PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

ABSTRACTED MONTHL Y FROM THE JOURNALS

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This document is divided into two parts

    The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

        HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent

            points of each article.

        EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based

            on his long-term reviews of the current literature and his 26-year publication

            of Practical Pointers.

    I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

Treating Everyone With A Statin Drug, Age Being The Only Indication

8-1 EFFECTS OF LOWERING LDL-CHOLESTEROL WITH STATIN THERAPY IN PEOPLE WITH LOW RISK OF VASCULAR DISEASE

The Cholesterol Treatment Trialists' (**CTT**) Collaboration previously (2010) reported a meta-analysis of individual data from 17 000 persons in trials of standard statin regimens vs controls.

Lowering LDL-c by 1 mmol/L (~40 mg/dL[a]) with a standard statin regimen reduced the incidence of major vascular events (**MVE**; nonfatal myocardial infarction, coronary death, stroke, or coronary revascularization) by around a fifth.

There was no evidence that lowering LDL-c increased the risk of non-vascular death or cancer.

However there remains uncertainty about whether statin therapy is of overall net benefit in primary prevention. This question is important because, although individuals without previous vascular disease are at lower absolute risk, at least half of all vascular events occur among them.

This study assessed the benefit / harm-cost ratio of lowering LDL-c in low- risk patients**.**

*(**a** I converted mmol/L to mg/dL because the latter is more commonly used in the US. Ed.)*

STUDY

1. The meta-analysis included individual participant data from 22 trials of statin vs controls
   (n = 134 537; mean LDL-c decrease with statin = 1.08 mmol/L. (~ 43 mg/dL; mean follow-up = 4.9 years)

2. Determined 5-year incidence of major vascular events as listed above.

3. At baseline, participants were separated into 5 categories based on risk of major vascular
   event over 5 years: < 5%; 5% to 9%; 10% to 19%; 20% to 29%; 30% and over.

3. Estimated the rate ratio (RR; statin vs control) per 40 mg/dL LDL-c reduction in each
   category.

4. Analysis by intention-to-treat.

(The study also included 5 trials of more vs less statin. I omit this data. Ed.)

RESULTS

1. Individual participant data were available from 22 trials comparing statin with controls

2. Baseline characteristics: (n = 134 537; mean LDL-c = 148 mg/dL; mean age 63)

	< 5% risk	5% to 9% risk	10% and above
LDDL-c (mg/dL)	137	148	
Previous vascular disease 4%	13%	56% to 93%	
Diabetes	7%	18%	24% to 44%

   (At baseline, much lower prevalence of vascular disuse and diabetes in those < 10% risk

   However, not all subjects with low risk could be considered as primary prevention. Ed.)

3. When trials were ordered by their median 5-year predicted risk of major vascular events, the 5 trials with the lowest predicted risk (all less than 10%) were primary prevention trials.

4. Almost all participants with a predicted 5-year risk over 20% were recruited into trials in patients with a definite history of CVD.

5. Risk reduction in major vascular events(**MVE**) per 40 mg/dl reduction in LDL-c at different levels of risk

Baseline 5-y risk (%)	Events (%) per year		RR*
	Statin	Control	
<5	167 (0.38)	254 (0.56)	0.62
5 to 9	604 (1.10)	847 (1.57)	0.69
10 to 19	3614 (2.96)	4195 (3.50)	0.79
20 to 29	4108 (4.74)	4919 (5.80)	0.81
30 and above	2787 (7.64)	3458 (9.82)	0.79
Overall	11280 (3.27)	13673 (4.04)	0.79

   * Risk Reduction per 40 mg/dL reduction in LDL-c

6. Trends on major coronary events, stroke, and coronary revascularization were similar.

7. Major vascular events and deaths per 1000 avoided for a 40 mg/dL reduction in LDL-c over 5-years: (Absolute numbers)

%	MVE	Vascular deaths
< 5	6	1.2
5 to 9	15	4
10 to 19	31	8
20 to 29	45	11
30 and over	61	20

7. In participants with no history of vascular disease, reduction of LDL-c lowered the risk of vascular mortality: RR per 40 mg/dL reduction = 0.85. The proportional reduction in major vascular events was at least as large in the 2 lowest risk groups as in those at higher risk. (RR = 0.61 vs 0.66.)

8. There was no statistically significant trend toward an increase in non-vascular mortality in those at lower risk.

10. There was no evidence of an increase in cancer incidence or cancer death at any level of major vascular event risk.

DISCUSSION

1. Overall, lowering LDL-c with standard statin regimens safely reduced the 5-year incidence of major coronary events, coronary revascularizations, and ischemic strokes by about one fifth per 40 mg/dL reduction in LDL-c.

