

PRACTICAL POINTERS
FOR
PRIMARY CARE
ABSTRACTED MONTHLY FROM THE JOURNALS

NOVEMBER 2008

THE FUTURE OF PRIMARY CARE IN THE UNITED STATES [11-1]
ROSUVASTATIN FOR PREVENTION OF VASCULAR EVENTS IN PATIENTS WITH ELEVATED C-REACTIVE PROTEIN—A GOOD IDEA? [11-2]
CALCIUM SUPPLEMENTATION IN HEALTHY NON-OSTEOPOROTIC MEN [11-3]
THE IMPACT ON BEING OVERWEIGHT OF EATING QUICKLY AND EATING UNTIL FULL [11-4]
ABDOMINAL OBESITY RELATED TO MORTALITY [11-5]
NON-FASTING TRIGLYCERIDES—A RISK FACTOR FOR ISCHEMIC STROKE [11-6]
HEALING SKILLS IN MEDICAL PRACTICE [11-7]
OBSERVATIONAL STUDIES REQUIRED DURING ENTIRE MARKET LIFE OF A DRUG [11-8]
LOW-DOSE ASPIRIN FOR PREVENTION OF CARDIOVASCULAR EVENTS [11-9]
LOW-DOSE ASPIRIN IN PATIENTS WITH DIABETES [11-10]
THE CAGE QUESTIONNAIRE AFTER 25 YEARS]11-11]

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
www.practicalpointers.org
A free public-service publication.

PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA
To request monthly issues go to Rjames6556@aol.com

This document is divided into two parts

1) 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 review of the current literature and his 20-year publication of *Practical Pointers*.

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

Practical Pointers is published every month on the internet as a public service. It is available on a more timely basis by e-mail attachment. It contains no advertising. It is completely without bias. There is never any charge.

Requests for "subscription" to rjames6556@aol.com

HIGHLIGHTS AND EDITORIAL COMMENTS NOVEMBER 2008

“More Money Will Not Be Enough To Revitalize Primary Care”

11-1 THE FUTURE OF PRIMARY CARE

The editors of NEJM asked several experts to share their perspectives on the crisis in U.S. primary care. They discuss our problems, suggestions for improvement, and add a comparison with the UK system of primary care.

They recommend extended primary care with expanded teams of professionals (nurses, administrators, as well as M.D.s). Primary care physicians need to learn to work in teams and adjust to the notion that much of primary care can be delivered by non-physician team members

Patient care delivered with a primary care orientation is associated with more effective, equitable, and efficient health services. Primary care physicians (**PCPs**) perform many tasks that do not require a medical degree, and could be delegated. Primary care must recapture its attraction for the next generation’s best trainees.

Primary care is not defined by who provides it. Rather, it is a set of functions—first-contact care; person (not disease)-focused care over time; comprehensiveness in attending to the needs of populations, subpopulations, and patients; and coordination of care when services have to be received elsewhere or from others.

Payment reform is necessary. But, “More money will not be enough to revitalize primary care”

Electronic record- keeping is essential.

If the team approach is clearly explained to patients, if patients are offered continuity with the team, and if team members provide patient-centered, high-quality care, it is likely that patients will transfer their trust to the team.

In the UK, primary care physicians hold each patient’s lifelong record, which includes a letter regarding every visit to a specialist.

Our healthcare system is broken. Can we fix it? How long will it take? I believe the change will not take place until a substantial majority of Americans support it.

Changing emphasis to primary care is more than a sea change. It is a revolution. Supplying a primary-care medical home for all citizens may be an insurmountable task.

Some will cry, “rationing”.

Please read the full abstract.

Is This Applicable To Primary Care?

11-2 ROSUVASTATIN TO PREVENT VASCULAR EVENTS IN MEN AND WOMEN WITH ELEVATED C-REACTIVE PROTEIN

Increased levels of the inflammatory biomarker C-reactive protein (**CRP**) predict cardiovascular events. Since statin drugs lower levels of CRP as well as cholesterol, these investigators hypothesized that people with elevated high sensitivity CRP, but without hyperlipidemia, might benefit from treatment with rosuvastatin.

This very large multicenter trial (over 1300 sites in 26 countries) screened over 89 000 subjects (men over age 50 and women over age 60). Over 72 000 were excluded for various reasons, leaving 17 802 “apparently healthy” subjects for randomization. (*Ie, 4 out of 5 screened were excluded.*)

All subjects who were entered had LDL-cholesterol levels below 130. and high sensitivity CRP levels 2.0 mg/L or higher. The authors state: “Nearly all study subjects had lipid levels at baseline that were well below the threshold for treatment according to current prevention guidelines.” (*See full abstract for details. RTJ*)

Randomized to: 1) rosuvastatin 20 mg daily (*Crestor*; Astra Zeneca), or 2) placebo.

Primary endpoint = a first major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or death from cardiovascular causes. Follow-up for median of 2 years.

Rosuvastatin was associated with a reduction of LDL-c by 50% and CRP by 37%.

End point	Rosuvastatin (n = 8901)		Placebo (n = 8901)		AD	NNT
	No. of Patients	Rate per 100-person-yr	No. of patients	Rate per 100-person-yr		
Primary end-point	142	0.77	251	1.36	0.59	169
Myocardial infarction	31	0.17	68	0.37	0.20	500
Stroke	33	0.18	64	0.34	0.16	625
Death	198	1.00	247	1.25	0.25	400

[AD = absolute difference NNT = number needed to treat for one year to benefit one patient

My calculations. RTJ.]

Conclusion: “In this randomized trial of apparently healthy men and women who did not have hyperlipidemia but did have elevated levels of high-sensitivity C-reactive protein, the rates of a first major cardiovascular event and death from any cause were significantly reduced among the participants who received rosuvastatin as compared with those who received placebo.”

Please read the full abstract.

High sensitivity CRP may be a valid, cost-effective and important risk factor. This trial does not convince me that it is. Rosuvastatin 20 mg vs placebo given to subjects with LDL-c < 130 (disregarding CRP), and lowering LDL-c by 50%, would certainly be associated with an incremental reduction of cardiovascular events. Would risk be lower in those with a high CRP vs those with a low CRP? Would the difference be clinically significant? Would treatment based on CRP alone (high vs low) be associated with clinically important benefit?

Are the results of this trial applicable to primary care practice? I think not:

- Complexity

1) Including high sensitivity CRP levels in addition to LDL-c adds complexity.

2) If primary care clinicians followed the procedures of the trial, additional screening would be needed to select patients: hepatic functions, creatine kinase, creatinine. And patients would be excluded on a clinical basis: history of cardiovascular disease, diabetes, uncontrolled hypertension, inflammatory diseases.

3) Over 1000 subjects would have to be screened to begin therapy in 200.

4) Primary care clinicians and their patients now have multiple risk factors to treat—without great success. We need to apply those we already have rather than look for others.

- Cost:

1) A single tablet of rosuvastatin 20 mg now costs \$3.45. One a day costs \$1259 a year

*2) The money needed to treat (**MNT**), by my calculation, to prevent one primary endpoint in one year, is $169 \times \$1259 = \$212\,771$. And a like amount every following year.*

3) The complexity of the treatment would add costs, including the cost of CRP screening.

4) Generalizability of rosuvastatin therapy would be limited due to cost alone. Most patients could not afford it.

- Adverse effects:

1) Rosuvastatin 20 mg is a moderately high dose. As the investigators state, we cannot now know all adverse effects that will occur over a period of years. There is a hint of an increased incidence of diabetes. Certainly, over time, adverse effects would be more frequent in those receiving 20 mg than in those receiving 5 or 10 mg.

2) To prevent one patient from experiencing a primary endpoint in one year, 168 patients would be exposed, without benefit, to adverse effects of rosuvastatin.

- Considering complexity, costs and adverse effects

I doubt few, if any, fully informed patients would accept this therapy.

The benefit /harm-cost ratio of rosuvastatin is very low.

1200 Mg Of Calcium Daily Had Beneficial Effects On BMD; 600 Mg Did Not

11-3 RANDOMIZED, CONTROLLED TRIAL OF CALCIUM SUPPLEMENTATION IN HEALTHY, NON-OSTEOPOROTIC, OLDER MEN

Calcium supplementation is widely regarded as a fundamental component of the prevention and treatment of postmenopausal osteoporosis in women. It has been assumed that calcium plays a similar role in men who have osteoporosis. The US Surgeon General recommends increases in calcium intake across the entire population, including men.

There has been no consistent evidence, however, that calcium supplements affects bone mineral density (**BMD**) in men.

