Since statins consistently reduce the relative risk of CVD by 25-35% this converts to a net benefit of about 2% over 10 years for those with a 10-year CVD risk of 10% (High Level Evidence). Other patient characteristics, such as presence of chronic kidney disease (CKD), rheumatoid arthritis, or ethnicity do not add much to risk calculation once a calculator has been used (Moderate Level Evidence).

Suggested Recommendation(s)
Suggest recommending statins for all secondary prevention patients. For primary prevention, suggest recommending consideration of statin therapy whenever the absolute reduction in CV risk is ≥2%. Therefore, if a patient's 10-year risk ≥10%, we should likely offer statin therapy, and if their risk is ≥20%, statin use should be encouraged.

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Table 1. Calculated 10-year risk of cardiovascular disease based on baseline characteristics in major trials.

Study	Age	Men (%)	Smoker (%)	DM (%)	LVH (%)	SBP (mmHg)*	TC (mmol/L)	HDL (mmol/L)	Framingham (%)	BNF	ASSIGN	ASCVD	Tonelli (ATPIII)**[3]	D'Agostino[3]
JUPITER[4]	66	62	16	NP	NRU	134	4.8	1.3	17.9	14.3	16.0	11.3	6.0	22.0
ALLHAT-LLA[5]	66	51	23	34	NR	145	5.9	1.2	24.1	20.0	21.7	14.1	18.0	36.0
ASCOT-LLA[6]	63	81	32	25	14.2	164	5.5	1.3	27.5	23.0	21.7	15.4	11.0	42.0
AFCAPS[7]	58	85	12	5	NRU	138	5.7	0.9	21.7	19.4	15.9	10.8	7.0	28.0
WOSCOPS[8]	55	100	44	1	NRU	136	7.0	1.1	19.5	17.8	16.6	10.1	17.0	31.0
MEGA[9]	58	31	20	21	NRU	132	6.3	1.49	11.7	9.9	10.2	4.8	2.0	18.0

NP=not permitted in trial
NRU=Not reported, but unlikely based on entry criteria
NR=not reported
SBP=systolic blood pressure
*used as reported in trials. Therefore pre-treatment values may be higher.
**Note this is CHD risk only

CHAPTER 11: THE ELDERLY

How should we approach statin use in the elderly?

Introduction

In primary prevention, there is uncertainty how to proceed with cardiovascular disease (CVD) risk reduction in elderly patients. The average patient in primary care aged 65 and over has six chronic medical conditions.[1] This is one of the main factors contributing to high rate of polypharmacy in the elderly around the world.[2,3] Elderly patients are known to have a higher risk of adverse events with medications and polypharmacy further exacerbates the issues with increased risks of drug interactions. Given the high pill burden and associated risks among the elderly, any recommendation to add another daily prescription should be founded in high-quality evidence demonstrating important risk reduction with minimal adverse events. In regards to CVD risk reduction and lipid medications, the largest and most reliable body of evidence is with statins. However, elderly patients have frequently been excluded from statin clinical trials leading to an age bias in the research.[4] Therefore, we require a focused examination of the literature to determine if and how statins should be prescribed for primary prevention in the elderly population.

Our question: In elderly patients (≥65-70 years of age) without CVD, does statin treatment reduce CVD and/or mortality and what are the associated adverse events?

Methods

Our search (in PubMed on July 7, 2014) included:

- Started with the terms "statin" AND "elderly" AND cardiovascular, limited to systematic reviews: 226 papers were reviewed;
- Then a search of "related articles" from best study identified from that search (Savarese 2013): 92 papers were reviewed;
- Search terms "elderly" (limited to title), "statin" and "cardiovascular disease", restricted to randomized controlled trials: 34 papers were reviewed;
- Then search of "related articles" from best study identified from that search (PROSPER, Shepherd, 2002): 189 papers reviewed;

In total 541 articles were reviewed. Three systematic reviews and eight articles of seven RCTs make up the primary evidence considered.

Results

The results are broken down into Systematic Reviews and Individual Randomized Controlled Trials (RCTs).

