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Incidence, mortality and bleeding rates associated with pulmonary embolism in England between 1997 and 2015

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ABSTRACT

Background: Improvements in availability and accuracy of diagnostic testing in pulmonary embolism (PE) in the last 20 years have more recently been paralleled by the introduction of additional anticoagulation agents and treatment strategies. These developments are likely to shape potentially important changes in PE incidence, associated mortality and treatment complications.
Methods: We investigated trends in PE incidence, PE-related mortality and bleeding risk by analysing Hospital Episodes Statistics for England.
Results: Between 1997 and 2015, 464,046 patients (53.9% female) were hospitalized with PE in England. The annual number of hospitalizations with an associated diagnosis of PE more than doubled over this period (24,366 in 1998 vs. 53,108 in 2014), with a corresponding increase in PE hospitalization rate (50.2 to 97.8 per 100,000 population/year), evident in all age categories. Mortality at 1 and 3 months decreased over the study period and was significantly associated with age, treatment era and comorbidities. The risk of bleeding resulting in hospitalization or death within 3 and 12 months after the index PE admission increased over the study period (4.3%/5.1% for 1998–2004 versus 6.1%/7.2% for 2010–2014, $p < 0.001$ for both comparisons).
Conclusions: The incidence of PE doubled in England between 1997 and 2015, likely attributable to raised awareness and ability to diagnose less severe cases. While PE-associated mortality decreased, there was an increase in bleeding risk. Renewed efforts directed at reducing the incidence of bleeding, including consideration of anticoagulation regimens and investigation of anticoagulation requirement in patients with low-risk features, are needed.

1. Introduction

Patients with pulmonary embolism (PE) have benefitted from significant developments in diagnostic and treatment pathways in the last 20 years, potentially shaping important trends in PE incidence and mortality [1,2]. These include enhanced diagnostic algorithms incorporating computed tomography (CT) and D-dimer testing as well as the adoption of new risk assessment scores and treatment guidelines. In the last few years there has been increasing use of direct oral anticoagulants (DOACs), which in Phase 3 studies appear to have equivalent efficacy to warfarin but with a safer bleeding profile. In addition, progressive ageing of the general population and increase in availability and sensitivity of diagnostic tests has contributed to an increasing PE incidence over the last two decades in many developed countries [3]. In spite of these advances, PE remains a common cause of morbidity and mortality in the general population of developed countries. As there has been very sparse literature describing experience in England [4,5], we aimed to investigate the longitudinal trends in PE incidence, associated hospitalisations and outcomes in the England from 1997 to 2015. Apart from providing important, novel information on a national level, we believe the data will provide an important benchmark for future studies given recent changes in PE prescribing practice toward greater use of DOACs.

2. Methods

We analysed the hospital episode statistics database (HSCIC) for England for years 1997 to 2015. This database contains records on the admissions under the National Health Service (NHS), which is the publicly funded national healthcare system for England. NHS Patients are assigned a unique identifier, which enables tracking of patients within the database. Each record for hospital admission contains up to twenty most relevant diagnoses and the most relevant procedures performed, as well as dates of admission, discharge and dates of procedures. Diagnoses are

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coded using the 10th revision of the International Classification of Diseases system (ICD-10), while procedures are reported using the 'Office of Population Censuses and Surveys' system (OPCS-4). Pseudo-anonymized data are released for research purposes and access to this database was granted for this project by the Health and Social Care Information Centre. We identified all patients diagnosed with PE (ICD-10 codes 'I26.x'). Data on mortality and primary cause of death were retrieved for all patients from the UK Office for National Statistics. The HSCIC database provides also information on approximate residency of the patient by assigning it to one of 6791 geographical regions in England, called Middle Layer Super Output Areas (MSOA), with 5–15 thousand population each. Information about the size of the general population and the age distribution for England for each MSOA was retrieved from the UK Office for National Statistics. Comorbidities were classified using Charlson Comorbidity Index [6]. Briefly, this score accounts for a range of diseases, such as heart disease, cancer or acquired immune deficiency syndrome, with a total of 22 categories of comorbid conditions. Each of these conditions is assigned a score, ranging from 1 to 6, and the sum of all scores represents the comorbidity index.

2.1. Statistical analysis

Continuous variables are presented as median with interquartile range (IQR) in square brackets while categorical variables are presented as number and percentage. Comparison between groups was performed for continuous variables using Mann-Whitney test or Analysis of Variance for multiple comparisons; distribution of categorical variables was assessed using chi-squared test. Changes of incidence of PE, mortality and bleeding over time were assessed by comparison across three treatment eras: early (1998–2004), middle (2005–2009) and late (2010–2015). Dependence of linear variables was assessed using Pearson correlation coefficient. The incidence of PE in each of the analysed regions in England was assessed for correlation with proportion of residents older than 65 years in each region and with social deprivation (IMD rank). As both parameters were significantly correlated with the incidence of PE, they were included in multiple linear regression analysis. Logistic regression analysis was used for assessing the association of independent variables with either death or bleeding, following PE. Kaplan–Meier method was used for assessing survival following the first PE episode in the entire cohort and in subgroups of patients. A two-sided p-value of <0.05 was considered indicative of statistical significance. Statistical analyses were performed using R-package version 3.2.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria) [7]. Tables were formatted using Microsoft Excel for Windows, version 2013.

