PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

MARCH 2008

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
www.practicalpointers.org

PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA

A free public-service publication. To request monthly issues go to Rjames6556@aol.co

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* MARCH 2008

Changing The Emphasis From Sugar To Fat

3-1 REINVENTING TYPE-2 DIABETES: Pathogenesis, Treatment, and Prevention

The lipocentric view depicts the hyperglycemia of DM-2 and the underlying insulin resistance and beta-cell loss as being secondary to the metabolic trauma caused by ectopic lipid deposition (lipotoxicity).

If this is the case, hyperglycemia could be corrected by eliminating the lipid overload.

For several decades, the position has been advanced that abnormal metabolism of lipids, not glucose, is the primary metabolic defect in DM-2. There is now evidence that fatty acids inhibit insulin-mediated glucose uptake in muscle. In the liver, fatty acids inhibit the insulin-mediated suppression of glycogenolysis and gluconeogenesis. (This leads to continuing glucose production and discharge from the liver despite the elevated blood glucose.)

There is broad consensus that ectopic accumulation of unoxidized fatty acids is a major factor in the production of insulin resistance.

Read the full abstract. It is quite convincing.

The consistent weight gain associated with insulin therapy fits nicely into this model.

Everyone Needs A "Medical Home"

3-2 COORDINATING CARE—A PERILOUS JOURNEY THROUGH THE HEALTH CARE SYSTEM

In the USA, 125 million people are living with chronic illness, disability, or functional limitations. These patients receive care from a number of different providers.

Care among multiple providers must be coordinated to avoid polypharmacy, wasteful duplication of diagnostic testing, and confusion about conflicting care plans. Care must be coordinated among primary care physicians, specialists, diagnostic centers, pharmacies, home care agencies, acute care hospitals, skilled nursing facilities, and emergency departments.

Coordination is also required between providers and patients and their families.

Failures in the coordination of care are common.

This report assesses the quality of care coordination, lists barriers to coordinated care, and discusses some solutions to improve care coordination.

Care coordination is virtually impossible without a strong primary care foundation to the health care system. "This foundation may be crumbling." With large patient panels, and a growing number of tasks

to be performed, PCPs can no longer provide high-quality short-term, long-term, and preventive care in a 15-minute consultation, let alone perform care-coordinating functions for which they are not reimbursed.

The patient-centered "medical home"[1] has become a prominent concept in health care reform. It envisions a medical practice that is based on: first-contact care, continuity of care over time, comprehensiveness, and responsibility to coordinate care throughout the healthcare system. The medical home is expected to contain health costs by reducing unnecessary hospital admissions and emergency department visits.

The article comments on a "Teamlet" Model to address the inadequacy of the 15-minute visit. It changes the care provider from the lone physician to a two-person (or more) team for patients needing support for self-management of long-term care. It provides care coordination by extending the 15-minute visit into care that is provided apart from the visit. With a two-person team that works together every day, the disadvantages of larger teams which require multiple person-to-person interactions is minimized.

The non-physician team member (a "coach") would ideally be a registered nurse or an advanced-practice clinician. The coach handles care before, after, and between visits, and may accompany the physician during the visit. The coach also assists with paperwork and authorizations, and can help patients obtain necessary tests and appointments. Using reminder systems and check lists, the coach makes sure that consultation reports come back from specialists and that results are transmitted to patients.

---

1 *See the full abstract for a statement from the ACP "Principles of the Patient-Centered Medical Home"*

I believe providing a Medical Home to all Americans would be a big step forward in solving our health-care problems. It would enable patients to access health care at an earlier stage of illness and enable greater reductions in risk factors. It would reduce hospitalizations and visits to the Emergency Department. The resultant lower costs would allow more patients to receive health care insurance.

I believe the added time and contact with the patient will allow the" coach" to educate patients and encourage adoption of health lifestyles. Patients must do their part in maintaining healthy life-styles.

They should also be encouraged to inform the physician's team about any out-of-the practice care and mediations they receive.

Common Clinical Signs And Symptoms Cannot Identify Patients With Sinusitis For Whom Treatment With Antibiotics Is Clearly Justified

3-3 ANTIBIOTICS FOR ADULTS WITH CLINICALLY DIAGNOSED ACUTE RHINO-SINUSITIS

This meta-analysis assessed whether common signs and symptoms could be used to identify a subgroup of patients with sinusitis who would benefit from antibiotics.

The study included 9 trials (over 2500 persons) in which adults with rhino-sinusitis-like complaints were randomly assigned to antibiotic treatment or placebo. Assessed overall effect of antibiotic treatment (mainly amoxicillin) and the prognostic value of common signs and symptoms by the number needed-to-treat with antibiotics to cure one additional person.

Excluded trials in which patients were recruited partly on the basis of results of imaging or laboratory tests or bacterial culture because in the primary care setting such methods are not routinely used or recommended.

The mean number needed-to-treat (NNT) with antibiotics to cure one patient = 15.

The NNT for patients with purulent discharge in the pharynx to cure one = 8.

For other patient-reported symptoms—a previous cold (or two stages of illness), pain on bending, unilateral face pain, and pain in the teeth—estimates were not precise enough to draw any conclusions about their prognostic value other than that these symptoms might not be reliable enough to be of any value.

The implication for primary care is that antibiotics offer little benefit for patients with acute rhino-sinusitis-like complaints.

Conclusion: Common signs and symptoms cannot identify a subgroup for which antibiotic treatment is clearly justified.

This study did not help me to decide when to prescribe antibiotics. Certainly symptomatic therapy will be prescribed.

When is the NNT low enough to justify antibiotics—eight? fifteen?

If X-ray is available and is positive for sinusitis would this tilt toward antibiotic treatment?

I believe primary care clinicians make judgments partially based on how sick and miserable the patient appears.

The "delayed" prescription may be applicable in some cases. Give the patient a prescription and tell him not to have it filled or take it unless within a week he feels much worse or is not getting better.

A New Protocol Maximizes Chest Compression And Minimizes Positive Pressure Ventilation

3-4 MINIMALLY INTERRUPTED CARDIAC RESUSCITATION BY EMERGENCY MEDICAL SERVICES FOR OUT-OF-HOSPITAL CARDIAC ARREST

Minimally interrupted cardiac resuscitation (**MICR**) is a new approach to out-of-hospital cardiac arrest (**CA**). MICR focuses on maximizing myocardial and cerebral perfusion through a series of coordinated interventions. It is intended to minimize interruption of chest compressions, provide immediate pre-shock chest compressions, delay or eliminate endotracheal intubation, minimize positive pressure ventilation, and decrease the time interval to intravenous epinephrine.

This study investigated whether MICR would improve survival from out-of-hospital CA. Emergency medical service (**EMS**) personnel received training in MICR which included:

1) 200 uninterrupted chest compressions over 2 minutes. (100 per minute)
2) Rhythm analysis with a single shock if indicated
3) Immediately followed by 200 post-shock compressions before any pulse check or rhythm reanalysis
4) Early administration of intravenous epinephrine 1 mg as soon as possible
5) Delayed tracheal intubation until after 3 cycles of chest compression
6) High flow oxygen (without positive pressure)

In 2460 patients with CA who received MICR, survival was 9.1% vs 3.8% in those who did not receive MICR

In 528 patients with witnessed VF who received MICR, 28% survived vs 12% of those who did not receive MICR

Conclusion: Survival to hospital discharge with out-of-hospital cardiac arrest increased after implementation of MICR as an alternate EMS protocol.

How fashions in medicine change! The AHA guidelines in 2000 instructed rescuers to give 15 chest compressions followed by 2 ventilations. It also called for 3 "stacked" shocks without performing chest compression in between defibrillation attempts. This resulted in prolonged time without any chest compression.

I doubt, however, that most bystanders will apply compressions with the force required for adequate perfusion.

Certainly more bystanders will be willing to perform CR if mouth-to-mouth breathing is not recommended.

"Antimicrobial Exposure Among Nursing Home Residents With Advanced Dementia Is Extensive And Steadily Increases Toward The End Of Life."

3-5 PATTERNS OF ANTIMICROBIAL USE AMONG NURSING HOME RESIDENTS WITH ADVANCED DEMENTIA

This study examined how infections in patients with advanced dementia are currently being managed.

Followed residents (n = 214) with advanced dementia in Boston-area nursing homes from 2003 to 2006. Mean age = 85; mean length of stay was 41 months. 46% died.

These patients had severe impairment of cognition, minimal or no verbal communication, dependence for eating and toileting, incontinence, and loss of ability to walk.

During the observation period, 66% received at least one dose of antimicrobials—a total of 540 courses.

Antibiotic exposure steadily increased toward the end of life—often administered parenterally.

In the 28 to 15 days before death, 18% of decedents received antibiotics.

In the 14 to 0 days before death, 42% of decedents received antibiotics.

Treatment decisions for infections in advanced dementia can be difficult for family members and caregivers.

The 2 purposes for antimicrobial therapy are: 1) prolongation of life, and 2) symptom control. Limited observational studies have failed to demonstrate that therapy achieves either outcome.

Parenteral administration adds to discomfort.

"Our findings further support that antimicrobials may not meaningfully extend the life of patients with advanced dementia." Palliation is the main goal of care. Antimicrobial therapy may relieve terminal symptoms, but it is not clear whether this provides symptomatic relief beyond what may be achieved by high quality palliation.

Antimicrobial use in nursing homes is a major public health issue because of increased antibiotic resistance. When these nursing home residents are admitted to the hospital, they carry resistant organisms with them.

This presents an important ethical dilemma encountered in primary care practice. Families can be seriously conflicted and can have different opinions about terminal care when a parent or spouse becomes demented.

