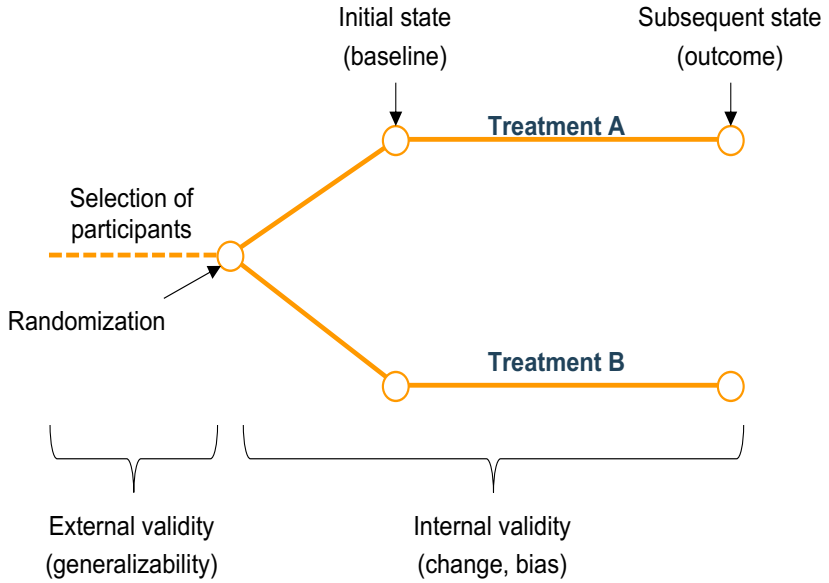
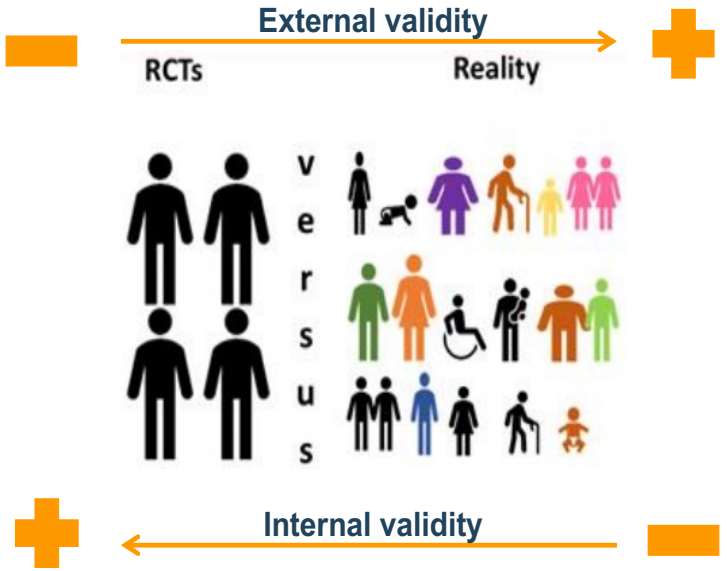
Trials Replication through Observational study by Yonsei (TROY)

Jaehyeong Cho, Chungsoo Kim, Kyungwon Kim, Seng Chan You

Background

Type of study	Strengths	Weaknesses
Randomized clinical trials	Best for studying an intervention Randomized High internal validity Unbiased distribution of confounders Evaluates efficacy	Expensive: time and money Short follow-up Volunteer bias Low generalizability to different or real-world population





Monti et al., Randomized Controlled Trials and Real-World Data: Differences and Similarities to Untangle Literature Data, *Rheumatology*, 2018

Background

Circulation

ORIGINAL RESEARCH ARTICLE

Estimation of DAPT Study Treatment Effects in Contemporary Clinical Practice: Findings From the EXTEND-DAPT Study

Neel M. Butala, MD, MBA; Kamil F. Faridi, MD, MSc; Hector Tamez, MD, MPH; Jordan B. Strom, MD, MSc; Yang Song, MSc; Changyu Shen, PhD; Eric A. Secemsky, MD, MSc; Laura Mauri, MD, MSc; Dean J. Kereiakes, MD; Jeptha P. Curtis, MD; C. Michael Gibson, MD, MS; Robert W. Yeh, MD, MSc

