Comparison of international normalised ratio audit parameters in patients enrolled in GARFIELD-AF and treated with vitamin K antagonists

GARFIELD-AF Investigators

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Comparison of international normalised ratio audit parameters in patients enrolled in GARFIELD-AF and treated with vitamin K antagonists

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Running short title: Comparing international normalised ratio audit parameters

Summary

Vitamin K antagonist (VKA) therapy for stroke prevention in atrial fibrillation (AF) requires monitoring of international normalised ratio (INR). We evaluated the agreement between two INR audit parameters, frequency in range (FIR) and proportion of time in the therapeutic range (TTR), using data from a global population of patients with newly diagnosed non-valvular AF, the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF). Among 17,168 patients with 1-year follow-up data available at the time of the analysis, 8445 received VKA therapy (±antiplatelet therapy) at enrolment, and of these patients, 5066 with ≥3 INR readings and for whom FIR and TTR could both be calculated were included in the analysis. In total, 70,905 INRs were analysed. At the patient level, TTR showed higher values than FIR (mean, 56.0% vs 49.8%; median, 59.7% vs 50.0%). Although patient-level FIR and TTR values were highly correlated (Pearson correlation coefficient [95% confidence interval; CI], 0.860 [0.852 to 0.867]), estimates from individuals showed widespread disagreement and variability (Lin's concordance coefficient [95% CI], 0.829 [0.821 to 0.837]). The difference between FIR and TTR explained 17.4% of the total variability of measurements. These results suggest that FIR and TTR are not equivalent and cannot be used interchangeably.

Keywords: atrial fibrillation, frequency in range, international normalised ratio, time in therapeutic range, vitamin K antagonists

Introduction

Vitamin K antagonists (VKAs) such as warfarin are effective in reducing the risk of stroke and thromboembolism in patients with atrial fibrillation (AF) (Hart*, et al* 2007). It is well known that quality of VKA control is related to clinical outcome. The optimal international normalised ratio (INR) range is 2.0–3.0, as levels below 2.0 and above 3.5–4.0 are associated with increased risk of ischaemic stroke and intracranial haemorrhage, respectively (Hylek and Singer 1994, Hylek*, et al* 1996, Singer*, et al* 2009).

The two most commonly reported audit parameters for INR control are frequency in range (FIR) – also known as proportion of INRs in the therapeutic range and number of tests in range – and the proportion of time in the therapeutic INR range (TTR) (Rosendaal*, et al* 1993). TTR is a relatively difficult measure to calculate, requiring computer software, whilst FIR, certainly at an individual patient level, is much easier to calculate and can effectively be done manually. Indeed, the National Institute for Health and Care Excellence (NICE) recommends using 'a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual dosing', whilst also using TTR of <65% as an indicator for poor anticoagulation control (NICE 2014). The European Society of Cardiology recommends a target TTR of at least 70% (Camm*, et al* 2012) and the Asia Pacific Heart Rhythm Society recommends a TTR of at least 60% (Ogawa*, et al* 2013) for optimal VKA control.

This paper aims to elucidate the agreement between these two measures at an individual patient level using the largest INR dataset to date, from the Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD-AF), a large contemporary prospective cohort study of patients newly diagnosed with non-valvular AF. We have chosen to compare TTR and FIR as these are reported in the majority of studies (Connolly*, et al* 2008, Fitzmaurice*, et al* 2000, Fitzmaurice*, et al* 2003, Franke*, et al* 2008, Singer*, et al* 2013, Van Spall*, et al* 2012, White*, et al* 2007).

Methods

Study design

GARFIELD-AF is an ongoing worldwide observational registry of adults with a new diagnosis of non-valvular AF (Kakkar*, et al* 2012). Patients are being enrolled **consecutively** in five sequential cohorts. The use of antithrombotic therapies is at the discretion of study investigators. **A site selection process was employed to ensure proportional representation of the spectrum of care settings in each country. First, the national coordinating investigator (NCI) identified the care settings they believed most accurately represented the management of patients with AF in their country. Then, from a list (sampling frame) of sites from various database searches that reflected the**

care settings in the country, the contract research organisation (CRO) contacted a random (ie, lack of selection of sites based on specific criteria rather than using random sampling) sample of sites for each care setting from the list, in accordance with the distribution specified by the NCI. A few sites were 'selected' by the CRO or NCI as replacement sites when sites dropped out or when we had exhausted the list and were still short of the required number of sites in a given country. This was very infrequent and only occurred in three countries. This article reports data for prospective patients enrolled from March 2010 to June 2013.

Ethics statement

Independent ethics committee and hospital-based institutional review board approvals were obtained, as necessary, for the registry protocol. The registry is being conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent to participate.

Data collection

Data **on consecutive patients** were collected using an electronic case report form (eCRF) and captured by trained data abstractors. The eCRF was designed by Dendrite Clinical Systems Ltd (Henley-on-Thames, UK) and the Thrombosis Research Institute (London, UK) is responsible for data management. **Source data verification (SDV) is regularly undertaken in the GARFIELD-AF study by monitoring 20% of the eCRF against source data. In the latest phase of SDV, the eCRF matched patient records 95.5% of the time.** Data for the analysis in this report were extracted from the GARFIELD-AF study database on 30 June 2014.

*VKA control**: inclusion and exclusion criteria***

INR readings during the first year of follow-up were analysed. Patients on VKA treatment at enrolment contributed to the analysis from enrolment to the date of discontinuation of VKA or to the last date of follow-up in the study.

The frequency of INR measurements is not mandated in the study. Patients on VKA treatment at enrolment but with fewer than three readings during the follow-up were excluded from the analysis. All INR readings after discontinuation of VKA were excluded even if the patient resumed VKA therapy. To exclude artifacts, INR readings of less than 0.8 were removed from the analyses in two cases.

Calculation of FIR and TTR

The target range of INR for this study was 2.0–3.0, based on the recommendations from international guidelines (Camm*, et al* 2012, January*, et al* 2014).

Patient-level FIR was calculated as the percentage of the total INR readings that were in range for each patient.

Patient-level TTR was estimated by assigning INR values to each day between consecutive INR readings by linear interpolation, as described by Rosendaal *et al* (1993). TTR was estimated between two consecutive INR readings only if the interval did not exceed 90 days**, based on the NICE-recommended INR testing interval of up to 12 weeks when values are stable (NICE 2015).** If a patient had at least three INR readings and one or more of the intervals between readings exceeded 90 days, the remaining intervals were used to calculate TTR for the patient.

