SGLT-2i from efficacy to effectiveness, what RWE can do: The CVD REAL Study

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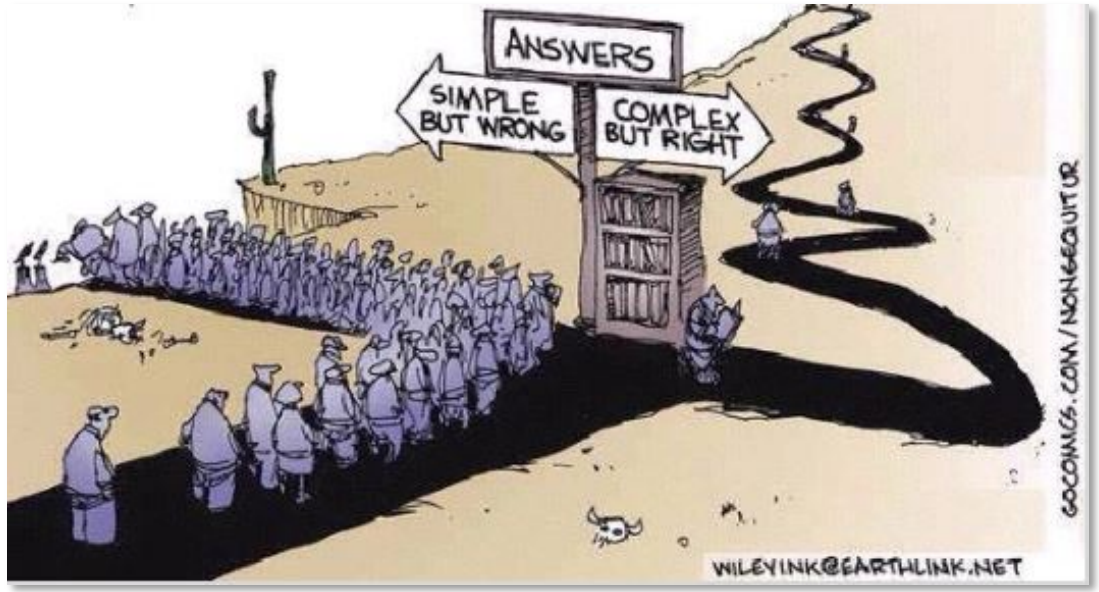
CVDREAL

Disclaimer and (Conflict) “Duality” of Interests

The opinions expressed in this presentation are the unique and very personal point of view of the author and do not necessarily reflect the position of any of the institutions or companies the author have been affiliated or is currently employed by

- AstraZeneca full time employee & Former Global Medical Affairs Senior Leader Diabetes (dapagliflozin)
- Conceived and developed the CVD REAL study, that is sponsored by AZ
- However, analyses and data interpretation by an independent Academic Scientific Committee
- Passionate about:
  - properly designed RWE
  - pragmatic trials
  - possibly, to impact clinical practice with robust evidence



Outlines

- Do we really need RWE, as we have RCTs already?
- Integrating CVD-REAL and CVOTs, where is the “true effect”?
- Is it the regulatory environment changing position about RWE?

- CVD-REAL: clinical implications, overall impact and future directions

What is Real World Evidence all about?

- "Everything that goes **beyond what is normally collected in the Phase 3 clinical trials program** in term of efficacy"[1]
- "Derived from **multiple sources outside typical clinical research setting**"[2]
- "A measure in **understanding health care data collected under real-life practice circumstances**"[1]
- "Data derived from medical practice among **heterogenous set of patients** in real-life practice settings"[3]

- Real world evidence (RWE) in medicine means evidence obtained from **real world data (RWD),** which are observational data obtained outside the context of randomized controlled trials (RCTs) and **generated during routine clinical practice**. RWE is generated by analysing data which is stored in electronic health records (EHR), etc.. It may be derived from retrospective or prospective observational studies and observational registries[8]

- **In the USA the 21st Century Cures Act required the FDA to expand the role of real world evidence**[8]

Opinion

VIEWPOINT

Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness

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For hundreds of years, the development of new medical treatments relied on "real-world" experience. Discoveries such as citrus fruit curing scurvy described in the 1700s or insulin as a treatment for diabetes in the 1920s long preceded the advent of the modern randomized clinical trial. What these diseases had in common was a reliable method of diagnosis, a predictable clinical course, and a large and obvious effect of the treatment.

In the late 1940s, the medical community began to adopt the use of randomized clinical designs for drug trials.[1] The recognition that anecdotal reports based on clinical practice observations were often misleading led to the nearly complete replacement of this "real-world evidence" (RWE) approach to evidence generated using the modern clinical trial model. Although moving medical science toward greater scientific rigor, this transformation simultaneously diminished the use (and minimized the value) of evidence generated from practice-based observations.

records (EHRs), together with rising costs and recognized limitations of traditional trials, has renewed interest in the use of real-world data (RWD) to enhance the efficiency of research and bridge the evidentiary gap between clinical research and practice. RWD can be defined as data relating to patient health status or the delivery of health care routinely collected from a variety of sources, such as the EHR and administrative data.

Under the 21st Century Cures Act, the Food and Drug Administration is tasked with developing a program to evaluate the use of RWE to support approval of new indications for approved drugs or to satisfy postapproval study requirements.[2] RWE can be defined as the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. A framework for this program will be published by the end of 2018.

The FDA routinely uses RWD to provide evidence about drug safety, drawing on claims and pharmacy data

> [Real-world data] can be defined as data relating to patient health status or the delivery of health care routinely collected from a variety of sources, such as the EHR and administrative data.

propriately matched study groups, modern clinical trials support drawing strong causal inferences regarding the efficacy of treatments, and thereby contribute to the substantial evidence of effectiveness necessary for regulatory approval. On the other hand, such trials do have important limitations, including high costs, extensive resource requirements, and often long timelines. Restrictive enrollment criteria and the concentration of trial sites in certain health systems make it challenging for some patients to enroll, including those with comorbidities, especially if mobility or cognitive abilities are affected. Thus, the trial population may not reflect the larger population that will use the drug.

The increasing accessibility of digital health data, spurred in large part by the transition to electronic health

The FDA is now focused on identifying additional areas in which RWD may be used to generate evidence of effectiveness. This will require both an assessment of the quality and suitability of underlying data that will be used, and the analytical methods to generate the evidence. Through Sentinel, the FDA has considerable experience with the use of claims data, but claims data will not capture many of the clinical end points used to support new indications for approved drugs. EHRs can provide more granular clinical data, including laboratory results, imaging, and clinical assessments; however, EHR data are often unstructured and at times inconsistent due to entry variations across providers and health systems. This is not surprising because EHR data are not presently generated with research goals in mind.

Corresponding Author: Janet Woodcock, MD, Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993 (janet.woodcock@fda.hhs.gov).

1. Real-Life Data. A Growing Need. Available at http://www.ispor.org/News/articles/Oct07/RLD.asp
2. Sherman RE et al. N. Engl J Med 2016;375:2293-7
3. Network for Excellence in Health 2015. RWE A new Era for Health Care Innovation. http://www.nehi.net/publications/66-real-wolrd-evidence-a-era-for-health-care-innovation/view
4. Real-World Evidence — What Is It and What Can It Tell Us? The New England Journal of Medicine, Dec. 6, 2016
5. Network for Excellence in Health Innovation. Real world evidence: a new era for health care innovation. September 2015. available at http://www .nehi .net/ writable/ publication_files/ file/ rwe_issue_ brief_final .pdf
6. Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices: draft guidance for industry and Food and Drug Administration staff. July 27, 2016.http://www.fda gov/ downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.pdf
7. Berger, Marc L. et al. "Good Practices for Real-world Data Studies of Treatment And/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-world Evidence in Health Care Decision Making." Pharmacoepidemiology and Drug Safety 26.9 (2017): 1033–1039. PMC. Web. 5 May 2018.
8. https://en.wikipedia.org/wiki/Real_world_evidence
9. Corrigan-Curay J et al. *JAMA*. 2018;320:867

RWE, RWD and "*CCPD" (Current Clinical Practice Data)*

- RWD: data derived from the real world
  - Routine healthcare, clinical or business operations
  - Observation of free-living humans
- RWE: evidence relevant to the real world
- **RWD does not always make RWE**
- RWE usually starts with RWD
- "CCPD" might not translate into "RW" at all

RWD, real world data; RWE, real world evidence

Academy of Medical Sciences. Next steps for using real world evidence. 2018. Available at: https://acmedsci.ac.uk/more/news/next-steps-for-using-real-world-evidence (Accessed June 2018)

Different stakeholders have different interests in RWE

PRESCRIBER

How a treatment performs in **real life practice** across different **age groups**, genders, races and ethnicities, disease severities and comorbid conditions to inform use in everyday clinical practice[1]

REGULATORY AUTHORITY

How clinical setting and provider and health-system characteristics influence treatment **effects and outcomes**[2]; real world **safety**[1]

PAYER

Economic impact (budget impact model, short term models, health care resource utilization/cost data), reimbursement;[3] pricing;[3] cost-effectiveness;[1] formulary placement[1]

PATIENT

To what extent a treatment is likely to work for **patients like them** in real life[4]

1. Cziraky M and Pollock M. Applied Clinical Trials 2015. Available at: http://www.appliedclinicaltrialsonline.com/real-world-evidence-studies (Accessed June 2018);
2. Sherman RE *et al. N Engl J Med* 2016;375:2293–7; 3. ISPOR. Real-Life Data: A Growing Need. Available at: https://www.ispor.org/News/articles/Oct07/RLD.asp (Accessed June 2018); 4. de Lusignan S *et al*. *J Innov Health Inform* 2015;22:368–73

Real world evidence can inform …

- Outcomes research
- Research on healthcare systems
- Quality improvement
- Safety surveillance
- Therapeutic development
- Well-controlled effectiveness studies
- And can provide information on how factors, such as clinical setting and provider, and health system characteristics influence treatment effects and outcomes

Sherman RE *et al. N Engl J Med* 2016;375:2293–7

What does real world evidence mean?

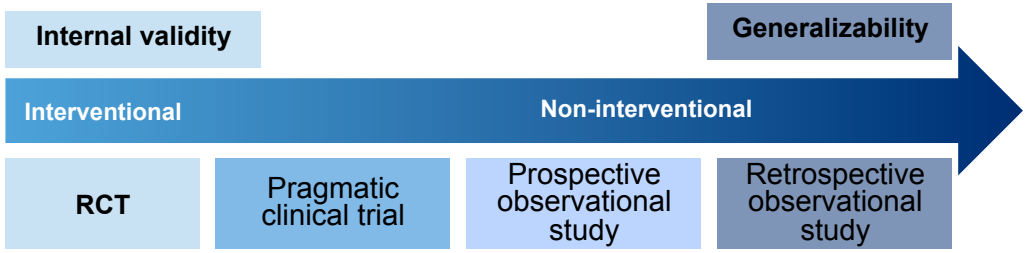
RWE is the use of RWD and analytics to discover, develop, deliver and provide new insights on healthcare interventions

1. Availability of **RWD** and use of appropriate **analytical methods** create a big opportunity to **accelerate/increase patient access to innovative medicines**

2. RWE **differs from the traditional RCT approach** because it **uses primary and secondary data from the real world** instead of data generated from a standard, randomized patient base

3. **RWE does not replace results from RCTs, but is complementary** because it offers a broader range of data to generate the evidence necessary for medical and healthcare decision-makers

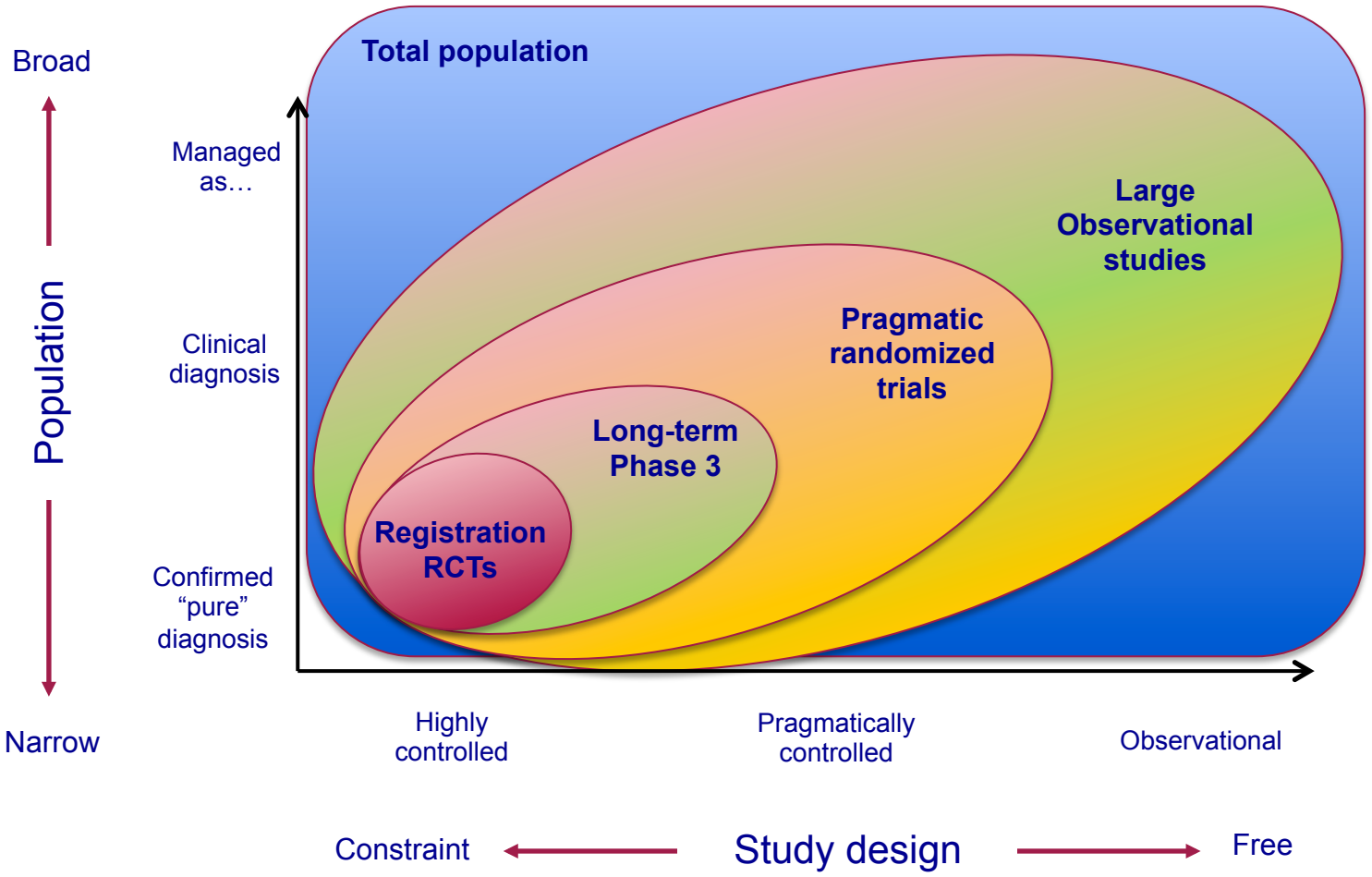
RCTs and RWE form a continuum of evidence



