Emulating randomized clinical trials with non-randomized real-world evidence studies

Results from the RCT DUPLICATE* initiative

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*Randomized Controlled Trials Duplicated Using Prospective Longitudinal Insurance Claims: Applying Techniques of Epidemiology

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Disclosures Dr. Schneeweiss

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Harvard study team:

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Research Staff: Dr. Pawar, Besette, Lee, Gautham, Chin, Dr. D'Andrea, Dr. Gopalakrishna, Jawaid, Jin, Lee, Dr. Mahesri, Sears, Tesfaye, Umarje, York, Zabotka, Zakoul

Aetion team: Drs. Garry, Rassen, and Isaman, Gibbs, Gilpin

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Expert advisor panel:*

Drs. Steve **Goodman**, Stanford; Miguel **Hernan**, Harvard; Wayne **Ray**, Vanderbilt; Samy **Suissa**, McGill; Alan **Brookhart**, Duke

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Real-World Evidence (RWE) studies

Randomized controlled trials are an accepted research study design to establish the efficacy of medical products

RWE is based on data produced by the routine operation of the healthcare system

It is thought to complement and expand the evidence generated by RCTs and often expands the line of inquiry into

- Different populations
- Different treatment patterns
- Different endpoints
- Different comparators

Can RWE studies estimate causal treatment effects?

We wish to calibrate RWE findings against the true causal treatment effect

-> Can we ever know the true treatment effect in a given population?

If not, what is the next best thing?

- Relying on expert opinion – no!
- Statistical simulation studies – no!
- Comparisons against RCT findings:
  Based on the assumption that a well-planned and well executed RCT is accepted as having a causal interpretation – possibly?

Why is this so important?

If RWE cannot estimate causal treatment effects, what is the point of doing RWE?

What some RWE proponents say:

"RWE studies answer different questions than RCTs and therefore you should never expect the same findings," "you should not compare; it may backfire"

Translates to: "We can never test the validity of RWE because we don't have an agreeable gold standard to test against"

> So where does that leave us? With the conclusion that, for RWE, there is no real upside to the RCT replication endeavor—only downside. *David Thompson, Value Health 2021*

Karl Popper noted that if a hypothesis evades testability it is not a viable hypothesis.

What some RCT proponents say:

"RWE studies have never been able to convincingly demonstrate that they have causal conclusions like RCTs have"

Translates to: "The bar is set high and we are open to listen but doubt that RWE will ever be trusted"

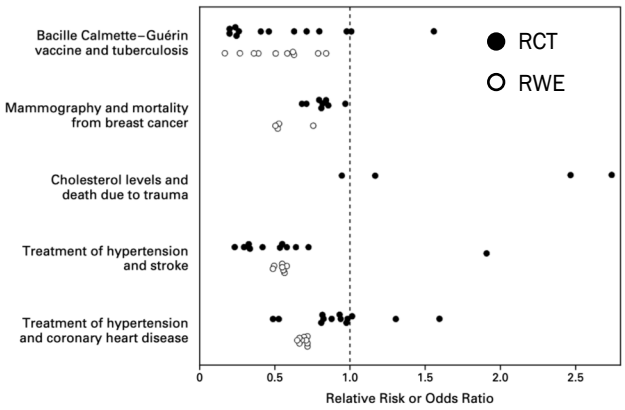
What we don't mean:

We don't want to imply that all RWE studies need to calibrate against an RCT – that would defeat the purpose of RWE as it is meant to complement RCT evidence

Variability in RCT-to-RCT and in RWE-to-RWE comparisons

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.



Considerations of RCT emulation

RCT $\overset{?}{\leftrightarrow}$ RCT $\overset{?}{\leftrightarrow}$ RWE $\overset{?}{\leftrightarrow}$ RWE

RCT $\overset{!}{\neq}$ RWE

This is what we are really interested in quantifying

1) Agreement with what?
- How variable are RCT results?
- What is the true treatment effect in the study population?

…

2) Emulation failure?
- Different population
- Different treatment pattern
- Different outcome measure
- Different follow-up duration

…

3) Bias?
- Confounding
- Differential surveillance
- Time-related biases

…

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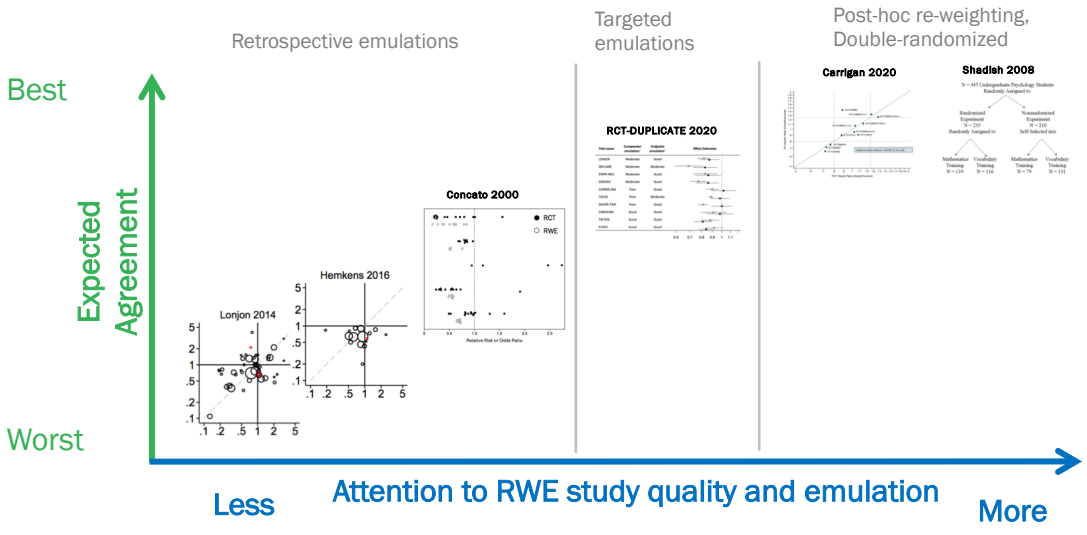
Range of RCT emulation successes by RWE studies



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RCT-DUPLICATE objectives

Aimed to understand and improve the validity of RWE studies for regulatory decision making

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Nonrandomized Real-World Evidence to Support Regulatory Decision Making: Process for a Randomized Trial Replication Project

Jessica M. Franklin[1]*, Ajinkya Pawar[1], David Martin[2], Robert J. Glynn[1], Mark Levenson[3], Robert Temple[3] and Sebastian Schneeweiss[1]

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Replicate **30 RCTs** and predict **7 RCTs** considered by FDA

Learnings:
Had we replaced an RCT with a single RWE study would we have come to the same decision?

2

Test a **process** with FDA to conduct and submit RWE studies

Learnings:
Can we successfully enable transparent and reproducible RWE and enable regulators to re-analyze data?

3

Factors that predict replication success, causal estimates

Learnings:
Identify factors that predictably increase validity of RWE studies.

