Should we only count randomized controlled trials for clinical practice guidelines?

Lars H Lindholm
Cairns, Australia, 20 February 2017
NO!

But RCTs are important!
EBM is an approach to medical practice intended to optimize decision making by use of evidence from well designed and well conducted research.
Evidence based medicine, EBM (2)

EBM classifies evidence by its strength and requires that only the strongest studies (RCTs, meta-analyses, and systematic reviews) can yield strong recommendations.
Evidence based medicine, EBM (3)

Lars Lindholm’s experience of EBM

• Chair, Moderately Elevated blood Pressure 1991-4
• Chair, Moderately Elevated Blood Pressure 2001-4

The Swedish Council on Technology Assessment in Health Care (SBU)
Evidence based medicine, EBM (4)

Four limitations

• The EBM definition of evidence is narrow and excludes important information

• For many reasons (cost, drop-out risk etc.), RCTs are only short-term (1-5 y.)

• Many populations are under-represented and vulnerable patients are often not included

• Management is highly controlled and the usefulness to individual patients “in the real world” is limited
Grade 1: At least two studies of high quality

Grade 2: At least one study of high quality + two studies of medium quality

Grade 3: At least two studies of medium quality
Q: How do you decide what is high, medium, and low quality?

A: ?
Appraising a medical article (1)
0-16 points and 1-5 points

- Design appropriate (0-2)
- Study sample representative (0-2)
- Control group acceptable (0-2)
- Quality of measurements and outcomes (0-2)
- Completeness (compliance, missing data) (0-2)
- Distorting influences (contamination, confounders) (0-2)
- Strategy for data analyses (0-2)
- Strategy for treatment (adequate dosages) (0-2)

- Overall judgement (1-5)

Fowler and Fulton, BMJ, 1991
Appraising a medical article (2)
Cut off points for high, medium, or low grades?

- Design appropriate (0-2)
- Study sample representative (0-2)
- Control group acceptable (0-2)
- Quality of measurements and outcomes (0-2)
- Completeness (compliance, missing data) (0-2)
- Distorting influences (contamination, confounders) (0-2)
- Strategy for data analyses (0-2)
- Strategy for treatment (adequate dosages) (0-2)

- Overall judgement (1-5)
Seven different types of studies

• RCT: High quality grade
• Subgroup of RCT: High quality grade, if pre-specified
• Post-hoc analyses of RCT: Low quality grade
• Meta analysis of RCTs: High to medium-high quality grade
• Case-control study: Low quality grade
• Observational study: Low quality grade
• Case reports: Low or very low quality grade
**LIFE: Cumulative event rates**

(n=9,222)

**Primary composite endpoint**
- **Atenolol**
- **Losartan**

ARR 13.0%, p = 0.021

**Fatal/non-fatal MI**
- **Atenolol**
- **Losartan**

ARR -7%, NS

**Fatal/non-fatal stroke**
- **Atenolol**
- **Losartan**

ARR 25%, p = 0.001

**CV mortality**
- **Atenolol**
- **Losartan**

ARR 11%, NS

Dahlof B et al. Lancet 2002
Seven different types of studies

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LIFE: Diabetes
Trial Profile of Subpopulation

10,778 assessed for eligibility
1,556 ineligible
9,222 randomized
29 excluded
7,998 without Diabetes Mellitus at baseline
1,195 with Diabetes Mellitus at baseline

Losartan
586 available for analysis

Atenolol
609 available for analysis

Lindholm LH Lancet 2002
LIFE: Diabetes - All cause mortality

Risk Reduction = 39%; $p = 0.002$

Lindholm L et al. Lancet 2002
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LI FE Albuminuria substudy: Changes from baseline

Ibsen H, Lindholm LH et al J Hypertens 2004

* p = 0.001, ** p < 0.0001, by Wilcoxon rank-sum test
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Atenolol in hypertension: is it a wise choice?

Bo Carlberg, Ola Samuelsson, Lars Hjalmar Lindholm

Summary
Background Atenolol is one of the most widely used β blockers clinically, and has often been used as a reference drug in randomised controlled trials of hypertension. However, questions have been raised about atenolol as the best reference drug for comparisons with other antihypertensives. Thus, our aim was to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients.

