

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

**Lars H Lindholm**

**Cairns, Australia, 20 February 2017**

NO !

But RCTs are important!

# Evidence Based Medicine, EBM (1)

## (25<sup>th</sup> anniversary)

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

# EBM: Quality grades for recommendations (1)

**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

# EBM: Quality grades for recommendations (2)

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)

# Appraising a medical article (2)

Cut off points for high, medium, or low grades?

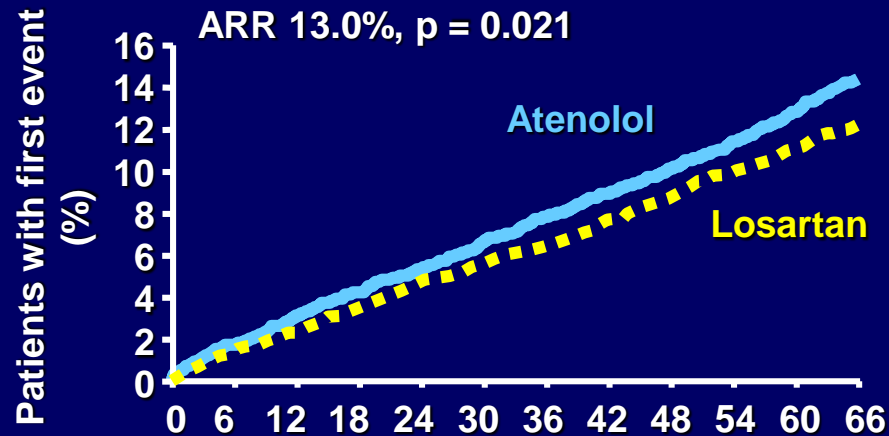
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- Strategy for data analyses (0-2)
- Strategy for treatment (adequate dosages) (0-2)
  
- Overall judgement (1-5)

# Seven different types of studies

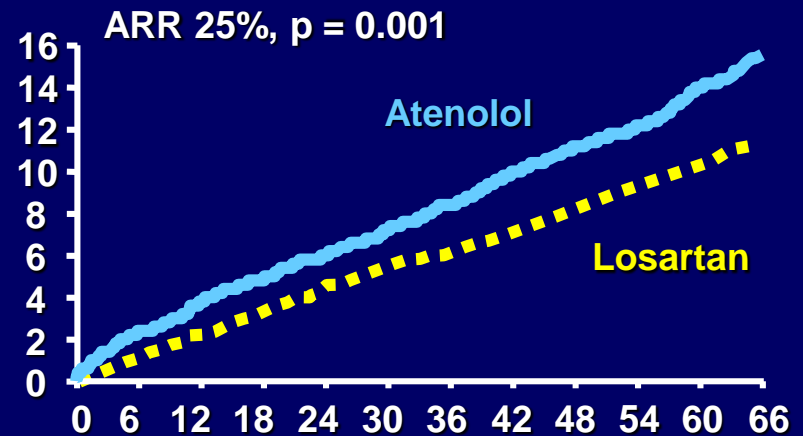
- RCT: High quality grade
- Subgroup of RCT: High quality grade, if pre-specified
- Post-hoc analyses of RCT: Low quality grade
- Meta analysis of RCTs: High to medium-high quality grade
- Case-control study: Low quality grade
- Observational study: Low quality grade
- Case reports: Low or very low quality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

