Update in General Internal Medicine

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Benefits of statin therapy

Effect of very high-intensity statin therapy on regression of coronary atherosclerosis. The ASTEROID Trial

BACKGROUND:
Prior intravascular ultrasound (IVUS) trials have demonstrated slowing or halting of atherosclerosis progression with statin therapy but have not shown convincing evidence of regression using percent atheroma volume (PAV), the most rigorous IVUS measure of disease progression and regression.

AIM:
To determine if high-intensity statin therapy, reaching very low levels of LDL-C in conjunction with substantial elevations of HDL-C, will result in regression of coronary atherosclerosis.

METHODS:
Open label, non-placebo controlled, blinded end-point study funded by the pharmaceutical manufacturer enrolling from 53 community and tertiary centers in the United States, Canada, Europe, and Australia from November 2002 to October 2003.

Patients were at least 18 years old and had a clinical indication for coronary angiogram that demonstrated at least 1 obstruction with greater than 20% luminal diameter narrowing. The target vessel could not have undergone previous angioplasty nor have greater than a 50% narrowing throughout the target segment of at least 40 mm. The patients were “statin-naïve,” defined as no more than 3 months during the previous 12 months. If taking a statin within 4 weeks of enrollment, they had a 4-week washout period. Patients with uncontrolled triglyceride levels (>500 mg/dL) or poorly controlled diabetes (A1c >10%) were excluded.

Of 1183 patients screened, 507 (42.9%) received rosuvastatin 40 mg/d, but only 349 (68.8% of enrolled) had IVUS data that could be evaluated. IVUS was performed at baseline and at the end of the 24-month trial. The primary endpoints were the percent atheroma volume (PAV) and nominal change in total atheroma volume (TAV) in the 10mm subsegment of the coronary artery with the largest plaque volume (most diseased segment).

RESULTS:
There was a statistically significant decrease in the median PAV and median TAV. Additionally, mean LDL-C decreased and HDL-C increased (see table). Elevated ALT >3x ULN and elevated CK >5x ULN on 2 consecutive visits occurred in 0.2% and 0.2% of patients, respectively.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>% Change</th>
<th># (% regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAV</td>
<td>Mean (S.D.)</td>
<td>39.6 (8.5)</td>
<td>38.6 (8.5)</td>
<td>-0.98 (3.15)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>39.9 (33.8-45.3)</td>
<td>38.5 (32.6-44.3)</td>
<td>-0.79 (-1.2to -0.5)*</td>
<td>NA</td>
</tr>
<tr>
<td>TAV</td>
<td>Mean (S.D.)</td>
<td>65.1 (27.0)</td>
<td>59.0 (24.5)</td>
<td>-6.1 (10.1)</td>
<td>-8.5 (13.7)</td>
</tr>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>65.1 (45.2-82.2)</td>
<td>58.4 (40.6-76.3)</td>
<td>-5.6 (-6.8 to -4.0)*</td>
<td>-9.1 (-10.8 to -7.2)*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Mean (S.D.)</td>
<td>130.4 (34.3)</td>
<td>60.8 (20.0)</td>
<td>-53.2% (-55.6 to -50.9)*</td>
<td>14.7% (12.3 to 17.1)*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Mean (S.D.)</td>
<td>43.1 (11.1)</td>
<td>49.0 (12.6)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001

CONCLUSIONS:
In patients with documented coronary artery disease, treatment with highest dose rosuvastatin is associated with a reduction of percent atheroma volume and total atheroma volume.

LIMITATIONS:
The study was unblinded and without control. Although the authors comment that a placebo or low intensity statin was ethically unacceptable, current national guidelines would allow a goal LDL-C of <100 mg/dL in many of the included patients. Since the mean LDL-C in the trial was 130 mg/dL, an average reduction of 23% would have been required, which could have been accomplished by a lower dose statin. Inclusion criteria required the patient to have
High-dose atorvastatin after stroke or transient ischemic attack

BACKGROUND:
Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease, whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established.

AIM:
To determine whether atorvastatin 80 mg given daily would reduce the risk of stroke in patients with no known coronary heart disease who had had a stroke or TIA within the previous six months.

METHODS:
Double blind, placebo-controlled, randomized trial funded by the pharmaceutical manufacturer enrolling from 205 centers in Australia, Africa, Europe, North America, Central America, and South America from September 1998 to March 2001.

Eligible patient were over 18 years of age and had an ischemic or hemorrhagic stroke or TIA (diagnosed by a neurologist within 30 days after the event) 1 to 6 months before randomization.  Patients were ambulatory, had a modified Rankin score of 3 or less, and had an LDL-C level greater than or equal to 100 mg/dL and less than or equal to 190 mg/dL.  Patients with atrial fibrillation, other cardiac sources of embolism, and subarachnoid hemorrhage were excluded.  All lipid lowering medications were stopped 30 days before screening.

Of 6670 screened, 4731 (70.9%) were randomized to receive 80 mg of atorvastatin (n=2365) or placebo (n=2366).  The primary endpoint was time to first nonfatal or fatal stroke.  There were multiple secondary endpoints.

RESULTS:
After a median 4.9 years of follow-up, the primary endpoint occurred in 265 (11.2%) of the atorvastatin group and 311 (13.1%) of the placebo group.  After controlling for prespecified baseline factors, atorvastatin was associated with a 16.0% relative reduction (HR, 0.84; 95% CI, 0.71 to 0.99; p=0.03).  Atorvastatin was also associated with a significant decrease in secondary outcomes, including major coronary events, major cardiovascular event, acute coronary event, any coronary event, revascularization, and any cardiovascular event, but no difference in overall mortality.  Post-hoc analysis revealed that atorvastatin was associated with different treatment effects based on the type of stroke: ischemic stroke (HR, 0.78; 95% CI, 0.66-0.94), hemorrhagic stroke (HR, 1.66; 95% CI, 1.08-2.55), and unclassified stroke (HR, 0.55; 95% CI, 0.21-1.40).  Persistently elevated ALT or AST >3x ULN on 2 consecutive visits occurred more frequently in the atorvastatin group.

CONCLUSIONS:
In patients with a recent history of stroke or TIA and no known history of coronary artery disease, treatment with highest dose atorvastatin reduced the risk of subsequent stroke and coronary and cardiovascular events.  The difference in all strokes was seen in fatal stroke, not nonfatal stroke.  However, there was an increase in the risk of
abnormal liver enzymes and hemorrhagic stroke, the latter also seen in the Heart Protection Study. In contrast, the HPS found no difference in stroke; however, patients were enrolled much later after their initial event.

LIMITATIONS:
Because stroke and coronary artery disease share many risk factors, one may suggest that patients with cerebrovascular disease have CAD. The average patient was higher risk (63-year-old, overweight male, and approximately 62% had hypertension, 60% were current or former smokers, 17% were diabetic) and would likely require reduction of LDL-C. Again, one can question the use of placebo in this trial. Additionally, we are unable to formulate conclusions on a target LDL-C.

RELATED ARTICLES:

IMPACT ON MEDICINE:
HMG-CoA reductase inhibitor therapy is the mainstay for management of hyperlipidemia. In the SPARCL trial, patients with stroke or TIA had no known, but at high risk for having, coronary artery disease, had a significant reduction in fatal and nonfatal stroke. As expected, the patients also had a reduction in cardiovascular endpoint, although they were secondary endpoints. However, it did show an increase in incidence of hemorrhagic stroke, which was also evident in the Heart Protection Trial. Given this possible risk, providers must weigh the risks and benefits of highest dose statin therapy. The ASTEROID trial is the first published trial demonstrating that we may be able to halt the progression or cause regression of atherosclerotic disease of the coronary vessels in “statin naïve” patients. Although this is a very intriguing endpoint, we still await the correlation with hard endpoints. Neither study used an active control; therefore we cannot conclude that a different dose or different statin would not have produced the same results. The additional studies evaluated surrogate endpoints, such as change in proteinuria or ejection fraction, thus we must wait for the longer term studies evaluating time to dialysis, doubling of creatinine, or cardiovascular mortality. It is well known that, in addition to lowering lipids, statins have other pleiotropic effect, such as being anti-inflammatory and antithrombotic. These studies would suggest that there are additional indications for HMG-CoA reductase inhibitor therapy.

Diabetes Mellitus

Prevention of diabetes mellitus

Effect of ramipril on the incidence of diabetes. The DREAM trial

BACKGROUND:
Previous studies have suggested that blockade of the renin-angiotensin system may prevent diabetes in people with cardiovascular disease or hypertension.

AIM:
To evaluate whether ramipril reduces the risk of diabetes in people who have impaired fasting glucose (IFG) levels or impaired glucose tolerance (IGT), but who are at low risk for cardiovascular event.

METHODS:
Double-blind, placebo-controlled, randomized trial with a 2x2 factorial design (ramipril and rosiglitazone) funded by the pharmaceutical manufacturer and the Canadian Institutes of Health Research enrolling from 191 centers from Australia, Asia, Europe, Central America, South America, and North America between July 2001 to August 2003.
Eligible patients were 30 years of age with impaired fasting glucose (>110 mg/dL but <126 gm/dL) or impaired glucose tolerance (>140 mg/dL but <200 mg/dL, 2 hours after a glucose load) and no history of diabetes, cardiovascular disease, or intolerance of either angiotensin-converting enzyme inhibitors or thiazolidinediones.

Of 24,592 patient screened, 5808 entered the run-in phase, and 5269 were randomly assigned to receive ramipril (dose increased from 5 mg/d to 15 mg/d at 1 year) or placebo. The primary endpoint was newly diagnosed diabetes or death.

RESULTS:
After a median of 3.0 years of follow-up, there was no significant difference in the primary outcome (see table). By the end of the study only 72.7% and 78.0% were taking ramipril and placebo study medication, respectively. The primary endpoint occurred in 18.1% of patient taking ramipril and 19.5% of those taking placebo (HR 0.91; 95% CI 0.81-1.03; P=0.15). Of the secondary endpoints, a greater proportion of patient had a regression to normoglycemia in the ramipril group (42.5% versus 38.2%, P=0.001) and the 2-hour postprandial glucose levels were significantly lower in the ramipril group (135.1 mg/dL vs. 140.5 mg/dL, P=0.01). Median fasting glucose, cerebrovascular events, and the number of hospitalizations were not different.

CONCLUSIONS:
Use of up to 15 mg of ramipril daily for 3 years does not significantly prevent diabetes or death in patients with impaired glucose tolerance or impaired fasting glucose and without cardiovascular disease. However, it did demonstrate an increase in regression to normal glucose levels.

LIMITATIONS:
Glucose levels were not available for 7.4% of the patients. Depending upon the distribution of missing data, the results could change in either direction. Assuming that a proportion of patients with either IFG or IGT will progress to overt diabetes over time, these results may slightly underestimate the actual rates. Additionally, there was no comment on side effects that may have revealed the treatment assignment to study personnel, possibly leading to difference in management. The authors note that although there was no statistical significance, the Kaplan-Meier curves appeared to diverge at 3.5 years. Therefore, the true difference may be evident after 4 years.

RELATED ARTICLE:
Barzilay JI, Davis BR, Cutler JA, et al. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes or antihypertensive treatment. Arch Intern Med 2006;166:2191-2201. [PMID: 17101936]

IMPACT ON MEDICINE:
Although previous studies demonstrate a decrease in diabetes incidence, it was evident only in secondary or post-hoc analysis, as is the one from the ALLHAT. The well-designed DREAM study refutes these data and proves that ramipril does not decrease new onset diabetes or death over a 3-year period. The unanswered questions are whether other antihypertensive medication increase risk of developing diabetes, and ultimately if they lead to difference in clinical outcomes. Patients should be counseled on lifestyle changes, particularly calorie reduction and regular exercise, to prevent the development of diabetes.

Management of diabetes mellitus

Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy

BACKGROUND:
The efficacy of thiazolidinediones, as compared with other oral glucose-lowering medications, in maintaining long-term glycemic control in type 2 diabetes is not known.

AIM:
To evaluate the durability of glycemic control in patients receiving monotherapy with a thiazolidinedione, rosiglitazone; a biguanide, metformin; or a sulfonylurea, glyburide in patients with recently diagnosed type 2 diabetes who had not received previous pharmacologic treatment

METHODS:
Double-blind, active controlled, randomized trial sponsored by the pharmaceutical manufacturer enrolling at 488 centers in the United States, Canada, and Europe between April 2000 and June 2002. The protocol was amended in March 2002 to increase the sample size due to a higher than expected drop out rate.

Patients were ages of 30 to 75 years old, with fasting plasma glucose between 126 and 180 mg/dL. Exclusion criteria were clinically significant hepatic disease, renal impairment, a history of lactic acidosis, unstable or severe angina, known congestive heart failure, or uncontrolled hypertension.

Of 6676 patient screened, 4360 initially randomized, 9 did not receive study drug, and 224 withdrew before first scheduled efficacy evaluation, yielding 4127 (95%) patients for analysis. They received initial daily doses of 4 mg rosiglitazone, 500 mg of metformin, or 2.5 mg glyburide. If the patients fasting blood glucose was greater than 140 mg/dL, the doses were increased to a maximum of 4 mg of rosiglitazone twice a day, 1 gm of metformin twice a day, or 7.5 mg of glyburide twice a day. The primary endpoint was time to treatment failure, defined as a fasting plasma glucose >180 mg/dL on consecutive testing after at least 6 weeks of treatment at the maximum dictated or tolerated dose.

RESULTS:
After a median 4.0 years of follow-up, monotherapy failed in 143 patients who received rosiglitazone (2.9 per 100 pt-yrs), 207 who received metformin (4.3 per 100 pt-yrs), and 311 who received glyburide (7.5 per 100 pt-yrs).

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure (cumulative incidence)</td>
<td>15%</td>
<td>21%</td>
<td>0.68 (0.55-0.85)</td>
<td>&lt;0.001</td>
<td>17</td>
<td>34%</td>
<td>0.37 (0.30-0.45)</td>
<td>&lt;0.001</td>
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<tr>
<td>A1c&lt;7% @ 4yrs</td>
<td>40%</td>
<td>36%</td>
<td>0.03</td>
<td>26%</td>
<td>&lt;0.001</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt change (kg) @ 5 yrs</td>
<td>+4.8</td>
<td>-2.9</td>
<td>&lt;0.001</td>
<td>+1.6</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

SELECTED AEs

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
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<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular event</td>
<td>62 (4.3%)</td>
<td>58 (4.0%)</td>
<td>NS</td>
<td>--</td>
<td>26 (1.8%)</td>
<td>≤0.05</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>22 (1.5%)</td>
<td>19 (1.3%)</td>
<td>NS</td>
<td>--</td>
<td>9 (0.6%)</td>
<td>≤0.05</td>
<td>167</td>
<td></td>
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</tr>
<tr>
<td>GI events</td>
<td>335 (23.0%)</td>
<td>557 (38.3%)</td>
<td>≥0.01</td>
<td>7</td>
<td>316 (21.9%)</td>
<td>NS</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>142 (9.8%)</td>
<td>168 (11.6%)</td>
<td>NS</td>
<td>--</td>
<td>557 (38.7%)</td>
<td>≥0.01</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>100 (6.9%)</td>
<td>18 (1.2%)</td>
<td>≥0.01</td>
<td>18</td>
<td>47 (3.3%)</td>
<td>≥0.01</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb fx, women</td>
<td>36 (5.6%)</td>
<td>18 (3.1%)</td>
<td>&lt;0.05</td>
<td>40</td>
<td>8 (1.3%)</td>
<td>≤0.01</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limb fx, women</td>
<td>36 (5.6%)</td>
<td>18 (3.1%)</td>
<td>≤0.05</td>
<td>40</td>
<td>8 (3.3%)</td>
<td>≤0.01</td>
<td>24</td>
<td></td>
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</tbody>
</table>

<0.01 4
P values compare to metformin, rosiglitazone, and glyburide.

Secondary analysis suggested that glyburide had the greatest decline in fasting plasma glucose and glycosylated hemoglobin within the first 6 months, but then increased the greatest rate. Both endpoints were significantly higher in glyburide than metformin and rosiglitazone at 5 years. Rosiglitazone maintained a significantly higher level of insulin sensitivity throughout the trial, and although demonstrated an increase in beta-cell function within the first year, the difference was not significant compared to glyburide by the end.

CONCLUSIONS:
Patients with type 2 diabetes mellitus, initially treatment with rosiglitazone slowed progression to monotherapy failure more effectively than metformin or glyburide. The relative costs of these medications, their profiles of adverse events, and their potential risks and benefits should be considered in making an informed decision.

LIMITATIONS:
An average of 4.5 patients were enrolled per site, which may suggest that it is a select population. The percentage of patients that withdrew from the study was large, 37%, 38%, and 44% receiving rosiglitazone, metformin, and glyburide, respectively. This number was not explained solely by the side effects of the medication and can significantly affect the results. Additionally, in practice, glycosylated hemoglobin level, not a FG of 180, usually
defines inadequate control and guides therapy changes. Lastly, although the maximum dose of rosiglitazone could be used, this was not the case for metformin or glyburide.

**IMPACT ON INTERNAL MEDICINE:**

There is no perfect medication. Rosiglitazone appears to produce the fewest monotherapy failures, but was associated with greater weight gain and a higher LDL-C resulting in greater use of diuretics and statins. Glyburide had the greatest number of failures and more than a third of the patients complained of hypoglycemic symptoms, but it was associated with the fewest cardiovascular events, particularly congestive heart failure. Metformin was associated with gastrointestinal events in more than a third of patients. This study corroborates previous data demonstrating a decline in beta-cell function in patients with diabetes mellitus, leading to an increase in fasting glucose and glycosylated hemoglobin, and ultimately to monotherapy failures. Those patients on medications known to affect insulin resistance fared better than those on a sulfonylurea. At 4 years, the percentage of subjects with an A1c <7% was also greatest in the rosiglitazone arm. Although we can infer from the improved glycemic control, we cannot assume, that starting with a specific monotherapy will have an effect on longer-term outcomes, such as incidence of retinopathy and nephropathy. Lastly, the study was not designed to determine the best second agent, as many patients require 2 or 3 oral medications.

**Effects of quality improvement strategies for type 2 diabetes on glycemic control. A meta-regression analysis.**


**BACKGROUND:**

There have been numerous reports of interventions designed to improve the care of patients with diabetes, but the effectiveness of such interventions is unclear.

**AIM:**

To assess the impact on glycemic control of 11 different categories of QI strategies to identify those that significantly augment intervention effectiveness.

**METHODS:**

Searching MEDLINE, EMBASE, and CINAHL, randomized controlled trials, quasi-randomized trials, and controlled before-after studies involving adult outpatients with type 2 diabetes were included if it conducted one of the following interventions: audit and feedback, case management, team changes, electronic patient registry, clinician education, clinician reminder, facilitated relay of clinical information to clinician, patient education, promotion of self-management, patient reminder systems, or continuous quality improvement. Fifty-eight studies, that included 66 studies, were analyzed.

**RESULTS:**

The mean decrease in A1c was 0.42% (95% CI, 0.29%-0.54%) over 13 months. Although all interventions except clinician reminders and continuous quality improvement, lead to a significant decrease in A1c levels, only team changes (0.33%, 95% CI 0.12%-0.54%) and case management (0.22%, 95% CI 0.00%-0.44%) remained statistically significant in the meta-regression model. Of the key components of case management, a post hoc analysis revealed that the ability to independently make medications changes increased its effectiveness.

**CONCLUSIONS:**

Most of the improvement strategies studied decreased A1c levels, although only to a modest degree. Case management, especially when managers were able to independently modify medications, and team changes demonstrated more robust improvements.

**LIMITATIONS:**

Because of the complexity of the interventions, there may have been misclassification and confounders that would have led to the differences. The primary studies were of modest sample sizes and had methodological shortcomings; and, there was a suggestion of publication bias, for which the authors controlled. Additionally, there were multiple comparisons without adjustment. No economic analysis was conducted.
Providing optimal care to our patients with chronic diseases, such as diabetes mellitus, is difficult. This meta-regression analysis supports the benefits of a multidisciplinary team in chronic disease management. Although the effect on A1c was modest, the majority of strategies were beneficial. However, adaptation and implementation of such strategies will require addition of resources.

**Recently Approved Medications**


This meta-analysis examined the efficacy, safety and patient acceptability of inhaled insulin therapy in nonpregnant adults with diabetes. Sixteen randomized, controlled trials were identified in MEDLINE and the Cochrane Controlled Clinical Trial Register. Subcutaneous insulin demonstrated a significant decrease in A1c (0.08%, 95% CI, 0.03%-0.14%) in patients with type 1 or type 2 diabetes. It was also favored in the longer-term studies (104 weeks) and type 1 diabetes. When compared to oral hypoglycemic agents, inhaled insulin resulted in a significant decrease in A1c (1.04%, 95% CI, 0.49%-1.59%). The percent of patients achieving a goal A1c <7% was significantly greater when compared to the oral hypoglycemic agents (30.9% vs. 16.9%) but not compared to subcutaneous insulin (27.1% vs. 24.6%). Severe hypoglycemia occurred in equal frequency between the insulin groups, but significantly more frequently than the oral hypoglycemic agent (9.4% vs. 3.5%). Cough was the most common pulmonary complaint (16.9% vs. 5.0%). Patient satisfaction was higher comparing inhaled to subcutaneous insulin. The studies included had methodological shortcomings, including no blinding and were short-term, <24 weeks.


These randomized, double-blind, placebo-controlled study compared the efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor, sitagliptin, added to ongoing pioglitazone or metformin therapy or as monotherapy in patients with type 2 diabetes and inadequate glycemic control. Adult patients with an A1c ≥7% and ≤10%, were randomized to receive a daily dose of 100 mg sitagliptin or placebo (add on trials) or sitagliptin 100 or 200 mg or placebo (monotherapy trial). The mean baseline A1c was approximately 8.1%. At 24 weeks, addition of sitagliptin to pioglitazone and metformin significantly decreased A1c by -0.70% and -0.68%, respectively. In the monotherapy trial, sitagliptin 100 and 200 mg significantly reduced A1c by -0.79% and -0.94%, respectively. Other measures of glucose metabolism were significantly affected; and, the proportion reaching target A1c was increased in the sitagliptin group. Sitagliptin was generally well tolerated, with no increased risk of hypoglycemia.

**Surgical management of obesity**

Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program

BACKGROUND:
Obesity is a major, growing health problem. Observational studies suggest that bariatric surgery is more effective than nonsurgical therapy, but no randomized, controlled trials have confirmed this.

AIM:
To ascertain whether surgical therapy for obesity achieves better weight loss, health, and quality of life than nonsurgical therapy.

METHODS:
Randomized, controlled trial in university departments of medicine and surgery and an affiliated private hospital. Eighty adults with mild to moderate obesity (body mass index, 30 kg/m² to 35 kg/m²) from the general community. Patients were assigned to a program of very-low-calorie diets, pharmacotherapy, and lifestyle change for 24 months (nonsurgical group) or to placement of a laparoscopic adjustable gastric band (LAP-BAND System, INAMED Health, Santa Barbara, California) (surgical group). The primary outcomes measures were weight change, presence of the metabolic syndrome, and change in quality of life at 2 years.

