Comparison of All-Cause Mortality Following VTE Treatment Between Propensity Score-Adjusted Observational Studies and Matched Randomized Controlled Trials

Meta-Epidemiologic Study

Claudia Coscia, MD; Ana Jaureguizar, MD; Carlos Andres Quezada; Alfonso Muriel, PhD; Manuel Monreal, PhD; Tomas Villén, MD; Esther Barbero, MD; Diana Chiliza, MD; Roger D. Yusen, MD; and David Jimenez, PhD

BACKGROUND: It is unknown whether propensity score-adjusted observational studies produce results comparable to those of randomized controlled trials (RCTs) that address similar VTE treatment issues.

METHODS: The PubMed and Web of Science databases were systematically searched for propensity score-adjusted observational studies, RCTs, and meta-analyses of RCTs that estimated all-cause mortality following VTE treatment. After identifying distinct clinical treatment issues evaluated in the eligible observational studies, a standardized algorithm was used to identify and match at least one RCT or RCT meta-analysis publication for paired study design analyses. Meta-analyses were used to summarize groups of studies. Treatment efficacy statistics (relative ORs) were compared between the paired observational and RCT studies, and the summary relative ORs for all study design pairs were also calculated.

RESULTS: The observational and RCT study pairs assessed seven clinical treatment issues. Overall, the observational study-RCT pairs did not exhibit significantly different mortality estimates (summary relative OR, 0.89; 95% CI, 0.32-1.46; $I^2 = 23\%$). However, two of the seven treatment issue study pairs (thrombolysis vs anticoagulation for pulmonary embolism; once- vs twice-daily enoxaparin for VTE) exhibited a significantly different treatment effect direction, and there was a substantial (nonsignificant) difference in the magnitude of the effect in another two of the study pairs (rivaroxaban vs vitamin K antagonists for VTE; home treatment vs hospitalization for DVT).

CONCLUSIONS: This systematic comparison across seven VTE treatment topics suggests that propensity score-adjusted observational studies and RCTs often exhibit similar all-cause mortality, although differences in the direction or the magnitude of estimated treatment effects may occasionally occur.

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ABBREVIATIONS: PE = pulmonary embolism; RCT = randomized controlled trial

AFFILIATIONS: From the Biostatistics Department (Drs Coscia and Muriel), Ramón y Cajal Hospital and Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS, CIBERESP, Madrid, Spain; Respiratory

Department (Drs Jaureguizar, Quezada, Barbero, Chiliza, and Jimenez), Hospital Ramón y Cajal, Medicine Department, Universidad de Alcalá (IRYCIS), Madrid, Spain; Department of Internal Medicine (Dr Monreal), Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Universidad Católica de Murcia, Murcia, Spain; Emergency

VTE, which encompasses DVT and pulmonary embolism (PE), remains a worldwide major health issue.¹ PE ranks as the third most common cause of vascular death following myocardial infarction and stroke, and it causes most preventable hospital deaths.² Different clinical practice guidelines provide recommendations for the management of acute VTE,³⁻⁶ but high-quality evidence only supports a minority of these recommendations.³ Therefore, a strong need exists for continued efforts to conduct studies that will further assist with decision-making regarding treatment for acute symptomatic PE.

To answer key VTE management questions and to fill data gaps, the randomized controlled trial (RCT) provides the strongest evidence regarding the efficacy and safety of new (or established) therapies while accounting for the effects of unmeasured confounders and selection bias by indication.⁷ However, feasibility or ethical issues may prevent the use of an RCT to address some important clinical questions. Feasibility concerns regarding RCTs include excess complexity, high expense, and long time for trial conduct; RCTs also have

representativeness limitations compared with more real-world studies.

When significant barriers to conducting an RCT exist, investigators may choose to use observational data to examine and infer treatment effects. Although observational studies may show a strong correlation between a treatment and an outcome, they do not provide evidence for causation as strong as that provided by the RCTs. To correct for measured imbalances in pretreatment patient characteristics and confounding in observational studies that compare treatment approaches, investigators have increasingly used propensity scores in the past 2 decades. However, propensity score matching does not address selection bias associated with unmeasured characteristics. Thus, concerns exist regarding the validity of propensity score-matched observational studies that attempt to answer vital clinical questions regarding VTE treatment.

