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Ramy Sedhom

Michael Megaly
Henry Ford Health, mmegaly1@hfhs.org

Ayman Elbadawi

Islam Y. Elgendy

Christian F. Witzke

See next page for additional authors

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Authors

Ramy Sedhom, Michael Megaly, Ayman Elbadawi, Islam Y. Elgendy, Christian F. Witzke, Sanjog Kalra, Jon C. George, Mohamed Omer, Subhash Banerjee, Wissam A. Jaber, and Mehdi H. Shishehbor

Contemporary National Trends and Outcomes of Pulmonary Embolism in the United States

Ramy Sedhom, MD, MS[a], Michael Megaly, MD, MS[b], Ayman Elbadawi, MD[c], Islam Y. Elgendy, MD[d], Christian F. Witzke, MD[e], Sanjog Kalra, MD[f], Jon C. George, MD[g], Mohamed Omer, MD[h], Subhash Banerjee, MD[i,j], Wissam A. Jaber, MD[k], and Mehdi H. Shishehbor, DO, MPH, PhD[l,*]

Contemporary data on the national trends in pulmonary embolism (PE) admissions and outcomes are scarce. We aimed to analyze trends in mortality and different treatment methods in acute PE. We queried the Nationwide Readmissions Database (2016 to 2019) to identify hospitalizations with acute PE using the International Classification of Diseases, Tenth Revision, Clinical Modification codes. We described the national trends in admissions, in-hospital mortality, readmissions, and different treatment methods in acute PE. We identified 1,427,491 hospitalizations with acute PE, 2.4% of them (n = 34,446) were admissions with high-risk PE. The rate of in-hospital mortality in all PE hospitalizations was 6.5%, and it remained unchanged throughout the study period. However, the rate of in-hospital mortality in high-risk PE decreased from 48.1% in the first quarter of 2016 to 38.9% in the last quarter of 2019 (p-trend <0.001). The rate of urgent 30-day readmission was 15.2% in all PE admissions and 19.1% in high-risk PE admissions. In all PE admissions, catheter-directed interventions (CDI) were used more often (2.5%) than systemic thrombolysis (ST) (2.1%). However, in admissions with high-risk PE, ST remained the most frequently used method (ST vs CDI: 11.3% vs 6.6%). In conclusion, this study showed that the rate of in-hospital mortality in high-risk PE decreased from 2016 to 2019. ST was the most frequently used method for achieving pulmonary reperfusion in high-risk PE, whereas CDI was the most frequently used method in the entire PE cohort. In-hospital death and urgent readmissions rates remain significantly high in patients with high-risk PE. **(Am J Cardiol 2022;176:132−138)**

Introduction

Pulmonary embolism (PE) remains a leading cause of cardiovascular morbidity and mortality.[1,2] Patients presenting with hypotension or shock (i.e., high-risk PE) have the highest mortality, which may reach >50%.[3] In recent years, treatment methods for achieving pulmonary reperfusion and supporting the circulation have evolved, including catheter-directed interventions (CDI), systemic thrombolysis (ST), surgical embolectomy (SE), and extracorporeal membrane oxygenation.[4] There are 2 main types of CDI: catheter-directed thrombolysis (CDT) and catheter-directed embolectomy (CDE). CDT involves the administration of thrombolytic agents directly into the pulmonary arteries, whereas CDE involves the mechanical disruption or aspiration of the PE. CDT can be combined with ultrasound CDT (US-CDT), which disrupts fibrin strands allowing effective thrombolysis at lower doses. Theoretically, CDI can achieve early restoration of blood flow, reduce the pulmonary vascular resistance, reduce right ventricular afterload and increase the cardiac output without the higher risk of bleeding observed with ST.[5−8] To better understand the real-world practice, including usage trends, we aimed to describe the national trends in mortality and outcomes of acute PE and to describe the trends in the use of different treatment methods using a comprehensive analysis of the Nationwide Readmissions Database (NRD).