Randomized	Observational
Protocol-driven	Usual care-driven
Internal validity	Relevance to clinical practice
Extensive exclusion and inclusion criteria	Few exclusions (including comorbidities)
High cost per patient	Lower cost per patient (large n values)

RCT, randomized controlled trial; RWD, real world data; RWE, real world evidence

What are we measuring, moving beyond clinical trials



Adapted from Roche et al. Lancet Respir Med 2013;1(10):e29–30
RCT, randomized controlled trial

In RCT:

- **Efficacy** is the extent to which an intervention does more good than harm under ideal circumstances

In RWE:

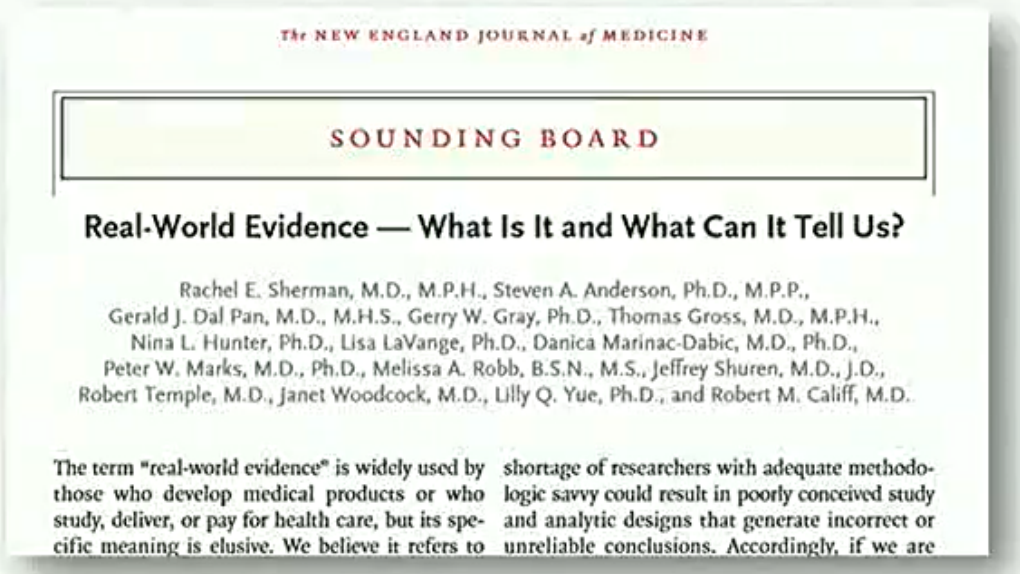
- **Effectiveness** is the extent to which an intervention does more good than harm when provided under the usual circumstances of healthcare practice

In HE:

- **Efficiency** is the analysis of the incremental cost related to the unity of quality of life gained or lost (e.g. QALY, ICER, NNT, NNH, DALY), however Patient's is different from HCP's or Payer's prospective

The importance of RWE for advancing drug safety

"…And at the end of a drug development program, RCTs can leave critical questions unanswered, particularly about the effects or impacts of a drug after it gets into the 'real world'…"[1]



The NEW ENGLAND JOURNAL of MEDICINE

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.

The term "real-world evidence" is widely used by those who develop medical products or who study, deliver, or pay for health care, but its specific meaning is elusive. We believe it refers to

shortage of researchers with adequate methodologic savvy could result in poorly conceived study and analytic designs that generate incorrect or unreliable conclusions. Accordingly, if we are

RCT, randomized controlled trial; RWE, real world evidence

1. CDER Drug Safety Priorities 2017. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM605229.pdf (Accessed 7 July 2018)
2. Sherman RE et al. *NEJM*. 2016;375:2293–7

Sampling in CVOTs… Size matters!

Deaths	Pts Randomized (Risk = 10%)	Chance of Type II Error*	Comments on Sample Size
0-50	< 500	> 0.9	Utterly inadequate
50-150	1000	0.7-0.9	Probably inadequate
150-350	3000	0.3-0.7	Possibly inadequate
350-650	6000	0.1-0.3	Probably adequate
> 650	10000	< 0.1	Adequate

**Probability of failing to achieve p < .01 if risk reduction = 25%*

Yusuf Progr CV Dis 1985

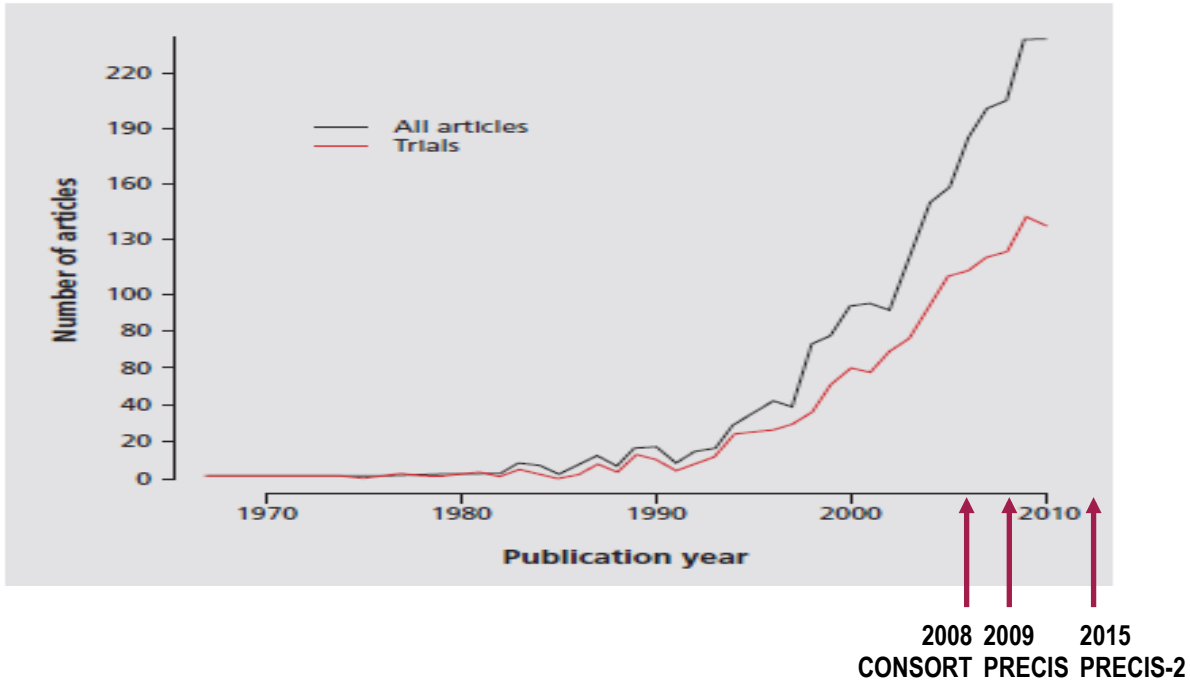
Is it feasible, affordable and cost effective? Do your maths

- Different types of studies require different amounts of resources
  - Are the resources required justified by the value of the study?

Study	Personnel	Finance	Time
Systematic literature review		$	
Analysis of administrative claims data/registry data		$	
Analysis of electronic medical records		$$	
Prospective, non-interventional study		$$$	
Pragmatic clinical trial		$$$$	
RCT		$$$$$	

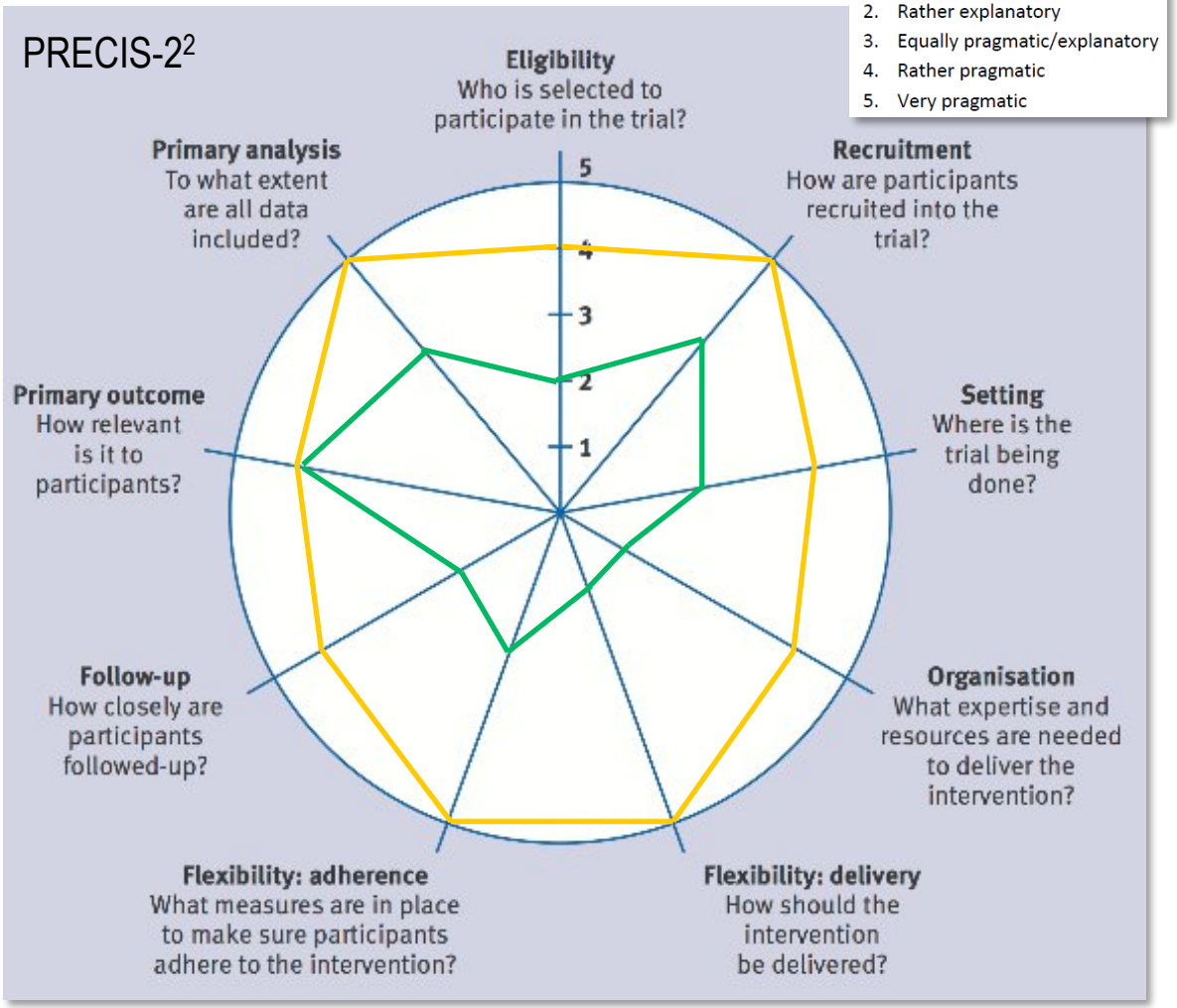
Why so many Pragmatic Trials?

MEDLINE search “pragmatic [tiab] OR naturalistic* [tiab] AND trial”[1]



Each domain is a 5-point Likert scale:

1. Very explanatory
2. Rather explanatory
3. Equally pragmatic/explanatory
4. Rather pragmatic
5. Very pragmatic



1. Modified from Dialogues Clin Neurosci 2011;13:217-224. 2. NEJM 2016;375 (5):454-463. Adapted from BMJ 2015;350:h2147 https://www.precis-2.org

Role of “RWE” and “Pragmatic design”… is it really so “all new stuffs”!

“Turn out your old clothes…
… some of them may have come back into fashion.”

From 1967 to 2009 … from 1984 to 2016 !

STATISTICS IN MEDICINE, VOL. 3, 375–384 (1984)

TYING CLINICAL RESEARCH TO PATIENT CARE BY USE OF AN OBSERVATIONAL DATABASE

MARK A. HLATKY, KERRY L. LEE, FRANK E. HARRELL, JR., ROBERT M. CALIFF, DAVID B. PRYOR, DANIEL B. MARK AND ROBERT A. ROSATI

Division of Cardiology, Department of Medicine and the Division of Biometry, Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina, U.S.A.

The proposition that some inherent logical incompetence attaches to an inference based on observational, as distinguished from experimental, evidence seems to have little to commend it beyond the great positiveness with which it is sometimes asserted.
JEROME CORNFIELD[1]

Careful observation forms the foundation upon which all science is built. Performing experiments is, of course, a major scientific activity, but there are several scientific disciplines, such as astronomy, geology and evolutionary biology to name but a few, in which meaningful experimentation is impossible and careful observation and analysis of data are the only methods available. Experimentation in clinical medicine takes the form of the randomized controlled trial (RCT), and it has been asserted that only randomized trials can provide valid conclusions about therapeutic efficacy. As in other fields, however, there have been important advances in medical therapeutics as a result of careful observation and analysis. Our thesis is that the credibility of any investigation depends mainly upon its adherence to high scientific standards in obtaining data and the care taken in analysing data. When proper methodology is used, we believe that the observational database can play an important complementary role to the RCT in assessing the efficacy of therapy.

In this article we first briefly outline the methods that should be used in modern observational studies. We then consider certain limitations to the use of RCT results in guiding clinical decisions about individual patients. Next we address the principal objections to the use of the observational database, and the methods used to control or reduce the bias introduced when treatment is not allocated randomly. Finally, we discuss the complementary roles of the RCT and observational database and the potential benefit of more frequent use of multivariable methods to analyse RCT data.