Using a meta-epidemiologic study design, the present study assessed the concordance in VTE treatment mortality effects between propensity score-adjusted observational study and RCT pairs.

Materials and Methods

Study Design

With the goal of assessing differences in mortality effects reported in propensity score-adjusted observational studies and RCTs that addressed similar clinical treatment issues, a systematic review was conducted of the medical literature to identify eligible observational studies. We then identified distinct treatment issues addressed by the studies and grouped the studies according to these issues. A systematic review was subsequently conducted of the medical literature to identify RCTs or RCT meta-analyses that addressed similar treatment issues. A standardized algorithm was then used to match each observational study publication or group of publications to at least one RCT or RCT meta-analysis publication for each treatment issue. For observational studies that we assigned to the same treatment issue group, meta-analysis was used to estimate treatment effects, and the treatment effects were then compared

between the matched observational study and RCT pairs. The systematic reviews were registered with the PROSPERO international prospective registry of systematic reviews on April 23, 2018 (CRD42018087819).

Eligibility Criteria

We required that each propensity score-adjusted observational study, RCT, and RCT meta-analysis include and clearly identify adult patients who presented with acute symptomatic VTE (PE, DVT, or both), compare a VTE intervention with a control group or another intervention, and estimate the effects of the treatments on all-cause mortality. Short-term (typically within 30 days of VTE diagnosis) mortality was chosen as the primary outcome because of its clinical importance and the fact that it is less prone to misclassification compared with other outcomes. As noted earlier, for eligibility, we required that the RCT(s) address one of the treatment issue categories assessed by the observational studies and have patient and setting characteristics similar to those in the paired studies.

Search Strategy

To identify eligible studies, the PubMed and Web of Science databases were searched; the search had no language restrictions. We required studies to have a publication date no later than February 1, 2018. To search for observational studies and observational study meta-analyses, we used a search string of “propensity” [All Fields] AND (“therapeutics” [MeSH Terms] OR “treatment” [All Fields]) AND (“venous thromboembolism” [MeSH Terms] OR “venous” [All Fields] AND “thromboembolism” [All Fields]) OR “venous thromboembolism” [All Fields]). Eligible publications included manuscripts and conference abstracts. We reviewed the references of relevant articles, assessed our own

Department (Dr Villén), Hospital Universitario La Paz, Madrid, Spain; and the Divisions of Pulmonary and Critical Care Medicine and General Medical Sciences (Dr Yusen), Washington University School of Medicine, St. Louis, MO.

Drs Coscia and Jaureguizar contributed equally to the manuscript.

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CORRESPONDENCE TO: Alfonso Muriel, PhD, Biostatistics Department, Ramón y Cajal Hospital, 28034 Madrid, Spain; e-mail: alfonso.muriel@hrc.es

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manuscript “files,” and contacted experts to try to identify eligible studies that the search did not include.

Identification of Eligible Observational Studies and Observational Study Meta-Analyses

To determine observational study and observational study meta-analysis eligibility, two reviewers (C. C. and D. J.) screened titles and abstracts of each publication that the search identified. For each study deemed potentially eligible, we obtained and searched the complete article to assess its eligibility. The two reviewers used consensus to resolve eligibility discrepancies, to eliminate duplicate publications, and to choose the most appropriate study for those that had overlapping data.

Data Extraction From Observational Studies

For each eligible observational study or observational study meta-analysis, the Patient, Intervention, Comparison, Outcome structure⁸ was used to guide data extraction. Using a standardized and data abstraction form that had undergone pilot testing and revision until deemed adequate, one reviewer (D. J.) extracted study characteristic and treatment effect (ie, mortality) data.