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Data sources

U.S. longitudinal claims data

- Enrollment and disenrollment dates
- Patient-level information on visits, hospitalizations, pharmacy fills, death
- Including service date, diagnoses, procedures, and drug ingredients

- Optum Clinformatics: Commercial, incl. Medicare Advantage
- IBM MarketScan: Commercial, incl. Medicare Advantage
- Medicare FFS: Beneficiaries 65 years and older

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RCT selection strategy: Breadth

1. Mix of regulatory submissions:
    1. Primary approvals
    2. Supplemental approvals
    3. Negative trials
    4. FDA special interest
2. Mix of therapeutic areas
3. Mix of comparator: Placebo, active
4. Mix of hypothesis testing intention: Superiority, non-inferiority

RCT selection strategy: Data fit-for-purpose

5. Outcome observable?
6. Treatment observable?
7. Key inclusion criteria observable?
8. Key exclusion criteria observable?
9. Key pre-exposure outcome predictors observable?

RWE study design and analysis strategy

1. Emulate the target trial -> new-user active-comparator cohort study
2. Emulate inclusion/exclusion criteria as best as possible given the data
3. Adjustment for baseline imbalances using 1:1 propensity score matching on >100 pre-exposure covariates
4. Validated outcome definitions when available w/ focus on highly specific definitions
5. We wanted to emulate an RCT ITT analysis with perfect compliance (>90%); in light of suboptimal real-world adherence we used an on-treatment analysis
6. One single pre-defined analysis
7. A single investigator team plus clinical and methodological advisors
8. Few sensitivity analyses if any for this iteration

Process and feasibility

- Trial Design
  - Treatment arms
  - Population and exclusions
- RWE Emulation Study Design
- Feasibility: power
- Feasibility: baseline balance

- Well emulated
- Sufficiently emulated
- Difficult to emulate

PARADIGM-HF (Phase 3)

Inclusion

Age>=18, HFrEF, HF hospitalization within 12 months
Stable on ACEis/ARBs and beta-blocker therapies

Exclusion

- Allergy, intolerance, and contraindication to any of the study drugs
- History of angioedema
- Treatment with both ACEis AND ARBs
- Acute decompensated HF
- Symptomatic hypotension
- Low eGFR/renal dysfunction
- Hyperkalemia
- ACS, Stroke, TIA, CABG, PCI, Other CV Procedures, Carotid Angioplasty within 3 months
- Coronary/carotid artery disease or PCI within 6 mo. after visit 1
- CRT device within 3 months prior to visit 1 or intent to implant
- History of heart transplant, on transplant list, or with LVAD
- History of severe pulmonary disease
- Peripartum- or chemotherapy- induced cardiomyopathy
- Untreated ventricular arrhythmia with syncopal episodes
- Symptomatic bradycardia or 2nd & 3rd degree AV block
- Hemodynamically significant mitral and/or aortic valve disease
- Active IBD, Duodenal/gastric ulcers
- Hepatic disease
- Cholestyramine or colestipol resins
- Presence of any disease with a life expectancy of <5 years
- *Ivabradine use*

Process and feasibility

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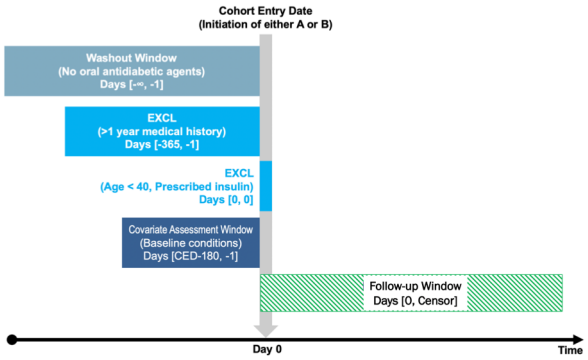
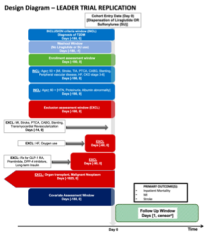


Target trial emulation:
New-user active-comparator cohort study

Clear temporality, no adjustment for intermediates, no immortal time bias, no depletion of susceptibles



This is an example;
all details are on clinicaltrials.gov

Process and feasibility

- Trial Design
  - Treatment arms
  - Population and exclusions
- RWE Emulation Study Design
- Feasibility: power
- Feasibility: baseline balance

	MarketScan		Optum		Medicare	
	Sacubitril/ Valsartan	ACEI	Sacubitril/ Valsartan	ACEI	Sacubitril/ Valsartan	ACEI
Unmatched						
N Patients	1,476	2,218	2,729	4,217	1,738	6,293
N Outcomes	592		1,435		1,992	
Follow Up	111	118	92	99	86	81
Matched						
N Patients	743	743	1278	1,278	1,008	1,008
N Outcomes	–		–		–	
Follow Up	137	126	109	118	107	102

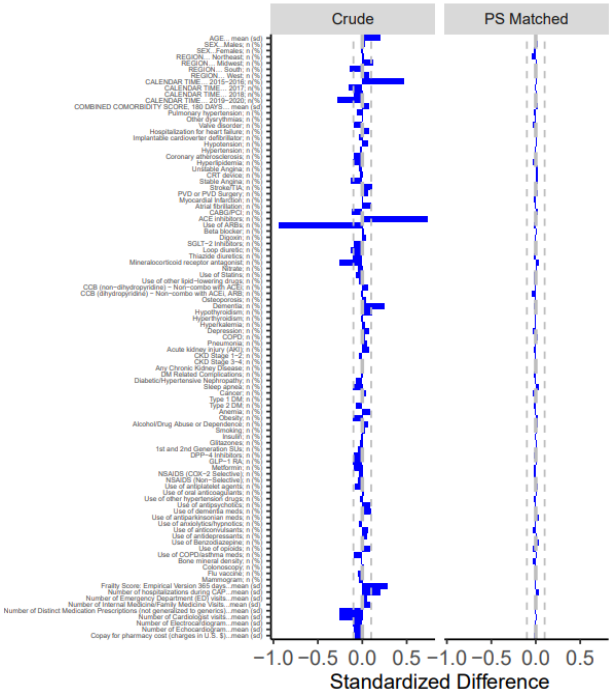
	MarketScan	Optum	Medicare	Pooled
# Matched patients	1,486	2,556	2,016	6,058
Risk per 1,000 patients	160.3	206.6	248.3	215.3
Desired HR from RCT	0.8	0.8	0.8	0.8
Alpha (2-sided)	0.05	0.05	0.05	0.05
Number of events expected	238	528	501	1,304
Power	0.41	0.73	0.70	0.98

