Recurrent Stroke in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial

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Key Words

Heart failure · Stroke · Ejection fraction

Abstract

Background and Purpose: WARCEF randomized 2,305 patients in sinus rhythm with ejection fraction (EF) $\leq 35\%$ to warfarin (INR 2.0–3.5) or aspirin 325 mg. Warfarin reduced the incident ischemic stroke (IIS) hazard rate by 48% over aspirin in a secondary analysis. The IIS rate in heart failure (HF) is too low to warrant routine anticoagulation but epidemiologic studies show that prior stroke increases the stroke risk in HF. In this study, we explore IIS rates in WARCEF patients with and without baseline stroke to look for risk factors for IIS and determine if a subgroup with an IIS rate high enough to give a clinically relevant stroke risk reduction can be identified. **Methods:** We compared potential stroke risk

factors between patients with baseline stroke and those without using the exact conditional score test for Poisson variables. We looked for risk factors for IIS, by comparing IIS rates between different risk factors. For EF we tried cut-off points of 10, 15 and 20%. The cut-off point 15% was used as it was the highest EF that was associated with a significant increase in IIS rate. IIS and EF strata were balanced as to warfarin/aspirin assignment by the stratified randomized design. A multiple Poisson regression examined the simultaneous effects of all risk factors on IIS rate. IIS rates per hundred patient years (/100PY) were calculated in patient groups with significant risk factors. Missing values were assigned the modal value. **Results:** Twenty of 248 (8.1%) patients with baseline stroke and 64 of 2,048 (3.1%) without had IIS. IIS rate in patients with baseline stroke (2.37/100PY) was greater than patients without (0.89/100PY) (rate ratio 2.68, $p < 0.001$). Fourteen of 219 (6.4%) patients with ejection fraction

(EF) <15% and 70 of 2,079 (3.4%) with EF ≥15% had IIS. In the multiple regression analysis stroke at baseline ($p < 0.001$) and EF <15% vs. ≥15% ($p = 0.005$) remained significant predictors of IIS. IIS rate was 2.04/100PY in patients with EF <15% and 0.95/100PY in patients with EF ≥15% ($p = 0.009$). IIS rate in patients with baseline stroke and reduced EF was 5.88/100PY with EF <15% decreasing to 2.62/100PY with EF <30%. **Conclusions:** In a WARCEF exploratory analysis, prior stroke and EF <15% were risk factors for IIS. Further research is needed to determine if a clinically relevant stroke risk reduction is obtainable with warfarin in HF patients with prior stroke and reduced EF.

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Introduction

The warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) randomized 2,305 patients in sinus rhythm with ejection fraction (EF) ≤35% to warfarin (INR 2.0–3.5) or aspirin 325 mg. Warfarin reduced the incident ischemic stroke (IIS) hazard rate by 48% over aspirin in a secondary analysis in terms of time to IIS (HR 0.52; 95% CI 0.33 to 0.82; $p = 0.005$ in a stratified cause-specific Cox model) [1]. Although this important finding is supported by a recent study [2], its clinical significance is difficult to assess due to several reasons: First, it is the result of a subgroup analysis, the primary combined endpoint (death, stroke and intracerebral hemorrhage) of WARCEF having been negative. Second, the reduction in IIS rate with warfarin over aspirin in WARCEF has been said to be offset by an increase in major systemic hemorrhages [3]. Third, we have found that the effect of warfarin on stroke in WARCEF is not homogenous and warfarin has a greater risk reduction effect in the cardio-embolic stroke subgroup [4].

The situation in atrial fibrillation (AF) bears similarities to that in HF in sinus rhythm [5]. The stroke risk reduction effect of warfarin is similar [6], but subgroups with a high risk for stroke have to be identified in whom the benefits of warfarin give a net clinical advantage. In AF, these subgroups have been defined by the use of scores, such as CHADS2 [7], for which there is no counterpart in HF. A recent study [8] using the decision analysis methodology showed that patients require at least a 0.8% absolute risk reduction (number needed to treat 125) in order to agree to initiate anticoagulation treatment. A 0.52 hazard rate with warfarin would not achieve this absolute risk reduction in patients with heart failure (HF) in sinus rhythm, who have stroke rates of 0.8–1.5%

per year [2, 9]. Although a previous incident of stroke also appears to increase the stroke rate in HF [10], it is unclear whether patients with recurrent stroke or some subgroup of them, would have a rate high enough to warrant routine anticoagulation. This study was initiated to look for risk factors for IIS and at the rate of IIS in patients with prior stroke in WARCEF to determine if a subgroup with a higher stroke rate can be identified.

