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Trends in management and outcomes of pulmonary embolism with a multidisciplinary response team

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Abstract

Multidisciplinary pulmonary embolism (PE) response teams have garnered widespread adoption given the complexities of managing acute PE and provide a platform for assessment of trends in therapy and outcomes. We describe temporal trends in PE management and outcomes following the deployment of such a team. All consecutive patients managed by our multidisciplinary PE response team activated by the Emergency Department were included over a 5-year calendar period. We examined temporal trends in management and rates of a composite primary endpoint (all-cause-death, major bleeding, recurrent venous thromboembolism, and readmission) at 30 days and 6 months. We assessed 425 patients between 2015 and 2019. We observed an increase in PE acuity and use of systemic thrombolysis. The primary endpoint at 30 days decreased from 16.3% in 2015 to 7.1% in 2019 (adjusted rate ratio per period, 0.63; 95%CI, 0.47–0.84), driven by a decrease in the adjusted rate of major bleeding. Among 406 patients with complete follow-up, the adjusted rate ratio per year for the primary outcome at 6 months was 0.37 (95%CI, 0.19–0.71), driven by a decrease in all-cause mortality. We observed evidence of temporal changes in clinical presentation, therapeutic strategies, and outcomes for acute PE, in parallel to, but not necessarily because of, the implementation of a multidisciplinary response team. Over time, major bleeding, mortality and readmission rates decreased, despite an increase in PE risk category.

Keywords Outcomes · Pulmonary embolism · Response team

Highlights

- Among 406 patients managed from 2015 to 2019, we observed that PE acuity increased over time.
- The use of unfractionated heparin and systemic thrombolysis increased, while there was a significant decrease in the composite 30-day endpoint of death, major bleeding, recurrent venous thromboembolism, or hospital readmission between 2015 and 2019.
- We provide evidence for temporal changes in the clinical characteristics and therapeutic strategies for acute PE, in parallel to the implementation of a multidisciplinary response team.

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Introduction

Thirty-day mortality for acute pulmonary embolism (PE) approaches 25%, especially for patients presenting with cardiogenic shock [1], despite improvements in our understanding of pathophysiology [2, 3] and innovations in anticoagulation and reperfusion. Therapeutic advances include broad integration of direct oral anticoagulants (DOACs) into PE therapy, development of catheter-based reperfusion strategies, and the application of extra-corporeal membrane oxygenation and open surgical embolectomy [4–9].

Gaps in evidence-based clinical practice guidelines and the increasing number of therapeutic options helped drive forward the concept of multidisciplinary PE response teams [10]. Beyond simply providing algorithms for management pathways, which are available in international guidelines, the interest of a dedicated response team resides in the multidisciplinary decision-making, which personalizes care based on each patient's individual risk profile. Burgeoning growth of these teams nationwide has led to formation of the Pulmonary Embolism Response Team (PERT) Consortium [11]. The 2019 European Society of Cardiology (ESC) guidelines issued a class IIA recommendation in support of institutional creation of multidisciplinary PE teams [12]. However, longitudinal changes in PE management and associated clinical outcomes in the era of such team-based care have not been fully delineated [10, 13–22].

We report a longitudinal time-based analysis of patients diagnosed with acute PE and managed by a multidisciplinary PE response team, first activated in the Emergency Department (ED). The aims were to describe temporal trends in patient characteristics, treatment delivered, and clinical outcomes since the deployment of a multidisciplinary PE team at our institution.

Methods

Study design

In December 2014, a multidisciplinary PE response team program, named CODE-PE, was established for the management of acute PE referred to the ED at Brigham and Women's Hospital (Boston, MA). The faculty of our CODE-PE program is comprised of specialists from Cardiovascular Medicine, including Cardiac Imaging, Interventional Cardiology and Vascular Medicine, Cardiothoracic Surgery, Emergency Medicine, Pulmonary and Critical Care Medicine, and Radiology, all of whom have a particular interest and competency in treating acute PE. CODE-PE team members were encouraged to follow evidence-based clinical practice guidelines when possible and to employ a collaborative case discussion when guidelines did not provide a clear management strategy. No internal treatment algorithms were utilized. The primary evaluation of a CODE-PE patient was provided in the ED and shared by the on-call Vascular Medicine and Pulmonary Vascular Disease teams on an alternating weekly basis. In the present analysis, we focus on patients for whom CODE-PE was activated by the ED team and who had imaging-confirmed PE (i.e., positive computed tomography [CT] pulmonary angiography [23], or high probability ventilation/perfusion scan [24]). The CODE-PE program was activated by the ED provider based on the following clinical criteria: (1) ESC-defined high-risk PE, including PE with sustained hypotension (i.e., systolic blood pressure < 90 mmHg, or "relative hypotension"), or recurrent hypotension despite resuscitative efforts such as IV fluids, or need for vasopressor support [12], (2) ESC-defined intermediate-risk PE, including acute PE with normotensive status and objective evidence of right ventricular (RV) dysfunction documented by CT angiography, transthoracic echocardiography, or increased levels in biomarkers of myocardial injury (e.g., troponin T) [12], (3) anatomically large PE not meeting criteria for high-risk or intermediate-risk, and (4) any patient with PE and contraindications to systemic anticoagulation. Primary responders for the on-call CODE-PE team rapidly congregated at the bedside, gathered information, and reviewed clinical data and radiologic images pertinent to the case. Then, the CODE-PE primary evaluation team decided whether to involve cardiac surgeons or interventional vascular medicine as appropriate, based on the team discussion [25]. If necessary, a conference call was held to discuss management options and patient-specific treatment challenges. After a consensus opinion was reached, the team provided management recommendations to the referring providers and the patient, along with his or her family. The team reconvened on an as-needed basis, in particular if there was deterioration in the patient's clinical condition. The CODE-PE program also included a multidisciplinary case review scheduled on an ad hoc basis to review presentations with challenging management and outcomes. The criteria for activation and intervention of the CODE-PE team were unchanged throughout the study period.