Identification of Eligible RCT Meta-Analyses and RCTs and Matching of Observational Studies/Observational Study Meta-Analyses to RCTs

One reviewer (D. J.) used a structured approach for attempting to match each observational study/observational study meta-analysis or group of observational studies that addressed the same treatment scenario to at least one RCT meta-analysis (or RCT). We conducted a stepwise RCT search, prioritizing the latest publication, of the following sources: (1) the Cochrane Database of Systematic Reviews; (2) Medline-indexed meta-analyses; (3) evidence-based guidelines from the American College of Chest Physicians/European Society of Cardiology; (4) focused Medline searches to identify eligible primary publications of RCTs; and (5) reference lists of the observational studies. For matching to the observational study or studies in each treatment scenario group, matched RCTs had to use the same pharmacologic or nonpharmacologic intervention, have the same VTE characteristics (PE, DVT, or both) for randomized participants, and have a similar clinical setting. We did not require but attempted to choose RCTs that had demographic or comorbidity characteristics similar to the observational study or studies in each treatment group. We did not use specific adult age subgroups or demographic subpopulations (sex, race, or ethnicity) for matching. Two physicians trained in quantitative methods (C. A. Q. and E. B.) independently verified that selected RCT and RCT meta-analysis publications met the matching criteria. A practicing respiratory physician (D. J.) then verified the appropriate selection of the studies and resolved any discrepancies.

Data Extraction From RCT Meta-Analyses and RCTs

One reviewer (D. J.) performed data extraction for each eligible RCT meta-analysis or RCT publication. Extracted data included the

number of randomized patients and the number of deaths for each treatment group. The follow-up period most similar to the one used in the comparator study was used for incidence of death (eg, in-hospital, 30-day mortality) comparisons.

Risk of Bias Assessment

The Cochrane risk of bias tools^{9,10} were used to assess the observational studies (A. M. and D. J.) and RCTs (C. A. Q. and D. J.). A Measurement Tool to Assess Systematic Reviews 2¹¹ was used to assess the risk of bias in each meta-analysis (C. C. and D. J.). Discrepancies were resolved through discussions that led to a consensus decision.

Statistical Analysis

For groups of observational studies that addressed a similar VTE treatment issue, meta-analysis was performed by using random effects models (per DerSimonian and Laird)¹² to obtain a summary estimate of treatment efficacy. For groups of RCTs that addressed a similar clinical treatment issue, we preferentially used data from the most recent published meta-analysis. Otherwise, meta-analytic procedures were used to combine multiple trials with random effects models to obtain a summary OR for mortality.¹³ Due to the low number of deaths in each study, we assumed that the reported relative risk or hazard ratio would approximate the OR.

To compare RCT and observational study treatment effect estimates (ie, mortality) for each distinct clinical treatment issue, the summary OR direction ($OR > 1$, $OR = 1$, $OR < 1$) and magnitude were compared; we also assessed for 95% overlap for the summary ORs.

For each distinct VTE treatment issue, the relative OR (ratio of ORs) was calculated by dividing the RCT summary OR by the observational study summary OR. CIs for the RCT and observational study relative ORs were calculated by summing the OR variances for each study design type. The summary relative OR was then calculated across all study pairs. By convention, a summary relative $OR > 1$ indicated a lower observational study treatment-associated mortality, and an $OR < 1$ indicated a lower RCT treatment-associated mortality.

To assess for the robustness of the findings, depending on the data available, four types of sensitivity analyses were performed: (1) including only observational studies with low risk of bias; (2) including only prospective observational studies; (3) using the single largest study (observational or randomized) instead of meta-analysis estimates for clinical questions where more than one observational or randomized study was available; or (4) repeating the meta-analysis under a fixed effect model.

Stata version 15.0 (Stata Corp.) was used for the analyses. Two-tailed *P* values were used for comparisons.

Results

Study Selection, Distinct Treatment Issue Identification, and Matching of RCTs to Observational Studies

The search for propensity score-adjusted observational studies identified 319 citations. Abstract review identified 25 potentially eligible studies we retrieved in full text.¹⁴⁻³⁸ e-Figure 1 presents the search strategy flow

and eligibility of studies reviewed in full text. We deemed 23 of the 25 reviewed observational studies¹⁶⁻³⁸ as eligible. Within the 13 observational studies used for analyses, seven distinct VTE treatment issues were identified that the observational studies addressed. Six of the seven treatments investigated included pharmacologic interventions (systemic thrombolysis vs no thrombolysis for PE [$n = 1$], systemic