# LIFE: Cumulative event rates (n=9,222)

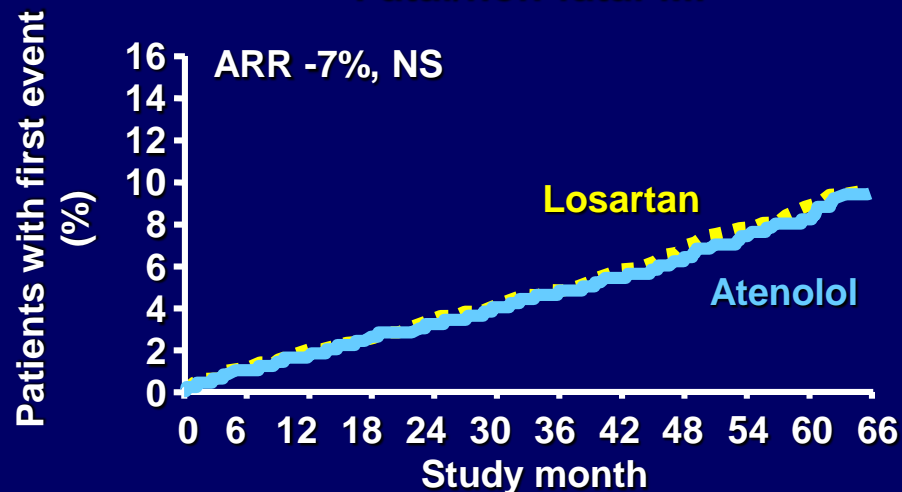
Primary composite endpoint



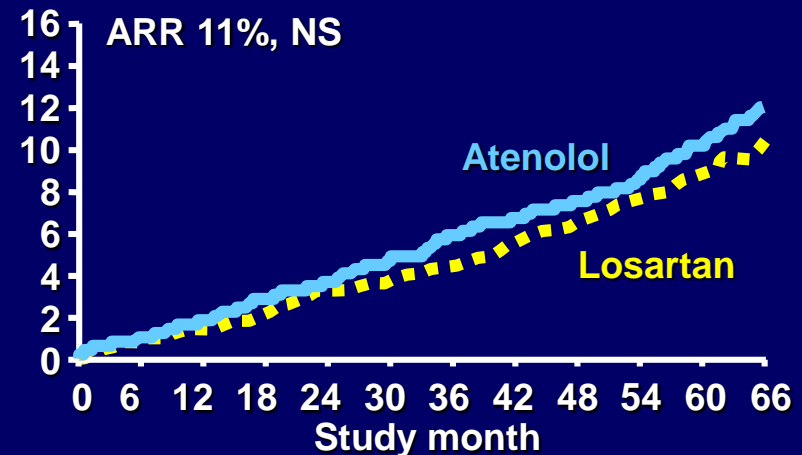
Fatal/non-fatal stroke



Fatal/non-fatal MI



CV mortality

