Prevention of venous thromboembolism and safe use of heparin in Spanish hospitals

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Abstract

Objective. To assess compliance with basic and actionable indicators in relation to prevention of venous thromboembolism (VTE) and safe use of heparin.

Design. We built, pilot tested and measured a set of evidence-based structure (existence of guidelines) and process (risk assessment for VTE, and dose adjustment to patient weight and renal function when prescribing heparin) indicators in a nation-wide random sample of 22 hospitals. Compliance with process indicators is estimated at national level and by groups of hospitals (stratified by size). At hospital level, compliance is assessed with Lot Quality Acceptance Sampling, for 85% compliance standard ($\alpha = 0.05$), 55% threshold ($\beta = 0.10$). Contents of existing guidelines are analyzed, and their influence on performance is assessed using logistic regression.


Interventions. None

Main Outcome Measures. Problem identification through indicators assessment.

Results. Less than half of hospitals have guidelines and their contents are very variable and incomplete. No hospital complies with the standard for VTE prevention and only one for heparin dose adjustment. Nationally, VTE risk assessment is performed in 5.8% of patients (95% CI: 5.6–6.0), and heparin dose is explicitly adjusted in 17.5% (95% CI: 16.8–18.2). Performance is relatively higher in large hospitals and it is associated with the existence of guidelines for VTE prevention (OR: 8.3; 95% CI: 2.1–32.1).

Conclusions. We have identified some actionable contributing factors to safety problems using evidence-based structure and process indicators. Explicit process design and key clinical interventions (risk assessment for VTE and heparin dose adjustment) should be addressed to improve the current situation.

Keywords: patient safety, prevention, safety indicators, thrombosis, embolism, prevention, heparin, (clinical practice) guidelines

Introduction

Venous thromboembolism (VTE) is an important safety problem in hospitals [1]. Postmortem studies have revealed that up to 1 in 10 in-hospital deaths are related to pulmonary thromboembolism (PE) [2, 3], and sudden death occurs in over one-third of patients with PE [4]. A study in six European countries estimated that 370 000 deaths per year are caused by this problem, almost three-quarters of which are hospital-related [5]. In the UK alone, it has been estimated that at least 25 000 deaths could be prevented annually [6]. Additionally, VTE unnecessarily increase comorbidity and health care costs [7].

To prevent VTE, both mechanical and pharmacologic interventions are available [8–10], the latter consisting of the use of anticoagulants after the risk for VTE, contraindications of anticoagulants and the risk of bleeding have been assessed [1, 10, 11]. At the same time, anticoagulants are high-risk drugs [12] and a prominent cause of adverse events [7, 13].

To address these safety problems, the National Quality Forum (NQF) recommends the evaluation of each patient

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for the risk of VTE, the use of appropriate methods to prevent VTE, and dedicated anticoagulation services for antithrombotic care management [14]. Under a contract with the Agency for Quality of the Spanish Ministry of Health, we have developed, pilot tested and measured in a representative sample of hospitals, a set of basic structure and process indicators that could be used to measure to what extent the NQF evidence-based recommendations are being implemented [15]. This article describes the indicators constructed, and the results of the nationwide baseline study on VTE prevention and initial management of patients treated with anticoagulants.

Methods

Construction and pilot testing of measures

A multidisciplinary team was formed to analyze NQF recommendations along with their supporting evidence and to convert them into indicators. The guidelines for this process were the following: (i) indicators should translate into measurable elements, the NQF recommendations; (ii) they should be structure and process indicators, reflecting what hospitals should have or do to prevent the addressed safety problems; (iii) few; try to achieve parsimony; (iv) take into account measurement feasibility.

The team was composed of experienced health professionals from all concerned areas (intensive care, surgery, medicine, pharmacy), and quality management experts. To review evidence for the indicators, we used primarily NQF document [14] and AHRQ Evidence Report No 43 [16], in addition to a PubMed search of more recent articles. The eventually approved indicators were pilot tested for reliability and feasibility in three hospitals, representing the three types of hospitals in which the eventual national sample was to be stratified. Pilot testing was performed independently but simultaneously by two health professionals (nurses) who had not participated in the development of the indicators. Reliability was assessed by calculating the kappa coefficient. Table 1 describes the indicators, measurement methods and source of data that we used.

