

In-home Compared With In-Clinic Warfarin Therapy Monitoring in Mechanical Heart Valves: A Population-Based Study

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Abstract

Objective: To evaluate differences in time in therapeutic range (TTR), major bleeding, thromboembolism, and survival comparing in-home and in-clinic international normalized ratio monitoring for patients with mechanical heart valves receiving warfarin anticoagulation.

Patients and Methods: An observational population-based study of 383 patients (mean \pm SD age, 61.5 \pm 14.1 years; 38.6% female) with mechanical heart valves (aortic, 77.8%; mitral, 31.1%; tricuspid, 1%; pulmonic 0.2%; and multiple, 9.7%) was performed from January 1, 2012, through December 31, 2017. The target international normalized ratio was 2.5 for 199 patients (52.0%) and 3.0 for 184 (48.0). Of these patients, 37.9% (n=145) were managed by in-home monitoring (cases) and 62.1% (n=238) were monitored in the clinic (controls).

Results: During median follow-up of 3.1 years, mean \pm SD TTR was similar between in-home (66.6% \pm 19.2%) and in-clinic (67.2% \pm 19.8%) monitoring ($P=.76$). There were no differences between the in-home and in-clinic groups regarding survival to major bleeding (5.7% per person-year vs 6.7% per person-year; $P=.66$) or thrombotic complications (2.3% vs 1.8%; $P=.56$). In-home monitoring was associated with reduced all-cause mortality (hazard ratio, 0.40; 95% CI, 0.19 to 0.83; $P=.01$) on univariate analysis; however, this was no longer apparent when controlling for age and baseline left ventricular ejection fraction.

Conclusion: In this real-world population-based study of patients with mechanical heart valves, in-home monitoring was equivalent to in-clinic monitoring regarding TTR and important clinical outcomes.

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Patients with mechanical heart valves have been bound to the same oral anticoagulants since the first mechanical valve was implanted in 1960.¹ Vitamin K antagonists are the only viable and approved option for oral anticoagulation therapy in these patients.²⁻⁴ Unique challenges accompany warfarin use given its narrow therapeutic window, including frequent plasma monitoring and vigilant awareness of drug and dietary interactions. The prothrombin time–based international normalized ratio (INR) becomes the harbinger of success or failure, and patients find refuge in a strictly defined target range. High time in therapeutic range (TTR) represents an important surrogate for

anticoagulation quality and has proved to be a longitudinal predictor of improved outcomes.^{5,6} Nonetheless, average TTR remains well below 70% even in the strict confines of randomized controlled trials (RCTs).⁷⁻¹²

Monitoring has become more convenient and accessible with the advent of point-of-care testing and patient self-testing (PST) at home. Prospective trials have found that these strategies improve quality of life and are equivalent to traditional in-clinic monitoring regarding cost-effectiveness and clinical outcomes.^{7,13-20} Participants in these studies were subject to a highly regulated environment with enforced compliance. Furthermore, only a small proportion of patients studied in



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the published literature had mechanical heart valves, and even fewer required a higher INR target range for mechanical mitral valves or previous thromboembolic events.

We sought to evaluate the contemporary experience of a health system using both conventional in-clinic and in-home INR monitoring in patients with mechanical heart valves.

METHODS

Study Population

The study evaluated all consecutive patients enrolled in the warfarin anticoagulation monitoring program for any indication through Mayo Clinic in Rochester, Minnesota, from January 1, 2012, through December 31, 2017. The analysis occurred in a retrospective cohort manner comparing those enrolled in the in-home INR monitoring program (cases) with those monitored exclusively in the clinic (controls). The inclusion criteria were age older than 18 years, use of warfarin for at least 30 consecutive days, implantation of a mechanical heart valve, and a target INR of 2.5 (range, 2.0-3.0) or 3.0 (range, 2.5-3.5). This study was approved by the Mayo Clinic Institutional Review Board.

Warfarin Dose Adjustment

Warfarin dosing was adjusted under the guidance of a nurse-administered standardized protocol developed by the Mayo Clinic Gonda Vascular Center ([Supplemental Data](#), available online at <http://mcpiqjournal.org>). This protocol applied to both the in-clinic and in-home INR monitoring groups. The data from the anticoagulation monitoring program provided a complete record of INR values obtained through phlebotomy with plasma testing, in-clinic fingerstick point-of-care testing, and in-home INR monitoring through PST. To be eligible for home INR monitoring patients were required to have been receiving warfarin anticoagulation for at least 3 months with stable dosing and good compliance with recommendations as determined at the discretion of staff. Before being enrolled patients also had to agree to record INR values on at least a weekly basis initially and to being required to pass a 2-session training program using the CoaguChek XS (Roche Diagnostics) test meter,

which was provided as the primary portable PST device. This device has been validated against plasma testing at Mayo Clinic.^{21,22} The in-home INR program required monthly data uploads to a centralized server as well as timely interactions for out-of-range INR values. All patients received dosing recommendations by nursing staff verbally in the clinic, by secure online messaging, or by telephone. Patients could be dismissed from the in-home INR monitoring program for medication or testing noncompliance or for failure to provide timely communication regarding collected INR values.

