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Assessing Heterogeneity of Treatment Effect in Real-World Data

Jodi B. Segal, MD, MPH*; Ravi Varadhan, PhD, PhD*; Rolf H.H. Groenwold, MD, PhD; Nicholas C. Henderson, PhD; Xiaojuan Li, PhD; Kaori Nomura, MPH, PhD; Sigal Kaplan, PhD; Shirin Ardeshirrouhanifard, PharmD, PhD; James Heyward, MHS; Fredrik Nyberg, PhD; and Mehmet Burcu, PhD

(Ann Intern Med. 2023;176:536-544)

Annals of Internal Medicine®

Presenter: Sureerat Suwatcharangkoon, MD

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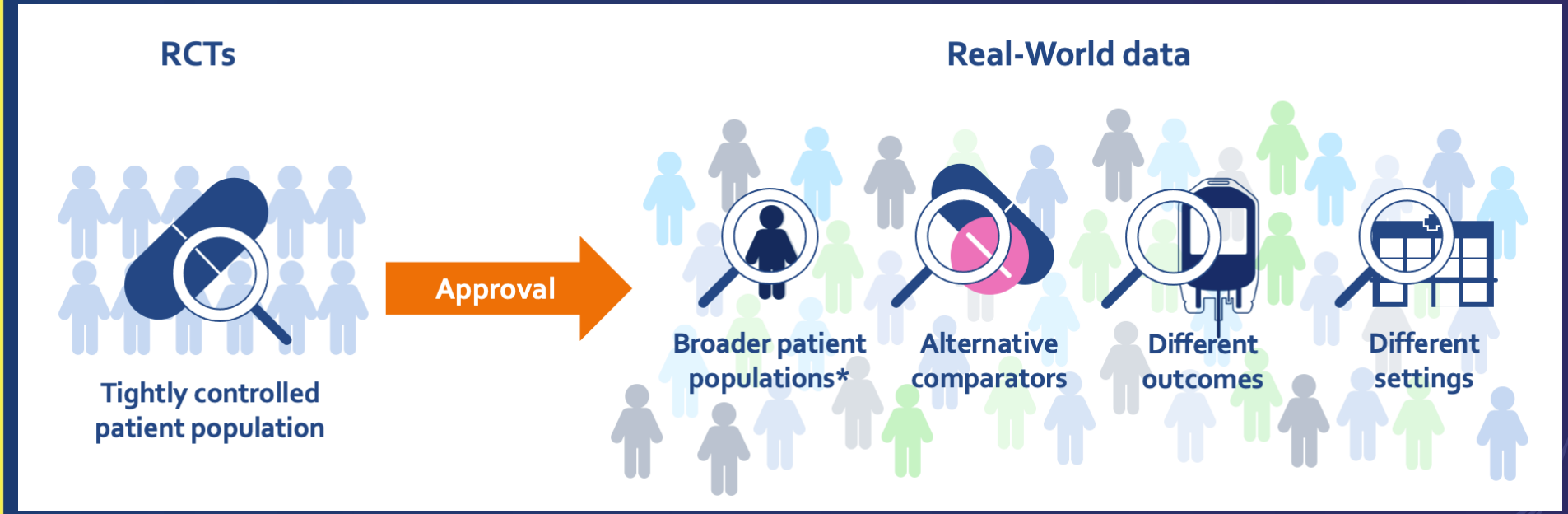
Heterogeneity of Treatment Effects (HTE)

- HTE describes how treatment effect varies across patients



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What are the Primary Sources of HTE?

- Intrinsic biological characteristics
- Extrinsic environmental factors
- Behaviors
- Others
  - Treatment access or delivery
  - Concomitant therapies
  - Clinician expertise
  - Site features

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What motivates HTE Assessment?