thrombolysis vs catheter-directed thrombolysis for PE [n = 2], once- vs twice-daily enoxaparin for VTE [n = 1], inferior vena cava filter insertion vs no insertion for VTE [n = 4], rivaroxaban vs vitamin K antagonists for VTE [n = 3], low-molecular-weight heparin vs unfractionated heparin for VTE [n = 1]) and one included nonpharmacologic approaches (home treatment vs hospitalization for DVT [n = 1]). Three of the seven distinct clinical treatment issue groups included more than one study. The 13 observational studies had publication dates between 2012 and 2017, and they used diverse types of data sources that included registries, hospital databases, and administrative data. Only two of the 13 observational studies (15%)^{34,35} had a prospective design. Eight of 13 studies (62%)^{27-29,34-38} compared two active interventions. We successfully matched 13 studies²⁶⁻³⁸ from the 23 eligible observational studies to seven RCTs or RCT meta-analyses.³⁹⁻⁴⁵

Risk of Bias and Study Quality Assessments

Although the risk of bias due to confounding was deemed moderate for all observational studies, most had a low risk of bias for other types of bias. Thus, the overall risk of bias was considered as low to moderate for the observational studies (e-Table 1).

In general, the observational study propensity score-based analyses followed current recommendations for statistical practice. All studies provided data for covariate selection for the construction of the propensity score model. Five studies used regression methods for covariate selection, and eight used preexisting knowledge of potential confounders of the treatment-mortality association. Eleven studies undertook matched analyses. Ten studies assessed the balance between the matched groups.

Among the observational studies, the smallest study included 368 patients and the largest included 8,910 patients; in total, these studies included 39,236 patients. The comparative effect estimates were based on a median of 2,942 patients per analysis (interquartile range, 733-4,638 patients per analysis) (Table 1).²⁶⁻³⁸ Figure 1 shows the meta-analyses (using random effects models) of comparative effects of interventions on mortality reported in the observational studies.

The seven eligible RCT publications that matched to the observational studies included three RCTs and four RCT meta-analyses (Table 2).³⁹⁻⁴⁵ We deemed the overall quality fair for two RCT publications, mainly due to lack

of blinding,^{41,42} and high for one publication⁴³ (e-Table 2). The four RCT meta-analyses provided an accurate and comprehensive summary of the results of the available studies that addressed the question of interest^{39,40,44,45} (e-Table 3).

Among the RCT and RCT meta-analysis studies, the smallest study included 400 patients and the largest included 9,663 patients. In total, the RCT and RCT meta-analysis studies included 25,345 patients and had 938 deaths. We based the comparative effect estimates on a median of 2,057 patients per analysis (interquartile range, 400-5,865 patients per analysis) (Table 1).

Treatment Effects and Comparisons

Among the seven distinct VTE treatment issues, the observational studies found significant treatment effects (ie, all-cause mortality reduction) in five (Fig 2). Among the seven distinct VTE treatment issues, two of the RCT and RCT meta-analysis studies found significant treatment effects.

For the comparison of treatment effects between each observational study and RCT pair, the overall mortality estimates did not significantly differ (summary relative OR, 0.89; 95% CI, 0.32-1.46; $I^2 = 23\%$). Five of the seven distinct VTE treatment issues had treatment effects that showed the same direction (OR +, 0, -). However, for two of the seven (29%) distinct VTE treatment issues, the direction of treatment effects differed between the paired observational study and the RCT publications (thrombolysis vs anticoagulation for PE; once- vs twice-daily enoxaparin for VTE), and these pairs showed significantly different estimates (no overlap in 95% CI) (Fig 2). The point estimates of the relative effect sizes comparing treatment effects in observational studies vs RCTs were occasionally far from the null (rivaroxaban vs vitamin K antagonists for VTE; home treatment vs hospitalization for DVT), despite being statistically nonsignificant.

Sensitivity Analyses

The sensitivity analyses showed results similar to the primary analyses (Table 3). Estimates of summary relative ORs ranged from 0.64 to 1.59, and their 95% CIs excluded the null in one of the four sensitivity analyses. We found the largest estimate of a difference between an observational study and RCTs pair (summary relative OR, 1.59) when only observational studies that had a low risk of bias were considered.

