Combining Real-world and Clinical Trial Data to Study the Effectiveness of Thrombolytics for Treating Patients with COVID-19 Associated Acute Respiratory Distress Syndrome

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Combining Real-World and Clinical Trial Data to Study the Effectiveness of Thrombolytics for Treating Patients with COVID-19 Associated Acute Respiratory Distress Syndrome

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Disclosures

I do not have any disclosures relevant to this presentation.

Identifying the Need

High Mortality in critically ill COVID-19 patients

Acute Respiratory Distress Syndrome

Thrombotic events in COVID-19 patients

- The suspicions of increased risk of thrombosis was seen in multiple sites, countries, and treated with anticoagulation and or thrombolytics based on clinical judgement and assessment of risks versus benefit.
- The therapy itself is not without potentially harmful side effects

Clinical judgement is a major driver of clinical decision making especially when there is lack of therapies, guidelines.

Anticoagulation and thrombolytic therapy

Evidence was urgently needed

Challenges

- Multi-center, multi-disciplinary collaborative effort
- STARS trial - Study of Alteplase for Respiratory Failure in SARS-CoV-2 COVID-19: A Vanguard Multicenter, Rapidly Adaptive, Pragmatic, Randomized Controlled Trial. Barrett CD, Moore HB, Moore EE, et al Chest 2022 Mar;161(3):710-727).
- Clinical trials were competing for the same patient population
  - Patient populations were also very heterogeneous and disease presentations were captured across a broad spectrum of impactful factors:
    - Comorbidities, medications, level of severity before hospitalization, etc.
- Staff shortages research, facing personal illness, deployment.
- Collaboration was needed between clinicians and investigators to meet the demands of in-patient studies of critically ill patients, a 24/7 operation.

The Benefits of Real-World Data

- Real-world outcomes from everyday clinical decisions is invaluable.
- RWD before and after interventions is available and easily accessible
- RWD can be used to enhance study data and study population.
- IRB approval process is quicker and expedites study start up.

Polling Question (Open Text Response):

What research challenges did your organization / institution face due to COVID?

Gathering Real-World Data in Parallel with Clinical Trials to Deliver Analytic Insights

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Disclosures

Employee and shareholder at Genentech, Inc - A Member of the Roche Group

Context: Rationale

Researchers at US universities identified a need for evidence informing treatment of COVID+ Acute Respiratory Distress Syndrome (ARDS).

ARDS is thought to cause pulmonary microemboli, which can lead to worsening respiratory failure and possibly death.

Alteplase* is a thrombolytic drug approved for use in *acute massive pulmonary embolism*.

Researchers have studied thrombolytics for use in treatment of ARDS.[1-4]

*Alteplase is not currently approved for use in treating COVID, ARDS, or pulmonary microemboli.

1. Hardaway RM, Harke H, Williams CH. Fibrinolytic agents: a new approach to the treatment of adult respiratory distress syndrome. Adv Ther. 1994;11(2):43-51.
2. Gram J, et al. Inhalation/intravenous recombinant tissue plasminogen activator and inhaled heparin in a patient with acute respiratory distress syndrome. In: Fibrinolysis and Proteolysis. 1999;13(4):209-212.
3. Greene R, et al. Pulmonary vascular obstruction in severe ARDS: angiographic alterations after iv fibrinolytic therapy. American Journal of Roentgenology. 1987 Mar 1;148(3):501-8.
4. Mahmoud AA, et al. Streptokinase versus unfractionated heparin nebulization in patients with severe acute respiratory distress syndrome (ARDS): a randomized controlled trial with observational controls. Journal of Cardiothoracic and Vascular Anesthesia. 2020 Feb 1;34(2):436-43.

ACTIVASE (Alteplase) and TNKase (Tenecteplase) Prescribing Information

Activase is a tissue plasminogen activator (tPA) indicated for the treatment of

- Acute Ischemic Stroke (AIS).
- Acute Myocardial Infarction (AMI) to reduce mortality and incidence of heart failure.

Limitation of Use in AMI: the risk of stroke may be greater than the benefit in patients at low risk of death from cardiac causes.

- Acute Massive Pulmonary Embolism (PE) for lysis.

TNKase® (Tenecteplase) is indicated for use in the reduction of mortality associated with acute myocardial infarction (AMI).

For full prescribing information please see
https://www.gene.com/download/pdf/activase_prescribing.pdf
https://www.gene.com/download/pdf/tnkase_prescribing.pdf

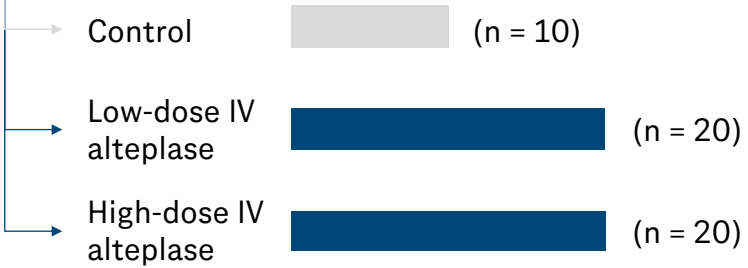
Context: Clinical Trials

Alteplase Phase 2 Trial

(NCT04357730)
PI: Ernest Moore, MD
CU Denver Health, CO
University of Colorado **Denver**

Primary outcome:

PaO2/FiO2 ratio



Tenecteplase Phase 2 Trial

(NCT04505592)
PI: Hooman Poore, MD
Mount Sinai Health System, NY
Mount Sinai

Primary outcome:

National Institute of Allergy and Infectious Diseases (NIAID) scale

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Objectives

Use RWD to urgently assess for associations between thrombolytic treatment and outcomes in patients with COVID+ ARDS

- Enhance the robustness of clinical trial analyses
- Inform future research to identify appropriate treatments for ARDS
- Provide evidence to support treatment decisions for COVID+ ARDS

Design and Implementation (1 of 2)

Design:

Cohort study with multiple sub-groups

- Alteplase trial
  - Controls
  - Alteplase treated (2 dosing groups)
- Tenecteplase trial
  - Placebo
  - Tenecteplase treated
- RWD
  - Controls
  - Alteplase treated (outside of trials)
  - Tenecteplase treated (outside of trials)

Polling question (Word Cloud):

What was the shortest timeline in which you were able to complete an observational study with primary data collection? Put your answer(s) in one-word.