Methods

We used the NRD, Healthcare Cost and Utilization Project (HCUP), and Agency for Healthcare Research and Quality to obtain our cohort. The NRD contains discharge data from 28 geographically dispersed states, accounting for 60% of the United States resident population and 58.2% of all United States hospitalizations. We

[a]Department of Medicine, Albert Einstein Medical Center, Philadelphia, Pennsylvania; [b]Division of Cardiology, Henry Ford Hospital, Detroit, Michigan; [c]Section of Cardiology, Baylor College of Medicine, Houston, Texas; [d]Department of Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar; [e]Division of Cardiology, Albert Einstein Medical Center, Philadelphia, Pennsylvania; [f]Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, Canada; [g]Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, Pennsylvania; [h]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; [i]Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas; [j]Veterans Affairs North Texas Healthcare System, Dallas, Texas; [k]Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; and [l]Harrington Heart and Vascular Institute and Case Western Reserve University School of Medicine, University Hospitals, Cleveland, Ohio. Manuscript received January 30, 2022; revised manuscript received and accepted March 23, 2022.

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*Corresponding author.

E-mail address: shishem@gmail.com (M.H. Shishehbor).

identified the cohort, procedures, and outcomes using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD 10-CM), and procedure (ICD 10-PCS) codes. The codes used are listed in Supplementary Table 1.

We identified hospitalizations with any diagnosis of acute PE for the years 2016 to 2019 using ICD 10-CM codes as listed in Supplementary Table 1. Admissions with STEMI (ST-segment elevation myocardial infarction), acute ischemic stroke, and acute limb ischemia were excluded from our analysis to avoid confounding as some of those patients might have received ST or CDI for other reasons than acute PE. We also excluded admissions with missing data on mortality. We then identified those who received ST, CDI, and SE. In the hospitalizations with CDI, we identified those who received CDT and CDE. Admissions with high-risk PE were identified as those with cardiogenic shock or those who received vasopressors.

Patient and hospital-level variables provided by the HCUP and NRD were used to identify demographics and baseline characteristics. The Elixhauser method was used to assess co-morbidities.[9] The rest of the co-morbidities were identified using appropriate ICD 10 CM codes (Supplementary Table 1). The NRD is a publicly available database with de-identified hospitalization records; therefore, this study was exempt from institutional review board approval.

We investigated the trends in the use of different treatment methods for achieving pulmonary reperfusion (i.e., CDI, CDT, CDE, ST, and SE) in acute PE across the 4 years by quarters. We then evaluated the trends in all-cause in-hospital mortality in all acute PE hospitalizations and in high-risk PE.

In addition, we described the unadjusted outcomes based on the treatment method. The outcomes of interest were all-cause in-hospital mortality, intracranial hemorrhage (ICH), non-ICH bleeding events, which included respiratory hemorrhage, hemothorax, gastrointestinal hemorrhage, retroperitoneal bleeding, hematuria, hemarthrosis, hemopericardium, intraocular hemorrhage, gynecological bleeding, and unspecified postprocedural bleeding. Admissions not receiving reperfusion therapy or inferior vena cava (IVC) filter were presumed to have received anticoagulation alone.

Finally, we investigated and described the urgent 30-day readmission rates. We used a limited cohort to identify readmissions after excluding those admitted in December of each calendar year (30-day readmissions for hospitalizations in December could not be obtained because the NRD does not cross the calendar year) and those who died during the index admission. We identified the proportion of urgent 30-readmissions because of PE and major bleeding using the ICD-10 codes of the first 3 recorded readmission diagnoses.

All analyses were conducted using the appropriate weighting, stratifying, and clustering samples following HCUP regulations.[10,11] We did not aim to compare the different methods given the limitations of the database and the lack of important variables that would be required for adequate matching. Therefore, we did not perform propensity-score matching. Continuous variables were summarized as medians and interquartile range (IQR) (25th and 75th percentiles). Categorical variables were displayed as numbers and percentages. Trend analysis was performed using the Poisson regression method. All p values were 2-sided with a significance threshold <0.05. Statistical analysis was performed using STATA *Statistical* Software for Windows Release16.0. (College Station, Texas. StataCorp LLC.)

Results

We identified a total of 1,427,491 weighted hospitalizations with acute PE during the study period, 2.4% of them (n = 34,446) were admissions with high-risk PE. In all PE admissions, 2.1% (n = 30,570) received ST, 2.5% (n = 36,332) underwent CDI, and 0.2% (n = 2,185) underwent SE (Figure 1). In high-risk PE, ST use was 11.3% (n = 3,884), CDI was 6.6% (n = 2,289), and SE was 3% (n = 1,033).

