Prescribing Trends for Dabigatran etexilate in Primary Care

Abstract:
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A retrospective analysis (January 2010–June 2011) of the National General Medical Services Prescription Database showed that 1929 patients had received prescriptions for dabigatran etexilate. Of these, 42% had received it for longer than the licensed maximum duration (at that time) of 35 days. The Eastern Health board dabigatran etexilate cohort (n = 510) was analysed further. Here 64.3% had received the drug for longer than 35 days. Seventy-six (32.5%) of the 234 patients who had received more than 90 days of dabigatran etexilate had concurrently received rate/rhythm control therapy. Likewise, 47 (31%) of the 152 patients who had received more than 180 days of dabigatran etexilate had been co-prescribed rate/rhythm control therapy. It is possible that dabigatran etexilate had been prescribed for stroke prevention in atrial fibrillation.

Introduction
Dabigatran etexilate (Pradaxa®; Boehringer Ingelheim) is an oral pro-drug of dabigatran, which directly inhibits thrombin. It does not require coagulation monitoring during routine clinical practice. In 2008, it became licensed in Ireland for the primary prevention of venous thromboembolism (VTE) in adults who have undergone elective total hip replacement (THR) and for total knee-replacement (TKR). Treatment should be continued for 28 to 35 days after THR and for ten days after TKR.

The National Centre for Pharmacoeconomics (NCPE) has conducted a rigorous assessment of the cost-effectiveness of dabigatran etexilate compared to enoxaparin for this indication. It concluded that the drug could be considered cost-effective. In 2008, dabigatran etexilate received a positive reimbursement status under the Community Drug Schemes (CDS) in Ireland for this indication.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1 to 2% of the general population. Over 6 million Europeans suffer from AF and its prevalence is estimated to almost double in the next 50 years. It has significant drug, food and alcohol interactions. It is possible that dabigatran etexilate had been prescribed for stroke prevention in atrial fibrillation.

In 2009, the Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial was published. It involved over 18,000 patients with AF and one stroke risk factor. It compared dabigatran etexilate 110 mg or 150 mg twice daily (BD) (this dose comparison was double blind) with open label adjusted dose warfarin (INR 2–3). The primary outcome was stroke or systemic embolism (SE). After database lock on August 15th 2009, several additional primary efficacy and safety outcome events were identified and these are reported here. After a median of two years follow-up, 21% of participants had discontinued dabigatran etexilate. 17% had discontinued warfarin.

When compared with warfarin, dabigatran etexilate 150 mg BD significantly reduced the rate of stroke or SE (relative risk (RR) 0.65, 95% confidence interval (CI) 0.52 to 0.81). No significant difference in the same outcomes was found between the 110 mg BD dose and warfarin.

Compared to warfarin, dabigatran etexilate 110 mg BD significantly reduced the rate of major bleeding (RR 0.60, 95% CI 0.70 to 0.93). No significant difference was found between the 150 mg BD dose and warfarin. Both doses of dabigatran etexilate were associated with significantly fewer intracranial bleeds than warfarin. The 110mg BD dose was associated with significantly fewer lifethreatening bleeding events. No significant difference was found between the 150mg BD dose and warfarin. The 150 mg BD dose significantly increased gastrointestinal bleeding compared with both warfarin and the lower dose dabigatran etexilate.

Of note, the antithrombotic effect of dabigatran etexilate is not rapidly reversible at the time of acute bleeding. Both doses were associated with a non-significantly increased risk of myocardial infarction (MI) compared with warfarin. The mechanism of increased MI is unclear. It has been postulated that it might be due to a superior effect of warfarin in MI prevention.

At the time of this investigation, dabigatran etexilate was awaiting European marketing authorisation for the indication of SPAF in patients with and one or more stroke risk factors.

Methods
A retrospective analysis (January 2010–June 2011) of the National General Medical Services (GMS) Prescription Database (data anonymised) was performed (data beyond June 2011 was not available at the time of analysis). The GMS scheme is the largest of the CDS. In 2010 the number of persons eligible was 1,611,138 (about 40% of the population). The database contains information on brand name, strength, formulation, pack size, utilisation and cost of the drug as well as patient-specific information such as age and gender. Medicines are coded using the WHO Anatomical Therapeutic Chemical (ATC) system. We determined the monthly volume of prescriptions for dabigatran etexilate (ATC code B01AE07) which had been dispensed throughout Ireland and in each health-board. We identified the number of patients who had received the drug and their age and gender. For the purposes of this analysis, we assumed the minimum age-group if more than one age-group had been recorded for a patient. We ascertained the number of patients who had received the drug for longer than the maximum licensed duration (at that time) of 35 days (at the VTE prophylaxis dose). Where the drug had been dispensed for longer than 90 days, we co-prescribed of a recommended AF rate/rhythm control agent.
Results
From January 2010 to June 2011, 1929 GMS patients (female 51%) had received at least one prescription for dabigatran etexilate in Ireland. The total number of prescriptions dispensed was 4920. The disaggregated monthly analysis, shown in figure 1, reveals that the national number of prescriptions increased steadily from 82 in January 2010 to 555 in June 2011 (6.8 fold increase). The gross GMS expenditure on dabigatran etexilate was €773,995. Of the 1929 patients who had received dabigatran etexilate, 58% had received it for 35 days or less, 21% had received it for between 36 and 90 days, 8% had received 91 to 180 days and 13% had received more than 180 days of treatment. The number of patients in each age-group (per 100,000 GMS eligible patients) who had received the drug is shown in figure 2; 52% were 70 years and over.

