Original Article

Bridging to Warfarin with Apixaban versus Conventional Heparin: An Open Label, Pilot, Randomized Controlled Trial

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Objective: Despite of non-vitamin K antagonist oral anticoagulants (NOACs) is a preferred oral anticoagulant but in limited-resource country, warfarin still be first line drug. Bridging parenteral anticoagulant with warfarin is required in particular circumstances. Since a NOACs contains rapid onset and steady activity characteristics, then the use of NOACs instead of traditional parenteral anticoagulant to bridging with warfarin is intriguing.

Materials and Methods: We conducted an open-label, randomized, pilot study in patients with atrial fibrillation (AF) and thromboembolism who considerably required bridging therapy to apixaban (5 mg orally bid) or enoxaparin (1 mg/kg subcutaneously every 12 hours) bridging to warfarin. The dose of warfarin was adjusted every 3 to 5 days to achieve the goal of international normalized ratio (INR) between 2 to 3 before stopping the bridging. The primary outcome was bleeding complication classified as the Bleeding Academic Research Consortium (BARC) criteria. The secondary outcome included thromboembolic complication, mean change of hemoglobin (Hb) level during bridging, and cost of anticoagulant.

Results: A total of 37 patients underwent randomization after stratified to AF and thromboembolism groups from 60 patients screened, which 19 assigned to apixaban and 18 to enoxaparin. Six patients were excluded after randomization (1 in apixaban group and 5 in enoxaparin group), the data before the patients were excluded were used in the analysis. The median (interquartile range) bridging duration was 7 (5 to 10) and 9 (6 to 14.5) days for apixaban and enoxaparin, respectively. There was null BARC bleeding in apixaban group whereas 3 patients developed BARC 1 bleeding in enoxaparin group (p=0.058). Thromboembolic complication was not occurred in any group during the bridging. The median cost of anticoagulant was 674 and 4,352 Thai Baht (p<0.001) and mean change of Hb level was +0.36 and -0.38 g/dl in apixaban and enoxaparin group (p=0.029), respectively.

Conclusion: Apixaban was as safe, effective, and less expensive than enoxaparin in bridging to warfarin in patients with AF and thromboembolism.

Keywords: Bridging anticoagulant; NOACs; Apixaban; Enoxaparin; Warfarin

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Atrial fibrillation (AF), arterial and venous thromboembolism (ATE, VTE) are relatively common in clinical practice. The most serious complication of these diseases are embolic complications such as systemic embolism included embolic stroke, coronary embolism and acute massive pulmonary embolism that can cause vary degree in severity of morbidity and mortality to the patient. To treat these diseases and prevent its complications, using of oral anticoagulant is a key of outpatient management. In spite of non-vitamin K antagonist anticoagulant (NOAC) is recommended as the first line drug to prevent thromboembolic events, Thailand universal healthcare coverage only provide warfarin, not NOAC, as the first line drug.

Initiation of warfarin may cause pro-coagulation effect due to inhibit anti-coagulating proteins (protein C and protein S) before pro-coagulating proteins (Clotting factor II, VII, IX, X)[1,2]. So using of parenteral anticoagulant e.g. Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) for bridging to warfarin is recommended at least 5 days and until achieve INR level between 2 to 3 for patient with VTE[2], but bridging in moderate to high risk group of AF patients is still equivocal because nearly two third of patient in the BRIDGE study has $CHADS_2$ score ≤ 2[3]. Due to lack of strong evidence for bridging in moderate to high risk group of AF patients, the use of parenteral anticoagulant for bridging is depended on clinician's judgement and individualized of the patients.

Bridging with subcutaneous enoxaparin, the patients need to do self-injection or may need healthcare worker to do injection and/or need longer hospital stay for waiting INR level. Incautious injection may cause subcutaneous bleeding, intramuscular hematoma or systemic bleeding. In order to avoid the inconvenience and risk of injection site related complications as well as to facilitate early patient discharge, an oral anticoagulant bridging regimen

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could be an alternative. Apixaban is an oral factor Xa inhibitor that has rapid onset of action with 12 hours half-life and has efficacy and safety profile for AF and VTE patients[4,5]. Furthermore, cost is cheaper than enoxaparin around five times (96.30 vs. 483.62 Thai baht per day; reference from Drug and Medical Supply information Center, Ministry of Public Health (DMSIC), Thailand, Since 9 December 2019). Therefore, this study aims to evaluate safety as well as to compare the cost of medications between the bridging with apixaban and subcutaneous enoxaparin for bridging to warfarin in setting where NOAC is inaccessible as the first line drug.

