Evidence-based health care: A look into the future

- McMaster perspective
- leaders - past, present, future
- new first principle of EBM
  - implications for evidence assessment
  - implications for searching
- information management
- shared decision-making
Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>RCTs</th>
<th>Pts</th>
</tr>
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<tbody>
<tr>
<td>1960</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>1965</td>
<td>3</td>
<td>149</td>
</tr>
<tr>
<td>1970</td>
<td>7</td>
<td>1793</td>
</tr>
<tr>
<td>1980</td>
<td>23</td>
<td>5767</td>
</tr>
<tr>
<td>1985</td>
<td>33</td>
<td>6571</td>
</tr>
<tr>
<td>1990</td>
<td>70</td>
<td>48154</td>
</tr>
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</table>

Cumulative Year

<table>
<thead>
<tr>
<th>Textbook/Review Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Odds Ratio (Log Scale)

- Favours Treatment
- Favours Control

P<.01
P<.001
P<.00001
First principle

* systematic summaries of the best available evidence should guide patient management decisions
GRADE

* system to guide interpretation of systematic reviews to inform clinical guidelines and clinical decisions
* system for developing recommendations
GRADE uptake
First principle: Hierarchy of Evidence for Therapy

- Randomized Trials
- Observational studies
  - patient-important outcomes
- Basic research
  - test tube, animal, human physiology
- Clinical experience
### Beyond the old hierarchy: Guides to confidence in estimates

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Confidence in estimates</th>
<th>Lower if</th>
<th>Higher if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised trial</td>
<td>High</td>
<td>Risk of bias</td>
<td>Large effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 Serious</td>
<td>+1 Large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 Very serious</td>
<td>+2 Very large</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Inconsistency</td>
<td>Dose response</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 Serious</td>
<td>+1 Evidence of a gradient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 Very serious</td>
<td>All plausible confounding</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Indirectness</td>
<td>+1 Would reduce a demonstrated effect or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 Serious</td>
<td>+1 Would suggest a spurious effect when results show no effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 Very serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very low</td>
<td>Imprecision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 Serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 Very serious</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Publication bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 1 Likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 2 Very likely</td>
<td></td>
</tr>
</tbody>
</table>
Further advances in GRADE: coming up

* application to systematic reviews of prognosis
  * overall prognosis of population
  * identification of risk factors
  * clinical prediction rules

* application to systematic reviews of diagnosis
  * confidence in estimates
  * utility – treat as an intervention
## Quality Assessment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of participants (studies)</th>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Publication Bias</th>
<th>Quality</th>
<th>Relative Effect (95% CI)</th>
<th>Absolute risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>10,125 (9)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>Not detected</td>
<td>High</td>
<td>0.71 (0.57 to 0.86)</td>
<td>1.5% fewer (0.7% fewer to 2.1% fewer)</td>
</tr>
<tr>
<td>Mortality</td>
<td>10,205 (7)</td>
<td>No serious limitations</td>
<td>Possibly inconsistent</td>
<td>No serious limitations</td>
<td>Imprecise</td>
<td>Not detected</td>
<td>Moderate or low</td>
<td>1.23 (0.98 – 1.55)</td>
<td>0.5% more (0.1% fewer to 1.3% more)</td>
</tr>
<tr>
<td>Stroke</td>
<td>10,889 (5)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>Not detected</td>
<td>High</td>
<td>2.21 (1.37 – 3.55)</td>
<td>0.5% more (0.2% more to 1.3% more)</td>
</tr>
</tbody>
</table>
Clinicians need pre-appraised evidence

Clinicians need guidance on applying that evidence
Review: Eplerenone is not more effective for reducing mortality than other aldosterone antagonists

Clinical impact ratings:  

Therapeutics  

Question  
In patients with left ventricular (LV) dysfunction, what is the relative efficacy of eplerenone and other aldosterone antagonists (AAs)?

Review scope  
Included studies compared eplerenone or other AAs with control (placebo, angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, or β-blocker) in patients >18 years of age with symptomatic or asymptomatic LV dysfunction, had ≥8 weeks of follow-up, and reported ≥1 outcome of interest. Studies comparing AAs with each other were excluded. Outcomes were all-cause mortality, cardiovascular (CV) mortality, gynecomastia [per trial definition in individual studies], and hyperkalemia (serum potassium >5.5 mEq/L).

