The management of pulmonary embolism in a regional Australian centre - A retrospective audit

[redacted]
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Abstract
Background: The current inpatient management of pulmonary embolism (PE) is heterogenous and international guidelines are often inconsistent.
Aim: The aim of this study was to compare the current management of PEs in a regional Australian hospital to international consensus guidelines particularly in the areas of duration of anticoagulant, inpatient investigation after diagnosis and malignancy screening.
Methods: This was a single centre, retrospective study performed at Cairns Hospital from the 1st of July 2017 to the 30th of June 2018. Data was collected from review of the electronic medical records.
Results: Among patients with unprovoked PE 28% (14/50) were recommended indefinite anticoagulation. In patients with provoked PE without active malignancy 9.6% (5/52) were prescribed anticoagulation for three months. There was no documentation of duration of anticoagulation in the medical records of 25.7% (27/144) of patients. Thrombophilia screening was undertaken in 20.1% (29/144). A CT abdomen for malignancy screening was performed in 8% (4/50) of patients.
Discussion: The management of PE in a regional centre differs from the most recent ACCP guidelines. Patients with unprovoked PE were largely undertreated with current guidelines recommending indefinite anticoagulation. Patients with provoked PE were over-treated with only a minority prescribed the recommended three months. Documentation in the clinical records was very poor particularly related to the recommended duration of anticoagulation. Thrombophilia screening and CT abdomen for malignancy screening are both low value investigations that were overutilised resulting in inappropriate resource allocation.
Conclusion: This audit has corroborated previous Australian research showing significant heterogeneity in the investigation and management of PEs in a regional centre and non adherence to international guideline recommendations and highlights a number of areas that require significant improvement.

Introduction
The majority of recent research into pulmonary embolism (PE) has focused on clinical decision making rules regarding investigation and has largely neglected management after diagnosis. This has lead to a diverse and non standardized approach to the management of pulmonary embolism in Australia and worldwide. Pulmonary embolism has a significant associated morbidity and mortality with death occurring in 12% of patients within one month of diagnosis. Venous thromboembolism causes more deaths than all falls and road traffic accidents combined. The health care burden of pulmonary embolism in Australian is significant with an estimated 8200 new cases per year and total cost of venous thromboembolism approaching two billion dollars. [1]

Despite this significant burden there are no Australian guidelines for the management of pulmonary embolism and international guidelines have changed considerably. Furthermore, in recent years there has been a paradigm shift in the management of venous thromboembolism with direct oral anticoagulants (DOACs) largely superseding vitamin K antagonists. This changing landscape has contributed to considerable variability in the inpatient management of patients with pulmonary thromboembolism affecting patient outcome, length of stay and increasing health expenditure.

International guidelines include those by the British Thoracic Society [2], American College of Chest Physicians (ACCP) [3] and European Society of Cardiology (ESC) [4]. Of these the ACCP guidelines (published in 2016) are the most recently updated and referenced and provide the standard by which the management of pulmonary embolism will be measured against.

The aim of this audit was to provide a 'real world' review of the management of pulmonary embolism in a regional Australian hospital compared with international guidelines and other published Australian data [5-8]. We aim to compare our current practice to guidelines by investigating the following areas;

1. Choice of anticoagulant
2. Recommended duration of anticoagulation
3. Use of thrombophilia screening and inpatient echocardiogram
4. Malignancy screening post PE
5. Thrombolysis both the indications and complications

This research will provide an opportunity to address the current landscape, identify low value investigations and to provide a standardised approach to the management of pulmonary embolism in a regional centre.

Methods

This was a single centre, retrospective study performed at Cairns Hospital from the 1st of July 2017 to the 30th of June 2018. Data was collected by a single investigator by reviewing electronic medical records (iEMR).

Cairns Hospital is a regional 530 bed hospital situated in Far North Queensland. There are 135,000 presentations through the emergency department per year. Cairns Hospital has inpatient computed tomography pulmonary angiogram (CTPA) and access to ventilation perfusion (VQ)scans via an offsite private radiology company.