TABLE 1] Description of All-Cause Mortality VTE Treatment Efficacy Comparisons Within Propensity Score-Adjusted Observational Studies

Source	Data Source	Total No. of Patients	Treatment Comparison	Condition or Disease	Follow-up	Study Results
Riera-Mestre et al, ²⁶ 2012	RIETE registry	622	Systemic thrombolysis vs no thrombolysis	Stable and unstable pulmonary embolism	30 d	All-cause mortality OR of 1.8 (95% CI, 1.2-2.6) in patients who received thrombolysis
Patel et al, ²⁷ 2015	Nationwide inpatient sample	868	Systemic thrombolysis vs catheter-directed thrombolysis	Acute pulmonary embolism	In-hospital	All-cause mortality OR of 1.8 (95% CI, 1.2-2.8) in patients who received systemic thrombolysis
Liang et al, ²⁸ 2017	Nationwide inpatient sample	2,868	Systemic thrombolysis vs catheter-directed thrombolysis	Acute pulmonary embolism	In-hospital	All-cause mortality OR of 1.1 (95% CI, 0.9-1.5) in patients who received systemic thrombolysis
Trujillo-Santos et al, ²⁹ 2017	RIETE registry	2,271	Once- vs twice-daily enoxaparin	VTE	30 d	Enoxaparin once daily 42% (95% CI, 0-67%) reduction in all-cause mortality
Muriel et al, ³⁰ 2014	RIETE registry	688	Inferior vena cava filter vs no filter	Pulmonary embolism and contraindication to anticoagulation	30 d	All-cause mortality OR of 0.6 (95% CI, 0.2-1.2) in patients who received a filter
Isogai et al, ³¹ 2015	Diagnosis procedure combination database	6,948	Inferior vena cava filter vs no filter	Pulmonary embolism	In-hospital	All-cause mortality OR of 0.6 (95% CI, 0.4-0.7) in patients who received a filter
White et al, ³² 2016	California patient discharge database	3,017	Inferior vena cava filter vs no filter	VTE and active bleeding	30 d	All-cause mortality OR of 0.7 (95% CI, 0.5-0.9) in patients who received a filter
Liang et al, ³³ 2017	Nationwide inpatient sample	...	Inferior vena cava filter vs no filter	Pulmonary embolism	In-hospital	All-cause mortality OR of 0.93 (95% CI, 0.89-1.01) in patients who received a filter
Agno et al, ³⁴ 2016	Prospective, noninterventonal XALIA study	4,515	Rivaroxaban vs standard anticoagulation	DVT	At least 12 mo	All-cause mortality OR of 0.5 (95% CI, 0.2-1.1) in patients who received rivaroxaban
Gaertner et al, ³⁵ 2017	REMOTEV registry	368	Rivaroxaban vs vitamin K antagonists	VTE	6 mo	All-cause mortality OR of 0.2 (95% CI, 0.1-0.7) in patients who received rivaroxaban
Larsen et al, ³⁶ 2017	Nationwide Danish health registries	4,679	Rivaroxaban vs warfarin	VTE	6 mo	All-cause mortality OR of 1.2 (95% CI, 0.8-1.9) in patients who received rivaroxaban
Lozano et al, ³⁷ 2014	RIETE registry	8,910	Home vs in-hospital management	DVT	7 d	All-cause mortality OR of 0.2 (95% CI, 0.1-0.7) in patients treated at home
Trujillo-Santos et al, ³⁸ 2013	RIETE registry	3,750	LMWH vs UFH	VTE with normal renal function ^a	15 d	2.9% mortality rate for LMWH group vs 4.6% for UFH group

LMWH = low-molecular-weight heparin; RIETE = Registro Informatizado de La Enfermedad TromboEmbólica; XALIA = XA Inhibition With Rivaroxaban for Long-Term and Initial Anticoagulation in Venous Thromboembolism; REMOTEV = Rivaroxaban Versus Standard Anticoagulation for Symptomatic Venous Thromboembolism; UFH = unfractionated heparin.

^aCreatinine clearance > 30 mL/min.