Prescribing patterns in the eight health boards were investigated. Figure 1 illustrates that the increasing monthly volume of prescriptions seen in Ireland was driven by the Eastern health board (EHB). The gross expenditure in the EHB was €353,224. Figure 3 shows that the drug was prescribed for longer than 35 days in all health boards. The percentage of patients who received more than 35 days ranged from 16% of the Mid-Western to 70.5% of the North-Western health board. A number of patients in all health boards had received the drug for more than 180 days. The EHB dabigatran etexilate cohort (n=510) was chosen for further analysis because of the high number of patients who had received long-term treatment. Here, 64.5% had received the drug for longer than 35 days. In total, 78 (32.5%) of the 234 patients who had received more than 90 days of dabigatran etexilate had concurrently received rate/rhythm control therapy. Patients on rate/rhythm control therapy were significantly more likely to receive more than 90 days of dabigatran etexilate compared to patients not receiving rate/rhythm control therapy (OR= 17.9; 95%CI 13.6, 23.5).

Discussion
The volume of prescriptions dispensed, in Ireland, for dabigatran etexilate has increased progressively from January 2010 to June 2011. In the main, there has been an increase in the monthly volume of prescriptions across all health boards, but this increase has been most dramatic within the EHB. Our study indicates that the drug has been prescribed for longer than its maximum licensed duration (at that time) across all health boards. The median follow up in RE-LY was two years. Those patients receiving dabigatran etexilate in RE-LY however, were permitted to continue receiving it after trial completion as part of the rollover study, RELY-ABLE. The study is on-going. After nearly six decades in clinical practice, much is know about long term treatment with warfarin. Pertinent long term safety issues include the increased risk of MI with dabigatran etexilate compared to warfarin seen in RE-LY and the lack of an antidote to the anticoagulant effect of dabigatran etexilate. Indeed, according to this analysis, 52% of all prescriptions for dabigatran etexilate (per 100,000 GMS eligible

GMS=General Medical Services; EHB=Eastern health board; MWHB=Mid-western health board; SHB=Southern health board; WHB=Western health board; NWHB=North-western health board; SEHB=South-eastern health board; NEHB=North-eastern health board; MHB=Midlands health board.
patients) were dispensed to patients over 70 years. It has been recognised elsewhere that elderly patients are at a higher risk of bleeding secondary to anticoagulant therapy. This study suggests that dabigatran etexilate has been prescribed outside its license (at the time of the study). It is possible that such indications might include VTE treatment. In the EHB, patients on rate/rhythm control therapy were significantly more likely to receive more than 90 days of dabigatran etexilate compared to patients not receiving rate/rhythm control therapy (OR= 17.9; 95%CI 13.6, 23.5). This raises the question was dabigatran etexilate prescribed for SPAF in these patients? In contrast to the short course of anticoagulant required for the primary prevention of VTE events secondary to THR and TKR, SPAF requires chronic therapy. There are financial implications associated with prescribing drugs for purposes for which the cost-effectiveness from the HSE perspective has not yet been established. These implications are particularly important given the current economic climate. Globally, the anticoagulant market is projected to grow. The growth will be driven by demographics of the ageing population and by the approval of new agents. It has been predicted that the direct oral anticoagulants are likely to take more than half of the anticoagulant market share between 2010 and 2014. There are a number of limitations to this study. It is likely that estimates of the percentage of patients who received long term anticoagulant treatment are conservative; those individuals who continued on treatment beyond June 2011 will not have been captured. Indeed, analysis here revealed that 76% of patients in the EHB cohort who had received more than 90 days of dabigatran etexilate were still receiving this drug in June 2011. In using rate/rhythm control agents as a surrogate for AF, we may have missed patients not receiving such therapy. Likewise, these drugs may have been prescribed for alternative indications. In conclusion, there has been a steady increase in the uptake of dabigatran etexilate on the GMS scheme from January 2010 to June 2011. The drug has frequently been prescribed for longer than its licensed duration (at that time). There are efficacy, safety and budget impact concerns surrounding the use of drugs for unlicensed indications. Analysis has shown that rate/rhythm control agents used in AF have commonly been co-prescribed in those patients who have received dabigatran etexilate for longer than 90 days. It is possible that dabigatran etexilate has been prescribed for SPAF. At the time of this analysis, the NCPE had not reported on the cost-effectiveness of dabigatran etexilate for SPAF. Likewise the HSE had not confirmed a reimbursement decision regarding its use for SPAF. Given the current economic climate, it would appear appropriate that medicines are only reimbursed for those indications which have received positive reimbursement decisions.

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References