- Postmarketing research
  - Treatment risks in subpopulations
- Clinical decision making
  - Heterogenous net clinical benefit

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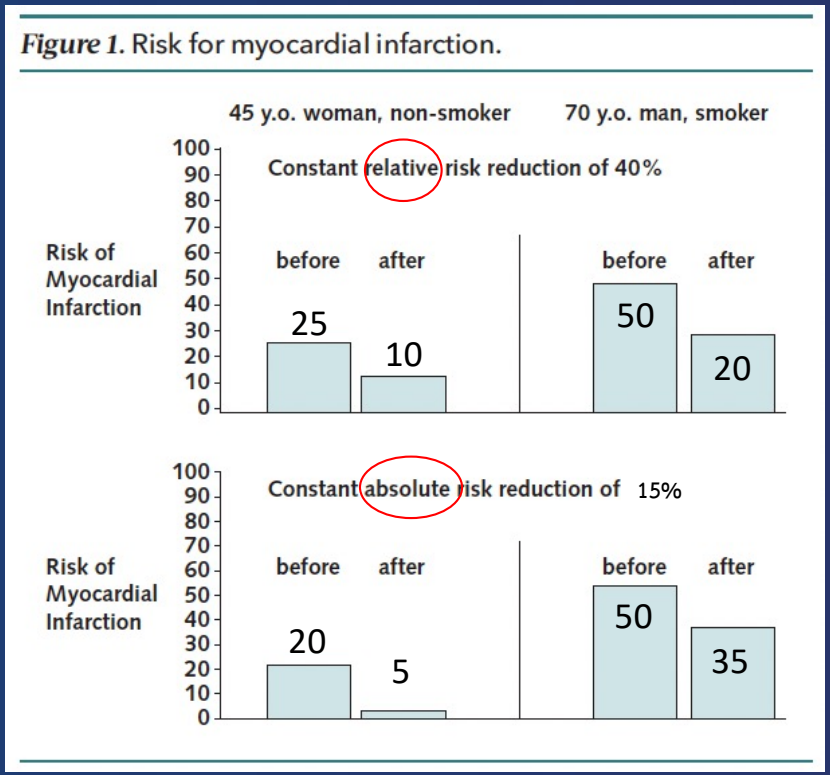
What are the Key Considerations when Using RWD?

1. Generate a valid estimate of the overall effect across all patients
2. Choose an appropriate approach to addressing missing data
3. Address issues of selection bias when reporting results
4. Consider the risk of measurement biases
5. Assess the sufficiency of information about potential confounders
6. Address potential confounding

Which Effect Scale should be used when Evaluating and Reporting HTE?



1. The additive (absolute) scale is most interpretable to guide clinical decisions
2. The additive (absolute) scale may give clues about interactions that are likely to be etiologic
3. Statistical modeling need not, necessarily, be conducted on the same scale as that with which results are communicated

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What are the Different Objectives of Conducting HTE analyses?

1. To confirm subgroup effects
2. To describe the magnitude of HTE
3. To discover clinically important subgroups
4. To predict individual effects

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Objective 1:

