Using Real-World Data to Extrapolate Evidence from Randomized Controlled Trials

4th EFSPI regulatory statistics workshop, Basel, 2019-09-23

PD Dr. Christoph Gerlinger

Acknowledgements

- Collaboration with
  - Prof. Schneeweiss' group at Harvard
  - Dr. Thomas Evers, Bayer

Problem statement

cleverly

"Drugs are tested by the people who manufacture them, in p~~o~~rly designed trials, on ***hopelessly small numbers*** *of* ***weird, unrepresentative patients****, and analysed using techniques which are flawed by design, in such a way that they* ***exaggerate the benefits*** *of treatments."*

Ben Goldacre, Bad Pharma *www.badscience.net*

Problem statement – 2

- Health technology assessors (IQWiG, HAS, …) need to assess the added benefit of new drugs
  - Based on phase III data, only.
  - No real world data on new drug yet, of course

- Health technology assessors (and prescribing physicians) need to extrapolate phase III RCT data
  - From clinical trial population to full population
  - From clinical trial duration to full treatment duration

- How can we augment the phase III data?

The “easy” solution

- Run a clinical effectiveness trial in parallel to phase III
  - Include whole population, i.e. those within the intended label
    - E.g., with co-morbidities
  - In non-specialist centers
  - With minimal requirements in study protocol
- Or use a hybrid of efficacy and effectiveness trial

- Use your phase III data for registration
- Use your clinical effectiveness data for
  - Payers
  - Prescribers


STATE OF THE ART

Efficacy and Effectiveness Too Trials: Clinical Trial Designs to Generate Evidence on Efficacy and on Effectiveness in Wide Practice

Harry P. Selker[1,2,*], Hans-Georg Eichler[3], Norman L. Stockbridge[4], Newell E. McElwee[5], Willard H. Dere[6], Theodora Cohen[1,2], John K. Erban[7], Vicki L. Seyfert-Margolis[8], Peter K. Honig[9], Kenneth I. Kaitin[10], Kenneth A. Oye[11] and Ralph B. D'Agostino Sr[12,13]

doi:10.1002/cpt.1347

The “easy” solution – caveats

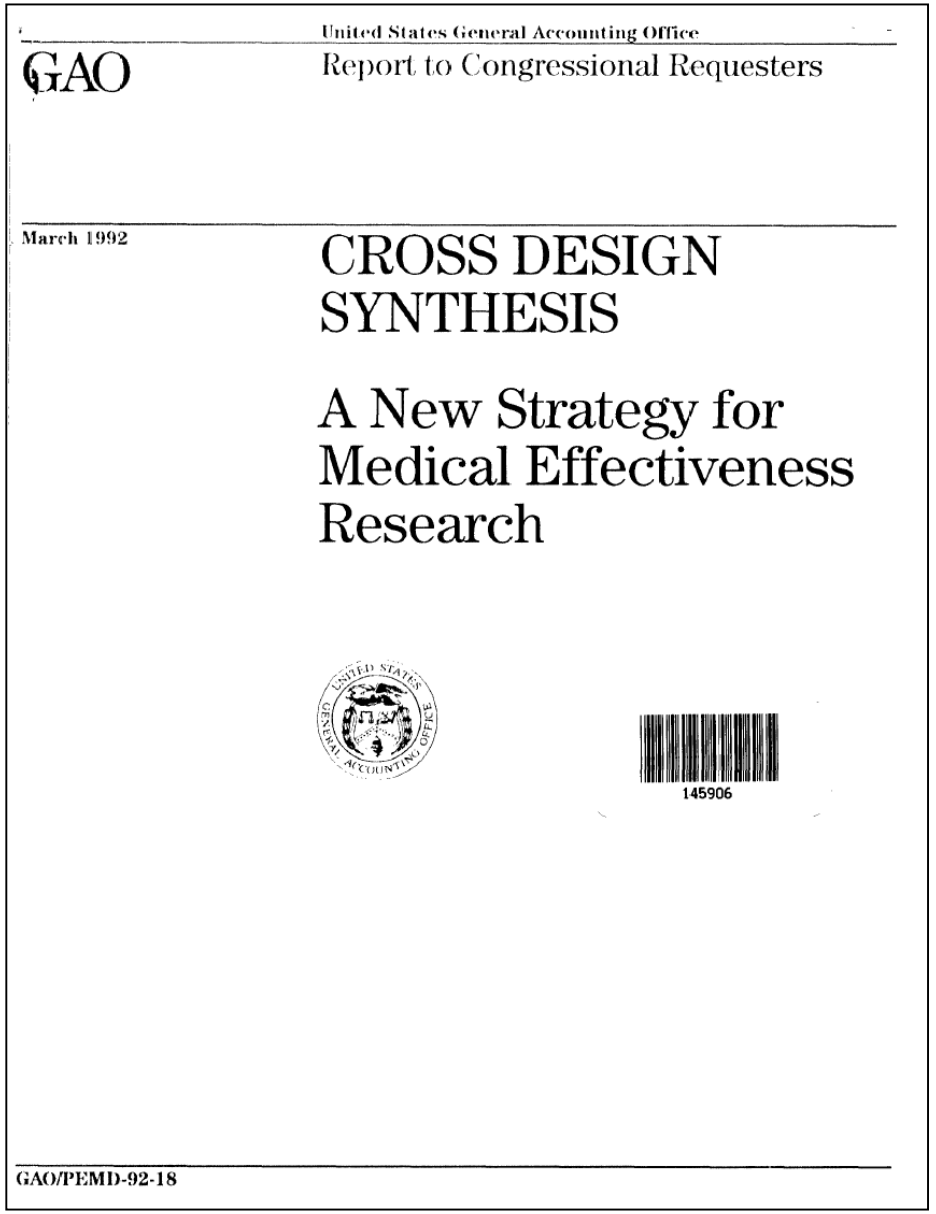
- Exposure of additional patients in clinical effectiveness part
  - Before benefit/risk is established
  - Ethics ?
  - Clinical trial setting required
    - selected centers, informed consent, dense safety assessments, …
    - Not really a real world stetting

