Does aspirin reduce cardiovascular events in patients with asymptomatic peripheral vascular disease identified by screening ABI?

Aspirin for Asymptomatic Atherosclerosis Trial
- 3350 patients aged 50-75 without prior known history of vascular disease with ABI ≤ 0.95
- 33% smokers, 3% diabetics
- Randomized to 100 mg enteric ASA vs. placebo
- Primary endpoint - CV event, CVA or revascularization
  - Secondary endpoint added angina, TIA, claudication, overall mortality
- Mean follow-up 8.2 years

<table>
<thead>
<tr>
<th></th>
<th>ASA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st endpoint</td>
<td>10.8%</td>
<td>10.5%</td>
</tr>
<tr>
<td>2nd endpoint</td>
<td>17.2%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>2.0%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Aspirin for Asymptomatic Atherosclerosis Trial-Conclusions
- Aspirin ineffective in preventing CV events in asymptomatic patients with low ABI.
- Insufficient evidence to support interventions in patients undergoing ABI screening
Does intensive blood pressure control reduce cardiovascular events in patients with diabetes?

Intensive Blood Pressure Control in Diabetic Patients- ACCORD BP
- 4,733 patients with HgBA1C ≥ 7.5%
  - Age ≥ 40-79 with CVD
  - Age ≥ 55-79 at high risk for CVD
  - Systolic BP 130-180 taking ≤ 3 BP drugs
  - Creatinine ≤ 1.5 mg/dl or < 1 gm proteinuria
- Intensive treatment- Goal BP ≤ 120 mm Hg
  - monthly visits x4, then q2mo
- Control group- Goal BP ≤ 140 mm Hg
  - visits month 1 and 4, then q4mo
- 1° outcome- non-fatal MI, CVA, CV death
- Mean follow-up 4.7 years

NEJM 2010 362: 1575-85

ACCORD BP Trial

<table>
<thead>
<tr>
<th></th>
<th>Intensive Therapy Events %/yr</th>
<th>Standard Therapy Events %/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>1.87</td>
<td>2.09 (NS)</td>
</tr>
<tr>
<td>CVA</td>
<td>0.32</td>
<td>0.53 (NNT x 5 yr 89)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.15</td>
<td>1.28</td>
</tr>
<tr>
<td>Death</td>
<td>1.28</td>
<td>1.19</td>
</tr>
</tbody>
</table>

ACCORD BP Trial

Similar use of ACEI/ARB, thiazides, beta blocker, calcium channel blocker

INVEST Trial

- Observational secondary analysis involving 6,400 diabetic patients with HTN and CAD
- Patients randomized to calcium channel blocker vs. beta blocker strategy to achieve BP <130/85
  - Added ACEI and thiazide
- Patients categorized
  - Tight control systolic BP <130
  - Usual control systolic BP 130-139
  - Uncontrolled systolic BP ≥ 140
- Primary outcome- mortality, non-fatal MI, CVA

JAMA 2010:304;61-68
INVEST TRIAL

<table>
<thead>
<tr>
<th>BP Control</th>
<th>BP &lt; 140</th>
<th>BP 140-159</th>
<th>BP ≥ 140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>12.7%</td>
<td>12.6%</td>
<td>19.8%</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>11.0%</td>
<td>10.3%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.3%</td>
<td>1.7%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Non-fatal CVA</td>
<td>1.0%</td>
<td>1.3%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

INVEST TRIAL - BP Control in CAD

BP Control in Diabetes and CAD - Conclusions
- Current BP goal for patients with diabetes is suspect
- Systolic BP < 140 may be adequate
- Particular caution in elderly patients with CAD
- Systolic target 140 and diastolic target seem optimal
- If already on ACEI/ARB may be beneficial to periodically assess diabetic patients for macroalbuminuria to determine need for more aggressive BP target

Does adding a fibrate to a statin reduce cardiovascular events in patients with diabetes?

Combination Lipid Therapy in Type 2 Diabetes - ACCORD Lipid
- 5518 patients with Type 2 DM at high risk for CVD
- LDL 60 - 180 mg/dl
- HDL < 55 mg/dl for women and blacks, <50 others
- All patients on open label simvastatin ≤ 40 mg/d
- Randomized to fenofibrate, dose adjusted for renal function
- 1st outcome non-fatal MI, CVA, CV death
- Follow-up 4.7 years

Combination Lipid Therapy in Type 2 Diabetes - ACCORD Lipid

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Fenofibrate + Statin</th>
<th>Placebo + Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>10.52%</td>
<td>11.26%</td>
</tr>
<tr>
<td>Primary outcome: HbA1C ≥ 6.5% and Triglyceride ≥ 200 mg/dl</td>
<td>12.17%</td>
<td>17.32%</td>
</tr>
<tr>
<td>Progressive retinopathy</td>
<td>6.3%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Drug D/C'd due to J-character</td>
<td>2.8%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