Methods

The primary outcome of this post-hoc analysis was the onset of IIS, previously defined [1]. We investigated the risk factors for IIS, comparing the IIS rates between patients with and without different potential stroke risk factors in the WARCEF baseline data (see table 1) using Poisson regression. For EF, we assessed cut-off points of 10, 15 and 20%. The cut-off point 15% was used as it was the highest EF showing a significant increase in the IIS rate. IIS and EF strata were balanced as to warfarin/aspirin assignment by the stratified randomized design. A multiple Poisson regression examined the simultaneous effects of all risk factors on the IIS rate. We also compared the IIS rate per hundred patient years (/100PY) between the group with EF <15% versus the group with EF ≥15% in patients with and without baseline stroke. p values and 95% CIs were calculated based on the Wald test. The missing values were assigned the modal value. IIS rates were calculated for different EF levels in patients with baseline stroke.

Results

Twenty of 248 (8.1%) patients with baseline stroke and 64 of 2,048 (3.1%) without had IIS. Descriptive statistics (according to onset of IIS) for the demographic and clinical covariates are shown in table 1. Results from univariable and multivariable Poisson regression are presented in table 2. For EF, 15% was the highest EF that was associated with a significant increase in the IIS rate ($p = 0.064$ at cutoff point 10%, $p = 0.009$ at 15%, and $p = 0.261$ at 20%). Only baseline stroke and EF <15% were significant risk factors for IIS in the univariable and multivariable models. IIS rates in patients with baseline stroke (2.37/100PY) were greater compared to the IIS rates in patients without baseline stroke (0.89/100PY): unadjusted RR = 2.68, $p < 0.001$; adjusted RR = 2.66, $p < 0.001$. Fourteen of 219 (6.4%) patients with EF <15% and 70 of 2,079 (3.4%) with EF ≥15% had IIS. IIS rates were 2.04/100PY in patients with EF <15% and 0.95/100PY in patients with EF ≥15% (unadjusted RR = 2.15, $p = 0.009$; adjusted RR = 2.33, $p = 0.005$). Comparison of IIS rates between groups with EF <15% versus EF ≥15% in patients

Table 1. Baseline characteristics of the study participants, according to the onset of IIS

Covariates	IIS (n = 84)	No IIS (n = 2,221)	p value*
Older patients (age ≥60)	46/84 (54.8)	1,229/2,221 (55.3)	0.917
Male	66/84 (78.6)	1,774/2,216 (80.1)	0.739
White non-Hispanic	64/84 (76.2)	1,669/2,215 (75.3)	0.861
Continent			0.508
EU	36/84 (42.9)	1,058/2,221 (47.6)	
NA	43/84 (51.2)	1,076/2,221 (48.4)	
Systolic BP ≥119.5	51/84 (60.7)	1,374/2,215 (62.0)	0.807
Ejection fraction <15%	14/84 (16.7)	205/2,214 (9.3)	0.023
NYHA class III or IV	27/84 (32.1)	681/2,206 (30.9)	0.804
Alcohol consumption			0.755
Current consumption, >2 oz/day	18/83 (21.7)	554/2,215 (25.0)	
Previous consumption, >2 oz/day	18/83 (21.7)	488/2,215 (22.0)	
Smoking status			0.989
Current smoker	15/83 (18.1)	393/2,213 (17.8)	
Former smoker	42/83 (50.6)	1,138/2,213 (51.4)	
Already on warfarin	8/84 (9.5)	171/2,221 (7.7)	0.540
Atrial fibrillation	3/84 (3.6)	83/2,211 (3.8)	0.931
Diabetes mellitus	31/84 (36.9)	691/2,210 (31.3)	0.275
Hypertension	49/81 (60.5)	1,318/2,151 (61.3)	0.888
Ischemic cardiomyopathy	37/84 (44.0)	954/2,209 (43.2)	0.876
Baseline stroke	20/84 (23.8)	228/2,212 (10.3)	<0.001
Myocardial infarction	47/84 (56.0)	1,065/2,210 (48.2)	0.162
Peripheral vascular disease	14/84 (16.7)	247/2,221 (11.1)	0.115

* p values were calculated using the Chi-square test.