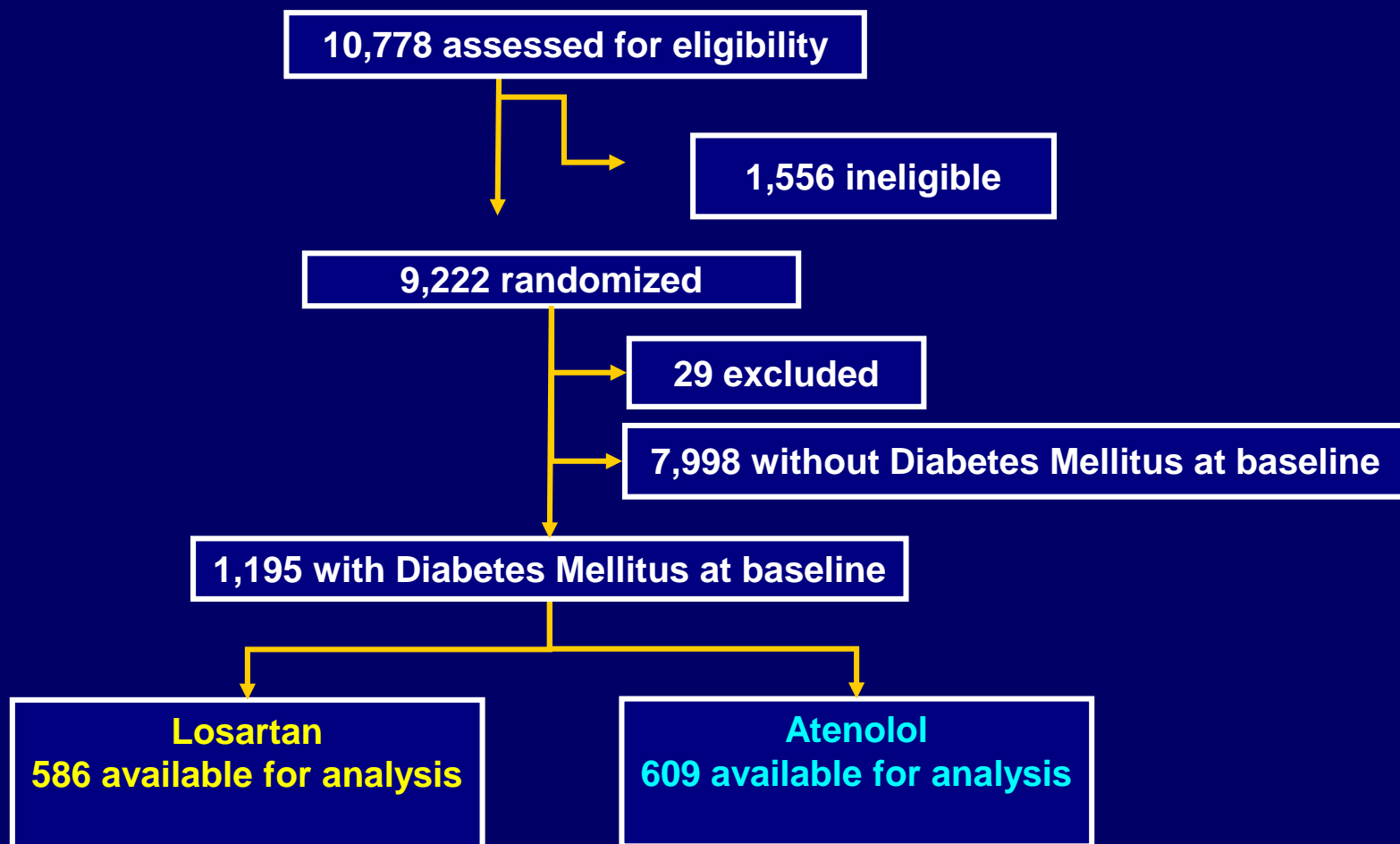


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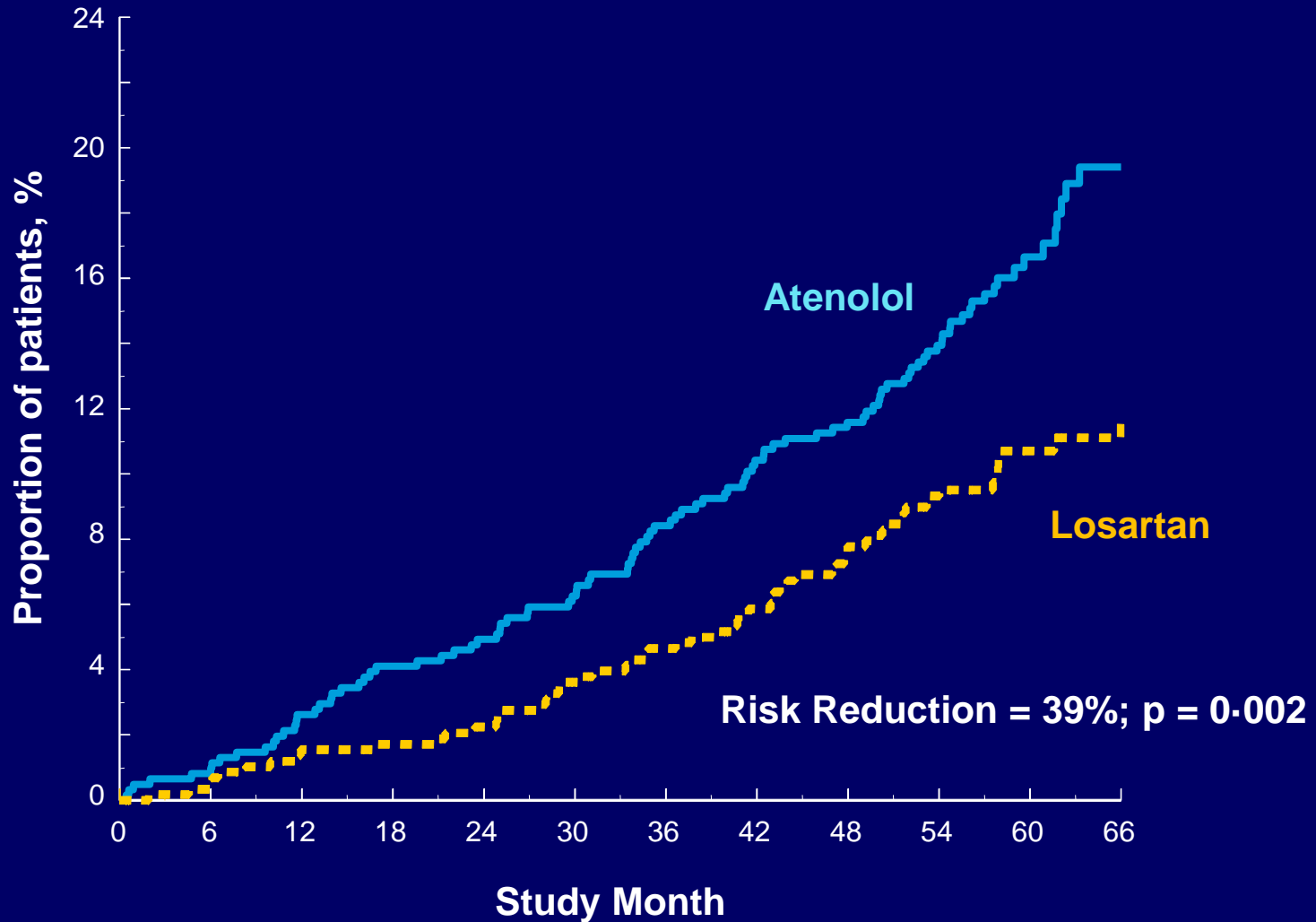
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# LIFE: Diabetes