- Substantial investment before
  - Drug license is granted
  - Re-imbursement is granted

The basic idea …

- … is more than 25 years old
- … is to formally combine RCT with observational data

- To (hopefully) combine the different strengths of the designs, but not their weaknesses


United States General Accounting Office

GAO

Report to Congressional Requesters

March 1992

CROSS DESIGN SYNTHESIS

A New Strategy for Medical Effectiveness Research

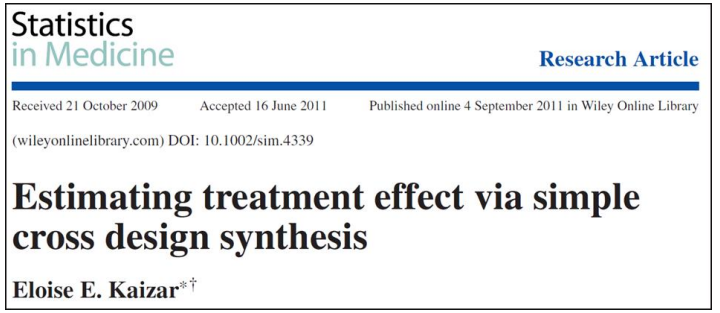
145906

GAO/PEMD-92-18

http://www.gao.gov/products/PEMD-92-18 2017-10-19

The basic idea – 2

- Usually, cross design synthesis is done for a drug of interest
  - We use cross design synthesis for RCT control arm
    - Estimate difference RCT to RWD for control short time
    - Estimate long time effects for control from RWD only
- Other methods considered
  - Reweighting (standardization) methods
  - Discrete event simulation
- Make some bold (and untestable) assumptions