The project was submitted to the Chair of the Far North Queensland Human Research Ethics Committee prior to commencement and was deemed to meet the definition of a Quality Assurance Project and therefore received exemption from the Health Service Human Research Ethics Committee (HREC reference number- HREC/18/QCH/102 – 1269 QA). International Classification of Disease (ICD-10) diagnostic codes were used to identify all adult inpatients admitted to Cairns Hospital with 126.0 pulmonary embolism with mention of acute cor pulmonale and 126.9 pulmonary embolism without mention of acute cor pulmonale. All patients managed in the outpatient setting and paediatric patients (age <18 years) were excluded. Patient details were de-identified and stored in a secure, password protected Microsoft Excel database only accessible to the investigator.

Clinical information on each patient was obtained using iEMR, discharge summaries, radiological and cardiac imaging reports and pathology results. The data collated included demographics, in hospital mortality, risk factors for VTE *(see table 1),* imaging modality chosen, location of embolus on imaging, thrombophilia and antiphospholipid screening, inpatient transthoracic echocardiogram, choice and duration of anticoagulant, documentation of long term anticoagulant prophylaxis, IVC filter insertion, and thrombolysis.

Table 1 Provoked PE [9]

Hormonal-related factors – pregnancy or early postpartum (<1 month), oral contraceptive pill, hormone replacement therapy
Malignancy-related factors – active malignancy, myeloproliferative neoplasms, cancer treatment
Recent major surgery or trauma (within three months) or immobility (best rest >3 days)

Table 2 Definitions

Thrombophilia screen - Protein C and protein S levels, antithrombin III level, activated protein C resistance and prothrombin gene mutation (PG202A) [6].
Age appropriate malignancy screen - Faecal occult blood test (age 50-74), mammography (women 50-74 years or depending on risk), cervical screening (women 25-74) [10].
Antiphospholipid syndrome - ICS criteria for definite antiphospholipid syndrome (APLS) used [11].
APLS testing - Anticardiolipin antibody, beta 2 glycoprotein, lupus anticoagulant [11].
Massive PE – Acute PE with sustained hypotension (systolic blood pressure <90mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE) [12].
Submassive PE - SBP >90mmHg with evidence of right heart dysfunction on CTPA/ECG/ echocardiogram, or elevated biomarkers, such as troponin or B-type natriuretic peptide [12].
Low risk PE - Haemodynamically stable with no evidence of RV dysfunction [12].

Results

Demographics

A total of 144 patients were admitted to Cairns Hospital with a diagnosis of pulmonary embolism from 1st of July 2017 to 30th of June 2018. The median age was 65. 57% of the patients were male. The average length of stay was 7.5 days *(table 3*). 63.2% of cases of PE were provoked. The most prevalent provoking factor was recent immobility or surgery present in 57.5% *(table 3).*

Diagnosis/ Location of embolus/ RV dysfunction

CTPA was the predominant imaging modality in 94.4% compared with a VQ scan in 4.2%. Two patients were diagnosed with PE 'on clinical grounds' and commenced on treatment without imaging. Of the 6 patients that underwent VQ scan one had anaphylaxis to contrast, three had a creatine clearance of 30 mL/min or less and one with a creatinine clearance of 32ml/min and one patient was pregnant *(table 3)*.

Amongst patients who underwent CTPA the majority had main pulmonary artery, lobar or segmental emboli (89%). 5.9% of patients had saddle emboli and 5.1% had subsegmental emboli.
A total of 2 patients met the American Heart Associated (AHA) definition of massive pulmonary embolism, 25.7% of patients had submassive PE and 72.9% were classified as 'low risk' embolism *(table 3).*