Confirm Subgroup HTE

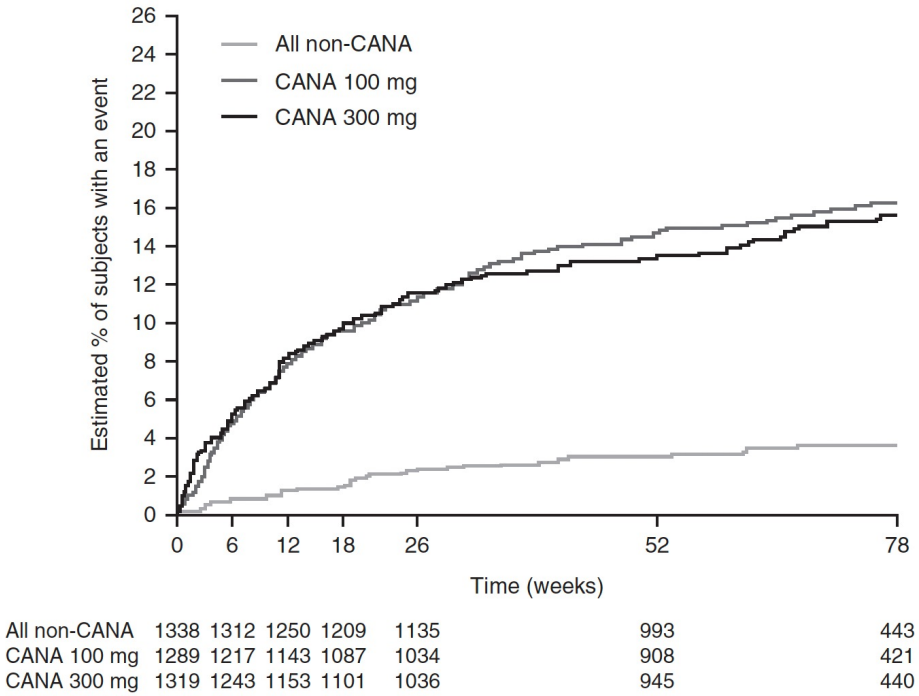
Obj 1: Confirm Subgroup HTE

To test whether the treatment effect in any subgroup is different from the overall treatment effect

- When there is a signal of possible HTE in a clinical trial—perhaps in the confirmatory trials regulators might require for drug approval
- When passive surveillance systems suggest possible harm in a subgroup

Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies

Paul Nyirjesy, Jack D. Sobel, Albert Fung, Cristiana Mayer, George Capuano, Kirk Ways & Keith Usiskin



Curr Med Res Opin. 2014 Jun;30(6):1109-19.

Table 4. Summary of genital mycotic infection adverse events in males (Population 1).

	Patients, *n* (%)		
	PBO (*n* = 334)	CANA 100 mg (*n* = 408)	CANA 300 mg (*n* = 404)
Any AE	2 (0.6)	17 (4.2)	15 (3.7)
AEs leading to discontinuation	0	2 (0.5)	2 (0.5)
AEs related to study drug*	2 (0.6)	12 (2.9)	12 (3.0)
Serious AEs	0	0	0
Specific terms			
Balanitis			
Balanitis car			
Balanoposth			
Genital infec			
Number of eve			
1			
2			
≥3			

PBO, placebo; C
*Possibly, proba
investigators.

Table 3. Summary of genital mycotic infection adverse events in females (Population 1).

	Patients, *n* (%)		
	PBO (*n* = 312)	CANA 100 mg (*n* = 425)	CANA 300 mg (*n* = 430)
Any AE	10 (3.2)	44 (10.4)	49 (11.4)
AEs leading to discontinuation	0	4 (0.9)	2 (0.5)
AEs related to study drug*	8 (2.6)	33 (7.8)	45 (10.5)
Serious AEs	0	0	0
Specific terms			
Genital infection fungal	1 (0.3)	0	0
Vaginal infection	2 (0.6)	5 (1.2)	7 (1.6)
Vulvitis	0	0	2 (0.5)
Vulvovaginal candidiasis	3 (1.0)	7 (1.6)	12 (2.8)
Vulvovaginal mycotic infection	4 (1.3)	25 (5.9)	23 (5.3)
Vulvovaginitis	0	8 (1.9)	7 (1.6)
Number of events experienced			
1	9 (2.9)	34 (8.0)	39 (9.1)
2	1 (0.3)	9 (2.1)	8 (1.9)
≥3	0	1 (0.2)	2 (0.5)

PBO, placebo; CANA, canagliflozin; AE, adverse event.
*Possibly, probably, or very likely related to study drug, as assessed by investigators.

