Thromboprophylaxis with dabigatran leads to an increased incidence of wound leakage and an increased length of stay after total joint replacement

Since the introduction of the National Institute for Health and Care Excellence (NICE) guidelines on thromboprophylaxis and the use of extended thromboprophylaxis with new oral agents, there have been reports of complications arising as a result of their use. We have looked at the incidence of wound complications after the introduction of dabigatran for thromboprophylaxis in our unit.

We investigated the rate of venous thromboembolism and wound leakage in 1728 patients undergoing primary joint replacement, both before and after the introduction of dabigatran, and following its subsequent withdrawal from our unit.

We found that the use of dabigatran led to a significant increase in post-operative wound leakage (20% with dabigatran, 5% with a multimodal regimen; p < 0.001), which also resulted in an increased duration of hospital stay. The rate of thromboembolism in patients receiving dabigatran was higher (1.3%) than in those receiving the multimodal thromboprophylaxis regimen, including low molecular weight heparin as an inpatient and the extended use of aspirin (0.3%, p = 0.047). We have ceased the use of dabigatran for thromboprophylaxis in these patients.

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Patients and Methods
Dabigatran was used between 1 December 2010 and 31 May 2011. Following the manufacturer's instructions, patients received 110 mg four hours following surgery, and then 220 mg daily for 14 days after TKR and 28 days after THR. Patients over the age of 75, or who had renal impairment, or were taking verapamil or amiodarone, received a reduced dose of 75 mg post-operatively followed by 150 mg daily. Following a perceived increase in wound leakage, it was decided to perform a prospective audit on all patients who were admitted for TJR. Routine monitoring of the wounds began on 1 March 2011 and continued until dabigatran use ceased on 31 May 2011, after analysis of the data confirmed an increase in the rate of wound leakage. Information was collected prospectively on wound leakage, surgical site infection and post-operative length of stay by a surveillance nurse, who is employed to inspect all wounds following TJR using strict criteria to record wound infection.**7** To our knowledge, there are no such criteria by which to assess wound leakage, and therefore for our purposes we defined significant leakage as 'a wound requiring at least two dressing changes per day due to it being soaked through'. We attempted to limit the subjective nature of this method by having the inspection carried out in all patients by the same person, who was trained in wound surveillance. Patients were not discharged with leaking wounds and patients taking aspirin for other reasons only recommenced their aspirin therapy after discharge.

Accurate wound leakage data were not available before the change to dabigatran for comparison, as this had previously not been identified as an issue in the unit. Therefore, in order to confirm that dabigatran was responsible for the increase in wound problems, the audit was repeated again between 1 September and 30 November 2011, following the introduction of a revised thromboprophylaxis policy. This policy was introduced in June 2011 and was identical to that which had previously been in place at GH; it involved the use of dalteparin as an inpatient, with 5000 units at 6pm on the day of surgery and then daily until discharge, followed by extended prophylaxis as an outpatient, with aspirin 150 mg for six weeks.

In the United Hospitals of Leicester NHS Trust, patients investigated for symptomatic VTE are either screened through an outpatient DVT clinic or are admitted for investigation. Positive imaging is recorded on a region-wide hospital-acquired thromboembolism events database. This database is analysed by a specialist nurse, and all positive VTE events occurring within 90 days of hospital admission for TJR are identified. In order to avoid the risk of introducing a seasonal variation in the incidence of VTE, we examined two cohorts of patients to establish who had suffered a VTE after TJR; first, between December 2010 and May 2011 when dabigatran was in routine use, and second between December 2009 and May 2010 when the previous regimens from GH and LGH were in use (LMWH alone and LMWH with aspirin). A flowchart outlining the numbers, thromboprophylaxis regimens and time periods studied is shown in Figure 1.

As a final assessment of the impact of the various methods of chemical thromboprophylaxis we examined the length of stay of our patients. We compared the dabigatran cohort (March to May 2011) with the multimodal cohort (September to November 2011). Using an enhanced recovery programme, our Trust aims for a length of stay of less than four days following primary TJR.

**Statistical analysis.** Statistical analysis was carried out using SPSS v19.0 (IBM SPSS Statistics, Armonk, New York). Contingency tables and Fisher's Exact test were used to compare wound leakage rates and the causes of delayed discharge. Length of stay, defined as within 4 days or greater than 4 days, was examined using a one-tailed t test. Contingency tables and a chi-squared test were used to compare venous thromboembolism rates between the LMWH alone, LMWH + aspirin and dabigatran cohorts. In all cases a p-value of < 0.05 was considered significant.