Retinopathy benefit in subgroup with baseline retinopathy
Combination Lipid Lowering in DM - Conclusions

- Combination fenofibrate and moderate dose simvastatin is safe
- CV may benefit patients with HDL < 35 and Triglyceride > 204 mg/dl
- Decreases progression of retinopathy
- Adjust dose for GFR

Meta-analysis: Age and Effectiveness of Prophylactic ICDs

- Meta-analysis of 5 clinical trials that reported mortality outcomes after ICD placement
- EF ≤ 30-40%
- Elderly defined as age 60-65
  - 44% of study population
  - 70% ICD's implanted in patients > 60
  - 40% ICD's implanted in patients > 70
- Complications occurred in 17% patients
  - 12% inappropriate ICD shocks

Do implantable cardioverter-defibrillators or cardiac resynchronization devices provide benefit in older patients?
Cardiac Resynchronization Therapy in Mild-Moderate Heart Failure

- 1798 patients with NYHA Class II or III CHF, EF ≤ 30%, QRS ≥ 120 msec
- Mean age 66
- 80% Class II CHF
- Randomized to CRT-ICD vs. ICD alone
- Primary outcome death from any cause or CHF hospitalization
- Mean follow-up 40 months

Meta-analysis: Age and Effectiveness of Prophylactic ICD’s

- Older patients with narrow QRS and systolic dysfunction do not conclusively benefit from ICD placement
- Note: Patients with low EF and QRS ≥ .12 seconds benefit from CRT regardless of age
- CRT reduces CHF morbidity and mortality
- Mortality in older patients more likely nonarrhythmic
- CRT-P (without defibrillator) may be more appropriate in elderly patients

Patients’ and Cardiologists’ Perceptions of the Benefits of PCI in stable CAD

- Survey of 153 patients undergoing elective cardiac catheterization with possible PCI and 27 cardiologists at Baystate Medical Center
- 77% patients had + stress test
- 65% patients had hx of angina
- 41% had angina < once per week
- 41% had activity limited by angina
- 77% who received PCI reported angina
- Cardiologists’ reported angina in 98% of these patients

Does CABG decrease mortality in patients with CHF?
Surgical Treatment for Ischemic Heart Failure- STICH Trial

- 1212 patients with CAD amenable to CABG and EF ≤ 35% randomized to CABG vs. medical therapy
- > 65% patients with > 75% proximal LAD
- ≈ 60% patients with 3 vessel disease
- ≈ 90% patients on optimal medical therapy
- Excluded patients with Class III or IV angina
- Surgeons had experience and mortality ≤ 5%
- Primary outcome: overall mortality
- Secondary outcome: CV hospitalization and/or death

NEJM published online April 4, 2011

Eplerenone in Patients with CHF and Mild Symptoms

- 2737 patients with NYHA Class II CHF and EF ≤ 35%
- Hospitalized within the last 6 months or increased BNP
- Randomized to eplerenone titrated to 50 mg qd vs. placebo
- Started 25 mg qd and increased to 50 mg qd at 4 weeks
- If CrCl 30-49 ml/min started 35 mg qd and titrated to qd if K+ ≤ 5.0
- Dose decreased if K+ 5.5-5.9
- Drug stopped for K+ ≥ 6.0, remeasured after 72 hours and restarted if K+ < 5.0

NEJM 2011;364:11-21

Eplerenone in Mild CHF

<table>
<thead>
<tr>
<th></th>
<th>Eplerenone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or CHF Hospitalization</td>
<td>18.3%</td>
<td>25.9%</td>
</tr>
<tr>
<td>Overall mortality or CHF Hospitalization</td>
<td>19.8%</td>
<td>27.4%</td>
</tr>
<tr>
<td>Hospitalization for worsening renal function</td>
<td>0.7%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>
**Aldosterone Use in CHF**

- Observational analysis of 43,625 patients admitted with CHF and discharged home
- 242 hospitals participating in the Get With The Guidelines-HF Program
- 12,565 patient eligible for aldosterone antagonist therapy
  - EF \(\leq\) 35%
  - Serum potassium \(\leq\) 5.0 mEq/L
  - Serum creatinine \(\leq\) 2.5 mg/dl in men
  - Serum creatinine \(\leq\) 2.0 mg/dl in women
- 34.5% eligible patients received aldosterone antagonist
- 10.55% inappropriate or potentially inappropriate use

**Dabigatran vs. Warfarin for Atrial Fibrillation-RE-LY Trial**

- 18,113 patients with atrial fibrillation with one of TIA or CVA
- EF < 40%
- Symptomatic CHF
- Age \(\geq\) 75
- Age 65-74 plus DM, HTN, or CAD
- Mean CHADS2 Score 2.1
- Excluded patients with liver disease and CrCl < 30
- Randomized to dabigatran (direct thrombin inhibitor) 110 mg BID or 150 mg BID, vs. warfarin
- Outcome: PE or systemic embolism
- Follow-up 2 years