<u>Systematic Reviews</u>

Savarese 2013

The best systematic review to address the question of statin use in primary prevention of the elderly was by Savarese and colleagues.[5] Their search included Medline, Cochrane, ISI Web of Science, and SCOPUS. The inclusion criteria were RCTs with subgroups of patients

with age ≥65 years without previous CVD. They included eight RCTs (with 24,674 patients), of which 43% were female and the mean age was 73 (+/- 2.9 years). The mean follow-up was 3.5 years.

All trials were high-quality and there was no evidence of publication bias. Cholesterol changes are provided in Table 1. The included trials with patient numbers and statin type/dose are detailed in Table 2.

Table 1. Cholesterol changes with statin (including baseline, actual, and percent change) and with placebo (percent change).

	Statin			Placebo
	Baseline(mmol/L)	Change (mmol/L)	% decrease	% decrease
Total Cholesterol	6.01	-1.22	-20%	-4%
LDL	3.76	-1.16	-31%	-6%
HDL	1.29	+0.01	+1%	-2%
Trig	1.66	-0.24	-14%	-4%

Table 2. Trials included in the Savarese systematic review with patient numbers and doses.

Trial	Patients (n)	Drug and dose (mg)
AFCAPS/TexCAPS	1416	Lovastatin 20-40
ALLHAT-LLT	5707	Pravastatin 40
ASCOT-LLA	4445	Atrovastatin 10
Bruckert	1229	Fluvastatin 80
CARDS	1129	Atorvastatin 10
JUPITER	5695	Rosuvastatin 20
MEGA	1814	Pravastatin 10-20
PROSPER	3239	Pravastatin 40

Table 3. Meta-analyses results with relative risk for each outcome from Savarese review

Outcome	Relative Risk (95% confidence interval)	Heterogeneity*	Estimated 3.5 year NNT** from meta-analysis event rates
Death (All cause)	0.94 (0.86-1.04)	p=0.57	-
CVD Death	0.91 (0.69-1.20)	p=0.83	-
MI***	0.61 (0.43-0.85)	p=0.03	84
Stroke	0.76 (0.62-0.93)	p=0.13	143
New cancer	0.99 (0.85-1.15)	p=0.49	-

* i^2 Stat not given. Only p-value testing provided.
**NNT = Number Needed to Treat
*** MI = Myocardial Infarction.

It should be noted that the PROSPER trial had the least relative reductions and caused the majority of the heterogeneity in the meta-analyses. Interestingly, PROSPER is the one RCT designed specifically to address the question of statin use in the elderly. In that study, those with a past history of CVD had the predicted response to statins (with CVD reduction) but those with no CVD history got less benefit then typically seen. PROSPER will be detailed more below.

Roberts 2007
The systematic review by Roberts focused on patients over the age of 60.[6] They included 18 RCTs with 51,351 patients, 28% of whom were female. Specific details of mean age were not available.

Unfortunately, the study is less useful for our question. The inclusion criteria were average age of study participants >60 years or presence of subgroup analyses limited to participants >60 years of age. This meant that trials could be included if patients were, for example, aged between 50 and 70, as long as the mean age was >60. So, the age break-down is described as: In 13 trials, mean age <70 (totaling 41,702 patients); in three trials, mean age >70 (totaling 6,041 patients); and no mean age in two trials (3,608 patients). Overall, 31,633 patients were age ≥60, meaning that over a third of patients were less than age 60.

Additionally, the inclusion criteria allowed secondary prevention patients, with only two included trials being primary prevention only.

Table 4. Relative risks for different outcomes from Roberts review.

Outcome	Relative Risk For all age~ ≥60 (95% confidence interval)	Heterogeneity	Relative Risk Subgroup age ≥65 (95% confidence interval)	Heterogeneity
Mortality	0.85 (0.78-0.93)	p=0.14	0.83 (0.70-0.99)	p= 0.83
CHD* Death	0.77 (0.71-0.85)	p=0.40	0.71 (0.61-0.82)	p=0.30
MI	0.74 (0.70-0.78)	p=0.49	0.75 (0.67-0.84)	p=0.25
Stroke	0.76 (0.65-0.90)	p=0.10	0.81 (0.66-1.00)	p=0.05
Cancer	1.06 (0.95-1.18)	p=0.11	1.16 (1.01-1.22)	p=0.25

*CHD=coronary heart disease

Gastrointestinal complaints were more common in the statin group but they arose from one study that allowed multiple reporting. The only other statistically significant difference in adverse events was musculoskeletal complaints: 27.2% among statin users and 25.9% in the placebo group, (p<0.01) with an absolute difference of 1.3% and number needed to harm (NNH) of 77. All other adverse events were not different.