Methods Reports were identified through searches of The Cochrane Library, MEDLINE, relevant textbooks, and by personal communication with established researchers in hypertension. Randomised controlled trials that assessed the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension were included.

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Summary
Background: β blockers have been used widely in the treatment of hypertension and are recommended as first-line drugs in hypertension guidelines. However, a preliminary analysis has shown that atenolol is not very effective in hypertension. We aim to substantially enlarge the data on atenolol and analyse the effect of different β blockers.
Half full ..........?

.............Half empty ?
Lindholm et al. meta-analysis: Overview

- **Design:** Meta-analysis comparing the efficacy of atenolol and other β-blockers with placebo and other antihypertensive drugs (n=127,879)

- **Trials:** 18 RCTs evaluating efficacy of β-blockers as first-line therapy in preventing CVD

- **Eligibility criteria for trials:**
  - Primary hypertension
  - β-blocker as first-line drug in at least 50% of the patients

- **Outcomes:** Stroke, MI, and death

Lindholm LH et al. Lancet 2005
β-blockers vs. placebo or no treatment

Outcomes

<table>
<thead>
<tr>
<th>End point</th>
<th>β-blocker n/N</th>
<th>Placebo n/N</th>
<th>RR (95% CI)</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>325/11025</td>
<td>518/16408</td>
<td>0.81 (0.71-0.93)</td>
<td>p = 0.23</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/11025</td>
<td>639/16408</td>
<td>0.93 (0.83-1.05)</td>
<td>p = 0.85</td>
</tr>
<tr>
<td>Mortality for all causes</td>
<td>606/11025</td>
<td>932/16408</td>
<td>0.95 (0.86-1.04)</td>
<td>p = 0.13</td>
</tr>
</tbody>
</table>

Lindholm LH et al. Lancet 2005
# Atenolol vs. other BP lowering drugs

## Outcomes

<table>
<thead>
<tr>
<th>End point</th>
<th>β-blocker n/N</th>
<th>Other drug n/N</th>
<th>RR (95% CI)</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1019/28132</td>
<td>810/28169</td>
<td>1.26 (1.15-1.38)</td>
<td>p = 0.70</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1216/28132</td>
<td>1167/28169</td>
<td>1.05 (0.91-1.21)</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>Mortality for all causes</td>
<td>2387/28132</td>
<td>2216/28169</td>
<td>1.08 (1.02-1.14)</td>
<td>p = 0.33</td>
</tr>
</tbody>
</table>

Lindholm LH et al., Lancet 2005
Lindholm et al. meta-analysis: Conclusion

- Effect of $\beta$-blockers less than optimum vs. other antihypertensive drugs
- $\beta$-blockers should not be considered first-line therapy to treat primary hypertension and should not be used as reference drugs in future randomized trials

Lindholm LH et al. Lancet 2005
For new treatment of high blood pressure, patients will only be reimbursed for β-blockers if they have tried other drug classes first.
“A meta-analysis is much like a bouillabaisse... no matter how much fresh seafood is added, one rotten fish will make it stink”

Messerli F, 1995
On the other hand,

"a spoonful of port will make a poor French wine drinkable…….."
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- Case reports: Low quality grade
Case-control studies

- Cases (e.g. patients with stroke) are selected and compared with controls (no stroke), matched for e.g. age and sex
- They are compared retrospectively for risk exposure e.g. smoking or coffee drinking
- OR (with 95% CI) is calculated as an estimate of RR
- Easily done and not expensive
- Hypothesis generating
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Framingham Heart Study
An observational study

• 5,209 men and women living in Framingham, aged 30-62 were examined in 1948-52 and followed since then

• More than 1,000 original papers (2016)

• Data on third generation offspring

• Hypertension (HT), 160/95 mm Hg and above; Normotension (NT) below 140/90 mm Hg
  - Risk of CVD death x 3 for HT compared with NT
  - Risk of Stroke x 4 for HT compared with NT
  - Risk of Heart Failure x 4 for HT compared with NT
  - Risk of MI x 2 for HT compared with NT
Post-marketing studies on treatment effectiveness

- RCT assesses if an intervention does more good than harm under ideal circumstances i.e. if a drug can work.
- Once the efficacy has been shown, a drug’s “effect in the real world” (with younger and older patients, fragile patients and those with co-morbidities) must be established.
- Post-marketing studies can provide these data as well as data on adverse events which may take a long time to appear e.g. SLE-type nephritis from hydralazine treatment.
Seven different types of studies

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Case reports

- Great importance many years ago, e.g. for getting drugs registered
- Could be hypotheses generating, if many reports point in the same direction
- Low or very low quality grade
Should we only count randomized controlled trials for clinical practice guidelines?

