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International normalized ratio control and subsequent clinical outcomes in patients with atrial fibrillation using warfarin

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Abstract

We explored associations between INR measures and clinical outcomes in patients with AF using warfarin, and whether INR history predicted future INR measurements. We included patients in ARISTOTLE who were randomized to and received warfarin. Among patients who had events, we included those with ≥ 3 INR values in the 180 days prior to the event, with the most recent ≤ 60 days prior to the event, who were on warfarin at the time of event (n = 545). Non-event patients were included in the control group if they had ≥ 180 days of warfarin exposure with ≥ 3 INR measurements (n = 7259). The median (25th, 75th) number of INR values per patient was 29 (21, 38) over a median follow-up of 1.8 years. A total of 87% had at least one INR value < 1.5; 49% had at least one value > 4.0. The last INRs before events (median 14 [24, 7] days) were < 3.0 for at least 75% of patients with major bleeding and > 2.0 for half of patients with ischemic stroke. Historic time in therapeutic range (TTR) was weakly associated with future TTR ($R^2 = 0.212$). Historic TTR ≥ 80% had limited predictive ability to discriminate future TTR ≥ 80% (C index 0.61). In patients with AF receiving warfarin, most bleeding events may not have been preventable despite careful INR control. Our findings suggest that INRs collected through routine management are not sufficiently predictive to provide reassurance about future time in therapeutic range or to prevent subsequent outcomes, and might be over-interpreted in clinical practice.

Keywords International normalized ratio · Clinical outcomes · Warfarin · Atrial fibrillation

Michael Hanna—Employee of Bristol-Myers Squibb at the time of the study.

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Highlights

- We explored associations between INR measures and clinical outcomes in patients with AF using warfarin, and whether INR history predicted future INR measurements.
- In this large randomized trial with structured visits and frequently collected INR measurements, two-thirds of patients with AF treated with warfarin had an INR value < 3.0 before bleeding and half of patients had an INR value > 2.0 before ischemic stroke around 2 weeks before the events.
- In patients with AF receiving warfarin, most bleeding events may not have been preventable despite careful INR control.
- Our results suggest that INRs collected through routine management are not sufficiently predictive to provide reassurance in preventing subsequent outcomes; therefore, INR control might be over-interpreted in clinical practice.

Introduction

Vitamin K antagonists, such as warfarin, have been the standard of care for stroke prevention in patients with atrial fibrillation (AF) for decades. The importance of achieving and maintaining the international normalized ratio (INR) in a therapeutic range (between 2.0 and 3.0) among warfarin users has been established. However, this can be challenging since multiple food and drug interactions plus dynamic changes over time are known to cause INR levels to vary [1].

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban was superior to warfarin in preventing thromboembolic and bleeding events in patients with AF and additional risk factors [2]. A previous post hoc analysis of ARISTOTLE showed that the treatment effects of apixaban in comparison with warfarin were similar across different levels of centers' and patients' predicted quality of INR control [3]. However, less is known about the association between individual INR history and subsequent clinical outcomes in patients with AF using warfarin. Additionally, the influence of the individual INR history on future INR levels has not yet been explored in the context of a large randomized trial with structured visits and frequent INR measurements. Therefore, we aimed to explore associations between measures of individual INR control and clinical outcomes in patients with AF using warfarin, and whether INR history predicted future INR measurements.

Methods

Patients and study design

The design and results of the ARISTOTLE trial have been previously published [2, 4]. In summary, it was a randomized, double-blind, controlled trial that enrolled patients with AF or atrial flutter and at least one risk factor for stroke. Participants were randomized to receive either apixaban 5 mg twice daily (n = 9120) or dose-adjusted warfarin (n = 9081) with a target INR of 2.0–3.0. Patients were excluded if they had clinically significant mitral stenosis, prosthetic mechanical heart valves, previous intracranial bleeding, severe renal insufficiency, recent stroke (within 7 days before randomization), and need for dual antiplatelet therapy. In this trial, INR monitoring started at the fourth day following initiation of treatment and was performed twice a week for 2 weeks, once a week for 2 weeks, and monthly thereafter once a stable INR was achieved. More frequent INR measurements were performed per discretion of the investigators. The central monitoring of INR measurements utilized encrypted point of care devices and centralized dosing recommendations. Results were blinded and showed either a true INR value when the patient received warfarin or a sham INR value when the patient received apixaban. The study protocol conforms to the Declaration of Helsinki and approval was received from appropriate ethics committees at participating sites. All patients provided written informed consent.

