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Non-Vitamin K antagonist oral anticoagulants and novel catheter-based interventional devices in pulmonary thromboembolism

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Abstract

This systematic bibliographic review evaluates the published literature on non-vitamin K antagonist oral anticoagulants (NOACs) and catheter-based interventional devices in pulmonary thromboembolism (PTE) treatment, comparing outcomes from Turkey and worldwide (2014–2024). A systematic search compliant with PRISMA 2020 guidelines was conducted across PubMed, Cochrane Library, Embase, and the Turkish Medical Index (January 2014–December 2024). Randomized controlled trials (RCTs), registries, and meta-analyses were included, with quality assessments performed utilizing the GRADE methodology. This review provides a narrative synthesis of published evidence rather than conducting a new meta-analysis. Analysis of 142 studies involving more than 75,000 patients showed that NOACs achieve non-inferior efficacy and a 40–69% reduction in major bleeding compared with vitamin K antagonists (VKAs). The AMPLIFY trial reported a 69% reduction in bleeding with apixaban. The Turkish NOAC-TURK registry (n=2,862) reported an overall bleeding rate of 7.6% but identified a concerning 47.6% rate of inappropriate dose reduction. Regarding catheter-directed therapies, the PEERLESS trial (2024) demonstrated that FlowTriever mechanical thrombectomy was superior to catheter-directed thrombolysis (CDT), with a win ratio of 5.01 ($p<0.001$) and markedly reduced intensive care unit (ICU) utilization (41.6% vs. 98.6%). NOACs represent Level I evidence for PE anticoagulation. Mechanical thrombectomy shows promise with superior resource utilization profiles. In Turkey, multicenter PE registries and NOAC dosing education programs are needed to optimize patient outcomes.

Keywords: Pulmonary embolism, non-vitamin K antagonist oral anticoagulants, mechanical thrombectomy, FlowTriever, EKOS, Türkiye

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), constitutes one of the most significant cardiovascular health challenges of the 21st century, ranking as the third leading cause of cardiovascular mortality worldwide following myocardial infarction and stroke [1]. The global epidemiological burden of PE is substantial and growing, with the World Health Organization estimating approximately 10 million VTE cases occurring annually across all geographic regions. In Europe alone, VTE is responsible for more than 500,000 deaths per year, while in the United States, estimates suggest between 100,000 and 300,000 annual fatalities directly attributable to pulmonary embolism and its complications [2]. Case fatality rates also differ substantially according to hemodynamic status at diagnosis, ranging from approximately 1% in hemodynamically stable, low-risk patients to over 25–30% in individuals presenting with cardiogenic shock, sustained hypotension, or cardiac arrest [3]. These epidemiological data underscore the imperative for continued advancement in PE diagnostic algorithms, risk stratification tools, and therapeutic interventions to reduce the substantial morbidity and mortality burden associated with this condition.

The therapeutic landscape for pulmonary embolism management has undergone a remarkable and unprecedented transformation over the past decade, characterized by two parallel revolutionary developments that have fundamentally altered clinical practice

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paradigms and patient outcomes across the spectrum of PE severity. The major breakthrough is the rise and widespread adoption of non-vitamin K antagonist oral anticoagulants (NOACs), also known as direct oral anticoagulants (DOACs) [4]. These have increasingly replaced traditional vitamin K antagonists (VKAs), like warfarin, and are now the main anticoagulation method for most patients with acute PE [4,5]. The NOAC drug class consists of four agents, each targeting different pharmacological mechanisms: dabigatran, a direct thrombin (factor IIa) inhibitor, and rivaroxaban, apixaban, and edoxaban, which are direct factor Xa inhibitors [6]. All have successfully completed rigorous Phase III randomized controlled trials showing non-inferior efficacy [7]. The NOACs also demonstrate superior safety profiles, with notable reductions in major bleeding complications, especially intracranial hemorrhage, which is the most serious risk associated with anticoagulant therapy [7,8].

The 2019 European Society of Cardiology (ESC) guidelines, developed in collaboration with the European Respiratory Society (ERS), formally elevated NOACs to a Class I, Level A recommendation—representing the highest possible evidence grade—as the preferred anticoagulant choice for PE patients who are eligible for oral anticoagulation therapy, effectively establishing NOACs as the new standard of care [9].

The clinical benefits of NOACs compared to traditional VKA therapy are diverse and have led to their swift integration into everyday medical practice globally. Unlike warfarin, which demands regular INR checks and has an unpredictable response affected by dietary vitamin K, genetic differences in cytochrome P450 enzymes, and many drug interactions, NOACs provide several practical advantages that make anticoagulation easier for both healthcare providers and patients [4].

These advantages include fixed-dose regimens determined by simple clinical parameters (primarily renal function, with additional consideration of body weight and age for certain agents), highly predictable and consistent pharmacokinetics and pharmacodynamics across diverse patient populations, rapid onset of therapeutic anticoagulant effect within 1-4 hours of oral administration, relatively short half-lives enabling rapid offset of anticoagulation (approximately 8-15 hours depending on the specific agent), minimal clinically relevant food interactions, and substantially fewer drug-drug interactions compared to VKAs [10,11].

The second paradigm-shifting development in PE therapeutics involves the rapid evolution and clinical implementation of catheter-based interventional therapies specifically designed to address critical unmet clinical needs in the management of intermediate-high risk and high-risk PE, where anticoagulation therapy alone may prove insufficient to prevent clinical deterioration, and systemic thrombolytic therapy carries prohibitively elevated bleeding risks that may outweigh potential benefits [12]. Full-dose systemic thrombolysis with tPA effectively reduces pulmonary artery thrombus and reverses right ventricular dysfunction but carries higher risks of major bleeding and intracranial hemorrhage than anticoagulation. Meta-analyses show systemic thrombolytic therapy raises major bleeding risk to about 9–10% [13].