It again emphasizes the need for advanced directives, but more than that, a need for clear and repeated informal instructions to the family before dementia begins. As persons age, I believe all should

appoint a chief advocate who will speak for them and express their autonomous decisions about end-of-life care. All members of the family should understand this decision. The primary care clinician should record it along with the more formal advanced directive. This may prevent a great deal of heartache.

I would be willing to wager that no primary care clinicians would opt for antibiotic treatment at the end of life should they be burdened by advanced dementia. They will remember Sir William Osler's observation that pneumonia is "the old man's friend".

Favors Insulin Glargine

3-6 ONCE-DAILY BASAL INSULIN GLARGINE VERSUS THRICE-DAILY PRANDIAL INSULIN LISPRO IN PEOPLE WITH TYPE-2 DIABETES ON ORAL HYPOGLYCAEMIC AGENTS

As type-2 diabetes (**DM-2**) progresses, oral hypoglycemic agents often fail to maintain blood glucose control, and insulin is needed.

This study, of inadequately-controlled patients with DM-2, investigated whether once-daily insulin glargine + oral hypoglycemic agents was non-inferior in controlling overall glucose control compared to prandial insulin lispro + oral hypoglycemic agents.

Insulin glargine (*Lantus*, Sanofi-Aventis), a basal insulin given once daily, has a duration of action of about 24 hours, with no discernable peak in insulin concentration. Insulin lispro (*Humalog*, Lilly) short acting is given three times a day at mealtimes.

Outcomes:	Glargine	Lispro
HbA1c		
Baseline	8.7%	8.7%
At 44 weeks	7.0	6.8
Reaching HbA1c less than 7%	57%	69%
Incidence of hypoglycemic events		
(events per patient per year):	5	24
Mean weight gain (kg)	3.0	3.5

Patient-satisfaction was greater in subjects taking glargine

"Our results suggest that treatment with once-daily insulin glargine is non-inferior to three-times daily insulin lispro in achieving overall glycemic control as represented by haemoglobin A1c."

Conclusion: Insulin glargine provides a simple and effective option that is more satisfactory to patients than is insulin lispro. It is associated with less frequent need for blood glucose monitoring, and lower incidence of hypoglycemia,.

Note the mean baseline BMI was 29, and subjects gained about 10 pounds over 44 weeks. This is a consistent effect of insulin therapy. As noted in a preceding article, increasing weight (and lipid deposition) related to overdriving the lowering of blood glucose with insulin may, in some respects, be counterproductive. It increases lipid deposition and lipid toxicity. See the preceding abstract. [3-1]

It Would Be Wise To Avoid Highly Intensive Management That Combines Multiple Insulin Injections With Multiple Oral Agents.

3-7 SAFETY OF VERY TIGHT BLOOD GLUCOSE CONTROL IN TYPE 2 DIABETES.

On February 8, 2008, the glucose arm of a large ongoing randomized, controlled trial of people with type 2 diabetes (**DM-2**) who were at high risk of vascular disease was stopped because of concerns about safety. Intensively controlling blood glucose to a HbA1c under 6% increased the risk of death compared with a less intensive treatment strategy (HbA1c 7.0% to 7.9%).

What should we conclude? It seems that moderately intensive management to targets of HbA1c less than 6.5% or lower—if easily obtained—need not be abandoned. Meanwhile, it would be wise to avoid highly intensive management that combines multiple insulin injections with multiple oral agents.

Cardiovascular disease is the major risk of diabetes. Blood concentrations of other constituents are more important than HbA1c in determining risk—LDL-cholesterol, HDL-cholesterol, triglycerides.

Hypertension, BMI, waist circumference, and a sedentary lifestyle are also major risk factors.

Controlling these factors will likely reduce risk more than reducing HbA1c, and will likely also reduce HbA1c.

Dose, Formulation, And Delivery Need To Be Adjusted According To The Age And Frailty Of The Patient

3-8 PRESCRIBING FOR OLDER PEOPLE

This review highlights some of the difficulties in prescribing for older patients and offers guidance to appropriate prescribing.

Increasing age is associated with changes in pharmacokinetics and pharmacodynamics. Prescribing for elderly patients presents many challenges.

Older patients are often prescribed unnecessary drugs; drugs that are contraindicated in their age group; and are given the wrong dose. They may be given drugs without a specific indication, and lacking an evidence base.

The article includes a discussion of:

Physiological changes occurring with aging

Multiple pathology and polypharmacy in the elderly

Inappropriate prescribing for the elderly

Drugs that pose a particular risk in the elderly

Some guidelines for good prescribing in the elderly:

Regular medication review

Prescribe new drugs that have a clear indication

Try to avoid drugs that pose a particular risk

Use the doses recommended for elderly patients

Use simple drug regimens and appropriate administration systems

Limit authorization for repeat prescriptions

Consider once daily formulations

Limit number of physicians who prescribe for the patient

Avoid treating adverse effects of drugs with other drugs

Enlist pharmacist's help. They have an important role in spotting adverse drug reactions and interactions

Follow the development of electronic prescribing. E-prescribing may reduce errors and improve patient care

---

This is an important clinical consideration for primary care.

I noted in a random review of the PDR, that many manufacturers (but far from all) mentioned reduced-dose recommendations for the elderly. I believe many times even these reduced doses may be too high. For long-term medications prescribed for the elderly (eg, for hypertension) I believe we can start with a lower than recommended doses. This may require a pill cutter.

Then, gradually raise the dose to a modest level. This may be acceptable and provide the desired response.

If the elderly patient then requires a still higher dose, we must choose between raising the dose above the modest level or adding a second drug. I believe adding a second drug would generally be preferable because adverse effects are more likely with higher doses of a single drug than with lower doses of two drugs.

The December 2007 issue of Practical Pointers reported a study of the adverse drug effects seen most commonly in the emergency department. These were not age-limited, but would likely be encountered in the elderly.

Anticoagulants and antiplatelet agents: warfarin, aspirin, and clopidogrel

Antidiabetes agents: insulin, metformin, glyburide, glipizide

Narrow therapeutic index agents: digoxin, phenytoin

Statically Significant Benefit; Questionable Clinical Benefit

3-9 CURRENT PHARMACOLOGICAL TREATMENT OF DEMENTIA: A Clinical Practice Guideline.

The American College of Physicians developed this guideline to present the available evidence on current pharmacological treatment of dementia. This was based on a literature search (59 studies) for evidence of effectiveness of FDA approved drugs for dementia for outcomes in domains of cognition, global function, behavior/mood, and quality of life/activities of daily living.

The drugs discussed in this review have shown statistically significant improvement in scores of various instruments evaluating changes in patients with dementia. Most of these outcomes are not used in routine clinical practice. Interpretation of clinical importance of improvements is challenging.

Many of the improvements demonstrated in the trials, although *statistically* significant, were not *clinically* important.

Adverse effects were tolerable.

No convincing evidence demonstrates that one drug is more effective than another.

Recommendations:

Decisions to initiate therapy should be individualized.

Benefits on average are not clinically significant for cognition, and are modest for global assessments. Summary estimates showed small effect sizes.

In more advanced dementia, decision makers may not view stabilization or slowing decline in cognition as a desirable goal if quality of life is judged to be poor.

Harms of drugs should be weighed against modest or even no benefit.

Limited evidence suggests, but does not demonstrate conclusively, that a subgroup of patients achieves clinically important improvement.

Currently, we have no way to predict which patients might have a clinically important response.

Evidence does not support prescribing these agents for every patient with dementia.

Evidence is insufficient to determine optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months. The effect may be an improvement or stabilization.

No evidence demonstrates when it is appropriate to stop treatment. If slowing decline is no longer a goal, treatment is no longer appropriate.

Faint praise.

I believe these drugs are over-used, and used for too long a time.

The benefit/harm-cost ratio approaches 1. These drugs are expensive.

I believe many patients and families choose treatment hoping for an outlier benefit.

A Model Based on Information Easily Obtained in One Outpatient Visit is No Worse Than, and Substantially Cheaper and Simpler To Implement, Than the Framingham Risk Equation.

3-10 LABORATORY-BASED VERSUS NON-LABORATORY-BASED METHOD FOR ASSESSMENT OF CARDIOVASCULAR RISK ***The NHANES I Follow-up study cohort***

The National Health and Nutrition Examination Survey (NHANES) is a prospective cohort study of over 14 000 participants ages 25-74 at the time they were first examined (between 1971 and 1978).

This follow-up study included participants (n = 6186) who did not report a history of cardiovascular disease (myocardial infarction, heart failure, stroke, angina) or cancer at baseline.

Compared how well non-laboratory-based risk factors could predict first-time fatal and non-fatal cardiovascular disease events as compared with laboratory-based risk factors.

A. Laboratory-based risk factors: age, systolic BP, smoking status, reported diabetes, current treatment for hypertension and total cholesterol.

B. Non-laboratory-based risk factors: substituted BMI for cholesterol.

Follow-up for over 21 years.

The study shows that a non-laboratory-based risk method that uses information easily obtained in one outpatient visit can predict cardiovascular disease outcomes as accurately as one that includes determination of total cholesterol.

At most, the rates of correct classification differed by less than 1%, and none of the differences were significant.

This simpler method is probably no worse, yet substantially cheaper and simpler to implement than the Framingham risk equation.

Conclusion: A method that uses non-laboratory-based risk factors (included BMI, but not total cholesterol determination) predicted cardiovascular events as accurately as one that included total cholesterol. This approach could simplify risk assessment.

Only total cholesterol was considered in the laboratory-based cohort. HDL- c, triglycerides, and HbA1c not measured. The investigators comment that the value of additional laboratory tests seems limited. Nevertheless, primary care clinicians will likely request them.