Sample of hospitals and patients

The list of National Health System (NHS) hospitals was stratified by size into three strata: small hospitals (<200 beds, \(N_1 = 79\)), medium size hospitals (from 200 to 500 beds, \(N_2 = 163\)) and large hospitals (>500 beds, \(N_3 = 64\)). A random sample of hospitals in each stratum was then taken. The number of hospitals sampled per stratum was determined to proportionally represent the contribution of each stratum to the total number of hospital admissions. The sample, devised and used previously to study the frequency of adverse events [17], consisted of 24 hospitals (5 large, 13 medium size and 6 small); 5 of which had to be substituted because they refused to participate. Two of the substituted medium size hospitals declined to participate and, in other two, data were incomplete and were excluded from the analysis, which finally included 20 hospitals. We asked for a copy of their guidelines for VTE prevention and anticoagulant therapy management, and two random samples of medical records were selected to assess the process indicators: one for VTE prevention, which applies to all patients, and another for prescription of anticoagulants, where patients who were treated with heparin were sampled. In both the cases, the sampling framework was 6 months previous to assessment and was provided by the Minimum Basic Data Set of the hospital (a homogeneous and compulsory administrative and clinical recording system in all hospitals). To assess VTE risk assessment, we focused on patients aged >65, a sample that was also used to assess other patient safety problems. To evaluate safe prescription of anticoagulants, we sampled all types of patients prescribed with heparin.

For the assessment of process indicators in individual hospitals, we used the Lot Quality Acceptance Sampling (LQAS) technique, a quality control procedure promoted by the World Health Organization for rapid assessments, that can be used in epidemiological studies, and that we had adapted as a problem identification tool for quality management [18, 19]. The parameters set for acceptance (‘good quality’) were a standard of 85% indicator compliance, \(\alpha < 0.05\), and \(\beta < 0.10\) for a 55% compliance threshold. These conditions require a random sample of 17 patients and a minimum of 12 compliance cases. Hospitals with <12 compliance cases in the sample may be identified as problematic. To estimate compliance, first by stratum (hospitals grouped by size) and then for the NHS, the sum of all the individual hospital samples is considered as a two-step (first hospitals, then patients) stratified (hospitals) clusters (patients) sample, with fixed (non-proportional) sample size for individual hospitals.

Data analysis

The presence of guidelines and a comparative analysis of their contents are described by hospital and by hospital size. For process indicators, LQAS classification (acceptance/rejection of compliance with the pre-established standard) is given by hospital, and non-biased estimates of compliance with 95% confidence interval are calculated by hospital groups (by hospital size) and for the NHS using the appropriate formula for the two-step cluster sampling. Finally, to ascertain whether compliance with process indicators was significantly associated with structural variables (hospital size and the existence of guidelines), we used stepwise logistic regression models where these variables are independent categorical variables and performance of VTE risk assessment and explicit adjustment to patient weight and renal function when prescribing heparin are dependent variables. We tested and compared models with and without interaction among structural variables using the \(-2\log\) likelihood chi-square test for the null hypothesis of no difference when including the interaction term.
<table>
<thead>
<tr>
<th>Safety recommendation</th>
<th>Title of the indicator</th>
<th>Description</th>
<th>Domain</th>
<th>Measurement method</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Assessment and prevention of VTE</td>
<td>1.1. Existence of guidelines for prevention of VTE.</td>
<td>This indicator is used to determine whether or not the hospital has a guideline approved by hospital for prevention of VTE.</td>
<td>Structure</td>
<td>Inspection</td>
<td>Guidelines used in the hospital</td>
</tr>
<tr>
<td></td>
<td>1.2. Percentage of patients over 64 years of age assessed in the first 24 h after admission to hospital for the risk of developing VTE.</td>
<td>This indicator is used to determine the percentage of patients &gt;64 years of age, who are assessed, with documented evidence, in the first 24 h after admission to hospital, for the risk of developing VTE.</td>
<td>Process ($k = 1)^a$</td>
<td>Medical record review</td>
<td>Medical record</td>
</tr>
<tr>
<td>2. Specific management of anticoagulants</td>
<td>2.1. Existence of guidelines for the management of oral anticoagulants by patients, for patients who receive anticoagulants from outpatient clinics or health centers.</td>
<td>This indicator is used to determine whether or not the hospital has a guideline for including patients in the management of oral anticoagulant therapy.</td>
<td>Structure</td>
<td>Inspection</td>
<td>Guidelines used in the hospital</td>
</tr>
</tbody>
</table>
| | 2.2. Existence of guidelines for correct heparin administration using a nomogram. | This indicator is used to determine whether or not the hospital has guidelines approved by the hospital for heparin administration using a nomogram. The document need to include the following minimum criteria:
- Initial dose
- Corresponding blood tests
- Modification of dose in light of results of blood tests | Structure | Inspection | Guidelines used in the hospital |
| | 2.3. Percentage of patients assessed for weight and renal function before starting anticoagulant therapy with heparin. | This indicator is used to determine the percentage of patients whose renal function (creatinine, when prescribing LMWH) and weight (both types of heparin) are assessed prior to administration of heparin. Patients’ weight should be assessed within 24 h before starting therapy and their creatinine levels at most 48 h before starting therapy. | Process ($k = 1)^a$ | Medical record review | Medical record |