This double-blind, randomized, controlled trial followed 323 healthy men (mean age 57) for 2 years. Randomized to: 1) placebo; 2) 600 mg calcium daily; 3) 1200 mg calcium daily [600mg twice daily]. None received vitamin D supplements.

At baseline (means):

Calcium intake	850 mg/d
Serum 25-OH vitamin D	37 ng/mL (SI reference = 18-36)
Bone density T score	
Lumbar spine	+0.2
Hip	- 0.2 (Not osteopenic or osteoporotic.)

Over 2 years, BMD increased at all sites in the group receiving 1200 mg/d by 1% to 1.5% compared with placebo. Lumbar spine BMD increased by 1.2% in the first 6 months, followed by a more gradual increase over the 2 years to 1.5%. BMD in those receiving 600 mg did not differ from placebo.

“The present data establish that 1.2 g of calcium given in a divided dose produces substantial benefit to BMD throughout the skeleton in vitamin-D-sufficient men.”

Conclusion: Calcium, 1200 mg/d had beneficial effects on BMD in men comparable with those found in postmenopausal women; 600 mg /d was ineffective.

The problem of osteopenia and osteoporosis in older men is becoming more publicized. Vitamin D and calcium supplements are as necessary as in women.

Auckland, the site of the study, is a northern city in NZ, closer to the equator. Its latitude is 37° south, a sunny climate. I doubt that the oral intake of vitamin D is any greater than any other city. Perhaps the sunlight maintained serum levels of 25-OH D.

Note that the mean dietary intake of calcium was 850 mg. When 1200 mg is added, the total grows to over 2000 mg. A two-year period is not long enough to detect adverse effects of this total intake.

The rapidity of increase in BMD surprised me.

The Volume Eaten Is Predicted By The Volume Served.

11-4 THE JOINT IMPACT ON BEING OVERWEIGHT OF SELF-REPORTED BEHAVIORS OF EATING QUICKLY AND EATING UNTIL FULL

Eating quickly, gouging, and binge eating have been associated with increased total energy intake, and may lead to overweight and obesity.

This study examined whether eating until full (eating a large amount of food in one meal) and eating quickly are associated with overweight.

A cross sectional survey in Japan of over 3200 adults (mean age 53) was carried out in two Japanese communities (2003-2006). All completed a self-administered questionnaire on diet history to assess dietary habits during the previous month. Asked whether they usually eat until full (yes or no) and speed of eating (very slow, slow, medium, fast and very fast).

Multivariate adjusted odds ratios of men for being overweight: (Similar OR for women.)

	Not eating until full	Eating until full	Eating quickly	Eating until full
	Not eating quickly	Not eating quickly	Not eating until full	Eating quickly
Odds ratio	1.00	1.61	1.42	3.13

Those eating quickly and eating until full had 3 times the risk of overweight.

The effect of our food environment on children is likely to be challenging for the future health of the population. As with adults, there is little evidence of short-term energy regulation in the face of changing environmental stimuli. The capacity for regulation seems to decrease as children age. A study of preschool children found that the strongest correlate of the amount of food consumed at a meal was the amount served, and that the amount consumed was not influenced by energy consumed as snacks between meals.

The majority of parents encourage children to eat more than they may have wanted. As a result many children eat substantially more. It seems likely that any early capacity for energy regulation may be overridden by parental pressure to eat more.

Because children find it difficult to regulate their energy intake, it is important to inform parents of the environmental stimuli that promote positive energy balance such as serving excessively large meals.

Conclusion: Eating until full and eating quickly were associated with overweight in Japanese men and women. The combination may have a substantial impact on being overweight.

Sitting down together, enjoying a meal, and discussing the events of the day is, I believe, is one of the most important means of facilitating family cohesiveness. Relax and enjoy each other !

Children will copy the habits of their parents.

The old admonition “clean up your plate” is certainly out of date now.

Serve small portions and eat slowly. Be a good role-model for your children. Take care of yourself.

The recent effort to limit snack foods, especially fructose-containing soft drinks, at school is welcome.

Both Associated With Increased Risk Of Death

11-5 GENERAL AND ABDOMINAL OBESITY AND RISK OF DEATH IN EUROPE

Waist circumference and waist/hip ratio, indicators of abdominal obesity, may be better predictors of the risk of disease than the BMI.

Current guidelines with respect to obesity recommend the measurement of waist and hip circumference, and propose cutoff points of 102 cm for men and 88 cm for women. And cutoff points for waist/hip ratio of 100/100 for men and 82/100 for women to define abdominal obesity..

Does the distribution of body fat contribute to the prediction of death?

This study entered and followed over 359 000 men and women age 25 to 70 at enrollment (1992-2000). All were recruited from the general population. At baseline, all participants underwent anthropological measurements and completed a questionnaire about socioeconomic and lifestyle characteristics. Ascertained causes and dates of death over 10 years. Examined the associations of BMI, waist circumference, and waist/hip ratio with risk of death.

The lowest risk of death was at a BMI of 25 for men and 24 for women.

Waist circumference and waist/hip ratio were strongly associated with relative risks (**RR**) of death: Circumference: RR of death in the highest quintile vs the lowest was 2.05 for men and 1.78 for women. Waist/hip: RR of the highest quintile vs the lowest was 1.51 for men and 1.66 for women.

Among persons with “normal” weight (BMI 18.5 to < 25), the relative risks in the highest quintile of circumference, as compared with the lowest quintile were 2.06 and 1.79.

General obesity was more strongly related to risk of death among participants who had never smoked, whereas underweight was more strongly related to risk of death among current smokers.

Conclusion: General and abdominal adiposity were associate with increased risk of death. This supports the use of waist circumference and waist/hip ratio in addition to BMI in assessing risk of death.

Measurement of waist circumference is simpler than the ratio. Indeed, measurement is not necessary for many patients. Abdominal obesity is self-evident.

If your weight is “normal”, but your abdominal girth is high, you are at increased risk.

If you are skinny and your abdominal girth is high, you are at increased risk.

Formerly, I considered persons at lower BMIs (eg, 20) to be at lower risk. Several studies now suggest the most favorable BMI is 24-25.

If the patient has a high waist circumference, what can the patient and the primary care clinician do about it? I suspect, very little.

The extra-abdominal fat (exterior to the muscular abdominal wall) is metabolically inert compared with the intraabdominal fat.

Associated With Increased Risk Of Stroke

11-6 NONFASTING TRIGLYCERIDES AND RISK OF ISCHEMIC STROKE

Two recent cohort studies reported a strong association between elevated levels of non-fasting triglycerides and increased risk of myocardial infarction, ischemic heart disease, and death.

This study asks, “Are non-fasting triglycerides (**NFTG**) associated with an increased risk of stroke?

The population-based prospective cohort Copenhagen City Heart Study, initiated in 1976, included over 13 000 men and women (interquartile age ranges 48 to 57), with follow-up through July 2007 (31 years).

NFTG levels were determined at baseline. All blood samples were drawn between 8 AM and 4 PM; 82% of subjects had eaten within the last 3 hours. The remaining had eaten more than 3 hours before.

During follow-up, 1529 ischemic strokes occurred.

The cumulative incidence of ischemic stroke increased with increasing levels of NFTG.

Multivariate adjusted hazard ratios (**HR**) for stroke for men according to NFTG levels:

< 89	1.00
89-176	1.30
177-265	1.60

266-353	1.50
354-442	2.20
> 442	2.50

There were corresponding values for women. The HR for each 89 mg/dL increase in NFTG was 1.24
 “By using nonfasting rather than fasting triglycerides, . . . we detected associations between linear increases in nonfasting triglycerides and stepwise increases in risk of ischemic stroke with no threshold effect.”

Conclusion: NFTG levels were associated with increased risk of ischemic stroke.

It has long been considered that TGs are a risk factor for cardiovascular disease. The association was related to fasting TG. What took so long for us to realize the association with NFTG? One reason NFTG were not used to determine risk was that there was no standard. It is difficult for us to move from an “established” risk factor (fasting TG) to a new one.

The relation between NFTG and cardiovascular disease makes sense to me. Will this lead to a renaissance of use of fibrates and niacin? Certainly it emphasizes the downside of high fat meals.

The Chief Delivery Vehicle For The Scientific Interventions Of Modern Medicine.

11-7 HEALING SKILLS FOR MEDICAL PRACTICE

Physician’s relationships with patients can have healing effects. Compassion and trusting relationships with patients are the chief delivery vehicle for the scientific interventions of modern medicine.

Relational skills are fundamental to success. Relationships themselves have potential therapeutic value—described in scientific terms as the “placebo effect”—and, in ethical terms, as the center of the healing relationship.

Relationships with patients are a large part of the intrinsic rewards of medical practice.

