

Leveraging Data to Inform Health Decision-Makers

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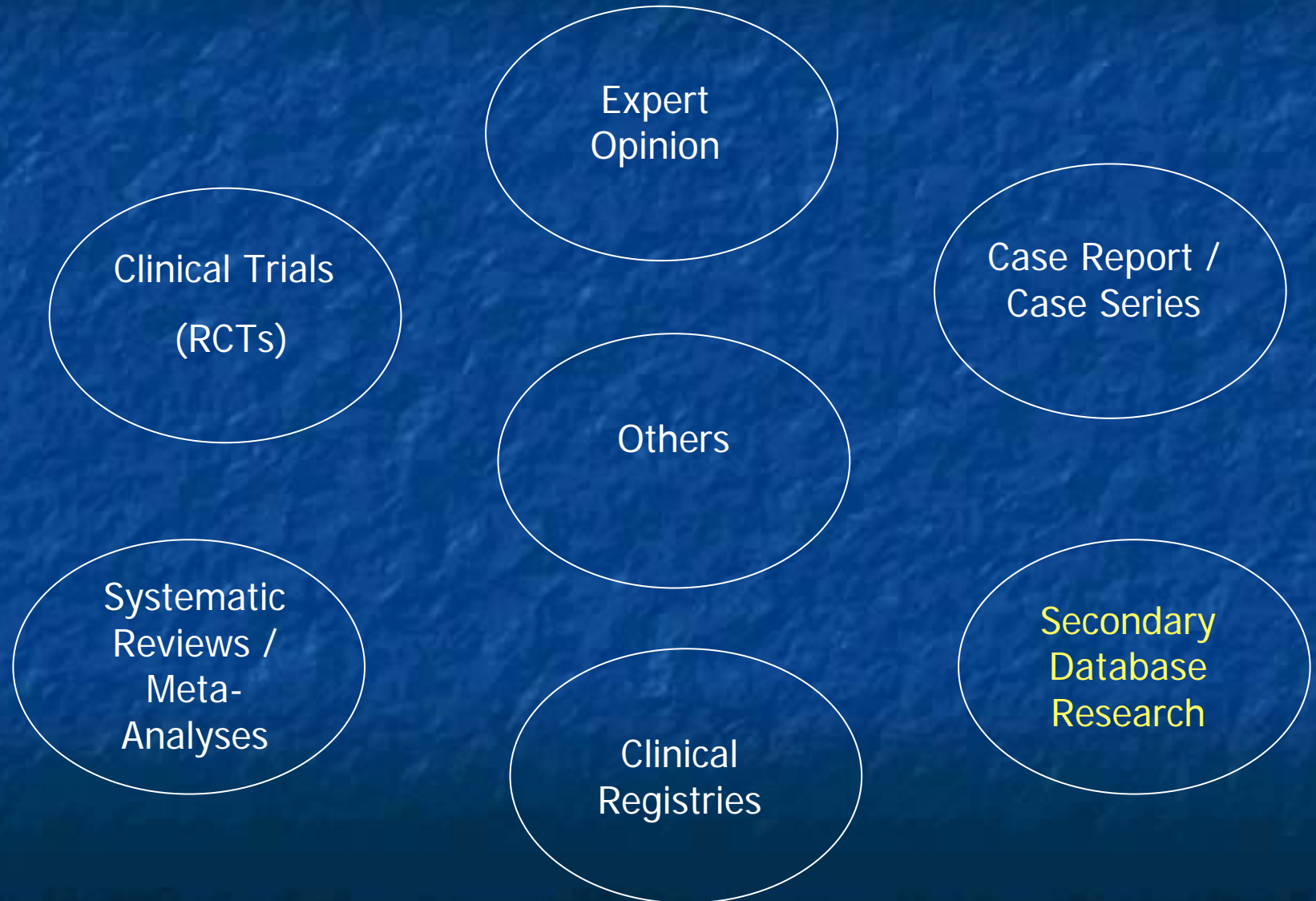


**"I now pronounce you husband and wife.
Side effects may include headaches, weight gain,
irritability, mild depression, tantrums...."**

Objectives

- To understand how different forms of clinical research can inform decision-making
- To understand how pharmacovigilance research can be useful in decision-making
- To understand key factors in leveraging pharmacovigilance research to inform decision-making

Sources of Drug-Related Research



Hierarchy of Evidence

Level of Evidence	Study Type
Level 1	RCTs
Level 2	Cohort Studies
Level 3	Case-Control Studies
Level 4	Case Series
Level 5	Expert Opinion

Adapted from Oxford Centre for Evidence-Based Medicine, 2002

The Risk of Being Narrowly Focused



The Trouble with RCTs

Example: *H. pylori* eradication and non-ulcer dyspepsia

■ McColl et al (NEJM, 1998)

- Treatment (n=154): Omeprazole 20 mg bid + amoxicillin 500 mg tid + 400 mg metronidazole tid x 2 weeks
- Comparison (n=154): omeprazole 20 mg bid x 2 weeks
- Symptom resolution at 1 year: Tx = 21% vs. Comparison = 7% (p<0.001)

■ Blum et al (NEJM, 1998)

- Treatment (n=164): Omeprazole 20 mg bid + amoxicillin 1000 mg bid + 500 mg clarithromycin bid x 1 week
- Comparison (n=164): omeprazole 20 mg bid x 1 week
- Symptom resolution at 1 year: Tx = 27% vs. Comparison = 21% (p=0.17)

Examining Secondary Endpoints: Is there Room for Uncertainty?

- Case Example: ELITE I vs ELITE II
 - Patient population
 - elderly patients with CHF
 - Comparison groups:
 - Losartan 50 mg qd vs Captopril 50 mg tid
 - ELITE I (Lancet 1997)
 - N = 722
 - Primary endpoint = change in serum creatinine
 - Secondary endpoint = total mortality; L:C RR=0.54 (0.31-0.95)
 - ELITE II (Lancet, 2000)
 - N = 3,152
 - Primary Endpoint = total mortality; L:C RR=1.13 (0.95-1.35)

The Trouble with Observational Studies

Example: HRT and cardiovascular disease

- Stampfer et al (NEJM, 1985) – ‘Nurse’s Health Study’
 - Cohort study beginning in 1976
 - 32,317 nurses age 30-55 years without a history coronary disease
 - Follow-up = approx. 4 years
 - Findings (ever vs. never users): RR=0.5 (0.3-0.8) for CV events
- Wilson et al (NEJM, 1985) – ‘Framingham Study’
 - 1,234 postmenopausal women age 50-83 years
 - Follow-up = approx. 8 years
 - Findings (past or current use vs. never): RR=1.8 ($p < 0.01$) for CV events
- Contrast to findings from two large RCTs:
 - HERS and WHI

Can Observational Studies and Clinical Trials Live in Harmony??