$a$ kappa coefficient from the pilot test; $n = 30.$
Results

Guidelines for preventing VTE and for anticoagulant therapy

Less than half of hospitals have guidelines for both processes (see first rows of Tables 2 and 3). The frequency of the presence of guidelines is not significantly different by hospital size. However, in relation to the active participation of the patient with anticoagulant therapy, we found guidelines in only one small hospital. This topic was not addressed in any of the large or medium size hospitals.

Contents of the existing guidelines are not uniform. A detailed comparative analysis (Tables 4 and 5) shows striking variability and, to some extent, incompleteness.

With regard to VTE prevention (Table 4), most guidelines (10 of 11) apply to surgical patients, fewer (7 of 11) to medical patients and less (6 of 11) to both surgical and medical patients. A risk assessment instrument is included in only 3 of 11 guidelines. All of them include recommendations for pharmacological prophylaxis, particularly low-molecular weight heparin (LMWH), but warnings on contraindications and adverse events are in 8 of 11 protocols, and recommended alternatives in 5 of 11. Mechanical/physical prevention methods are recommended in 8 of 11 guidelines.

All guidelines for heparin therapy (Table 5), present in fewer than half of the hospitals (9 of 20), contain recommendations on the initial dose, adjustment by weight and lab test controls. However, explicit consideration of potential adverse events is included in only two of nine guidelines, and of renal function (creatinine level) in one. Clear applicability (target patients) is described in two of nine guidelines.

LQAS assessment

Both VTE prevention and management of patients under heparin treatment processes were identified as problem areas for patient safety (non-compliance with the 85% standard) in the vast majority of hospitals (Tables 2 and 3). Only one medium size hospital had enough compliance cases (≥12) in the heparin prescription sample to accept compliance with the standard. None of the hospitals complied with the standard for the assessment of VTE risk.

Estimates of indicators compliance

Less than 6% (5.8%; 95% CI: 5.6–6.0) of patients are explicitly assessed for the risk of VTE (Table 2). There are some differences according to hospital size: the assessment is relatively more frequent in large hospitals; however, even in this group, it is documented in only 10.4% patients (95% CI: 9.3–11.5).

The assessment of patient weight and, when appropriate, renal function at the time of heparin prescription is documented in <20% of cases (17.5%; 95% CI: 16.8–18.2). Again, as for the assessment of the risk of VTE, compliance is relatively higher in large hospitals (29.6%; 95% CI: 27.3–31.9). Explicit dose adjustment for patient weight is the most frequent failure. Weight is not documented in ~75% of patients treated with heparin (Table 3). When LMWH is prescribed, creatinine is not assessed in 17.2 ± 4.2% of patients.

Multivariate logistic regression shows the influence of hospital size and the existence of guidelines on risk assessment for VTE (odds ratio for large hospitals, adjusted for existence of guidelines: 4.1; 95% CI: 1.1–15.5); the model including an interaction variable provides significantly better fit (P = 0.032) and the adjusted odds ratio for large hospitals with guidelines is 8.3 (95% CI: 2.1–32.1). However, we found no significant association between these structural variables and the explicit adjustment to patient’s weight and creatinine level when prescribing heparin.

Discussion

The need and importance of guidelines

A salient result of our study is the lack of guidelines for both VTE risk assessment and anticoagulants management, in...
approximately half of the hospitals assessed. The existence of guidelines does not ensure performance [20]. However, a systematic review of studies on strategies to improve VTE prophylaxis concluded that, with guidelines as the basis for all strategies, a multifaceted strategy is also needed (electronic reminders, audit and feedback, etc.) [11]. A clear recommendation from the American College of Chest Physicians [21], and one of the main conclusions in epidemiological studies and health policy documents, such as the ENDORSE study [22] and the report on the prevention of VTE in UK hospitals [6], is that every hospital develop a formal institution-wide strategy to address VTE prevention [21], together with measures that ensure that risk assessment of every patient on admission becomes a reality [6]. Our study confirms the association between the existence of guidelines and the performance of risk assessment for VTE, but not so for the adjustment of heparin dosage to the patient’s characteristics. A possible explanation may be that guidelines for anticoagulant therapy are relatively less frequent and somehow of lower quality, one of the many barriers influencing non-compliance with guidelines [23]. However, some studies have shown that the implementation of evidence-based guidelines for anticoagulant therapy resulted in a significant increase of appropriate use, fewer anticoagulant-associated adverse events and lower costs [24, 25]. The lack of this type of guideline may be considered then as a relevant structural contributing factor to the less than optimal practice we found [20].