THE MODERN OBSERVATIONAL DATABASE

A primary purpose of an observational database is to collect and then distil accumulated clinical experience to make accurate predictions for individual patients. To attain this goal, the factors which are most predictive of diagnosis and prognosis must first be identified, and then predictive models must be developed and validated. The primary purpose of the observational database therefore differs from that of the randomized controlled trial, which is designed to assess the effect of therapy in a population of patients.

J. chron. Dis. 1967, Vol. 20, pp. 637–648. Pergamon Press Ltd. Printed in Great Britain

EXPLANATORY AND PRAGMATIC ATTITUDES IN THERAPEUTICAL TRIALS

DANIEL SCHWARTZ and JOSEPH LELLOUCH

Unité de Recherches Statistiques, Institut National de la Santé et de la Recherche Medicale, 94 Villejuif, France

(*Received* 6 *January* 1967; *in revised form* 24 *March* 1967)

IT IS the thesis of this paper that most therapeutic trials are inadequately formulated, and this from the earliest stages of their conception. Their inadequacy is basic, in that the trials may be aimed at the solution of one or other of two radically different kinds of problem; the resulting ambiguity affects the definition of the treatments, the assessment of the results, the choice of subjects and the way in which the treatments are compared.

It often occurs that one type of approach is ethically less defensible than the other, or may even be ruled out altogether on ethical grounds. We postpone consideration of this aspect of the question until a later section.

Journal of Clinical Epidemiology

Journal of Clinical Epidemiology 62 (2009) 499–505

ORIGINAL ARTICLE

Explanatory and Pragmatic Attitudes in Therapeutical Trials

Daniel Schwartz, Joseph Lellouch

Unité de Recherches Statistiques, Institut National de la Santé et de la Recherche Medicale, 94 Villejuif, France

Accepted 30 January 2009

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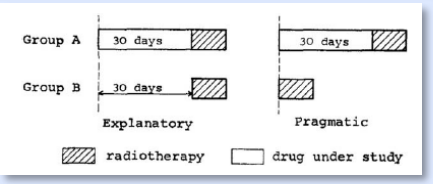

		Approach	
		Explanatory.R	Pragmatic R
Results	Research	Yes	Only if DR > R
	Immediate application	Only if DR ≤.R	Yes

R, immediate therapy, R, delayed radiotherapy, DR, drug followed by radiotherapy.

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N Engl J Med. 2016 Dec 8;375(23):2293-2297

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REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Pragmatic Trials

Ian Ford, Ph.D., and John Norrie, M.Sc.

N Engl J Med. 2016; 375:454-63

European Committee - Innovative Medicines Initiative (IMI)

https://www.imi-getreal.eu/

Trying to integrate CVOTs with RWE…

- Do we really need RWE?
- Can we rely on the results?
- Is RWE relevant to my clinical practice?

RCTs (vs placebo)

- High internal validity
- Limited external validity
- Efficacy and safety
- Gold standard

RWE (vs standard of care)

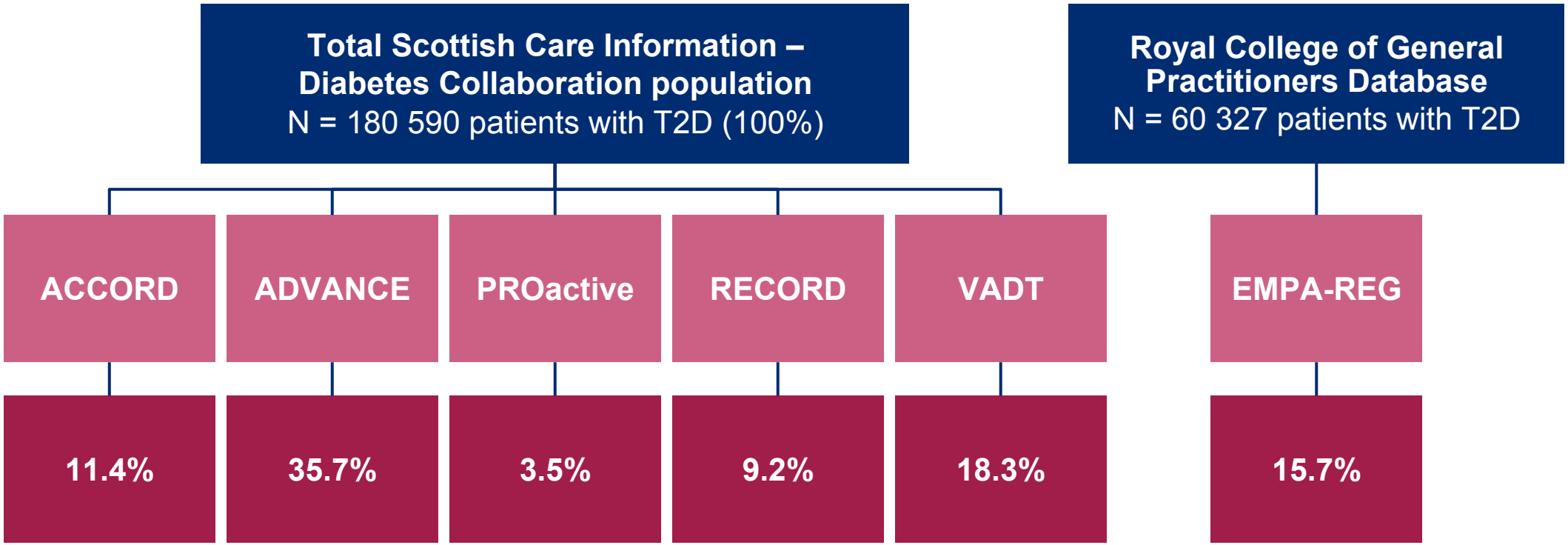
- Higher external validity (current clinical practice)
- Residual confounding
- Established for safety monitoring
- Effectiveness

CVOT, cardiovascular outcomes trial; RCT, randomized controlled trial; RWE, real world evidence

Silverman L. *Am J Med* 2009;122:114-120

The majority of patients are not represented in RCTs

How many real world patients with T2D would be eligible for landmark diabetes RCTs?

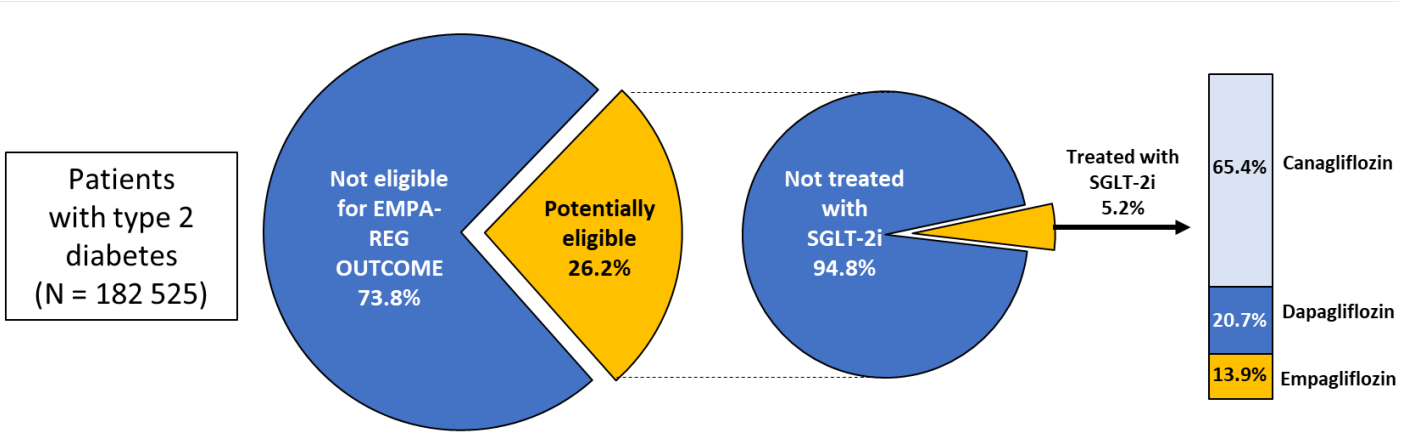


RCT, randomized controlled trial; T2D, type 2 diabetes

Saunders C *et al. Diabet Med* 2013;30:300–8; McGovern A *et al. Diabetes Ther* 2017 Apr;8:365–76. doi: 10.1007/s13300-017-0254-7 [Epub ahead of print]

Eligibility for EMPA-REG OUTCOME

- **Diabetes Collaborative Registry[1]**
  - In a large US-based outpatient registry, ~1 in 4 patients with T2D met the main eligibility criteria for EMPA-REG OUTCOME



- **Royal College of General Practitioners Research and Surveillance Centre database[2]**
  - 16% of patients with T2D from the UK-eMR database met the inclusion criteria for EMPA-REG OUTCOME

	RCGP-RSC total type II diabetes group (n = 60,327)
	Risk factor present % (95% CI)[1]
Myocardial infarction	4.9 (4.8 to 5.1)
Coronary artery disease	5.9 (5.7 to 6.0)
Unstable angina	0.9 (0.8 to 0.9)
Stroke	4.3 (4.2 to 4.5)
Peripheral artery disease	4.4 (4.3 to 4.6)
Any major CV risk factor	15.7 (15.5 to 16.0)

CV, cardiovascular; eMR, electronic medical record; T2D, type 2 diabetes

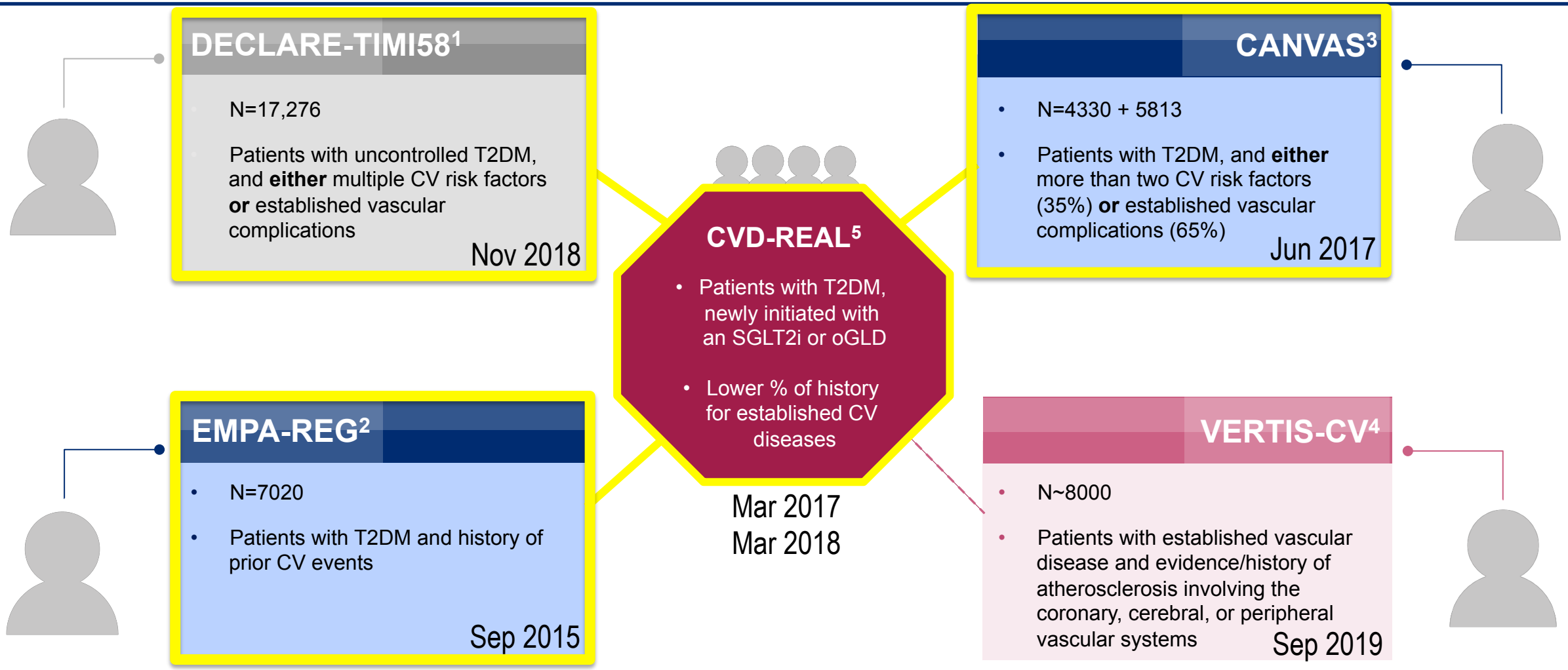
1. Arnold S et al. Eur J Prev Cardiol 2017;24:1637–45; 2. McGovern A et al. Diabetes Therapy 2017. doi:10.1007/s13300-017-0254-7

Ethical implications: Possible Events Avoided in the DCR Registry Study

	Event rate (total)		Event rate (annualized)		Potential events avoided	
	Rate in drug	Rate in placebo	Rate in drug	Rate in placebo	Total (3.1 y)	Per year
All-cause death	5.7%	8.3%	1.94%	2.86%	1441	510
CV death	3.7%	5.9%	1.24%	2.02%	1219	432
CHF hospitalization	2.7%	4.1%	0.94%	1.45%	776	283

DCR, Diabetes Collaborative Registry
Arnold S, et al. Presented at: 52nd EASD Annual Meeting; September 12th–16th, 2016; Munich, Germany

Real-world Evidence and Ongoing CVOTs



CV, cardiovascular; CVOT, cardiovascular outcome trial; MI, myocardial infarction; SGLT2i, sodium–glucose co-transporter 2 inhibitor; T2DM, Type 2 diabetes mellitus

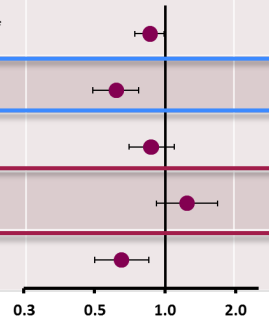
1. NCT01730534. Available at: https://clinicaltrials.gov/ct2/show/NCT01730534 (Accessed Oct 2018); 2. Zinman B, et al. N Engl J Med 2015;373:2117–2128;
3. NCT01032629. Available at: https://clinicaltrials.gov/ct2/show/NCT01032629; https://clinicaltrials.gov/ct2/show/NCT01989754 (Accessed Oct 2018); 4. NCT01986881. Available at: https://clinicaltrials.gov/ct2/show/NCT01986881 (Accessed Oct 2018); 5. https://clinicaltrials.gov/ct2/show/NCT02993614?term=cvd+real&rank=1 (Accessed Oct 2018). Kosiborod M et al. Circulation 2017;136:249–59; Kosiborod M et al. J Am Coll Cardiol 2018;71:2628–39.