2. The present study also shows that reductions of LDL-c with statin therapy significantly lowered the risk of major vascular events in individuals with 5-year risk lower than 10%, even in those with no previous history of vascular diseases or diabetes.

3, The estimated absolute reduction in major vascular events even in patients with a 5-year risk lower than 10% was around 11 per 1000 over 5 years for each 40 mg/dL reduction in LDL-c.

4. Modern statin regimens can often reduce LDL-c by more than 40 mg/dL, which would yield even larger absolute reductions.

5. These benefits in apparently healthy low-risk people might be worthwhile provided they are not accompanied by any definite hazard that is of comparable severity. Although there was no evidence of increased risk of death from non-vascular causes or cancer in those at low risk, several known or potential hazards of statins need to be considered to evaluate the net effects.

   1) Statins are associated with a small increase in myopathy (exercises induced) of about 0.5 per 1000 over 10 years. And rhabdomyolysis of by about 0.1 per 1000 over 10 years. The risks of myopathy are dose-related.

   2) Statins might increase the risk of hemorrhagic stroke. The present analyses suggest that the excess risk of reducing LDL-c by 40 mg/dL might be in the order of 0.5 per 1000 per 5 years. But since statins produce a clear reduction in overall stroke, the increase in hemorrhagic stroke would be outweighed by the reduction in ischemic stroke (as well as the reductions in

other occlusive vascular events and deaths) even in individuals whose 5-year risk of major vascular events is lower than 5%.

     3) Statins might be associated with a proportional increase in diabetes of about 10%. More intensive therapy produces a greater increase. The authors suggest that risks from diabetes over 5 years is more than 50 times smaller than the absolute benefit of statin therapy.

6. Under current guidelines people with 5-year risk of major vascular events lower than 10% would typically not be judged suitable for statin therapy No guidelines now recommend statin treatment of patients with less than 10% risk.

7. Judgment about the appropriateness of widespread prescription of statins for primary prevention of vascular events in patients at lower risk also depends on costs. Generic statins, if effective, are likely to be cost-effective in individuals with an annual vascular disease risk down to at least 1%.

8. The present report shows that statins are indeed both effective and safe for people with a 5-year risk of major vascular events lower than 10%. Guidelines might need to be reconsidered.

INTERPRETATION

    In individuals with 5-year risk of major vascular events lower than 10%, each 40 mg/dL reduction in LDL-c produced an absolute reduction in major vascular events of about 11 per 1000 persons over 5 years. This benefit greatly exceeds any known hazards of statin therapy.

This is a complex, difficult-to-abstract article.

I do not understand how they determined the baseline risk percentages. They did not use the Framingham Risk Score. The annual rate of MVE in the subjects with 5 year baseline risk under 10% was lower than the rate in the 30% risk group. (~1% vs 9%). The 2 lowest risk groups had LDL-c

levels averaging 142 mg/dL. A few subjects in the lowest risk groups also had diabetes, previous CHD and other vascular events. The mean age of the entire cohort was 63.

The main point of the study was to establish that statin therapy reduced relative risk of MVE in those with baseline risks < 10% to a similar extent as relative risk reductions of subjects with higher baseline risks. In the lowest risk group, statin therapy also resulted in a small absolute reduction in MVE and deaths. Would it be reasonable to treat all patients with statins regardless of the baseline risk? Ie, treat everyone. Would pre- and post-treatment determination of LDL-c be eliminated? Would the baseline LDL-c level be ignored? At what age should statin treatment be started?

They suggest that the guidelines should be changed. At present no guideline recommends statin treatment for subjects with estimated risk under 10%.

This recalls the "polypill" principle, which suggested that preventive therapy for all persons over age 55 would reduce CVD mortality. Wald and Law first proposed the "polypill" principle in 2003. "A Strategy to Reduce Cardiovascular Disease by more than 80%" BMJ June 28 2003; 316. (See Practical Pointers June 2003.) The pill contained 5 drugs designed to lower LDL-c, BP, and platelet adherence. The recommendation was for everyone over age 55 to take it. Age was the only indication. There would be no pre-testing or post-testing.

Debate on this principle has continued.

To an elderly primary care internist, there is something wrong with advising all healthy people to take a daily foreign substance (a drug) for years even if it benefits some.

Many potentially treatable factors other than LDL-c increase risk of MVE: hypertension, obesity, sedentary lifestyle, unhealthy diet, smoking—all determined by screening. All should be considered. I believe most persons over age 55 have at least one risk factor.

