2020

Quality of anticoagulation with warfarin in rural Chhattisgarh, India

Puja Chebrolu

Sushil Patil

Timothy S. Laux

Noor Al-Hammadi

Yogesh Jain

See next page for additional authors

Authors

Puja Chebrolu, Sushil Patil, Timothy S. Laux, Noor Al-Hammadi, Yogesh Jain, and Brian Gage

Indian J Med Res 152, September 2020, pp 303-307
DOI: 10.4103/ijmr.IJMR_1201_18

Quick Response Code:

Quality of anticoagulation with warfarin in rural Chhattisgarh, India

Puja Chebrolu[1], Sushil Patil[4], Timothy S. Laux[3], Noor Al-Hammadi[2], Yogesh Jain[4] & Brian Gage[1]

[1]Department of Medicine, Washington University in St. Louis, [2]Division of Biostatistics, Washington University in St. Louis, St. Louis, Missouri, [3]Department of Hospital Medicine, Columbia University Medical Center, New York, USA & [4]Jan Swasthya Sahyog, Chhattisgarh, India

Received June 29, 2018

***Background & objectives*: In most of rural India, warfarin is the only oral anticoagulant available. Among patients taking warfarin, there is a strong association between poor control of the international normalized ratio (INR) and adverse events. This study was aimed to quantify INR control in a secondary healthcare system in rural Chhattisgarh, India.**

***Methods*: The INR data were retrospectively obtained from all patients taking warfarin during 2014-2016 at a secondary healthcare system in rural Chhattisgarh, India. Patients attending the clinic had their INR checked at the hospital laboratory and their warfarin dose adjusted by a physician on the same day. The time in therapeutic range (TTR) was calculated for patients who had at least two INR visits.**

***Results*: The 249 patients had 2839 INR visits. Their median age was 46 yr, and the median body mass index was 17.7 kg/m^2. They lived a median distance of 78 km (2-3 h of travel) from the hospital. The median INR was 1.7 for a target INR of 2.0-3.0 (n=221) and 2.1 for a target of 2.5-3.5 (n=28). The median TTR was 13.0 per cent, and INR was subtherapeutic 66.0 per cent of the time. Distance from the hospital was not correlated with TTR.**

***Interpretation & conclusions*: INR values were subtherapeutic two-thirds of the time, and TTR values were poor regardless of distance from the health centre. Future studies should be done to identify interventions to improve INR control.**

Key words Anticoagulation - international normalized ratio - stroke - TTR - warfarin

Atrial fibrillation (AF), both valvular and non-valvular, carries an increased risk of stroke and systemic embolism, which leads to major social and economic burden. Without thromboprophylaxis, stroke risk averages four per cent/year among patients with non-valvular AF and 17-18 per cent/year among patients with valvular AF[1]. Anticoagulation reduces this risk by 64 per cent compared to placebo and halves the risk compared with antiplatelet therapy[2,3]. The cost of treating stroke can be ₹500,000 in the first year[4], a major burden given the 1.44-1.64 million strokes diagnosed each year in India alone[5].

In most of the rural India, warfarin is the only oral anticoagulant available, but there are many barriers to its optimal use. Warfarin requires frequent monitoring and adjustment to maintain a therapeutic range. Subtherapeutic values increase the risk of

stroke and embolism in patients with AF[6], whereas supratherapeutic values increase the risk of intracranial haemorrhage. Alternatives such as direct oral anticoagulants (DOACs) are as effective as warfarin, but these are prohibitively expensive for most rural Indians and not approved for use in patients with severe mitral stenosis or mechanical heart prostheses[7].

Time in therapeutic range (TTR) is the standard method of estimating the quality of anticoagulation with warfarin[8], and a goal of 70 per cent or more improves outcomes[9]. Although some anticoagulation clinics in high-income countries could meet this goal[10], US clinics average was 55 per cent[11], and outside of North America and Europe, TTR was often lower including 46.5 per cent in South Africa and 50.1 in Latin America[12-14]. Compared to patients with a TTR of approximately >70 per cent, patients with a TTR of approximately <50 per cent have double the risk of ischaemic stroke, bleeding or death[15].

Of the 45 countries that enrolled participants in the ROCKET-AF trial, India had the lowest TTR of any region, averaging 35.9 per cent[14]. These data were collected from an urban centre, a setting with more robust healthcare infrastructure than rural India. The present study was aimed to characterize the quality of anticoagulation with warfarin in a rural, secondary healthcare system in Chhattisgarh, India, by quantifying the TTR of warfarin patients and determining the correlation of TTR with factors such as socio-economic status, caste and distance from the hospital.