Figure 1 – Meta-analyses of comparative effects of medical interventions on all-cause mortality reported in propensity score-adjusted observational studies for each of seven distinct VTE treatment issues. CDT = catheter-directed thrombolysis; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

Discussion

For seven distinct VTE treatment issues, we compared mortality results in publications of propensity score-adjusted observational studies and matched RCTs or RCT meta-analyses. The majority of the matched pairs of studies showed similar treatment efficacy, although two of the seven matched pairs (thrombolysis vs anticoagulation for PE; once- vs twice-daily enoxaparin for PE) exhibited statistically significantly different mortality results, and the direction of treatment effects actually differed between the pairs. Although there was a substantial (although not statistically significant) difference in the magnitude of the effect in two of the seven distinct VTE treatment issues (rivaroxaban vs vitamin K antagonists for VTE; home treatment vs hospitalization for DVT), no evidence was found that propensity score-adjusted observational study estimates systematically underestimated or overestimated the treatment efficacy shown in RCTs.

The results from the present study agree with a Cochrane review meta-analysis of 14 meta-analyses that

compared > 1,000 pairs of observational studies and RCTs across 228 medical conditions.⁴⁶ The review found that effect estimates from observational studies did not significantly differ from those of RCTs (relative OR, 1.08; 95% CI, 0.96-1.22). The majority (71%) of the meta-analyses found minimal disagreement between RCTs and observational studies. In general, well-conducted observational studies and RCTs have results that show agreement.⁴⁷ Interestingly, significant discrepancies in results may occur among randomized trial-randomized trial pairs as frequently among observational study-randomized trial pairs.⁴⁸

The point estimates of the relative effect sizes comparing treatment effects in observational studies vs RCTs were occasionally far from the null (rivaroxaban vs vitamin K antagonists for VTE; home treatment vs hospitalization for DVT), despite being statistically nonsignificant. Despite the imprecision, the results showed consistency of direction. RCTs often use strict enrollment criteria to improve the likelihood of identifying efficacious interventions. Previous research has well documented how little RCT populations

TABLE 2] Description of All-Cause Mortality VTE Treatment Efficacy Comparisons Within RCTs and RCT Meta-Analyses

Source	Design	Total No. of Patients	Treatment Comparison	Condition or Disease	Follow-up	Study Results
Marti et al, ³⁹ 2015	Meta-analysis of RCTs	2,057	Systemic thrombolysis vs no thrombolysis	Acute pulmonary embolism	...	All-cause mortality OR of 0.64 (95% CI, 0.35-1.17) in patients who received thrombolysis
Jimenez et al, ⁴⁰ 2018	Network meta-analysis of RCTs	2,494	Systemic thrombolysis vs catheter-directed thrombolysis	Acute pulmonary embolism	...	All-cause mortality OR of 1.93 (95% CI, 0.07-51.33) in patients who received systemic thrombolysis
Merli et al, ⁴¹ 2001	RCT	610	Once- vs twice-daily enoxaparin	VTE	3 mo	3.7% mortality rate for once-daily enoxaparin group vs 2.2% for twice-daily enoxaparin group
Decousus et al, ⁴² 1998	RCT	400	Inferior vena cava filter vs no filter	DVT at risk for pulmonary embolism	12 d	All-cause mortality OR of 0.99 (95% CI, 0.29-3.42) in patients who received an IVC filter
Prins et al, ⁴³ 2013	Pooled analysis of 2 RCTs	8,282	Rivaroxaban vs vitamin K antagonists	DVT and pulmonary embolism	3, 6, or 12 mo	2.3% mortality rate for rivaroxaban vs 2.4% for vitamin K antagonists
Othieno et al, ⁴⁴ 2018	Meta-analysis of RCTs	1,839	Home vs in-hospital management	DVT	...	All-cause mortality OR of 0.69 (95% CI, 0.44-1.09) in patients who were treated at home
Robertson and Jones, ⁴⁵ 2017	Meta-analysis of RCTs	9,663	LMWH vs UFH	VTE ^a	...	All-cause mortality OR of 0.84 (95% CI, 0.70-1.01) in patients who received LMWH

IVC = inferior vena cava; RCT = randomized controlled trial. See Table 1 legend for expansion of other abbreviations.

^aCreatinine clearance > 30 mL/min.