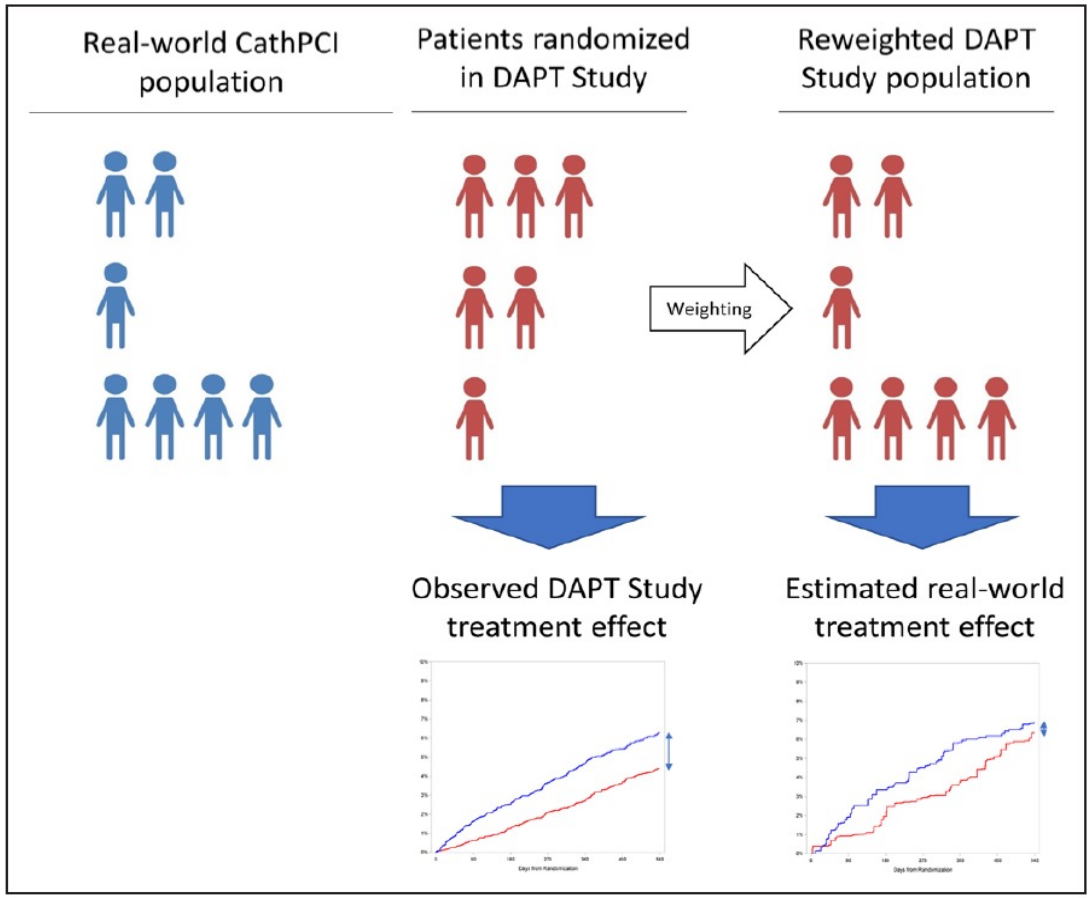
BACKGROUND: Differences in patient characteristics, changes in treatment algorithms, and advances in medical technology could each influence the applicability of older randomized trial results to contemporary clinical practice. The DAPT Study (Dual Antiplatelet Therapy) found that longer-duration DAPT decreased ischemic events at the expense of greater bleeding, but subsequent evolution in stent technology and clinical practice may attenuate the benefit of prolonged DAPT in a contemporary population. We evaluated whether the DAPT Study population is different from a contemporary population of US patients receiving percutaneous coronary intervention and estimated the treatment effect of extended-duration antiplatelet therapy after percutaneous coronary intervention in this more contemporary cohort.

METHODS: We compared the characteristics of drug-eluting stent–treated patients randomly assigned in the DAPT Study to a sample of more contemporary drug-eluting stent–treated patients in the National Cardiovascular Data Registry CathPCI Registry from July 2016 to June 2017. After linking trial and registry data, we used inverse-odds of trial participation weighting to account for patient and procedural characteristics and estimated a contemporary real-world treatment effect of 30 versus 12 months of DAPT after coronary stent procedures.