RESULTS:
At 2 years, the surgical group had greater weight loss, with a mean of 21.6% (95% CI, 19.3% to 23.9%) of initial weight lost and 87.2% (95% CI, 77.7% to 96.6%) of excess weight lost, while the nonsurgical group had a loss of 5.5% (95% CI, 3.2% to 7.9%) of initial weight and 21.8% (95% CI, 11.9% to 31.6%) of excess weight (P < 0.001). The metabolic syndrome was initially present in 15 (38%) patients in each group and was present in 8 (24%) nonsurgical patients and 1 (3%) surgical patient at the completion of the study (P < 0.002). Quality of life improved statistically significantly more in the surgical group (8 of 8 subscores of Short Form-36) than in the nonsurgical group (3 of 8 subscores).

CONCLUSIONS:
Surgical treatment using laparoscopic adjustable gastric banding was statistically significantly more effective than nonsurgical therapy in reducing weight, resolving the metabolic syndrome, and improving quality of life during a 24-month treatment program.

LIMITATIONS:
The study was limited to mildly and moderately obese participants and was not powered for comparison of adverse events. This is important, as surgical treatment is not currently indicated in this population. In addition, while outcomes were measured at 24 months, the authors do not describe the lifestyle and pharmacological treatment administered to patients for maintenance after the first 6 months.

IMPACT ON INTERNAL MEDICINE:
Laparoscopic gastric banding is effective treatment for mild to moderate obesity. However, practitioners should not overlook the importance of limited weight loss (i.e. 5% to 10%) on comorbidities such as hypertension or diabetes. It is still unclear in which patients with mild to moderate obesity the benefits of surgical weight loss outweighs the risk of the surgical procedure itself. Until further information is available, this procedure should be limited to patients who fail lifestyle modification in whom significant medical complications are likely to improve with this intervention.

Vascular Medicine

Cardiovascular disease

Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events

BACKGROUND:
Dual antiplatelet therapy with clopidogrel plus low-dose aspirin has not been studied in a broad population of patients at high risk for atherothrombotic events.
AIM:
To demonstrate the efficacy of long-term treatment with a combination of clopidogrel plus aspirin over aspirin alone in the reduction of cardiovascular events in a high-risk population.

METHODS:
This industry-sponsored trial randomly assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Patients were excluded from the trial if they were on long-term NSAIDs or oral anticoagulants.

RESULTS:
The rate of the primary efficacy end point was 6.8 percent with clopidogrel plus aspirin and 7.3 percent with placebo plus aspirin (RR, 0.93; 95% CI, 0.83 to 1.05; P=0.22). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7% and 17.9% (RR, 0.92; 95% CI, 0.86 to 0.995; P=0.04), and the rate of severe bleeding was 1.7% and 1.3% (RR, 1.25; 95% CI, 0.97 to 1.61%; P=0.09). The rate of the primary end point among patients with multiple risk factors was 6.6% with clopidogrel and 5.5% with placebo (RR, 1.2; 95% CI, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel (3.9% vs. 2.2%, P=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel and 7.9% with placebo (RR, 0.88; 95% CI, 0.77 to 0.998; P=0.046).

CONCLUSIONS:
In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.

LIMITATIONS:
Well-designed industry sponsored study. The predetermined subgroups described in this study are difficult to translate into clinical practice and the blur the applicability of this study.

IMPACT ON INTERNAL MEDICINE:
While the addition of clopidogrel to aspirin has demonstrated major incremental clinical benefits in the setting of acute vascular injury (i.e. acute coronary syndrome, COMMIT trial) and has even supplanted ticlopidine for reduction of restenosis and cardiovascular events after stent placement, this short-term benefit has been extrapolated to long-term use clopidogrel in clinical practice. The results of this trial in combination with the results of other trials (i.e. ACTIVE and MATCH) convincingly demonstrate no benefit and potential harm of dual therapy when used long-term for primary prevention of CAD or secondary prevention in patients with stable disease.
417 men and women with PAD were evaluated in this prospective cohort study with a median follow-up of 36 months (interquartile range, 24 to 36 months) in academic medical center. Participants were classified at baseline and annually according to the number of times they reportedly walked for exercise each week. Functional assessments (6-minute walk distance, 4-meter walking speed, summary performance score) were measured at baseline and annually. Results were adjusted for age, sex, ethnicity, comorbid conditions, body mass index, ankle–brachial index, education, leg symptoms, cigarette use, geriatric depression score, previous year's level of functioning, and patterns of missing data.

RESULTS:
Compared with those who exercised less frequently, patients who walked for exercise 3 or more times per week had a significantly smaller average annual decline in 6-minute walking distance (–48.0 feet per year compared with –56.6 feet per year for those who walked 1 to 2 times per week and –79.4 feet per year for nonexercisers; P for trend = 0.037). Patients who walked for exercise at least 3 times per week experienced a smaller average annual decline in the usual-paced 4-meter walking velocity (–0.014 m/s per year compared with –0.022 m/s per year for those who walked 1 to 2 times per week and –0.045 m/s per year for nonexercisers; P = 0.005). Similar findings were observed for the fast-paced 4-meter walk. The subset of asymptomatic patients who walked for exercise 3 or more times per week had annual declines in 6-minute walking performance (P = 0.107), normal-paced walking velocity (P = 0.065), and the summary performance score (P = 0.115); however, these declines were smaller than those observed in asymptomatic participants who walked fewer than 3 times per week.

CONCLUSIONS:
Among patients with PAD, self-directed walking exercise performed at least 3 times weekly is associated with significantly less functional decline during the subsequent year. Similar trends were observed in the subset of asymptomatic patients with PAD. These findings may be particularly important for the numerous patients with PAD who do not have access to supervised walking exercise programs.

LIMITATIONS:
Because this was an observational study, associations reported here cannot be construed as causal relationships. Specifically, the authors did not control for the use of other interventions such as the use of pentoxyphylline and cilastazol. In addition, sample sizes for subgroup analyses were small, which limited statistical power.

IMPACT ON INTERNAL MEDICINE:
Self-directed walking for exercise may benefit a much larger proportion of patients with PAD than is currently being served by supervised rehabilitation programs and should be recommended in patients with symptomatic PAD.

Ramipril markedly improves walking ability in patients with peripheral arterial disease

BACKGROUND:
Peripheral arterial disease (PAD) affects up to 12% of adults older than 50 years of age. Conventional therapies have only modest effects in improving symptoms.

AIM:
To examine the effects of angiotensin-converting enzyme inhibition on walking ability in patients with PAD.

METHODS:
Randomized, double-blind, placebo-controlled trial initiated in March 2003 and completed in January 2005 in the Alfred Hospital, Melbourne, Australia. Forty older adults with symptomatic PAD and no history of diabetes or hypertension received 10 mg of ramipril (n = 20) or placebo (n = 20) once daily for 24 weeks. All patients completed the trial. Pain-free and maximum walking time were recorded during a standard treadmill test, and the standard Walking Impairment Questionnaire was administered.

RESULTS:
After adjustment for the baseline pain-free walking time, mean pain-free walking time after ramipril treatment was 227 seconds (95% CI, 175 seconds to 278 seconds; P < 0.001) longer than that after placebo treatment. Similarly,
maximum walking time improved by 451 seconds in the ramipril group (CI, 367 seconds to 536 seconds; P < 0.001) but did not change in the placebo group. Ramipril improved the Walking Impairment Questionnaire median distance score from 5% (range, 1% to 39%) to 21% (range, 12% to 58%; P < 0.001), speed score from 3% (range, 3% to 39%) to 18% (range, 8% to 50%; P < 0.001), and stair-climbing score from 17% (range, 4% to 80%) to 67% (range, 38% to 88%; P < 0.001). No adverse events were reported.

CONCLUSIONS:
Ramipril improved pain-free and maximum walking time in some adults with symptomatic PAD.

LIMITATIONS:
The sample size is modest, and the strict inclusion criteria limit the applicability of the results to nondiabetic patients with claudication and infrainguinal disease with restricted mobility and limited exercise tolerance. The study population represents approximately 50% of patients with PAD.

IMPACT ON INTERNAL MEDICINE:
In addition to reducing cardiovascular morbidity and mortality in patients with PAD, ramipril may improve symptoms in patients with PAD.

Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis

AIM:
Carotid artery stenting (CAS) is less invasive than carotid endarterectomy (CEA), but it is unclear whether it is as safe in patients with symptomatic carotid-artery stenosis.

METHODS:
We conducted a multicenter, randomized, noninferiority trial to compare stenting with endarterectomy in patients with a symptomatic carotid stenosis of at least 60%. The primary end point was the incidence of any stroke or death within 30 days after treatment.

RESULTS:
The trial was stopped prematurely after the inclusion of 527 patients for reasons of both safety and futility. The 30-day incidence of any stroke or death was 3.9% after CEA (95% CI, 2.0 to 7.2) and 9.6% after CAS (95% CI, 6.4 to 14.0); the relative risk of any stroke or death after CAS as compared with CEA was 2.5 (95% CI, 1.2 to 5.1). The 30-day incidence of disabling stroke or death was 1.5% after CEA (95% CI, 0.5 to 4.2) and 3.4% after CAS (95% CI, 1.7 to 6.7); the relative risk was 2.2 (95% CI, 0.7 to 7.2). At 6 months, the incidence of any stroke or death was 6.1% after CEA and 11.7% after CAS (P=0.02). There were more major local complications after CAS and more systemic complications (mainly pulmonary) after CEA, but the differences were not significant. Cranial-nerve injury was more common after CEA than after CAS.

CONCLUSIONS:
In this study of patients with symptomatic carotid stenosis of 60% or more, the rates of death and stroke at 1 and 6 months were lower with CEA than with CAS.

LIMITATIONS:
It is possible that there was a significant “learning curve” with regard to the CAS procedure accounting for increased complications in this group. Information regarding the specific etiology of perioprocudural strokes or other potential factors related to strokes in patients treated with CAS was not provided.

IMPACT ON INTERNAL MEDICINE:
The benefits of any intervention must be weighed against the potential complication of the procedure. While CAS appears attractive as a less invasive procedure the current study questions the efficacy of this procedure compared to the well-studied standard of CEA. Currently CAS is FDA-approved for symptomatic patients with stenosis of the internal carotid exceeding 60% who are at high risk after surgery. This recommendation is based on the SAPPHIRE trial that demonstrated that CAS was safer than CEA with lower risk of perioperative myocardial infarction. There
was no difference in stroke or death at 1 year for the two procedures (2.1% 30-day incidence of any stroke or death). Why conflicting results? The Saphire trial included a large proportion of patients who were asymptomatic internal carotid lesions who were not at high surgical risk because of severe CAD, where as the present study only enrolled symptomatic patients. Both a meta-analysis and a recently published CAS v. CEA trial (SPACE) have demonstrated similar rates of 30-day incidence of any stroke or death at 5.5% and 6.84% respectively. So while the present study raises concern for the safety of CAS, it underscores the need for standardize training and credentialing requirements as well as limiting the procedure to those patients with symptomatic internal carotid stenosis > 60% with a high risk for surgical morbidity and mortality.

**RELATED ARTICLE**

Retrospective multicenter cohort of 1998 patients undergoing CEA. Perioperative complications were recorded. Logistic regression and ROC analyses assessed the predictive abilities of the Goldman, Detsky, American Society Anesthesiologists, and Revised Cardiac Risk indices and of 2 CEA-specific risk models (the Halm and Tu scores). All 6 were equivalent in predicting noncardiac medical complications. However, only the Revised Cardiac Risk Index and the CEA-specific scores predicted death or stroke.

**Venous thromboembolic disease**

**An evaluation of D-dimer in the diagnosis of pulmonary embolism**

**BACKGROUND:**
It may be safe to omit additional diagnostic testing in selected patients with suspected pulmonary embolism (PE) who have a negative D-dimer test, but this approach has never been evaluated in a randomized, controlled trial.

**AIM:**
To determine if additional diagnostic testing can be safely withheld in patients with suspected PE who have negative erythrocyte agglutination D-dimer test results.

**METHODS:**
Randomized comparisons in 2 subgroups of a prospective multicenter study in 7 university hospitals. 1126 outpatients or inpatients with suspected PE; of these, 456 patients with negative erythrocyte agglutination D-dimer test results were randomly assigned to the intervention groups. Patients were classified into 2 clinical probability groups: those with a low clinical probability of PE (low-probability group) and those with a moderate or high clinical probability of PE, a nondiagnostic ventilation–perfusion lung scan, and no evidence of proximal deep venous thrombosis on bilateral ultrasonography (moderate- or high-probability group).

The experimental intervention for both probability groups was no further diagnostic testing for PE. The control intervention for the low-probability group was a ventilation–perfusion lung scan followed by ultrasonography of the proximal deep veins of the legs on the same day. If the lung scan was nondiagnostic, ultrasonography of the legs was repeated 7 and 14 days later. The control intervention for the moderate- or high-probability group was ultrasonography of the proximal deep veins of the legs after 7 and 14 days. In the control and experimental groups, anticoagulation was withheld or withdrawn if PE was not diagnosed. The primary outcome was symptomatic venous thromboembolism (VTE) during 6 months of follow-up.

**RESULTS:**
Prevalence of VTE was 15.2% in the 1126 enrolled patients. In the low-probability group, VTE occurred during follow-up in 0 of 182 patients who had no additional diagnostic testing and in 1 of 185 patients who had additional testing (difference, −0.5 percentage points [95% CI, −3.0 to 1.6 percentage points]). In the moderate- or high-probability group, VTE occurred during follow-up in 1 of 41 patients who had no additional diagnostic testing and in 0 of 41 patients who had additional testing (difference, 2.4 percentage points [CI, −6.4 to 12.6 percentage points]).
CONCLUSIONS:
In patients with a low probability of PE who have negative D-dimer results, additional diagnostic testing can be withheld without increasing the frequency of VTE during follow-up. Low clinical probability and negative D-dimer results occur in 50% of outpatients and in 20% of inpatients with suspected PE.

LIMITATIONS:
One half of eligible patients who satisfied the inclusion criteria were excluded from participation and thus the authors could not enroll 2000 patients as originally planned reducing study precision; 3 randomly assigned patients did not receive the allocated intervention, and 7 received inadequate follow-up. Personnel who performed follow-up evaluations were not blinded to the results of diagnostic testing at enrollment or to allocation group assignments. Most patients were low-probability patients and therefore the validity of the results may not be applicable to a high-risk population in which the prevalence of VTE is significantly higher than the study group.

Multi-detector computed tomography for acute pulmonary embolism

BACKGROUND:
The use of CT angiography has largely replaced ventilation-perfusion scans and limited the use of pulmonary angiography to diagnose or exclude pulmonary embolism in suspected patients. However, accuracy of this modality varies widely with sensitive ranging from 60 to 100 percent.

AIM:
To determine whether multidetector CTA can reliably detect and rule out acute pulmonary embolism and whether the addition of CTV improves the ability to detect and rule out pulmonary embolism.

METHODS:
The Prospective Investigation of Pulmonary Embolism Diagnosis II trial was a prospective, multicenter investigation of the accuracy of multidetector CTA alone and combined with venous-phase imaging (CTA–CTV) for the diagnosis of acute pulmonary embolism. We used a composite reference test to confirm or rule out the diagnosis of pulmonary embolism.

RESULTS:
Among 824 patients with a reference diagnosis and a completed CT study, CTA was inconclusive in 51 because of poor image quality. Excluding such inconclusive studies, the sensitivity of CTA was 83% and the specificity was 96%. Positive predictive values were 96% with a concordantly high or low probability on clinical assessment, 92% with an intermediate probability on clinical assessment, and nondiagnostic if clinical probability was discordant. CTA–CTV was inconclusive in 87 of 824 patients because the image quality of either CTA or CTV was poor. The sensitivity of CTA–CTV for pulmonary embolism was 90%, and specificity was 95%. CTA–CTV was also nondiagnostic with a discordant clinical probability.

CONCLUSIONS:
In patients with suspected pulmonary embolism, multidetector CTA–CTV has a higher diagnostic sensitivity than does CTA alone, with similar specificity. The predictive value of either CTA or CTA–CTV is high with a concordant clinical assessment, but additional testing is necessary when the clinical probability is inconsistent with the imaging results.

LIMITATIONS:
Over 80% of patients were outpatients at the time of their evaluation and thus this study may have limited applicability to the inpatient population in who clinical probability of VTE is traditionally higher than in the outpatient setting. Noninvasive diagnostic test were in part used as the reference standard. In fact, 238 patients did not complete the diagnostic reference testing.

RELATED ARTICLE:
This was a randomized, open-label, adjudicator-blinded, noninferiority trial of 708 patients aged 18 years or older with acute venous thromboembolism (VTE) from 6 university-affiliated clinical centers. Unfractionated heparin (UFH) was administered subcutaneously as an initial dose of 333 U/kg, followed by a fixed dose of 250 U/kg every 12 hours. Dalteparin or enoxaparin was administered subcutaneously at a dose of 100 IU/kg every 12 hours. Both treatments could be administered out of hospital and both were overlapped with 3 months of warfarin therapy. The primary outcomes of recurrent VTE within 3 months of treatment occurred in 13 patients in the UFH group (3.8%) and 12 patients in the low-molecular-weight heparin (LMWH) group (3.4%; absolute difference, 0.4%; 95% CI, –2.6% to 3.3%). Major bleeding within 10 days of randomization was not statistically different. The observed rate of VTE was lower than expected with limited follow up for recurrences of only 3 months. The majority of study enrollees were outpatients presenting with isolated DVT and thus the results can not be generalizable to patients presenting with symptomatic pulmonary embolism or those sick enough to be admitted to the hospital. In addition, 74% of the LMWH preparation used in this study is not currently FDA approved for treatment of symptomatic VTE in the United States.

IMPACT ON INTERNAL MEDICINE:
Dr. Kearon et al. provides compelling evidence that weight-based use of UFH may provide an alternative therapeutic strategy for non-massive pulmonary embolism. While the results of this trial will require confirmation by other trials, in the meanwhile, clinicians should continue to manage patients with continuous intravenous heparin, an FDA approved LMWH regimen or fondaparinux as a bridge to warfarin therapy. This subcutaneous weight-based regimen of UFH should be reserved for the limited group of patients in whom intravenous access proves difficult or in whom alternative approved regimens are not available.

Deciding who can reliably avoid unnecessary testing or potentially avoid exposure to potentially harmful treatment such as anticoagulation is at the center of all management strategies for pulmonary embolism. While D-dimers have been readily incorporated into management strategies for deep vein thrombosis, physicians have been reluctant to use D-dimers in the management of pulmonary embolism. Dr. Kearon’s study evaluating the utility of D-dimer in the management of pulmonary embolism provides convincing data that anticoagulation and additional diagnostic testing can be avoided in patients with low pretest probability and a negative D-dimer in both the inpatient and outpatient settings.

The management of VTE provides a direct empirical demonstration of Bayes’ theorem as applied to diagnosis which states that the probability of disease after testing is not only dependent on the sensitivity and specificity of the test, but also on the clinical probability before testing. Therefore clinicians should use validated models to assess the risk of patients with suspected pulmonary embolism. The PIOPED II convincingly establishes the diagnostic performance of multi-detector CTA, at least in outpatients. However, the clinician should be wary and consider further testing whenever there the results of CT are discordant with the clinical pretest likelihood (ie. high pretest likelihood with negative CTA).

Cancer Screening

Lung cancer

Survival of patients with stage I lung cancer detected on CT screening.

BACKGROUND:
The outcome among patients with clinical stage I cancer that is detected on annual screening using spiral computed tomography (CT) is unknown.
AIM:
To report the results of all patients in the study with stage I lung cancer detected with the use of spiral CT screening, including those who underwent surgical resection.

METHODS:
This screening study followed the protocol of the International Early Lung Cancer Action Project (I-ELCAP). Although the technique for baseline and annual screening with low-dose spiral CT was standardized, each institution specified their enrollment criteria. A protocol for evaluation of abnormalities noted at baseline and the annual screening are detailed in the article, and could include repeat CT scanning at 3 months, immediate positron-emission tomography (PET) scan, fine-needle aspiration, or 2 week course of antibiotics with follow up CT. The protocol was a recommendation; the ultimate diagnostic decision making was left to patient and provider. The interventions following diagnosis of cancer was also left to the discretion of the patient and provider.

Baseline screening CT scans were completed in 31,567 asymptomatic men and women, between 1993 and 2005. All participants were considered acceptable candidates for thoracic surgery and were at risk for lung cancer because of a history of cigarette smoking, occupational exposure, or second hand smoke exposure.

RESULTS:
The median age was 61 years (range, 40-85) and the median pack-years was 30 (range, 1 to 141) at baseline. Of the 4186 (13%) patients with a positive scan necessitating further workup, 405 (1.3%) lung cancers were identified. Five additional lung cancers were identified in the interim before the first annual screening CT scan. The median age was 62 years (range, 41 to 86) and the median pack-years was 35 (range, 0 to 141) for the 27,456 patients who had annual screenings. Of the 1460 (5%) patients with a positive scan necessitating further workup, 74 (0.3%) lung cancers were diagnosed. No interim lung cancers were diagnosed. Biopsies directed by the protocol occurred in 535 patients, of which 479 (89.5%) were lung cancer and 13 (2.4%) were lymphoma or metastases from cancers other than lung. The median tumor size was 13 mm at baseline and 9 mm on annual CT. The patients with a diagnosis of lung cancer had a median followed up of 40 months.

The 484 patients with a diagnosis of lung cancer had a 10-year lung cancer-specific survival of 80% (95% CI, 74% to 85%). Of these, 412 (85%) were clinical stage I and received treatment that included surgical resection (91%); chemotherapy, radiation or both (7%); and nothing (2%). They had a 10-year survival of 88% (95% CI, 84% to 91%). Only 347 (92.5%) of the 375 patients with clinical stage I disease who had resection, actually had pathological stage I disease. They had a 10-year survival of 94% (95% CI, 91% to 97%). The overall operative mortality was 0.5%.

CONCLUSIONS:
Annual spiral CT screening can detect lung cancer that is curable.

LIMITATIONS:
Allowing study centers to develop enrollment criteria may create a bias. A center that has an extremely low complication rate for biopsies and resections may allow lower risk patients to be enrolled, while another center may only screen higher risk patient for fear of complications. Selection criteria are very important and can alter the results of economical analyses. Use of PET scans (only performed in 166 of 484 patients) could have decreased the proportion of clinical stage I lung cancers. PET scans consistent with more extensive disease, may “upstage” those tumors initially felt to be stage I by CT alone. This inconsistency may affect the survival rate of the clinically stage tumors, but not those staged by pathology. Other biases typically associated with screening studies including lead-time and overdiagnosis have not been completely ruled out in the I-ELCAP.

