



# A Randomized Controlled Trial of Multidisciplinary Telephone-based Management of Oral Anticoagulant Therapy

Bhuritat Maungboon, MD<sup>1</sup>, Krisada Sastravaha, MD<sup>1</sup>

<sup>1</sup>Cardiology Unit, Department of Medicine, Bhumibol Adulyadej Hospital RTAF

## Abstract

**Background:** Monitoring warfarin therapy is crucial. A multidisciplinary team evaluates the appropriateness and duration of warfarin therapy, monitors international normalized ratio (INR), regulates warfarin dose, and educates patients. A multidisciplinary telephone-based management team has been operating but has not been compared to the traditional office-based visits management team.

**Objective:** Compared the warfarin-related complications between the telephone-based management team with the traditional office-based visit management team.

**Methods:** We conducted a single center, PROBE trial of eligible adults with inappropriate INRs level that received multidisciplinary management through telephone or traditional in-office-based visits. Data analyses to compare warfarin-related outcomes and clinical end points between groups was done.

**Results:** Three hundred nineteen patients were evaluated, and 102 patients were included in the study. They were divided into three groups. The first two groups, which had 34 patients each, were managed by multidisciplinary telephone and regular period visits at two- and three-month respectively. The third group, which included 34 patients, was managed in office-based clinic visits as the control group. There were no differences in demographic between the groups. There was no statistically significant difference in rate of INRs level achievable (67.6%, 82.4%, 88.2%,  $p = 0.096$ ), thrombotic and/or bleeding event (17.6%, 8.8%, 8.8%,  $p = 0.427$ ), and hospitalization with warfarin-related (2.9%, 2.9%, 0%,  $p = 0.600$ ). There were significantly fewer incidences of emergency department visit rate causing adverse events in the telephone-managed groups as compared with the face-to-face-managed group ( $p = 0.045$ ). However, there was no statistical significant in adverse events and INRs achievable rate between patients in group 2 (2-month interval) and 3 (3-month interval).

**Conclusion:** The multidisciplinary telephone-based management of patients with unachievable INRs level through a physician-staffed warfarin clinic resulted in clinical outcomes that were at least as safe as those managed with office-based visits. Telephone-based education can be added to manage warfarin therapy in patients who INRs level are not able to reach the target.

**Key words:** anticoagulation, telephone management, warfarin

Thai Heart J 2017; 27 : 1-8

E-Journal : <http://www.thaiheartjournal.org>

## Introduction

The use of warfarin is an extremely important issue in clinical practice. Because of warfarin's narrow therapeutic index and its many drug and dietary interactions, patients who take warfarin must have their international normalized

ratio (INR) monitored and their warfarin dose adjusted on a regular basis<sup>(1)</sup>. INR level must meet the criteria for treatment for each indication. If the INR level is out of therapeutic range, it can cause all kinds of bleeding complications and thrombotic event. Therefore, narrowing the range is important. The challenge is still significant when the bleeding is particularly severe. Depending on the duration of warfarin, the dosing is critical<sup>(2)</sup>. Traditionally, physicians provided these services. However, with the rise of multidisciplinary

health management over the past decade, non-physician-based clinical management programs such as telephone-based, anticoagulation services have become more popular. In an anticoagulation clinic (ACC), physicians turn over the warfarin-related care of their anticoagulated patients to a multidisciplinary team of health-care providers who monitor patients' INRs, prescribe warfarin, and educate patients about their therapy. Research suggests that patients treated in an ACC spend more time in a therapeutic INR range and have lower bleeding and thromboembolic rates than patients receiving standard physician care<sup>(3-4)</sup>.

Reduced patient knowledge have been shown to influence compliance of drug usage, produce poorer health therapeutic outcomes, and increase patients risks of serious complication from warfarin, even when the patients are in ACC programs<sup>(5-6)</sup>. Thus, the possibility to increase the patient knowledge and compliance with telephone-based clinical management programs is important, not only for patients who take warfarin, but also for patients with related disease management programs<sup>(7)</sup>.