Despite this recognition, relational skills are rarely studied systematically, and are often consigned to the unscientific and mystified “art” of medicine.

The authors of this study interviewed 50 practitioners regarded by their professional peers as especially good at establishing and sustaining excellent patient relationships. This included 10 non-MD practitioners in complementary and alternative medicine. 50% were women. They were asked: “How do you go about establishing and maintaining healing relationships with your patients?” “We believe that our interviews reveal a sound preliminary portrait of core relational skills from the practitioner’s perspective.”

Eight themes emerged:

1. Do the little things
 2. Take time and listen
 3. Be open
 4. Find something to like, to love
 5. Remove barriers
 6. Let the patient explain
 7. Share authority
 8. Be committed and trustworthy
-

Read the full abstract.

Although these themes can begin at the first consultation, it takes time to develop them fully. Fortunately, primary care clinicians are more likely to develop long-lasting relationships than specialists. Nevertheless, there is much opportunity for specialists to apply the themes.

Long ago, when I was in training in an academic center, we young-ones were often somewhat dismissive of the older physicians who we thought had a good “bedside manner” but who did not keep up with the latest in “scientific” medicine. How wrong we were !

Note that half of those interviewed were women. Women are innately more compassionate than men, and are more open in expressing it. Men can learn.

Both Benefits And Risks Need To Be Evaluated And Integrated During The Entire Market Life Of A Drug

11-8 BENEFITS AND RISKS OF DRUG TREATMENTS: *How to combine the best evidence on benefits with the best data about adverse effects*

The US Institute of Medicine states that a life-cycle approach to drug evaluation is needed. Both benefits and risks need to be evaluated and integrated during the entire market life of a drug.

To understand the full spectrum of adverse effects—those that occur late, that are not known beforehand, and that are rare but nevertheless serious—and to be able to investigate the true incidence of known adverse effects in circumstances of actual prescribing, well designed observational studies will be necessary.

Guidelines from the Agency for Health Research and Quality clearly separate the use of observational evidence for beneficial effects, for which the possibilities are scant; and the use of the same type of evidence for harms, for which the possibilities are rich.

For a future that combines benefit and harm assessment, systematic reviews will need to incorporate the best information from both randomized and observational studies.

This bears repeating:

Efficacy (as determined by RCTs) answers the question—Can it work?

Effectiveness (as determined by observational studies) answers the question—Does it work in the general population? Is it generalisable?

Efficiency (as determined by cost-effectiveness studies) answers the question—How much does it cost?

“Pragmatic trials” also attempt to judge if results are generalisable to the population.

There have been many accepted drugs and interventions, which have become entrenched in medical practice, that later were found to be misleading. For example:

The long-held view that estrogen prevents cardiovascular events.

The recent discovery that rosiglitazone is harmful to the cardiovascular system.

Primary care clinicians should wait for 2 to 3 years before prescribing a new drug unless the application of the drug is unique and important and if there is no reasonable substitute.

No Benefit in The Primary Prevention Of Cardiovascular Events, Even in High Risk Groups.

11-9 ASPIRIN FOR PREVENTION OF CARDIOVASCULAR EVENTS: Is only effective in established cardiovascular disease.

The use of aspirin for the *secondary* prevention of cardiovascular events in patients with coronary or cerebrovascular disease is well established. A meta-analysis reported that aspirin was beneficial in patients with acute myocardial infarction (**MI**), ischemic stroke, unstable or stable angina, and those with previous MI, stroke, or cerebral ischemia. However, not all patients with cardiovascular disease benefit from aspirin as shown by a recent meta-analysis of aspirin trials in peripheral artery disease.

Studies evaluating the possible benefits of aspirin for the *primary* prevention of cardiovascular disease have consistently been negative. A review by the FDA in 2004 evaluated five primary prevention trials and found that they were all negative for their end-points. Further examination of trials in the higher risk subgroups (Framingham scores > 8-10% / decade) also failed to show a benefit of aspirin. The FDA did not extend the labeling of aspirin for primary prevention.

Despite the consistently negative evidence, some guidelines recommend aspirin to prevent cardiovascular events in subjects at higher risk who do not have existing cardiovascular disease, and in patients with diabetes. The assumption is that the positive findings of aspirin in patients with symptomatic coronary or cerebrovascular disease can be extrapolated to high-risk populations who have no clinical evidence of cardiovascular disease.

Risk assessment alone cannot predict which patients will benefit from aspirin. In fact, the only predictor of clinical benefit from aspirin is a history of major coronary or cerebral ischemic events. This is in sharp contrast to evidence that statin drugs and anti-hypertension drugs have clinical benefit that extends to all risk groups, including those with and without CVD. In these examples, the differences between primary and secondary prevention is the absolute reduction in risk. Primary prevention populations have a lower absolute risk, but receive the same relative risk reduction.

A total of 7 well controlled trials now show that aspirin has no benefit for *primary* prevention of cardiovascular events, even in people at high risk. Aspirin should be prescribed only in patients with established cardiovascular disease (*secondary* prevention).

See the following abstract for a contrary view.

“The Role Of Antiplatelet Therapy For Primary Prevention In Individuals With Diabetes Remains To Be Elucidated.”

11-10 ASPIRIN FOR PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN DIABETES: Still an Open Question

This issue of JAMA presents a trial from Japan specifically designed to address the issue of antiplatelet therapy for *primary* prevention of cardiovascular events in patients with diabetes. It reported no benefit in reducing the risk of a composite endpoint of atherosclerotic events and mortality.

Aspirin was associated with an increased risk of gastrointestinal bleeding and retinal hemorrhage. Four patients in the aspirin group required blood transfusion.

Should this study be considered as definite proof that aspirin is less effective in patients with diabetes than in other high-risk groups? The editorialist believes the question is not settled. The trial poses some problems in terms of generalizability of results. There was a very low baseline risk of cardiovascular disease in the study groups.

“The role of antiplatelet therapy (*for primary prevention*) in the context of the overall approach to cardiovascular risk reduction in individuals with diabetes remains to be elucidated.”

How should the primary care clinician now respond? The decision to prescribe aspirin should be made on an individual patient basis after careful evaluation of the balance between the expected benefits and the risk of major bleeding.

I believe low-dose aspirin still has a place in primary prevention of cardiovascular disease, in high risk patients including those with diabetes. It should be used in conjunction with reduction in all other risk factors. Used alone, the absolute benefit in reducing cardiovascular events will be very small, and the NNT will be very high.

The editorialists agree that low-dose aspirin is indicated in patients with established cardiovascular disease (a history of myocardial infarction or ischemic stroke).

Considered two patients age 60:

A has an acute MI. He had not previously received low dose aspirin. Now it is prescribed based on its putative effectiveness in secondary prevention. It will be continued indefinitely.

Treatment results in improvement of dyslipidemia, BP, BMI and abdominal girth, and fitness. He stops smoking. Aspirin is likely to be continued despite his risk of a recurrent cardiovascular event being greatly reduced.

B has not experienced a MI. His risk factors are just as high as patient A at the time of his MI. He is at high risk for a cardiovascular event. Aspirin is not prescribed because his clinician does not consider it indicated for primary prevention.

Benefits of aspirin will be very low in both patients, I believe risk is higher in B than in A. And aspirin may be beneficial in B. Some patients who have never experienced a cardiovascular event may be at higher risk than some who have experienced a myocardial infarction. Benefit of primary prevention may be as great as secondary prevention in select patients.

Low-dose prophylactic aspirin has become engrafted in our medical practice. I believe use will continue. Primary care clinicians should limit use to very high risk patients along with other more important interventions to reduce risk. Whether diabetes per se is a high enough risk factor is a matter of debate. Most patients with diabetes have other risk factors.

Long-term aspirin use depends on the individual choice of an informed patient. Individualization is key.

Fashions in medicine change. At times, doubt about well-accepted practices may begin to creep in regarding applications that have been generally accepted for years, and advised by guidelines.

“Should Be Included Among The Standard History Questions”

11-11 THE CAGE QUESTIONNAIRE FOR DETECTION OF ALCOHOLISM: A Remarkably Useful but Simple Tool

“Some of the most remarkable advances in medicine are deceptively simple.” The CAGE questionnaire, published in the USA 25 years ago, is an example. Four simple questions have a major role in detecting alcoholism:

Have you ever:

- 1) felt the need to Cut down on our drinking?
- 2) felt Annoyed by criticism of your drinking?
- 3) had Guilty feelings about drinking?
- 4) taken a morning Eye opener?

A score of 2 or 3 indicates a high index of suspicion. A score of 4 is virtually diagnostic.