IMPACT ON INTERNAL MEDICINE:
The Surveillance, Epidemiology, and End Results registry estimates the 8-year survival for pathological stage I lung cancers <15 mm to be approximately 75%; however these are typically found incidentally. These may be biologically different from those identified on CT screening, as those found in this trial. Based on the distribution of lung cancers that were identified, CT screening can identify an earlier stage lung cancer. However, improvements in mortality, either overall or cancer-specific, due to management of these malignancies have not been definitively demonstrated. Ultimately the results of the ongoing randomized controlled trials of screening processes will provide additional insight.
Prostate cancer

PSA screening among elderly men with limited life expectancies

BACKGROUND:
Most guidelines do not recommend prostate-specific antigen (PSA) screening in elderly men who have limited life expectancies because the known harms of screening outweigh potential benefits. However, there are no large-scale studies of actual PSA screening practices in elderly men, according to life expectancy.

AIM:
To characterize the extent of PSA screening among elderly men, including those with limited life expectancies.

METHODS:
Cohort study of 597,642 male veterans aged 70 years and older with at least one or more outpatient visits to one of 104 US Department of Veterans Affairs facilities during both 2002 and 2003. Patients were excluded if they had a history of prostate cancer, elevated PSA, prostate cancer symptoms, or in Medicare managed care. Charlson comorbidity scores were used to stratify men into 3 groups ranging from best health (score = 0) to worst health (score ≥ 4). In addition, age was used with health status to predict the probability of 10-year survival.

The primary outcome was receipt of PSA testing during 2003 was based on US Department of Veterans Affairs data and Medicare claims. A random sample of medical records in the cohort were reviewed to ensure that PSA testing was in deed for screening.

RESULTS:
In 2003, 56% of elderly men had a PSA test performed. Although PSA screening rates decreased with advancing age, within each 5-year age group the percentage of men who underwent a PSA test did not substantially decline with worsening health. For example, among men aged 85 years and older, 34% in best health had a PSA test compared with 36% in worst health. In multivariate analyses, many nonclinical factors, such as marital status and region of the country, had a greater effect on PSA screening than health, and screening rates exceeded 60% for some subgroups of men in worst health.

CONCLUSIONS:
Prostate-specific antigen screening rates among elderly veterans with limited life expectancies should be much lower than current practice given the known harms of screening. More attention to prognosis is needed when making screening PSA recommendations to elderly men.

LIMITATIONS:
This cohort study was limited to men in the VA system and therefore the results may not be generalizable to the greater male elderly male population. Claim data provide limited information for the rationale for ordering a screening test. The Charlson Comorbidity Index while strongly predicting overall mortality of a population, has not been validated for an individual patient and excludes other important variables such as physical function.

Survival associated with treatment vs. observation of localized prostate cancer in elderly men

BACKGROUND:
Prostate cancer is the most common cancer affecting US men and therefore routine screening prostate specific antigen (PSA) has been advocated by several organized consensus and interest groups. PSA screening has led to an increase in the diagnosis and treatment of localized prostate cancer. However, the role of active treatment of low- and intermediate-risk disease in elderly men is controversial.
AIM: To estimate the association between treatment (with radiation therapy or radical prostatectomy) compared with observation and overall survival in men with low- and intermediate-risk prostate cancer.

METHODS: NIH-sponsored study of this observational US cohort from Surveillance, Epidemiology, and End Results Medicare database. At total of 44,630 men aged 65 to 80 years who were diagnosed between 1991 and 1999 with organ-confined, well- or moderately differentiated prostate cancer and who had survived more than a year past diagnosis. Patients were followed up until death or study end (December 31, 2002). Patients were classified as having received treatment (n=32,022) if they had claims for radical prostatectomy or radiation therapy during the first 6 months after diagnosis. They were classified as having received observation (n=12,608) if they did not have claims for radical prostatectomy, radiation, or hormonal therapy. Patients who received only hormonal therapy were excluded. The primary outcome was overall survival and was defined as the interval from the date of diagnosis to the Medicare date of death.

RESULTS: At the end of the 12-year study period, 4663 men (37%) in the observational group and 7639 men (23.8%) in the treatment group had died. The treatment group had longer 5- and 10-year survival than the observation group. After using propensity scores to adjust for potential confounders (tumor characteristics, demographics, and comorbidities), there was a statistically significant survival advantage associated with treatment (hazard ratio, 0.69; 95% confidence interval, 0.66-0.72). A benefit associated with treatment was seen in all subgroups examined, including older men (aged 75-80 years at diagnosis), black men, and men with low-risk disease.

CONCLUSIONS: This study suggests a survival advantage is associated with active treatment for low- and intermediate-risk prostate cancer in elderly men aged 65 to 80 years. Because observational data cannot completely adjust for potential selection bias and confounding, these results must be validated in randomized controlled trials of alternative management strategies in elderly men with localized prostate cancer.

LIMITATIONS: The study utilized an observational cohort rather than a randomized controlled trial therefore not allowing for control of a number of important variables such as “selection of the fittest” for treatment. These results may not be generalizable to an “unscreened” population of US males. Lastly, the results may be further biased by stage migration in patients undergoing the surgical intervention.

IMPACT ON INTERNAL MEDICINE: Although not supported by any organization, prostate cancer screening in elderly men with limited life expectancy occurs frequently. The elderly patient often fears mortality from prostate cancer and overestimates the benefits of therapy and their respective life expectancy. Alternatively, physicians recommend PSA screening because the treatment of a diagnosed early cancer may be rewarding and the penalty for failing to diagnose may be severe. In the midst of the unproven benefit in elderly patients with limited life expectancy and the potential harm associated with treatment in this population, physicians should strongly consider an individual patient’s prognosis when making the decision to screen for prostate cancer. Limited observational data suggest a survival advantage in men when active treatment for early stage prostate cancer compared to patients who undergo a watchful waiting strategy.

RELATED ARTICLE

Nested case control of 71,661 patients at 10 VA medical Centers in New England identified 501 cases of men diagnosed with prostate cancer. Control patients were matched (1:1 ratio) for age and VA facility. The exposure variable was whether PSA testing or DRE was performed. Screening for prostate cancer was not associated with overall or cause-specific (prostate cancer) mortality after adjustment for race and comorbidity.
Colorectal cancer

Colonoscopy in colorectal-cancer screening for detection of advanced neoplasm

BACKGROUND:
Recommendations for colorectal-cancer screenings are based solely on age and family history of cancer, not sex.

AIM:
To derive and validate a model for the detection of advanced neoplasia in the large bowel during screening colonoscopy.

METHODS:
This cross-sectional study, evaluated patients aged 40 to 49 years with a family history of any cancer and 50 to 66 years of age, in whom cancer was not suspected, who were advised and participated in this Polish national colonoscopy-based screening program for colorectal cancer. Exclusion criteria included recent changes in bowel habits, anemia, unexplained weight loss, bleeding in the lower GI tract not attributable to hemorrhoids, characteristics that met criteria for hereditary nonpolyposis colorectal cancer of familial adenomatous polyposis, inflammatory bowel disease, or colonoscopy within 10 years. Advanced neoplasm was defined as adenoma or cancer ≥10 mm, high grade dysplasia, villous tubulovillous histology, or any combination. A total of 50,148 participants underwent colonoscopy at one of 40 centers.

RESULTS:
Of the participants, 64.1% were women; and 13.3% of those between 50 and 66 years of age and 66.3% of those 40 to 49 years had a family history of colorectal cancer. Advanced neoplasm was diagnosed in 5.9% of the population, 5.9% in those 50 to 66 years of age and 3.4% in those 40 to 49 years of age. Adenocarcinoma was diagnosed in 0.8% of those screened. Age greater than 49 years, family history of colorectal cancer, and male sex (OR 2.08, 95% CI, 1.89-2.28, P<0.001) were independent predictors of advanced neoplasm. Complications from colonoscopy occurred in 0.1% of subjects.

CONCLUSIONS:
Male sex was an independent predictor of finding advanced neoplasia on screening colonoscopy.

LIMITATIONS:
The patients included in the study were exclusively from Poland, which limits the generalizability. Also, the study was purely observational yielding only prevalence data. It does not appear that the authors controlled for other possible risk factors for colorectal cancer, including smoking, obesity, alcohol intake, or diet.

RELATED ARTICLES:

This study evaluated the results of a mail survey of 500 physicians of the American College of Physicians and 500 physicians from the American Academy of Family Physicians who were asked to recommend follow-up colonoscopy for six hypothetical patients. Of the 57% of respondents, most providers referred patients for repeat colonoscopy at a more intense frequency than recommended by national organizations.


This retrospective cohort study calculated the life expectancy of patients diagnosed with earlier stage colorectal cancer linked to the Surveillance, Epidemiology, and End Results (SEER) Program-Medicare database. Chronic conditions were identified by Medicare encounter claims. As expected, life expectancy...
was inversely correlated with increasing age, cancer stage, and comorbidities. Also, male sex was associated with a shorter life expectancy. The authors concluded that age and comorbid conditions should be used in guiding screening decisions.


This study is a secondary analysis of a single Veterans Affairs Medical Center study, initially designed to determine the prevalence of diabetes mellitus. Only 45.9% of the eligible cohort, at least 50 years of age who had not had previous been screening, underwent colorectal cancer screening. A high rate of screening was seen in those with moderate (44.9%) and severe (45.8%) comorbidities.


Of 7882 colonoscopies performed by 12 experienced gastroenterologists, neoplastic lesions were detected in 23.5% of the 2053 studies. Higher rates of any neoplasia (28.3% vs. 11.8%, P<0.001) and advanced neoplasia (6.4% vs. 2.6%, P=0.005) were identified more frequently when the mean withdrawal time for a normal colonoscopy was greater than 6 minutes compared to less.


This retrospective cohort study evaluated the complication rates associated with colonoscopies performed within the Kaiser Permanente, Northern California health care system. The majority of colonoscopies were conducted because symptoms or a family history of colorectal cancer. Biopsies were obtained in 67.9% (range 33.3% to 91.5%) of cases. Serious complications occurred in 0.5% (95% CI, 0.4% to 0.6%) examinations.

**IMPACT ON INTERNAL MEDICINE:**
Colorectal cancer screening is recommended for all patients over 50 years of age and possibly earlier for those with increased risk. Although the United States Preventive Services Task Force recommends multiple modalities for screening, use of colonoscopy has increased. Use of any screening process depends upon an expectation of years of life saved; and, in the case of colonoscopy, it may be 5 years before the benefits are realized. The observational studies above provide support that patients should undergo risk-benefit analysis before colonoscopy. It is clear that guideline dissemination and adherence is poor and that neoplastic lesion detection is related to technique.

**Gender Medicine**

**Osteoporosis**

**Calcium plus vitamin D supplementation and the risk of fractures**

**BACKGROUND:**
The efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in healthy postmenopausal women remains equivocal.

**METHODS:**
We recruited 36,282 postmenopausal women, 50 to 79 years of age, who were already enrolled in a Women's Health Initiative (WHI) clinical trial. We randomly assigned participants to receive 1000 mg of elemental calcium as calcium carbonate with 400 IU of vitamin D3 daily or placebo. Fractures were ascertained for an average follow-up period of 7.0 years. Bone density was measured at three WHI centers.
RESULTS:
Hip bone density was 1.06 percent higher in the calcium plus vitamin D group than in the placebo group (P<0.01). Intention-to-treat analysis indicated that participants receiving calcium plus vitamin D supplementation had a hazard ratio of 0.88 for hip fracture (95 percent confidence interval, 0.72 to 1.08), 0.90 for clinical spine fracture (0.74 to 1.10), and 0.96 for total fractures (0.91 to 1.02). The risk of renal calculi increased with calcium plus vitamin D (hazard ratio, 1.17; 95 percent confidence interval, 1.02 to 1.34). Censoring data from women who ceased to adhere to the study medication reduced the hazard ratio for hip fracture to 0.71 (95 percent confidence interval, 0.52 to 0.97). Effects did not vary significantly according to prerandomization serum vitamin D levels.

CONCLUSIONS:
Among healthy postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip-bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones.

LIMITATIONS:
This study was evaluated as an intention-to-treat trial and the interpretation of adherence to the prescribed regimen may have a significant impact on the results. For example, only 59% of women in the trial were taking the correct dose of the study drug at the end of the trial. In addition, the dose of Vit D supplementation used (400 IU) was lower than the dose used in studies finding benefit of vitamin D supplementation (≥ 600 IU). Lastly, participants of the WHI trial were health postmenopausal women living in the community free of disability with high baseline calcium intake as well as baseline BMD measurements. Therefore the population studied may limit application of such results to higher risk women with more to lose without adequate calcium and vitamin D intake.

IMPACT ON INTERNAL MEDICINE:
Overall this study probably should have no significant impact on the current recommendations for prevention of fracture in postmenopausal women. The current guidelines recommend at least 1200 mg of elemental calcium per day as well as 800 IU of vitamin D per day – the amount usually required to raise serum levels of 25-hydroxyvitamin D levels to that needed to lower the risk of fracture (≥ 75 nmol per liter). In addition, this trial may simply punctuate the need for adequate supplementation of vitamin D and elemental calcium, without which the habitual use of inadequate intake of these supplements is ineffective.

RELATED ARTICLES

Thirteen randomized controlled trials were identified that gave participants oral vitamin K supplements for longer than 6 months. Overall this reviewed suggests that supplementation with vitamin K reduces bone loss and may reduce incident fractures in specific populations.


Randomized controlled trial of 48 adults randomized to 1 of 3 groups for 1 year: caloric restriction (CR), regular exercise (EX) or healthy lifestyle (HL). CR-induced weight loss, but not EX induced weight loss, is associated with reductions in BMD at clinically important sites of fractures.


The efficacy and safety of subcutaneously administered Denosumab (receptor activator of nuclear factor-RANKL) were evaluated over a 12-month period in 412 postmenopausal women. Subjects were randomly assigned various regimens of Denosumab vs. 70 mg of weekly of alendronate vs. placebo. Denosumab administered subcutaneously (30 mg every 3 months or 60 mg every 6 months) was as effective as alendronate and more effective than placebo in increasing BMD. This preliminary data suggest that Denosumab may be an effective treatment for osteoporosis.
Complementary and alternative medicine

Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo

The authors recruited 351 women after mailing over 157,000 brochures with 3443 responses. This very selective population of highly symptomatic (ie. average of 6 vasomotor symptoms/24 hours) well-educated mostly white females was randomly assigned to herbal treatments (black cohosh, multi-botanicals, or multibotanicals plus counseling about dietary soy), estrogen with or without progesterone, or placebo. Using the Wiklund Vasomotor Symptom Subscale at 3, 6, and 12 months, patients receiving the herbal interventions had the same change in vasomotor symptoms as those receiving placebo (except for more severe symptoms at 12 months for patients taking multi-botanicals plus dietary soy). Alternatively, conjugated estrogen substantially decreased vasomotor symptoms compared to placebo and the botanicals. It should be noted that the placebo group experienced an approximately 30% reduction in the severity and frequency of vasomotor symptoms during follow up.

RELATED REFERENCE

Systematic review of randomized controlled trials comparing a complementary or alternative therapy with placebo or control for treatment of menopausal symptoms. A total of 70 RCT met inclusion criteria. Although individual trials suggested benefit, overall data provided insufficient support for use and effectiveness of any complementary and alternative therapy in this review for the management of menopausal symptoms.

Saw palmetto for benign prostatic hyperplasia

Well conducted double-blind randomized controlled trial of 225 men over the age of 49 years with moderate-to-severe symptoms of benign prostatic hyperplasia (BPH) assigned subjects to one year of treatment with saw palmetto extract (160 mg twice daily) or placebo. The primary outcome measures were changes in the scores on the American Urological Association Symptom Index (AUASI) and the maximal urinary flow rate. At one year there was no significant difference in the primary outcome between active treatment and placebo group.

IMPACT ON INTERNAL MEDICINE:
The use of botanicals for menopausal symptoms or symptomatic BPH has been well described in previous trials. However, the results of these two trials contrast with the results of other studies comparing the respective botanical to an established active treatment on placebo. While firm conclusion related to efficacy and safety can not be drawn as these trials represent comparison of specific preparation and therefore may not be representative of other brands or preparations, it is clear that botanicals used for medicinal purposes deserve similar scientific rigor and product standardization to ensure consistent efficacy and safety of the product.

The good and bad of ACE inhibition

Efficacy and safety of benazepril for advanced chronic renal insufficiency

BACKGROUND:
Angiotensin-converting–enzyme inhibitors provide renal protection in patients with mild-to-moderate renal insufficiency (serum creatinine level, 3.0 mg per deciliter or less). The effect of ACE inhibition on advanced renal disease is less clear.

**AIM:**
To determine whether benazepril could slow the progression of renal dysfunction in patients without diabetes who have advanced renal insufficiency,

**METHODS:**
We enrolled 422 patients in a randomized, double-blind study. After an eight-week run-in period, 104 patients with serum creatinine levels of 1.5 to 3.0 mg per deciliter (group 1) received 20 mg of benazepril per day, whereas 224 patients with serum creatinine levels of 3.1 to 5.0 mg per deciliter (group 2) were randomly assigned to receive 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed for a mean of 3.4 years. The dose was administered in a divided fashion with 10 mg in the morning and 10 mg at night. All patients received conventional antihypertensive therapy. The primary outcome was the composite of a doubling of the serum creatinine level, end-stage renal disease, or death. Secondary end points included changes in the level of proteinuria and the rate of progression of renal disease.

**RESULTS:**
Of 102 patients in group 1, 22 (22 percent) reached the primary end point, as compared with 44 of 108 patients given benazepril in group 2 (41 percent) and 65 of 107 patients given placebo in group 2 (60 percent). As compared with placebo, benazepril was associated with a 43 percent reduction in the risk of the primary end point in group 2 (P=0.005). This benefit did not appear to be attributable to blood-pressure control. Benazepril therapy was associated with a 52 percent reduction in the level of proteinuria and a reduction of 23 percent in the rate of decline in renal function. The overall incidence of major adverse events in the benazepril and placebo subgroups of group 2 was similar.

**CONCLUSIONS:**
Benazepril conferred substantial renal benefits in patients without diabetes who had advanced renal insufficiency.

**LIMITATIONS:**
The safety endpoints of this study may underestimate the risk in other populations. Approximately 5% of the patients in group 2 were excluded from the study as they developed hyperkalemia during the run in phase. It is also possible that the potassium intake of Chinese patients may be substantially lower than that of most Western patients. In addition, a large proportion of the patients in group 2 received a diuretic which protects against hyperkalemia.

**IMPACT ON INTERNAL MEDICINE:**
Many physicians are reluctant to use ACE inhibitors in patients with advanced renal insufficiency because of concern that serum creatinine or potassium levels will rise. Still others simply believe that the real benefits of the drug in advanced renal disease is simply related to the effect on blood pressure and therefore opt to use other antihypertensive agents. This study demonstrates the ACE inhibitors can be given safely to patients with stage 4 chronic kidney disease and compared to placebo lowers the risk of disease progression (including proteinuria) and death. The observed effect was independent of blood pressure control. However, enthusiastic and widespread use of benazepril in patients with advanced renal disease should be tempered with generalizability of the safety of this intervention in this high-risk population. Although the dose of benazepril used in this study was almost twice as much used in other studies of ACE inhibition and advance renal disease, physicians should carefully consider the concomitant use of diuretic therapy and potassium intake (consider measuring 24 hour urinary potassium excretion) before prescribing benazepril as well as starting as a lower dose while carefully monitoring electrolytes. Overall, it appears that the safe use of benazepril confers a protective and survival advantage in patients with nondiabetic advanced renal disease.

**Major congenital malformations after first-trimester exposure to ACE inhibitors**

**BACKGROUND:**
Use of angiotensin-converting–enzyme (ACE) inhibitors during the second and third trimesters of pregnancy is contraindicated because of their association with an increased risk of fetopathy. In contrast, first-trimester use of ACE inhibitors has not been linked to adverse fetal outcomes. We conducted a study to assess the association between exposure to ACE inhibitors during the first trimester of pregnancy only and the risk of congenital malformations.

METHODS:
We studied a cohort of 29,507 infants enrolled in Tennessee Medicaid and born between 1985 and 2000 for whom there was no evidence of maternal diabetes. We identified 209 infants with exposure to ACE inhibitors in the first trimester alone, 202 infants with exposure to other antihypertensive medications in the first trimester alone, and 29,096 infants with no exposure to antihypertensive drugs at any time during gestation. Major congenital malformations were identified from linked vital records and hospitalization claims during the first year of life and confirmed by review of medical records.

RESULTS:
Infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations (risk ratio, 2.71; 95% CI, 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. In contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (RR, 0.66; 95% CI, 0.25 to 1.75). Infants exposed to ACE inhibitors were at increased risk for malformations of the cardiovascular system (RR, 3.72; 95% CI, 1.89 to 7.30) and the central nervous system (RR, 4.39; 95% CI, 1.37 to 14.02).

CONCLUSION:
Exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided.

LIMITATIONS:
This observational cohort provides indirect evidence that exposure to ACE inhibition in the first trimester is associated with fetal death or malformation. Despite attempts to control for confounders, no causal relationship can be attributed to ACE inhibition based on the observational design.

IMPACT ON INTERNAL MEDICINE:
This exploratory study raises the possibility that maternal ACE-inhibitor treatment early in pregnancy may sometimes cause birth defects. As indications for ACE inhibitors have expanded, their use among women of childbearing age has increased. While further study is needed to determine the precise risk, mechanism and its relationship to individual drugs, this demonstrated increase risk should likely be discussed with all women of reproductive age who are prescribed ACE inhibition. Birth defects caused by teratogenic treatments are preventable.

- Detailed ultrasonography and echocardiography should be obtained of the fetus in all women who have taken such drugs during the first trimester.
- A woman who learns that she is pregnant while taking an ACE inhibitor should immediately be switched to another antihypertensive agent to minimize the risk of fetopathy.

Perioperative Medicine

The effects of perioperative beta-blockade: Results of the metoprolol after vascular surgery (MaVS) study, a randomized controlled trial

BACKGROUND:
Patients undergoing vascular surgery comprise the highest risk group for perioperative cardiac mortality and morbidity after noncardiac procedures. Many current guidelines recommend the use of beta-blockers in all patients undergoing vascular surgery. We report a trial of the perioperative administration of metoprolol and its effects on the incidence of cardiac complications at 30 days and 6 months after vascular surgery.
METHODS:
Patients undergoing abdominal aortic surgery and infrainguinal or axillofemoral revascularizations were recruited to a double-blind randomized controlled trial of perioperative metoprolol versus placebo. Patients were randomized to receive study medication, starting 2 hours preoperatively until hospital discharge or maximum of 5 days postoperatively. Primary outcome were postoperative 30-day composite incidence of nonfatal myocardial infarction, unstable angina, new congestive heart failure, new atrial or ventricular dysrhythmia requiring treatment, or cardiac death.

RESULTS:
Patients were randomized to receive either metoprolol (n = 246) or placebo (n = 250). Primary outcome events at 30 days postoperative occurred in 25 (10.2%) versus 30 (12.0%) (P = .57) in metoprolol and placebo groups, respectively (RRR 15.3%, 95% CI, 38.3% to 48.2%). Observed effects at 6 months were not significantly different (P = .81) (RRR 6.2%, 95% CI, 58.4% to 43.8%). Intraoperative bradycardia requiring treatment was more frequent in the metoprolol group (53/246 vs 19/250, P = .00001), as was intraoperative hypotension requiring treatment (114/246 vs 84/250, P = .0045).