Statistical analysis

Patient-level FIR and TTR were compared using the Pearson correlation coefficient (Pearson 1896) and Lin's concordance coefficient for agreement (Lin 1989, Lin 2000). The Pearson correlation coefficient measures the linear association between two continuous variables. Lin's concordance coefficient for agreement combines measures of both precision and accuracy to determine how far the observed data deviate from the line of perfect concordance.

We also estimated a variance component model to model the dependence between FIR and TTR for the same patient, by splitting the total variance of INR quality control measurements into two components: between-patient variance and within-patient (or residual) variance. The within-patient variability is due to the disagreement between FIR and TTR. The within-patient variability would be zero if FIR and TTR agreed perfectly. Lin's concordance coefficient can be viewed as an intraclass coefficient estimated through variance components (Carrasco and Jover 2003).

We also studied whether the number of INR readings affected the agreement between FIR and TTR, by plotting Lin's concordance coefficient against the number of INR readings.

A sensitivity analysis was performed by repeating all analyses except the variance component model and the analysis of the effect of number of INR readings on the agreement between FIR and TTR, but excluding INR readings in the first 90 days of VKA treatment.

Analyses were performed using SAS statistical software, release 9.4 (SAS Institute, Cary, NC, USA) and Stata statistical software, version 13.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics of patients

Overall, 17,168 prospective patients enrolled into GARFIELD-AF from March 2010 to June 2013 had 1-year follow-up data available at the time of the analysis. Among these patients, 8445 were on VKA therapy (with or without antiplatelet therapy) at enrolment, and of these patients, 5066 with at least three INR readings and for whom FIR and TTR could both be calculated were included in the analysis. **The majority of these patients received warfarin (62.3%), followed by acenocoumarol (22.3%) and phenprocoumon (9.4%); 2.6% received other types of VKA and 3.4% received unknown VKAs. Of the patients,** 963 (19.0%) had 3–5 INR readings and 4103 (81.0%) had ≥6 INR readings. The mean age of these patients was 71.2 years and 43.9% were women (Table I). The mean CHA_2DS_2-VASc score was 3.4.

INR readings

A total of 70,905 INR readings were analysed. At the population level, the mean INR value was 2.4 and the median was 2.3 (Table II). Slightly more than half of the INR readings (51.8%) were in the therapeutic range (2.0–3.0) and of the remainder, a greater proportion were under the therapeutic range than above the range (31.2% and 17.0%, respectively; Table II and Fig 1).

FIR and TTR

Overall, TTR values were higher than FIR values at the patient level. The mean TTR and FIR were 56.0% and 49.8%, respectively, and the median TTR and FIR were 59.7% and 50.0%, respectively (Table II). Using equal-sized intervals for histograms of patient-level FIR and TTR, the distribution of FIR showed greater variation between consecutive quantiles than TTR (Fig 2).

FIR and TTR showed high correlation (Fig 3), with a Pearson correlation coefficient of 0.860 (95% confidence interval [CI]: 0.852 to 0.867). However, concordance was poor according to McBride criteria (McBride 2005), with clear deviation from the line of perfect concordance (**Fig 3**). Lin's concordance coefficient was 0.829 (95% CI: 0.821 to 0.837).

In the variance component model, between-patient and within-patient variability explained 82.6% (between-patient variance = 542.0) and 17.4% (within-patient variance = 113.9), respectively, of the total variance. In other words, the disagreement between FIR and TTR was responsible for 17.4% of the total variance.

Although, on average, FIR increased as TTR increased, in the group of patients with a TTR of 70–80%, 25% had an FIR of less than 57.1% (Fig 4).

Analysis of the agreement between FIR and TTR by the number of INR readings showed that Lin's concordance coefficient decreased as the number of readings increased (Fig 5). Lin's concordance coefficient did not show good agreement between FIR and TTR for any number of INR readings, although it was highest between 6 and 12 readings, ie, a frequency of one INR test every 1–2 months.

Sensitivity analysis

We performed a sensitivity analysis by excluding INR readings in the first 90 days of VKA treatment, to evaluate the effect of excluding INR readings during the period when patients were settling into their therapy regimen. The distribution of INR readings (n=42,036) is shown in Table III. The median was the same as that from the main analysis (2.3) but the mean was slightly higher (2.5 vs 2.4). The percentage of INR readings in the therapeutic range at the population level was higher than in the main analysis (56.6% vs 51.8%, respectively).

The distribution of patient-level FIR and TTR is shown in Fig 6. The mean patient-level FIR and TTR were higher than those from the main analysis (FIR, 55.4% vs 49.8%; TTR, 60.3% vs 56.0%).

Pearson and Lin's coefficients (Pearson, 0.875 [95% CI: 0.867 to 0.882]; Lin, 0.858 [0.850 to 0.865]) were similar to those from the main analysis (Pearson, 0.860 [0.852 to 0.867]; Lin, 0.829 [0.821 to 0.837]).

Discussion

FIR and TTR are two commonly used parameters for assessing quality of VKA control. FIR is based on a discrete number of visits, whereas TTR is estimated for each day of the follow-up period; however, FIR has the advantage of being simpler to calculate. We evaluated the agreement between these two measures at an individual patient level. Our analysis showed that FIR was not equivalent to TTR, with TTR values being higher than FIR values overall. Although the two parameters were highly correlated, there was widespread disagreement and variability between them. In the variance component model, the within-patient variability, which is due to differences between FIR and TTR, was high enough to have clinical relevance. In general, FIR increased as TTR increased; however, the great variability between the measures meant that, for example, in a subset of patients with good VKA control according to TTR (70–80%), a quarter had an FIR of less than 57%, which would indicate inadequate VKA control. These results suggest that clinical assessment of the quality of VKA control at the patient level may change considerably if FIR is used instead of TTR.

The agreement between FIR and TTR decreased as the number of INR readings increased, and was greatest between 6 and 12 INR readings (ie, an INR test every 1–2 months). We speculate that the highest numbers of INR tests were done on patients with very unstable INR, for whom the linear interpolation assumption in the estimation of TTR may not hold. The mean patient-level FIR and TTR were higher in the sensitivity analysis (excluding INR readings in the first 90 days of VKA treatment) than in the main analysis, although the degree of correlation and concordance between FIR and TTR was similar to that found in the main analysis. This suggests that for meaningful results, INR readings in the early period of VKA therapy, when patients are settling into the therapy regimen, should be treated with caution in analyses.

