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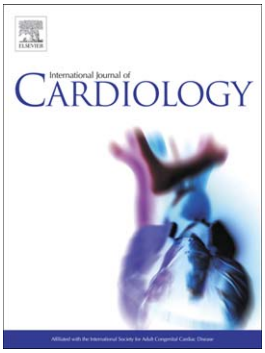
Shaffer, Jonathan A.; Thompson, John; Cheng, Bin; Ye, Siqin; Lip, Gregory; Mann, Douglas L.; Sacco, Ralph L.; Pullicino, Patrick M.; Freudenberger, Ronald S.; Graham, Susan; Mohr, J.p.; Labovitz, Arthur J.; Estol, Conrado J.; Lok, Dirk J.; Ponikowski, Piotr; Anker, Stefan D.; Di Tullio, Marco R.; Homma, Shunichi

DOI:
10.1016/j.ijcard.2014.10.012

Document Version
Peer reviewed version

Citation for published version (Harvard):
Shaffer, JA, Thompson, JLP, Cheng, B, Ye, S, Lip, GYH, Mann, DL, Sacco, RL, Pullicino, PM, Freudenberger, RS, Graham, S, Mohr, JP, Labovitz, AJ, Estol, CJ, Lok, DJ, Ponikowski, P, Anker, SD, Di Tullio, MR & Homma, S 2014, 'Association of quality of life with anticoagulant control in patients with heart failure: The Warfarin and Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial', International Journal of Cardiology, vol. 177, no. 2, pp. 715-717. https://doi.org/10.1016/j.ijcard.2014.10.012



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PII: S0167-5273(14)01939-1
DOI: doi: 10.1016/j.ijcard.2014.10.012
Reference: IJCA 18993

To appear in: *International Journal of Cardiology*

Received date: 27 August 2014
Revised date: 3 October 2014
Accepted date: 4 October 2014

Please cite this article as: Shaffer Jonathan A., Thompson John L.P., Cheng Bin, Ye Siqin, Lip Gregory Y.H., Mann Douglas L., Sacco Ralph L., Pullicino Patrick M., Freudenberger Ronald S., Graham Susan, Mohr JP, Labovitz Arthur J., Estol Conrado J., Lok Dirk J., Ponikowski Piotr, Anker Stefan D., Di Tullio Marco R., Homma Shunichi, Association of quality of life with anticoagulant control in patients with heart failure: The Warfarin and Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, *International Journal of Cardiology* (2014), doi: 10.1016/j.ijcard.2014.10.012

Running head: WARFARIN AND QUALITY OF LIFE

Association of quality of life with anticoagulant control in patients with heart failure: The Warfarin and Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial

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Total word count: 1,057

Clinical Trial Registration: NCT00041938; http://clinicaltrials.gov/show/NCT00041938

Chronic heart failure (HF) imposes a large public health burden in terms of morbidity, mortality, and economic cost. HF with reduced left ventricular ejection fraction (LVEF) is associated with a hypercoagulable state, formation of left ventricular thrombus, cerebral embolism, and death from atherothrombotic events [1]. As such, anticoagulation is recommended for HF patients with atrial fibrillation (AF), and considered for those without AF but with previous embolic events [2].

Warfarin, the current mainstay of anticoagulation in HF, requires frequent monitoring and dosing adjustment, and is thus difficult to manage. This difficulty is concerning given that poor warfarin control is associated with increased risk of death, myocardial infarction, and stroke [3]. Further, as most HF patients have reduced heart failure-related quality of life (HFQoL) [4], a characteristic that has been associated with medication non-adherence in other patient populations [5], treatment with warfarin may present even greater challenges in this population. Although some studies have examined patient factors that predict anticoagulant control [6], the effect of HFQoL—a potentially modifiable factor—on anticoagulant control in HF has never been investigated.

In this ancillary analysis of 1,142 participants from the Warfarin and Aspirin in Reduced Cardiac Ejection Fraction **(**WARCEF) trial, we tested whether reduced HFQoL was independently associated with poor warfarin control.

Details of the WARCEF trial have previously been published [1]. Briefly, patients who were 18 years of age or older and had HF in normal sinus rhythm, no contraindication to warfarin, and a LVEF < 35% or wall-motion index ≤ 1.2 were randomized to receive either warfarin or aspirin therapy. Additional eligibility criteria included a modified Rankin score ≤ 4 and planned treatment with a beta-blocker, angiotensin-converting-enzyme inhibitor, or

hydralazine and nitrates. Patients randomized to receive warfarin were managed by local practice guidelines with at least monthly international normalized ratio (INR) testing.

For this study, we included 1,142 participants randomized to warfarin therapy with targeted INR between 2.0 and 3.5. The trial was performed in 168 centers from 11 countries around the world. All local institutional review committees approved the study protocol, and all patients provided informed consent for trial entry.

A modified time in therapeutic range (TTR) metric was calculated to estimate warfarin control [7]. This method interpolates all available INR values to calculate percentage of days when the INR is between 2.0 and 3.5.