Telephone-based management of anticoagulant therapy has been described in several reports, so far<sup>(7-8)</sup>. A survey of patients who were enrolled in a telephonic anticoagulation clinic found that these patients had a high degree of satisfaction with care and a high level of knowledge about warfarin therapy<sup>(9)</sup>. One report described monitoring outcomes and clinical events in a telephone-based anticoagulation management service that were similar to previously reported outcomes in traditional office-based anticoagulation clinics<sup>(6)</sup>. In addition, the results of a study of a centralized, telephonic, pharmacist-managed anticoagulation monitoring service showed that it reduced the risk of anticoagulation therapy-related complications compared to usual care<sup>(10)</sup>.

However, to our knowledge, no randomized trial has analyzed patients that received reinforcement knowledge of warfarin management by a telephone-based ACC multidisciplinary team<sup>(8)</sup>. We assessed the therapeutic INR range (TTR) of patients taking warfarin who were treated either at a control health center with traditional ACC access or randomly selected to have access to a telephone-based ACC. We hypothesized that patients who received an added telephone-based health center support would be more in therapeutic INR range. Therefore, they would use less

medical resource and have less warfarin-related complications than patients who receive only traditional multidisciplinary clinic setting care at a control health center. Furthermore, we hypothesized that the appropriate duration of follow-up on a patient that is unachievable TTR, both short and long period, can be achieved with an added telephone-based program, with no difference of adverse event.

## Methods

### Participant Randomization of Bhumibol Adulyadej hospital RTAF

We established the single center of study at ACC of Cardiovascular Research and Prevention Centre (CRPC) and medical outpatient units. We used a *block randomization* matching two variables in the CRPC and medical outpatient units by gender and baseline unachievable INR level, low or high. The patients assigned to ACC were in group 1, as a control, group 2 as the short follow-up (8 weeks), or group 3, as the long follow-up (12 weeks) after completing a two weeks run-in period.

Physicians could choose to enroll eligible patients in the intervention group or could continue to monitor their patients in the conventional treatment group. Physicians could change the patients between groups with written consent until the end of the study, which operates with the research protocol. Finally, 319 patients were enrolled and 34 patients participated in each group.

### Selection of Study Participants

Between March and December 2013, to select potential study participants, we used physicians and pharmacists claims to identify all patients who had warfarin prescribed. Patients recruited to the study signed an informed consent. We have chosen to separate groups by gender and INR prior to treatment goals. The appropriate INR level was defined following specific conditions such as between 2.0 and 3.0 in cases of atrial fibrillation or aortic prosthetic heart valves or between 2.5 and 3.5 for patients whose had mitral prosthetic valves to prevent thrombotic or bleeding complicated therapy. After the medical examination and pharmacists educated to patient or their caregivers, patients were recruited to the study. Patients

were required to use the telephone to communicate on their own or through their caregivers under the hotline safety protocol. They also had to meet the team regularly.

