The Magic of Randomization versus the Myth of Real-World Evidence

Presented by

Songporn Oranratnachai, M.D.

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SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

N ENGL J MED 375;23 NEJM.ORG DECEMBER 8, 2016

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Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P., and Richard Peto, F.R.S.

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What is RWE?

- Information on health care that is derived from multiple sources outside typical clinical research settings
  - Electronic health records (EHRs)
  - Claims and billing data
  - Product and disease registries
  - Personal devices and health applications

Usefulness

- Generalization
- Reflect actual use in practice
  - Provide information how factors (clinical setting, provider, health-system characteristics) influence treatment effects and outcomes
- Saving time and money

Quality of data

Methodology

Analytic tools

2 Key dimensions

Research settings

Population
Data collection

Methodologic approach

Research settings

RCT vs Real world

RCTs	
Pros	**Cons**
✤ Specific populations ✤ Control variability and quality of data ✤ Evaluate safety and efficacy of medical product	✤ Uncertain generalizability ✤ Expense

Real-world setting		
Data access	**What to concern?**	**How to fix?**
Point of care data ✤ EHR ✤ Claims databases ✤ Registries	✤ Not collected or organized with the goal of supporting research	✤ Harmonized data collection ✤ Create a unified system ✤ Developing and implementing methods for incorporation data from EHRs and other source to research
Monitoring ✤ Personal devices ✤ Applications	✤ Accuracy and reliability of data	
Epidermiologic ✤ Social media	✤ Quality of data ✤ Privacy	

Research method, treatment allocation, and definition of RWE

incorrect !!!

RWE ≠ RCTs

Appropriate **analytic approaches**
Study design: planned interventions
Setting: tertiary care / academic centers

▶ **RWE ~ RCTs**

Useful of observational setting

- Generate hypothesis for prospective trials
- Assess generalizability of finding from interventional trials
- Conduct safety surveillance
- Examine changes in patterns of therapeutics use
- Measure and implement quality in health care delivery

Cautions

Small effect size

True effect?
or
Confounding factors

Flawed conclusion

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Nonrandomized observational analysis

Pros

- Detect
  - Rare events that cannot plausibly be attributed to bias (large relative risk)
- Large benefit effects

Cons

- Misleading conclusion due to potential biases
- If the effects of treatment are actually null or only moderate (RR < 2x)

RCTs of adequate size are required to ensure any **moderate** benefits/harms of treatment to guide patient care appropriately

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2012;367:1792-802.

ORIGINAL ARTICLE

Statin Use and Reduced Cancer-Related Mortality

The Danish Civil Registration system — **Baseline Characteristics Health Outcomes**

The Danish Cancer Registry — **Cancer diagnosis**

The Danish Registry of Medicinal Products Statistics — **Statin use**

Nonrandomized observational study

The NEW ENGLAND JOURNAL of MEDICINE

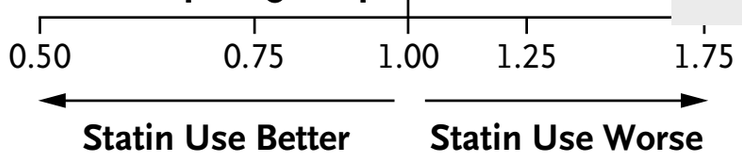
N Engl J Med 2012;367:1792-802.

ORIGINAL ARTICLE

Statin Use and Reduced Cancer-Related Mortality

A Nationwide Study

Cause of Death and Statin Dose	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Any cause				
0.00	277,204	184,895		
0.01–0.75	9,780	5,730		
0.76–1.50	6,181	3,438		
>1.50	2,760	1,531		
Cancer				
0.00	277,204	153,327		
0.01–0.75	9,780	4,680	1.00	
0.76–1.50	6,181	2,810	0.83 (0.81–0.86)	<0.001
>1.50	2,760	1,250	0.87 (0.83–0.91)	<0.001
Cardiovascular cause			0.87 (0.81–0.92)	<0.001
0.00	277,204	13,512		
0.01–0.75	9,780	529	1.00	
0.76–1.50	6,181	314	1.08 (0.99–1.19)	0.08
>1.50	2,760	134	1.25 (1.21–1.41)	<0.001
Other cause			1.24 (1.03–1.48)	0.01
0.00	277,204	18,056		
0.01–0.75	9,780	521		
0.76–1.50	6,181	314		
>1.50	2,760	147		