Methods

This was a retrospective observational study. De-identified data were obtained from the Jan Swasthya Sahyog (JSS) electronic medical record (EMR). All patients who received warfarin between 2014 and 2016 at JSS or its subcentres were included. Patients who lacked two or more INR values in any eight-week period were excluded from the analysis.

Demographic, clinical and laboratory data were abstracted from the EMR for all patients. Indication for warfarin was abstracted manually. Distance to the medical centre was ascertained from Google Maps. All patients who had INR measured at least twice during an eight-week period were included. A Behnk Elektronik's Thrombostat magnet-based monitor (Norderstedt, Germany) was used to measure INR values. Patients attending the clinic had their INR checked in the hospital laboratory prior to their appointments, and the results were uploaded into the EMR by the time of their appointment 1-3 h later. Warfarin was adjusted by the physician on the same day after seeing and interviewing the patient in the clinic.

Ethical approval for the study was obtained by the Ethics Committee of the Emmanuel Hospital Association, New Delhi and by the Washington University School of Medicine's IRB (#201612042).

Mean TTR was determined using the Rosendaal linear interpolation method[8]. Analyses were done using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results

Demographic information of the patients is shown in Table I. There were 249 patients receiving warfarin, and 162 of them had more than one INR visit (87 were excluded as they did not have at least two INR readings in any eight-week period). There was a median of nine INR visits per included patient during the three-year study period. The median age was 46 yr; 135 (54.2%) were female, and the median body mass index was 17.7 kg/m^2. Most patients were form Chhattisgarh (n=175, 70.3%) and the remaining were from Madhya Pradesh. Most patients were in the scheduled tribe (ST, n=86, 34.5%) or other backward class groups (OBC, n=86, 34.5%); 44 (7.7%) were from scheduled caste group. The median distance from the main JSS hospital was 78 km, which was slightly lower (72 km) among patients with two or more INR values greater than eight week apart. Indication for warfarin is shown in Table II. Most patients (62.6%) required warfarin for AF, and 10.0 per cent of patients had mechanical valves. The median INR was 1.7 for patients whose target INR was 2.0-3.0 and 2.1 for those with a target of 2.5-3.5 (Table II). Most (n=221, 88.8%) patients had a target INR of 2.0-3.0 and 11.2 per cent (n=28) had a target of 2.5-3.5. All patients with the higher target had mechanical mitral valve replacements (MVRs). The median TTR of the entire group of patients was 13.0 per cent (IQR 0-34.8). The median time subtherapeutic was 77.5 per cent (45-100), and the median time supratherapeutic was 0.0 per cent (0-11.6). Distance showed no correlation with TTR (Spearman's rho <1%). TTR was greatest among the scheduled caste [median 26.4 (IQR 10.7-44.5)] and lowest among scheduled tribes (median 0.0, IQR 0-13.4, P<0.001). Median TTR

Table I. Details of patients included in the study

Demographics	n (%)	Median	IQR
Age (yr)	249	46	36-53
Height (cm)	222	155	250-162
Weight (kg)	226	47.7	39.3-54.8
BMI (kg/m^2)	188	17.7	13.1-20.8
Distance (km)	249	78	33-149
Distance (km) (for patients with a TTR)	162	72	28-143

BMI, body mass index; IQR, interquartile range; TTR, time in therapeutic range

Table II. Indications for warfarin, INR targets, and median INRs in the study patients

Indication for warfarin	n (%)
AF without mechanical valve	156 (62.6)
Mechanical valve	25 (10.0)
LA or LV thrombus	12 (4.8)
DVT, PE or DVT prophylaxis	54 (21.6)
Unclear	2 (0.8)
Target INR	
2.0-3.0	221 (88.8)
2.5-3.5	28 (11.2)
INR (target 2-3), median (IQR)	1.7 (1.2-2.4)
INR (target 2.5-3.5), median (IQR)	2.1 (1.6-2.8)
INRs per person, median (IQR)	9 (3-19)

AF, atrial fibrillation; LA, left atrial; LV, left ventricular; DVT, deep-vein thrombosis; PE, pulmonary embolism; INR, international normalized ratio

Table III. Time in therapeutic range

TTR	Median (%)	IQR
Median TTR	13.0	0-34.8
Time below range	77.5	45.0-100.0
Time above range	0.0	0-11.6
TTR by caste		
General category	11.3	0-34.7
OBC	20.0	0-35.6
SC	26.4	10.7-44.5
ST	0.0	0-13.4
Other	2.8	2.8-37.3
TTR versus distance	Spearman's ρ=0.009, P=0.906	

SC, scheduled caste; ST, scheduled tribe; OBC, other backward class

in OBCs was 20.4 (0-35.6) and 11.3 (0-34.7) in the general category patients (Table III).