This is one in the series “JAMA Classics”. I believe it merits a reminder.

ABSTRACTS NOVEMBER 2008

“More Money Will Not Be Enough To Revitalize Primary Care”

11-1 THE FUTURE OF PRIMARY CARE

The editors of NEJM asked several experts to share their perspectives on the crisis in U.S. primary care. I abstracted select portions. RTJ

THE PROBLEM:

“A growing chorus of discontent suggests that the once-revered doctor-patient relationship is on the rocks.”¹

The U.S. now ranks 15th to 40th worldwide on various key health measures, such as life expectancy and years of life lost owing to preventable causes.²

Primary care has been one of the best jobs in medicine, and can be again. Primary care must recapture its attraction for the next generation’s best trainees—or the chaos and inefficiency of our health care system will worsen.

Primary care physicians (**PCPs**) perform many tasks that do not require a medical degree, and could be delegated. Overstressed by large patient panels, many primary care practices are performing below par. This can be attributed primarily to the overburdened 15-minute clinic visit.

Primary care is not defined by who provides it. Rather, it is a set of functions—first-contact care; person (not disease)-focused care over time; comprehensiveness in attending to the needs of populations, subpopulations, and patients; and coordination of care when services have to be received elsewhere or from others.

Today, more than half of specialist visits are routine follow-up—a misuse of expensive resources. There are large interregional variations in referral rates and use of specialist services that cannot be explained by differences in patients’ needs. Patients are often referred to specialists for problems—such as conditions requiring minor surgery or joint aspirations—that are common in the population and should therefore be addressed in primary care. Primary care is underused, and specialist care is overused. .

Money is only part of the problem, and therefore can be only part of the solution. When payments to PCPs are increased, they respond by reducing the number of patients they see. Physicians place a higher priority on trying to do a good job and having a sane life than on making a higher income. More money will not be enough to revitalize primary care. Payment reform is necessary—from volume-based payment to comprehensive payment for the delivery of comprehensive primary care—a “base payment”

supplemented by a “bonus” for achieving desired outcomes in the areas of cost, quality, and patient satisfaction.

Our multiple-payer system retards development of quality-improvement activities.

SUGGESTIONS FOR IMPROVEMENT:

Long-term relationships are a great source of satisfaction for providers and comfort for patients. Such relationships can be instrumental in providing effective and efficient care.

Patient care delivered with a primary care orientation is associated with more effective, equitable, and efficient health services. Residents of countries that are more oriented to primary care have better health at lower costs. PCP services in most industrialized countries are more comprehensive than those in the U.S.

Important functions of primary care include serving as first point of contact for all health needs and problems, delivering long-term person-focused care, comprehensively meeting all health needs except those whose rarity renders it impossible for a generalist to maintain competence in, and coordinating care that must be received elsewhere.

We must learn how to surround primary care physicians with teams that help them care for their populations of patients. Primary care physicians need to learn to work in teams and adjust to the notion that much of primary care can be delivered by non-physician team members, some of whom are located in non-traditional settings. Reorganization of primary care into a team-based endeavor, and off loading many functions from the 15-minute visit requires fundamental payment reform that uncouples reimbursement from the clinician visit and creates incentives for team building.

Electronic medical records can help manage the flood of information that moves through their offices every day.

A panel manager (perhaps a retrained medical assistant) must systematically and repeatedly review the registry and use physician-related standing orders to ensure that all tasks related to preventive and chronic care (subject to patient preference) are performed.

Healthy patients needing preventive care should be served largely by panel managers, who would order preventive services, send patients normal test results, and arrange clinician visits, telephones calls, or e-mail encounters for patients who need or want a discussion of abnormal results or other issues.

Patients with one or two chronic conditions could be cared for by a team under physician supervision. The team would plan visits (ideally for groups of patients) focused on patient education, lifestyle changes, clinical data tracking, and medication intensification. Health coaches (registered

nurses) could provide much of this care. The 15-minute visit with the PCP could then be devoted to patient-generated agenda items.

PCPs would become team leaders with a dramatically different daily schedule, having at most 10 visits per day and spending more time consulting with team members, handling physician-level telephone and electronic encounters, and ordering medication changes, which would be carried out by health coaches who would contact patients, explain the changes, listen to concerns, and follow-up on adherence.

If the team approach is clearly explained to patients, if patients are offered continuity with the team, and if team members provide patient-centered, high-quality care, it is likely that patients will transfer their trust to the team.

Primary care management for the vast majority of health problems should be the rule for most diagnosis and care, with specialty interventions when diagnosis requires confirmation with the use of special technology that is impractical in the primary care setting.

LESSONS FROM THE U.K.

There are some features of primary care in the United Kingdom that might warrant adaptation in the US. The UK takes the importance of primary care for granted. The UK government has become more convinced that strong primary care needs to be at the heart of the country's health care system—quite the reverse of the situation in the US.

UK primary care physicians increasingly work in multidisciplinary teams, with nurses taking on an increasing proportion of the work. Nurses see patients with minor illnesses and assume responsibility for the routine management of chronic diseases.

Having a single payer system helps a great deal in terms of organizing quality-improvement activities. Having a single-payer system defines common standards to which all suppliers of electronic records must adhere. Having a single-payer system means that UK primary care physicians hold each patient's lifelong record, which includes a letter regarding every visit to a specialist.

Virtually all primary care physicians use electronic medical records. Laboratories now download lab results directly into PCP computer systems.

NEJM November 13, 2008; 359: 2085-92 "Perspective", commentary by

Thomas H Lee, Partners Health-Care System, Boston, Mass

Katherine Treadway, Harvard Medical School, Boston, Mass

Thomas Bodenheimer, University of California, San Francisco, CA

Allan H Goroll, Harvard Medical School, Boston Mass

Barbara Starfield, Johns Hopkins University, Baltimore, MD

Mark Roland, University of Manchester, U.K.

1 New York Times July 29, 2008

2 The US lags behind 7 other advanced countries in:

Access to medical care due to cost

Coordination of care (availability of test results, reordering tests already done)

Medical and lab errors

US Health Care System Earns Poor Marks JAMA December 24/31, 2008; 300: 2843-44

“Medical News and Perspective” by Rebecca Voelker, JAMA Staff.

Is This Applicable To Primary Care?

11-2 ROSUVASTATIN TO PREVENT VASCULAR EVENTS IN MEN AND WOMEN WITH ELEVATED C-REACTIVE PROTEIN

Increased levels of the inflammatory biomarker C-reactive protein (**CRP**) predict cardiovascular events. Since statin drugs lower levels of CRP as well as cholesterol, these investigators hypothesized that people with elevated high sensitivity CRP, but without hyperlipidemia, might benefit from treatment with rosuvastatin.

STUDY

1. This very large multicenter trial (over 1300 sites in 26 countries) screened over 89 000 subjects (men over age 50 and women over age 60). Over 72 000 were excluded for various reasons, leaving 17 802 “apparently healthy”¹ subjects for randomization. (*Ie, 4 out of 5 screened were excluded.*)
 2. All subjects who were entered had LDL-cholesterol levels below 130, and high sensitivity CRP levels 2.0 mg/L or higher.
 3. Randomized to: 1) rosuvastatin 20 mg daily (*Crestor*; Astra Zeneca), or 2) placebo.
 4. Baseline characteristics²

	Rosuvastatin	Placebo
Body mass index		
Median	28	28
Interquartile range	25-32	25-32
Current smoker	16%	16%

Metabolic syndrome	41%	41%
High sensitivity CRP (mg/L)		
Median	4.2	4.3
Interquartile range	2.8-7.1	2.8-7.2
LDL-c (mg/dL)		
Median	108	108
Interquartile range	94-119	94-119
HDL -cholesterol (mg/dL)		
Median	49	49
Interquartile range	40-60	40-60
Triglycerides (mg/dL)		
Median	118	118
Interquartile range	85-169	86-169
Total cholesterol mg/dL)		
Median	186	185
Interquartile range	168-200	169-199
Glucose		
Median	94	94
Interquartile range	87-102	88-102

5. The authors state: “Nearly all study subjects had lipid levels at baseline that were well below the threshold for treatment according to current prevention guidelines.”² (*Compare with the NCEP treatment panel below. RTJ*)

6. Primary endpoint = a first major cardiovascular event: non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or death from cardiovascular causes.

RESULTS

1. Lipids and high –sensitivity CRP during a median follow-up of 2 years:

	Rosuvastatin	Placebo
CRP (mg/L)	2.2	3.5
LDL-c (mg/dL)	54	108
HDL-c (mg/dL)	52	50
Triglycerides (mg/dL)	99	116

[Rosuvastatin 20 mg was associated with a reduction of LDL-c by 50% and CRP by 37%.]