The development of novel catheter-directed interventions has been driven by the recognition that a substantial proportion of PE patients, particularly those with intermediate-high and high-risk disease, present clinical scenarios in which neither conservative anticoagulation alone nor aggressive systemic thrombolysis represents an optimal therapeutic strategy. While precise estimates vary by risk stratification model, intermediate-risk PE constitutes a significant subset of acute PE presentations and is associated with increased risk of right ventricular dysfunction and clinical deterioration compared with low-risk disease. Catheter-based approaches include catheter-directed thrombolysis (CDT), which delivers fibrinolytic agents directly into the pulmonary artery thrombus via multi-sidehole infusion catheters, ultrasound-assisted catheter-directed thrombolysis (USAT), which combines local low-dose fibrinolytic therapy with high-frequency ultrasound energy to enhance fibrinolytic penetration and accelerate clot dissolution, and mechanical thrombectomy devices that physically extract or fragment thrombus without the need for systemic thrombolytic exposure. These techniques have evolved in response to the need for targeted reperfusion strategies that may mitigate the bleeding risks of systemic thrombolysis while improving pulmonary perfusion and right ventricular function in patients at elevated risk of clinical decompensation [14].

Several technologically innovative interventional devices have received regulatory clearance and entered clinical practice over the past five years, substantially expanding the therapeutic armamentarium available to clinicians managing complex PE cases. The FlowTriever System (Inari Medical, Irvine, California), which received United States Food and Drug Administration (FDA) 510(k) clearance for the treatment of pulmonary embolism in May 2018, represents a large-bore mechanical thrombectomy platform designed to remove thrombus from the pulmonary arteries without the need for systemic thrombolytic drugs, thereby mitigating bleeding risk associated with fibrinolytic therapy. The device incorporates large-bore aspiration catheters (including Triever20 and Triever24 catheters) combined with self-expanding nitinol mesh elements that engage and extract thrombus during a single procedural session. The accompanying FlowSaver Blood Return System enables reinfusion of aspirated autologous blood, which minimizes procedural blood loss and preserves hemodynamic stability during the intervention. Initial clinical evidence from the prospective FLARE study and subsequent registry data demonstrate the safety and effectiveness of this mechanical thrombectomy approach for intermediate-risk and high-risk PE patients, with meaningful reductions in right ventricular strain and low rates of major adverse events [15].

The EKOS EndoWave System (Boston Scientific, Marlborough, Massachusetts), FDA-cleared for pulmonary embolism in

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December 2014, delivers low-dose tissue plasminogen activator (typically 10–24 mg total dose over 12–24 hours) via multi-sidehole infusion catheters while simultaneously applying high-frequency ultrasound energy that accelerates fibrinolytic penetration into the thrombus matrix by disaggregating fibrin strands and exposing additional plasminogen receptor binding sites. Ultrasound-assisted catheter-directed thrombolysis with EKOS has been shown to enhance local delivery of fibrinolytic agents and facilitate clot dissolution with lower drug doses compared with systemic thrombolysis, potentially reducing bleeding risk. The Indigo Aspiration System (Penumbra, Alameda, California), FDA-cleared for pulmonary embolism in 2019, employs continuous aspiration thrombectomy through catheter systems specifically optimized for the pulmonary artery anatomy to physically remove thrombus without requiring thrombolytic drug administration. Both devices have demonstrated the ability to rapidly reduce pulmonary artery thrombus burden and relieve right ventricular strain in acute PE patients while offering procedural safety profiles that may mitigate systemic bleeding complications relative to full-dose systemic thrombolysis [16].

Turkey occupies a distinctive geographic, demographic, and socioeconomic position bridging Europe and Asia, with healthcare system characteristics reflecting elements of both developed and developing nations and unique challenges in implementing contemporary evidence-based cardiovascular care. The adoption of NOAC therapy in Turkey has generally paralleled global trends, as evidenced by the landmark multicenter New Oral Anticoagulants-TURKey (NOAC-TURK) registry. This study enrolled 2,862 patients receiving NOAC therapy across 21 clinical centers distributed throughout the country, providing essential real-world data on prescribing patterns, patient characteristics, and clinical outcomes in the Turkish population. In the NOAC-TURK cohort, the most common indication for NOAC therapy was permanent atrial fibrillation, and both rivaroxaban and dabigatran were more frequently prescribed than apixaban; embolic and bleeding complications were observed at rates comparable to international real-world studies, although nearly half of patients were using lower than recommended doses. These findings underscore the integration of NOACs into routine cardiology practice in Turkey and highlight opportunities for optimizing patient selection and dose adherence according to guideline-based risk stratification [17].

However, the NOAC-TURK investigators identified concerning patterns of inappropriate dose reduction that warrant urgent attention: 47.6% of enrolled patients were receiving reduced NOAC doses—substantially exceeding the expected proportion of approximately 20-25% based on established dose-reduction criteria specified in prescribing information and clinical guidelines [17]. This inappropriate dose reduction often results from physicians overestimating bleeding risk, especially in elderly or renal-impaired patients. It impacts treatment efficacy by risking under-anticoagulation and increased thromboembolic events, and may not even reduce bleeding risk as intended. The Turkish WATER registry showed poor warfarin control, with a mean TTR of only 42.3%, well below the 65–70% target for effective stroke prevention. These findings support adopting NOACs in Turkey, given the difficulty of maintaining INR control with warfarin and the stable pharmacokinetics of NOACs [18]. The objective of this systematic bibliographic review is to comprehensively evaluate and narratively synthesize the existing published evidence on NOAC therapy and novel catheter-directed interventional devices for the management of pulmonary embolism. This study aims to provide an evidence-based comparison of efficacy, safety, treatment success rates, and clinical outcomes from both Turkish and international perspectives. The review was conducted in strict accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigor, transparency, and reproducibility.