## Trial Profile of Subpopulation



# LIFE: Diabetes – All cause mortality

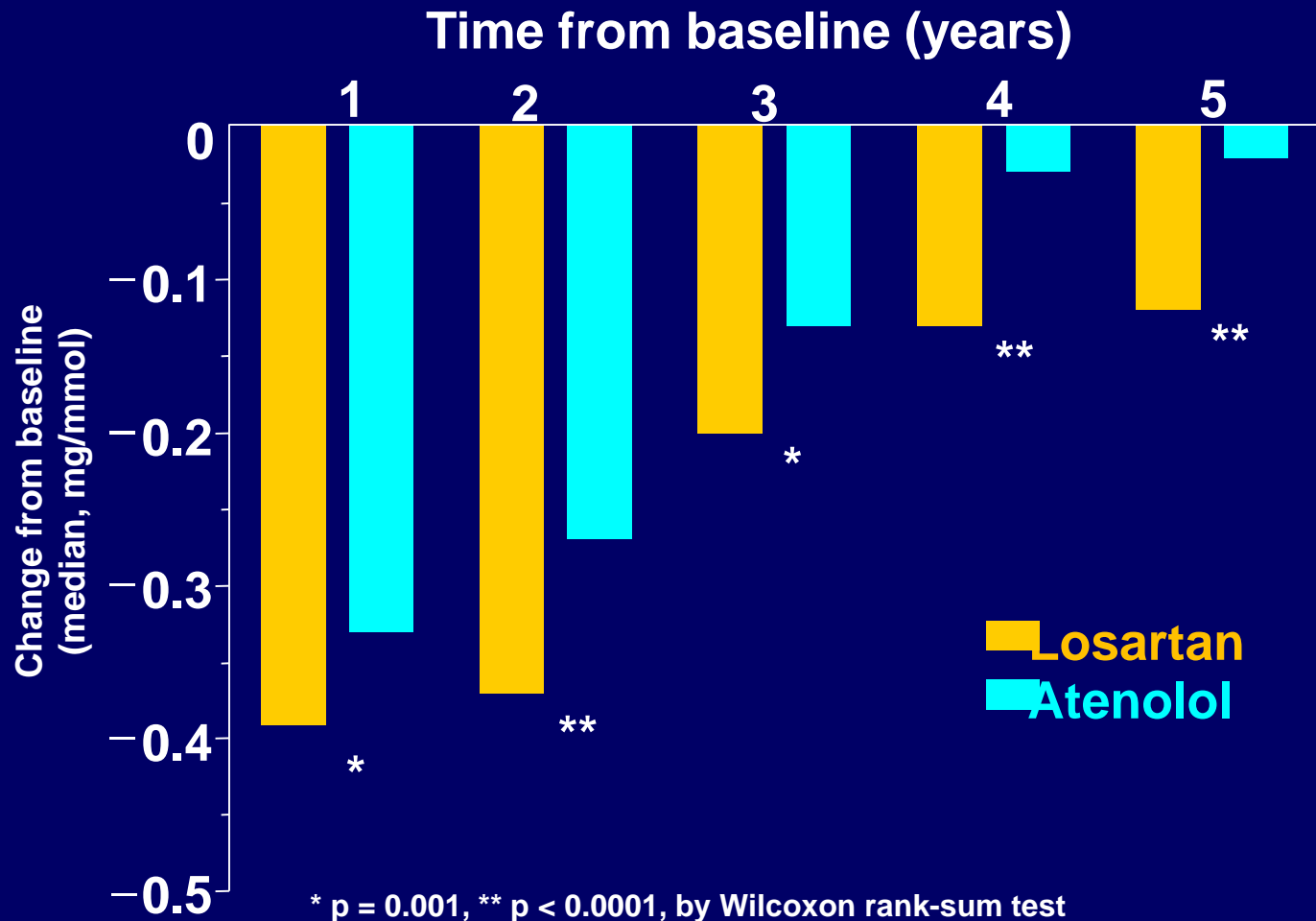


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# LIFE Albuminuria substudy: Changes from baseline



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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  $\beta$  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.



.....ASCOT

## Should $\beta$ blockers remain first choice in the treatment of primary hypertension? A meta-analysis



Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

## Summary

**Background:**  $\beta$  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  $\beta$  blockers.

*Lancet* 2005; 366: 1545-53  
Published online  
October 18, 2005

Half full.....?



.....Half empty ?