2. End point	Rosuvastatin		Placebo		AD	NNT	HR ³	P Value ³
	(n = 8901)		(n = 8901)					
	No. of patients	Rate per 100-person-yr	No. of patients	Rate per 100-person-yr				
Primary end-point	142	0.77	251	1.36	0.59	169	0.56	0.0001
Myocardial infarction	31	0.17	68	0.37	0.20	500	0.46	0.0002
Stroke	33	0.18	64	0.34	0.16	625	0.53	0.0001
Death	198	1.00	247	1.25	0.25	400	0.80	0.02

[AD = absolute difference NNT = number needed to treat for one year to benefit one patient

HR = hazard ratio. My calculations RTJ]

3. Subgroup analysis: groups typically assumed to be at very low risk also benefited: non-smokers, BMI < 25, no metabolic syndrome, a calculated Framingham risk score under 10%, or a LDL-c less than 100 mg/dL. The observed hazard ratios for the primary end point were similar to those in higher-risk groups. [No details given.]

4. Adverse effect: Physician –reported diabetes was more frequent in the rosuvastatin group (n = 270 vs 216 in the placebo group) and a small but significant increase in glycated hemoglobin. Myopathy, hepatic injury and cancer did not occur more frequently in the rosuvastatin group vs the placebo group. “Since the median follow-up was 1.9 years, we cannot rule out the possibility that the rate of adverse effects might increase in this population during longer courses of therapy.”

DISCUSSION

1. In this trial of generally healthy men and women with elevated levels of high-sensitivity CRP, rosuvastatin significantly reduced incidence of major cardiovascular events, despite the fact that nearly all study participants had lipid levels at baseline that were well below the threshold for treatment according to current prevention guidelines.
2. These effects were consistent in subgroups customarily considered to be at low risk.
(No details given.)

CONCLUSION

“In this randomized trial of apparently healthy man and women who did not have hyperlipidemia

but did have elevated levels of high-sensitivity C-reactive protein, the rates of a first major cardiovascular event and death from any cause were significantly reduced among the participants who received rosuvastatin as compared with those who received placebo.”

NEJM November 20. 2008; 359: 2195-207 Original investigation by the Justification for the Use of statins to Prevention: and Interventions Trial Evaluating Rosuvastatin (JUPITER) study group
first author Paul M Ridker, Brigham and Women’s Hospital and Harvard Medical School, Boston Mass

Study supported by Astra Zeneca

I detect a high degree of “spin” in this report. RTJ

1 *The authors describe the cohort as “generally healthy”. Note that 41% had the metabolic syndrome; 16% were smokers; ¼ had a BMI over 32, a HDL-c under 40, triglycerides over 169, a total cholesterol over 200, and a fasting glucose over 102. I would not describe these subjects as being “generally healthy”. They were more representative of patients seeking primary care. Some were at high risk.*

2 *The NCEP Adult Treatment Panel III classification of lipids:*

LDL-c

<100	<i>Optimal</i>
100-129	<i>Near or above optimal</i>
130-159	<i>Borderline high</i>
160-180	<i>High</i>

Total cholesterol

< 200	<i>Desirable</i>
200-239	<i>Borderline high</i>
<u>≥240</u>	<i>High</i>

HDL-c

< 40	<i>Low (Low HDL-c is a risk factor)</i>
≥60	<i>High</i>

Triglycerides

<150	<i>Normal</i>
150-199	<i>Borderline</i>
200-499	<i>High (Triglycerides are a risk factor)</i>

Risk categories that modify LDL-c goals New goal

CHD and CHD equivalents <100

2 or more risk factors	<130 (I suspect many subjects in the treatment group had
0-1 risk factor	<160 2 or more risk factors.)

3 Authors insist, and publishers persist, in reporting hazard ratios and P values even though they are misleading and clinically meaningless. Some readers may be impressed.

1200 Mg Of Calcium Daily Had Beneficial Effects On BMD; 600 Mg Did Not

11-3 RANDOMIZED, CONTROLLED TRIAL OF CALCIUM SUPPLEMENTATION IN HEALTHY, NON-OSTEOPOROTIC, OLDER MEN

Calcium supplementation is widely regarded as a fundamental component of the prevention and treatment of postmenopausal osteoporosis in women. It has been assumed that calcium plays a similar role in men who have osteoporosis. The US Surgeon General recommends increases in calcium intake across the entire population, including men.

There has been no consistent evidence, however, that calcium supplements affects bone mineral density (**BMD**) in men.

This trial determined the effects of calcium supplementation on BMD in men.

Conclusion: 1200 mg of calcium daily had beneficial effects on BMD; 600 mg did not.

STUDY

1. Double-blind, randomized, controlled trial followed 323 healthy men (mean age 57) for 2 years.
2. Randomized to: 1) placebo; 2) 600 mg calcium daily; 3) 1200 mg calcium daily [600mg twice daily]. None received vitamin D supplements. A few were taking multivitamin supplements.
3. At baseline (means):

Calcium intake	850 mg/d
Serum 25-OH vitamin D	37 ng/mL (SI reference = 18-36)
Bone density T score	
Lumbar spine	+0.2
Hip	- 0.2 (Not osteopenic or osteoporotic.)

RESULTS

1. Over 2 years, BMD increased at all sites in the group receiving 1200 mg/d by 1% to 1.5% compared with placebo. Lumbar spine BMD increased by 1.2% in the first 6 months, followed by a more gradual increase over the 2 years to 1.5%.

2. BMD in those receiving 600 mg did not differ from placebo.
3. There were dose-related decreases in serum levels of: parathyroid hormone; alkaline phosphatase; and procollagen type-1 in the group receiving 1200 mg.
4. Urinary calcium excretion increased by 57% in the 1200 mg group.
5. Falls tended to be less common in the 1200 mg group; vascular events more common.
6. No difference in multiple assessed adverse events between groups, including renal calculi (0 in 1200mg group; 2 in placebo group). No differences between groups in prevalence of cramps.
7. Withdrawals were few in all 3 groups.

DISCUSSION

1. "The present data establish that 1.2 g of calcium given in a divided dose produces substantial benefit to BMD throughout the skeleton in vitamin-D-sufficient men."
2. The failure of 600 g daily to influence BMD is surprising in view of the clear impact on parathyroid hormone

CONCLUSION

Calcium, 1200 mg/d had beneficial effects on BMD in men comparable with those found in postmenopausal women; 600 mg /d was ineffective.

Archives Int Med November 10, 2008; 2276-82 Original investigation, first author Ian R Reid, University of Auckland, New Zealand.

The Volume Eaten Is Predicted By The Volume Served.

11-4 THE JOINT IMPACT ON BEING OVERWEIGHT OF SELF-REPORTED BEHAVIORS OF EATING QUICKLY AND EATING UNTIL FULL

Eating quickly, gouging, and binge eating have been associated with increased total energy intake, and may lead to overweight and obesity.

This study examined whether eating until full (eating a large amount of food in one meal) and eating quickly are associated with overweight.

Conclusion: Eating until full and eating quickly were associated with being overweight.

STUDY

1. This cross sectional survey in Japan of over 3200 adults (mean age 53) was carried out in two Japanese communities (2003-2006).
2. All completed a self-administered questionnaire on diet history to assess dietary habits during the previous month. Asked whether they usually eat until full (yes or no) and speed of eating (very slow, slow, medium, fast and very fast).
3. Determined height and weight and calculated BMI. Considered a BMI of 25 or more as indicating overweight.
4. Interviewed participants to ascertain data on smoking, occupation, and use of regular physical exercise.
5. Determined whether there was an additive effect of eating until full and eating quickly.

RESULTS

1. Multivariate adjusted odds ratios of overweight for men:

	Not eating until full	Eating until full	Eating quickly	Eating until full
Odds ratio	1.00	1.61	1.42	3.13
	Not eating quickly	Not eating quickly	Not eating until full	Eating quickly

2. Those eating quickly and eating until full had 3 times the risk of overweight.

3. Results were similar in women.

DISCUSSION

1. Eating until full and eating quickly were associated with overweight. The combination of the two had an additive effect on overweight.
2. Participants who ate until full had higher total energy intake than those reporting binge eating.

CONCLUSION

Eating until full and eating quickly were associated with overweight in Japanese men and women. The combination may have a substantial impact on being overweight.

BMJ November 8, 2008; 337: 1091-93 Original investigation, first author Koutatsu Maruyama. Osaka University, Japan

A linked editorial in this issue of BMJ (pp 1064-65), First author Elizabeth Denney-Wilson, University of NSW, Sydney, Australia comments and expands on this study:

Humans are relatively ineffective at regulating energy intake.

