



# **Generalizability of results from randomized trials; A systematic overview of possible approaches**

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# Background

- RCTs are conducted in restricted populations
- many patients seen in practice excluded

# Objective

- When are RCT results generalizable to patients *not* represented in RCTs?
- How can we decide this?

# Methods (I)

- Systematic review of the literature
- Systematic search of:
  - Textbooks in clinical epidemiology from 1980
  - Medline and Embase from 1990

# Results

- 3 approaches identified
  - 1. Resemblance with eligibility criteria
  - 2. Use observational studies
  - 3. Assume generalizability unless compelling reasons not to do so

# 1. Resemblance with eligibility criteria

- Check whether your patient was represented
  - If yes: generalize
  - If no: do not generalize

## 2 Use observational studies

- Evidence from observational studies
  - broader patiënt group

# 3. Assume generalizability unless

- Check whether biological, social and economic and epidemiological issues could limit generalizability



# Example: spironolactone

- Spironolactone appeared to reduce both morbidity and death among patients with severe heart failure
- Does this apply to patients >70 years?

Pitt et al, *N Engl J Med* 1999;341(10):709-17.

# . 1. Check eligibility criteria

- Patients >70 not represented
  - Do not generalize

## 2. Observational studies

- In 1999: no guidance
- In 2004: increased morbidity and mortality due to hyperkalaemia (Juurlink, 2004)
  - Do not generalize

Juurlink et al. N Engl J Med 2004;351:543-51.

# 3. Assume generalizability unless

- Generalize?
- Check issues that could limit generalizability
  - In 1999 RCT no hyperkalemia
  - but exclusion patients with  $K > 5$  mmol/l
  - phase 2 trial in 1996:

# Results of phase 2 trial (1996)

- Am J Cardiol 1996;78:902-90
- Spironolactone increases risk of hyperkalaemia
- “We recommend careful monitoring of serum potassium levels.”

# Overview of the three approaches

- Avantanges and disadvantages

# 1. Resemblance with eligibility criteria

- Very strict approach
- No guidance if not represented
- Eligibility criteria incompletely reported

## 2. Observational studies

- If conflicting with RCT evidence
  - RCT result would be more trustworthy
  - Observational study evidence would not provide guidance



# 3. Assume generalizability

- Time consuming
- Subjective judgement?

# Recommendations

- Assume generalizability unless compelling reasons
  - Check whether biological, social and economic and epidemiological issues could limit generalizability
  - Use evidence from observational studies (adverse effects) to help decide on these issues

# Discussion point

- Who should do the assessment of generalizability?
- Guideline developers (?)