This is an example;
all details are on clinicaltrials.gov

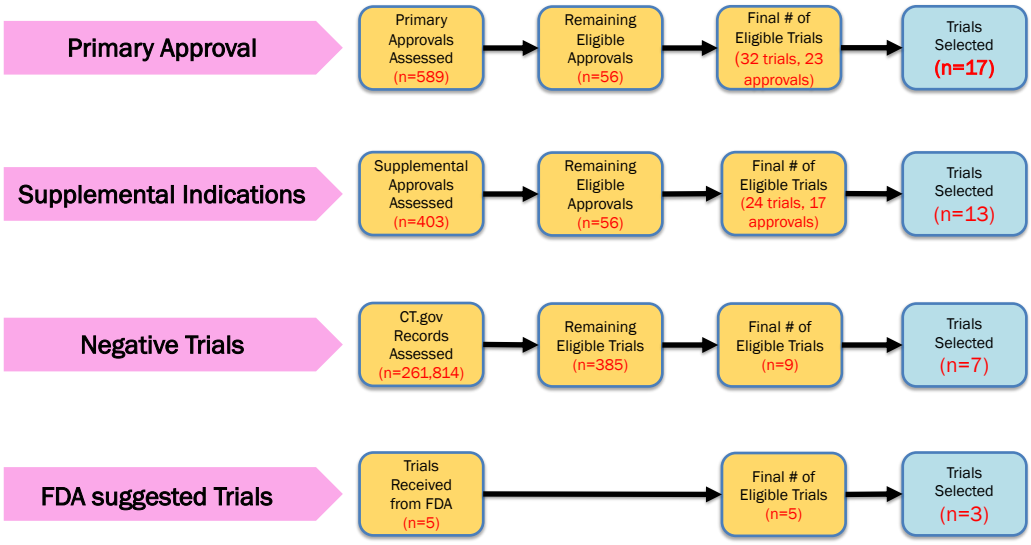
Process and feasibility

- Trial Design
  - Treatment arms
  - Population and exclusions
- RWE Emulation Study Design
- Feasibility: power
- Feasibility: baseline balance

Adjusted for >100 pre-exposure covariates:
- Demographics, region, calendar time, disease risk score
- CVD and non-CVD comorbidities
- CVD and non-CVD medications
- Proxies of healthcare utilization, SES



Selecting 30 regulatory-standard RCTs for replication



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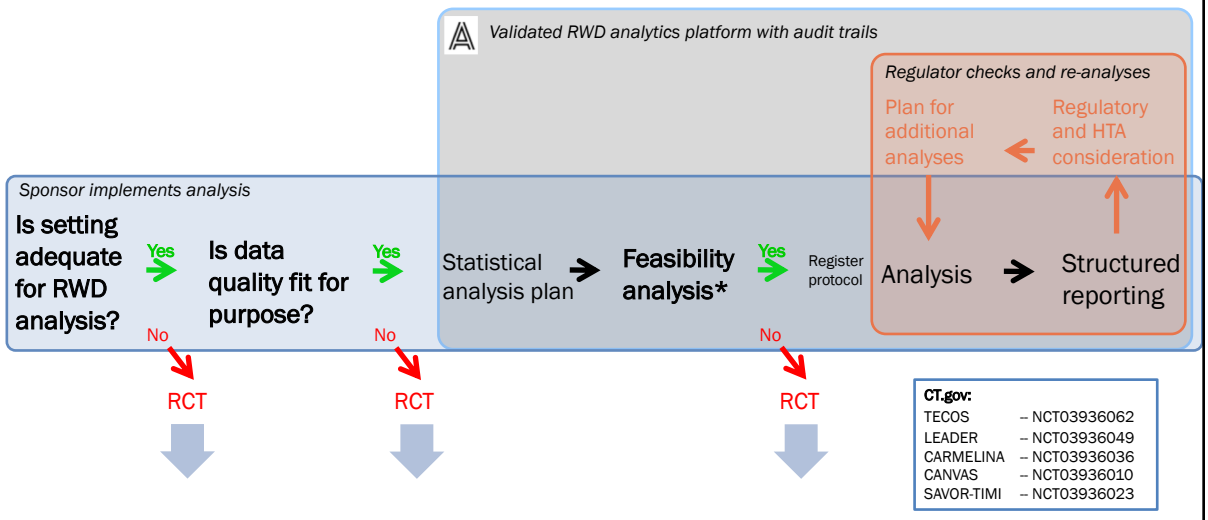
A pathway with regulatory validation



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* Feasibility analysis can include 1) checking covariate balance after applying the chosen confounding adjustment strategy, 2) checking statistical power, 3) evaluating positive or negative control outcomes, and 4) other analyses, *without* evaluating the study outcomes in the two treatment groups.

Examples for dropping RCTs during feasibility check

Trial Group	Trial Name	Reason for Dropping
Antiplatelet	CLARITY-TIMI 28	Assessed treatments given during hospitalization and cannot be emulated with outpatient dispensing data
Antiplatelet	COMMIT	Assessed treatments given during hospitalization and cannot be emulated with outpatient dispensing data
Antiplatelet	TRA 2P - TIMI 50	Low number of vorapaxar users
Antiplatelet	PROFESS	Low number of aspirin/dipyridamole users
Antiplatelet	PEGASUS-TIMI	Low number of patients using ticagrelor beyond 1 year after myocardial infarction

Study implementation with the Aetion Evidence Platform to reduce error, increase transparency

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AETION

Transparency

CT.gov registration:

- Complete protocol of each emulation

Comparative analysis starts after registration

1. **RCT Details**
2. **Person responsible for implementation of replication in Aetion**
3. **Data Source(s)**
4. **Study Design Diagram**
5. **Cohort Identification**
   - 5.1 Inclusion/exclusion criteria for cohort entry
   - 5.2 Flowchart of the study cohort assembly
6. **Variables**
   - 6.1 Exposure-related variables:
   - 6.2 Preliminary Covariates:
   - 6.3 Outcome variables and study follow-up:
7. **Initial Feasibility Analysis**
   - Aetion report name:
   - Date conducted:
8. **Initial Power Assessment**
9. **Balance Assessment after PS matching**
   - Aetion report name:
   - Date conducted:
10. **Final Power Assessment**
    - Aetion report name:
    - Date conducted:
11. **Study Confidence and Concerns**
12. **Register study protocol on clinicalTrials.gov**
13. **Comparative Analyses**
    - Aetion report name:
    - Date conducted:
14. **Requested Results**
15. **References**

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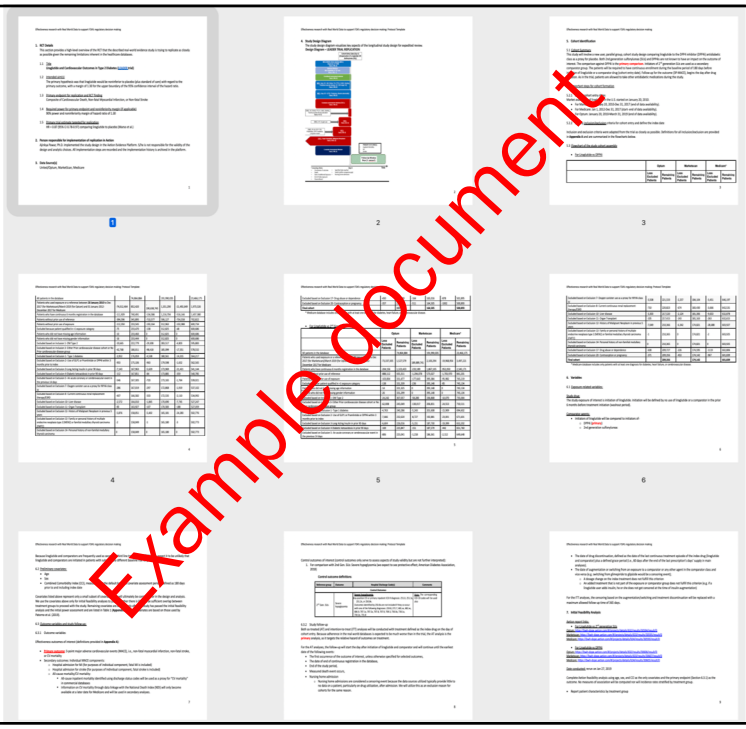
Transparency