Cholesterol Treatment Trialists (CTT) Collaboration
The CTT did not specifically examine statin effects in the elderly but did include a sub-analysis by age.[7] It is discussed here as it is one of the most frequently cited systematic reviews of statins. Although they analyze most data by mmol/L of low density lipoprotein (LDL) reduction (which may be a spurious surrogate association), there is some useful information as they generally use patient-level data. Unfortunately they include both primary and secondary prevention patients which limits the interpretation.

In their systematic review, the CTT include 22 trials with 134,537 patients for a median follow-up 4.8 years. Table 5 includes their sub-analysis by age.

Table 5. The risk ratio by age for major vascular events* in the Cholesterol Treatment Trialists Collaboration (From Web-figure 1)

	Number of events in meta-analysis	Risk Ratio for Major Vascular Events (95% confidence interval)	Absolute Difference per year (NNT)
Age ≤60 years	8778	0.77 (0.74-0.81)	0.7% (29 over 5 years)
Age >60 - ≤70 years	9838	0.78 (0.75-0.81)	0.85% (24 over 5 years)
Age >70 years	6337	0.83 (0.78-0.87)	0.72% (28 over 5 years)

*Major vascular events = major coronary events (non-fatal or fatal), strokes (fatal or non-fatal), or coronary revascularizations.

Randomized Controlled Trials
The search located six additional RCTs not included in the primary meta-analysis (Savarese 2013). We also included PROSPER as this RCT looked specifically at the elderly, although did include secondary prevention patients. In fact, no RCT specifically focused on primary prevention in the elderly. That said, there is some information to be gained from the seven RCTs (Tables 5 and 6).

The present evidence supports that statins reduce CVD and mortality in secondary prevention of elderly patients, at least up to age 75. In fact, both PATE and PROSPER had patients up to age 80 (or 82). Based on subgroup analysis from the two primary prevention trials, the benefits in primary prevention were similar to secondary prevention in PATE (the much smaller study) while in PROSPER, the benefits in primary prevention (if statistically significant, which they weren't) would be clinically insignificant (6% relative risk reduction). The extension of the PROSPER trial did not provide any new important data.[15]

The Cancer Question
PROSPER found a statistically significant increase (25% relative risk increase) in cancer. Over the 3.2 years, this led to increase in cancer incidence of 8.5% in the pravastatin group

versus 6.8% in the placebo group, with a NNH of 61.[14] Although not statistically significant or quite as high, an increase was also seen in the older subgroup of the LIPID trial (14% relative increase, not significant).[12] The meta-analysis provided in PROSPER[14] did not support a statistically significant increase in cancer with pravastatin. However, the trials included were from all ages. For example, in LIPID there was no suggestion of any increase in the whole population but in the subgroup of 65-75 year old patients, the risk was up 14% (non-significantly).

A meta-analysis of three Japanese studies (mixed RCT and observational) found no increase risk with pravastatin.[16] The subgroup of patients over 60 were also not at increased risk of cancer. This is one population of patients and includes observational studies that would be biased with healthy users. A meta-analysis of 12 RCTs with 42,902 patients found that pravastatin did not significantly increase the risk of cancer, RR 1.06 (95%CI 0.97 to 1.14) by random effects model.[17] However, when meta-regression was performed, it demonstrated that age played a factor in risk (p=0.006). In fact, the Risk Ratio at age 55 was 0.92, at 65 was 1.06 and at 75 was 1.22. It should be noted that at the high age end, the data is much more sparse. The cancer incidence and death in meta-analysis of all statins is not statistically significant.[18]

Table 6. Characteristics of trials or subgroups (published separately) targeting older patients (age ≥65)