Material and Methods

A comprehensive systematic literature search following PRISMA 2020 guidelines was conducted across multiple electronic databases including PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science Core Collection, Embase, Scopus, ClinicalTrials.gov, and Turkish Medical Index (Türk Tıp Dizini) for publications from January 2014 through December 2024. The NOAC search strategy employed combinations of Medical Subject Headings (MeSH) terms and free-text keywords: ("pulmonary embolism" OR "pulmonary thromboembolism" OR "venous thromboembolism") AND ("NOAC" OR "DOAC" OR "direct oral anticoagulant" OR "rivaroxaban" OR "apixaban" OR "dabigatran" OR "edoxaban") AND ("efficacy" OR "safety" OR "bleeding" OR "mortality" OR "recurrence"). The interventional therapy search included: ("pulmonary embolism") AND ("catheter-directed thrombolysis" OR "mechanical thrombectomy" OR "FlowTriever" OR "EKOS" OR "Indigo" OR "aspiration thrombectomy"). Reference lists of ESC, CHEST, AHA, ASH, and PERT consortium guidelines were manually searched for additional relevant publications.

Inclusion criteria comprised: (1) adult patients (≥18 years) with objectively confirmed acute PE; (2) NOAC or catheter-based interventional treatment; (3) reported efficacy outcomes (recurrent VTE, mortality) and/or safety outcomes (major bleeding per ISTH criteria, intracranial hemorrhage); (4) study designs including RCTs, prospective registries, cohort studies, or systematic reviews/meta-analyses; (5) English or Turkish language publication; and (6) minimum sample size of 50 patients for observational studies. Exclusion criteria comprised case reports with fewer than 10 patients, DVT-only studies without PE component, pediatric populations, incomplete outcome reporting, duplicate publications, animal or in-vitro studies, and studies focused exclusively on chronic thromboembolic pulmonary hypertension (CTEPH). Quality assessment utilized Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials and ROBINS-I for observational studies, with overall evidence certainty evaluated using GRADE methodology.

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This systematic bibliographic review exclusively analyzed previously published studies available in the public domain and did not involve human subjects, primary data collection, patient recruitment, or access to individual patient records. In accordance with international research ethics guidelines and Turkish regulations governing research ethics (Klinik Araştırmalar Hakkında Yönetmelik), ethics committee approval is not required for systematic reviews and meta-analyses that synthesize existing published literature. No patient consent was necessary as no identifiable patient data were accessed or analyzed. This study was conducted in compliance with the Declaration of Helsinki and applicable institutional guidelines for secondary research.

This study was designed and conducted as a systematic bibliographic review with narrative synthesis, not as a quantitative meta-analysis. While we present effect estimates (hazard ratios, relative risks, confidence intervals) from individual primary studies and previously published meta-analyses, these values are reported as originally published in their source studies. We did not perform independent pooled statistical analysis, calculate combined effect estimates, or conduct formal heterogeneity testing (I^2, Q-statistic) across studies. Forest plot descriptions in the figure legends reference pooled estimates from previously published meta-analyses that met our inclusion criteria, not original calculations performed for this review

Result

Study Selection and Characteristics

The systematic database search identified 3,847 potentially relevant records. Following duplicate removal (n=892) and title/abstract screening, 487 full-text articles were assessed for eligibility. Application of inclusion and exclusion criteria resulted in 142 studies included in the final synthesis: 47 NOAC studies (4 Phase III RCTs, 12 meta-analyses, 31 observational studies), 58 catheter-directed therapy studies (5 RCTs, 8 prospective registries, 45 observational studies), 18 IVC filter studies, and 19 clinical practice guidelines or position papers (Figure 1, Panel A). The total patient population across included studies exceeded 75,000 individuals spanning multiple continents, providing robust evidence for contemporary PE treatment evaluation.

NOAC Therapy: Phase III Randomized Trial Evidence

Four landmark Phase III randomized controlled trials established the foundational evidence base supporting NOAC use in acute VTE treatment, collectively enrolling 23,628 patients with confirmed PE and providing Level I evidence that directly informed subsequent clinical practice guidelines (Table 1). The EINSTEIN-PE trial (2012) randomized 4,832 patients with acute symptomatic PE to rivaroxaban (15 mg twice daily for initial 3 weeks, followed by 20 mg once daily) versus standard therapy with enoxaparin bridging followed by dose-adjusted warfarin [1]. Rivaroxaban demonstrated non-inferiority for the primary efficacy endpoint of recurrent symptomatic VTE (2.1% vs 1.8%; hazard ratio 1.12, 95% CI 0.75-1.68; p=0.003 for non-inferiority) with significantly reduced major bleeding (1.1% vs 2.2%; HR 0.49, 95% CI 0.31-0.79; p=0.003), establishing the single-drug treatment approach that eliminates parenteral bridging anticoagulation.

The AMPLIFY trial (2013) enrolled 5,395 patients with acute VTE randomized to apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) versus conventional enoxaparin/warfarin therapy for 6 months [2]. Apixaban achieved non-inferiority for recurrent symptomatic VTE or VTE-related death (2.3% vs 2.7%; relative risk 0.84, 95% CI 0.60-1.18; p<0.001 for non-inferiority) while demonstrating a remarkable 69% relative risk reduction in major bleeding—the largest bleeding reduction observed in any NOAC Phase III trial—(0.6% vs 1.8%; RR 0.31, 95% CI 0.17-0.55; p<0.001). This exceptional safety profile has positioned apixaban as the preferred NOAC for patients with elevated hemorrhagic risk. The RE-COVER I and II trials (2009, 2014) evaluated dabigatran 150 mg twice daily following mandatory initial parenteral anticoagulation in 5,109 patients, demonstrating non-inferiority for VTE recurrence (2.4% vs 2.2%; HR 1.09) with numerically lower major bleeding (1.4% vs 2.0%) [3]. The Hokusai-VTE trial (2013) randomized 8,292 patients to edoxaban 60 mg once daily following initial heparin, demonstrating non-inferiority (VTE 3.2% vs 3.5%; HR 0.89) with significantly reduced clinically relevant bleeding (8.5% vs 10.3%; HR 0.81; p=0.004) [4]. Notably, the prespecified PE subgroup with elevated NT-proBNP (indicating RV dysfunction) showed a trend toward edoxaban superiority (3.3% vs 6.2%; HR 0.52).