Statistics in Medicine

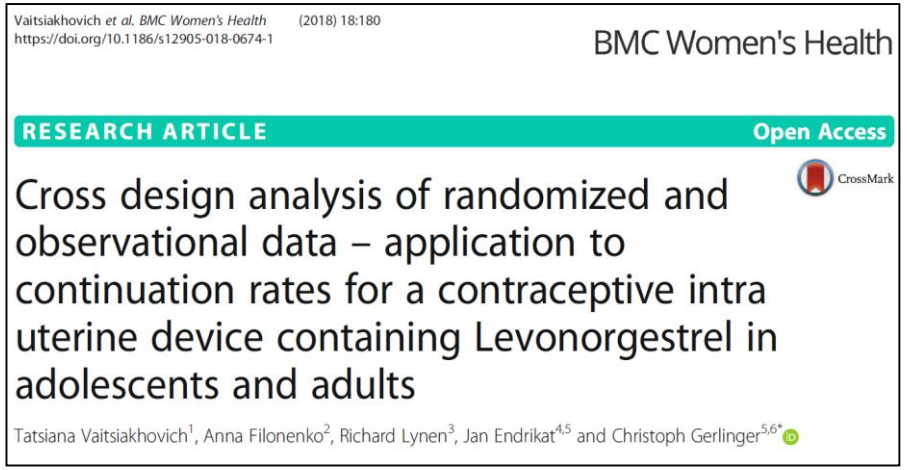
Research Article

Received 21 October 2009 Accepted 16 June 2011 Published online 4 September 2011 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.4339

Estimating treatment effect via simple cross design synthesis

Eloise E. Kaizar*†


Vaitsiakhovich *et al. BMC Women's Health* (2018) 18:180
https://doi.org/10.1186/s12905-018-0674-1