Overall, the rate of all-cause in-hospital mortality in all PE hospitalizations was 6.5%, and it remained unchanged throughout the study period. The overall mortality in high-risk PE was 42.3%, and it showed a favorable trend from 48.1% in the first quarter of 2016 to 38.9% in the last quarter of 2019 (p-trend <0.001) (Figure 2).

The use of CDI and ST increased throughout the study period, whereas SE trends showed a slight decrease. ST was the predominant treatment method in 2016, but CDI became more frequently used from 2017 to 2019 (Figure 3). However, in admissions with high-risk PE, ST remained the most commonly used method for reperfusion throughout the study period, with an increase in its use from 171 cases in the first quarter of 2016 to 307 cases in the last quarter of 2019 (p-trend <0.001). Patients with high-risk PE who received CDI increased from 80 in the first quarter of 2016 to 205 in the last quarter of 2019 (p-trend <0.001) (Figure 4).

The overall urgent 30-day readmission rate was 15.2% (184,449 of 1,215,904 admissions), with a median time to readmission of 10 days (IQR 5 to 18 days). In urgent readmissions, 12.1% were because of recurrent PE, 4.8% because of deep venous thrombosis (DVT), 3.7% because of non-ICH bleeding, and 0.8% because of ICH.

In the high-risk PE cohort, the urgent 30-day readmission rate was 19.2% (3.434 of 17,861) with a median time to readmission of 10 days (IQR 5 to 18 days). In those urgent readmissions, 7.3% were because of recurrent PE, 3% because of DVT, 2.9% because of non-ICH bleeding, and 1.1% because of ICH.

The baseline demographics, co-morbidities, hospital characteristics, and outcomes of all PE admissions are listed in Table 1. In all PE admissions, the median age was 65 years (IQR 53 to 76 years), and 51.7% were female. The most common co-morbidities were hypertension, chronic pulmonary disease, diabetes mellitus, anemia, and heart failure. Concomitant DVT was present in one-third of admissions, whereas both saddle PE and acute cor pulmonale were present in approximately 6% of cases. Most of the admissions received anticoagulation alone, whereas CDI was the most common method for achieving pulmonary reperfusion.