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Cardiac Death</th>
<th>Non-fatal MI</th>
<th>Non-Cardiac Death</th>
<th>New onset CHF</th>
<th>Intraop ↓BP or ↓HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>25 (1.1%)</td>
<td>0 (0.0%)</td>
<td>19 (7.7%)</td>
<td>1 (0.4%)</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>30 (12.0%)</td>
<td>1 (0.4%)</td>
<td>21 (8.4%)</td>
<td>6 (2.4%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.4</td>
<td>1</td>
<td>0.87</td>
<td>0.12</td>
<td>0.5</td>
</tr>
</tbody>
</table>

CONCLUSIONS:
Our results showed metoprolol was not effective in reducing the 30-day and 6-month postoperative cardiac event rates. Prophylactic use of perioperative Beta-blockers in all vascular patients is not indicated.

LIMITATIONS:
Use of perioperative beta-blockade did not begin to 2 hours prior to surgery without bradycardic or sympatholytic targets before the initiation of anesthesia. In addition, the study was open-labeled potentially influencing the management of the patient and therefore outcome. Lastly, this study enrolled beta-blocker naïve patients and therefore the results of this study may not be generalizable to patients with higher risk or known CAD.

Effect of perioperative beta-blockade in patients with diabetes undergoing major non-cardiac surgery: randomized placebo controlled, blinded multicentre trial

AIM:
To evaluate the long term effects of perioperative blockade on mortality and cardiac morbidity in patients with diabetes undergoing major non-cardiac surgery.

METHODS:
Randomized placebo controlled and blinded multicenter trial conducted in University anaesthesia and surgical centers and one coordinating center. 921 patients aged > 39 scheduled for major non-cardiac surgery were randomized to 100 mg metoprolol controlled and extended release or placebo administered from the day before surgery to a maximum of eight perioperative days. The composite primary outcome measure was time to all cause mortality, acute myocardial infarction, unstable angina, or congestive heart failure. Secondary outcome measures were time to all cause mortality, cardiac mortality, and non-fatal cardiac morbidity. Analyses were by ITT.

RESULTS:
Mean duration of intervention was 4.6 days in the metoprolol group and 4.9 days in the placebo group. Metoprolol significantly reduced the mean heart rate by 11% (95% CI, 9% to 13%) and mean blood pressure by 3% (1% to 5%). The primary outcome occurred in 99 of 462 patients in the metoprolol group (21%) and 93 of 459 patients in the placebo group (20%) (hazard ratio 1.06, 0.80 to 1.41) during a median follow-up of 18 months (range 6-30). All
cause mortality was 16% (74/462) in the metoprolol group and 16% (72/459) in the placebo group (1.03, 0.74 to 1.42). The difference in risk for the proportion of patients with serious adverse events was 2.4% (-0.8% to 5.6%).

CONCLUSIONS:
Perioperative metoprolol did not significantly affect mortality and cardiac morbidity in these patients with diabetes. Confidence intervals, however, were wide, and the issue needs reassessment.

LIMITATIONS:
While this is the largest placebo-controlled randomized trial assessing the effect of beta-blockade on perioperative cardiac events, the intervention was once again started immediately prior to induction. Although parameters were provided to guide withholding treatment, no specific sympatholytic targets were provided. Fewer events comprising the primary outcome occurred than anticipated limiting the studies ability to detect a mild to moderate benefit of the study drug.

Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control?

BACKGROUND:
Treatment guidelines of the American College of Cardiology/American Heart Association recommend cardiac testing in these patients to identify subjects at increased risk. This policy delays surgery, even though test results might be redundant and beta-blockers with tight HR control provide sufficient myocardial protection. Furthermore, the benefit of revascularization in high-risk patients is ill-defined.

OBJECTIVES:
The purpose of this study was to assess the value of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate (HR) control scheduled for major vascular surgery.

METHODS:
All 1,476 screened patients were stratified into low-risk (0 risk factors), intermediate-risk (1 to 2 risk factors), and high-risk (≥3 risk factors). All patients received beta-blockers. The 770 intermediate-risk patients were randomly assigned to cardiac stress-testing (n = 386) or no testing. Test results influenced management. In patients with ischemia, physicians aimed to control HR below the ischemic threshold. Those with extensive stress-induced ischemia were considered for revascularization. The primary end point was cardiac death or myocardial infarction at 30-days after surgery.

RESULTS:
Testing showed no ischemia in 287 patients (74%); limited ischemia in 65 patients (17%), and extensive ischemia in 34 patients (8.8%). Of 34 patients with extensive ischemia, revascularization before surgery was feasible in 12 patients (35%). Patients assigned to no testing had similar incidence of the primary end point as those assigned to testing (1.8% vs. 2.3%; odds ratio [OR] 0.78; 95% confidence interval [CI] 0.28 to 2.1; p = 0.62). The strategy of no testing brought surgery almost 3 weeks forward. Regardless of allocated strategy, patients with a HR <65 beats/min had lower risk than the remaining patients (1.3% vs. 5.2%; OR 0.24; 95% CI 0.09 to 0.66; p = 0.003).

CONCLUSIONS:
Cardiac testing can safely be omitted in intermediate-risk patients, provided that beta-blockers aiming at tight HR control are prescribed.

IMPACT ON INTERNAL MEDICINE:
Reduction of perioperative cardiovascular events continues to challenge the practicing internist. While quality indicators and the recently updated ACC/AHA (Circulation 2006) guidelines support more broad use of perioperative beta-blockers not only in patients with known CAD, but in patients with multiple risk factors. The studies by Juul et al. and Yang et al. provide evidence to suggest limiting the use of perioperative beta-blockers to very select patients as both studies failed to show benefit against placebo. Furthermore, both studies also provided
strong evidence that beta-blockers, if given to naïve patients immediately prior to anesthesia and surgery, may come at a risk of significant bradycardia and hypotension as seen in up to 30% of patients randomized to active treatment in these well conducted trials. We anxiously await the results of a 10,000 patient placebo-controlled randomized controlled trial to more clearly define the role of perioperative beta-blockade in the asymptomatic at risk for CAD undergoing elective noncardiac surgery.

The role of risk stratification is extremely important in making decisions about the use of additional diagnostic tests or use preoperative interventions such as PTCA or CABG. Polderman et al. demonstrate perioperative beta-blockade that even in intermediate risk patients undergoing vascular surgery with stable CAD symptoms that additional diagnostic testing and/or other interventions do not provide change 30-day cardiovascular event rates or death. These data provide additional support to the findings of the previously reported CARP trial. Therefore, it is essential that the practicing clinician thoughtfully consider the risk and benefits of both testing and interventions as all decisions have consequences and may ultimately not provide improve outcomes but unnecessary risk in an attempt to make more informed decisions related to elective surgery.

**Common office-based problems (interesting articles)**

**Skin and Soft tissue infection**

**Methicillin-resistant S. aureus infections among patients in the emergency department**


**BACKGROUND:**
Methicillin-resistant Staphylococcus aureus (MRSA) is increasingly recognized infections among persons in the community without established risk factors for MRSA.

**AIM:**
To determine the prevalence of MRSA as a cause of skin infections among adult patients presenting to emergency departments in several geographically diverse, metropolitan areas in the United States.

**METHODS:**
Prospective, prevalence study of adult patients with skin and soft-tissue infections who were seen at hospitals in the EMERGEncy ID Net (network of university affiliated emergency department in 11 US cities).

Patients were at least 18 years of age and presented in August 2004 with purulent skin and soft-tissue infections of less than one week’s duration. Perirectal abscesses were excluded. Emergency department physicians determined on the individual management of each patient. Specimens were collected, processed, and cultured in standardized fashion at each site. S. aureus isolates were sent to the CDC for characterization with PCR and pulsed-field gel electrophoresis (PFGE).

**RESULTS:**
Of the 422 patients with skin and soft-tissue infections that were enrolled, 320 (76%) were S. aureus. MRSA was identified in 59% (range 15%-74%) of the patients, and accounted for 78% of the S. aureus isolates. It accounted for the majority of isolates from abscesses and half of the purulent wounds and cases of cellulitis with purulent exudates. Cultures were MSSA (17%), streptococcus (7%), coagulase-negative staphylococci (3%), and Proteus mirabilis (1%). The CDC characterized 218 MRSA isolates, determined that 216 (99%) were consistent with community-acquired MRSA, and 98% were type USA 300. Seventy four percent of type USA 300 were a single strain (strain USA 300-0114). The MRSA were susceptible to rifampin (100%), trimethoprim-sulfamethoxazole (100%), clindamycin (95%), tetracycline (92%), fluoroquinolones (60%), and erythromycin (6%). The patients were treated with incision and drainage with or without antibiotics in 85% of cases. However, only 75 of 175 MRSA infections treated with antibiotics were appropriate.

**CONCLUSIONS:**
MRSA has become the most common identifiable etiologic agent for skin and soft-tissue infections in several metropolitan areas in the United States. Empiric antibiotic therapy was initiated in more than 80% of MRSA infections; however, only 43% were susceptible to the antibiotic.

**LIMITATIONS:**
A case finding audit revealed only 42% of eligible patients were enrolled in this study, thus possibly introducing a selection bias.

**RELATED ARTICLE:**

**IMPACT ON INTERNAL MEDICINE:**
Community-acquired MRSA appears to becoming the most common identifiable bacteria associated with skin and soft-tissue infections. These two studies demonstrate that approximately 60-70% of isolates are MRSA and the majority are USA 300. Therapy may include incision and drainage, but should empiric therapy be indicated, antibiotics, such as rifampin, trimethoprim-sulfamethoxazole, or clindamycin should be selected.

**Pulmonary problems**

**The salmeterol multicenter asthma research trial. A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.**

**BACKGROUND:**
Published studies have suggested a rise in asthma-related deaths over the past decades. There are identified risk factors that are associated with this. Currently, there is debate as to the link between β2-agonists and this increasing mortality.

**AIM:**
To evaluate the effects of salmeterol xinafoate when added to usual asthma care on respiratory- and asthma-related deaths or life-threatening episodes.

**METHODS:**
Starting June 1996, patients were enrolled by 1316 investigators from 6163 sites in the United States into this triple-blind, parallel-group, placebo-controlled, randomized observational trial funded by the pharmaceutical company.

Participants were ≥12 years of age, with a diagnosis of asthma, based on the investigator’s clinical judgment, and being treated with prescription medication. Exclusion criteria included use of inhaled long-acting β2-agonists; pregnancy and/or lactation, or any significant systemic disease that placed the patient at risk; history of adverse reaction to any sympathomimetic amine drug; or current use of β-blockers. Patients were recruited in 2 phases because of decreasing enrollment. The first was via print, radio, and television advertisement, the second was by direct recruitment by the study investigators.

There were 26,355 subjects randomly assigned to salmeterol (n=13,176) or placebo (n=13,179) for 28 weeks. The initial visit was the only face-to-face contact the patients received throughout the trial. At that visit, they received the 28 weeks of medication and instructions on its use, as well as instructions to continue other asthma medications. Every 4 weeks patients were contacted by phone. At the end of the trial, unused medication was returned. The primary endpoint was the occurrence of combined respiratory-related deaths or respiratory-related life-threatening experiences (intubation and mechanical ventilation).

**RESULTS:**
The baseline characteristics revealed that African Americans greater disease severity than Caucasians, and a lower rate of inhaled corticosteroid use (38% vs 47%). There was no significant difference in the primary endpoint over the 28-week period (0.38% in salmeterol and 0.27% in placebo). Of the secondary endpoints, combined asthma-related death or life-threatening experiences; respiratory-related deaths; and asthma-related deaths were slightly statistically significant. When subgrouped by race (Caucasian vs African American), there was a statistically significant increase in the primary endpoint seen in those treated with salmeterol (0.85% vs 0.22%; RR=4.1; 95% CI, 1.5-10.9). Estimates of NNT=159 (47 to 859). Post hoc analysis stratifying based on use of inhaled corticosteroid (ICS) revealed that the primary endpoint was only significant in African Americans not using ICS.

CONCLUSIONS:
For the primary endpoint in the total population, there was no significant difference between the salmeterol and placebo. Although the prespecified termination criteria were not met, the trial was terminated at the interim analysis by the pharmaceutical manufacturer because of the preliminary findings in African Americans and difficulty recruiting subjects.

LIMITATIONS:
The study had a number of methodological issues. Selection of the patients is very important for any study. One should call into question the diagnosis of asthma that was based on clinical judgment. Additionally, recruitment from advertisement will result in a population that differs from those directly recruited. It may attract a population that was initially sicker or not on appropriate medications because they did not regularly seek medical care. Interestingly, the greater discrepancy of the primary endpoint occurred in this phase, although it was not statistically significant. Throughout the study, compliance with medications was estimated to be 80% for both groups and ultimately, only 73% completed treatment. The sample size was subsequently increased because the primary outcome was occurred at half the expected rate; but the trial was terminated early due to a small but significant difference in one of multiple post hoc analyses. Although statistically significant, it did not meet the prespecified criteria for study termination. Without statistical adjustment they may have been purely by chance. Finally, it appears that most patients were not treated appropriate to national guidelines for asthma care. From the baseline data, 51% of the Caucasians and 62% of the African Americans did not receive ICS.

RELATED ARTICLES:

IMPACT ON INTERNAL MEDICINE:
With the release of the data for the SMART trial, the FDA added a black box warning to salmeterol and salmeterol/fluticasone to warn patients of a significant, but small increase in asthma-related deaths. This was a secondary endpoint within the study, but an increase was also seen in the meta-analysis by Salpeter et al. Unfortunately, the largest study providing data to the meta-analysis was the SMART study. Like all meta-analyses the results depend upon the quality of the individual studies. In contrast, previous Cochrane reviews published in 2005 found no difference in the risk of severe exacerbations requiring hospitalization. In these, included studies required continued use of ICS. Inhaled corticosteroids have been recommended for treatment of persistent asthma because of their anti-inflammatory properties, whereas long-acting β-agonists are recommended as add-on therapy. Because of the methodological problems of the SMART trial, the link between long-acting β-agonists and asthma-related deaths will continue to be debated. For now informed decision making between the patient and provider must occur and hopefully we will continue to follow the current evidence-based guidelines.

Systematic Review: Smoking cessation intervention strategies for adults and adults in special populations

BACKGROUND:
While smoking cessation interventions have been shown to work, questions remain about how to increase their efficacy.

AIM:
To examine strategies for effective tobacco treatment in adults and special populations.

METHODS:
The authors searched MEDLINE, CINAHL, Cochrane Library, Cochrane Clinical Trials Register, Psychological Abstracts and Sociological Abstracts from January 1980 to June 2005 for systematic reviews, randomized, controlled trials (>30 patients) or experimental/observational trials (>100 patients) in humans 13 years and older, in developed countries, in English, with a duration >6 months. Of 1288 studies screened, 488 were reviewed, and 42 were relevant to the review. The 28 studies, not included in previous reviews, of fair and good quality were included.

RESULTS:
Alternative approaches to smoking cessation
• Self-help approach (2 studies): The two studies differed in the direction of their results. There is insufficient evidence of its efficacy.
• Counseling (5 studies): Previous reviews demonstrated the effectiveness of counseling. The new studies included patients from various setting, and yielded conflicting results (2 were effective and 3 not).
• Pharmaceutical monotherapy (5 studies): As the bupropion studies were mixed, 2 effective and 1 ineffective, there was insufficient evidence to change the existing recommendation for its use as first line pharmacological therapy. Both nicotine replacement strategies had favorable results; therefore, the current recommendation of its efficacy should remain unchanged.
• Combined pharmacotherapies (3 studies): Nicotine patch and nicotine inhaler and bupropion and nicotine patch improved rates of abstinence, but transdermal system and paroxetine did not. Thus, insufficient evidence to make a recommendation about combined therapies.
• Pharmacotherapy and psychological interventions (6 studies): Included paroxetine, nortriptyline, nicotine replacement, and bupropion combined with various counseling methods. Five of the studies yielded positive results, thus the studies suggest pharmacotherapy with psychological interventions are effective.

Special populations
• Hospitalized patients by diagnosis (3 studies): No differences were noted; thus, intensive counseling during a hospitalization for a smoking-related clinical diagnosis, does not improve abstinence rates.
• Hospitalized patients by intensity of intervention (4 studies): Mixed results, therefore, there is insufficient evidence to recommend the most effective level of intensity for smoking cessation in hospitalized patients.
• Psychiatric and substance abuse conditions (4 studies): Two studies evaluated smoking cessation in patients with depression. In this population, counseling combined with pharmacotherapy significantly improved abstinence rates for adherent patients, as did tailored smoking cessation counseling in some depressed smokers. Due to lack of studies, there was insufficient evidence to formulate a recommendation. Two studies evaluated smoking cessation programs for adults in alcohol and substance abuse disorder programs. In this population, counseling with pharmacotherapy significantly improved abstinence rates, however, alcohol abstinence may be negatively affected.

CONCLUSIONS:
Self help strategies marginally affect rates of abstinence, however, combined and individual pharmacotherapies with or without counseling significantly improves a patient’s chances to quit.

LIMITATIONS:
Several methodological issues are present, including inadequate description of sampling techniques; high refusal, attrition, and nonadherence rates; and self-selection.

RELATED ARTICLES:
In these randomized, double-blind, placebo- and active-treatment-controlled, phase 3 clinical trial, subjects were 18 to 75 years old, smoked 10 or more cigarettes per day, had less than 3 months of abstinence in the last year, and were motivated to stop. Between the 2 studies, 2052 subjects received 12 weeks of titirated varenicline, titrated bupropion SR, or placebo. The primary endpoint of exhaled carbon monoxide-confirmed 4-week abstinence rate for weeks 9 through 12 was similar between the studies and was significantly higher in those receiving varenicline (44% and 43.9%) compared to both bupropion (29.5% and 29.8%; P<0.001) and placebo (17.7% and 17.6%; P<0.001). The longer term, 9 to 24 week and 9 to 52 week, 4-week abstinence rates were also significantly greater. Any adverse events occurred with equal frequency among the three groups, and nausea was the most common event in the varenicline group. Weight increased in all groups.

Low back pain

Surgical vs nonoperative treatment for lumbar disk herniation. The spine patient outcomes research trial (SPORT): a randomized trial

BACKGROUND:
Lumbar discectomy is the most common surgical procedure performed for back and leg symptoms in US patients, but the efficacy of the procedure relative to nonoperative care remains controversial.

AIM:
To compare the outcomes of surgical and nonoperative treatment for lumbar intervertebral disk herniation, spinal stenosis, or degenerative spondylolisthesis.

METHODS:

Patients were 18 years and older, diagnosed by participating physicians with intervertebral disk herniation and persistent symptoms despite nonoperative treatment for at least 6 weeks. Inclusion criteria were radicular pain and evidence of nerve-root irritation with a positive nerve-root irritation sign or a corresponding neurologic deficit. All were considered surgical candidates with advanced imaging demonstrating a herniated disk that corresponded to
their symptoms. Exclusion criteria were prior lumbar surgery, cauda equina syndrome, scoliosis >15 degrees, segmental instability, vertebral fractures, spine infection or tumor, inflammatory spondyloarthropathy, pregnancy, comorbid conditions contraindicating surgery or inability/unwillingness to have surgery within 6 months.

Of 2720 screened, 729 were ineligible and 747 refused study participation, and 743 refused to be randomized (enrolled in the SPORT observational cohort). Five hundred one patients were randomized to receive standard open diskectomy with examination of the involved nerve root (n=245) and “usual care” (n=256), which included active physical therapy, education/counseling with home exercises, and nonsteroidal anti-inflammatory medications, if tolerated. The primary outcome was the change from baseline in the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) bodily pain and physical function scales and the American Academy of Orthopaedic Surgeons MODEMS version of the Oswestry Disability Index (ODI) at 6 weeks, 3 months, 6 months, and 1 and 2 years.

RESULTS:
The mean age was 42 years and most patients were white, with some college education, and employed. There were a large number of patients that crossed-over between study groups. Only 50% of those assigned to surgery at 3 months and 60% at 2 years underwent surgery; and, 30% of those assigned to usual care at 3 months and 45% at 2 years underwent surgery. The primary outcomes improved substantially in both groups; and, although favored surgery at each time point, did not reach statistical significance. The secondary outcomes Sciatica Bothersomeness Index and Self-rated progress demonstrated small statistically significant differences favoring surgery.

CONCLUSIONS:
Both groups improved over the 2 years period. None of the primary endpoints were statistically significant.

LIMITATIONS:
The high number of missing data (24%-27% at 2 years) and patients that crossed-over make interpretation of the intention-to-treat data difficult. In the observational cohort, despite controlling for many covariates, interpretation is also limited, as one can only draw an association and not causation. The population of the randomized controlled trial appears to be very selective. Thirteen sites were only able to enroll 501 patients over a 4.75-year study (~8 pts per site per year). Other limitations include use of subjective endpoints, which is prone to bias in an unblinded study, and nonstandardization of the actual care in the usual care group.

RELATED ARTICLES:

The patients who were eligible to the SPORT, but refused to be randomized, were included an observational trial of the same interventions and outcomes. Of the 743 enrolled, 521 (70%) chose surgery and 481 of 503 patients with available data underwent the procedure at 2 years. Twenty-two percent of the usual care group crossed-over to have surgery at 2 years. There was a significantly greater improvement in both primary outcomes at all times in the cohort that had standard open diskectomy with examination of the involved nerve root.


In this unblinded, randomized controlled trial, 129 patients with >4 months of chronic low back pain from a specialist orthopedic clinic in Taiwan, had either acupressure (provided by a single specialist) or physical therapy (referred by orthopedist but at discretion of the therapist). The mean age was 51 and most patients were married women with an education level of high school or below. The primary outcome, the Roland and Morris disability questionnaire, and secondary measures, core outcome, pain visual scale, and modified Oswestry disability questionnaire, were significantly lower in the acupressure group post treatment and at 6 months. Acupressure conferred a 89% reduction in significant disability compared to physical therapy. The NNT to reduce cases with severe disability by one was 6.
IMPACT ON INTERNAL MEDICINE:
This trial reinforces the need to evaluate many treatments that we prescribe in medicine that have not undergone rigorous testing. If we accept the gold standard for the evaluation of interventions, the RCT, standard discectomy with examination of the involved nerve root is not statistically different from the usual care group. For those undergoing the procedure, the intraoperative and postoperative complication rates are low (~5%) and 84% stayed in the hospital for 1 night or left the same day.

Inguinal hernia

Watchful waiting vs. repair of inguinal hernia in minimally symptomatic men. A randomized controlled trial

In this unblinded, randomized controlled trial at 5 North American centers, 720 men with asymptomatic or minimally symptomatic inguinal hernia were randomly assigned to watchful waiting or to receive standard Lichtenstein open tension-free repair. Cross over from watchful waiting to surgery occurred in 85 (23%) of patients and 62 (17%) assigned to surgery never had repair. After a median follow up of 3.2 years, pain and discomfort interfering with usual activities 2 years after enrollment occurred in 5.1% of patients watchfully waiting and 2.2% of surgical repairs (difference 2.86%; 95% CI, -0.04% to 5.77%; p=0.52). An additional primary endpoint, the change from baseline to 2 years in the physical component score of the SF-36, improved by 0.29 and 0.13 (of 100) in the watchful waiting and surgical repair groups, respectively (difference 0.16; 95% CI, -1.2 to 1.5). The complication rates of surgery were 21.7% and 27.9% (p=0.30) in patients assigned to surgical repair and those in watchful waiting who had repair, respectively. Only 1 acute hernia incarceration occurred and none of the 22 deaths were attributed to the study.