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

ORIGINAL ARTICLE

Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: A population-based study of older women and men with diabetes

Iliana C. Lega MD, Susan E. Bronskill PhD, Michael A. Campitelli MSc, Jun Guan MSc, Nathan M. Stall MD, Kenneth Lam MD, Lisa M. McCarthy MSc, Andrea Gruneir PhD, Paula A. Rochon MD

	Overall			Women			Men		
Outcome within 30 days	Number exposed with outcome	Unadjusted HR (95% CI)	Adjusted HR (95% CI)†	Number exposed with outcome	Unadjusted HR (95% CI)	Adjusted HR (95% CI)‡	Number exposed with outcome	Unadjusted HR 95% CI)	Adjusted HR (95% CI)‡
TOTAL EXPOSED	21,444	-	-	8,848		-	12,596		-
Outcome within 30 days									
Genital mycotic infection	487	2.15 (1.84-2.51)	2.47 (2.08-2.92)	305	2.45 (2.01-2.98)	2.56 (2.06-3.17)	182	1.91 (1.48-2.45)	2.30 (1.74-3.02)
UTI	489	0.67 (0.60-0.76)	0.88 (0.78-1.00)	278	0.71 (0.61-0.83)	0.89 (0.76-1.05)	211	0.67 (0.56-0.80)	0.88 (0.73-1.07)

Diabetes Obes Metab. 2019 Nov;21(11):2394-2404.

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Required Elements

1. Prespecification of subgroups
2. Scientific rationale and prior evidence for hypotheses
3. Prespecification of the analytic plan
4. Control of family wise type I error
5. The presence of a significant overall treatment effect
6. Adequate power to test subgroup hypotheses

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Objective 2:

Describe the Magnitude and Nature of HTE

Obj 2: Describe the Magnitude and Nature of HTE

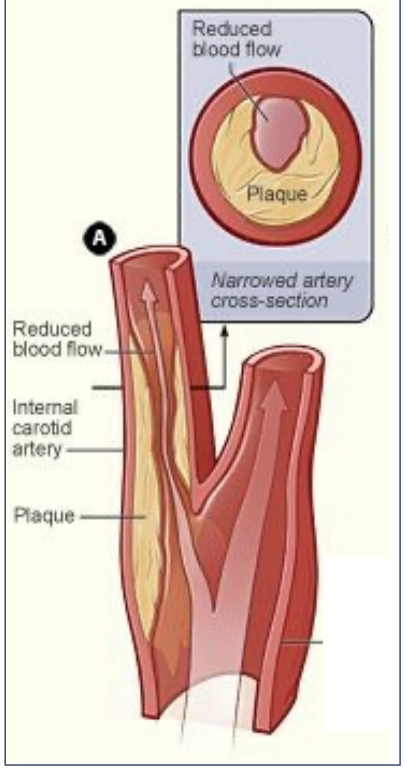
Descriptive HTE

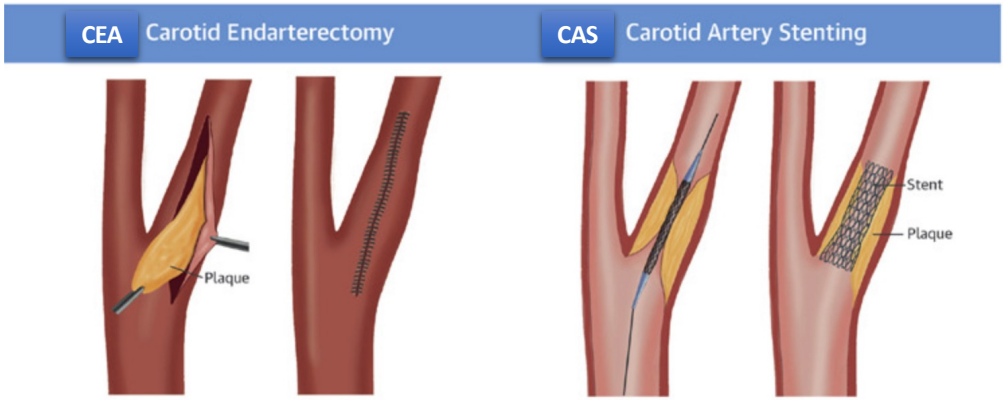
- The process of reporting on TEs, and their CIs, in prespecified subgroups but without testing hypotheses about the differences between subgroups or about differences between subgroup effects and the overall TE
- To estimate and report the magnitude of the TE in known subgroups of interest

Frailty & Stroke

Impact of frailty on 30-day death, stroke, or myocardial infarction in severe carotid stenosis: Endarterectomy versus stenting

Vivien Chan [a,b,*], Alan R. Rheaume [a], Michael M. Chow [a]





Rate of 30-day death, stroke, or MI in CEA and CAS patients stratified by frailty.

