Turk Kardiyol Dern Ars 2021;49(4):254-256 doi: 10.5543/tkda.2021.94055

Perspective Görüş

Time in therapeutic range among warfarin users in Turkey: Are there enough data to set definitive criteria for reimbursement?

Türkiye'deki varfarin kullanıcılarında terapötik aralıktaki süre: Geri ödemede kesin kriterler belirlemek için yeterli veri var mı?

Mehmet Akif Topcuoglu, M.D., Ethem Murat Arsava, M.D.

Units of Neuro Critical Care & Stroke, Department of Neurology, Hacettepe University School of Medicine, Ankara, Turkey

In Turkey, reimbursement of nonvitamin K oral anticoagulants (NOAC) mandates a time in therapeutic range (TTR) of <60% during warfarin use for the prevention of stroke in people with atrial fibrillation (AF). The Health Implementation Directive (SUT: "Sağlık Uygulama Tebliği" in Turkish) Drug Use Principles are stated in 4.2.15 exactly as follows: "If the target International Normalized Ratio (INR) value cannot be kept between 2-3 with warfarin in at least three of the last 5 measurements made at least one week apart, warfarin may be discontinued and rivaroxaban or dabigatran or apixaban or edoxaban treatment can be started." There is no doubt that TTR is one of the main parameters determining the efficacy and safety of oral anticoagulation with warfarin. For the treatment to be considered successful, it is suggested that TTR should be above 60% or at least not below 55%. This threshold had been achieved in the major NOAC trials in the AF population; the TTR value was 64% in RELY,[1] 62% in ARISTOTLE,[2] 55% in ROCKET-AF,[3] and 68% in ENGAGE-AF TIMI-48.[4] However, outside the rigorously ordered environment of randomized controlled trials, the TTR value is often below 50% in real-life. We have performed a systematic literature review and pooled analysis to investigate the TTR status in Turkey with the goal of providing guidance to change the current problematic prescribing rules.

Abbreviations:

AF	*Atrial fibrillation*
INR	*International Normalized Ratio*
NOAC	*Nonvitamin K oral anticoagulants*
TTR	*Time in therapeutic range*
WoS	*Web of Science*

The latest manual of Preferred Reporting Items for Systematic Reviews and Meta-analyses was followed for reporting.[5] A total of 1,658 articles were detected in PubMed between 1980 and 30 October 2020 after a search with the keywords "Turkey" and "atrial fibrillation." After a review of the titles, 40 articles related to the subject were identified, and their abstracts were evaluated. Thirteen of them were not related to the subject studied. The full texts of the remaining 27 articles were reviewed in detail, and 5 articles were considered suitable for the analysis.[6-11] With the Snowball technique, 720 additional articles were screened from the sources of these articles and the articles they referred to in PubMed. This led to the identification of 6 additional articles suitable for the analysis herein.[12-17] No additional studies could be extracted from further search in Google Scholar (1,230 articles were detected with "therapeutic range", used in addition to the same keywords, up to 4 February, 2021) and WoS (Web of Science) databases (with the same keywords for the topic, total 95 articles, up to 4 February, 2021).

We performed an inverse variance, fixed-effects meta-analysis to calculate the pooled TTR estimates.

Received: January 7, 2021 *Accepted:* February 23, 2021
Correspondence: Mehmet Akif Topcuoğlu, M.D. Units of Neuro Critical Care & Stroke, Department of Neurology, Hacettepe University School of Medicine, Ankara, Turkey
Tel: +90 536 575 36 34 e-mail: mat@hacettepe.edu.tr

