ASPIRIN AS PREVENTIVE THERAPY FOR ASYMPTOMATIC VASCULAR DISEASE [3-1]

THE METABOLIC SYNDROME--IS THE WHOLE GREATER THAN THE SUM OF ITS PARTS? [3-2]

LIRAGLUTIDE, (VICTOZA): RISKS AND BENEFITS [3-3]

RISKS OF HIGH HbA1c IN NON-DIABETIC PATIENTS [3-4]

A SHORT LEG MAY INCREASE RISK OF OSTEOARTHRITIS OF THE KNEE [3-5]

VITAMIN D: WHERE DO WE STAND NOW? [3-6]

DOES REMOTE ISCHEMIC CONDITIONING REDUCE MYOCARDIAL DAMAGE AFTER AN ACUTE MI? [3-7]

USE OF PNEUMOCOCCAL VACCINE IN NURSING HOME PATIENTS [3-8]
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.

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   **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 25-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.

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Marginal Benefits and Higher Rates of Bleeding.

3-1 ASPIRIN AS PREVENTIVE THERAPY IN PATIENTS WITH ASYMPTOMATIC VASCULAR DISEASE [Editorial]

Antiplatelet therapy has been a cornerstone of prevention and therapy. Strong data support aspirin in the setting of acute MI or stroke. In patients with suspected acute MI, early vascular mortality has been reduced by 23%. In stroke trials, low-dose aspirin was associated with a significant reduction in recurrent ischemic stroke and mortality. A meta-analysis of trials in patients with symptomatic stable CVD demonstrated a consistent association between aspirin and reduction of cardiovascular morbidity and mortality.

This issue of JAMA reports a double-blind randomized trial of aspirin in 3350 patients age 55-75 with screening-detected low ankle-brachial index in persons with no previous history of CVD events. Participants received: 1) aspirin 100 mg/d or 2) placebo for a mean of over 8 years. Aspirin was no more effective than placebo at reducing fatal or non-fatal coronary events, stroke, or revascularization, and had no significant effect on secondary endpoints.

Aspirin was associated with a statistically non-significant increase in major hemorrhage. (2% vs 1.2%; hazard ratio = 1.7). Intracranial hemorrhage (3 fatal) occurred in 11 patients in the aspirin group vs 7 in the placebo group.

Why does the available evidence suggest that aspirin has little benefit in reducing rates of cardiovascular events in primary prevention? The majority of participants in primary prevention trials were at low absolute risk of coronary disease. The annual risk of vascular events was only about 10% of that in high risk patients. Benefits of aspirin are more modest when used in primary prevention than when used for patients with established CVD.

Aspirin remains an effective therapeutic agent for secondary prevention.

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Use of aspirin in primary prevention of CVD depends on physicians' judgment of benefit vs risk of bleeding in the individual patient. A history of MI or ischemic stroke will automatically place an individual at high risk, and is an indication for aspirin.

Aspirin has been routinely recommended for patients with diabetes. However, the individual risk of a vascular event varies widely. I believe not all patients with diabetes should be exposed to the risk of bleeding (eg, younger patients with short history of diabetes and no other risk factors). For older patients with diabetes, attention to other risk factors (BP, lipids, BMI) may be more productive than aspirin. The patient's fully-informed preference also plays an important role.
The MetS Does Not Provide Better Disease Prediction Than Its Individual Components. Unhealthy Lifestyles Are the Root Cause

3-2 THE METABOLIC SYNDROME AS A CLUSTER OF RISK FACTORS [Editorial]

Is the Whole Greater Than the Sum of Its Parts?

The MetS is a combination of 5 components.

- Greater waist circumference
- Hypertriglyceridemia
- Hyperglycemia
- Hypertension
- Low HDL-cholesterol

(Any combination of 3 defines the syndrome):

Cardiovascular disease risks associated with the MetS are unstable and substantially heterogeneous, depending on which of the 5 components is included.

Each of the components of the MetS is already part of routine clinical assessment. Because treatment strategies are available for the individual risk factors rather than for the MetS itself, it is not clear whether the diagnosis of the MetS can improve treatment strategies.

A study in this issue of Archives conducted a pooled analysis from 7 clinical trials using intravascular ultrasound to compare the effects of MetS and its individual components on coronary plaque progression.

Results indicate that MetS does not predict coronary plaque progression beyond the independent risk contributions of its individual components. It does not represent a distinct disease syndrome.

Obesity, especially abdominal adiposity, is a driving force for other components of MetS. Many obese individuals possess some, but may not possess all components. Non-obese individuals can also possess several components.

Central obesity is at least one factor commonly shared by all other components, with waist circumference serving as a point of further clinical emphasis. MetS has increased attention to central adiposity.

Because all 5 components are modifiable by changes in diet and physical activity, the recognition of MetS is highly relevant for prevention. Identifying “fellow travelers” of MetS such as sleep apnea, fatty liver, gout, gallstones, and polycystic ovary syndrome will help identify high-risk patients.

Unhealthy lifestyles are the root cause of all components of MetS.

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In this group of patients with established CHD, 58% had the MetS. I would have thought that almost 100% would have the syndrome.

Since we do not have a “pill” for the MetS, we rely on treatment of all components in individual patients. As each component, added to others, increases risk, treating each component will decrease risk. Will informing a patient that he has 4 or 5 combined risk factors for CAD impress him enough to change lifestyle? It may impress some individuals.

Insulin resistance is the basic metabolic defect related to the syndrome. This, I believe, is largely due to intra-abdominal obesity.

I call the MetS the “Mall syndrome”. Observing people in a busy shopping mall will reveal how many Americans have increased abdominal girth.

“May Benefit Patients Who Have Inadequate Control Despite Use Of Other Antidiabetes Therapy”

3-3 WEIGHING RISKS AND BENEFITS OF LIRAGLUTIDE: The FDA’s Review of a New Anti-diabetic Therapy

New therapies are needed to achieve glycemic goals because beta-cell function declines over time in patients with diabetes.


In clinical trials, liraglutide resulted in reductions in the mean glycated hemoglobin (HbA1c) of 0.8 to 1.4 percentage points as compared with placebo. Compared as monotherapy with a sulfonylurea, liraglutide was associated with a lower risk of hypoglycemia. There was also greater weight loss and an absence of need to adjust the dose for patients with renal impairment.

There are potential serious safety concerns: In rodents, liraglutide was associated with increased risk of thyroid C-cell focal hyperplasia and C-cell tumors. The relevance to humans is not known. The FDA concluded that there is a low risk for humans, but did require additional studies in animals and establishment of a cancer registry to monitor the annual incidence of medullary cancer over the next 15 years. There is a possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway. The FDA requires a post-approval study to rule out any cardiovascular disease risks.

A. Incretins are a group of natural gastrointestinal peptide hormones released from the small bowel in response to presence of nutrients. They have a number of actions, which improve blood glucose control:
Increase insulin secretion from the pancreas in a glucose-dependent manner
Decrease glucagon secretion from the alpha cells of the pancreas further reducing blood glucose
Inhibit acid secretion in the stomach and gastric emptying
May produce weight loss by increasing satiety, and decreasing food intake.

