Optimal INR Level in Patients Receiving the Triple Therapy

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บทคัดย่อ: ระดับ INR ที่เหมาะสมในผู้ป่วยที่ได้รับยา Warfarin ร่วมกับ Clopidogrel และ Aspirin

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กลุ่มงานอายุรศาสตร์หัวใจ สถาบันโรคทรวงอก ตำบลบางกระสอ อำเภอเมือง จังหวัดนนทบุรี 11000

ภูมิหลัง: ผู้ป่วยที่จำเป็นต้องได้รับยา Aspirin, Clopidogrel และ Warfarin (Triple therapy) ร่วมกัน เช่น ผู้ป่วยหัวใจสั่นพลิ้วที่มีโรคหลอดเลือดหัวใจและได้รับการทำบอลลูนร่วมกับการใส่ขดลวดค้ำยันมีความเสี่ยงที่จะเกิดภาวะเลือดออกได้มากกว่ากลุ่มที่ได้รับยา Warfarin เพียงชนิดเดียว แต่ยังไม่มีงานวิจัยใดที่ทำการศึกษาชี้ชัดว่าระดับ International normalized ratio (INR) ที่เหมาะสมสำหรับผู้ป่วยที่ได้รับ Triple therapy ควรจะเป็นเท่าใด **วัตถุประสงค์:** เพื่อหาระดับ INR ที่เหมาะสมสำหรับผู้ป่วยไทยที่ได้รับ Triple therapy **วิธีการ:** เก็บข้อมูลตั้งแต่วันที่ 1 มกราคม 2545 ถึง 31 มีนาคม 2556 และแบ่งผู้ป่วยเป็น 5 กลุ่มตามระดับ INR คือ INR < 1.5, INR 1.5-2.0, INR 2.1-2.5, INR 2.6-3.0 และ INR > 3.0 และทำการสืบค้นเวชระเบียนของผู้ป่วยว่ามีการเกิดภาวะลิ่มเลือดอุดตันหรือภาวะเลือดออกในระดับ INR ขณะที่เกิด events นั้นๆ เป็นอย่างไร ระดับ INR ที่เหมาะสมคือ ระดับ INR ที่ค่า incidence density ของภาวะลิ่มเลือดอุดตันและภาวะเลือดออกต่ำที่สุด **ผล**: การศึกษานี้เป็นการศึกษาแบบย้อนหลังในผู้ป่วยจำนวน 235 คน เป็นผู้ชาย 78.7% อายุเฉลี่ย 61.3 ± 10.9 ปี ระยะเวลาที่ได้รับยา Triple therapy เฉลี่ย 190 ± 180 วัน ระยะเวลาที่ผู้ป่วยอยู่ใน INR < 2.0, 2.0-3.0 และ > 3.0 คือ 76.3%, 18.2%, 5.5% ตามลำดับ ผู้ป่วยเกิดภาวะสมองขาดเลือด 1 คน (0.82 ต่อ 100 patient-years) ในกลุ่ม INR < 1.5 เมื่อเทียบกับกลุ่มอื่นแล้วไม่แตกต่างอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยเกิดภาวะเลือดออกรุนแรงเสี่ยงต่อการเสียชีวิต 3 คน (2.45 ต่อ 100 patient-years), ภาวะเลือดออกรุนแรงไม่เสี่ยงต่อการเสียชีวิต 1 คน (0.82 ต่อ 100 patient-years) และภาวะเลือดออกไม่รุนแรง 31 คน (34.33 ต่อ 100 patient-years) ในกลุ่ม INR > 1.5 มีภาวะเลือดออกทั้งหมดเพิ่มขึ้นมากกว่ากลุ่ม INR < 1.5 อย่างมีนัยสำคัญ ($p < 0.001$, 95% CI = 2.35-44.01, RR = 8.22) **สรุป:** ระดับ INR ที่เหมาะสมในผู้ป่วยไทยที่ได้รับ Triple therapy อาจน้อยกว่า 1.5 ซึ่งมีความสัมพันธ์กับการเกิดภาวะเลือดออกน้อยที่สุดในขณะที่ไม่เพิ่มการเกิดลิ่มเลือดอุดตัน การศึกษาแบบไปข้างหน้าขนาดใหญ่ควรจะมีขึ้นเพื่อยืนยันผลการศึกษานี้ต่อไปในอนาคต
คำสำคัญ: ยาต้านเกล็ดเลือด 2 ชนิด ยาต้านเกล็ดเลือด 2 ชนิดร่วมกับยาละลายลิ่มเลือด สมองขาดเลือด เลือดออก หัวใจสั่นพลิ้ว