	CEA	CAS	
Non-frail	2.4 % (45/1837)	1.9 % (8/423)	$p = 0.59$
Pre-frail	2.9 % (211/7253)	1.0 % (17/1719)	$p < 0.001$*
Frail	3.9 % (182/4662)	1.2 % (15/1239)	$p < 0.001$*
Severely frail	6.5 % (44/676)	3.0 % (8/265)	$p = 0.04$*
	$p < 0.001$	$p = 0.08$	

Clin Neurol Neurosurg 2022 Nov;222:107469., J Am Coll Cardiol. 2017;69(18):2266-75.

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The Four Main Clinical Indications for Subgroup Analysis

Potential heterogeneity of treatment effect related to risk

- Differences in risks of treatment
- Differences in risk without treatment

Potential heterogeneity of treatment effect related to pathophysiology

- Multiple pathologies underlying a clinical syndrome
- Differences in the biological response to a single pathology
- Genetic variation

Clinically important questions related to the practical application of treatment

- Does benefit differ with severity of disease?
- Does benefit differ with stage in the natural history of disease?
- Is benefit related to the timing of treatment after a clinical event?
- Is benefit dependent on comorbidity?

Underuse of treatment in routine clinical practice due to uncertainty about benefit

- Underuse of treatment in specific groups of patients eg, elderly people
- Confinement of treatment according a narrow range of values of a relevant physiological variable—eg, treatment thresholds for cholesterol level or blood pressure

Lancet 2005 Jan;365(9454):176-86

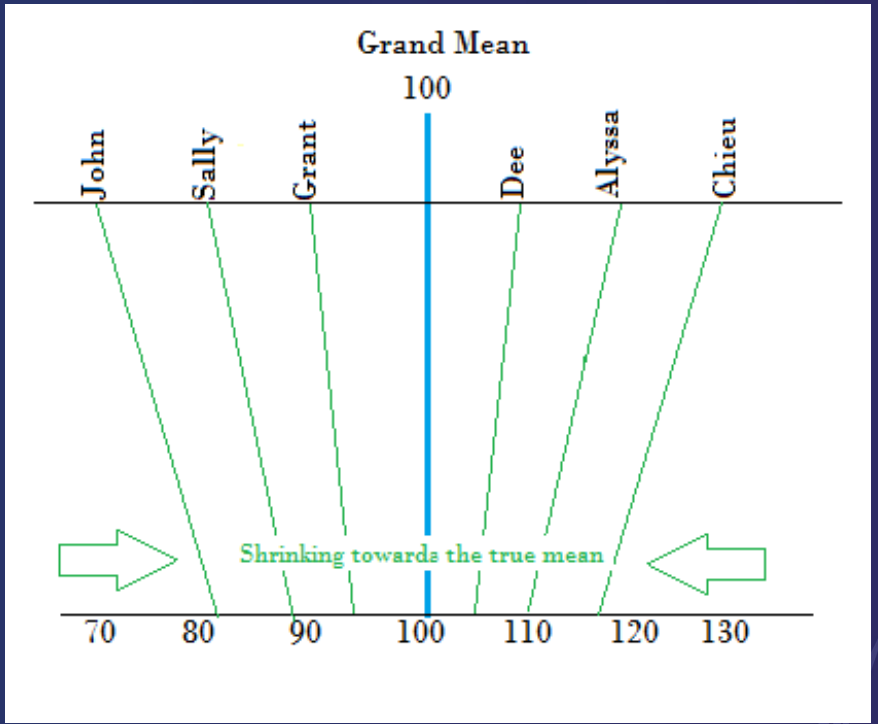
Descriptive HTE Based on Bayesian Methods

- A Bayesian subgroup analysis can be an effective approach for descriptive HTE when the subgroups are prespecified in the protocol.
- Investigators need only unconfounded subgroup-specific effects, and their variances, to use the methodology.
- These subgroup estimates can be obtained from propensity score–based matching or by weighting within each subgroup,

Descriptive HTE Based on Bayesian Methods

Shrinkage estimation

- TE in a subgroup is estimated as a compromise between the “raw” or “observed” TE in that group and the overall (average) TE.
- The degree of compromise depends on the size of the subgroup and the shrinkage method. The smaller the subgroup the greater the compromise.