A study by Schmitt *et al* (2003) compared three methods for assessing quality of VKA control, FIR, TTR and cross-section of the files, and showed that TTR gave a significantly shorter mean time in therapeutic range versus each of the other methods over six 2-month intervals. Similar differences were found when analyses were performed for 3-month and 6-month time intervals. The study was a retrospective analysis of 633 patients managed by a university hospital-based, pharmacist-managed anticoagulation clinic in the USA, with 1 year of follow-up. Recently, a retrospective cohort study of 377 VKA-treated outpatients attending the cardiology anticoagulation clinic of a Portuguese hospital showed that FIR and TTR were significantly correlated but not equivalent, due to high variability between the parameters (Caldeira*, et al* 2015). Our study extends these findings by analysing data from an international cohort of 8445 prospective patients.

Overall, 60% (5066/8445) of patients on VKA with at least three INR readings and for whom FIR and TTR could both be calculated were included in the analysis. However, because the frequency of INR testing is not mandated in this real-world study, a significant proportion of patients had fewer than three INR readings and this is clearly a limitation of the study. Based on clinical input, it was felt that a criterion for the minimum number of readings required over the 1-year period of follow-up should be at least three. The best agreement between FIR and TTR was found between 6 and 12 readings, ie, a frequency of one INR test every 1–2 months; it should be noted that 81% (4103/5066) of patients included in the analyses had at least six INR readings over the 1-year follow-up period. Although the target INR range used in this study is based on recommended international guidelines (Camm*, et al* 2012, January*, et al* 2014), we recognise that investigators in each country may have been guided by national guidelines that differ from this target range; for example, Japanese guidelines (J.C.S. Joint Working Group 2014). This represents a further limitation of this study.

In conclusion, our data show that FIR and TTR are not equivalent and cannot be used interchangeably. FIR gives a lower value than TTR overall. **It is not possible to conclude from our data that one measure is better than the other. However, we suggest that TTR is reported if only one INR audit parameter is reported, and that FIR is only used if it is not possible to calculate TTR. The reason is that TTR takes into account the time between INR readings and may also be a better proxy for clinical outcomes, as observed by Wan et al (2008).** We also suggest that patients who are receiving warfarin (or any other VKA) are managed utilising computerised decision support systems, so that the generation of these data for both an individual and a population is straightforward.

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Author contributions

DAF, SH, GK, FM and AKK contributed to the study design; DAF, HLL and HtC contributed individual patient data; GA performed the statistical analyses; all authors assisted in the

interpretation of the analyses and in the writing, editing and/or critical review of the manuscript; all authors provided final approval of the manuscript for submission.

Disclosures

DAF has acted as an advisory board member for Bayer. GA, GK and HLL have no conflicts of interest to disclose. SH has acted as a consultant for Aspen, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer and Sanofi and has participated in Speakers' Bureaux for Bayer, Bristol-Myers Squibb and Sanofi. FM is an employee of Bayer Healthcare. KP has received honoraria from Bayer Healthcare and AstraZeneca. HtC has given invited talks for Bayer, Boehringer Ingelheim, GSK, Leo and Roche, has acted as a consultant for Stago and Philips, and is Chair of the board for the Dutch Federation of Anticoagulation Clinics. He has received research funding from Bayer, Boehringer Ingelheim and AstraZeneca. AGGT has acted as a consultant for Bayer Pharma AG and has participated in Speakers' Bureaux for Janssen. AKK has received research support or acted as the principal investigator for Bayer HealthCare and Armetheon. He has acted as a consultant or advisory board member for or received honoraria from Bayer HealthCare, Sanofi-Aventis, Boehringer Ingelheim, Daiichi Sankyo, Armetheon and Aspen.

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Table I. Baseline characteristics in patients on vitamin K antagonist at enrolment with at least two INR readings and for whom both frequency in range and proportion of time in the therapeutic range could be calculated.

Variable	N=5066
Age	
Mean (SD), years	71.2 (10.2)
Age group, n (%)	
<65 y	1195 (23.6)
65–74 y	1752 (34.6)
≥75 y	2119 (41.8)
Gender, n (%)	
Women	2223 (43.9)
Race, n (%)	
Caucasian	3761 (76.3)
Asian	860 (17.5)
Other	307 (6.2)
Unwilling to declare	138
Smoking habits	
Current smoker	420 (9.3)
Ex-smoker	1266 (27.9)
No	2850 (62.8)
Unknown	530
CHA_2DS_2-VASc	
Mean (SD)	3.4 (1.5)
Median (interquartile range)	3.0 (2.0–4.0)
0, n (%)	86 (1.7)
1, n (%)	422 (8.5)
2, n (%)	857 (17.3)
≥3, n (%)	3589 (72.5)
Unknown	112

INR, international normalised ratio; SD, standard deviation

Table II. Distribution of INR readings, patient-level frequency in range and patient-level proportion of time in the therapeutic range.

	INR	FIR	TTR
N	70,905 readings	5066 patients*	5066 patients*
Median (IQR)	2.3 (1.9–2.8)	50.0 (33.3–66.7)	59.7 (38.6–76.2)
Mean (SD)	2.4 (0.9)	49.8 (23.8)	56.0 (26.9)
INR <2.0, n (%)	22,149 (31.2)	-	-
INR 2.0–3.0, n (%)	36,676 (51.8)	-	-
INR >3.0, n (%)	12,080 (17.0)	-	-

FIR, frequency in range; INR, international normalised ratio; IQR, interquartile range; SD, standard deviation; TTR, proportion of time in the therapeutic range