 Primary care clinicians in the US usually treat individual risk factors as they appear regardless of estimated risk. The mean LDL-c in the study, even in those with risk < 10% was high (~ 150 mg/dL). This would be treated regardless of the 5- or 10-year risk. But, when to screen and start treatment is debated. Some have advised screening select adolescents for dyslipidemia. We should not wait until age 55 or 63 to start treatment. The earlier the treatment, the greater the benefit later in life.

Strict lifestyle interventions may be advised before drug therapy. They are the safest approach. In primary care practice they generally fail. It is easier to take a pill. We often prescribe a drug in combination with lifestyle advice.

Whether Populations Will Be Well Served By Present Pharmacologically Dominated Research Findings For Lifestyle-Related Diseases Is Debatable

8-2 STATINS FOR EVERYONE BY AGE 50 YEARS?

(This editorial comments and expands on the previous study. Ed.)

The Cholesterol Treatment Trialists' (**CTT**) collaborators report an overall relative risk reduction (statin vs control) in major vascular events (**MVE**) per 40 mg/dL reduction in LDL-c.

"Men and women, old and young; and people with and without CVD all benefit."

These findings confirm the efficacy of statins for primary prevention, resolving concerns about possible serious adverse effects and potential sources of bias in randomized trials.

The report extends findings to lower levels of MVE risk than recommended by current guidelines. And shows that benefits of statins outweigh any conceivable serious adverse effects.

The study raises questions for clinical practice: Are the costs acceptable? Can reductions of 40 mg/dL be sustained in routine primary care? Are statins cost-effective for patients at low CVD risk?

The CTT analysis predicts that 6 MVE would be prevented per 1000 persons with a baseline risk less than 5% treated with a statin over 5 years, and 15 MVE would be prevented in those with baseline risks 5% to 9%. This gives a number needed to treat of 167 and 67.

In England, half of men older than 50 years and 30% of women older than 60 years have a 10-year risk of MVE equal or higher than 20%, the present threshold for treatment. Adopting a lower, 10% threshold would classify 83% of men older than 50 and 56% of women older than 60 as needing a statin.

In primary care, long-term reductions in the order of 1 mmol/L might be difficult to achieve.

The CTT analysis provides reassurance to primary care clinicians to prescribe higher doses of statins to achieve greater benefit. It dissipates uncertainty about any potential serious adverse risks of statins.

Cost-effectiveness studies in the US, show that statins are cost-saving, even in people at low risk of MVE. To gain maximum effect, 64 million people in the US and (just under half of the population older than 35 years) would need to be put on treatment at a cost of $2800 per QALY gained.

Because most people over age 50 are likely to be at greater risk of MVE, it would be more pragmatic to use age as the only indication for statins, as originally proposed for the polypill. This approach would save costs.

However, whether populations will be well served by present pharmacologically dominated research findings for lifestyle-related diseases is debatable.

For a patient with risk under 10%, I believe choosing statin treatment becomes an individual's choice and preference after being fully informed. If long term statin therapy is chosen, it should be a low-dose generic. Pushing the dose upward and prescribing stronger, more powerful statin would increase adverse effects. I believe some benefit would occur even if LDL-c were not lowered by 40 mg/dL.

Patients should be informed about possible adverse effects and look for them. It would be reasonable to take care in patients more likely to become diabetic. The problem of long-term compliance would remain.

Ask would you be willing to take this drug every day for 5 years if it has 1 chance in 167 of benefit? Would you be willing to take it if you had 166 chances in 167 that would do no good.

There is an ethical issue here. By prescribing statin for everyone, we are placing many patients at risk of an adverse event and increased costs knowing than we may be doing no good.

The individual patient's lifestyle must be considered. It seems futile to me to treat a patient with statins if he continues to smoke.

If we treat everyone over age 55 with statins, when do we stop treatment? At age 65, 75, 85?

The article mentions treatment of hypertension. The approach differs. I have yet to encounter any advice to treat everyone over a certain age with anti-hypertension drugs in order to lower the risk of a subsequent MVE. We wait until the BP rises enough to warrant treatment.

Is Screening With Coronary Artery Calcium Score Appropriate In Primary Care?
8-3 CARDIOVASCULAR RISK ASSESSMENT IN THE 21ST CENTURY

The Framingham Risk Score (FRS) uses a number of risk factors to predict the likelihood of a cardiovascular event in the next 10 years.

Guidelines now suggest that this type of risk estimation may be useful as part of a general CHD prevention evaluation before embarking on various prevention strategies.