Enrollment and data collection

The study period extended from December 2014 through December 2019. The population was divided by calendar year of admission from 2015 to 2019. The study was conducted according to the Declaration of Helsinki, and

Institutional Review Board approval was obtained. The requirement for informed consent was waived. All patients who were evaluated by the CODE-PE program were prospectively included in the cohort study at the time of initial consultation. The CODE-PE program establishes clinical follow-up for patients in the Cardiovascular Medicine or Pulmonary Vascular Disease clinic. Any missing or follow-up data (around 20%) were retrospectively retrieved from the Electronic Health Record (EHR, EPIC) for the Massachusetts General Brigham Healthcare system to complete the files for the purposes of the present analysis. Two research physicians (RC, UC), both trained in cardiovascular medicine and with expertise in PE management, performed the data audits and confirmed the abstraction using standard definition. Definitions for each variable recorded were defined in advance based on the literature and were validated by all authors prior to the start of data collection. Quality control was maintained by random audit of the data. Using this method, we were able to obtain complete 30-day follow-up for 100%, and 6-month follow-up for 95.5% of patients.

Outcomes and definitions

The primary study outcome was assessed at 30 days and 6 months. This endpoint was a composite of all-cause mortality, major bleeding, recurrent venous thromboembolism (VTE), and hospital readmission. Secondary study outcomes were each individual component of the primary outcome, at 30 days and 6 months.

PE was considered the cause of death if there was objective documentation by autopsy, imaging, objectively confirmed deep vein thrombosis (DVT) in patients with clinical signs and symptoms of PE, or if PE was not objectively-confirmed, but was most likely the main cause of death, as stipulated by the International Society on Thrombosis and Haemostasis (ISTH) [26]. Cause of death was unknown if there was not enough clinical information to decide [26]. Recurrent VTE included PE confirmed by visualization of new filling defects on contrast-enhanced chest CT scan, new mismatched perfusion and ventilation images on V/Q scan, or DVT confirmed by a non-compressible venous segment consistent with a diagnosis of DVT on ultrasonography. Major bleeding was defined according to the criteria proposed by the ISTH [27]. An additional composite endpoint which included PE-related death, major bleeding, recurrent VTE, and rehospitalization was used in a sensitivity analysis at 30 days. All suspected outcome events were classified by a central adjudication committee comprised of three cardiovascular medicine specialists (UC, KJ, and ZA) according to standard definitions derived from the evidence-based literature.

PE was risk-stratified according to the ESC 2019 guidelines [12]. Right ventricular dysfunction was defined on echocardiogram by RV dilatation, hypokinesis of the RV free wall, RV/left ventricular (LV) end-diastolic diameter ratio > 0.9, or elevated RV systolic pressure defined by tricuspid regurgitation gradient > 30 mmHg or tricuspid systolic velocity > 2.6 m/s, and on CT scan by a RV/LV end-diastolic diameter ratio > 0.9 [12, 28]. Full dose of systemic thrombolysis was 100 mg of recombinant tissue-type plasminogen activator (rt-PA) administered over 2 h. Half-dose of systemic thrombolysis was 50 mg of rt-PA administered over 2 h. Catheter-directed therapy (CDT) was performed using ultrasound-facilitated, catheter-directed, low-dose fibrinolysis with the EKOSonic system (Boston Scientific, Marlborough, MA, USA), or the FlowTriever retrieval and aspiration system (Inari Medical, Irvine, CA, USA).

Statistical analysis

We report the study methods and results in accordance with the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines, based on the Recommendations for Statistical Reporting in Cardiovascular Medicine from the American Heart Association [29, 30]. Continuous variables are reported as mean (SD) or median and interquartile range, as appropriate. Discrete variables are described as number and percentage. To evaluate changes in baseline characteristics by calendar period of one year, we used the Cochran-Armitage test for binary variables and the Jonckheere-Terpstra test for continuous variables to determine the statistical significance of changes over time [31].

To assess outcome rates over time, we constructed penalized multivariable models to reduce the bias related to a low event rate [32], using logistic regression for 30-day outcomes, and Cox models for 6-month outcomes. We adjusted multivariable models for baseline characteristics and in-hospital therapies that yielded a p value < 0.10 by univariable analysis. Continuous variables that were statistically significant were categorized, choosing the most discriminative cut-off points, based on the best-subset selection [33]. The full list of candidate covariates is available in Supplemental Table S1. We included the independent covariate "calendar year", a categorical variable with 2015 as the reference. The use of multiple imputation was not required, as the rate of missing data was < 2% for all covariates (Supplemental Table S1) [34]. We multiplied the adjusted rate ratio for each year by the observed outcome rates for the reference year to obtain risk-adjusted outcome rates for the study period. These rates represent the estimated rate of outcomes if the patient case mix was similar to that of the reference year. The crude incidence of 30-day major bleeding per calendar year across ESC-defined risk stratification categories was estimated using the cumulative incidence function [35]. The rate of the primary outcome at 6 months across calendar years is displayed by Cox-model-derived adjusted curves.

We also examined whether primary outcome trends differed between PE risk categories by including an interaction term with calendar period in the model [31]. The temporal trend of length of stay over time was assessed using a penalized multivariable logistic regression.

To assess the robustness of the findings, we performed sensitivity analyses for mortality and bleeding within the first 7 days. We also analyzed the temporal trend of an additional composite endpoint at 30 days, which included PE-related death, major bleeding, recurrent VTE, and rehospitalization.

All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

A total of 425 patients were evaluated in the ED with a confirmed diagnosis of acute PE and prompted consultation of the multidisciplinary PE response team (mean age, 61.9 ± 16.1 years; 46.1% male). In-hospital and 30-day outcomes were available for all 425 patients. Four hundred and six patients (95.5%) had complete 6-month follow-up (Fig. 1). Overall, 91 (21.4%) had low-risk PE, 70 (16.5%) had intermediate-low risk PE, 213 (50.1%) had intermediate-high risk PE, and 51 (12.0%) had high-risk PE. All low-risk PE patients had anatomically large PE on the CT-scan. The number of PE patients managed with the consultation of the multidisciplinary PE response team spanned from 71 in 2015 to 98 in 2016 and 2018 (median, 82 patients; interquartile range 22) (Table 1).