Time in Therapeutic Range

The Rosendaal linear interpolation method for calculating TTR was used with respect to each patient's individual INR target range.²³ All INR values in the first 30 days after initiating warfarin therapy were excluded to allow for initial dosing titration before assessing TTR. To control for periods of anticoagulation interruption for invasive procedures or critical illness when calculating TTR, INR values were excluded if obtained during inpatient hospitalization and during periods of receiving an additional anticoagulant, such as heparin for bridging purposes. The TTR was calculated separately for patients with target INR ranges of 2.0 to 3.0 and 2.5 to 3.5.

Ascertainment of Clinical Data

Clinical data on baseline comorbid conditions and outcomes were obtained using *International Classification of Diseases, Ninth and Tenth Revision* codes from inpatient and outpatient encounters ([Supplemental Table 1](#), available online at <http://mcpiqjournal.org>). Baseline serum creatinine level, height, weight, aspirin use, mechanical valve position, and mortality were manually abstracted from the medical record at the time of first eligible INR value. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault method.²⁴ Left ventricular ejection fraction (LVEF) was pulled from the institution's transthoracic echocardiography database if measured within 12 months before enrollment; visual estimation or the calculation method for determining ejection fraction was chosen at the discretion of the independent clinical diagnostician. Major bleeding was

defined as intracranial hemorrhage or any bleeding diagnosis requiring transfusion or hospital admission. The circumstances and management of *International Classification of Diseases* code diagnoses of bleeding were confirmed by manual abstraction from the medical record.

Statistical Analyses

Normally distributed continuous variables are reported as mean \pm SD, nonnormally distributed variables as median (interquartile range [IQR]), and categorical variables as percentages, unless otherwise specified. Comparisons between groups for categorical data were made using χ^2 and Fisher exact tests as appropriate. Continuous data were compared using 2-sample *t* tests for normally distributed variables and Wilcoxon rank sum tests for nonnormally distributed variables. The effects of several factors on TTR values were tested using a multiple linear regression model. The Kaplan-Meier survival analysis method was used to plot survival to outcome events. Univariate and multivariate Cox proportional hazards regression models were used to determine the association between outcomes and clinical variables. Patients enrolled in the in-home group were analyzed in an intention-to-treat manner regardless of whether they returned to conventional in-clinic monitoring. All analyses were performed using JMP Pro Software, Version 14.1.0 (SAS Institute Inc). A 2-tailed $P \leq .05$ was considered statistically significant.

RESULTS

Patient Characteristics

Of the 6092 patients enrolled in the anticoagulation management program, 434 were identified as having mechanical heart valves. Fifty-one patients were excluded due to short (<30 days) follow-up ($n=9$) and nonstandard target INR ranges ($n=42$). The final study cohort consisted of 383 patients with a mean \pm SD age of 61.5 ± 14.1 years; 38.6% were female ($n=148$) and 89.3% identified as white race ($n=342$). The home monitoring program enrolled 145 patients (37.9%), and 238 (62.1%) received monitoring exclusively in the clinic. Mechanical valve positions were aortic in 77.8% of patients ($n=298$), mitral

in 31.1% ($n=119$), tricuspid in 1% ($n=4$), and pulmonic in 0.2% ($n=1$). Multiple mechanical valves were present in 9.7% of patients ($n=37$).

Patients enrolled in the in-home monitoring program were younger (mean \pm SD age: 59.6 ± 13.7 years vs 62.6 ± 14.3 years; $P=.04$), had lower serum creatinine values (1.0 ± 0.3 mg/dL vs 1.1 ± 0.7 mg/dL [to convert to $\mu\text{mol/L}$, multiply by 88.4]; $P=.04$), higher LVEF ($59.0\% \pm 10.9\%$ vs $55.1\% \pm 12.6\%$; $P=.008$), and were more likely to have an available ejection fraction measurement within the preceding 12 months (77.9% vs 58.8%; $P<.001$). In the in-home group, eGFR was higher, but the difference did not reach significance (98.0 ± 39.8 mL/min vs 88.7 ± 39.4 mL/min; $P=.055$) and there was a similar proportion with eGFR of 30 mg/dL or less (0.9% vs 3.1%; $P=.23$). Fewer patients in the in-home group had LVEF of 40% or less (8.0% vs 17.9%; $P=.02$). There were no differences between groups regarding body mass index, mechanical valve position, number of valves, target INR range, aspirin use, presence of atrial fibrillation, or other thrombotic comorbidities (Table 1).