Figure 2 – Comparison of all-cause mortality treatment effects between propensity score-adjusted observational study and randomized controlled trial matched pairs for seven distinct VTE treatment issues. The left panel shows comparative effects of medical interventions on mortality reported in propensity score-adjusted observational study (or meta-analyses of observational studies) and randomized trial (or meta-analyses of randomized trials) matched pairs for each VTE treatment issue. Red circles = effect estimates reported in observational studies; blue circles = effect estimates from randomized trials; lines = 95% CIs. The right panel shows the ratio of mortality effects (relative ORs) reported in propensity score-adjusted observational study and randomized controlled trial matched pairs that addressed the same VTE treatment issue. An ROR > 1 indicates more favorable, an ROR < 1 indicates less favorable, and an ROR of 1 indicates no difference in mortality outcomes between a propensity score-adjusted observational study and randomized trial matched pairs. Gray squares (lines) = RORs (95% CIs); blue diamond = pooled summary ROR (meta-analysis of ROR) across all clinical treatment issues. ROR = relative OR. See Figure 1 legend for expansion of other abbreviations.

resemble real-world populations, and differences in baseline characteristics might account for differences in the magnitude of the effect sizes.

Unlike RCTs, observational studies have a high risk of bias due to unmeasured confounders or inadequate control for measured confounders. The use of falsification end points may assist with the evaluation for residual

confounding in observational comparative effectiveness studies, and this method might help to strengthen the validity of nonrandomized studies. RCTs may also have deficiencies in study methods and conduct (poor allocation concealment, lack of blinding, baseline imbalances, and selective dropout) that could affect study validity. Both types of study designs may also report variation in results among the populations and clinical

TABLE 3] Agreement of Treatment Effects Reported in Propensity Score-Adjusted Observational Studies and Randomized Controlled Trials

Analysis	No. of Treatment Comparisons	Summary Relative OR (95% CI)	I^2 (%)
Main analysis			
Random effect models for combining observational studies	7	0.89 (0.32-1.46)	22.5
Sensitivity analyses			
Observational studies with low risk of bias	1	1.59 (0.66-3.82)	10.9
Prospective observational studies	1	0.64 (0.01-1.27)	90.7
Single largest observational study for each comparison	7	0.81 (0.61-1.05)	81.1
Fixed effect models for combining observational studies	7	0.80 (0.75-0.85)	89.3

settings studied. Biases in either type of study may make it difficult to compare them. Thus, treatment effectiveness discrepancies between observational and RCT study designs should not automatically lead to an assumption of bias in the observational studies and discrediting of the results. Instead, discrepancies should trigger a careful search for possible clinical or methodologic explanations.

Regarding the matching process for each of the distinct VTE treatment issues, a systematic approach⁴⁹ was applied similar to that used to evaluate studies for inclusion in systematic reviews or practice guidelines. This approach had multiple checkpoints and required consensus among reviewers regarding study eligibility, matching, and outcomes. However, we acknowledge the subjective component of this matching process. Despite our attempts to minimize bias, this study highlights the complex processes needed to appraise the comparative effectiveness of competing interventions. We also acknowledge the limitations in the precision of effect estimates from some of the included studies. Of note, this study's focus exclusively on all-cause mortality does not address potential differences among study pairs in other important outcomes, such as recurrent VTE or bleeding.

In addition, the extent of agreement between study design types may differ among the outcomes being studied.

Conclusions

This systematic comparison within seven diverse VTE treatment issues suggests that propensity score-adjusted observational studies and RCTs often report similar all-cause mortality, although differences in the direction of estimated treatment effects may occasionally occur. In addition, the imprecision of the estimates lowers our certainty about the difference in outcomes between the paired studies. Thus, well-conducted propensity score-adjusted observational studies may confirm and supplement the results from RCTs, or they may raise important questions regarding internal and external validity of the findings. Thus, an important part of interpreting study results includes comparing treatment effect estimates across different study designs and seeking explanations for discrepancies. In situations in which medical treatments have significant treatment efficacy and/or harm evidence provided from one or more propensity score-adjusted observational studies but not from an RCT, thoughtful interpretation of study methods, results, and external validity will help to guide clinical practice.

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