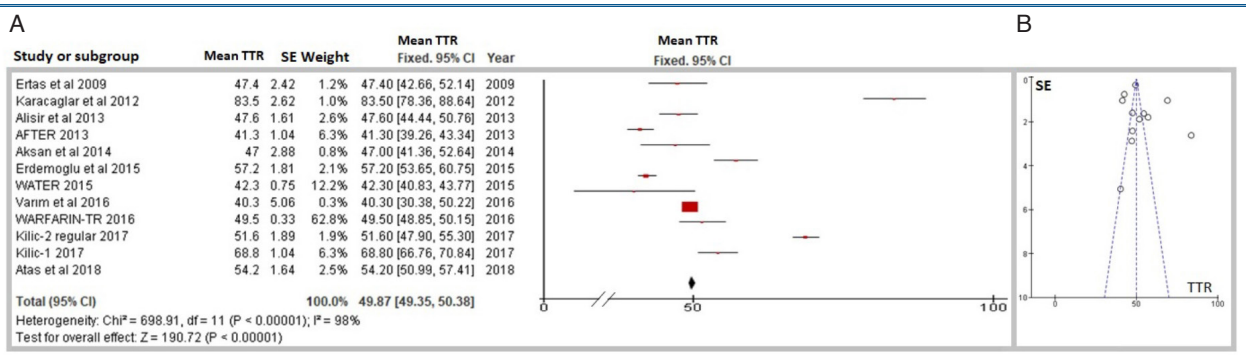

Figure 1. (A) Forrest plot, **(B)** funnel plot.
TTR: time in therapeutic range; SE: standard error; CI: confidence interval.

The standard errors were calculated with the formula "SD/SQRT(n)" [n: population number, SQRT: square root, SD: standard deviation) if SD were provided in the original article, and with the formula of "SQRT(p*(1-p)/n)" [p: prevalence] if it were not given. Inter-study heterogeneity was assessed by the Cochran-Q and I^2 statistics. I^2 values greater than 75% indicated substantial heterogeneity. The significance level for the Q statistic was set at 0.1. The small-study bias effect was assessed using Funnel plot inspection. All statistical analyses were conducted with the Cochrane Collaboration's Review Manager Software Package (RevMan 5.3) (The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen, 2014).

A total of 11 studies and 10,501 patients were analyzed. About 60% of the cases came from 2 studies.[6,9] Ten studies were conducted on outpatients.[6,9-17] Three studies were multicenter studies[6,9,17] Study design was retrospective in 4 trials,[11,12,15,18] snapshot in 1,[6] prospective follow-up in 5,[8-10,13,17] and not clear in the final study (Supplementary Table 1). The weighted average age of the whole population was 63.1±11.3 years and the female gender frequency was 57.1%. Valvular AF status was reported in all the studies except one,[15] and the frequency of nonvalvular AF was 52%. Stroke/transient ischemic attack/systemic embolism frequencies were provided in 6 studies, with a weighted average of 11.4%.[6,8-10,15,18]

A single INR measurement was used for TTR determination in 3 studies,[6,12,18] the traditional method in another 3 studies,[8,11,15] and the Roosendaal method in the remaining 6.[9,10,13,16,17,19] The pooled average of TTR was 49.87% (95% confidence interval [CI]: 49.35% to 50.38%) with substantial heterogeneity (I^2=98%, z=190,72, p<0.001). The Forrest plots of all studies are displayed in Figure 1A. The Funnel plot of comparison indicated acceptable publication bias (Figure 1B). Pooled mean INR values did not show a significant change when the studies with a single INR measurement were excluded (50.57%, 95% CI: 50.03%-51.11%) or when only those using the Rosendaal method were included (50.26%, 95% CI: 49.71%-50.80%).