Materials and Methods

Study design

Randomized, open-label, pilot, controlled trial to evaluate safety use of apixaban comparing with LMWH as bridging to warfarin in clinical practice. The study was conducted at the Queen Sirikit Heart Center of Northeast (QSHC) and Srinagarind Hospital, Khon Kaen University, Thailand, since 20 March 2020 till 31 December 2020. The trial was approved by Center for Ethics in Human Research, Khon Kaen University (HE621566) and all participants provided written informed consent. Study was funded by Queen Sirikit heart center and there was no conflict of interest (Figure 1).

Study participants

Inclusion criteria included both in-patient department (IPD) or out-patient department (OPD) patients with age ≥18-year-old plus at least one of these diagnoses, AF with CHA_2DS_2VASc ≥3, systemic embolism or VTE. Major exclusion criteria included patient with mechanical prosthetic heart valves, moderate to severe mitral stenosis, recent history of bleeding or bleeding tendency, severe hepatic and renal dysfunction (estimated glomerular filtration rate (eGFR) <30 ml/min), currently use of anticoagulants and/or INR >1.3, pregnancy and patient that could not comply the study protocol.

Randomization and treatment assignment

This trial used open-label permuted block of 4 randomization of two stratified data divided by diagnosis, AF and thromboembolism group. Intervention group was received apixaban 5 mg orally every 12 hours and control group was received enoxaparin 1 mg/kg/dose (maximum 60 mg/dose) subcutaneously every 12 hours for bridging, apixaban was reduced dose according to specific dose reduction criteria. Bridging could be IPD or OPD setting, INR level was rechecked and warfarin dosage was adjusted every 3 to 5 days until achieved INR level ≥2. Then trial drug was stopped and INR with other laboratories (included complete blood count (CBC), blood chemistries and

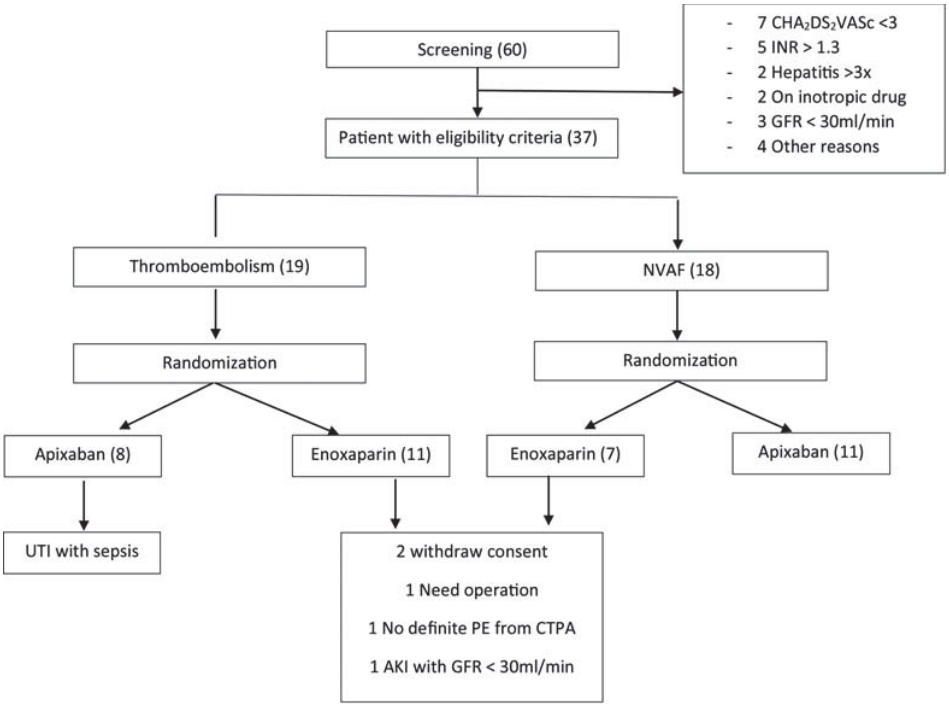

Figure 1. Patients flow.