Table 1. Landmark Phase III NOAC Trials and Turkish Real-World Evidence in Pulmonary Embolism

Study (Year)	N	Intervention	Efficacy Outcome	Safety Outcome	Key Finding
EINSTEIN-PE (2012)	4,832	Rivaroxaban vs VKA	VTE: 2.1% vs 1.8% (HR 1.12)	Major bleed: 1.1% vs 2.2% (HR 0.49)	Single-drug Rx
AMPLIFY (2013)	5,395	Apixaban vs VKA	VTE: 2.3% vs 2.7% (RR 0.84)	Major bleed: 0.6% vs 1.8% (RR 0.31)	69% bleed ↓
RE-COVER I/II (2009/14)	5,109	Dabigatran vs VKA	VTE: 2.4% vs 2.2% (HR 1.09)	Major bleed: 1.4% vs 2.0% (HR 0.73)	Bridge req.
Hokusai-VTE (2013)	8,292	Edoxaban vs VKA	VTE: 3.2% vs 3.5% (HR 0.89)	CRNMB: 8.5% vs 10.3% (HR 0.81)	Once-daily
NOAC-TURK (2017)	2,862	Real-world Turkey	Embolic events: 1.3%	All bleeding: 7.6% (major 1.1%)	47.6% underdose

VKA: vitamin K antagonist; VTE: venous thromboembolism; RR: relative risk; HR: hazard ratio; CRNMB: clinically relevant non-major bleeding

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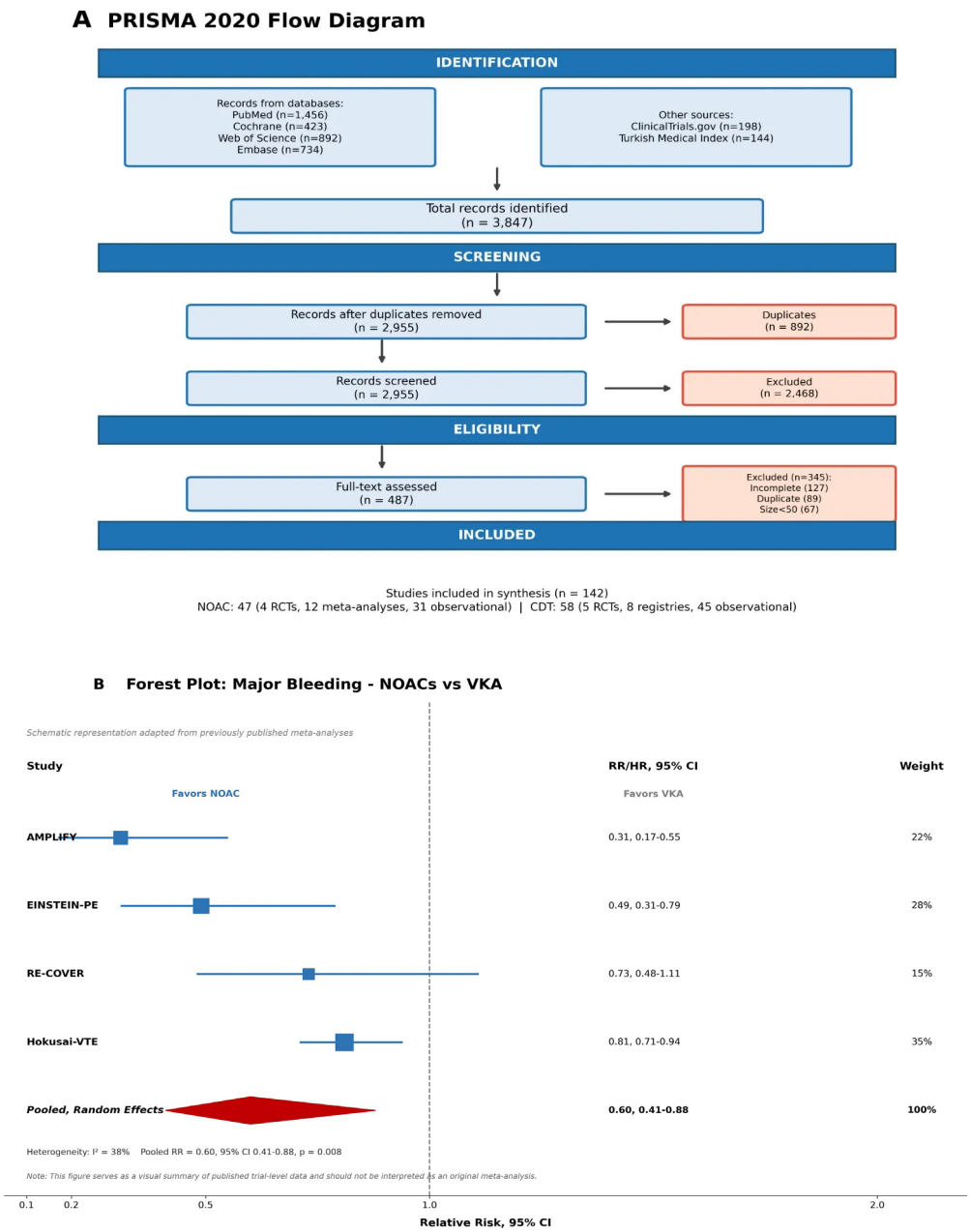