Design and Implementation (2 of 2)

Implementation

Complex project management:

Multi-site collaboration agreements, separate institutional IRBs, flexible meeting options

Data collection:

Clinical Operations, Clinical Research Organization, Site-based informatics services and research staff

Data infrastructure:

Custom electronic case report forms to capture key clinical trial and real-world data elements (computer scientists, software developers), Clinical Operations, Clinical Research Organization, Medical Affairs data scientists and biostatisticians

Analyzing Combined Real-world and Clinical Trial Data

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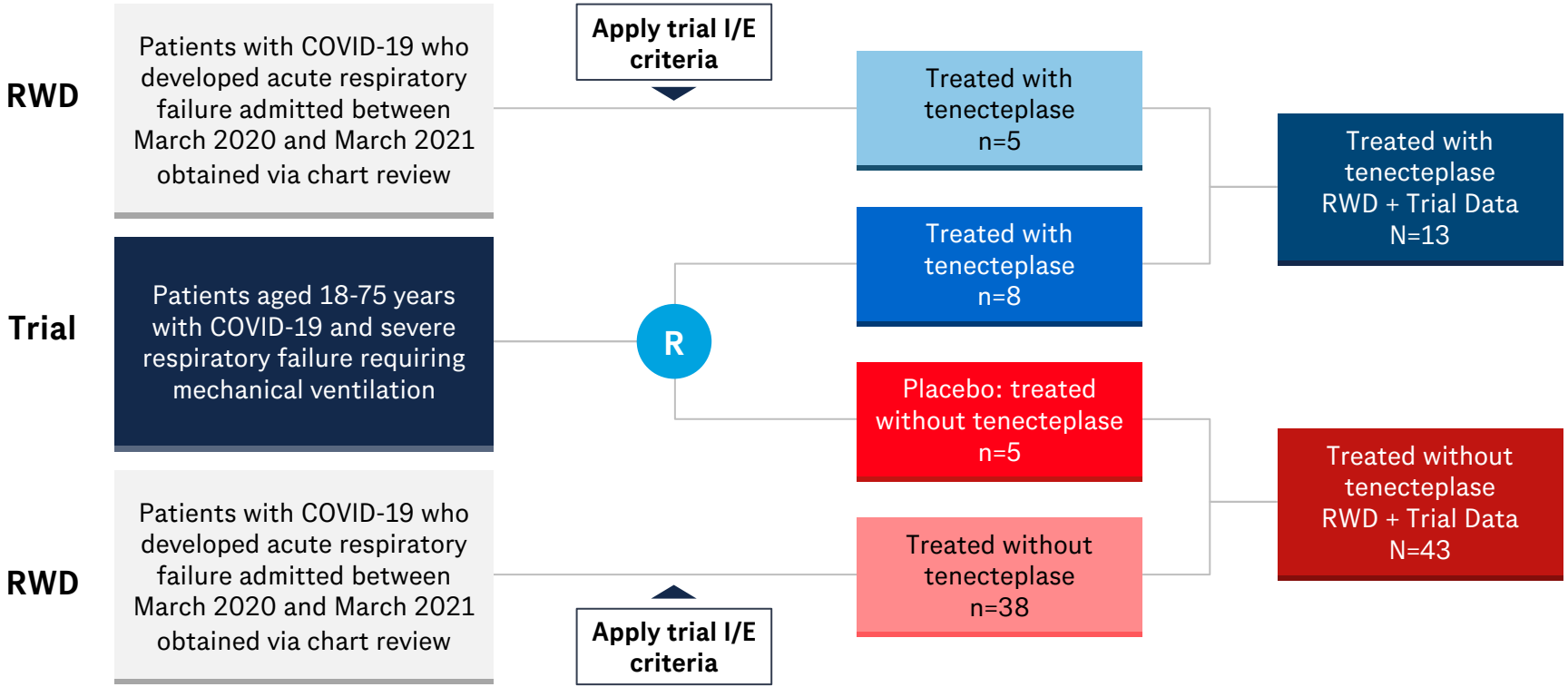
Disclosures

Employee and shareholder at Genentech, Inc - A Member of the Roche Group

Cohort Includes 2 Sources: Tenecteplase Trial and RWD



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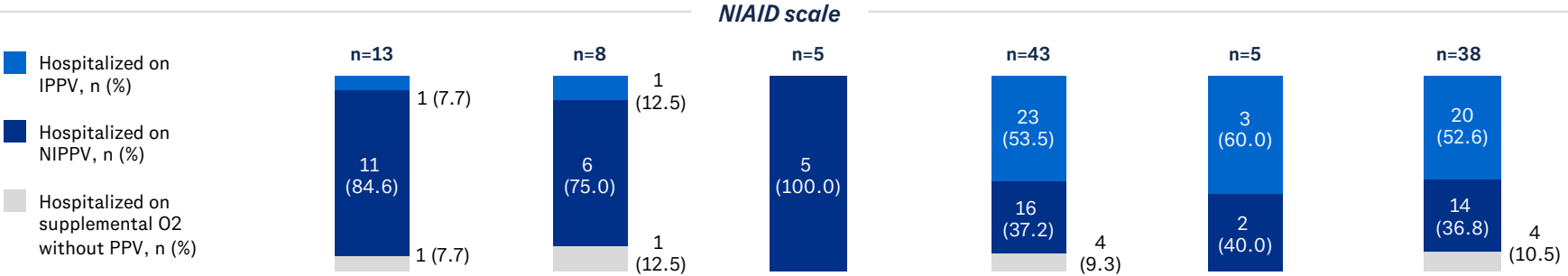
Patients in RWD cohort were older and had more comorbid conditions

Demographics and clinical characteristics	Tenecteplase Clinical Trial Data: All (n=13)	Tenecteplase Clinical Trial Data: Treated with tenecteplase (n=8)	Tenecteplase Clinical Trial Data: Treated without tenecteplase (n=5)	RWD: All (n=43)	RWD: Treated with tenecteplase (n=5)	RWD: Treated without tenecteplase (n=38)
Age, years	**60.9 (14.5)**	60.3 (15.5)	61.8 (14.4)	**63.1 (9.1)**	67.6 (7.7)	62.5 (9.2)
Male, n (%)	9 (69.2)	7 (87.5)	2 (40.0)	29 (67.4)	3 (60.0)	26 (68.4)
BMI	32.6 (9.4)	36.3 (10.1)	27.5 (5.7)	32.2 (10.6)	29.5 (4.1)	32.5 (11.2)
Elixhauser Comorbidity Index score	**2.2 (0.4)**	2.3 (0.5)	2.0 (0.0)	**2.9 (0.9)**	2.6 (0.6)	3.0 (1.3)



Data are presented as mean (SD) or n (%)
BMI, body mass index; IPPV, invasive positive pressure ventilation; NA, not applicable; NIAID, National Institute of Allergy and Infectious Diseases; NIPPV, noninvasive positive pressure ventilation; RWD, real-world data; SD, standard deviation.