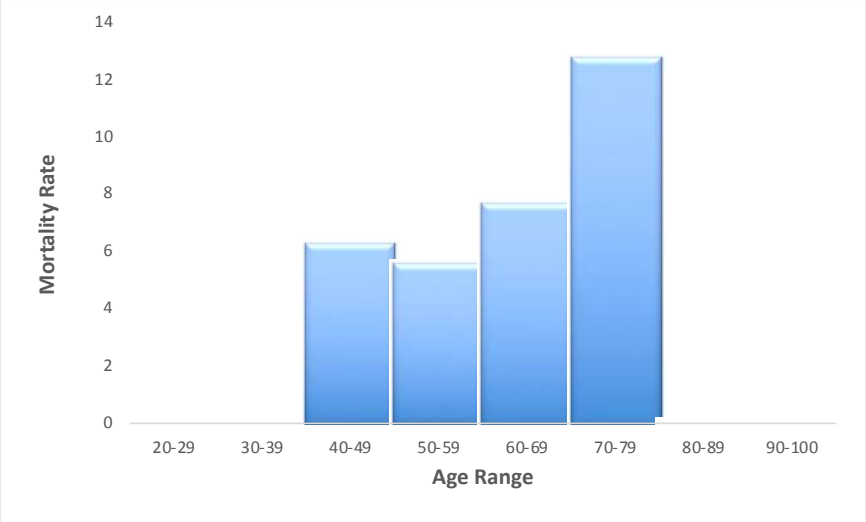
Table 3 Characteristics of Study Population

Mean age	65 years (range 21-94)
Male	57.0% (82/144)
Provoked PE	63.2% (91/144)
• Recent surgery or immobilisation	59.3% (54/91)
• Malignancy related factors	46.1% (42/91)
• Hormonal related factors	4.4% (4/91)
Previous VTE	14.6% (21/144)
Thrombophilia	2.8% (4/144)
In Hospital Mortality	
• all patients	6.9% (10/144)
• no active malignancy	3.9% (4/102)
• active malignancy	14.3% (6/42)
Average Length Of Stay	7.5 days
Haemodynamics and RV dysfunction	
• Massive	1.4% (2/144)
• Submassive	25.7% (37/144)
• Low risk	72.9% (105/144)
Location of emboli	
• Saddle	5.9% (8/136)
• Main pulm art/Lobar/segmental	89.0% (121/136)
• subsegmental	5.1% (7/136)
Imaging modality	
• CTPA	94.4% (136/144)
• VQ	4.2% (6/144)
• neither	1.4% (2/144)
Thrombophilia screen	20.1% (29/144)
APLS screen	17.4% (25/144)
Age related malignancy screen recommended	20.0% (10/50)
Screening CT abdomen to exclude malignancy	8.0% (4/50)
Acute inpatient TTE performed	30.3% (45/144)
Thrombolysis	1.4% (2/144)
• massive PE	100% (2/2)
• submassive PE	2.7% (1/37)
• low risk	0.0% (0/105)
IVC filter inserted	1.4% (2/144)

Inpatient Mortality

The overall inpatient mortality rate in all patients admitted for pulmonary embolism was 6.9% (10/144). When patient with active malignancy were excluded (42 patients excluded) the mortality rate reduced to 3.9% (4/102).

Figure 1 Inpatient mortality rate of PE among different age ranges



Anticoagulant Chosen

In patients without active malignancy rivaroxaban was the most commonly prescribed anticoagulant (51.0%) followed by apixaban (35.3%), enoxaparin (8.8%) and then warfarin (4.9%). Of the five (4.9% - 5/102) patients prescribed warfarin, DOACs were contraindicated in two due to renal dysfunction and one had a relative contraindication with morbid obesity. The remaining two patients were prescribed warfarin due to clinician preference. In patients with active malignancy, enoxaparin was prescribed in 59.5% with the rest prescribed DOACs or warfarin.

Table 4 Anticoagulant prescribed

Anticoagulation Prescribed	**PE (no malignancy) n=102**	**PE (malignancy) n=42**
Rivaroxaban	51.0% (52)	14.3% (6)
Apixaban	35.3% (36)	16.7% (7)
Enoxaparin	8.8% (9)	59.5% (25)
Warfarin	4.9% (5)	9.5% (4)