This is not to say that lipids and HbA1c, and BP should be neglected. They should be treated vigorously—but not to the neglect of weight and diet control, maintenance to a slim waist circumference, and maintenance of fitness.

If a 50-year old man has a systolic BP of 120, does not have diabetes, never smoked, has a BMI of 22, and is physically fit, how much would laboratory results add to determination of his risk? If his LDL-cholesterol is 120, should he be treated with statins? How much would treatment reduce his risk?

We can determine at a glance that a middle-aged man who is obviously obese and has an expanded waist circumference is at high risk. How much would lipid determinations add to assessment of risk and his willingness and ability to reduce risk?

The American public seems obsessed with "cholesterol", and, I believe, often neglects to consider other, likely more important risk factors. This is due in part because taking daily pill for cholesterol is much easier than controlling diet, losing weight, stopping smoking, and maintaining fitness.

Empirical Acid Suppression Is An Appropriate First Choice.

3-11 HELICOBACTER PYLORI TEST AND TREAT VERSUS PROTON PUMP INHIBITOR IN INITIAL MANAGEMENT OF DYSPEPSIA IN PRIMARY CARE

The aim of this study was to determine the effectiveness of *H pylori* "test and treat" compared with empirical acid suppression in the initial management of dyspepsia in primary care.

Randomized, controlled trial, conducted in 80 general practices, followed 699 patients (age 18-65) who presented with dyspepsia. None had "alarm" symptoms.

Randomized to:

1) *H pylori* carbon-13 urea breath test:

A. Patients with a positive *H pylori* test were offered eradication therapy followed by 3 weeks of 20 mg omeprazole once daily. A follow-up breath test was offered at 12 weeks. (The test is available as a kit and is quite feasible in primary care.)

B.. Patients who tested negative received omeprazole 20 mg once daily for 4 weeks.

2) Proton pump inhibition alone—omeprazole 20 mg daily for 4 weeks.

Test and treat group:	No. tested	No. positive for *H pylori*	Successful eradication
	343	100 (29%)	78%
Proton pump-only (PP-only)	356		

Outcomes at 12 months:

A. Continuing symptoms at 12 months	PP-only	Test and treat
	83%	82%

B. No significant difference in quality-adjusted life-years and costs between groups. The cost of test and treat was higher at the beginning, but costly resource use was higher in the PP-only group. The two cancelled each other.

C. The score for satisfaction was similar between groups

"This study shows that an *H pylori* test and treatment strategy offers no significant advantage over a proton pump inhibitor for the initial management of dyspepsia in primary care."

There was no difference in outcome between patients with heartburn-predominant and epigastric-pain predominant dyspepsia. (One problem has been the shifting role of heartburn in the definition of functional dyspepsia.)

Treatment of dyspepsia is difficult because it is a syndrome, not a disease. Many different symptoms are included, and vary from individual to individual. Severity and duration also vary.

The type and duration of treatment relies heavily on clinical judgment and patient preference.

In this trial, neither treatment was particularly effective at one year.

I believe most primary care clinicians would choose empirical proton pump inhibition. It will be required for longer than one month in many patients.

The antibiotic treatment protocol can be burdensome.

I believe primary care clinicians in the USA would be more likely to recommend endoscopy at an earlier stage in patients with disturbing symptoms.

Is This Screening Program Clinically, Socially, Economically, And Ethically Acceptable?

3-12 CORONARY CALCIUM AS A PREDICTOR OF CORONARY EVENTS IN FOUR RACIAL OR ETHNIC GROUPS

The study presents data that allows determination of the excess risk related to increasing coronary calcium (CC) scores.

This population-based study collected data on risk factors for cardiovascular disease in over 6700 subjects. All received CT scanning to determine CC score. None had cardiovascular disease at baseline.

Over 4 years, there were 162 coronary events (2.5%): 89 myocardial infarction or death from coronary disease (17 died); 73 angina

CC score as a predictor of CHD (any event)

Score	No. /No. at risk	Hazard ratio
0	8/3409	1.00
1-100	25/1728	3.6
101-300	24/752	7.7
> 300	32/833	10

The score contributed to risk independently of other risk factors.

Conclusion: Measurement of CC score added incremental value to the prediction of CHD over that of standard coronary risk factors.

Determining the CC score by CT entails risks from radiation that are not negligible.

The American public is enamored with the latest and most expensive (and "better") drugs and diagnostic interventions.

Note that the subjects who developed a coronary event were at much greater baseline risk as determined by the usual risk factors (including age and sex). We must ask:

1) How would we treat a patient considered to be at high risk as determined by usual risk factors?

2) How would we treat a patient considered to be at high risk as determined by the usual risk factors + a high CC score? (Note that the patients who developed an event over the subsequent 4 years had higher risk factors at baseline and were, on this account already considered at high risk.)

3) Would there be any difference in treatment between 1) and 2)? What additional measures to reduce risk factors would be taken in patients because they had a high CC score?

4) Would knowing that the CC score is high motivate individual patients to be more adherent to risk-factor reductions?

See Practical Pointers April 2006 for a suggested list of key criteria for screening. This includes:

The screening test should be safe, simple, precise, and validated. A suitable cut-off value should be defined and agreed.

Effective treatment should be identified through the screening program, with evidence that

early treatment leads to better outcome.

High quality randomized, controlled trials should provide evidence that the screening program effectively reduces morbidity.

The screening program should be clinically, socially, economically, and ethically acceptable.

In addition, individuals who may request the screen, or to whom it is offered by medical personnel, should be fully informed about pros and cons of screening, including costs.

Does CC screening meet these criteria?

ABSTRACTS MARCH 2008

Changing The Emphasis From Sugar To Fat

3-1 REINVENTING TYPE-2 DIABETES: Pathogenesis, Treatment, and Prevention

The conventional glucocentric perspective of type-2 diabetes (**DM-2**) views hyperglycemia as a primary disease caused by an etiologically uncertain combination of obesity-associated insulin resistance and beta-cell loss. It is viewed as a disease of glucose metabolism to be treated with anti-hyperglycemia agents, including high-dose insulin.

A novel lipocentric view depicts the hyperglycemia of DM-2 and the underlying insulin resistance and beta-cell loss as being secondary to the metabolic trauma caused by ectopic lipid deposition (lipotoxicity).

If this is the case, hyperglycemia could be corrected by eliminating the lipid overload.

During the past half century, Americans have been exposed to 2 historically unprecedented changes in their caloric environment that would predispose to lipid overload:

1) Meal preparation has been outsourced from family kitchens to commercial processors and purveyors of lipid-rich, caloric-dense foods. This has resulted in a 150 to 300 kcal/d increase in caloric intake.
2) Physical activities that have always been a part of normal life have substantially decreased.

This has dramatically altered the body habitus. More than 2/3 of Americans are now overweight.

Overweight individuals with normal glucose levels have higher insulin levels than normal-weight individuals. This implies insulin resistance.

For several decades, the position has been advanced that abnormal metabolism of lipids, not glucose, is the primary metabolic defect in DM-2. There is now evidence that fatty acids inhibit insulin-mediated glucose uptake in muscle. In the liver, fatty acids inhibit the insulin-mediated suppression of glycogenolysis and gluconeogenesis. (This leads to continuing glucose output by the liver at a time when production should be shut down.)

There is broad consensus that ectopic accumulation of unoxidized fatty acids is a major factor in the production of insulin resistance:

A. Ectopic lipids accumulate in the pancreatic islets, in parallel with other tissues, and can cause lipotoxic destruction of beta cells.

B. The liver continues to synthesize fatty acids while resisting insulin-mediated suppression of hepatic glucose production.

The lipocentric pathway to hyperglycemia:

The editorialist proposes a plausible pathway with increased caloric balance as the primary perturbation:

1) Caloric surplus
2) Hyperinsulinemia
3) Increased lipogenesis
4) Increased adiposity
5) Ectopic lipid deposition
6) Insulin resistance
7) Beta cell lipotoxicity
8) Hyperglycemia.

Insulin promotes disposition of unused calories—initially as fat in adipocytes—but ultimately as ectopic fat in non-adipocytes such as myocytes and hepatocytes.

Clinical applications of the lipocentric concept:

The concept may have 2 important clinical implications:

1) Relatively modest weight loss by caloric restriction, by exercise, or both, can reduce insulin resistance and hyperglycemia, even if the desired cosmetic goal is not achieved.
2) The concept raises questions about the preferred therapy for obese patients with DM-2. Insulin resistance can be overcome with adequate insulin without eliminating caloric excess. (The now-available U500 insulin makes this easier.) Might the superimposition of exogenous hyperinsulinemia on preexisting endogenous hyperinsulinemia worsen the ectopic lipid overload by providing still more substrate for lipogenesis from the continuing surplus of calories? If so, intensive insulin therapy would be relatively contraindicated. (In February 2008 the National Heart, Lung, and Blood Institute halted a clinical trial of aggressive lowering of blood glucose levels in patients with high risk DM-2 because of an increase in death, myocardial infarction, and stroke.) Overpowering the insulin resistance may be harmful because doing so forces lipogenesis and promotes ectopic deposition of lipids.

This should in no way be construed as minimizing the importance of treating hyperglycemia. It merely advocates a strategy that would eliminate hyperglycemia without amplifying the underlying abnormality—the ectopic lipid overload.

JAMA March 12, 2008; 299: 1185-87 Commentary by Roger H Unger, University of Texas, Southwestern Medical Center, Dallas.