NO!

We need other types of data as well!
Finally, an EBM analysis of:
Parachute use to prevent death related to gravitational challenge (free fall)
Parachute use to prevent death related to free fall

- **Question**: Are parachutes effective in preventing major trauma and death when jumping from an aircraft?
- **Design**: Systematic review of Trials (RCTs and others)
- **Outcome**: (1) Only observational data exist, (2) most show a positive effect of using a parachute

Gordon CS, BMJ 2003;327:1459
Dr. Gordon’s suggestion

Enthusiastic EBM supporters should participate themselves in a RCT of the effects of a parachute

Gordon CS, BMJ 2003;327:1459
Double blind RCT of the effects of the parachute; 50% active and 50% placebo
Dr. Gordon’s suggestion

Enthusiastic EBM supporters should participate themselves in a RCT of the effects of a parachute

This would lower their numbers by half, I (Lars Lindholm) guess!

Gordon CS, BMJ 2003;327:1459
However, you always have the outlier.
A man jumped from 7 600 m without a parachute on 31 July 2016.
He made it and survived (1)
He made it and survived (2)
Thank You
EBM: Quality grades for recommendations (2)

Q: How do you decide what is high, medium, and low quality?
ASCOT: Stroke (n=19,342)

Risk reduction 23%, p<0.001

Dahlöf B et al. Lancet 2005
ALPINE study (1 year)

Compare the drug effects on metabolic variables in drug naive patients with high BP (DB, RCT, n=362, mean age 55 years, BP 155/97 mm Hg)

- HCTZ 25 mg + atenolol 50-100 mg (84%)
- Candesartan 16 mg + felodipine 2.5-5 mg (71%)

No cross-over
No lipid lowering drugs
No other BP lowering drugs
BP lowering 22/13 mm Hg

Metabolic variables from baseline to 1 year in ALPINE

S-insulin

P-glucose

TG

D/β-b

ARB/CaA

Lindholm LH et al. J Hypertens 2003
New-onset diabetes in ALPINE NE

No of patients

D+BB
ARB+CaA

Difference 3.6% [0.6-6.5%]

28 [15-159] patients treated for 1 year to avoid 1 diabetes case

p<0.05

Lindholm LH et al. J Hypertens 2003
### β-blockers vs. other BP lowering drugs

#### Outcomes

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<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td>1650/51963</td>
<td>1594/53882</td>
<td>1.16 (1.04-1.30)</td>
<td>p = 0.02</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>1935/51963</td>
<td>2042/53882</td>
<td>1.02 (0.93-1.12)</td>
<td>p = 0.04</td>
</tr>
<tr>
<td><strong>Mortality for all causes</strong></td>
<td>3525/52016</td>
<td>3766/53935</td>
<td>1.03 (0.99-1.08)</td>
<td>p = 0.20</td>
</tr>
</tbody>
</table>

Lindholm LH et al. Lancet 2005
Lifetime risk of hypertension in Framingham from 65 years*

*People with BP <140/90

Vasan RS et al. JAMA 2002
Hence, to avoid hypertension in Framingham…

Lindholm LH, 2006
Lifetime risk of hypertension in Framingham

Hence, to avoid hypertension in Framingham you must die young

Lindholm LH, 2006
Parachute use to prevent death related to free fall

- **Question:** Are parachutes effective in preventing major trauma and death when jumping from an aircraft?
Parachute use to prevent death related to free fall

• **Question**: Are parachutes effective in preventing major trauma and death when jumping from an aircraft?

• **Design**: Systematic review of trials (RCTs and others)
NO !