The FRS sets a high bar because it predicts, fairly well, using several simple risk factors that are inexpensive and easy to obtain. It explains a fair amount of the variability of risk in a population. Adding some conventional risk factors does not add materially to the model largely because of the

high correlation with factors already in the model. Obesity and body mass index are clearly associated with risk of cardiovascular events, but they are correlated with other factors such as lipid levels and BP that are already in the FHS model. The basic FRS is not improved when these factors are added.

In this issue of JAMA, two articles address the utility of additional techniques designed to enhance the predictive value of the FRS.

1) Carotid-intima-media thickness (**CIMT**). A pooled analysis of a number of studies demonstrates that CIMT does not add meaningful information to the standard FRS.

2) Coronary artery calcium score (**CACS**): Extensively evaluated a number of laboratory and imaging ancillary risk markers (ankle-brachial index, high sensitivity C-reactive protein). Only CACS was associated with substantially improved estimation of risk in patients at modest risk.

The CACS substantially reclassified individuals as being at higher risk, but requires additional assessment to determine whether the added information is truly useful. It involves radiation exposure, which raises some concerns and limits rescreening. The costs of the scan and the costs of additional interventions must be considered.

Although many guidelines stress the importance of understanding overall risk, a few simple questions can provide substantial information. Does the patient have known cardiovascular disease? If yes, there is no need to use a risk calculator. Does the patient have diabetes? If yes, aggressive management should be considered because the long-term risk of CVD is so high. If a simple risk calculator, such as the FRS identifies the patient at low risk (under 5% over 10 years) or high risk (over 20% over 10 years) then risk refinement is not informative. For those with risk 5% to 20%, a CAC scan may refine risk.

JAMA August 22/29 2-12; 308: 816-17 Editorial, first author J Michael Gaziano, Harvard Medical School, Boston Mass.

1 "Common Carotid Intima-media Thickness Measurements in Cardiovascular Risk Prediction"   First author Hester M Den Ruijter, University Medical Center, Utrecht, Netherlands

2 "Comparison of Novel Risk Markers for Improvement in Cardiovascular Risk Assessment in Intermediate-Risk Individuals" First author Joseph Yeboah, Wake Forest University, Winston-Salem NC

The editorialist is no fan of the CAC. I think with good reason. It is too cumbersome and costly to be applied to primary care practice.

The editorialist advocates the FRS because it is simple, less costly, and readily available to primary care practice. It has been useful for decades. Rapid calculators for the risk score are readily available on the internet. We should remember that all risk scores set boundaries for action that are arbitrary. Clinical judgment is still required.

FRS includes age, gender, total cholesterol, HDL cholesterol, smoking, systolic BP, treated hypertension. Diabetes is excluded because it is already a risk factor equivalent to a history of CVD.

FRS is easy to use; the risk factors are easy to obtain; they are safe; it is worth the cost; the risk score can monitor changes over time.

Age is the chief risk factor. Smoking is next to age as a risk factor, especially in younger patients.

A risk of less than 5% over 10 years indicates low risk and no need for therapy. A score over 20% indicates high risk and requires therapy.

I do not think the FRS and similar risk scores are helpful in primary care practice. Primary care looks far beyond 10 years.

It is possible for a male age 35 with a total cholesterol over 280 and no other risk factors to have a score under 5%; and a 35 year old male to have a systolic BP over 160 and no other risk factors to have a score under 5%. These patients should be treated. The longer the risk factor persists, the greater the risk of CVD events and death.

"Set Appropriate Treatment Goals And Focus On QOL, Not Solely On Survival At Any Costs."

8-4 IMPROVING PATIENTS QUALITY OT LIFE AT THE END OF LIFE

In the Coping With Cancer study in this issue of Archives,[1] patients and their caregivers provided various demographic, medical, and psychosocial data at enrollment and followed the patient until death (a mean 4 months later).

Identified key predictors of QOL just before death:

A. Associated with worse QOL: Intensive care unit stay in the final week; hospital death; patient worry; feeding tube use; chemotherapy in the final week.

B. Associated with better QOL: Religious prayer or meditation; pastoral care; patient-physician therapeutic alliance.

However, the study states that the factors included in the study account for only about 20% of the variance of quality of life at EOL.

Health-related QOL defies exact definition. QOL has various applications, including care for patients with other terminal illness, such as dementia.

There is a significant role for physicians when cure is unavailable by cultivating a therapeutic alliance, promoting introspection through pastoral services, reducing worrying, and avoiding unnecessary hospitalizations.