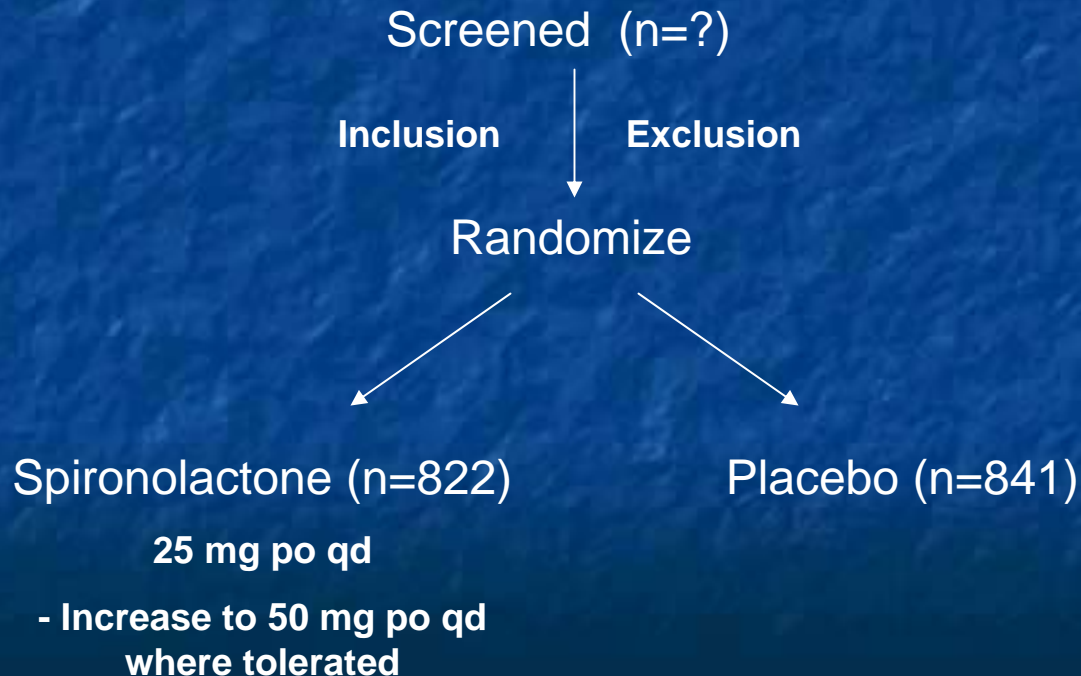


RALES

Randomized ALdactonE Study

Pitt et al, N Engl J Med, 1999

- Double-blind randomized controlled trial in patients with congestive heart failure
- Primary endpoint: all-cause mortality



RALES Criteria

■ Inclusion / Exclusion

- NYHA class III or IV at time of enrolment
- LVEF < 35% within 6 months
- Exclude patients with serum creatinine \geq 2.5 mg/dL or serum potassium > 5 mmol/L

■ Follow-up

- Lab and clinic follow-up at 4 weeks and 3 and 6 months
- Appropriate use of ACE inhibitors and beta-blockers
- D/c K-sparing diuretics and K⁺ supplements
- Holding spironolactone for hyperkalemia or creatinine > 4 mg/dL

RALES - Results

Outcome	Absolute Risk	Relative Risk
Death	PI=46% Spir=35% p<0.001	0.70 (0.60-0.82)
Readmission for HF	PI=36% Spir=26% p<0.001	0.65 (0.54-0.77)
Serious Hyperkalemia	PI=1.2% Spir=1.7% p=0.42	NS

BUT in the 'Real World'....

- Different patients may get the drug
 - > 50% of population that would normally use the drugs in clinical practice often do not meet inclusion / exclusion criteria of RCTs (e.g. Gill et al, CJCP, 2004)
- Patients may not be monitored as carefully
- Patients may not take their drug as they should
- Patients may take interacting drugs that they shouldn't be on
- Patients may not adhere to their drugs optimally

What's the Problem?

Life-threatening Hyperkalemia during Combined Therapy with Angiotensin-converting Enzyme Inhibitors and Spironolactone: An Analysis of 25 Cases

Hans Schepkens, MD, Raymond Vanholder, MD, PhD, Jean-Marie Billiouw, MD, Norbert Lameire, MD, PhD

Hyperkalaemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study

Morten Svensson, Finn Gustafsson, Søren Galatius, Peter

Spironolactone reduces disease and death in patients with severe congestive heart failure and is well tolerated with regard to renal function and serum potassium concentrations.¹ Guidelines recommend taking spironolactone in addition to angiotensin converting enzyme inhibitors and β blockers,^{2,3} but since spironolactone can lead to renal dysfunction or hyperkalaemia, we followed up a cohort of patients taking spironolactone to identify predictors of harmful effects.

Lesson of the week

Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases

Eike Wrenger, Regina Müller, Michael Moesenthin, Tobias Welte, Jürgen C. Frölich, Klaus H Neumann

The randomised aldactone evaluation study (RALES) proved a substantial (30%) reduction in risk of mortality in patients with severe congestive heart failure by treatment with low dose spironolactone (25-50 mg a day) in addition to standard treatment.¹ Exclusion criteria for treatment in the study were a plasma potassium concentration >5.0 mmol/l and serum creatinine concentration >221 μ mol/l. A pilot study had previously shown that the higher the dosage

mean age was 76 (standard deviation 11) years. The mean dosage of spironolactone was 88 (SD 45, range 25-200) mg daily. All patients also received ACE inhibitors or AT₁ receptor blockers (table). Fourteen patients were treated with β receptor blockers and 40 with loop diuretics.

Thirty five of the 44 patients had diabetes mellitus type 2. Symptoms on admission were vomiting (19), diarrhoea (8), bradyarrhythmia (14), muscle weakness

plasma bicarbonate was
acute renal failure were
heart failure (n = 9). The
57 ± 23 mg and 12 mg