coagulation) was rechecked again at next 1 week. For the patient needed to treat as OPD setting, they were received logbook for record dosage and duration of medication use and patients would be required to have INR test at either the hospital nearby patient's house or at QSHC. If patients checked INR level at the nearby hospital, investigator would ask INR level and adjusted warfarin dosage via telephone. Starting dose of warfarin was 3 mg orally every night and adjusted as the adapted warfarin adjustment protocol (adapted from: 1) Chiangrai Prachanukroh Study, 2) Ann Rose and Lee Vermeulen. Guidelines for Ambulatory Warfarin Management in Adults. Review and approved by Anticoagulation Task Force, Pharmacy and Therapeutics Committee of University of Wisconsin Hospital. June 2009) and depended on clinician's judgement base on individualized basis.

End points

Primary end point was bleeding complication during bridging period, classified severity with BARC criteria. Secondary end point included the following: thromboembolism complication, cost of medication, duration for bridging and mean change of hemoglobin level during bridging.

Statistical analysis

This study was a pilot study aim to prove hypothesis that bridging with apixaban was not inferior to subcutaneous enoxaparin. Sample size was set as 50 patients. Categorical data were presented as percentage, continuous data were presented as mean with standard deviation and median with interquartile range as appropriate. Comparisons of continuous variables using a t-test for normally distributed continuous data and a Wilcoxon rank-sum test for non-normally distributed data. Comparisons of categorical variables using a Chi-square test. All outcomes analysis was performed according to intention to treat analysis, missing of outcome data was analysis by the basis of best case and worst-case scenario. The p-value less than 0.05 was considered to indicate statistically significant.

Results

Out of 60 screening patients, 23 were screening failure, only 37 eligible patients were randomly allocated to intervention and control group within each strata of AF and thromboembolism group. There were 6 patients excluded after randomization with the following reasons; needed for further operation (1), unconfirmed VTE by imaging (1), could not follow-up INR as protocol (2), developed acute kidney injury and eGFR decline to <30 ml/min during bridging (1) and developed urinary tract infection (UTI) and septic shock (1), the first 5 patients were in enoxaparin group and the last one was in apixaban group. No patient loss follows-up (99% compliance rate in both groups). All baseline characteristics were comparable between two groups. Most of the patients was male (67%), mean age was 64 years. Diagnosis was: AF (48.6%), arterial site thromboembolism (37.8%) and VTE (13.5%). Comorbidities were CHF (56.8%), hypertension (51.4%), DM (35.1%), stroke (32.4%), ACS (29.7%), CCS (21.2%) and DCM (18.9%). Current medications were PPI (51.3%), clopidogrel (35.1%) and ASA (24.3%). Biochemical test results were comparable, except for baseline BUN, creatinine and eGFR; mean (SD) of creatinine was 1.08 (0.23) mg/dl and mean (SD) of eGFR was 66.18 (14.11) ml/min in apixaban group and mean (SD) of creatinine was 0.91 (0.24) mg/dl and mean (SD) of eGFR was 81.72 (18.53) ml/min in enoxaparin group, p=0.042 and p=0.007 respectively. Median (IQR) of number for INR test was 2 (1 to 2) and 3 (2 to 5) in apixaban and enoxaparin group, p=0.005. Median (IQR) of INR level before stopped trial drugs was 2.46 (2.13 to 3.18) and 2.37 (2.10 to 2.55) in apixaban and enoxaparin group, p=0.409. Median (IQR) of INR level at 1 week after stopped trial drugs was 2.53 (1.97 to 2.96) and 2.48 (2.10 to 2.86) in apixaban and enoxaparin group. Most of the patients were treated as OPD setting (46.9%) (Figure 2 and 3).