Acute pharyngitis

Management of acute pharyngitis in adults

Swiss prospective cohort study of 372 patients with acute pharyngitis based on use of a clinical criteria (Centor score - 2 or 4 of the following: temperature ≥ 38 C, tonsillar exudates, tender cervical adenopathy, and no cough or rhinitis) underwent rapid streptococcal antigen test (RSAT) and throat culture. RSAT had a high sensitivity (91%) and specificity (95%). Use of clinical criteria and systematic RSAT led to optimal treatment in 94% of this cohort with antibiotic prescriptions limited to 37% and therefore minimal antibiotic overuse (3%) and underuse (3%). Empiric therapy in patients with 3 or 4 Centor criteria resulted in a high rate of antibiotic use (60%) with significant overuse (32%) compared to incorporation and systematic use of RSAT.

Evaluation and treatment of pharyngitis in primary care practice

Retrospective analysis of 2097 adults with a diagnosis of pharyngitis. The 4-point Center criteria as recommended by ACP and IDSA were not predictive of the use of streptococcal testing but weakly predictive of a positive streptococcal test and antibiotic prescriptions. Adherence to ACP’s empiric strategy was 12% and to the testing strategy in 30% of visits, adherence to the IDSA in 30% of visits, and to none of the strategy in 66% of visits. Most commonly, testing or antibiotic prescription was performed in patients at low risk for pharyngitis (78%) based on the guidelines. Physicians should avoid unnecessary testing and treatment in low risk patients.
STD counseling

Condom use and the risk of genital human papillomavirus infection in young women

Prospective follow up study of 82 college female students without previous sexual intercourse or first sexual with one male during the three months prior to enrollment. Sexual history was recorded via web-based diary and subjects underwent gynecological evaluation every four weeks. Specifically the frequency of condom use by their male partners and the number of new partners. Cervicle and vaginal samples for HPV DNA and Papanicolaou testing were collected every four months. Condom use by male partners significantly reduced the likelihood of new infection with sexually transmitted disease (STD). Physicians should counsel female patients that condom is an effective method to reduced the risk of newly acquired STD.

New and important guidelines for the practicing internist

Disease prevention – influenza, tetanus, diphtheria, and pertussis

Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine

To reduce pertussis morbidity among adults and maintain the standard of care for tetanus and diphtheria prevention and to reduce the transmission of pertussis to infants and in health-care settings, the Advisory Committee on Immunization Practices (ACIP) recommends that:

- Adults aged 19--64 years should receive a single dose of Tdap to replace tetanus and diphtheria toxoids vaccine (Td) for booster immunization against tetanus, diphtheria, and pertussis if they received their last dose of Td ≥10 years earlier and they have not previously received Tdap
- Intervals shorter than 10 years since the last Td may be used for booster protection against pertussis
- Adults who have or who anticipate having close contact with an infant aged <12 months (e.g., parents, grandparents aged <65 years, child-care providers, and health-care personnel) should receive a single dose of Tdap to reduce the risk for transmitting pertussis. An interval as short as 2 years from the last Td is suggested; shorter intervals can be used. When possible, women should receive Tdap before becoming pregnant. Women who have not previously received Tdap should receive a dose of Tdap in the immediate postpartum period
- Health-care personnel who work in hospitals or ambulatory care settings and have direct patient contact should receive a single dose of Tdap as soon as feasible if they have not previously received Tdap. An interval as short as 2 years from the last dose of Td is recommended

Prevention and control of influenza

The 2006 recommendations include new and updated information. Principal changes include

- Recommending vaccination of children aged 24--59 months and their household contacts and out-of-home caregivers against influenza.
- Highlighting the importance of administering 2 doses of influenza vaccine for children aged 6 months--<9 years who were previously unvaccinated
- Advising health-care providers, those planning organized campaigns, and state and local public health agencies to a) develop plans for expanding outreach and infrastructure to vaccinate more persons than the previous year and b) develop contingency plans for the timing and prioritization of administering influenza vaccine, if the supply of vaccine is delayed and/or reduced
• Reminding providers that they should routinely offer influenza vaccine to patients throughout the influenza season
• Recommending that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A in the United States until evidence of susceptibility to these antiviral medications has been re-established among circulating influenza A viruses
• Using the 2006-07 trivalent influenza vaccine virus strains.

HIV screening

Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

Major revisions from previously published guidelines are as follows:
For patients in all health-care settings
• HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
• Persons at high risk for HIV infection should be screened for HIV at least annually.
• Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
• Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.
For pregnant women
• HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women.
• HIV screening is recommended after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
• Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
• Repeat screening in the third trimester is recommended in certain jurisdictions with elevated rates of HIV infection among pregnant women.

AHA – Beta-blocker perioperative medicine

ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: Focused on perioperative beta-blocker therapy

This expedited update was provided to help aid the practicing physician with the interpretation of the increasingly complicated data supporting the use of Beta-blockers perioperatively. This guideline reviews the strength of the evidence and makes recommendations that can be used in national quality initiatives.

• Class I benefit>>>risk (tx should be administered)
  1. β-blockers required in the recent past to control symptoms of angina or patients with symptomatic arrhythmias or hypertension, or other ACC/AHA Class I guideline indication (Level of evidence C)
  2. β-blockers: patients at high cardiac risk owing to the finding of ischemia on perioperative testing who are undergoing major vascular surgery (B)

• Class IIa benefit>>risk (tx is reasonable )
  1. β-blockers: perioperative assessment identifies untreated HTN, known CAD, or major risk factors for CAD (B)
2. β-blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk as defined by the presence of multiple clinical risk factors (B)

3. β-blockers are probably recommended for patients in whom preoperative assessment identifies CAD or high cardiac risk as defined by the presence of multiple clinical risk factors and who are undergoing intermediate- or high-risk procedures (B)

- **Class IIb benefit>risk (tx may be considered)**
  1. β-blockers may be considered for patients who are undergoing intermediate- or high-risk procedures as defined in these guidelines, including vascular surgery, in whom preoperative assessment identifies intermediate cardiac risk as defined by the presence of a single clinical risk factor (C)
  2. β-blockers may be considered in patients undergoing vascular surgery with low cardiac risk who are not currently on β-blockers (C)

- **Class III risk>benefit tx (not helpful and may be harmful)**
  1. β-blockers: should be avoided in patients with absolute contraindications to β-blockade (C)

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**Postoperative Pulmonary Complications**

**Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: A guideline from the American College of Physicians**


Recommendation 1: All patients undergoing noncardiothoracic surgery should be evaluated for the presence of the following significant risk factors for postoperative pulmonary complications in order to receive pre- and postoperative interventions to reduce pulmonary risk: chronic obstructive pulmonary disease, age older than 60 years, American Society of Anesthesiologists (ASA) class of II or greater, functionally dependent, and congestive heart failure. The following are not significant risk factors for postoperative pulmonary complications: obesity and mild or moderate asthma.

Recommendation 2: Patients undergoing the following procedures are at higher risk for postoperative pulmonary complications and should be evaluated for other concomitant risk factors and receive pre- and postoperative interventions to reduce pulmonary complications: prolonged surgery (>3 hours), abdominal surgery, thoracic surgery, neurosurgery, head and neck surgery, vascular surgery, aortic aneurysm repair, emergency surgery, and general anesthesia.

Recommendation 3: A low serum albumin level (<35 g/L) is a powerful marker of increased risk for postoperative pulmonary complications and should be measured in all patients who are clinically suspected of having hypoalbuminemia; measurement should be considered in patients with 1 or more risk factors for perioperative pulmonary complications.

Recommendation 4: All patients who after preoperative evaluation are found to be at higher risk for postoperative pulmonary complications should receive the following postoperative procedures in order to reduce postoperative pulmonary complications: 1) deep breathing exercises or incentive spirometry and 2) selective use of a nasogastric tube (as needed for postoperative nausea or vomiting, inability to tolerate oral intake, or symptomatic abdominal distention).

Recommendation 5: Preoperative spirometry and chest radiography should not be used routinely for predicting risk for postoperative pulmonary complications. Preoperative pulmonary function testing or chest radiography may be appropriate in patients with a previous diagnosis of chronic obstructive pulmonary disease or asthma.
Recommendation 6: The following procedures should not be used solely for reducing postoperative pulmonary complication risk: 1) right-heart catheterization and 2) total parenteral nutrition or total enteral nutrition (for patients who are malnourished or have low serum albumin levels).

Travel Medicine

The practice of travel medicine: Guidelines by the Infectious Diseases Society of America

This updated guideline provides detailed information regarding the several important competencies in travel medicine to include: pre-travel risk assessment, travel medicine advice, records and procedures, immunization, traveler’s diarrhea, malaria, personal safety and environmental health, and post-travel care.

Other articles of interest

Heart failure


Preventive cardiology


Anticoagulation and thromboembolism


**Obesity**


**Geriatrics**


Update in General Internal Medicine

Darrell W. Harrington, M.D.
and
Mark T. Munekata, M.D., MPH

Society of General Internal Medicine
April 2007
Disclosure of Financial Relationships

Mark T. Munekata, M.D., MPH

Has no relationships with any proprietary entity producing health care goods or services consumed by or used on patients.
Disclosure of Financial Relationships

Darrell W. Harrington, M.D.

Has relationship(s) with the following proprietary entity(s) producing health care goods or services:

Consultantship - Sanofi-Aventis, Eisai, GlaxoSmithKline, Bristol Myer Squib
Speakers Bureau - Sanofi-Aventis, Eisai, and GlaxoSmithKline
Research Support - Sanofi-Aventis, Eisai, and UMass
Goals and Objectives . . .

- Provide concise and critical evaluation of important articles relevant to the practicing internist from an “internist perspective”
  - Articles limited to those published in 2006 in “High Impact” journals
Updates

Beginning to 2006:
“The Year’s Most Important Papers in Internal Medicine Subspecialties”

2007:
“The Year’s Most Important Papers Published in ____ in Internal Medicine and the Subspecialties”
“The Year’s Most Important Published Papers for the Practicing Internist”
Methods of the Update

• Methodology:
  - Developed “categories” common in IM practice
  - Articles from 7 “High impact” journals were reviewed independently by two academic internists and ranked in order of importance.
  - There was a high level of inter-rater concordance.
  - Highly ranked articles were then collated into specific content categories and once again ranked in order of importance.

• External validity: A total of 82 articles selected for Update in GIM.
  - 28 Primary Articles reviewed (16 unique content areas)
  - 34 Related references
  - 20 Other articles of interest
## ACP GIM Update - Content

<table>
<thead>
<tr>
<th>Topics covered</th>
<th>2007</th>
<th>2006</th>
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<td><strong>Primary articles (detail)</strong></td>
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<td><strong>Related references</strong></td>
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<td><strong>Articles of interest</strong></td>
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**Topics covered:**
1. Lipids - statins have remained a hot topic
2. Diabetes Mellitus - prevention and treatment
3. Vascular Medicine - therapy for CAD, PAD, VTE, and prevention
4. Perioperative Medicine - controversial and hot topics
5. Gender Medicine - osteoporosis, HRT (male and female), BPH,
6. Cancer Screening - prostate, colon, breast, lung, cervical
7. Common office problems - Asthma, STD, ID, LBP, HA, surgical referral, geriatrics, CHF, smoking cessation, depression, thyroid dz +
Format for Today’s Update

• Review of articles in the context of a daily practice.

  - Dr. M and Dr. H share a pod together in a busy urban practice and have just arrived to a full day’s work...
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<td>50M</td>
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<td>LR</td>
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<td>57M</td>
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<td>GB</td>
<td>follow up</td>
<td>40M</td>
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<tr>
<td>11:00</td>
<td>IR</td>
<td>new</td>
<td>65F</td>
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<td>GD</td>
<td>follow up</td>
<td>59F</td>
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<tr>
<td>10:10</td>
<td>BK</td>
<td>sorethroat</td>
<td>45y</td>
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</table>
To statin or not to statin?

60 year old male with a long standing history of hypertension (BP 135/78). Current medication include aspirin 81 mg and hydrochlorothiazide 25 mg daily

T chol= 200 mg/dL; LDL-C= 135 mg/dL; HDL-C= 45 mg/dL

Framingham Risk score= 14 (10 year risk= 16%)

Target LDL-C <130 mg/dL
Key Question:
To statin or not to statin?

Should he start taking a statin?

Are statins effective at reducing coronary artery disease?
Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis

- Open label, non-controlled, blinded end-point study

- **Inclusion:**
  - At least 18 years of age with a clinical indication for coronary angiogram
  - At least 1 obstruction with >20% but <50% luminal diameter narrowing (at least 40mm). No previous intervention
  - “Statin-naïve,” defined as no more than 3 months during the previous 12 months..

- **Exclusion:**
  - Uncontrolled triglyceride levels (>500 mg/dL)
  - Poorly controlled diabetes (A1c ≥10%)

## Table 1. Baseline Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients Completing the Trial (n = 349)</th>
<th>Patients Not Completing the Trial (n = 158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.5 (10.0)</td>
<td>58.5 (10.3)</td>
</tr>
<tr>
<td>Male</td>
<td>245 (70.2)</td>
<td>115 (72.8)</td>
</tr>
<tr>
<td>White race</td>
<td>338 (96.8)</td>
<td>139 (88.0)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>85.5 (16.8)</td>
<td>86.2 (16.7)</td>
</tr>
<tr>
<td>Body mass index, median (IQR)†</td>
<td>28.4 (25.8-31.4)</td>
<td>28.9 (25.7-32.2)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>335 (96.0)</td>
<td>148 (93.7)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>46 (13.2)</td>
<td>18 (11.4)</td>
</tr>
<tr>
<td>History of acute coronary syndrome</td>
<td>60 (17.2)</td>
<td>24 (15.2)</td>
</tr>
<tr>
<td>History of prior myocardial infarction</td>
<td>86 (24.6)</td>
<td>35 (22.2)</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>292 (83.7)</td>
<td>132 (83.5)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>186 (53.3)</td>
<td>72 (45.6)</td>
</tr>
<tr>
<td>Angiotensin receptor antagonists</td>
<td>64 (18.3)</td>
<td>21 (13.3)</td>
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<tr>
<td>Organic nitrates</td>
<td>297 (85.1)</td>
<td>138 (87.3)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>294 (84.2)</td>
<td>116 (73.4)</td>
</tr>
</tbody>
</table>

*Data are expressed as number (percentage) unless otherwise specified.
†Calculated as weight in kilograms divided by the square of height in meters.

• Of 1183 patients screened, 507 (42.9%) received rosuvastatin 40 mg/d, but only 349 (68.8% of enrolled) had IVUS data that could be evaluated

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Median (IQR)</th>
<th>During Treatment</th>
<th>Median (IQR)</th>
<th>Percent Change, Least-Square Mean (95% CI)†</th>
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<tr>
<td>Total cholesterol, mg/dL</td>
<td>204 (41.2)</td>
<td>197 (179-224)</td>
<td>133.8 (25.4)</td>
<td>130 (116-148)</td>
<td>−33.8 (−35.6 to −31.9)</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>130.4 (34.3)</td>
<td>127 (109-145)</td>
<td>60.8 (20.0)</td>
<td>58 (47-72)</td>
<td>−53.2 (−55.6 to −50.9)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>43.1 (11.1)</td>
<td>41 (35-49)</td>
<td>49.0 (12.6)</td>
<td>47 (41-54)</td>
<td>+14.7 (12.3 to 17.1)</td>
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<table>
<thead>
<tr>
<th>Primary efficacy parameters</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change</th>
<th>Percent Change</th>
<th>No. (%) With Regression</th>
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</thead>
<tbody>
<tr>
<td>Percent atheroma volume</td>
<td>39.0 (8.5)</td>
<td>35.5 (8.5)</td>
<td>−3.5 (3.15)</td>
<td>NA</td>
<td>222 (63.6)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>39.9 (33.8-45.3)</td>
<td>38.5 (32.6-44.3)</td>
<td>−0.79 (−1.21 to −0.53)*†</td>
<td>NA</td>
<td>249 (78.1)</td>
</tr>
<tr>
<td>Atheroma volume in most</td>
<td>55.1 (37.0)</td>
<td>50.0 (34.5)</td>
<td>5.1 (10.4)</td>
<td>8.5 (13.7)</td>
<td>249 (78.1)</td>
</tr>
<tr>
<td>diseased 10-mm subsegment, mm² (n = 319)</td>
<td>65.1 (45.2-62.2)</td>
<td>58.4 (40.6-76.3)</td>
<td>−5.6 (−6.82 to −3.96)*†</td>
<td>−9.1 (−10.83 to −7.23)*†</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3. Relationship Between Mean Low-Density Lipoprotein Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Trials

There is a close correlation between these 2 variables ($r^2=0.97$). REVERSAL indicates Reversal of Atherosclerosis With Aggressive Lipid-Lowering; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; A-Plus, Avasimibe and Progression of Lesions on Ultrasound; and ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden.
ASTEROID- limitations

- The study was without control. The mean LDL-C was 130 mg/dL.
- Limited applicability
- 158 (31.2%) patients not analyzed due to lack of data.
- Atheroma volume may not correlate with clinical outcomes.
Case Resolution

- This patient does not fit the inclusion criteria for the trial.
- His target remains the same: <130 mg/dL
- No statin therapy needed.
NCEP ATP III Guidelines

• Coronary Heart Disease risk equivalent:
  - Diabetes
  - Multiple risk factors that confer a 10-year risk for CHD >20%
  - Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
To statin or not to statin?

68 year old female with a long standing history of hypertension. A few months ago, she woke feeling that her left arm was clumsy. The symptoms resolved by dinner. A work-up at that time, including carotid ultrasound and head CT were negative.

Current medication include aspirin 81 mg, hydrochlorothiazide 25 mg, lisinopril 10mg, atorvastatin 80 mg daily. She is a former smoker.
To statin or not to statin?

BP = 140/85

Baseline lipid profile:
T chol = 212 mg/dL; LDL-C = 135 mg/dL; HDL-C = 50 mg/dL

Current: LDL-C 68 mg/dL

Framingham Risk = 10 year risk = 10%
Is there benefit to aggressive lowering of LDL-C in patient with cerebrovascular disease?
High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

• Double blind, placebo-controlled, randomized trial.
• Inclusion:
  - Ambulatory subjects over 18 years of age
  - Ischemic or hemorrhagic stroke or TIA within 1 to 6 months
  - Modified Rankin score of 3 or less
  - LDL-C >100 mg/dL and ≤ 190 mg/dL
• Exclusion:
  - Atrial fibrillation
  - Other cardiac sources of embolism
  - Subarachnoid hemorrhage
• The average patient was...


**Table 1. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atorvastatin (N = 2365)</th>
<th>Placebo (N = 2366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>63.0±0.2</td>
<td>62.5±0.2</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>1427 (60.3)</td>
<td>1396 (59.0)</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>138.9±0.4</td>
<td>138.4±0.4</td>
</tr>
<tr>
<td>Diastolic blood pressure — mm Hg</td>
<td>82.0±0.2</td>
<td>81.4±0.2</td>
</tr>
<tr>
<td>Body-mass index†</td>
<td>27.5±0.1</td>
<td>27.4±0.1</td>
</tr>
<tr>
<td>Entry event — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1655 (70.0)</td>
<td>1613 (68.2)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>1595 (67.4)</td>
<td>1559 (65.9)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>45 (1.9)</td>
<td>48 (2.0)</td>
</tr>
<tr>
<td>Other type or not determined</td>
<td>15 (0.6)</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>TIA</td>
<td>708 (29.9)</td>
<td>752 (31.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Time since entry event — days</td>
<td>87.1±1.0</td>
<td>84.3±1.0</td>
</tr>
<tr>
<td>Risk factors — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>452 (19.1)</td>
<td>456 (19.3)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>963 (40.7)</td>
<td>918 (38.8)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>1476 (62.4)</td>
<td>1452 (61.4)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>395 (16.7)</td>
<td>399 (16.9)</td>
</tr>
</tbody>
</table>
### SPARCL

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior statin therapy — no. (%)</td>
<td>57 (2.4)</td>
<td>63 (2.7)</td>
</tr>
<tr>
<td>Concomitant therapy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin or other antiplatelet drug, excluding heparin</td>
<td>2067 (87.4)</td>
<td>2063 (87.2)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>683 (28.9)</td>
<td>667 (28.2)</td>
</tr>
<tr>
<td>Dihydropyridine derivative</td>
<td>350 (14.8)</td>
<td>359 (15.2)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>414 (17.5)</td>
<td>422 (17.8)</td>
</tr>
<tr>
<td>Angiotensin II–receptor antagonist</td>
<td>110 (4.7)</td>
<td>102 (4.3)</td>
</tr>
<tr>
<td>Vitamin K antagonist, including warfarin</td>
<td>139 (5.9)</td>
<td>154 (6.5)</td>
</tr>
</tbody>
</table>

### Lipids — mg/dl:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>132.7±0.5</td>
<td>133.7±0.5</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>50.0±0.3</td>
<td>50.0±0.3</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>211.4±0.6</td>
<td>212.3±0.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>144.2±1.9</td>
<td>143.2±1.4</td>
</tr>
<tr>
<td>Apolipoprotein A1</td>
<td>149.1±0.6</td>
<td>149.6±0.6</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>133.1±0.5</td>
<td>134.1±0.5</td>
</tr>
</tbody>
</table>

• 6670 screened, 4731 (70.9%) randomized to receive 80 mg of atorvastatin (n=2365) or placebo (n=2366).
• LDL-C in atorvastin group 73 mg/dL during study.
• After 4.9 years of follow-up, the primary endpoint was significantly decreased in the atorvastatin group.

SPARCL


<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Atorvastatin (N=2365)</th>
<th>Placebo (N=2366)</th>
<th>Unadjusted P Value†</th>
<th>Prespecified Adjusted Model‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal or fatal stroke§</td>
<td>265 (11.2)</td>
<td>311 (13.1)</td>
<td>0.05</td>
<td>0.84 (0.71–0.99)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>247 (10.4)</td>
<td>280 (11.8)</td>
<td>0.14</td>
<td>0.87 (0.73–1.03)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>24 (1.0)</td>
<td>41 (1.7)</td>
<td>0.04</td>
<td>0.57 (0.35–0.95)</td>
</tr>
</tbody>
</table>

NNT 51

124
Table 3. Incidence of Adverse Events and Elevated Laboratory Values.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin (N=2365)</th>
<th>Placebo (N=2366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>2199 (93.0)</td>
<td>2156 (91.1)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>988 (41.8)</td>
<td>975 (41.2)</td>
</tr>
<tr>
<td>Any adverse event resulting in discontinuation of study treatment</td>
<td>415 (17.5)</td>
<td>342 (14.5)</td>
</tr>
<tr>
<td>Musculoskeletal adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>129 (5.5)</td>
<td>141 (6.0)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>7 (0.3)</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>Rhabdomyolysis†</td>
<td>2 (0.1)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Laboratory value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT or AST &gt;3× ULN at 2 consecutive measurements</td>
<td>51 (2.2)</td>
<td>11 (0.5)</td>
</tr>
<tr>
<td>Creatine kinase &gt;10× ULN at 2 consecutive measurements</td>
<td>2 (0.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Hemorrhagic stroke 55 (2.3%) 33 (1.4%) 110

SPARCL- limitations

• The study was without an active control.