Discussion

Our study demonstrated that the quality of anticoagulation in rural Chhattisgarh was poor. Overall, TTR was very low with a median of 13.0 per cent. The low TTR is a cause of concern because among patients taking warfarin, mortality rises with lower TTR, with the highest mortality seen in patients with <30 per cent TTR[16]. Several factors may have contributed to the low TTR in this rural population such as lack of infrastructure and poverty. Although we hypothesized that distance also would contribute to low TTR, there was no correlation between distance and TTR. One explanation for this negative finding is that distance may not capture the difficulty of reaching the healthcare centre in terms of mode of transport (private vehicle, public transport or on foot), lost wages, childcare or cost of travel. However, a more likely explanation may be that in an area where poor public health infrastructure is ubiquitous, being closer to an overwhelmed institution makes little difference compared to being farther away.

Poverty also might have interfered with INR control. TTR correlates with socio-economic level[17], and higher TTRs have been noted in anticoagulation clinics in high-income countries[10]. TTR increased in countries that implemented warfarin management programmes[18]. However, a more sustainable, long-term solution for rural India may lie in focusing on bolstering the public health infrastructure rather than establishing warfarin management programmes alone. Targeting women may also improve impact, as women are known to have poorer INR control than men[19].

The TTR was low because patients spent 77.5 per cent of their time below their target INR. The effectiveness of warfarin therapy declines exponentially with subtherapeutic INR values, both in patients with AF[20] and among those with mechanical valves[21]. Thus, these patients with subtherapeutic TTR

received only a fraction of the potential benefit of their warfarin therapy and would have high risks of stroke, which could be reduced with better INR control.

The DOAC therapy, if available, would have been an option for up to 84.2 per cent (210 of 249) of these patients based on their indication for anticoagulation. Warfarin is a fraction of the upfront cost of DOACs, but has a greater monitoring burden and risk of intracranial haemorrhage[22]. Although DOACs are not cost saving, but these appear cost-effective among populations that have low TTR values with warfarin[23].

Patient self-testing may also be an option to improve INR control. In a US Veteran's Affairs study, INR control was improved among patients who used individual home point-of-care (POC) devices, even when they had access to a managed anticoagulation clinic[24]. Though individual POC devices would be very expensive for the rural poor, a POC device shared in a rural community (perhaps with the help of a community health worker) could improve laboratory and clinical outcomes.

Reducing the thrombotic tendency of mechanical valves may also lead to improved TTR. The newly designed On-X valve, for example, requires an INR of only 1.5-2.0[25], which was common in this study. If these valves were available for the rural poor who required a MVR, their risk of stroke might decline.

The study had several limitations. First, only 162 of the 249 patients on warfarin had more than one visit, allowing TTR to be calculated. It is unknown which of the excluded patients established care elsewhere and continued to take warfarin and who discontinued warfarin. It is possible that because of this loss to follow up, INR monitoring may actually be worse than reported. Second, some patients might have run out of warfarin for several days before they were seen in clinic, which would have exaggerated the amount of time that they were presumed to be subtherapeutic. Third, as we did not have data on income or education level, we used caste as a surrogate marker of socio-economic status. Although several studies show that health indicators vary by caste[26], it would have been better to have additional socio-economic variables. Finally, we did not assess whether dietary factors contributed to the subtherapeutic INR values in this population. In a previous study, dietary vitamin K has had an inconsistent effect on the therapeutic warfarin dose[27].

In conclusion, the quality of anticoagulation in rural Chhattisgarh was below standards, even among patients with access to JSS health centres. Future studies should focus on identifying potential interventions in this population, such as access to POC monitoring, genetic risk-based dosing, DOAC therapy and the overall improvement of public health infrastructure in this neglected area.

***Financial support & sponsorship*:** This study was financially supported by the Heal Initiative, University of California San Francisco, and the Washington University in St Louis Mentors in Medicine International Grant.

