A Retrospective Evaluation of the Impact of Multi-disciplinary Approach for Improving the Quality of Anticoagulation Therapy in Ambulatory Patients with Non-valvular Atrial Fibrillation Receiving Warfarin

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While percent time within therapeutic range (%TTR) of international normalized ratio of prothrombin time (PT-INR) represents the quality of anticoagulation therapy with warfarin, it is often maintained less than 50% in patients with non-valvular atrial fibrillation (NVAF). We aimed to study if implementation of a multi-disciplinary ambulatory anticoagulation service (MAAS) may improve %TTR. Collaborating with cardiologists at Kanto Rosai Hospital, we conducted a MAAS for NVAF patients receiving warfarin from April 2013 to December 2015. Patients who agreed to utilize the service in addition to their appointments with cardiologists visited pharmacists to have counseling about diet, concomitant medications, and lifestyle. According to a protocol, pharmacists made dose adjustment proposals to cardiologists, if necessary. Upon approval by cardiologists, dose modifications were made. We retrospectively reviewed medical records of the patients who participated in the MAAS before and during the service. The study protocol was approved by the institutional review board. We identified 78 eligible patients (44 males and 34 females, aged 51 to 91 years). Their median %TTR increased significantly (p < 0.05) from 57% during the pre-MAAS period to 77% during the MAAS period. In addition, the median percent time below therapeutic range (%TBTR) decreased significantly (p < 0.05) from 35% during the baseline period to 11% during the MAAS period. The present study indicates that MAAS improves the quality of anticoagulation therapy with warfarin in ambulatory patients with NVAF. Further prospective, randomized studies with a greater number of patients are required to confirm the results of the present study.

Key words—non-valvular atrial fibrillation; warfarin; prothrombin time; time in therapeutic range; multidisciplinary service

BACKGROUND

Warfarin is an orally active vitamin K antagonist that has been used for over 60 years for the prevention of thromboembolic diseases in patients with non-valvular atrial fibrillation (NVAF). Despite the introduction of direct oral anticoagulants (DOACs),1–4 warfarin is still widely prescribed. According to the guidelines issued by Japanese Circulation Society, international normalized ratio of prothrombin time (PT-INR) between 2 to 3 has been recommended as the therapeutic window for NVAF patients younger than 70 years.5) Nevertheless, it has often been difficult to maintain PT-INR within the therapeutic range in real-world ambulatory patients. The quality of anticoagulation therapy with warfarin may be assessed by percent time within the therapeutic range (%TTR) of PT-INR.6) A previous study demonstrated that NVAF patients receiving warfarin had greater benefit over an antiplatelet therapy only when their %TTR was maintained greater than 65%,7) indicating that the efficacy of warfarin depends critically on %TTR.8) As a result, in head-to-head randomized clinical trials comparing the efficacy and adverse drug reactions between warfarin and DOACs, %TTR of patients receiving warfarin was maintained above 65%.1–4) While the Japanese guidelines recommend that %TTR should be maintained at
60% or greater for NVAF patients receiving warfarin,\(^5\) %TTR of patients in ambulatory service has been reported to be approximately 50% or less.\(^9\)

Among many attempts conducted for improving the quality of warfarin therapy in ambulatory care, a multi-disciplinary ambulatory anticoagulation service (MAAS) may be of interest. A recent systematic review revealed that implementation of MAAS in patients receiving warfarin reduced the risk of hospitalization compared with routine medical care and was associated with a lower or equal risk of major bleeding or thromboembolic events.\(^10\) While a study demonstrated that a physician-led point-of-care approach was effective in improving the quality of anticoagulation therapy with warfarin in Japan,\(^11\) to our knowledge, the impact of MAAS on warfarin therapy has not been reported. Here, we report our attempts aiming to improve the quality of warfarin therapy by MAAS in our institution.

**METHODS**

**Study Design and Patients**  
Our hospital with 610 beds is located in the suburbs of the Tokyo metropolitan area. Most of the patients who had been initiated on warfarin therapy for NVAF during hospitalization were followed at the ambulatory clinic of the hospital after discharge. They visited the ambulatory clinic every 2 to 3 months for PT-INR monitoring and counseling with cardiologists. In order to provide more extensive follow-up, we launched a temporal, team-based routine medical service for patients receiving warfarin (i.e., MAAS) from April 2013 after obtaining an institutional approval.

Briefly, having explained the purpose of the service and obtained oral informed consent from the patient, the cardiologist made an appointment for the patient to attend the MAAS at the midpoint of regular visits to cardiologists. During the visit to MAAS, patients underwent a PT-INR measurement and had an interview with pharmacists. The pharmacist reviewed the patient’s adherence to warfarin therapy, diet, concomitant medications including non-prescription drugs and supplements, lifestyle, and signs and symptoms of adverse drug reactions with reference to the PT-INR value measured before the interview. Pharmacists not only gave pharmaceutical advice to patients, but also provided feedback to cardiologists by telephone about dosage adjustment if deemed necessary, according to the protocol that had been agreed between cardiologists and pharmacists prior to the initiation of the service (Supplementray Table 1).\(^12\) Cardiologists made the final decision about dosage modification. MAAS was terminated in December 2015.