The first part of this analysis aimed to summarize INR measures among ARISTOTLE participants who were randomized to and received warfarin, and had at least three INR measures (n = 8822) (Fig. 1). These measures are shown in the overall cohort and stratified by warfarin-naïve and warfarin-experienced patients.

The second part of this analysis aimed to summarize INR measures preceding events. Among patients who had events, we included those with at least three INR values in the 180 days prior to the event, with the most recent no more than 60 days prior, who were still on warfarin at the time of event (n = 545). Non-event patients were included in the control group if they had at least 180 days of warfarin exposure with at least three INR values (n = 7259). To provide a consistent approach across groups—i.e., looking back 180 days from a specific time point—INR data from the period between 3 and 9 months post-randomization was used in the control group; thus, patients must have been on warfarin during this period. Patients not meeting these criteria were excluded from this part of the analysis. Patients who experienced both ischemic stroke/systemic embolism (SE) and major bleeding while on warfarin (n = 5) were counted in each of those groups. This yielded a total of 7805 patients

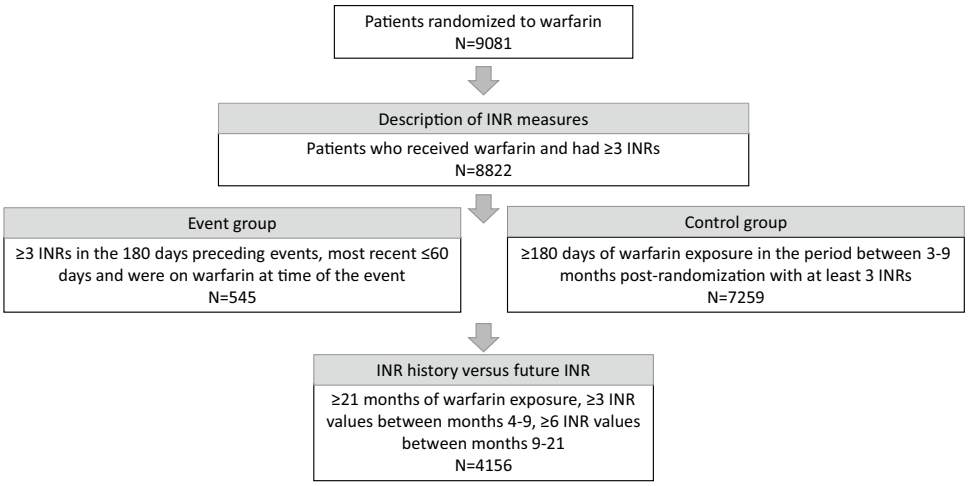

Fig. 1 CONSORT diagram

included in this second part of the analysis. We also stratified this part of the analysis by warfarin-naïve (n = 4630) or warfarin-experienced (n = 3175) patients. We performed four sensitivity analyses: 1) excluding patients with clinical events occurring in the first 3 months after enrollment (n = 100 patients excluded), which removed 15 ischemic stroke/SE and 87 major bleeding events from this analysis; 2) excluding patients with events occurring during or after study drug interruptions (n = 60 patients excluded; events that occurred during a study drug interruption of at least 7 days, or in the 30 days after resumption of study drug were excluded, which removed 14 ischemic stroke/SE, 48 major bleeding events, three intracranial hemorrhages [ICHs], and 13 gastrointestinal [GI] bleeding events from this part of the analysis); 3) including only patients with at least one INR measure in the 14–30 days before clinical events (n = 351); and 4) including only patients not receiving aspirin the day prior to the event (n = 388).

The third part of this analysis examined the relationship between INR history and future INR. We included patients who had at least 21 months of warfarin exposure, at least three INR values between months 4 and 9, and at least six INR values between months 9 and 21 (n = 4156).

The authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Outcomes

The clinical outcomes analyzed were ischemic stroke or SE, major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria (clinically overt bleeding with a hemoglobin drop of at least 2 g/dL or transfusion of ≥ 2 units of packed red cells, bleeding occurring at a critical site, or resulting in death), ICH, and GI bleeding. A clinical events classification committee, blinded to study assignment, adjudicated all endpoints according to pre-specified criteria.

Statistical analysis

INR measures from the warfarin-treated population are summarized: number of INR values per patient, lowest INR value for each patient, highest INR value for each patient, time in therapeutic range (TTR), percentage of time with INR < 2.0, percentage of time with INR > 3.0, at least one INR out of 2.0–3.0 range, at least one INR < 1.5, at least one INR > 4.0, and at least one INR < 1.5 or > 4.0. For the first part of the analysis, we included patients with at least three INR values (n = 8822). Values are presented as medians (25th, 75th percentiles) for continuous variables and numbers with percentages for categorical variables. Interpolation of data for time in, above, or below therapeutic range used the Rosendaal method [5].

To examine the relationship between INR history and future INR values, INR data from baseline to month 3 were omitted, allowing patients to reach a point of dose stability. The "landmark" for these summaries was the end of month 9. Historic INR was determined using INR values from months 4 through 9 (6 months), and future INR was determined using INR values from months 10 through 21 (1 year). The relationship between historic and future INR stability was assessed in the following ways: a) an R^2 value explored the association between historic TTR and future TTR (both continuous); b) C index determined whether historic TTR ≥ 80% discriminated TTR ≥ 80% in the subsequent year, using univariate logistic regression; c) C index determined whether historic TTR ≥ 80% discriminated the occurrence of any future INR out of range (< 2.0 or > 3.0); and d) C index determined whether historic TTR = 100% discriminated future TTR ≥ 80% or the occurrence of any future INR out of range (< 2.0 or > 3.0). In addition, future TTR, both as a continuous and categorical variable, was summarized by historic bins in 20% increments.

Results

Summary of INR measures

The summary of INR measures among patients with AF receiving warfarin is presented in Table 1. Overall, the median (25th, 75th) number of INR values per patient was 29 (21, 38) over a median follow-up of 1.8 years. The median lowest and highest INR values per patient were 1.1 (0.9, 1.3) and 4.0 (3.5, 4.7), respectively. Median TTR was 66% (52, 76) overall, 63% (48, 74) among warfarin-naïve patients and 70% (59, 79) among warfarin-experienced patients. A total of 91% of warfarin-naïve patients had at least one INR value < 1.5 (81% for warfarin-experienced) whereas 51% had at least one INR value > 4.0 (47% for warfarin-experienced).

INR measures preceding clinical events

INR measures preceding clinical events are presented in Fig. 2. The last INR values before clinical events (median 14 [24, 7] days) were 2.0 (1.5, 2.5) for patients with ischemic stroke/SE and 2.5 (2.0, 2.9) for those with major bleeding (Table 2). The lowest INR value within 6 months before stroke/SE was 1.3 (1.0, 1.6), while the highest for patients with major bleeding was 3.4 (2.9, 4.1). In the control group, which included patients without clinical events, the lowest INR value between 3 and 9 months of follow-up was 1.6 (1.2, 1.8) and the highest was 3.3 (2.8, 3.8). The percentage of time with INR < 2.0 was 20% (8, 49) for patients with stroke/SE, while the percentage of time with INR > 3.0 was 10% (0, 25) for those with major bleeding.

Among warfarin-naïve patients (n = 4630), the last INR values before clinical events were 1.9 (1.4, 2.5) for patients with ischemic stroke/SE and 2.4 (2.0, 3.0) for those with major bleeding. (eTable 1). Among warfarin-experienced patients (n = 3175), the last INR values before a clinical event were 2.1 (1.7, 2.6) for patients with ischemic stroke/SE and 2.5 (2.2, 2.9) for those with major bleeding (eTable 2).

