Introduction of Point-of-Care Testing in Japanese Outpatient Clinics Is Associated With Improvement in Time in Therapeutic Range in Anticoagulant-Treated Patients

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Background: Warfarin reduces the risk of stroke in patients with atrial fibrillation (AF), but requires a moderate-to-high time in therapeutic range (TTR). We hypothesized that point-of-care (POC) testing for prothrombin time-internationalized normalized ratio (PT-INR) could improve the TTR in patients receiving warfarin.

Methods and Results: Eight outpatient clinics that introduced POC testing for PT-INR participated in this study. We identified 148 consecutive patients who received warfarin for at least 12 months before and after the introduction of POC testing. We compared the TTR before and after the introduction of POC testing for each patient. TTR after the introduction of POC testing was significantly higher than that beforehand (51.9%±33.0% vs. 69.3%±26.3%; P<0.0001). The improvement in TTR was statistically significant in patients who had low TTR (<70%) before the introduction of POC testing. After the introduction of POC, the time spent above the target INR showed no significant change (3.7%±10.6% vs. 3.3%±6.3%, P=0.7322), while that spent below the target INR improved significantly (44.4%±34.4% vs. 27.4%±27.6%, P<0.0001).

Conclusions: The introduction of POC testing was associated with an improvement in TTR, mainly through a reduction in the time spent below the target INR.

Key Words: Outpatient clinic; Point-of-care testing; Prothrombin time-internationalized normalized ratio; Time in therapeutic range; Warfarin

Strong evidence from clinical trials has shown that warfarin reduces the risk of stroke and mortality in patients with atrial fibrillation (AF). Warfarin, however, is often underused because it is believed to be associated with an increased risk of bleeding. A long time in therapeutic range (TTR) is required for warfarin therapy to be maximally effective. This reduces the risk of not only stroke and systemic embolism, but also bleeding. Patients with optimal international normalized ratios (INR) experience less severe disability than those with sub-therapeutic INR, when affected by stroke or systemic embolism. In addition, when assessed at 30 days after admission, the prognosis of patients with optimal INR was found to be better than that of patients with sub-therapeutic INR. Therefore, it is critical that the INR of patients receiving warfarin is maintained within the target therapeutic range. In patients with mechanical heart valve(s) and mitral stenosis, INR should also be maintained within the target therapeutic range. This is a major challenge, however, in actual clinical practice. Although the TTR of AF patients managed at specialized cardiology centers in Japan has been reported to be 64%, that of patients attending outpatient clinics has not yet been investigated. In Japan, many elderly patients are followed up at outpatient clinics.

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Okuyama Y et al.

The POC testing device, CoaguChek® (Roche Diagnostics), was introduced in outpatient clinics of Japan; the use of this device was expected to increase the quality of warfarin therapy in these clinics. An important disadvantage of TTR control in these clinics is that blood samples for PT-INR measurement are sent to an offsite laboratory, and the results become available half a day or a full day after blood sampling. In 2007, CoaguChek®, a device used for point-of-care (POC) testing of PT-INR, was introduced in outpatient clinics of Japan. The device was expected to increase the quality of warfarin therapy in terms of TTR, because POC testing could overcome the time delay in the availability of PT-INR test results. In this study, we sought to test the hypothesis that the introduction of POC testing of PT-INR improved the TTR of patients visiting different outpatient clinics in Japan.

### Methods

Eight outpatient clinics located in the Osaka Prefecture in Japan participated in this retrospective observational study. The POC testing device, CoaguChek® (Roche Diagnostics), was made available to all the participating clinics >1 year before participation in this study. The study protocol was approved by the ethics committee of Osaka University Hospital. Written informed consent was waived because the analyzing center was blinded to the pre-existing data, as stipulated by the Japanese epidemiological study guidelines.