Since MAAS appeared to improve the quality of anticoagulation therapy with warfarin, we planned to undertake a retrospectively study where we evaluate the clinical efficacy of MAAS. We reviewed medical records of all NVAF patients receiving warfarin under ambulatory care of the Kanto Rosai Hospital between April 2013 and December 2015. Among the patients retrieved, we identified those who participated in MAAS. For the relevant patients, we further reviewed their medical records before the service. Patients with rheumatic mitral valve disease or prosthetic valve were excluded from the analysis. Demographic (age, gender, height, and weight) and relevant clinical variables (renal function, CHADS\(_2\) score, PT-INR, duration of warfarin therapy, and numbers of visit to the ambulatory clinic including MAAS) were retrieved from the medical records. By scrutinizing the medical records, we identified concomitant medications that might have interfered with the anticoagulation effect of warfarin (including antiplatelet drugs, acetaminophen, allopurinol, amiodarone, systemic azole antifungals, cimetidine, fluoroquinolone, macrolide antibiotics, metronidazole, propafenone, selective serotonin reuptake inhibitors, hydroxyl methylglutaryl coenzyme A reductase inhibitors, and sulfonamide antimicrobials).

**Assessment of the Quality of Anticoagulation Therapy**  
Quality of anticoagulation therapy with warfarin was assessed according to the Rosendaal method.\(^6\) Briefly, %TTR for a patient was calculated as the proportion of time during which his/her PT-INR was maintained within the target range over the entire observation period. Therapeutic windows of PT-INR for those aged <70 and ≥70 years were set at 2.0–3.0 and 1.6–2.6, respectively, according to the guidelines issued by Japanese Circulation Society.\(^5\) For comparing %TTR data before and during MAAS, we performed the analysis using data obtained from comparable observational periods before and during MAAS. First, we identified a relevant observation period during MAAS period in each patient from the first day of his/her participation to the service to the end of the service (i.e., December 2015). Then, we tracked back PT-INR data for the same
patient in the pre-MAAS period on the medical records from the latest visit before the commencement of MAAS as long as possible. When an observation period during MAAS was shorter than that of the pre-MAAS period in a patient, we adopted the pre-MAAS data that were obtained within the same length of observation period from the latest visit before MAAS, and vice versa. We excluded the PT-INR data obtained during periods when warfarin was suspended for clinical reasons (e.g., elective surgery, invasive medical procedure, and unexpected elevations of PT-INR above the therapeutic range) and those obtained within 7 d after resuming administration of warfarin. Patients with a follow-up period shorter than 100 d and patients who had only a single point of PT-INR measurement were excluded from the analysis. We also modified the Rosendaal method to calculate percent time below the therapeutic range (%TBTR) and percent time above the therapeutic range (%TATR) for each patient.

Ethics Approval The present study was conducted in compliance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the Guidelines for Proper Handling of Personal Information in Medical Care/Nursing Care Service Providers. Patients’ names were replaced with randomly generated 4-digit numbers before analysis and the data were analyzed anonymously thereafter. We had an official approval for our new service at the ambulatory clinic (MAAS) from the institutional authority before it was started. We did not obtain written informed consents from patients when they participated in the MAAS, because it was conducted as a routine, protocol-based pharmacotherapy service, but not as a research. MAAS was begun for improving the quality of anticoagulation therapy with warfarin. The protocol of the present retrospective study was submitted to the IRB of Kanto Rosai Hospital after the service had been terminated, and it was approved (No. 2015-23) with a condition of the official announcement of the research protocol on the hospital Web site.

Statistical Analysis Data are presented as mean ± S.D. or median [upper limits of the first quartile (Q1) and third quartile (Q3) ranges], unless stated otherwise. Continuous variables were compared using Wilcoxon signed-rank test. Categorical variables were compared using McNemar’s test. A p value less than 0.05 by two-tailed test was considered statistically significant. We did not conduct a power calculation for detecting clinically relevant difference in %TTR before the study. However, our post-hoc analysis estimated that 51 patients were required for obtaining a statistically significant difference by implementing MAAS under an assumption of $\alpha = 0.05$, $\beta = 0.2$; mean %TTR during the baseline period ($\mu_{\text{baseline}}$) and that during the MAAS period ($\mu_{\text{MAAS}}$) would be 48% and 60%, respectively, and S.D. of %TTR would be 30%. We considered that at least a 10% difference in %TTR between the baseline period and during the MAAS period would be clinically relevant. Since mean %TTR observed in our ambulatory clinic was 48% with S.D. of approximately 30%9 and the guidelines recommended %TTR of 60% for ambulatory patients, we considered that a 10 to 12% improvement in %TTR in our patients by implementing MAAS would be a realistic goal for the present study. Statistical analyses were performed with JMP Pro ver. 11 software (SAS Institute Inc., Cary).