B. Glucagon-like peptide-1 (GLP-1) is a natural incretin. It is rapidly inactivated by the enzyme dipeptidyl peptidase. It has a half-life of less than 2 minutes. It is not useful clinically.
(Termed “glucagon-like” not because GLP-1 has glucagon activity--quite the opposite. The term comes from the proglucagon gene. GLP-1 is derived from the transcription product of that gene.)

C. Liraglutide (Victoza; Novo Nordisk) is a GLP-1 receptor agonist, an analogue of native GLP-1 with a fatty acid attached. A single daily subcutaneous injection provides action for about 12 hours. It improves control of blood glucose by the same mechanisms as natural incretins. It acts in a glucose-dependent manner--ie, stimulating insulin secretion only when blood glucose is higher than normal. It has negligible risk of hypoglycemia. It leads to a lowering of triglyceride levels. It can be used alone, or in combination with other anti-diabetes drugs. Hypoglycemia is rare, but may result when used with sulfonylureas. It is not approved for use with insulin. It reduces HbA1c by about 1%. The most common adverse effects are gastrointestinal. It is expensive. One daily injection of 1.8 mg costs over $800.00 a month.

D. Exenatide (Byetta; Amylin; Lilly) is also a GLP-1 analogue--a 39 amino acid peptide with a 50% amino acid homology with GLP-1. It is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. It has biological properties similar to human GLP-1. Its half-life is much longer than half-life of GLP-1, but shorter than liraglutide. It must be given s.c. twice a day before meals. It is used at times as primary monotherapy and as adjunctive therapy combined with other anti-diabetes drugs.

E. Sitagliptin (Januvia; Merck) is a dipeptidyl peptidase inhibitor. It prolongs the half-life of native GLP-1. It may be used alone or in combination with other anti-diabetes drugs. It is given by mouth. Adverse effects are rare.

As usual, we will not know all possible important adverse effects for some years.
Higher GH Values in the Normal Range Can Identify Increased Risk of Diabetes and Cardiovascular Complications

3-4 GLYCATED HEMOGLOBIN, DIABETES, AND CARDIOVASCULAR RISK IN NON-DIABETIC ADULTS

This study characterized and compared the relationships between glycated hemoglobin (GH; HbA1c) and fasting glucose and the risk of developing diabetes, coronary heart disease (CHD), ischemic stroke, and death from any cause in a large cohort of middle-aged community-dwelling adults.

Measured GH in over 11,000 adults at baseline (1990-1992). None had a history of diabetes or cardiovascular disease. Obtained blood for determination of GH.

Followed periodically for up to 15 years.

Baseline characteristics:

<table>
<thead>
<tr>
<th>GH (%)</th>
<th>&lt;5</th>
<th>5.0 to 5.4</th>
<th>5.5 to 5.9</th>
<th>6.0 to 6.4</th>
<th>6.5 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of persons</td>
<td>949</td>
<td>4950</td>
<td>3683</td>
<td>1031</td>
<td>479</td>
</tr>
</tbody>
</table>

Fasting glucose

<table>
<thead>
<tr>
<th></th>
<th>&lt; 100 mg/dL (%)</th>
<th>100 to 125 (%)</th>
<th>126 &amp; over (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 mg/dL</td>
<td>61</td>
<td>53</td>
<td>33</td>
</tr>
<tr>
<td>100 to 125</td>
<td>39</td>
<td>45</td>
<td>64</td>
</tr>
<tr>
<td>126 &amp; over</td>
<td>0.8</td>
<td>1.1</td>
<td>3.0</td>
</tr>
<tr>
<td>BMI</td>
<td>26</td>
<td>27</td>
<td>28</td>
</tr>
</tbody>
</table>

During follow-up, the cumulative incidence of diabetes was 20%:

<table>
<thead>
<tr>
<th>Incidence (%)</th>
<th>&lt;5%</th>
<th>5.0 to 5.4</th>
<th>5.5 to 5.9</th>
<th>6.0 to 6.4</th>
<th>6.5 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>6</td>
<td>12</td>
<td>21</td>
<td>44</td>
<td>79</td>
</tr>
</tbody>
</table>

Incidence rates per 1000 person-years rose steadily from about 5 in the lowest GH quintile to over 100 in the highest. Baseline GH of less than 5% was associated with approximately half the risk of development of diabetes as those with GH 5.0 to 5.4.

There was an increasing risk of CHD, ischemic stroke, and death from any cause with higher levels of GH.

There was no evidence of a threshold value of GH for development of diabetes.

But for death from any cause, there was “J shaped” association. Those in the less than 5% group had a significantly higher death rate than those with GH 5.0 to 5.4. (Hazard ratio = 1.48).

“Our findings show that people with glycated hemoglobin value of 6% or higher are at high risk for development of diabetes, even after adjustment for other risk factors, and independently of baseline fasting glucose levels.”
GH is also a marker for cardiovascular risk and death even after accounting for baseline fasting glucose levels—“suggesting that glycated hemoglobin may be superior to fasting glucose for characterizing long-term risk”.

“Our data suggest that glycated hemoglobin values within the normal range can identify persons at increased risk of coronary heart disease, stroke and death before the diagnosis of diabetes.”

Conclusion: In this community-based population of non-diabetic adults, GH was associated with risk of diabetes, and risks of cardiovascular disease and death from any cause as compared with fasting glucose.

This is an interesting study. And I believe a helpful one.

Are we headed toward a more convenient and perhaps a less costly single test, which will offer a helpful prognosis before development of diabetes, as well as a diagnosis of diabetes?

(The ADA states that an HbA1c of 6.5% and over is diagnostic of diabetes.)

Will adding another risk factor lead patients to better lifestyles? A HbA1c of 6.0, indicating considerably increased risk, may induce some patients to adopt more healthful lifestyles.

The test must be done in a certified and standardized laboratory.

A Potentially Modifiable Risk Factor For Knee OA.

3-5 ASSOCIATION OF LEG-LENGTH WITH KNEE OSTEOARTHRITIS

Leg-length inequality (LLI) is common. It has been implicated in: low back pain, trochanteric bursitis, osteoarthritis (OA) of the hip and knee, knee pain, and Achilles rupture.

LLI increases ground-reaction forces on the lower leg. Because it has to come from a higher level to reach the ground during walking, a shorter leg would likely incur an increased ground-reaction force compared with the legs that are equal in length.

Like walking down hill

The study followed over 2900 participants age 50-79 (mean age 63); at high risk for OA due to knee pain, obesity (mean body mass index = 31), knee injury or surgery. Performed standard knee radiography and full-limb radiography to determine length.. Follow-up = 30 months.

Risk of incident symptomatic OA of the knee, and progressive OA increased in the shorter leg over 30 months

Leg-length inequality may be an important risk factor for knee OA, primarily in the shorter leg.

LLI may be under-recognized and under treated in patients with knee OA. It is easily corrected with shoe modification. This raises the possibility that correction of LLI may be a simple and cost-effective method for preventing and treating and knee OA.
Conclusion: Radiographic LLI was associated with prevalent, incident symptomatic and progressive knee OA. LLI is a potentially modifiable risk factor for knee OA.

