

## Original Article

# Non-vitamin K Oral Anticoagulant prescription for stroke prevention in atrial fibrillation : Perceptions among physicians in a metropolis

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**Objective :** To study the trend in use of the NOACs amongst the physicians and also to explore the reasons behind the choice of a particular NOAC.

**Methods :** An on-line survey was conducted amongst the physicians of a metropolis, based on an arbitrary case scenario

**Results :** Dabigatran was found to be preferred by majority of physicians. Inappropriate low dosing was more common with dabigatran and rivaroxaban. Of the Dabigatran brands, the original research brand was mostly preferred. Efficacy and safety were the predominantly cited reasons for preferring one NOAC over the others. Although not statistically significant, there were some differences in prescription habit for NOACs between the cardiologists and internists.

**Conclusion :** Dabigatran was the NOAC most preferred by the physicians practising in Kolkata. The reason for choosing one NOAC over the others was largely driven by perceived efficacy and safety, rather than cost or availability of an antidote.

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**Key words :** Atrial fibrillation, Kolkata, NOAC, prescription preference, physicians, stroke, survey.

Over the last decade, vitamin K antagonist (VKA) is being gradually replaced by non-VKA oral anticoagulant (NOAC) as the oral anticoagulant of choice in nonvalvular atrial fibrillation (NVAF). This trend is more obvious in the urban setting compared to rural, and in private sector compared to the government-run health sectors. The reason for this discrepancy is likely economical, as the NOACs are considerably more costly than VKA. The complexity of VKA use and the need for regular blood tests cannot fully overcome the financial constraints to the use of NOACs<sup>1</sup>.

However, the introduction of generic dabigatran in the Indian market has changed the scenario. Many more people now can afford these cheaper generic drugs. On the other hand there are issues of compliance with a single daily dose of rivaroxaban versus the twice daily doses of dabigatran and apixaban. When prescribing, clinicians also consider the real or perceived side effects of NOACs such as higher incidence of myocardial infarction and gastrointestinal bleeding with dabigatran, and less thromboembolic protection with the lower dose of

### Editor's Comment :

- The survey brought out useful information on the practice of use of novel oral anticoagulants in atrial fibrillation by physicians practicing in and around Kolkata.
- It showed that of the four considerations to choose one NOAC over others, namely, efficacy, safety, cost and availability of antidotes, the first two were prime factors.
- Dabigatran was the NOAC of choice as revealed in this survey.
- Original brand molecule was still preferred over cheaper generic versions.

apixaban. The high prescription of lower doses of NOACs as compared to the doses used in the setting of the clinical trials with NOAC, is also an issue of concern.

We conducted a survey in the metropolitan city of Kolkata to find out the trend in use of the NOACs amongst the internists, Cardiologists and Neurologists and also to explore the reasons behind the choice of a particular NOAC.

### MATERIALS AND METHODS

#### Survey Questionnaire :

A short and simple survey was designed to test physicians' perception and mindset regarding prescription of NOACs [Fig1]. The survey consisted of three questions set in reference to a given clinical

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**A 69 year old man with hypertension and diabetes presents with AF. No other comorbidity. No history of bleeding. He is on Telmisartan and Metformin. Renal and liver functions are normal. CHA<sub>2</sub>DS<sub>2</sub>VaSc score 3, HAS-BLED score 2.**

**Q1. Which of the following NOACS will you choose and at what dosage?**

- Dabigatran 150 mg BD
- Dabigatran 110 mg BD
- Apixaban 5 mg BD
- Apixaban 2.5 mg BD
- Rivaroxaban 20 mg OD
- Rivaroxaban 15 mg OD
- Generic Dabigatran 150 mg BD
- Generic Dabigatran 110 mg BD

**Q2. What is the most important reason for your choice?**

- Effectiveness
- Safety
- Compliance
- Cost

**Q3. What describes you best?**

- Cardiologist
- Neurologist
- Internist

**Fig 1** — Clinical scenario and the survey questionnaire

scenario. The first question was designed to test which of the three available NOACs (apixaban, dabigatran or rivaroxaban) would be of choice to a physician in a clinical situation where any of the three NOACs could be used. Dabigatran was further divided into the branded and the generic types that were available. For each NOAC, there was the option to use the higher or the lower dose. The second question was about the reason for the choice. The third question was to determine whether the physician was a cardiologist, neurologist or internist. Only one answer was allowed for each question stem and the participant was required to choose the answer from a drop-down menu.