Descriptive HTE Based on Prognostic and Propensity Scores

- Captures HTE dependent on
  - the risk for outcome (a prognostic score)
  - the probability that a person receives a treatment of interest (a propensity score)

Risk of chronic kidney disease in people living with HIV by tenofovir disoproxil fumarate (TDF) use and baseline D:A:D chronic kidney disease risk score

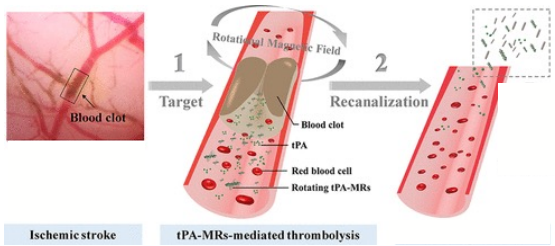
R Hsu,[1,2] L Brunet [3] J Fusco [3] A Beyer,[4] G Prajapati,[4] C Wyatt,[5] M Wohlfeiler[6] and G Fusco[3]

Table 1. Association Between TDF Exposure, D:A:D CKD Risk Strata, and Incidence of CKD*

TDF/D:A:D Risk Group	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No TDF		
Low-risk	1.00 (Ref)	1.00 (Ref)
Medium-risk	4.69 (1.70–12.96)	2.32 (0.72–7.52)
High-risk	37.56 (17.20–82.02)	19.55 (7.35–52.00)
TDF		
Low-risk	0.42 (0.16–1.11)	0.55 (0.19–1.54)
Medium-risk	5.37 (2.40–12.01)	3.96 (1.38–11.39)
High-risk	18.30 (8.42–39.78)	12.84 (4.57–36.07)

CKD = chronic kidney disease; **D:A:D = Data Collection on Adverse Events of Anti-HIV Drugs**; OR, odds ratio; TDF = tenofovir disoproxil fumarate.

HIV Med 2021 May;22(5):325-333.



Results of Multivariable Logistic Regression, Propensity Matching, Propensity Adjustment, and Propensity-based Weighting under Conditions of Nonuniform Effect

Tobias Kurth[1,2,3], Alexander M. Walker[3,4], Robert J. Glynn[1,5,6], K. Arnold Chan[3,4], J. Michael Gaziano[1,2,7], Klaus Berger[8], and James M. Robins[3,6]

Table 2. Proportion of Deaths Among 6,269 Ischemic Stroke Patients Registered in a German Stroke Registry Between 2000 and 2001 Who Were Treated or Not Treated With Tissue Plasminogen Activator, According to Percentiles of the Propensity Score for the Entire Study Population

Percentile	Treated (n = 212)				Not treated (n = 6,057)				Empirical OR*
	Score†	No.	Deaths		Score†	No.	Deaths		
			No.	%			No.	%.	
99 to 100	0.5809	36	3	8.3	0.5474	26	7	26.9	0.25
95 to <99	0.3143	73	13	17.8	0.2912	178	27	15.2	1.21
90 to <95	0.1393	55	8	14.6	0.1363	258	19	7.4	2.14
75 to <90	0.0585	31	3	9.7	0.0459	910	82	9.0	1.08
50 to <75	0.0115	10	4	40.0	0.0084			5.6	11.27
25 to <50	0.0017	5	2	40.0	0.0014	1,561	54	3.5	18.60
10 to <25	0.0004	2	1	50.0	0.000267	940	36	3.8	25.11
5 to <10		0	0	0	0.000066	313	6	1.9	
1 to <5		0	0	0	0.000027	251	8	3.2	
0 to <1		0	0	0	0.000007	62	1	1.6	
Overall	0.2521	212	34	16.0	0.0262	6057	327	5.4	3.35

*Propensity-stratum-specific-treatment–mortality odds ratio.

