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The Efficacy and Safety of Dabigatran (Pradaxa) for *SPAF* among PPUKM patients (*ESPADA*)

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ABSTRACT

Background: Dabigatran is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. It was first introduced into Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) in July 2011. Dabigatran and warfarin are both used for stroke prevention in atrial fibrillation (SPAF) but there is lack of data on the efficacy and safety of dabigatran in an Asian population.

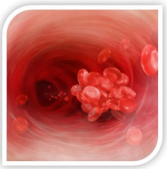
Aim: To investigate the efficacy and safety of dabigatran for SPAF amongst PPUKM patients. The compliance of PPUKM patients on dabigatran was also examined. The study also investigated the appropriateness of dabigatran prescribing amongst our medical practitioners.

Methods: This is a retrospective study where a data collection form was created to clerk the data of patients on dabigatran who were chosen via the Pharmacy System in PPUKM from July 2011 to May 2013. The data collection period started in August 2013 till October 2013. Correlation analysis were used using SPSS v20 with $p<0.05$ was considered statistically significant.

Results: Stroke occurred in 2 patients (3.4%) in the dabigatran 110mg twice daily group but none in the 150mg twice daily group, where dose was a significantly correlated with stroke events ($p = 0.05$). Bleeding of any degree occurred in 6 patients (10.1%, n = 59) on dabigatran, with HAS-BLED score being a significant positive predictor of bleeding ($p = 0.04$). Dyspepsia was the most common minor adverse event of dabigatran (8.5%), where the rate of adverse events is associated with discontinuation ($p < 0.01$). The overall compliance in this study was estimated to be 74.6% (15 defaulted, n = 59), which includes those with or without the discounted card. The compliance measured in terms of the discounted card system was 55.9% (15 defaulted, n = 34).

Conclusion: Our study showed that dabigatran 150mg twice daily is more effective than dabigatran 110mg twice daily in SPAF. Bleeding events was not observed to be higher in our study for dabigatran 150mg twice daily dosing. Adverse events (particularly gastrointestinal) affect discontinuation and compliance significantly. All patients in this study that are prescribed dabigatran 110mg twice daily dosing met the appropriate criteria.

INTRODUCTION



Dabigatran is a reversible direct thrombin inhibitor which prevents the development of thrombus. It is indicated for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

Dabigatran is also indicated for reduction of the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Table 1: Characteristics of patients included in the study

Characteristics	Dabigatran (n = 59)
Age	69.3 ± 9.99
Sex	
Male	27 (45.8%)
Female	32 (54.2%)
CHA_2DS_2-VASc score	3.92 ± 1.96 (high stroke risk)
0	0 (0%)
1	3 (5.1%)
≥ 2	56 (94.9%)
HASBLED score	1.64 ± 1.17 (moderate bleeding risk)
Medical history	
Diabetes mellitus	21 (35.6%)
Hypertension	50 (84.7%)
Dyslipidaemia	35 (59.3%)
Elderly	20 (33.9%)
Previous stroke/TIA	18 (30.5%)
Ischaemic heart disease	31 (52.5%)
Congestive heart failure	9 (15.3%)
Chronic kidney disease	4 (6.8%)
History of gastric bleeding	3 (5.1%)
Previously on warfarin	14 (23.7%)
Event (Efficacy outcome)	Dabigatran (n = 59)
Stroke	2 (3.4%)
Haemorrhagic	1 (1.7%)
Ischaemic	1 (1.7%)
Death from stroke	1 (1.7%)
Death from any other cause	1 (1.7%)

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RESULTS & DISCUSSIONS [Key Findings of *ESPADA* study]

Event (Safety outcome)	Dabigatran (n = 59)
Major bleeding	1 (1.7%)
Intracranial bleeding Patient had cerebellar haemorrhage with intraventricular extension and was on concomitant antiplatelet drugs	1 (1.7%)
Minor bleeding	5 (8.5%)
Hemoptysis	1 (1.7%)
Gastrointestinal (GI) bleeding	4 (6.8%)
Adverse event	Dabigatran (n = 59)
Dyspepsia	4 (8.5%)
Vomit	1 (1.7%)
Chest pain	1 (1.7%)
Nausea	1 (1.7%)
Bleeding	6 (10.1%)

Variable	Dabigatran 110 mg (n = 21)	Dabigatran 150 mg (n = 38)
Stroke events	2 (9.5%)	0 (0%)
Bleeding events	3 (14.3%)	3 (7.9%)
Major bleeding	1 (4.8%)	0 (0%)
Minor bleeding	2 (9.5%)	3 (7.9%)
Adverse events	4 (19.0%)	9 (23.7%)
Discontinuation events	3 (14.3%)	6 (15.8%)

% Patients free of stroke event after taking dabigatran for a duration of at least 3 months = **96.6%**

The **overall compliance** in this study was estimated at **74.6%** (n = 59) which includes those with or without the discounted card. However, the compliance rate measured in terms of the **discounted card system was only 55.9%** (n = 34). (15 defaulted and 19 compliant)

Ho et al (2012) in the Hong Kong study postulated that Asians in general could have been more prone to the gastrointestinal adverse events of dabigatran.

In our study, **5 patients (8.47%, n = 59) discontinued dabigatran** due to **adverse events** which were unrelated to bleeding, which includes 4 patients that had dyspepsia and 1 patient had vomiting. Similar trend were seen in the Hong Kong study which showed that the most common reason for discontinuation of dabigatran was dyspepsia (4.92%, n = 122)

Despite the convenience of lesser need for frequent monitoring and fewer dietary restrictions compared to warfarin, other studies and our current findings reflected that dabigatran cost of treatment, gastrointestinal adverse events are and compliance issues need to be addressed for a successful therapy.

Our findings show that there was a ***significant negative correlation*** between dabigatran dose and stroke incidence, indicating that **patients on a lower dabigatran dose were more likely to experience stroke events**.

CONCLUSIONS

Our study shows that dabigatran 150mg twice daily is more effective than dabigatrain 110mg twice daily in SPAF. Bleeding events was not observed to be higher in our study for Dabigatran 150mg twice daily dosing. Adverse events (particularly gastrointestinal) affect discontinuation and compliance significantly. All patients in this study that are prescribed dabigatran 110mg twice daily dosing met the appropriate criteria. It may be useful to compare dabigatran's efficacy and safety profile with other anticoagulants such as warfarin in order to help prescribers make a better choice of treatment.

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