ClinicITrials.gov registration:

- Complete protocol of each emulation
- Incl. hotlinks to the Aetion Evidence Platform:
  - Inspect definitions
  - Inspect audit trails
  - Reproduce analyses
  - Make changes and run sensitivity analyses
  - Produce additional reports



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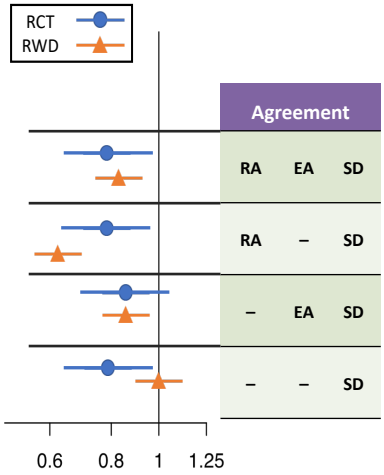
Pre-defined agreement assessment

Regulatory agreement (RA)
Interpretation of the RWE and RCT results would lead to equivalent regulatory decisions based on p<0.05

Estimate agreement (EA)
Estimates for RWE fell within the 95% confidence interval of the RCT results

Numeric difference in estimate (SD)
Difference between the RWE and RCT estimates, on a standardized scale



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Emulation quality assessment

Comparator emulation:

Good	if RCT has active comparator
Moderate	if RCT has placebo comparator that was emulated by other drug (unrelated to outcome) and used in similar patients
Poor	if RCT has placebo comparator that was emulated by other drug (unrelated to outcome) and used in different patients

Endpoint emulation:

Good	if endpoint measurement has high specificity
Moderate	if endpoint measurement has moderate specificity

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Overview 1-10

		Trial name	RCT Exposure	RCT Comparator	RWE emulation Exposure	RWE emulation Comparator	RCT Outcome	RWE Emulation
2nd-line Antidiabetics	1	LEADER	Liraglutide (GLP1)	Placebo	Liraglutide	DPP4i	3p MACE	
	2	DECLARE	Dapagliflozin (SGLT2)	Placebo	Dapagliflozin	DPP4i	HHF + CV death	
	3	EMPA-REG	Empagliflozin (SGLT2)	Placebo	Empagliflozin	DPP4i	3p MACE	
	4	CANVAS	Canagliflozin (SGLT2)	Placebo	Canagliflozin	DPP4i	3p MACE	
	5	CARMELINA	Linagliptin (DPP4i)	Placebo	Linagliptin	Sulfonylureas	3p MACE	
	6	TECOS	Sitagliptin (DPP4i)	Placebo	Sitagliptin	Sulfonylureas	3p MACE+ angina	
	7	SAVOR-TIMI	Saxagliptin (DPP4i)	Placebo	Saxagliptin	Sulfonylureas	3p MACE	
	8	CAROLINA	Linagliptin (DPP4i)	Glimerpiride	Linagliptin	Glimerpiride	3p MACE	
Antiplatelets	9	TRITON	Prasugrel	Clopidogrel	Prasugrel	Clopidogrel	3p MACE	
	10	PLATO	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	3p MACE	

MACE = Major adverse cardiovascular events

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Comparator emulation:

Good | Moderate | Poor

			RCT		RWE emulation		RCT	RWE
		Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
2nd-line Antidiabetics	1	LEADER	Liraglutide (GLP1)	Placebo	Liraglutide	DPP4i	3p MACE	
	2	DECLARE	Dapagliflozin (SGLT2)	Placebo	Dapagliflozin	DPP4i	HHF + CV death	
	3	EMPA-REG	Empagliflozin (SGLT2)	Placebo	Empagliflozin	DPP4i	3p MACE	
	4	CANVAS	Canagliflozin (SGLT2)	Placebo	Canagliflozin	DPP4i	3p MACE	
	5	CARMELINA	Linagliptin (DPP4i)	Placebo	Linagliptin	Sulfonylureas	3p MACE	
	6	TECOS	Sitagliptin (DPP4i)	Placebo	Sitagliptin	Sulfonylureas	3p MACE+ angina	
	7	SAVOR-TIMI	Saxagliptin (DPP4i)	Placebo	Saxagliptin	Sulfonylureas	3p MACE	
	8	CAROLINA	Linagliptin (DPP4i)	Glimerpiride	Linagliptin	Glimerpiride	3p MACE	
Antiplatelets	9	TRITON	Prasugrel	Clopidogrel	Prasugrel	Clopidogrel	3p MACE	
	10	PLATO	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	3p MACE	

MACE = Major adverse cardiovascular events

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Endpoint emulation:

Good | Moderate

			RCT		RWE emulation		RCT	RWE
		Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
2nd-line Antidiabetics	1	LEADER	Liraglutide (GLP1)	Placebo	Liraglutide	DPP4i	3p MACE	
	2	DECLARE	Dapagliflozin (SGLT2)	Placebo	Dapagliflozin	DPP4i	HHF + CV death	HF IP any position, no cause of death
	3	EMPA-REG	Empagliflozin (SGLT2)	Placebo	Empagliflozin	DPP4i	3p MACE	
	4	CANVAS	Canagliflozin (SGLT2)	Placebo	Canagliflozin	DPP4i	3p MACE	
	5	CARMELINA	Linagliptin (DPP4i)	Placebo	Linagliptin	Sulfonylureas	3p MACE	
	6	TECOS	Sitagliptin (DPP4i)	Placebo	Sitagliptin	Sulfonylureas	3p MACE+ angina	Angina non-specific
	7	SAVOR-TIMI	Saxagliptin (DPP4i)	Placebo	Saxagliptin	Sulfonylureas	3p MACE	
	8	CAROLINA	Linagliptin (DPP4i)	Glimerpiride	Linagliptin	Glimerpiride	3p MACE	
Antiplatelets	9	TRITON	Prasugrel	Clopidogrel	Prasugrel	Clopidogrel	3p MACE	
	10	PLATO	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	3p MACE	