Time in Therapeutic Range

The median follow-up duration for the whole cohort was 3.1 years (IQR, 0.9-4.7 years). The TTR and clinical outcomes are presented in Table 2. Median (IQR) follow-up duration did not differ between in-home and in-clinic monitoring (3.2 [1.6-4.2] years vs 2.9 [0.3-5.6] years; $P=.99$). A median of 61 (IQR, 20-85) INR data points were available per person, with a mean \pm SD interval between points of 19.3 ± 18.2 days. Significantly more median (IQR) points per patient were available for those in the in-home group (58 [27-91] vs 47 [13-84]); $P=.03$) but with a similar mean \pm SD interval between points (20.0 ± 18.5 days vs 18.8 ± 18.0 days; $P=.55$). For patients enrolled in the in-home program, 75.2% of all data points originated from home PST devices, with the remaining from phlebotomy and in-clinic point-of-care testing. The mean \pm SD Rosendaal TTR percentage was $67.0\% \pm 19.5\%$ for the whole cohort, and there was no significant difference between the

TABLE 1. Baseline Characteristics by Anticoagulation Program^{a,b}

Characteristic	All (n=383)	In-home (n=145)	In-clinic (n=238)	P value
Age (y), mean ± SD	61.5±14.1	59.6±13.7	62.6±14.3	.04 ^c
Female sex (No. [%])	148 (38.6)	58 (40.0)	90 (37.8)	.67
Mechanical valve position (No. [%]) ^d				
Mitral	119 (31.1)	42 (29.0)	77 (32.4)	.49
Aortic	298 (77.8)	119 (82.1)	179 (75.2)	.12
Tricuspid	4 (1.0)	1 (0.7)	3 (1.3)	.59
Pulmonic	1 (0.2)	0	1 (0.4)	.43
Multiple mechanical valves	37 (9.7)	16 (11.0)	21 (8.8)	.48
Target INR range (No. [%])				
2.0-3.0	199 (52.0)	70 (48.3)	129 (54.2)	.26
2.5-3.5	184 (48.0)	75 (51.7)	109 (45.8)	.26
Body mass index, mean ± SD	29.4±9.1	29.4±8.6	29.5±9.5	.90
LVEF (%), mean ± SD	56.8±12.0	59.0±10.9	55.1±12.6	.008 ^c
LVEF ≤40% (No. [%])	33 (13.0)	9 (8.0)	24 (17.9)	.02 ^c
LVEF unavailable (No. [%])	130 (33.9)	32 (22.1)	98 (41.2)	<.001 ^c
Low-dose aspirin use (No. [%])	168 (43.9)	63 (43.4)	105 (44.1)	.90
Creatinine (mg/dL), mean ± SD	1.1±0.6	1.0±0.3	1.1±0.7	.04 ^c
eGFR (mL/min), mean ± SD	92.5±39.8	98.0±39.8	88.7±39.4	.055
eGFR ≤30 mg/dL (No. [%])	6 (2.2)	1 (0.9)	5 (3.1)	.23
Creatinine unavailable (No. [%])	103 (26.9)	32 (22.1)	71 (29.8)	.10
Additional indication (No. [%])				
Atrial fibrillation	72 (18.8)	24 (16.6)	48 (20.2)	.38
Stroke	49 (12.8)	22 (15.2)	27 (11.3)	.28
Nonstroke arterial thromboembolism	9 (2.4)	5 (3.5)	4 (1.7)	.27
Venous thromboembolism	8 (2.1)	1 (0.7)	7 (2.9)	.14
Subtotal	138 (36.0)	52 (35.8)	86 (36.1)	.85

^aeGFR = estimated glomerular filtration rate; INR = international normalized ratio; LVEF = left ventricular ejection fraction.
^bSI conversion factor: To convert creatinine values to μmol/L, multiply by 88.4.
^cStatistically significant at P≤.05.
^dColumn totals exceed 100% due to patients with mechanical valves in multiple positions.

in-clinic (67.2%±19.8%) and in-home (66.6%±19.2%) monitoring groups ($P=.76$). When further stratified by target INR range, the TTR was higher for 2.0 to 3.0 as opposed to 2.5 to 3.5 in each group (Figure 1).