Review methods  
MEDLINE, EMBASE/Excerpta Medica, CINAHL, and Cochrane Central Register of Controlled Trials (all to Jul 2011); reference lists; and reviews were searched for randomized controlled trials (RCTs). 16 RCTs (n = 12,505, mean age 55 to 69 yr, 54% to 87% men) met selection criteria. 4 RCTs included patients after acute myocardial infarction LV dysfunction, and 12 included patients with heart failure. Study drugs were spironolactone (10 RCTs), canrenone (3 RCTs), and eplerenone (3 RCTs). Risk for bias (Cochrane criteria) was low for 8 RCTs, intermediate for 7, and high for 1.

Main results  
Eplerenone and other AAs reduced all-cause mortality and CV mortality compared with no AA (Table). Eplerenone increased risk for hyperkalemia, and other AAs increased risk for gynecomastia, compared with no AA (Table). Based on an indirect comparison, other AAs reduced mortality more than eplerenone (P*<0.009).  

Eplerenone or other AAs vs control in patients with left ventricular dysfunction  

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>At 2 to 24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Eplerenone)</td>
<td>Control</td>
<td>RRR (95% CI)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2 (9569)</td>
<td>14%</td>
<td>16%</td>
</tr>
<tr>
<td>CV mortality</td>
<td>2 (9569)</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>2 (9561)</td>
<td>0.49%</td>
<td>0.66%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3 (4849)</td>
<td>6.1%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Other AAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>12 (2561)</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>CV mortality</td>
<td>4 (2553)</td>
<td>20%</td>
<td>34%</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>10 (3342)</td>
<td>0.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>6 (2279)</td>
<td>5.4%</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

References  


Conclusion  
Based on a indirect comparison, eplerenone is not more effective for reducing mortality in adults with left ventricular dysfunction than other aldosterone antagonists.

*Information provided by author.

Source of funding: No external funding.

For correspondence: Dr. S. Chatterjee, Maimonides Medical Center, Brooklyn, NY, USA. E-mail suavachatterjeejm@gmail.com.

Commentary  
In their thorough review of the use of AAs in systolic heart failure, Chatterjee and colleagues conclude that data are insufficient to recommend eplerenone over spironolactone. Only 2 large outcome trials actually address the issue: RALES, assessing spironolactone (1), and EMPHASIS-HF (2), assessing eplerenone. Although the populations evaluated in each study were quite different, the relative reductions in mortality were similar (25%, 34%, and 19%, respectively). Indirect comparisons of drug efficacy across clinical trials with different patient populations and study protocols are challenging. Without head-to-head trials of AAs, we should not draw conclusions about their relative efficacy.

Chatterjee and colleagues confirm that spironolactone increases risk for gynecomastia. Hyperkalemia is a known adverse effect of any AA, although potassium increases were “not clinically important” in RALES (1). After RALES was published, however, there was a marked increase in the number of spironolactone prescriptions, with an increase in hyperkalemia and associated mortality (4). Gynecomastia can be distressing to male patients, but hyperkalemia may be fatal to other sex.

A strict, evidence-based practitioner would base drug and dosage selection on the clinical trial most closely matching a patient’s presentation. While waiting for a definitive head-to-head trial—note that benefits seem similar in the studied populations—I start with the less expensive spironolactone, switching to eplerenone if troublesome sexual adverse effects develop (while closely monitoring potassium).
Evidence-Based Journals

Critical Appraisal Filters

30,000 articles/y from 120 journals

~3,500 articles/y meet appraisal and content criteria (93% ‘noise’ reduction)
~3,500 articles/y meet critical appraisal and content criteria

~20 articles/yr for clinicians (99.96% noise reduction)

~5-50 articles/y for authors of evidence-based guidelines and reviews

Health Knowledge Refinery
## What is the problem?

Lacking trustworthiness of guidelines - GRADE

Inefficient guideline authoring, adaptation and dynamic updating

Inefficient guideline dissemination to clinicians at the point of care

Suboptimal presentation formats of guideline content

Inconsistent and under-developed systems for integration in EMRs

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### Table 5—(Sections 2.1.1.8.1.5) Aspirin Plus Clopidogrel vs Aspirin in the Secondary Prevention of Cardiovacular Events