Figure 2 Anticoagulant chosen in patients without active malignancy

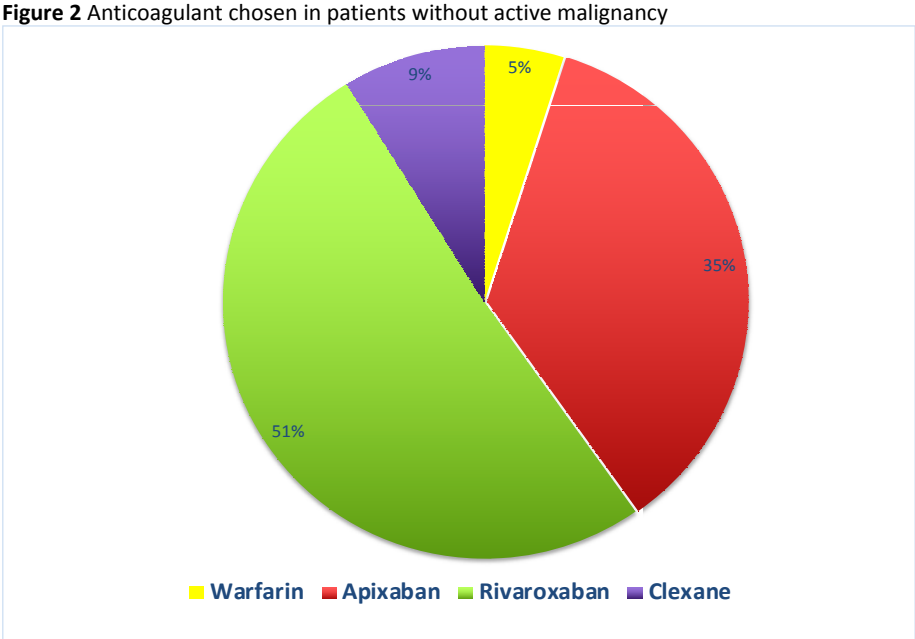
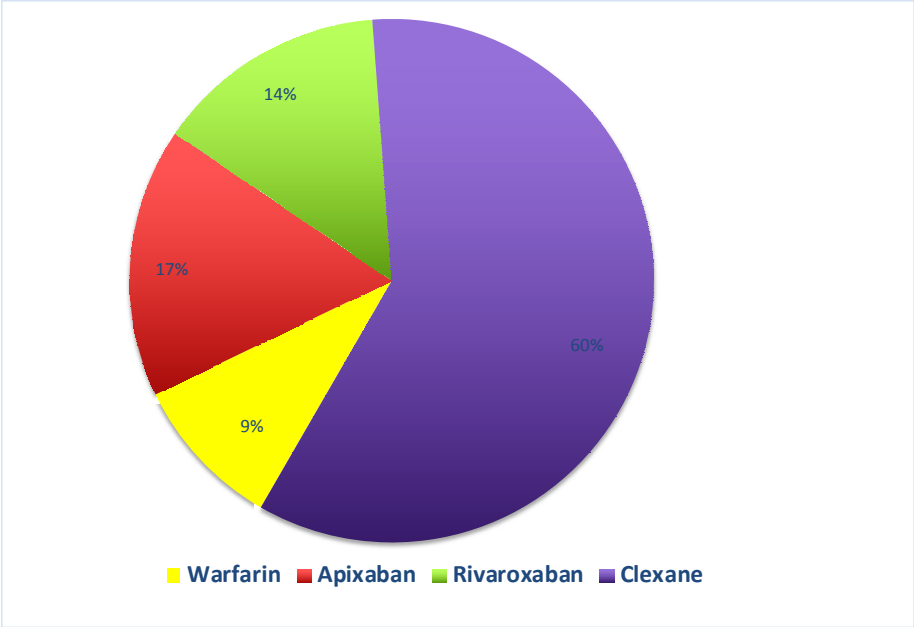


Figure 3 Anticoagulant chosen in patients with active malignancy



Duration of anticoagulation

The duration of anticoagulation for unprovoked PE varied significantly with 28% prescribed indefinite anticoagulation. In patients with a provoked PE without active malignancy 9.6% were prescribed anticoagulation for three months. Duration of anticoagulation was not documented in inpatient notes or on the discharge summary in 25.7% of patients *(table 5).*

Table 5 Duration of anticoagulation

Duration	Unprovoked (n=50)	Provoked- no malignancy (n=52)	Active Malignancy (n=42)
3 months	0% (0)	9.6% (5)	4.7% (2)
6 months	36% (18)	57.7% (30)	21.4% (9)
12 months	8% (4)	0% (0)	0.0% (0)
Indefinite	28% (14)	11.5% (6)	23.8%(10)
Other	2% (1)	7.7% (4)	9.5% (4)
Not documented	26% (13)	13.5% (7)	40.5% (17)

Subsegmental PE

All seven patients diagnosed with subsegmental PEs (SSPE) were treated with anticoagulation.