**ACC Role, Trial Protocol, and Structured Telephone-based Protocol**

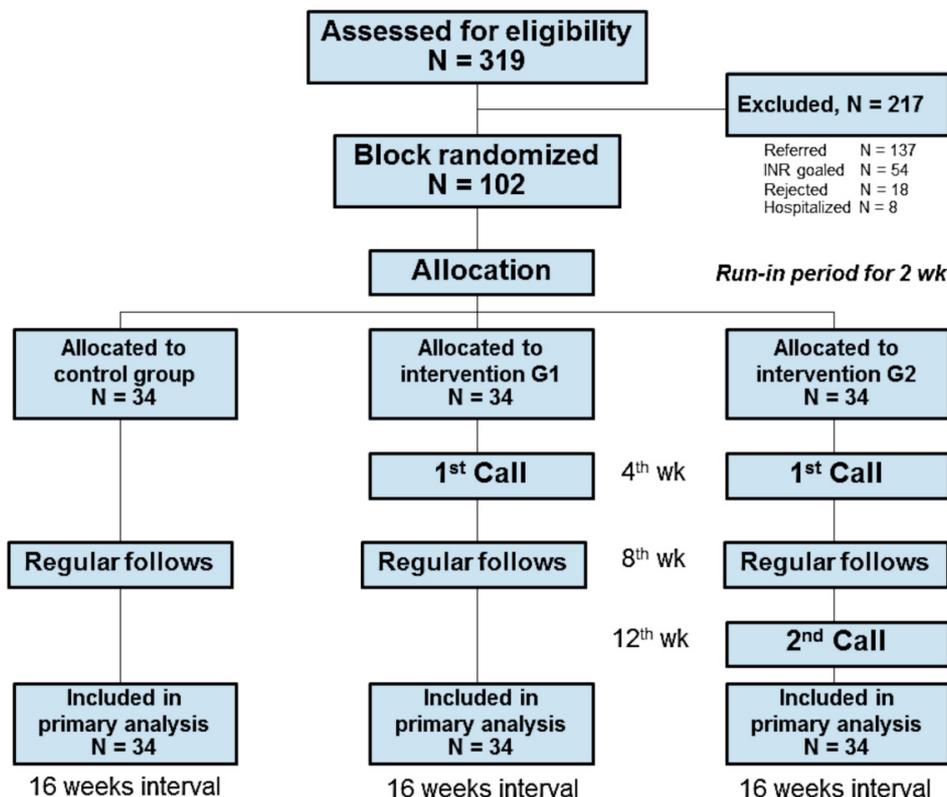
The ACC regrouped a multidisciplinary team, consisting of a physician, a nurse, and a pharmacist. The ACC facilitates a clinical point of cares for patients receiving warfarin continuously. When they meet the physician, clinical data and physical examination are collected. Then, a special nurse and a pharmacist attending the ACC will give the necessary warfarin education to patients. They will promote compliance, drug-to-drug and drug-to-food interaction. They will also explained the complication of warfarin. Finally, they will answers all questions from the patients<sup>(8)</sup>. In this study, an added telephone-based educational program was conducted by a well-trained physician, a practical nurse, and a clinical pharmacist. This was done between appointment and contained all issues as discussed during the routine visits. Following the the protocol and guidelines, a structured

program was initiated. The only difference between the groups was the fixed duration and frequency of follow up between the three groups. The medical staff communicated with the patients primarily by telephone. The staff completed the initial patient education over the telephone. A single call was made to the patients of group 2 and two calls were made to the patients in group 3. However, there were no office-based group educational session.

**Measures**

A new case record form was created to collect the clinical data. The form was validated and redesigned. The data about clinical issues, drug compliance to assess over or under usage, food or herb remedies, other drugs used such as over-counter-drug, and NSAIDs or drug suspected to interfere directly warfarin level were collected. Moreover, the adverse events including bleeding or thrombotic event, emergency room visit, or hospitalization related to warfarin were also collected. As a safety protocol, a hotline was available to all enrolled patients to contact the multidisciplinary team (Figure 1).

**Figure 1.** Randomization, Follow-up, and Analysis Populations



## Statistical Analyses

We used a non-parametric statistic, Chi square test, and univariate analysis to compare INR achievable by TTR, and warfarin dosage differences in patients at the telephone-based and in ACC centers. The intent-to-treat analyses compared the adverse events of all patients at the telephone-based and the control warfarin centers. We calculated basic descriptive statistics for the patient demographic data and created graphs. We used two-sided tests for all comparisons and considered a  $p$  value less than .05 to be statistically significant. We performed our analyses in SPSS (Version 13; SPSS; Chicago, IL).