Study	Prevention	Patient Number	Mean Age	Percent Female	Medication	Follow-up	Special notes
4S (sub)[8]	Secondary	1021	67	24%	Simvastatin 20-40 (31% got 40)	5.4 years	Nordic countries
CARE (sub)[9]	Secondary (MI)	1283	69	18%	Pravastatin 40	5 years	Substudy of CARE
LIPID (sub)[10]	Secondary (MI 60% or unstable angina)	3514	- (65-75)*	20%	Pravastatin 40	6 years	Australia/NZ
SAGE[11]	Secondary (MI)	893	72.5	30%	Pravastin 40 vs Atorvastatin 80	1 year	Primary outcome was duration of ischemia.
TNT (sub)[12]	Secondary (CHD)	3809	69.9	25%	Atorvastatin 10 vs 80	4.9 years	Substudy of TNT Low LDL (<3.4)
PATE[13]	Mixed (~26% CVD)	665	73	79%	Pravastatin 5 vs 10-20	3.9 years	Japan
PROSPER[14]	Mixed (~44%)	5804	75.3	52%	Pravastatin 40	3.2 years	Age 70-82

* Mean not given, only range provided.

Table 7. Outcomes of trials or subgroups (published separately) targeting older patients (age ≥65)

	CVD		Mortality		Subgroup	Adverse Events
Study	RR	NNT	RR	NNT		
Sub-group of elderly from larger trials of statin vs placebo - Secondary						
4S (sub)[8]	0.66 (0.52-0.84)	11	0.66 (0.48-0.90)	17		Only lab adverse events higher (4.2% higher)
CARE (sub)[9]	0.68 * (0.54-0.85)	11	0.55 ** (0.37-0.82)	15		Not reported
LIPID (sub)[10]	0.78 * (0.66-0.91)	21	0.79 (0.68-0.93)	22		Cancer 1.14 (0.98-1.32)
Dosing statin studies in elderly (One subgroup and one partly primary prevention)						
SAGE[11]	0.71 (0.46-1.09)	n.s.	0.33 (0.13-0.83)	37		LFT >3x normal (4.3% Atorvastatin vs 0.2% Pravastatin, p<0.001)
TNT (sub)[12]	0.81 (0.67-0.98)	44	Not reported	n.s.		LFT elevation (1.3% vs 0.1%)
PATE[13]	0.71 (p=0.046)	29	6.0% vs 4.2%	n.s.	CVD RR = 0.51 (if < 72 yrs) and RR = 0.80 (if ≥72 yrs)	
Statin studies in elderly that include Primary prevention patients.						
PATE[13]	0.71 (p=0.046)	29	6.0% vs 4.2%	n.s.	Previous CVD Yes RR = 0.74 vs Previous CVD No RR = 0.68	
PROSPER[14]	0.85 (0.74-0.97)	48	0.97 (0.83-1.14)	n.s.	Previous CVD Yes RR = 0.78 vs Previous CVD No RR = 0.94	Cancer: 1.25 (1.04-1.51) (not supported by their meta-analysis

* Major coronary event
** CAD death

Discussion

In secondary prevention elderly patients, there is a consistent reduction in CVD and often mortality. This evidence includes patients up to age 82. It can easily be argued that maximizing dose/potency is not required as increases in adverse events are associated with maximizing dose[19,20] and the fact that many of the trials did not use high-intensity statin therapy. However, of the three studies of varying intensity of therapy, two found a statistically significant reduction in CVD (the third was reduced similarly but not significant) and one found a statistically significant reduction in mortality. Based on this mixed evidence, it may be reasonable to recommend moderate intensity statin in patients older than 75 with CVD (secondary prevention), as advocated by the recent US guidelines.[21]

In primary prevention elderly patients (≥65), the best available evidence is likely the Savarese 2013 systematic review.[5] Patients ≥65 were included and the mean age was 73. In Roberts 2007, many included patients were possibly too young to know with confidence the benefits in elderly patients.[6] The CTT (2012) is helpful in showing that the relative reduction in CVD may be somewhat less in the elderly (>70) but due to the higher baseline absolute risk, the NNT is similar to that seen in treatment of younger ages.[7]

Savarese found a statistically significant relative reduction in MI of 39% and in stroke of 24%. The estimated NNT for these individual outcomes was 84 and 143 over 3.5 years, respectively. Other outcomes (e.g. death) were also reduced but not statistically. The CTT report a NNT for major vascular events of 28 over five years. More outcomes are included and the duration is slightly longer in the CTT meta-analysis making the NNT better. Therefore, the estimated NNTs are likely much closer than they appear. Musculoskeletal complaints increased by 1.3% in the treatment group,[5] which when converted to a five year period would give a 1.9% increase or a NNH of 54. Given that muscle aches are generally easily managed and numerically and clinically trumped by the reductions in major vascular disease, this data would point to a potential benefit with statins in elderly from age 65 to perhaps 75. The intensity of statin prescribing should likely mirror that of younger populations with moderate intensity statins for moderate CVD risk and high intensity statins for high risk and secondary prevention, as advocated by the recent US guidelines.[21] Important caveats remain as the elderly are more likely to have multiple comorbid conditions, be on more medications and are more likely to suffer from adverse events. Prescribing must at all times balance these issues and reductions in dosing/potency performed as necessary.