==========

Everyone Needs A "Medical Home"

3-2 COORDINATING CARE—A PERILOUS JOURNEY THROUGH THE HEALTH CARE SYSTEM

In the USA, 125 million people are living with chronic illness, disability, or functional limitations. These patients receive care from a number of different providers. Between 2000 and 2002, typical Medicare beneficiaries saw a median of 2 primary care physicians, and 5 specialists each year, in addition to accessing diagnostic, pharmacy, and other services.

Care among multiple providers must be coordinated to avoid polypharmacy, wasteful duplication of diagnostic testing, and confusion about conflicting care plans. Care must be coordinated among primary care physicians, specialists, pharmacies, home care agencies, acute care hospitals, skilled nursing facilities, and emergency departments.

Coordination is also required between providers and patients and their families.

Failures in the coordination of care are common, and can increase serious quality concerns.

"Given this level of complexity, the coordination of care among multiple independent providers becomes an enormous challenge."

This report assesses the quality of care coordination, lists barriers to coordinated care, and discusses some solutions to improve care coordination.

Examples of studies reporting difficulties in care coordination:

Between primary care physicians (**PCPs**) and specialists: At times, no (or little) information was sent from the PCP to the specialist. Feedback from specialists to PCP was lacking and late.

Between PCPs and emergency departments: In 1/3 of cases the PCP was not informed about the care the patient received.

Between physicians and sources of diagnostic data: Often medical records and laboratory data were not available at the time of a scheduled visit. Duplicate tests were often done.

Between hospital based physicians and PCPs: About 1/3 of PCPs reported that no follow-up arrangements had been made after hospital discharge. PCPs were not informed about discharge plans and medications. Discharge summaries were often delayed. Some never reached the PCP.

Between physicians and patients and their families: 75% of physicians did not routinely contact patients about normal lab results, and 1/3 did not consistently notify patients about abnormal results. Many patients received conflicting information from various doctors. Many left the office with important questions unanswered, and reported that the physician had not reviewed their medication and had not explained side effects. Fifty % left the office not understanding what they were told. Few participated in medical decisions.

Between hospitals and patients and their families: Many patients reported they did not receive information about whether they should take their pre-hospital medications. Few received information about adverse effects of prescribed drugs.

Care coordination is virtually impossible without a strong primary care foundation to the health care system. "This foundation may be crumbling." With large patient panels, and a growing number of tasks to be performed, PCPs can no longer provide high-quality short-term, long-term, and preventive care in a 15-minute consultation, let alone perform care-coordinating functions for which they are not reimbursed.

The patient-centered "medical home"[1] has become a prominent concept in health care reform. It envisions a medical practice that is based on first-contact care, continuity of care over time, comprehensiveness, and responsibility to coordinate care throughout the healthcare system. The medical home is expected to contain health costs by reducing unnecessary hospital admissions and emergency department visits.

The article comments on a "Teamlet" Model to address the inadequacy of the 15-minute visit. It changes the care provider from the lone physician to a two-person (or more) team for patients needing support for self-management of long-term care. It provides care coordination by extending the 15-minute visit into care that is provided apart from the visit. With a two-person team that works together every day, the disadvantages of larger teams which require multiple person-to-person interactions is minimized.

The non-physician team member (a "coach") would ideally be a registered nurse or a retrained medical assistant. The coach handles care before, after, and between visits, and may accompany the physician during the visit. The coach also assists with paperwork and authorizations, and can help patients obtain necessary tests and appointments. Using reminder systems and check lists, the coach makes sure that consultation reports come back from specialists and that results are transmitted to patients.

Each clinician-coach team works out which functions the coach is adequately trained to perform.

This model becomes financially viable because the coach handles some routine duties. This allows the clinician to see more patients.

NEJM March 6, 2008; 358: 1064-71 "Health Policy Report" by Thomas Bodenheimer, University of California at San Francisco, CA,

1 JOINT PRINCIPLES OF THE PATIENT-CENTERED MEDICAL HOME

http://www.medicalhomeinfo.org/Joint%20Statement.pdf

Proposed by the American College of Physicians, American Academy of Pediatrics, American Academy of Family Physicians, and American Osteopathic Association March 2007

- The Patient-Centered Medical Home provides each patient an ongoing relationship with a personal physician and the physician's team to provide first contact, continuous, and comprehensive care.
- The personal physician is responsible for providing for all the patient's health care needs and taking responsibility for appropriately arranging care with other qualified professionals. This includes all stages of life: acute care, chronic care, preventive services, and end-of-life care.
- Care is coordinated and integrated across all elements of the complex health care system. This includes the patient's family, and public and private community-based services.
- It assures that patients get the indicated care where and when they need it in a culturally and linguistically appropriate manner.
- Patients actively participate in decision-making.
- Enhanced access to care is available through open scheduling, expanded hours and new options for communication.
- Compensation to physicians and non-physician staff reflects work that falls outside the face-to-face visit.
- Adopts and uses health-information technology.

==========

Common Clinical Signs And Symptoms Cannot Identify Patients With Sinusitis For Whom Treatment With Antibiotics Is Clearly Justified

3-3 ANTIBIOTICS FOR ADULTS WITH CLINICALLY DIAGNOSED ACUTE RHINO-SINUSITIS

About one third of consultations for upper respiratory infections are diagnosed as acute rhino-sinusitis. Eighty percent of these patients are now treated with antibiotics. Primary care clinicians continue to prescribe antibiotics because the distinction between viral and bacterial sinus infection is difficult. In primary care, no test, sign, or symptom, or combination of these can clearly identify patients who benefit from antibiotics.

Increased rates of antibiotic resistance occur where antibiotic use is high. Antibiotic resistance has led to increased morbidity, mortality, and cost throughout the world.

Guidelines therefore recommend deferral of antibiotic treatment until a patient has had symptoms for at least 7 days. This recommendation was made based on the time usually taken to progress from a viral to a secondary bacterial infection. However, both discomfort and cost of additional office visits would be reduced if patients with bacterial infections did not have to wait.

This study assessed whether common signs and symptoms could be used to identify a subgroup of patients who would benefit from antibiotics.

Conclusion: Common symptoms and signs cannot identify patients with rhino-sinusitis for whom antibiotic treatment is clearly justified.

STUDY

1. This meta-analysis included 9 trials (over 2500 persons) in which adults with rhino-sinusitis-like complaints were randomly assigned to antibiotic treatment or placebo.
2. Assessed overall effect of antibiotic treatment (mainly amoxicillin) and the prognostic value of common signs and symptoms by the number needed-to-treat with antibiotics to cure one additional person.
3. Excluded trials in which patients were recruited partly on the basis of results of imaging[1] or laboratory tests or bacterial culture because in the primary care setting such methods are not routinely used or recommended.

RESULTS

1. The mean number needed-to-treat (NNT) with antibiotics to cure one patient = 15. The NNT for patients with purulent discharge in the pharynx to cure one = 8.
2. Patients with more severe symptoms and older patients took longer to cure, but they were no more likely to benefit from antibiotics than other patients.
3. For other patient-reported symptoms—a previous cold (or two stages of illness), pain on bending,

unilateral face pain, and pain in the teeth—estimates were not precise enough to draw any conclusions about their prognostic value other than that these symptoms might not be reliable enough to be of any value.

DISCUSSION

1. “Our analysis of 2547 patients from nine trials showed that 15 patients with rhino-sinusitis-like complaints need to be given antibiotics before one additional patient benefits from treatment.”
2. There was a slightly higher cure rate among patients treated with antibiotics.
3. “Our results are more realistic for a primary-care setting than those of previous meta-analyses, and support the guidelines that do not recommend antibiotic treatment for clinically diagnosed rhino-sinusitis unless confirmed by imaging[1] or bacterial culture.”
4. The most common signs and symptoms do not help distinguish a bacterial infection from a viral infection. Patient-reported symptoms such as a previous common cold or facial pain do not seem as reliable as some guidelines suggest. They are equally common in viral as in bacterial infections.
5. Purulent nasal discharge is consistently associated with bacterial infection in diagnostic studies, but the results of this study suggest that its prognostic value is not sufficient to justify antibiotic treatment.
6. These results suggest that antibiotics are not warranted even when a patient reports symptoms for over a week.
7. As patients aged, and as symptom duration and severity increased, cure took longer, but antibiotics were no more likely to benefit.
8. The implication for primary care is that antibiotics offer little benefit for patients with acute rhino-sinusitis-like complaints. Common signs and symptoms cannot identify a subgroup for which antibiotic treatment is clearly justified.
9. High fever, periorbital swelling, erythema, or intense facial pain suggest a serious complication and warrant antibiotic treatment.

CONCLUSION

Common clinical signs and symptoms cannot identify patients with rhino-sinusitis for whom treatment with antibiotics is clearly justified, even if the patient reports symptoms lasting longer than a week.

Lancet March 15, 2008; 371: 908-14 original investigation, first author Jim Young, University Hospital, Basel, Switzerland.

1 X-rays are often available in primary care practice. Does this indicate that, if sinusitis is diagnosed by X-ray, antibiotic treatment is more acceptable?

An editorial in this issue of Lancet, first author Morten Lindbaek, University of Oslo, Norway comments and expands on this study:

Many patients with sinusitis expect antibiotic treatment, and associate the drug with recovery. At the same time, evidence mounts that antibiotics confer little average benefit.

However, a possible benefit in subgroups has not been ruled out. This leads to variation in antibiotic prescribing.

Clinical guidelines reflect this unsatisfactory evidence: two guidelines have come to different conclusions. However, they shared the recommendation to wait 7 – 10 days before starting antibiotics.

In the face of uncertainty, clinicians generally give the individual patient the benefit of the doubt when weighing up chances of benefit from an antibiotic against possible contribution to antibiotic resistance..

Can a new meta-analysis provide a change in the evidence base that is required for the management of sinusitis in primary care?