## Results

Three hundred nineteen patients were enrolled and after selection, 102 patients, divided in three groups, were included in this study. Table 1 summarizes the demographic characteristics of the patients in each management group. The differences in sex, age, duration of therapy, indications for oral anticoagulation, medical comorbidity, baseline INR level, mean dosage of warfarin and warfarin-naive patients did not reach statistical significance. As described in Table 2, the differences in monitoring outcomes such as achievable INR by TTR, clinical end points both bleeding or thrombotic events, and the use of health-care resources between the three groups did not reach statistical significance.

Patients who were managed by an added telephone-based had a similar number of INRs compared to patients who were managed during office encounters (67.6% vs 85.2%, respectively;  $p = 0.096$ ). The INR achievable by TTR was not statistically significant different between control and telephone-based management at the end of study (67.6%, 82.4%, 88.2%,  $p = 0.096$ ), recurrent thromboembolism and/or bleeding event (17.6%, 8.8%, 8.8%;  $p = 0.427$ ; RR 0.89; 95% CI, 0.32 to 2.34), and hospitalization with warfarin-related (2.9%, 2.9%, 0%;  $p = 0.600$ ; RR 0.21; 95% CI, 0.02 to 0.16). There were significantly fewer incidences of emergency department visit rate caused adverse events between telephone-managed and ACC centers -managed ( $p = 0.045$ ). However, there was no statistically significant difference in adverse events and INRs achievable rate between patients in group 2 (2-month interval) and 3 (3-month interval).

## Discussion

Telephone-based management of oral anticoagulation therapy has been described in several reports. In addition to our knowledge, this is the first randomized controlled study to evaluate differences in monitoring clinical outcomes, clinical end points, and health-care resource utilization between the added telephone-based and office-based patients within an anticoagulation clinic setting in Thailand. The results showed no significant differences between the three groups, indicating that the added telephone-based to conventional clinic education and follow-up were at least as effective as in-person visits to manage oral anticoagulation. It is important to highlight that the structured and rigidity of our telephone-based interview and patient evaluation replicated the model of our in-clinic visit<sup>(8,11-12)</sup>. Therefore, our findings may be generalizable to add telephonic anticoagulation education services that merely serve to reinforce screening out-of-range INR values and to increase safety when managing warfarin.

However, in new oral anticoagulants (NOAC) era, warfarin is the cornerstone medication for patient whose risk of thromboembolic event because of its low cost and high effectiveness. Furthermore, many healthcare providers such as physicians, practical nurses, and clinical pharmacists have more experience with this drug<sup>(13)</sup>.

The economic impact of using the added telephone-based management with a multidisciplinary team has not been considered in this study<sup>(14)</sup>. However, in previous studies, it has been shown that using a telephone-based approach for follow-up of patients in a primary care clinic setting resulted in decreased costs because of the reduced utilization of medical resources, including clinic visits, hospital admissions, lengths of stay, and ICU days. Another study showed that one third of patients who succeeded in consulting a clinician by telephone would have otherwise gone to an emergency department. No formal pharmacoeconomic study has been conducted to evaluate the impact of telephone-based management<sup>(15,16)</sup>. However, as telephone management is not reimbursed by most payers, anticoagulation clinics with a business model that requires a particular level of reimbursement may find that telephone management is not economically feasible. The study showed safety impact to all patients whose warfarin-labile