• The average patient was higher risk (63-year-old, overweight male, and approximately 62% had hypertension, 60% were current or former smokers, 17% were diabetic) and would require reduction of LDL-C.

• Cannot draw conclusions on a target LDL-C
Case Resolution

- High dose atorvastatin decreases the risk of second cerebrovascular event, as well as cardiovascular events. However, there was an increase in hemorrhagic stroke.

- Continue patient on current therapy.

- Optimize other cardiovascular risk (BP)
"To statin or not to statin"- that may not be the question

• Must weigh the risks and benefits of highest dose statin therapy.

• Calculate Framingham Risk for patients to determine LDL-C goal.

• It is well known that, in addition to lowering lipids, statins have other pleiotropic effect. These studies suggest additional indications for HMG CoA reductase inhibitor therapy.

• Unanswered questions
  - Class effect or drug effect?
  - How low should we go?
“An ounce of prevention…”

43 year old white, overweight, smoking female is following up for impaired fasting glucose levels. She is not taking any medications, but has been attempting lifestyle changes for the last few months.

Family history significant for diabetes and osteoporosis in her mother.

Ht=67 inches, Wt=173 lbs, BMI 27
Waist=34 inches
BP= 135/85
“An ounce of prevention...”

• Diabetes “prevention” in patients with impaired fasting glucose or impaired glucose tolerance:
  - Intensive lifestyle modification.
  - Metformin
  - Acarbose
  - Troglitazone (withdrawn from market)

Are ACE inhibitors effective at preventing diabetes?

Effect of Ramipril on the Incidence of Diabetes (DREAM)

- Double-blind, placebo-controlled, RCT
- Inclusion:
  - 30 years of age
  - impaired fasting glucose or impaired glucose tolerance
  - no history of diabetes, cardiovascular disease, or intolerance of either angiotensin-converting enzyme inhibitors or thiazolidinediones.
## Table 1. Baseline Characteristics of the Study Participants.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ramipril (N = 2523)</th>
<th>Placebo (N = 2646)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>54.7±10.9</td>
<td>54.7±10.9</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Median local fasting plasma glucose level — mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>106.3</td>
<td>106.5</td>
<td>0.46</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>97.3–113.5</td>
<td>97.3–115.3</td>
<td></td>
</tr>
<tr>
<td><strong>2-Hr local plasma glucose level — mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>155.6</td>
<td>157.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>144.1–173.7</td>
<td>144.1–175.6</td>
<td></td>
</tr>
<tr>
<td><strong>Weight — kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>84.8±18.9</td>
<td>85.0±19.0</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Body-mass index</strong></td>
<td>30.9±5.6</td>
<td>30.9±5.7</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Waist-to-hip ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.96±0.07</td>
<td>0.96±0.07</td>
<td>0.31</td>
</tr>
<tr>
<td>Women</td>
<td>0.86±0.08</td>
<td>0.87±0.08</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Blood pressure — mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136.1±18.6</td>
<td>136.0±18.1</td>
<td>0.80</td>
</tr>
<tr>
<td>Diastolic</td>
<td>83.4±10.8</td>
<td>83.4±10.8</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Isolated impaired glucose tolerance — no. (%)</strong></td>
<td>1513 (57.7)</td>
<td>1515 (57.3)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Isolated IFG — no. (%)</strong></td>
<td>366 (14.0)</td>
<td>373 (14.1)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Impaired glucose tolerance and IFG — no. (%)‡</strong></td>
<td>744 (28.4)</td>
<td>758 (28.6)</td>
<td>0.83</td>
</tr>
</tbody>
</table>
24,592 patient screened, 5808 entered a run-in phase, and 5269 were randomized to ramipril (dose increased from 5 mg/d to 15 mg/d at 1 year) or placebo.

After a median of 3.0 years of follow-up, there was no significant difference in the primary outcome.

### Table 2. Hazard Ratios for Primary Outcome and Regression to Normoglycemia.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ramipril (N = 2623)</th>
<th>Placebo (N = 2646)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>475 (18.1)</td>
<td>517 (19.5)</td>
<td>0.91 (0.81–1.03)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diagnosed on the basis of fasting plasma glucose level and 2-hr post-load glucose level</td>
<td>375 (14.3)</td>
<td>411 (15.5)</td>
<td>0.91 (0.79–1.04)</td>
<td></td>
</tr>
<tr>
<td>Diagnosed by physician</td>
<td>74 (2.8)</td>
<td>78 (2.9)</td>
<td>0.95 (0.69–1.30)</td>
<td></td>
</tr>
<tr>
<td>Death*</td>
<td>31 (1.2)</td>
<td>32 (1.2)</td>
<td>0.98 (0.60–1.60)</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Regression to normoglycemia (%)</th>
<th>Ramipril</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-hour postprandial glucose (mg/dL)</td>
<td>135.1</td>
<td>140.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year of Follow-up</th>
<th>Placebo</th>
<th>Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2646</td>
<td>2623</td>
</tr>
<tr>
<td>1</td>
<td>2510</td>
<td>2498</td>
</tr>
<tr>
<td>2</td>
<td>2277</td>
<td>2287</td>
</tr>
<tr>
<td>3</td>
<td>1240</td>
<td>1218</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>194</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.91; 95% CI, 0.81–1.03; P=0.15

Hazard ratio, 1.16; 95% CI, 1.07–1.27; P=0.001

Regression to normoglycemia (%)

2-hour postprandial glucose (mg/dL)
In the other arm, rosiglitazone decreased the incidence of diabetes from 26% to 11.6%, but increased risk of CHF from 0.1% to 0.5%.
“...a pound of cure”

- Her likelihood of developing diabetes is about 6% per year.

What are the best treatments to initiate for diabetics?
Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

- Multinational, double-blind, randomized trial.
- Inclusion:
  - ages of 30 to 75 years old
  - fasting plasma glucose between 126 and 180 mg/dL.
- Exclusion
  - clinically significant hepatic disease
  - renal impairment
  - hx of lactic acidosis
  - unstable or severe angina
  - known congestive heart failure
  - uncontrolled hypertension.

• Of 6676 patient screened, 4360 initially randomized, but 4127 (95%) patients for analysis.

• The average patient: 57 year old male with diabetes <2 years, BMI 32, FBG 152 mg/dL, A1c 7.36%

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>4 mg daily</td>
<td>4 mg bid</td>
</tr>
<tr>
<td>Metformin</td>
<td>500 mg daily</td>
<td>1000 mg bid</td>
</tr>
<tr>
<td>Glyburide</td>
<td>2.5 mg daily</td>
<td>7.5 mg bid</td>
</tr>
</tbody>
</table>

The primary endpoint was time to treatment failure, defined as a fasting plasma glucose >180 mg/dL on consecutive testing after at least 6 weeks of treatment at the maximum dictated or tolerated dose.
<table>
<thead>
<tr>
<th>Treatment failure (cum. incidence)</th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>21%</td>
<td>0.68 (0.55-0.85)</td>
<td>&lt;0.001</td>
<td>17</td>
<td>34%</td>
<td>0.37 (0.30-0.45)</td>
<td>&lt;0.001</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>A1c&lt;7% @ 4yrs</td>
<td>40%</td>
<td>36%</td>
<td>0.03</td>
<td>26%</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt change (kg) @ 5 yrs</td>
<td>+4.8</td>
<td>-2.9</td>
<td>&lt;0.001</td>
<td>+1.6</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SELECT AEs**

<table>
<thead>
<tr>
<th>CV event</th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>62 (4.3%)</td>
<td>58 (4.0%)</td>
<td>NS</td>
<td>26 (1.8%)</td>
<td>&lt;0.05</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>22 (1.5%)</td>
<td>19 (1.3%)</td>
<td>NS</td>
<td>9 (0.6%)</td>
<td>&lt;0.05</td>
<td>167</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GI events</th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>335 (23.0%)</td>
<td>557 (38.3%)</td>
<td>&lt;0.01</td>
<td>7</td>
<td>316 (21.9%)</td>
<td>NS</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>142 (9.8%)</td>
<td>168 (11.6%)</td>
<td>NS</td>
<td>557 (38.7%)</td>
<td>&lt;0.01</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight gain</th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 (6.9%)</td>
<td>18 (1.2%)</td>
<td>&lt;0.01</td>
<td>18</td>
<td>47 (3.3%)</td>
<td>&lt;0.01</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower limb fx, women</th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 (5.6%)</td>
<td>18 (3.1%)</td>
<td>&lt;0.05</td>
<td>40</td>
<td>8 (1.3%)</td>
<td>&lt;0.01</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upper limb fx, women</th>
<th>Rosiglitazone</th>
<th>Metformin</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
<th>Glyburide</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 (3.4%)</td>
<td>10 (1.7%)</td>
<td>NS</td>
<td>9</td>
<td>&lt;0.05</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P values compare to metformin rosiglitazone and glyburide to rosiglitazone.

ADOPT-limitations

• **Rosiglitazone**
  - *Plus:* fewest monotherapy failures
  - *Minus:* more fractures in women; and, greater weight gain and a higher LDL-C resulting in use of diuretics and statins

• **Metformin:**
  - *Minus:* More than a third of patients noted gastrointestinal events.

• **Glyburide**
  - *Plus:* fewer cardiovascular events, particularly congestive heart failure
  - *Minus:* greatest number of failures and hypoglycemic symptoms.

Case Resolution & Impact on IM

- Effect on long term outcomes?
- Best second agent?
- There may be no perfect medication.
- In addition to pharmacological therapy, a multidisciplinary approach, including case management and team changes, to chronic disease is necessary.
- Start metformin.

The American Diabetes Association and European Association for the Study of Diabetes consensus statement

64 year old male former smoker with known HTN, hyperlipidemia and type 2 DM has been followed for 3 years. He is compliant with all meds and complains of claudication at two block.

**Meds:**
- Aspirin 81 mg/day
- Fluvastatin 20 mg/day
- Amlodipine 10 mg/day
- Maxzide 50 mg/day
- Metformin 1000 mg bid
- Glipizide 10 mg bid
- Lisinopril 40 mg/day
- Cilastazol 100 mg bid
Vascular Medicine

- **Exam: BP - 135/74  HR - 66**
  - His exam is unremarkable except for evidence of decreased peripheral pulses in both lower extremities - DP/PT pulses trace to 1+. No edema or ulcers present.
  
- **Most recent studies:**
  - Lipids LDL - 102 mg/dl, HDL - 44 mg/dl
  - ABI = 0.68 (Mild to moderate)
Key Questions

• What additional therapy might benefit the patient?

• Is there a role for exercise?
  - Are non-supervised programs effective?
Peripheral Arterial Disease

• 20-30% of older patients in general medical practices

• Symptomatic PAD = increased risk for CV mortality.

• Aggressive lifestyle modification and appropriate use of optimal medical therapy (ACE-I, Statin, Anti-HTN, Anti-Plt Tx)
  - Cilostozal and Pentoxyphylline are the only FDA approved drugs for claudication.

• Supervised walking program - 30 mins, 3 d/week
Physical Performance in PAD: A Slower Rate of Decline in Patients who Walk More

- 417 men and women with PAD were evaluated prospectively with a median follow up of 36 months. Subjects were classified at baseline and annually according to weekly walking frequency.
  - **Primary Outcome**: Functional assessments using 6-minute walk distance, 4-meter walking speed, and a summary performance score were measured at baseline and annually.
  - The average patient was 72 years old, white, BMI ~ 27, ABI= 0.66, high-school educated with Arthritis (40%), Diabetes (~30%), CV disease (~57%)

Results: Compared with those who exercised less frequently, patients who walked for exercise ≥ 3/week had a significantly reduced average annual decline.

Conclusions: Among patients with PAD, self-directed walking exercise performed at least 3 times weekly is associated with less functional decline in subsequent years.
Self-directed exercise and functional decline in **asymptomatic** patients with PAD

- Asymptomatic patients with PAD are at risk of functional decline.
- Medical therapies have unknown benefit in this population.
- A strong trend towards benefit of a self-directed walking program was also observed for this asymptomatic subgroup.

The Long-term Prognostic Value of the Resting and Postexercise ABI

- Prospective cohort of 3209 patients with resting and postexercise ABI values.
- Primary Endpoint: overall survival
- Results: During the 8 year follow-up 41% of patients died. Post exercise ABI values were associated with increased mortality even in patients with normal resting ABIs.
- Conclusion: Postexercise ABIs may identify additional patients at risk of subsequent mortality.

Case Resolution & Impact on IM

- Self-directed programs may be an effective alternative in the management of symptomatic PAD.
  - In a posthoc analysis, the results remained robust even after control for use of cilostazol and pentoxifylline.

- This study also underscores the importance of routine screening of at risk patients for PAD with ABIs as PAD is underdiagnosed in the Primary Care setting.

- Post exercise ABI may be a more sensitive test in diagnosing the asymptomatic patient.
Vascular Medicine

- 61 year old female with well controlled HTN and type 2 DM. She had a TIA 6 weeks ago while traveling in Italy. Carotid duplex results are unknown. No recurrent symptoms. No history of CAD with fair functional status (vacuums one room at a time).

- Meds:
  - Aspirin 81 mg/day
  - Fluvastatin 20 mg/day
  - Amlodipine 10 mg/day
  - Maxzide 50 mg/day
  - Metformin 1000 mg bid
  - Glipizide 10 mg bid
  - Lisinopril 40 mg/day
Vascular Medicine

- Exam: BP – 122/64  HR – 66
  - Her exam is unremarkable except for Loud bruit heard in left carotid. Normal upstroke. No murmurs were appreciated. Evidence of decreased peripheral pulses in both lower extremities – 1+ was also noted.
  - ABIs = 0.88; were performed 2 months ago
Key Question

- Should this patient be placed on dual anti-platelet therapy for primary prevention of CAD or secondary prevention of CVA?
Clopidogrel and ASA vs. ASA Alone for the Prevention of Atherothrombotic Events

- DBRCT of 15,603 patients with clinically evident CV dz or multiple risk factors.
  - Clopidogrel (75 mg/day) + ASA (75 - 162 mg/day) vs. ASA + Placebo

- Primary endpoint - composite of MI, CVA, or death from CV cause (Follow up = 28 mos)
  - Exclusions - recent ACS, long-term use of NSAIDs, recent/indication for PCI.

- Average Patient - 64 y/o white male, documented CVD, hx of smoking, HTN. ↑lipids, on ASA, 75% on statins, 55% on BB.

CHARISMA

- Primary endpoint: no difference
- Subgroup analysis
  - Multiple Risk Factors - 3.9 vs. 2.2% (P=0.01) for CV death.
  - Clinically evident atherothrombotic events - 6.9 vs. 7.8% (P=0.046) for CV death.
- Secondary endpoints:
  - Composite of Primary endpoint and hospitalization/revascularization
  - Sev. Bleeding (1.7 vs. 1.3%), P=0.09
  - Mod. Bleeding (2.1 vs. 1.3%), P<0.001
- Conclusions: Dual therapy was overall not more effective than ASA alone, but may be associated with increased harm.

Case Resolution & Impact on IM

• While combination anti-platelet therapy has proven useful in the setting of ACS (ie. COMMIT Trial), the benefits can not be extrapolated to long-term use for primary and secondary prevention.

• This trial is consistent with other recently published data which demonstrate superiority of oral anticoagulation over dual therapy in the setting of atrial fibrillation (ACTIVE IV)*.

• Dual antiplatelet therapy has limited long-term use and may be associated with increased risk of bleeding complications and death.

• The clinic nurse interrupts and states that she found a fax from Italy (already translated) with the results of the Carotid Duplex.

70% stenosis of Right Internal Carotid Artery
Key Questions

• Should I refer this patient to carotid endarterectomy?
  - Isn’t this a safer alternative given her poor functional status?
  - The results stenting are just as good as CEA, right?
CEA versus Stenting in Patients with Symptomatic Severe Carotid Stenosis

- Multi-center RCT of symptomatic (>60%) carotid stenosis randomized to CEA vs. CAS. Qualifying event must be within 120 days before enrollment.
- Primary endpoint: Stroke or death within 30 days of procedure.
- Exclusion: history of disabling stroke, severe tandem lesions, previous revascularization, life expectancy < 2 yrs, uncontrolled HTN or DM.
- Average patient: 70 y/o male (~75%), HTN, ↑ lipids, antiplatelet Rx (50%), with TIA/CVA (84%)

### CEA versus Stenting in Patients with Symptomatic Severe Carotid Stenosis

**Table 3. Risk of Stroke or Death and Other Treatment-Related Outcomes within 30 Days after Endarterectomy or Stenting.**

<table>
<thead>
<tr>
<th>Outcome Event</th>
<th>Endarterectomy (N = 259)</th>
<th>Stenting (N = 261)</th>
<th>Unadjusted Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7 (2.7) †</td>
<td>23 (8.8) ‡</td>
<td>3.3 (1.4–7.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Symptoms lasting 7 days or more</td>
<td>6 (2.3)</td>
<td>20 (7.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondisabling</td>
<td>6 (2.3)</td>
<td>16 (6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabling§</td>
<td>1 (0.4)</td>
<td>7 (2.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3 (1.2)</td>
<td>2 (0.8)</td>
<td>0.7 (0.1–3.9)</td>
<td>0.68</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>2 (0.8) †</td>
<td>1 (0.4) ‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other cause</td>
<td>1 (0.4) †</td>
<td>1 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any stroke or death</td>
<td>10 (3.9)</td>
<td>25 (9.6)</td>
<td>2.5 (1.2–5.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Any disabling stroke or death</td>
<td>4 (1.5)</td>
<td>9 (3.4)</td>
<td>2.2 (0.7–7.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.8)</td>
<td>6 (2.3)</td>
<td>3.0 (0.6–14.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>Myocardial infarction**</td>
<td>2 (0.8)</td>
<td>1 (0.4)</td>
<td>0.5 (0.04–5.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Bradycardia or hypotension††</td>
<td>0</td>
<td>11 (4.2)</td>
<td>Not computable</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic complications</td>
<td>8 (3.1) ††</td>
<td>5 (1.9) ‡‡</td>
<td>0.6 (0.2–1.9)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Results: The trial was stopped prematurely after the inclusion of 527 patients for reasons of safety and futility. Overall, CAS was associated with a RR = 2.5 for any stroke or death within 30 days. In addition, there were more major local complications after CAS.

<table>
<thead>
<tr>
<th>Event</th>
<th>Endarterectomy Group N=262</th>
<th>Stenting Group N=265</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke or death at 30 days† plus ipsilateral stroke between 31 days and 6 mo</td>
<td>11 (4.2)</td>
<td>27 (10.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Any stroke or death at 30 days† plus any stroke between 31 days and 6 mo</td>
<td>12 (4.6)</td>
<td>29 (10.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Any stroke or death within 6 mo†</td>
<td>16 (6.1)</td>
<td>31 (11.7)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Case Resolution & Impact on IM

- CEA remains the procedure of choice for asymptomatic patients and symptomatic patients not at high risk for adverse surgical outcomes.

- The SAPPHIRE Trial showed that perioperative risk (esp. MI) were reduced with CAS and no difference was seen in stroke or death at 30 days. However, CAS is only FDA approved for symptomatic patients.

  - A significant learning curve for CAS is still prevalent. Therefore, it is important to ensure standardized training and credentialing requirements for operators of this new approach.
59 year old obese male with history of HTN on hormone therapy for prostate cancer presents to ED with one day history of sudden onset of shortness of breath and right posterior chest pain. Symptoms have improved slightly over the last few hours.

- **Exam:** BP – 154/94   HR – 108 (↓ to 92 with fluids)   RR – 20
- ECG with sinus tachycardia without ST-TW △
  - CT angiogram - no evidence of thrombus. Small RLL atelectasis. No cardiomegaly or effusions. (official read).
- The ED physician calls for an appointment and close follow up after this “negative” work evaluation.
Key Questions

- Should I be satisfied that this patient has been sufficiently evaluated for pulmonary embolism?
  - What is the role of D-dimer in patients with high probability PE?
  - Is a CT angiogram adequate to rule out disease?
Clinical Probability Score Used in Patients with Suspected Pulmonary Embolism (Well’s Criteria)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (swelling and pain)</td>
<td>3</td>
</tr>
<tr>
<td>PE as likely or more likely than an alternative diagnosis</td>
<td>3</td>
</tr>
<tr>
<td>Immobilization (bedrest &gt;3 days or recent surgery &lt; 4 wks)</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Heart Rate &gt; 100/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Active Cancer (treatment ongoing or w/in past 6 mos)</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

Low Probability < 2  (2.8%)
Moderate Probability 2-6 (28%)
High Probability > 6 (79%)

Clinical Probability Score Used in Patients with Suspected Pulmonary Embolism (Revised Geneva Score)

Risk Factors
- Age > 65 years 1
- Previous DVT or PE 3
- Surgery (with GA) or Fracture 2
- Active Malignancy 2

Symptoms
- Unilateral lower-limb pain 3
- Hemoptysis 2

Clinical Signs
- Heart Rate
  - 75-94 beats/min 3
  - >95 beats/min 5
- Pain on lower-limb deep palpation and unilateral edema 4

Low Prob. 0 - 3 (7.3%)
Moderate Prob. 4-10 (35.1%)
High Prob. > 11 (76.9%)

• 3 University Hospital ED in Europe.
• 956 in derivation cohort and 749 in validation cohort.

Arch Int Med. 2004;164:2483-87
Increased thrombin Production due to:
• Surgery
• Trauma
• Infection
• Inflammation
• Disseminated intra-vascular coagulation
• Pregnancy and delivery
• Thrombosis

Plasmin Degradation of a Fibrin Clot
Sensitivity Analysis of D-dimer for Acute VTE

<table>
<thead>
<tr>
<th>Cutoff 500 ng/mL: Tier 3 analysis (all data)†</th>
<th>Deep Venous Thrombosis</th>
<th>Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity (95% CL)</td>
<td>Specificity (95% CL)</td>
</tr>
<tr>
<td>ELISA</td>
<td>0.94‡ (0.89–0.98)</td>
<td>0.43 (0.36–0.50)</td>
</tr>
<tr>
<td>Quantitative rapid ELISA</td>
<td>0.97‡ (0.92–1.00)</td>
<td>0.42 (0.32–0.52)</td>
</tr>
<tr>
<td>Semi-quantitative rapid ELISA</td>
<td>0.91‡ (0.85–0.98)</td>
<td>0.43 (0.34–0.52)</td>
</tr>
<tr>
<td>Qualitative rapid ELISA</td>
<td>0.93‡ (0.87–0.99)</td>
<td>0.53 (0.43–0.64)</td>
</tr>
<tr>
<td>Quantitative latex</td>
<td>0.88 (0.80–0.95)</td>
<td>0.59 (0.49–0.69)</td>
</tr>
<tr>
<td>Semi-quantitative latex</td>
<td>0.78 (0.69–0.87)</td>
<td>0.70 (0.62–0.78)</td>
</tr>
<tr>
<td>Whole-blood</td>
<td>0.82 (0.76–0.89)</td>
<td>0.70 (0.64–0.76)</td>
</tr>
</tbody>
</table>

D-dimer in Clinical Practice

Conclusions:
1. A non-invasive and quick test can be used to reliably exclude both DVT and PE.
2. The ultimate use of a D-dimer will depend on the clinical context (pretest probability) and specific D-dimer method employed.