Patient characteristics

There was a calendar-year trend toward an increasing proportion of men (35.2% in 2015 and 60.2% in 2018; p = 0.002 for trend), whereas the mean age did not vary (60.0 to 60.7 years; p = 0.19 for trend). The prevalence of comorbidities, such as chronic lung disease, chronic heart failure, or cancer remained constant over time as did history of recent bleeding (p for trend > 0.10 for all comparisons). Conversely, our analysis showed increases in PE with transient or reversible VTE factors (29.6% in 2015 to 47.4% in 2019; p = 0.004 for trend). Over time, the proportion of patients with elevated troponin and RV dysfunction on echocardiogram or CT scan increased, yielding an increase in PE risk classification severity (p < 0.001 for trend) (Table 1).

Temporal trends in pharmacological management and adjusted length of hospital stay

During the study period, patients were less frequently managed with low-molecular weight heparin (LMWH) (p = 0.02 for trend), whereas a concomitant increase of the use of unfractionated heparin (UFH) (p < 0.001 for trend) at admission was noted. Systemic thrombolysis was administered in 0.8% of intermediate-low-risk, 5.1% of intermediate-high risk, and in 29.4% of high-risk PE patients. CDT was used in 3.1% of low-risk, 9.5% of intermediate-low risk, 19.9% of intermediate-high risk and 11.8% of high-risk PE. The rate of systemic thrombolysis increased over time (+ 5.9% [95%CI, − 0.2 to 0.2]; p = 0.01 for trend), especially the prescription of half-dose systemic thrombolysis (p = 0.03 for trend). Surgical embolectomy decreased between 2015 and 2019, from 5.6% to 1.3% (p = 0.04 for trend), whereas CDT, extra-corporeal membrane oxygenation, and inferior

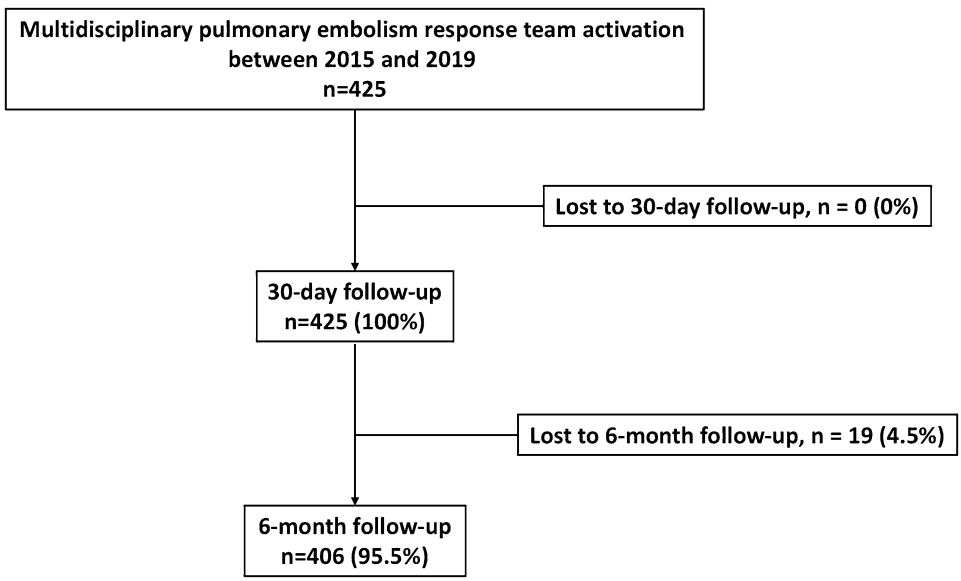

Fig. 1 Study flow-chart

Table 1 Baseline characteristics of 425 patients with acute pulmonary embolism managed by the multidisciplinary pulmonary embolism team from 2015 to 2019