Table 1 Demographic characteristics

Demographic	Strata 1N, (%)	Strata 2N, (%)	Strata 3N, (%)	p
<b>Mean age, years</b>	56.0±13.7	59.8±12.5	54.0±10.4	0.127
<65	23 (67.6)	20 (58.8)	27 (79.4)	0.087
≥65	11 (32.3)	14 (41.1)	7 (20.5)	
<b>Male</b>	15 (44.1)	20 (58.8)	22 (64.7)	0.063
<b>INR goal</b>				
2.0-3.0	25 (35.7)	22 (31.4)	23 (32.8)	0.271
2.5-3.5	9 (28.1)	12 (37.5)	11 (34.3)	
<b>Indication to treat</b>				
AF/AFI	10 (29.4)	15 (44.1)	17 (50.0)	0.664
PHV	18 (52.9)	11 (32.3)	14 (41.1)	
VTE/PE	3 (8.8)	4 (11.7)	0 (0)	
LV thrombus	1 (2.9)	1 (2.9)	1 (2.9)	
CHF	1 (2.9)	1 (2.9)	1 (2.9)	
Other	1 (2.9)	2 (5.8)	1 (2.9)	
<b>Comorbidities</b>				
0	5 (14.7)	6 (17.6)	4 (11.7)	0.482
1-2	19 (55.8)	17 (50.0)	21 (61.7)	
≥3	10 (29.4)	11 (32.3)	9 (26.4)	
<b>Non-therapeutic INR</b>				
Low level	19 (55.8)	20 (58.8)	19 (55.8)	0.961
High level	15 (44.1)	14 (41.1)	15 (44.1)	
<b>Initial INR (mode, range)</b>	1.22 (0.63-4.59)	1.98 (0.65-4.94)	5.12 (0.52-6.57)	0.335
<b>Final INR (mode, range)</b>	2.14 (1.44-3.95)	2.23 (1.57-4.24)	2.53 (1.52-4.51)	0.619
<b>Inappropriate INR</b>				
Dose-related	24 (70.5)	22 (64.7)	23 (67.6)	0.874
Non-dose related	10 (29.4)	12 (35.2)	11 (32.3)	
<b>Warfarin dose (mean of mg per week)</b>				
Initial	19.8±3.5	19.1±2.7	19.8±3.3	0.833
End period	20.1±1.8	19.9±1.9	20.0±2.0	

**Table 2** Monitoring outcomes, clinical end points, and the warfarin-related complications\*

Outcomes	Stratum 1N = 34	Stratum 2N=34	Stratum 3N=34	p
TTR achievable	23 (67.6%)	28 (82.4%)	30 (88.2%)	0.096
Adverse event	6 (17.6%)	3 (8.8%)	3 (8.8%)	0.427
ED visit	1 (2.9%)	2 (5.9%)	2 (5.9%)	0.045
Hospitalization	1 (2.9%)	1 (2.9%)	0 (0%)	0.600

\*Major bleeding; any bleeding that resulted in hospital admission; Thromboembolism; any objectively confirmed thromboembolic event; Warfarin-related emergency department visit; emergency department visit due to a complication of warfarin therapy (most commonly ecchymoses); Warfarin-related hospital admission; any hospital admission specifically due to a complication of warfarin therapy, including major bleeding complications, strokes, other thromboembolic events, and over anticoagulation.

was demonstrated, particularly for patients who are unable to come to the clinic due to personal preference, distance, transportation, or disability issues. The telephone management was used as a reinforcement between short and long-period follow-ups.

There were several limitations to this study that are typical of PROBE evaluations. First, because it is a short duration to follow-up in office-based patients, the programmed education could have memorable effect to many patients. Second, the protocol of warfarin guided the dosage adjustment to achieve the goals by expert clinicians. Third, the rigid structured telephone-based education and commentary may not have allowed natural communication. However, the telephone-based education actively interrogated for serious complication of warfarin usage. Finally, certain adverse events, particularly serious bleeding, was associated with warfarin exposure duration.

## Conclusion

The study demonstrated no significant differences were found in INR clinical goal achievable by TTR, number of bleeding events, thromboembolic events, warfarin-related emergency department visits, or warfarin-related hospital admissions between patients whose oral anticoagulant therapy was managed by the added telephone-based of a multidisciplinary team compared to patients whose therapy was managed during office-based encounters in an

anticoagulation clinic setting. However, it was feasible and safe to use for reinforcement therapy. While these findings may be not demonstrated clinical impact to achieve INR goal by TTR they enhance the perception for patient evaluation and education when they visit the clinic.