**Subjects :**

Requests for survey were sent to 150 physicians who are practicing in Kolkata. Physicians were chosen at random from the directories of the Cardiological Society of India and the Association of Physicians of India (seventy-five from each of the directories). Only Cardiologists, Neurologists and Internists (with MD qualification) were chosen for the survey.

**Methodology :**

The software ‘Survey Monkey’ was used to get the response from the participants. Only first 100 responses were planned to be considered as per the existing software capability. The survey was anonymous and was designed so that it cannot be taken more than once by a participant.

**Analysis :**

The result was further analysed by the software. The higher dose of the chosen NOAC was considered to be the appropriate dose in the given situation as there was no reason to prefer the lower dose. Chi-square test was used to assess statistical significance.

**RESULTS**

**Responders :**

Of 150 surveys sent, 112 responded. The first 100 of the responses were considered. 18 responses were incomplete and therefore excluded from the study. Out of 82 respondent physicians who were considered for the study, 45 (54.9%) were Cardiologist, 4 (4.9%) were Neurologist and 33 (40.2%) were Internists

**Results, all Specialties Combined :**

The choice and the dose of NOAC all specialty combined, is given in Table1. Of the 82 respondents, dabigatran was preferred by 58 (70.7%), apixaban 13 (15.9%) and rivaroxaban 11 (13.4%) [Fig 2]. This greater preference for dabigatran among physicians compared to apixaban and rivaroxaban was statistically significant (p<0.00001).

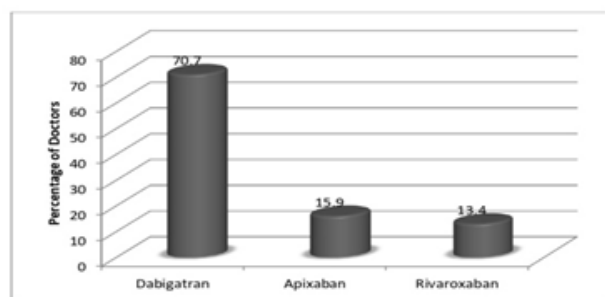
The higher dose of any NOAC (the appropriate dose in this case) was considered by 48 (58.5%) of 82 respondents. The inappropriate lower dose in this case was selected by 28 (48.3%) out of 58 of dabigatran prescribers, 1 (7.7%) of 13 apixaban prescribers and 5 (45.5%) of 11 rivaroxaban prescribers.

Of the 58 physicians preferring dabigatran, the generic dabigatran were considered only by 9 (15.5%) physicians.

The reasons for preference among all specialty

**Table 1** — Overall choice of NOAC and dosage (NOAC= Non-vitamin K oral anticoagulant)

Dosage of NOAC	Number (n=82)	Percent
Dabigatran 150 mg twice daily	23	28.0
Dabigatran 110 mg twice daily	26	31.7
Apixaban 5 mg twice daily	12	14.6
Apixaban 2.5 mg twice daily	1	1.2
Rivaroxaban 20 mg once daily	6	7.3
Rivaroxaban 15 mg once daily	5	6.0
Generic Dabigatran 150 mg twice daily	7	8.5
Generic Dabigatran 110 mg twice daily	2	2.4



**Fig 2** — Percentage of physicians of all specialties choosing a particular NOAC

combined, were cited as effectiveness by 28 (34.1%), safety 25 (30.5%), better compliance 10(12.2%), cost 10 (12.2%) and availability of antidote 9 (11%) [Table 2]. This difference between efficacy and safety on one hand and compliance, cost and antidote availability on the other hand, appeared statistically significant ( $p < 0.00001$ ).

**Results Filtered as per the Specialties :**

When the data were filtered as per the specialties, among the cardiologist [Table 3], (n=45), thirty-two (71.1%) opted for dabigatran, 5 (11.1%) for apixaban and 8 (17.8%) for rivaroxaban. Twenty-nine (64.4%) considered the appropriate dosage. Of the 32 who considered dabigatran, only 6 (18.8%) preferred generic dabigatran. The reason for preference was cited as effectiveness by 17 (37.8%), safety 10 (22.2%), better compliance 5(11.1%), cost 8 (17.8%) and availability of antidote 5 (11.1%).