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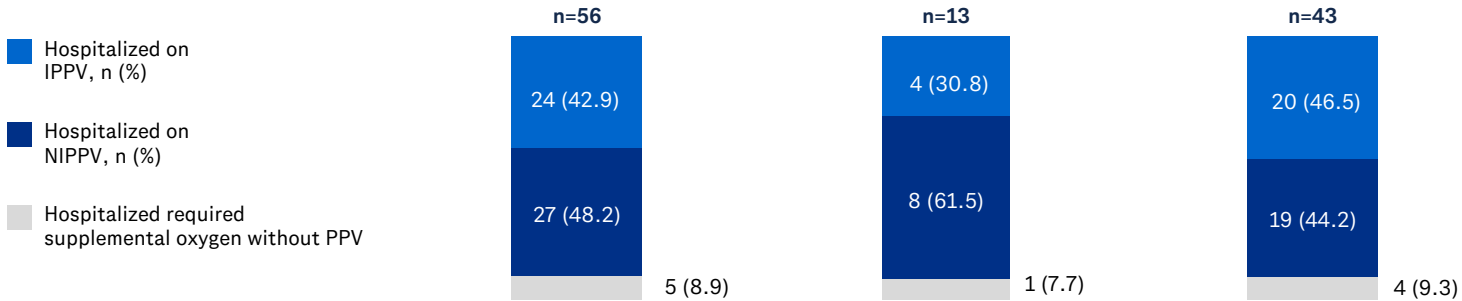
In the combined data, differences of baseline characteristics were observed between the treatment groups

Demographics and clinical characteristics	Tenecteplase RWD plus trial data: Overall (n=56)	Tenecteplase RWD plus trial data: Treated with Tenecteplase (n=13)	Tenecteplase RWD plus trial data: Treated without Tenecteplase (n=43)	*SMD*
Age, years	62.5 (10.5)	63.1 (13.2)	62.4 (9.7)	**0.02**
Male, n (%)	38 (67.9)	10 (76.9)	28 (65.1)	**0.16**
BMI	32.3 (10.3)	33.5 (8.6)	32.0 (10.7)	**0.17**
Elixhauser Comorbidity Index score	2.7 (0.9)	2.4 (0.5)	2.8 (1.0)	**0.82**

NIAID scale score at Day 1 of use of MV



0.20

Data are presented as mean (SD; range) or n (%).
BMI, body mass index; IPPV, invasive positive pressure ventilation; MV, mechanical ventilation; NIAID, National Institute of Allergy and Infectious Diseases; NIPPV, noninvasive positive pressure ventilation; RWD, real-world data; SD, standard deviation.

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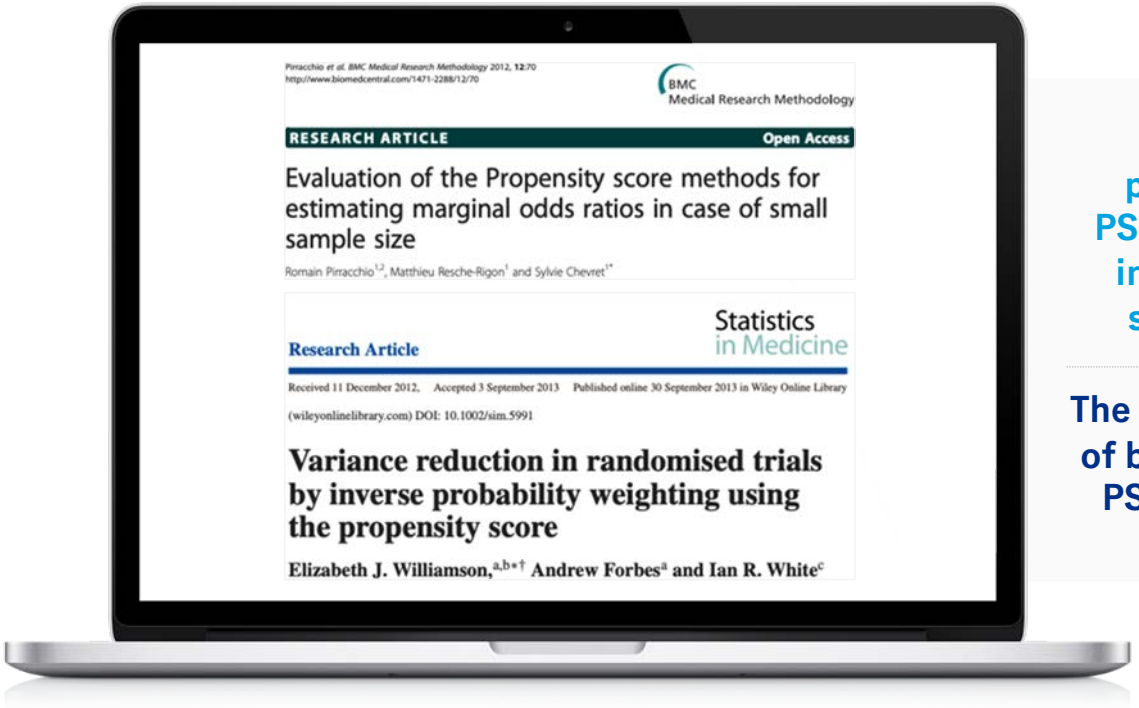
Polling question (Multiple Choice):

What approaches have you used to adjust for potential confounders when analyzing cohorts with small sample sizes?

- Stratification
- Multivariate Models (e.g. linear regression, logistic regression)
- Propensity Score Matching
- Inverse probability of treatment weighting
- Other

The small cohort size posed some statistical challenges and considerations on using the Propensity Score (PS) methods (1 of 4)



What is the performance of PS- based methods in the context of small samples?

PS matching might lead to a further decrease in the sample size.

The limited sample size restricts the number of baseline covariates to be included in the PS regression model to avoid overfitting.