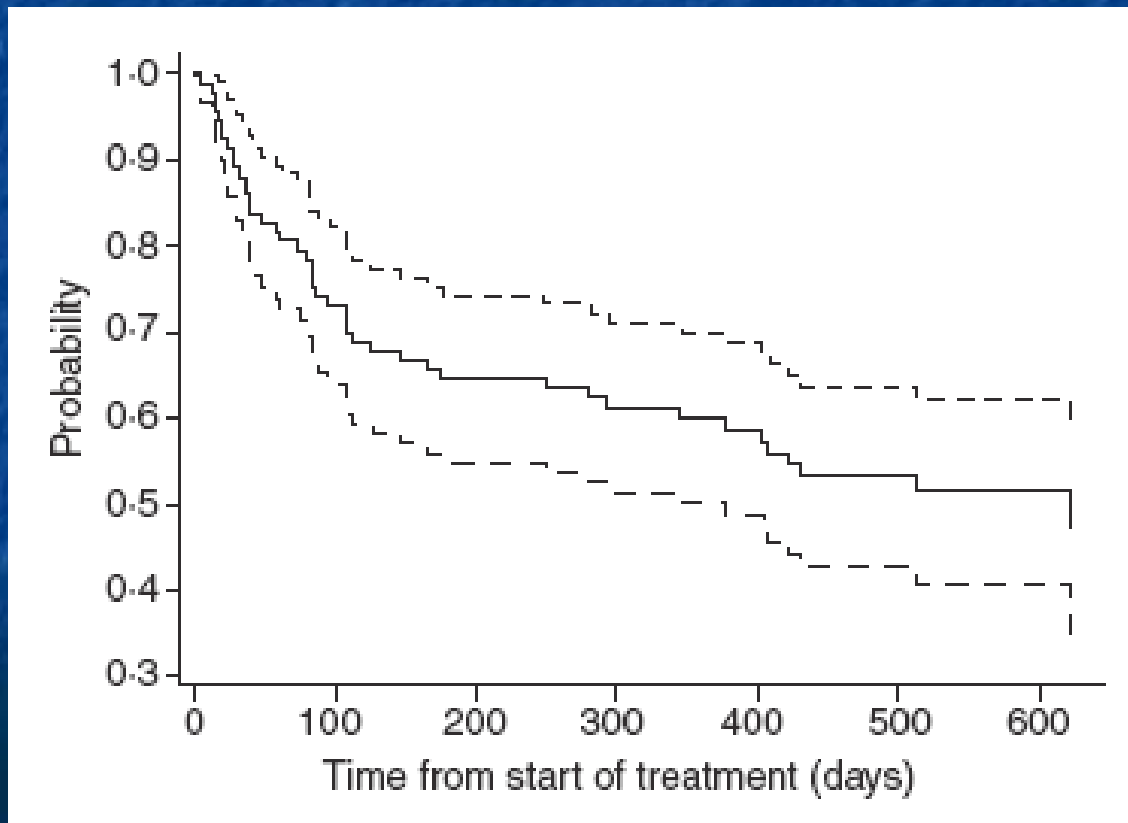
Anton et al

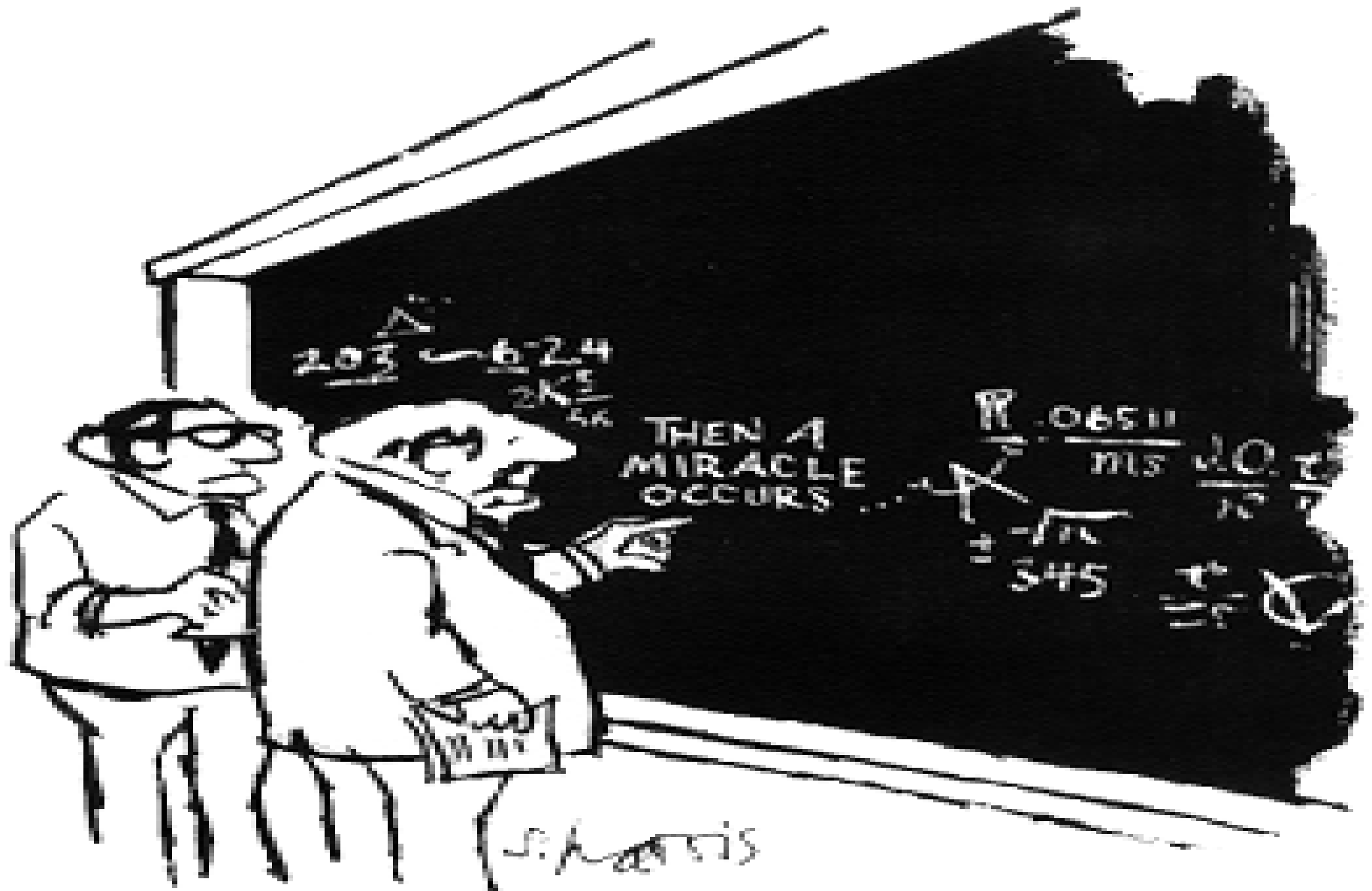
J Clin Pharm Ther 2003; 28: 285-7

- Anton et al. *J Clin Pharm Ther* 2003;28:285-7
- Retrospective cohort
 - Single hospital
 - 110 patients Rx spironolactone + ACEI
 - Mean age 71 years, half with DM
 - Outcomes
 - Cessation of spironolactone
 - Hyperkalemia

Findings

- 24% developed $\uparrow K^+$ (> 5.5 mEq/L) at 1 year
- Many stopped spironolactone





"I think you should be more explicit here in step two."

Bozkurt et al

J Am Coll Cardiol 2003;41:211-4

Criteria	Bozkurt et al (n=104)	RALES (n=822)
NHYA (% patients)		
I	4.5%	0%
II	4.5%	0.5%
III	15.3%	72%
IV	10.3%	27%
Undocumented	65.4%	0%
% Patients with LVEF < 35%	54.8%	100%
% Patients with renal insufficiency at baseline	30.7%	Excluded
Use of beta-blockers	34.6%	11%

What RALES said...

- In a highly selected group of patients with severe heart failure who are largely free of other risk factors for hyperkalemia and who can be monitored closely, the addition of spironolactone to standard therapy (as defined in 1994) decreases hospitalization for heart failure and saves lives, with no significant risk of hyperkalemia.

What we heard...

- In patients with heart failure, spironolactone saves lives.

How Do We Study What's Happening in the 'Real World'?

- Experimental studies
 - Often problematic given typically stringent inclusion / exclusion criteria
 - Compromised generalizability
 - Large-scale 'pragmatic' RCTs are often difficult to conduct and very costly
- Non-experimental studies
 - Typical problems with selection bias and confounding make interpretation of findings difficult
 - Compromised validity

Study Design

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

■ Study Design

- Population-based cross-sectional time series analysis using administrative databases from 1994-2001
- Time horizon broken into 120-day intervals