**Results**

**Wound leakage.** A total of 92 THRs (92 patients) and 129 TKRs (129 patients) were performed between March and May 2011, all of whom received dabigatran. The mean
The mean age of these patients was 69 years (26 to 92); 229 were men and 302 were women. These results demonstrated a statistically significant difference in wound leakage rates with the use of dabigatran (p < 0.001, Fisher’s Exact test) (Table I).

VTE rates. During the first study period a total of 415 THRs and 457 TKRs were performed (872 TJRs); all of these patients received dabigatran. In the second study period a total of 856 TJRs were performed: 185 THRs and 366 TKRs using inpatient LMWH alone, and 164 THRs and 141 TKRs using inpatient LMWH and aspirin for six weeks as an outpatient (Table II). No patient died within 90 days of the operation in either group.

The reasons for the delayed discharge are summarised in Table V. Other reasons included patients not being fit for discharge for either medical or social reasons, or those requiring extra physiotherapy input to improve range of movement or mobility.

We compared the presence of a leaking wound alone against any patient with delayed discharge for other reasons. The dabigatran cohort were more likely to have a delayed discharge due to a leaking wound than for any other reason, compared with the multimodal cohort. This was statistically significant (p = 0.002, Fisher’s Exact test).

Table I. Incidence of leaking wounds on both thromboprophylaxis regimes

<table>
<thead>
<tr>
<th>Wound status</th>
<th>Dabigatran [n, %]</th>
<th>Multimodal - LMWH + aspirin [n, %]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaking wound</td>
<td>44 [20]</td>
<td>25 [5]</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>No wound leakage</td>
<td>175 [79]</td>
<td>500 [94]</td>
<td></td>
</tr>
<tr>
<td>Not recorded</td>
<td>2 [1]</td>
<td>6 [1]</td>
<td></td>
</tr>
</tbody>
</table>

Table II. Rates of venous thromboembolism following total joint arthroplasty by thromboprophylaxis regime

<table>
<thead>
<tr>
<th>Procedure/regime*</th>
<th>Thromboembolic event†</th>
<th>PE</th>
<th>AKDVT</th>
<th>BKDVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH alone (n = 185)</td>
<td>1.1% (n = 2)</td>
<td>1.1% (n = 2)</td>
<td>0.5% (n = 1)</td>
<td></td>
</tr>
<tr>
<td>LMWH + aspirin (n = 164)</td>
<td>0.6% (n = 1)</td>
<td>0%</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Dabigatran (n = 415)</td>
<td>0.5% (n = 2)</td>
<td>0.2% (n = 1)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Total knee replacement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH alone (n = 366)</td>
<td>0.3% (n = 1)</td>
<td>0.5% (n = 2)</td>
<td>1.4% (n = 5)</td>
<td></td>
</tr>
<tr>
<td>LMWH + aspirin (n = 141)</td>
<td>0%</td>
<td></td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Dabigatran (n = 457)</td>
<td>0.4% (n = 2)</td>
<td>0.4% (n = 2)</td>
<td>0.7% (n = 3)</td>
<td></td>
</tr>
<tr>
<td>All total joint replacements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMWH alone (n = 551)</td>
<td>0.5% (n = 3)</td>
<td>0.7% (n = 4)</td>
<td>1% (n = 6)</td>
<td></td>
</tr>
<tr>
<td>LMWH + aspirin (n = 305)</td>
<td>0.3% (n = 1)</td>
<td>0%</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Dabigatran (n = 872)</td>
<td>0.5% (n = 4)</td>
<td>0.3% (n = 3)</td>
<td>0.3% (n = 3)</td>
<td></td>
</tr>
</tbody>
</table>

* LMWH, low-molecular-weight heparin
† PE, pulmonary embolism; AKDVT, above knee DVT; BKDVT, below knee DVT

Table III. Rates of venous thromboembolism (VTE) in all total joint replacements by thromboprophylaxis regime

<table>
<thead>
<tr>
<th>Regime*</th>
<th>VTE (n, %)</th>
<th>No VTE (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH alone (n = 551)</td>
<td>13 (2.4)</td>
<td>538</td>
<td>p = 0.047</td>
</tr>
<tr>
<td>LMWH + aspirin (n = 305)</td>
<td>1 (0.3)</td>
<td>304</td>
<td></td>
</tr>
<tr>
<td>Dabigatran (n = 872)</td>
<td>11 (1.3)</td>
<td>861</td>
<td></td>
</tr>
</tbody>
</table>

* LMWH, low-molecular-weight heparin
Discussion

The most appropriate type of thromboprophylaxis for patients undergoing TJR remains controversial. The high rates of VTE seen in the early days of arthroplasty have decreased considerably, and the incidence of significant symptomatic VTE after TJR, with modern management, is probably about 2% to 3%. Factors contributing to this include shorter operating times, less blood loss, earlier mobilisation, good hydration and the increasing use of regional anaesthesia, in addition to changes in chemical and mechanical thromboprophylaxis.