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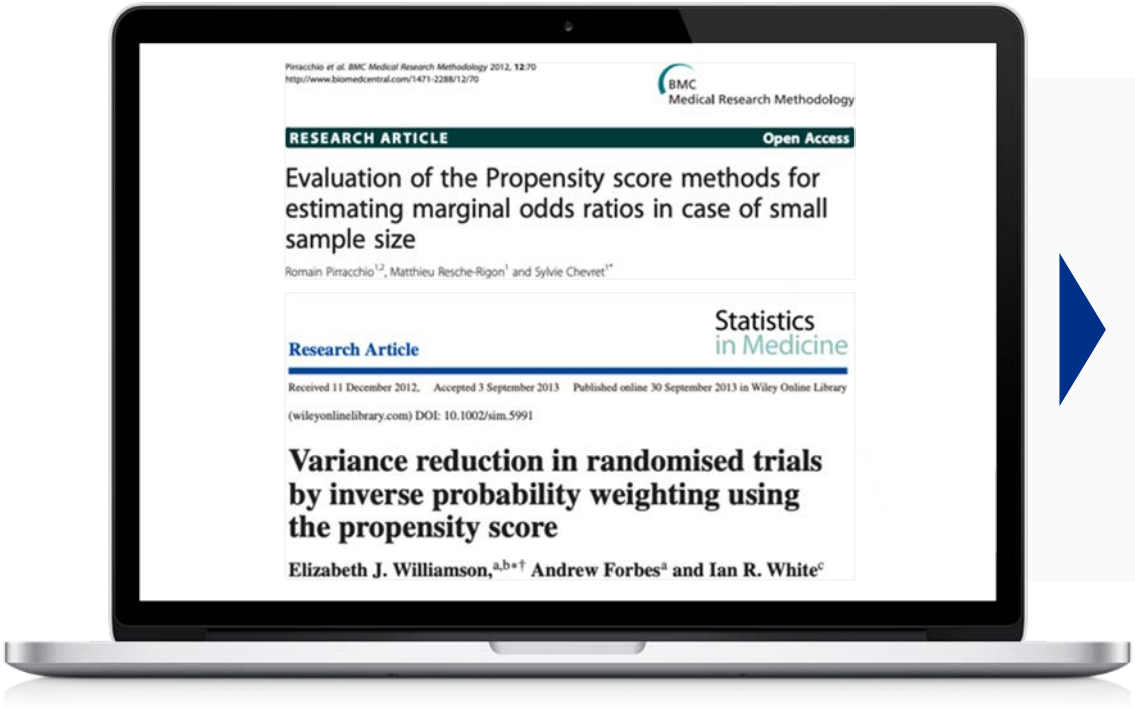
The small cohort size posed some statistical challenges and considerations on using the Propensity Score (PS) methods (2 of 4)



What is the performance of PS- based methods in the context of small samples?

Simulation studies have shown that even in case of small study samples (e.g. N = 40), PS- matching and IPTW can yield correct estimations of treatment effect.

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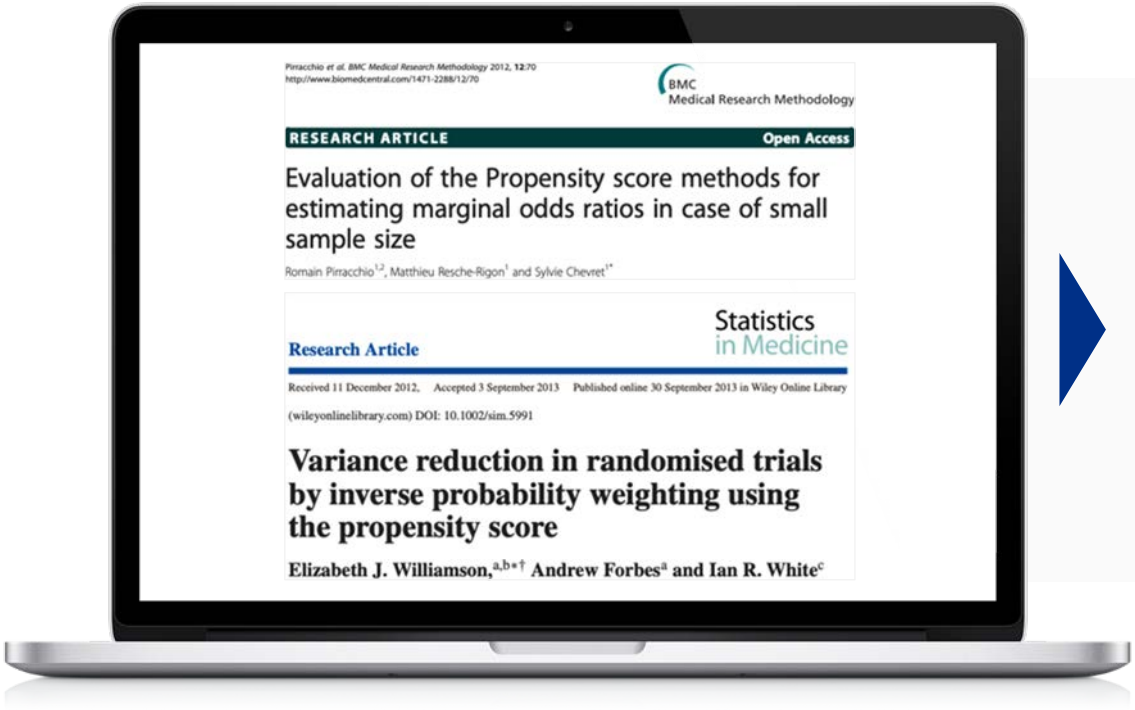
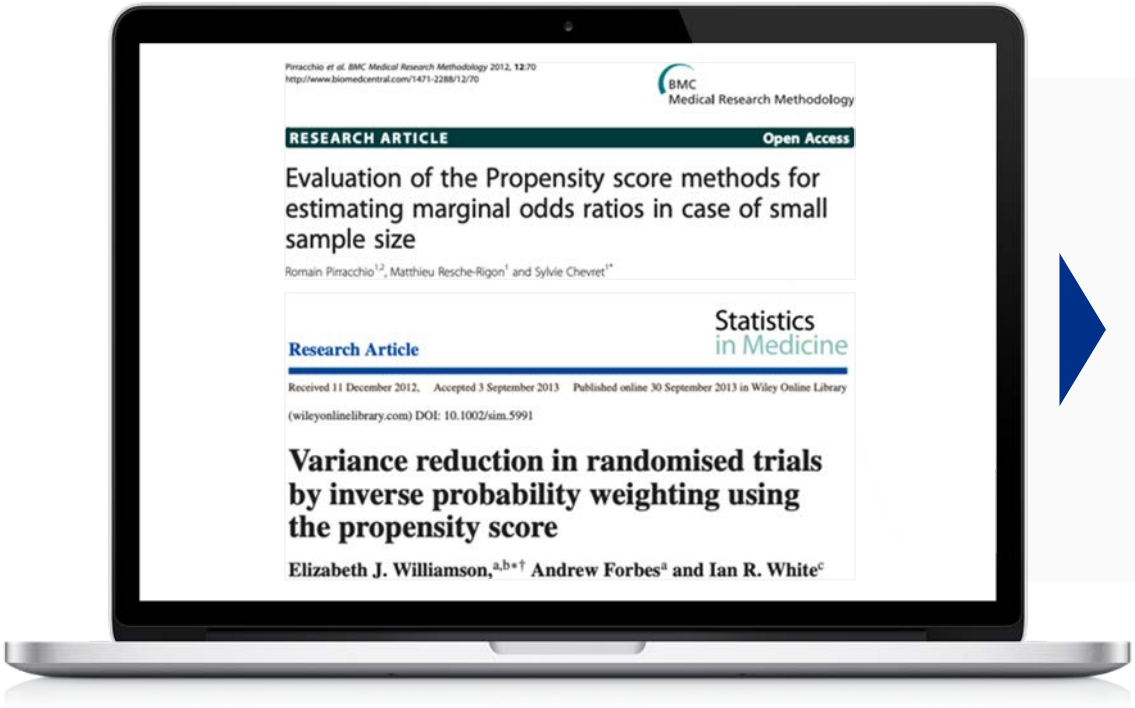
The small cohort size posed some statistical challenges and considerations on using the Propensity Score (PS) methods (3 of 4)