■ Patient Population

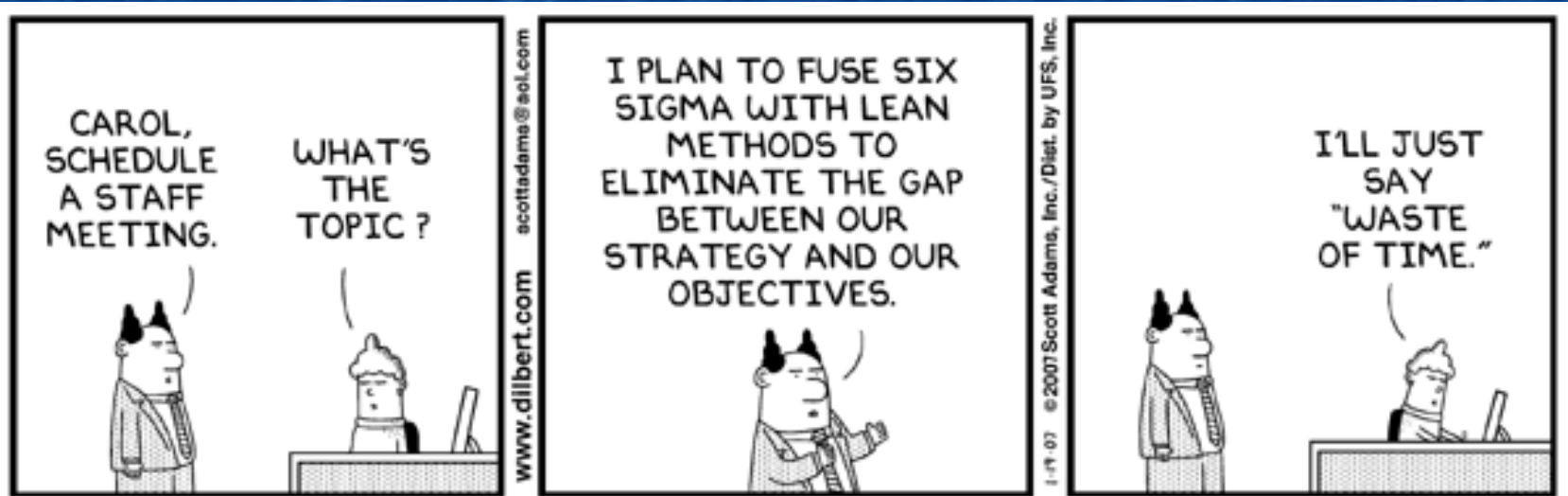
- 1.3 million elderly residents of Ontario age ≥ 66 years
- Patients hospitalized for CHF within 3 years prior to study interval and filling a Rx for an ACEI in study interval (20-30K/study interval)

■ Endpoints of Interest

- Spironolactone prescription utilization
- Hyperkalemia-associated hospital admissions
- Hyperkalemia-associated in-hospital deaths

■ Statistical Analysis

- Autoregressive integrated moving average (ARIMA) models



CAROL,
SCHEDULE
A STAFF
MEETING.

WHAT'S
THE
TOPIC ?

I PLAN TO FUSE SIX
SIGMA WITH LEAN
METHODS TO
ELIMINATE THE GAP
BETWEEN OUR
STRATEGY AND OUR
OBJECTIVES.

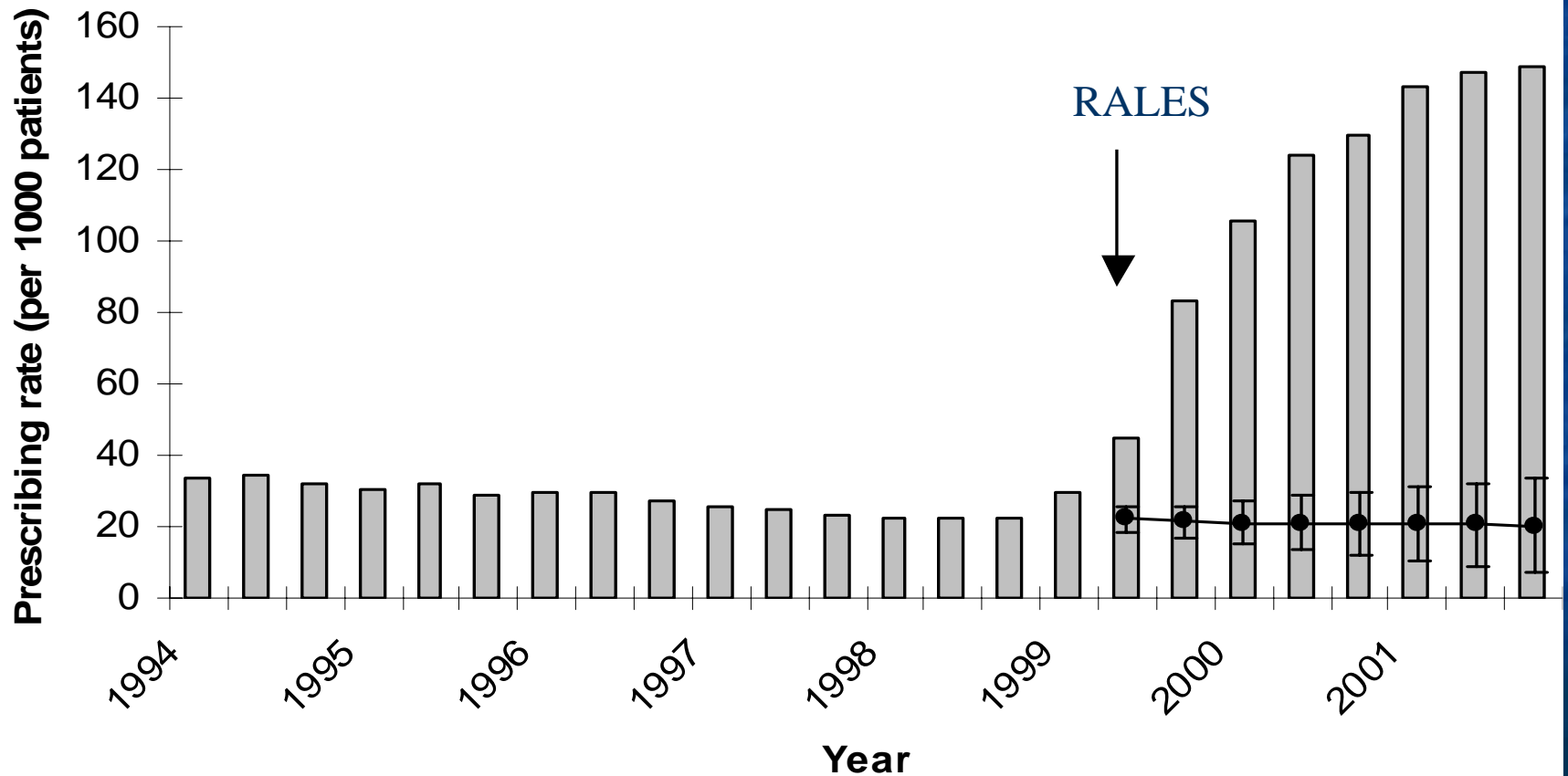
I'LL JUST
SAY
"WASTE
OF TIME."

