A national audit on the utilisation and documentation of dabigatran checklist for patients initiated on dabigatran

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ABSTRACT

Background: Direct oral anticoagulants (DOACs) especially dabigatran, have gain popularity for their efficacy, fixed dosing and favourable safety profile. A dabigatran prescribing checklist has been prepared by the Ministry of Health, Malaysia (MOH) to ensure rational and safe prescribing of dabigatran. This study therefore aimed to audit the utilization and documentation of this checklist and use of dabigatran in the government healthcare facilities.

Methods: This is a nationwide retrospective audit on the documentation of Dabigatran Prescribing and Dispensing Checklist for a period of two years from January 2013 till December 2014. Data from these Dabigatran Checklists (indication, dose, duration, renal function and adverse drug reactions encountered) were extracted by the pharmacist at MOH healthcare facilities.

Results: A total of 52 out of 56 (92.9%) of MOH facilities complied to usage of checklist at their centres involving a total of 582 patients of which 569 (97.7%) patients were initiated on dabigatran for the approved indications. The recommended dose of dabigatran was used correctly in 501 (99.6%) of patients. Reason for switching to DOACs use was only documented in 76.7% (131/171) of patients. The most common reason for switching from warfarin was poor INR control (n=39), history of bleeding/overwarfarinisation (n=22) and unable to attend regular INR clinic (n=21).

There were 75 cases of adverse events reported. The most common adverse event reported were abdominal discomfort (n=10) followed by gum bleeding (n=9) and dizziness (n=5).
Conclusions: Compliance to the dabigatran check list was high with 70% of patients prescribed the appropriate dosing.

KEY WORDS:
Direct oral anticoagulant; dabigatran; Malaysia; checklist; compliance

INTRODUCTION

Direct oral anticoagulants (DOACs) have been introduced in recent years in place of warfarin in the prevention of thromboembolic events among high risk patients such as many of those with non-valvular atrial fibrillation. DOACs comprises of thrombin inhibitor (e.g., dabigatran) or factor Xa inhibitors (e.g., rivaroxaban, apixaban and edoxaban). Dabigatran, the first DOAC launched in Malaysia, was approved in 2010 for use in Ministry of Health (MOH) Malaysia healthcare facilities for the prevention of venous thromboembolism (VTE), total knee replacement (TKR) and total hip replacement (THR). Later, dabigatran was approved for stroke prevention in non-valvular atrial fibrillation. In 2015, it was also approved for pulmonary embolism (PE) and deep vein thrombosis (DVT).

Despite DOACs costs, these agents especially dabigatran, have achieved popularity among both patients and health care providers due to multiple reasons including their efficacy, ease of use such as fixed dosing and favourable safety profile including less bleeding rates.[1-6] Moreover, in contrast to warfarin, dabigatran does not require regular International Normalized Ratio (INR) monitoring and has fewer known drug or food interactions. In this perspective, prescribing dabigatran may seem less complex compared to warfarin. However, there are some contraindications, precautions and dose adjustments based on renal function to be considered before prescribing DOACs.[1-6] Pharmacy Practise and Development Division (PP&DD), Ministry of Health (MOH) of Malaysia introduced a checklist for dabigatran use known as Dabigatran Prescribing and Dispensing Checklist for all patients initiated with dabigatran at the MOH facilities. This was meant to ensure safer prescribing and monitoring at the healthcare facilities. Dabigatran Prescriber Checklist (which contains details on indication, dose, renal function, contraindications and precautions) were made compulsory to be filled up by hospitals and health clinics under MOH, Malaysia and send to pharmacists together with the prescription and followed by the Dabigatran Dispensing Checklist for patient counselling and follow-up counselling. To date, no audit on utilization of dabigatran checklist was documented in health care facilities in Malaysia.

We therefore aimed to audit the utilisation and documentation of this checklist and use of dabigatran in the MOH healthcare facilities.

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MATERIALS AND METHODS

Study Type and Design

This is a nationwide retrospective audit on the documentation of Dabigatran Prescribing and Dispensing Checklist for a period of two years from January 2013 till December 2014. Data from these Dabigatran Checklists (indication, dose, duration, renal function and ADR encountered) were extracted by the pharmacist from each of the MOH healthcare facility. Request for data extraction was obtained with the help of PP&DD, MOH with letter sent out to all the State Health Department and institutions of MOH requesting all the hospitals and health clinics to provide the researchers with the required data. Anonymised data as recorded in the checklist was extracted by the collectors at the respective sites. All data collected was keyed into an Excel Data Collection Form (EDCF). Site pharmacists entered the anonymised data into an EDCF. All the EDCFs was then compiled based on the respective state health facilities to PP&DD and compiled data was finally sent to the investigators for analysis.