PS matching might lead to a further decrease in the sample size.

Use inverse probability of treatment weighting (IPWT) with a robust variance estimator

The small cohort size posed some statistical challenges and considerations on using the Propensity Score (PS) methods (4 of 4)



The limited sample size restricts the number of baseline covariates to be included in the PS regression model to avoid overfitting.

To include the true confounder and the variable related only to the outcome in the PS model.

To report several models controlling for additional variables as sensitivity analysis.

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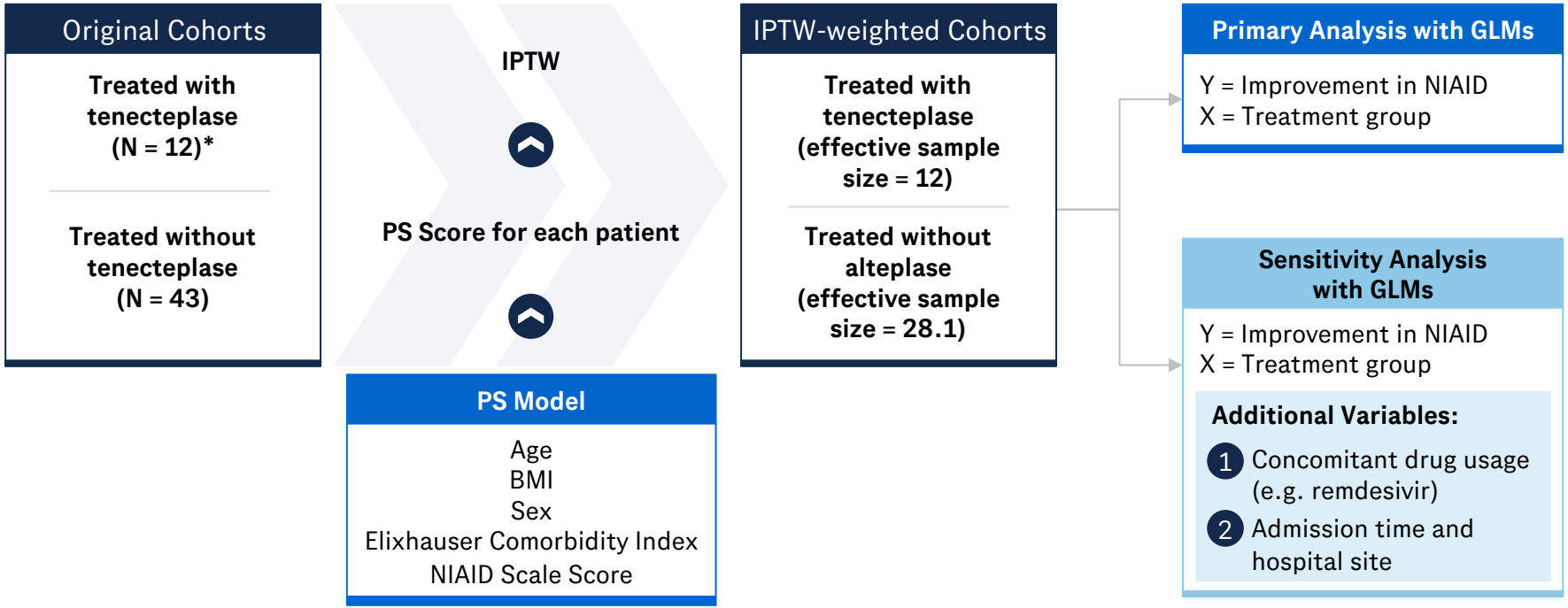
Treatment effect was assessed in the IPTW-weighted cohorts using Generalized Linear Models (GLMs)