Clinical characteristics	2015 (n = 71)	2016 (n = 98)	2017 (n = 82)	2018 (n = 98)	2019 (n = 76)	*P* for trend	Percent change from 2015 to 2019, (95% CI)
Age, mean (SD)	60.0 ± 16.3	61.8 ± 16.5	63.8 ± 15.4	62.7 ± 16.2	60.7 ± 15.8	0.19	0.7 (−2.0 to 3.4)
Male sex (%)	25 (35.2)	38 (38.8)	36 (43.9)	59 (60.2)	38 (50.0)	0.002	14.8 (−12.1 to 30.8)
BMI, mean (SD)	30.0 ± 8.0	29.4 ± 7.7	29.5 ± 6.8	31.8 ± 9.4	30.7 ± 8.6	< 0.001	0.7 (−2.0 to 3.4)
Comorbidities (%)							
Chronic pulmonary disease	8 (11.3)	13 (13.3)	12 (14.6)	9 (9.2)	10 (13.2)	0.88	1.9 (−8.7 to 12.5)
Heart failure	4 (5.6)	3 (3.1)	4 (4.9)	5 (5.1)	6 (7.9)	0.37	2.3 (−5.8 to 10.4)
Active cancer[a]	26 (36.6)	37 (37.8)	31 (37.8)	33 (22.7)	20 (26.3)	0.14	−10.3 (−25.3to 4.7)
Prior stroke	3 (4.2)	3 (3.1)	12 (14.6)	89 (9.2)	4 (5.3)	0.31	1.1 (−5.8 to 8.0)
Prior bleeding	6 (8.4)	16 (16.3)	6 (7.3)	7 (6.1)	5 (6.6)	0.10	−1.8 (−8.9 to 5.3)
Prior VTE	17 (23.9)	24 (24.5)	19 (23.2)	26 (26.5)	21 (27.6)	0.53	3.7 (−8.1 to 15.5)
Family history of VTE	7 (9.9)	3 (3.1)	7 (8.5)	7 (7.1)	15 (19.7)	0.02	9.8 (0.1 to 19.5)
Major transient or reversible factors	21 (29.6)	28 (28.6)	26 (31.7)	40 (40.8)	36 (47.4)	0.004	17.8 (4.6 to 31.0)
Associated DVT	41 (57.7)	55 (56.1)	54 (65.8)	58 (59.2)	53 (69.7)	0.12	12.0 (−3.4 to 27.6)
Long-term medications (%)							
Estrogen-containing oral contraception	10 (14.1)	6 (6.1)	2 (2.4)	10 (10.2)	8 (10.5)	0.93	−3.5 (−14.1 to 7.0)
Anticoagulant	5 (7.0)	14 (14.3)	9 (11.0)	11 (11.2)	10 (13.2)	0.12	−1.1 (−1.2 to 1.0)
Antiplatelet	13 (18.3)	14 (14.3)	24 (29.3)	24 (28.7)	16 (29.5)	0.12	11.2 (−0.2 to 23.0)
Clinical characteristics							
Cardiac arrest	1 (1.4)	3 (3.1)	2 (2.4)	2 (2.0°	1 (1.3)	0.75	−0.1 (−3.8 to 3.6)
Syncope (%)	10 (14.1)	9 (9.2)	14 (17.1)	15 (15.3)	10 (17.2)	0.62	3.1 (−0.8 to 14.9)
HR at admission, bpm	101.9 ± 21.3	98.2 ± 19.1	95.8 ± 20.2	98.6 ± 21.6	109.6 ± 20.7	< 0.001	7.6 (0.8 to 14.5)
SBP at admission, mmHg	124.1 ± 24.3	125.0 ± 25.7	120.1 ± 27.5	117.2 ± 26.8	116.0 ± 23.5	< 0.001	−8.1 (−15.9 to 3.1)
SaO_2 at admission, %	93.6 ± 9.1	93.4 ± 5.4	90.7 ± 9.4	92.1 ± 7.9	90.9 ± 8.3	< 0.001	−2.7 (−5.5 to 0.1)
Biological data							
Glomerular filtration rate, mL/min/1.73 m^2	57.4 ± 8.1	57.8 ± 10.6	56.1 ± 6.7	71.4 ± 24.9	77.9 ± 25.4	< 0.001	20.5 (14.2 to 26.7)
Positive troponin	25 (35.2)	45 (45.9)	51 (62.2)	78 (79.6)	62 (81.6)	< 0.001	46.4 (30.5 to 62.3)
Echocardiography data	32 (45.1)	55 (57.3)	55 (67.9)	65 (67.0)	59 (78.7)	< 0.001	33.6 (17.9 to 49.3)
RV dysfunction[b]	32 (45.1)	55 (57.3)	55 (67.9)	65 (67.0)	59 (78.7)	< 0.001	33.0 (17.3 to 48.7)
Systolic PAP, mmHg	35.2 ± 17.0	38.1 ± 14.0	36.5 ± 14.0	40.7 ± 11.8	45.3 ± 14.4	< 0.001	10.1 (4.9 to 15.2)
sPESI, mean (SD)	1.3 (1.1)	1.2 (0.9)	1.3 (1.0)	1.5 (1.0)	1.5 (1.2)		0.1 (−27 to −0.46)
ESC PE-risk Stratification (%)						< 0.001	
Low-risk	32 (45.1)	32 (32.6)	13 (15.8)	8 (8.2)	6 (7.9)		−37.2 (−51.3 to −23.0)
Intermediate-low risk	13 (18.3)	20 (20.4)	16 (19.5)	12 (12.2)	9 (11.8)		−6.6 (−18.0 to 5.0)
Intermediate-high risk	21 (29.6)	35 (35.7)	42 (51.2)	63 (64.3)	52 (68.4)		38.8 (22.6 to 54.9)
High-risk	5 (7.0)	11 (11.2)	11 (13.4)	15 (15.3)	9 (11.8)		4.8 (−4.7 to 14.3)

CI confidence interval; *SD* standard deviation; *BMI* body mass index; VTE, venous thrombo-embolism; *DVT* deep vein thrombosis; HR, heart rate; SBP, systolic blood pressure; *SaO_2* oxygen saturation; *PAP* pulmonary artery pressure; *sPESI* simplified Pulmonary Embolism Severity Index; *PE* pulmonary embolism; *RV* right ventricle; *ESC* European Society of Cardiology

[a]Active or anti-tumor therapy within the last 6 months, or metastatic state; [b]defined by at least one of the following parameters: RV/left ventricle ratio > 1.0, hypokinesia of RV free wall, and elevated right ventricular systolic pressure (tricuspid regurgitation gradient > 30 mmHg or tricuspid systolic velocity > 2.6 m/s)

vena cava filter insertion all had similar rates of utilization over time. During the study period, the trend was towards more frequent discharges with a prescription for a DOAC (45.1% vs 68.4%) and fewer with LMWH (32.4% vs 11.8%) (Table 2). Figure 2 summarizes acute PE management according to the ESC-defined risk categories. The

Table 2 In-hospital therapies and adjusted length of hospital stay among 425 patients with acute pulmonary embolism managed by the multidisciplinary pulmonary embolism team between 2015 and 2019

Clinical characteristics	2015 (n = 71)	2016 (n = 98)	2017 (n = 82)	2018 (n = 98)	2019 (n = 76)	*P* for trend	Percent change from 2015 to 2019, (95% CI)
Anticoagulant at admission (%)						–	–
Unfractionated heparin	40 (56.3)	83 (84.7)	67 (81.7)	88 (89.0)	68 (89.5)	< 0.001	33.2 (18.9 to 47.5)
LMWH	28 (39.4)	11 (11.2)	13 (15.8)	15 (15.3)	10 (13.2)	0.002	− 26.2 (− 40.4 to 12.0)
DOAC	3 (4.2)	1 (1.0)	1 (1.2)	12 (12.2)	3 (3.9)	0.07	− 0.3 (− 0.6 to 0.6)
VKA	0 (0)	0 (0)	1 (1.2)	1 (1.0)	0 (0)	0.61	–
Advanced therapy (%)	–	–	–	–	–	–	–
Systemic thrombolysis	1 (1.4)	1 (1.0)	10 (12.2)	11 (11.2)	5 (6.6)	0.01	5.9 (− 0.2 to 0.2)
Full-dose of systemic thrombolysis*	0 (0)	1 (1.0)	4 (4.9)	8 (8.2)	1 (1.3)	0.31	1.3 (− 1.3 to 3.9)
Half-dose of systemic thrombolysis**	0 (0)	0 (0)	6 (7.3)	3 (3.1)	4 (5.3)	0.03	5.3 (0–10.5)
Surgical embolectomy	4 (5.6)	3 (3.1)	4 (4.9)	0 (0)	1 (1.3)	0.04	7.6 (− 1.9 to 1.7)
Catheter directed therapy	11 (15.5)	15 (15.3)	8 (9.8)	14 (14.3)	14 (18.4)	0.72	2.9 (− 9.2 to 15.1)
Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis	11 (15.5)	14 (14.3)	8 (9.8)	14 (14.3)	13 (17.1)	–	–
Mechanical retrieval and aspiration thrombectomy	0 (0)	1 (1.0)	0 (0)	0 (0)	1 (1.3)	–	–
ECMO	1 (1.4)	0 (0)	1 (1.2)	0 (0)	1 (1.3)	0.98	0.1 (− 0.4 to 3.8)
IVC filter implantation	7 (9.9)	8 (8.2)	11 (13.4)	4 (4.1)	7 (9.2)	0.53	0.07 (− 0.09 to 10.1)
Anticoagulant at discharge (%)							
None	0 (0)	5 (5.1)	1 (1.2)	0 (0)	3 (3.9)	0.86	3.9 (2.6 to 5.2)
LMWH	23 (32.4)	27 (27.5)	21 (25.6)	24 (24.5)	9 (11.8)	0.005	21.5 (8.1 to 34.8)
VKA	11 (15.5)	16 (16.3)	13 (15.8)	16 (16.3)	9 (11.8)	0.59	− 3.6 (− 14.7 to 7.4)
DOAC	32 (45.1)	47 (47.8)	40 (48.8)	53 (54.1)	52 (68.4)	0.003	23.3 (7.3 to 39.34)
Adjusted hospital length of stay*	5.2 ± 5.8	5.9 ± 6.9	6.0 ± 6.1	6.4 ± 6.7	6.5 ± 6.1	0.44	1.3 ± 0.7