Data collected in the anonymised EDCF comprises demographics of patients (age, gender, ethnicity), dabigatran usage indication and dosing, reasons for initiating dabigatran, previous use of warfarin, baseline renal function (determined based on creatinine clearance) and adverse events (AEs) as documented in the checklist with addition of AEs reported to the Malaysia Adverse Drug Reaction Committee (MADRAC). Data reported by facilities were verified with National Drug Usage and Costing Database. The Dabigatran related ADR reports were cross-checked with MADRAC. Reasons of discrepancies in data provided by facilities with the two verification sources were later confirmed by contacting the site directly for further clarification.

Audit Indicators

The *approved indication* for use of dabigatran at the initiation of the audit was stroke prevention in nonvalvular atrial fibrillation (SPAF) and venous thromboembolism prevention (VTE) in patients undergoing total hip replacement (THR) or total knee replacement (TKR).

The *approved dose* for dabigatran use for SPAF in Malaysia is 150mg twice daily and reduced dose of 110mg twice daily in special population patients. Special population patients are patients with reduced creatinine clearance of 30-50mls per minute, advanced age of 75 years and above, and concurrent use of amiodarone (an anti-arrhythmic drug), due to increased risk of major bleeding with amiodarone or other drugs such as fluconazole, rifampicin or phenytoin.[7] Dosing for VTE prevention in patients undergoing TKR or THR is 110mg once daily on the first day followed by 220mg once daily for 10 days in TKR and up to 35 days in THR. In the special population of patients with creatinine clearance of 30 to 50mls per minute, and advanced age of 75 years and above, first dose is reduced to 75mg once daily and then continues at 150mg once daily for similarly above mentioned duration.

In patients with creatinine clearance of less than 30 ml per minute, the use of dabigatran is absolutely contraindicated in Malaysia as stated in the checklist in the 'Garis Panduan Pemantauan Peggunaan Tablet Dabigatran / Rivaroxaban di Fasiliti' by the Ministry of Health Malaysia (online).

Corrected dose is when patient's dose is adjusted based on the age, creatinine clearance and interacting drugs. For e.g. in page 14 of the checklist as in the 'Garis Panduan Pemantauan Peggunaan Tablet Dabigatran / Rivaroxaban di Fasiliti' by the Ministry of Health Malaysia (online) in an 80 years old patient undergoing hip replacement surgery, dabigatran with a dose of 75mg on day one and 150mg daily for four to five weeks is given instead 110mg on day one and subsequently 220mg daily for the same duration of time.

Study Population

The study was conducted at all Ministry of Health (MOH) healthcare facilities which comprises of 139 hospitals and 145 health centres in Malaysia (a total of 284 facilities). Letter from PP&DD were send to all the facilities regardless of whether dabigatran was purchased and used at the facilities. All patients on dabigatran that completed at least one-year follow-up in these facilities were included in the study.

Statistical Analysis

Data was analysed using SPSS version 21. Continuous variable is reported as mean (standard deviation, SD). Categorical data is reported as number (percentage) and Chi Square test were used to compare difference between the approved use dabigatran and non-approved used of dabigatran.

RESULTS

Usage of Dabigatran Prescribing and Dispensing Checklist

A total 50 hospitals and two health clinics reported that Dabigatran Prescribing and Dispensing Checklist was used upon initiating patients on dabigatran, which was subsequently monitored during drug counselling. There were also four hospitals that did not comply with the usage of the checklist when initiating patients on dabigatran. Hence a total of 52 out of 56 (92.9%) of MOH facilities that purchased dabigatran complied with usage of checklist at their centres as shown in Figure 1.

Demographic of Patients Monitored using Checklist

There were a total of 582 patients on dabigatran that was monitored using this checklist. The average age of patients was 67.2 (SD 11.0) years. There almost equal number of male and female patients with males comprising 294 (50.3%) of the total number of patients monitored. Majority of the patients were Malays, 282 (48.2%) followed by Chinese 220 (37.6%), Indian 44 (7.5%) and Iban 9 (1.5%), corresponding very much to Malaysia's own ethnic group composition.