None of patients in apixaban group had bleeding but occurred in 3 patients (all BARC 1; subcutaneous bleeding at injection site) in enoxaparin group, p=0.058, Risk of bleeding was lower in apixaban group (RR 0.1; 95% CI 0.0056 to 1.7876), p=0.1175. Due to lacked of 5 end point data because of patient were excluded after randomization. We calculated RR base on the best-worse-case scenario analysis, RR for best case scenario was 0.1357; (95% CI 0.0075 to 2.4565), p=0.1765, and worst-case scenario, RR 0.0559; (95% CI 0.0035 to 0.9028), p=0.0421.

For secondary end point; there was no thrombo-embolism event in both groups. Median cost of medication was 674 versus 4,352 Thai Baht in apixaban and enoxaparin group, p<0.001. Median (IQR) duration for bridging was 7 (5 to 10) days versus 9 (6 to 14.5) days in apixaban and

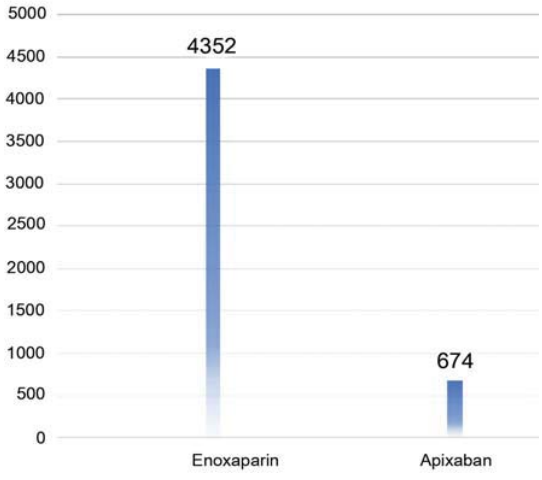

Figure 2. Cost of medication.

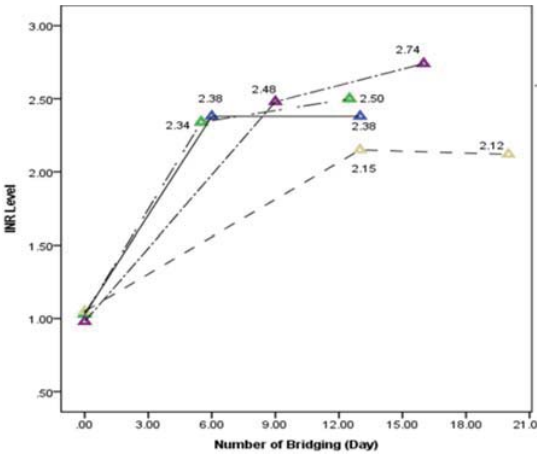

Figure 3. Duration for bridging and median INR level.

enoxaparin group, p=0.384. Mean (SD) change of Hb during bridging was +0.36 (0.84) g/dl in apixaban group versus -0.38 (0.94) g/dl in enoxaparin, p=0.029 (Table 1 and 2).

Discussion

Apixaban is a factor X inhibitor, and enoxaparin is a factor X and factor II inhibitor with more effect on factor X around 4: 1. Many landmark studies shown that apixaban has efficacy and safety to treat and prevent complications for AF and VTE[6–9]. So, by theoretical apixaban might not so much difference in efficacy from enoxaparin. Data from ENGAGE AF-TIMI 48 trial shown that bridging to warfarin with half dose edoxaban is safe[8]. Luis Diaz also shown case series of VTE patients (19 cases) bridging to warfarin with NOAC (apixaban and rivaroxaban) without minor, major bleeding or thrombosis events over 3 and 6 months of observation[6] but data when compare to conventional therapy is lacking. This pilot study shown the safety and cost saving of apixaban instead of enoxaparin for bridging to warfarin. The bleeding outcome was not significant difference between two groups, no injection site complications in apixaban group and comfortable to use as OPD setting. Cost of medication is significant lower in apixaban group about 6.5 times (674 vs. 4,352 Baht) and this not included cost for hospitalization that might higher if the patients are needed for hospitalization when use parenteral heparin. Median INR is not difference between two groups but mean INR level before stopped trial drug is not surprising slightly, not significantly, higher in apixaban group because apixaban has some effect to INR level but less than other NOACs[10]. At the next follow-up 1 week INR level was not significantly difference. The mean Hb is slightly increase in apixaban group and slightly decrease in enoxaparin group during bridging period, p=0.029, without clinically relevant bleeding.