# Lindholm et al. meta-analysis: Overview

- **Design:** Meta-analysis comparing the efficacy of atenolol and other  $\beta$ - blockers with placebo and other antihypertensive drugs (n=127,879)
- **Trials:** 18 RCTs evaluating efficacy of  $\beta$ - blockers as first-line therapy in preventing CVD
- **Eligibility criteria for trials:**
  - Primary hypertension
  - $\beta$ -blocker as first-line drug in at least 50% of the patients
- **Outcomes:** Stroke, MI, and death

# $\beta$ -blockers vs. placebo or no treatment

## Outcomes

End point	$\beta$ -blocker n/N	Placebo n/N	RR (95% CI)	Test for heterogeneity
Stroke	325/11025	518/16408	0.81 (0.71-0.93)	p = 0.23
Myocardial infarction	413/11025	639/16408	0.93 (0.83-1.05)	p = 0.85
Mortality for all causes	606/11025	932/16408	0.95 (0.86-1.04)	p = 0.13

# Atenolol *vs.* other BP lowering drugs

## Outcomes

End point	$\beta$ -blocker n/N	Other drug n/N	RR (95% CI)	Test for heterogeneity
Stroke	1019/28132	810/28169	1.26 (1.15-1.38)	p = 0.70
Myocardial infarction	1216/28132	1167/28169	1.05 (0.91-1.21)	p = 0.04
Mortality for all causes	2387/28132	2216/28169	1.08 (1.02-1.14)	p = 0.33

# 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



# Pharmaceutical Benefits Board Sweden, 1 September 2008

For new treatment of high blood pressure, patients will **only** be reimbursed for  $\beta$ -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”

*On the other hand,*

” a spoonful of port will  
make a poor French wine  
drinkable.....”

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# 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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- **Observational study: Low quality grade**
- Case reports: Low quality grade

# 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



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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