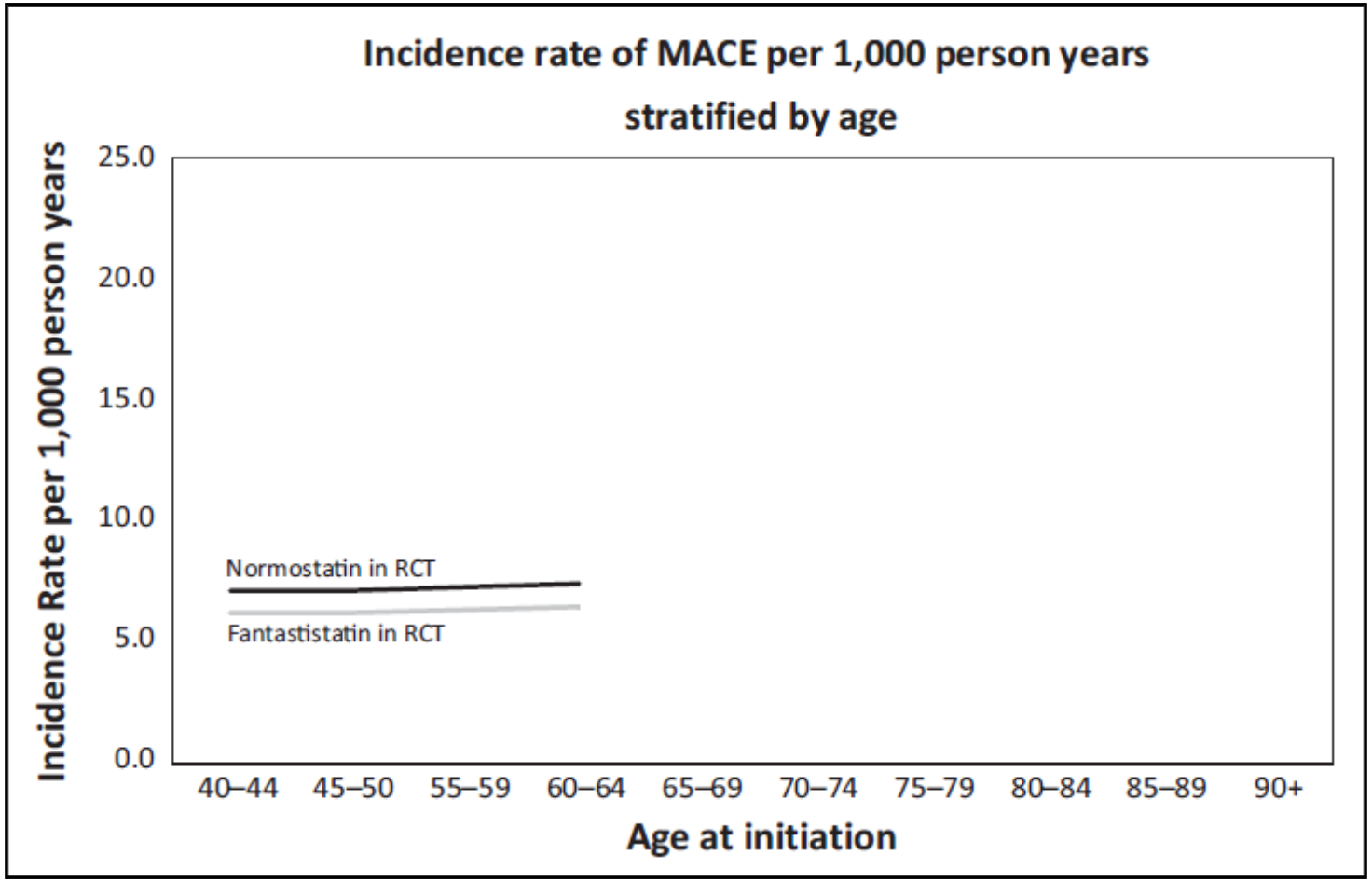
BMC Women's Health

RESEARCH ARTICLE Open Access

Cross design analysis of randomized and observational data – application to continuation rates for a contraceptive intra uterine device containing Levonorgestrel in adolescents and adults

Tatsiana Vaitsiakhovich[1], Anna Filonenko[2], Richard Lynen[3], Jan Endrikat[4,5] and Christoph Gerlinger[5,6*]