**Dabigatran- Conclusions**

- Dabigatran 150 mg dose modestly more effective than warfarin
- Expense an issue, especially for Medicare patients
- Useful in patients difficult to control or monitor
- May be less effective in non-adherent patients due to shorter half life

**Dabigatran vs. Warfarin for Atrial Fibrillation-RE-LY Trial**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic embolism</td>
<td>1.53%</td>
<td>1.11%</td>
<td>1.48%</td>
</tr>
<tr>
<td>MI</td>
<td>0.72%</td>
<td>0.74%</td>
<td>0.11%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.71%</td>
<td>3.31%</td>
<td>3.36%</td>
</tr>
</tbody>
</table>

Dabigatran - 11.5% dyspepsia
Elevated liver enzymes similar in all groups

**Population Based Prostate Cancer Screening Trial- Göteberg Trial**

- 20,000 age 50-64 randomized to PSA every 2 years vs. no screening
- Screening discontinued at age 69
- Elevated PSA, defined as 2.5-3, offered DRE, ultrasound and biopsy
- Men with negative evaluation re-screened every 2 years and biopsied for repeat PSA elevation
- Primary endpoint: prostate cancer specific mortality
- Median follow-up 14 years

Does PSA screening reduce prostate cancer mortality?

Lancet 2010
Prostate CA diagnosed

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Invited to screen</th>
<th>Attendees</th>
<th>Non-attendants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>2.0%</td>
<td>6.1%</td>
<td>7.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>2.5%</td>
<td>1.6%</td>
<td>4.5%</td>
<td>1.0%</td>
</tr>
<tr>
<td>High Risk</td>
<td>1.3%</td>
<td>1.0%</td>
<td>1.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Advanced</td>
<td>0.9%</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Low risk: T1, Gleason score ≤ 6, PSA <10
Moderate risk: T1-2, Gleason score ≤ 7, PSA <20
High risk: T1-4, Gleason score ≥ 8, PSA <100

# invited to screen to prevent one death = 293
# diagnosed to prevent one death = 12

PSA Screening: Norköping Trial
- 1494 men aged 50-69 randomly allocated to screening
- 7532 men in control group
- First 2 screens - DRE
- PSA screening instituted 1993
- Men aged < 70 received a second PSA in 1996
- PSA cutoff > 4 μg/L
- Patients with prostate cancer offered surgery or radiotherapy if it were considered possible to prolong survival
- Primary outcome- prostate cancer specific mortality

**Table 3: Treatments for prostate cancer, by study group**

**BMJ 2011;342:d1539**
PSA Screening: Norköping Trial

- 5.7% screened vs. 3.9% control patients diagnosed with prostate cancer
- ≈ 50% cases in screened group were interval cancers

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised tumor</td>
<td>26.7%</td>
<td>56.5%</td>
</tr>
<tr>
<td>Watchful waiting</td>
<td>34.6%</td>
<td>43.5%</td>
</tr>
<tr>
<td>Surgery</td>
<td>7.9%</td>
<td>10.8%</td>
</tr>
<tr>
<td>RT</td>
<td>6.1%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Hormonal</td>
<td>50.3%</td>
<td>31.8%</td>
</tr>
</tbody>
</table>

How are men with low risk prostate cancer treated?

Risk Profiles and Treatment Patterns in Men with Prostate Cancer

- Analyzed 123,934 newly diagnosed prostate cancer patients from SEER database
- Men categorized into 3 risk groups
  - Low: Stage ≤ T2a, PSA ≤ 10, Gleason score ≤ 6
    - Stage T2a involves < ½ one lobe
  - Intermediate: Stage T2b, PSA 10-20, Gleason ≤ 7
    - Stage T2b involves > ½ one lobe
  - High: Stage ≥ T2c, PSA > 20, Gleason ≥ 8

Archives of Int Medicine 2010;170:1256-1261
NCCN Guidelines

- Active surveillance reasonable option for men with
  - Stage T1-2a, Gleason score ≤ 6, PSA < 10
- Active surveillance
  - PSA at least every 6 months
  - DRE at least every 12 months
  - Biopsy 6 months if initial bx. < 10 cores
  - Biopsy 18 months if initial bx. ≥ 10 cores

---

Prostate Cancer Screening-Conclusions

- PSA screening may provide small survival benefit
- Pre-screening, contamination, biopsy threshold and
treatment differences limits data interpretation
- Survival curves start to diverge at about 10 years
- Significant benefit may take longer
- Overdiagnosis is a serious health hazard
- Over 1 million treated
- Side effects immediate
- Impact of overdiagnosis could be dramatically reduced if active
surveillance was initial treatment strategy in appropriate
patients
- Shared decision making should emphasize delayed benefit,
short term risk and option for delayed curative treatment
- Collaboration with urology community is essential