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I wonder--Will the NIH now sponsor a long-term treatment trial?
This may be a simple application for primary care. Patients with obvious LLI are not uncommon.
Would it be reasonable to advise them to obtain a shoe lift?
Would it be reasonable to tape-measure the lower extremities in patients with established knee OA to determine if LLI is present, and if a lift would possibly benefit? This might be helpful especially in younger individuals to retard development of knee OA.

Is D going the way of antioxidants and folic acid?

3-6 VITAMIN D SUPPLEMENTATION IN THE AGE OF LOST INNOCENCE [Editorial]

Two systematic reviews and editorial comment update the present status of the association between D and cardiovascular disease, diabetes, hypertension, and mortality. (Please read the full abstract. RTJ)

Some observations:

The widespread claims of health benefits of D from increased intake follow decades of research that led to the collapse of similar claims regarding antioxidant vitamins and folic acid supplementation. Will history repeat itself?

For clinical CVD outcomes, 4 of 7 analyses found that low blood concentrations of D were associated with increased risk. For incident diabetes, 3 of 6 analyses found low D status associated with increased risk. For both clinical cardiovascular and diabetes outcomes, the methods of the original studies were too heterogeneous to consider pooling. For hypertension, 3 cohorts reported that low D concentrations were associated with an overall 79% increase in the odds of incident hypertension.

Evidence from limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk. Generalizability is uncertain. Further research is needed.

Two randomized trials reported no significant effect on risk of ischemic heart disease or stroke. There was a significant reduction in fractures.

A meta-analysis of 18 trials found that D supplementation was associated with a reduced all-cause mortality by 7%.

Observational studies may be subject to various biases for estimating the effect of vitamin and mineral supplementation on disease endpoints.

The editorialist concludes:
“The effect of vitamin D supplements on cardiovascular disease, diabetes, and hypertension remains uncertain. However, the available evidence in favor of vitamin D supplementation is far more promising than for other vitamin or mineral supplements.”

From a biological perspective, the presence of D receptors in many cell types and organs support the potential broad-ranging effects of D.

“We believe that the evidence for widespread use of high dose vitamin D supplementation in the general population remains insufficient.”

Trials of antioxidant vitamins have taught us that we cannot anticipate small risks of presumed safe interventions that, when applied to hundreds of millions of persons, could result in thousands of detrimental events.

We must define the optimal dose, and the real benefits and potential harmful effects of supplementation. Enthusiasm for supplementation must be tempered by the loss of innocence from trials of antioxidant supplements that showed not only benefits, but also harms.

“Conducting large randomized trials of high-dose vitamin D should be a public health priority.”

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*What do we understand at this time?*

- *D deficiency is common*
- *Replacement to normal levels seems reasonable*
- *Replacement does reduce risk of falls and fractures, especially in the elderly, resulting in a reduction in mortality*
- *Evidence of benefit is conflicting*
- *Long-term harms when large numbers of persons receive moderately high doses is not known*
- *We must wait for a definitive answers*

*Questions:*

- *Must we wait until blood levels reach normal levels before judging benefits and harms?*
- *Who will conduct a very large RCT? Certainly not the drug companies. There would be no profit.*
- *I believe many individuals will continue to take moderately high doses of D. The putative benefit / harm-cost ratio is high.*
“Increases Myocardial Salvage, And Has A Favorable Safety Profile.”

3-7 REMOTE ISCHAEMIC CONDITIONING BEFORE HOSPITAL ADMISSION AS A COMPLEMENT TO ANGIOPLASTY, AND EFFECT ON MYOCARDIAL SALVAGE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Remote ischemic conditioning (RIP) is a simple procedure: 1) applying a BP cuff to the arm and inflating to 200 mm Hg and continuing inflation for 5 minutes. 2) Deflating the cuff and leaving it deflated for 5 minutes. 3) repeating the cycle a total of 4 times (total of 40 minutes if the final deflation period of 5 minutes is included). The procedure can be applied immediately after symptoms of a suspected MI occur. It may be given by ambulance or other personnel at the scene and continued during transport.

This study used myocardial imaging with repeated 99technicium scans to examine whether RIP done before percutaneous coronary intervention (PCI) increases myocardial salvage in patients with an evolving first MI.

The primary outcome was myocardial salvage index at 30 days after PCI measured by myocardial perfusion imaging as the proportion of the area at risk salvaged by treatment. Salvage index was calculated as (area at risk - final infarct size) / area at risk.

251 subjects with acute ST elevation MI were randomized telemedically to: 1) RIP, and 2) no RIP. Patients received RIP during transport to the hospital, started by ambulance personnel.

Mean salvage index was 0.69 treated vs 0.57 controls, a difference of 0.12.

Salvage as a percentage of left ventricle was (statistically) significantly higher in the RIP group (16% vs 11%). Differences in final infarct size were not significant (median 7% of left ventricle in both groups).

Peak troponin T release, the proportion of patients achieving 70% ST segment resolution within 90 minutes, and NYHA class of disease at 30 days did not differ between groups.

Major adverse coronary events were similar in each group: 3 deaths; 1 reinfarction; 3 heart failure.

Conclusion: “Remote ischemic conditioning before hospital admission increases myocardial salvage, and has a favorable safety profile.”

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Ordinarily, I would not include this study. It is not a practical point at this time. Will it ever be? I included it because it is so provocative. I will be on the lookout for further developments.

How does RIP influence the coronary circulation? The authors did not discuss this. There are no studies about the effect of RIP on the coronary circulation (Personal communication from Dr. Botker)
They seem, however, enthusiastic about the benefits of the procedure. I remain skeptical. The procedure resulted in no clinical benefits.

**Reduces Incidence Of Pneumonia And Death From Pneumonia. But Should We Recommend It?**

**3-8 EFFICACY OF A 23-VALENT PNEUMOCOCCAL VACCINE IN PREVENTING PNEUMONIA AND IMPROVING SURVIVAL IN NURSING HOME RESIDENTS**

This trial determined the efficacy of a 23-valent vaccine in nursing homes (NH) in Japan.

At baseline, about 90% of subjects were over age 75; 47% age 85-94; 9% age 95-1005. About 10% were bedridden, 5% had a “psychological disorder”. The majority had 1 to 3 or more co-morbid conditions. Written informed consent was obtained from participants or their next of kin.

Excluded patients who were immunocompromised and those who were unable to follow instructions.

<table>
<thead>
<tr>
<th>Incidence of pneumonia over 3 years:</th>
<th>Vaccine (n = 502)</th>
<th>Placebo (n = 504)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>Non-pneumococcal</td>
<td>49</td>
<td>67</td>
</tr>
<tr>
<td>All-cause pneumonia</td>
<td>63</td>
<td>104</td>
</tr>
</tbody>
</table>

**Death rates**

<table>
<thead>
<tr>
<th></th>
<th>Vaccine (n = 502)</th>
<th>Placebo (n = 504)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal pneumonia</td>
<td>0/14</td>
<td>13/37</td>
</tr>
<tr>
<td>Non-pneumococcal pneumonia</td>
<td>13/49</td>
<td>13/67</td>
</tr>
<tr>
<td>All cause pneumonia</td>
<td>13/63</td>
<td>26/104</td>
</tr>
</tbody>
</table>

The death rates from all-cause pneumonia and non-pneumococcal pneumonia and the incidence of non-pneumococcal pneumonia were not significantly reduced in the vaccine group.