* One patient with missing BMI was excluded from the analysis

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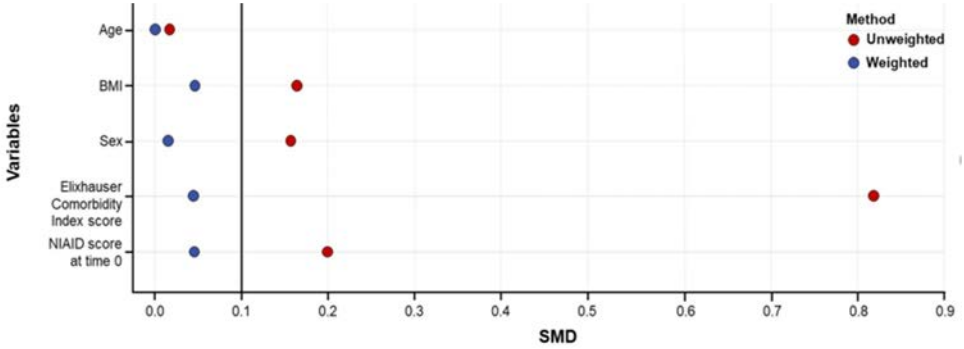
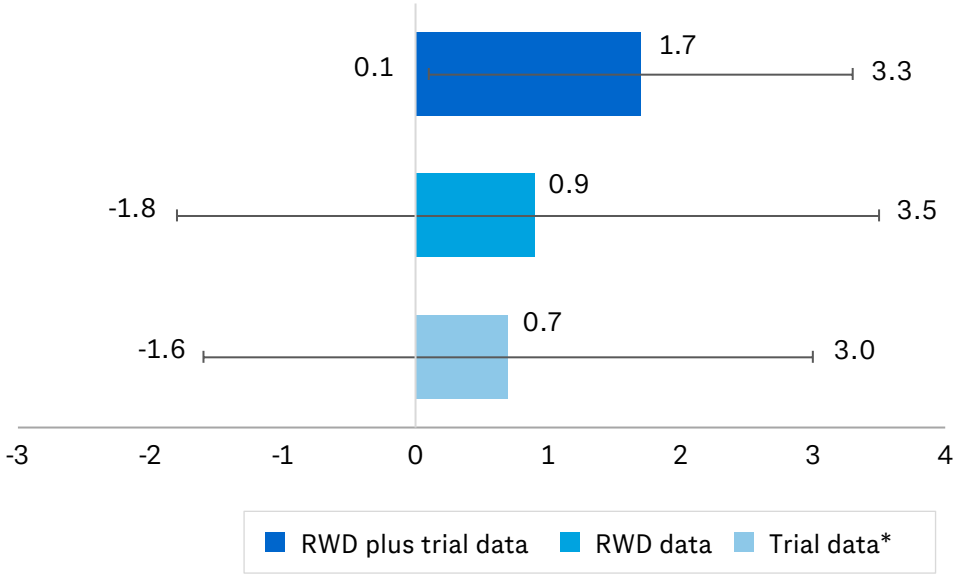
Association between tenecteplase treatment and improvements in NIAID was measured



Outcomes	RWD plus trial data			
	Tenecteplase treatment coefficient (95% CI)	Robust SE	Odds Ratio (OR, 95% CI)	*P value*
Primary Analysis				
NIAID improvement	**1.7 (0.1 to 3.3)**	**0.8**	**5.4 (1.1 – 27.8)**	**0.04**
Sensitivity Analysis				
Concomitant remdesivir	1.7 (–0.1 to 3.5)	0.9	5.3 (0.9 – 32.7)	0.07
Concomitant corticosteroids	2.1 (0.4 to 3.8)	0.9	7.8 (1.4 – 43.4)	0.02
Concomitant antimalarials	Analysis not performed because only 1 patient in the study received antimalarials			
Admission time, hospital site and interaction of admission time and hospital site	-0.3 (–1.4 to 0.7)	0.6	0.7 (0.2 – 2.1)	0.54

Supplementing trial data with RWD provided greater precision of estimates

Outcomes	Tenecteplase treatment coefficient (95% CI)	Robust SE	*P value*
Primary Analysis – NIAID improvement		**0.8**	**0.04**
		1.3	**0.51**
		1.2	**0.56**

**Results for trial data was calculated for illustration purpose only. Final trial analysis methods differ.*

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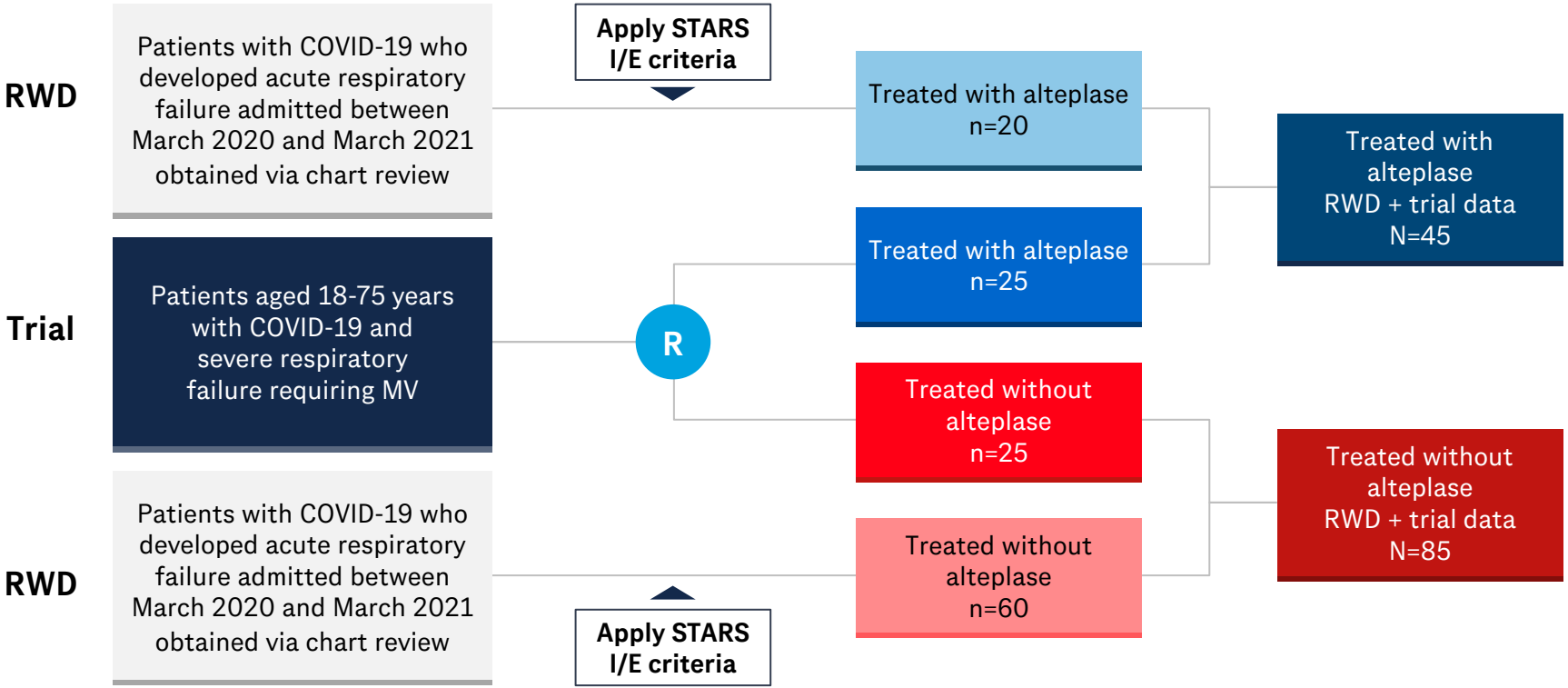
Cohort Includes 2 Sources: Alteplase Trial and RWD