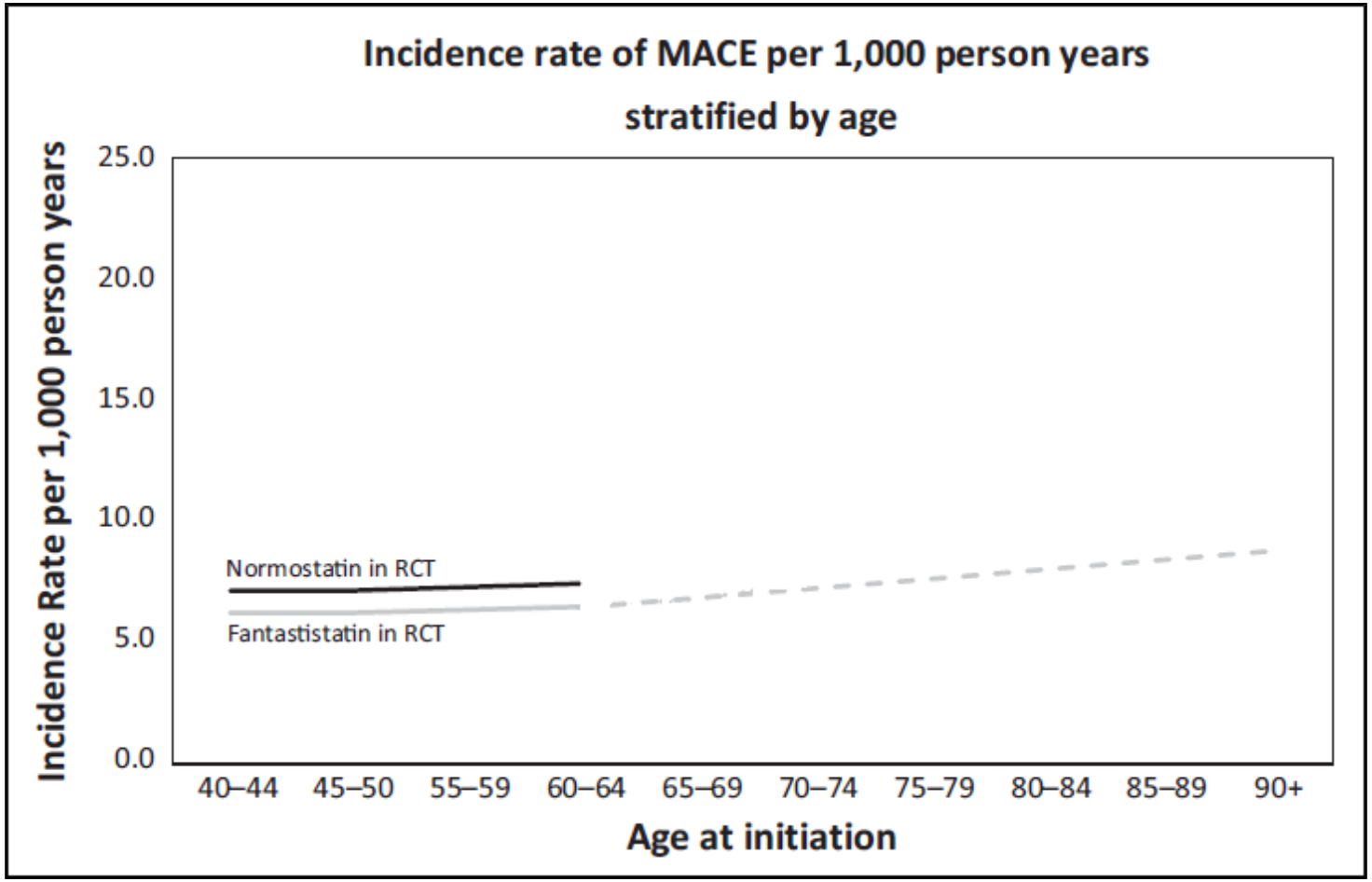
The basic idea – illustrated



MACE: major adverse cardiac event

Wang et al. fig 2

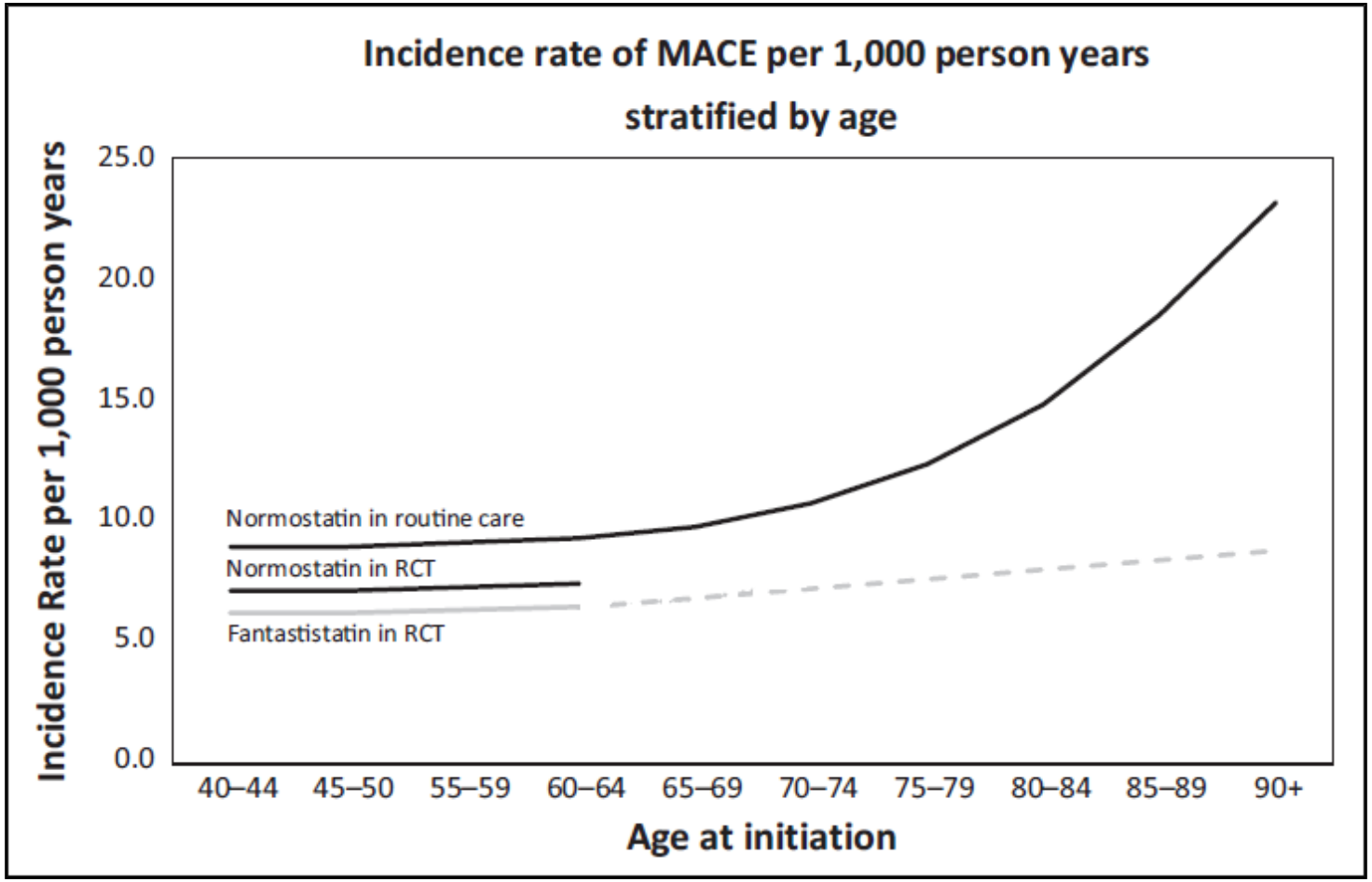
The basic idea – illustrated



MACE: major adverse cardiac event