Clinical Outcomes

The clinical outcomes of the whole cohort as well as stratified by anticoagulation monitoring setting are presented in Table 2. There was no significant difference in the incidence per person-year (PPY) of major bleeding (5.7% PPY vs 6.7% PPY; $P=.66$) or thrombotic events (2.3% PPY vs 1.8% PPY; $P=.56$) when comparing the in-home and in-clinic monitoring groups. In the in-home group there

was a lower rate of all-cause mortality during follow-up (2.1% PPY vs 5.6% PPY; $P=.01$). Kaplan-Meier survival analyses for in-clinic vs in-home monitoring are highlighted in Figure 2. Survival to major bleeding ($P=.66$) or thrombotic complications ($P=.56$) was similar between groups. Enrollment into in-home INR monitoring was associated with a reduced all-cause mortality rate (hazard ratio [HR], 0.40; 95% CI, 0.19 to 0.83; $P=.01$).

To explore the relationship further with all-cause mortality, univariate and multivariate analysis was performed using baseline characteristics and INR testing variables (Supplemental Table 2, available online at <http://mcpiqjournal.org>). Of several variables

TABLE 2. Clinical Outcomes Stratified by Anticoagulation Monitoring Setting^a

Outcome	All (n=383)	In-home (n=145)	In-clinic (n=238)	P value
Follow-up (y), median (IQR)	3.1 (0.9-4.7)	3.2 (1.6-4.2)	2.9 (0.3-5.6)	.99
Time in therapeutic range (%), mean \pm SD	67.0 \pm 19.5	66.6 \pm 19.2	67.2 \pm 19.8	.76
Major bleeding event (No. [% PPY])				
Intracranial	12 (1.1)	2 (0.4)	10 (1.4)	.17
Gastrointestinal	21 (1.9)	8 (1.8)	13 (1.8)	.78
Other	40 (3.5)	15 (3.4)	25 (3.5)	.96
Subtotal	73 (6.4)	25 (5.7)	48 (6.7)	.66
Major thrombotic event (No. [% PPY])				
Stroke or TIA	15 (1.3)	5 (1.1)	10 (1.4)	.57
Nonstroke arterial thromboembolism	6 (0.5)	4 (0.9)	2 (0.3)	.11
Valve thrombosis	2 (0.2)	1 (0.2)	1 (0.1)	.67
Subtotal	23 (2.0)	10 (2.3)	13 (1.8)	.56
All-cause mortality (No. [% PPY])	49 (4.3)	9 (2.1)	40 (5.6)	.01 ^b

^aIQR = interquartile range; PPY = per person-year; TIA = transient ischemic attack.

^bStatistically significant at $P \leq .05$.

that reached significance in the univariate analysis, the only factors that retained significance after multivariate analysis were age (HR, 1.08 per 1-year increase; 95% CI, 1.04 to 1.12 per 1% increase; $P < .001$), LVEF at baseline (HR, 0.96 per 1% increase; 95% CI, 0.93 to 0.9996 per 1% increase; $P = .04$), and Rosendaal TTR (HR, 0.93 per 1% increase; 95% CI, 0.90 to 0.97 per 1% increase; $P < .001$). When stratified by INR target range there were no significant differences in survival to major bleeding, thrombotic complications, or all-cause mortality (Figure 3).

DISCUSSION

In a population-based study of mechanical heart valves in various positions and with 2 different INR target ranges, in-home INR monitoring resulted in similar TTR as well as major bleeding and thromboembolic outcomes compared with in-clinic INR monitoring. A significant reduction in all-cause mortality was seen in the in-home monitoring group. After adjustment for differences in age and LVEF, this survival advantage was no longer apparent.