MACE = Major adverse cardiovascular events

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Overview 11-20

		Trial name	RCT Exposure	RCT Comparator	RWE emulation Exposure	RWE emulation Comparator	RCT Outcome	RWE Emulation
DOAC AF	11	ARISTOTLE	Apixaban	Warfarin	Apixaban	Warfarin	Stroke/Systemic Embolism	
DOAC AF	12	RE-LY	Dabigatran	Warfarin	Dabigatran	Warfarin	Stroke/Systemic Embolism	
DOAC AF	13	ROCKET-AF	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin	Stroke/Systemic Embolism	
DOAC DVT	14	EINSTEIN-DVT	Rivaroxaban	Enoxaparin/ VKA	Rivaroxaban	Warfarin	VTE	
DOAC DVT	15	RE-COVER II	Dabigatran	Warfarin	Dabigatran	Warfarin	VTE / VTE Related Death	
DOAC DVT	16	AMPLIFY	Apixaban	Enoxaparin/ warfarin	Apixaban	Warfarin	VTE / VTE Related Death	
Heart failure	17	PARADIGM-HF	Sacubitril/ Valsartan	Enalapril	Sacubitril/ Valsartan	ACEi	HHF/ Mortality	
Anti-HTN	18	TRANSCEND	Telmisartan	Placebo	Telmisartan + Loop/CCB /TZ	Loop/CCB/ TZ	3p MACE + HHF	
Anti-HTN	19	ON-TARGET	Telmisartan	Ramipril	Telmisartan	Ramipril	3p MACE + HHF	
Osteoporosis	20	HORIZON	Zoledronic Acid	Placebo	Zoledronic Acid	Raloxifene	Hip Fracture	

Comparator emulation:

Good | Moderate | Poor

		Trial name	RCT Exposure	RCT Comparator	RWE emulation Exposure	RWE emulation Comparator	RCT Outcome	RWE Emulation
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DOAC AF	13	ROCKET-AF	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin	Stroke/Systemic Embolism	
DOAC DVT	14	EINSTEIN-DVT	Rivaroxaban	Enoxaparin/ VKA	Rivaroxaban	Warfarin	VTE	
DOAC DVT	15	RE-COVER II	Dabigatran	Warfarin	Dabigatran	Warfarin	VTE / VTE Related Death	
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Osteoporosis	20	HORIZON	Zoledronic Acid	Placebo	Zoledronic Acid	Raloxifene	Hip Fracture	

Endpoint emulation:

Good | Moderate

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	13	ROCKET-AF	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin	Stroke/Systemic Embolism	
DOAC DVT	14	EINSTEIN-DVT	Rivaroxaban	Enoxaparin/ VKA	Rivaroxaban	Warfarin	VTE	May include some rule-out Dx
	15	RE-COVER II	Dabigatran	Warfarin	Dabigatran	Warfarin	VTE / VTE Related Death	May include some rule-out Dx
	16	AMPLIFY	Apixaban	Enoxaparin/ warfarin	Apixaban	Warfarin	VTE / VTE Related Death	May include some rule-out Dx
Heart failure	17	PARADIGM-HF	Sacubitril/ Valsartan	Enalapril	Sacubitril/ Valsartan	ACEi	HHF/ CV death	HF IP any position, no cause of death
Anti-HTN	18	TRANSCEND	Telmisartan	Placebo	Telmisartan + Loop/CCB /TZ	Loop/CCB/ TZ	3p MACE + HHF	HF IP any position, no cause of death
	19	ON-TARGET	Telmisartan	Ramipril	Telmisartan	Ramipril	3p MACE + HHF	HF IP any position, no cause of death
Osteoporosis	20	HORIZON	Zoledronic Acid	Placebo	Zoledronic Acid	Raloxifene	Hip Fracture	Shorter follow-up

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Event rates 1-10

Good | Moderate

Generally lower event rates in RWE studies

	Trial name	Outcome	RCT Exposure Events	RCT Exposure N	RCT Exposure Rate*	RCT Comparator Events	RCT Comparator N	RCT Comparator Rate	RWE Exposure Events	RWE Exposure N	RWE Exposure Rate	RWE Comparator Events	RWE Comparator N	RWE Comparator Rate
1	LEADER	3p MACE	608	4,668	3.4	694	4,672	3.9	1,352	84,346	2.1	1,955	84,346	2.6
2	DECLARE	HHF +CV death	417	8,582	1.2	496	8,578	1.5	242	24,895	1.6	367	24,895	2.4
3	EMPA-REG	3p MACE	490	4,687	3.7	282	2,333	4.4	416	51,875	1.5	478	51,875	1.9
4	CANVAS	3p MACE	564	5,795	2.7	496	4,347	3.2	772	76,099	1.5	990	76,099	1.9
5	CARMELINA	3p MACE	434	3,494	5.8	420	3,485	5.6	1,540	50,913	4.6	1,826	50,913	5.2
6	TECOS	3p MACE+ angina	839	7,257	4.1	851	7,266	4.2	8,106	174,739	7.3	9,692	174,739	8.3
7	SAVOR-TIMI 53	3p MACE	613	8,280	3.6	609	8,212	3.6	1,662	91,064	2.4	2,390	91,064	3.1
8	CAROLINA	3p MACE	356	3,023	2.1	362	3,010	2.1	373	24,131	2.7	458	24,131	3.0
9	TRITON-TIMI 38	3p MACE	643	6813	7.9	781	6795	9.7	718	21,932	3.8	960	24,446	3.9
10	PLATO	3p MACE	864	9333	9.3	1014	9291	11.7	649	13,980	8.0	858	13,980	7.1

3P MACE = 3-point major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death); HHF = hospitalization for heart failure
* Incidence rate per 100 person-years.

Higher event rates in RWE studies: Less specific endpoint definitions

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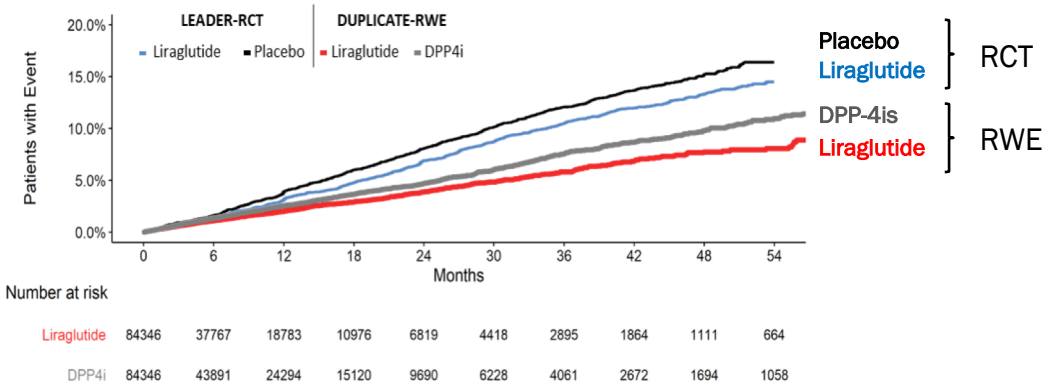
Example of a K-M plot: LEADER trial and emulation



Second-line anti-diabetics: SGLT2-is and GLP-1 RAs

	Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
1	LEADER	Liraglutide (GLP1)	Placebo	Liraglutide	DPP4i	3p MACE	
2	DECLARE	Dapagliflozin (SGLT2)	Placebo	Dapagliflozin	DPP4i	HHF + CV death	HF IP any position, no cause of death
3	EMPA-REG	Empagliflozin (SGLT2)	Placebo	Empagliflozin	DPP4i	3p MACE	
4	CANVAS	Canagliflozin (SGLT2)	Placebo	Canagliflozin	DPP4i	3p MACE	