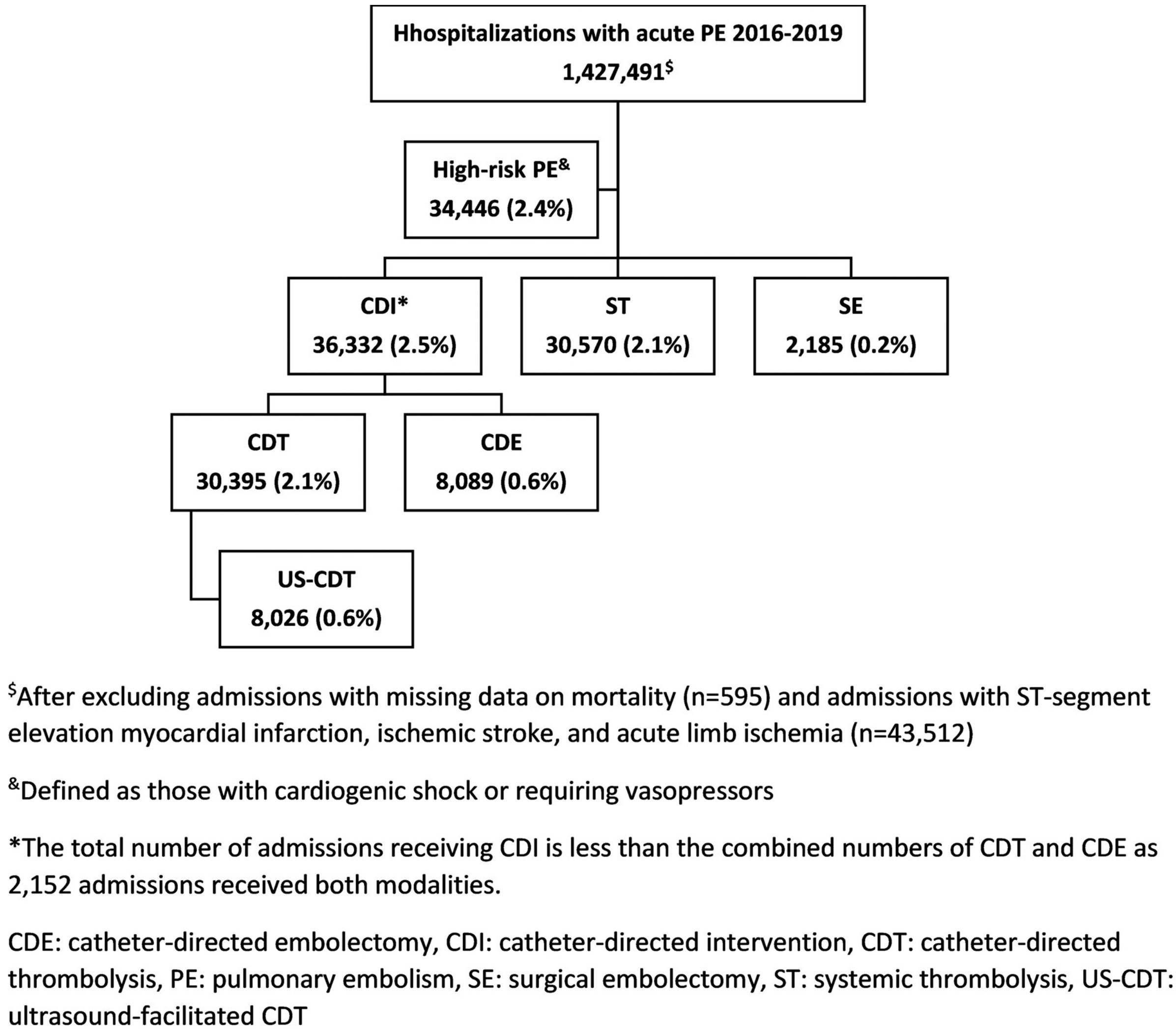

Figure 1. Flowchart of the study.

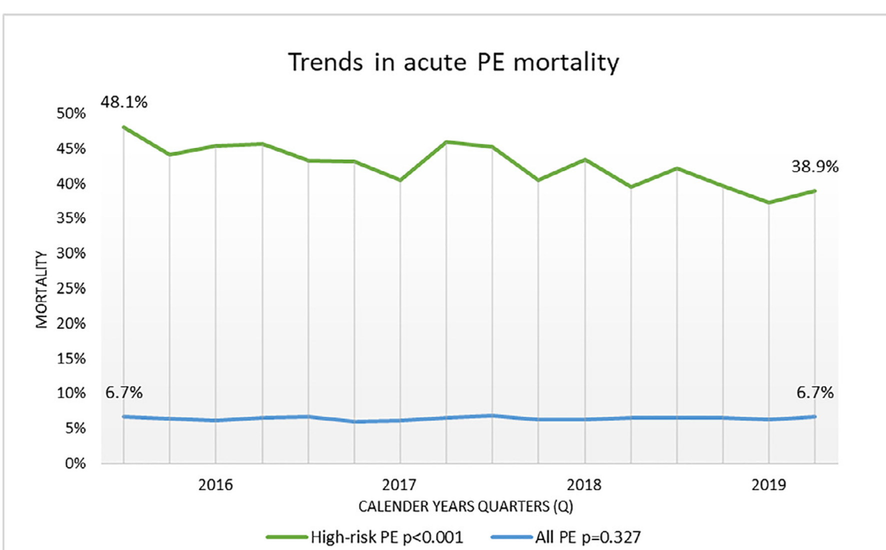

Figure 2. National trends in in-hospital mortality in pulmonary embolism.