3. Results

Between 1997 and 2015, 464,046 patients (53.9% female) were hospitalized with a diagnosis of PE in England. The annual number of PE hospitalizations more than doubled over this period (24,366 in 1998 to 53,108 in 2014, Fig. 1) with a corresponding increase of PE incidence from 50.2 to 97.8 per 100,000 population/year. The rise in PE incidence was evident in all age categories (Table 1, Fig. 2), with the highest relative increase in seniors (115.0% in those aged 85–90 years and 206.7% in those above 90 years of age).

In children, the relative increase was high (331.3%), but was small in absolute terms (0.2 to 0.6 per 100,000 population for 0–14 year-olds). The incidence of PE increased exponentially with age between 1998 and 2015, and rose by 294.1/100,000 in 85–90 year-olds and by 355.3/100,000 in those above 90 years of age.

There were significant geographical differences in the incidence of PE, with the lowest incidence seen in densely populated urban areas (Fig. 1). Population density was negatively correlated with the proportion of over 65 years-year-olds in each region (MSOA, $r = -0.62$, 95% CI −0.65 to −0.58, $P < 0.001$). The incidence of PE was moderately correlated to the proportion of over 65-year-olds in each region ($r = 0.37$, 95% CI 0.32–0.42, $P < 0.001$) and weakly correlated to social deprivation (IMD rank; $r = -0.12$, 95% CI −0.17 to −0.6, $P < 0.001$). On multiple linear regression analysis, both parameters remained in the model, but only explained 30.0% of the variability in PE incidence ($P < 0.001$).

The number of patients re-admitted to hospital with PE within 2 years from the first episode increased over the study period, from 7.5% (95% CI 7.2–7.9%) in 1998 to 14.8% in 2012 (95% CI 14.5–15.2%, $P < 0.001$). The increase in the number readmitted within 2 years was highest in younger patients (13.8%, 95%CI 13.5–14.2% for age ≤ 40) as opposed to 40–60 year-olds (12.9%, 95% CI 12.7–13.1%, $p < 0.001$) and