Might a particular patient benefit significantly from antibiotics despite what is known about average effects? Can primary care clinicians now confidently tell all patients that antibiotics will not help their sinusitis symptoms? The issue is never that simple because all the familiar problems with meta-analyses remain.

Meta-analyses can never overcome weaknesses of, or important differences between, the combined studies.

Nevertheless, this new meta-analysis has shown that if any group of patients with mild sinusitis respond substantially to antibiotics, these subgroups are not easy to identify.

==========

A New Protocol Maximizes Chest Compression And Minimizes Positive Pressure Ventilation

3-4 MINIMALLY INTERRUPTED CARDIAC RESUSCITATION BY EMERGENCY MEDICAL SERVICES FOR OUT-OF-HOSPITAL CARDIAC ARREST

Although early defibrillation with automated external defibrillators improves survival, early defibrillation is rarely available, and few patients with out-of-hospital cardiac arrest (**CA**) survive.

Minimally interrupted cardiac resuscitation (**MICR**) is a new approach to out-of-hospital cardiac arrest.

MICR focuses on maximizing myocardial and cerebral perfusion through a series of coordinated interventions. It is intended to minimize interruption of chest compressions, provide immediate pre-shock chest compressions, delay or eliminate endotracheal intubation, minimize positive pressure ventilation, and decrease the time interval to intravenous epinephrine.

This study investigated whether MICR would improve survival from out-of-hospital CA.

Conclusion: Survival to hospital discharge improved after a program of MICR was instituted.

STUDY

1. This 3-year prospective study determined survival to hospital discharge before and after institution of MICR for out-of-hospital CA
2. Emergency medical service (**EMS**) personnel received training in MICR which included:
   1) 200 uninterrupted chest compressions over 2 minutes. (100 per minute)
   2) Rhythm analysis with a single shock if indicated
   3) Immediately followed by 200 post-shock compressions before any pulse check or rhythm reanalysis
   4) Early administration of intravenous epinephrine 1 mg as soon as possible
   5) Delayed tracheal intubation until after 3 cycles of chest compression
   6) High flow oxygen (without positive pressure)
3. Main outcome measure = survival to hospital discharge.

RESULTS

1. Outcomes:

	Before MICR	After MICR
A. Survival to hospital-discharge		
Among 886 patients with CA	1.8%	5.4%
B. Subgroup of 174 patients with witnessed CA and VF	4.7%	17.6%

2. In 2460 patients with CA who received MICR, survival was 9.1% vs 3.8% in those who did not receive MICR
3. In 528 patients with witnessed VF who received MICR, 28% survived vs 12% of those who did not receive MICR

DISCUSSION

1. MICR discourages early and excessive ventilation by advocating passive oxygen insufflation

rather than positive pressure ventilation. Positive pressure ventilation during CA may be harmful because it increases intra-thoracic pressure, thereby decreasing venous return and subsequent myocardial and cerebral blood flow. High oxygen flow is administered without positive pressure.

2. One major contributor to the poor survival rates of patients with out-of-hospital CA is prolonged, inadequate myocardial and cerebral perfusion. During resuscitation efforts, the foreword blood flow produced by chest compressions is so marginal that any interruption of chest compression is deleterious, especially for favorable neurological outcomes. Even 10- to 20-second pauses in pre-shock compressions decrease defibrillation success.
3. Studies indicate that pre-shock chest compression for prolonged VF can improve the rate of successful resuscitation.
4. "Stacked" shocks (2 or 3 in succession) decreases the time of chest compressions and lead to inadequate cerebral and myocardial perfusion. Thus, single shocks are used in MICR.
5. Chest compressions can provide adequate oxygen delivery. Immediately after CA due to sudden VF, aortic oxygen and carbon dioxide concentrations do not vary from the pre-arrest state because there is no blood flow and oxygen consumption is minimal.
7. When chest compression is initiated, the blood flowing from the aorta to the coronary and cerebral circulations provides adequate oxygenation at an acceptable pH. At that time, myocardial oxygen delivery is limited more by blood flow than oxygen content. Adequate oxygenation and ventilation can continue without rescue breathing because substantial ventilation occurs from chest compression-induced gas exchange. (Ie, small volumes exhaled with each compression and spontaneous gasping during cardiac resuscitation.)
8. The greatest improvement in survival occurred in the subgroup of patients most likely to survive. (Ie, those with documented witnessed CA and a shockable rhythm.)

CONCLUSION

Survival to hospital discharge with out-of-hospital cardiac arrest increased after implementation of MICR as an alternate EMS protocol.

JAMA March 12, 2008; 299: 1158-65 Original investigation, first author Bentley J Bobrow, Mayo Clinic, Scottsdale, Arizona.

An Editorial in this issue of JAMA, first author Mary Ann Peberdy, Virginia Commonwealth University, Richmond comments and expands on this study:

Survival from CA declines rapidly if defibrillation is not performed in the first few minutes because myocardial adenosine triphosphate (**ATP**) levels begin to decrease and the fibrillating myocardial cells continue to consume ATP at a nearly normal rate.

By the time EMS personnel arrive, myocardial ATP stores often have declined to critical levels. While defibrillation shock will usually terminate VF, it frequently results in either asystole or pulseless electrical activity as myocardial cells run out of high-energy phosphate "fuel".

A brief period of effective chest compression before defibrillation can boost myocardial ATP stores, and increase the likelihood that a perfusing rhythm will follow defibrillation.

Thus, the strategy for resuscitation has evolved from "shock first and often" to a time-critical orchestrated approach to high quality CPR, defibrillation, and post-resuscitation care.

The new approach highlights the importance of high-quality, minimally interrupted chest compression to maximize tissue oxygen delivery and intracellular high-energy phosphate levels. High quality chest compression (adequate depth, force, and duration—ie, complete chest wall compression) are needed to maximize stroke volume and improve venous filling during the upstroke.

Chest compression alone (with an open airway) generates significant minute ventilation.

==========

"Antimicrobial Exposure Among Nursing Home Residents With Advanced Dementia Is Extensive And Steadily Increases Toward The End Of Life."

3-5 PATTERNS OF ANTIMICROBIAL USE AMONG NURSING HOME RESIDENTS WITH ADVANCED DEMENTIA

About 70% of the more than 5 million Americans with dementia will reside in nursing homes during the final stage of their disease.

Nursing home residents with advanced dementia are at high risk for infections.

Administration of antibiotics to these patients may be potentially burdensome, and may not confer any symptomatic or life-prolonging benefit.

From a broader point of view, antimicrobial use is the primary factor leading to the emergence of resistant bacteria. Older patients harbor relatively high rates of antimicrobial-resistant bacteria.

This study examined how infections in advanced-dementia patients are currently being managed.

Conclusion: These patients are frequently exposed to antimicrobials, especially during the last few weeks of life.

STUDY

1. Followed residents (n = 214) with advanced dementia in Boston-area nursing homes from 2003

to 2006. Mean age = 85; mean length of stay was 41 months; 46% died.

2. These patients had severe impairment of cognition, minimal or no verbal communication, dependence for eating and toileting, incontinence, and loss of ability to walk.
3. During the observation period, 66% received at least one dose of antimicrobials—a total of 540 courses.
4. Infections treated: respiratory tract (47%); urinary tract (36%). Quinolones were the most frequently prescribed antibiotics; third generation cephalosporins the next.
5. Antibiotic exposure steadily increased toward the end of life—often administered parenterally.

   In the 28 to 15 days before death, 18% of decedents received antibiotics.

   In the 14 to 0 days before death, 42% of decedents received antibiotics.

DISCUSSION

1. "This prospective cohort study demonstrated that antimicrobial exposure among nursing home residents with advanced dementia is extensive and steadily increases toward the end of life."
2. During a follow-up period of 322 days, two thirds of the subjects were prescribed at least one course of antimicrobial therapy—on average a total of 4 courses. Up to one-third of antimicrobials used in nursing homes are prescribed for conditions for which they are not indicated.
3. This extensive use of antimicrobials raises concerns about development of resistant organisms in nursing homes.
4. Treatment decisions for infections in advanced dementia can be difficult for family members and caregivers.
5. The 2 purposes for antimicrobial therapy are: 1) prolongation of life, and 2) symptom control. Limited observational studies have failed to demonstrate that therapy achieves either outcome. Parenteral administration adds to discomfort.
6. "Our findings further support that antimicrobials may not meaningfully extend the life of patients with advanced dementia." Palliation is the main goal of care. Antimicrobial therapy may relieve terminal symptoms, but it is not clear whether this provides symptomatic relief beyond what may be achieved by high quality palliation.
7. Older persons are particularly susceptible to adverse events of antimicrobials owing to altered pharmacokinetics, polypharmacy, dosing errors and increased risk of *Clostridium difficile* infections.
8. Antimicrobial use in nursing homes is a major public health issue because of increased antibiotic resistance. When these nursing home residents are admitted to the hospital, they carry resistant organisms with them.

Archives Intern Med February 4, 2008; 168 : 357-62 Choices, Attitudes, and Strategies for Care of Advanced Dementia at the End-of-life study (CASCADE) first author Erika D'Agata, Beth Israel Deaconess Medical Center, Boston Mass

==========

Favors Insulin Glargine

3-6 ONCE-DAILY BASAL INSULIN GLARGINE VERSUS THRICE-DAILY PRANDIAL INSULIN LISPRO IN PEOPLE WITH TYPE-2 DIABETES ON ORAL HYPOGLYCAEMIC AGENTS (APOLLO)

As type-2 diabetes (**DM-2**) progresses, oral hypoglycemic agents often fail to maintain blood glucose control, and insulin is needed. Secondary failure occurs in abut a half of patients after a few years.