# Dr. Gordon's suggestion

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

**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!

**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)



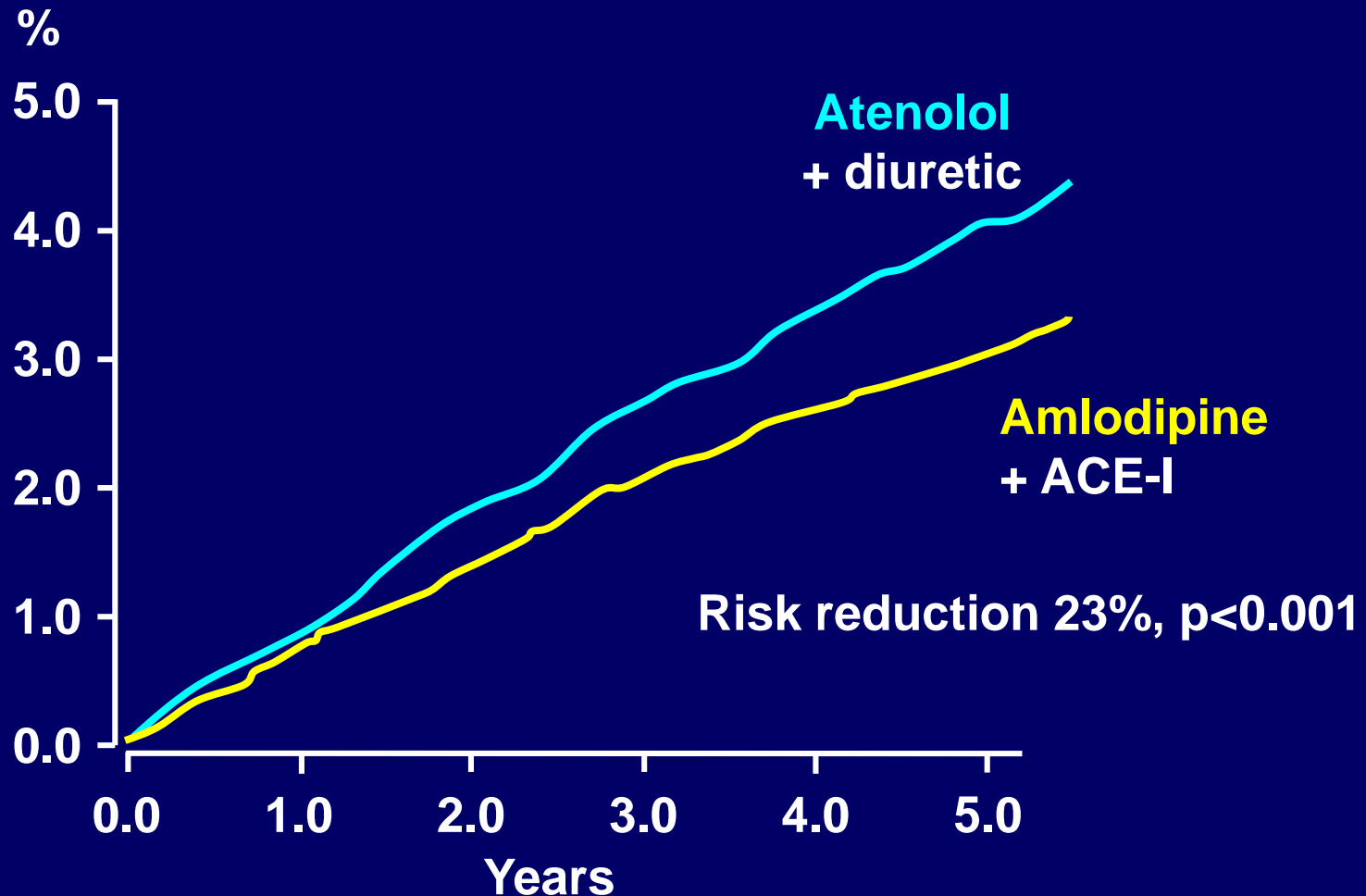
**Thank You**

# EBM: Quality grades for recommendations (2)

Q: How do you decide what is high, medium, and low quality?

# ASCOT: Stroke

(n=19,342)