The authors have no conflicts of interest.

## References

1. Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126 (suppl):204S–233S.
2. Ansell JE, Buttaro ML, Thomas VO, et al. Consensus guidelines for coordinated outpatient oral anticoagulation therapy management. *Annals Pharmacotherapy*. 1997;31:604–615.
3. Witt DM, Sadler MA, Shanahan RL, et al. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest*. 2005;127:1515–1522.
4. Pal B. Following up outpatients by telephone: pilot study. *British Medical Journal*. 1998;316:1647–1650.
5. Car J, Sheikh A. Telephone consultations. *British Medical Journal*. 2003;326:966–969.
6. Goldberg Y, Meytes D, Shabtai E, et al. Monitoring oral anticoagulant therapy by telephone communication. *Blood Coagulation and Fibrinolysis*. 2005;16:227–230.
7. Samer Hassan, Ali Naboush, Jared Radbel, et al. Telephone-based anticoagulation management in the homebound setting: a retrospective observational study Telephone-based anticoagulation management in the homebound setting: a retrospective observational

- study. *Journal of International Journal of General Medicine*. 2013;6:869–875.
8. Scalley RD, Kearney E, Jakobs E. Interdisciplinary inpatient warfarin education program. *American Journal of Hospital Pharmacy*. 1979;36:219–220.
  9. Dolor RJ, Ruybalid RL, Uyeda L, et al. An evaluation of patient self-testing competency of prothrombin time for managing anticoagulation: pre-randomization results of VA Cooperative Study #481–The Home INR Study (THINRS). *Journal of Thrombosis and Thrombolysis*. 2010;30(3):263–275.
  10. Stafford L, van Tienen EC, Peterson GM, et al. Warfarin management after discharge from hospital: a qualitative analysis. *Journal of Clinical Pharmacy and Therapeutics*. 2012;37(4): 410-414.
  11. Waterman AD, Banet G, Milligan PE, et al. Patient and Physician Satisfaction with a Telephone-based Anticoagulation Service. *Journal of General Internal Medicine*. 2001;16:460-463.
  12. Wofford JL, Wells MD, Singh S. Best strategies for patient education about anticoagulation with warfarin: a systematic review. *BMC Health Services Research*. 2008;8:40.
  13. Davis NJ, Billett HH, Cohen HW, Arnsten JH. Impact of adherence, knowledge, and quality of life on anticoagulation control. *Annals Pharmacotherapy*. 2005;39:632–636.
  14. Gadisseur AP, Breukink-Engbers WG, van der Meer FJ, van den Besselaar AM, Sturk A, Rosendaal FR. Comparison of the quality of oral anticoagulant therapy through patient self-management and management by specialized anticoagulation clinics in the Netherlands: a randomized clinical trial. *Archives Internal Medicine*. 2003;163:2639–2646.
  15. Newall F, Monagle P, Johnston L. Patient understanding of warfarin therapy: a review of education strategies. *Hematology*. 2005; 10:437–442.
  16. Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB. Management of venous thromboembolism: A systematic review for a practice guideline. *Annals of Internal Medicine*. 2007;146:211–222.

# การเสริมความรู้เรื่องยาละลายลิ่มเลือดทางโทรศัพท์ด้วยสหสาขาวิชาชีพ ในผู้ป่วยที่ยังไม่เข้าเกณฑ์รักษา

ภุริทัต เมืองบุญ พบ.<sup>1</sup>, กฤษฎา ศาสตร์ราหา พบ.<sup>1</sup>

<sup>1</sup>หน่วยโรคหัวใจและหลอดเลือด, กองอายุรกรรม, โรงพยาบาลภูมิพลอดุลยเดช

## บทคัดย่อ

**ภูมิหลัง:** การรักษาระดับ INR ในผู้ป่วยที่รับประทานยาออร์ฟารินในอยู่ในช่วงการรักษาด้วยสหสาขาวิชาชีพในโรงพยาบาลนั้นมีความสำคัญเพราะสามารถประเมินผลการรับประทาน, ความร่วมมือรวมถึงการให้ความรู้และประเมินความเข้าใจการใช้จ่ายยาได้ดี อย่างไรก็ตามการใช้โทรศัพท์เสริมเพื่อให้ความรู้ด้วยสหสาขาวิชาชีพอาจให้ผลการเข้าถึงระดับ INR ได้เพิ่มขึ้น