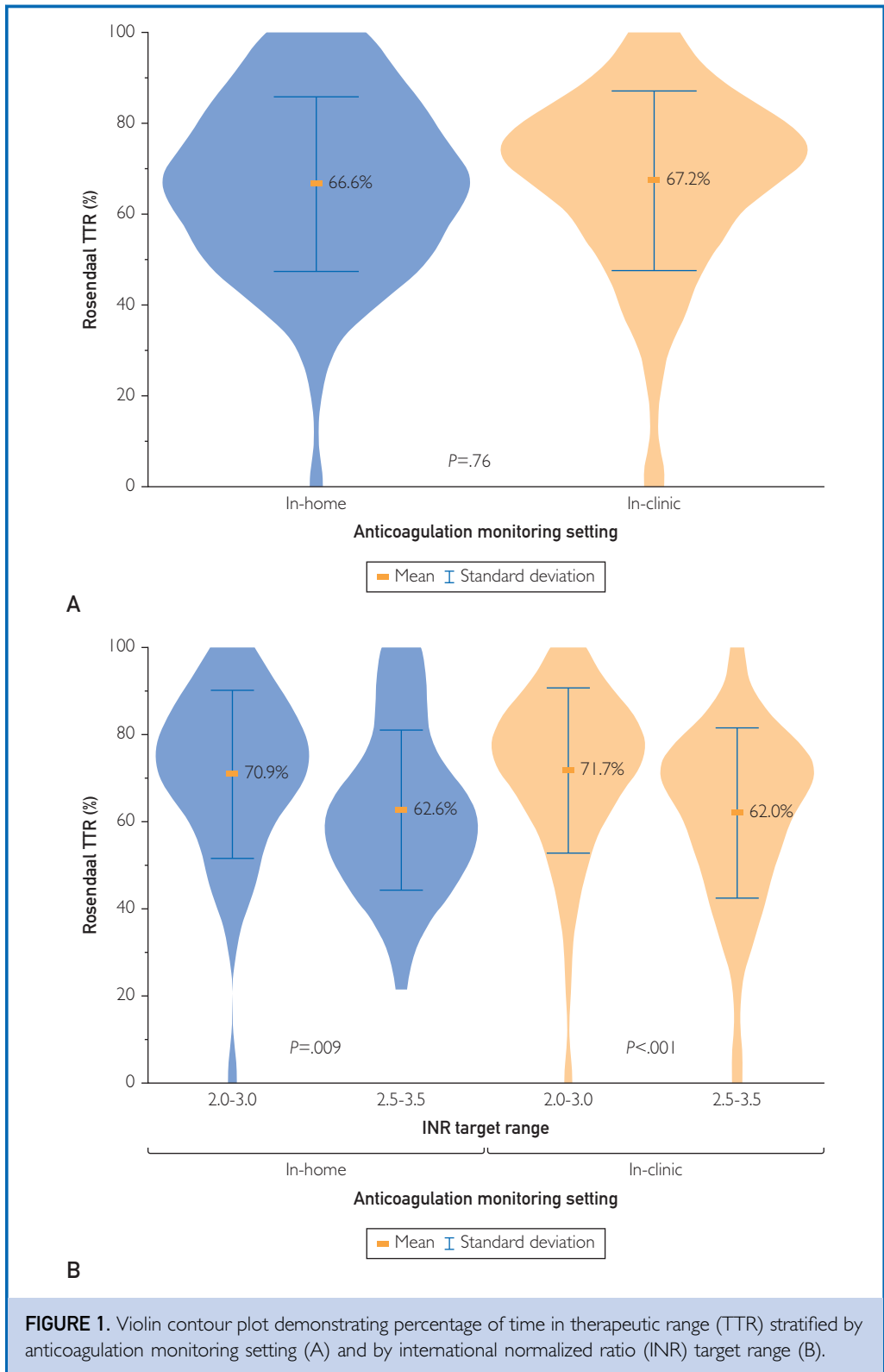
Comparison With Existing Data

There have been several important prospective studies comparing in-home and in-clinic INR monitoring for patients with mechanical heart valves, but these have had multiple important

factors that limit generalizability to contemporary clinical practice.^{16-18,25} A German trial enrolled 600 patients immediately after mechanical valve replacement and reported an improvement in a composite outcome of combined major bleeding and thrombotic events favoring in-home INR monitoring.¹⁶ The INR target ranges (2.5-4.5) and a self-management warfarin dosing strategy for the in-home group differed from those in the present study. Furthermore, INR data points in range were reported rather than TTR. A second study from the United Kingdom randomized 100 patients with a mechanical valve to self-management vs conventional monitoring and found improved TTR with the former strategy (76.5% vs 63.8%; $P < .001$).¹⁷ There were no differences in bleeding, thrombosis, or mortality rates between management strategies. Of note, an INR range of 2.0 to 3.0 was targeted for all patients, including the 37% with mechanical mitral valves and the 4% with multiple mechanical valves. A third RCT of patients with a mechanical valve did not report outcomes but found improved TTR (43% vs 22%) with a self-management strategy at an optimal testing interval of once per week.¹⁸