Sensitivity analysis

When excluding patients with clinical events occurring in the first 3 months after enrollment, the last INR was 2.0 (1.5, 2.5) for patients with ischemic stroke/SE and 2.4 (2.0, 2.9) for those with major bleeding (eTable 3). When excluding patients with events during or after study drug interruptions, the last INR was 1.9 (1.5, 2.5) for patients with ischemic stroke/SE and 2.5 (2.1, 3.0) for those with major bleeding (eTable 4). Among patients with at least one INR value within 14 to 30 days before clinical events, the last INR was 2.2 (1.7, 2.8) for patients with ischemic stroke/SE and 2.4 (1.8, 2.9) for those with major bleeding (eTable 5). When considering only patients not receiving aspirin on the day before the event, results were similar (eTable 6).

Historic INR versus future INR

Historic TTR was weakly associated with future TTR ($R^2 = 0.212$). Using TTR as a categorical variable, historic TTR ≥ 80% had limited predictive discrimination of future TTR ≥ 80% (C index = 0.61). Among patients with historic TTR ≥ 80%, 43% had future TTR ≥ 80%. When

Table 1 INR measures in warfarin-treated ARISTOTLE patients

INR measure	All patients in analysis cohort (n = 8822*)	Warfarin-naïve patients (n = 5320*)	Warfarin-experienced patients (n = 3502*)
Lowest INR value for each patient	1.1 (0.9, 1.3)	1.1 (0.9, 1.2)	1.2 (1.0, 1.4)
Highest INR value for each patient	4.0 (3.5, 4.7)	4.1 (3.5, 4.8)	4.0 (3.6, 4.5)
TTR	66 (52, 76)	63 (48, 74)	70 (59, 79)
Percent of time with INR < 2.0	19 (11, 32)	22 (13, 36)	15 (8, 25)
Percent of time with INR > 3.0	11 (5, 18)	11 (5, 18)	11 (6, 18)
At least one INR out of 2.0–3.0 range, no. (%)	8815 (99.9)	5319 (99.9)	3496 (99.8)
At least one INR < 1.5, no. (%)	7682 (87.1)	4857 (91.3)	2825 (80.7)
At least one INR > 4, no. (%)	4348 (49.3)	2698 (50.7)	1650 (47.1)
At least one INR < 1.5 or > 4, no. (%)	8110 (91.9)	5064 (95.2)	3046 (87.0)
Variance of INR	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)	0.5 (0.3, 0.7)