Table 2. Predictors of IIS rate in univariable and multivariable Poisson regression models

Covariates	Unadjusted (univariable) model		Adjusted (multivariable) model	
	rate ratio (95% CI)	p value*	rate ratio (95% CI)	p value*
Older patients (age ≥60)	1.11 (0.72, 1.70)	0.641	1.02 (0.65, 1.59)	0.946
Male	0.96 (0.57, 1.61)	0.869	0.96 (0.55, 1.66)	0.875
White, non-Hispanic	1.03 (0.63, 1.71)	0.893	0.99 (0.58, 1.69)	0.981
Systolic BP ≥119.5	0.95 (0.61, 1.48)	0.827	0.96 (0.61, 1.52)	0.874
Ejection fraction <15%	2.15 (1.21, 3.82)	0.009	2.33 (1.30, 4.18)	0.005
NYHA class III or IV	1.14 (0.72, 1.80)	0.570	1.04 (0.65, 1.66)	0.882
Alcohol consumption		0.637		0.740
Current consumption, >2 oz/day	0.79 (0.46, 1.35)		0.86 (0.49, 1.51)	
Previous consumption, >2 oz/day	0.85 (0.49, 1.45)		0.81 (0.45, 1.45)	
Smoking status		0.992		0.977
Current smoker	0.98 (0.52, 1.84)		0.93 (0.47, 1.84)	
Former smoker	0.97 (0.60, 1.58)		0.95 (0.57, 1.60)	
Already on warfarin	1.20 (0.58, 2.49)	0.620	1.03 (0.49, 2.15)	0.937
Atrial fibrillation	1.00 (0.32, 3.17)	0.998	1.07 (0.34, 3.42)	0.905
Diabetes mellitus	1.34 (0.86, 2.09)	0.193	1.19 (0.74, 1.91)	0.471
Hypertension	1.01 (0.65, 1.57)	0.965	0.91 (0.57, 1.46)	0.694
Ischemic cardiomyopathy	1.20 (0.78, 1.84)	0.415	0.96 (0.58, 1.60)	0.887
Myocardial infarction	1.42 (0.92, 2.18)	0.111	1.36 (0.81, 2.28)	0.249
Peripheral vascular disease	1.74 (0.98, 3.09)	0.058	1.59 (0.87, 2.89)	0.132
Baseline stroke	2.68 (1.62, 4.42)	<0.001	2.66 (1.59, 4.45)	<0.001

* p values were calculated using the Wald test. Score tests for overdispersion were not significant.

Table 3. IIS rate by baseline stroke and EF categories

	EF <15%	EF ≥15%	Rate ratio	p value*
With baseline stroke, PY	51.0 (n = 21)	793.4 (n = 227)		
Events, n (n/100PY)	3 (5.88)	17 (2.14)	2.75	0.107
Without baseline stroke, PY	635.7 (n = 198)	6,597.4 (n = 1,859)		
Events, n (n/100PY)	11 (1.73)	53 (0.80)	2.15	0.021

* p values were calculated using the Wald test.

Table 4. Warfarin/aspirin effect by the presence of prior ischemic stroke

	Warfarin	Aspirin	Rate ratio	p value*
With baseline stroke, PY	444.7 (n = 128)	399.7 (n = 120)		
Events, n (n/100PY)	8 (1.80)	12 (3.00)	0.60	0.262
Without baseline stroke, PY	3,600 (n = 1,014)	3,633.1 (n = 1,043)		
Events, n (n/100PY)	21 (0.58)	43 (1.18)	0.49	0.008

* p values were calculated using the Wald test.