RESULTS: The US drug-eluting stent–treated trial cohort included 8864 DAPT Study patients, and the registry cohort included 568 540 patients. Compared with the trial population, registry patients had more comorbidities and were more likely to present with myocardial infarction and receive 2nd-generation drug-eluting stents. After reweighting trial results to represent the registry population, there was no longer a significant effect of prolonged DAPT on reducing stent thrombosis (reweighted treatment effect: −0.40 [95% CI, −0.99% to 0.15%]), major adverse cardiac and cerebrovascular events (reweighted treatment effect, −0.52 [95% CI, −2.62% to 1.03%]), or myocardial infarction (reweighted treatment effect, −0.97% [95% CI, −2.75% to 0.18%]), but the increase in bleeding with prolonged DAPT persisted (reweighted treatment effect, 2.42% [95% CI, 0.79% to 3.91%]).

CONCLUSIONS: The differences between the patients and devices used in contemporary clinical practice compared with the DAPT Study were associated with the attenuation of benefits and greater harms attributable to prolonged DAPT duration. These findings limit the applicability of the average treatment effects from the DAPT Study in modern clinical practice.

Key Words: percutaneous coronary intervention ■ platelet aggregation inhibitors ■ pragmatic clinical trials as topic



Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. New England Journal of Medicine. 2014;371(23):2155-66.
Butala NM, Faridi KF, Tamez H, Strom JB, Song Y, Shen C, et al. Estimation of DAPT Study Treatment Effects in Contemporary Clinical Practice: Findings From the EXTEND-DAPT Study. Circulation. 2022;145(2):97-106.

Background

Circulation

EDITORIAL

The Evolution of Evidence-Based Medicine: When the Magic of the Randomized Clinical Trial Meets Real-World Data

Seng Chan You, MD, PhD; Harlan M. Krumholz, MD, SM

The central principle of evidence-based medicine is the prioritization of evidence, and the results from well-designed randomized clinical trials are regarded as the gold standard of evidence. The PCI-CURE clinical trial (Percutaneous Coronary Intervention–Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), published in 2001, provided the evidence to establish a standard dual antiplatelet therapy (DAPT) strategy with 12-month aspirin and P2Y12 inhibitors after implantation of drug-eluting stents (DES). The researchers found that prolonged DAPT up to 12 months can prevent the risk of a subsequent fatal cardiac event, stent thrombosis.[1] The DAPT trial, published in 2014, found that prolonged duration (up to 30 months) of DAPT lowers the risk of stent thrombosis and recurrent myocardial infarction, compared with a 12-month duration, at the cost of more bleeding.[2] The DAPT study remains the largest trial on this topic and has generated considerable debate.

over, decades after initial publication, questions may emerge surrounding the generalizability of the results to contemporary populations. The newer generation of DES, with the alteration of the antiproliferative drug, structure of stent polymer, and stent platform, reduced the risk of late and very late stent thrombosis compared with the previous generation and challenged the strategy of 12-month or longer DAPT duration.[3]

As reported in this issue of *Circulation*, Butala and colleagues[4] investigated the generalizability of the DAPT study. By leveraging data from the National Cardiovascular Data Registry CathPCI Registry from 2016 to 2017, they evaluated the differences in characteristics between the participants in the DAPT trial and contemporary patients in the United States who undergo percutaneous coronary intervention. Compared with the trial population, registry patients were older and had more comorbidities. Although first-generation DES was implanted in ≈40% of patents in the trial, 100%

- The characteristics of enrolled patients passing eligibility criteria in the trial may differ from the patients under routine clinical practice
- Over time, the characteristics of people of indication have changed
- The evidence from trials may not be durable

You SC, Krumholz HM. The Evolution of Evidence-Based Medicine: When the Magic of the Randomized Clinical Trial Meets Real-World Data. Circulation. 2022;145(2):107-9.