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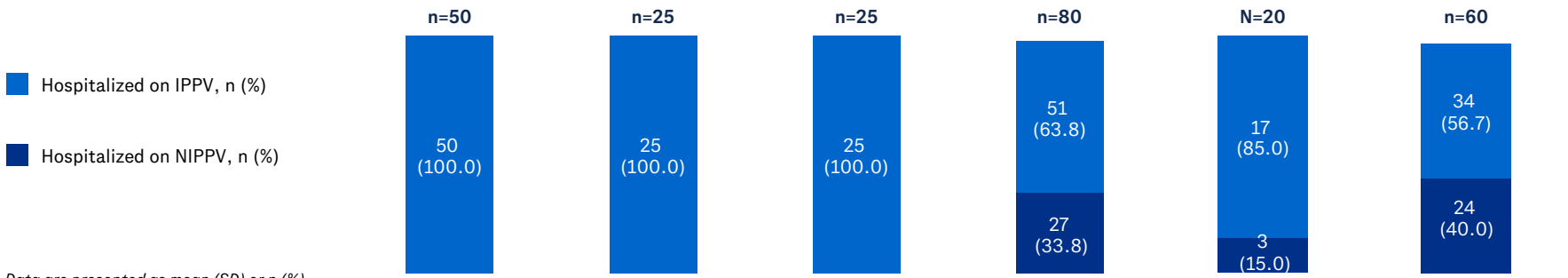
Patients in RWD cohort were older and had more comorbid conditions

Demographics and clinical characteristics	Alteplase Clinical Trial Data: Overall (n=50)	Alteplase Clinical Trial Data: Treated with alteplase (n=25)	Alteplase Clinical Trial Data: Treated without alteplase (n=25)	RWD: Overall (n=80)	RWD: Treated with alteplase (n=20)	RWD: Treated without alteplase (n=60)
Age, years	**58.1 (9.5)**	57.0 (11.0)	59.2 (7.9)	**61.5 (11.2)**	59.1 (11.5)	62.3 (11.1)
Male, n (%)	37 (74.0)	21 (84.0)	16 (64.0)	60 (75.0)	14 (70.0)	46 (76.7)
BMI	34.5 (7.3)	35.2 (7.8)	33.8 (6.8)	32.2 (9.1)	29.8 (7.3)	33.0 (9.6)
Elixhauser Comorbidity Index score	**2.00 (0.0)**	2.00 (0.0)	2.00 (0.0)	**3.2 (1.3)**	3.0 (1.0)	3.3 (1.3)



Data are presented as mean (SD) or n (%)
BMI, body mass index; IPPV, invasive positive pressure ventilation; NA, not applicable; NIAID, National Institute of Allergy and Infectious Diseases; NIPPV, noninvasive positive pressure ventilation; RWD, real-world data; SD, standard deviation.

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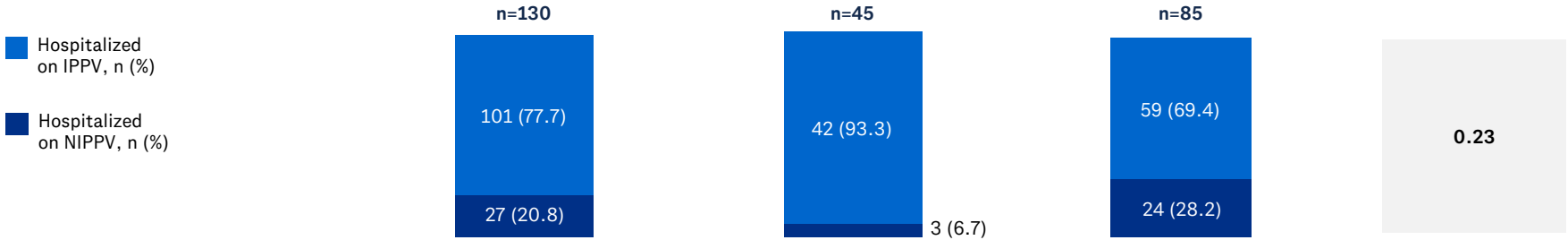
In the combined data, differences of baseline characteristics were observed between the treatment groups

Demographics and clinical characteristics	Overall (n=130)	Alteplase RWD plus trial data: Treated with alteplase (n=45)	Alteplase RWD plus trial data: Treated without alteplase (n=85)	*SMD*
Age, years	60.2 (10.7)	58.0 (11.2)	61.4 (10.3)	**0.32**
Male, n (%)	97 (74.6)	35 (77.8)	62 (72.9)	**0.02**
BMI	33.1 (8.5)	32.8 (8.0)	33.2 (8.8)	**0.03**
Elixhauser Comorbidity Index score	2.8 (1.2)	2.4 (0.8)	2.9 (1.3)	**0.5**

NIAID scale score at time zero



0.23

Data are presented as mean (SD) or n (%)
BMI, body mass index; IPPV, invasive positive pressure ventilation; NA, not applicable; NIAID, National Institute of Allergy and Infectious Diseases; NIPPV, noninvasive positive pressure ventilation; RWD, real-world data; SD, standard deviation; SMD, standardardized mean difference