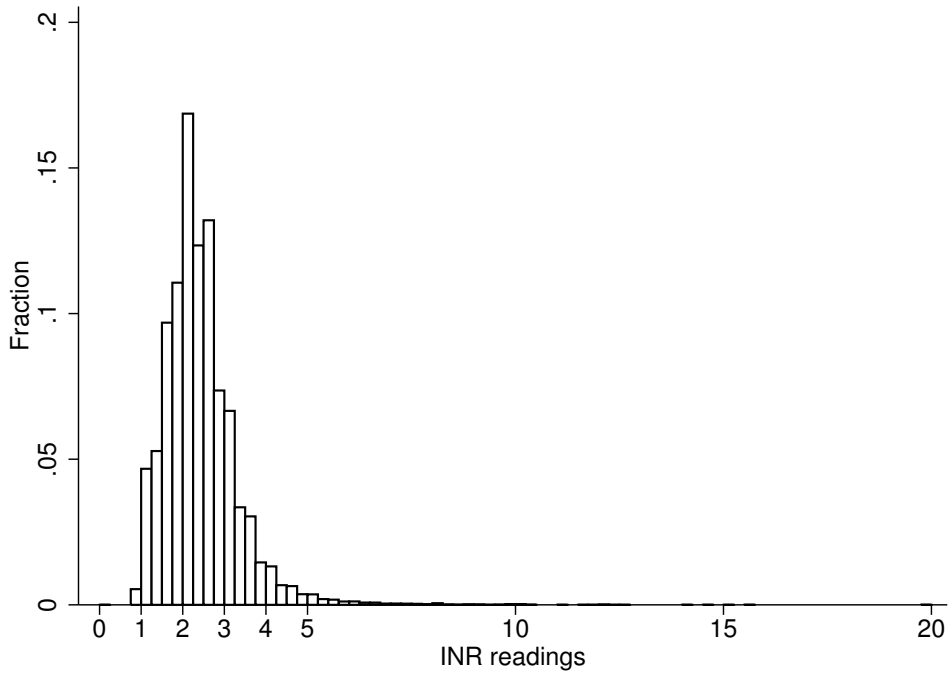
*The number of INR readings was the same for FIR and TTR but for TTR, intervals between INR readings that were >90 days were excluded

Table III. Distribution of INR readings, patient-level frequency in range and patient-level proportion of time in the therapeutic range, excluding readings in the first 90 days of treatment.

	INR	FIR	TTR
N	42,036 readings	4191 patients	4191 patients
Median (IQR)	2.3 (2.0–2.8)	58.3 (38.5–73.7)	64.3 (42.8–81.9)
Mean (SD)	2.5 (0.8)	55.4 (25.6)	60.3 (27.7)
INR <2.0, n (%)	10,878 (25.9%)	-	-
INR 2.0–3.0, n (%)	23,771 (56.6%)	-	-
INR >3.0, n (%)	7387 (17.6%)	-	-

FIR, frequency in range; INR, international normalised ratio; IQR, interquartile range; SD, standard deviation; TTR, proportion of time in the therapeutic range

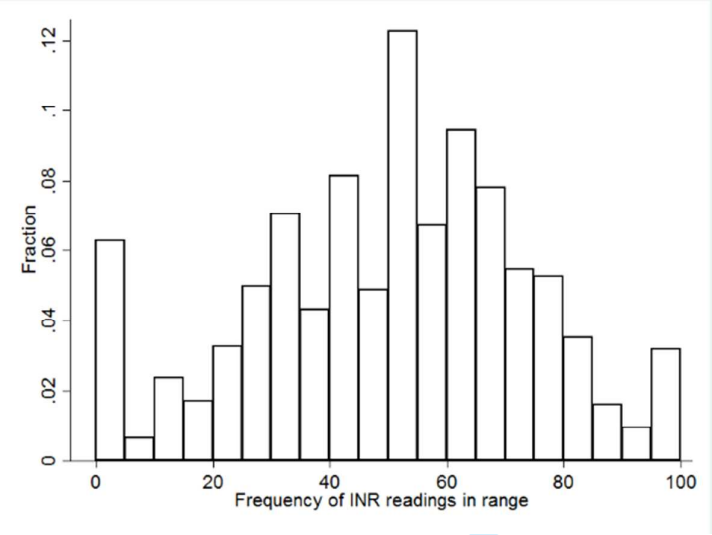
Fig 1. Distribution of INR readings.



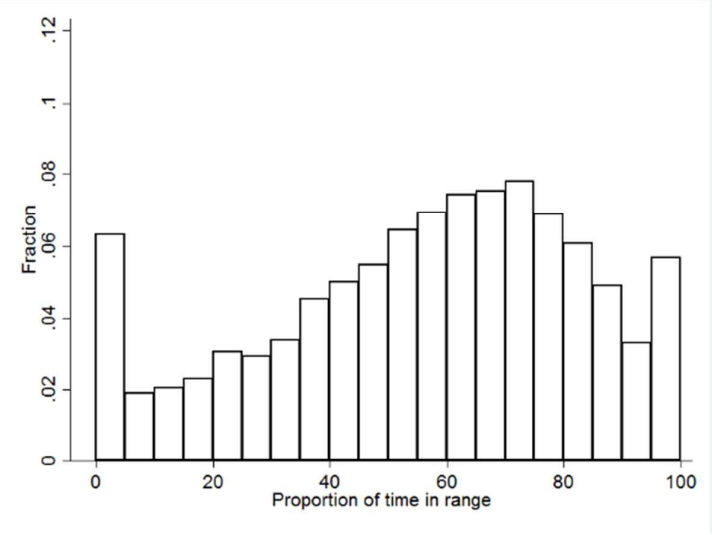
INR, international normalised ratio

Fig 2. Distribution of patient-level frequency in range (A) and proportion of time in the therapeutic range (B).

(A)

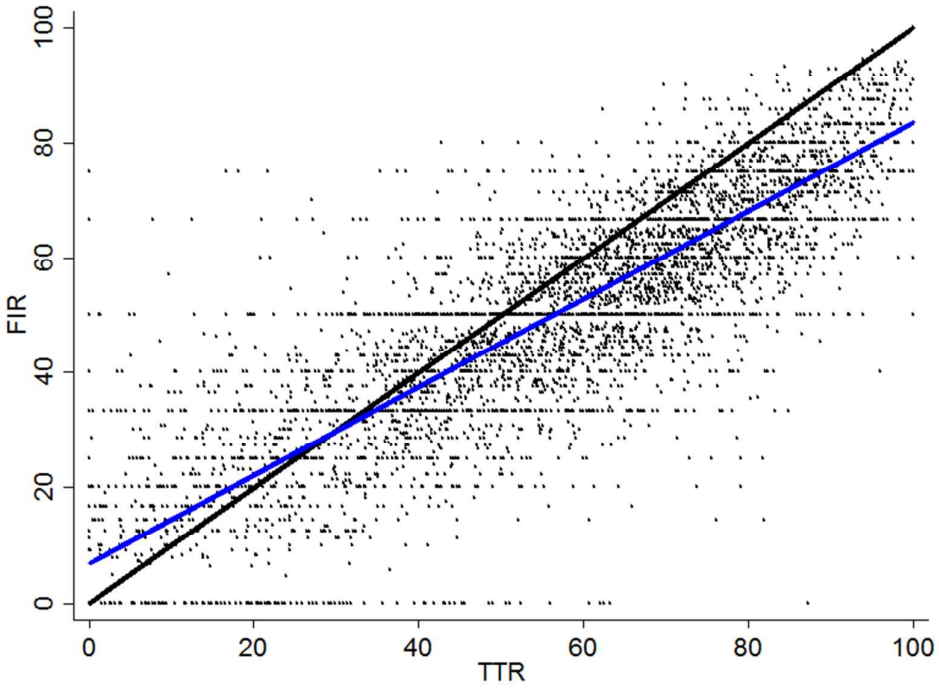


(B)