	Trial name	Comparator emulation	Endpoint emulation+	RCT result	RWE results	Stand. Diff.	Test	Agreement		
1	LEADER	Moderate	Good	**0.87** (0.78, 0.97)	**0.82** (0.76, 0.87)	0.90	NI	**RA**	**EA**	**SD**
2	DECLARE	Moderate	Moderate	**0.83** (0.73, 0.95)	**0.69** (0.59, 0.81)	1.76	NI	**RA**	–	**SD**
3	EMPA-REG	Moderate	Good	**0.86** (0.74, 0.99)	**0.83** (0.73, 0.95)	0.35	NI	**RA**	**EA**	**SD**
4	CANVAS	Moderate	Good	**0.86** (0.75, 0.97)	**0.77** (0.70, 0.85)	1.34	NI	**RA**	**EA**	**SD**

Second-line anti-diabetics: DPP4is

	Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
5	CARMELINA	Linagliptin (DPP4i)	Placebo	Linagliptin	Sulfonylureas	3p MACE	
6	TECOS	Sitagliptin (DPP4i)	Placebo	Sitagliptin	Sulfonylureas	3p MACE+ angina	Angina non-specific
7	SAVOR-TIMI	Saxagliptin (DPP4i)	Placebo	Saxagliptin	Sulfonylureas	3p MACE	
8	CAROLINA	Linagliptin (DPP4i)	Glimerpiride	Linagliptin	Glimerpiride	3p MACE	

	Trial name	Comparator emulation	Endpoint emulation+	RCT result	RWE results	Stand. Diff.	Test	Agreement		
5	CARMELINA	Poor	Good	**1.02** (0.89, 1.17)	**0.90** (0.84, 0.96)	1.61	NI	*	EA	SD
6	TECOS	Poor	Moderate	**0.98** (0.88, 1.09)	**0.89** (0.86, 0.91)	1.71	NI	*	EA	SD
7	SAVOR-TIMI	Poor	Good	**1.00** (0.89, 1.12)	**0.81** (0.76, 0.86)	3.16¶	NI	*	–	–
8	CAROLINA	Good	Good	**0.98** (0.84, 1.14)	**0.91** (0.79, 1.05)	0.70	NI	RA	EA	SD

Note:
Positive interpretation of CAROLINA; very similar to TECOS yet no Reg Agreement

Antiplatelets: Prasugrel and Ticagrelor

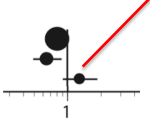
	Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
9	TRITON	Prasugrel	Clopidogrel	Prasugrel	Clopidogrel	3p MACE	
10	PLATO	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	3p MACE	

	Trial name	Comparator emulation	Endpoint emulation+	RCT result	RWE results	Stand. Diff.	Test	Agreement		
9	TRITON	Good	Good	**0.81** (0.73, 0.90)	**0.88** (0.79, 0.97)	-1.11	Sup	RA	EA	SD
10	PLATO	Good	Good	**0.84** (0.77, 0.92)	**0.92** (0.83, 1.02)	-1.31	Sup	–	EA	SD

1) PLATO's treatment effect was not established among US participants possibly due to high aspirin dosing in the US compared to Europe

PLATO and regional variation:*

	N	Ticagrelor	Clopidogrel	HR (95% CI)
All Countries	18624	9.8	11.7	0.84 (0.77, 0.92)
	2666	7.5	10.8	0.69 (0.53, 0.90)
USA	1413	12.6	10.1	1.27 (0.92, 1.75)



Note: RCT-DUPLICATE used U.S. data sources only

** Mahaffey KW et al. Circ 2011*

DOAC treatment for Afib

	Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
11	ARISTOTLE	Apixaban	Warfarin	Apixaban	Warfarin	Stroke/Systemic Embolism	
12	RE-LY	Dabigatran	Warfarin	Dabigatran	Warfarin	Stroke/Systemic Embolism	
13	ROCKET-AF	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin	Stroke/Systemic Embolism	

	Trial name	Comparator emulation	Endpoint emulation⁺	RCT result	RWE results	Stand. Diff.	Test	Agreement		
11	ARISTOTLE	Good	Good	**0.79** (0.66, 0.95)	**0.65** (0.59, 0.72)	1.81	NI	**RA**	–	**SD**
12	RE-LY	Good	Good	**0.66** (0.53, 0.82)	**0.69** (0.57, 0.83)	-0.31	NI	**RA**	**EA**	**SD**
13	ROCKET-AF	Good	Good	**0.79** (0.66, 0.96)	**0.77** (0.69, 0.86)	0.22	NI	**RA**	**EA**	**SD**

DOAC treatment for VTE

	Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
14	EINSTEIN-DVT	Rivaroxaban	Enoxaparin/ VKA	Rivaroxaban	Warfarin	VTE	Can't measure clinical parameter
15	RE-COVER II	Dabigatran	Warfarin	Dabigatran	Warfarin	VTE / VTE Related Death	Can't measure clinical parameter
16	AMPLIFY	Apixaban	Enoxaparin/ warfarin	Apixaban	Warfarin	VTE / VTE Related Death	Can't measure clinical parameter

	Trial name	Comparator emulation	Endpoint emulation⁺	RCT result	RWE results	Stand. Diff.	Test	Agreement		
14	EINSTEIN-DVT	Good	Moderate	**0.68** (0.44, 1.04)	**0.75** (0.63, 0.89)	-0.42	NI	*	**EA**	**SD**
15	RE-COVER II	Good	Moderate	**1.08** (0.64, 1.80)	**1.10** (0.76, 1.60)	-0.06	NI	**RA**	**EA**	**SD**
16	AMPLIFY	Good	Moderate	**0.84** (0.60, 1.18)	**0.76** (0.53, 1.09)	0.40	NI	**RA**	**EA**	**SD**

Heart failure: Sacubitril/ Valsartan (Entresto)

17	PARADIGM-HF	Sacubitril/ Valsartan	Enalapril	Sacubitril/ Valsartan	ACEi	HHF/ CV death	HF IP any position, no cause of death

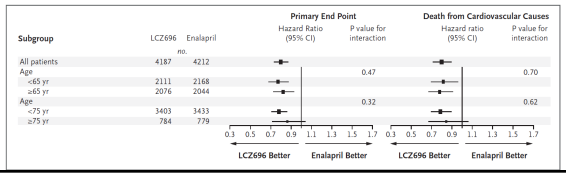
	Trial name	Comparator emulation	Endpoint emulation⁺	RCT result	RWE results	Stand. Diff.	Test	Agreement		
17	PARADIGM-HF	Moderate	Moderate	**0.80** (0.73, 0.87)	**0.97** (0.87-1.08)	-3.17	Sup	–	–	–

1) HR by data source

2) Treatment effect reduced in those 75+

Optum	0.98 (0.84, 1.16)
MarketScan	0.85 (0.67, 1.08)
Medicare FFS	1.02 (0.85, 1.22)
pooled	0.97 (0.87-1.08)
<= 75 yrs	0.89 (0.77-1.02)
> 75 yrs	1.04 (0.89-1.23)