Dabigatran Use

Patients that were oral anticoagulant naïve totalled 303 (52.1%). 171 (29.4%) patients were previously on warfarin and only 1 patient was switched from rivaroxaban to dabigatran. The rest of patient's data on previous use of warfarin was not available. Reason for switching to DOAC use was only documented in 76.7% (131/171) of patients. The most common reason for switching from warfarin was poor

Table I: Reasons for Switching from Warfarin to Dabigatran as Documented in The Prescriber's Checklist (N=131)

Reasons for Switching	Patients
Poor INR Control	39
History of Bleeding with warfarin and Overwarfarinisation - Overwarfarinisation (8) - Intracranial bleeding (3) - Non-specific bleeding (4) - Upper gastrointestinal bleed (3) - Heamaturia (2) - Heamotypsis (1) - Knee hematoma (1)	22
Unable to Attend INR Clinic - Non-specific reason (6) - Poor social support (3) - Bedbound (2) - Job constraints (1) - Finance constrains (1)	21
Non-Compliance Defaulted clinic visits (3) Non-compliance to dietary advise (1)	17
Referral from Other Centers National Heart Center (5) Private medical facilities (4)	9
Doctor's Preferences	7
Contraindication to warfarin Recent CVA (3) Recent surgery (3)	6
Refused warfarin	4
Adverse drug reaction Insomnia (1), Nausea, vomiting & joint pain (1) Intolerant (1)	3
Others High bleeding risk (1) severe OA (1) Drug interaction with allopurinol (1)	3

Table II: Adverse Events as Documented in the Dispensing Checklist (Not Reported to MADRAC) and Reported Adverse Events to MADRAC from 2013 – 2014 (N=75)

Adverse Events Documented in Checklist	Total	Adverse Events Reported to MADRAC	Total
Bleeding Adverse Event	20	Bleeding Adverse Event	12
Gum bleeding	9	Gastrointestinal bleeding	4
Heamaturia	4	Hematuria	3
Brusing	2	Gum bleeding	1
Bleeding (not specified)	2	Hemorrhagic Stroke	1
Tarry Stool	2	Rectal bleeding	1
Heamoptysis	1	Bruising	1
		Prolonged prothrombin time	1
Non-Bleeding Adverse Event	**21**	**Non-Bleeding Adverse Event**	**22**
Abdominal discomfort	10	Abdominal discomfort	8
Dizziness	5	Itch and rash	6
Ankle swelling	1	Skin tear	1
Hair Loss	1	Skin thinning	1
Reduced creatinine clearance	1	Eye irritation	1
Thrombocytopenia	1	Backache	1
Fatigue	1	Drowsy	1
Itch	1	Headache	1
		Chest pain	1
		Shortness of breath	1
Total	**41**	**Total**	**34**

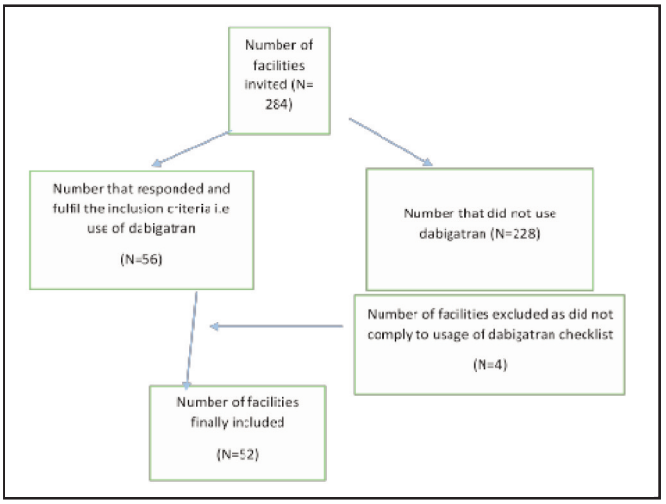

Fig. 1: Flow chart showing on how the health facilities were invited and finally recruited into this study.

INR control (n=39), history of bleeding / overwarfarinisation (n=22) and unable to attend regular INR clinic issues (n=21). Other reasons for switching to dabigatran are as stated in Table I.

Approved Indication

A total of 569 (97.7%) patients were initiated on dabigatran for the approved indications as stated stated above, i.e., stroke prevention in nonvalvular atrial fibrillation (SPAF) and venous thromboembolism prevention (VTE) in patients undergoing total hip replacement (THR) or total knee replacement (TKR). One patient was wrongly initiated on a totally contraindicated indication of stroke prevention in valvular heart disease, of which action was taken to stop the use of drug in this patient. The rest of the patients were using dabigatran for indications that were not yet approved in MOH at the time of audit, including treatment of seven patients with deep vein thrombosis (1.2%) and two patients with pulmonary embolism (0.4%).

Use of Approved Dose

The recommended dose of dabigatran was used correctly in 501(99.6%) of patients. Only 2 patients were on not approved doses of 150mg once daily for stroke prevention in patients with non-valvular atrial fibrillation (SPAF). Fifty-four patients that were on dabigatran for prevention of VTE in TKR or THR were on approved doses of either 220mg once daily or 150mg once daily maintenance dose (81.8%).