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Participants/Study, Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Aspirin</th>
<th>Risk Difference With Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>15,659 (1 RCT, 18 mo)</td>
<td>Moderate due to imprecision</td>
<td>RR 0.89 (0.86-0.94)</td>
<td>120 per 1,000</td>
<td>No significant difference; 1 fewer (from 17 fewer to 17 more)</td>
</tr>
<tr>
<td>MI nonfatal events</td>
<td>15,659 (1 RCT, 18 mo)</td>
<td>Moderate due to imprecision</td>
<td>RR 0.84 (0.75-0.94)</td>
<td>80 per 1,000</td>
<td>No significant difference; 5 fewer (from 20 fewer to 14 more)</td>
</tr>
<tr>
<td>Stroke and/or nonfatal ischemic and hemorrhagic strokes</td>
<td>15,659 (1 RCT, 18 mo)</td>
<td>Moderate due to imprecision</td>
<td>RR 0.84 (0.74-0.94)</td>
<td>110 per 1,000</td>
<td>No significant difference; 21 fewer (from 40 fewer to 2 more)</td>
</tr>
<tr>
<td>Major extracranial bleed</td>
<td>15,659 (1 RCT, 18 mo)</td>
<td>Moderate due to imprecision</td>
<td>RR 0.85 (0.77-0.93)</td>
<td>60 per 1,000</td>
<td>No significant difference; 10 fewer (from 1 fewer to 24 more)</td>
</tr>
</tbody>
</table>

See Table 1 through 3 legends for expansion of abbreviations.

+ The deaths in the CHA2DS2-VASc (History of Cardiovascular Disease, Age, Sex, Diabetes, Hypertension, Stroke, Vascular disease, Age > 75) trial, 17 of 1671 (1%) with aspirin were fatal bleed, and 44 (4.4%) with clopidogrel, and aspirin were fatal bleed.

+ Rated down for imprecision because of wide CIs for absolute effects, suggesting important benefit, or benefit, or important harm with clopidogrel for all outcomes. Not rated down for it, although subgroup analysis found no significant effect of clopidogrel on vascular mortality in patients with established cardiovascular disease in contrast with increased mortality in asymptomatic patients. We judged clinical effect to be not credible (high number of subgroup hypothesis tested, and analysis appropriate test for interaction used).

+ Central group risk estimate for total mortality come from the aspirin arm of the CHA2DS2-VASc trial. Estimates for MI and stroke come from observed events in a meta-analysis. 36 RCTs in prevention (Diogenz et al.), adjusted to a 5-year time frame.

+ Of the strokes in CHA2DS2-VASc, 27 of 105 (25%) with aspirin were intracranial hemorrhage, and 20 of 141 (14%) with clopidogrel were intracranial hemorrhage.

+ We excluded fatal bleeding and intracranial hemorrhage to avoid the double counting of events in the CHA2DS2-VASc trial. Proportion of severe GI bleed in CHA2DS2-VASc was 0.05% (not reported for each treatment arm).

+ Central group risk estimate come from observed major bleeding events in the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Intracranial Events) trial, adjusted to a 5-year time frame, and the 16 studies included in the meta-analysis from CHA2DS2-VASc because these studies did not report major bleeds consistently.
STEP 1 develops:
- Authoring tool template
- Electronic outputs
- Optimal formats
- Integration in EMR
- Adaptation
- Decision aids

Electronic outputs
Web + App

Integrated in the EMR

Decision aids for patients and clinicians

Database
Structured content
XML language

GRADE GUIDELINE
SNAP-IT DECIDE

Electronic authoring tool

PICO
Individual studies
Descriptive tables
Evidence profiles

Recommendations
Key information
Rationale

SNAP-IT
SHARE-IT

PLUGGED IN

SNAP-IT

Adaptation
National/ local or EBM Textbooks
1.0 Primary prevention of cardiovascular disease

For persons age 50 years or older without symptomatic cardiovascular disease we suggest low dose aspirin 75-100 mg daily over no aspirin therapy.

2. Secondary prevention of cardiovascular events

For patients with established CAD

We recommend long-term single antiplatelet therapy with aspirin 75-100 mg daily or clopidogrel 75 mg daily over no antiplatelet therapy.

We suggest single over dual antiplatelet therapy with aspirin plus clopidogrel.

For patients in the first year after an ACS who have not undergone PCI

We recommend dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily or clopidogrel 75 mg daily plus low dose aspirin 75-100 mg daily) over single antiplatelet therapy.

We suggest ticagrelor 90 mg daily plus low dose aspirin over clopidogrel 75 mg daily plus low dose aspirin.