www.dilbert.com scottadams@aol.com

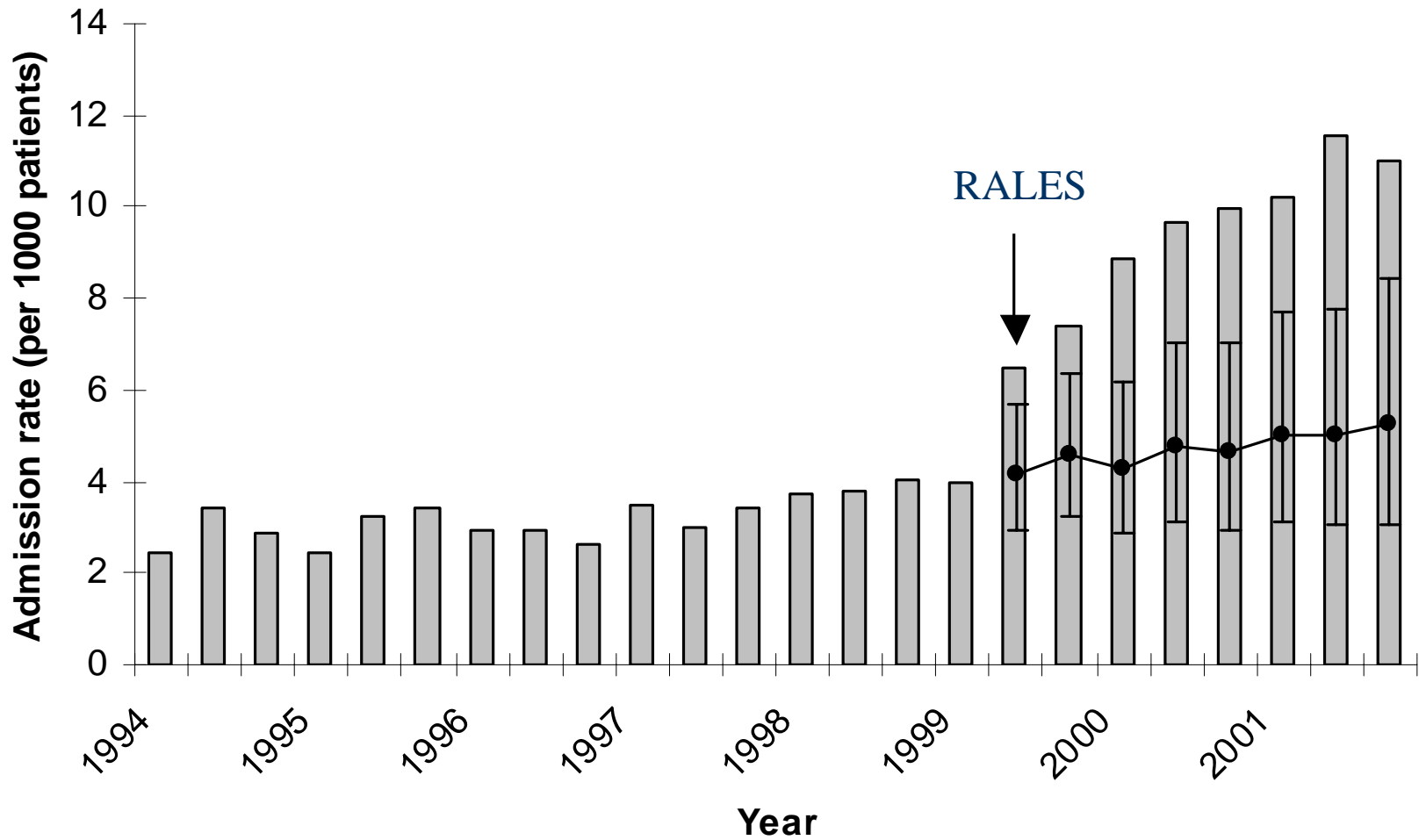
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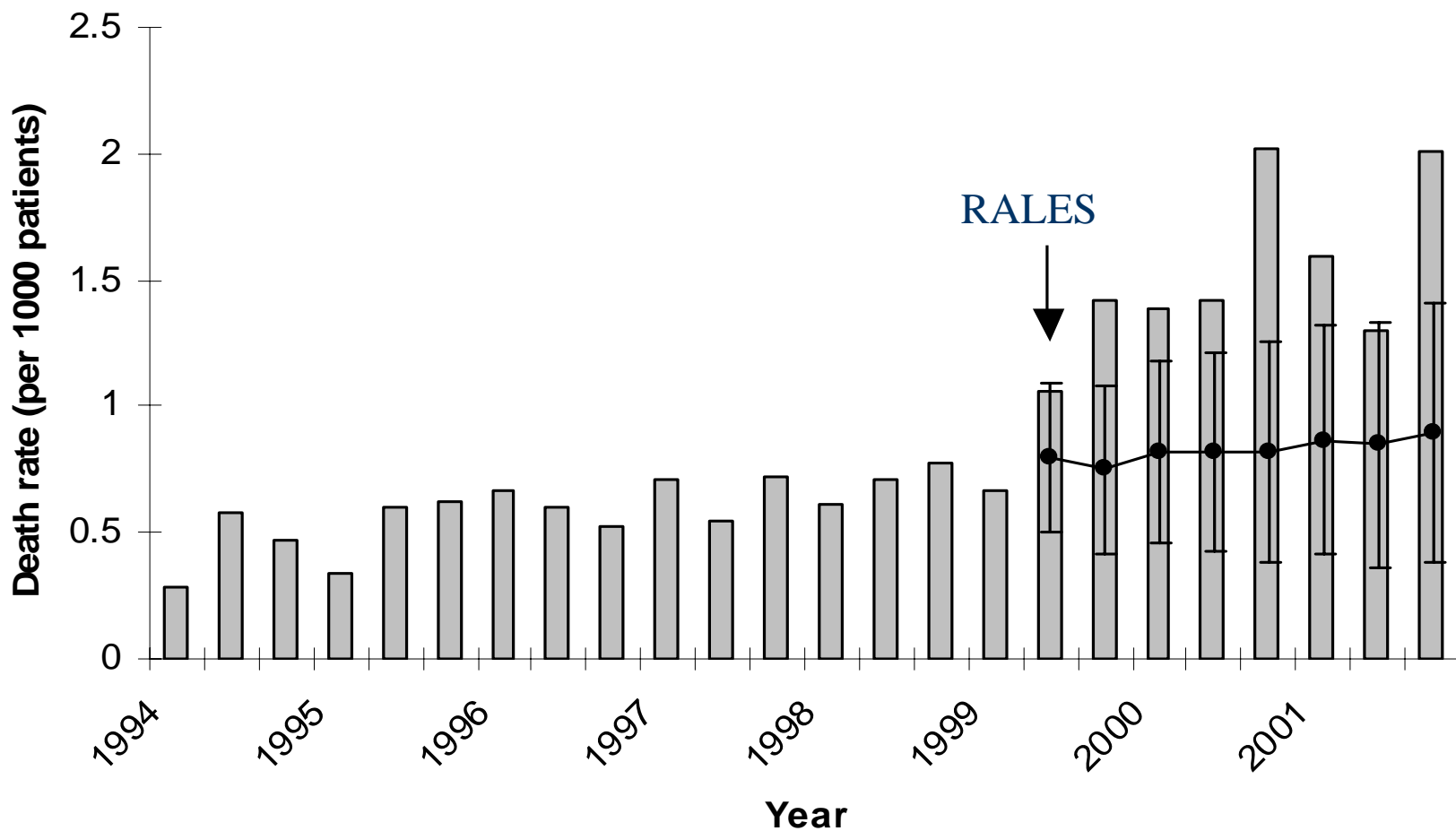
Spironolactone Prescription Uptake 1994-2001