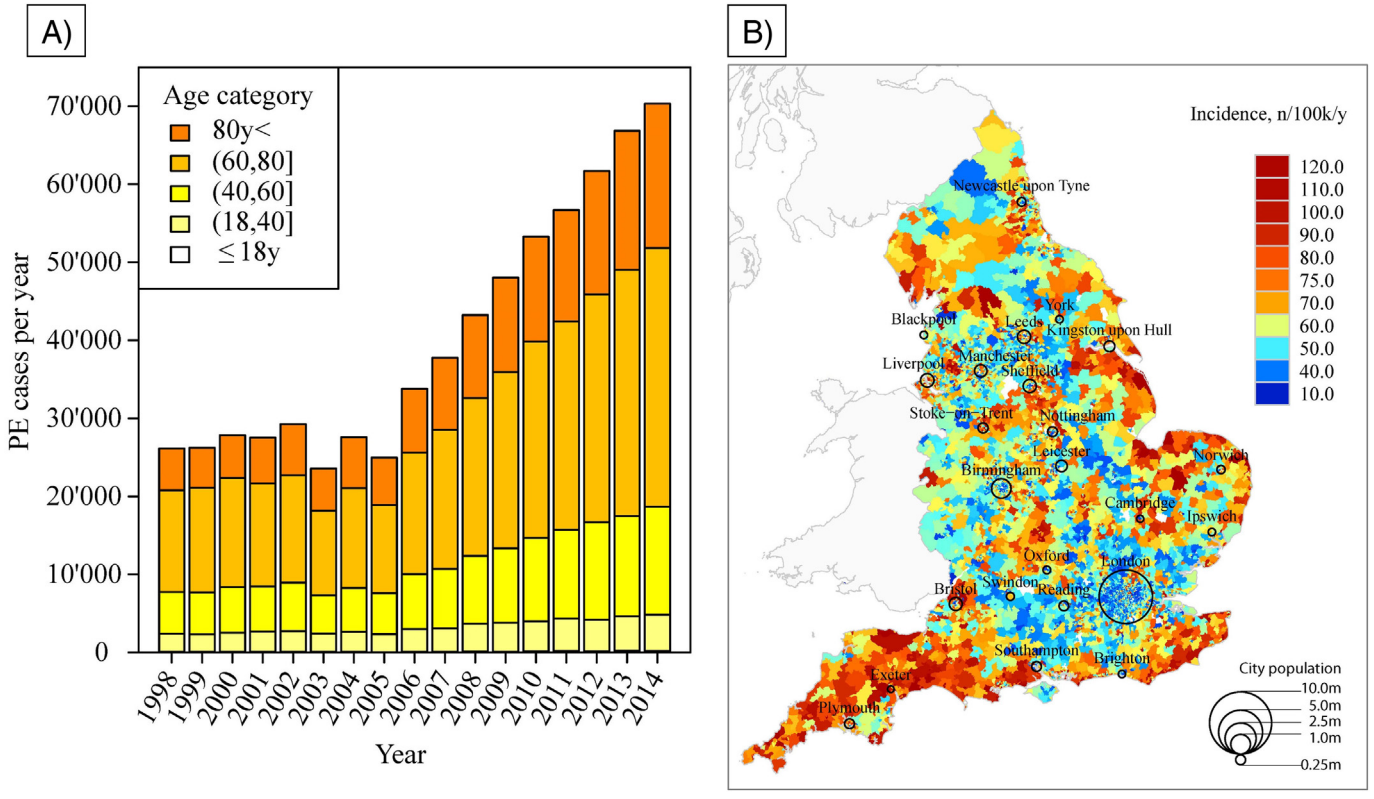

Fig. 1. Hospitalizations with pulmonary embolism in England by year and age category and geographical distribution of incidence. A) Distribution of hospitalizations by year and age category. There was a significant increase in the number of hospitalizations with pulmonary embolism over time, which was evident in all age categories. B) Regional incidence of pulmonary embolism in England. Incidence of pulmonary embolism for 1997–2015, based on patients' residential address and calculated for each 'middle layer super output area' (geographic areas with population ranging from 5000 to 15,000 resident population). Circle area proportional to city population.

Table 1
Incidence of pulmonary embolism by year of diagnosis and age at diagnosis.

	0–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89	90≤
2014	0.8	5.9	15.0	22.2	30.5	35.6	46.1	66.4	81.8	114.9	162.0	226.3	310.4	387.1	460.7	549.7	527.2
2013	0.9	6.2	16.0	20.2	28.8	35.4	47.2	62.4	78.0	105.6	159.2	215.8	298.4	379.5	457.1	541.5	531.5
2012	0.3	6.0	13.4	21.7	25.4	34.1	47.1	63.7	77.4	102.5	151.2	205.6	292.8	365.1	421.5	497.1	475.5
2011	0.6	6.3	14.6	21.8	26.1	34.2	44.5	58.2	69.9	98.6	138.5	197.6	276.3	347.6	403.9	459.6	424.2
2010	0.4	5.5	13.3	18.6	25.6	31.9	43.1	51.2	72.2	95.6	131.7	191.3	260.3	342.3	390.5	453.1	397.6
2009	0.2	5.6	14.0	19.3	23.9	32.2	40.3	49.4	60.2	91.5	123.1	180.8	252.5	307.2	375.4	415.9	351.9
2008	0.2	5.4	13.7	19.3	23.7	30.1	34.1	45.9	59.7	85.9	116.6	180.0	224.8	279.2	342.2	368.3	343.4
2007	0.2	3.7	11.0	15.1	22.6	25.3	34.4	37.7	51.4	74.0	111.1	159.6	206.8	250.5	307.6	334.0	315.8
2006	0.2	4.9	10.8	14.3	21.5	24.0	29.3	38.7	50.5	65.9	95.5	141.1	192.8	238.6	283.2	320.5	280.9
2005	0.1	4.2	8.4	13.7	15.9	18.4	23.9	29.2	38.1	53.0	77.0	104.7	142.8	180.2	223.2	250.9	243.1
2004	0.3	3.7	9.5	15.1	19.2	20.2	25.9	34.1	39.2	55.8	85.7	114.4	162.3	210.8	244.9	279.8	244.2
2003	0.2	3.8	10.0	13.9	17.1	18.3	22.1	29.5	37.9	50.0	75.8	104.6	135.5	181.0	211.5	246.4	201.5
2002	0.2	4.1	10.0	14.9	19.3	21.8	27.4	37.1	50.4	64.2	96.5	135.0	169.6	226.8	256.6	298.7	247.1
2001	0.1	4.3	9.6	15.1	19.1	21.7	26.5	35.0	47.3	63.9	90.2	130.5	168.4	227.8	252.9	279.5	207.4
2000	0.2	4.8	8.0	14.3	16.8	22.7	26.8	35.0	49.6	69.2	94.9	140.0	175.6	244.2	248.2	270.6	201.8
1999	0.3	3.7	9.0	12.2	16.6	18.9	23.9	36.0	45.5	63.1	93.1	135.8	172.3	225.7	251.5	257.4	186.2
1998	0.2	3.7	10.5	13.7	16.8	19.3	25.0	32.4	47.0	65.2	100.1	134.8	175.6	203.5	273.9	255.7	171.9

Incidence of pulmonary embolism per 100,000 population. Incidence was higher in older patients and increased between 1998 and 2014. Colour of each cell reflects its numerical value, to aid visual perception of presented data, with a tri-colour gradient used, ranging from green (low-range values), through yellow (mid-range values) to red (high-range values).

over 60 years of age (10.1%, 95% CI 10.0–10.2%, $P < 0.001$). In the overall population, readmission for PE was also more likely in males compared to females (11.3%, 95% CI 11.1–11.4% vs 10.8%, 95% CI 10.7–10.9%, $P < 0.001$), but in younger patients (age ≤ 40y), females were more likely to be readmitted with PE (14.4%, 95% CI 13.9–14.8% vs 13.1%, 95% CI 12.6–13.6% in men, $P < 0.001$).