Barriers to initiation of insulin include risk of hypoglycemia, and concerns about daily injections and restrictions in lifestyle. New insulin analogues offer the possibility of reducing some of these concerns:

Insulin glargine (*Lantus*, Sanofi-Aventis) a basal insulin given once daily has a duration of action of about 24 hours with no discernable peak in insulin concentration.

Insulin lispro (*Humalog*, Lilly) short acting given three times a day at mealtimes.

There is ongoing debate as to the most beneficial treatment: 1) to target postprandial blood glucose concentrations with meal-related insulin, or 2) to target fasting blood glucose concentrations with basal insulin.

Postprandial blood glucose contributes more to glycemic control in patients with mild or moderate hyperglycemia. In poorly controlled DM-2, fasting blood glucose is the main contributor to overall hyperglycemia.

This study, of inadequately-controlled patients with DM-2, investigated whether once-daily insulin glargine + oral hypoglycemic agents was non-inferior[1] in controlling overall glucose control compared to prandial insulin lispro + oral hypoglycemic agents.

Conclusion: Insulin glargine was just as effective in lowering HbA1c as insulin lispro, and was more satisfactory to patients.

STUDY

1. Multicenter parallel, open study followed 415 patients (mean age 60; mean BMI = 29) with DM-2. All were inadequately controlled by oral therapy. (Mean baseline HbA1c = 8.7%)
   At baseline, most were taking metformin..

2. Randomized to: 1) Insulin glargine (starting at 10 U daily and titrated upward) + continuation of oral agents, or 2) Insulin lispro (starting at 4 U 3 times daily before meals and titrating upward) + continuation of oral agents. Doses of oral agents were kept stable during the study.
3. All subjects monitored their own blood glucose concentrations.
5. Follow-up = 44 weeks. Primary objective = change in HbA1c from baseline.
6. Tested the hypothesis that glargine was non-inferior to lispro.

RESULTS

1.	Glargine	Lispro
HbA1c		
Baseline	8.7%	8.7%
At 44 weeks	7.0	6.8 *
Reaching HbA1c less than 7%	57%	69%
Mean fall in fasting blood glucose		
at 44 weeks:	-77 mg/dL	- 32 mg/dL
Mean fall in nocturnal glucose	- 59	-47
Incidence of hypoglycemic events		
(events per patient per year):	5	24
Mean weight gain (kg)	3.0	3.5

(*The difference of 0.2% at 44 weeks was considered to be within the predefined limit for non-inferiority.)

2. Control of blood glucose during the day was better in the lispro group.
3. Improvement in patient-satisfaction was greater in subjects taking glargine

DISCUSSION

1. “Our results suggest that treatment with once-daily insulin glargine is non-inferior to three-times daily insulin lispro in achieving overall glycemic control as represented by haemoglobin A1c.
2. In practice, monotherapy fails to achieve or maintain HbA1c levels of 7% or less in most patients with DM-2. Additional therapeutic options need to be introduced without delay,
3. If HbA1c targets are not obtained with insulin glargine or insulin lispro, the addition of the other insulin could be helpful in reaching the target.
4. The two treatment regimens showed different effects on circadian regulation of blood glucose: 1) Insulin glargine led to greater decreases in fasting and nocturnal blood glucose.

2) Insulin lispro was associated with lower postprandial concentrations.

5. Targeting fasting blood glucose or postprandial glucose were equally effective in improving HbA1c.
6. Despite similar improvements in glycemic control, the addition of insulin glargine to existing treatment with oral agents was associated with a much lower incidence of overall hypoglycemia.
7. When insulin glargine is used, only one daily injection is required, and a single blood glucose test before breakfast guides therapy.
8. Study participants taking insulin glargine reported greater overall treatment satisfaction.
9. Whether patients with DM-2 and established cardiovascular disease benefit from a strategy of intensive glycemic control continues to be debated. The recent ACCORD trial was stopped early because of a 20% increased risk of mortality in the intensive group (HbA1c targeted to less than 6% compared with the standard group targeted to 7%-7.9%).
10. In the present APOLLO trial, the rate of acute cardiovascular event was 11 per 1000 patient-years. No deaths occurred.
11. The addition of insulin glargine to oral hypoglycemic agents is a simple and well-tolerated intervention that can be helpful in overcoming major barriers to timely insulin initiation in primary care. It can be regarded as a first-line insulin-initiation approach.

CONCLUSION

Insulin glargine provides a simple and effective option that is more satisfactory to patients than is insulin lispro. It is associated with less frequent need for blood glucose monitoring, and lower incidence of hypoglycemia,.

Lancet March 29, 2008; 371: 1073-84 Original investigation by A Parallel design comparing and Oral antidiabetic drug combination therapy with either Lantus once daily or Lispro at mealtime in type 2 diabetes patients failing Oral treatment (APOLLO), first author Reinhard G Bretzel, Justus-Liebig-Universitat, Glessen, Germany.

1 Non-inferiority trials, comparing a new drug with an established drug, should be designed only if the new drug is likely to have advantages of lower cost, convenience, or fewer adverse effects.

==========

3-7 SAFETY OF VERY TIGHT BLOOD GLUCOSE CONTROL IN TYPE 2 DIABETES.

On February 8, 2008, the glucose arm of a large ongoing randomized, controlled trial (ACCORD) of people with type 2 diabetes (**DM-2**) who were at high risk of vascular disease was stopped because of concerns about safety. Intensively lowering blood glucose below current recommendations (to a HbA1c under 6%) increased the risk of death compared with a less intensive treatment strategy (HbA1c 7.0% to 7.9%).

Several guidelines have recommended target values of HbA1c less than 6.5%, or less than 7%. Targets of this kind are rarely tested in clinical trials.

For DM-2, the core data used in target-setting come from the UK Prospective Diabetes Study. This study achieved HbA1c values around 6.5%. It reported benefits for vascular outcomes in the more intensive therapy group. It also reported that vascular event rates were lower at HbA1c values as low as 5.5%.

In practice, HbA1c of about 6.5% can be achieved in many people for a variable number of years. Once insulin is started, however, studies that treat to target have struggled to achieve values much lower than 7%.

Would achieving a level of less than 6% (considered the normal range) achieve better vascular outcomes than a higher HbA1c, such as that used in people with type-1 DM (< 7.5%)?

If insensitivity to insulin is actually a protective mechanism, rather than the pathological outcome of overeating as it is perceived today, then perhaps trying aggressively to overcome it may have adverse cellular effects that we have not yet begun to understand.

Conclusion: It seems that moderately intensive management to targets of HbA1c less than 6.5% or lower—if easily obtained—need not be abandoned. Meanwhile, it would be wise to avoid highly intensive management that combines multiple insulin injections with multiple oral agents.

BMJ March 1,2008: 336: 458-59 Editorial by Philip Home, Newcastle University, Newcastle, UK

==========

Dose, Formulation, And Delivery Need To Be Adjusted According To The Age And Frailty Of The Patient.

3-8 PRESCRIBING FOR OLDER PEOPLE

In the UK, people over age 60 receive almost 2/3 of all prescriptions. These account for more than half of the national drug costs. They often have several co-existing problems, and take multiple drugs.

This review highlights some of the difficulties in prescribing for older patients and offers guidance to appropriate prescribing.

Increasing age is associated with changes in pharmacokinetics and pharmacodynamics. Prescribing for elderly patients presents many challenges, most of which have not changed in the past 20 years.

Older patients are often prescribed unnecessary drugs; drugs that are contraindicated in their age group; and the wrong dose. They may be given drugs without a specific indication, and lacking an evidence base.

Physiological changes occurring with aging:

With age, the body undergoes several changes that can affect the distribution, metabolism, and excretion of drugs:

Reductions may occur in renal clearance, liver size, hepatic enzyme activity, lean body mass, and serum albumin. The most clinically important is the reduction in renal clearance which results in reduced excretion of water-soluble drugs. This is especially important for drugs with a narrow therapeutic window (ratio of desired effect to toxic effect), such as digoxin, lithium, and gentamicin.

Older people are also more sensitive to the effects of some drugs, especially those that act on the central nervous system—eg, benzodiazepines are associated with an increase in falls.

The elderly often need lower doses.

Multiple pathology and polypharmacy:

About 1/5 of people over age 70 take 5 or more drugs. All may have an appropriate indication.

Periodic review is especially warranted for patients who take 4 or more drugs.

The presence of multiple medical problems and subsequent polypharmacy makes adverse drug reactions and interactions more common. It increases risk of falls, hospital admissions, length of hospital stay, readmission rates, and mortality.

Inappropriate prescribing:

Inappropriate prescribing is especially relevant in older people because they often take a large number of drugs. This increases the chance of having an adverse event. Dose, formulation, and delivery need to be adjusted according to the age and frailty of the patient.

Problems arise when older patients are assumed to respond to drugs in the same way as an average adult. Careful monitoring the introduction of new drugs is advised, often starting at low doses and titrating upwards.

The *British National Formulary for Children* highlights the importance of taking age into account for dose adjustment. We might need a similar publication for elderly patients.

Drugs that pose a particular risk in the elderly:

Long-term NSAIDs	G.i. hemorrhage; renal impairment; hypertension
Benzodiazepines	Falls; impaired balance
Anticholinergic drugs	Unmasking Alzheimer disease; urinary retention
Tricyclic antidepressants.	Orthostatic hypotension; sedation
Doxazocin	Orthostatic hypotension; dry mouth; urinary problems.