### Subjects

We enrolled patients who received warfarin for the treatment of AF, heart valve replacement, as well as mitral stenosis, and who were followed up at any of the participating clinics between 28 June 2010 and 31 May 2012. Patients were enrolled only if they had received warfarin for more than 15 months at the time of introducing the POC testing device at the respective clinic. This was necessary because we intended to compare the data on the TTR for >1 year before and 1 year after implementation of the POC testing device. We reviewed patient charts and collected data on patient profile, concomitant antiplatelet drug use, and PT-INR measurements. PT-INR measurements were made every 1 or 2 months for at least 1 year before and 1 year after the introduction of the POC testing device. During follow-up, warfarin dosage for patients with non-valvular AF was adjusted according to the Japanese Guidelines for Pharmacotherapy of Atrial Fibrillation to maintain INR at 2.0–3.0 and 1.6–2.6 for patients aged <70 years and ≥70 years, respectively. Warfarin dosage for patients with mechanical heart valve(s) and mitral stenosis was also adjusted according to the Guidelines to maintain INR at 2.0–3.0. For the present study, we used the PT-INR results obtained at least 3 months after the initiation of warfarin. Patients who had an interval >100 days between 2 PT-INR measurements were excluded because the calculated TTR in such cases may not accurately reflect the quality of warfarin control.

### Study Protocol

We analyzed the data with software designed specifically for the study (Medi-Skette, Tokyo, Japan). Successive PT-INR of each patient were entered into the computer program, and the TTR was calculated. The software program automatically drew successive demarcations between any 2 consecutive PT-INR obtained during the observation period and calculated the percentage of the total time within the preset therapeutic range over the specified period. The therapeutic range of the INR was set as described in the previous section. We defined TTR before the introduction of the POC testing device (TTRBefore), as the TTR obtained for the period between the first visit to the outpatient clinic for PT-INR evaluation and the last visit within 1 year before the POC testing device was introduced at that clinic. TTR after the introduction of the POC testing device (TTRAfter) was defined as TTR obtained in the time period between the introduction of the device at a clinic and the last visit for PT-INR evaluation within 1 year after the introduction of the POC testing device. We also defined the time periods “time spent under therapeutic range (TUTR)” and “time spent over therapeutic range (TOTR)” to investigate reasons for change in TTR.

We first compared factors related to TTRAfter with those for TTRBefore, as well as the TUTR and TOTR before and after the introduction of POC testing. We then analyzed the following factors with the potential to influence a change in TTR: TTRBefore, age, gender, history of concomitant antiplatelet drug use, CHADS2 score,13 and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score.14

### Statistical Analysis

All data are expressed as mean±SD. We used a 2-tailed paired t-test to assess the TTR change before and after the introduction of the POC testing device, and 1-way analysis of variance with Bonferroni post-hoc test to compare the TTR of 3 or more groups. We used the Tukey range test to compare TTR between clinics. P<0.05 was regarded as statistically significant.

### Table 1. Clinical Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
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<tr>
<td>(n=109)</td>
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<tr>
<td>Age (years)</td>
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<td>Men (n=57)</td>
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<td>Women (n=52)</td>
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<td>Indication for warfarin</td>
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<tr>
<td>AF</td>
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<tr>
<td>Mechanical heart valve</td>
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<tr>
<td>Mitral stenosis</td>
<td>4</td>
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<tr>
<td>Warfarin dose at introduction of POC testing (mg/day)</td>
<td>2.6±1.0</td>
</tr>
<tr>
<td>AF</td>
<td>2.6±1.0</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>2.6±1.2</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>2.6±1.3</td>
</tr>
<tr>
<td>Mean TTRBefore of all patients (%)</td>
<td>51.9±33.0</td>
</tr>
<tr>
<td>AF</td>
<td>55.2±32.1</td>
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<tr>
<td>Mechanical heart valve</td>
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<tr>
<td>Mitral stenosis</td>
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<td>CHADS2 score of AF patients</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
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<tr>
<td>3–6</td>
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<td>HAS-BLED score of all patients</td>
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<tr>
<td>0–2</td>
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<tr>
<td>3–9</td>
<td>22</td>
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</tbody>
</table>

Data given as mean±SD or n. Four patients did not have data for HAS-BLED score.

AF, atrial fibrillation; POC, point of care; TTRBefore, time in therapeutic range before the introduction of POC testing.

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**Editorial p????**
Improvement in TTR

TOTR was low, at 3.7%±10.6% and 3.3%±6.3%, respectively, both before and after the introduction of POC testing (P=0.7322). In contrast, TUTR decreased after the introduction of POC testing (44.4%±34.4% vs. 27.4%±27.6%; P<0.0001; Figure 2). The mean interval between PT-INR measurements before the introduction of POC testing was greater than that after its introduction (42.7±14.4 and 35.2±10.2 days, respectively; P<0.0001).