**วิธีการศึกษา:** เป็นการศึกษาชนิดสุ่มที่มีกลุ่มควบคุมแบบ PROBE แบ่งผู้ป่วยที่ระดับ INR ยังไม่เข้าเกณฑ์การรักษาออกเป็น 3 กลุ่ม กลุ่มควบคุมได้รับการรักษาในโรงพยาบาลด้วยสหสาขาวิชาชีพ ในขณะที่กลุ่มที่ 2 และ 3 ได้รับโทรศัพท์ที่ให้ความรู้เสริมเกี่ยวกับการใช้ยาออร์ฟารินเพิ่มอีก 1 และ 2 ครั้งตามลำดับโดยมีระยะเวลาติดตามระดับ INR ทุก 2 และ 3 เดือนตามลำดับและติดตามระดับ INR ที่สิ้นสุดการศึกษา โดยผลลัพธ์หลักได้แก่ therapeutic time in range (TTR) ตามเกณฑ์รักษาและผลลัพธ์รองได้แก่ภาวะเลือดออกผิดปกติและภาวะลิ่มเลือดอุดตันที่เกี่ยวข้องด้วยยาออร์ฟาริน

**ผลลัพธ์:** ลักษณะทั่วไปของผู้ป่วยทั้ง 3 กลุ่มๆ ละ 34 ราย จำนวน 102 รายจาก 319 ที่เข้าเกณฑ์คัดเลือกไม่มีความแตกต่างกันเมื่อพ้นระยะเตรียมการ (run-in) ส่วนใหญ่เป็นเพศชาย อายุเฉลี่ย  $56.0 \pm 13.7$  ปี ร้อยละ 70.0 มีระดับ INR ไม่เข้าเกณฑ์การรักษาเพราะเหตุเกี่ยวข้องกับขนาดยาออร์ฟาริน เมื่อสิ้นสุดการศึกษาไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติของผลลัพธ์หลักและรอง ได้แก่ การเพิ่มระดับ INR ตามเกณฑ์ด้วยวิธี TTR ทั้ง 3 กลุ่ม (67.6%, 82.4%, 88.2%,  $p = 0.096$ ), ภาวะลิ่มเลือดและ/หรือเลือดออกผิดปกติ (17.6%, 8.8%, 8.8%,  $p = 0.427$ ) และการเข้ารับการรักษาในโรงพยาบาลด้วยเหตุเกี่ยวข้องกับยาออร์ฟาริน (2.9%, 2.9%, 0%,  $p = 0.600$ ) อย่างไรก็ตามกลุ่มผู้ป่วยที่ได้รับโทรศัพท์เสริมมีแนวโน้มที่อัตราเข้ารับการรักษาที่ห้องฉุกเฉินมากกว่า ( $p = 0.045$ ) และไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มผู้ป่วยที่มีระยะเวลาติดตามผล INR ทุก 2 และ 3 เดือนตามลำดับ

**สรุป:** การเสริมโทรศัพท์เพื่อให้ความรู้แก่ผู้ป่วยที่รับประทานยาออร์ฟารินที่ระดับ INR ยังไม่เข้าเกณฑ์การรักษาด้วยสหสาขาวิชาชีพไม่เพิ่มอัตราการรักษาตามความจำเป็นของระดับ INR แต่ละเป้าหมาย

**คำสำคัญ:** ยาเม็ดละลายลิ่มเลือด, โทรศัพท์, ยาออร์ฟาริน