The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was administered at randomization [8] as a measure of HFQoL. This 21-item measure requires respondents to indicate how much their HF symptoms have interfered with their daily lives during the past 30 days, using a scale from 0 (not very much) to 5 (very much). Scores on the MLHFQ range from 0 to 105, with higher scores indicating worse HFQoL.

Differences in baseline characteristics by TTR were compared using *t* tests for continuous variables and chi-square tests for discrete characteristics. Beta-logit regression analyses, which are used to analyze proportions and yield an odds ratio (OR), were conducted to assess whether HFQoL was associated with TTR. We first controlled for age (years) and sex, and then additionally controlled for other clinical-demographic factors that have been associated with TTR. These included race/ethnicity, education (years), body mass index (kg/m^2), hypertension, diabetes, history of ischemic stroke, recent stroke or transient ischemic attack (within 12 months of randomization), peripheral vascular disease, hematocrit, and hemoglobin (g/dL) [9].

The median TTR was 63% (interquartile range, 39%). Participants whose TTR was

below the median were younger, and less likely to be White, non-Hispanic than those with TTR was above the median (**Table 1)**. These participants were also more likely to have had hypertension and ischemic stroke.

In an age- and sex-adjusted regression model (**Table 2)**, baseline HFQoL was significantly associated with TTR such that each 10-point increase on the MLHFQ (i.e., worsening of HFQoL) corresponded to an 8% decrease in the odds of being in therapeutic range (95% confidence interval [CI] = 0.89 – 0.95, $p < 0.001$). In the fully-adjusted model, HFQoL remained significantly associated with TTR (OR = 0.91, 95% CI = 0.87 – 0.96, $p < 0.001$). Additionally, having a recent stroke was associated with a 42% decrease in the odds of being in therapeutic range ($p = 0.01$), and White, non-Hispanic race/ethnicity was associated with a 74% increase in the odds ($p < 0.001$) of being in therapeutic range.

In this large cohort of 1,142 patients with HF, we examined for the first time whether HFQoL is associated with warfarin control, and found that reduced HFQoL was independently associated with reduced odds of being in therapeutic range. Although a previous study found no association of quality of life with anticoagulation control, that study was limited by a small sample of 52 non-HF patients, a cross-sectional design, and a non-validated measure of quality of life [10]. Consistent with previous literature [9], however, we observed associations of White, non-Hispanic race/ethnicity with greater odds and recent stroke with reduced odds of being in therapeutic range. Given that those with recent stroke have a high recurrent stroke rate, special attention needs to be placed on effective anticoagulant control in this population. Apostolakis and colleagues recently derived a prediction model for anticoagulant control that included both race/ethnicity and stroke (among other medical comorbidities); however, this model did not include HFQoL, and thus the incremental value of adding this parameter to their model may be

worth examining. Further, although age independently predicted TTR in their model as well as in our minimally-adjusted prediction model, its predictive value was attenuated to non-significance in our fully-adjusted model. This curious finding may reflect limited statistical power or a confounding or mediating effect of other covariates on the age-TTR association—scenarios that could be tested in future studies.

Of note, we did not assess all potential patient characteristics known to interfere with anticoagulant therapy. In addition, we did not include a measure of medication adherence to test whether this factor partially explains the association of HFQoL with warfarin control.

In conclusion, we found that reduced HFQoL is associated with reduced warfarin control among HF patients with reduced LVEF in normal sinus rhythm. Future research could consider whether intervening to improve HFQoL has beneficial downstream effects on TTR or whether newer anticoagulants that do not require frequent dosing adjustments on the basis of a TTR have a role in the management of HF patients with poor HFQoL who require systemic anticoagulation.

Funding Acknowledgments

This work was supported by the National Heart. Lung, and Blood Institute of the National Institutes of Health (grant number K23 HL112850 to Dr. Shaffer) and by the American Heart Association (grant number CRP8870004 to Dr. Shaffer). The WARCEF trial was supported by the National Institute of Neurological Diseases and Stroke of the National Institutes of Health (grant numbers U01-NS-043975 to Dr. Homma and U01-NS-039143 to Dr. Thompson). Warfarin and warfarin placebo were provided by Taro Pharmaceuticals USA, and aspirin and aspirin placebo by Bayer HealthCare.