*In addition, the D-dimer assay may remain elevated for several months following an acute VTE.
Diagnostic Management and Outcomes of Suspected PE

• Prospective cohort of 1529 pts in 116 ED with 3 mo f/u
• Each patient was assessed for adherence to appropriate diagnostic criteria and standards

• Results: Diagnostic mgmt was inappropriate in 43% of patients including 8% of confirmed PE and 57% PE ruled out.

Ann Intern Med. 2006;144:157-164
# Diagnostic Management and Outcomes of Suspected PE

**Table 3. Patient Outcomes at 3 Months after Exclusion of Pulmonary Embolism**

<table>
<thead>
<tr>
<th>Diagnostic Work-up</th>
<th>Patients Receiving Appropriate Management (n = 418)</th>
<th>Patients Receiving Inappropriate Management (n = 506)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thromboembolic events, n (%)</td>
<td>5 (1.2)</td>
<td>39 (7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal thromboembolic event, n</td>
<td>2</td>
<td>10</td>
<td>0.045</td>
</tr>
<tr>
<td>Unexplained sudden death, n</td>
<td>3</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Patients who received anticoagulation for reasons other than thromboembolic disease were excluded from follow-up analysis.
PIOPED II

- Prospective multi-center study to investigate the accuracy of multi-detector CTA alone and with venous phase imaging for the diagnosis of PE compared to a reference standard.

  - 824 adult patients (~ 90% outpatient) suspected of PE and underwent 4-row multi-detector CTA after clinical assessment using Wells Criteria. (7284 patients suspected of PE were initially screened with 3262 eligible patients – 2172 of these not enrolled.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pulmonary Embolism (N=192)</th>
<th>No Pulmonary Embolism (N=632)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>DSA</td>
<td>33 (17)</td>
<td>192 (30)</td>
</tr>
<tr>
<td>Ventilation-perfusion scanning†</td>
<td>109 (57)</td>
<td>146 (23)</td>
</tr>
<tr>
<td>Ultrasonography of lower extremities with abnormal findings, no previous DVT at same site, and nondiagnostic ventilation-perfusion scanning</td>
<td>50 (26)</td>
<td>NA</td>
</tr>
<tr>
<td>Ventilation-perfusion scanning indicating low or very low probability of disease, low clinical probability, and normal findings on ultrasonography‡</td>
<td>NA</td>
<td>294 (47)</td>
</tr>
</tbody>
</table>

PIOPED II

• **Results:** Overall 23% of patients diagnosed with PE. Overall Sensitivity of 83% and Specificity of 96%.

<table>
<thead>
<tr>
<th>Variable</th>
<th>High Clinical Probability</th>
<th>Intermediate Clinical Probability</th>
<th>Low Clinical Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./Total No.</td>
<td>Value (95% CI)</td>
<td>No./Total No.</td>
</tr>
<tr>
<td>Positive predictive value of CTA</td>
<td>22/23</td>
<td>96 (78–99)</td>
<td>93/101</td>
</tr>
<tr>
<td>Positive predictive value of CTA or CTV</td>
<td>27/28</td>
<td>96 (81–99)</td>
<td>100/111</td>
</tr>
<tr>
<td>Negative predictive value of CTA</td>
<td>9/15</td>
<td>60 (32–83)</td>
<td>121/136</td>
</tr>
<tr>
<td>Negative predictive value of both CTA and CTV</td>
<td>9/11</td>
<td>82 (48–97)</td>
<td>114/124</td>
</tr>
</tbody>
</table>

• **Conclusions:**
  - MDS are better than single detector scanners.
  - CTV added very little overall to the diagnostic accuracy
  - Clinicians should incorporate proven clinical judgment as discordant CTA results may be misleading.

### Clinical Assessment & V/Q Lung Scan Probability:

<table>
<thead>
<tr>
<th>Clin Prob</th>
<th>V/Q Lung Scan Prob</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Lo</td>
<td>2%</td>
</tr>
<tr>
<td>Int</td>
<td>6%</td>
</tr>
<tr>
<td>Hi</td>
<td>0%</td>
</tr>
</tbody>
</table>

PIOPED Study, JAMA 1990
The British Thoracic Society

Assess clinical probability

<table>
<thead>
<tr>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer N/A</td>
<td>SimpliRED available</td>
<td>Vidas/MDA available</td>
</tr>
</tbody>
</table>

D-dimer assay

Positive | Negative

Start LMWH
CT pulmonary angiogram

PE present | No PE

Add warfarin | Another diagnosis
Case Resolution & Impact on IM

• D-dimers reliably exclude Pulmonary embolism in patients with low PTP in both the inpatient and outpatient setting and can avoid unnecessary additional testing. (This may also be true for more sensitive D-dimers in the moderate PTP patient).

• Clinicians should consider further testing in patients with discordant PTP and results on multidetector CTA.

• Clinicians should use validated models and consistent methodology when ruling patients out for clinically significant VTE.

• How confident do you want to be when you “rule out” PE?
Unresolved Dilemma

• 6-30% of patients with documented PE present with clots only in subsegmental and smaller arteries.

• Controversy still exists about the treatment of such emboli and whether this alters clinical outcome.

• It is assumed that the presence of such emboli may indicate current DVT and thus subsequent events.

• Small peripheral emboli may have prognostic relevance in individuals with cardiopulmonary disease and for the development of chronic pulmonary HTN.

• But remember how satisfied we were with a “Normal V/Q scan”!
current time=12:15pm

Lunch break
The general internist is always multi-tasking!
35 year old male you saw as a walk-in presented with a spider bites on the upper leg and another on the abdomen. On the abdomen, there was a 1 cm area of fluctuance with surrounding erythema and on the leg, 3 cm fluctuance. After incising and draining the larger, the material is sent for culture. The patient was given a prescription for cephaalexin.
# University Hospital Laboratory Results

**Name:** Mr. Sa  
**Number:** 123-45-67  
**Date:** 4/19/2007

## Wound Culture
- **Specimen:** Leg abscess
- **Gram Stain:** Rare WBC, GPCs
- **Culture:**
  - Moderate Growth *Staphylococcus aureus* - Methicillin Resistant (MRSA)

## MIC:

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin-Sulbactam</td>
<td>&gt;=32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;=32</td>
<td>Resistant</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&lt;=0.5</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt;=8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>&gt;=8</td>
<td>Resistant</td>
</tr>
<tr>
<td>Penicillin G (beta-lactamase)</td>
<td>&gt;=16</td>
<td>Resistant</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&lt;=1</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>&lt;=1</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>&lt;=10</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>
Methicillin-resistant *S. Aureus* Infections Among Patients in the Emergency Department

- Prospective, prevalence study of adults seen at hospitals in the EMERGEncy ID Net.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>422</td>
<td>100%</td>
</tr>
<tr>
<td>S. Aureus</td>
<td>320 (76%)</td>
<td>100%</td>
</tr>
<tr>
<td>MRSA</td>
<td>249 (59%)</td>
<td>100%</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>99%</td>
<td>95%</td>
</tr>
</tbody>
</table>

- Antibiotic therapy was inadequate in 57% of MRSA infections.

Emergence of Community-Acquired Methicillin-Resistant Staphylococcus Aureus USA 300 Clone as the Predominant Cause of Skin and Soft-tissue Infections

- Prospective laboratory surveillance of infections from Grady Memorial Hospital or its affiliated outpatient clinics

<table>
<thead>
<tr>
<th>S. Aureus</th>
<th>389</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>279 (72%)</td>
</tr>
<tr>
<td>CA-MRSA</td>
<td>87%</td>
</tr>
</tbody>
</table>

- Empiric antibiotic therapy was inadequate in 65% of MRSA infections.

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>100%</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>100%</td>
</tr>
<tr>
<td>Rifampin</td>
<td>99%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>97%</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>90%</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>13%</td>
</tr>
</tbody>
</table>

Dear Provider,

Sexually transmitted infection identified. Please refer to the following CDC link.

http://www.cdc.gov/mmwr

Laboratory
Chlamydia PCR
   Specimen: Urine
   Results: Positive
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

For patients in all health-care settings
- HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Persons at high risk for HIV infection should be screened for HIV at least annually.
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.

Voicemail: Patient Requesting Information

• A message from a middle aged couple asks what they need to prepare for their a trip to Brunei in the summer
The Practice of Travel Medicine: Guidelines by the Infectious Diseases Society of America

Important competencies
pre-travel risk assessment
travel medicine advice
records and procedures
immunization
traveler’s diarrhea
malaria
personal safety and environmental health
post-travel care

www.idsociety.org
www.cdc.gov/travel

• **Recommended vaccines:**
  - Hepatitis A
  - Hepatitis B
  - Japanese encephalitis
  - Rabies
  - Typhoid
  - As needed tetanus-diphtheria, measles, and polio

• **Required vaccines:** none

• **Malaria:** there is no risk in Brunei

• **Yellow Fever:** there is no risk in Southeast Asia
Voicemail: Referral for Back Surgery

• Your referral for a 42 year old overweight female with a history of diabetes mellitus and low back pain for 1 year was rejected because of lack of information.
Surgical vs Nonoperative Treatment of Lumbar Disk Herniation

• Non-blinded, randomized controlled trial.
• Inclusion:
  - 18 years and older
  - Symptoms consistent with disk hernation for ≥6 weeks.
  - Surgical candidates with advanced imaging.
• Exclusion criteria:
  - Prior lumbar surgery
  - Scoliosis >15 degrees
  - Vertebral fractures
  - Inflammatory spondyloarthropathy
  - Comorbid conditions contraindicating surgery
  - Cauda equina syndrome
  - Segmental instability
  - Spine infection or tumor
  - Pregnancy
  - Inability/unwillingness to have surgery within 6 months.

SPORT

- Of 2720 screened, 729 were ineligible and 747 refused study participation, and 743 refused to be randomized.
- The average patient: 42 years, BMI 28

<table>
<thead>
<tr>
<th>Assignment</th>
<th>% surgery @ 3 mos.</th>
<th>% surgery @ 2 yrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Usual Care</td>
<td>30%</td>
<td>45%</td>
</tr>
</tbody>
</table>

- Results: The primary outcomes improved substantially in both groups; and, although favored surgery at each time point, did not reach statistical significance.

Voicemail: Prior Authorization Form

• The pharmacy has phoned about a prescription for fluticasone/salmeterol inhaled (250/50). Since salmeterol alone is covered by the carrier, they request a substitution; otherwise a prior authorization form must be completed.

• The prescription is for Mr. Lopez who has moderate persistent asthma.
The Salmeterol Multicenter Asthma Research Trial

• Triple-blind, placebo-controlled, RCT.
• Inclusion:
  - ≥12 years of age
  - Diagnosis of asthma (investigator’s judgment)
  - Treated with prescription medication
• Exclusion:
  - Use of inhaled long-acting β2-agonists
  - Pregnancy and/or lactation
  - Current use of β-blockers

SMART

- There were 26,355 subjects randomly assigned to salmeterol (n=13,176) or placebo (n=13,179) for 28 weeks.
- The trial was terminated at the interim analysis because of a preliminary finding in African Americans.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Caucasians</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Salmeterol (n = 9281)</td>
<td>Placebo (n = 9,361)</td>
</tr>
<tr>
<td>Primary end point</td>
<td>29 (&lt; 1)</td>
<td>28 (&lt; 1)</td>
</tr>
<tr>
<td>Combined respiratory-related deaths or life-threatening experiences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary end points</td>
<td>17 (&lt; 1)</td>
<td>16 (&lt; 1)</td>
</tr>
<tr>
<td>Combined asthma-related death or life-threatening experiences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>29 (&lt; 1)</td>
<td>22 (&lt; 1)</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>323 (3)</td>
<td>317 (3)</td>
</tr>
<tr>
<td>Combined all-cause death or life-threatening experience</td>
<td>44 (&lt; 1)</td>
<td>44 (&lt; 1)</td>
</tr>
<tr>
<td>Respiratory-related death</td>
<td>16 (&lt; 1)</td>
<td>7 (&lt; 1)</td>
</tr>
<tr>
<td>Asthma-related death</td>
<td>6 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
</tbody>
</table>

SMART-limitations

• Because of the methodological problems of the SMART trial, the link between long-acting β-agonists and asthma-related deaths will continue to be debated.
  - Selection bias
  - Uncertain compliance
  - Early termination NOT meeting prespecified criteria
  - Inadequate use of inhaled corticosteroids

• Follow current national guidelines, and continue to use informed decision making between patient and provider.
DH paperwork
Voicemail: Referral for Hernia Repair

• 57 year old male, well known, with reducible inguinal hernia and mild pain for 6 month. Referral for repair is rejected.
Watchful Waiting vs Repair of Inguinal Hernia in Minimally Symptomatic Men

- **RCT** of 720 men with minimal symptoms from inguinal hernia randomized to watchful waiting vs. surgical repair.

- **Primary endpoint**: Pain and discomfort, as well as, impairment of usual activities.

- **Results**: No difference in outcomes at 2 yrs. Only 1 (0.3%) experience acute incarceration during in the WW group.

- **Conclusion**: It is safe to delay surgical repair until symptoms increase without significant morbidity.

Voicemail: Referral for Bariatric Surgery

• 40 year old female with BMI of 33 kg/m² request referral from her provider (a NP supervised by me in the office).

• The patient has no significant co-morbidities with LDL = 135 mg/dl and HDL = 54 mg/dl.
Treatment of Mild to Moderate Obesity with LapBand (Adjustable) or an Intensive Medical Program

- RCT of 80 adults with BMIs 30 - 35 kg/m² to surgical tx vs. intense medical tx (500-550 kcal/day diet using Optifast).
- Results: At 2 years surgery had greater weight loss (21.6% vs. 5.5% of initial body wt, P<0.001); significant reduction in metabolic syndrome (97 vs. 76%, P=0.002)

*Conclusions:* Surgery using the LapBand procedure is more effective than intensive weight loss.

“Someday, son, all this will be yours!”
University Hospital Laboratory Results

Name: Ms. XXXXX        Number: 123-00-00
Date: 4/19/2007

Microbiology
Culture
   Specimen: Throat
   Results: Moderate Growth Group A beta-hemolytic Streptococcus
Management of Acute Pharyngitis
ACP/IDSA recommendations

4 point Centor score (Modified-adult only):
- $T \geq 38\,^C$,
- Tonsillar exudates,
- Tender cervical adenopathy
- No cough or rhinitis

ACP Test Strategy:
- Empiric tx with antibiotics for Centor score of 4.
- Throat culture should be limited to patients with (-) RSAT and Centor score of 2 or 3.
- Patients with Centor score of < 1, do not require further testing or treatment.

ACP Empirical Strategy:
- Empiric tx for patients with Centor score of 3 or 4

Management of Acute Pharyngitis

- Prospective cohort of 372 patients with acute pharyngitis (Centor score - 2 or 4) underwent RSAT and throat culture. RSAT had a high sensitivity (91%) and specificity (95%).

<table>
<thead>
<tr>
<th></th>
<th>Antibiotic use</th>
<th>Antibiotic overuse</th>
<th>Appropriate antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>37%</td>
<td>3%</td>
<td>94%</td>
</tr>
<tr>
<td>Empiric</td>
<td>60%</td>
<td>32%</td>
<td>68%</td>
</tr>
</tbody>
</table>

- Retrospective analysis of 2097 adults with a diagnosis of pharyngitis. Adherence to ACP’s empiric strategy was 12% and to the testing strategy in 30% of visits, adherence to the IDSA in 30% of visits, and to none of the strategy in 66% of visits. Testing or antibiotic prescription was performed in patients at low risk for pharyngitis (78%) based on the guidelines.
<table>
<thead>
<tr>
<th>Time</th>
<th>Provider</th>
<th>Type</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:00</td>
<td>WR</td>
<td>follow up</td>
<td>30M</td>
</tr>
<tr>
<td>1:10</td>
<td>GH</td>
<td>follow up</td>
<td>45M</td>
</tr>
<tr>
<td>1:30</td>
<td>JM</td>
<td>new</td>
<td>75F</td>
</tr>
<tr>
<td>2:00</td>
<td>TI</td>
<td>follow up</td>
<td>38F</td>
</tr>
<tr>
<td>2:10</td>
<td>KR</td>
<td>follow up</td>
<td>95F</td>
</tr>
<tr>
<td>2:30</td>
<td>EE</td>
<td>follow up</td>
<td>35F</td>
</tr>
<tr>
<td>2:40</td>
<td>MP</td>
<td>follow up</td>
<td>77F</td>
</tr>
<tr>
<td>2:50</td>
<td>UP</td>
<td>follow up</td>
<td>69F</td>
</tr>
<tr>
<td>3:00</td>
<td>GC</td>
<td>new</td>
<td>18M</td>
</tr>
<tr>
<td>3:15</td>
<td>AR</td>
<td>follow up</td>
<td>62F</td>
</tr>
<tr>
<td>3:30</td>
<td>HG</td>
<td>follow up</td>
<td>58M</td>
</tr>
<tr>
<td>3:45</td>
<td>MT</td>
<td>follow up</td>
<td>40M</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Provider</th>
<th>Type</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:00</td>
<td>II</td>
<td>new</td>
<td>75M</td>
</tr>
<tr>
<td>1:15</td>
<td>OO</td>
<td>follow up</td>
<td>55M</td>
</tr>
<tr>
<td>1:30</td>
<td>NF</td>
<td>follow up</td>
<td>66F</td>
</tr>
<tr>
<td>1:45</td>
<td>IR</td>
<td>needs form</td>
<td>78F</td>
</tr>
<tr>
<td>2:00</td>
<td>VM</td>
<td>new</td>
<td>57F</td>
</tr>
<tr>
<td>2:10</td>
<td>ME</td>
<td>follow up</td>
<td>52F</td>
</tr>
<tr>
<td>2:30</td>
<td>QT</td>
<td>follow up</td>
<td>44M</td>
</tr>
<tr>
<td>2:45</td>
<td>JK</td>
<td>follow up</td>
<td>88M</td>
</tr>
<tr>
<td>3:00</td>
<td>EF</td>
<td>new</td>
<td>60F</td>
</tr>
<tr>
<td>3:15</td>
<td>PR</td>
<td>follow up</td>
<td>90F</td>
</tr>
<tr>
<td>3:30</td>
<td>LK</td>
<td>follow up</td>
<td>62F</td>
</tr>
<tr>
<td>3:45</td>
<td>FF</td>
<td>pre-op</td>
<td>66M</td>
</tr>
</tbody>
</table>
PLEASE SEE ME

BEFORE YOU SEE

THIS PATIENT!

-MCRW
Dr. M  current time= 1:25pm
Cancer Screening

75 year old male being seen as an initial visit. He is accompanied by his grandson who demands that he get a repeat colonoscopy, PSA, and spiral CT to screen for lung cancer.

PMH: CAD
- CHF, Class II, EF 25%
- diabetes x 15 years
- tubular adenoma (‘06)
- tobacco use (45 pk-yrs)

Labs: PSA=2.7 (1/06)

Meds: aspirin 81mg daily
- metoprolol 50mg bid
- lisinopril 20mg daily
- atorvastatin 20mg daily
- furosemide 10mg daily
- glargine insulin 20 U daily
- insulin lispro 10 U w/ meals
• When should the patient be referred for colonoscopy surveillance?

• Is screening for lung cancer effective? Can it detect earlier cancers? Can we improve survivals of those that are found?

• In whom should be screen for prostate cancer?
Colorectal Screening After Polypectomy: A National Survey Study of Primary Care Physicians

- This study evaluated the results of a mail survey of 500 physicians of the American College of Physicians and 500 physicians from the American Academy of Family Physicians who were asked to recommend follow-up colonoscopy for six hypothetical patients.

US Multi-Society Task Force on Colorectal Cancer and American Cancer Society

| Small rectal hyperplastic polyp                  | 10 years  |
| 1 or 2 small (<1 cm) tubular adenoma w/ only low grade dysplasia | 5-10 years |
| Three to ten adenomas                           | 3 years   |
| Any adenoma ≥1 cm                               |           |
| Any adenoma with villous features              |           |
| High grade dysplasia                            |           |
| More than ten adenomas                          | <3 years  |
| Sessile polyps                                  | ensure complete removal 2-6 mos |

# Colorectal Screening After Polypectomy: A National Survey Study of Primary Care Physicians

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Physicians Who Recommended Surveillance, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In ≤1 Year</td>
</tr>
<tr>
<td>6-mm hyperplastic polyp</td>
<td>16</td>
</tr>
<tr>
<td>6-mm tubular adenoma</td>
<td>25</td>
</tr>
<tr>
<td>12-mm tubular adenoma with high-grade dysplasia</td>
<td>85</td>
</tr>
<tr>
<td>12-mm tubulovillous adenoma</td>
<td>59</td>
</tr>
<tr>
<td>Two 6-mm tubular adenomas</td>
<td>37</td>
</tr>
<tr>
<td>No polyps in a patient with a 12-mm tubular adenoma 3 years earlier</td>
<td>2</td>
</tr>
</tbody>
</table>

Impact on Internal Medicine

• Primary care physicians are referring patients for surveillance too frequently.

• Understand the current recommendations for repeating colonoscopy after polypectomy.

Survival of Patients with Stage I Lung Cancer Detected on CT Screening

• Screening study followed the protocol of the International Early Lung Cancer Action Project (I-ELCAP).

• Baseline screening CT scans were completed in 31,567 asymptomatic men and women. All participants were at risk for lung cancer because of a history of cigarette smoking, occupational exposure, or second hand smoke exposure.

Survival of Patients with Stage I Lung Cancer Detected on CT Screening

Limitations and Impact on IM

- SEER data estimates 8 year survival of pathological stage I CA at 75%
- Inconsistent use of PET in evaluation
- Lead time and overdiagnosis bias

- Although screening CT can detect lung cancer that are potentially curable, more comparative studies are needed before it is routinely used.