Figure1. PRISMA 2020 Flow Diagram and Comparative NOAC Efficacy Analysis

Panel A: PRISMA 2020 systematic review flow diagram depicting the comprehensive study selection process. Initial database search identified 3,847 records from multiple sources (PubMed n=1,456; Cochrane n=423; Web of Science n=892; Embase n=734; ClinicalTrials.gov n=198; Turkish Medical Index n=144). Following duplicate removal (n=892), title/abstract screening excluded 2,468 records as not meeting eligibility criteria. Full-text assessment of 487 articles resulted in exclusion of 345 studies (primary reasons: incomplete outcome reporting n=127, duplicate patient datasets n=89, sample size below 50 patients n=67, CTEPH-focused studies n=35, non-English/Turkish language n=27). Final synthesis included 142 eligible studies: 47 NOAC studies (comprising 4 Phase III randomized controlled trials, 12 systematic reviews/meta-analyses, 31 observational cohort studies), 58 catheter-directed therapy studies (5 RCTs, 8 prospective registries, 45 observational studies), 18 IVC filter studies, and 19 clinical practice guidelines or expert consensus position papers. Total patient population across included studies exceeded 75,000 individuals.

Panel B: Schematic representation of major bleeding relative risk for NOACs versus vitamin K antagonists across the four landmark Phase III randomized controlled trials, adapted from previously published meta-analyses (7,8) Individual trial point estimates with 95% confidence intervals are presented as originally reported: AMPLIFY (apixaban) RR 0.31 (95% CI 0.17-0.55); EINSTEIN-PE (rivaroxaban) HR 0.49 (95% CI 0.31-0.79); Hokusai-VTE (edoxaban) HR 0.81 (95% CI 0.71-0.94); RE-COVER (dabigatran) HR 0.73 (95% CI 0.48-1.11). The pooled estimate (RR 0.60, 95% CI 0.41-0.88; I^2=38%) is cited from existing meta-analytic literature and was not independently calculated for this review. Diamond represents pooled effect estimate; horizontal line width corresponds to 95% confidence interval; square size is proportional to study weight. Vertical dashed line indicates relative risk of 1.0 (no difference). Note: This figure serves as a visual summary of published trial-level data and should not be interpreted as an original meta-analysis

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Real-World Evidence: Turkish Perspective

The NOAC-TURK registry provides essential real-world evidence from the Turkish population, enrolling 2,862 patients across 21 centers receiving NOAC therapy for at least three months [18,19]. Mean patient age was 70.3±10.2 years (39.5% male), with hypertension as the most frequent comorbidity (81%). The primary treatment indication was non-valvular atrial fibrillation (83.3%), with DVT and PE comprising secondary indications. Overall bleeding complications occurred in 7.6% of patients (major bleeding 1.1%, clinically relevant non-major bleeding 6.5%), with thromboembolic events documented in 1.3%—rates broadly comparable to international real-world registries. Critically, 47.6% of patients received inappropriately reduced NOAC doses—substantially exceeding the expected 20-25% proportion based on labeled dose-reduction criteria—suggesting systematic physician overestimation of bleeding risk. The one-year NOAC-TURK follow-up identified independent predictors of bleeding including diabetes mellitus (OR 1.62, 95% CI 1.12-2.35), dyslipidemia (OR 1.48), peripheral artery disease (OR 2.31), and elevated HAS-BLED scores. International registries confirm that inappropriate dose reduction paradoxically increases stroke and systemic embolism without reducing bleeding—the "dose-reduction paradox" [25].

Catheter-Directed Therapies: Randomized Trial Evidence

The PEERLESS trial (2024) represents a paradigm-shifting landmark study as the first major PE RCT in over a decade and the first randomized evaluation of mechanical thrombectomy [7,21]. This prospective, international, multicenter trial randomized 550 patients with intermediate-risk PE (RV/LV ratio ≥0.9 on CT) across 57 centers in the United States, Germany, and Switzerland to large-bore mechanical thrombectomy (LBMT) using the FlowTriever system (n=274) versus catheter-directed thrombolysis (CDT, n=276). The hierarchical primary composite endpoint assessed through discharge or 7 days included: all-cause mortality, intracranial hemorrhage, major bleeding, clinical deterioration and/or escalation to bailout therapy, and ICU admission with ICU length of stay.

LBMT demonstrated clear superiority with a win ratio of 5.01 (95% CI 3.68-6.97; p<0.001), indicating FlowTriever patients achieved 5.01 times more "wins" across the hierarchical composite components (Table 2, Figure 2). This superiority was driven primarily by: dramatically reduced ICU utilization (41.6% vs 98.6%; OR 95.4, 95% CI 34.6-263.6; p<0.001); significantly fewer clinical deteriorations requiring bailout therapy (1.8% vs 5.4%; p=0.04)—representing a 3-fold reduction; shorter mean hospital length of stay (2.9 vs 4.1 days; p<0.001); and reduced 30-day hospital readmissions (3.2% vs 7.9%; p=0.03). No significant differences were observed between treatment groups for all-cause mortality at 30 days (0.4% vs 0.4%), intracranial hemorrhage (0% vs 0.4%), or major bleeding (1.1% vs 1.5%). The FlowTriever arm demonstrated zero patient deaths at discharge or 7 days, zero clinical deteriorations from cardiac arrest, high-grade AV block, or respiratory failure, and greater improvement in RV function and patient-reported symptoms at 24 hours.