Disclosures

Dr. Homma received payment from AGA Medical (now St. Jude Medical) for his work as a member of a data and safety monitoring board and consulting fees from Boehringer Ingelheim; Dr. Graham, owning stock in March Pharmaceuticals, Medtronic, and Pfizer; Dr. Labovitz received grant support from Boehringer Ingelheim on behalf of his institution, lecture fees from Boehringer Ingelheim, and fees for the development of educational presentations from the American College of Cardiology; Dr. Anker received consulting fees from Amgen, Bosch Healthcare, GlaxoSmithKline, Helsinn, LoneStar Heart, Novartis, Professional Dietetics, PsiOxus, Relypsa, SHL Telemedicine, and Thermo Fisher, grant support from Vifor Pharma, and lecture fees from Novartis, holding patents with Brahms AG and Charité Berlin, and received royalties from Imperial College; Dr. Ponikowski received consulting fees from Bayer, Boehringer Ingelheim, Coridea, Corthera, Johnson & Johnson, Pfizer, Respicardia, and Vifor Pharma, grant support from Vifor Pharma on behalf of himself and his institution, and lecture fees from Abbott, Boehringer Ingelheim, Merck Serono, Pfizer, Respicardia, Sanofi-Aventis, Servier, and Vifor Pharma; and Dr. Lip received consulting fees from Astellas, AstraZeneca, Bayer, Biotronik, Boehringer Inhelheim, Bristol-Myers Squibb, Pfizer, Merck, Medtronic, and Sanofi-Aventis, speakers bureau fees from Bayer, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Medtronic, and Sanofi-Aventis, and payment for the development of educational presentations from Bayer, Boehringer Ingelheim, and Merck. No other potential conflict of interest relevant to this article was reported.

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Table 1. Baseline parameters for patients above and below the median time in therapeutic range of warfarin

	Overall		TTR ≥ 63%		TTR < 63%		
Parameter	*N*	Value*	*N*	Value	*N*	Value	*P*
Age, years	1,142	60.8 ± 11.6	527	62.2 ± 11.3	540	59.2 ± 11.7	< 0.01
Female		221 (20.7)		102 (19.4)		119 (22.0)	0.28
Race/Ethnicity							< 0.01
White, non-Hispanic		809 (75.8)		448 (85.0)		361 (66.9)	
Black, non-Hispanic		149 (14.0)		32 (6.1)		117 (21.7)	
Hispanic		81 (7.6)		33 (6.3)		48 (8.9)	
Other		28 (2.6)		14 (2.7)		14 (2.6)	
Education							0.09
≤ Some high school		455 (42.6)		235 (44.6)		220 (40.7)	
High school		458 (42.9)		209 (40.0)		249 (46.1)	
≥ College		154 (14.4)		83 (15.8)		71 (13.2)	
Body mass index, kg/m^2	1,135	29.0 ± 5.9	524	29.1 ± 5.6	539	29.0 ± 6.3	0.79
Hypertension		620 (60.1)		286 (56.5)		334 (63.6)	0.02
Diabetes		347 (32.6)		166 (31.6)		181 (33.6)	0.48
Ischemic stroke		116 (10.9)		45 (8.6)		71 (13.2)	0.02
Recent stroke		59 (8.3)		21 (6.6)		37 (9.5)	0.24
Recent TIA†		26 (2.4)		9 (1.7)		17 (3.2)	0.13
Peripheral vascular disease		130 (12.2)		59 (11.2)		71 (13.2)	0.33
Hematocrit	1,045	41.7 ± 4.6	481	41.8 ± 4.4	501	41.6 ± 4.8	0.61
Hemoglobin, g/dL	1,042	14.0 ± 1.6	488	14.0 ± 1.5	489	14.0 ± 1.6	0.72
MLHFQ§	1,132	34.1 ± 23.7	523	29.7 ± 21.6	538	38.9 ± 25.1	<0.01
NYHA Class III & IV‖	1,067	337 (31.6)	527	137 (26.0)	540	200 (37.0)	<0.01

*All values are mean ± standard deviation or *N* (%).

†TIA, transient ischemic attack

§MLHFQ, Minnesota Living with Heart Failure Questionnaire

‖NYHA, New York Heart Association

Table 2 Beta-logit regression analysis of predictors of anticoagulant control during warfarin therapy

	Model 1			Model 2		
Parameter	OR*	95% CI†	*P*	OR	95% CI	*P*
Age, years	1.01	1.003 - 1.016	0.004	1.002	0.99 - 1.01	0.72
Female	1.20	1.003 - 1.432	0.047	1.15	0.88 - 1.51	0.41
MLHFQ§, per 10-point increase	0.92	0.89 - 0.95	< 0.001	0.91	0.87 - 0.96	< 0.001
White, Non-Hispanic				1.74	1.33 - 2.29	< 0.001
Education, years				0.96	0.83 - 1.13	0.65
Body mass index, kg/m^2				1.00	0.98 - 1.02	0.66
Hypertension				1.18	0.95 - 1.46	0.15
Diabetes				1.16	0.92 - 1.48	0.21
Ischemic stroke				1.11	0.80 - 1.53	0.54
Recent stroke				0.58	0.38 - 0.88	0.01
Recent transient ischemic attack				0.89	0.45 - 1.77	0.74
Peripheral vascular disease				0.77	0.55 - 1.06	0.11
Hematocrit				0.98	0.94 - 1.02	0.23
Hemoglobin, g/dL				1.00	0.88 - 1.14	0.99
NYHA Class III & IV‖				0.88	0.69 - 1.12	0.30

*OR, odds ratio

†CI, confidence interval;

§MLHFQ, Minnesota Living with Heart Failure Questionnaire

‖NYHA, New York Heart Association