Table 5. Warfarin/aspirin effect by EF categories

	Warfarin	Aspirin	Rate ratio	p value*
EF <15%, PY	341.5 (n = 110)	345.2 (n = 109)		
Events, n (n/100PY)	8 (2.34)	6 (1.74)	1.35	0.580
EF ≥15%, PY	3,703.2 (n = 1,032)	3,687.6 (n = 1,054)		
Events, n (n/100PY)	21 (0.57)	49 (1.33)	0.43	0.001

* p values were calculated using the Wald test.

with and without baseline stroke are presented in table 3. The IIS rate among the 21 patients with baseline stroke and EF <15% was 5.88/100PY and in patients without baseline stroke and EF <15% was 1.73/100PY. Table 4 shows the warfarin/aspirin effect by the presence of prior ischemic stroke. Table 5 shows the warfarin/aspirin effect by EF categories.

Discussion

We found that EF <15% is a risk factor for IIS in HF in sinus rhythm. This is a new finding but previous studies have suggested that EF <20% is a risk factor for stroke

[11]. We have also confirmed previous studies [9, 10] showing prior stroke to be a risk factor for stroke in HF. Unlike previous studies, we did not find age [9], diabetes [9, 10] or hypertension [12], to be risk factors for IIS in HF. In addition to prior stroke (and HF), risk factors for stroke in HF in sinus rhythm are therefore different from those in AF.

A warfarin stroke risk reduction effect was not apparent in the WARCEF primary endpoint because it included a large number of deaths not reduced by warfarin. However, stroke in HF can be fatal and is disabling [4] and should be assessed for treatment in its own right. Although there were more major hemorrhages in the warfarin than aspirin arms in WARCEF, it is only intracere-

bral and not a major systemic hemorrhage that offsets a risk reduction effect of warfarin because nonfatal systemic hemorrhage is treatable [4]. A recent study has shown that patients are willing to sustain 4.4 major systemic hemorrhages to prevent one stroke [8]. The rate of major systemic hemorrhage in WARCEF was well below this rate.

In WARCEF, warfarin gave a hazard ratio of 0.52 for IIS versus aspirin and patients on warfarin had 0.07 intracerebral hemorrhage events/100PY more than aspirin. We found a rate of IIS of 5.88/100PY in patients with both prior stroke and EF <15%, which is a rate similar to that of patients with AF with a moderate stroke risk [7] and who are routinely anticoagulated. This suggests that there are subgroups of patients with HF with a stroke rate high enough to have a clinically relevant benefit from anticoagulation. The rate of IIS in all patients with baseline stroke (2.37/100PY) is still however quite low, and we did not find a significant stroke risk reduction effect by warfarin over aspirin in this subgroup; so we cannot advise anticoagulation of all HF patients with prior stroke. Our findings are based on small numbers and hence do need confirmation in a separate population, preferably in patients who are not on antithrombotics. We are planning a similar analysis in the warfarin versus Antiplatelet Therapy in Chronic Heart Failure (WATCH) Study [2].

Since AF is a strong risk factor for stroke and paroxysmal AF gives a similar risk to overt AF, the question arises whether the increased stroke risk in HF in sinus rhythm could be totally or partly due to undiagnosed paroxysmal AF. Patients with a prior history of AF or AF on baseline electrocardiogram were excluded from WARCEF. None of the 84 patients with IIS in WARCEF had overt atrial fibrillation. Non-invasive cardiac monitoring in patients with acute stroke detects up to 7.7% of patients to have

paroxysmal AF [13]. About 6 of the IIS in WARCEF could therefore have been due to paroxysmal AF on this basis. If paroxysmal AF accounted for more than a small proportion of patients with IIS we would have expected known risk factors for AF including hypertension, diabetes and particularly age, to become significant risk factors for IIS in HF too.

The major limitation of this study is that the number of patients with both prior stroke and EF <15% is very small and represents only 9% of patients with prior stroke. The group was too small to show a significant warfarin hazard ratio. We have recently reported that the warfarin effect is the greatest in the cardioembolic stroke subtype in WARCEF [4] and strokes with EF <15% are likely to be cardioembolic. Mortality and intracerebral hemorrhage rates could however be greater in this subgroup. Although the overall impact of treating this small subgroup with warfarin would be small, our findings do establish the presence of a high stroke risk subgroup in patients with HF. Thrombin inhibitors need to be studied in HF in sinus rhythm since the current guidelines [14] recommend their use in AF with a thromboembolic rate 2.5 [1.98–3.15]/100PY. This rate is similar to the rate of IIS in all HF patients with baseline stroke in WARCEF and potentially gives a larger subgroup in which anticoagulation with these agents might be clinically indicated.

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