Factors Influencing Improvement of TTR

A recent study reported that TTR <40% could be associated with a tendency toward worse outcome in stroke incidence. In that study, only warfarin-treated patients with TTR >70% had significantly fewer strokes than those not treated with warfarin. To assess the effects of an improvement in TTR, we divided the present patients into the following 3 groups according to TTRBefore: those with TTR ≤40%; those with TTR 41–70%; and those with TTR ≥71% (Figure 3); the average TTRBefore in the 3 different groups was 15.8%±14.4% (n=40), 55.0%±8.9% (n=34), and 90.2%±9.2% (n=35), respectively. TTR of the 2 groups with low TTR Before (≤40%, 41–70%) improved significantly after the introduction of POC testing (51.0%±26.1% and 75.4%±24.1%, respectively; both P≤0.0001), while that of the group with the highest TTRBefore (≥71%) decreased significantly (84.3%±13.4%, P=0.0299).

The patients were classified into 3 groups according to CHADS2: score 0–1 (n=20), 2 (n=19), and 3–6 (n=41) to examine the relationship between the risk of stroke and improvement in TTR. TTRAfter improved in patients with CHADS2 score 0–1 (38.0%±34.5% to 58.1%±31.0%, P=0.0019) and those with CHADS2 score 3–6 (63.1%±29.9% to 79.5%±19.7%, P=0.0007). TTRAfter in patients with CHADS2 score 2 showed a tendency for improvement, but statistical significance was not reached (56.1%±28.2% to 69.3%±23.1%, P=0.0572).

**Results**

**Patient Clinical Characteristics**

We identified 148 patients who were treated with warfarin. Thirty-nine of these 148 patients were excluded because they had an interval >100 days between 2 PT-INR measurements. Thus, data from 109 patients were included in the analysis: 80 patients received warfarin for AF; 25 patients for heart valve replacement; and 4 patients for mitral stenosis (Table 1). The mean interval between PT-INR measurements was 37.7±9.9 days. The mean patient age was 72.6±9.5 years (range, 45–97 years), and the mean age of the male (n=57) and female (n=52) patients was 71.5±9.7 years and 73.9±9.3 years, respectively. The INR range used for the calculation of TTR was maintained at 2.0–3.0 for patients with non-valvular AF who became older than 70 years of age during the study period. The mean CHADS2 score in patients with non-valvular AF was 2.4±1.3 (median, 2), and the mean warfarin dose given at the first visit during the observational period was 2.6±1.0 mg/day (range, 0.75–5.5 mg/day). In all, 23 warfarin-treated patients were given antiplatelet drugs concomitantly (21.1%), and over the 2-year study period, 5 cases of symptomatic brain infarction and 1 case of brain hemorrhage were recorded. Bleeding associated with gastric cancer was reported in 1 other patient.

**Change in TTR**

TTRBefore was 51.9%±33.0%; TTRAfter was significantly higher: 69.3%±26.3% (P<0.0001; Figure 1). Improvements in TTR were observed in patients with AF (55.2%±32.1% to 71.8%±25.1%, P<0.0001) and mechanical heart valve (43.3%±33.8% to 62.5%±27.1%, P=0.0013), but only a tendency for improvement was noted in patients with mitral stenosis (41.4%±42.6% to 62.7%±42.0%, P=0.3319).
HAS-BLED score is a predictor of major bleeding in patients receiving warfarin, and HAS-BLED score ≥3 is thought to indicate a high bleeding risk. Improvements in TTR were observed in patients with HAS-BLED score 0–2 (n=83; these patients improved from 50.0%±33.4% to 68.1%±27.1%; P<0.0001). The change in TTR in patients with HAS-BLED score ≥3 (n=22), however, showed the same trend but did not reach statistical significance (58.2%±33.7% vs. 71.1%±24.2%, P=0.0551).