Hospital Admission Associated with $\uparrow K^+$

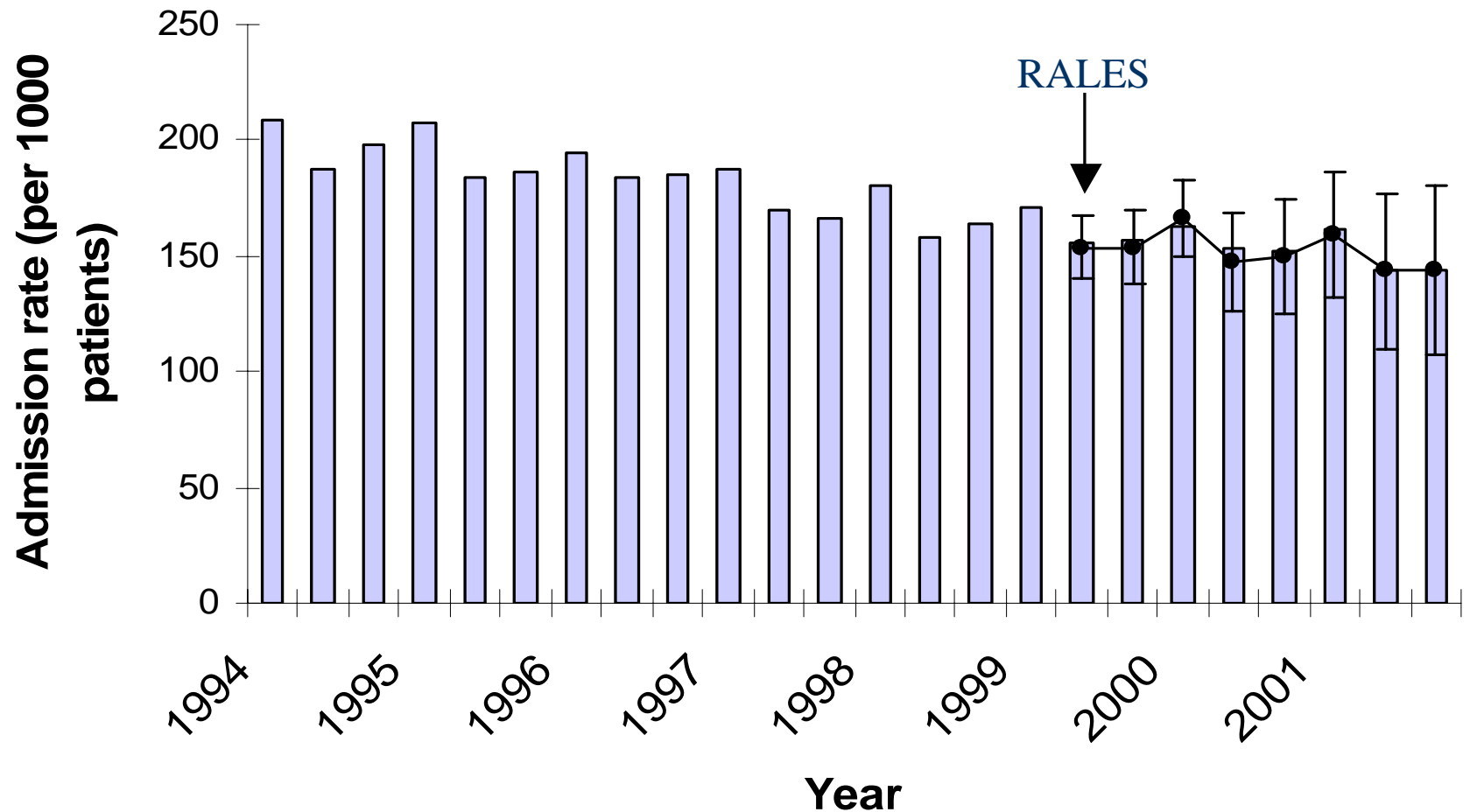


Admission Associated with ↑K⁺ Ending in Death

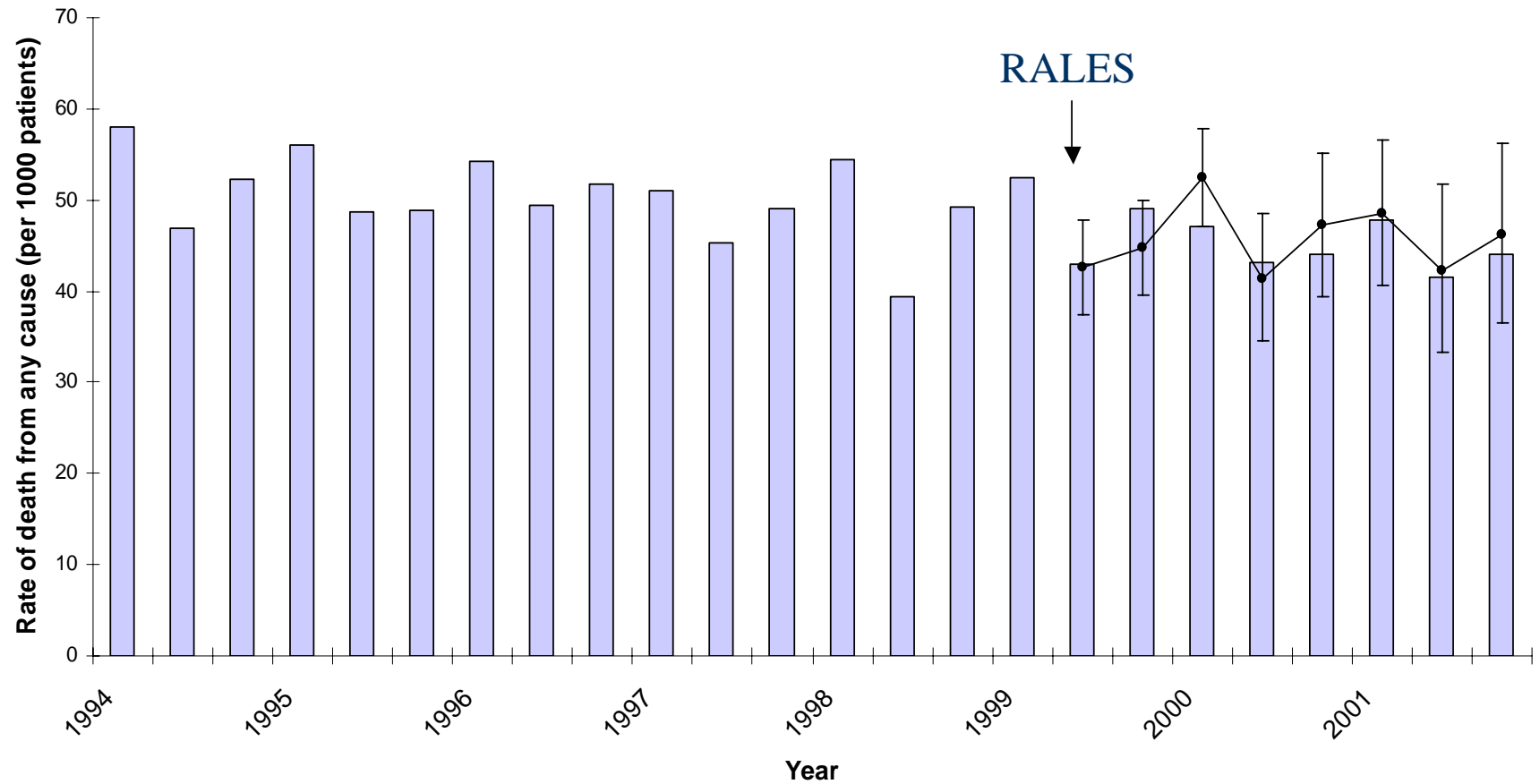


What about the expected
benefits?