CVOTs mostly in prevalent “established CVD” T2D population

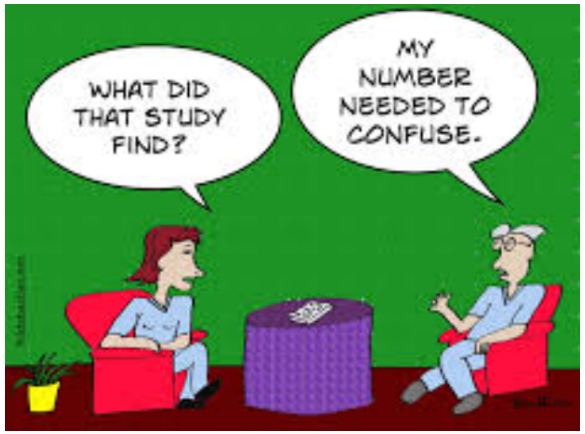
EMPA-REG OUTCOME

Sep 2015

Outcome	Patients with event / analyzed: Empagliflozin	Patients with event / analyzed: Placebo	Hazard ratio	95% CI	*P* value
3-point MACE	490/4687	282/2333	0.86	0.74, 0.99*	0.04
CV death	172/4687	137/2333	0.62	0.49, 0.77	<0.001
Nonfatal MI	213/4687	121/2333	0.87	0.70, 1.09	0.22
Nonfatal stroke	150/4687	60/2333	1.24	0.92, 1.67	0.16
Hospitalization for heart failure	126/4687	95/2333	0.65	0.50, 0.85	0.002



NNT
NNH
NNTBC

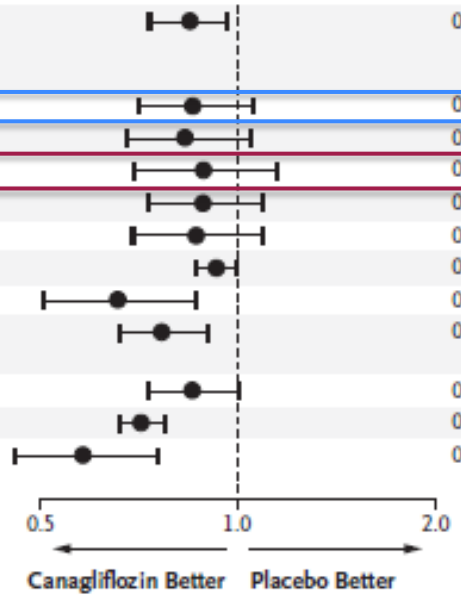


CANVAS Program

CANVAS-R

Jun 2017

Outcome	Canagliflozin (N=5795)	Placebo (N=4347)	Hazard Ratio (95% CI)
	no. of participants per 1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	26.9	31.5	0.86 (0.75–0.97)
Death from cardiovascular causes	11.6	12.8	0.87 (0.72–1.06)
Nonfatal myocardial infarction	9.7	11.6	0.85 (0.69–1.05)
Nonfatal stroke	7.1	8.4	0.90 (0.71–1.15)
Fatal or nonfatal myocardial infarction	11.2	12.6	0.89 (0.73–1.09)
Fatal or nonfatal stroke	7.9	9.6	0.87 (0.69–1.09)
Hospitalization for any cause	118.7	131.1	0.94 (0.88–1.00)
Hospitalization for heart failure	5.5	8.7	0.67 (0.52–0.87)
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78 (0.67–0.91)
Death from any cause	17.3	19.5	0.87 (0.74–1.01)
Progression of albuminuria	89.4	128.7	0.73 (0.67–0.79)
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60 (0.47–0.77)



Primary outcome was defined as death from CV causes, nonfatal myocardial infarction, or nonfatal stroke

CI, confidence interval; CV, cardiovascular; EMPA-REG, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; HF, heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium–glucose co-transporter 2; T2DM, Type 2 diabetes mellitus

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128.
2. Neal B, et al. N Engl J Med 2017;376:644-57.

Baseline characteristics from CVOTs and RWE studies (1)

	CVOTs			Observational studies				
	EMPA-REG OUTCOME[1] (EMPA vs placebo)[1] N = 7020	**CANVAS** (CANA vs placebo)[2] N = 10 142	**DECLARE Total** (DAPA vs placebo) N = 17 160	**CVD-REAL** (SGLT-2i vs oGLD)[3] N = 306 156	**CVD-REAL Nordic** (SGLT-2i vs oGLD)[4] N = 91 320	**CVD-REAL Nordic vs DPP-4i** (DAPA vs DPP-4i)[5] N = 40 908	**CVD-REAL 2** (SGLT-2i vs oGLD)[7] N = 470 128	**EASEL** (SGLT-2i vs oGLD)[6] N = 25 258
	63	63	64	57	61	61	57	66
Women, %	28	36	37	44	40	41	45	44
White race, %	72	78	79	-	-	-	NA	35
eCVD, %	> 99	66	41	13	25	23	27	100
Previous HF, %	10	14	10	3	5	5	7	23

These studies differ in design, patient population, comparator and follow-up period; the table does not represent a direct H2H comparison between studies
CKD, chronic kidney disease; CVD, cardiovascular disease; CVD-REAL CardioVascular events in Diabetes – Reduction of Events According to real Life data; CVOT, cardiovascular outcomes trial; DAPA, dapagliflozin; DPP-4i, dipeptidylpeptidase-4 inhibitor; EMPA, empagliflozin; eCVD, estimated CVD; GLP-1 glucagon-like peptide-1; H2H, head-to-head; HF, heart failure; oGLD, other glucose-lowering drug; RWE, real world evidence; SGLT-2i, sodium–glucose co-transporter 2 inhibitor

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28; 2. Neal B *et al. N Engl J Med* 2017;376:644–57; 3. Kosiborod M *et al. Circulation* 2017;136:249–59; 4. Birkeland KI *et al. Lancet Diabetes Endocrinol* 2017;5:709–17; 5. Persson F *et al. Diabetes Obes Metab* 2018;20:344–51; 6. Udell JA *et al. Circulation* 2018;137:1450–59; Nov 13 [Epub ahead of print];
7. Kosiborod M *et al. J Am Coll Cardiol* 2018;71:2628–39.

Baseline characteristics from CVOTs and RWE studies (2)

CVDREAL

	CVOTs			Observational studies				
	EMPA-REG OUTCOME (EMPA vs placebo)[1] N = 7020	**CANVAS** (CANA vs placebo)[2] N = 10 142	**DECLARE Total** (DAPA vs placebo) N = 17 160	**CVD-REAL** (SGLT-2i vs oGLD)[3] N = 306 156	**CVD-REAL Nordic** (SGLT-2i vs oGLD)[4] N = 91 320	**CVD-REAL Nordic vs DPP-4i** (DAPA vs DPP-4i)[5] N = 40 908	**CVD-REAL 2** (SGLT-2i vs oGLD)[7] N = 470 128	**EASEL** (SGLT-2i vs oGLD)[6] N = 25 258
Metformin, %	74	77	79	79	77	84	75	81
Insulin, %	49	50	40	29	30	29	20	20
SU, %	43	43	41	39	27	26	52	45
DPP-4i, %	11	12	16	33	19	-	56	44
GLP-1 RA, %	3	4	4	19	15	8	3	14
AHTN, %	95	-	89	80	76	73	63	-
ARB/ACEi, %	81	80	77	72	67	64	56	74
Statin, %	77	75	71	68	68	63	65	82*

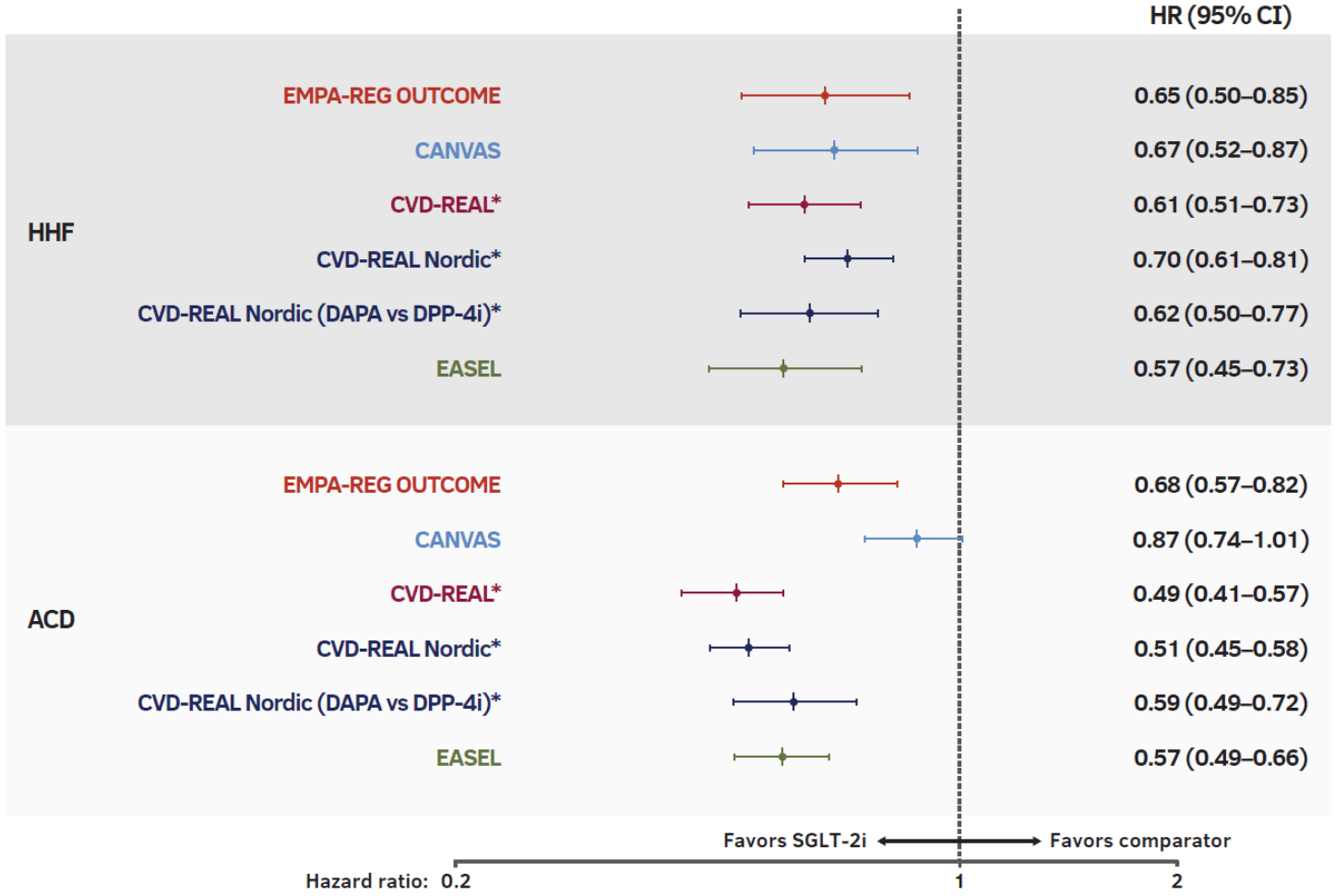
These studies differ in design, patient population, comparator and follow-up period, the table does not represent a direct H2H comparison between study results

ACEi angiotensin-converting-enzyme inhibitor; AHTN, arterial hypertension; ARB, angiotensin receptor blocker; CANA, canagliflozin; CKD, chronic kidney disease; CVD, cardiovascular disease; CVD-REAL, CardioVascular events in Diabetes – Reduction of Events According to real Life data; CVOT, cardiovascular outcomes trial; DAPA, dapagliflozin; DPP-4i, dipeptidypeptidase-4 inhibitor; EMPA, empagliflozin; GLP-1 RA, glucagon-like peptide receptor agonist; H2H, head-to-head; oGLD, other glucose-lowering drug; RWE, real world evidence; SU, sulphonylurea

1. Zinman B *et al. N Engl J Med* 2015;373:2117–28; 2. Neal B *et al. N Engl J Med* 2017;376:644–57; 3. Kosiborod M *et al. Circulation*. 2017;136(3):249–59; 4. Birkeland KI *et al. Lancet Diabetes Endocrinol*. 2017; 5:709–17; 5. Persson F *et al. Diabetes Obes Metab*. 2018;20:344–51; 6. Udell JA *et al. Circulation*. 2018;137:1450–59; 7. Kosiborod M *et al. J Am Coll Cardiol.* 2018;71:2628–39

What we know today
Side by side plot of the CVOTs and RWEs results

CVDREAL 2



Hospitalization for Heart Failure

P-value for SGLT2i vs. oGLD: p=0.001

Database	N	# of events	HR (95% CI)
Korea	336,644	5149	0.87 (0.82, 0.92)
Japan	67,780	565	0.75 (0.63, 0.89)
Singapore	2726	67	0.62 (0.38, 1.02)
Israel	19,472	128	0.53 (0.37, 0.75)
Canada	16,064	88	0.36 (0.24, 0.56)
Total	442,686	5997	0.64 (0.50, 0.82)

Heterogeneity p-value: p<0.001

ITT, unadjusted analysis

Favor SGLT2i ← → Favor oGLD

Hazard Ratio: 0.25 0.50 1.00 2.00

All-Cause Death

P-value for SGLT2i vs. oGLD: p<0.001

Database	N	# of events	HR (95% CI)
Korea	336,644	3445	0.72 (0.67, 0.77)
Japan	67,780	557	0.56 (0.47, 0.67)
Singapore	2726	36	0.75 (0.38, 1.47)
Israel	19,472	199	0.41 (0.30, 0.55)
Canada	16,064	261	0.51 (0.41, 0.65)
Australia	27,442	718	0.32 (0.27, 0.38)
Total	470,128	5216	0.51 (0.37, 0.70)