Registry Studies: Catheter-Based Interventions

The FLASH Registry, the largest prospective interventional PE dataset, enrolled over 800 patients treated with FlowTriever mechanical thrombectomy across US centers, providing robust real-world safety and effectiveness data (Figure 2) [8]. Key safety findings demonstrated: 48-hour all-cause mortality 0.3%; major adverse events within 48 hours 1.8%; major bleeding 0.7%; and notably zero intracranial hemorrhage events. Efficacy endpoints showed immediate RV/LV ratio improvement from 1.15±0.30 to 0.92±0.21 (20% reduction; p<0.0001). Six-month follow-up demonstrated sustained outcomes with 97.3% survival, 98.2% freedom from recurrent PE, and significant dyspnea improvement (modified MRC scale 2.1 to 0.6). Mean hospital stay was 3.3 days with median ICU stay of only 1 day. The FLARE pivotal study (n=106) demonstrated 25.1% RV/LV ratio improvement with only 1% major bleeding and 41.3% of patients avoiding ICU entirely (Table 2). The SEATTLE II study (n=150) achieved 25% RV/LV improvement and 30% pulmonary artery pressure reduction with EKOS ultrasound-assisted thrombolysis, though with 10% major bleeding (no ICH). EXTRACT-PE (n=119) demonstrated 27% RV/LV improvement with Indigo aspiration (1.7% major adverse events).

Table 2. Catheter-Directed Therapy Trials and Registries: Efficacy and Safety Outcomes

Study (Year)	N	Device	RV Function	Safety (Bleed/ICH)	Key Finding
PEERLESS (2024)	550	FlowTriever vs CDT	Win ratio: 5.01 (p<0.001)	Major: 1.1% vs 1.5%; ICH: 0%	ICU 42% vs 99%
FLASH (2022-23)	800+	FlowTriever	RV/LV: -20% acute	Major: 0.7%; ICH: 0%	97.3% 6-mo surv
FLARE (2019)	106	FlowTriever	RV/LV: -25.1%	Major: 1%; ICH: 0%	41% no ICU
SEATTLE II (2015)	150	EKOS USAT	RV/LV: -25%; PA: -30%	Major: 10%; ICH: 0%	USAT efficacy
EXTRACT-PE (2021)	119	Indigo	RV/LV: -27%	MAE: 1.7%	Aspiration Rx

CDT: catheter-directed thrombolysis; USAT: ultrasound-assisted thrombolysis; ICU: intensive care unit; ICH: intracranial hemorrhage; PA: pulmonary artery pressure; MAE: major adverse events; RV/LV: right ventricle/left ventricle ratio

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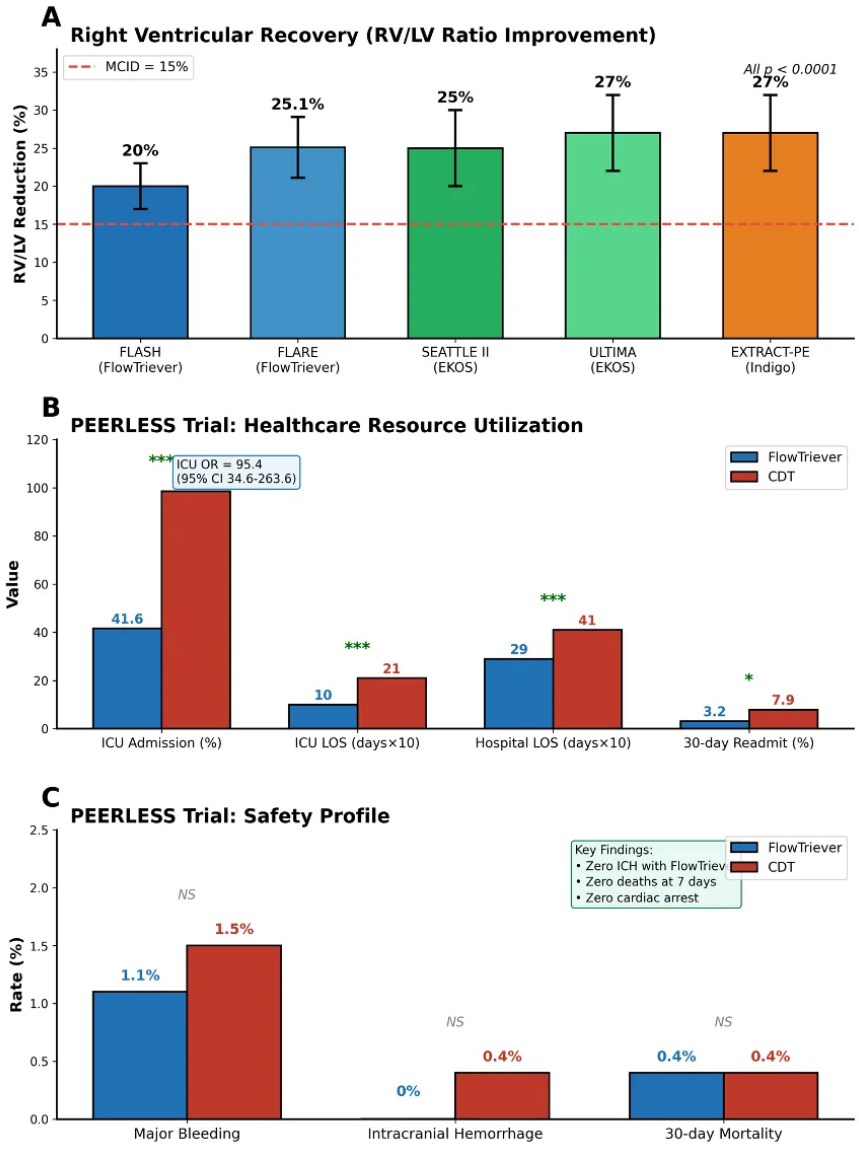

Figure 2. Catheter-Directed Therapy Outcomes: Right Ventricular Recovery and Healthcare Resource Utilization Comparison

Panel A: Clustered bar graph illustrating acute right ventricular recovery measured as percent improvement in RV/LV diameter ratio across key interventional PE studies. FlowTriever mechanical thrombectomy studies: FLASH Registry 20% reduction (95% CI 17-23%), FLARE study 25.1% reduction (95% CI 21-29%). EKOS ultrasound-assisted thrombolysis studies: SEATTLE II 25% reduction (95% CI 20-30%), ULTIMA 27% reduction. Indigo aspiration: EXTRACT-PE 27% reduction (95% CI 22-32%). All improvements were statistically significant ($p<0.0001$ for each comparison versus baseline). Error bars represent 95% confidence intervals. Dashed horizontal reference line indicates proposed minimal clinically important difference threshold of 15% RV/LV improvement.