Overall, death rates did not differ between groups; (80 patients in each group died from all causes).

“The findings of this study suggest the need for a national policy that recommends the systematic vaccination of residents living in institutions to reduce morbidity as well as the cost of health care in Japan.”

Conclusion: The 23-valent pneumococcal vaccine prevented pneumococcal pneumonia and reduced mortality from pneumococcal pneumonia in nursing home residents.

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*I did not abstract this study because of its conclusions, but to ask: Should we give pneumococcal vaccine to NH patients? If so, to whom? If not, to whom?*

The investigators noted that: “A placebo controlled trial of vaccine efficacy has been deemed unethical in developed nations where the vaccine is considered standard of care, even in the absence of
any proved efficacy.” In Japan there is no national recommendation for its use. Does the “standard of care” of NH residents in the USA include pneumococcus vaccine?

The trial did place some restriction on participants. Only 5% had a “psychological disorder”. Although participants were very old and had co-morbidities, only 160 of the 1006 residents died over 3 years. Terminal cancer patients must have been excluded.

The prevalence of dementia in NH in the USA, I believe, is much higher than 5%. The study excluded those who were unable to follow directions. The investigators did obtain informed consent from the patient or surrogate.

If vaccination were universal in NH in the USA, all patients would have to give informed consent. Many would lack decisional capacity to give informed consent. This would involve finding, fully informing, and obtaining consent from surrogates.

I believe the kindest and most appropriate approach would be to be very restrictive in asking individual patients if they wish to receive vaccine. Many patients in NH do not wish to extend a demented life. (At any rate, vaccination did not reduce the death rate.) Should we bring up the subject up very often? I believe not.

Remember Osler’s comment: “Pneumonia is the old man’s friend”

As usual, the decision rests on the individual patient’s informed consent. I would ask only those who have a reasonable remaining length of enjoyable life.
Assessing patients’ cardiovascular risk may be used to target preventive treatments to asymptomatic individuals at high risk for future CVD events.

For those at high risk, strategies including medications, diet, and comprehensive lifestyle approaches improve cardiovascular morbidity and mortality.

Antiplatelet therapy has been a cornerstone of prevention and therapy. Strong data support aspirin in the setting of acute MI or stroke. In patients with suspected acute MI, early vascular mortality has been reduced by 23%. In stroke trials, low-dose aspirin was associated with a significant reduction in recurrent ischemic stroke and mortality. A meta-analysis of trials in patients with symptomatic stable CVD demonstrated a consistent association between aspirin and reduction of cardiovascular morbidity and mortality.

Use of aspirin has been extrapolated to high-risk patients without established CVD. However, preventive therapy is associated with risks. Aspirin’s major risk is bleeding.

This issue of JAMA reports a double-blind randomized trial of aspirin in 3350 patients age 55-75 with screening-detected low ankle-brachial index in persons with no previous history of CVD events. Participants received: 1) aspirin 100 mg/d or 2) placebo for a mean of over 8 years. Aspirin was no more effective than placebo at reducing fatal or non-fatal coronary events, stroke, or revascularization, and had no significant effect on secondary endpoints.

Aspirin was associated with a statistically non-significant increase in major hemorrhage. (2% vs 1.2%; hazard ratio = 1.7). Intracranial hemorrhage (3 fatal) occurred in 11 patients in the aspirin group vs 7 in the placebo group.

To take a closer look at primary prevention:

Twenty years ago, the British Doctors Trial randomized over 5100 healthy males to 500 mg aspirin / day vs no treatment. No benefits from aspirin were observed.

The Physicians Health Study randomized over 22 000 males to 325 mg aspirin/d vs placebo. Aspirin was associated with a 44% reduction in fatal and non-fatal MI, yet did not significantly reduce the primary endpoint of cardiovascular death.
Four more recent randomized controlled trials of aspirin in primary prevention showed reductions in several secondary cardiovascular end points, but no reduction in the primary endpoint.

Why does the available evidence suggest that aspirin has little benefit in reducing rates of cardiovascular events in primary prevention?

Most participants in primary prevention trials were at low absolute risk of coronary disease. The annual risk of vascular events was only about 10% of that in high risk trials. Benefits of aspirin are more modest when used in primary prevention (about a 12% risk reduction) than when used for patients with established CVD.

Use of enteric-coated aspirin in many trials may have resulted in lower bioavailability and inadequate platelet inhibition, especially in obese patients.

Recent primary prevention trials have failed to demonstrate the superiority of aspirin added to standard medical therapy, such as statins. The data do not support recommendations for ABI screening in an effort to reduce CVD events. The clinical benefit of aspirin for patients with peripheral arterial disease remains unproven.

“Aspirin appears to have marginal benefits for reducing initial CVD events when used for patients without clinically evident CVD, and is associated with higher rates of bleeding.”

Aspirin remains an effective therapeutic agent for secondary prevention.

JAMA March 3, 2010; 303: 880-82 Editorial by Jeffrey S Berger, New York University School of Medicine, New York.


A low A/B index indicates atherosclerosis and an increased risk of cardiovascular and cerebrovascular events. This double-blind trial (1998-2008) involved over 28 000 men and women age 50-76 living in the general population of Scotland. All were free of CVD. All had a A/B screening test.

Over 3300 had a low A/B index, defined as equal to, or less than 95/100. Randomized the 3300 to 1) aspirin 100 mg daily, or 2) placebo.

Primary end point = composite of fatal or non-fatal coronary events and stroke.

After a mean of 8 years, 357 had a primary event.

Aspirin group: 13.3 per 1000 person-years
Control: 13.7 per 1000 person-years.

No significant difference in all-cause mortality.

Major hemorrhage requiring admission to a hospital occurred in 34 participants (2.5 per 1000 person-years in the aspirin group, and 1.5 per 1000 person-years in the control group. Hazard ratio = 1.7)

“The data do not support recommendations for ABI screening”

The MetS Does Not Provide Better Disease Prediction Than Its Individual Components. Unhealthy Lifestyles Are the Root Cause

3-2 THE METABOLIC SYNDROME AS A CLUSTER OF RISK FACTORS [Editorial]

Is the Whole Greater Than the Sum of Its Parts?

Debate continues. Is the MetS a real syndrome? Is it an informative clinical tool?

The MetS is a combination of 5 components:

Greater waist circumference
Hypertriglyceridemia
Hyperglycemia
Hypertension
Low HDL-cholesterol

(Any combination of 3 defines the syndrome)

CVD risks associated with the MetS are unstable and substantially heterogeneous, depending on which of the 5 components is included.

There are 2 main questions:

1) Does the MetS improve prediction and better characterize people at risk of CVD, rather than simply identifying the presence of individual component risk factors.

2) Does it possess an underlying pathophysiological characteristic, or is it merely an aggregate collection of CVD risk factors?