Readmission for Heart Failure



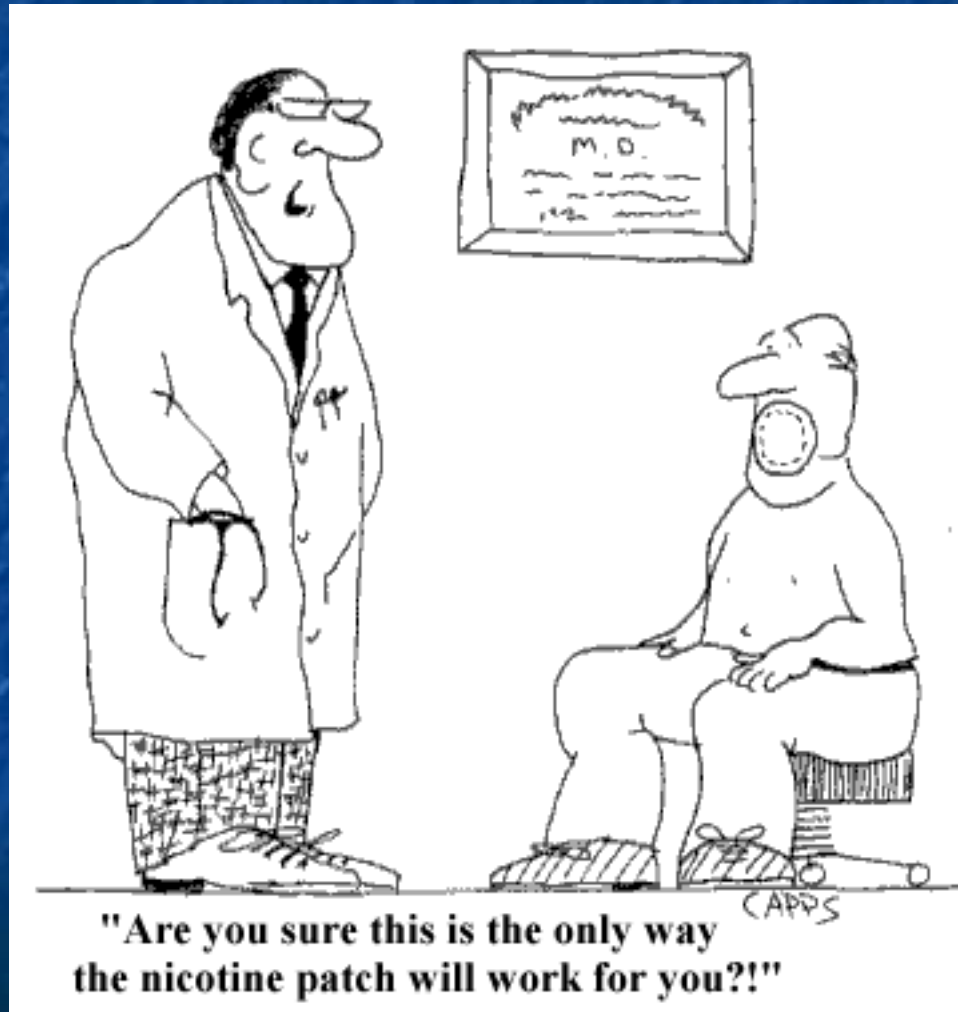
All-Cause Mortality



Basic Messages

- Spironolactone CAN work in the right patients with minimal risk of hyperkalemia (clinical trial data)
- As it is currently being used, spironolactone may significantly increase the population rate of hyperkalemia admissions without a major decrease in readmission rates or total mortality (observational study data)
- Perhaps a better job needs to be done in selecting the right patients or monitoring those heart failure placed on spironolactone

Example: Gatifloxacin (Tequin)



Background

- A particular group of antibiotics called 'fluoroquinolone' antibiotics have become the most widely prescribed group of antibiotics
 - About 22 million prescriptions dispensed annually in US
 - 16 individual fluoroquinolone antibiotics have been available on the market; In 2005, gatifloxacin (Tequin) was the fluoroquinolone antibiotic of choice for US public health system
- Some of these drugs have problems: serious adverse events have led to the withdrawal or restriction of several fluoroquinolones in recent years
 - Temafloxacin (blood sugar and kidney problems)
 - Grepafloxacin and sparfloxacin (heart problems)
 - Trovafloxacin (liver problems)
- In 2005, a clinician noticed major changes in blood sugar levels in patients receiving Tequin and approached researchers to investigate this observation

So We Conducted a Study

(Park-Wyllie et al, NEJM, 2006)

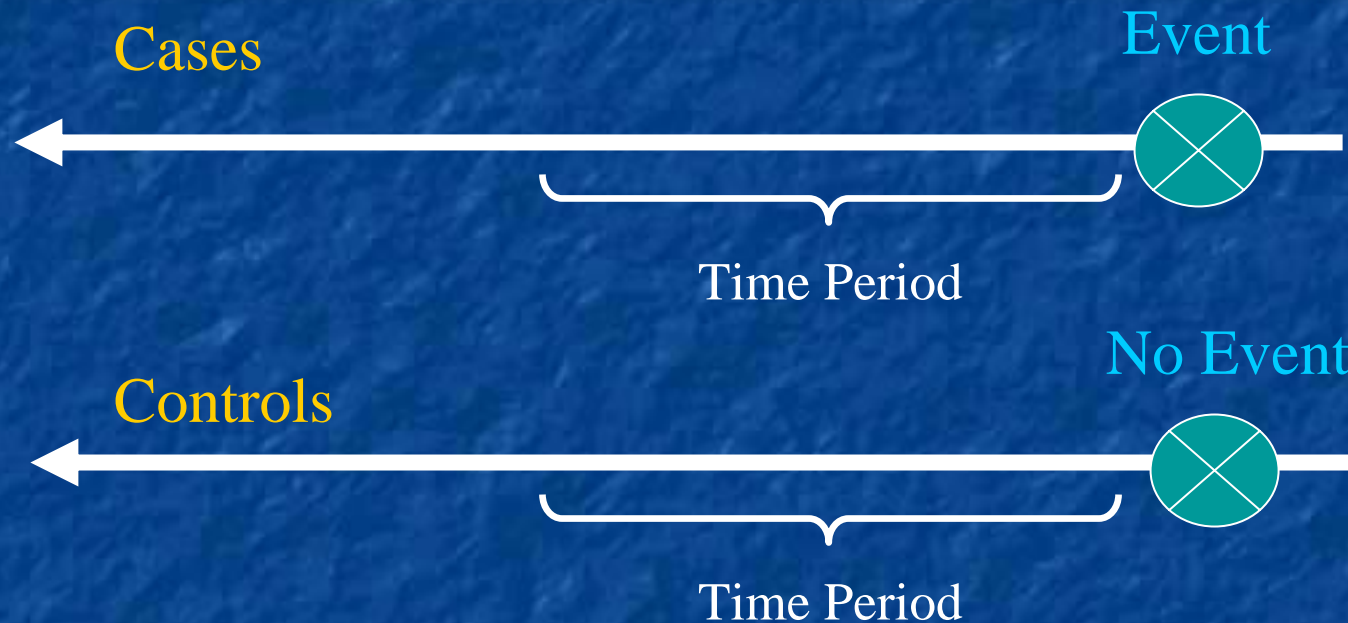
■ Population

- Examined records of over 1.4 million elderly residents of Ontario age 66 years and older between 2002-2004
- Analysis limited to individuals who were using one of several selected antibiotics

■ Outcomes

- Hospital admission related to severe changes in blood sugar level

Basic Schematic for Case-Control Study



What Were the Results?