Abstract

Background: There are many patients receiving both dual antiplatelets and warfarin who are at risk of bleeding complication. However, no study on the optimal INR level in patients receiving triple therapy has been reported. **Objectives:** To identify optimal INR level in Thai patients receiving triple therapy that caused the lowest thromboembolic and bleeding events. **Methods:** Triple therapy patients were retrospectively enrolled since 1st January 2002 to 31st March 2013. The INR range were divided into 5 groups (less than 1.5, 1.5 to 2.0, 2.1 to 2.5, 2.6 to 3.0 and more than 3.0). Thromboembolic and bleeding events in each group were collected. The optimal INR level was the level that patients had the least thromboembolic and bleeding events. **Results:** A total of 235 patients (the mean age 61.3±10.9 years) were eligible, contributing to 122.35 patient-years of observational period. The patient-time spent within therapeutic INR range (2-3), less than 2 and more than 3 was 28.2%, 76.3%, 5.5%, respectively. Of 235 patients, one patient experienced one ischemic stroke (0.82 per 100 patient-years), 3 patients experienced 3 major life-threatening bleeding events (2.45 per 100 patient-years), one patient experienced one major non life-theatening bleeding event (0.82 per 100 patient-years), and 31 patients experienced 42 minor bleeding events (34.33 per 100 patient-years). Each group of INR level was not statistically significant in thromboembolic event. Total bleeding events was found to be significantly increased in INR level more than 1.5 ($p < 0.001$, 95%CI CI = 2.35-44.01, RR = 8.22). **Conclusions:** The INR level less than 1.5 had the least total bleeding events and comparable ischemic stroke compared with the INR level more than 1.5 in patients with triple therapy. Further larger prospective study should be conducted to confirm these results in the future.

Keywords: Dual antiplatelets, Triple therapy, Warfarin, Stroke, Bleeding, Atrial fibrillarion

Introduction

There are many patients receiving both dual antiplatelets and oral anticoagulant (triple therapy) because of several indications such as those patients with atrial fibrillation (AF) and coronary artery disease (CAD) following percutaneous coronary stent placement. According to 2010 ESC guidelines for management

of atrial fibrillation[1] recommends that AF patients with CAD who received any stent placement should be prescribed triple therapy to achieve the INR target range of 2.0-2.5.

To date, there have been many patients who receive triple therapy. Those patients have not been achieved INR target range of 2.0 to 3.0 with no thromboembolic event. In contrast to other ones with INR level less than 2.5 have had bleeding events. In addition, combined oral anticoagulant and dual antiplatelets have more bleeding events than patients who received only warfarin alone.

Previous study revealed that low INR level (1.8-2.5) was optimal in AF and CAD patient with stents placement received triple therapy[2]. Furthermore, there have been Asian studies have been shown the lower INR level (INR between 1.5-3.0) in Chinese and Japanese atrial fibrillation patients who received warfarin could effectively prevent thromboembolism and had more safety profile[3-5]. Recently, Methavigul K et al studied the optimal INR in Thai AF patients with warfarin and have demonstrated the optimal INR target range of 1.5 to 2.9[6]. The results from these trials in Asian population have shown that the lower INR level may be more suitable[7-8]. This study was conducted to identify the optimal INR level in Thai patients who received triple therapy.

Materials and Methods

This study was a retrospective study in patients with triple therapy (warfarin, clopidogrel and aspirin) in Central Chest Institute of Thailand since 1st January 2002 to 31st March 2013. Those patients who were 18 years old or more and had indication for triple therapy i.e. stable CAD , acute coronary syndrome , coronary ectasia, renal artery stenosis with stents, AF, deep vein thrombosis, pulmonary embolism, left ventricular thrombus were included.