Survival Associated with Treatment vs. Observation of Localized Prostate Cancer in Elderly Men

- A US cohort from SEER Medicare database.
- 44,630 men, aged 65 to 80 years who were diagnosed between 1991 and 1999 with organ-confined, well- or moderately differentiated prostate cancer and who had survived more than a year past diagnosis.
- Patients were followed up until death or study end.
- 32,022 received treatment; 12,608 received observation
- Exclusion: those who received only hormonal therapy or death within 1 year of diagnosis

Survival Associated with Treatment vs. Observation of Localized Prostate Cancer in Elderly Men

Table 4. Association Between Active Treatment and Overall Mortality

<table>
<thead>
<tr>
<th>Propensity Score Quintile</th>
<th>Mean Propensity Score (Range)</th>
<th>HR for Death (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire cohort*</td>
<td>0.72 (0.06-0.97)</td>
<td>0.69 (0.66-0.72)</td>
</tr>
<tr>
<td>Entire cohort stratified by quintile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1†</td>
<td>0.43 (0.06-0.59)</td>
<td>0.69 (0.64-0.74)</td>
</tr>
<tr>
<td>2</td>
<td>0.66 (0.59-0.72)</td>
<td>0.70 (0.65-0.76)</td>
</tr>
<tr>
<td>3</td>
<td>0.76 (0.72-0.80)</td>
<td>0.66 (0.61-0.73)</td>
</tr>
<tr>
<td>4</td>
<td>0.83 (0.80-0.86)</td>
<td>0.67 (0.60-0.75)</td>
</tr>
<tr>
<td>5‡</td>
<td>0.89 (0.86-0.97)</td>
<td>0.57 (0.50-0.65)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Adjusted for tumor size, grade, and number of comorbidities.
†Lowest propensity for treatment.
‡Highest propensity for treatment.

PSA Screening Among Elderly Men with Limited Life Expectancies

- Cohort study of 597,642 male veterans aged 70 years and older.
- Excluded
  - history of prostate cancer, elevated PSA, prostate cancer symptoms, or in Medicare managed care.
- The primary outcome was receipt of PSA testing during 2003 was based on US Department of Veterans Affairs data and Medicare claims.

PSA Screening Among Elderly Men with Limited Life Expectancies

**Figure 2.** Percentage of Men in Cohort With PSA Screening in 2003 vs Percentage of Men in the General US Population Who Will Live 10 Years or More According to Age

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Received PSA Test</th>
<th>Expected to Live ≥10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-74</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>75-79</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>80-84</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>≥85</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>

**Figure 3.** Percentage of Men Who Received PSA Screening in 2003 According to Health Status and Age (N=597 642)

<table>
<thead>
<tr>
<th>Charlson Score</th>
<th>Men With PSA Test, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Best Health); n=178 222</td>
<td>70-74: 60, 75-79: 50, 80-84: 40, ≥85: 30</td>
</tr>
<tr>
<td>1-3; n=327 334</td>
<td>70-74: 50, 75-79: 40, 80-84: 30, ≥85: 20</td>
</tr>
<tr>
<td>≥4 (Worst Health); n=92 086</td>
<td>70-74: 40, 75-79: 30, 80-84: 20, ≥85: 10</td>
</tr>
</tbody>
</table>

Case Resolution

• Colon CA screening: NO, too early
• Lung Cancer screening: NO, not ready for prime time
• Prostate CA screening: NO, based on patient’s long term survival
Osteoporosis - Mrs. E

- 52 year old healthy postmenopausal Caucasian female without significant PMHx followed in practice for health maintenance. She only complains of occasional hot flashes which she says is controlled with *Black Cohosh*.
- Today she returns for scheduled annual pap smear, mammogram, lipids and refill of meds.
- **Meds:**
  - Vit D 400 IU/day
  - Calcium Carbonate 800 mg/day
- Of note she has a BMI = 22, never smoked, but has a family history of osteoporosis.
Key Questions

• Should I keep giving this woman Vitamin D and CaCO3 for primary prevention of osteoporosis?
  - Is this a waste of time and money?
National Osteoporosis Foundation 2007

Recommendations:
For women over > 50 years:

1. Consume at least 1200 mg of elemental calcium (primarily from the diet)
2. Use of supplemental calcium only if inadequate dietary intake.
*3. Vit D daily intake of 400-600 IU

*Many experts recommend at >800 IU if at risk for osteoporosis.
Calcium plus Vitamin D Supplementation and the Risk for Fractures

• **Methods**: RCT of 36,282 postmenopausal women aged 50-79 years already enrolled in the WHI. Subjects were randomly assigned to receive 1000 mg of elemental calcium with 400 IU of vitamin D₃. Average follow up was 7 years.

• **Primary endpoint**: Bone density and Fracture rates.

• **Exclusion**: Hypercalemia, renal calculi, corticosteroids use, and calcitriol use.

• **Noted observations of the trial**:
  - 1. Personal supplementation of calcium (up to 1000 mg/day) was allowed, as well as, vitamin D (up to 600 IU/day). Therefore, the placebo are had significant supplementation use.
  - 2. A nested case-control was performed to determine the effect of prerandomization vitamin D levels on fracture rates.
  - 3. The overall rate of adherence was 59% at 7 yrs.

• **Average patient**: 62 y/o female, BMI=29, white (84%), hormone use (50%).
Calcium plus Vitamin D Supplementation and the Risk for Fractures

Results: Total-Hip BMD was preserved in patients receiving supplementation. (P=0.01). Fractures: Overall no reduction in hip, vertebral or lower arm/wrist fracture rates. - Subgroup analysis of those adherent to therapy did show significant reduction of Hip fracture rates. - The nested study of prerandomization vitamin D levels did not show an interaction with fracture rates.

Calcium plus Vitamin D Supplementation and the Risk for Fractures


Conclusion: Supplementation in healthy postmenopausal women with Vit D and calcium did not reduce fracture risk.
Case Resolution & Impact on IM

- Supplementation should not substitute for adequate risk stratification and evaluation for osteoporosis.
- Appropriate doses of calcium and vitamin D should be administered to patients with inadequate intake.
HPI: A 66 year old male with Type 2 DM (insulin requiring), and HTN and severe DJD scheduled for elective total knee replacement under regional anesthesia. He has no complaints of chest pain or SOB. He is inactive at home and has difficulty ambulating or climbing stairs secondary to pain.

MEDS: Novolin (70/30) 18/8 units, Benazepril 40 mg qDay, Metformin 1000 mg BID, ASA 81 mg q Day.
**EXAM:** VS: BP - 132/78  HR - 76  RR - 14  T - 98.2 F; BMI=27

Male in NAD. No JVD, no carotid bruises and normal upstroke. Lungs both clear w/o crackles. Heart with RRR, with occ ectopy, no murmurs appreciated. Abdomen - benign. Lower ext w/o edema and good pulses.

**DATA:** Preop labs - normal. Last Hgb A1C = 7.8% (1 mo prior). His ECG shows only a few PACs per minute, normal axis, ↓precordial voltage V1-2 (unchanged from 6 months ago), and LVH. CXR - No obvious disease. LDL = 127 mg/dl 3 months ago.
Key Questions

1. “What is the risk of an adverse cardiac event?”

2. “What can be done to reduce this risk?”
   - Should I send this patient for further diagnostic tests?
   - Maybe I should just give this guy a beta-blocker and send him to surgery?
ACC/AHA Step-by-step Steps:
1. What is the urgency?
2. Revasc within 5 yrs?
3. Cardiac testing < 2 yrs
4. Major clinical predictor?
5. Intermediate clinical Predictors
6. Evaluate functional status
7. Risk of surgery

Consider Noninvasive testing

J Am Coll Cardiol or Circulation 2002
Cardiac Assessment –
The Rule “2 out of 3” - a short cut

- Intermediate clinical predictor
- Poor functional status (< 4 mets)
- High-risk surgical procedure

- If patient with 2 or more of the above one should **consider** preoperative cardiac risk assessment and/or procedures to reduce perioperative cardiac events.
### Derivation and Validation of a Predictive Index

#### Revised Cardiac Risk Index

<table>
<thead>
<tr>
<th>RCR Index</th>
<th>Adjusted OR (95% CI)</th>
<th>Derivation Set (n=2893)</th>
<th>Validation Set (n=1422)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk type of surgery</td>
<td>2.8 (1.6,4.9)</td>
<td>2.6 (1.3,5.3)</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2.4 (1.3,4.2)</td>
<td>3.8 (1.7,8.2)</td>
<td></td>
</tr>
<tr>
<td>History of CHF</td>
<td>1.9 (1.1,3.5)</td>
<td>4.3 (2.1,8.8)</td>
<td></td>
</tr>
<tr>
<td>History of Cerebrovasc. Dz</td>
<td>3.2 (1.8,6.0)</td>
<td>3.0 (1.3,6.8)</td>
<td></td>
</tr>
<tr>
<td>Insulin therapy for DM</td>
<td>3.0 (1.3,7.1)</td>
<td>1.0 (0.3,3.8)*</td>
<td></td>
</tr>
<tr>
<td>Preop serum creat &gt; 2.0 mg/dl</td>
<td>3.0 (1.4,6.8)</td>
<td>0.9 (0.2,3.3)*</td>
<td></td>
</tr>
</tbody>
</table>

Lee et al. *Circulation*. 1999;100:1043-1049
How does the RCI compare vs. Original CI ROC = 0.701 Modified CI ROC = 0.582

Lee et al. *Circulation*. 1999;100:1043-1049

<table>
<thead>
<tr>
<th>Class</th>
<th>Events/Patients, n/n</th>
<th>Event Rate (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (0 risk factors)</td>
<td>2/488</td>
<td>0.4 (0.05–1.5)</td>
</tr>
<tr>
<td>II (1 risk factor)</td>
<td>5/567</td>
<td>0.9 (0.3–2.1)</td>
</tr>
<tr>
<td>III (2 risk factors)</td>
<td>17/258</td>
<td>6.6 (3.9–10.3)</td>
</tr>
<tr>
<td>IV (≥3 risk factors)</td>
<td>12/109</td>
<td>11.0 (5.8–18.4)</td>
</tr>
<tr>
<td>ROC curve area</td>
<td></td>
<td>0.806†</td>
</tr>
</tbody>
</table>
No good data that revascularization prior to elective surgery reduces perioperative cardiovascular risk!
Perioperative Cardiac Risk of Death or MI in a RCT of Major Vascular Surgery (DECREASE II)

- 1476 patients screened for 770 intermediate risk patients (1 to 2 RF; including age > 70 yrs). All patients received beta-blockers (Bisoprolol) to target HR < 65 bpm.
- Patients randomized to cardiac testing (DSE) versus no cardiac testing. Primary endpoint - 30d MI or cardiac death

- **Results:**
  - Likelihood of primary endpoint highly correlated with number of risk factors (ie. 0 < < 1 or 2 < < 3 or more risk factors; p < .002 for all)
  - Overall incidence of primary endpoint in randomized groups - No difference 1.8% vs. 2.3% (p=0.62).
  - 287 (74%) without e/o ischemia, 34 (8.8%) with extensive ischemia. (12/34 underwent revascularization)
  - **Tight HR control (<65 bpm) was associated with a lower incidence of the primary endpoint ( 1.3% vs. 5.2%; p=0.006).** Only 1.7% of patients with HR < 50 bpm.

Indications for Perioperative Beta-blockers (ACC/AHA 2006)- in *Circulation*

1. β-blockers required in the recent past to control symptoms of angina or patients with symptomatic arrhythmias or hypertension, or other ACC/AHA Class I guideline indication (Level of evidence C)

2. β-blockers: patients at high cardiac risk owing to the finding of ischemia on perioperative testing who are undergoing major vascular surgery (B)

3. β-blockers: perioperative assessment identifies untreated HTN, known CAD, or major risk factors for CAD (B)

4. β-blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies *high cardiac risk* as defined by the presence of multiple clinical risk factors (B)

5. β-blockers are probably recommended for patients in whom preoperative assessment identifies CAD or *high cardiac risk* as defined by the presence of multiple clinical risk factors and who are undergoing intermediate- or high-risk procedures (B)
Metoprolol After Vascular Surgery (MaVS)

- RDBCT of 497 pts: 247 Metoprolol and 250 placebo undergoing elective vascular surgery.
- Patients treated with either Metoprolol IV/oral or placebo 2hrs pre-op and continued until discharge or max 5 days post-op.
- Primary outcome: 30-day postop composite endpoint (non-fatal MI, USA, new CHF, new arrhythmia, or cardiac death.
- Results: no reduction in cardiac event rates at 30 days post-op (10.1 vs. 12.0%, p=0.4), even when stratified for RCR index.

<table>
<thead>
<tr>
<th></th>
<th>Primary Outcome</th>
<th>Cardiac Death</th>
<th>Non-fatal MI</th>
<th>Non-Cardiac Death</th>
<th>New onset CHF</th>
<th>Intraop ↓BP or↓HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metoprolol</strong></td>
<td>25(10.1%)</td>
<td>0(0.0%)</td>
<td>19(7.7%)</td>
<td>1(0.4%)</td>
<td>5(2.0%)</td>
<td>53(21.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84(34.0%)</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>30(12.0%)</td>
<td>1(0/4%)</td>
<td>21(8.4%)</td>
<td>6(2.4%)</td>
<td>3(1.2%)</td>
<td>19(7.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26(10.4%)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.4</td>
<td>1</td>
<td>0.87</td>
<td>0.12</td>
<td>0.5</td>
<td>P=0.00001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P=0.0045</td>
</tr>
</tbody>
</table>

Diabetic Postoperative Mortality & Morbidity Trial (DIPOM)

- RDBPCT of Metoprolol XL 100 mg/day
- 921 β-blocker naïve diabetic patients older than 40 undergoing non-cardiac surgery
- **Primary outcome**: composite of all-cause mortality, MI, USA, HF
- **Result**: no benefit from β-blocker
- **Limitation**: small, too low of a dose of β-blocker (100 mg) and too short of a course (4.5 days). Only 32% with HR < 65 bpm.

Juul et al. BMJ.2006;332:1482.

<table>
<thead>
<tr>
<th>Endpoint (%)</th>
<th>Metoprolol (n = 462)</th>
<th>Placebo (n = 459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>
Dose of B-Blockers and Tight HR

- 272 vascular pts
- Screened for cardiac risk factors and B-blocker dose
- HR, 12 lead ECG, troponin were monitored

**Conclusion:** Higher doses of B-blockers and tight HR are associated with reduced perioperative ischemia and troponin release

Key Messages - Impact on IM

• The ACC/AHA guideline is a sensitive tool to decide who does **not** require additional testing or interventions.

• Patients with an RCRI score of < 2 do not routinely require additional diagnostic testing or preoperative interventions.

• An accurate history is the most important preoperative tool available to minimize unnecessary harm to a specific patient.

• Beta-blockers are not a substitute for responsible and vigilant preoperative evaluation.
  - If used preoperatively they should be used days to weeks before surgery to ensure adequate sympatholysis (HR < 65)
The Lightning Round

A Few “Successes and Failures” for 2006
Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency.

- **RDBCT of 422 patients with CKDz.**
  - Group 1 - $S_{cr} = 1.5-3.0$ mg/dl + benazapril 20 mg/day
  - Group 2 - $S_{cr} = 3.1 - 5.0$ mg/dl + benazapril 20 mg/day.
  - Group 2 - $S_{cr} = 3.1 - 5.0$ mg/dl + placebo

- **Primary endpoint:** doubling of $S_{cr}$, ESRD, or death.

- **Average patient:** 45 y/o with HTN and proteinuria. (DM pts excluded)

- **Conclusions:** Use of ACEI in advanced CKDz is safe and suggest that discontinuing ACEI in the face of progression of kidney disease may hasten the onset of ESRD.

*Compared to Placebo, ACEI had a 43% RRR of endpoint*

Sitagliptin

- **Dipeptidyl peptidase-4 inhibitor**
  - Inhibits degradation incretins, that stimulate insulin and suppress glucagon release (both in a glucose-dependent manner), delay gastric emptying, and increase satiety.

- As monotherapy or in addition to metformin or pioglitazone, 24 weeks of therapy lead to a decrease in A1c (-0.65% to -0.79%), fasting plasma glucose, and 2-h postmeal glucose.

- No hypoglycemia, probably weight neutral

- The 3 studies had approximately 1800 pts, short term.

Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

- 29,507 cohort of infants enrolled in Tennessee’s Medicaid program yielded 209 infants with exposure to ACE-I during the 1st trimester and 202 with exposure to other anti-HTN.

- Patients - mean maternal age ~28, 50% AA, >85% multigravida, > 90% with timely prenatal care

- **Results:** Only babies exposed to ACE-I had an increased risk of major congenital abnormalities.

### Table 4. Alternative Analyses of Risk of Major Congenital Malformations among Study Infants with Fetal Exposure to ACE Inhibitors during the First Trimester Alone.*

<table>
<thead>
<tr>
<th>Alternative Analysis</th>
<th>Any Malformation</th>
<th>Cardiovascular Malformation</th>
<th>Central Nervous System Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Ratio (95 Percent Confidence Interval)</td>
<td>Risk Ratio (95 Percent Confidence Interval)</td>
<td>Risk Ratio (95 Percent Confidence Interval)</td>
</tr>
<tr>
<td>Entire study group</td>
<td>2.71</td>
<td>1.72–4.27</td>
<td>3.72</td>
</tr>
<tr>
<td>ACE inhibitor prescription filled after first 14 days of last menstrual period</td>
<td>2.96</td>
<td>1.83–4.79</td>
<td>4.04</td>
</tr>
<tr>
<td>Broader definition of diabetes†</td>
<td>2.77</td>
<td>1.76–4.37</td>
<td>3.81</td>
</tr>
<tr>
<td>Patent ductus arteriosus excluded</td>
<td>2.51</td>
<td>1.54–4.09</td>
<td>3.35</td>
</tr>
</tbody>
</table>

Impact on IM - ACE-I in Pregnancy

• This observation provides caution to the use of ACE-I in women of childbearing years unless there are clear indications and the risk of associated with use have been clearly explained to the patient.

• Women who learn of an early pregnancy should likely be immediately switched to an alternative antihypertensive.
Inhaled Insulin

- Inhaled powder form of recombinant human insulin
- Meta-analysis
  - 16 RCTs in nonpregnant diabetics
  - Subcutaneous insulin favored (A1c reduction 0.08%)
  - Insulins had equivalent hypoglycemic episodes (greater than oral agents)
  - Patients preferred the inhaled insulin
  - Increase in dry cough and mild decrease in PFTs.
- A noninvasive alternative to injected insulin, but lack of long term studies should limit its use.

Inhaled Insulin

- Contraindication: current smoker or recently quit smoking (within the last 6 months).
- Not recommended in patients with asthma, bronchitis, or emphysema.
- Baseline tests for lung function are recommended after the first 6 months of treatment and every year thereafter, even if there are no pulmonary symptoms.

Treatment of Vasomotor Symptoms of Menopause with Black Cohosh, Multibotanicals, Soy, Hormone Therapy or Placebo

- RDBPCT of 351 women (peri- or postmenopausal) with one of 3 herbal regimens or hormone therapy for the relief of vasomotor symptoms compared to placebo.
- Primary endpoint: Vasomotor symptoms measured by standardized tool @ 3, 6, and 12 months.
- Results: No difference in herbal regimens vs. placebo; except that symptoms were worse for herbal at 12 months (P=0.016). Hormone Tx significantly improved symptoms at all points during follow up.

Varenicline tartrate

- $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist
- Phase 3 studies (12 week) ~2050 subjects

<table>
<thead>
<tr>
<th>Abstinence rates (est.)</th>
<th>9-12 wks</th>
<th>9-24 wks</th>
<th>9-52 wks</th>
<th>NNT @ 12 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline</td>
<td>44%</td>
<td>30%</td>
<td>23%</td>
<td>$\sim$4</td>
</tr>
<tr>
<td>Bupropion</td>
<td>30%</td>
<td>20%</td>
<td>15%</td>
<td>$\sim$9</td>
</tr>
<tr>
<td>Placebo</td>
<td>18%</td>
<td>13%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

- Mild nausea occurred in 29%

Still no Fountain of Youth!

- 2-year DBPRCT of 164 elderly men and women randomized to DHEA tablets (75 mg/d for men, 50 mg/d for women), transdermal testosterone (5 mg/d for men only), or placebo for 2 years.

- **Primary endpoints**: physical performance, body composition, BMD, insulin sensitivity, and QOL.

- **Results**: Treatment was well tolerated. Despite significant increases in plasma DHEA only mild decreases in fat-free mass (testosterone group only) and a minimal inconsistent effect on bone density.

- **Conclusion**: restoration of DHEA levels in the elderly to those of healthy young people had little benefit.

For the last time . . .

“Use of Folic Acid and B$_{12}$ to prevent major CV events does not work!”

The NORVIT and HOPE 2 investigators

What have we learned today?
**DO**

- **SPARCL** = statin use indicated for patients with cerebrovascular disease (caution about adverse events)
- **Cancer screening** = ensure age-appropriate screening, frequency of follow-up, and assess risk-benefit for each procedure.
- **VTE** - Confirmatory testing is required when there is discordance between pretest probability and diagnostic test. It is important to follow evidence based pathways.
- Treat suspected **CA-MRSA** appropriately.
- **HIV testing** for all patients unless they opt-out.
DO

• Self-directed exercise programs for all patients with PAD
• Screening ABIs for at risk patients.
• Testing strategy for acute pharyngitis decreases overuse of antibiotics.
• ACE inhibitors should be used in non-diabetic patients with chronic kidney diseases
• Varenicline is effective in smoking cessation
• Sitagliptin is useful in the management of diabetes
DON’T

• Carotid stenting should be reserved for symptomatic patients at high risk for surgical morbidity and mortality
• Supplementation should not substitute for adequate risk stratification and evaluation for osteoporosis.
• Dual platelet inhibition has limited utility in primary and secondary prevention of cardiovascular disease
• SPORT does not support back surgery
• Minimally symptomatic inguinal hernias do not need immediate intervention
• DREAM= do not use ACE inhibitors to prevent diabetes
• ACE inhibitors should not be used in the first trimester of pregnancy
• DHEA and testosterone replacement in older men and women has little effect.
• Perioperative medicine: LESS IS MORE!
DOESN’T CHANGE PRACTICE

- ASTEROID = interesting, but must await clinical outcome data
- ADOPT = although rosiglitazone was most effective, each had significant adverse events.
- SMART = continue to follow NHLBI guidelines, but discuss risk with patient
Summary

• “Lifelong learning” is one of our most important professional values
• Apply what we learn in our daily practice
• Physician = Teacher
• We are responsible not only for teaching the community we serve but each other.
• Both professional and personal satisfaction are not only related to the breadth, but depth of our experiences.
Satisfaction in Internal Medicine

- National survey of physicians examining factors associated with career satisfaction
- ~12,000 respondents in each of 3 rounds of surveys over a 4 year period

Results:
- Overall primary care and specialist physicians equal with significant regional differences.
  - Related to autonomy, interactions with patients and colleagues, the ability to provide high quality care and not income.

A Charge for the Internist

We should [each] try to develop areas of special interest and become "experts", thereby enabling us to be resources for each other.
Thank you

• The following people assisted in optimizing this presentation:
  - Dr. Karen Kwan
  - Dr. Melissa Chin
  - Dr. John Ford
  - Yvonne Shears
  - Claudia Mazzei, NP
  - Irene Dolan, NP
Thank you for your attention.

Remember life is a JOURNEY of continuous Learning.

Don’t forget the milk Dr. H!