†Mean propensity score in percentile.

Am J Epidemiol. 2006 Feb 1;163(3):262-70.

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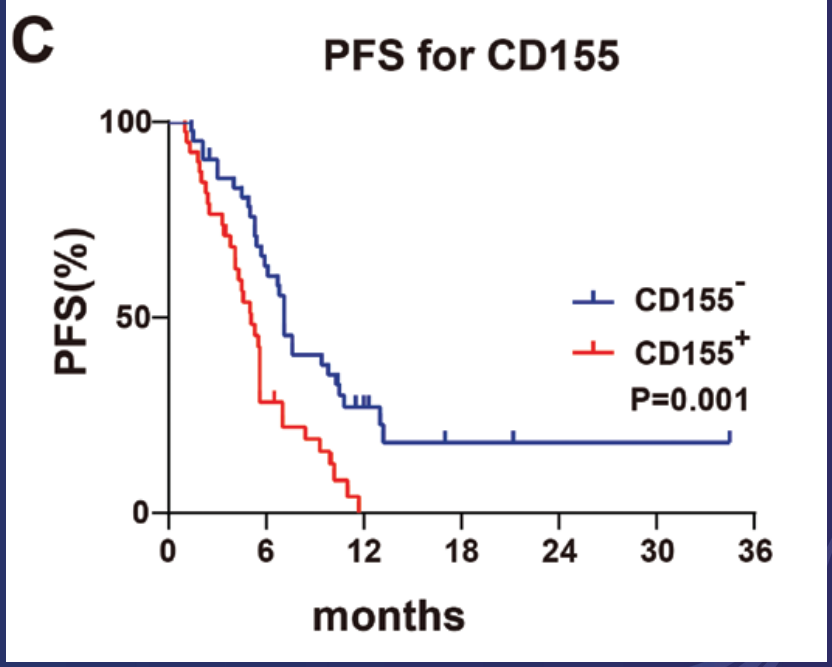
Objective 3:

Discover Subgroups With Important HTE

Obj 3: Discover Subgroups With Important HTE

- To identify subgroups that might benefit from treatment more than the average patient and with lower risk for harm
- There is less concern about adequate power and multiple comparisons, but attention to bias and confounding cannot be ignored

Association of tumor CD155− vs CD155+ with progression-free survival in NSCLC patients treated with αPD1



Clin Exp Immunol. 2022 Jun 11;208(2):220-232.

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Key Elements to Prespecify in Subgroup Search

1. Prespecification
2. Biomarker effects
3. Interactions
4. Adjusting for multiplicity
5. Bias correction
6. Partition

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Key Elements to Prespecify in Subgroup Search

1. Prespecification

- algorithm/methodology to be used for identifying subgroups
- list of biomarkers
- complexity of subgroup definitions
- other options/decisions in the analysis process

Key Elements to Prespecify in Subgroup Search

2. Biomarker effects

allows for separating prognostic biomarker effects from predictive biomarker effects.

3. Interactions

allows for multiple biomarkers to be included in the definition of a subgroup.

Key Elements to Prespecify in Subgroup Search

4. Adjusting for multiplicity

how statistical significance (i.e., p-values) of a subgroup finding will be adjusted for multiplicity.

5. Bias correction

how estimates of treatment effect are corrected for bias due to the selection bias associated with searching multiple subgroups.

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Key Elements to Prespecify in Subgroup Search

6. Partition

allows for identification of a cut-off value for a continuous biomarker that separates lower treatment effects from higher treatment effects.