Long term prophylaxis

No patients were prescribed low dose DOAC prophylaxis. One patient was planned to be initiated on aspirin prophylaxis after completion of anticoagulation.

Thrombolysis

Three patients were thrombolysed. Two of these patients met the AHA criteria [12] for massive PE and both survived their hospital admission. The other patient met criteria for a submassive PE. This patient developed profound hypoxaemia in the setting of poor respiratory reserve with a saddle embolus and died in hospital post lysis. Of the thrombolysed patients, none experienced clinically significant bleeding.

IVC filter

A total of two patients received IVC filters. Both were inserted whilst anticoagulation was withheld for surgical procedures (one tracheostomy, one split skin graft). One was retrieved during the same admission. There was no documented plan for retrieval of the other filter.

Thrombophilia screening

Thrombophilia screening was performed in 20.1% (29/144) of all patients, and a considerable proportion of these were performed in provoked PEs (*table 6*). Of the 29 patients who underwent screening one patient was found to be a heterozygote for factor V Leiden mutation. This patient had a massive unprovoked PE and thus prior to screening already had a strong indication for indefinite

anticoagulation [3]. One patient tested positive for lupus anticoagulant but did not return for repeat testing. Five patients had low protein C or S but these were performed during the index admission. A repeat test for clarification was only performed in one patient and was negative indicating a false positive.

Table 6 Thrombophilia and Antiphospholipid Screening

	All (n=144)	**Unprovoked (n=50)**	**Provoked (n=94)**
Thrombophilia screen	20.1% (29/144)	30.0% (15/50)	14.9% (14/94)
APLS screen	17.4% (25/144)	24.0% (12/50)	13.8% (13/94)

Malignancy screening
In the unprovoked PE population an age appropriate malignancy screen was recommended in 20% of patients. Of the 102 patients without a known malignancy, a screening CT abdomen was ordered in 7.8%. None of these eight patients were diagnosed with an occult malignancy as a result of the CT abdomen. The index CTPA diagnosed 2.9% of patients with a new malignancy.

Inpatient TTE
An inpatient transthoracic echocardiogram (TTE) was ordered in 30.3% of patients and 19.0% of patients with low risk PE. Two of these patients had features of RV strain or pulmonary hypertension on TTE. 62.2% of submassive PE had an inpatient TTE and of these 65.2% had RV dysfunction or elevated pulmonary pressures.
The length of stay in patients receiving TTE was longer at 9.3 days compared with the average length of stay of 7.5 days.

Discussion

The goal of consistent and up-to-date clinical practice is difficult with inconsistent and changing guidelines. It is therefore unsurprising that the management of PE in a regional centre differs from the most recent ACCP guidelines *(table 7)*. This study identifies the following key areas where improvement in practice could be undertaken, namely; the duration and choice of anticoagulation, the inpatient investigation of patients following diagnosis with PE, and the documentation of the anticoagulation plan in the medical records.

Table 7 Regional practice compared to ACCP guidelines [3]

	Guidelines recommendations	**Regional Practice**
Choice of anticoagulant		
• **Patients without active malignancy**	DOAC recommended first line	Prescribed in 86.3%
• **Patients with active malignancy**	LMWH recommended	Prescribed in 59.5%
Duration of anticoagulation		
• **Provoked PE**	3 months	3 months in 9.6%, 6 months in 57.7%
• **Unprovoked PE (low bleeding risk)**	Indefinite	Indefinite in 28.0%, 6 months in 36.0%
Anticoagulation in subsegmental PE in low risk patients	Not recommended	3 patients were anticoagulated that may have been observed
Thrombophilia screen	Not recommended	Performed in 20.1%
Malignancy screen in unprovoked PE		
• **Age appropriate malignancy screen**	Recommended	Recommended in 10.0%
• **CT abdomen**	Not recommended	Performed in 7.8%
Thrombolysis		
• **Massive**	Recommended	Performed in 2/2 patients
• **Submassive with cardiorespiratory decompensation**	Recommended	Performed in 1/1 patient
• **Submassive with no cardiorespiratory decompensation**	Not recommended	Not performed - 0/36 patients

In this series there was significant variation in duration of anticoagulation prescribed for PE. Research has shown that unprovoked PE has a high rate of recurrence of around 31% and therefore indefinite anticoagulation is recommended in all patients who are low bleeding risk [3, 13]. Surprisingly, in this series less than one third of patients with unprovoked PEs were prescribed long term anticoagulation. A finite six or twelve months of anticoagulation was more commonly prescribed. This is a significant deviation from international guidelines.