Improvements in TTR were consistently observed in both men and women enrolled in the present study (52.9%±29.2% to 70.9%±25.2%, P<0.0001; 50.9%±36.9% to 67.5%±27.5%, P=0.0002, respectively). In addition, similar levels of improvement in TTR were noted in patients treated with or without antiplatelet drugs (45.0%±34.9% to 60.4%±24.3%, P=0.0334; 53.8%±32.4% to 71.7%±26.4%, P<0.0001). There was no difference in TTR before between patients aged <70 years (49.0%±32.6%) and ≥70 years (53.4%±33.3%, P=0.514). Improvement in TTR was significant in all the subgroups of age (<70 years: 49.0%±32.6% to 60.8%±27.5%, P=0.0126; ≥70 years: 53.4%±33.3% to 73.5%±24.8%, P<0.0001). Calculation of TTR using the target ranges of 1.6–2.6, 2–3, and 1.6–3.0 indicated consistent improvement in TTR associated with POC testing in all subgroups of age.

**Figure 2.** The time spent over the therapeutic range (TOTR) remained low after the introduction of point-of-care (POC) testing, but the time spent under the therapeutic range (TUTR) decreased. Column and bar, mean and SD, respectively. Yellow, before the introduction of POC testing; green, after the introduction of POC testing.

**Figure 3.** Effect of time in therapeutic range (TTR) before the introduction of point-of-care (POC) testing (TTR before) on change in TTR after the introduction of POC testing. In patients with TTR before ≤40% and 41–70%, TTR improved significantly, whereas in patients with TTR before ≥71% it decreased significantly. Column and bar, mean and SD, respectively. Yellow, before the introduction of POC testing; green, after the introduction of POC testing.
There were statistically significant differences in TTR before between clinics 3 and 7, and between clinics 6 and 7 (Table 2; Tukey range test, P<0.05). A strong tendency for improvement in TTR was observed at all of the clinics except for clinic 5. Statistically significant improvement in TTR was noted at 2 clinics (Nos. 4 and 7).

**Discussion**

**Major Findings**

The major findings are as follows: (1) overall, TTR\textsubscript{After} was considerably higher than TTR\textsubscript{Before}; this improvement could mainly be ascribed to a decrease in the TUTR; (2) improvement in TTR was consistent, independent of gender, age, and antiplatelet drug use; (3) improvement in TTR was significant in patients who had CHADS\_2 score 0–1 or 3–6, and HAS-BLED score ≤2; and (4) only patients with high TTR before the introduction of the POC testing device had significant but small decreases in TTR.

**Advent of POC Testing**

The POC testing devices have been developed in recent years in order to provide quick results for the monitoring of INR in patients receiving oral anticoagulants. Before the advent of POC, general practitioners were required to wait for half a day or even a full day for INR results. Because POC testing devices enable quick measurement of INR, adjustments to warfarin dose can be made in a timely manner. Several studies comparing the INR results obtained with POC testing devices and conventional laboratory methods have shown that the former provide accurate test results.

**High TTR**

Good INR control is critical to improvement in patient outcome. In sub-studies of SPORTIF III and V, 3,587 patients with AF treated with warfarin were divided into 3 groups according to TTR (<60%, 60–75%, >75%). The rates of stroke or systemic embolic events, as well as of bleeding, were higher among patients with poor INR control (<60%) than among those with moderate (60–75%) or good INR control (>75%). A sub-study of ACTIVE W, which originally compared the effect of a dual antiplatelet regimen and warfarin on the prevention of stroke and systemic embolism, also showed that patients who were treated at centers that had mean TTR above the study median of 65% had a marked benefit against stroke and total vascular events. That study also showed that warfarin therapy was effective only when TTR reached the lower limit of 58% (this value was based on a population-average model). Nevertheless, in community medical practices, INR control within the therapeutic range is typically achieved only in approximately 50% of measurements. Okumura et al reported that the average TTR at 5 Japanese centers for cardiovascular disease was 64%. These findings indicate the need for the establishment of strategies to improve TTR in actual clinical practice. Several studies have shown that clinical practices are important determinants of TTR. The introduction of anticoagulation clinics and computer-assisted decision-support tools can improve TTR. In contrast, patient education is important for improvements in TTR and for the outcome of warfarin therapy, because poor adherence is potentially a major source of poor anticoagulation control. The present study clearly showed that the use of a POC testing device in an outpatient clinic was associated with improvement in TTR. Although the present study was not designed to ascertain why the introduction of POC in outpatient clinics may be associated with significant increases in TTR, there are some plausible explanations for the improvement in TTR observed in this study. First, it was easy for clinicians to adjust a patient’s warfarin dosage because PT-INR could be measured on site. Before the introduction of the POC testing devices, clinicians had to adjust the dose after the patient had already left the clinic because the PT-INR result would not be available until 1 day after blood sampling. We do not have information regarding the frequency of dose adjustments and the final dose of warfarin. The frequency of dose adjustments, however, could be increased because the interval between PT-INR measurements was shortened by approximately 10 days after the introduction of POC testing devices. Rose et al showed that longer time between INR monitoring, and the failure to recheck INR promptly after out-of-range values are recorded, closely relate to poor INR control. Therefore, a shorter interval between INR measurements in the present study could have facilitated the improvement in INR control. Second, the quality of warfarin therapy is, to some extent, dependent on a patient’s understanding of the need for this treatment as well as of the importance of maintaining PT-INR within the therapeutic range. Education programs have an important role in improving clinical outcome. One possible reason for this is the improvement in treatment adherence. The use of POC testing devices could facilitate the education of patients on these issues on-site and thereby could contribute to good adherence to
therapy. Further studies are needed to elucidate the effect of the introduction of POC testing devices on patient understanding and adherence to therapy.