Each of the components of the MetS is already part of routine clinical assessment, and because treatment strategies are available for the individual risk factors rather than for the MetS itself, it is not clear whether the diagnosis of the MetS can improve treatment strategies.

A study in this issue of Archives conducted a pooled analysis from 7 clinical trials using intravascular ultrasound to compare the effects of MetS and its individual components on coronary plaque progression.
Results indicate that MetS does not predict coronary plaque progression beyond the independent risk contributions of its individual components. It does not represent a distinct disease syndrome.

Several other studies have come to the same conclusion.

There is one positive resulting from the syndrome-- the diagnosis of MetS may help to motivate lifestyle changes.

The use of MetS in clinical practice is complicated by inconsistencies in risks and substantial variations in the magnitude of the association depending on which of the 5 components is included in the diagnosis. For example, inclusion of a higher BMI and elevated triglycerides had a stronger association with plaque progression than did the MetS defined without either component. Inclusion of elevated fasting glucose or hypertension in the MetS criteria predicts total and CVD mortality differently than does MetS diagnosed without these components. Obesity, especially abdominal adiposity is a driving force for other components of MetS. Many obese individuals possess some, but not all components. Non-obese individuals can also possess several components.

Central obesity is at least one factor commonly shared by all other components, with waist circumference serving as a point of further clinical emphasis. MetS has helped increase attention to central adiposity.

Because all 5 components are modifiable by changes in diet and physical activity, the recognition of MetS is highly relevant for prevention. Identifying “fellow travelers” of MetS such as sleep apnea, fatty liver, gout, gallstones, and polycystic ovary syndrome will help identify high-risk patients.

Unhealthy lifestyles are the root cause of all components of MetS.

Archives Internal Medicine March 8, 2010; 170: 484-85 “Invited commentary” first author Eric L Ding, Harvard School of Public Health, Boston, Mass.

1 See Practical; Pointers January 2010 for more details

2 “The Metabolic Syndrome, Its Component Risk Factors, and Progression of Coronary Atherosclerosis” Archives Internal Medicine March 8, 2010, 170: 478-84 Original investigation, first author Ozgur Bayturan, Cleveland Clinic, Cleveland, Ohio

Over 3400 patients were included in this systematic review of 7 clinical trials. All had established coronary heart disease (CHD). Coronary atheroma progression was monitored by intravascular ultrasonography. Patients with and without the MetS were compared with regard to clinical characteristics, coronary atheroma burden at baseline, and change on serial evaluation. Investigated relationships between plaque progression (increase in percent atheroma volume [PAV]) and its component risk factors.

The MetS was highly prevalent (58%). It was associated with greater progression of PAV.
After adjusting for its individual components, MetS was no longer an independent predictor. Although accelerated disease progression is observed in the setting of MetS, this is owing to presence of individual component risk factors rather than to the presence of the syndrome itself.

Although each component produced greater disease progression, hypertriglyceridemia (HTG) and elevated BMI (> 30) had the highest hazard ratios for atheroma progression. The finding that HTG independently predicted disease progression supports the increasing body of evidence demonstrating that elevated fasting triglycerides are an established risk factor—even in patients with LDL-cholesterol levels considered to be normal. This suggests that a more aggressive approach to manage even mild elevations of triglycerides should be integrated into risk reduction strategies.

Targeting abdominal obesity for aggressive preventive measures may be of greater utility than identification of MetS.

This does not diminish the importance of other risk factors. LDL-c remains important. Similarly, the importance of diabetes, even after controlling for associated risk factors, underscores the importance of disordered glucose homeostasis. When each component was considered individually, a greater chance of progression was observed.

Note that all patients in this study had established CAD. It is not known whether the findings can be extrapolated to asymptomatic patients in the primary prevention setting.

“Although accelerated disease progression is observed in patients with MetS, this appears to be largely driven by individual component risk factors rather than by the presence of the syndrome itself.”

“May Benefit Patients Who Have Inadequate Control Despite Use Of Other Antidiabetes Therapy”

3-3 WEIGHING RISKS AND BENEFITS OF LIRAGLUTIDE: The FDA’s Review of a New Anti-diabetic Therapy

New therapies are needed to achieve glycemic goals because beta-cell function declines over time in patients with diabetes.


In clinical trials, liraglutide resulted in reductions of the mean glycated hemoglobin (HbA1c) of 0.8 to 1.4 percentage points as compared with placebo. Compared as monotherapy with a sulfonylurea, liraglutide was associated with a lower risk of hypoglycemia. There was also greater weight loss and an absence of need to adjust the dose for patients with renal impairment.

There are potential serious safety concerns:

1) In rodents, liraglutide was associated with increased risk of thyroid C-cell focal hyperplasia and C-cell tumors. C-cell hyperplasia is a pre-neoplastic lesion leading to medullary thyroid cancer.
C-cell carcinomas were also observed in rodents—a statistically significant increase in incidence at doses resulting in high plasma levels. Overall survival rates were not affected. The relevance to humans is not known.

Calcitonin, a hormone secreted by the thyroid C cells, is used clinically as a biomarker for the detection of medullary thyroid cancer. In controlled trials, increases in calcitonin levels occurred in a slightly higher percentage of patients treated with liraglutide than in controls. However levels were still within normal.

The FDA concluded that this translates into a low risk for humans, but did require additional studies in animals and establishment of a cancer registry to monitor the annual incidence of medullary cancer over the next 15 years.

2) There is a possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway. So far, the incidence of pancreatitis, although low, is about 4 times higher in users of liraglutide than in comparator groups. The true incidence is difficult to determine because of limitations of postmarketing reporting and the possibility that pancreatitis may be high in patients with diabetes. The FDA has required GLP-like drugs to carry a label noting an increased risk of pancreatitis, and to conduct additional studies.

Common side effects of liraglutide include nausea and vomiting. Persistent or severe nausea should be carefully evaluated. This may be an early sign of pancreatitis.

3) Is it possible to rule out increased risks of cardiovascular disease? Analyses of CVD events in phase 2 and 3 trials showed that liraglutide met the standard for ruling out an unacceptable increase in CVD risk. The overall rates of CVD events was low. However, more stringent criteria outlined for postapproval evaluations were not met. The FDA requires a postapproval study.

In approving liraglutide, the FDA recognized that it may benefit patients who have inadequate diabetes control despite use of other antidiabetes therapy. The FDA recognizes that all products approved for treating type-2 diabetes, including long-marketed products, carry risks. A risk mitigation strategy is required that includes a guide and a communication plan for educating prescribers about the drug’s risks and benefits.

The FDA expects to learn more about liraglutide’s safety from required postapproval studies. Meanwhile, physicians need to carefully review the prescribing information and decide whether the benefit-risk profile is favorable for each individual patient.

NEJM March 4, 2010; 362: 77-77  “Perspective”, first author Mary Parks, Center for Drug Evaluation and Research, FDA, Silver Spring, MD
Higher GH Values in the Normal Range Can Identify Increased Risk of Diabetes and Cardiovascular Complications

3-4 GLYCATED HEMOGLOBIN, DIABETES, AND CARDIOVASCULAR RISK IN NON-DIABETIC ADULTS

New clinical practice guidelines from the ADA advocate the use of glycated hemoglobin (GH; HbA1c) in the diagnosis of diabetes, largely on the basis of the established association between GH and micro-vascular disease. GH has several advantages over fasting glucose as a diagnostic test: it is assessed in the non-fasting state and has higher repeatability. It is the preferred test to monitor glucose control.