Previous studies suggested that a key question is whether the patient was asked to place a value on their lives.

There seems to be a paradox in assessing QOL when the expected death is hours or days away. Nevertheless, the concept persists. It speaks to the absence of unnecessary pain and discomfort, and acceptance of the inevitability of the short time left.

Dispositions and personality characteristics (particularly optimism) are related to self-rated QOL. Personality attributes are important for predicating QOL. Other attributes include: Science and health literacy levels among patients and caregivers; race; ethnicity; language and cultural competence among physicians and other providers; consistency of longitudinal care; and quality of physician-patient bidirectional communication.

The Americana Society of Clinical Oncology urges physicians to individualize care that will set appropriate treatment goals and focus on QOL, not solely on survival at any costs.

The challenge of providing care for patients with advanced cancer lies not in knowing which modalities may offer the best chance of disease response and prolonged survival, but in developing and maintaining effective caregiver-patient relationships. Physicians must convey the emotionally difficult message of prognosis, the true efficacy and futility of treatment, and when palliation is the best treatment.

Primary care clinicians are often involved in EOL care of their patients. This is a lifetime challenge. The challenge becomes much greater when a young patient is dying.

In the past, we have been admonished not to say "there is nothing else we can do". There is always "something else we can do". We should know when to stop active therapy and pass on to earlier palliation and Hospice care.

I believe patients in transition to death will be more at peace if they:

Believe in a Creator

Believe the Creator created the universe

Believe the Creator loves all creation, especially humankind

Respond by loving the Creator, all creating, and all fellow humans.

It Takes Decades For Alzheimer's Disease To Develop

8-5 LIFELONG MANAGEMENT OF AMYLOID-BETA METABOLISM TO PREVENT ALZHEIMER'S DISEASE

Alzheimer's disease (**AD**) is characterized by accumulation of amyloid-beta (**A***B*) in the CNS.

Twenty five years ago, an A*B* precursor protein (**APP**) was localized to chromosome 21. This made it clear that early-onset AD that occurs in all patients with Down's syndrome (trisomy 21) is attributable to an extra copy of APP.

Subsequently, APP mutations were identified in families with autosomal dominant AD. A substantial proportion of cases of autosomal dominant AD have been linked to more than 200 pro-amyloidogenic mutations that are responsible for the liberation of A*B* from APP.

In 2003, a postmortem study showed that participants vaccinated with AB had extraordinarily sparse levels of cortical amyloid plaques. In 2010. passive immunotherapy with monoclonal anti- A*B* antibody was shown to retard the progression of the cerebral amyloid burden by up to 25%. However, this modest reduction in the plaque burden was associated with no obvious clinical benefit.

The absence of cognitive benefit may have been because the antibody treatment was too late.

Interest in A*B* -lowering therapy for pre-symptomatic disease continues. A study in this issue of NEJM[1] focuses on imaging and biomarker assessment of pre-symptomatic autosomal dominant AD.

A study in this issue of NEJM[1] followed families with autosomal dominant AD worldwide. It showed that the changes in A*B* in the cerebrospinal fluid that accompany A*B* deposition can be detected as long as 25 years before AD symptoms begin Within a particular kindred of autosomal AD and its own mutation, the age at onset of AD breeds true. Ie, the age of onset is relatively invariable from generation to generation. Each mutation carrier knows approximately how many more pre-symptomatic years he or she can expect.

This implies that primary prevention in persons with autosomal dominant AD might need to begin 25 years or more before expected symptom onset. The 20 billion dollar question is: How early must one intervene to delay onset of symptoms?

A recent study from Iceland described an APP mutation leading to extremely low levels of plasma and cerebrospinal fluid A*B*. It identified 25 persons who were protected against AD. These data solidify the notion that A*B* accumulation is required for AD pathogenesis. And inhibition of APP is an attractive and potentially effective target.

We now know that, at least for autosomal dominant AD, the onset of A*B* accumulation is likely to be 25 years earlier than formerly guessed. Initiation of anti- A*B* therapy at the first signs of A*B* accumulation may be too late to avoid dementia.

Should patients with Down's syndrome be treated with A*B* -lowering therapy as babies? As children? As adolescents?

Should we begin to think of lifetime control of A*B* metabolism the same way we think of cholesterol metabolism?

Reduction on the risk of late-life AD requires a long-term effort.

A comprehensive strategy aimed at late-life dementia risk will almost certainly include monitoring and control of AB metabolism.

I abstracted this article mainly to learn the latest about AD. Patients will be asking about it.