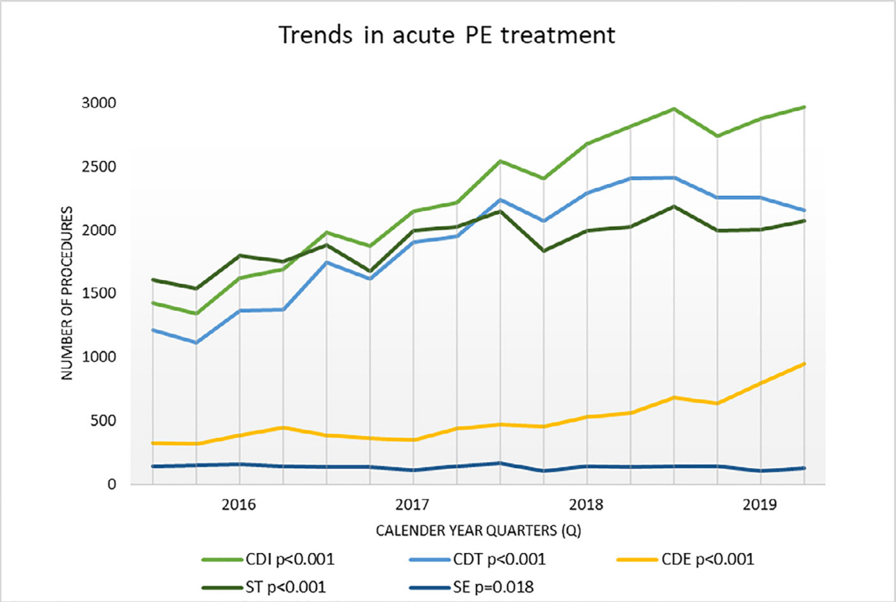

Figure 3. National trends in the use of different treatment methods in pulmonary embolism

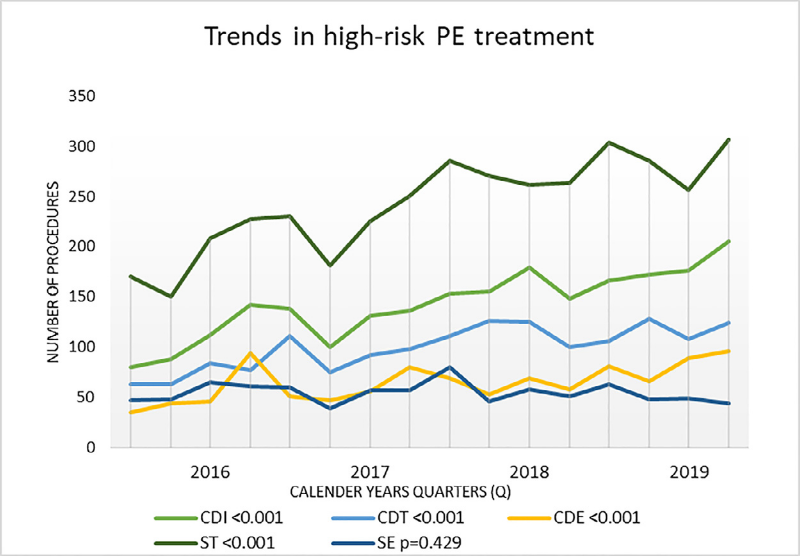

Figure 4. National trends in the use of different treatment methods in high-risk pulmonary embolism

The rate of all-cause in-hospital mortality was 6.5%, ICH was 1.1% and non-ICH bleeding was 10.2%. The median length of stay was 4 days (IQR 2 to 8 days) (Table 1). When stratified by treatment method, the rate of in-hospital mortality was highest in ST (16.5%) and lowest in CDT (4.7%). The ICH was highest in SE (6%), whereas non-ICH was highest in the IVC filter (27.4%) (Table 2).

Discussion

The salient findings of our study are as follows: (1) the overall rate of in-hospital mortality in high-risk PE decreased during the study period from 48.1% in the first quarter of 2016 to 38.9% in the last quarter of 2019. The rate of urgent 30-day readmission in high-risk PE was 19%. (2) the number of admissions who underwent CDI for acute PE increased over the study period, exceeding those who received ST in 2017−2019. However, ST remained the most commonly used treatment method for achieving pulmonary reperfusion in high-risk PE.

In our study, we have noticed a reduction in in-hospital mortality and increased use of CDI and ST in high-risk PE over the study period. One possible explanation is the acceptance of the "PERT team" (pulmonary embolism response team) concept by many hospitals. Multidisciplinary PERTs were introduced in 2013.[12] These teams are

Table 1
Baseline characteristics and in-hospital outcomes in admissions with pulmonary embolism from 2016 to 2019