Data presented as median (25th, 75th), unless otherwise indicated

INR international normalized ratio, *TTR* time in therapeutic range

*Number of patients with at least three INR values

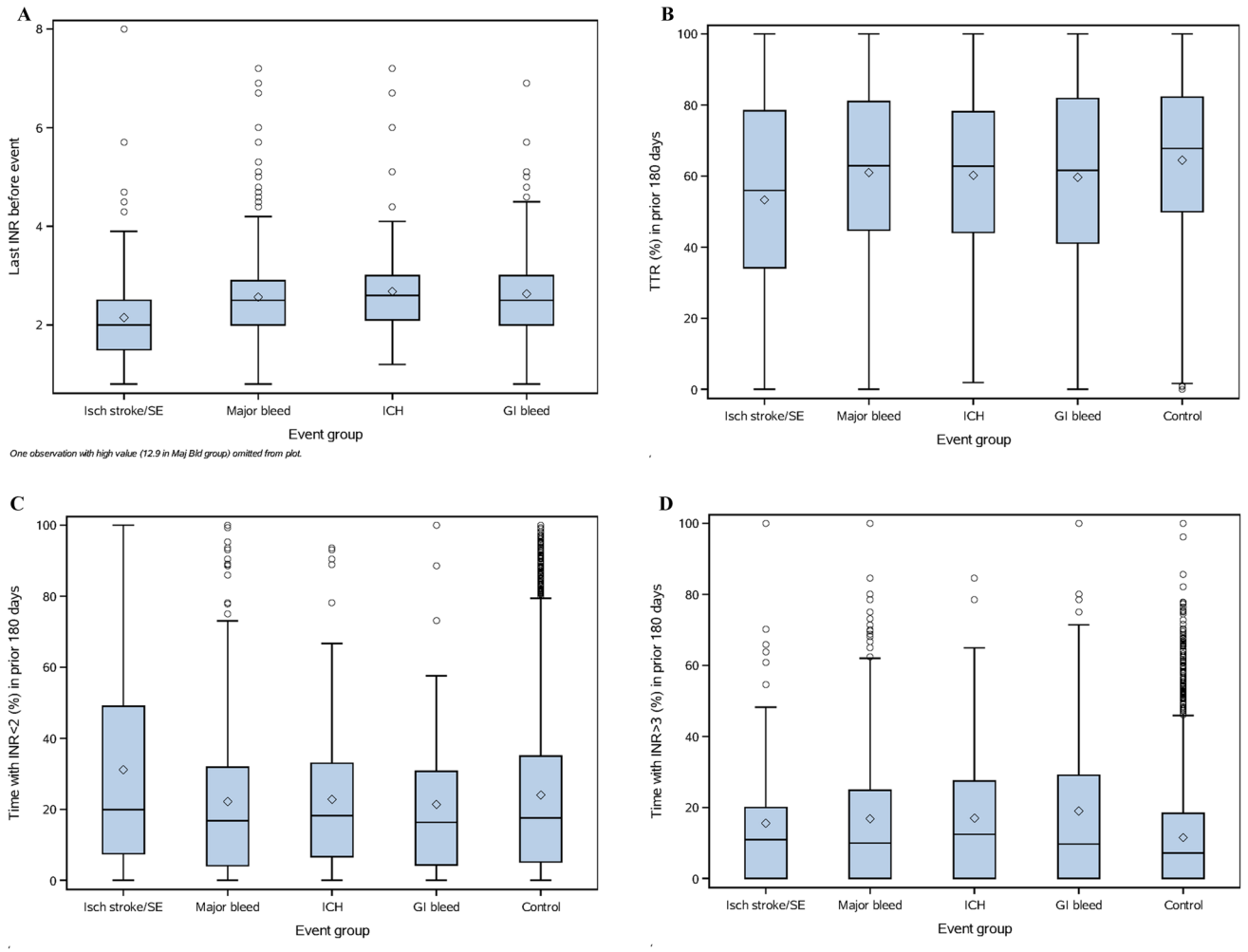

Fig. 2 INR measures preceding clinical events. **a** Last international normalized ratio (INR) before event. **b** Time in therapeutic range in the prior 180 days. **c** Percentage of time with INR < 2.0 in prior 180 days. **d** Percentage of time with INR > 3.0 in prior 180 days. *GI* gastrointestinal, *ICH* intracranial hemorrhage, *INR* international normalized ratio, *SE* systemic embolism, *TTR* time in therapeutic range

Table 2 INR measures preceding clinical events in warfarin-treated patients

INR measures from 180 days prior to event	Ischemic stroke or SE (n = 102)	Major bleeding (n = 448)	Intracranial bleeding (n = 117)	GI bleeding (n = 130)	Control (n = 7259)
Days from last INR to event	12 (5, 22)	14 (7, 24)	13 (6, 22)	12 (5, 22)	–
Number of INR values	7 (6, 9)	7 (6, 9)	7 (6, 9)	7 (6, 8)	7 (6, 8)
Last INR value prior to event	2.0 (1.5, 2.5)	2.5 (2.0, 2.9)	2.6 (2.1, 3.0)	2.5 (2.0, 3.0)	–
Lowest INR value	1.3 (1.0, 1.6)	1.4 (1.1, 1.7)	1.4 (1.2, 1.7)	1.5 (1.1, 1.7)	1.6 (1.2, 1.8)
Highest INR value	3.6 (3.0, 4.2)	3.4 (2.9, 4.1)	3.4 (3.0, 4.0)	3.3 (2.9, 4.2)	3.3 (2.8, 3.8)
Variance of INR	0.5 (0.2, 1.0)	0.4 (0.2, 0.9)	0.5 (0.2, 0.9)	0.4 (0.2, 1.0)	0.3 (0.2, 0.6)
TTR (%)	56 (34, 78)	63 (45, 81)	63 (44, 78)	62 (41, 82)	68 (50, 82)
Percent time with INR < 2.0	20 (8, 49)	17 (4, 32)	18 (7, 33)	16 (4, 31)	18 (5, 35)
Percent time with INR > 3.0	11 (0, 20)	10 (0, 25)	12 (0, 27)	10 (0, 29)	7 (0, 18)

Data presented as median (25th, 75th), unless otherwise indicated

GI gastrointestinal, *INR* international normalized ratio, *SE* systemic embolism, *TTR* time in therapeutic range

looking at the association between historic TTR ≥ 80% and the occurrence of any future INR out of range, the C index was 0.54. Of 160 patients with historic TTR of 100%, 44% had future TTR ≥ 80%. Historic TTR of 100% had limited predictive discrimination of future TTR ≥ 80% (C index = 0.51). When looking at the association between historic TTR of 100% and the occurrence of any future INR out of range, the C index was 0.53.