4. Mortality and bleeding risk after pulmonary embolism

The survival at 1, 3 and 6 months following the first PE episode was 85.0% (95% CI 84.9–85.1%), 76.9% (95% CI 76.8–77.1%) and 72.4% (95% CI 72.3–72.5%), respectively (Table 2, Fig. 3).

Mortality was highest in older patients, those with higher comorbidity score, lower socio-economic status and those who had PE in the early treatment era (1998–2004). The association between mortality and gender was age-dependent (Table 3); mortality was lower in females compared to males below the age of 40 years (HR 0.88, 95% CI 0.80–0.97, $P = 0.013$), but was higher in those aged 40–60 years, while there was no significant association of gender with mortality for age of above 60 years.

The risk of bleeding resulting in hospitalization or death within 3 or 12 months after the index PE admission increased over the study period (4.3% and 5.1%, respectively, for 1998–2004 versus 6.1% and 7.2% for 2010–2014, $P < 0.001$ for both comparisons).

On logistic regression analysis, bleeding risk within 12 months from the first PE episode was related to age (OR 1.36 per 10 years, 95% CI 1.34–1.38, $P < 0.001$), comorbidity index (OR 1.23/1CCI, 95% CI 1.22–1.24, $P < 0.001$) and PE occurring during the more recent treatment era (OR 1.75, 95% CI 1.71–1.78 for years 2010–2014 compared to 1998–2004, $P < 0.001$), while there was no significant association with gender ($P = 0.16$) or socioeconomic status ($P = 0.06$, for the most deprived quartile vs. the remainder).

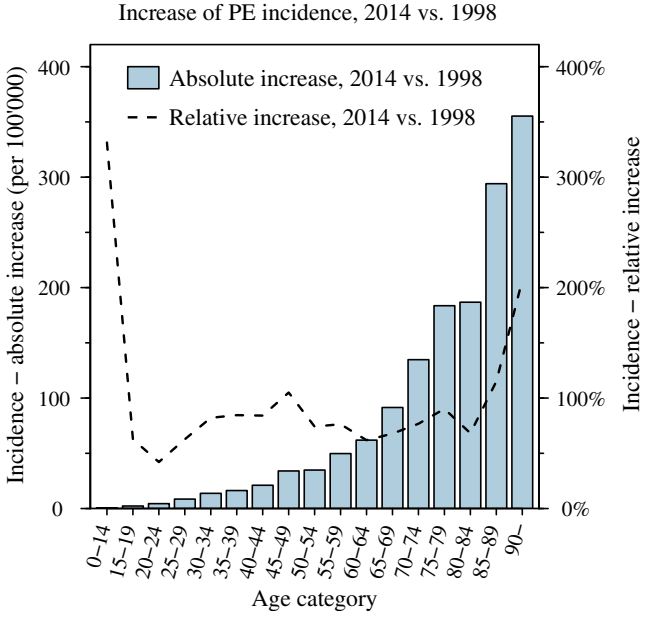

Fig. 2. Absolute and relative increase of pulmonary embolism incidence in 2014 compared to 1998. While the relative increase in pulmonary embolism (PE) incidence was highest in children and in seniors (by approximately 300% and 200%, respectively), the absolute rise in PE incidence was increased with older age (blue bars).

5. Discussion

This large population study based on Hospital Episode Statistics in England between 1998 and 2015 has highlighted the following important messages. Firstly, the rate of hospitalization with an associated diagnosis of PE more than doubled over the study period; this was evident in all age categories. Secondly, and reassuringly, mortality rates diminished. Thirdly, there appeared to be an important trend of increasing bleeding rates resulting in hospitalization or death. This final result indicates a pressing requirement for renewed attention toward anticoagulation risk assessment and safety measures to maintain both low PE mortality and low bleeding risk in this growing population.

5.1. Incidence

We believe this is the largest contemporary study investigating the demographics and outcome of PE in England to date. In fact, there have been surprisingly few previous national studies. Goldacre et al. reported hospital admissions and mortality rates for VTE in the Oxford region between 1975 and 1998 [5]. The authors noted a steady increase in hospital admissions from the early 1990s onwards; admission rates in those patients under 50 were higher in women and higher in men in the over 50s. Aylin et al. used Hospital Episode Statistics for England to study the admission rates of patients admitted with any mention of

Table 2
Absolute mortality and bleeding risk after hospitalization for pulmonary embolism.

(A) Absolute mortality after pulmonary embolism.