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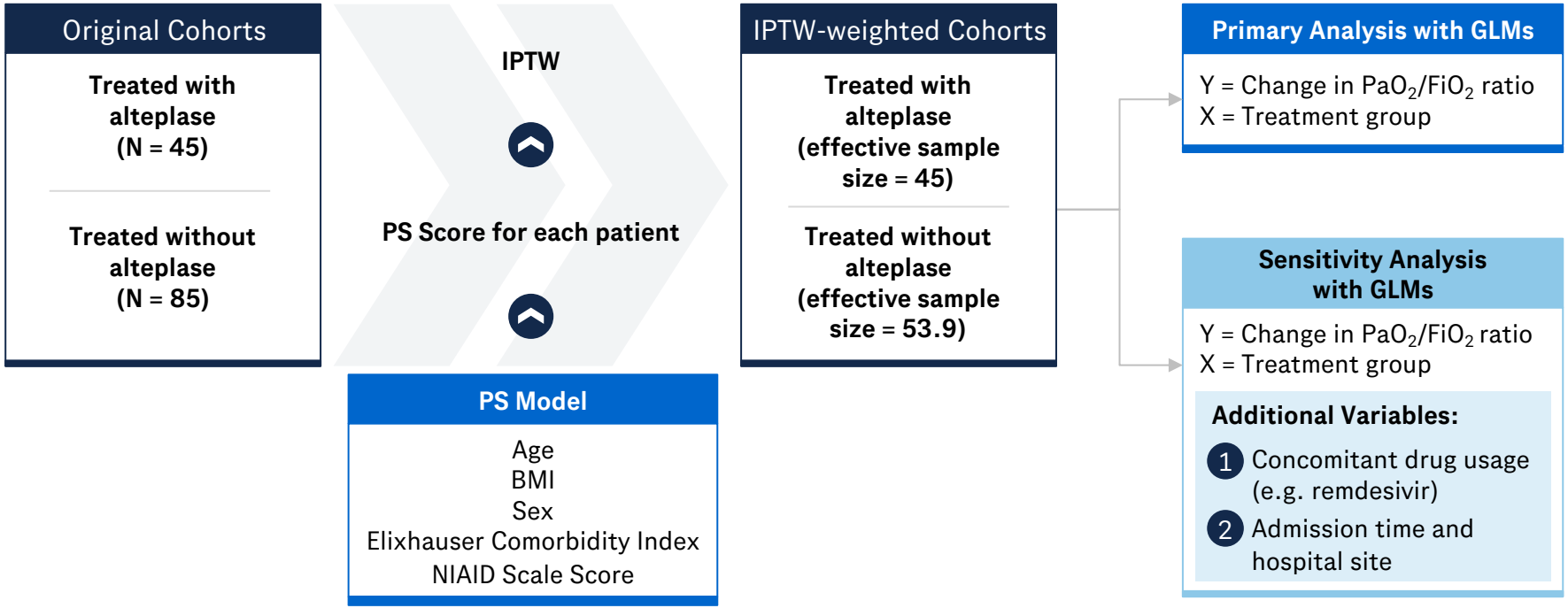
Treatment effect was assessed in the IPTW-weighted cohorts using Generalized Linear Models (GLMs)



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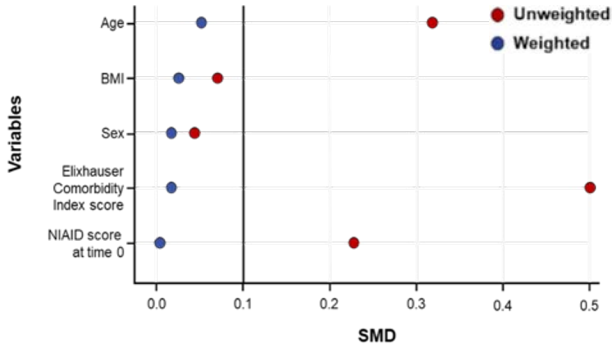
Association between alteplase treatment and improvements in PaO_2/FiO_2 ratios was measured



Outcomes	RWD plus trial data		
	Alteplase treatment coefficient (95% CI)	Robust SE	*P value*
Primary Analysis			
PaO_2/FiO_2 ratio improvement	22.1 (−1.1 to 45.2)	11.8	0.06
Sensitivity Analysis			
Concomitant remdesivir	20.1 (−6.3 to 46.4)	13.5	0.14
Concomitant corticosteroids	20.9 (−2.7 to 44.4)	12	0.08
Concomitant antimalarials	14.3 (−9.5 to 38.1)	12.2	0.24
Admission time, hospital site and interaction of admission time and hospital site	9.0 (−14.3 to 32.4)	11.9	0.45
Hospital site and interaction of hospital site and treatment	13.3 (−18.8 to 45.4)	16.4	0.42

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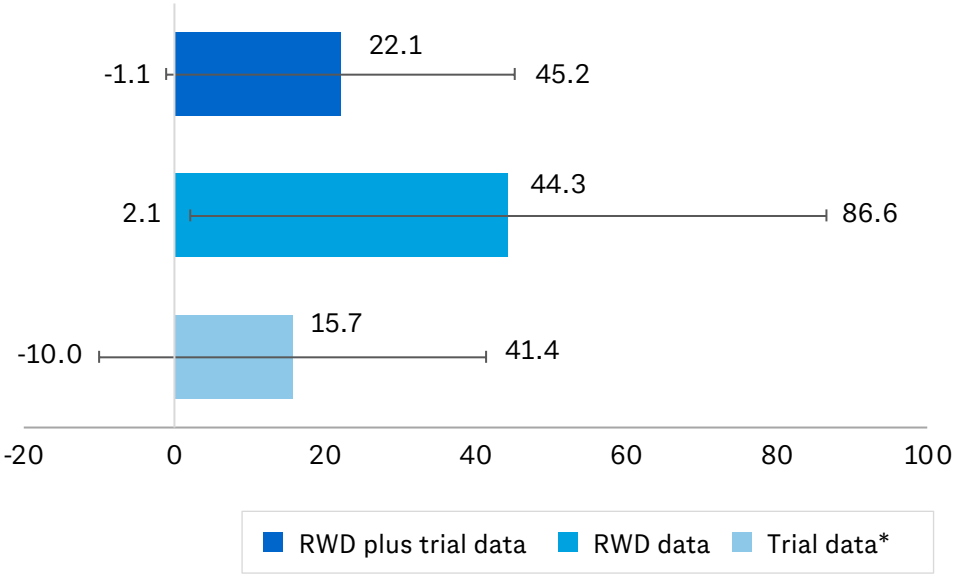
Supplementing trial data with RWD provided greater precision of estimates

Outcomes	Alteplase treatment coefficient (95% CI)	Robust SE	*P value*
Primary Analysis – PaO_2/FiO_2 ratio improvement		**11.8**	**0.06**
		21.6	**0.04**
		13.1	**0.23**

**Results for trial data was calculated for illustration purpose only. The original clinical trial study compared outcomes for tPA Bolus + Heparin group and tPA Drip + Heparin group separately.*

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Conclusion

RWD can enhance, inform, and accelerate analytic insights from small clinical trials in new therapeutic areas

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Questions & Answers

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