Heterogeneity p-value: p<0.001

ITT, unadjusted analysis

Favor SGLT2i ← → Favor oGLD

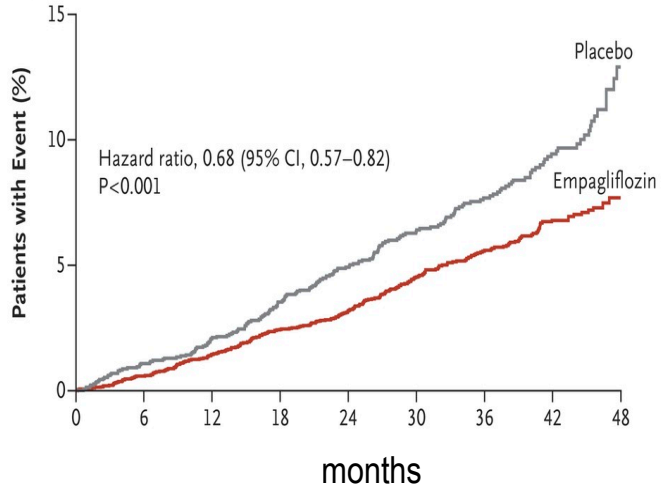
Hazard Ratio: 0.25 0.50 1.00 2.00

These studies differ in design, patient population, comparator and follow-up period. The graph does not represent a direct H2H comparison between studies. *On-treatment population. ACD, all-cause death; HR, hazard ratio; HHF, hospitalization for heart failure

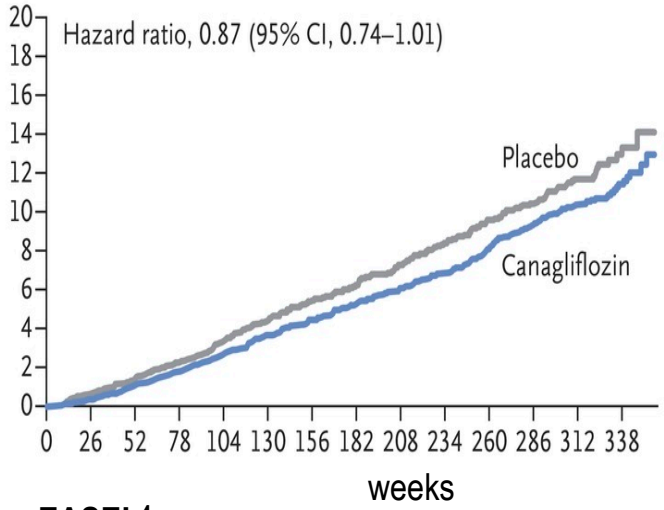
1. Zinman B, et al. N Engl J Med 2015;373(22):2117-28
2. Neal B, et al. N Engl J Med 2017;376:644-57
3. Kosiborod M, et al. Circulation. 2017;136(3):249-59
4. Birkeland KI, et al. Lancet Diabetes Endocrinol. 2017; 5(9):709-717
5. Persson F, et al. Diabetes Obes Metab. 2017;1–8
6. Udell JA, et al. Circulation. 2017; Nov 13 [Epub ahead of print]
7. Kosiborod M, et al.. J Am Coll Cardiol (in press). DOI: 10.1016/j.jacc.2018.03.009

Kaplan-Meier side by side plots from CVOTs and RWEs for all-cause death

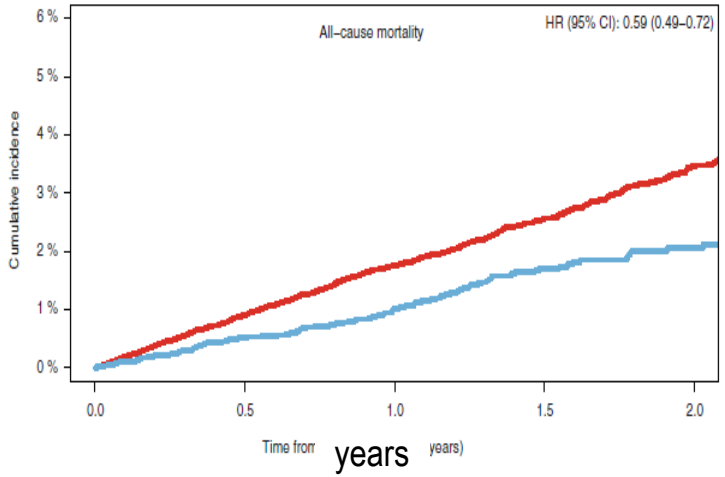
EMPA REG Outcome[1]



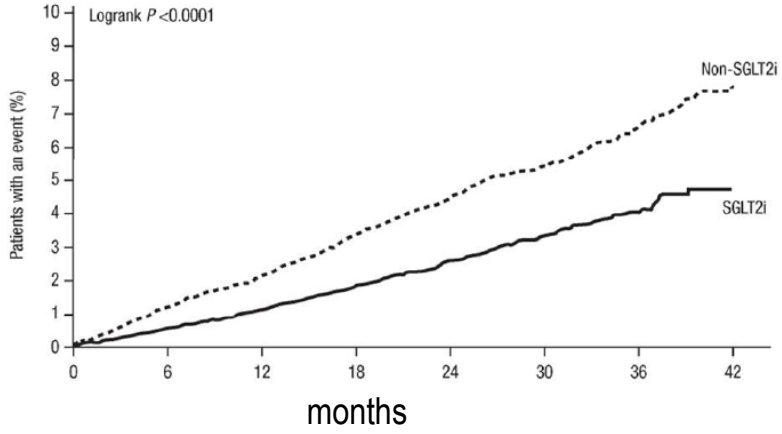
CANVAS[2]



CVD-REAL DPP4-i[3]



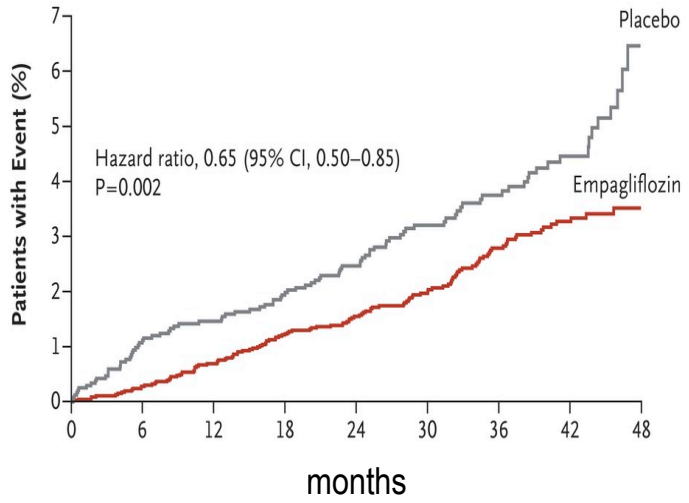
EASEL[4]



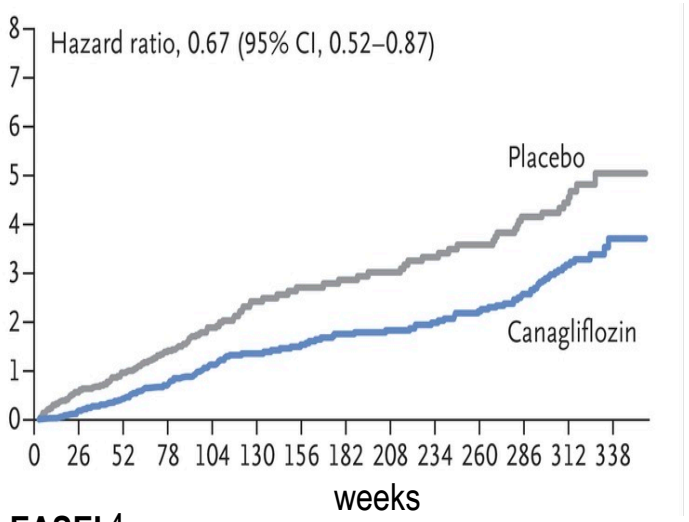
1. Zinman B, et al. N Engl J Med 2015;373(22):2117-28
2. Neal B, et al. N Engl J Med 2017;376:644-57
3. Persson F, et al. Diabetes Obes Metab. 2017;1–8
4. Udell JA, et al. Circulation. 2017; Nov 13 [Epub ahead of print]

Kaplan-Meier side by side plots from CVOTs and RWEs for HHF

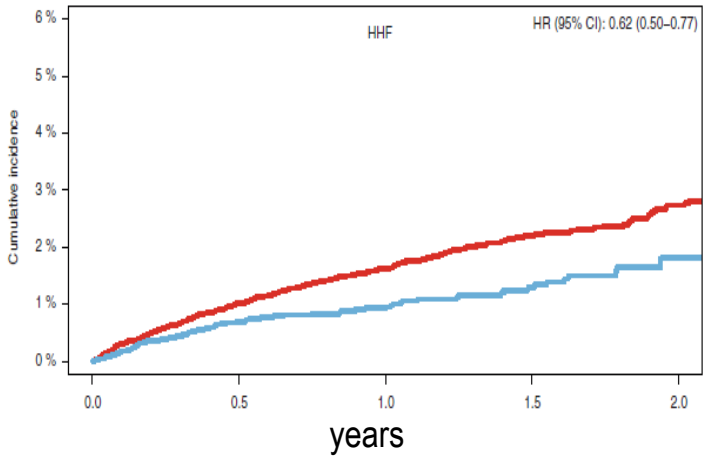
EMPA REG Outcome[1]



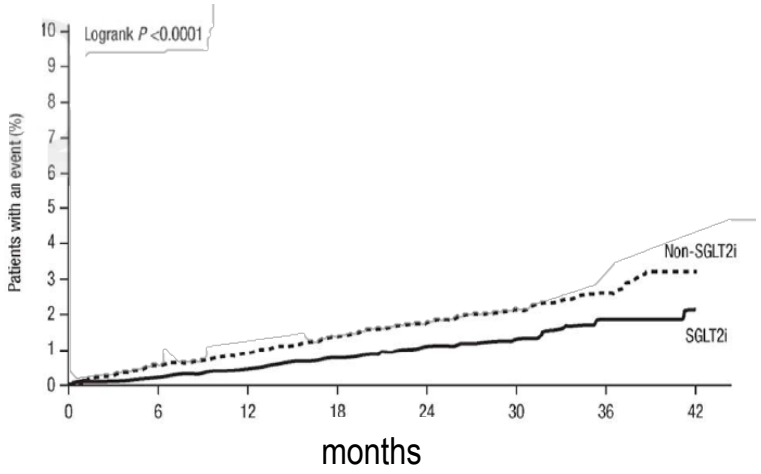
CANVAS[2]



CVD-REAL DPP4-i[3]



EASEL[4]

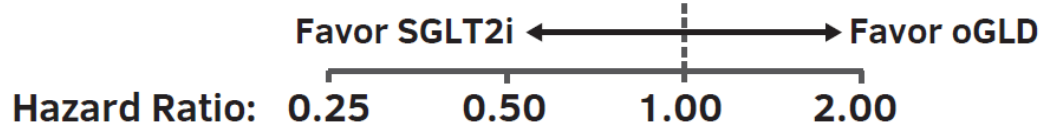


1. Zinman B, et al. N Engl J Med 2015;373(22):2117-28
2. Neal B, et al. N Engl J Med 2017;376:644-57
3. Persson F, et al. Diabetes Obes Metab. 2017;1–8
4. Udell JA, et al. Circulation. 2017; Nov 13 [Epub ahead of print]

Stroke? Role of RWE in hypothesis generation

CVDREAL 2

Database	N	# of events	HR (95% CI)
Korea	336,644	5972	0.82 (0.78, 0.86)
Japan	67,780	272	0.66 (0.52, 0.84)
Singapore	2726	34	0.34 (0.15, 0.75)
Israel	19,472	116	0.66 (0.47, 0.94)
Canada	16,064	45	0.55 (0.32, 0.94)
Total	442,686	6439	0.68 (0.55, 0.84)



P-value for SGLT2i vs. oGLD: p<0.001

Heterogeneity p-value: p=0.029

ITT, unadjusted analysis

Too Good To Be True?

CVDREAL

EDITORIAL

Reality and Truth

Balancing the Hope and the Hype of Real-World Evidence

Article, see p 249

Anushka Patel, MD, PhD
Laurent Billot, MRes

Comment

SGLT2 inhibitors in the real world: too good to be true?

Despite recent therapeutic advances, type 2 diabetes remains associated with a high incidence of premature cardiovascular disease and reduced life expectancy. Glucose lowering alone has not been shown to have any short-term effects on cardiovascular disease. Until recently, no individual glucose-lowering agent had been

95% CI 0·69–0·87), cardiovascular mortality (0·53, 0·40–0·71), and all-cause mortality (0·51, 0·45–0·58), and led to a 30% reduction in hospital events for heart failure (0·70, 0·61–0·81). Non-fatal myocardial infarction and non-fatal stroke were not reduced by SGLT2 inhibitors. Notably, only 25% of participants in CVD-REAL Nordic

Lancet Diabetes Endocrinol 2017
Published Online
August 3, 2017
http://dx.doi.org/10.1016/
S2213-8587(17)30259-0
See Online/Articles
http://dx.doi.org/10.1016/
S2213-8587(17)30258-9

Comparison of outcomes using SGLT-2is in CVOTs vs CVD-REAL 2

Data source	Death	Heart failure hospitalization	Myocardial infarction	Stroke
RCT meta-analysis	0.79 (0.70–0.88)	0.67 (0.55–0.80)	0.84 (0.73–0.98)	1.03 (0.86–1.24)
Observational data	0.51 (0.37–0.70)	0.64 (0.50–0.82)	0.81 (0.74–0.88)	0.68 (0.55–0.84)

"Each of the observational studies and clinical trials are informative and valuable, and there are complementary but only trials tell the truth about treatment effects."

Values are hazard ratios (95% confidence interval) for each outcome, SGLT-2i vs placebo/alternative glucose-lowering therapy
McMurray JJV. *J Am Coll Cardiol* 2018;71:2640–42

Can we really “trust” effect seen in observational studies?

The New England Journal of Medicine

Special Articles

A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS

KJELL BENSON, B.A., AND ARTHUR J. HARTZ, M.D., PH.D.