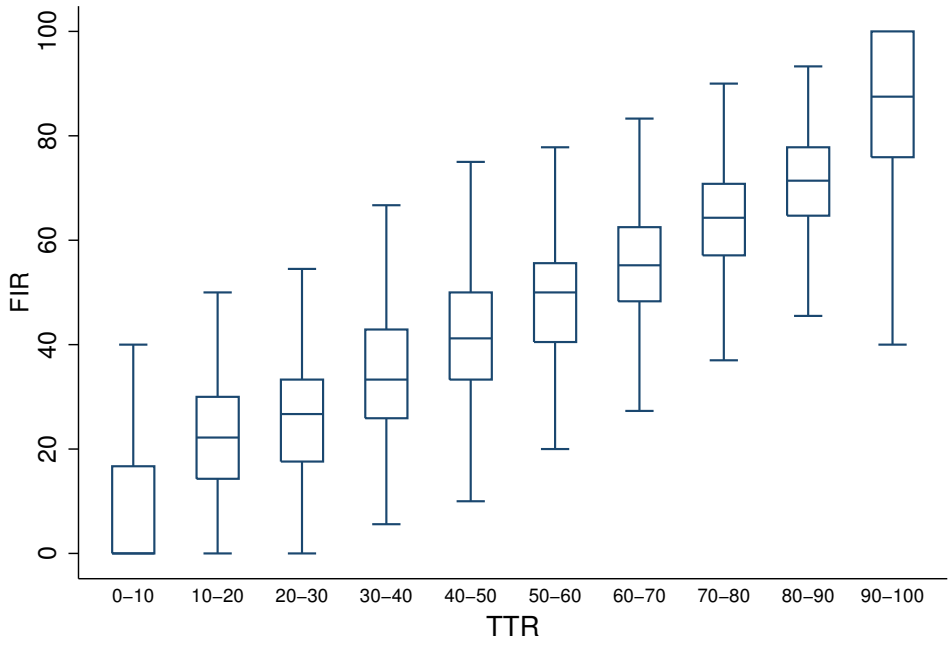
INR, international normalised ratio

Fig 3. Concordance between patient-level frequency in range and proportion of time in the therapeutic range. The black line is the line of perfect concordance and the blue line is the line of regression.



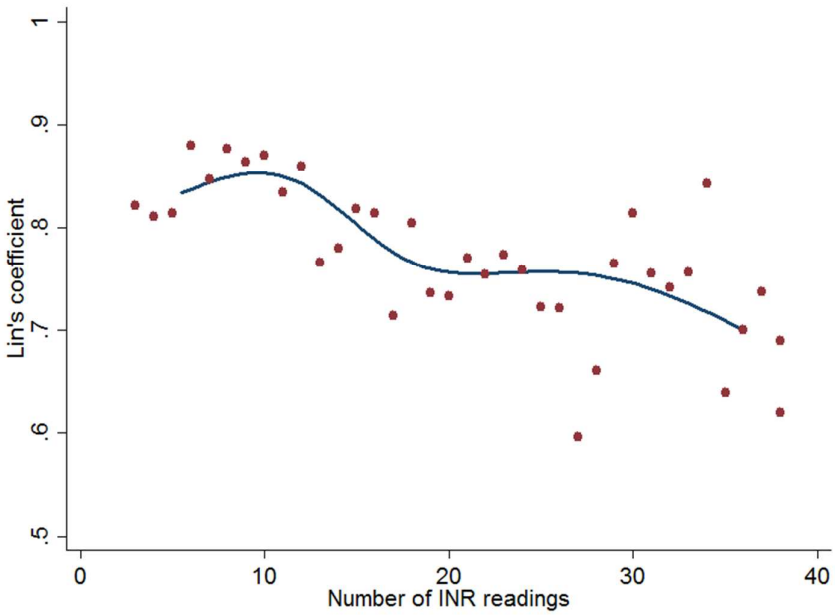
FIR, frequency in range; TTR, proportion of time in the therapeutic range

Fig 4. Frequency in range by level of proportion of time in the therapeutic range at the patient level.



FIR, frequency in range; TTR, proportion of time in the therapeutic range

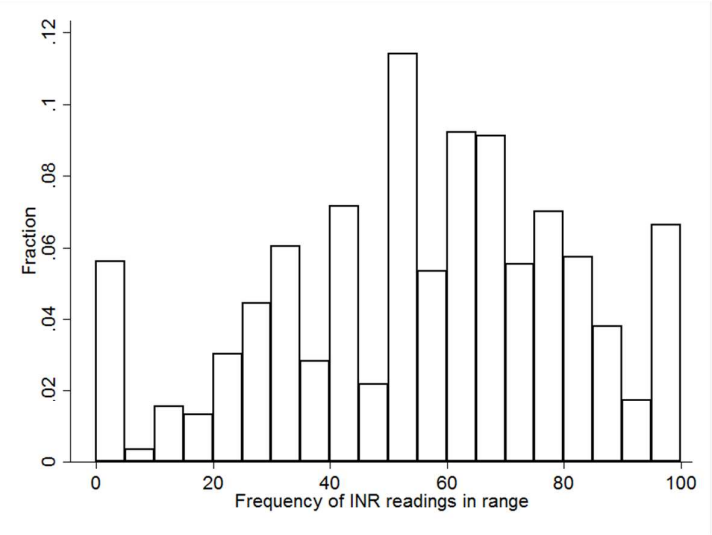
Fig 5. Agreement between frequency in range and time in the therapeutic range by number of INR readings.