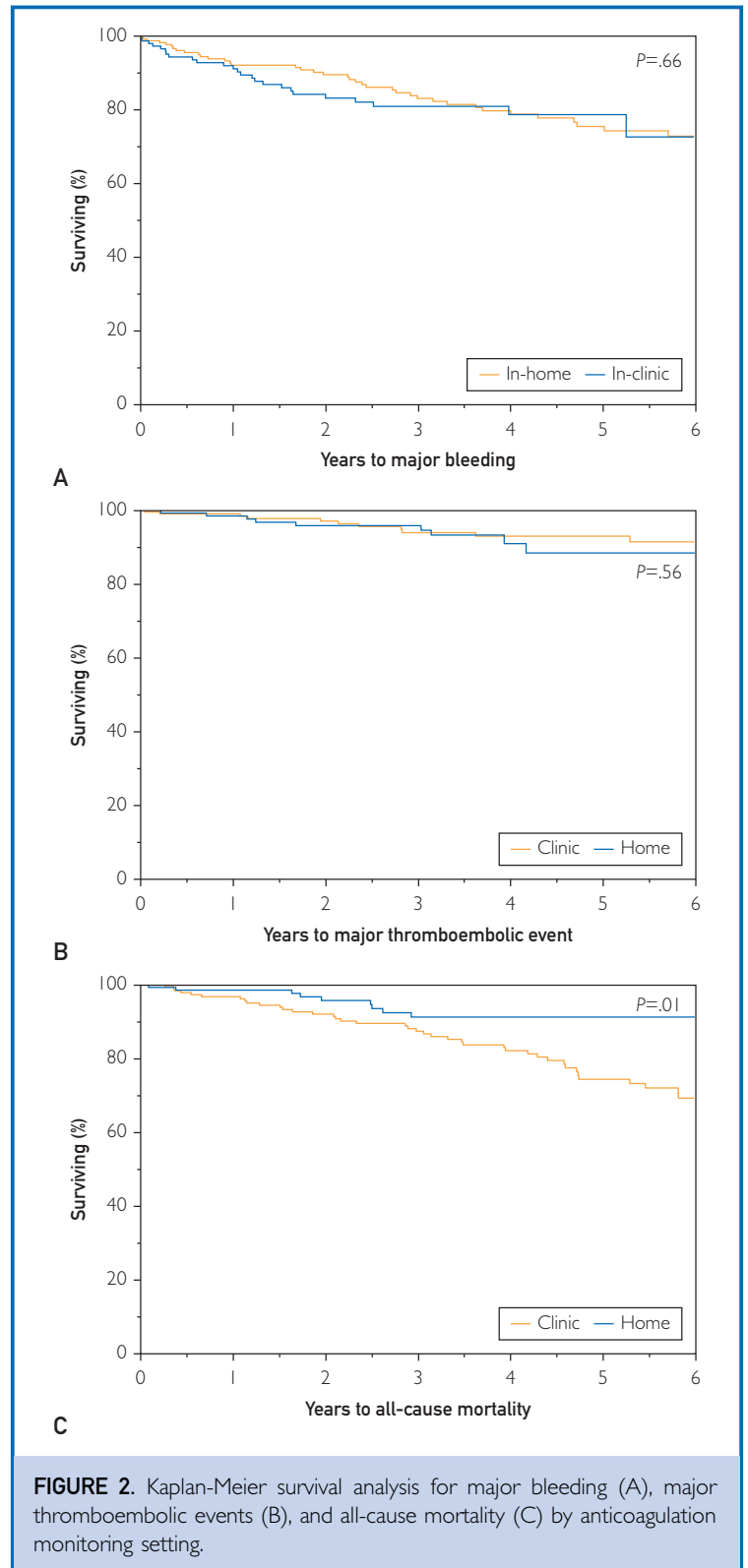
Monitoring of Anticoagulation

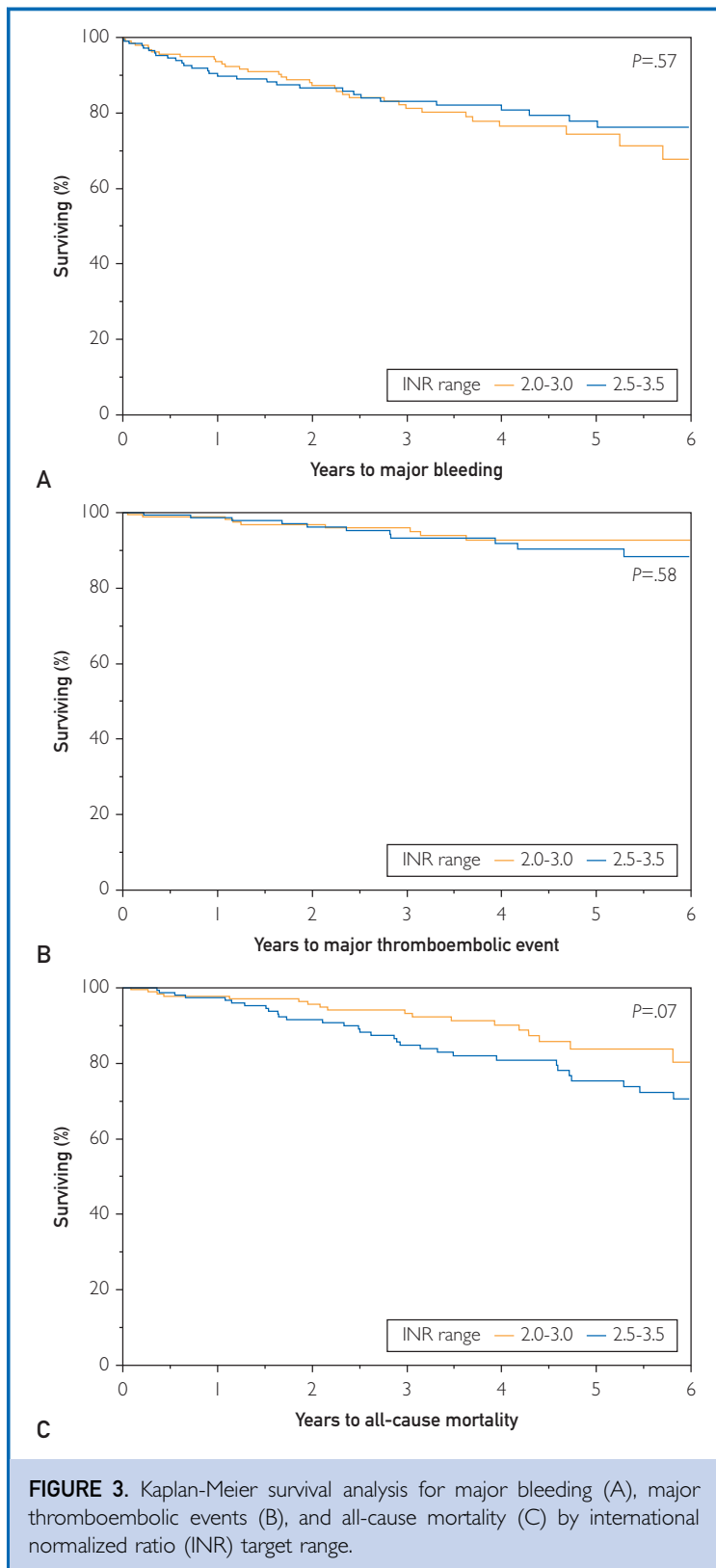
In this observational study, no difference in TTR was noted between anticoagulation monitoring setting groups. This is an important



finding and differs from previous literature that has shown increased TTR with the use of home PST devices in prospective clinical trial settings.^{7,17} Despite the lack of difference between groups, the mean Rosendaal TTR of 67% in the entire cohort actually exceeded those seen in previously published clinical trials. In the direct oral anticoagulant atrial fibrillation trials (which all excluded mechanical valves and used a target INR of 2.0-3.0), average TTR varied between 55% and 65% in the warfarin groups.⁹⁻¹² Similarly, The Home INR Study (THINRS), which included mechanical valves in less than one-quarter of patients, reported a mean TTR of 66% in the in-home arm and 62% in the in-clinic arm ($P<.001$).⁷ The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) was the only direct oral anticoagulant study to include patients with mechanical heart valves. In this study, the warfarin group achieved a TTR of 51% at best for those who had remotely implanted mechanical mitral valves, perhaps owing to the higher INR target range of 2.5 to 3.5 for these patients.⁸ Despite this, the warfarin arm in the RE-ALIGN trial had significantly fewer thrombotic and bleeding events than the dabigatran arm, leading to guideline recommendations to avoid the use of direct oral anticoagulants in those with mechanical prosthetic valves.^{2,3} Note that even in those with the higher INR target range of 2.5 to 3.5, the present study found a mean TTR of 62%. The higher TTR values seen in this population-based study likely reflect the efficacy of the institution's contemporary outpatient anticoagulation program, which governs both in-home and in-clinic INR monitoring.