CI confidence interval; LMWH low molecular weight heparin; *DOAC* direct oral anticoagulant; *VKA* vitamin K antagonist; *ECMO* extra-corporeal membrane oxygenation; *IVC* inferior vena cava

*Adjusted for covariates identified by a causal directed acyclic graph (i.e. diabetes mellitus, heart failure, prior intra-cranial bleeding, history of heart failure, family history of venous thromboembolism, recent hospitalization, concomitant deep vein thrombosis, cardiogenic shock, and surgical embolectomy)

temporal increased rate of use of DOAC mainly occurred in high-risk PE patients. The adjusted length of stay was similar across calendar years, from 5.2 to 6.5 days (p = 0.44 for trend) (Table 2).

Temporal trends in the primary outcome

The entire cohort had a 30-day composite endpoint frequency of 106 events (24.9%). There was a temporal trend toward a decrease in the crude incidence of the composite endpoint and in all individual components of the composite endpoint except for recurrent VTE at 30 days (supplemental Figure S1). Covariates included in the adjusted multivariable model for the primary outcome at 30 days are displayed in Supplemental Table S2. After adjustment for temporal trends in patient characteristics and clinical status at the time of PE diagnosis, the primary outcome at 30 days decreased from 16.3% (95%CI, 7.8–32.1) in 2015 to 7.1% (95%CI, 1.9–17.3) in 2019 (risk-adjusted rate ratio per period, 0.63; 95% CI, 0.47–0.84; p = 0.001 for trend) (Fig. 3, and Table 3). The temporal trends in the primary outcome at 30 days were similar according to the PE risk stratification (p = 0.65 for interaction), with decreased rates in low, intermediate-low, intermediate-high, and high-risk PE between 2015 and 2019 (Supplemental Figure S2). The trend toward a decrease in the primary endpoint at 30 days was driven by a decrease in the risk-adjusted rate of major bleeding (adjusted rate ratio per period, 0.71 (0.52–0.96); p = 0.02 for trend) (Table 3). The individual major bleeding components are summarized per calendar year in Supplemental Table S3. The decrease