Amongst patients with a transient, reversible risk factor for PE the ACCP guidelines and most other international guidelines recommend three months total duration of anticoagulation [3, 4]. This is because the rate of recurrent PE post cessation of anticoagulation in this group has been found to be

low at 2.5% per year [14]. The Haematology Society of Australia and New Zealand's EVOLVE guidelines list extending anticoagulation over three months in provoked PE in their top five low value practices and interventions [15]. In the audit, the majority of patients were over treated and prescribed anticoagulation for six months.

The duration of anticoagulation was not defined in 25.7% of patients during their admission. This figure although high is lower than cross-sectional data from the CareTrack Australian study which identified that 41% of Australian patients hospitalised for VTE are not given a duration for anticoagulation [5]. This demonstrates a failure of clinical documentation which is vital for handover to primary care physicians.

In patients with active malignancy enoxaparin was only prescribed in just over half of cases (59.5%). This is despite evidence that warfarin is less effective in preventing recurrent VTE than low molecular weight heparin (LMWH) [16]. Edoxaban has been shown to be non-inferior to LMWH in this group however is not available on the PBS in Australia and not yet recommended in guidelines [17].

The accessibility of imaging and introduction of highly sensitive CT has led to the increased detection of small insignificant pulmonary emboli. Patients with isolated subsegmental PEs (SSPEs) without a DVT or risk factors for PE are at a low risk of recurrence and VTE guidelines recommend clinical surveillance over anticoagulation [3]. In this series all seven cases of SSPEs received anticoagulation, three of which occurred in patients without risk factors who could have been considered for clinical surveillance if Doppler examination of the lower limbs was negative.

Recent studies show that low dose apixaban (2.5mg twice daily) and low dose rivaroxaban (10mg daily) are effective at preventing VTE when used as long term prophylaxis [18, 19]. Currently apixaban is available on the PBS for this indication but not rivaroxaban. As an alternate option in patients with first unprovoked PE, low dose DOAC prophylaxis can be considered following six to twelve months of therapeutic anticoagulation although this is yet to be recommended in guidelines. In this audit, DOAC prophylaxis was not recommended to any of the patients.

The utility of thrombophilia testing in PE is controversial as results rarely influence clinical management[20]. Indiscriminate thrombophilia testing can result in a positive test with an associated 'label' and rarely any clinical significance and a negative test may well provide false reassurance. Furthermore, when testing is performed in the acute inpatient setting a number of factors such as acute thrombus and anticoagulant use may cause inaccurate results. Most international guidelines [3, 4, 21] do not recommend routine thrombophilia screening. Thrombophilia screening in provoked VTE was also listed in the Haematology Society of Australia and New Zealand's EVOLVE guidelines as a low value test [15]. Even in patients at significant risk of a thrombophilia (eg strong family history) there are no clear recommendations to screen. Despite guidelines, thrombophilia and antiphospholipid screening were performed in one in five patients in this study. Even amongst patients with provoked emboli where the yield of such tests are very low nearly one in six patients were tested for a thrombophilia or antiphospholipid syndrome. The results of the thrombophilia test did not change management in any of the patients in this audit further highlighting their lack of clinical utility.