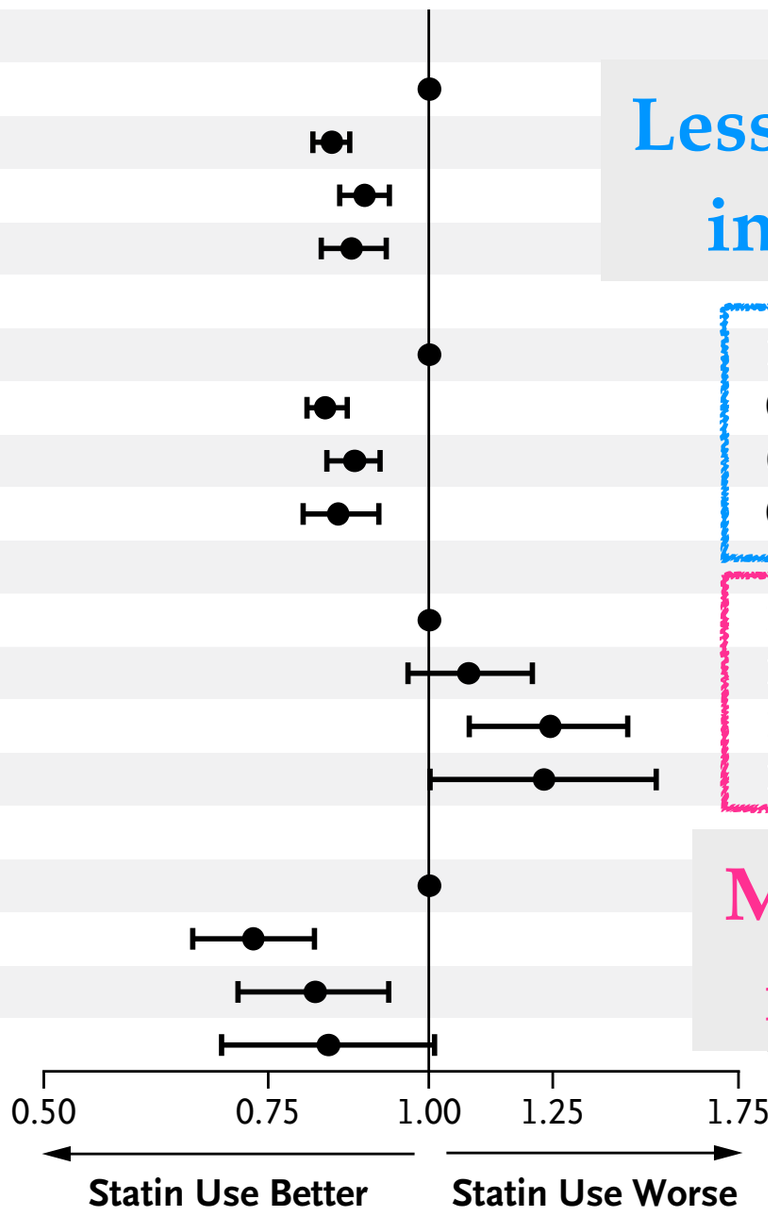


Less cancer death in statin user

More CV death in statin user

B Matched Study

Cause of Death and Statin Dose	No. of Patients	No. of Deaths	Hazard Ratio (95% CI)	P Value
Any cause				
0.00	45,741	26,271		
0.01–0.75	8,162	4,741		
0.76–1.50	4,927	2,721		
>1.50	2,158	1,176		
Cancer				
0.00	45,741	22,584	1.00	
0.01–0.75	8,162	3,844	0.82 (0.80–0.86)	<0.001
0.76–1.50	4,927	2,203	0.87 (0.82–0.91)	<0.001
>1.50	2,158	946	0.85 (0.80–0.91)	<0.001
Cardiovascular cause				
0.00	45,741	1,373	1.00	
0.01–0.75	8,162	468	1.08 (0.95–1.21)	0.19
0.76–1.50	4,927	258	1.24 (1.08–1.42)	0.002
>1.50	2,158	108	1.23 (1.00–1.50)	0.05
Other cause				
0.00	45,741	2,314		
0.01–0.75	8,162	429		
0.76–1.50	4,927	260		
>1.50	2,158	122		