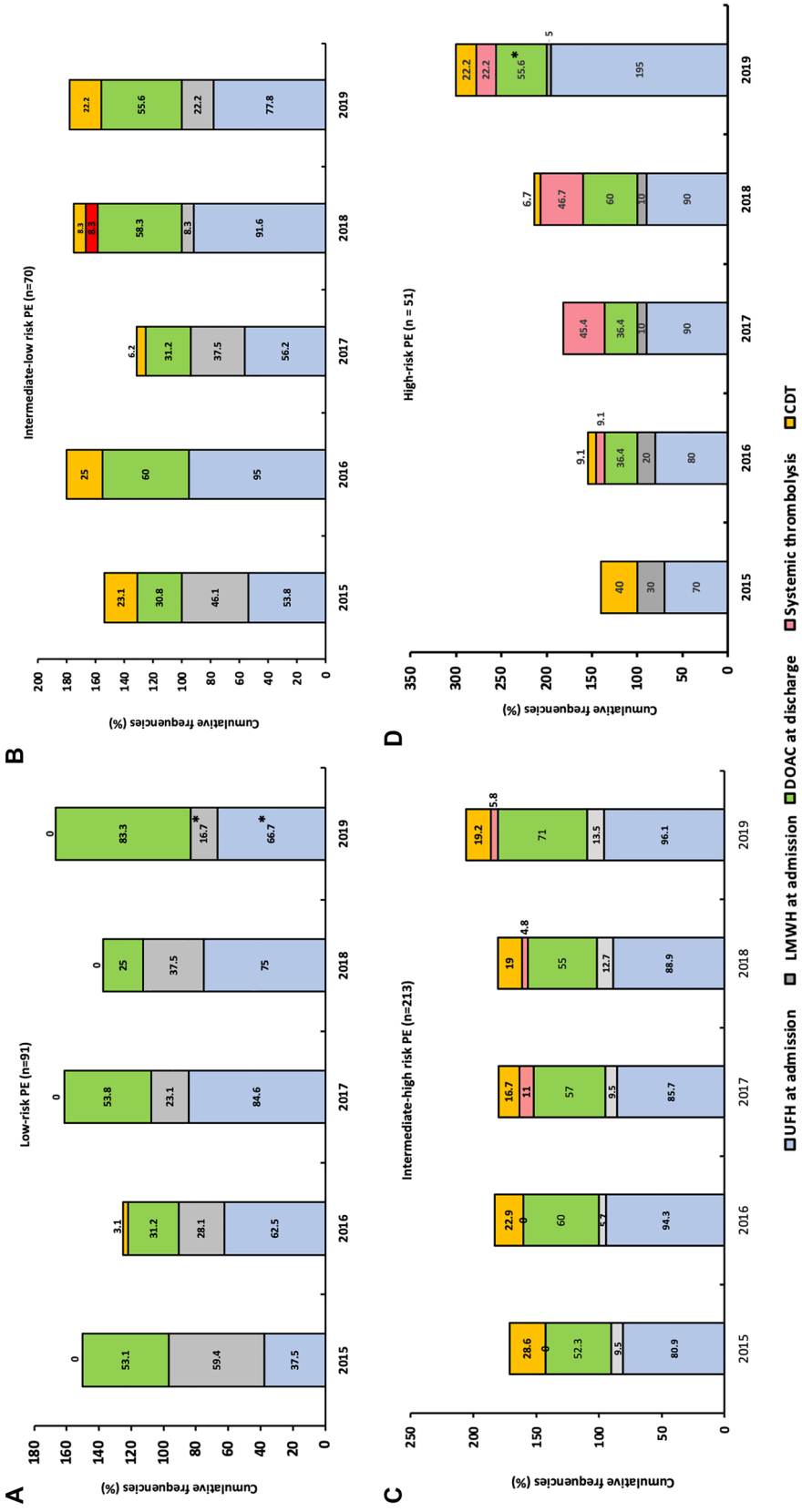

Fig. 2 Cumulative frequencies of acute pulmonary embolism management strategies, according to the ESC-defined risk category, and by year. *UFH* unfractionated heparin; *LMWH* low molecular weight heparin; *DOAC* direct oral anticoagulant; *CDT* catheter-directed therapy. *p for trend <0.05 over the study period, within the ESC-defined risk category

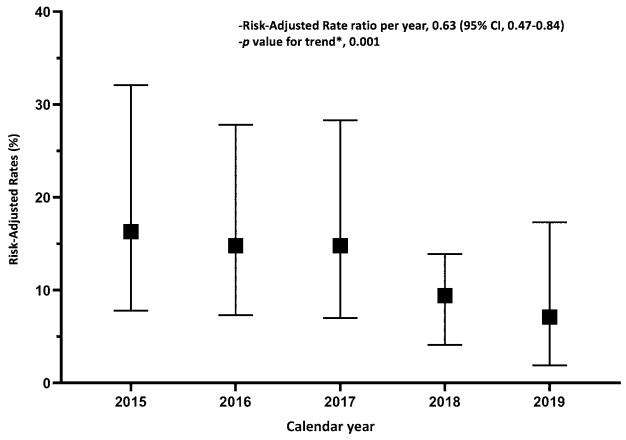

Fig. 3 Adjusted temporal trends in composite outcomes at 30 days. *Risk-adjusted rates of the composite endpoint pulmonary embolism-related death, major bleeding, recurrent VTE, and rehospitalization for each calendar period are reported for the overall cohort. Rates were adjusted for temporal changes in cancer, body mass index > 30 kg/m^2, estimated glomerular filtration rate < 60 mL/min, systolic blood pressure < 100 mmHg at admission, elevated troponin at admission, right ventricular dysfunction at admission, and in-hospital systemic thrombolysis. Adjusted risk ratios and p values for trend were determined with a model evaluating calendar period as a continuous variable

in the crude incidence of 30-day major bleeding during the study period was observed primarily in ESC-defined high-risk PE (Supplemental Figure S3). There was no significant temporal trend in the risk-adjusted rates of all-cause mortality and hospital readmission at 30 days (9.2% in 2015 vs 1.9% in 2019 for mortality [p = 0.07] for trend, and 18.6% in 2015 vs 4.0% in 2019 for readmission [p = 0.12 for trend]) (Table 3). Cancer was the main cause of death across the entire study period (from 11.2% in 2015 to 3.1% in 2019), followed by PE-related mortality (from 4.2% in 2015 to 2.0% in 2019) (Supplemental Table S4).

The crude incidence of the 6-month composite outcome is displayed in Supplemental Fig. 1. Covariates associated with the composite outcome at 6 months are summarized in Supplemental Table S2. The risk-adjusted rate ratio per year for the primary outcome at 6 months was 0.37 (95%CI, 0.19–0.71) with a decrease from 15.8% in 2015 to 9.5% in 2019 (Fig. 4, and Table 3). The risk-adjusted rate of all-cause mortality decreased significantly over time (14.6% to 8.6%; p < 0.001 for trend), especially the rate of cancer-related death (Supplemental Table S4). There was no significant temporal trend in hospital readmissions (18.2% in 2015 vs 6.5% in 2019, p = 0.19). The rates of major bleeding and recurrent VTE at 6 months did not change across calendar years (Table 3).

Sensitivity analyses

Sensitivity analyses showed a significant trend toward a decrease in major bleeding with similar rate of all-cause death (Fig. 5). Risk-adjusted rates of the additional composite endpoint (PE-related death, major bleeding, recurrent VTE, and rehospitalization) decreased from 21.8% in 2015 to 6.9% in 2019 (p for trend = 0.003) (supplemental Figure S4).

Table 3 Trends in outcomes included in the primary composite end-point at 30 days and 6 months

Outcome	Risk-Adjusted Rates (%, 95%CI)*					Risk-Adjusted Rate ratio per year (95% CI)**	*p* value for trend**
	2015	2016	2017	2018	2019		
30 days							
Primary outcome	16.3 (7.8–32.1)	14.8 (7.3–27.8)	14.8 (7.0–28.3)	9.4 (4.1–13.9)	7.1 (1.9 (17.3)	0.63 (0.47–0.84)	0.001
All-cause death	9.2 (3.1–23.5)	4.4 (1.2–13.2)	5.3 (1.4–1.2)	2.2 (0.3–8.9)	1.9 (0.1–9.3)	0.73 (0.51–1.03)	0.07
Major bleeding	6.4 (2.1–18.5)	7.2 (2.6–17.3)	6.0 (1.8–16.3)	2.1 (0.3–8.3)	5.5 (1.4–15.5)	0.71 (0.52–0.96)	0.02
Recurrent VTE	1.4 (0.06–11.9)	1.5 (0.1–10.6)	0.6 (0.01–8.2)	0 (0–3.2)	0 (0–2.1)	0.50 (0.20–1.22)	0.12
Hospital readmission	18.6 (8.2–37.9)	10.3 (4.1–23.2)	11.3 (4.4–25.8)	6.3 (2.0–16.6)	4.0 (0.2–13.7)	0.78 (0.57–1.07)	0.12
6 months							
Primary outcome	15.8 (5.9–39.2)	14.5 (5.6–35.2)	15.7 (6.0–38.4)	10.1 (3.7–26.6)	9.5 (2.9–27.3)	0.37 (0.19–0.71)	0.02
All-cause death	14.6 (7.8–24.5)	11.4 (6.4–19.8)	15.2 (3.7–24.8)	12.5 (6.9–20.9)	8.2 (3.3–17.0)	0.57 (0.49–0.66)	< 0.001
Major bleeding	11.3 (4.8–21.5)	12.3 (6.3–20.9)	11.0 (4.9–10.2)	3.2 (5.8–9.1)	11.2 (4.4–22.2)	1.0 (0.97–1.02)	0.84
Recurrent VTE	2.9 (0.4–10.4)	5.5 (1.8–12.5)	2.4 (0.3–8.8)	1.0 (0.02–5.8)	0 (0–4.6)	1.0 (0.02–5.6	0.63
Hospital readmission	19.2 (9.1–40.7)	12.4 (5.1–26.9)	12.6 (5.0–28.3)	6.7 (2.1–17.6)	6.5 (1.6–19.7)	0.80 (0.58–1.11)	0.19