136 Reports, 19 different treatments

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

99 Reports, 5 clinical topics

…results of well-designed observational studies do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic

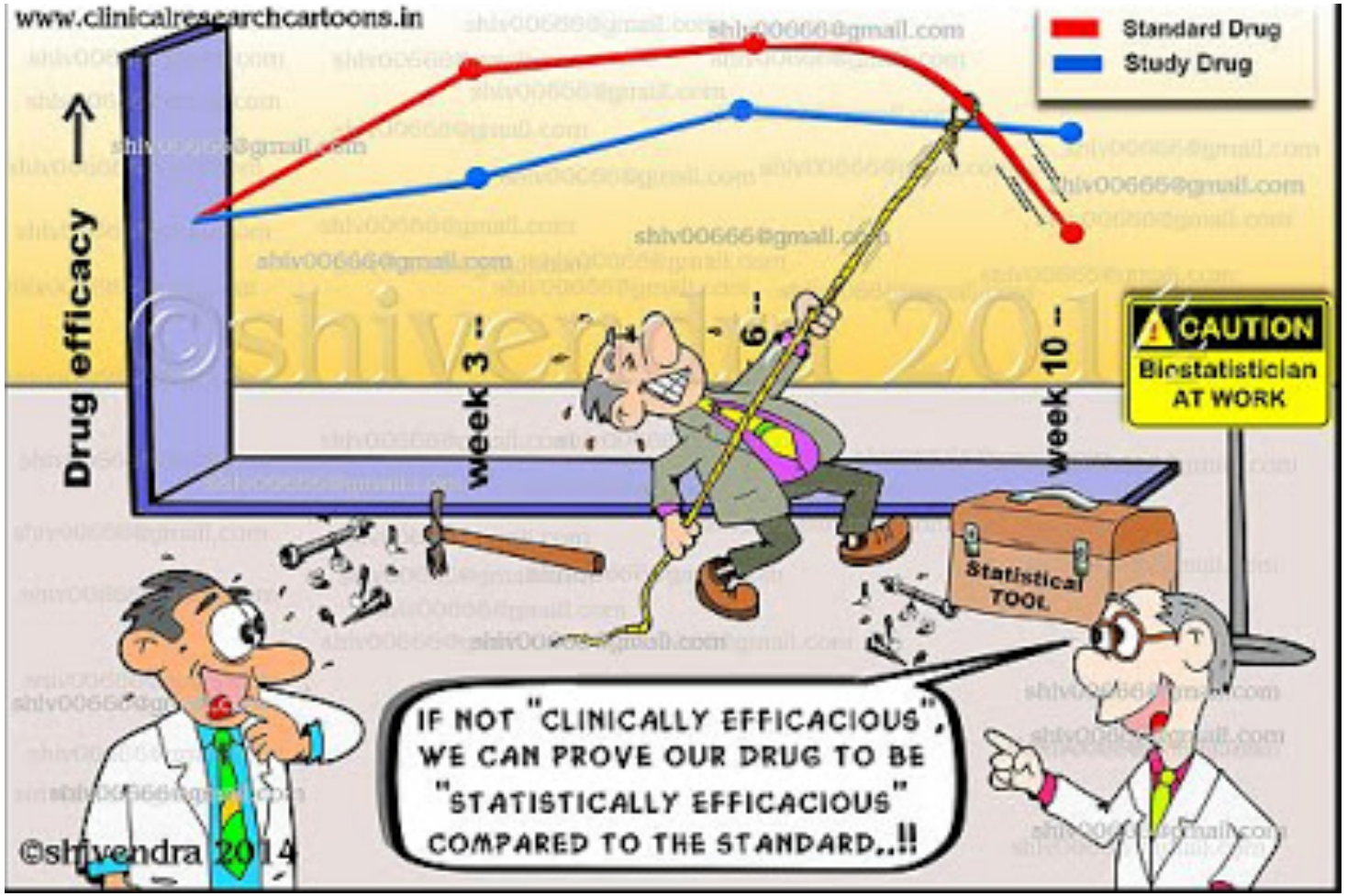
Benson et al. NEJM 2000; 342:1878-1886. 2. Concato J et al. NEJM 2000; 342:1887-1892

However, in RCTs biases might still be there…
…hidden somewhere

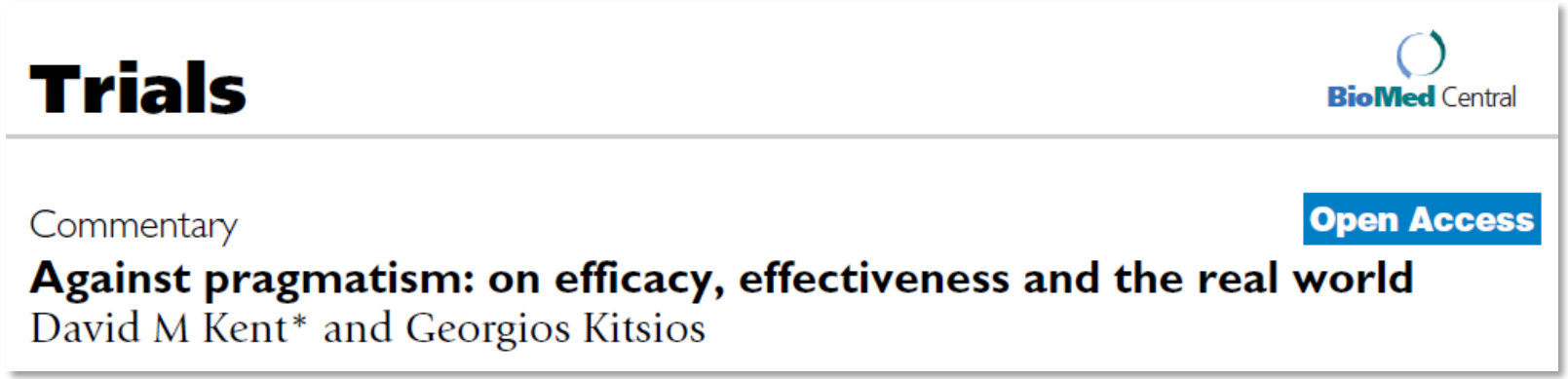
- Subversion Bias (poor concealment)
- Technical Bias
- Attrition Bias
- Consent Bias
- Ascertainment Bias
- Dilution Bias
- Recruitment Bias
- Resentful demoralisation
- Delay Bias
- Chance Bias
- Hawthorne effect
- Analytical Bias
- …

- Schulz JAMA 1995;274:1456. Hewitt et al. BMJ 2005. Brown et al. Stats in Medicine, 2005,24:3715. Kinley et al., BMJ 2002 325:1323
- Berger VW, Weinstein S (2004). Ensuring the Comparability of Comparison Groups: Is Randomization Enough? *Controlled Clinical Trials* 25, 515-524
- Schor, S. (1971). The University Group Diabetes Program: A Statistician Looks at the Mortality Results. *JAMA* 217, 12, 1671-1675.
- Altman, D. G. (1985). Comparability of Randomized Groups. *The Statistician* 34, 125-136.
- Marcus SM (2001). Sensitivity Analysis for Subverting Randomization in Controlled Trials. *Statistics in Medicine* 20, 545-555.
- Jordhoy, M. S., Fayers, P. M., Ahlner-Elmqvist, M., Kaasa, S. (2002). Lack of Concealment May Lead To Selection Bias in Cluster
- Randomized Trials of Palliative Care. *Palliative Medicine* 16, 43-49.
- Matts, J. P. and McHugh, R. B. (1983). Conditional Markov chain design for accrual clinical trials. *Biometrical Journal* 25, 563-577.
- Berger, VW, Christophi, CA (2003). "Randomization Technique, Allocation Concealment, Masking, and Susceptibility of Trials to
- Selection Bias", *JMASM* 2, 1, 80-86.
- Berger, VW (2004). "Selection Bias and Baseline Imbalances in Randomized Trials", *Drug Information Journal* 38, 1-2.
- Berger, VW (2005). *Selection Bias and Covariate Imbalances in Randomized Clinical Trials*, John Wiley & Sons, Chichester.
- Berger, VW (2005). "Quantifying the Magnitude of Baseline Covariate Imbalances Resulting from Selection Bias in Randomized Clinical Trials" (with discussion), *Biometrical Journal* 47, 2, 119-139.
- Berger, VW, Exner, DV (1999). "Detecting Selection Bias in Randomized Clinical Trials", *Controlled Clinical Trials* 20, 319-327.
- Berger, VW (2005). "The Reverse Propensity Score To Manage Baseline Imbalances in Randomized Trials", *Statistics in Medicine* 24
- Berger VW. Selection Bias and Covariate Imbalances in Randomized Clinical Trials 2005: Wiley, Chicester.
- Rosenberger WF, Lachin JM. Randomisation in clinical trials: Theory and practice. Wiley Interscience, 2002, John Wiley and Sons, NY
- …

Where is the “true” effect?



Where to find the “true” effect of a treatment?



- The main point we wish to emphasize is that while both types of trials yield useful information, **pragmatic trials do not provide a more accurate measure of the 'true' treatment effect**, since **the concept of a true effect is fundamentally illusory.**

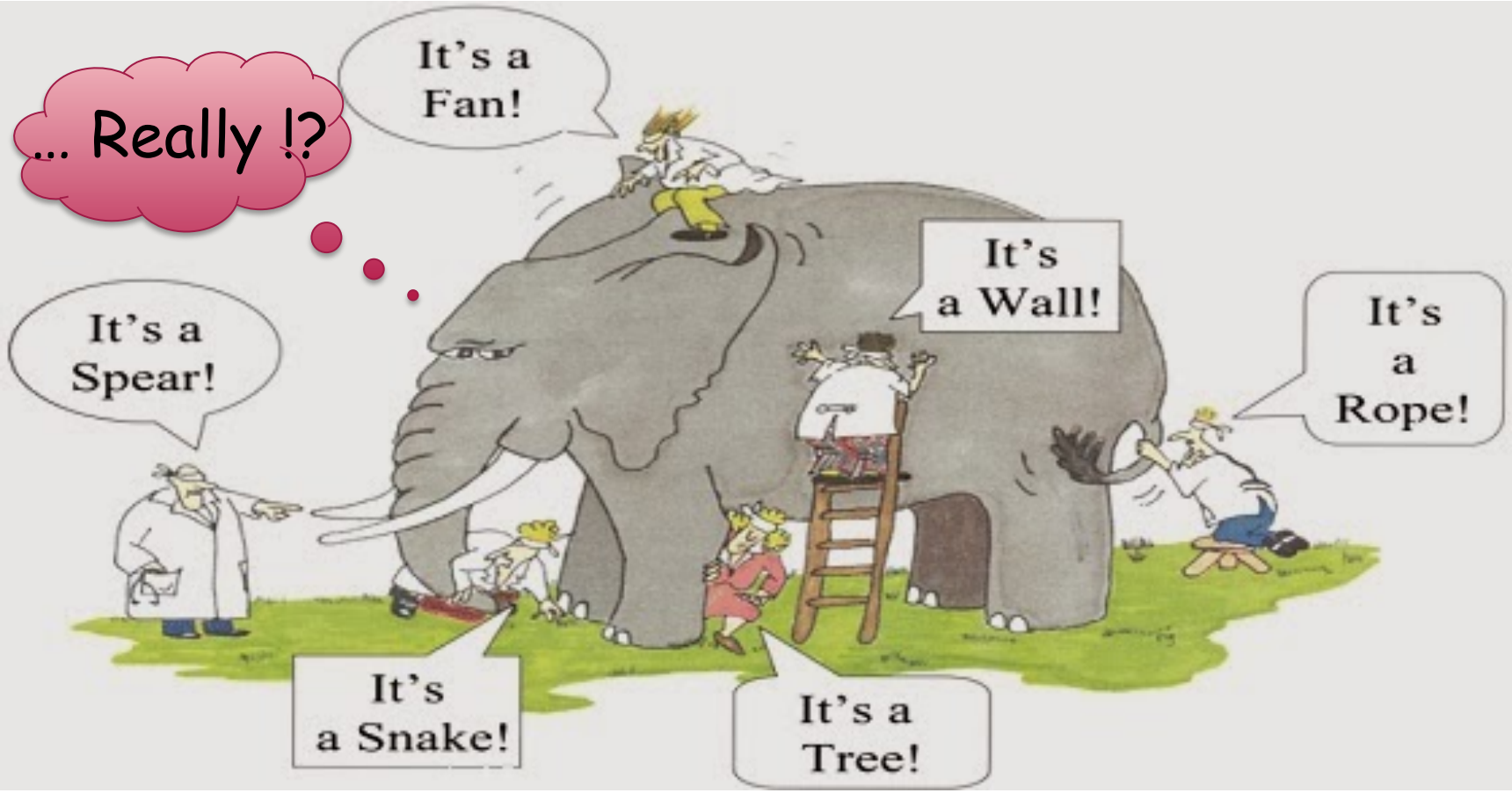
- While **extrapolating the results of efficacy trials to the care of individual patients in the real world can be problematic**, and **requires careful physician judgment and decision-making**, **the same is unfortunately true for the results of effectiveness trials.**

From “double blinded” RCT to the “real” clinical practice

RCTs… it should not be an unconditional “trust”…?