When the dose of dabigatran was corrected based on age, creatinine clearance, previous bleeding events and concomitant use of amiodarone, it was found that only 404 (71.0%) of the patients had correct dosing for either SPAF or prevention of VTE in TKR or THR. Most of the incorrect dosing were noted to be due to the dose not being adjusted to age or/and creatinine clearance (75 patients, 13.4%). Another reason for incorrect dosing were use of lower than recommended dosing despite of the absence of potential drug-drug interaction or presumed bleeding risk, which was found in 73 (12.6%) of the patients.

There were four patients (0.7%) that were started on dabigatran despite their creatinine clearance being lower than 30ml per min in the last six months. In Malaysia, as stated earlier dabigatran is not approved to be used in patients with creatinine clearance lower than 30ml per min. Dabigatran was also given erroneously as twice daily dosing in another four patients (5%) that were on dabigatran for the prevention of VTE in TKR or THR. There were nine patients in whom correct dosing could not be determined due to missing data. Patients on correct dosing for SPAF was significantly higher (365/494 patients, 73.9%) than patients on correct dosage of dabigatran for the prevention of VTE in TKR o THR (39/66 patients, 59.1%) with the difference being statistically significant (p=0.012, χ^2=6.34).

Baseline Renal Function and Adverse Events (AEs) Monitoring

Baseline renal function was only done in 469 (80.2%) of patients initiated with dabigatran. There was no difference between baseline renal function monitoring among patients with either AF or post THR/TKR patients (p = 0.24, χ^2= 1.38).

Based on the dispensing checklist, 41 patients complained of AEs during the follow up by pharmacist. The most common adverse events reported were abdominal discomfort (n=10) followed by gum bleeding (n=9) and dizziness (n=5). Once the patients developed bleeding, they were usually admitted for further management. Other bleeding related events documented were haematuria (n=4), black tarry stools (n=2) and haemoptysis (n=1). Other AEs document in checklist are listed in Table II. At the same period of time, 29 types of AE were submitted to MADRAC, accounting to a total of 34 patients. The most common reported AEs were abdominal related (n=8) complaints followed by gastrointestinal bleeding (n=4). After cross-checking both data sources for patient's age, gender and site of reports, we found that none of the AEs reported at MADRAC and the checklists were similar. Pharmacist at the study sites also were contacted and confirmed that they did not report any of the AEs that they documented in the checklist to MADRAC. Therefore, there were a total of 75 cases of AEs for dabigatran documented or reported from 2013 till 2014 without any duplication of data.

DISCUSSION

Based on this audit project, the Dabigatran Prescribing and Dispensing Checklist implemented by PP&DD is used in most of the MOH healthcare facilities using dabigatran. It is possible to incorporate the checklist both in clinical practice as well as a monitoring tool for patients on dabigatran provided information filled are accurate and complete.

Many other studies conducted previously retrospectively and prospectively revealed that dabigatran has been used for non-approved indications in about 5-10% percentage of patients although the rates in this study was lower at 2.3%.[8-13] The reason could be that the prescription for dabigatran has to be counter signed by a specialist or consultant in the relevant disciplines in the Malaysian setting, mainly cardiologists, thereby reducing unnecessary or wrong prescription.

Incorrect dosing and dose not adjusted for age, creatinine clearance, bleeding risks and concomitant drug use, were found to be as high as 5-33% in retrospective studies and in prospective studies incorrect dosing were as high as 19-42%, compared to this study finding of 29.9 %, indicating that more training need to be given to the prescriber regarding the correct prescribing doses.[9-11,13-15] Despite very clear dosing guidelines issued by the manufacturer for DOAC, incorrect dosing prescription for dabigatran is still prevalent. Dosing of DOAC based on age of the patients and medical background is important to provide best possible safe care to patients in ensuring efficacy as well as reducing risk of unwanted side effects, including non-reversible torrential haemorrhage especially intracranial bleeds. This is especially important as higher dosing was associated with increased all-cause mortality and lower than recommended dosing were associated with increased cardiovascular hospitalisation in patients with AF due to under coagulation.[16]