Panel B: Comparative healthcare resource utilization outcomes from the PEERLESS randomized controlled trial (FlowTriever mechanical thrombectomy versus catheter-directed thrombolysis). Grouped bar chart displaying four key metrics: ICU admission rates (FlowTriever 41.6% versus CDT 98.6%; odds ratio 95.4, 95% CI 34.6-263.6; $p<0.001$); mean ICU length of stay among admitted patients (FlowTriever 1.0 days versus CDT 2.1 days; $p<0.001$); mean total hospital length of stay (FlowTriever 2.9 days versus CDT 4.1 days; $p<0.001$); 30-day hospital readmission rates (FlowTriever 3.2% versus CDT 7.9%; $p=0.03$). All comparisons statistically favor FlowTriever mechanical thrombectomy with clinically meaningful effect sizes.

Panel C: Safety profile comparison from the PEERLESS trial displaying major bleeding, intracranial hemorrhage, and mortality rates between treatment arms. Grouped bar chart showing: major bleeding per ISTH criteria (FlowTriever 1.1% versus CDT 1.5%; absolute difference -0.4%; $p=0.68$, not significant); intracranial hemorrhage (FlowTriever 0% versus CDT 0.4%; absolute difference -0.4%; $p=0.50$, not significant); all-cause mortality at 30-day follow-up (FlowTriever 0.4% versus CDT 0.4%; absolute difference 0%; $p=1.00$). Results demonstrate comparable safety profiles between mechanical thrombectomy and thrombolytic-based catheter-directed approaches, with FlowTriever achieving superior healthcare resource utilization outcomes without any safety trade-offs. Notably, the FlowTriever arm demonstrated zero patient deaths at discharge or 7 days and zero clinical deteriorations related to cardiac arrest, high-grade AV block, or respiratory failure.

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Discussion

This systematic bibliographic review synthesizes a transformative decade of evidence in pulmonary embolism treatment, encompassing both the maturation of NOAC therapy as an established first-line anticoagulation standard and the emergence of catheter-directed interventions as increasingly viable options for selected higher-risk patient populations. The Phase III NOAC trial portfolio, including EINSTEIN-PE, AMPLIFY, RE-COVER, and Hokusai-VTE, collectively provides Level I, Grade A evidence for NOAC use in acute PE, demonstrating consistent non-inferior efficacy with superior bleeding safety profiles that directly informed the 2019 ESC Class I recommendation for NOACs as preferred anticoagulation for eligible PE patients [19].AMPLIFY's exceptional 69% major bleeding reduction has positioned apixaban as the preferred agent for patients with elevated hemorrhagic risk, given that major bleeding events are associated with significant morbidity, treatment discontinuation, and increased thrombotic risk [20].

The NOAC-TURK findings regarding 47.6% inappropriate dose reduction parallel international observations of the "dose-reduction paradox," where underdosing increases thromboembolic risk without reducing bleeding, and underscore the urgent need for targeted physician education on evidence-based NOAC dosing algorithms in Turkey [17]. The clinical implication is unequivocal: there is a critical and urgent need to enhance physician education concerning evidence-based NOAC dosing algorithms, to ensure the appropriate and limited application of specific dose-reduction criteria (including renal function thresholds, body weight considerations, advanced age, and concomitant interacting medications), and to adopt objective, individualized bleeding risk assessments utilizing validated scoring tools such as HAS-BLED. These initiatives are vital for improving anticoagulation quality and enhancing patient outcomes within Turkish clinical practice.

The PEERLESS trial represents a paradigm shift in interventional PE treatment, establishing that mechanical thrombectomy achieves outcomes equivalent or superior to thrombolytic-based approaches while dramatically reducing resource utilization. The marked difference in ICU admission rates reflects the practical burden of thrombolytic infusion protocols requiring prolonged monitoring versus FlowTriever's single-session approach, with implications for healthcare costs, hospital capacity, patient experience, and reduced exposure to ICU-associated complications [21].

However, critical and clinically important knowledge gaps remain regarding catheter-directed PE therapies that must be definitively addressed through additional well-designed randomized trials before establishing definitive treatment paradigms and clinical practice guidelines. Most fundamentally, neither the PEERLESS trial nor prior randomized studies of catheter-directed therapy have demonstrated mortality reduction compared to anticoagulation alone—the ultimate unanswered question for intermediate-risk PE management that has limited widespread adoption of interventional approaches [21]. While PEERLESS convincingly demonstrated FlowTriever superiority over CDT for a hierarchical composite endpoint emphasizing resource utilization, ICU admission, and clinical deterioration, both treatment arms received catheter-based intervention, precluding conclusions about benefit over standard anticoagulation. The ongoing HI-PEITHO trial (NCT04790370), which is randomizing approximately 406 patients with intermediate-high risk PE to EKOS ultrasound-assisted thrombolysis versus anticoagulation alone with a primary composite endpoint of 7-day PE-related mortality, hemodynamic decompensation, or recurrent VTE, will provide essential evidence regarding whether any catheter-based intervention offers meaningful clinical benefit beyond optimal anticoagulation [21]. Similarly, the PEERLESS II trial (NCT06055920) will directly compare FlowTriever mechanical thrombectomy plus anticoagulation versus anticoagulation alone in up to 1,200 patients with intermediate-risk PE and additional clinical risk factors, using a hierarchical win ratio primary endpoint encompassing mortality, clinical deterioration, hospital readmission, bailout therapy, and dyspnea outcomes. Until these pivotal trial results become available—anticipated in 2025-2026—the optimal role for interventional PE therapies in clinical practice remains uncertain [22].