***Conflicts of Interest*:** None.

References

1. Narasimhan C, Verma JS, Ravi Kishore AG, Singh B, Dani S, Chawala K, *et al*. Cardiovascular risk profile and management of atrial fibrillation in India: Real world data from RealiseAF survey. *Indian Heart J* 2016; *68* : 663-70.
2. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2007; *3* : CD006186.
3. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; *146* : 857-67.
4. Marfatia S, Monz B, Suvarna V, Bhure S, Sangole N. Treatment costs of stroke related to nonvalvular atrial fibrillation patients in India - a multicenter observational study. *Value Health Reg Issues* 2014; *3* : 205-10.
5. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol* 2009; *8* : 355-69.
6. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, *et al*. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003; *349* : 1019-26.
7. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet* 2014; *383* : 955-62.
8. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; *69* : 236-9.
9. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, *et al*. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation* 2008; *118* : 2029-37.

10. Sjögren V, Grzymala-Lubanski B, Renlund H, Friberg L, Lip GY, Svensson PJ, *et al*. Safety and efficacy of well managed warfarin. A report from the Swedish quality register Auricula. *Thromb Haemost* 2015; *113* : 1370-7.
11. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm* 2009; *15* : 244-52.
12. Haim M, Hoshen M, Reges O, Rabi Y, Balicer R, Leibowitz M. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. *J Am Heart Assoc* 2015; *4* : e001486.
13. Mwita JC, Francis JM, Oyekunle AA, Gaenamong M, Goepamang M, Magafu MG. Quality of anticoagulation with warfarin at a tertiary hospital in Botswana. *Clin Appl Thromb Hemost* 2018; *24* : 596-601.
14. Singer DE, Hellkamp AS, Piccini JP, Mahaffey KW, Lokhnygina Y, Pan G, *et al*. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: Data from the ROCKET AF clinical trial. *J Am Heart Assoc* 2013; *2* : e000067.
15. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, *et al*. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: Results from SPORTIF III and V. *Arch Intern Med* 2007; *167* : 239-45.
16. Morgan CL, McEwan P, Tukiendorf A, Robinson PA, Clemens A, Plumb JM. Warfarin treatment in patients with atrial fibrillation: Observing outcomes associated with varying levels of INR control. *Thromb Res* 2009; *124* : 37-41.
17. Razouki Z, Ozonoff A, Zhao S, Rose AJ. Pathways to poor anticoagulation control. *J Thromb Haemost* 2014; *12* : 628-34.
18. de Lima Silva RG, Bertollo CM, Ferreira IG, Brant LC, Martins MAP. Assessment of oral anticoagulation control at two pharmacist-managed clinics in Brazil. *Int J Clin Pharm* 2017; *39* : 1157-61.
19. García-Sempere A, Hurtado I, Bejarano-Quisoboni D, Rodríguez-Bernal C, Santa-Ana Y, Peiró S, *et al*. Quality of INR control and switching to non-vitamin K oral anticoagulants between women and men with atrial fibrillation treated with vitamin K antagonists in Spain. A population-based, real-world study. *PLoS One* 2019; *14* : e0211681.
20. Reynolds MW, Fahrbach K, Hauch O, Wygant G, Estok R, Cella C, *et al*. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: A systematic review and metaanalysis. *Chest* 2004; *126* : 1938-45.
21. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briët E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995; *333* : 11-7.
22. Marshall S, Fearon P, Dawson J, Quinn TJ. Stop the clots, but at what cost? Pharmacoeconomics of dabigatran etexilate for the prevention of stroke in subjects with atrial fibrillation: A systematic literature review. *Expert Rev Pharmacoecon Outcomes Res* 2013; *13* : 29-42.
23. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation* 2011; *123* : 2562-70.
24. Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS, *et al*. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med* 2010; *363* : 1608-20.
25. Puskas J, Gerdisch M, Nichols D, Quinn R, Anderson C, Rhenman B, *et al*. Reduced anticoagulation after mechanical aortic valve replacement: Interim results from the prospective randomized On-X valve anticoagulation clinical trial randomized food and drug administration investigational device exemption trial. *J Thorac Cardiovasc Surg* 2014; *147* : 1202-10.
26. Nayar KR. Social exclusion, caste health: A review based on the social determinants framework. *Indian J Med Res* 2007; *126* : 355-63.
27. Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM, *et al*. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin Pharmacol Ther* 2008; *84* : 326-31.

For correspondence: Dr Puja Chebrolu, 7595 River Crest Dr, Columbus, GA 31904, USA
e-mail: pujachebrolu@gmail.com