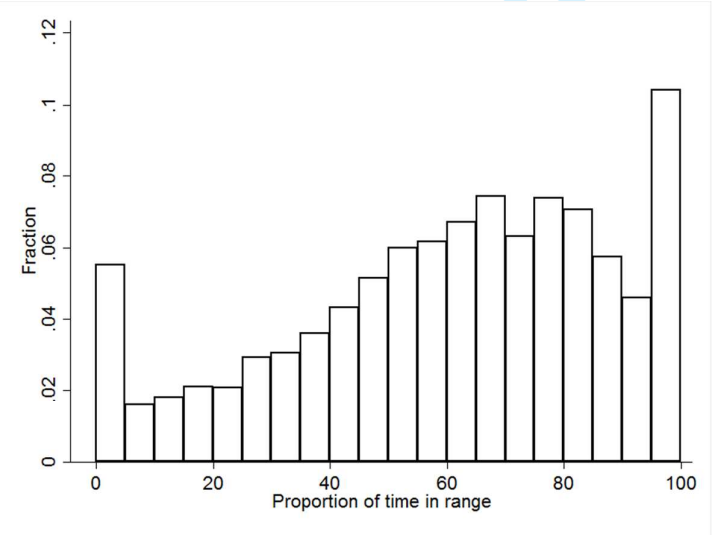
INR, international normalised ratio

Fig 6. Distribution of patient-level frequency in range (A) and proportion of time in the therapeutic range (B), excluding INR readings in the first 90 days of treatment.

(A)



(B)



INR, international normalised ratio

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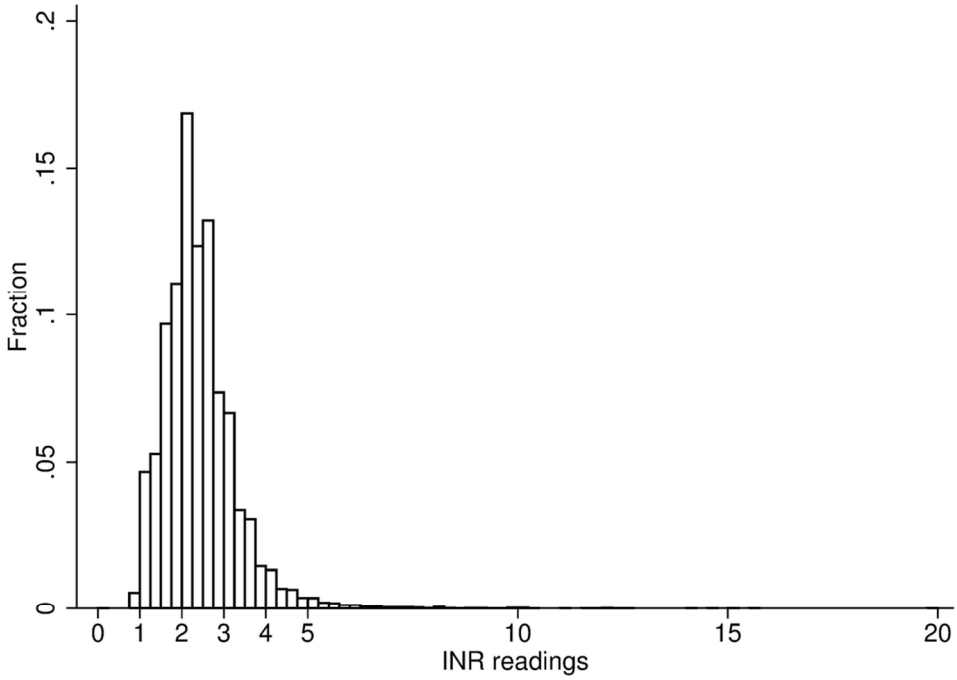


Fig 1. Distribution of INR readings.
INR, international normalised ratio
101x73mm (300 x 300 DPI)

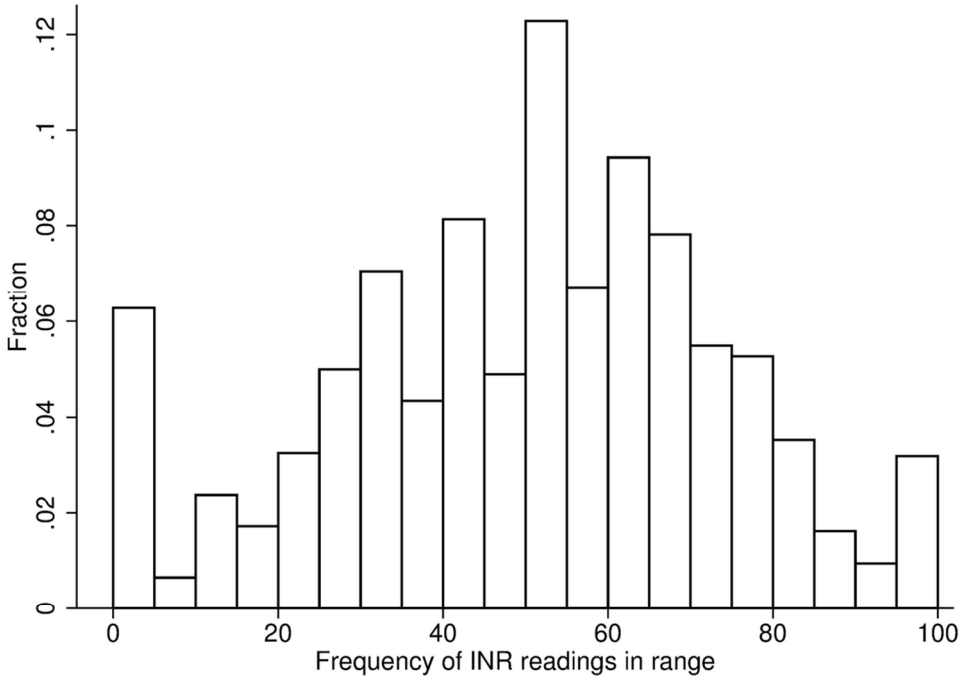
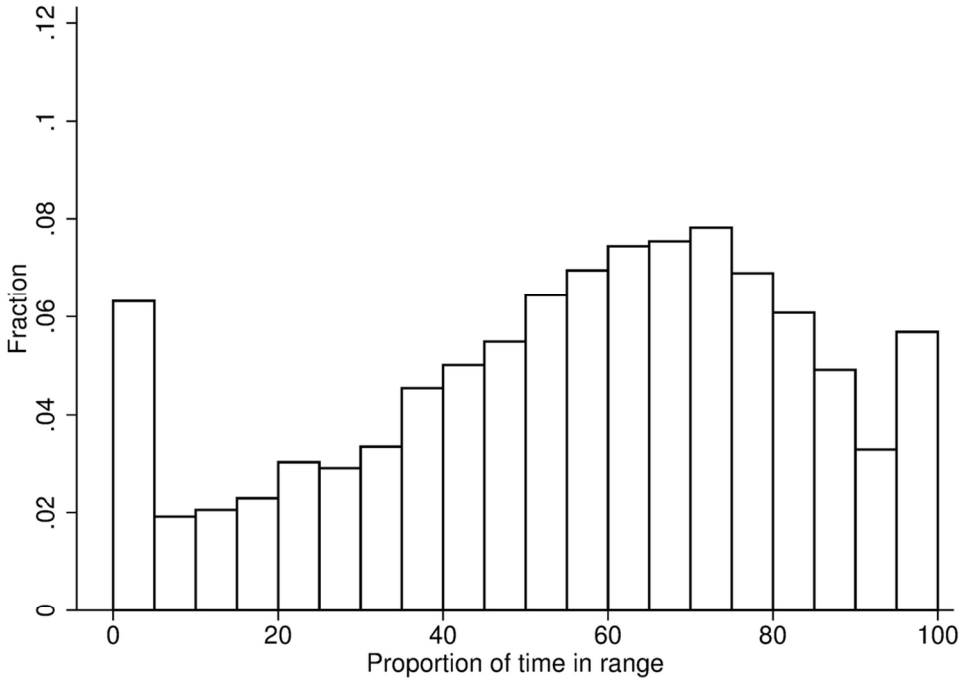