# ALPINE study (1 year)

*ALPINE*

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

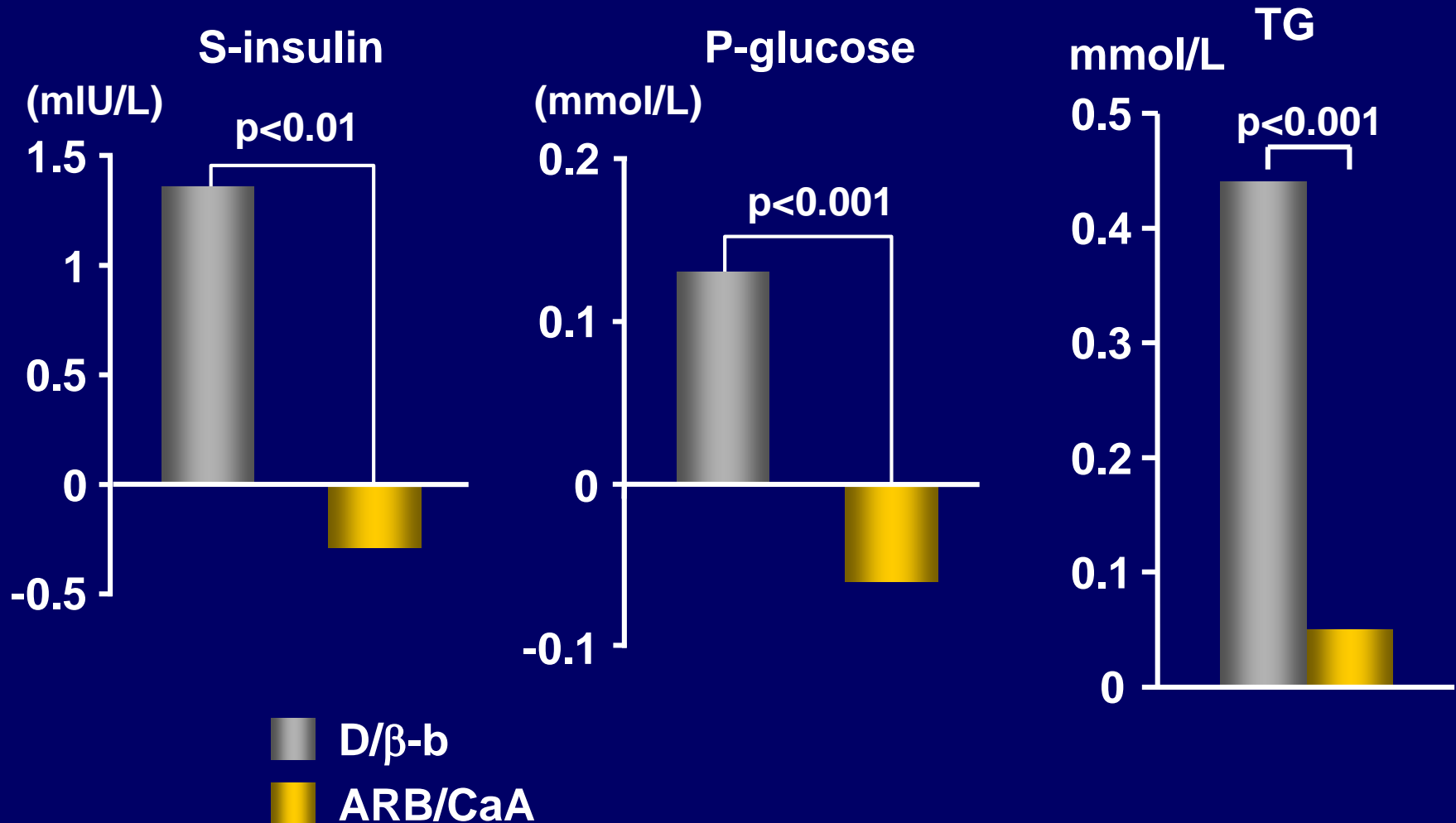
No other BP lowering drugs

**BP lowering 22/13 mm Hg**



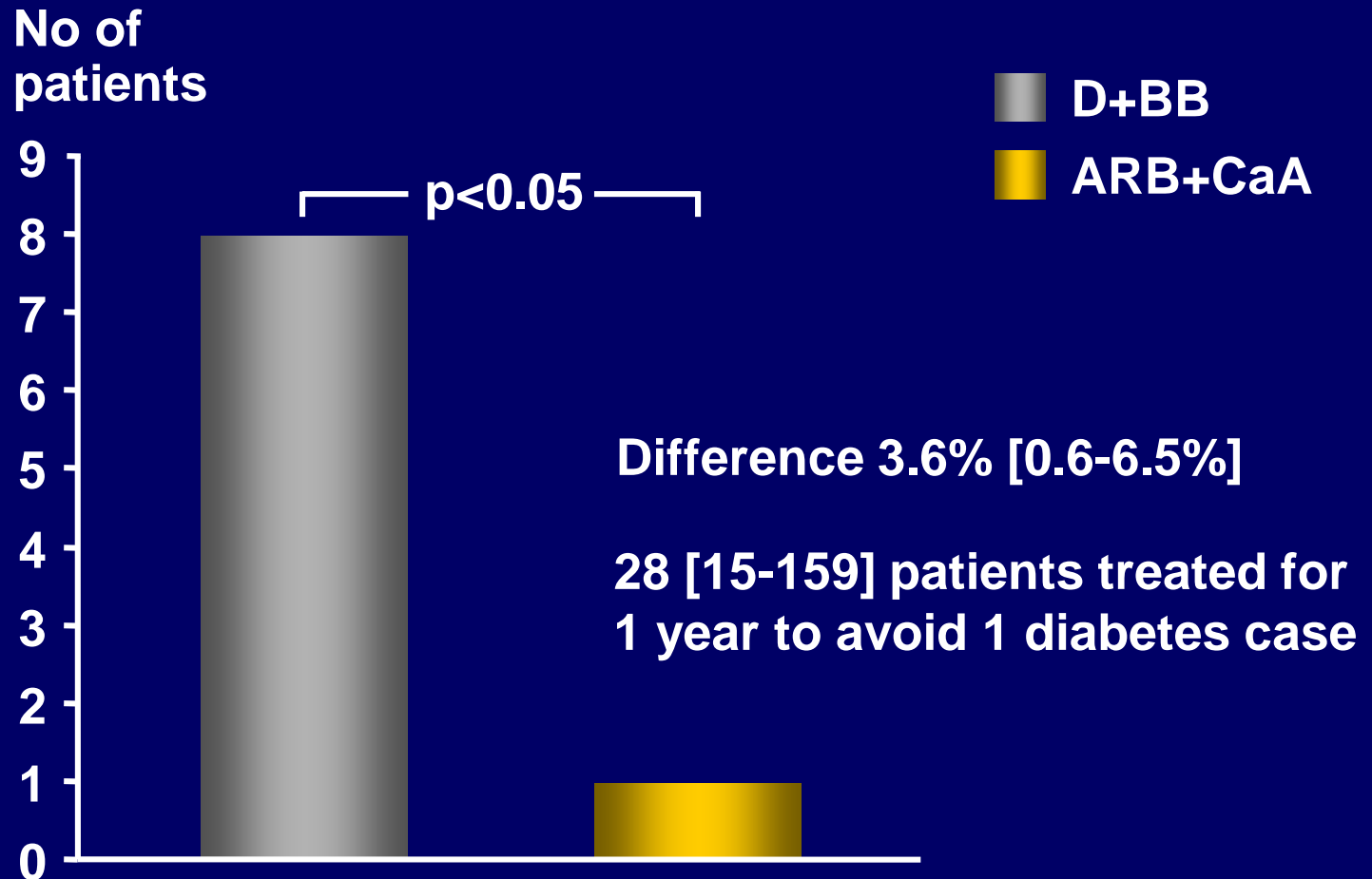
# Metabolic variables from baseline to 1 year in ALPINE