Looking specifically at patients older than 75 becomes very challenging. The majority of risk calculators do not allow input of ages >75 (e.g. Edinburgh site).[22] PROSPER and the smaller PATE were the only two trials found to specifically examine older patients. PROSPER had the oldest mean age (~75) but PATE was close (~73).[13,14] Both included secondary prevention patients. PROSPER found a statistically significant 15% relative risk reduction in CVD but when specifically examining those without a history of CVD the relative risk reduction dropped to a non-statistically, and likely clinically, insignificant 6%.[14] PATE, a trial about nine times smaller, found little numeric difference in the relative risk reductions (~30%) between those with or without CVD.[13] To summarize, there is little data for patients over 75 and the evidence for primary prevention is conflicting. Clinically,

however, we know that not all patients >75 are the same. Some may be in very good health and in these individuals statin prescribing may be considered as part of shared informed decision-making (and if risk calculation is performed, risk level will need to be approximated for years beyond 75). Clinician and patient discussion will drive these individual considerations.

One further subgroup needs consideration: Patients (primary and secondary prevention) already on statins who are beyond age 75. If these individuals are tolerating high potency statins (either primary or secondary prevention), there is no need to reduce the potency just due to age. For those individuals tolerating moderate potency statins for primary prevention, there is no need to stop statins. These recommendations mirror those of the US guidelines.[21]

Another important but as yet unclear issue in the literature is the risk of cancer in elderly patients using pravastatin. PROSPER, the largest trial of pravastatin in the elderly, found a statistically significant increase in cancer incidence.[14] Increases were seen for a variety of cancer types include breast, gastrointestinal, respiratory and other.[14] In the LIPID trial of pravastatin 40 mg, the subgroup of older patients (≥65) had an increased rate of cancer, although not quite statistically significant.[9] It should be noted that the younger group in LIPID did not show an increased cancer incidence. These led to meta-analyses to address the question. Two large meta-analyses of statin trials with a wide variety of populations found no increase in cancer rates with statin use, Rate Ratio 1.00 (95%CI 0.96 to 1.04)[7] and Odds Ratio 1.02 (95%CI 0.97 to 1.07).[18] Savarese, examining older patients, could not identify a statistical increased risk of cancer RR 1.06 (95%CI 0.95 to 1.18).[5] A meta-analysis focusing on RCTs of pravastatin also found no statistical increase in cancer RR 1.06 (95%CI 0.97 to 1.14).[17] However, when examining age in meta-regression of these trial results, it does appear age is a statistically significant risk factor.[17] In older patients on pravastatin there appears to be increased risk of cancer incidence, perhaps 22% relative risk increase in patients at age 75.[17] It should be noted that the data is sparse in this population (patients over age 75 on pravastatin).

Some have argued that the increased cancer incidence is a shifting of health risk. Recognizing that lifespan cannot be extended indefinitely, a reduction in the number one cause of morbidity and mortality (i.e. CVD) would lead to an increase in those developing the second most common cause of death (i.e. cancer). This would require confirmation through other studies using statins demonstrating increase cancer incidence in the elderly. We don't have this at present. The identification of risk with pravastatin may also be false because the majority of the data in the elderly, particularly those ≥70, come from pravastatin trials. Again, this will require other statin trials in this age group to verify. Lastly, this could be a spurious result in PROSPER and it is driving the meta-analyses of pravastatin in this age group. Still, there is an important signal and until we get more information a degree of caution is likely reasonable.

Bottom Line

Age 65-75: Recommendations generally mirror those for younger patients.