NOAC is recommended to be first line drug for patient with AF and VTE in many current guidelines[11,12] but in limited resource countries, warfarin still be drug of choice. Bridging to warfarin with conventional heparin might be uncomfortable to the patient and might need hospitalization and/or prolonged hospital stay, that could result in increase in healthcare expenditure looking from either patients or healthcare provider perspectives. Therefore, apixaban is about 6.5 times lower cost than enoxaparin and no serious bleeding events during the bridging period, apixaban may be another alternative bridging drug, especially in those area where limited healthcare resources are obvious or widely presence, and also increase patient's satisfaction.

The present study has some limitations, first this is a hypothesis generating study, so, do not have power to test primary end point. Second warfarin adjustment and duration for bridging is depended on individualized response and difference between hospital protocol. Third, the necessary for bridging in moderate to high-risk AF patient is still equivocal and depend on clinician's judgement on case by case.

Conclusion

Bridging to warfarin with apixaban is safe as subcutaneous enoxaparin but more cost saving and comfortable than enoxaparin.

What is already known on this topic?

According to ENGAGE-AF TIMI 48 study, bridging to warfarin with half dose edoxaban is safe[8]. But, the data of apixaban from ARISTOTLE trial, the two-day switching protocol from apixaban to warfarin shown high event rate stroke or systemic embolism and major bleeding[7].

What this study adds?

Bridging to warfarin with apixaban is safe as subcutaneous enoxaparin but more cost saving and comfortable to the patient than subcutaneous enoxaparin.

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Potential conflicts of interest

The authors declare no conflict of interest.

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Table 1. Baseline characteristic

Variables	Over all (n=37)	Enoxaparin (n=18)	Apixaban (n=19)	p-value
Sex, male	25 (67.6)	13 (72.2)	12 (63.2)	0.556
Age, mean (SD)	64.97 (11.65)	63.17 (12.66)	66.68 (10.66)	0.366
Diagnosis				0.589
NVAF	18 (48.6)	7 (38.9)	11 (57.9)	
Arterial site embolism	14 (37.8)	8 (44.4)	6 (31.6)	
Venous site thrombosis	5 (13.5)	3 (16.7)	2 (10.5)	
Co morbidities				
DM	13 (35.1)	7 (38.9)	6 (31.6)	0.642
HTN	19 (51.4)	8 (44.4)	11 (57.9)	0.413
Ischemic stroke	12 (32.4)	4 (22.2)	8 (42.1)	0.197
CAD	19 (51.4)	7 (38.9)	12 (63.2)	0.140
ACS	11 (57.9)	3 (42.9)	8 (66.7)	
CSA	8 (42.1)	4 (57.1)	4 (33.3)	
DCM	7 (18.9)	3 (16.7)	4 (21.1)	>0.999
CHF	21 (56.8)	8 (44.4)	13 (68.4)	0.141
Other	17 (45.9)	11 (61.1)	6 (31.6)	0.072
Current medication				
Aspirin	9 (24.3)	5 (27.8)	4 (21.1)	0.714
Clopidogrel	13 (35.1)	4 (22.2)	9 (47.4)	0.109
ACEI	8 (21.6)	3 (16.7)	5 (26.3)	0.693
Diuretic	13 (35.1)	5 (27.8)	8 (42.1)	0.362
PPI	19 (51.4)	9 (50.0)	10 (52.6)	0.873
Statin	23 (62.2)	11 (61.1)	12 (63.2)	0.898
Digoxin	7 (18.9)	2 (11.1)	5 (26.3)	0.405
BB	20 (54.1)	11 (61.1)	9 (47.4)	0.402
MRA	12 (32.4)	6 (33.3)	6 (31.6)	0.909
Other	24 (64.9)	12 (66.7)	12 (63.2)	0.823
Baseline laboratory				
Hb	12.45 (1.76)	13.01 (2.07)	11.93 (1.24)	0.068
PT	12.34 (1.27)	12.43 (1.37)	12.25 (1.19)	0.672
INR				0.260
Mean	1.01 (0.10)	1.03 (0.10)	1.00 (0.09)	
Median (IQR)	1.00 (0.94 to 1.07)	1.04 (0.94 to 1.10)	0.98 (0.95 to 1.04)	
BUN	19.42 (9.52)	16.16 (4.80)	22.34 (11.70)	0.045
BUN, median (IQR)	17.4 (13.12 to 21.50)	15.6 (12.45 to 20.65)	18.8 (14.30 to 27.60)	0.106
Cr	0.99 (0.25)	0.91 (0.24)	1.08 (0.23)	0.042
GFR	73.74 (17.99)	81.72 (18.53)	66.18 (14.11)	0.007
Last laboratory				
Hb	12.35 (1.57)	12.45 (1.75)	12.30 (1.50)	0.801
PT, mean (SD)	30.77 (11.13)	27.83 (4.44)	32.63 (13.61)	0.168
INR				
Mean	2.75 (1.38)	2.35 (0.42)	3.03 (1.72)	0.117
Median (IQR)	2.37	2.37 (2.10 to 2.55)	2.46 (2.13 to 3.18)	0.409
BUN	18.03 (9.74)	15.30 (4.75)	19.75 (11.67)	0.221
BUN, median (IQR)	15.4 (12.10 to 20.80)	15.15 (11.95 to 19.90)	16.2 (12.10 to 22.20)	0.361