CI confidence interval; *VTE* venous thromboembolism

*Rates were adjusted for temporal changes in patient characteristics, and in-hospital therapies (see Table 4 for all model covariates)

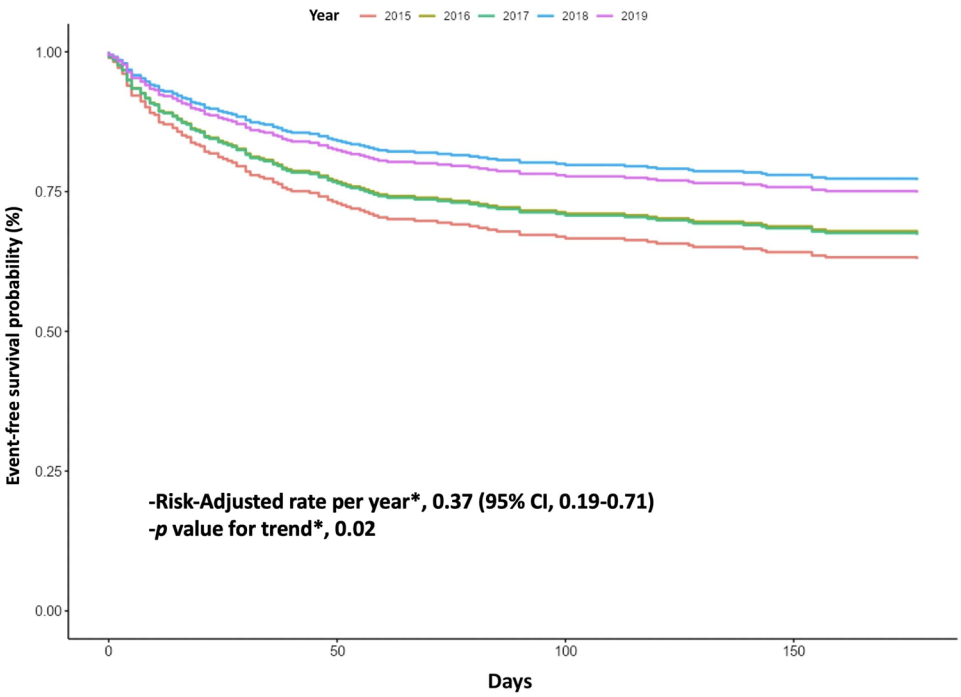

Fig. 4 Cox model-derived adjusted curves for the 6-month primary composite outcome by calendar year. *Risk-adjusted rates of the composite endpoint pulmonary embolism-related death, major bleeding, recurrent VTE, and rehospitalization for each calendar period are reported for the overall cohort. Rates were adjusted for temporal changes in cancer, recent traumatic injury, dementia, and cardiogenic shock at admission Adjusted risk ratios and p values for trend were determined with a model evaluating calendar period as a continuous variable

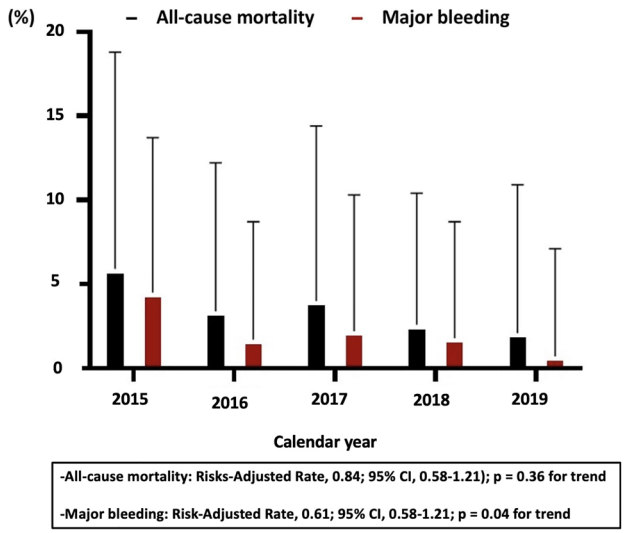

Fig. 5 Sensitivity analyses comparing trends in all-cause mortality and major bleeding within the first 7 days after acute pulmonary embolism managed by a multidisciplinary pulmonary embolism team between 2015 and 2019

Discussion

Using data collected through our multidisciplinary PE response team program, we found evidence of temporal changes in clinical characteristics, therapeutic strategies, and clinical outcomes for acute PE, in parallel to, but not necessarily because of, its implementation. Decreases in risk-adjusted primary outcome rates were driven by a temporal decrease in 30-day major bleeding, especially in high-risk PE patients. A reduction in all-cause mortality at 6 months accompanied these changes despite an increase in PE severity.

It is plausible that changes in practice, in particular more widely integrated use of DOACs, and perhaps implementation of the multidisciplinary PE response team, may have played a role in the observed improvements in outcomes during the time period.