		Age <40y			Age 40–60y			Age > 60 y		
		1m	3m	1y	1m	3m	1y	1m	3m	1y
CCI=0	2010–2015	1.1%	1.3%	2.1%	1.8%	2.5%	4.2%	5.8%	8.9%	15.3%
	2005–2009	1.6%	2.0%	2.7%	2.4%	3.3%	5.5%	9.0%	12.6%	19.4%
	1998–2004	2.4%	2.8%	3.7%	4.1%	5.2%	7.6%	15.2%	19.3%	25.6%
CCI=1	2010–2015	2.2%	3.2%	4.6%	4.3%	6.0%	9.3%	11.2%	17.1%	27.3%
	2005–2009	3.1%	4.0%	5.1%	6.3%	8.3%	11.9%	16.1%	23.0%	33.3%
	1998–2004	5.0%	6.1%	8.0%	11.2%	14.2%	19.0%	25.2%	33.1%	43.1%
CCI=2	2010–2015	6.4%	10.8%	20.0%	8.2%	14.7%	28.6%	14.5%	24.9%	41.8%
	2005–2009	6.5%	11.6%	21.9%	11.5%	19.8%	35.9%	20.2%	31.8%	48.3%
	1998–2004	10.5%	17.2%	28.1%	19.0%	28.5%	43.7%	31.2%	42.9%	57.1%
CCI≥ 3	2010–2015	17.9%	31.7%	52.5%	23.3%	42.3%	65.2%	26.9%	45.8%	66.6%
	2005–2009	19.5%	33.8%	52.6%	26.4%	46.5%	68.8%	30.8%	50.8%	70.6%
	1998–2004	22.9%	35.5%	53.4%	32.9%	49.8%	70.3%	39.8%	56.3%	72.4%

(B) Absolute bleeding risk after pulmonary embolism

		Age <40y			Age 40-60y			Age>60y		
		1 m	3 m	1 y	1 m	3 m	1 y	1 m	3 m	1 y
CCI=0	2010–2015	3.5%	4.1%	5.7%	3.5%	4.2%	6.0%	4.0%	4.9%	7.3%
	2005–2009	3.6%	4.2%	5.9%	3.7%	4.3%	5.9%	3.5%	4.2%	6.5%
	1998–2004	3.3%	3.9%	5.6%	2.7%	3.4%	5.2%	3.1%	3.8%	5.9%
CCI=1	2010–2015	7.4%	8.3%	10.1%	6.9%	7.8%	10.3%	7.0%	8.2%	11.3%
	2005–2009	6.0%	6.7%	9.0%	6.8%	7.8%	10.6%	6.8%	7.7%	10.6%
	1998–2004	5.6%	7.1%	9.4%	6.2%	7.1%	9.8%	5.6%	6.4%	9.2%
CCI=2	2010–2015	6.9%	8.7%	13.5%	6.0%	7.4%	10.8%	7.4%	8.8%	12.4%
	2005–2009	4.8%	6.7%	10.1%	4.7%	5.8%	9.4%	6.2%	7.4%	11.0%
	1998–2004	6.4%	7.1%	10.3%	4.1%	5.4%	8.5%	5.7%	6.9%	10.3%
CCI≥ 3	2010–2015	9.8%	11.8%	16.1%	7.2%	9.2%	14.4%	7.8%	9.6%	14.1%
	2005–2009	8.0%	9.7%	13.2%	6.1%	7.5%	12.4%	7.0%	8.5%	13.0%
	1998–2004	7.2%	8.9%	13.6%	5.2%	6.7%	10.8%	6.5%	7.9%	11.9%

Absolute observed (A) mortality and (B) bleeding resulting in hospitalization or death following the index hospitalization for pulmonary embolism (PE), by age, treatment era and Charlson comorbidity index (CCI; 0 = no relevant comorbidities). Mortality within 3 months after PE increased with older age (Odds ratio 1.55 per 10 y), higher CCI (OR = 1.45 per 1 point) but declined over the study period. In contrast, bleeding risk within 1 year after index PE increased over time (OR = 1.36/decade) and was higher in older patients (OR = 1.07/10 y) and those with comorbidities (OR = 1.72 for CCI > 0; P < 0.001 for all presented odds).
Colour of each cell reflects its numerical value, to aid visual perception of presented data, with a bi-colour gradient used, ranging from pale-red (low-range values) to red (high-range values).

PE (similar to our study) between 1996 and 2006 [4]. There were 251,449 admissions with a diagnosis of PE in the study period with non-elective admission rates rising from 28.0 per 100,000 in 1996/7 to 32.1 per 100,000 in 2005/6. The increasing incidence reported in our study therefore extends the observations of these previous studies.

So what are the reasons behind the increasing incidence? Despite the largest increase in PE incidence occurring in the 80 years and above age groups and the apparent similarity between the geographic distribution maps of incident PE and age-distribution map of England, increased PE incidence was only partially accounted for by older age and social deprivation ($R^2 = 0.30$) [8]. This discrepancy can be explained by increased likelihood of diagnosing PE over the study period. In turn, this is most likely to reflect the increased use of diagnostic algorithms advocating pre-test probability testing, wider availability of CT pulmonary angiography and D-dimer testing, as well as a greater tendency to investigate elderly patients who are more at risk. For instance, at one extreme, a randomized study in 2012 suggested the combination of Well's score and qualitative D-dimer testing may be used to safely exclude a PE diagnosis in primary care [9]. However, lack of available D-dimer testing in UK community practices has precluded widespread adoption of this approach suggesting more UK evidence may be needed in the community-based PE diagnostic pathway [10]. The advent of multidetector row CT pulmonary angiography revolutionized diagnostic approaches to PE around 1998. In the RIETE study the proportion of patients diagnosed with PE using a CT scan has increased from 47% to 90% over the period 2001 to 2013 [11]. Inevitably this has led to the discovery of asymptomatic or 'incidental' PEs, which predominate in sub-segmental pulmonary vessels [12]. Even discounting for false positive diagnoses due to breathing motion or beam-hardening artefacts on CT, there remains considerable uncertainty over the clinical relevance of sub-segmental thrombi and the risk/benefit of treatment with anticoagulation. [3,13–15].