Be Evidence Based, however…. careful about being too much “blinded”…

The metaphor of the blind men *(“scientists”)* and the elephant



Levels of evidence and grades of recommendation: in any case we need 'well-conducted' clinical trials and studies

CVDREAL

Table 2. Oxford Centre levels of the evidence scheme[24]

Level	Description	
1a	Systematic review with homogeneitya of RCTs	
1b	Individual RCT with narrow CI	
1c	All or none[b]	
2a	Systematic review with homogeneity of cohort studies	B: Level 2 or 3 (provided studies are consistent; extrapolations from level 1 studies)
2b	Individual cohort study; low quality RCT (eg, < 80% follow-up)	
2c	Outcome research; ecological studies	
3a	Systematic review with homogeneity of case-control studies	
3b	Individual case-control studies	
4	Case series; poor quality cohort or case-control studies	
5	Expert opinion omitting explicit critical appraisal (includes opinion based upon physiology, bench research, or first principles	ies from any level)

[a]Free of heterogeneity in direction and degree of results between individual studies
[b]Met when all patients used to die before treatment became available, but now some survive. Or, met when some patients used to die but now all survive

Table 1—ADA evidence-grading system for "Standards of Medical Care in Diabetes"

Level of	
	adequately powered, including • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
	• Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including
- Evidence from a well-conducted multicenter trial
- Evidence from a meta-analysis that incorporated quality ratings in the analysis

Supportive evidence from well-conducted cohort studies
- Evidence from a well-conducted prospective cohort study or registry
- Evidence from a well-conducted meta-analysis of cohort studies

Supportive evidence from a well-conducted case-control study

CEBM CENTRE FOR EVIDENCE BASED MEDICINE
UNIVERSITY OF OXFORD
Levels of Evidence (March 2009) www.cebm.net

ADA, American Diabetes Association; CI, confidence interval; RCT, randomized controlled trial

RCT + RWE + NMA = A More Comprehensive Base of Evidence

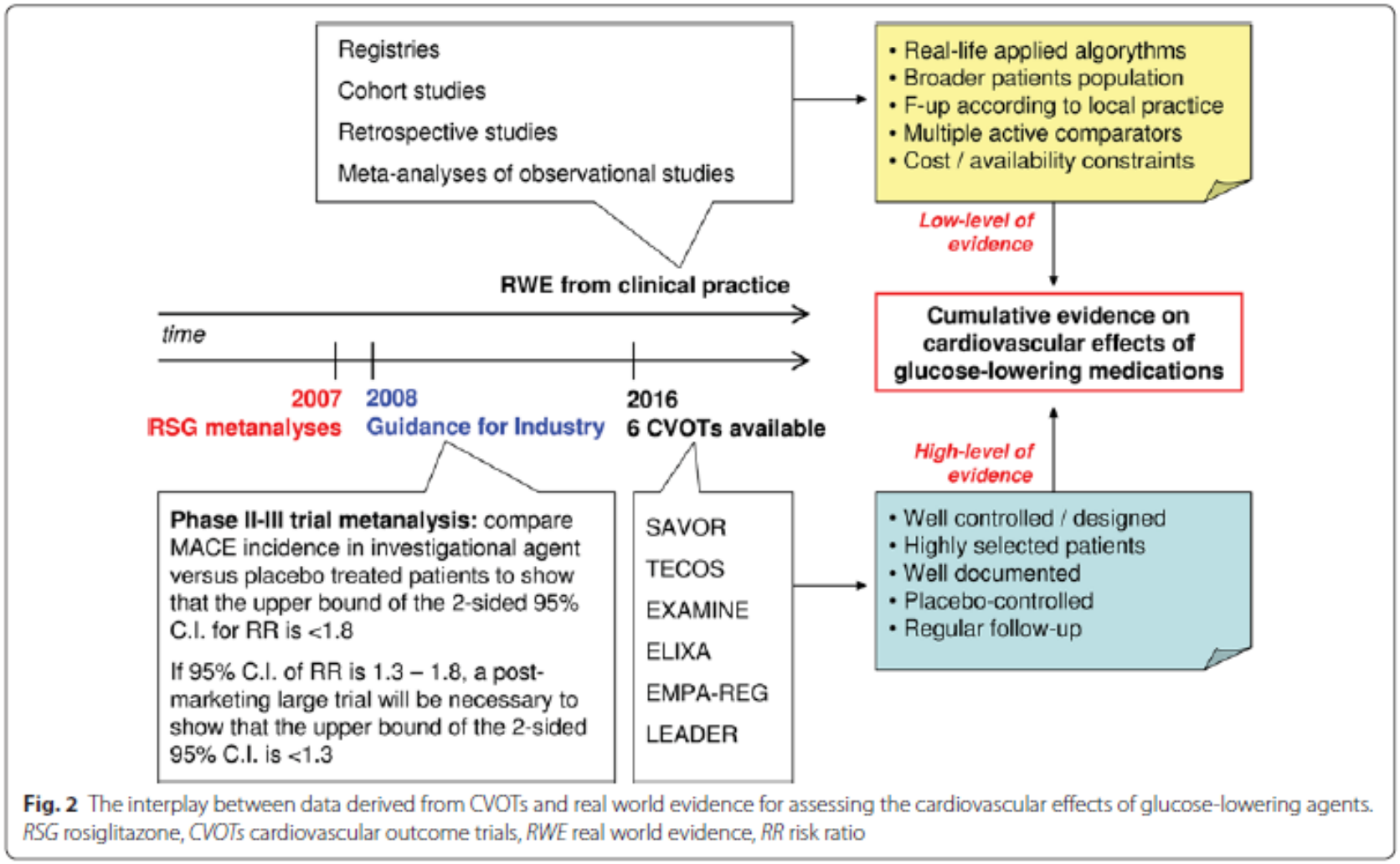
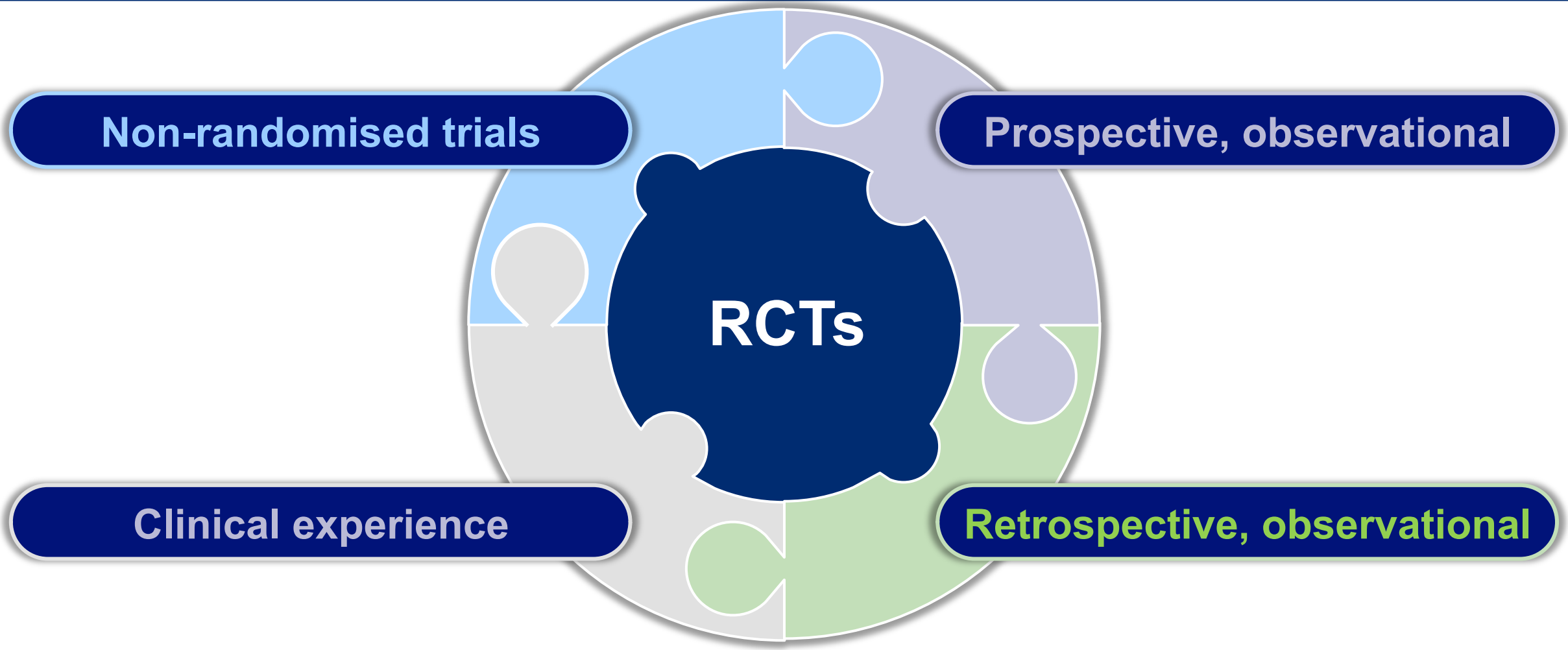


Fig. 2 The interplay between data derived from CVOTs and real world evidence for assessing the cardiovascular effects of glucose-lowering agents. *RSG* rosiglitazone, *CVOTs* cardiovascular outcome trials, *RWE* real world evidence, *RR* risk ratio

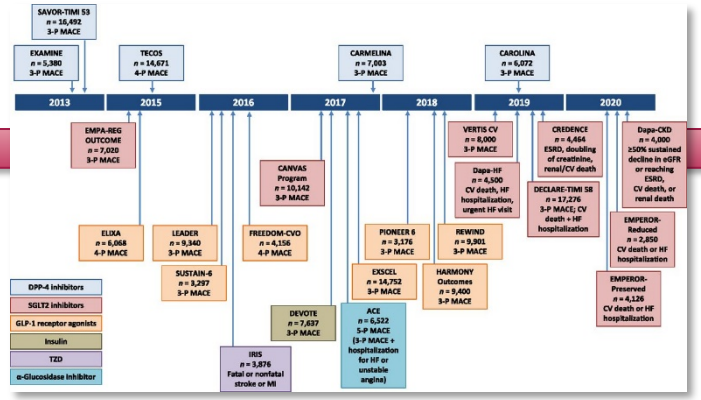
A. Avogaro *et al. Cardiovasc Diabetol (2016) 15:111*

Totality of evidence requires studies that complement



Then “re-thinking” about the need for CVOTs in T2D?…

2008



2018

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

$,$$$ Millions

Summary of New CVOTs in Diabetes

	Study	Composite MACE*	CV Death	MI	Stroke	Any Death	HHF
DPP-4	SAVOR-TIMI53 (saxagliptin)	⇔	⇔	⇔	⇔	⇔	⇑
DPP-4	EXAMINE (alogliptin)	⇔	⇔	⇔	⇔	⇔	⇔
DPP-4	TECOS (sitagliptin)	⇔	⇔	⇔	⇔	⇔	⇔
SGLT2	EMPA-REG OUTCOME (empagliflozin)	⇓	⇓	⇔	⇔	⇓	⇓
GLP-1	ELIXA (lixisenatide)	⇔	⇔	⇔	⇔	⇔	⇔
GLP-1	LEADER (liraglutide)	⇓	⇓	⇔**	⇔	⇓	⇔
GLP-1	SUSTAIN-6 (semaglutide)	⇓	⇔	⇔	⇓ (non-fatal)	⇔	⇔

CVOT: Cardiovascular outcome trial
MACE: Major adverse cardiovascular event
HHF: hospitalization for heart failure
*all studies use 3-point MACE of CV death, MI, and stroke except TECOS and ELIXA which adds hospitalization for unstable angina.
** p<0.05 for individual components of fatal, nonfatal, and silent MI; p=0.046 for composite of fatal, nonfatal, and silent MI

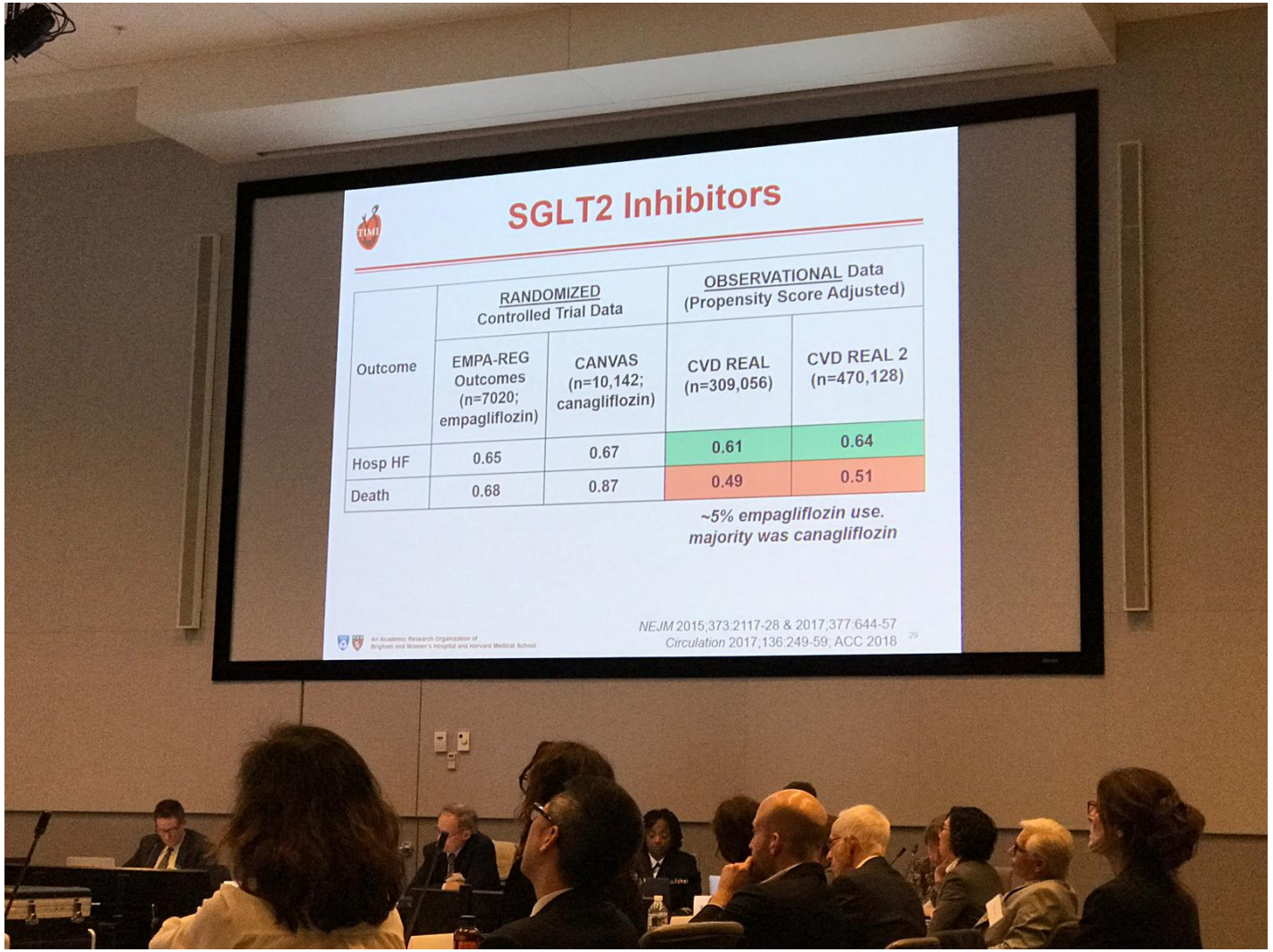
	GLP-1			SGLT2		DPP-4		
MNIADs	Liraglutide	Semaglutide	Lixisenatide	Empagliflozin	Canagliflozin*	Saxagliptin	Alogliptin	Sitagliptin*
CVOT	LEADER	SUSTAIN 6	ELIXA	EMPA-REG	CANVAS	SAVOR	EXAMINE	TECOS
Composite MACE	0.87*	0.74*	1.02	0.86*	0.86*	1.00	0.96	0.98
CV death	0.78*	0.98	0.98	0.62*	0.87	1.03	0.79	1.03
Non-fatal MI	0.88	0.74	1.03^	0.87*	0.85	1.95	1.08	0.95^
Non-fatal stroke	0.89	0.61*	1.12^	1.24	0.90	1.11	0.91	0.97^
Hospitalization for HF	0.87	1.11	0.96	0.65*	0.67	1.27*	1.07	1.00
All-cause mortality	0.85*	1.05	0.94	0.68*	0.87	1.11	0.88	1.01

Oct 25-26, 2018
FDA EMDAC Consultation Meeting:

- Should an unacceptable increase in cardiovascular risk be excluded for all new drugs to improve glycemic control in patients with type 2 diabetes, regardless of the presence or absence of a signal for cardiovascular risk in the development program?