Some guidelines for good prescribing in the elderly:

Regular medication review

Prescribe drugs that have a clear indication

Try to avoid drugs that pose a particular risk (as in the above list)

Use the doses recommended for elderly patients

Use simple drug regimens and appropriate administration systems

Limit authorization for repeat prescriptions

Consider once daily formulations

Limit number of physicians prescribing for the patient

Avoid treating adverse effects of drugs with other drugs

Enlist pharmacist's help. They have an important role in spotting adverse drug reactions and interactions

Follow the development of electronic prescribing. E-prescribing may reduce errors and improve patient care

BMJ March 15, 2008; 336: 606-09 "Clinical Review", first author James C Milton, King's College Hospital Foundation Trust, London, UK

==========

Statically Significant Benefit; Questionable Clinical Benefit

3-9 CURRENT PHARMACOLOGICAL TREATMENT OF DEMENTIA: A Clinical Practice Guideline.

The American College of Physicians developed this guideline to present the available evidence on current pharmacological treatment of dementia. This was based on a literature search (59 studies) for evidence of effectiveness of FDA approved drugs for dementia for outcomes in domains of cognition, global function, behavior/mood, and quality of life/activities of daily living.

Current drug interventions are used primarily to improve symptoms and delay progression.

Does pharmacological treatment of dementia with any of the drugs improve cognitive symptoms and outcomes?

Clinically important improvement versus statistical significance:

Most studies reported *statistical* significance on the basis of changes in various scores of various scales: Alzheimer's Disease Assessment Scale [ADAS-cog]; non-cognitive subscale ADAS-noncog; Mini-mental State Examination [MMSE] and Clinician-based Impression of Change with caregiver input [CUBIC-plus].

The guideline panel also assessed *clinically* important effects of treatment regimens based on the minimum change in scores judged to define clinical importance.

A clinically relevant treatment can be defined as one in which the change is both relevant and important to the patient or caregiver, and to clinicians. Caregiver burdens can be heavy.

A statically significant difference does not always reflect clinically relevant meaningful changes.

Cholinesterase inhibitors approved by the FDA for mild to moderate dementia.

Donepezil (*Aricept*; Eisai)

Galantamine (*Razadyne*; Ortho-McNeil)

Rivastigmine (*Exelon*; Novartis)

(The article also discussed tacrine. I omit this data. Tacrine is rarely used because of toxicity. RTJ)

*T*he non-cholinergic neurotransmitter (neuropeptide-modifying) agent approved by the FDA for treatment of moderate to severe Alzheimer disease.

Memantine (*Namenda*; Forrest)

Donepezil (24 studies compared with placebo)

The average change in cognitive scores was statistically significant. The evidence is insufficient to determine whether a subgroup of patients had a clinically important improvement.

Adverse effects included diarrhea, insomnia, nausea, abnormal dreams, muscle and leg cramps—all statistically significant.

The duration of all but one trial was less than one year, so the long-term effect is unknown.

Galantamine (12 studies compared with placebo)

Although the pooled evidence showed a statistically significant average improvement, the change did not reach the level of clinical improvement.

Adverse effects included nausea; vomiting; diarrhea; anorexia/weight loss; and dizziness.

The duration of trials was less than one year, so the long-term effect is unknown.

Rivastigmine (9 studies compared with placebo)

Did not improve cognition as measured by the ADAS-cog, but did result in clinically important cognitive improvements determined by the CIBIC-plus. Behavior and quality of life outcomes did not significantly improve.

Adverse effects included dizziness; nausea; vomiting; eating disorder/weight loss; and headache.

The duration of trials was less than 7 months, so the long-term effect is unknown.

Memantine (5 studies compared with placebo)

Statically significant, but not clinically important, improvement in cognition scores for all levels of severity of Alzheimer disease and vascular dementia as measured by the CIBIC-cog

Limited evidence showed improvement in quality of life, caregiver burden, and resource utilization.

Adverse effects included nausea, dizziness, diarrhea, and agitation.

Summary:

The drugs discussed in this review have shown *statistically* significant improvement in scores of various instruments evaluating changes in patients with dementia. Most of these outcomes are not used in routine clinical practice. Interpretation of *clinical* importance of improvements is challenging.

Many of the improvements demonstrated in the trials, although statistically significant, were not clinically important.

Evidence of improvement on global assessment was available for donepezil, galantamine, rivastigmine, and memantine, although changes were generally modest. The evidence about quality of life was mixed.

Adverse effects were tolerable.

No convincing evidence demonstrates that one drug is more effective than another.

Recommendations:

Decisions to initiate therapy should be individualized.

In more advanced dementia, decision makers may not view stabilization or slowing decline as a desirable goal if quality of life is judged to be poor.

Harms of drugs should be weighed against modest or even no benefit.

Benefits on average, are not clinically significant for cognition, and are modest for global assessments. Summary estimates showed small effect sizes.

Limited evidence suggests, but does not demonstrate conclusively, that a subgroup of patients achieves clinically important improvement.

Currently, we have no way to predict which patients might have a clinically important response.

Evidence does not support prescribing these agents for every patient with dementia.

Evidence is insufficient to determine optimal duration of therapy. A beneficial effect, if any, would generally be observed within 3 months. The effect may be an improvement or stabilization.

No evidence demonstrates when it is appropriate to stop treatment if the patient becomes unresponsive or shows decline in various domains of dementia. If slowing decline is no longer a goal, treatment is no longer appropriate.

Annals Int Med March 4, 2008; 148: 370-78 "Clinical Guideline" from the American College of Physician, and the American Academy of Family Physicians, first author Amir Qassem, American College of Physicians, Philadelphia, PA

An evidence review on which the clinical guideline was based is reported in this issue of Annals (pp 379-96).

The ACP adds that these guidelines are "guides" only and may not apply to all patients, and all clinical situations. They are not intended to override clinical judgment.

Kenneth Schellase, Medical College of Wisconsin, Milwaukee comments:

Even though statistically significant improvements are reported in clinical trials, outcomes may not be clinically meaningful.

He uses a weight-loss analogy: “If you lose a half a pound after taking a weight-loss drug of 6 months, it’s significant if you power the study with enough people, but is that really a meaningful benefit?”

JAMA April 16, 2008;299:1763

==========

Substantially Cheaper And Simpler To Implement Than The Framingham Risk Equation.

3-10 LABORATORY-BASED VERSUS NON-LABORATORY-BASED METHOD FOR ASSESSMENT OF CARDIOVASCULAR RISK ***The NHANES I Follow-up study cohort***

A well-established primary prevention strategy uses prediction rules to identify those at higher risk.

This long follow-up study determined if a risk prediction method that does not require any laboratory tests could be as accurate as one requiring laboratory information.

Conclusion: A method that used non-laboratory-based risk factors predicted cardiovascular events as accurately as one that included a laboratory-based factor (total cholesterol).

STUDY

1. The National Health and Nutrition Examination Survey (NHANES) is a prospective cohort study of over 14 000 participants ages 25-74 at the time they were first examined (between 1971 and 1978).
2. This follow-up study included participants (n = 6186) who did not report a history of cardiovascular disease (myocardial infarction, heart failure, stroke, angina) or cancer at baseline.
3. Compared how well non-laboratory-based risk factors could predict first-time fatal and non-fatal cardiovascular disease events as compared with laboratory-based risk factors.
   A. Laboratory-based risk factors: age, systolic BP, smoking status, reported diabetes, current treatment for hypertension and total cholesterol.
   B. Non-laboratory-based risk factors: substituted BMI for cholesterol
4. Follow-up for over 21 years.

RESULT S

1. Baseline (mean) values for men:

Age	48
Current smoking	48%
Past smoking	25%
Diabetes	4%

BMI	26
Current hypertension	7%
Total cholesterol	221 mg/dL

2. Over follow-up there were 1529 first-time cardiovascular events, and 578 deaths due to cardiovascular disease.
3. In men, the c-statistic[1] was 0.784 for the laboratory-based model, and 0.783 for the non-laboratory –based model. (Similar in women.)
4. Both models correctly classified over 80% of women, and 70% of men when the threshold for risk of an outcome during follow-up (over 5 years) was set at 10% or greater.

DISCUSSION

1. The study shows that a non-laboratory-based risk method that uses information easily obtained in one outpatient visit can predict cardiovascular disease outcomes as accurately as one that includes determination of total cholesterol.
2. At most, the rates of correct classification differed by less than 1%, and none of the differences were significant.
3. In addition to the overall predictive discrimination, there are other reasons for focusing on a non-laboratory screening method:
    1) Ability to correctly classify patients at the threshold that most prevention guidelines choose for initiating treatment.
    2) Practicality, cost, and feasibility.
4. Costs of lipid screens add up as the test is repeated over time, with little or no added benefit beyond what is already available without laboratory testing.
5. Most cases of cardiovascular disease occur in low-income countries. Developing countries have limited resources for prevention strategies that require laboratory testing.
6. For people at the boundary of low risk and high risk, laboratory testing might be useful for further risk stratification.
7. The non-laboratory method is probably no worse, yet substantially cheaper and simpler to implement than the Framingham risk equation. (Includes age, gender, total-cholesterol, HDL-cholesterol, smoking, systolic BP, and history of hypertension)
8. The benefit of additional laboratory tests (eg, HDL-cholesterol, triglycerides, HbA1c)

seems limited. The predictive discrimination might improve if these laboratory factors were included. However, even if the model was marginally improved, whether it would be worth the added cost and inconvenience (especially in developing countries) is not clear.

CONCLUSION

A method that uses non-laboratory-based risk factors (ie, no total cholesterol determinations) predicted cardiovascular events as accurately as one that relied on laboratory-based values. This approach could simplify risk assessment.

Lancet March 15, 2008; 371: 923-31 Original investigation, first author Thomas A Graziano, Brigham and Woman's Hospital, Boston Mass.