The study builds on evidence that eating behaviors are important in promoting positive energy balance and may contribute to the current epidemic of obesity.

We do not know what drives us to eat quickly or to eat until we are full. Are these drivers modifiable? It may be that the changing sociology of food consumption with fewer families eating together, more people eating while distracted (eg, while watching TV), and people eating fast food while on the go, all promote eating quickly. The increased availability of relatively inexpensive food, served in larger portions, may promote eating beyond satiety.

We rely on visual clues (such as the amount of food that has been removed from the plate) more than the internal clues of fullness. The volume of food eaten is not modified in response to increased energy density of the food served. Food consumption increases with the variety offered. The volume eaten is predicted by the volume served.

The effect of our food environment on children is likely to be challenging for the future health of the population. As with adults, there is little evidence of short-term energy regulation in the face of changing environmental stimuli. The capacity for regulation seems to decrease as children age. A study of preschool children found that the strongest correlate of the amount of food consumed at a meal was the amount served, and that the amount consumed was not influenced by energy consumed as snacks between meals.

The majority of parents encourage children to eat more than they may have wanted. As a result many children eat substantially more. It seems likely that any early capacity for energy regulation may be overridden by parental pressure to eat more.

Clinicians should recognize that behavioral counseling can help management of this aggressively “eat more” food environment. Adults can successfully modify the speed of eating, and in turn, the energy intake of their children. Young children can be taught to recognize internal cues and alter their consumption accordingly.

Clinicians should encourage parents to adopt a child-led feeding strategy that acknowledges a child’s desire of when to stop eating that begins with birth.

Reassure parents that well children don’t starve.

Because children find it difficult to regulate their energy intake, it is important to inform parents of the environmental stimuli that promote positive energy balance such as serving excessively large meals.

Both Associated With Increased Risk Of Death

11-5 GENERAL AND ABDOMINAL OBESITY AND RISK OF DEATH IN EUROPE

Previous studies have relied predominantly on body mass index (**BMI**) to assess the association of adiposity with the risk of death.

Waist circumference and waist/hip ratio, indicators of abdominal obesity, may be better predictors of the risk of disease than the BMI.

Current guidelines with respect to obesity recommend the measurement of waist and hip circumference, and propose cutoff points of 102 cm for men and 88 cm for women. And cutoff points for waist/hip ratio of 100/100 for men and 82/100 for women to define abdominal obesity.

This study asks: Does the distribution of body fat contribute to the prediction of death?

Conclusion: Abdominal obesity (both increased circumference and increased waist/hip ratio) were associated with increased risk of death.

STUDY

1. The European Prospective Investigation into Cancer and Nutrition (EPIC) entered and followed over 359 000 men and women age 25 to 70 at enrollment (1992-2000). All were recruited from the general population.
2. At baseline, all participants underwent anthropological measurements and completed a questionnaire about socioeconomic and lifestyle characteristics.
3. Ascertained causes and dates of death over 10 years. Examined the associations of BMI, waist circumference, and waist/hip ratio with risk of death.

RESULTS

1. Over 14 000 participants died during the 10-year follow-up.
2. The lowest risk of death was at a BMI of 25 for men and 24 for women.
3. Waist circumference and waist/hip ratio were strongly associated with relative risks (**RR**) of death:
 - A. Circumference: RR of death in the highest quintile vs the lowest was 2.05 for men and 1.78 for women.
 - B. Waist/hip: RR of the highest quintile vs the lowest was 1.51 for men and 1.66 for women.
4. There was a significant association of BMI with relative risk of death:
 - A. Men: The lowest relative risk of death was at a BMI of 25
 - B. Women: The lowest risk of death was a BMI of 24.

(Relative risks of death rose below and above 25 for men; below and above 24 for women.)

5. For a given BMI, a waist circumference that was 5 cm larger was associated with an increased risk of death by a factor of 1.17 in men and 1.13 in women
6. The associations of circumference and waist/hip ratio tended to be stronger among persons with a lower BMI as compared with a higher BMI.
9. Persons in the lowest third of BMI and the highest quintile of waist circumference, as compared with the middle third of BMI with the lowest quintile of circumference (the reference group) had the highest risk of death.
10. Among persons with “normal” weight (BMI 18.5 to < 25), the relative risks in the highest quintile of circumference, as compared with the lowest quintile were 2.06 and 1.79.
11. The associations of a high BMI and high circumference with increased risk of death was stronger in young men than in older men, especially from circulatory causes.

DISCUSSION

1. General and abdominal adiposity were independently related to the risk of death.
2. Circumference is easier to measure and to interpret than the ratio.
3. “The current results underscore the importance of assessing the distribution of body fat even in persons of normal weight.”
4. General obesity was more strongly related to risk of death among participants who had never smoked, whereas underweight was more strongly related to risk of death among current smokers.
5. The addition of abdominal circumference to BMI more accurately stratifies persons into higher- and lower-risk categories.

CONCLUSION

General and abdominal adiposity were associate with increased risk of death. This supports the use of waist circumference and waist/hip ratio in addition to BMI in assessing risk of death.

NEJM November 13, 2008; 359: 2105-20 Original investigation, first author T Pischon, German Institute of Human Nutrition, Potsdam-Rehbruecke, Germany

Associated With Increased Risk Of Stroke

11-6 NONFASTING TRIGLYCERIDES AND RISK OF ISCHEMIC STROKE

Two recent cohort studies^{1,2} reported a strong association between elevated levels of nonfasting triglycerides and increased risk of myocardial infarction, ischemic heart disease, and death.

This study asks, “Are non-fasting triglycerides (**NFTG**) associated with an increased risk of stroke?

TG levels are usually measured in the fasting state. This excludes most remnant lipoproteins.

Except for the few hours before breakfast, most individuals are in the non-fasting state.

Conclusion: Nonfasting TG levels were associated with increased risk of stroke.

STUDY

1. The population-based prospective cohort Copenhagen City Heart Study, initiated in 1976, included over 13 000 men and women (interquartile age ranges 48 to 57), with follow-up through July 2007 (31 years). Fewer than 2% were receiving lipid-lowering therapy.
2. All had NFTG levels determined at baseline.
3. All blood samples were drawn between 8 AM and 4 PM; 82% of subjects had eaten within the last 3 hours. The remaining had eaten more than 3 hours before.
4. Stratified TG levels into 6 groups (mg/dL): < 89; 89-176; 177-265; 266-353; 354-442; and > 432.
5. Also studied a cross section of over 10 000 persons examined in 1991-94. This study calculated remnant lipoprotein cholesterol [Total cholesterol – (HDL-c + LDL-c)] Determined history of stroke related to levels of remnants and age.

RESULTS

1. During follow-up, 1529 ischemic strokes occurred.
2. The cumulative incidence of ischemic stroke increased with increasing levels of NFTG.
3. Multivariate adjusted hazard ratios (**HR**) for stroke for men according to NFTG levels:

< 89	1.00
89-176	1.30
177-265	1.60
266-353	1.50
354-442	2.20
> 442	2.50

4. There were corresponding values for women.
5. The HR for each 89 mg/dL increase in NFTG was 1.24

6. In both sexes, the absolute 10-year risk of ischemic stroke increased with increasing NFTG and age.

Men younger than 55; TG < 89 2.6%

Men age 55 and older; TG > 442 16.7%

7. In the cross sectional study (1991-94) in men with previous ischemic stroke:

NFTG: 191 mg/dL vs controls 148.

Remnant lipoprotein cholesterol: 38 mg/dL vs controls 29.