Wang et al. fig 2

The basic idea – illustrated



MACE: major adverse cardiac event

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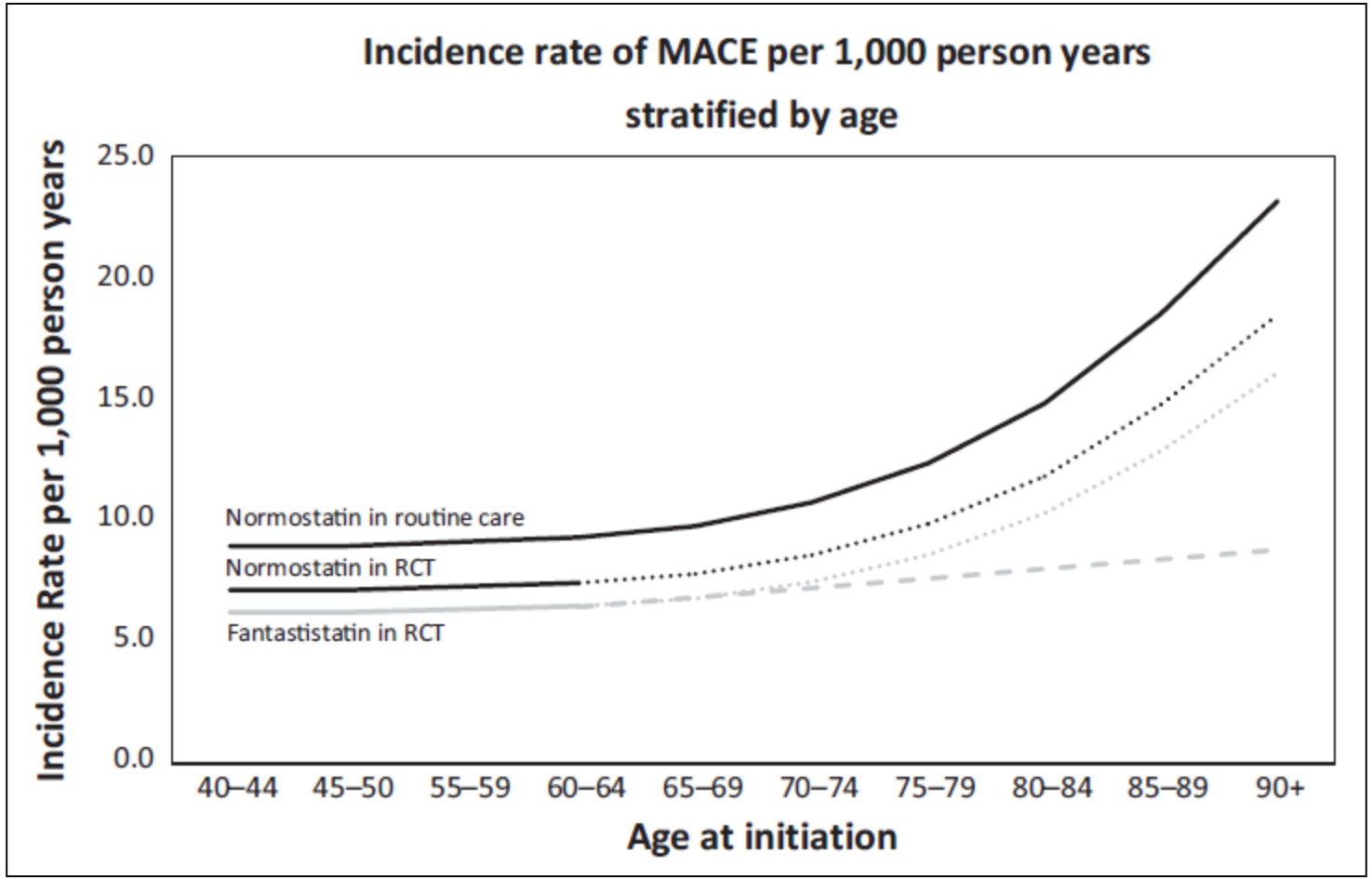
The basic idea – illustrated