The number of patients re-admitted to hospital with PE within 2 years from the first PE episode increased over the study period, with the highest re-admission rate observed in younger patients. The reason for the general increase of re-admissions appears multifactorial and may be related to the increasing age of the population but, also, to increased availability of tests aiding PE diagnosis, including imaging and D-dimers. The higher proportion of younger patients re-admitted with PE compared to older patients is, however, surprising. Diagnosis of PE may be clinically challenging, particularly in older patients with significant comorbidities. Moreover, re-admissions due to recurrent events may be less often observed in old individuals, as recurrent PE may be fatal [12].

5.2. Mortality

Despite the increase in incidence over the study period, there was a steady decrease in mortality. This was seen over all age groups and co-morbidity score. Unsurprisingly, the highest mortality was seen in older patients with higher co-morbidity score. An improvement in mortality was also reported in the previous national studies as well as in more prevalent international studies such as the RIETE Registry [4,5,11]. The reasons for this improvement in mortality are likely to include both a real improvement in patient care and "over-diagnosis" of incidental and sub-segmental PE [13,16]. In more recent treatment era, patients were older with greater comorbidity scores supporting the conclusion that improved mortality is due, at least in part, to improved patient care. Potential contributors to improvements in care include more effective guidelines and treatments, more judicious use of systemic thrombolysis in the acute setting [3,17], as well as a paradigm shift in cancer-associated PE treatment toward low molecular weight heparin in place of vitamin K antagonists [18].

5.3. Bleeding

A surprising result of this study is the apparent increase in bleeding rates. Previous studies have clearly demonstrated that one of the most important parameters associated with increased risk of bleeding related to anticoagulation is age [19–21]. Yet, our analysis suggests that increasing age of the general population in England may be only one of the factors associated with increased likelihood of bleeding following PE-episode over the years. Although we did not have anti-coagulation details for the patients included in this study, analysis of prescriptions of anticoagulants in the United Kingdom performed by Loo et al. demonstrates, that there was an increase of prescriptions since 2011 with an exponential increase in use of DOACs and decline of prescriptions for Vitamin K antagonists [22]. Multiple clinical studies support the safer bleeding profile of DOACs over Vitamin K antagonists, the importance of prolonged anticoagulation in symptomatic VTE as well as the benefit of low dose DOACs in the chronic term. [23–26] This suggests that greater DOAC use in the modern treatment era should reduce anticoagulation complications and ameliorate bleeding risk [27], However, the use of DOACs remains relatively novel [24] and we found that the majority of bleeding complications occurred in more elderly patients with greater comorbidity. Notably, this group has been underrepresented in current clinical trials of DOACs. Even the most recent "real-world" evidence suggesting no worse bleeding with DOACs in a large Canadian population are only short-term results. The only safe