Among the Internists [Table4](n=33), 24(72.7%) opted for dabigatran, 7 (21.2%) for apixaban and 2

**Table 4** — Choice of NOAC and dosage among Internists (NOAC= Non-vitamin K oral anticoagulant)

Dosage of NOAC	Number (n=33)	Percent
Dabigatran 150 mg twice daily	7	21.2
Dabigatran 110 mg twice daily	14	42.4
Apixaban 5 mg twice daily	6	18.2
Apixaban 2.5 mg twice daily	1	3.0
Rivaroxaban 20 mg once daily	1	3.0
Rivaroxaban 15 mg once daily	1	3.0
Generic Dabigatran 150 mg twice daily	2	6.1
Generic Dabigatran 110 mg twice daily	1	3.0

(6.1%) for rivaroxaban. Fourteen (42.4%) considered the appropriate dosage. Of the 24 who considered dabigatran, 3 (12.5%) preferred generic dabigatran. The reason for preference was cited as effectiveness by 9 (27.3%), safety 15 (45.5%), compliance 4(12.1%), cost 2 (6.1%) and availability of antidote 3 (9.1%).

Among the Neurologist (n=4), 2(50%) opted for dabigatran, 1 (25%) for apixaban and 1 (25%) for rivaroxaban]. Three (75%) considered the appropriate dosage. Of the 2 who considered dabigatran, none preferred generic dabigatran. The reason for preference was cited as effectiveness by 2 (50%), safety 0 (0%), compliance 1(25%), cost 0 (0%) and availability of antidote 1 (25%).

**DISCUSSION**

To the best of our knowledge this is the first survey of physicians' perception regarding NOAC prescription in Eastern India. Several interesting findings came out of our survey.

Firstly, dabigatran is the clear first choice by majority of clinicians. Dabigatran, both the branded and the generic versions together, was the choice of 70.7% of responders. Apixaban was chosen by 15.9% and rivaroxaban by 13.4%. At first thought it may appear that this preference for dabigatran is due to the availability of the cheaper generic version of dabigatran and that it is the only NOAC which has got an antidote. But the survey reveals a completely different story.

Of the 58 dabigatran prescribers, 84.5% preferred the more expensive branded molecule and only 15.5% opted for the cheaper generic version. Therefore cost was not prime consideration for the choice as branded drug prices were similar for all three NOACS. Cost was a consideration for only 12.2% of clinicians.

Also, the reason for the choice was not the availability of antidote (only 11%), but rather efficacy or safety. Why dabigatran scored over the other two NOACS in terms of safety or efficacy could not be explored by this survey as that was beyond the scope of our study, but this opens up an interesting aspect of physicians' prescribing habits and the factors that

**Table 2** — Most important reason for the choice of a particular Non-vitamin K oral anticoagulant

	Number (n=82)	Percent
Effectiveness	28	34.1
Safety	25	30.5
Compliance	10	12.2
Cost	10	12.2
Availability of antidote	9	11

**Table 3** — Choice of NOAC and dosage among Cardiologists (NOAC= Non-vitamin K oral anticoagulant)

Dosage of NOAC	Number (n=45)	Percent
Dabigatran 150 mg twice daily	15	33.3
Dabigatran 110 mg twice daily	11	24.4
Apixaban 5 mg twice daily	5	11.1
Apixaban 2.5 mg twice daily	0	0
Rivaroxaban 20 mg once daily	4	8.9
Rivaroxaban 15 mg once daily	4	8.9
Generic Dabigatran 150 mg twice daily	5	11.1
Generic Dabigatran 110 mg twice daily	1	2.2

influence such habits. Perhaps physicians' familiarity with dabigatran may be an important factor in their decision making process, as dabigatran has been available in the market few years ahead of the other two NOACs.

In the pioneering trials of the three NOACs, namely, RE-LY<sup>2</sup>, ROCKET-AF<sup>3</sup> and ARISTOTLE<sup>4</sup>, there was hardly any difference with the outcome when used in proper dosing. There was initial concern about dabigatran causing more acute myocardial infarction which was later refuted by large registry data mostly from the USA. Incidence of GI bleed is higher with dabigatran and rivaroxaban compared to apixaban<sup>5</sup>. Also, as dabigatran is extensively excreted via urine, its use is to be carefully monitored below creatinine clearance (CrCl) of 50 ml/min and it is not recommended below of 30 ml/min. Rivaroxaban and apixaban, on the other hand, has less renal excretion and can safely be used upto CrCL 30 ml/min or even lower. Thus, there is no evidence to suggest that dabigatran is safer than the other NOACs.