Less cancer death in statin user

More CV death in statin user

Lancet 2016; 388: 2532–61

Meta-analysis of RCTs

Interpretation of the evidence for the efficacy and safety of statin therapy

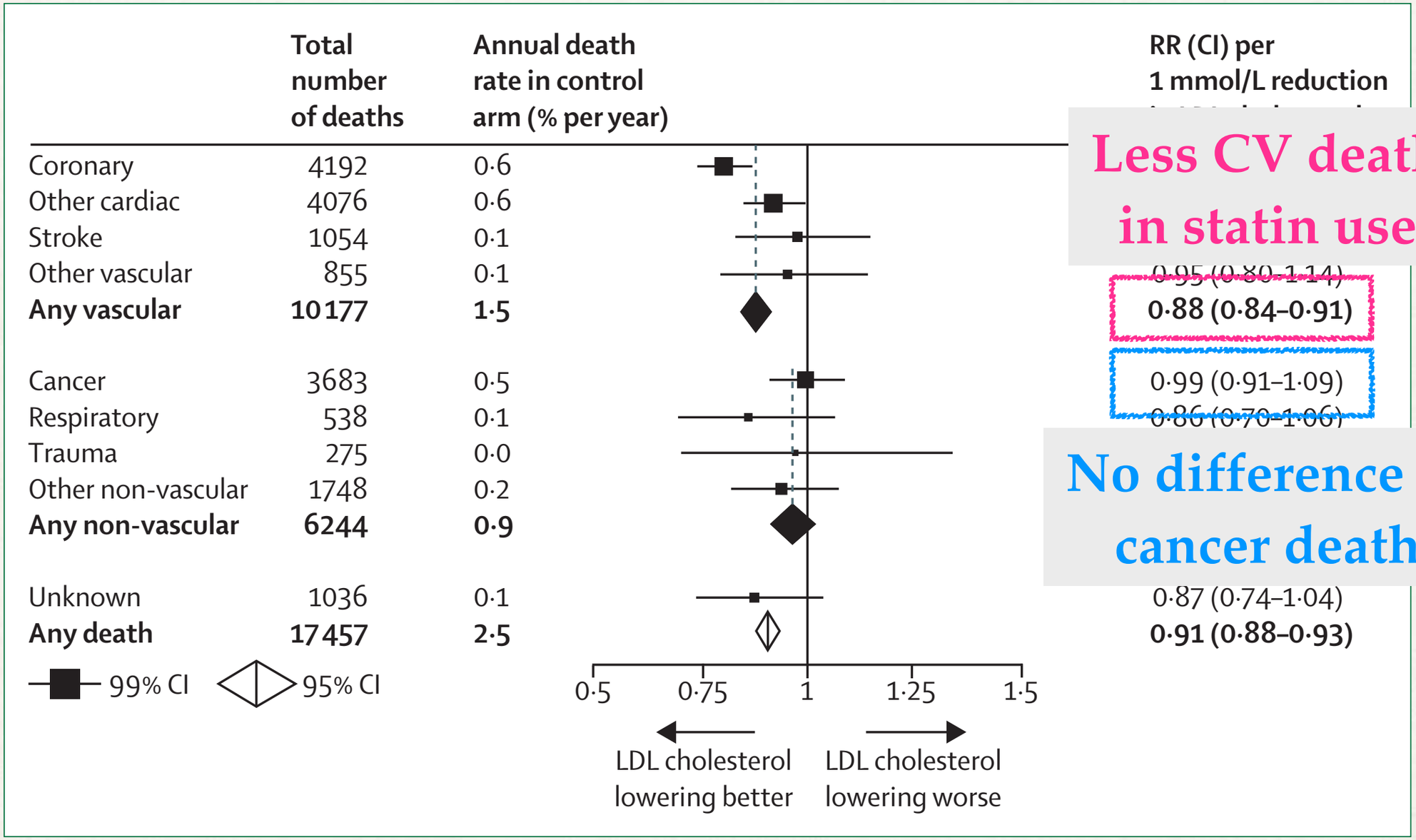


Figure 6: **Effects of lowering LDL cholesterol with statin therapy on cause-specific mortality in meta-analyses of randomised trials of statin therapy**

Adapted from CTT Collaboration website. Combined comparisons in randomised trials of routine statin therapy versus no routine statin therapy and of more versus less intensive statin therapy. RR=rate ratio.