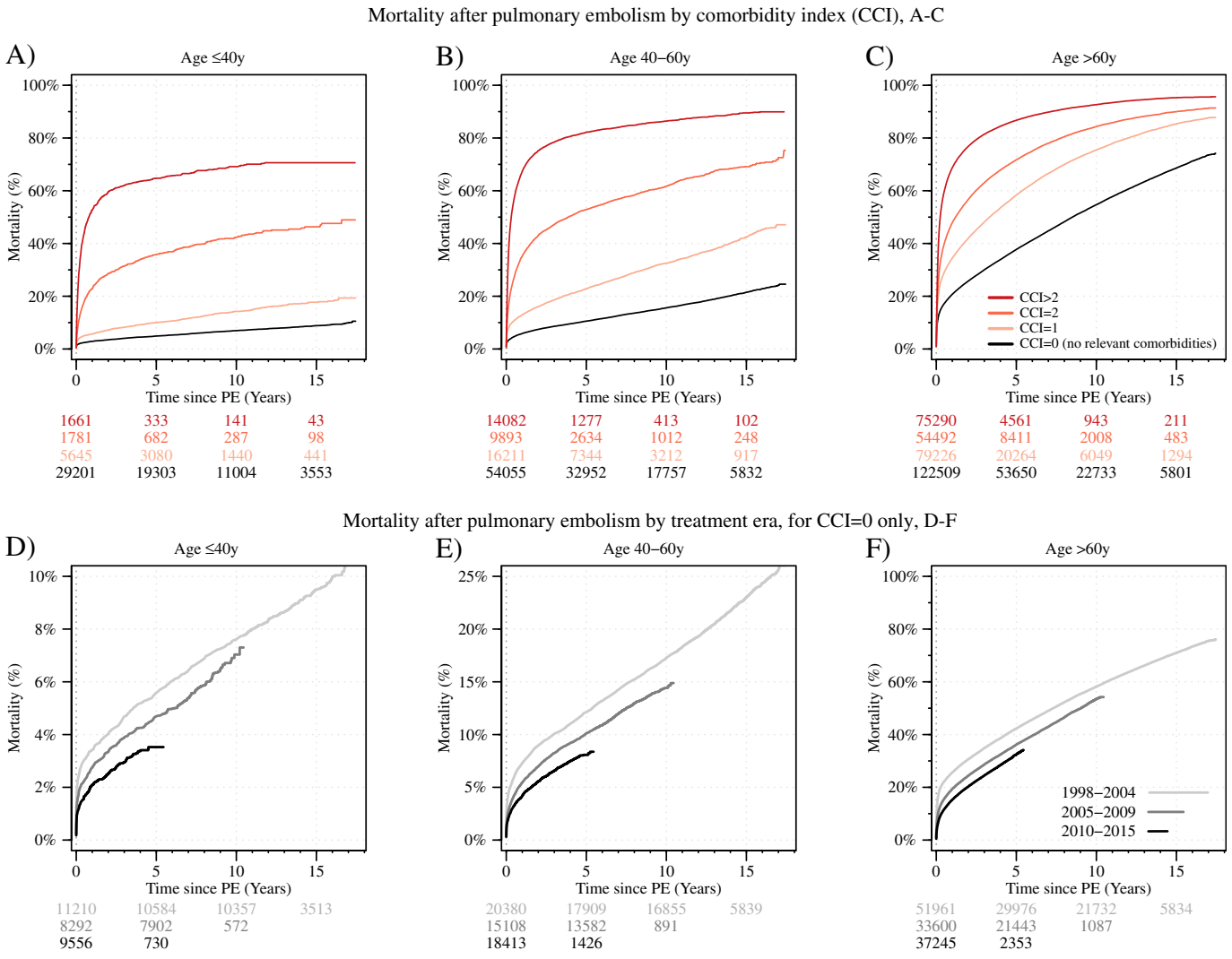

Fig. 3. Mortality after pulmonary embolism by treatment era, age category and comorbidity index (CCI). Mortality after the first episode of pulmonary embolism (PE) by (A–C) age category and Charlson Comorbidity Index (CCI) and (D–F) by treatment era (for patients without comorbidities, i.e. CCI = 0, only) showing declining mortality over the years (Logrank $P < 0.001$ for D–F).

conclusion is that we must remain observant of bleeding rates in future cohorts that will mainly be treated with DOACs. Therefore, we believe our results present an important bench-mark for future studies. Given heightened interest in PE follow up, future national investment in specialized PE clinics and personalisation of treatment plans will be key.

Table 3
Predictors of mortality at 3 months following the first episode of pulmonary embolism.

Parameter	OR (95% CI)	P-value
Age (/10 y)	1.55 (1.54–1.56)	<0.0001
Female gender	1.07 (1.06–1.09)	<0.0001
Age < 40 y	0.88 (0.80–0.97)	0.013
Age 40–60 y	1.28 (1.23–1.33)	<0.0001
Age > 60 y	1.01 (1.00–1.03)	0.087
Charlson comorbidity score		
0	0.22 (0.22–0.22)	<0.0001
1	0.87 (0.85–0.88)	<0.0001
2	1.57 (1.54–1.59)	<0.0001
>2	4.89 (4.81–4.97)	<0.0001
Event era		
2010–2015	0.82 (0.81–0.84)	<0.0001
2005–2009	0.88 (0.87–0.90)	<0.0001
1998–2004	Reference	
Social deprivation[a]		
Most affluent	0.93 (0.91–0.94)	<0.0001
Most deprived	1.03 (1.01–1.05)	0.0002

[a] Analysed for quartiles of indices of multiple deprivation rank.

5.4. Limitations

This study did not include complete data on anticoagulation prescription and duration; therefore it is difficult to judge the relevance of recent changes in anticoagulation prescribing practice to our findings. In addition, Hospital Episode Statistics gathered over such a broad treatment era are non-standardised and come with limitations inherent to using hospital coding data for diagnosis.

6. Conclusions

The documented incidence of PE doubled over the period 1997–2015 in England, with a significant increase across all age categories. Mortality significantly declined, which may be associated with both improvements in treatment and identification of less severe cases. However, the risk of bleeding associated with PE, requiring admission or resulting with death, increased modestly over the study period. Considering the trend of both increasing documented PE incidence as well as increasing bleeding risk, management strategies

should remain focused on the most appropriate method and duration of PE anticoagulation.

Conflict of interest

Dr. Kempny has received unrestricted educational grant support from Actelion Global. Prof Gatzoulis and the Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension have received support from the British Heart Foundation. Dr. Wort and Dr. Dimopoulos have acted as Consultants and received unrestricted educational grants from Actelion, GSK, Bayer and Pfizer. This project was supported by the NIHR Cardiovascular Biomedical Research Unit of Royal Brompton and Harefield NHS Foundation Trust and Imperial College London. This report is independent research by the National Institute for Health Research Biomedical Research Unit Funding Scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