Variable	PE Admissions in 2016−2019 (n=1,427,492)
Age (years), median (IQR)	65 (53−76)
Women	738,700 (51.7%)
Pregnancy	10,336 (0.7%)
Year of admission	
2016	347,108 (24.3%)
2017	355,114 (24.9%)
2018	360,499 (25.3%)
2019	364,772 (25.6%)
History of tobacoo use	345,689 (24.2%)
Morbid obesity	169,902 (11.9%)
Hypertension	882,764 (61.8%)
Diabetes mellitus	354,360 (24.8%)
Anemia	314,087 (22%)
Coagulopathy	157,402 (11%)
Pulmonary hypertension	85,780 (6%)
Chronic pulmonary disease	382,461 (26.8%)
Atrial fibrillation/flutter	227,898 (16%)
Heart failure	291,157 (20.4%)
Prior MI	71,253 (5%)
Prior PCI	6,438 (0.5%)
Prior CABG	48,122 (3.4%)
Prior stroke	80,184 (5.6%)
Severe renal disease	48,424 (3.4%)
Severe liver disease	14,356 (1%)
Presentation and severity	
Concomitant DVT	475,256 (33.3%)
Saddle PE	82,454 (5.8%)
Acute cor pulmonale	80,177 (5.6%)
Cardiogenic shock	23,647 (1.7%)
High-risk PE	34,446 (2.4%)
Hospital and payer	
Large hospital	796,033 (55.8%)
Teaching hospital	997,259 (69.9%)
Medicare	783,396 (54.9%)
Treatment modalities	
CDI	36,332 (2.5%)
CDT	30,395 (2.1%)
CDE	8,089 (0.6%)
ST	30,570 (2.1%)
SE	2,185 (0.2%)
IVC filter	103,411 (7.2%)
Anticoagulation alone	1,269,394 (88.9%)
Circulatory and ventilatory support	
Vasopressors	13,382 (0.9%)
Mechanical ventillation	105,942 (7.4%)
Impella	887 (0.1%)
ECMO	2,512 (0.2%)
Outcomes	
In-hospital mortality	92,455 (6.5%)
Discharge to facility	271,011 (19%)
Urgent 30-day readmission	184,449 (15.2%)*
ICH	15,534 (1.1%)
Non-ICH bleeding	145,544 (10.2%)
Respiratory hemorrhage	43,740 (3.1%)
Hematuria	28,023 (2%)
Gastrointestinal bleeding	54,956 (3.8%)
Hemarthrosis	6,488 (0.5%)
Gynecological bleeding	8,767 (0.6%)
Retroperitoneal bleeding	6,563 (0.5%)
Hemothorax	3,534 (0.2%)
Hemopericardium	516 (0%)
Intraocular hemorrhage	260 (0%)
Unspecified postprocedural bleeding	2,561 (0.2%)
Blood transfuison	78,327 (5.5%)
LOS in days, (median, IQR)	4 (2−8)

* Of 1,215,904 admissions.

CABG = coronary artery bypass surgery; CDE = catheter-directed embolectomy; CDI = catheter-directed intervention; CDT = catheter-directed thrombolysis; DVT = deep venous thrombosis; ECMO = extracorporeal membrane oxygenation; ICD = implantable cardioverter-defibrillator; ICH = intracranial hemorrhage; IQR = interquartile range; IVC = inferior vena cava; MI = Myocardial infarction; PCI = percutaneous coronary intervention; PE = pulmonary embolism.

composed of experts from different specialties aiming at providing better care to patients with high-risk PE in a timely manner.[13] They help in rapid risk stratification of patients and choosing the most appropriate management strategy.[12] Studies have shown that with the introduction of PERTs, there has been an increase in the use of advanced therapies for PE (ST/CDI), with a possible decrease in in-hospital mortality.[3,12] Another explanation for the decreased mortality in our study is the advances in the management of shock,[4] including the use of mechanical circulatory support (i.e., Impella and extracorporeal membrane oxygenation). However, we found that the overall in-hospital mortality remained elevated (42.3%), reperfusion therapies remained underused (11.3% and 6.6% for ST and CDI, respectively), and the urgent 30-day readmission rate was substantial (19%) in admissions with high-risk PE. These findings reflect the high burden of the disease and should raise awareness of the limitations of the current risk stratification methods, which have not been shown to improve the outcomes of patients.[14]