PARADIGM-HF effect estimates by age:



Antihypertensives: Telmisartan

	Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
18	TRANSCEND	Telmisartan	Placebo	Telmisartan + Loop/CCB /TZ	Loop/CCB/ TZ	3p MACE + HHF	HF IP any position, no cause of death
19	ON-TARGET	Telmisartan	Ramipril	Telmisartan	Ramipril	3p MACE + HHF	HF IP any position, no cause of death

	Trial name	Comparator emulation	Endpoint emulation⁺	RCT result	RWE results	Stand. Diff.	Test	Agreement		
18	TRANSCEND	Moderate	Moderate	**0.92** (0.81, 1.05)	**0.88** (0.81, 0.96)	0.55	Sup	*	**EA**	**SD**
19	ON-TARGET	Good	Moderate	**1.01** (0.94, 1.09)	**0.83** (0.77, 0.90)	3.46	NI	*	–	–

1) We investigate subtle differences in exposure, outcome, inclusion-exclusion criteria, covariates, follow-up

ON-TARGET	1.0 (0.9-1.1)
Fralick et al. RWE JAMA-IM	1.0 (0.9-1.1)
RCT-DUPLICATE	0.8 (0.8-0.9)

Osteoporosis: Zoledronic acid

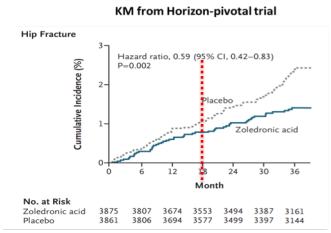
	Trial name	Exposure	Comparator	Exposure	Comparator	Outcome	Emulation
20	HORIZON	Zoledronic Acid	Placebo	Zoledronic Acid	Raloxifene	Hip Fracture	Time-varying hazard

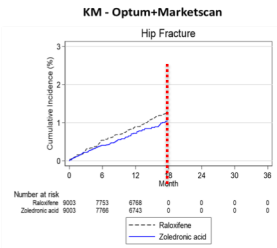
	Trial name	Comparator emulation	Endpoint emulation⁺	RCT result	RWE results	Stand. Diff.	Test	Agreement		
20	HORIZON	Moderate	Moderate	**0.59** (0.42, 0.83)	**0.75** (0.58, 0.97)	-1.10	Sup	**RA**	**EA**	**SD**

1) Time-varying treatment effects

RCT: HR_{36mo} = 0.59 RWE: HR_{36mo} = ?? Emulation mismatch

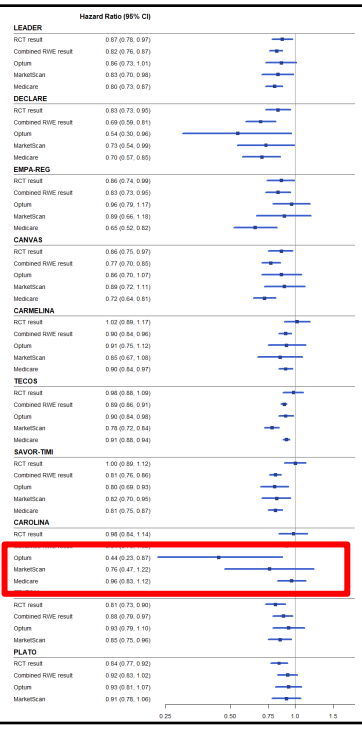
HR_{18mo} = 0.75 HR_{18mo} = 0.75 Calibration success

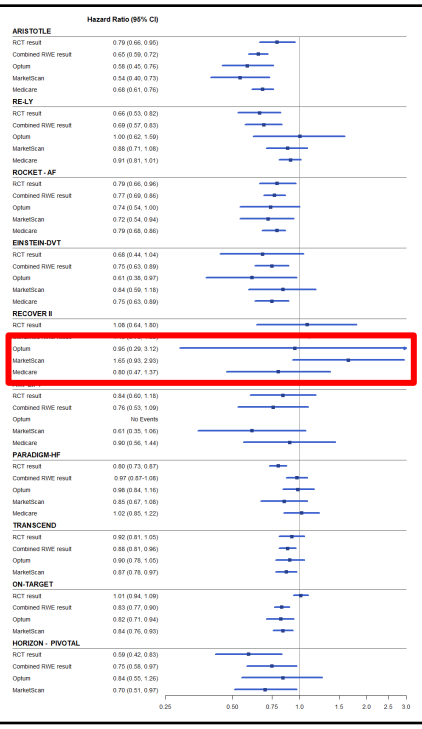




Variation between data sources

Limited variation between US commercial claims data sources





Conclusion

- With data that are fit-for-purpose and proper design and analysis, non-randomized real-world evidence studies usually come to the same conclusion about a drug's treatment effect as randomized trials
- These initial findings of the RCT-DUPLICATE program indicate circumstances when RWE may offer causal insights in situations where RCT data is either not available or cannot be quickly or feasibly generated.

Some learnings

- We need to take into account the uncertainty inherent in any single RCT
- One wouldn't likely take only the primary result of a single RCT in isolation
  - It is important to have planned sensitivity analyses to help interpret findings as a whole
- A single binary success metric will not do justice
- In any emulation, despite best efforts, there will remain differences in population, measurement, and drug use:
  - For our emulation success most critical seemed:
    - Population, comparator, and outcome emulation
    - Data fit-for-purpose and study design choices are most important considerations
  - We remain concerned about 3 emulations with an opportunity for more learnings:
    - PARADIGM-HF: some emulation differences, effect modification,
    - ON-TARGET: ??? (we are investigating multiple issues)
    - SAVOR-TIMI: Residual confounding by correlates of soc-econ factors?

Calibrating our RWE tool kit

- Repository of well-documented studies that illustrate the agreement between RCTs and RWE, in specific situations when the RWE study is explicitly designed to answer the same question as the RCT.

- May serve as reference points to assess validity in RWE:
  - By therapeutic area
  - By data source
  - By type of comparator
  - By type of outcome
  - Further categorization:
    - Population
    - Follow-up

- A repository of case studies would
  - Increase predictability of future RWE studies
  - Increase the use of common methodological approaches emulating target trials
  - Point out areas that are currently difficult to address with RWE and highlight the need to improve data sources

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Tracer outcomes to calibrate methodology performance