Table 1. Cont.

Variables	Over all (n=37)	Enoxaparin (n=18)	Apixaban (n=19)	p-value
Cr	1.03 (0.31)	0.94 (0.26)	1.09 (0.33)	0.186
GFR	70.50 (17.85)	75.93 (18.08)	67.06 (17.30)	0.182
Follow-up INR				
Mean times of INR check	2.50 (1.29)	3.15 (1.2)	2.05 (1.17)	0.016
Median (IQR) times of INR check	2 (2 to 3)	3 (2 to 5)	2 (1 to 2)	0.005
INR after stop trial drugs 1 week				
Mean	2.53 (0.71)	2.43 (0.51)	2.60 (0.82)	0.544
Median (IQR)	2.48 (2.00 to 2.90)	2.48 (2.10 to 2.86)	2.53 (1.97 to 2.96)	-
Method of INR follow-up				0297
OPD setting	15 (46.9)	4 (30.8)	11 (57.9)	
IPD setting	12 (37.5)	6 (46.2)	6 (31.6)	
Both	5 (15.6)	3 (23.1)	2 (10.5)	
Compliance	99.26 (2.39)	99.34 (1.72)	99.20 (2.81)	0.876
Median (IQR)	100	100	100	0.738

Table 2. Outcome

Outcome	Over all	Enoxaparin (n=18)	Apixaban (n=19)	p-value
Bleed	3 (9.4)	3 (23.1)	0	0.058
Thromboembolism	0	0	0	-
Cost of medication; mean (SD)	2,724 (3,401)	5,487 (3,945)	833.75 (508.82)	0.001
Median (IQR)	1,275.97 (589.83 to 3,264.57)	4,352.76 (2,901 to 7,133)	674.1 (481.50 to 1,011.15)	<0.001
Duration for bridging (E)				
Mean	9.44 (5.42)	10.23 (5.52)	8.89 (5.43)	0.503
Median (IQR)	7.00 (6 to 11)	9.00 (6 to 14.5)	7.00 (5 to 10)	0.384
Mean difference of last Hb and baseline Hb				
Mean	0.07 (0.94)	-0.38 (0.94)	0.36 (0.84)	0.029
Median (IQR)	0.10 (-0.70 to 0.70)	-0.25 (-0.97 to 0.55)	0.30 (-0.2 to 1.10)	-

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