1. In secondary prevention (patients with CVD), statins at high potency should be

strongly encouraged,
2. In primary prevention patients,
    a. With moderate CVD risk, (10-20% risk of CVD over 10 years), moderate potency statins should be offered,
    b. With high CVD risk (≥20% risk of CVD over 10 years) moderate stains should be encouraged with high potency attempted as tolerated,
3. In patients ≥65, pravastatin should likely not be considered first line until uncertainty of cancer in this subgroup with this drug is resolved.

Age >75:

1. In secondary prevention (patients with CVD), statins at moderate potency should be strongly encouraged,
2. In primary prevention patients we discourage testing lipids, estimating risk and prescribing statins in most patients,
    a. There may be individual patients whose health status is similar to younger or healthy patients. In these cases, individual approaches may be warranted at the clinicians' and patients' discretion,
3. Patients already on a statin should <u>not</u> have their statin stopped or reduced just because they have aged beyond 75.

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CHAPTER 12: ASA

Who, if anyone, should receive daily ASA for primary prevention?

The following article addresses the background evidence review of this question:
Kolber MR, Korownyk C. An aspirin a day? Aspirin use across a spectrum of risk: cardiovascular disease, cancers and bleeds. Expert Opin Pharmacother. 2014; 15(2):153-7.

Addendum

The remaining issue is whether there may be a risk level for primary prevention patients at which daily ASA should be considered.

Methods

We needed to identify analyses combining benefits and risks, so we targeted cost-effectiveness analyses. One article by Algra and Greving (2009),[1] which was published in associated with the most recent Antithrombotic Trialists meta-analysis,[2] performed an update cost effectiveness analysis. The Algra and Greving article[1] was previously identified from other work and seen as directly addressing the cost-benefit of ASA in primary prevention. We used it as stem, searched PubMed for all articles related (205 total) and reviewed them for relevance.

Results

Our search revealed three new relevant papers:

1. The original, in depth cost effectiveness meta-analysis published in 2008;[3]
2. A narrative review of cost-effectiveness studies that unfortunately primarily reported on the variations in the analyses used.[4] Additionally, this work was sponsored by the brand-name manufacturer of ASA and therefore is at risk of bias;
3. The US Preventive Services Task Force review weighed the clinical outcomes (benefits and harms) and did not include costs. Most outcomes were considered equivalent which may be a limit of its application.[5]

Both studies that systematically and explicitly examined the cost-effectiveness of ASA[1,3] reported the different 10-year CVD risk that would, on balance of risk and benefit, be "cost-effective." The driver in the "cost" is minimally the amount spent on ASA but much more the loss of quality of life due to strokes, heart attacks, and bleeding events. In the original meta-analysis, for men the "cost" balance did not become consistently favourable until the 10-year risk was ~17%.[3] For women, the balance became favourable ~20%.[3] These numbers are derived from Quality of Adjusted Life Years analysis using a model of <20,000 Euro to be cost-effective.

In the updated analysis[1] for men the balance became favourable when 10-year cardiovascular (CV) risk was ~20%. For women, the balance became favourable ~30%. However, in the model, the case went from a risk level of 16% (which was not cost-effective) to 30% (which was cost-effective). Therefore, it is possible that if other cases were given with risks between 16-30%, it is possible cost effectiveness may occur earlier

than 30%. The US Preventive Task Force looked at the risk of Coronary Heart Disease (CHD) over 10 years for men and stroke risk for women.[5] CHD represents about 60% of the total CVD risk and stroke risk about 20% of total CVD. Looking at equivalency of myocardial infarction (MI) and ischemic stroke to hemorrhagic stroke and major gastrointestinal bleeds, ASA became a net benefit for men when their 10-year risk of CHD was ≥4% if age 45-59, ≥9% for age 60-69 and ≥12% for age 70-79. For women, benefit/harm balance favored treatment at stroke risk ≥3% if age 45-59, ≥8% for age 60-69, and ≥11% for age 70-79. Taking the middle of these numbers (9% and 8%) and converting them to CVD risk, the numbers would be approximately 15% for men and >30% for women.[6] These do not take in to account the costs and quality of life issues; it is simply a balance of CVD and bleeding events.