Fig 2. Distribution of patient-level frequency in range (A) and proportion of time in the therapeutic range (B).
INR, international normalised ratio
101x73mm (300 x 300 DPI)



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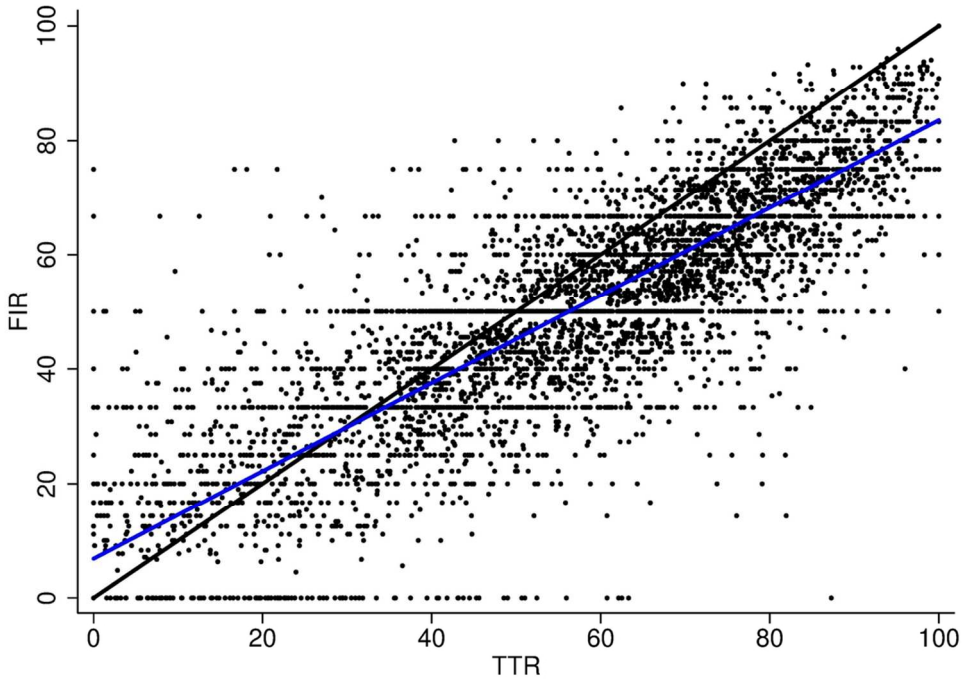

Fig 3. Concordance between patient-level frequency in range and proportion of time in the therapeutic range. The black line is the line of perfect concordance and the blue line is the line of regression. FIR, frequency in range; TTR, proportion of time in the therapeutic range
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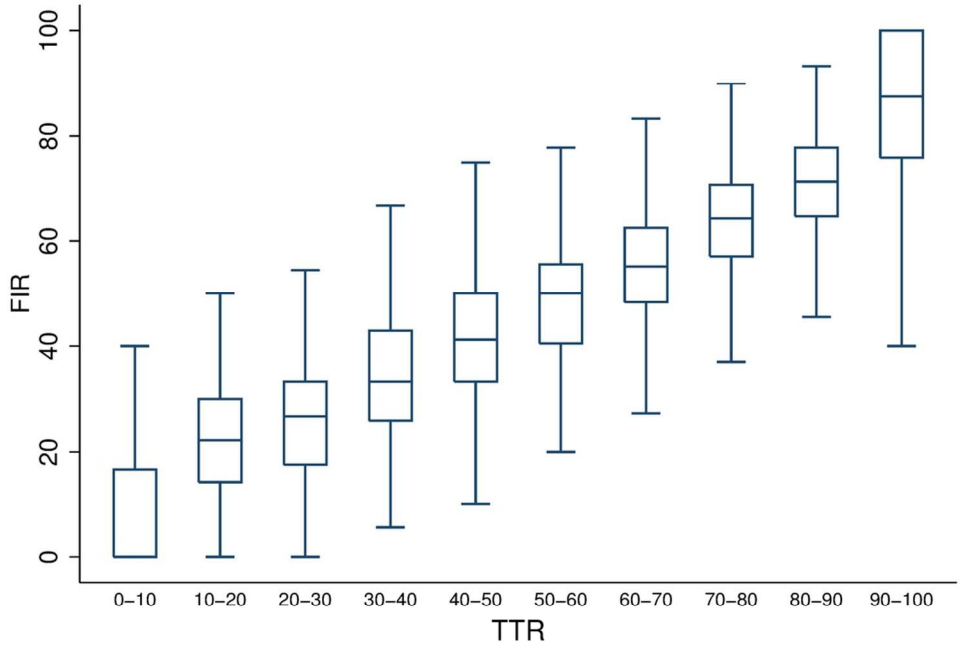


Fig 4. Frequency in range by level of proportion of time in the therapeutic range at the patient level.
FIR, frequency in range; TTR, proportion of time in the therapeutic range
101x73mm (300 x 300 DPI)