TROY

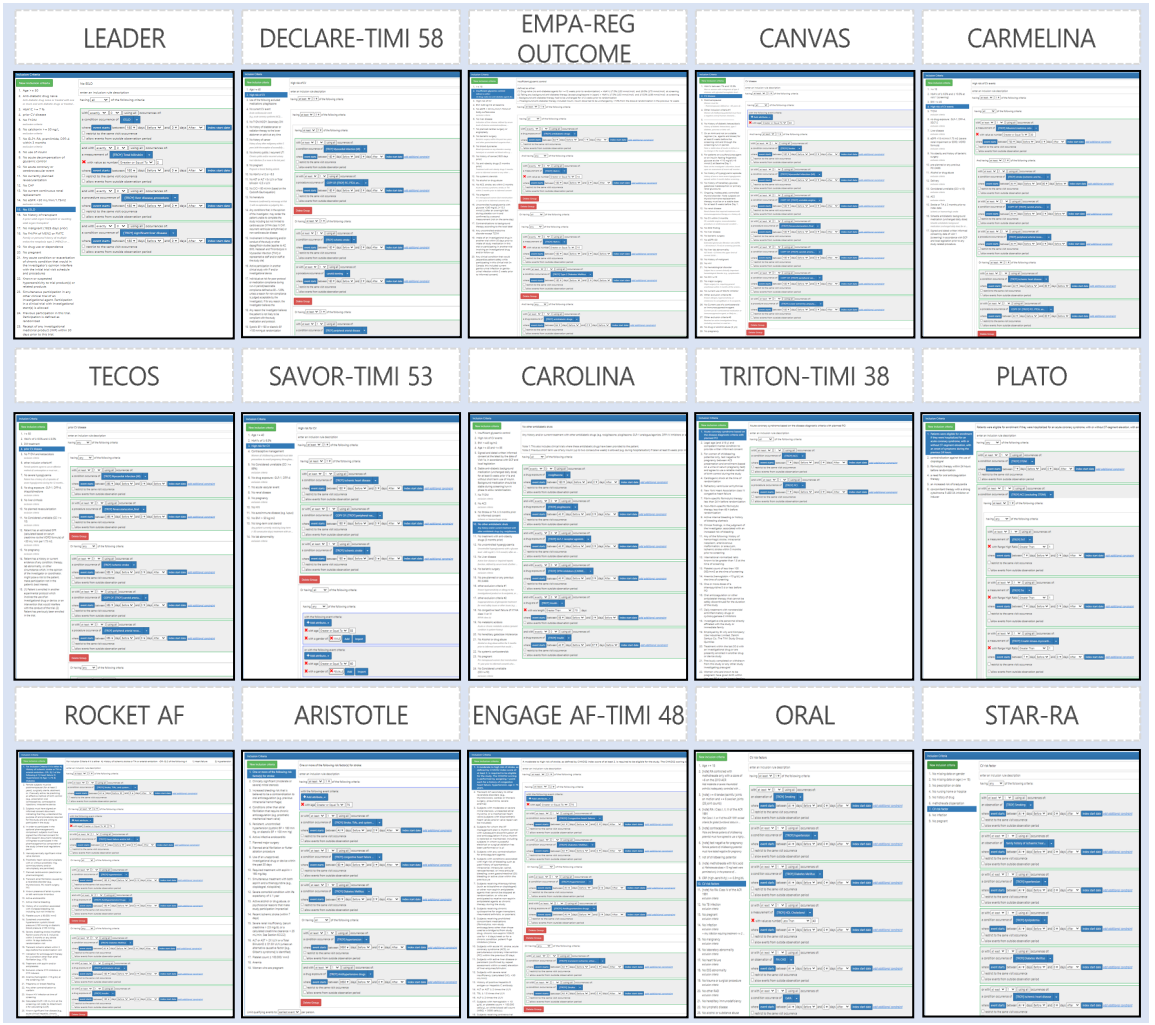
- **Trials replication through observational study by Yonsei (TROY)**
  - Replicate 15 major clinical trials
    - Based on OMOP-CDM
    - Replicating RCT eligible criteria

  - In populations based on RCT criteria, FDA indication, and clinical trial
    - Differences in baseline characteristics
    - Differences in crude incidences of outcomes
    - Estimating heterogeneous treatment effects

TROY

https://github.com/ohdsi-studies/Troy

Study	Target drug (class)	Comparator drug (class)	Primary endpoint
LEADER	Liraglutide (GLP-1)	DPP-4	3P MACE
DECLARE-TIMI 58	Dapagliflozin (SGLT-2)	DPP-4	HHF + CV death
EMPA-REG OUTCOME	Empagliflozin (SGLT-2)	DPP-4	3P MACE
CANVAS	Canagliflozin (SGLT-2)	DPP-4	3P MACE
CARMELINA	Linagliptin (DPP-4)	Sulfonylureas	3P MACE
TECOS	Sitagliptin (DPP-4)	Sulfonylureas	4P MACE
SAVOR-TIMI 53	Saxagliptin (DPP-4)	Sulfonylureas	3P MACE
CAROLINA	Linagliptin (DPP-4)	Glimepiride (Sulfonylureas)	3P MACE
TRITON-TIMI 38	Prasugrel + Aspirin	Clopidogrel + Aspirin	3P MACE
PLATO	Ticagrelor + Aspirin	Clopidogrel + Aspirin	3P MACE
ROCKET AF	Rivaroxaban	Warfarin	Stroke+systemic embolism
ARISTOTLE	Apixaban	Warfarin	Stroke+systemic embolism
ENGAGE AF-TIMI 48	Edoxaban	Warfarin	Stroke+systemic embolism
ORAL	Tofacitinib	TNF inhibitor	Cancer
STAR-RA	Tofacitinib	TNF inhibitor	Cancer, MI + stroke