RESULTS

We identified 98 patients who participated in the MAAS project. Twenty patients were excluded from analysis, because their follow-up periods were less than 100 d or multiple PT-INR measurements were not available in either or both of the observation periods. The demographic and relevant clinical characteristics of the 78 eligible patients are summarized in Table 1. They were old (mean age, 74 ± 10 years) and had a moderate risk of thromboembolic complications as indicated by the mean CHADS2 score of 2 ± 1. The median follow-up period of the patients was 830 [469, 899] d, and the median values for the total number of hospital visits was 19 times [10, 24], and the corresponding value for PT-INR measurement was 19 time [10, 24]. Dose adjustments were made for a median of 3 [1, 7] times per patient (Table 2).

Figure 1 shows the changes in %TTR from the pre-MAAS period to the MAAS period in individual patients. The median %TTR improved from 57% [26, 74] during the pre-MAAS period to 77% [60, 92] during the MAAS period ($p < 0.05$) (Table 2). The median %TBTR decreased significantly from 35% [10, 73] during the pre-MAAS period to 11% [2, 23] during the MAAS period. In addition, the median %TATR increased significantly from 0% [0, 3] during the pre-MAAS period to 6% [0, 12] during
the MAAS period. The proportion of patients who achieved %TTR ≥ 60% improved significantly from 47% during the pre-MAAS period to 74% during the MAAS period (Table 2).

Among the 37 patients who exhibited %TTR ≥ 60% during the pre-MAAS period, five patients showed %TTR < 60% during the MAAS period. In two patients, warfarin was suspended because they underwent surgery for diseases unrelated to NVAF. One patient withdrew from warfarin therapy due to accidental traumatic injury. One patient was temporarily withdrawn from MAAS, since the patient was cared in a non-cardiology department for the treatment of non-cardiac medical problems. In the remaining patient, PT-INR was maintained intentionally at lower values of the therapeutic range according to a cardiologist’s judgement, because the patient had a lower risk of thromboembolic events as indicated by CHADS$_2$ scores of 0.

**DISCUSSION**

The present study revealed that implementation of MAAS for patients with NVAF receiving warfarin significantly ($p < 0.05$) improved the quality of anticoagulation therapy assessed by %TTR and %TBTR (subtherapeutic coagulation) (Fig. 1 and Table 2). Along with a trend of upward shift in PT-INR during the MAAS period, a significant ($p < 0.05$), albeit small, increase in the median value for %TATR (excessive anticoagulation) from 0% to 6% during the baseline period and MAAS period, respectively (Table 2). The improvement in quality of anticoagulation during MAAS as compared to the pre-MAAS period might have been attributed either to more frequent ($p < 0.05$) counseling with pharmacists or PT-INR measurement at the MAAS. Indeed, the patients underwent more frequent ($p < 0.05$) dose adjustments during the MAAS period compared to the pre-MAAS period. Nevertheless, it would be difficult to attribute favorable changes in the quality of anticoagulation therapy to one of the factor(s) including changes in patients’ adherence, diet, intakes of over-the-counter drugs or supplements, since the present study was retrospective and observational in design and did not include a concurrent comparator group. Collectively, further prospective cohort or randomized studies are warranted to confirm the external validity of MAAS for improving the quality of anticoagulation therapy with warfarin and to identify major factors associated with the improvement.

It is well established that antithrombotic efficacy and risk of bleeding during warfarin therapy are associated with PT-INR, and PT-INR ranging from 2.0 to 3.0 has been shown to be the therapeutic window in terms of the balance between efficacy and risks of adverse reactions. In addition, most of the recent guidelines for anticoagulation therapy with warfarin recommend to assess the quality of anticoagulation therapy with warfarin using %TTR, and %TTR of 60% or greater has been considered a hallmark of good quality of anticoagulation. Various attempts have been made to attain and maintain a high quality of anticoagulation with warfarin. For instance, implementation of computerized dosing algorithm during the initiation phase of warfarin therapy in hospitals, utilization of point-of-care (POC) PT-INR monitoring at pharmacist-led ambulatory warfarin clinics, and self-monitoring at home in U.S. and Europe. To our knowledge, however, only a few attempts have been reported in Japan. Okuyama et al. reported that the implementation of POC testing of PT-INR using the CoaguChek® XS system (Roche...
Table 2. Comparisons of Quality of Anticoagulation Therapy with Warfarin between the Pre- and During the Multi-disciplinary Ambulatory Anticoagulation Service (MAAS) Periods

| Observation period (d)                  | Pre-MAAS | During MAAS | p value |
|----------------------------------------|----------|-------------|---------|
| Quality of warfarin therapy            |          |             |         |
| %TTR ≥ 60%, n (%)                      | 37 (47)  | 58 (74)     | <0.05*  |
| %TTR                                   | 57 (26, 74) | 77 (60, 92) | <0.05*  |
| %TBTR                                  | 35 (10, 73) | 11 (2, 23)  | <0.05*  |
| %TATR                                  | 0 (0, 3)  | 6 (0, 12)   | <0.05*  |