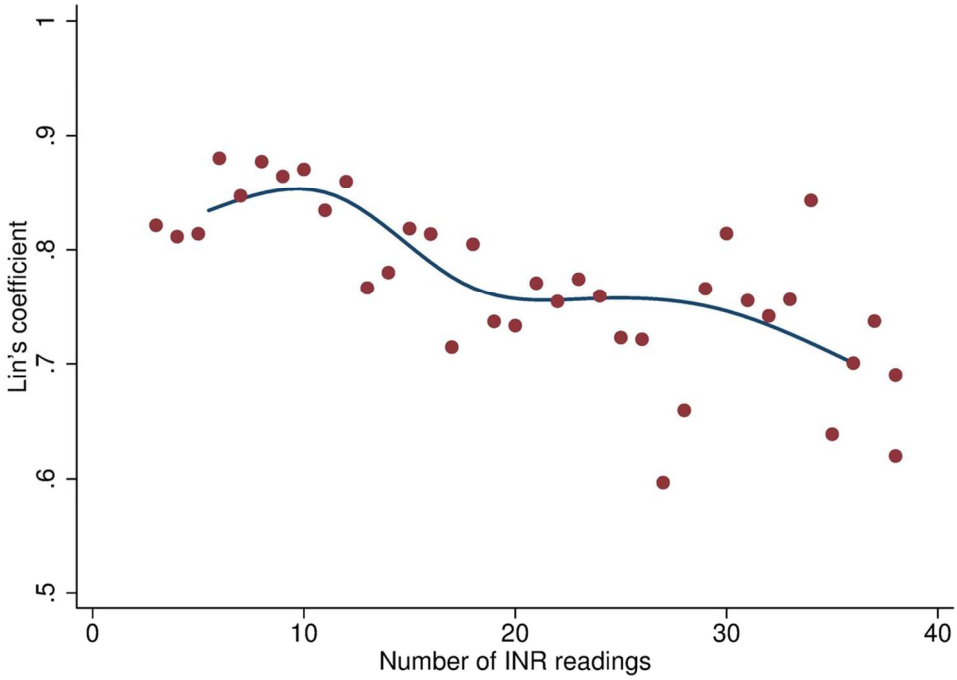


Fig 5. Agreement between frequency in range and time in the therapeutic range by number of INR readings.
INR, international normalised ratio
101x73mm (300 x 300 DPI)

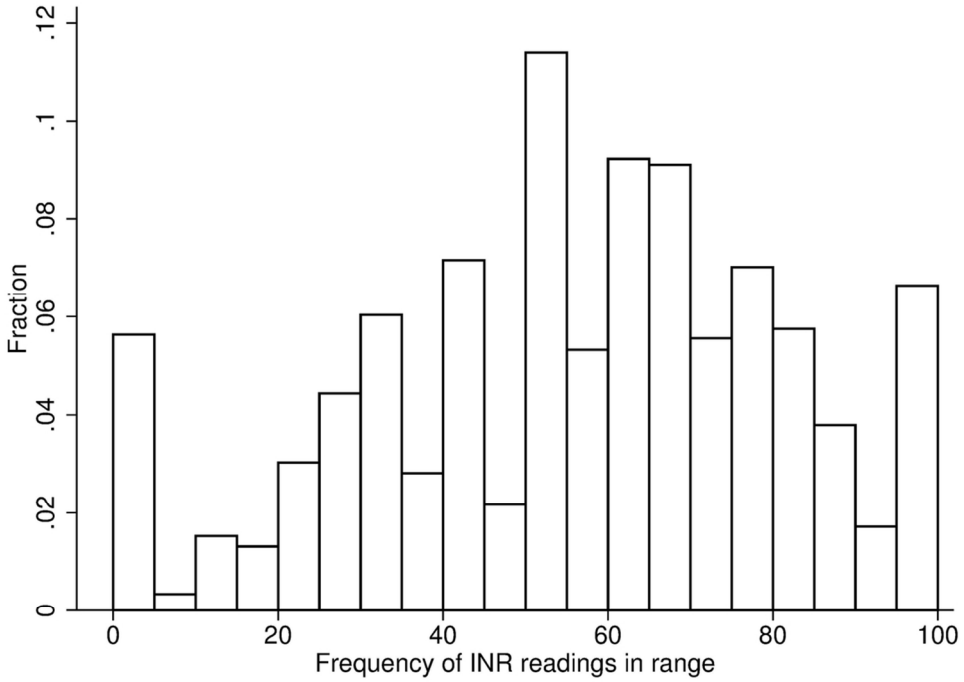
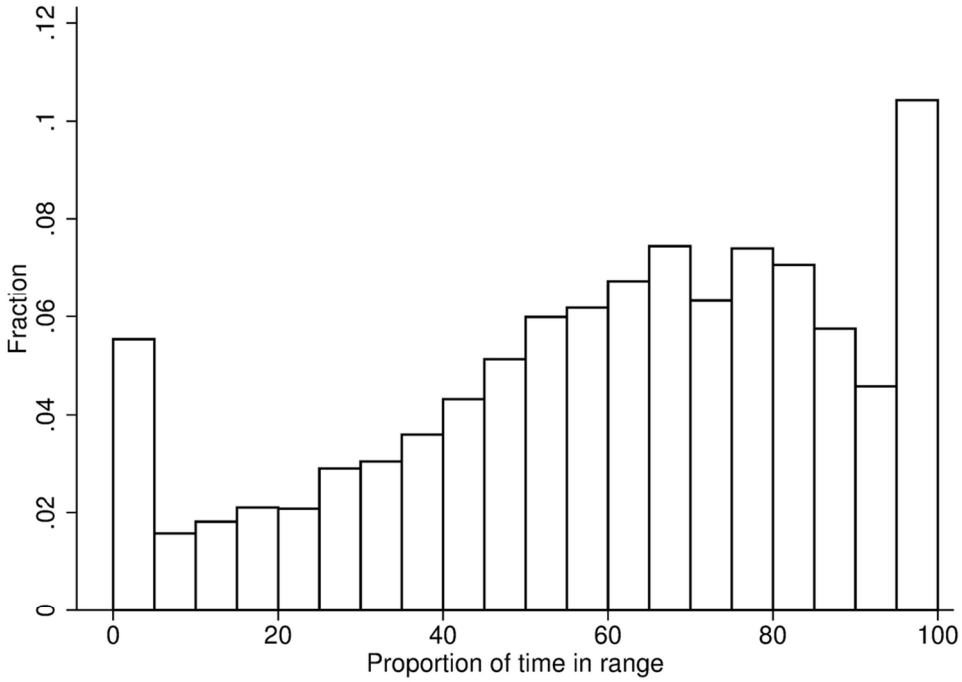


Fig 6. Distribution of patient-level frequency in range (A) and proportion of time in the therapeutic range (B), excluding INR readings in the first 90 days of treatment.
INR, international normalised ratio
101x73mm (300 x 300 DPI)



101x73mm (300 x 300 DPI)