The role of CDI in the treatment of PE is rapidly evolving.[5] Current guidelines do not support the routine use of CDI in patients with PE given the low level of evidence based mainly on retrospective or prospective single-arm studies.[15−17] These guidelines recommend ST as the first reperfusion therapy in patients with high-risk PE, whereas CDI is considered an alternative to SE in patients who fail or have a contraindication to ST.[13,14,18,19] Although we found that ST is the most commonly used method in high-risk PE, CDI was more used in the overall PE cohort than ST (2.5% vs. 2.1%). This contrasts to previous analyses from the Nationwide Inpatient Sample (years 2010 to 2012) and NRD (year 2016), which showed that ST was more frequently used than CDI.[20,21] In addition, we found that the trends in CDI use increased over time. A similar trend was found in an analysis of Medicare beneficiaries showing a 10-fold increase in CDT use from 2004 to 2016, increasing from 0.1% to 1.0%.[22] The increase in CDI use in our study reflects the advancements in the percutaneous endovascular techniques, with more operators and specialties familiar with those techniques.[22] During our study period, there

Table 2
Outcomes stratified by treatment method

Variable	In-Hospital Mortality	ICH	Non-ICH
Anticoagulation alone (n=1,269,394)	78,940 (6.2%)	9,491 (0.7%)	154,289 (12.2%)
IVC filter (n=103,411)	7,100 (6.9%)	5,507 (5.3%)	28,362 (27.4%)
Systemic thrombolysis (n=30,570)	5,033 (16.5%)	556 (1.8%)	4,181 (13.7%)
Catheter-directed thrombolysis (n=30,395)	1,415 (4.7%)	185 (0.6%)	3,090 (10.2%)
Catheter-directed embolectomy (n=8,089)	898 (11.1%)	234 (2.9%)	1,209 (14.9%)
Surgical embolectomy (n=2,185)	279 (12.8%)	66 (6%)	425 (19.5%)

ICH = intracranial hemorrhage; IVC = inferior vena cava.

were 3 Food and Drug Administration-approved interventional devices for use in PE; the EkoSonic Endovascular system in 2014 (EKOS Corporation, Bothell, Washington), which uses US-CDT,[15] FlowTriever System in 2018 (Inari Medical, Irvine, California), which is a suction embolectomy catheter[23] and most recently the Penumbra Indigo aspiration system in 2019 (Penumbra Inc., Alameda, California).[24]

Our analysis showed that the risk of ICH was 0.6% with CDT and 1.8% with ST, which is consistent with previous reports from the Nationwide Inpatient Sample and NRD showing an ICH rate of 0% to 0.7% with CDT compared with 1.4% to 2.1% with ST.[20,21,25] By delivering lower doses of thrombolytics directly into the pulmonary arteries, the risk of major bleeding including ICH is expected to be lower with CDT. Recently, lower doses (8 mg) and shorter duration of tPA infusion (2 to 4 hours) were as effective as longer infusions (6 hours), and higher doses (12 to 24 mg) in decreasing the right ventricular/left ventricular ratio in patients who underwent US-CDT.[26] In contrast, we found that ICH and non-ICH bleeding occurred more frequently in admissions receiving IVC filter, CDE, and SE, which is to be expected as these treatment methods are used predominantly in patients with high bleeding risk and/or contraindication to anticoagulation therapy or thrombolysis. It is important to note that our study is mainly descriptive, further observational or randomized studies are needed to ascertain the risk of bleeding, ICH, and mortality in patients based on treatment methods.

The strengths of our study are driven by its large sample size with national representation. However, the findings should be interpreted in the context of some limitations. First, our study is a retrospective observational study with its inherent limitation of selection bias. Second, given the administrative database structure of NRD, the study is subject to coding errors and data quality at the site of collection, without the ability to adjudicate accuracy. Third, the temporal relationship of certain outcomes cannot be reliably established. Fourth, data on discharge medications, including anticoagulation, and compliance are lacking which could influence the readmission rates and outcomes. Fifth, the clinical reasoning for choosing one method of reperfusion therapy versus the other could not be determined. The NRD lacks data on imaging and cardiac biomarkers which could help better risk-stratify patients and could potentially influence the decision to proceed with advanced therapies.

In conclusion, in this contemporary nationwide observational study, the risk of in-hospital mortality in high-risk PE decreased over the study period. ST was the most frequently used method for achieving pulmonary reperfusion in high-risk PE, whereas CDI was the most frequently used method in the entire PE cohort.

Disclosures

Dr. Sanjog Kalra is a consultant and Speakers' bureau and/or Advisory Board participant for Boston Scientific, Cardiovascular Systems Inc, Translumina Therapeutics, Abiomed Inc., and Philips Healthcare. Dr. Wissam Jaber receives consultation fees and research grants from Inari Medical. All other authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.03.060.

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