Patients were excluded if they had myeloproliferative disorders (polycythemic vera, chronic myeloid leukemia, essential thrombocythemia, agnogenic myeloid metaplasia), thrombocytopenia (platelets < 100,000/mm^3) during event occurrence, on triple therapy less than 1 month or had prosthetic heart valves.

Those patients were divided into 5 groups according to target INR: INR less than 1.5, INR 1.5 to 2.0, INR 2.1 to 2.5, INR 2.6 to 3.0 and INR more than 3.0. The thromboembolic events and bleeding events in each INR group were determined. The INR level during events were recorded. Data was collected from the first day of triple therapy until patients gived up the drugs or end of the study. The study protocol was approved by the Institutional Review Board. The present study complied with the Declaration of Helsinki.

Triple therapy was defined as aspirin and clopidogrel plus warfarin. Thromboembolic events included embolic stroke and peripheral arterial emboli. Bleeding events were classified into 3 groups: 1) major life-threatening bleeding including fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or hemoglobin reduction more than 5.0 g/dl or need more than 4 units of blood transfusion; 2) major non life-threatening bleeding including bleeding that less severe than major life-threatening bleeding such as disability, reduction of hemoglobin more than 3.0 g/dl or need more than 2-3 units of blood transfusion and 3) minor bleeding including bleeding other than major life-threatening and non life-threatening bleeding[9].

The INR level during thromboembolic events and bleeding events (the blood sample must be tested within 5 days of the events) were collected. Time between 2 follow-up visits was divided by half time between the first and next INR range. The first half-time period was considered that the patient was in the first INR range. The last half-time period was considered that the patient was in the next INR range[10]. The summation of time stayed in each INR groups was presented as patient-years.

The incidence density of thromboembolic and/or bleeding events was calculated by divided the numbers of thromboembolic events and/or bleeding events in each INR level with the summation of the time that each patients stayed in each INR level as shown below.

Incidence density = Number of events / observational time (Patient-year)

Overall thromboembolic events and bleeding events in INR level < 1.5, 1.5-1.9, 2.0-2.5, 2.6-3.0, > 3.0 were 15.1, 2.9, 4.4, 3.3, 20.5 per 100 patient-years, respectively[3]. In this study, the INR levels were divided into 5 groups; INR level < 1.5, 1.5-2.0, 2.1-2.5, 2.6-3.0 and > 3.0. Weighing INR group by the duration that patients stayed in each group including 146, 310, 271, 90, 39 patient-years, respectively. Compare proportion for independent G groups, we determined 0.05 for α-error, 0.20 for β error with 80% power. The calculated sample size was 235 patients.

The categorical data (i.e. sex, underlying diseases) are presented as the frequency and percentage. The numerical data (i.e. age and LVEF) are presented as mean ± S.D.

The optimal INR level was defined as the INR level that had the lowest incidence density of thromboembolic and bleeding events. We compare thromboembolic events and bleeding events between INR groups with chi-square test for two rates.

Results

A total of 235 patients receiving triple therapy since 1st January 2002 to 31st March 2013 were enrolled. The average age was 61.3±10.9 years. Most patients were male (78.7%) and 41.7% of patients had nonvalvular AF. One-third of patients had left ventricular thrombus. The mean CHA_2DS_2-VASc score was 3.44 in AF patients. The most common indication for dual

antiplatelets was coronary stent placement (70.64%). The patient-time spent within therapeutic INR range (2-3), less than 2 and more than 3 was 18.2%, 76.3%, 5.5%, respectively. The average duration during triple therapy was 190 ± 180 days. Baseline characteristics were summarized in table 1.