This systematic review of published studies, mostly from academic cardiology centers in Turkey, points to a TTR rate of approximately 50%. This value is expected to be much lower in non-academic/smaller centers. Therefore, a 60% threshold, which could be barely achieved in ideal settings such as randomized trials, is not realistic as a reimbursement criterion. Thus, it cannot be regarded as a contemporaneously acceptable practice to leave patients without treatment during the most perilous period by setting a criterion that cannot be reached and cannot be maintained even if it is reached. Anticoagulation with warfarin or NOAC for stroke prophylaxis in AF should be a medical decision, and be left to the discretion of the treating physician. The revision of the reimbursement statement for NOAC prescription appears to be a scientific necessity and has become a must, considering that inpatient and outpatient INR monitoring has become more difficult during the pandemic period. Our pooled analysis clearly indicates this net result and the need for change, albeit our study has some limitations such as not including some individual characteristics of the studies analyzed, such as exclusion criteria and their remarkable heterogeneity.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51. [Crossref]
2. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92. [Crossref]
3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91. [Crossref]
4. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104. [Crossref]
5. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1. [Crossref]
6. Ertas F, Kaya H, Kaya Z, Bulur S, Kose N, Gul M, et al. Epidemiology of atrial fibrillation in Turkey: preliminary results of the multicenter AFTER study. Turk Kardiyol Dern Ars 2013;41:99-104. [Crossref]
7. Ertas F, Kaya H, Ozhan H. Epidemiology of atrial fibrillation in Turkey: preliminary results in the multicenter AFTER study. Author reply. Turk Kardiyol Dern Ars 2013;41:370. [Crossref]
8. Aksan G, Soylu K, Demircan S, Aksoy O, Yanik A, Gedikli O, et al. Oral anticoagulant therapy and clinical outcomes in patients with atrial fibrillation: a pilot study from a single center registry. Blood Coagul Fibrinolysis 2014;25:688-94. [Crossref]
9. Celik A, Izci S, Kobat MA, Ates AH, Cakmak A, Cakilli Y, et al. The awareness, efficacy, safety, and time in therapeutic range of warfarin in the Turkish population: WARFARIN-TR. Anatol J Cardiol 2016;16:595-600. [Crossref]
10. Atas H, Sahin AA, Barutcu Atas D, Sunbul M, Kepez A, Agirbasli M. Potential causes and implications of low target therapeutic ratio in warfarin-treated patients for thrombosis prophylaxis: a single-center experience. Clin Appl Thromb Hemost 2018;24:536-41. [Crossref]
11. Varim P, Varim C, Ergenc H, Uyanik M, Yaylaci S, Vatan M, et al. Assessment of warfarin treatment efficacy by means; of using coagulation test results within the therapeutic range. Georgian Med News 2016;255:62-6.
12. Alisir M, Kecebi M, Besli F, Caliskan S, Gungoren F, Ahmet Yildirim A, et al. The rates of effective INR levels and the relationship with etiology in patients with warfarin treatment. Turkiye Klinikleri J Med Sci;33:868-73. [Crossref]
13. Erdemoğlu E, Uzunlulu M, Oğuz A, Köstek O, Telci-Çaklılı O. Frequency of coagulation test results being in the therapeutic range in patients using warfarin treatment. Medeniyet Medical Journal 2015;30:105-9.
14. Ertaş F KH, Atılgan ZA, Elbey MA, Aydin M, Akil MA. Predictors of warfarin use in patients with non-valvular atrial fibrillation who presented to the cardiology outpatient clinic of a tertiary hospital in Turkey: an observational study. Turk J Med Sci 2012;42:1172-9.
15. Karacaglar E, Atar I, Yetis B, Corut H, Ersoy B, Yilmaz K, et al. [The frequency of embolic risk factors and adequacy of anti-embolic treatment in patients with atrial fibrillation: a single tertiary center experience]. Anadolu Kardiyol Derg 2012;12:384-90. [Crossref]
16. Kilic S, Soner Kemal H, Yuce EI, Simsek E, Yagmur B, Memisoglu Akgul N, et al. Comparison of Warfarin use in terms of efficacy and safety in two different polyclinics. Anatol J Cardiol 2017;18:328-33. [Crossref]
17. Turk UO, Tuncer E, Alioglu E, Yuksel K, Pekel N, Ozpelit E, et al. Evaluation of the impact of warfarin time in therapeutic range on outcomes of patients with atrial fibrillation in Turkey: perspectives from the observational, prospective WATER Registry. Cardiol J 2015;22:567-75. [Crossref]
18. Ertas F, Duygu H, Acet H, Eren NK, Nazli C, Ergene AO. [Oral anticoagulant use in patients with atrial fibrillation]. Turk Kardiyol Dern Ars 2009;37:161-7.
19. Kilic S, Celik A, Cakmak HA, Afsin A, Tekkesin AI, Aciksari G, et al. The time in therapeutic range and bleeding complications of warfarin in different geographic regions of Turkey: a subgroup analysis of WARFARIN-TR study. Balkan Med J 2017;34:349-55. [Crossref]