This study characterized and compared the relationships between GH and fasting glucose and the risk of developing diabetes, coronary heart disease (CHD), ischemic stroke, and death from any cause in a large cohort of middle-aged community-dwelling adults.

The investigators hypothesized that GH would be superior to fasting glucose as an indicator of risk of developing diabetes.

STUDY

1. Measured GH in over 11,000 adults at baseline (1990-1992). None had a history of diabetes or cardiovascular disease. Obtained blood for determination of GH.
2. The diagnosis of diabetes was based on glucose measurements, a self-reported diagnosis of diabetes, or diabetes-medication use.
3. Followed periodically for up to 15 years. (Mean = 14 years)
4. Divided GH into quintiles.

RESULTS

1. Baseline characteristics:

<table>
<thead>
<tr>
<th>GH (%)</th>
<th>&lt;5</th>
<th>5.0 to 5.4</th>
<th>5.5 to 5.9</th>
<th>6.0 to 6.4</th>
<th>6.5 and over</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of persons</td>
<td>949</td>
<td>4950</td>
<td>3683</td>
<td>1031</td>
<td>479</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fasting glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100 mg/dL (%)</td>
</tr>
<tr>
<td>100 to 125 (%)</td>
</tr>
<tr>
<td>126 &amp; over (%)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
</tbody>
</table>
(Note increase in fasting glucose and BMI as GH increased. GH and fasting glucose were highly correlated. RTJ)

2. Participants with elevated GH were more likely to be black, have fewer years of education, a higher BMI and to be dyslipidemic.

3. During follow-up, the cumulative incidence of diabetes was 20%:

<table>
<thead>
<tr>
<th>GH Category</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>6</td>
</tr>
<tr>
<td>5.0 to 5.4</td>
<td>12</td>
</tr>
<tr>
<td>5.5 to 5.9</td>
<td>21</td>
</tr>
<tr>
<td>6.0 to 6.4</td>
<td>44</td>
</tr>
<tr>
<td>6.5 and over</td>
<td>79</td>
</tr>
</tbody>
</table>

4. Incidence rates per 1000 person-years rose steadily from about 5 in the lowest GH quintile to over 100 in the highest.

5. Baseline GH of less than 5% was associated with approximately half the risk of development of diabetes as those with GH 5.0 to 5.4.

6. There was an increasing risk of CHD, ischemic stroke, and death from any cause with higher levels of GH.

7. There was no evidence of a threshold value of GH for development of diabetes.

8. But for death from any cause, there was “J shaped” association. Those in the less than 5% group had a significantly higher death rate than those with GH 5.0 to 5.4. (Hazard ratio = 1.48)

   (The investigators only comment was that the J shaped relation between the GH and risk of death from any cause suggests that further exploration of the health risks associated with the low-normal glycemic state and possible non-glycemic determinants of GH is warranted. RTJ)

9. Race appeared to modify the association between GH and risk of developing diabetes during 15 years of follow-up. As compared with whites, blacks had lower adjusted hazard ratios within each category of GH.

   (The investigators surmise that this was due to delay in diagnosis. RTJ)

DISCUSSION

1. Among people in the US who do not have diagnosed diabetes, over 2.4 million have a GH higher than 6.5%, and 7 million have a value over 6.0%.

2. “Our findings show that people with glycated hemoglobin value of 6% or higher are at high risk for development of diabetes, even after adjustment for other risk factors, and independently of baseline fasting glucose levels.”

3. GH is also a marker for cardiovascular risk and death even after accounting for baseline fasting glucose levels--“suggesting that glycated hemoglobin may be superior to fasting glucose for characterizing long-term risk.”
4. “Our data suggest that glycated hemoglobin values within the normal range can identify persons at increased risk of coronary heart disease, stroke and death before the diagnosis of diabetes.”

5. “Glycated hemoglobin values exceeding 6% may be a clinically useful marker to identify persons at risk of, not only diabetes, but also cardiovascular disease and death.”

CONCLUSION

In this community-based population of non-diabetic adults, GH was associated with risk of diabetes, and risks of cardiovascular disease and death from any cause.

These data support use of GH as a diagnostic test for diabetes.

NEJM March 4, 2010; 362: 800-11 Original investigation, first author Elizabeth Selvin, Johns Hopkins University, Baltimore MD for the Atherosclerosis Risk in Communities (ARIC) study.

1 The ADA recently stated that a HbA1c of 6.5% and above is diagnostic of diabetes.

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A Potentially Modifiable Risk Factor For Knee OA.

3-5 ASSOCIATION OF LEG-LENGTH WITH KNEE OSTEOARTHRITIS

Leg-length inequality (LLI) is common. It has been implicated in: low back pain, trochanteric bursitis, osteoarthritis (OA) of the hip and knee, knee pain, and Achilles rupture.

Various imaging techniques have been used to measure LLI. Full length radiography with measurement from the femoral head to the ankle is the most commonly used method.

LLI increases ground-reaction forces on the lower leg. Because it has to come from a higher level to reach the ground during walking, a shorter leg would likely incur an increased ground-reaction force compared with the legs that are equal in length.

Like walking down hill.

LLI may increase the risk of OA of the knee. Conversely, because articular cartilage is lost with the development of knee OA, LLI may develop as a result of OA.

The study describes the relationship between LLI and both incident and progressive knee OA.

STUDY

1. Followed over 2900 participants age 50-79 (mean age 63); at high risk for OA due to knee pain,
obesity (mean body mass index = 31), knee injury or surgery. Performed standard knee radiography and full-limb radiography to determine length. Follow-up = 30 months.

2. Defined leg length as the distance from the center of the femoral head to the center of the end of the tibia.
3. Repeated knee radiography at 30 months
4. Defined radiographic OA progression of the knee as an increase in joint-space narrowing.
5. Defined LLI as a difference of 1 cm or more.

RESULTS
1. At baseline, 15% of the cohort had LLI of 1 cm or more. 1% had LLI of 2 cm or more.
2. At baseline:
   There was an association between LLI and symptomatic knee OA. Compared with those with LLI less than 1 cm, inequality of 1 cm or more was associated with increased odds of radiographic OA in the shorter leg. (53% vs 37%), but not in the longer leg (42% vs 37%; not significant).
   Inequality of as little as 0.5 to 1.0 cm increased the risk for prevalent OA, primarily in the shorter leg.
3. Incident knee OA:
   A gradient-response relationship existed between increasing LLI and increased odds of incident symptomatic OA in the shorter leg over 30 months.
4. Progressive radiological knee OA:
   LLI of 1 cm or more was associated with increased odds of progression in the shorter leg over 30 months.