Table 1 Baseline characteristics of the patients

Characteristics	Total n = 235 n (%) or mean ±SD
Age – yr	61.3 ± 10.9
Male sex - no. (%)	185 (78.7)
Follow-up time - days	190 ± 180
Time spent in INR range - yr (%)	
< 2.0	93.16 (76.3)
2.1-3.0	22.27 (18.2)
> 3.0	6.68 (5.5)
Comorbidities - no. (%)	
Coronary artery disease	220 (93.6)
Hypercholesterolemia	172 (73.2)
Hypertension	157 (66.8)
Diabetes	85 (36.2)
Valvular heart disease	62 (26.4)
Chronic kidney disease	20 (8.5)
Previous stroke or TIA	27 (11.5)
AF and/or atrial flutter	117 (49.8)
Coronary ectasia	19 (8.1)
Previous CABG	10 (4.3)
Peripheral arterial disease	9 (3.8)
Echocardiographic parameters	
LVEF ≤ 40%	97 (41.3)
LV thrombus	83 (35.3)
LV aneurysm	53 (22.6)
Indication for dual antiplatelets - no. (%)	
Coronary stents	166 (70.6)
DES	143 (60.9)
BMS	23 (9.8)
UA/NSTEMI	26 (11.1)
STEMI	22 (9.4)
Chronic stable angina	2 (0.9)
Ischemic cardiomyopathy	1 (0.4)
ASD device closure	4 (1.7)
Others	14 (6.0)
Indication for oral anticoagulant - no. (%)	
Nonvalvular AF	98 (41.7)
LV thrombus	72 (30.6)
Coronary artery thrombosis	14 (6)
Coronary ectasia	12 (5.1)
Mitral stenosis with AF	8 (3.4)
Deep venous thrombosis	6 (2.6)
MV repair	3 (1.3)
Pulmonary embolism	1 (0.4)

Table 1 Baseline characteristics of the patients (Cont.)

Characteristics	Total n = 235 n (%) or mean ±SD
More than 1 indications	15 (6.4)
AF with LV thrombus	8 (3.4)
AF with LV thrombus and coronary thrombus	1 (0.4)
AF with coronary ectasia	1 (0.4)
Coronary ectasia with coronary thrombus	4 (1.7)
Venous thromboembolism	1 (0.4)
Others	6 (2.6)
Dose of Aspirin - Mean (Range)	143.7 (81-325)
- Aspirin 81 mg/day - no. (%)	143 (60%)
- Aspirin 162 mg/day - no. (%)	47 (20%)
- Aspirin 300 mg/day - no. (%)	2 (0.9%)
- Aspirin 325 mg/day - no. (%)	43 (18.3%)
Dose of clopidogrel - Mean (Range)	75.64 (75-150)

S.D. = standard deviation, n = numbers, AF = atrial fibrillation, TIA = transient ischemic attack, LVEF = left ventricular ejection fraction, LV = left ventricular, DES = drug-eluting stent, BMS = bare-metal stent, UA/NSTEMI = unstable angina/non-ST elevation myocardial infarction, STEMI = ST elevation myocardial infarction, ASD = atrial septal defect

Of 235 patients, one patient experienced one ischemic stroke (0.82 per 100 patient-years), 3 patients experienced 3 major life-threatening bleeding events (2.45 per 100 patient-years), one patient experienced one major non life-theatening bleeding event (0.82 per 100 patient-years), and 31 patients experienced 42 minor bleeding events (34.33 per 100 patient-years).The characteristics of patients with major life-threatening and major non life-threatening bleeding was shown in table 2

The incidence density of thromboembolic event of INR < 1.5 group was 1.77 per 100 patients –year. Other INR group had no thromboembolic event. However, the incidence density of thromboembolic event of the INR < 1.5 group was higher than those of other INR groups without statistically significance (p = 0.42, 95%CI = 0 - 60.09, rate ratio = 0) (Figure 1). The INR level more than 1.5 was more total bleeding events than the INR level less than 1.5 with statistically significance (p < 0.001, 95%CI CI = 2.35-44.01, rate ratio = 8.22) (Figure 2).

The incidence density of stroke and total bleeding events of INR < 1.5 group was still statistically significant lower than other INR groups (P < 0.001, 95% CI = 0.2-0.57) (Figure 3). The optimal INR that had the lowest thromboembolic event and bleeding events was INR < 1.5 in the patients with triple therapy.