Supplementary Table 1. General characteristics of studies

Study	Ertas[18]	Karacaglar[15]	Alisir[12]	AFTER[6]	Aksan[8]	Erdemoğlu[13]	WATER[17]	WARFARIN-TR[9]	Varim[11]	Kilic-1 INR Clinic[19]	Kilic-2 Regular[16]	Atas[10]
Year	2009	2012	2013	2013	2014	2015	2015	2016	2016	2017	2017	2018
n	426	202	971	2242	301	155	572	4987	94	233	148	170
Population	Cardiology units	Cardiology outpatient clinic	Outpatient clinic	Cardiology outpatient clinic	Inpatients	Internal medicine or cardiology outpatient clinics	Outpatient clinic	Patients using warfarin for any reason	Outpatients undergoing at least 10 INR in the last 6 months	INR clinic	Cardiology outpatient clinic	Not stated
Number of centers	1	1	1	17	1	1	3	42	1	1	1	1
Mean age (if given±SD)	66±11	70.4	59.15	67±12	67.5±10.1	68±12	67.3±12	60.7±13.5	64.9±11	62±13.2	62±12.3	62.2±13.3
Female	60%	58.5%	57.7%	60%	48.2%	59.4%	60%	55.1%	62%	54.5%	59.4%	69.2%
NVAF	80.8%	Not stated	17.7%	78%	97.7%	77.4%	71%	38.4%	50%	59.1%	46.2%	56.4%
Stroke/TIA/ systemic embolism	12.9%	17.1%	Not given	15%	10%	Not given	Not given	9.3%	Not given	Not given	Not given	17.1%
Use of OAC	30.1%	100%	100%	50%	59.8%	100%	100%	100%	100%	100%	100%	100%
TTR (if given±SD)	47.4%	83.5%	47.6%	41.3%	47.4%	57.2±22.5%	42.3±18%	49.52±22.93	40.3%	68.8±15.9%	51.6±23.04%	54.2±21.4%
TTR in therapeutic range	61/128	167/202	462/971	460/1115	143/301	45.8% (criterion 60%)	318/572 (limit 40%)	2470/4987	38/94	None	None	Not given
Risk factors for TTR not within range	Not given	Not given	None	Advanced age	Advanced age	None	Advanced age, NVAF, CHA2DS2VASc score	Non-AF indication, comorbid diseases (HT, CAD, CHF, smoking), not undergoing INR	Not given	Not applicable	Not applicable	Advanced age, heart failure, renal insufficiency
TTR technical	Single measurement	Conventional	Single measurement	Single measurement	Conventional	Rosendaal	Rosendaals	Rosendaal	Conventional	Rosendaal	Rosendaal	Rosendaal
TTR time	Retrospective	Retrospective	Retrospective	Single point	Follow-up: 9.5 months	At least 4 measurements	Follow-up: 22 months	Follow-up: 9.6 months	Retrospective	Not given	Not given	Follow-up 20±8.4 months
Only NVAF TTR% efficient	Not given	Not given	51.7%	Not given	Not given	Not given	40.3±18%	50.1±22.9%	36.8%	Not given	Not given	53.8±20.7%
Only NVAF TTR efficient number	Not given	Not given	89/172	Not given	Not given	Not given	Not given	961/1918	17/47	Not given	Not given	51/94

AF: atrial fibrillation; HT: hypertension; CAD: coronary artery disease; CHF: congestive heart failure; NVAF: non-valvular atrial fibrillation; OAC: oral anti-coagulant; SD: standard deviation; TIA: transient ischemic attack; TTR: time in therapeutic range.