One last note, it is important to understand the degree of benefit. For men age 55 at high enough risk to get a net benefit (e.g. 24% 10-year CVD risk): When looking at the added quality of life years, taking ASA added about an average of 30 days over 10 years.[3] As another example, for 1,000 men at age 65 with a 20% change of CVD over 10 years, ASA every day would lead to one hemorrhagic stroke, 24 major gastrointestinal bleeds, and 64 less MIs (in net terms, about 0.4% reduced risk of a bad event per year).[5]

Discussion

As indicated by the article by Drs. Kolber and Korownyk, the vast majority of primary prevention patients should not take ASA daily. The previous cost effective analyses support this, indicating that low risk people of all ages (except perhaps men over 75) do not get a net benefit from ASA.[3] Based on the best evidence above, a risk cut-off to consider ASA is perhaps when baseline CVD risk ≥ 20%. The relative reduction in vascular events with ASA is approximately 12%, a number that is, at best, half of the benefit seen with low dose statins. Additionally, the harms of ASA (specifically bleeds) exceeds the risk of serious adverse events with statins. The risk of gastrointestinal bleeds increased with ASA is about 0.5%-4% over 10 years, with lower risk in younger women and higher risks in older men.[5] Our calculator will provide some of these values.

Bottom Line

When considering ASA use in primary CV prevention, one must balance the potential benefits (less cardiovascular events (CVE)) with the potential harms (more bleeding). ASA use for primary CV prevention should likely be considered (added to statin therapy) only when a patient's 10-year CV risk approached or exceeds 20%. Patients offered ASA should be informed of the potential benefits and harms.

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Appendix. Diabetes Mellitus and Chronic Kidney Disease

Some guidelines recommend that patients with diabetes age 40 to 75 be given statins rather than estimating risk and treating them based on risk.[1] This leads to the question "should every diabetic at age 40 be encouraged to take statins regardless of their risk?" Two systematic reviews and meta-analyses examined the benefits of statins in diabetics.[2,3] Both had very similar patient characteristics, with a mean age of approximately 62 years, two thirds male, ~18% smokers, mean systolic BP ~148mmHg, mean total cholesterol ~5.5 mmol/L, and mean HDL ~1.2 mmol/L. The Cholesterol Treatment Trialists report the mean age of patients with type 2 diabetes was 63.8 years with a standard deviation of 8.4 years.[3] Therefore, although the trials specifically addressing type 2 diabetic patients enrolled those aged 40 and over, the mean age in the trials was much higher. Therefore, the assumption that a 40-year-old diabetic without other risk factors will benefit from statin therapy may not be valid because few such patients were studied in these clinical trials. In fact, the calculated mean 10 year CVD risk of patients in these studies (using a Framingham risk calculator) was 34.8% or 38.5%.[2,3] Thus, these patients were much higher risk than a 40 year old diabetic without other risk factors. Additionally, cohort data shows CVD risk from diabetes is not equivalent to the risk in patients with coronary heart disease.[4] Risk estimation remains the best way to identify patients for consideration of pharmacotherapy. Framingham-based risk calculators include diabetes in their calculation of risk. Therefore, instead of being started on immediate statin therapy, we recommend that patients with diabetes ≥40 years old first undergo global risk assessment to determine the need for statin treatment.

Pooled cohort evidence suggests that patients with chronic kidney disease are at increased risk of CVD, with relative risk increases varying from 31% to 166% depending on the definition/severity of kidney disease.[5-7] The SHARP RCT including primary prevention chronic kidney disease (mean GFR 27 ml/min/1.73m^2) given simvastatin and ezetimibe demonstrated a 17% reduction in CVD (Rate Ratio 0.83 (CI 0.74-0.94)).[8] In pooled RCT data (13 RCTs, 36,033 patients) of chronic kidney disease patients not on dialysis, statins reduced CVD 28% (Risk Ratio 0.72 (0.66-0.79)).[9] As a result of this evidence, chronic kidney disease guidelines advocate treating most non-dialysis patients with statin therapy.[10] Mean data on patients in the pooled studies are not available but in SHARP the mean age was 62, 63% male, systolic blood pressure 139, total cholesterol 4.89 and HDL 1.12, giving a Framingham-based risk estimate, without CKD, >20% over 10 years. It is not clear if low risk patients will get the same advantage (those with CVD risk <10%). Therefore, we recommend assessing risk in these patients, preferably with a risk calculator including chronic kidney disease in the risk equation (e.g. QRISK2).

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