Another notable difference from prospective clinical trials is reflected in the interval between INR data points as well as the percentage of data points that arose from home PST testing in the in-home monitoring group of this observational analysis. Whereas most published trials mandate at least weekly INR testing in all patients,^{7,16-19,25} all patients in the present study followed a nurse-administered protocol that allowed extension





of the testing interval up to once a month depending on INR stability and other clinical factors (Supplemental Data, available online at <http://mcpiqjournal.org>). As a consequence of this and perhaps reduced compliance in some patients, the average interval between INR points was more than 2 weeks in all patients, and 75.2% of total INR data points arose from PST home INR testing in the in-home group. If a higher percentage of data points arose from home PST testing with a shorter testing interval in the in-home group, it is possible that a between-group difference may have become apparent in Rosendaal TTR and, perhaps, clinical outcomes compared with those who were followed exclusively in the clinic. That being said, real-world patient behavior and reasonable protocols designed to improve health care costs, autonomy, and quality of life are important factors to consider. These may enhance generalization of this study's results to clinical practice.

Clinical Outcomes

The event rates in the present study did differ from those in previously published RCTs in patients with mechanical valves. The aforementioned German prospective study reported a similar thrombotic rate (1.7% PPY) but a lower rate of mortality (1.9% PPY) and a lower bleeding rate (2.2% PPY).¹⁶ Note that a smaller proportion of patients with mechanical mitral valves were included (18% vs 31%). Also, 22% of all INR readings submitted were considered subtherapeutic as opposed to only 3% supratherapeutic, which may indicate that the risk of thrombosis was favored over bleeding in this study population. The event rates from the present study did closely resemble those from a Swedish anticoagulation registry of patients with mechanical heart valves that reported a thromboembolic rate of 1.8% PPY, a bleeding rate of 4.2% PPY, and a mortality rate of 4.5% PPY.²⁶

In-home monitoring enrollment was associated with a small decrease in all-cause mortality in this study. This has not been demonstrated previously in individual RCTs^{7,16,17} but was insinuated by an older meta-analysis of multiple RCTs of patients

with various anticoagulation indications, including mechanical valves.¹⁴ When interpreting the results of this observational analysis, one must take into account the differences in baseline characteristics between groups. Prerequisite INR stability, compliance, and demonstrated competency with using the PST device are likely to result in preferential selection for a younger, healthier population with less comorbidity. This is supported by the younger age, higher LVEF, and lower serum creatinine levels at baseline in the in-home monitoring group. Therefore, the loss of significance in the association between anticoagulation monitoring setting and all-cause mortality when controlling for age and LVEF by multivariate analysis would suggest that baseline characteristic differences are strongly at play.

Finally, multivariate analysis demonstrated that every 1% increase in Rosendaal TTR was associated with a 7% reduction in risk of all-cause mortality. This is similar to trends from other studies in patients with mechanical valves.^{5,25} Although TTR was not improved with the use of in-home INR monitoring in this study, we feel strongly that optimizing TTR remains an important goal for any anticoagulation monitoring program.

Limitations

This single-center observational study relied on independent clinician judgment to enroll patients in in-home as opposed to in-clinic INR monitoring. In the absence of randomization, there was opportunity for both measured and unmeasured confounding variables. Patients enrolled in the in-home INR monitoring program were analyzed in an intention-to-treat fashion, and crossover to conventional monitoring could not be definitively determined, although this would have affected PST percentages. Testing equipment and health care visit costs were subject to individual insurance coverage, and there may have been possible financial influences on testing frequency and setting. Because the data originated from a tertiary referral center, complications managed through outside institutions would have been missed in the analysis. Similarly, patients who periodically had anticoagulation managed through another health care system would

have had a resultant gap in INR information not available to the investigators.

CONCLUSION

In-home INR monitoring was equivalent to exclusive in-clinic monitoring regarding TTR and important clinical outcomes in real-world patients with mechanical heart valves, including those with a higher INR target range. Patient self-testing has been reported to be cost-effective on a population basis compared with in-clinic monitoring, especially when taking into account quality of life.¹³ Because vitamin K antagonists continue to be the only viable oral anticoagulants in this population, PST should be considered for all patients with mechanical heart valves.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://mcpiqjournal.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: eGFR = estimated glomerular filtration rate; HR = hazard ratio; INR = international normalized ratio; IQR = interquartile range; LVEF = left ventricular ejection fraction; PPY = per person-year; PST = patient self-testing; RE-ALIGN = Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement; RCT = randomized controlled trial; THINRS = The Home International Normalized Ratio Study; TIA = transient ischemic attack; TTR = time in therapeutic range

Potential Competing Interests: The authors report no competing interests.

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