Few studies have evaluated the temporal changes in PE-related characteristics, treatment, and outcomes in programs that have implemented multidisciplinary team care of acute PE [10, 13–20]. Kabrhel et al. reported, in the initial description of the multidisciplinary PE response team organization, a 30-day all-cause mortality rate of 12% in a population that comprised 26% high-risk PE [36]. The authors subsequently compared clinical outcomes of PE patients cared for before (n = 212) and after (n = 228) the creation of their multidisciplinary team, covering 10 years of experience. After multivariable adjustment for PE severity, the rates of 30-day major bleeding and mortality did not differ between the two periods, while the use of advanced therapies increased after the multidisciplinary team creation [19]. Moreover, further historical comparison showed an unadjusted decrease in 30-day mortality between pre- and post- multidisciplinary PE response team eras [17], whereas these findings were not observed in other studies [13, 22]. Finally, the Prognostication in Acute Pulmonary Embolism (IPEP) trial, which randomized 500 PE patients, demonstrated that a management

pathway involving risk stratification followed by mobilization and discharge based on predefined criteria, was associated with a shorter length of stay (4.0 vs 6.1 days, $p < 0.001$), reduced costs, and similar rates of 30-day readmission and death compared to the conventional management group [21].

Critical changes in acute management over the course of the present study period may have contributed to a decline in the rate of major bleeding. A Cochrane review published in 2010 that included 23 randomized controlled trials comparing fixed dose subcutaneous LMWH with adjusted dose UFH in patients with VTE found that fixed dose LMWH was more effective and safer than adjusted dose UFH for the initial treatment of VTE [37]. However, the more frequent use of UFH rather than LMWH by our team may have been related to the increasing number of patients who were candidates for systemic thrombolysis or advanced reperfusion therapies. Indeed, UFH may offer advantages in such situations, including greater control over the intensity of anticoagulation, due to its short half-life, and the possibility to reverse of heparin's anticoagulant activities with protamine sulfate [38]. In other cases, UFH may have been started in anticipation of advanced therapy that ultimately was not deemed to be necessary. The ESC guidelines recommend initiation of anticoagulation with UFH, including a weight-adjusted bolus injection without delay in patients with high-risk PE (class of recommendation IC) [12].

We observed a switch from full- to half-dose systemic thrombolysis, which was most likely driven by the providers' concern about thrombolysis-related bleeding. Initial enthusiasm for this strategy was based on limited international and single-center experiences [39, 40]. A more recent propensity score-matched study comparing half versus full-dose alteplase for PE demonstrated that half-dose systemic thrombolysis was associated with an increased frequency of treatment escalation, driven largely by secondary fibrinolysis and catheter-directed therapy with similar rates of the rates of in-hospital mortality and bleeding [41].

We also observed an increase in DOAC use over time by our multidisciplinary response team. DOACs are associated with a lower risk of bleeding, including major bleeding, ICH, and fatal bleeding, than the standard heparin/vitamin K antagonist regimen [42].

Surprisingly, we did not observe an increase in the rate of CDT use over time, as previously described in multidisciplinary PE response analyses [13, 17, 19, 22], even though the ultrasound-facilitated, catheter-directed, low-dose fibrinolysis EKOSonic system (Boston Scientific, Marlborough, MA, USA) was approved by the Food and Drug Administration at the beginning of our study period. Two mechanical thrombectomy catheters (the Indigo system [Penumbra, Alameda, CA, USA], and the FlowTriever system [Inari Medical, Irvine, CA, USA]) are used without any thrombolytic agent and have demonstrated reversal of RV dysfunction and dilatation within 48 h of intermediate-risk PE in single arm, non-randomized studies [6, 7]. These techniques have not been supported by evidence-based guidelines due to a lack of randomized controlled trials [12, 43]. In our cohort, CDT were infrequently used.

Finally, we can neither confirm nor exclude a causal relationship between the deployment of our multidisciplinary PE response team and the downward trend in 6-month mortality, especially regarding cancer-related death. A nationwide cohort analysis of 350,272 cancer-associated VTE demonstrated a similar trend toward declining 1-year mortality over an eleven-year period. These findings may reflect improvements in overall supportive care, especially for cancer patients [44].

Our study has some limitations. First, the relationship with clinical outcomes should be interpreted with caution because multidisciplinary PE response team activation was not randomly allocated. In addition, our data collection was limited to the data available in our medical records. Next, we did not compare therapeutic strategies and outcomes with PE patients managed during the year prior to implementation of the CODE PE team, as a reference period. Furthermore, we did not have data about the overall number of PE patients assessed in the ED during the study period. We did not record which initial team (Vascular Medicine or Pulmonary Vascular Disease) assessed the patient and, accordingly, could not analyze whether strategies varied in a systematic way. Lastly, practices of our CODE-PE team may not represent actual practices overall in the hospital or in other institutions, even though the management implemented by our multidisciplinary response team is based on the latest international guidelines [12], and therefore, theoretically represents best practices.

The strengths of our analysis include the large sample size, long-term follow-up, independent adjudication of outcomes, and the robustness of the statistical approaches for temporal studies [31–34]. The number of program activations per year in our study (between 71 and 98) was high compared to the number of multidisciplinary care team activations in a multicenter analysis from the National PERT Consortium Research Committee [16].

Conclusion

We observed temporal changes in clinical characteristics, therapeutic strategies, and clinical outcomes for acute PE, in parallel to, but not necessarily because of, the implementation of a multidisciplinary response team at our institution. The rate of major adverse clinical outcomes decreased, especially major bleeding in high-risk PE patients at 30 days. All-cause mortality decreased at 6 months.

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Author contributions Study conception and design: RC, UC, GP; data collection: RC, UC, KSJ, ZIA, ABW, SZG, GP; data curation: RC, UC, JES, SR, GP; writing—first draft: RC, GP; writing—critical revision: RC, UC, LM, KSJ, ZIA, JES, SR, ABW, SZG, GP.

Declarations

Conflict of interest RC, ABW, SR have no relevant competing interests to declare. KJ is supported by the National Institutes of Health (Training Grant 5-T32 HL007604). GP receives research grant support from BMS/Pfizer Alliance, Amgen, BSC, Janssen, Bayer, and Alexion. SZG receives research grant support from Bayer Healthcare, Boehringer Ingelheim, BMS, Boston Scientific BTG EKOS, Daiichi, Jansen, NHLBI, and Pfizer, and consultant grant from Agile, Bayer Health-care, Boehringer Ingelheim, and Pfizer.

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