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Objective 4:

Predict Individualized Treatment Effects

Obj 4: Predict Individualized Treatment Effects

- Estimate ITE, which rely on modeling assumptions about how the TE varies according to individual characteristics
- Individualized estimates = conditional average treatment effects (CATEs)

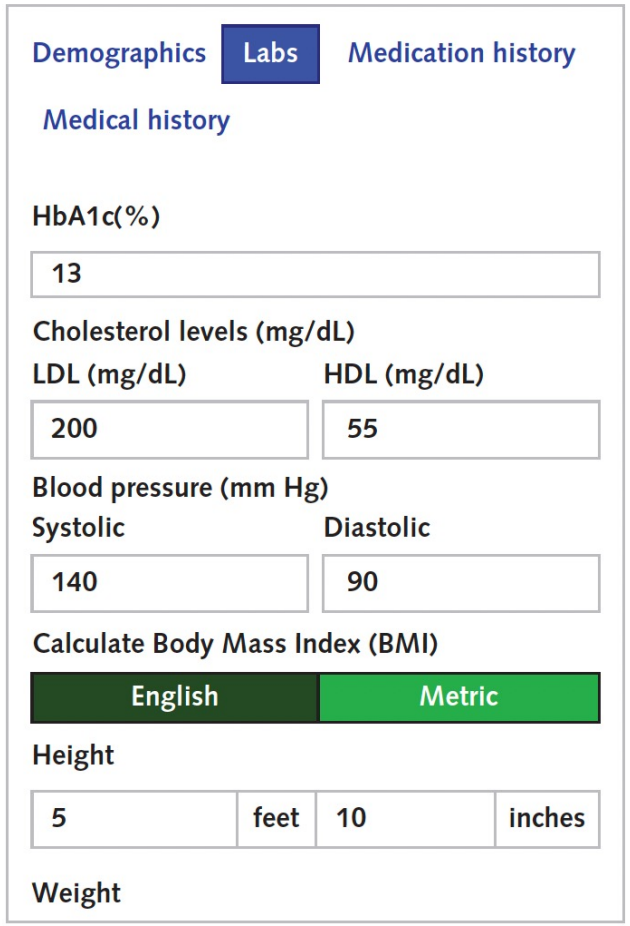
AACE Endocrine Practice™

Development and Internal Validation of A Prediction Tool To Assist Clinicians Selecting Second-Line Therapy Following Metformin Monotherapy For Type 2 Diabetes

Caroline E. El Sanadi, PhD, MS • Kevin M. Pantalone, DO • Xinge Ji, MS • Michael W. Kattan, PhD

Endocr Pract. 2021 Apr;27(4):334-341.

Figure 2. Screenshot of the clinical decision support tool "labs" page and prediction outputs for an example "Patient X".



Run Calculator

Predicted 5-year risk of outcomes

	SGLT2	GLP1	DPP4	TZO	SFU	Insulin
Death	1.5%	2.7%	4.7%	4.9%	6.3%	11.3%
Stroke	6.4%	8.4%	7%	7%	7.6%	8.8%
MI	4%	3.2%	4.3%	3.6%	4.2%	5.4%
Renal failure	3%	1.9%	2.8%	2.8%	3.4%	5.3%
Hypertension	31.4%	34.9%	36.1%	35.3%	37.8%	44.3%

Note:
Drugs predicted to be inferior for all outcomes are displayed in gray shading in the table above.
DPP4: Dipeptidyl peptidase-4 inhibitor;
GLP1: Glucagon-like Peptide-1 agonist;
SGLT2: Sodium-Glucose Co-transporter 2 inhibitor;
SFU: Sulfonylurea;
TZO: Thiazolidinedione;
Insulin: Insulin-Basal or Bolus or Mixed insulin

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What is still needed?

- Principled approaches to using information about newly discovered subgroups
- Presenting results clearly to decision makers
- A framework for determining whether evidence on HTE is actionable for decision makers
- Methods that can incorporate sources of heterogeneity beyond patient level characteristics (provider-level and health system–level factors)
- Consensus on methods to evaluate THE => Expert-based guidelines

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Conclusion

- The greater heterogeneity among real-world patients compared with trial participants creates opportunities to generate meaningful evidence for more personalized practice decisions
- Consider HTE always when interpreting the results of studies and when generating new evidence