DISCUSSION
1. “We observed leg-length inequality of 1 cm or greater in 14.5% of participants at baseline, and this was significantly associated with prevalent radiographic and symptomatic osteoarthritis at baseline, and predicted incident knee osteoarthritis 30 months later.”
2. The shorter leg was at high risk of progression.
3. Leg-length inequality may be an important risk factor for knee OA, primarily in the shorter leg.
4. The pathogenesis of increased risk in the shorter leg probably depends on the bio-mechanical mechanisms used to adapt to the inequality. The shorter leg has to travel a greater distance (even if minimal) to reach the ground, and therefore has a higher impact velocity. The shorter leg may in effect be going “down hill”.
5. Leg length differences as little as 0.5 cm may be associated with increased odds of prevalent symptomatic OA. But, physical examination may not provide sufficiently accurate or reproducible measurement of LLI of this magnitude.

6. LLI may be underrecognized and under treated in patients with knee OA. It is easily corrected with shoe modification. This raises the possibility that correction of LLI may be a simple and cost-effective method for treating and preventing knee OA.

CONCLUSION
Radiographic LLI was associated with prevalent, incident symptomatic and progressive knee OA. LLI is a potentially modifiable risk factor for knee OA.


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Is D going the way of antioxidants and folic acid?

3-6 VITAMIN D SUPPLEMENTATION IN THE AGE OF LOST INNOCENCE [Editorial]
We have witnessed an explosion of scientific and media attention to the health care effects of vitamin D (D).

The pivotal role of D in regulating calcium homeostasis has long been recognized.

Evidence has mounted suggesting that D may also influence non-skeletal conditions: cardiovascular disease (CVD), hypertension, diabetes, cancer, and mortality.

Claims that large segments of the population have inadequate D concentrations have prompted calls for increased D intake through supplementation or fortification.

The widespread claims of health benefits of D from increased intake follow decades of research that led to the collapse of similar claims regarding antioxidant vitamins and folic acid supplementation. Will history repeat itself?

Two systematic reviews in the issue of Annals Internal Medicine summarize the role of D in CVD and provided insight into the type of evidence that is necessary to fully understand the effects of D.

1) The first article reviewed the prospective observational studies on the association between D,
assessed by blood levels of 25(OH)D or reported D intake, and incident cardio-metabolic outcomes:

For clinical CVD outcomes, 4 of 7 analyses found that low concentrations were associated with increased risk.

For incident diabetes, 3 of 6 analyses found low D status associated with increased risk.

For both clinical cardiovascular and diabetes outcomes the methods of the original studies were too heterogeneous to consider pooling.

For hypertension, 3 cohorts reported that low D concentrations were associated with an overall 79% increase in the odds of incident hypertension with no heterogeneity.

2) The second article, using observational data, identified consistent inverse associations between D supplementation and CVD mortality in 6 prospective cohorts (5 were in patients receiving kidney dialysis).

Conclusion: Evidence from limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk. Generalizability is uncertain. Further research is needed.

Observational studies may be subject to various biases for estimating the effect of vitamin and mineral supplementation on disease endpoints. Randomized, controlled trials are more likely to provide unbiased evidence. “The evidence for the efficacy of vitamin D supplementation on clinical cardiovascular end points hinges on only 2 trials, neither of which showed significant benefits.”

1) One trial randomized over 2600 men and women over age 65 to receive 100 000 units of oral D3 placebo every 4 months. (Average of over 800 units daily). After 5 years, the hazard ratios (HR) of D vs placebo was 0.94 for ischemic heart disease, and 1.02 for stroke (neither statistically significant). For fracture prevention, HR of 0.78 was significant.

2) The Women’s Heath Initiative randomized over 36 000 women to 400 IU of D3 plus calcium 1000 mg carbonate, or placebo. After 7 years, the HRs were 1.04 for coronary disease and 0.95 for stroke. (Neither statistically significant) However, the dose of D was considered low, and compliance with taking D was low.

From a clinical perspective, a meta-analysis of 18 trials (over 57 000 individuals) found that D supplementation reduced all-cause mortality by 7%, with no evidence of heterogeneity. The effect on mortality in trials that used low-dose D (equal or less than 800 IU daily) was virtually identical to that of trial with high-doses. The trials included frail, elderly patients with low blood D levels, and a high rate of falls.
“Even with these limitations, this meta-analysis provides solid justification for conducting large randomized trials of high-dose vitamin D supplementation in general population settings.”

“The effect of vitamin D supplements on cardiovascular disease, diabetes, and hypertension remains uncertain. However, the available evidence in favor of vitamin D supplementation is far more promising than for other vitamins or mineral supplements.”

From a biological perspective, the presence of D receptors in many cell types and organs support the potential broad-ranging effects of D.

Debate about the optimal of D and the serum concentrations of 25(OH )D associated with optimal health is ongoing. Although circulating levels of 25(OH)D less than 20 nmol/L represent severe deficiency, and are likely to cause overt bone problems.

Two thresholds for deficiency have been proposed: less than 50 nmol/L and less than 75 nmol/L. With these definitions, up to one billion people in the world would be insufficient and would require high-dose supplements.

“We believe that the evidence for widespread use of high dose vitamin D supplementation in the general population remains insufficient.”

Trials of antioxidant vitamins have taught us that we cannot anticipate small risks of presumed safe interventions that, when applied to hundreds of millions of persons, could result in thousands of detrimental events.

We must define the optimal dose, the real benefits and potential harmful effects of supplementation. Enthusiasm for supplementation must be tempered by the loss of innocence from trials of antioxidant supplements that showed not only benefits, but also harms.

“Conducting large randomized trials of high-dose vitamin D should be a public health priority.”

Annals Internal Medicine March 2,2010; 152: 327-29  Editorial, first author Elisco Guallar, Johns Hopkins Bloomberg School of Public Health, Baltimore MD

1 Systematic Review: Vitamin D and Cardiometabolic Outcomes  Annals Internal Medicine March 2, 2010;152: 307-14  First author Anastassios G Pittas, Tufts University, Boston Mass

Conclusion: “The association between vitamin D status and cardiometabolic outcomes is uncertain.”

2 “Systematic Review: Vitamin D and Calcium Supplementation in Prevention of Cardiovascular Events Annals Internal Medicine March 2, 2010;152: 315-23  First author Lu Wang, Brigham and Women’s Hospital, Boston Mass
Conclusion “Evidence from limited data suggests that vitamin D at moderate to high doses may reduce CVD risk.”
Both studies were funded by the National Institutes of Health

“Increases Myocardial Salvage, And Has A Favorable Safety Profile.”

3-7 REMOTE ISCHAEMIC CONDITIONING BEFORE HOSPITAL ADMISSION AS A COMPLEMENT TO ANGIOPLASTY, AND EFFECT ON MYOCARDIAL SALVAGE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

After acute ST elevation myocardial infarction (STEMI), reduction of myocardial injury is best achieved by early reperfusion through primary percutaneous coronary intervention (PPCI). However, even when the procedure is done soon after symptom onset, significant myocardial injury may occur.

Remote ischemic preconditioning (RIP) induced by repeated brief periods of limb ischemia before index ischemia reduces myocardial injury in patients exposed to predictable ischemia.

These investigators have shown that conditioning by intermittent limb ischemia after the onset of myocardial ischemia, and before reperfusion reduces infarct size in a porcine model.