Table 2 Characteristics of patients with major life-threatening and major non life-threatening bleeding

No.	Age (yr)	Sex	Events	Antiplatelet regimen during event		Duration of triple therapy	INR during event
				ASA (mg/day)	Clopidogrel (mg/day)		
1	82	M	Intracerebral hemorrhage	325	75	42	4.3
2	66	M	Subdural hematoma	300	75	32	5.8
3	58	M	UGIB (Hb decrease > 5.0 g/dl)	81	75	215	6.9
4	58	M	UGIB (Hb decrease > 3.0 g/dl)	325	75	74	7.0

No = number, yr = years, M = male, UGIB = upper gastrointestinal bleeding, ASA = aspirin

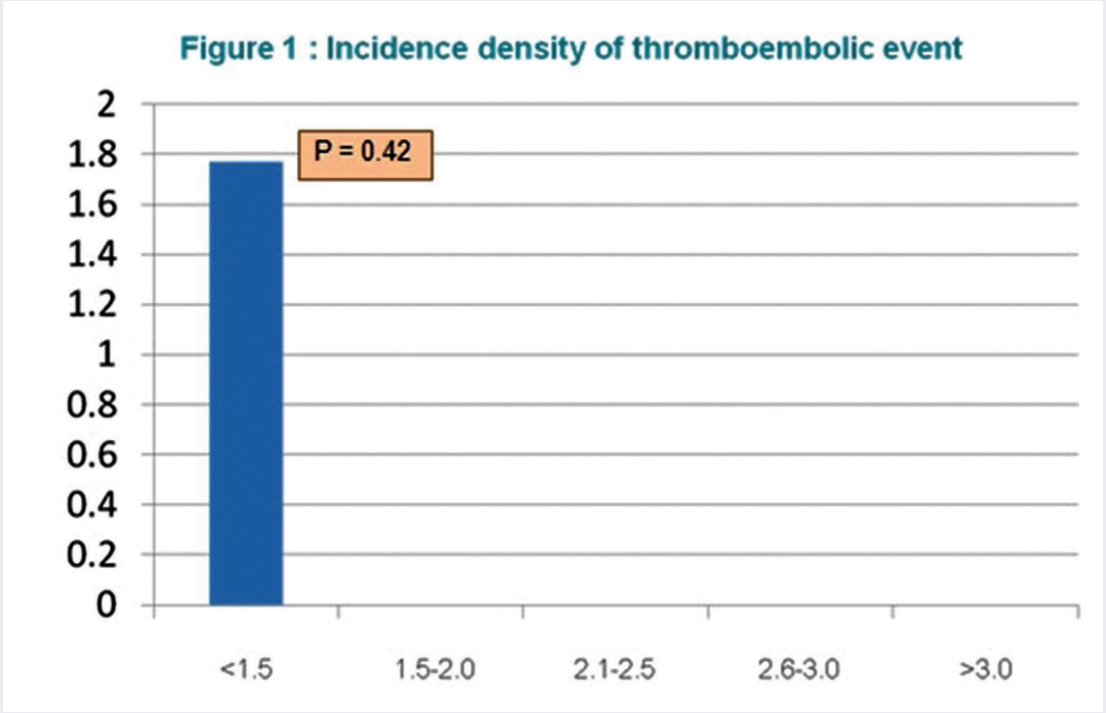


Figure 1 : Incidence density of thromboembolic event
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
P = 0.42
<1.5
1.5-2.0
2.1-2.5
2.6-3.0
>3.0