*ALPINE*



# New-onset diabetes in ALPINE

*ALPINE*

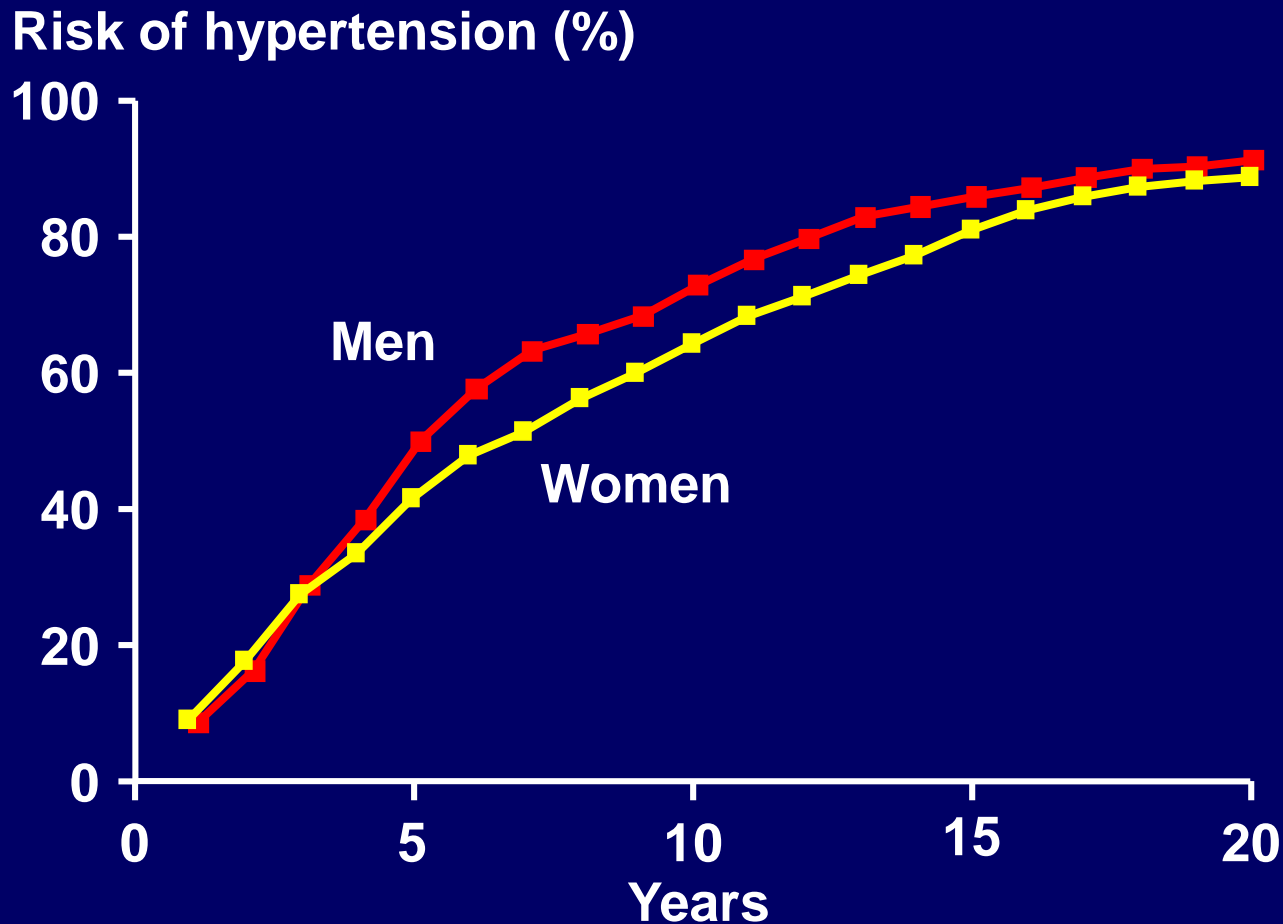


# $\beta$ -blockers vs. other BP lowering drugs

## Outcomes

End point	$\beta$ -blocker n/N	Other drug n/N	RR (95% CI)	Test for heterogeneity
Stroke	1650/51963	1594/53882	1.16 (1.04-1.30)	p = 0.02
Myocardial infarction	1935/51963	2042/53882	1.02 (0.93-1.12)	p = 0.04
Mortality for all causes	3525/52016	3766/53935	1.03 (0.99-1.08)	p = 0.20

# Lifetime risk of hypertension in Framingham from 65 years\*



\*People with BP <140/90

Vasan RS et al. JAMA 2002

# Lifetime risk of hypertension in Framingham

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 !