### Variability and insufficiency of the existing guidelines

Contents of the existing guidelines are widely different among hospitals, as it was found to some but less extent in other studies [26]. In relation to VTE prophylaxis, each institution seems to be unique, with the exception of recommending LMWH, and none of guidelines are complete. We expected to find guidelines for both surgical and medical patients. The ENDORSE study [22] found, probably overestimating it, that 41.5% of medical inpatients aged >40 and 64.4% of surgical patients aged >18 were at risk for VTE; however, most of the guidelines we found apply only to surgical patients. Furthermore, recommended risk assessment instruments are included in a minority of guidelines, while the explicit and structured consideration of procedural and

#### Table 3 Management of anticoagulation therapy

<table>
<thead>
<tr>
<th>Indicator</th>
<th>&gt;500-bed hospitals, n = 5</th>
<th>200–500-bed hospitals, n = 10</th>
<th>&lt;200-bed hospitals, n = 5</th>
<th>Total, n = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>The hospital has guidelines for anticoagulation therapy management</td>
<td>0/5</td>
<td>0/10</td>
<td>1/5</td>
<td>1/20</td>
</tr>
<tr>
<td>The hospital has guidelines for heparin therapy that includes dose adjustment to patient characteristics</td>
<td>4/5</td>
<td>5/10</td>
<td>0/5</td>
<td>9/20</td>
</tr>
<tr>
<td>% of patients treated with heparin whose weight (all types of heparin) and renal function (creatinine, for LMWH) are assessed before heparin prescription</td>
<td>n = 85</td>
<td>n = 168</td>
<td>n = 68</td>
<td>n = 321</td>
</tr>
<tr>
<td>Estimates of compliance (95% CI)</td>
<td>29.6 (27.3–31.9)</td>
<td>12.7 (12.2–13.2)</td>
<td>22.9 (20.3–25.5)</td>
<td>17.5 (16.8–18.2)</td>
</tr>
<tr>
<td>Single hospital compliance (LQAS)</td>
<td>0/5</td>
<td>1/10</td>
<td>0/5</td>
<td>1/20</td>
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<tr>
<td>Type of failure</td>
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<tr>
<td>Heparin prescription without explicit assessment of patient’s weight (95% CI)</td>
<td>67.2 (62.3–72.1)</td>
<td>75.9 (72.8–79.0)</td>
<td>76.0 (72.2–79.8)</td>
<td>73.8 (73.0–74.6)</td>
</tr>
<tr>
<td>LMWH prescriptions without explicit assessment of renal function, i.e. creatinine level (95% CI)</td>
<td>14.6 (7.0–22.2)</td>
<td>19.4 (13.3–25.5)</td>
<td>14.8 (5.9–23.7)</td>
<td>17.2 (13.0–21.4)</td>
</tr>
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</table>

Acceptance of compliance with an 85% standard, 55% threshold; \( \alpha = 0.05, \beta = 0.1; n = 17 \), minimum compliance = 12. LMWH, low-molecular-weight heparin; CI, confidence interval; LQAS, Lot Quality Acceptance Sampling.
patient risks may be more relevant for guiding appropriate decision-making [1]. The relatively less frequent presence of recommendations regarding mechanical or physical methods may be partially explained by the limited evidence of their comparative effectiveness. However, they may be useful as an interim alternative or complementary measure to pharmacological prophylaxis, fostering the collaboration of health personnel other than physicians (nurses, physiotherapists) to prevent this safety problem [9, 27]. In general, the lack of recommended alternatives is another frequent feature that we found in the guidelines for VTE prophylaxis.

The most striking feature among the few guidelines for heparin management that we found is the relative lack of attention to precautions for preventing adverse events (target

Table 4  Variability in the contents and recommendations of guidelines (G) for prevention of VTE

<table>
<thead>
<tr>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>G7</th>
<th>G8</th>
<th>G9</th>
<th>G10</th>
<th>G11</th>
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</thead>
<tbody>
<tr>
<td>&gt;500-bed hospitals (n = 5 hospitals; 3 with guidelines)</td>
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<td>200–500-bed hospitals (n = 10 hospitals, 6 with guidelines)</td>
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<tr>
<td>&lt;200 bed-hospitals (n = 5 hospitals, 2 with guidelines)</td>
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<tr>
<td>Total (n = 20 hospitals, 11 with guidelines)</td>
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</table>