From the Turkish healthcare system perspective, published clinical experience with catheter-directed PE therapies remains remarkably limited compared to international centers, representing both a significant gap in current evidence and an important opportunity for Turkish investigators and institutions to contribute meaningfully to the rapidly evolving international evidence base for interventional PE management. Several strategic priorities emerge from this analysis for advancing PE care quality in Turkey: first, establishing multicenter Turkish PE registries that systematically capture comprehensive data on both medical and interventional treatment outcomes with standardized data collection protocols enabling meaningful comparison with international benchmarks; second, expanding Pulmonary Embolism Response Team (PERT) programs—which now carry a Class IIa recommendation in ESC guidelines—to optimize multidisciplinary patient selection, treatment decision-making, procedural timing, and care coordination across departments and institutions (9); third, developing formal structured training programs for interventional cardiologists, interventional radiologists, and vascular surgeons in emerging catheter-based PE treatment techniques with credentialing standards; fourth, implementing standardized risk stratification protocols incorporating validated clinical scores (sPESI, PESI, ESC algorithm) and biomarker assessment (troponin, NT-proBNP) to guide appropriate treatment intensity selection; and fifth, urgently addressing the 47.6% inappropriate NOAC dose reduction rate identified in NOAC-TURK through targeted educational interventions, electronic health record decision support tools, pharmacist-led anticoagulation stewardship programs, and quality improvement initiatives with audit and feedback mechanisms.

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Several methodological limitations of this systematic bibliographic review warrant acknowledgment when interpreting findings. The bibliographic synthesis approach employed, while enabling comprehensive qualitative evidence evaluation across heterogeneous study designs and outcomes, precludes formal quantitative meta-analysis with pooled effect estimates, statistical heterogeneity assessment, and meta-regression to explore sources of between-study variation. Publication bias may systematically favor positive results, particularly for industry-sponsored device registry studies where negative or neutral findings may be less likely to reach publication. The rapidly evolving nature of interventional device technology means that some findings may become outdated as newer-generation devices with improved technical characteristics, enhanced deliverability, and optimized procedural protocols enter clinical use and are evaluated in prospective studies. The heterogeneity of PE risk classification schemes across included studies—with evolving definitions of intermediate-high risk PE incorporating variable combinations of imaging findings (RV dysfunction on echocardiography or CT), biomarker elevation (troponin, NT-proBNP), and clinical risk factors—complicates direct comparison of treatment outcomes across different patient populations, study eras, and geographic regions. Finally, the limited Turkish interventional therapy literature identified through systematic searching precluded detailed national comparison for this treatment modality and represents an important area requiring future research investment and infrastructure development.

The interpretation of findings across the included studies must be tempered by the recognition of substantial heterogeneity in several critical domains that limit direct comparisons. Risk stratification of PE varied considerably among studies; while some trials employed the ESC 2019 algorithm, which distinguishes low, intermediate-low, intermediate-high, and high-risk categories based on hemodynamic status, imaging findings, and biomarkers, others utilized earlier classification schemes, simplified PESI alone, or institution-specific protocols. Consequently, "intermediate-risk" PE patients in one study may not be directly comparable to those in another. Definitions of outcomes also exhibited variability across trials, with major bleeding variably defined according to the International Society on ISTH criteria, GUSTO classification, or TIMI criteria. Methods for ascertaining recurrent VTE ranged from routine surveillance imaging to symptom-driven evaluation only, and composite endpoints incorporated different component events with follow-up durations spanning from 7 days to 12 months. Additionally, baseline anticoagulation protocols in trials involving catheter-directed therapy displayed variation in heparin dosing, timing of NOAC initiation, and duration of parenteral overlap. Procedural techniques and operator experience in interventional studies reflected early adoption periods versus mature programs, potentially influencing outcomes independently of device characteristics. These heterogeneities preclude definitive quantitative comparisons across studies and underscore why a formal meta-analysis was not undertaken. Therefore, readers should interpret cross-study comparisons as hypothesis-generating rather than as definitive conclusions.

Conclusion

This PRISMA 2020-compliant systematic bibliographic review of pulmonary embolism treatment demonstrates that NOACs have achieved high-quality Level I evidence as first-line anticoagulation therapy for low and intermediate-risk PE, offering non-inferior efficacy with significantly reduced major bleeding compared to conventional VKA-based anticoagulation—a Grade A recommendation now established in international guidelines. The NOAC-TURK registry confirms real-world applicability in Turkish practice while highlighting the urgent need to address inappropriate dose reduction patterns (47.6%) through targeted educational and quality improvement interventions.

Catheter-directed therapies, particularly large-bore mechanical thrombectomy with FlowTriever, demonstrate substantial promise for intermediate-high risk PE with favorable safety profiles and dramatically reduced healthcare resource utilization compared to thrombolytic-based approaches. The PEERLESS trial establishes mechanical thrombectomy superiority over CDT (win ratio 5.01), primarily driven by reduced ICU utilization (41.6% vs 98.6%), fewer clinical deteriorations, and shorter hospital stays. However, mortality benefits over anticoagulation alone remain unproven pending HI-PEITHO and PEERLESS II trial completion. Key recommendations include: (1) strict NOAC dosing guideline adherence; (2) CDT consideration in intermediate-high risk PE with deterioration monitoring; (3) PERT program establishment; (4) Turkish multicenter PE registries; (5) standardized ESC-based risk stratification.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

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Ethical Approval

Ethics committee approval was not required as this study is based solely on previously published data and did not involve human subjects.

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