It is perceived that rivaroxaban improves compliance because of its once daily dosing schedule. Across the speciality of medical practice, compliance is an important issue and there are enough data to show that compliance is inversely proportional to the number of pills. But in our survey, only 12.2% of clinicians considered this as an important issue for choice of a NOAC. One explanation may be that they were allowed to give only one response, and efficacy and side effects of drugs took priority over compliance in their decision making process. An all-choice option with relative scoring might have revealed the compliance issue as also an important co-factor while choosing a drug.

Another interesting observation was the difference of choice between the Cardiologists and the Internists. We do not consider the opinions of the Neurologists separately as they were only four out of a total of 82 prescribers. Though the trend is same in favour of dabigatran, the differences are also interesting. Of the Cardiologists, 71.1% chose Dabigatran, 11.1% apixaban and 17.8% rivaroxaban. For the internists the corresponding values were 72.7%, 21.2% and 6.1%. Although not statistically significant ( $p=0.19$ ), more Cardiologists seem to prefer rivaroxaban over apixaban and the reverse is true for the internists. Also, among the physicians prescribing dabigatran, the generic version was more often chosen by the Cardiologists (18.8% of all dabigatran prescription by Cardiologists) compared to the Internists (12.5% of all dabigatran prescriptions). There is no obvious

explanation for this. We did not explore the socioeconomic status (SES) of the patients that the clinicians see in their practice, though it is unlikely to be a big difference between the SES of patients seen by Cardiologists and the Internists.

The inappropriate use of the lower dose of a NOAC is a problem all over the world. Real world data<sup>5,6</sup> show that the use of lower dose (15mg) of rivaroxaban was 20.1% and that for apixaban (2.5 mg) was 26.9%. On the contrary, in our study the lower dose of rivaroxaban was prescribed by 45.5% of rivaroxaban prescribers and the lower dose of apixaban was prescribed by 7.7% of apixaban prescribers. Moreover, for the given scenario 35.6% of Cardiologists preferred the low dose of dabigatran, whereas among internists it was 57.6%. For rivaroxaban, 50% of both Cardiologists and Internists used low dose. For apixaban, no Cardiologist preferred the low dose, but 14% of Internists prescribing apixaban preferred the low dose. It appears that the Internists are less likely to use the standard full dose of the NOACs compared to the cardiologists. This may be because the internists tend to be more concerned with the side effects of their treatment as reflected in our survey where 45.5% of internists cited safety as the main consideration, whereas only 22.2% of cardiologists did so. It highlights the need of more exposure of the internists to the need for appropriate dosing of the NOACs as the inappropriate low dose may not give the patients the added benefit of NOAC over VKA<sup>7,8</sup>.

#### Limitations of the Study :

We studied the mindset of physicians when prescribing NOACs. Their actual prescribing pattern may differ depending on individual circumstances, where the cost of NOAC and patients' preference about compliance and availability of antidotes may modify their prescription. A larger sample size could have also made a difference to our results.

#### Conclusion :

Dabigatran was the NOAC most preferred by the physicians practising in Kolkata. The reason for choosing one NOAC over the others was largely driven by perceived efficacy and safety, rather than cost or availability of an antidote. Some differences exist between the practice of the Cardiologists and the Internists. The survey also opens up the issue of inadequate or inappropriate usage of the NOACs, which should be addressed for improving quality of patient care.

#### What is Already Known?

It is known that prescriptions for NOAC are gradually

increasing in the recent years. The mindset of doctors while prescribing NOAC in the real world is not known

**What this Survey Adds ?**

Dabigatran is the most preferred NOAC among the physicians of Kolkata. The reason for choosing one NOAC over others was largely driven by perceived efficacy and safety, rather than consideration for compliance, cost or availability of an antidote. Inappropriate dosage of NOAC prescription is a matter of concern among both Internists and Cardiologists.

**Conflict of Interest : None**

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