The role of inpatient TTE in acute PE is to assess for RV dysfunction in patients at risk of clinical deterioration and risk stratify patients at risk of chronic thromboembolic pulmonary hypertension. The rate at which an inpatient TTE was ordered in this audit approximated those previously reported in the literature in Australia and America [22, 23]. ACCP propose that echocardiography should not be measured routinely in all patients with PE [3]. Acute TTE in haemodynamically stable patients with PE does not have clear therapeutic implications and should be reserved for patients in which the clinician is considering more intensive monitoring or thrombolysis [3]. A number of inpatient TTEs were ordered in patients with low risk PEs and were highly unlikely to have altered management. A study by Cohen et al showed that hospitals with high rates of inpatient TTE performed on haemodynamically stable patients with PEs had no difference in mortality outcomes but resulted in higher resource use and costs [24]. Length of stay was longer for patients with low risk PE who received an inpatient TTE. However, this data is confounded by the higher likelihood of inpatient TTE being performed on frail patients with more comorbidities, particular preexisting cardiovascular disease.

The hypercoagulable state of malignancy was first described by Trousseau in 1865 [25]. Only a minority (20%) of patients were advised that they should participate in age appropriate cancer screening. This is an area which needs considerable improvement. The reported incidence of malignancy after an unprovoked thrombotic event is approximately 5% with the majority of cases diagnosed within one year post initial VTE. Half of these cases are diagnosed with the index CTPA [26]. A CTPA not only images the chest but also upper abdomen and can diagnose thoracic and abdominal solid organ malignancies. The role of an additional CT abdomen post CTPA is of limited value and it is not endorsed by the guidelines. In this series a screening CT abdomen was performed in 8% of patients after the diagnosis of pulmonary embolism.

In this series thrombolysis and IVC insertion were infrequently used but met international consensus guideline indications.

Warfarin therapy, once the mainstay of anticoagulation in VTE, has been superseded by the advent of DOACs. The predictable pharmacokinetics with no requirement for monitoring or bridging enoxaparin, fewer drug interactions and lack of food interactions have now led to the ACCP recommendation that DOACs be used preferentially over warfarin [3]. In a recent analysis of the practice of Australian hematologists and respiratory physicians 76% would preference prescribing DOACs over warfarin for patients without cancer [7]. This audit corroborated this paradigm shift in anticoagulation with the majority of patients prescribed DOACs for acute PE. Both rivaroxaban and apixaban are as efficacious as warfarin for treatment of PE with comparable or fewer rates of bleeding [18, 27].

There are a number of limitations with this audit which warrant consideration. Firstly, this is a retrospective audit and information collected relies on the quality of documentation in the medical records and electronic notes. The audit relied on identification of subjects by ICD codes. If a patient with a PE was incorrectly coded they were missed. Furthermore, two of the patients included were diagnosed with PEs based on clinical grounds without an imaging diagnosis. The small sample size increases the chance of sampling bias. However, the sample group's demographic and characteristics do reflect national data [5-8]. The patients were not followed over time just during their acute admission so potentially important longitudinal data was not collected. For example, the duration of anticoagulation was determined by the documented plan not what actually happened after discharge. Other potentially important information such as results of repeat thrombophilia testing, post discharge mortality, recurrence of VTE may also have been missed.

Multiple disparate guidelines and the advent of new anticoagulant options are some of the factors giving rise to significant heterogeneity in the management of PE. Most research to date has focused on clinical decision making tools for the investigation of PE but based on this study there needs to be a focus on the standardisation of the management of PE, particularly in regards to duration of anticoagulation, investigation and documentation. Achieving change in a complex organisation requires a multifaceted approach. An anticoagulation stewardship program, similar to the antimicrobial stewardship program, could provide a nationwide system including current guidelines for the safe and appropriate prescribing and surveillance of the management of VTE. Furthermore, the prescription of anticoagulation for VTE should trigger mandatory documentation of whether the incident is provoked or unprovoked and the intended duration of anticoagulation. The introduction of the statewide electronic prescribing system could greatly simplify this process and provides an opportunity for such change.

Conclusion

This 'real world' data provides an overview of the state of play in the management of pulmonary embolism in a regional Australian centre. Rather than provide reassurance, this audit has corroborated previous Australian research showing significant heterogeneity in the investigation and management of PEs. Low value tests such a thrombophilia testing, inpatient TTE in haemodynamically stable patients and a CT abdomen to screen for occult malignancy are over-utilised and result in inappropriate resource allocation. The duration of prescribed anticoagulation and subsequent documentation in the medical records differed from international guidelines and fell far short of expectations.

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