Compared with no treatment, giving Aspirin for 10 years to 100 people will result in 2 less vascular events (MI and Stroke), with no significant differences in deaths or bleeds.

Our confidence in the results is high (mortality, major bleeds, MI, Stroke)

Some patients would probably be reluctant to take aspirin to achieve the modest reduction in vascular events.

Although Aspirin have little costs attached to it, it is not cost effective to treat all patients.
Third principle: evidence insufficient

* always tradeoffs
* many decisions value and preference sensitive
* low risk atrial fibrillation
  * anticoagulants or no anticoagulants
* screening
  * breast and colon cancer
* primary prevention
  * aspirin, statins, bisphosphonates
* cancer toxic chemotherapy
GRADE response: Strong and Weak Recommendations

* variability in patient preference
  * strong, almost all same choice (> 90%)
  * weak, choice varies appreciably

* interaction with patient
  * strong, just inform patient
  * weak, ensure choice reflects values
Values and preferences

- at point of care
- decision aids to ensure decisions consistent with individual patient values and preferences
Blood Sugar
(A1c Reduction)

Weight Change

Daily Routine
(Schedule and monitoring)

Low Blood Sugar
(Hypoglycemia)

Daily Sugar Testing
(Monitoring)

Side Effects

Exenatide
After starting Exenatide, some patients may have nausea or diarrhea. In some cases, the nausea may be severe enough that a patient has to stop taking the drug.

Insulin
There are no other side effects associated with insulin.

Glitazones
Over time, 10 in 100 people may have fluid retention (edema) while taking Glitazones. For some, it may be as little as ankle swelling. For others, fluid may build up in the lungs making it difficult to breathe.

Sulfonylureas
Some patients get nausea, rash and/or diarrhea when they first start taking Sulfonylureas. This type of reaction may force them to stop taking the drug.

Metformin
In the first few weeks after starting Metformin, patients may have some nausea, indigestion or diarrhea.
Blood Sugar
(A1c Reduction)

Exenatide ½ - 1%

Daily Routine
(Schedule and monitoring)

Low Blood Sugar
(Hypoglycemia)

Daily Sugar Testing
(Monitoring)

Side Effects

Exenatide
After starting Exenatide, some patients may have nausea or diarrhea. In some cases, the nausea may be severe enough that a patient has to stop taking the drug.

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Sulfonylureas
Some patients get nausea, rash and/or diarrhea when they first start taking Sulfonylureas. This type of reaction may force them to stop taking the drug.

Metformin
In the first few weeks after starting Metformin, patients may have some nausea, indigestion or diarrhea.

Weight Change

Metformin
- None

Insulin
- 4 to 6 lb. gain

Glitazones
- More than 2 to 6 lb. gain

Exenatide
- 3 to 6 lb. loss

Sulfonylureas
- 2 to 3 lb. gain
**Blood Sugar (A1c Reduction)**

- **Exenatide**: ½ - 1%
- **Insulin**: unlimited %

**Low Blood Sugar (Hypoglycemia)**

**Daily Sugar Testing (Monitoring)**

- **Metformin**

**Side Effects**

- **Exenatide**: After starting Exenatide, some patients may have nausea or diarrhea. In some cases, the nausea may be severe enough that a patient has to stop taking the drug.

- **Insulin**: There are no other side effects associated with Insulin.

- **Glitazones**: Over time, 10 in 100 people may have fluid retention (edema) while taking Glitazones. For some, it may be as little as ankle swelling. For others, fluid may build up in the lungs making it difficult to breathe.

- **Sulfonylureas**: Some patients get nausea, rash and/or diarrhea when they first start taking Sulfonylureas. This type of reaction may force them to stop taking the drug.

- **Metformin**: In the first few weeks after starting Metformin, patients may have some nausea, indigestion or diarrhea.

**Weight Change**

- **Metformin**: None
- **Insulin**: 4 to 6 lb. gain
- **Glitazones**: More than 2 to 6 lb.
- **Exenatide**: 3 to 6 lb. loss
- **Sulfonylureas**: 2 to 3 lb. gain

**Daily Routine**

- **Metformin**

- **Insulin**

- **Glitazones**

- **Exenatide (KEEP COLD)**: Take in the hour before meals.