References

[1] S.V. Konstantinides, A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galie, et al., ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 35 (3033-69) (2014) 69a-69k 2014.
[2] I.A. Naess, S.C. Christiansen, P. Romundstad, S.C. Cannegieter, F.R. Rosendaal, J. Hammerstrom, Incidence and mortality of venous thrombosis: a population-based study, J. Thromb. Haemost. 5 (2007) 692–699.
[3] S.V. Konstantinides, S. Barco, M. Lankeit, G. Meyer, Management of pulmonary embolism: an update, J. Am. Coll. Cardiol. 67 (2016) 976–990.
[4] P. Aylin, A. Bottle, G. Kirkwood, D. Bell, Trends in hospital admissions for pulmonary embolism in England: 1996/7 to 2005/6, Clin. Med. (Lond.) 8 (2008) 388–392.
[5] M.J. Goldacre, S. Roberts, D. Yeates, M. Griffith, Hospital admission and mortality rates for venous thromboembolism in Oxford region, UK, 1975–98, Lancet 355 (2000) 1968–1969.
[6] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (1987) 373–383.
[7] R Development Core Team, R: a Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2015 , Retrieved from http://www.R-project.org.
[8] Annual Mid-year Population Estimates for Clinical Commissioning Groups: Mid-2011 (Census Based). , Office for National Statistics, United Kingdom, 2012.
[9] G.J. Geersing, P.M. Erkens, W.A. Lucassen, H.R. Buller, H.T. Cate, A.W. Hoes, et al., Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study, BMJ 345 (2012) e6564.
[10] W.A. Lucassen, R.A. Douma, D.B. Toll, H.R. Buller, H.C. van Weert, Excluding pulmonary embolism in primary care using the Wells-rule in combination with a point-of care D-dimer test: a scenario analysis, BMC Fam. Pract. 11 (2010) 64.
[11] D. Jimenez, J. de Miguel-Diez, R. Guijarro, J. Trujillo-Santos, R. Otero, R. Barba, et al., Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry, J. Am. Coll. Cardiol. 67 (2016) 162–170.
[12] A.T. Cohen, G. Agnelli, F.A. Anderson, J.I. Arcelus, D. Bergqvist, J.G. Brecht, et al., Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality, Thromb. Haemost. 98 (2007) 756–764.
[13] M. Carrier, M. Righini, P.S. Wells, A. Perrier, D.R. Anderson, M.A. Rodger, et al., Subsegmental pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies, J. Thromb. Haemost. 8 (2010) 1716–1722.
[14] G. Le Gal, M. Righini, F. Parent, M. van Strijen, F. Couturaud, Diagnosis and management of subsegmental pulmonary embolism, J. Thromb. Haemost. 4 (2006) 724–731.
[15] B.D. Hutchinson, P. Navin, E.M. Marom, M.T. Truong, J.F. Bruzzi, Overdiagnosis of pulmonary embolism by pulmonary CT angiography, AJR Am. J. Roentgenol. 205 (2015) 271–277.
[16] R.S. Wiener, L.M. Schwartz, S. Woloshin, Time trends in pulmonary embolism in the United States: evidence of overdiagnosis, Arch. Intern. Med. 171 (2011) 831–837.
[17] G. Meyer, E. Vicaut, T. Danays, G. Agnelli, C. Becattini, J. Beyer-Westendorf, et al., Fibrinolysis for patients with intermediate-risk pulmonary embolism, N. Engl. J. Med. 370 (2014) 1402–1411.
[18] G.H. Lyman, A.A. Khorana, A. Falanga, D. Clarke-Pearson, C. Flowers, M. Jahanzeb, et al., American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer, J. Clin. Oncol. 25 (2007) 5490–5505.
[19] F.A. Klok, V. Hosel, A. Clemens, W.D. Yollo, C. Tilke, S. Schulman, et al., Prediction of bleeding events in patients with venous thromboembolism on stable anticoagulation treatment, Eur. Respir. J. 48 (2016) 1369–1376.
[20] F.A. Klok, J. Kooiman, M.V. Huisman, S. Konstantinides, M. Lankeit, Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review, Eur. Respir. J. 45 (2015) 201–210.
[21] D. Caldeira, F.B. Rodrigues, M. Barra, A.T. Santos, D. de Abreu, N. Goncalves, et al., Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis, Heart 101 (2015) 1204–1211.
[22] S.Y. Loo, S. Dell'Aniello, L. Huiart, C. Renoux, Trends in the prescription of novel oral anticoagulants in UK primary care, Br. J. Clin. Pharmacol. 83 (2017) 2096–2106.
[23] W. Ageno, L.G. Mantovani, S. Haas, R. Kreutz, D. Monje, J. Schneider, et al., Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study, Lancet Haematol. 3 (2016) e12–e21.
[24] T. van der Hulle, J. Kooiman, P.L. den Exter, O.M. Dekkers, F.A. Klok, M.V. Huisman, Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis, J. Thromb. Haemost. 12 (2014) 320–328.
[25] G. Agnelli, H.R. Buller, A. Cohen, M. Curto, A.S. Gallus, M. Johnson, et al., Apixaban for extended treatment of venous thromboembolism, N. Engl. J. Med. 368 (2013) 699–708.
[26] J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, et al., Rivaroxaban or aspirin for extended treatment of venous thromboembolism, N. Engl. J. Med. 376 (2017) 1211–1222.
[27] D. Keeling, T. Baglin, C. Tait, H. Watson, D. Perry, C. Baglin, et al., Guidelines on oral anticoagulation with warfarin - fourth edition, Br. J. Haematol. 154 (2011) 311–324.