Future TTR, both as a continuous and a categorical variable, is summarized by historic bins in 20% increments in Table 3. We observed an increased median future TTR as categories of historic TTR increased. Among those with historic TTR of 81–99%, 43% had future TTR ≥ 80%, and among those with historic TTR of 100%, 44% had future TTR ≥ 80%.

Discussion

Our study provides an overview of the associations between INR patterns and subsequent clinical outcomes and future INR in patients with AF using warfarin in a large randomized trial with structured visits and frequently collected INR measurements. Our study has three main findings: 1) approximately 14 days before a bleeding event, two-thirds of patients with AF treated with warfarin had an INR value < 3.0; 2) around 12 days before an ischemic stroke, half of patients with AF on warfarin had an INR value > 2.0; 3) historic TTR had limited predictive ability to discriminate future TTR and future out of range INR values. There is a perception that for patients on warfarin with stable INR, the risk of bleeding [6] or stroke events is low and they are likely to continue to have good INR control, and therefore may derive less benefit from switching to a direct acting oral anticoagulant. Our results suggest that it is difficult to identify patients with AF using warfarin who would have a low likelihood of clinical events based on INR measurements.

INR values and clinical events

In this large cohort of patients with AF using warfarin, with a median of 29 (21, 38) INR values per patient, we observed that TTR was 66%, the majority of patients had at least one INR value < 1.5 (87%) whereas half of them had at least one value > 4.0. It is well established that INR levels should be in therapeutic range for warfarin to be effective without an important increase in the risk of bleeding. However, important challenges are associated with warfarin therapy and achieving and maintaining INR values within range can be difficult [1]. The need for INR monitoring, frequent dose adjustments, and numerous food and drug interactions are just some of the challenges to maintaining therapeutic INR values. Recently, direct acting oral anticoagulants have been shown to be at least as effective as warfarin in the prevention of thromboembolic events in patients with AF, with the advantage of having a more predictable effect with no need for laboratory monitoring and causing lower rates of intracranial hemorrhage [2, 7–9]. These agents were reported to have consistent efficacy and safety benefits, regardless of quality of INR control in different sites [9–11].

We found that INRs were frequently within therapeutic range 2 weeks before clinical events. Similar findings were seen when analyzing only patients with INR values within 14–30 days before events, when excluding those with events occurring during or after study drug interruptions, when excluding those with events in the first 3 months of randomization, or when including only those patients not receiving aspirin on the day prior to events. Additionally, TTR was lower for patients experiencing stroke/SE or major bleeding (56% and 63%, respectively) than in the control group who did not present with clinical events (68%). In a previous analysis, we have shown that approximately 80% of the warfarin-treated patients with ICH had an INR within or below therapeutic range around 2 weeks before the event [12]. Our current findings are consistent with a meta-analysis of studies of patients with AF receiving vitamin K antagonists that reported 58% of bleeding events occurred at an INR < 3.0 and 43% of embolic events occurred at an INR > 2.0 [13].

Table 3 Future time in therapeutic range by historic time in therapeutic range

	Historic					
	TTR 0–20% (n = 219)	21–40% (n = 434)	41–60% (n = 950)	61–80% (n = 1334)	81–99% (n = 1059)	100% (n = 160)
Future TTR, median (25th, 75th)	39 (17, 61)	59 (45, 73)	65 (54, 77)	72 (61, 82)	78 (67, 87)	78 (66, 88)
Future TTR ≥ 80%, no. (%)	13 (6)	63 (15)	180 (19)	407 (31)	456 (43)	70 (44)

TTR indicates time in therapeutic range

These results suggest that a significant proportion of events still occur in patients with therapeutic INRs. An analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial showed that the median INR at the time of a major bleeding event was 2.6 (2.0, 4.0), and of all patients with major hemorrhages and INR values available (n = 211), 63% had INR < 3.0 at the time of the event [14]. Our results add to the available evidence, demonstrating that among 448 patients experiencing a major bleeding event in ARISTOTLE, the median INR around 2 weeks before the event was 2.5. These findings provide unique insights about the use of vitamin K antagonists for patients with AF and might inform national and international scientific guidelines.