	Tracer outcome	Expected HR*	Exposure IR#	Comparator IR#	Observed HR	
2nd-line Antidiabetics	LEADER	Severe hypoglycemia	< 1	7.8	10.5	0.73 (0.65-0.81)	✓
	DECLARE	Diabetic ketoacidosis	> 1	2.0	1.4	1.36 (0.78-2.37)	✓
	EMPA-REG	HF hospitalization	< 1	2.6	7.7	0.35 (0.27-0.46)	✓
		Diabetic ketoacidosis	> 1	2.9	2.3	1.25 (0.89-1.76)	✓
	CANVAS	HF hospitalization	< 1	2.8	7.8	0.36 (0.30-0.44)	✓
		Diabetic ketoacidosis	> 1	2.6	1.5	1.70 (1.29-2.25)	✓
	CARMELINA	ESRD	~ 1	3.2	3.2	1.04 (0.81-1.33)	✓
	TECOS	Sever hypoglycemia	< 1	12.3	30.8	0.40 (0.38-0.43)	✓
	SAVOR-TIMI	Severe hypoglycemia	< 1	5.9	16.3	0.37 (0.33-0.41)	✓
	CAROLINA	Severe hypoglycemia	< 1	6.0	16.0	0.42 (0.32-0.56)	✓
		ESRD	~ 1	3.0	3.2	1.08 (0.66-1.79)	✓
Antiplatelets	TRITON	Major bleeding	> 1	20.2	16.0	1.17 (1.01-1.34)	✓
		Pneumonia hosp.	~ 1	11.5	12.3	0.83 (0.73-0.95)	–
	PLATO	Major bleeding	~ 1	29.4	23.0	1.16 (0.98-1.39)	✓
		Pneumonia hosp.	~ 1	23.4	22.0	1.01 (0.84-1.22)	✓

✓ = successfully in negative/positive tracer outcome test

*An expected hazard ratio (HR) of ~1 indicates an approximately null effect.
IR = incidence rate per 1000 person-years

Impact of confounding adjustment

	Trial name	Comparator emulation	RCT result	1:1 PS matched RWE results	Unadjusted RWE results
2nd-line Antidiabetics	1 LEADER	Moderate	**0.87** (0.78, 0.97)	**0.82** (0.76, 0.87)	**0.57** (0.54-0.61)
	2 DECLARE	Moderate	**0.83** (0.73, 0.95)	**0.69** (0.59, 0.81)	**0.47** (0.41-0.53)
	3 EMPA-REG	Moderate	**0.86** (0.74, 0.99)	**0.83** (0.73, 0.95)	**0.63** (0.57-0.70)
	4 CANVAS	Moderate	**0.86** (0.75, 0.97)	**0.77** (0.70, 0.85)	**0.58** (0.54-0.62)
	5 CARMELINA	Poor	**1.02** (0.89, 1.17)	**0.90** (0.84, 0.96)	**0.90** (0.86-0.95)
	6 TECOS	Poor	**0.98** (0.88, 1.09)	**0.89** (0.86, 0.91)	**0.81** (0.79-0.84)
	7 SAVOR-TIMI	Poor	**1.00** (0.89, 1.12)	**0.81** (0.76, 0.86)	**0.65** (0.62-0.69)
	8 CAROLINA	Good	**0.98** (0.84, 1.14)	**0.91** (0.79, 1.05)	**0.92** (0.83-1.01)
Antiplatelets	9 TRITON	Good	**0.81** (0.73, 0.90)	**0.88** (0.79, 0.97)	**0.70** (0.65-0.76)
	10 PLATO	Good	**0.84** (0.77, 0.92)	**0.92** (0.83, 1.02)	**0.84** (0.78-0.91)

Meaningful change in estimate

Impact of confounding adjustment

		Trial name	Comparator emulation	RCT result	1:1 PS matched RWE results	Unadjusted RWE results
DOACs – AF	11	ARISTOTLE	Good	**0.79** (0.66, 0.95)	**0.65** (0.59, 0.72)	**0.66** (0.62-0.71)
DOACs – AF	12	RE-LY	Good	**0.66** (0.53, 0.82)	**0.69** (0.57, 0.83)	**0.67** (0.58-0.78)
DOACs – AF	13	ROCKET-AF	Good	**0.79** (0.66, 0.96)	**0.77** (0.69, 0.86)	**0.76** (0.69-0.84)
DOACs – DVT	14	EINSTEIN-DVT	Good	**0.68** (0.44, 1.04)	**0.75** (0.63, 0.89)	**0.86** (0.76-0.96)
DOACs – DVT	15	RE-COVER II	Good	**1.08** (0.64, 1.80)	**1.10** (0.76, 1.60)	**1.52** (1.13-2.04)
DOACs – DVT	16	AMPLIFY	Good	**0.84** (0.60, 1.18)	**0.76** (0.53, 1.09)	**0.64** (0.50-0.82)
Heart failure	17	PARADIGM-HF	Moderate	**0.80** (0.73, 0.87)	**0.97** (0.87-1.08)	**0.95** (0.89-1.01)
Anti-HTN	18	TRANSCEND	Moderate	**0.92** (0.81, 1.05)	**0.88** (0.81, 0.96)	**0.80** (0.74-0.85)
Anti-HTN	19	ON-TARGET	Good	**1.01** (0.94, 1.09)	**0.83** (0.77, 0.90)	**0.68** (0.64-0.72)
Osteoporosis	20	HORIZON	Moderate	**0.59** (0.42, 0.83)	**0.75** (0.58, 0.97)	**1.08** (0.86-1.35)

Event rates 11-20

Good | Moderate

Similar event rates

Higher event rates in RWE studies: Less specific endpoint

	Trial name	Outcome	RCT Exposure Events	RCT Exposure N	RCT Exposure Rate	RCT Comparator Events	RCT Comparator N	RCT Comparator Rate	RWE Exposure Events	RWE Exposure N	RWE Exposure Rate	RWE Comparator Events	RWE Comparator N	RWE Comparator Rate
11	ARISTOTLE	Stroke/ Sys Embol	212	9,120	1.3	265	9,081	1.6	545	110,259	0.9	694	110,259	1.5
12	RE-LY	Stroke/ Sys Embol	134	6,076	1.1	199	6,022	1.7	172	39,070	0.9	221	39,070	1.3
13	ROCKET-AF	Stroke/ Sys Embol	188	6,953	1.7	241	7,004	2.2	419	51,318	1.5	518	51,318	2.4
14	EINSTEIN-DVT	VTE	36	1,731	2.1	51	1,718	3.0	207	12,985	4.9	271	12,985	6.2
15	RECOVER II	VTE / VTE Death	30	1,279	2.3	28	1,289	2.2	46	2,671	5	48	2,671	5.1
16	AMPLIFY	VTE / VTE Death	59	2,609	2.3	71	2,635	2.7	155	3,570	11.6	99	3,570	8.2
17	PARADIGM-HF	HHF/ Mortality	914	4,187	21.8	1,117	4,212	26.5	645	3,033	46.4	636	3,033	44.6
18	TRANSCEND	3p MACE + HHF	465	2,954	15.7	504	2,972	17.0	826	20,024	7.4	1,383	20,024	7.6
19	ON-TARGET	3p MACE + HHF	1,412	8,576	16.5	1,423	8,542	16.7	874	17,626	6.4	1,306	17,626	8.2
20	HORIZON-PIV	Hip Fracture	88	3,876	2.5	52	3,861	1.4	78	9,003	0.7	97	9,003	0.9

3P MACE = 3-point major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death); Sys Embol = systemic embolism; HHF = hospitalization for heart failure
* Incidence rate per 100 person-years.

Lower event rates in RWE studies: Lower sensitivity endpoint definitions