In community medical practice, PT-INR often does not reach the therapeutic range, which is reflected by TUTR. Possible reasons for prolonged TUTR may be clinician or patient concerns regarding the bleeding complications associated with excessive warfarin therapy. Recent clinical trials, however, reported that warfarin therapy did not increase the risk of intracranial bleeding until PT-INR exceeded 3.5–4.0, and that the risk of intracranial hemorrhage in patients with PT-INR 2.0–3.0 was not higher than that in patients with lower PT-INR. In the present study, significant improvement in TTR was observed because of a decrease in TUTR, without any increase in TOTR. Therefore, POC testing devices may help maximize the preventive effect of warfarin in patients affected by the risk of stroke and systemic thromboembolism while also minimizing the increase in the risk of bleeding complications.

Only patients with high TTR (≥71%) before the introduction of POC testing had significant but small decreases in TTR (Figure 3; 90.2% to 84.3%). The reason for the decrease in TTR is not known, but both TTR before and TTR after were high enough to prevent stroke and systemic embolization.

New anticoagulants such as dabigatran are known to be effective in the prevention of stroke, and some of the novel therapies have been shown to be equally effective or better than warfarin. Although new anticoagulants have favorable pharmacologic profiles overall, there are several disadvantages to the use of novel therapies, including the cost of individual treatment. TTR in patients receiving warfarin in the recent studies on new anticoagulants ranged from 55% to 64.4%. Therefore, warfarin therapy that achieves TTR >70% could be similar or even superior to almost all the new anticoagulants for the prevention of stroke and systemic thromboembolism. In addition, warfarin is cost-effective and therefore an economical choice.

Study Limitations
The present findings should be interpreted in the light of some limitations. First, the study design was retrospective in nature, and it is not known whether the present results can be generalized to all outpatient clinics. It is possible that the clinicians at the clinics where POC was introduced were more enthusiastic than those at other clinics. This enthusiasm could have affected the results. Second, given that the number of subjects was relatively small, we were unable to examine how the use of POC testing devices affected the risk of bleeding or thromboembolism. Nevertheless, TTR is a strong and consistent predictor of bleeding and thromboembolism, and improvement in TTR without an increase in TOTR may reduce the risk of both bleeding and thromboembolism. We did not observe improvement in TTR in several subgroups, such as in patients with CHADS: score 2 and HAS-BLED score ≥3, probably because the subject group was relatively small. Finally, it is possible that the TTR in the present patients improved over time. Okumura et al. reported that TTR increased slightly, although not significantly, during the second year of treatment in a 2-year observation period. In addition, Rose et al. showed that TTR during an “experienced” period of warfarin therapy was higher than that during the “inception” period. The improvements observed in the present study, however, were statistically significant, and we ensured that there was an interval of at least 3 months between the initiation of warfarin therapy and TTR measurements recorded in this study. Therefore, a change in TTR over time alone could not explain the improvement of TTR that we observed.

Conclusions
The introduction of POC was associated with improvements in TTR, mainly through a reduction in the TUTR of INR. The widespread use of POC testing devices for the measurement of INR may improve the management of patients receiving warfarin.

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Disclosures
No other conflicts of interest are reported.

References