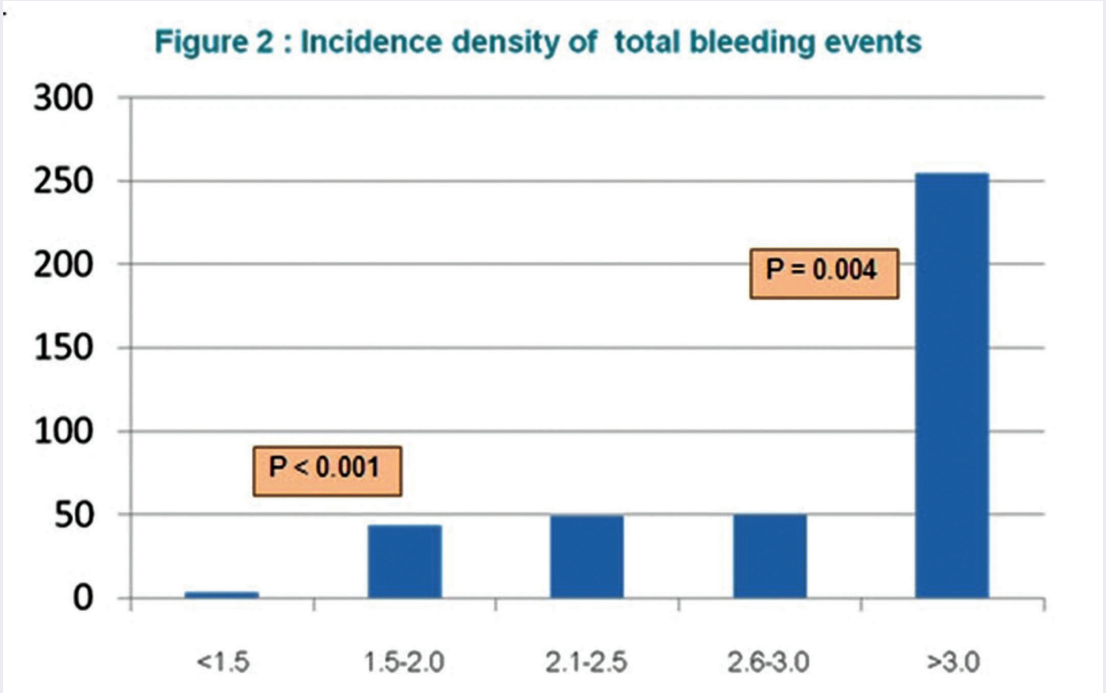
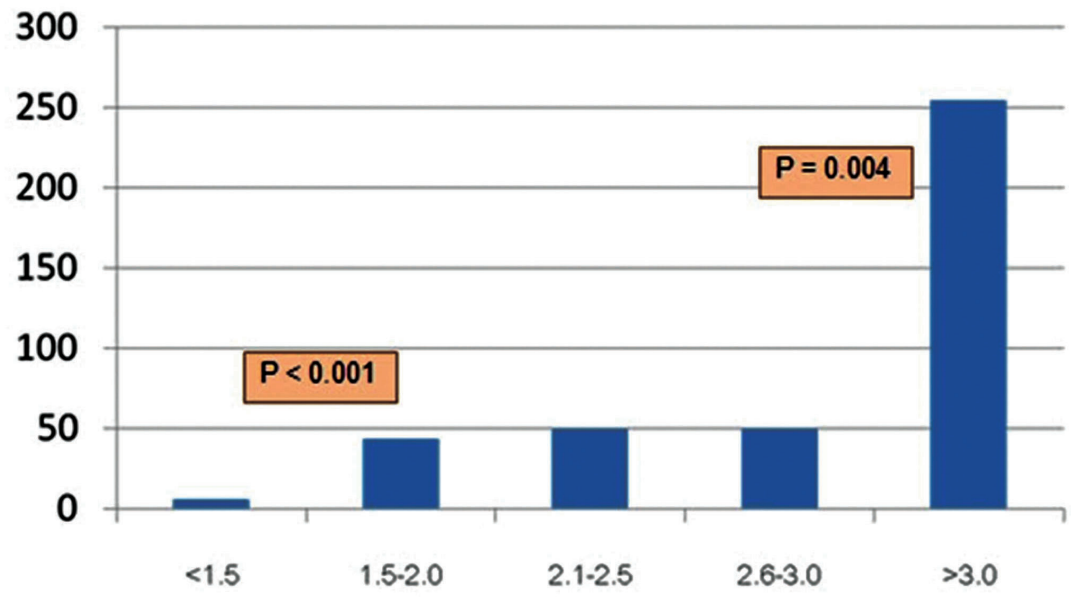