- Hospital admissions related to severe drops in blood sugar levels (hypoglycemia)
 - Gatifloxacin associated with 4x the risk of hospital admission compared to other antibiotics
- Hospital admissions related to severe increases in blood sugar levels (hypoglycemia)
 - Gatifloxacin associated with almost 17x the risk of hospital admission compared to other antibiotics
- Comparable antibiotic alternatives WITHOUT identifiable risks of hyper- and/or hypoglycemia exist

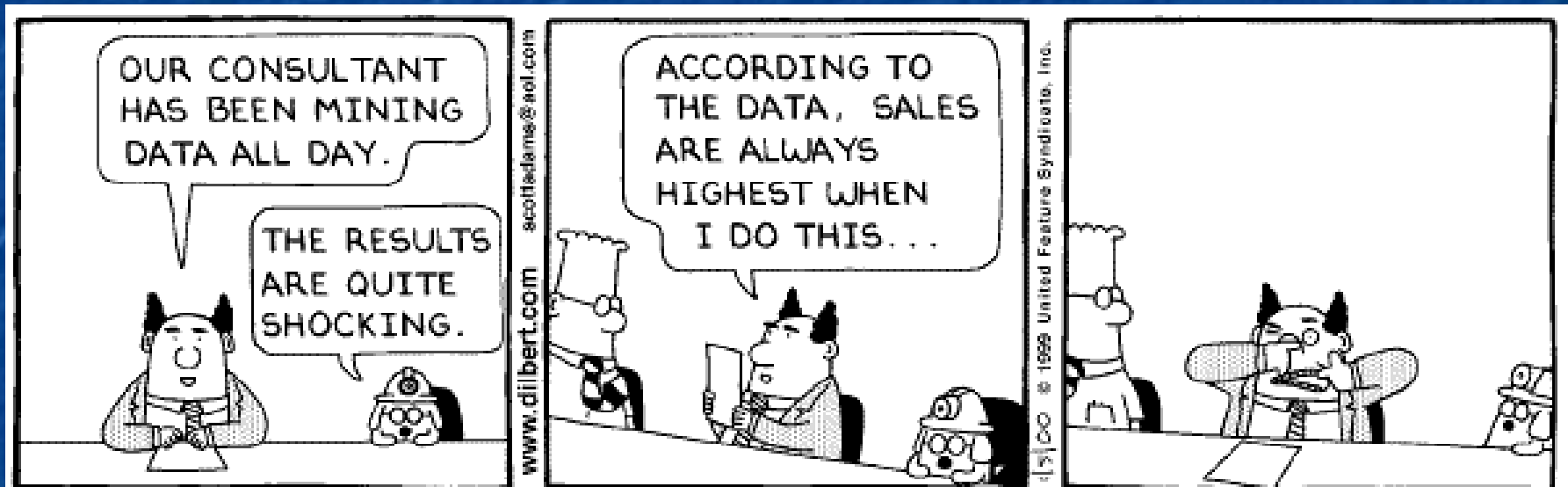
Making the Numbers Tangible

- If we consider the 1.4 million elderly residents of Ontario during the study timeframe:
 - There were nearly 17,000 courses of gatifloxacin treatment administered
 - For every 100 courses of gatifloxacin, we may expect 1 hospital admission for dysglycemia
 - On average, it was estimated that at least 1 elderly person in Ontario was hospitalized every week as a result of dysglycemia that was likely associated with gatifloxacin

Impact

- Published early online (March 1st, 2006) in the New England Journal of Medicine given its clinical relevance
- Recognized nationally as a significant research contribution:
 - Canadian Society of Clinical Pharmacology
 - Best Publication Award for 2006
- Gatifloxacin withdrawn from market in May 2006

Observational Research Has Its Challenges



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Leveraging Canadian Healthcare Data to Inform Decision-Makers

The Evolution of Pharmacovigilance Research

- Limitations of Pharmacovigilance Research
 - Generalizability and validity
 - Selection bias
 - Coding inaccuracies
 - Detection Bias
 - Survivor Treatment Selection Bias
- Advances in Pharmacovigilance Research
 - Advanced computing and biostatistical techniques
 - Better 'bridging' between disciplines to leverage research methodologies (e.g. econometric approaches)
 - Better understanding of biases involved in pharmacovigilance research

Challenges with Pharmacovigilance Research

- Key Challenges
 - Understanding the data sources – local expertise
 - Understanding and applying the appropriate scientific methodology – academic expertise
 - Creating the optimal environment – infrastructure resources; direct data access
 - Establishing the governance and operational models – coordination of the people, the science, and the resources
- Understanding these challenges can help devise a research approach that yields **high quality information** in a **timely** manner

The Quality Agenda: Canada's Research Talent

COMMENTARY

Case-Crossover Designs Compared With Dynamic Follow-up Designs

Malcolm Maclure,†‡ and Murray A. Mittleman†§¶*

Epidemiology • Volume 19, Number 2, March 2008

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BMJ

"Breakthrough" drugs and growth in expenditure on prescription drugs in Canada

Steven G Morgan, Kenneth L Bassett, James M Wright, Robert G Evans,
Morris L Barer, Patricia A Caetano and Charlyn D Black

BMJ 2005;331:815-816; originally published online 2 Sep 2005;
doi:10.1136/bmj.38582.703866.AE

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BMJ

Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review

Dean T Eurich, Finlay A McAlister, David F Blackburn, Sumit R Majumdar, Ross T Tsuyuki, Janice Varney and Jeffrey A Johnson

BMJ 2007;335:497-; originally published online 30 Aug 2007;
doi:10.1136/bmj.39314.620174.80

BMJ

expenditure on prescription drugs in Canada

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COMMENTARY

Pharmaceutical Use among Older Adults: Using Administrative Data to Examine Medication-Related Issues

Colleen Metge,^{1,2} Ruby Grymonpre,² Matthew Dahl,^{1,2} and Marina Yogendran^{1,2}



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COMMENTARY

Atenolol as initial antihypertensive therapy: an observational study comparing first-line agents

David F. Blackburn^a, Darcy A. Lamb^a, Dean T. Eurich^c, Jeffrey A. Johnson^c,
Thomas W. Wilson^b, Roy T. Dobson^a and James L. Blackburn^a

Colleen Metge,^{1,2} Ruby Grymonpre,² Matthew Dahl,^{1,2} and Marina Yogendran^{1,2}



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COMMENTARY

BMJ

Reader's guide to critical appraisal of cohort studies: 1. Role and design

Paula A Rochon, Jerry H Gurwitz, Kathy Sykora, Muhammad Mamdani, David L Streiner, Susan Garfinkel, Sharon-Lise T Normand and Geoffrey M Anderson

BMJ 2005;330:895-897
doi:10.1136/bmj.330.7496.895

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COMMENTARY

BMJ Reader's guide to critical appraisal of cohort
**Effectiveness of statins for secondary prevention
in elderly patients after acute myocardial infarction:
an evaluation of class effect**

Zheng Zhou, Elham Rahme, Michal Abrahamowicz, Jack V. Tu, Mark J. Eisenberg,
Karin Humphries, Peter C. Austin, Louise Pilote

BMJ

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BMJ Reader's guide to critical appraisal of cohort
Effectiveness of statins for secondary prevention
The Effect of Deinsuring Chlorpropamide on the
Prescribing of Oral Antihyperglycemics for
Nova Scotia Seniors' Pharmacare Beneficiaries

Ingrid S. Sketris, Pharm.D., George C. Kephart, Ph.D., Dawn M. Frail, M.Sc.,
Chris Skedgel, M.D.E., and Michael J. Allen, M.D.

 Steven C Morgan, Norman E Sackett, James M Wright, Robert C Evans,
Morris L Barer, Patricia A Caetano and Charlyn D Black

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A National Pharmacovigilance Program

- Scientific talent exists across Canada to establish a world-class pharmacovigilance program
- Canada has extensive healthcare databases that can yield useful information
- Pharmacovigilance research is/should be only one (but an important) part of the decision-making process
 - The evidence: quantifying and weighing risks and benefits
 - Objective and subjective assessments
 - Compared to alternative treatment options
 - Population vs. Individuals / Subgroups
 - 'Other' considerations
- A coordinated approach to pharmacovigilance research to inform decision-makers would be in the best interest of Canadians

Discussion

off the mark by Mark Parisi
www.offthemark.com