Historic INR and future INR

An analysis that included 3749 patients with AF using warfarin enrolled in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT AF) assessed whether historic INR stability (≥ 80% of INRs within therapeutic range) could predict future INR stability [15]. Among patients with stable INRs during the first 6 months of treatment, only 34% had stable INRs in the subsequent year. Historic INR stability had limited ability to predict INR values to stay stable over the next year (C index = 0.61). Our study included a larger population of patients with AF, with systematic INR measurement and collection, and we analyzed the ability of historic TTR ≥ 80% to predict future INR levels instead of looking at historic individual INR values. Our results reinforce the findings from ORBIT AF, since we also observed that less than half of patients with historic TTR ≥ 80% had future TTR ≥ 80%. As in the ORBIT AF analysis, we found that historic TTR ≥ 80% had limited predictive ability of future TTR ≥ 80% (C index = 0.61).

An analysis of 2841 patients with AF on warfarin in the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study showed that 41% of patients achieved TTR ≥ 70% in the initial period of 6 months [16]. Of those who had TTR ≥ 70% and INR values available (n = 987), only 60% achieved a TTR ≥ 70% over the next 6 months. Although prior publications on this topic have reached differing conclusions, our results are consistent with these studies and suggest that the data are not incompatible. While historic INR is related to future INR, the magnitude of association is not strong and many people with excellent INR history will experience poor INR control in the future. Moreover, even though TTR has been commonly used to assess quality of warfarin treatment in clinical trials, it may be influenced by multiple factors such as geographic region and the frequency of INR measurement [17].

Our study has several limitations. As an observational analysis, unmeasured confounding is always present and our results should be interpreted as hypothesis generating. We analyzed clinical outcomes in patients with AF who were randomized in a trial with specific inclusion and exclusion criteria. Thus, the results may be not generalizable to every patient with AF. We did not have data on INR at the time of event for most of the patients; therefore, we showed the last INR values before events. However, the median time between the last INR value and the clinical event was 14 days.

Conclusion

In patients with AF receiving warfarin in the ARISTOTLE trial, most bleeding events may not have been preventable, despite careful INR control. At least half of the strokes occurred shortly after measuring a "therapeutic" INR. INR history did not adequately predict future levels of INR control. Thus, our findings suggest that INRs collected through routine management are not sufficiently predictive to provide reassurance about future time in therapeutic range or to prevent subsequent outcomes, and might be over-interpreted in clinical practice.

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Compliance with ethical standards

Conflict of interest Lopes: Research grant: Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer; Consultant/Advisory Board: Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Medtronic, Merck, Portola, GlaxoSmithKline, Pfizer. Alexander: Research grant: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, CSL Behring, Sanofi, Tenax Therapeutics; Consultant/Advisory Board: Cempra, CryoLife, CSL Behring, Pfizer, Portola Pharmaceuticals, VasoPrep Surgical. Hijazi: Honoraria: Boehringer Ingelheim, Roche Diagnostics, Pfizer and Bristol-Myers Squibb; Consultant/Advisory board: Pfizer, Bristol-Myers Squibb, Roche Diagnostics, and Merck, Sharp & Dohme. Hylek: Consultant: Bayer, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Daiichi-Sankyo, Johnson & Johnson; Research grant: Bristol Myers Squibb/Pfizer, Johnson & Johnson. Gersh: Consulting fees/Honoraria: Xenon Pharmaceuticals; Data monitoring board: Armetheon Inc, Baxter Helathcare Corporation, CardioVascular Research Foundation, Janssen Research & Development, MEDTRONIC, Mount Sinai St. Lukes, Teva Pharmaceuticals, Thrombosis Research Institute; Other: Boston Scientific, Cipla Limited, Janssen Scientific Affairs LLC, St. Jude Medical, Inc. Garcia:

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Ethical approval All procedures performed in studies involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the study.

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