Figure 2 : Incidence density of total bleeding events
300
250
200
150
100
50
0
P = 0.004
P < 0.001
<1.5
1.5-2.0
2.1-2.5
2.6-3.0
>3.0

Figure 3 : Incidence density of stroke and total bleeding events



Discussion

This study is the first study to find out the optimal INR level in patients with triple therapy. From this study, the incidence density of thromboembolic events in INR level < 1.5 was higher than INR ≥ 1.5 without statistically significance (P = 0.42, 95%CI = 0 - 60.09, RR = 0), whereas the total bleeding incidence density in INR ≥ 1.5 was significantly higher than INR < 1.5 (P < 0.001, 95%CI = 2.35-44.01, RR = 8.22). This result is different from the previous studies in Chinese and Japanese nonvalvular AF patients who received warfarin. These trials showed that lower INR level (INR 1.5-3.0) did not increase the thromboembolic events, but also had less bleeding events than higher INR level[3, 4, 5]. The majority of the population in these studies[3, 4, 5] received only warfarin which is different from our population who received triple therapy that the risk of bleeding is higher than warfarin alone. This can be explained why the optimal INR in patients receiving warfarin and dual antiplatelets in this study was lower than previous studies of warfarin alone.

This study showed that the INR level < 1.5 is the optimal level because there was the lowest total bleeding events and thromboembolic events in this INR range. This result leads to the hypothesis that Thai patients who received dual antiplatelets may not need to get additional warfarin until INR 2.0-2.5 as recommended by the 2010 ESC guidelines for the management of atrial fibrillation[1] and 2012 ACCF/AHA Focused Update Incorporated Into the ACCF/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction[11] to prevent thromboembolism. However, The risk of thromboembolism in nonvalvular AF patients is also dependent on CHA_2DS_2-VASc score. Although these population had high risk thromboembolism because a median CHA_2DS_2-VASc score was 3.44, INR < 1.5 were not increased thromboembolism in nonvalvular AF patients receiving triple therapy as well.

The thromboembolic events in INR < 1.5 was higher than INR ≥ 1.5 without statistically significance may be result from the rate of thromboembolism in Thai population is usually lower than the Western population. Therefore, the chance to occur thromboembolic events is lower than Western population as well. Whereas the higher bleeding events that occurred in INR ≥ 1.5 may be resulted from smaller stature, lower body weight, or genetic polymorphism in Thai patients compared to Western patients[12].

The 2012 American College of Chest Physicians guideline recommends AF patients received PCI with stent placement whom $CHADS_2$ score 0-1 to take only dual antiplatelets for 12 months. However, if the $CHADS_2$ score ≥ 2, the recommendation suggested that the patient should receive triple therapy for 1 month for BMS and 3-6 months for DES then take warfarin and single antiplatelet (either aspirin or clopidogrel) thereafter until 12 months[13]. Despite this study used CHA_2DS_2-VASc score instead, the previous data revealed that for those who were not been prescribed warfarin, CHA_2DS_2-VASc score of 4 had an equal risk of stroke (4% per year) to $CHADS_2$ score of 2[1]. So in Thai nonvalvular AF population whom the CHA_2DS_2-VASc score < 4 and had one or more stents placement and received dual antiplatelets may not necessarily to get warfarin in conjunction with the dual antiplatelet. If the CHA_2DS_2-VASc score ≥ 4, it can be considered triple therapy (warfarin plus aspirin and clopidogrel) and the level of INR less than 1.5 is sufficient.

However, this study has some limitations. First, this is a retrospective study, so there are confounding factors, missing data, and some patients were lost to follow-up visit. However, this retrospective study can provides preliminary data about the optimal INR level in Thai patients with triple therapy. Second, this study had the small sample size. Although this is a small sample size study, this study can demonstrate the statistically significant difference of each INR level and the trend of having bleeding increased as the INR increased.

Conclusions

The INR level less than 1.5 had the least total bleeding events and comparable ischemic stroke compared with the INR level more than 1.5 in patients with triple therapy. Further larger prospective study should be conducted to confirm these results in the future.

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