TROY

Pivotal trial	RCT Eligibility			FDA Indication			RCT trials/Indication (%)		
	YUHS	AUSOM	DSMC	YUHS	AUSOM	DSMC	YUHS	AUSOM	DSMC
LEADER (Liraglutide + DPP-4)	2,417	3,099	892	27,686	20,329	6579	9%	15%	14%
DECLARE-TIMI 58 (Dapagliflozin + DPP-4)	249	398	497	16,110	10,025	2244	2%	4%	22%
EMPA-REG OUTCOME (Empagliflozin + DPP-4)	3,395	2,366	637	24,502	19,523	7691	14%	12%	8%
CANVAS (Canagliflozin + DPP-4)	1,993	2,060	487	25,222	19,093	6405	8%	11%	8%
CARMELINA (Linagliptin + sulfonylureas)	1,162	904	478	22,835	16,148	5349	5%	6%	9%
TECOS (Sitagliptin + sulfonylureas)	543	701	62	25,965	19,299	4644	2%	4%	1%
SAVOR-TIMI 53 (saxagliptin + sulfonylureas)	4,219	2,367	474	19,128	14,397	3116	22%	16%	15%
CAROLINA (linagliptin + glimepiride)	NA	NA	154	18,060	14,856	3006	NA	NA	5%
TRITON-TIMI 38 (prasugrel + clopidogrel)	378	742	52	5,064	4,984	1111	7%	15%	5%
PLATO (ticagrelor + clopidogrel)	4,670	4,551	1089	5,527	5,137	1210	84%	89%	90%
ROCKET AF (rivaroxaban + warfarin)	27	5	3	5,617	1,355	623	0%	0%	0%
ARISTOTLE (apixaban + warfarin)	2,518	448	429	5,820	1,197	1136	43%	41%	38%
ENGAGE AF-TIMI 48 (edoxaban + warfarin)	639	222	75	3,107	1,277	526	21%	17%	14%
ORAL (tofacitinib + TNFi)	NA	NA	NA	NA	NA	NA	NA	NA	NA
STAR-RA (tofacitinib + TNFi)	NA	NA	NA	NA	NA	NA	NA	NA	NA

TROY

[Call for collaborators: Trial Replication Through Observational Study of Yonsei (TROY) Project]

https://forums.ohdsi.org/t/call-for-collaborators-trial-replication-through-observational-study-of-yonsei-troy-project/19640

Call for collaborators: Trial Replication Through Observational Study of Yonsei (TROY) Project

Researchers

Chungsoo_Kim 3 Aug '23

Aug 2023

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Aug 2023

Dear OHDSI community,

This is a broad call for inviting collaborators (especially data partners) for exciting research on replicating clinical trials based on the OHDSI network.

Last year we (@Jaehyeong_Cho , @Chungsoo_Kim , @kyulee.jeon , and @SCYou) initiated a project related to key issues pointed out by many observational researchers.

1. Different clinical characteristics between RCT and RWD patients with similar eligibility criteria
2. Controversial generalizability of RCT effects in real clinical settings.

Therefore, through this TROY study, we would like to investigate the following three points based on multiple OMOP CDM databases.

1. Proportion of patients meeting eligibility criteria among patients with FDA-approved indications
2. Comparison of differences in clinical characteristics between clinical trial patients and patients extracted from actual data
3. Comparative analysis of efficacy between target drug and reference drug (experimental emulation)

Aug 2023

We look forward to the active participation of data partners, and we will set up a meeting to outline the study once an appropriate number of data partners have been recruited. (Even if you don't have OMOPed data, please feel free to contact us about how you can participate in this study.)

For more information, please see the Study Repo 4 , Protocol, Selected clinical trial information 2 , and 2022 OHDSI Symposium video 2 .

If you are interested or have any questions, please comment on this thread or please contact us via email → ted9219@ajou.ac.kr

Thank you
Chungsoo Kim

Thank you

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