DISCUSSION

1. "By using non-fasting rather than fasting triglycerides . . . we detected associations between linear increases in nonfasting triglycerides and stepwise increases in risk of ischemic stroke with no threshold effect." (Even the most recent guidelines on stroke prevention do not recognize elevated NFTG as a risk factor.)
2. The explanation for this is straightforward. Elevated levels of NFTG mark elevated levels of remnant lipoprotein cholesterol contained in chylomicrons and very low density lipoproteins. Chylomicrons and very low density lipoproteins can penetrate into the arterial lumen and may preferentially be trapped within the subendothelial space. Because all human cells can degrade triglycerides, but not cholesterol, it may not be the triglycerides that causes atherosclerosis, but rather the cholesterol in these particles.
3. Since cholesterol in remnant lipoprotein particles cannot be degraded when taken up by the intimal macrophages, these cells are transformed into cholesterol-laden foam cells, leading to fatty streak formation and development of atherosclerosis.
4. Double-blind trials have reported that, among patients with elevated fasting TG levels, a 20% to 40% reduction in fasting TG achieved by fibrates was associated with a 20% to 40% reduction in risk of ischemic heart disease. A reduction in fasting TG levels of 24% achieved by niacin reduced risk of cerebrovascular events by 24%.
- 5.. An association between high TG and cardiovascular disease has previously been questioned because extremely high TG levels (> 2200 mg/dL), as seen in familial lipoprotein lipase deficiency, do not lead to accelerated atherosclerosis. The explanation is that at such extreme TG levels, lipoproteins are very large and cannot penetrate the intima of arteries.
6. Another argument against use of nonfasting TG for assessment of cardiovascular risk, is that TG levels vary greatly after intake of fatty meals. (There is no standard.)
7. The potential difficulty of using NFTG levels in clinical practice without standardization of the time and content of the last meal should be considered:

- 1) Lipid levels are usually measured in the fasting state. NFTG levels would require yet another blood sampling unless NFTG were to become the standard in the future.
- 2) In this study, however, even random levels of NFTG are associated with ischemic stroke. Whether standardization of the time and content of the most recent meal would further improve the association with ischemic stroke needs to be studied.

CONCLUSION

NFTG levels were associated with increased risk of ischemic stroke.

JAMA November 12, 2008; 300: 2142-52 Original investigation, first author Jacob J Freiberg, University of Copenhagen, Denmark.

- 1 JAMA July 2007 298: 299-308 “Nonfasting triglycerides and risk of myocardial infarction in men and women.”
- 2 JAMA July 2007; 298: 309-16 “Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women.”
- 3 Practical Pointers July 2007 [7-6] and [7-7]

The Chief Delivery Vehicle For The Scientific Interventions Of Modern Medicine.

11-7 HEALING SKILLS FOR MEDICAL PRACTICE

Physician's relationships with patients can have healing effects. Compassion and trusting relationships with patients are the chief delivery vehicle for the scientific interventions of modern medicine.

Relational skills are fundamental to success. Relationships themselves have potential therapeutic value—described in scientific terms as the “placebo effect”—and, in ethical terms, as the center of the healing relationship.

Relationships with patients are a large part of the intrinsic rewards of medical practice.

Despite this recognition, relational skills are rarely studied systematically, and are often consigned to the unscientific and mystified “art” of medicine.

The authors of this study interviewed 50 practitioners regarded by their professional peers as especially good at establishing and sustaining excellent patient relationships. This included 10 non-MD practitioners in complementary and alternative medicine. 50% were women. They were asked: “How do you go about establishing and maintaining healing relationships with your patients?”

Eight themes emerged:

1. Do the little things:

Small courtesies and congenial manners, such as shaking hands, acknowledging others in the room and maintaining eye contact, often turn out to be highly significant, especially at the beginning of a relationship. The practitioner has enormous power to set the tone and direction to the first encounter.

Give your undivided attention.

If someone feels connected, then you are miles ahead in terms of feeling able to affect some sort of positive impact on the patient. Touch (shaking hands, a pat on the shoulder) is extremely important.

2. Take time and listen:

Be still, be quiet, be interested, and be relaxed, do not interrupt.
Listen to the patient's life story.
Let some silence take place.

3. Be open

Patients bring their wounds to the practitioner.

It takes courage on the part of the practitioner to be willing to be open to the patient's vulnerability. Such willingness and courage makes healing possible.

Be honest. You might be able to help many times—it depends. You have wounds yourself. You are not perfect.

If the patient becomes tearful, don't become more clinical. Allow yourself to feel the emotion.
Although difficult, this can be very rewarding.

4. Find something to like, to love:

Love manifests most authentically and most powerfully in compassion and understanding.
Seek in every patient a quality, an achievement, or even just a mannerism the you can appreciate or admire. Your feeling must be genuine. Be willing to walk the wounded path with them.

5. Remove barriers:

Seek to remove barriers. Develop a genuine person-to-person encounter.
This may be as simple as removing a physical barrier (a desk) between you and the patient.
Remove attitudinal barriers. This involves an appreciation of the power differential between physician and patient. It requires humility.

6. Let the patient explain:

Patients are the best source of information about their own condition. Allow them to express their understanding about their illness. Ask what they understand about their illness.

This provides the opportunity for a reinterpretation, which itself is often an essential part of healing.

Ask open-ended questions.

Reply in language and terminology that patients understand and is meaningful to them.

7. Share authority:

Establish an expectation of a shared responsibility for healing at the very beginning.

View the patient as a fellow expert. Who knows more about them than themselves?

“I will make some recommendations to you. You will always dictate what you want to do.”

Provide guidance as you move together down the “wounded path”.

8. Be committed and trustworthy:

Intentionally plan to sustain the relationship and carry it forward. Patients fear abandonment.

Make sure the patient leaves with a plan.

Healing is about connections. Connections are about listening to patient’s stories. Listening is what makes us trustworthy.

Building relationships based on real trust. Such relationships are the principal rewards of being a physician.

Archives Int Med November 18, 2008; 149: 720-24 “Improving Patient Care” Original investigation, first author Larry R Churchill, Vanderbilt University Medical Center, Nashville TN

Both Benefits And Risks Need To Be Evaluated And Integrated During The Entire Market Life Of A Drug

11-8 BENEFITS AND RISKS OF DRUG TREATMENTS: *How to combine the best evidence on benefits with the best data about adverse effects*

The US Institute of Medicine states that a life-cycle approach to drug evaluation is needed.

Both benefits and risks need to be evaluated and integrated during the entire market life of a drug.

The Congress has called on the FDA to improve its methods of communicating risks and benefits to patients and physicians in postapproval as well as preapproval settings. New methods are needed to combine evidence about risks and benefits.

To judge the benefits of drugs, randomized controlled trials (**RCTs**) provide information. For adverse effects, the situation is different. Given the average duration of RCTs (often months to 1 or 2 years) and the average number of patients in them (often a few dozen to a few hundred) such trials are at most able to detect and quantify frequent adverse events that occur only during early treatment. The study population in trials, which often includes young persons with a single diagnosis and without concurrent disease, is often not representative of those who will eventually use the drug in the community.

The situation does not much improve in meta-analysis. The typical meta-analysis of RCTs covers 1000 to 2500 individuals, only half of which will have taken the new drug. This sample size precludes a good quantification of adverse effects unless they occur at least with a frequency of about 1 in 200 person-years. Meta-analyses do not solve the problem of late adverse effects, or the narrow populations included in the trials.

Thus, to understand the full spectrum of adverse effects—those that occur late, that are not known beforehand, and that are rare but nevertheless serious—and to be able to investigate the true incidence of known adverse effects in circumstances of actual prescribing, well designed observational studies will be necessary.

Clinical trial data and observational evidence complement each other. For example, the interaction between selective serotonin reuptake inhibitors (**SSRI**) and NSAIDs, which led to an excess of upper GI bleeding, was missed in SSRI trials. The number needed to harm determined by a meta-analysis of observational studies was close to 1 in 100.

Guidelines from the Agency for Health Research and Quality clearly separate the use of observational evidence for beneficial effects, for which the possibilities are scant; and the use of the same type of evidence for harms, for which the possibilities are rich.

For a future that combines benefit and harm assessment, systematic reviews will need to incorporate the best information from both randomized and observational studies.

JAMA November 26, 2008; 300: 2417-19 “Commentary” first author Jan P Vandenbroucke, Leiden University the Netherlands.

No Benefit in The Primary Prevention Of Cardiovascular Events, Even in High Risk Groups.

11-9 ASPIRIN FOR PREVENTION OF CARDIOVASCULAR EVENTS

The use of aspirin for the *secondary* prevention of cardiovascular events in patients with coronary or cerebrovascular disease is well established. A meta-analysis¹ reported that aspirin was beneficial in patients with acute myocardial infarction (**MI**), ischemic stroke, unstable or stable angina, and those with previous MI, stroke, or cerebral ischemia. However, not all patients with cardiovascular disease benefit from aspirin as shown by a recent meta-analysis of aspirin trials in peripheral artery disease.

Studies evaluating the possible benefits of aspirin for the *primary* prevention of cardiovascular disease have consistently been negative. A review by the FDA in 2004² evaluated five primary prevention trials and found that they were all negative for their end-points. Further examination of higher risk subgroups (Framingham risk scores > 8-10% / decade) also failed to show a benefit of aspirin. The FDA did not extend the labeling of aspirin for primary prevention.

Subsequently, the Women's Health Study of over 39 000 healthy women³ also failed to show a significant improvement for the end-point (prevention of non-fatal MI, non-fatal stroke, or death from cardiovascular disease).