1. Objectives  
2. Includes surgical patients  
3. Includes medical (non-surgical) patients  
4. Includes a VTE risk assessment instrument  
5. Includes a risk classification scale  
6. Mechanical/physical prevention methods  
7. Pharmacological prophylaxis  
8. Warnings on contraindications and adverse events  
9. Duration of prophylactic treatment  
10. Recommended alternatives (flexibility)
patients, contraindications and creatinine control when prescribing LMWH), and to patient involvement. Guidelines for patient involvement are practically nonexistent. However, anticoagulant therapy is normally initiated and controlled in hospital services, and there seems to be enough evidence on the benefits of actively involving patients in this process [28, 29]. A meta-analysis [28] concluded that some kind of patient self-management significantly decreases the incidence of thromboembolism, major hemorrhages and mortality. Other studies have shown that self-management increases treatment efficiency and the patient’s quality of life [29]. All these findings have not been included in the clinical guidelines of our hospitals.

**Risk for VTE is not routinely and explicitly assessed**

Little is known about the current practices regarding risk assessment for VTE in hospitals. Risks for VTE may be present both in medical and in surgical patients, and studies such as ENDORSE [22] have attempted to quantify it. However, in that study, risk assessment was performed by the researchers and, whereas data are given about the proportion of at-risk patients that received prophylaxis, there are no data about the actual risk assessment performed by the health professionals providing care to the patients. Assessing risk for VTE probably does not ensure a correct prophylaxis, nor does failure to explicitly assess risk mean that prophylaxis is not prescribed [22]. However, it would seem logical to assume that this first step is a cornerstone of VTE prevention, and it is usually treated as such in international guidelines and studies [6, 21, 22]. Our data show that there is sizeable room for improvement in clinical practice in this regard.

**Additional risk of adverse events when prescribing heparin**

Anticoagulants are high-risk drugs [12, 13]. They are one of the top five medication types associated with patient safety incidents, and heparin ranks third in the top 10 drugs involved in reported harmful medication errors [30]. In Spain, anticoagulants are involved in 3% of adverse events in hospitals [17]. Probably, using a nomogram and controlling renal function will likely not fully guarantee the absence of heparin-related complications, but a potential consequence of the not explicitly adjusted use of this drug, as we found in our study, is an uncontrolled risk of hemorrhagic or thrombotic events [7, 13, 21].

Heparin may be used prophylactically and therapeutically. We did not make this distinction when assessing clinical practice. In some cases, particularly for cardiac patients, heparin may be prescribed as emergency care and fine adjustments may not be as relevant or easy to perform as its prophylactic use in surgery or in other type of patients. However, the very low compliance with the indicator for the dose adjustment that we used, along with the practically nonexistent of hospital-wide evidence-based guidelines for this process, lead us to conclude that we have an enormous opportunity to improve anticoagulant therapy management.

**Study limitations**

Sample size by hospital using LQAS is small and cannot be used to give estimates, but only to accept/reject compliance with the preset standard, identifying centers with significant low-quality performance. However, the strict randomization of both hospitals and cases for evaluation allow us to give estimates of indicator compliance for groups of hospitals and for the NHS very efficiently, aggregating LQAS samples. The use of clinical records for data abstraction may be a problem when there is under-registration or when indicators and data abstraction methods have not been tested for reliability. In our case, reliability was pilot tested before the study and data abstraction was performed by a trained team of health professionals. We cannot estimate to what extent there is under-registration, but estimates of compliance are so low.

Table 5 Variability in the contents and recommendations included in the existing guidelines (G) for heparin administration

<table>
<thead>
<tr>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>G7</th>
<th>G8</th>
<th>G9</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500-bed hospitals (n = 5 hospitals, 4 with guidelines)</td>
<td>2/9</td>
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<tr>
<td>200–500-bed hospitals (n = 10 hospitals, 5 with guidelines)</td>
<td>2/9</td>
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<tr>
<td>Total (n = 20 hospitals, 9 with guidelines)</td>
<td>2/9</td>
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*a For low-molecular-weight heparin.
Conclusions

Rather basic evidence-based structure and process indicators have proved to be very useful in identifying some potential contributing factors for important safety problems in hospitals. In addition, we point out some specific actions that should be taken (clinical process design with evidence-based guidelines) and key performance failures (risk assessment for VTE and dose adjustment to patient characteristics when prescribing heparin) that should be addressed to lessen the burden of unnecessary morbidity and mortality they may be causing.

Acknowledgements

We are most grateful to the 22 hospitals which participated in the study and made their documents and data available for the analysis.

Funding

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Appendix: The ISEP group

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