RIP preconditioning attenuates cardiac injury at elective surgery and angioplasty.

RIP is a simple procedure: 1) applying a BP cuff to the arm and inflating to 200 mm Hg and continuing inflation for 5 minutes. 2) Deflating the cuff and leaving it deflated for 5 minutes. 3) repeating the cycle a total of 4 times (total of 40 minutes if the final deflation period of 5 minutes is included). The procedure can be applied immediately after symptoms of a suspected MI occur. It may be given by ambulance or other personnel at the scene and continued during transport.

The study tested the hypothesis that RIP during evolving STEMI, and done before primary percutaneous intervention, increases myocardial salvage.

Used 99technicium CT myocardial imaging to examine whether RIP done before PPCI increases myocardial salvage in patients with an evolving first MI.

STUDY
1. Randomly assigned 333 consecutive patients with a suspected first acute MI. All were admitted to hospital within 12 hours of onset of pain. All had ST elevation in the first ECG recorded on the scene.
2. Randomized telemedically to: 1) RIP, and 2) no RIP. Patients received RIP during transport to
the hospital, started by ambulance personnel. If the 4 cycles were not completed in the ambulance the cycle was completed in the hospital.

3. Before PPCI, all received 99technicium to quantify the area at risk of infarction with a photon-emission CT. All then received PPCI. The injection of 99technicium and scan were repeated at 30 days to determine a myocardial salvage index.

5. The primary outcome was myocardial salvage index at 30 days after PPCI measured by myocardial perfusion imaging as the proportion of the area at risk salvaged by treatment. Salvage index was calculated as (area at risk - final infarct size) / area at risk.

RESULTS
1. 82 patients did not fulfill entry requirements. They were excluded, leaving 251 for analysis.
2. Of the 251 patients, paired scans were available to calculate the salvage index in 142.
3. Median salvage index was 0.75 (IQR 0.50-0.93; n = 73) in the RIP group vs 0.55 (IQR 0.35-0.88; n = 69) in controls.
4. Mean salvage index was 0.69 vs 0.57, a difference of 0.12.
5. Salvage as a percentage of left ventricle was (statistically) significantly higher in the RIP group (16% vs 11%). Differences in final infarct size were not significant (median 7% of left ventricle in both groups).
6. Peak troponin T release, the proportion of patients achieving 70% ST segment resolution within 90 minutes, and NYHA class of disease at 30 days did not differ between groups.
7. Major adverse coronary events were the same in each group: 3 deaths; 1 reinfarction; 3 heart failure.

DISCUSSION
1. “Our study shows that remote ischaemic conditioning, induced by intermittent upper arm ischaemia and done before primary percutaneous coronary intervention can attenuate reperfusion injury in patients with evolving myocardial infarction, thereby resulting in increased myocardial salvage.”
2. “Since the safety profile of remote conditioning is favourable, no patient should be denied this treatment.”
3. “The intervention’s simplicity, low cost and effectiveness make it attractive for testing in large-scale clinical trials.”
CONCLUSION

“Remote ischemic conditioning before hospital admission increases myocardial salvage, and has a favorable safety profile.”

Lancet, February 27, 2010; 375L 727-34  Original investigation, first author Hans Erik Betker, Aarhus University Hospital Skejby, Aarhus N, Denmark.

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Reduces Incidence Of Pneumonia And Death From Pneumonia. But Should We Recommend It?

3-8  EFFICACY OF A 23-VALENT PNEUMOCOCCAL VACCINE IN PREVENTING PNEUMONIA AND IMPROVING SURVIVAL IN NURSING HOME RESIDENTS

Pneumonia-related morbidity and mortality are high in nursing homes (NH). *S. Pneumoniae* is the most common pathogen.

The vaccine is generally recommended for those at high risk of pneumococcal pneumonia, but the vaccination rate in patients in NH is low, perhaps because there is little evidence of it’s efficacy. Most evidence is based on studies in the community.

In Japan, incidence of pneumococcal pneumonia in NH is about 20 times that in elderly community-dwelling persons.

This trial determined the efficacy of a 23-valent vaccine in NH in Japan.

STUDY

1. Randomized 1006 NH residents to: 1) 23-valent vaccine [*Pneumovax; Merck*] or 2) placebo [saline injection].
2. At baseline, about 90% of subjects were over age 75; 47% age 85-94; 9% age 95-1005. About 10% were bedridden, 5% had a “psychological disorder”. The majority had 1 to 3 or more co-morbid conditions. Written informed consent was obtained from participants or their next of kin.
3. Excluded patients who were immunocompromised and those who were unable to follow instructions.
4. All participants received a medical examination once weekly during the study.
5. Pneumonia was diagnosed on the basis of clinical symptoms and chest X-ray. Pneumococcal infection was diagnosed by blood culture, sputum culture, and/or antigen test in urine.
6. Primary endpoints were incidence of all-cause pneumonia and pneumococcal pneumonia.
7. Follow-up for 3 years.
RESULTS

1. Incidence of pneumonia over 3 years:* Vaccine (n = 502) Placebo (n =504)
   Pneumococcal 14 37
   Non-pneumococcal** 49 67
   All-cause pneumonia 63 104

   (* First episode only. Some had multiple episodes of pneumonia. **Non-pneumococcal pneumonia was caused by Staph aureus; Enterobacteriaceae, H influenza. and P aeruginosa)

2. No person in the vaccine group developed invasive pneumococcal disease (+ blood culture).
   Three in the placebo group did.

3. Death rates
   Pneumococcal pneumonia 0/14 13/37
   Non-pneumococcal pneumonia 13/49 13/67
   All cause pneumonia 13/63 26/104

4. Overall, 80 patients in each group died from all causes. (No difference between groups.)

5. There were no serious adverse effects from the vaccine

DISCUSSION

1. “The 23-valent pneumococcal polysaccharide vaccine significantly prevented pneumococcal pneumonia and reduced death from pneumococcal pneumonia in nursing home residents.”

2. The death rates from all-cause pneumonia and non-pneumococcal pneumonia and the incidence of non-pneumococcal pneumonia were not significantly reduced in the vaccine group.

3. Overall, death rates did not differ between groups.

4. Evidence for the efficacy of the 23-valent vaccine has been mainly obtained from studies on patients with community-acquired pneumonia. A large community-based cohort study reported a 29% reduction in the incidence of all-cause pneumonia, a 44% reduction in the incidence of invasive pneumococcal infection, and a 35% reduction in death from all-cause pneumonia.

5. However, recent under-powered randomized, controlled trials were unable to show efficacy of the vaccine.

6. Because of a steadily increasing elderly population in developed countries, nursing homes are often over-crowded. The incidence of infectious diseases such as pneumonia is common in elderly populations because of their impaired host defense mechanisms.

7. “The findings of this study suggest the need for a national policy that recommends the systematic
vaccination of residents living in institutions to reduce morbidity as well as the cost of health care in Japan.”

CONCLUSION

The 23-valent pneumococcal vaccine prevented pneumococcal pneumonia and reduced mortality from pneumococcal pneumonia in nursing home residents.


“Research” original investigation, first author Takaya Maruyama Mie University Graduate School of Medicine, Japan.