1 The c –statistic (or area under the ROC curve) is a useful single-number summary. It represents an estimate of the probability that the model assigns higher risk to those who have cardiovascular disease events than those who do not. A c statistic of 0.5 denotes no difference between the two groups.

A c-statistic of 0.75 and above (as in this study) is considered clinically meaningful.

The difference of 0.001 in the c statistic between the two groups in this study indicates no clinical difference between groups.

The ROC (receiver operator characteristic) curve measures the discrimination of a prediction model. It is the graph of the true-positive rate (sensitivity) against the false-positive rate (1 – specificity).

The article presents color risk-prediction charts based on:

Smoking vs non-smoking

Diabetes vs no-diabetes.

BMI rising from 15-20 to 30-40

Systolic BP 111-120 to 171-180

Age 35-45 to 65-74

Those with the highest number of risk factors had a 30% or higher risk of an event over 5-years. Those with the lowest number had risk under 5%.

==========

Empirical Acid Suppression Is An Appropriate First Choice.

3-11 HELICOBACTER PYLORI TEST AND TREAT VERSUS PROTON PUMP INHIBITOR IN INITIAL MANAGEMENT OF DYSPEPSIA IN PRIMARY CARE

The aim of this study was to determine the effectiveness of *H pylori* "test and treat" compared with empirical acid suppression in the initial management of dyspepsia in primary care.

Dyspepsia was defined broadly as a symptom complex consisting of one or more recurrent symptoms of: pain centered in the upper abdomen, heartburn, acid regurgitation, nausea, fullness, and early satiety of more than 4 weeks duration.

Conclusion: Empirical acid suppression is an appropriate first choice.

STUDY

1. Randomized, controlled trial, conducted in 80 general practices, followed 699 patients (age 18-65) who presented with dyspepsia. None had "alarm" symptoms.
2. Randomized to:
   1) *H pylori* carbon-13 urea breath test:
      A. Patients with a positive *H pylori* test were offered eradication therapy with one week of omeprazole 20 mg once daily; clarithromycin 250 mg twice daily, and metronoidazole 20 mg once daily followed by 3 weeks of 20 mg omeprazole once daily. A follow-up breath test was offered at 12 weeks.
      B.. Patients who tested negative received omeprazole 20 mg once daily for 4 weeks.
   2) Proton pump inhibition alone—omeprazole 20 mg daily for 4 weeks.
3. Main outcome measure = effect on dyspeptic symptoms as measured by a short-form dyspepsia questionnaire. Also cost effectiveness in cost per quality-adjusted-life-years (QALYs)

RESULTS

1. Test and treat group:	No. tested	No. positive for *H pylori*	Successful eradication
	343	100 (29%)	78%
2. Proton pump-only (PP-only)			
	356		

3. Outcomes at 12 months:

A. Continuing symptoms at 12 months	PP-only	Test and treat
	83%	82%

   B. No significant difference in QALYs and costs between groups. The cost of test and treat was higher at the beginning, but costly ongoing resource use was higher in the PP-only group. The two cancelled each other.
   C. The score for satisfaction was similar between groups

4. Adverse events: Eradication treatment—seven consultations for adverse effects.

DISCUSSION

1. "This study shows that an *H pylori* test and treatment strategy offers no significant advantage over a proton pump inhibitor for the initial management of dyspepsia in primary care." Effects, costs, and satisfaction were similar between groups at 12 months.
2. As this was a pragmatic study, the protocol did not recruit a closely defined subgroup of patients, rather a broad group with both heartburn and epigastric pain.
3. There was no difference in outcome between patients with heartburn-predominant and epigastric-pain predominant dyspepsia. (One problem has been the shifting role of heartburn in the definition of functional dyspepsia.)

CONCLUSION

Test and treat and empirical acid suppression with a proton pump inhibitor are equally effective in reducing symptoms, and improving quality-of-life at 12 months.

Empirical acid suppression is an appropriate first choice.

Practitioners should discuss with individual patients at which point to consider *H pylori* testing.

BMJ March 22, 2008; 336: 651-54 Original investigation , first author Brendan C Delaney, University of Birmingham, UK

An editorial in this issue of BMJ by Naoki Chiba, McMaster University, Hamilton, ON, Canada comments and expands on the study.

Dyspepsia is a common symptom complex of epigastric pain or discomfort—which includes symptoms of heartburn, acid regurgitation, excessive belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion, or early satiety—for which patients seek medical care.

Upper g.i. endoscopy should be performed in patients with alarm symptoms.

Most patients can be safely managed with empirical treatment. It is not cost-effective to perform endoscopy before treatment.

Guidelines in the UK recommend that patients with epigastric pain and heartburn should be managed in the same way rather than arbitrarily considering that epigastric pain represents dyspepsia (which is not a diagnosis) and that heartburn diagnoses gastro-esophageal reflux disease.

One randomized trial in Canada of patients positive for *H pylori* reported that eradication was more successful at 12 months in reducing symptoms than empirical PP inhibition (50% vs 36%)..

Eradicating *H pylori* may be beneficial in curing ulcers and reducing potential risk of gastric cancer and mucosa-associated lymphoid tissue lymphoma. It may also may provide a small benefit in people with functional dyspepsia. Primary care patients at first presentation could have any of these diagnoses, so the strategy of eradication as a first-line strategy continues to have merit.

Where prevalence of *H pylori* is lower, empirical proton pump inhibition may be more cost effective.

Clinicians can choose what strategy to use according to the predominant symptom complex.

Where prevalence of *H pylori* is high, we cannot go wrong with either strategy.

Choice still depends on individual considerations for each patient.

==========

Is This Screening Program Clinically, Socially, Economically, And Ethically Acceptable?

3-12 CORONARY CALCIUM AS A PREDICTOR OF CORONARY EVENTS IN FOUR RACIAL OR ETHNIC GROUPS

In white populations, computed topographic (**CT**) measurements of coronary calcium (**CC**) score predict coronary heart disuse (**CHD**) independently of traditional risk factors. The chief aim of this study was to determine if CC score would predict CHD in other ethnic groups (It did.)

The study also presents data that allows determination of the excess risk related to increasing CC scores.

STUDY

1. Population-based study collected data on risk factors for cardiovascular disease in over 6700 subjects.

   All received CT scanning to determine CC score. None had cardiovascular disease at baseline.

2. Also determined cardiovascular risk factors at baseline in all subjects and in those who sustained a cardiac event:

	All participants	Coronary events
Age	62	68
Male sex	47%	70%
Total cholesterol	194	200
Current or former smoker	50%	67%
Diabetes	12%	24%
Hypertension	45%	67%

3. Follow-up for 4 years to determine coronary events. Correlated risk of events related to CC scores.

RESULTS

1. Over 4 years, there were 162 coronary events (2,5%): 89 myocardial infarction or death from coronary disease (17 died); 73 angina
2. Any coronary event occurred in 162 of 6722 patients.
3. CC score as a predictor of CHD (any event)

Score	No. /No. at risk	Hazard ratio
0	8/3409	1.00
1-100	25/1728	3.6
101-300	24/752	7.7
> 300	32/833	10

DISCUSSION

1. Over 4 years, a doubling of the CC score increased the estimated probability of coronary events by 25%. (From a mean of age 62 to age 66.)
2. The score contributed to risk independently of other risk factors.
3. The study was limited due to the small number of events which occurred over 4 years.

CONCLUSION

Measurement of CC score added incremental value to the prediction of CHD over that of standard coronary risk factors.

NEJM March 27, 2008' 358: 1336-45 Original investigation by the Multi-Ethnic Study of Atherosclerosis (MESA), first author Robert Detrano, University of California at Irvine.
An editorial in this issue of NEJM, first author William S Weintraub, Christiana Care Heath System, Newark, Del comments and expands on this article:

"The thoughtful clinician takes it to be self-evident that intensity of therapy should be proportional to the risk of disease."

"'Risk stratification' has become something of a mantra for rational, evidence-based clinical management."

What is necessary is that reasonable steps can be taken to prevent events. In the case of coronary heart disease, multiple steps can be taken based on established risk factors such as published by the Framingham Study. (Age, sex, total cholesterol, high density cholesterol, smoking status, and systolic BP.)

"Discrimination" is the ability of a model to predict who will and who will not have an event. The discrimination of a model is often assessed by the c-index (equivalent to the area under the receiver-operating-characteristic curve) which is the fraction of pairs of subjects (one who has an event, and one who does not) for

which the probability of an event is higher in the subject who has an event. The c-index can vary from 0.5 (no ability to discriminate, with half the pairs predicted correctly) to 1.0 (perfect discrimination with all pairs predicted correctly).

The Framingham score remains the most common way to predict the 10-year cardiovascular risk. It consists of a few readily available clinical and laboratory variables. It has a discriminant accuracy of approximately 75%.

New risk factors are continually being proposed.

A new risk factor will have limited effect on discrimination unless its relative risk is quite high—in the range of 10 or so. For a new risk factor to be useful, it must offer both a large relative risk and a therapeutic target.

The CC score correlates strongly with age and sex. It does not point out sites of present or future unstable atherosclerotic plaques. The discriminant accuracy (measured with the c-index) increased from 0.77 for risk factors alone to 0.82 for risk factors plus CC score for all CHD events.

The CC score does predict events. But, is the relatively small improvement in accuracy worth it?

There can be value only if patient outcomes improve (ie, if the CC score can be shown to change care in such a way that there are fewer events in the future). This could happen if patients controlled lipids and BP more aggressively as a result of an increased score.

Would the CC score be cost effective? There are not sufficient data available to offer a robust assessment of cost-effectiveness.

Thus, the CC score remains an interesting concept for predicting events in addition to the Framingham score. Its role remains unknown.

==========