- **Sulfonylureas**: Take 30 min. before meal.
**Blood Sugar**
(A1c Reduction)

- **Exenatide**: ½ - 1%
- **Insulin**: unlimited %

**Low Blood Sugar**
(Hypoglycemia)

**Daily Sugar Testing**
(Monitoring)

- **Metformin**

**Side Effects**

- **Exenatide**: After starting Exenatide, some patients may have nausea or diarrhea. In some cases, the nausea may be severe enough that a patient has to stop taking the drug.

- **Insulin**: There are no other side effects associated with Insulin.

- **Glitazones**: Over time, 10 in 100 people may have fluid retention (edema) while taking Glitazones. For some, it may be as little as ankle swelling. For others, fluid may build up in the lungs making it difficult to breathe.

- **Sulfonylureas**: Some patients get nausea, rash and/or diarrhea when they first start taking Sulfonylureas. This type of reaction may force them to stop taking the drug.

- **Metformin**: In the first few weeks after starting Metformin, patients may have some nausea, indigestion or diarrhea.

---

**Weight Change**

- **Metformin**: None

- **Insulin**: 4 to 6 lb. gain

- **Glitazones**: More than 2 to 6 lb.

- **Exenatide**: 3 to 6 lb. loss

- **Sulfonylureas**: 2 to 3 lb. gain

---

**Daily Routine**

**Metformin**

- AM
- PM

**Insulin**

- AM
- PM

**Glitazones**

- AM
- PM

**Exenatide** (KEEP COLD) Take in the hour before meals.

**Sulfonylureas** Take 30 min. before meal.
**Blood Sugar**

- **Exenatide** 1.5 - 1%
- **Insulin** unlimited %
- **Glitazones** 1%

**Daily Sugar Testing**

- **Metformin**

**Side Effects**

- **Exenatide**
  
  After starting Exenatide, some patients may have nausea or diarrhea. In some cases, the nausea may be severe enough that a patient has to stop taking the drug.

- **Insulin**
  
  There are no other side effects associated with Insulin.

- **Glitazones**
  
  Over time, 10 in 100 people may have fluid retention (edema) while taking Glitazones. For some, it may be as little as ankle swelling. For others, fluid may build up in the lungs making it difficult to breathe.

- **Sulfonylureas**
  
  Some patients get nausea, rash and/or diarrhea when they first start taking Sulfonylureas. This type of reaction may force them to stop taking the drug.

- **Metformin**
  
  In the first few weeks after starting Metformin, patients may have some nausea, indigestion or diarrhea.

**Weight Change**

**Low Blood Sugar**

- **Exenatide**
  
  - Severe = No Risk
  - Minor = 0 - 1%

- **Insulin**
  
  - Severe = 1 - 3%
  - Minor = 30 - 40%

- **Glitazones**
  
  - Severe = No Risk
  - Minor = 1 - 2%

- **Sulfonylureas**
  
  - Severe = less than 1%
  - Minor = 21%

- **Metformin**
  
  - Severe = No Risk
  - Minor = 0 - 1%

**Daily Routine**

- **Insulin** (KEEP COLD) Take in the hour before meals.

- **Sulfonylureas** Take 30 min. before meal.

- **Glitazones** OR
  
  **Exenatide**
Combination of opportunities

**GRADE:**
Weak recs are ideally framed for SDM

Evolution of decision aids for the clinical encounter

Enhancing EBM & SDM conversations

Technology

Interactive DA on iPads
- For the clinical encounter
- Info tailored to patients' needs

Adaptive To Local circumstances

Semi-Automated Production

Continuous Update When evidence modified
New oral anticoagulants vs warfarin

Over 1 year, among 1000 patients:

**Mortality**
- Intervention: 24 per 1000
- Comparison: 30 per 1000
- 6 fewer per 1000 patients

**Stroke**
- Intervention: 24 per 1000
- Comparison: 40 per 1000
- 16 fewer per 1000 patients

**Major bleeding**
- Intervention: 60 per 1000
- Comparison: 50 per 1000
- 10 more per 1000 patients

Certainty:
- Mortality: Very low
- Stroke: High
- Major bleeding: High

**Aspirin vs warfarin**

**No treatment vs warfarin**

**No treatment vs aspirin**
Conclusion: Look into future

* dissemination of GRADE
  * GRADE principles
  * GRADE evidence summaries

* searching and evidence access
  * guidelines and pre-appraised evidence
  * evidence improved presentation
  * guidelines/evidence summaries on smart phones, EMR
  * push services

* Shared decision making
  * increasingly central: joint conference 2015
  * decision aids, including electronic from guidelines