Whether the increased use of potent chemical thromboprophylaxis has had a significant effect on rates of symptomatic VTE, however, remains uncertain. In 1996, it was noted that the fatal PE rate was lower than had previously been considered, even when no prophylaxis was used. In Scotland, separate guidelines were introduced in 1995 recommending the routine use of LMWH following TJR, but a ten-year review showed no significant change in the rate of VTE between 1992 and 2002. Furthermore, a study of > 200 000 patients before and after implementation of the NICE guidelines showed that despite a significant increase in the use of LWMH, there was a non-significant increase in 90-day VTE rates for patients undergoing THR, and no change for those undergoing TKR. This study also showed that there was a significant increase in the number of patients with heparin-induced thrombocytopenia, the mortality of which may be > 20%. A recent meta-analysis reported that potent anticoagulation does not reduce the overall mortality or the proportion of deaths due to PE.

Anticoagulation has its own complications. Tinzaparin has been linked with haematoma formation and sciatic nerve palsy following THR, and rivaroxaban has been associated with a significant increase in the number of patients returning to theatre within 30 days of TJR. Dabigatran has already been shown, in one small study, to increase wound leakage compared to LMWH, and the authors of this study suggested the inpatient use of LMWH followed by dabigatran as an outpatient. A meta-analysis of different VTE regimens in 2012 suggested that the use of rivaroxaban was associated with an increased bleeding tendency compared with enoxaparin, but that for dabigatran and enoxaparin the rates of bleeding were broadly similar. Sharrock et al, in a systematic review, showed that the use of potent anticoagulants had both a higher all-cause mortality and a higher non-fatal PE rate than a multimodal prophylaxis regimen.

The use of aspirin is not recommended by NICE, and until recently was not recommended by the ACCP in their equivalent guidelines. However, there are several recently published studies showing very low rates of symptomatic VTE and fatal PE when aspirin is used alone as chemical thromboprophylaxis, and it has the benefit of being inexpensive, protective in cardiovascular disease, and having an acceptable safety profile. In a meta-analysis, Brown showed that aspirin was equivalent to other forms of thromboprophylaxis in terms of VTE prevention, as well as being associated with a much lower risk of bleeding than any other form of anticoagulant. This is backed up by a recent study examining records from the National Joint Registry for England and Wales, although this study did demonstrate an increase in the rate of return to theatre with aspirin alone. In our study aspirin was used for extended thromboprophylaxis once the patient was discharged with a satisfactory wound, and had lower VTE rates than either dabigatran or LMWH alone, although all three regimens compare well with previously reported studies.

Our multimodal approach is evidence based. As well as the use of aspirin as described above, the risks for the development of VTE are routinely assessed. Anti-embolic stockings are used for six weeks post-operatively. Regional anaesthesia is used whenever possible, with early mobilisation. Our rates of VTE compared favourably with those using other thromboprophylactic regimens and are within the rates proposed as acceptable by the ACCP.

We accept that this study has limitations. Although we have included data on > 1700 patients, this is still a relatively small number when looking at rates of VTE. We did not set inclusion or exclusion criteria, as we included all patients undergoing TJR, so that although there may be discrepancies in the demographic make-up of the groups we feel this is unlikely, as there was no selection bias in the study. Although we are confident that we have captured all patients who suffered a symptomatic VTE following appro-
The use of dabigatran in our unit appeared to confer no advantage in terms of preventing VTE after TJR, but caused significant wound leakage with the associated inconvenience for patients, increased length of stay and theoretical increased risk of deep infection. We therefore discontinued the use of dabigatran and have subsequently confirmed a significant drop in wound leakage rates.

We felt compelled to implement the guidance laid down by NICE and were initially enthusiastic in our use of the new oral thromboprophylactic agents. However, our experience has shown that such guidance, although well meaning, does not always result in better outcomes for patients, and indeed may be associated with a significant risk of complications.

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References