Box 1. Facilitation of Randomization to Enhance Patient Care and Protect Public Health.

Randomization Provides Evidence about Treatment Effects That Can Be Trusted

Randomization results in groups of patients that are balanced (give or take the play of chance) with respect to their risks of all types of health outcomes. Consequently, in sufficiently large randomized trials, the effects of a treatment can be reliably assessed.

Nonrandomized observational studies may be able to detect large treatment effects. However, the potential biases can be appreciable, so such studies cannot be trusted when the benefits or harms of a treatment are actually null or only moderate.

Obstacles to Randomized Trials Should be Removed to Protect Patients >> Box 2

Increased focus on adherence to rules rather than on the scientific principles that underlie randomized trials has substantially increased the complexity and cost of trials.

Promotion of nonrandomized analyses of databases as a rapid source of "real-world evidence" about the effects of treatments is a false solution to the problems caused by the bureaucratic burdens imposed on randomized trials.

Instead, obstacles to randomized trials should be removed to allow more new treatments to become available and to facilitate the reliable assessment of existing treatments.

Treatment effect can be trusted

in RCTs > Observational study

Obstacles to RCTs should be removed

to reduce cost and complexities of RCTs

Box 2. Opportunities to Improve the Quality and Efficiency of Randomized Trials of New and Existing Interventions.

1 Appropriate trial guidelines

Based on scientific principles: Focus on issues that can materially affect the reliability of the results (including randomization with concealed assignment, adherence to trial intervention, completeness of follow-up, and intention-to-treat analyses).

Developed in partnership: Create new guidelines that can be adapted for many different types of trials through a collaboration of regulators, investigators, patients, and funders.

2 Enhanced recruitment

Faster and more predictable: Access electronic health care record systems and specialized registries to identify large numbers of potentially eligible patients.

Broader and more generalizable: Avoid unduly restrictive inclusion and exclusion criteria so that the results are relevant to a wide range of patients.

3 Improved quality

Better adherence: Implement interactive electronic case-report forms to help ensure complete and consistent data collection and to enhance adherence to the protocol and safety procedures.

Centralized monitoring: Improve patient safety and trial performance through real-time monitoring and analysis of electronic data from local trial sites.

4 Effective follow-up

Complete and comprehensive: Minimize loss to follow-up and facilitate prolonged follow-up of health outcomes by linkage to electronic health record systems.

Extended range of outcomes: Enhance the assessment of the safety and efficacy of treatment by incorporating technological advances (e.g., smartphones and digital sensors).

'Magic' of Randomization

- Balance known and unknown risk factors
- Outcome ascertainment
- Continue follow-up
- Reliable subjective outcome by masking intervention
- Ensure that causal effect come from intervention

Limitaions

My opinion
cannot apply to all scenario esp. personalized medicine with known prognostic/predictive biomarkers

- **Generalization**
  - Proportional effects should be similar in difference circumstances
  - Absolute benefits and harms ??
- **Costs** and **complexities**
  - Leading to a shift toward seeking treatments with
    - Larger effects in less common conditions
    - More restrict eligible criteria
    - Short duration of trials
  - Reduce generalizability and reliability of efficacy and safety

Summary

- Replacement of RCTs with non-RCTs is a false solution to the serious problems of ensuring both safety and efficacy of treatments

- Developing comprehensive guideline based on scientific principles is urgent needed

  - Generating reliable findings and ensuring patient safety

  - Take advantage of technological advances

My opinions

- Make use of nonrandomized observational study
  - First choice for some specific research questions eg. harm study, behavioral/social science research
- Confirm result of RCTs
  - Post-marketing surveillance of effectiveness and adverse events/safety
  - Evaluate health system performance of each centers (comparable outcome to result from RCTs?)

Your opinions ?