10 Yes vs 9 No

…However…


SGLT2 Inhibitors
RANDOMIZED Controlled Trial Data
OBSERVATIONAL Data (Propensity Score Adjusted)
Outcome
EMPA-REG Outcomes (n=7020; empagliflozin)
CANVAS (n=10,142; canagliflozin)
CVD REAL (n=309,056)
CVD REAL 2 (n=470,128)
Hosp HF
0.65
0.67
0.61
0.64
Death
0.68
0.87
0.49
0.51
~5% empagliflozin use. majority was canagliflozin
NEJM 2015;373:2117-28 & 2017;377:644-57
Circulation 2017;136:249-59; ACC 2018

Next Steps for the Real World Evidence Endeavour

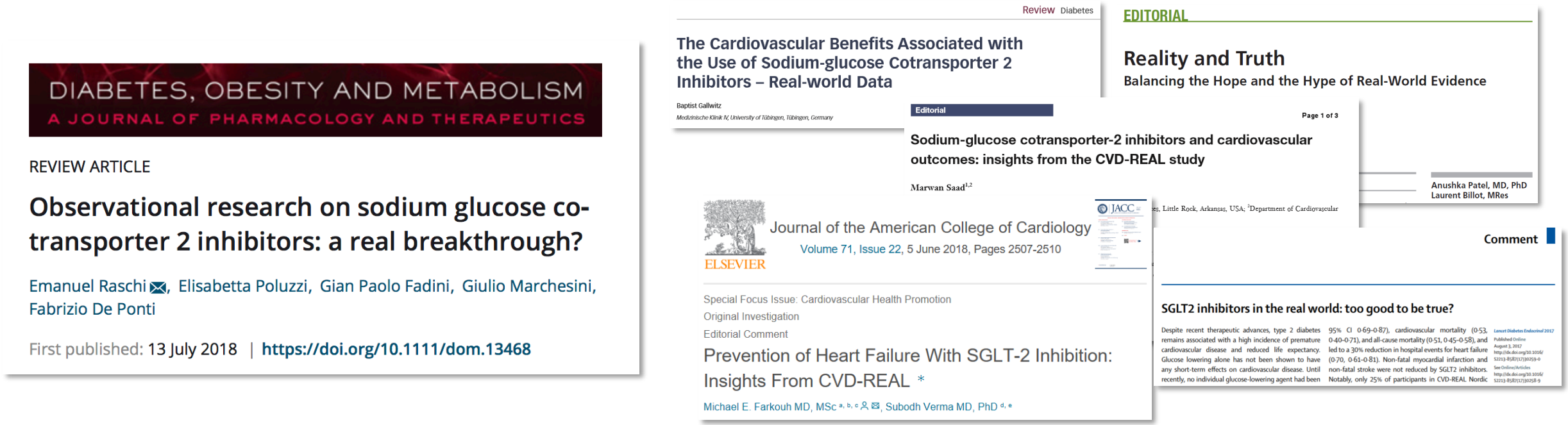
"…traditional concepts of hierarchies of evidence should be replaced by instead selecting evidence based on the research question"

"A need for regulators and health technology assessment (HTA) bodies to provide further clarity on the acceptability of RWE and provide guidance on where different types of RWE might be applied to assess safety, efficacy and effectiveness"

Academy of Medical Sciences. Next steps for using real world evidence, 2018. Available at: https://acmedsci.ac.uk/more/news/next-steps-for-using-real-world-evidence (Accessed June 2018)

https://professional.diabetes.org/meeting/clinical-and-research-symposia/2018-research-symposium

CVD-REAL: in the literature



DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

REVIEW ARTICLE

Observational research on sodium glucose co-transporter 2 inhibitors: a real breakthrough?

Emanuel Raschi, Elisabetta Poluzzi, Gian Paolo Fadini, Giulio Marchesini, Fabrizio De Ponti

First published: 13 July 2018 | https://doi.org/10.1111/dom.13468

Review Diabetes

The Cardiovascular Benefits Associated with the Use of Sodium-glucose Cotransporter 2 Inhibitors – Real-world Data

Baptist Gallwitz
Medizinische Klinik IV, University of Tübingen, Tübingen, Germany

EDITORIAL

Reality and Truth
Balancing the Hope and the Hype of Real-World Evidence

Anushka Patel, MD, PhD
Laurent Billot, MRes

Editorial

Page 1 of 3

Sodium-glucose cotransporter-2 inhibitors and cardiovascular outcomes: insights from the CVD-REAL study

Marwan Saad[1,2]

[1]...es, Little Rock, Arkansas, USA; [2]Department of Cardiovascular

ELSEVIER

Journal of the American College of Cardiology
Volume 71, Issue 22, 5 June 2018, Pages 2507-2510

JACC

Special Focus Issue: Cardiovascular Health Promotion
Original Investigation
Editorial Comment

Prevention of Heart Failure With SGLT-2 Inhibition: Insights From CVD-REAL *

Michael E. Farkouh MD, MSc [a, b, c], Subodh Verma MD, PhD [d, e]

Comment

SGLT2 inhibitors in the real world: too good to be true?

Despite recent therapeutic advances, type 2 diabetes remains associated with a high incidence of premature cardiovascular disease and reduced life expectancy. Glucose lowering alone has not been shown to have any short-term effects on cardiovascular disease. Until recently, no individual glucose-lowering agent had been

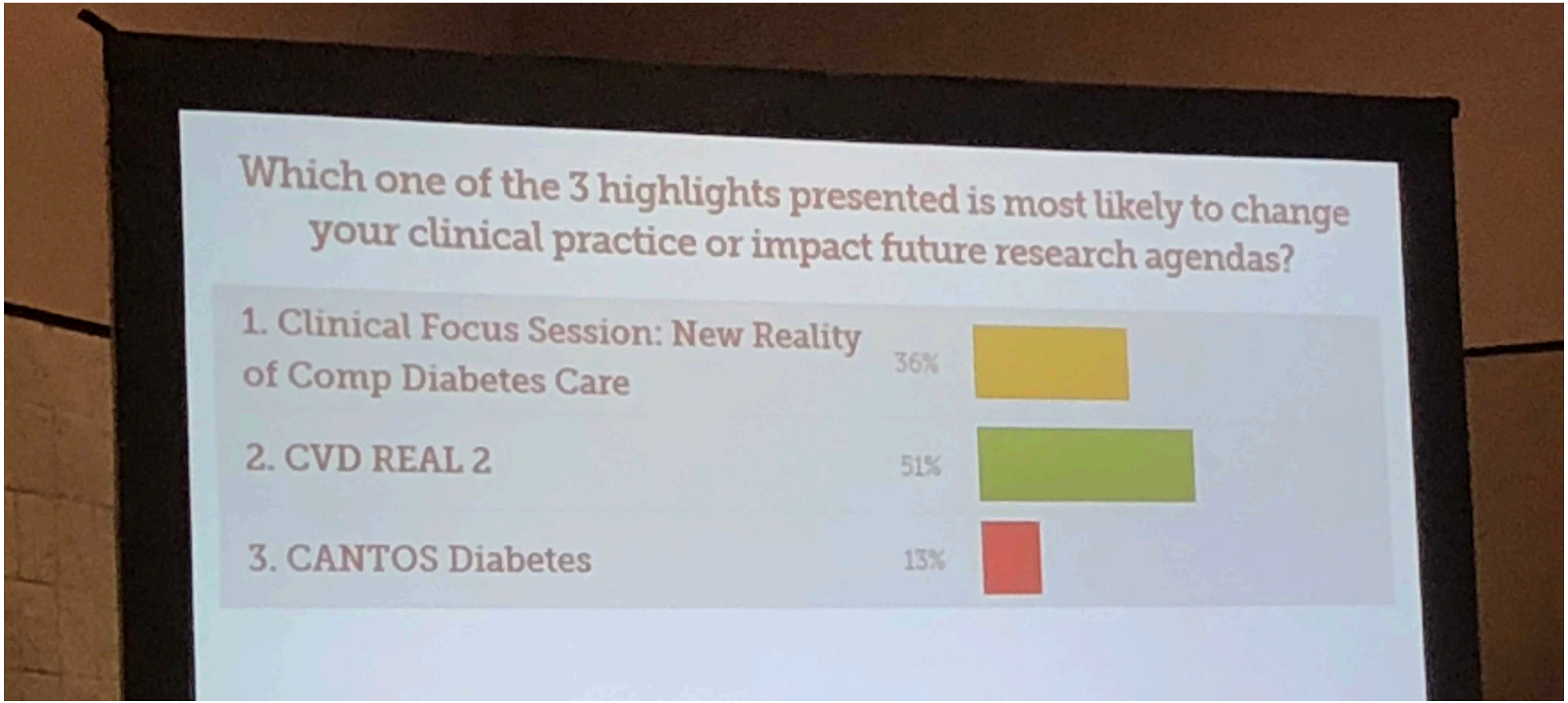
95% CI 0·69–0·87), cardiovascular mortality (0·53, 0·40–0·71), and all-cause mortality (0·51, 0·45–0·58), and led to a 30% reduction in hospital events for heart failure (0·70, 0·61–0·81). Non-fatal myocardial infarction and non-fatal stroke were not reduced by SGLT2 inhibitors. Notably, only 25% of participants in CVD-REAL Nordic

"Large pharmaco-epidemiological research studies such CVD-REAL should be commended for advancing knowledge by pooling such a large amount of prescription data and providing data on a heterogeneous cohort of patients with T2DM. Overall, data from observational cohort studies are not only in agreement with those from RCTs, but also found a larger benefit as compared to CVOTs in a population with lower CV risk. Notwithstanding these impressive results and sophisticated statistical techniques, we cannot firmly conclude for a class effect yet, and uncertainty remains especially on safety issues

…the heterogeneity of cohorts stresses the importance of assessing patients for comparability before data pooling"

CV, cardiovascular; CVD-REAL, CardioVascular events in Diabetes – Reduction of Events According to real Life data; CVOT, cardiovascular outcomes trial; RCT, randomized controlled trial; RWE, real world evidence; T2DM, type 2 diabetes mellitus

What Science Can Do… What RWE Can Do!



CVD-REAL: Impact on Treatment Guidelines

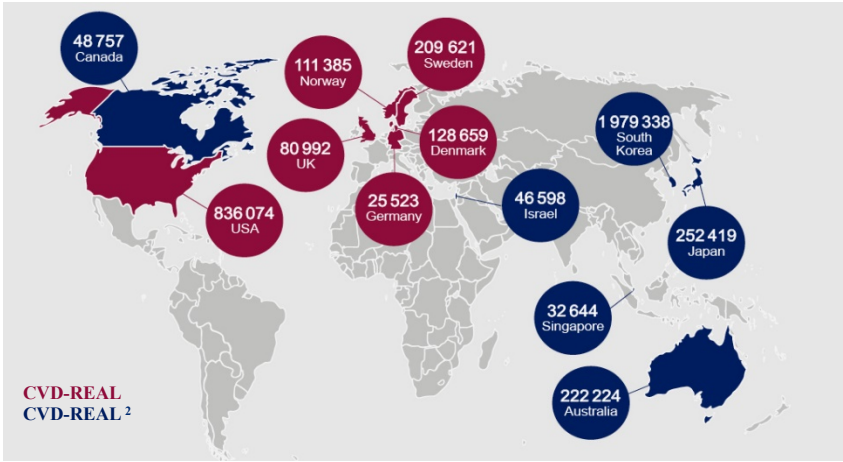
- CVD-REAL data incorporated in international guidelines
  - HF guidelines in Japan[1]
  - Diabetes guidelines in Taiwan[2], Singapore[3] and Denmark[4]
- Being included in various documents that are currently in development
  - AHA
  - ACC
  - ADA
  - Others
- Interest from major payers in US, EU, and Asia

ACC, American College of Cardiology; ADA, American Diabetes Association; AHA, American Heart Association; HF, heart failure

1. Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (JCS 2017/JHFS 2017) http://www.j-circ.or.jp/guideline/pdf/JCS2017_tsutsui_h.pdf
2. Chiang *et al.* Journal of the Chinese Medical Association 81 2018:189-222
3. Appropriate care guide for Oral glucose-lowering agents in type 2 diabetes mellitus – an update – July 2017
4. Farmakologisk behandling af type 2-diabetes 2018. https://vejledninger.dsam.dk/media/files/4/guidelines-2018-final.pdf

CVD-REAL: Future Directions

- Drilling down for answers
- Laboratory data
  - eGFR
- Imaging data
  - LVEF
- New countries being added (Finland, Taiwan, Spain, Portugal, …)
- Potential ability to examine epidemiologic trends in the adoption of T2D therapies, use in clinical practice, and associated outcomes
  - Across geographic regions
  - Temporal trends
- Potential ability to monitor safety
  - Across classes and specific agents



eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction. Adapted from www.cvdreal.com. Last accessed 26th September 2018

Easy to Navigate the Real World Evidence Sea?

- *Yes*
  - *with specific expertise and caution… &… full understanding of what we are talking about…&*

  - *…keeping always a "fair and balanced" mindset and interpretation of the results!*


THANKS!
THIS IS JUST THE BEGINNING