MACE: major adverse cardiac event

Wang et al. fig 2

Worked example

// We planned to present the proposed method with real data from a real trial

// Unfortunately the trial is delayed

// Coming soon to a paper near you …

Limitations

- Works only for active controlled phase III trials

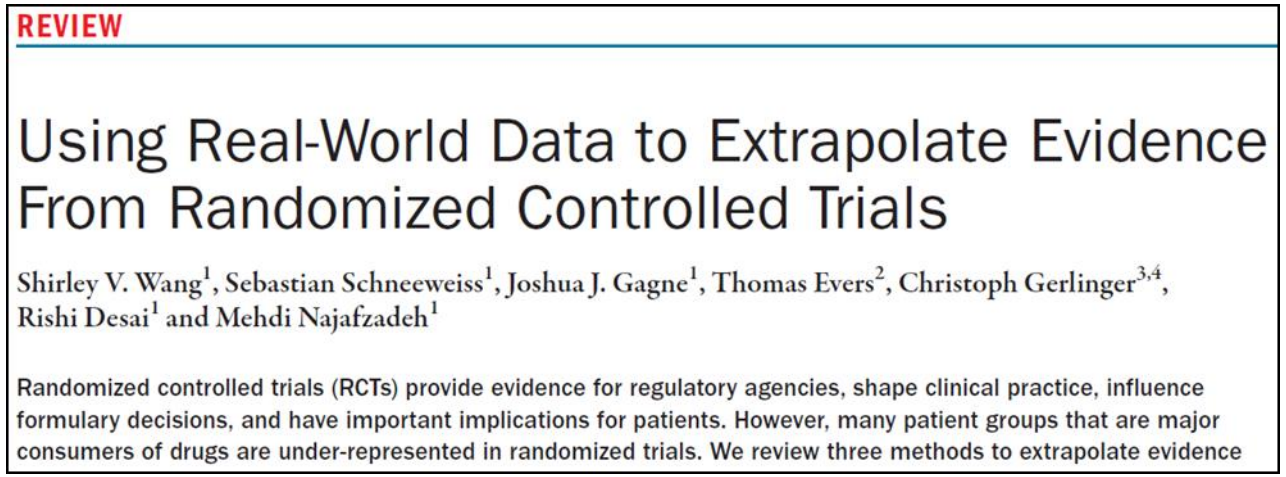
- Works only for endpoints sufficiently captured in real world data sources
  - E.g. for hospitalization
  - But not, e.g., for pain

- Strong assumptions needed
  - New drug has similar time course as reference drug
  - Loss between RCT efficacy and RWD effectiveness similar between new drug and reference drug

Summary of method

- RCT data can be extrapolated (in time span and in population) using RWD
- Many caveats and strong assumptions needed

- In essence:
  - replace rule of thumb by rule of 3 *(ok, maybe rule of 5)*



REVIEW

Using Real-World Data to Extrapolate Evidence From Randomized Controlled Trials

Shirley V. Wang[1], Sebastian Schneeweiss[1], Joshua J. Gagne[1], Thomas Evers[2], Christoph Gerlinger[3,4], Rishi Desai[1] and Mehdi Najafzadeh[1]

Randomized controlled trials (RCTs) provide evidence for regulatory agencies, shape clinical practice, influence formulary decisions, and have important implications for patients. However, many patient groups that are major consumers of drugs are under-represented in randomized trials. We review three methods to extrapolate evidence

Clinical Pharmacology & Therapeutics, doi:10.1002/cpt.1210

Thank you!

Bye-Bye