In this study, it was found that incorrect dosing was higher in patients receiving DOAC for VTE prophylaxis. Dosing difference in AF and VTE prophylaxis can sometimes confuse junior doctors who usually help in determining the dabigatran dose as VTE prophylaxis in post TKR or THR surgery patients. Methods to simplify in-house protocols and introducing dabigatran dosing charts in both clinics and hospitals can be implemented to improve prescription rates with the correct accurate dosing.[17] Active pharmacist intervention by correcting the dosing based on the prescriber checklist can improve the rate of correct dabigatran dosage besides reminding the specialist or consultant that counter signs the prescription to verify the dosing with the recommended dosing guidelines. In this study pharmacists when called for incorrect dosing claimed that prescriber insisted on the dose despite correct dosing recommendation especially the lower dosing of 110mg twice daily for SPAF. Ho JCS et al. based on his study in Hong Kong also reported that this dose is preferred among Asian prescribers due to preference for lower anticoagulation status for Asian patients.[18] However, the checklist has been an important mode of communication for pharmaceutical interaction between the pharmacists and the prescribers. Possibly there is an element of physician's inertia which need to be modified to ensure the best interests of the patients.

A retrospective cohort study of 500 patients on dabigatran from 2009 to 2013 was conducted at the National Heart Institute, Malaysia previously. A total of 70 ADRs was reported in this study with 27 AEs being associated with bleeding while 43 events were non-bleeding related AEs. The most common AE reported in that paper also was gastrointestinal related AEs, similar to our study as almost all drugs invariably will cause gastrointestinal related AEs.[19]

In this audit, there were 61 patients among 582 patients on dabigatran presenting with AEs related to dabigatran over a period of two years. Therefore, it can be estimated that about 10.5% of patients on dabigatran experiences AEs in Malaysia every 2 years. Half of it are bleeding related AEs. The rate of AEs related with dabigatran only an arbitrary estimate. This is because, the documented AEs are often not reported even though compulsory notification to MADRAC is a must as demonstrated in this study. Hence, the value is possibly an underestimation. In the RELY study, total bleeding rates among Asian patients were 11.71% and 15.27% for dabigatran 110mg and 150mg respectively.[20] The lower rate in our study could be also due to the problems due to underestimation and under reporting.

It was found that all the AEs reported at the healthcare facilities were not forwarded to MADRAC. Therefore, MADRAC has to come out with stiffer penalties for non-reporting of these AEs and ADRs as dabigatran is an expensive drug and represents a huge burden to the Malaysian public and therefore the prescription should only be continued if its morbidity and/or mortality rates remains lower than warfarin and the prescribers are able to follow the guidelines on its' prescribing.

STRENGTHS AND LIMITATIONS

The strength of this study remains in the fact that it was conducted in all MOH facilities, hence representing the practice of the prescribing pattern of dabigatran in the MOH healthcare facilities in Malaysia.

Considering that it is a retrospective audit, hence incomplete data extraction is unavoidable. Classification of inappropriate use of dabigatran was based on approved indication and dosing recommendation by MOH. Meanwhile incorrect dabigatran prescribing is based on the local package insert of dabigatran. Therefore, comparison of the correct prescribing practice of dabigatran was not possible in this study.

CONCLUSION

Dabigatran Prescribing and Dispensing checklist is utilized correctly in a large percentage of MOH healthcare facilities i.e., >90% and can be used to monitor patients on dabigatran in regards to indication, accurate dosing and monitoring of AEs. Patients on correct dosing of dabigatran are around 70% and correct dosing is more prevalent in the patients requiring dabigatran for SPAF due to simpler prescribing dosage. However, serum creatinine documentation in the checklist is only 80% and needs to be made a mandatory requirement before prescribing dabigatran. Another viable suggestion will be a plan to re-audit in six to twelve months to monitor for improvement.

Adherence to the checklist by both the prescriber and pharmacists will ensure the problems identified in this audit won't reoccur such as inaccurate dosing or wrong indications as the checklist is very comprehensive and includes essential elements such as patient counselling, dose modifications in patients with chronic kidney disease and accurate dosing according to specific indications, among others. Perhaps the implementation of a master training course involving a few prescribers and pharmacists from each of the health facilities would be a start. They can then disseminate the knowledge on proper documentation and usage of the checklist.

Another viable suggestion will be a plan to re-audit in six to twelve months to monitor for improvement.

The differing dosing regimen for atrial fibrillation and venous thromboembolism as well as the need for dose adjustment for age and renal function had created suboptimal dosing in a significant proportion of study subjects. Therefore, the use of a simplified dosing workflow would help to remedy the problem highlighted with suboptimal dosing.

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ETHICAL CONSIDERATION

This study has been registered with National Medical Research Registry (NMRR) and obtained ethics approval from the Medical Research Ethics Committee (MREC). The ethics approval number is NMRR-16-2306-31225, and while the publication approval number KKM/NIHSEC/800-4/4/1 Jld. 49(1).

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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