A subgroup analysis of the Physician's Health Study⁴ of over 22 000 healthy men randomized to aspirin or placebo found no benefit for the end point of cardiovascular mortality, although a subgroup analysis found that aspirin prevented non-fatal MI in men.

The major cardiovascular event rates in these two key primary prevention studies were less than 1% a year.

Despite the consistently negative evidence, some guidelines recommend aspirin to prevent cardiovascular events in subjects at higher risk who do not have existing cardiovascular disease, and in patients with diabetes. The assumption is that the positive findings of aspirin in patients with established coronary or cerebrovascular disease can be extrapolated to high-risk populations who have no clinical evidence of cardiovascular disease.

Other groups at high risk include patients with markers of systemic atherosclerosis, such as patients with peripheral atherosclerosis. In a recent meta-analysis an ankle/brachial index of less than 90/100 (indicating peripheral vascular disease) was associated with a doubling of the 10-year risk of major cardiovascular events. In this context, a trial reported in this issue of BMJ⁵ compared aspirin vs placebo on prevention of fatal and non-fatal major cardiovascular events in over 1200 high risk patients with diabetes and peripheral vascular disease. After 8 years, there was no difference in outcomes. There was a trend toward more gastrointestinal symptoms in the aspirin group. This again supports the observation

that there is no benefit from aspirin in the *primary* prevention of cardiovascular events, even in high risk groups.

Risk assessment alone cannot predict which patients will benefit from aspirin. In fact, the only predictor of clinical benefit from aspirin is a history of major coronary or cerebral ischemic events. This is in sharp contrast to evidence that statin drugs and anti-hypertension drugs have clinical benefit that extends to all risk groups, including those with and without CVD. In these examples, the differences between primary and secondary prevention is the absolute reduction in risk. Primary prevention populations have a lower absolute risk, but receive the same relative risk reduction.

A total of 7 well controlled trials now show that aspirin has no benefit for *primary* prevention of cardiovascular events, even in people at high risk. Aspirin should be prescribed only in patients with established cardiovascular disease (*secondary* prevention).

BMJ November 1, 2008; 337: 1005-06 Editorial by William R Hiatt, University of Colorado School of Medicine.

1 Collaborative Meta-analysis of Randomized Trials of Antiplatelet Therapy for Prevention of Death, Myocardial Infarction, and Stroke in High-risk Patients BMJ 2002; 324: 71-86

2 Report from the 100th Cardiovascular and Renal Drugs Advisory Committee Meeting: US Food and Drug Administration Circulation 2004; 109: e9004-5

3 A Randomized Trial of Low-dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women NEJM 2005; 352: 1293-304

4 Final Report on the Aspirin Component of the Ongoing Physician's Health Study Research Group NEJM 1989; 321: 129-35

This trial started interest in aspirin for primary prevention. At the time, it garnered a great deal of interest. Many primary care clinicians over age 50 began to take low-dose aspirin as a result.

The trial entered over 22 000 subjects, and continued for 5 years. Subjects were randomized to:

1) 350 mg aspirin every other day or 2) placebo.

In the aspirin group there were 255 myocardial infarctions per 100 000 person-years vs 440 in the placebo group—a reduction of 44%, but only in those over age 50. (By my calculation, the absolute yearly reduction in MI was 0.185%; NNT for one year to benefit one patient = 540.) There was a non-statistically significant increase in hemorrhagic stroke in the aspirin group.

The evidence concerning prevention of stroke and total cardiovascular deaths was inconclusive because of inadequate numbers of subjects with these endpoints.

5 The Prevention of Progression of Arterial Disease and Diabetes Trial BMJ November 1, 2008; 337: 1030-34

Reported that aspirin vs placebo was *not* effective in primary prevention of cardiovascular events and mortality in a population of patients with peripheral vascular disease and diabetes. (The study included a trial of antioxidants, which were likewise ineffective.)

“The Role Of Antiplatelet Therapy For Primary Prevention In Individuals With Diabetes Remains To Be Elucidated.”

11-10 ASPIRIN FOR PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN DIABETES: Still an Open Question

Many guidelines recommend low-dose aspirin for prevention of cardiovascular events in patients with diabetes. (Including those who have no history of cardiovascular disease.) The evidence supporting its efficacy is scarce. Indeed, an increasing amount of evidence suggests that the efficacy of antiplatelet therapy in patients with diabetes may be lower than in individuals without diabetes.

This issue of JAMA presents a trial ¹ from Japan specifically designed to address the issue of antiplatelet therapy for *primary* prevention of cardiovascular events in patients with diabetes. It reported no benefit in reducing risk of the composite endpoint of atherosclerotic disease and mortality. In a subgroup analysis of subjects over age 60, there was a marginally significant reduction in incidence of the primary endpoint in patients treated with aspirin compared with controls.

Aspirin was associated with an increased risk of gastrointestinal bleeding and retinal hemorrhage. Four patients in the aspirin group required blood transfusion.

Should this study be considered as definite proof that aspirin is less effective in patients with diabetes than in other high-risk groups? The editorialist thinks not. The trial poses some problems in terms of generalizability of results. There was a very low baseline risk of cardiovascular disease in the study groups.

The last meta-analysis ² of efficacy of antiplatelet therapy in prevention of major cardiovascular events showed a clear benefit (a 22% reduction in cardiovascular events) for the entire population of more than 140 000 patients. But no statistically significant benefit in the subgroup of diabetic patients.

“The role of antiplatelet therapy (*for primary prevention*) in the context of the overall approach to cardiovascular risk reduction in individuals with diabetes remains to be elucidated.”

How should the primary care clinician now respond? The decision to prescribe aspirin should be made on an individual patient basis after careful evaluation of the balance between the expected benefits and the risk of major bleeding.

JAMA November 12, 2008; 300: 2180-81 Editorial by Antonio Nicolucci, Consorzio Mario Negri Sud, Imbaro, Italy

1 JAMA November 12, 2008; 300: 2134-40 “Low-dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type-2 Diabetes.”, first author Hisano Ogawa, Kumamoto University, Kumamoto City, Japan.

The trial included over 2300 patients with type-2 diabetes. None had a history of atherosclerotic disease. Randomized to: 1) Aspirin 80-100 mg daily, or 2) Control group without aspirin.

After a median follow-up of 5 years, aspirin was associated with a non-significant reduction (hazard ratio = 0.80) in risk of the primary composite end point (fatal and non-fatal ischemic heart disease, fatal or non-fatal stroke, transient ischemic attack, and peripheral vascular disease.)

There were no differences in total mortality.

The author of the editorial comments that the study has methodological and generalizability problems. Cardiovascular disease in Japan differs from that of non-Japanese populations..

2 BMJ 2002; 324: 71-86 “Collaborative Meta-analysis of Randomized Trials of Antiplatelet Therapy for Prevention of Death, Myocardial Infarction, and Stroke in High-risk Patients.

This article was cited in the preceding article—with a different interpretation.

“Should Be Included Among The Standard History Questions”

11-11 THE CAGE QUESTIONNAIRE FOR DETECTION OF ALCOHOLISM: A Remarkably Useful but Simple Tool

“Some of the most remarkable advances in medicine are deceptively simple.” The CAGE questionnaire, published in the USA 25 years ago,¹ is an example. Four simple questions have a major role in detecting alcoholism:

Have you ever:

- 1) felt the need to Cut down on our drinking?
- 2) felt Annoyed by criticism of your drinking?
- 3) had Guilty feelings about drinking?
- 4) taken a morning Eye opener?

A score of 2 or 3 indicates a high index of suspicion. A score of 4 is virtually diagnostic.

Few primary care clinicians integrate evaluations for alcoholism into their standard workup. Of those who do, the majority use the CAGE. It is one of the most efficient and effective screening tools. It identifies patients who will require more extensive testing and possible treatment.

CAGE is a screening tool. It does not provide information about quantity, frequency, or pattern of drinking. Other instruments (Michigan Alcohol Screening Test; Alcohol Use Disorders Identification Test) are more detailed and are designed to inquire about drinking behavior and adverse consequences and dependence. Primary care clinicians may use CAGE as the simple, brief, easy-to-remember screen and go on to more detailed screens if CAGE is positive.

The degree to which physicians tend to overlook alcoholism and other addictions is substantial. There seems to be little motivation to detect and treat alcoholism. Moving a patient into recovery with psychotherapy, medication, and self-help such as AA, can save a life, a marriage, and a family.

CAGE should be included among the standard history questions.

JAMA November 5,2008; 300: 2054-56 Commentary "JAMA Classics" by Charles P O'Brien,
University of Pennsylvania, Philadelphia, PA.

1 JAMA 1984; 252: 1905-07