Management of warfarin therapy in ambulatory clinic

Total number of visits and PT-INR assays [ordered by MAAS] 12 (9, 14) 19 (10, 24) <0.05*

Total number of dose adjustments [according to pharmacists’ advice at MAAS] 2 (1, 3) 3 (1, 7) <0.05*

* McNemar’s test, † Wilcoxon’s signed rank test. Data are shown as median and interquartile values (Q1 = first quartile and Q3 = third quartile), † unless stated otherwise. %TTR = percent time within therapeutic range, %TBTR = percent time below therapeutic range, %TATR = percent time above therapeutic range, PT-INR = prothrombin time-international normalized ratio, NA = not applicable.

![Fig. 1. Comparison of Percent Time within Therapeutic Range (%TTR) between the Pre- and during Multi-disciplinary Ambulatory Anticoagulation Service (MAAS) Periods](image)

Diagnostics, K.K., Tokyo) in Japanese outpatient clinics improved the quality of anticoagulation therapy with warfarin. However, their study appeared to be physician-led with no mention of the contributions of pharmacists. In this context, the present study demonstrates that pharmacists in collaboration with cardiologists can also make significant contribution via MAAS for improving the quality of warfarin therapy under the Japanese healthcare system. For attaining high-quality warfarin therapy, a systematic coordinated approach to patient education, implementation of regular PT-INR testing, tracking, follow-up, and communication with patients are considered essential. Pharmacists may play an important role in this system.

Scrutinizing the data, we recognized that many patients having %TTR > 85% during pre-MAAS showed a reduction in %TTR during MAAS period (Fig. 1). We have no reasonable explanation for this finding. These changes might have been explained by random variations during the therapeutic range of PT-INR. To our knowledge, it remains unclear whether the variability of PT-INR within the therapeutic range may be associated with relevant clinical outcomes. In addition, there were several patients who showed %TTR < 60% in the pre-MAAS period and showed no apparent improvements in the values during the MAAS period (Fig. 1). No definite explanation may be offered for these findings. Nevertheless, in most of the patients, we considered that cardiologists intentionally kept their PT-INRs at the lower therapeutic range (e.g., around 1.6), since they had higher clinical risks of bleeding according to the data retrieved from medical records. For these patients, %TTRs calculated with use of the Rosendaal method would show lower values irrespective of the participation to MAAS.

Cost-effectiveness of the MAAS for warfarin therapy needs to be discussed. The implementation of MAAS was associated with a 60% increase in total number of patients’ visits as compared that in the pre-MAAS period (Table 2). While we anticipated that
the number of visits would increase two-fold during the MAAS period, it was much less than expected. This is probably due to the fact that the pharmacists proposed to prolong the interval of ambulatory check-up in patients with stable PT-INR. According to the American College of Chest Physicians (ACCP) Guidelines (Grade 2B) in 2012, the interval of PT-INR measurement may be extended up to a maximum of 12 weeks in patients with stable PT-INR.\(^{20}\) Collectively, we consider that the additional economic burden to patients by utilizing MAAS may be well balanced by the improvement of the quality of anticoagulation therapy. Nevertheless, at present we are not able to show hard data indicating the real benefits of MAAS with respect to efficacy and adverse events of warfarin therapy, due mainly to the small number of patients participating in the study.

The present study has several drawbacks for external validation. First, the present study was retrospective and observational in design. Comparisons were made in the same group of patients before and after the implementation of MAAS. As a result, a period effect cannot be excluded. In addition, it is possible that patients having low %TTR may have been recruited preferentially by cardiologists, since they were aware of the purpose of the MAAS. In order to identify factor(s) that were associated with the improvement of %TTR, we should have performed stratified analysis in terms of patients' characteristics and pharmacists' intervention. Unfortunately, complete data collection was impossible due to the design of the present study. Despite these limitations, our results would warrant further studies for validating the impact of MAAS in improving the outcome of warfarin therapy.

**CONCLUSION**

The present study demonstrated that implementation of MAAS for NVAF patients receiving warfarin improved the quality of anticoagulation therapy. Further studies are required to verify whether our approach can be generalized to other institutions.

**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Materials** Supplementary materials are available online with the present manuscript.

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