RESEARCH LETTER

Time to Cardioversion for Acute Atrial Fibrillation and Thromboembolic Complications

In 1995, practice guidelines recommended a limit of 48 hours after the onset of atrial fibrillation (AF) for cardioversion without anticoagulation.[1-3] Whether the risk of thromboembolic complications is increased when cardioversion without anticoagulation is performed in less than 48 hours is unknown.

Methods | In the retrospective Finnish CardioVersion study,[4] all patients with a primary diagnosis of AF, aged 18 years or older, with successful cardioversion in the emergency department within the first 48 hours of AF, and residence in the catchment areas of Turku and Kuopio university hospitals from 2003 to 2010 and Pori central hospital during 2010 were included. Clinical details and the occurrence of thromboembolic complications within 30 days after cardioversion were retrospectively collected from medical reports.

The primary outcome, a thromboembolic event, was defined as a clinical stroke or systemic embolism confirmed by computerized tomography or magnetic resonance imaging, surgery, or autopsy. Time to cardioversion was determined as the difference between the beginning of arrhythmic symptoms to the exact time of cardioversion. If the duration of arrhythmia was uncertain, the cardioversion

Table 1. Time to Cardioversion for Acute Atrial Fibrillation and Thromboembolic Complications[a]

	Total No. of Patients	No. (%) of Patients by Time to Cardioversion[b]			*P* Value[c]
		<12 h (n = 2440)	12-<24 h (n = 1840)	24-<48 h (n = 836)	
Age, mean (SD), y	5116	61.0 (12.2)	60.6 (12.7)	61.7 (12.5)	.04
Female sex	1638	851 (34.9)	551 (30.0)	236 (28.2)	<.001
Hypertension	2324	1117 (45.8)	833 (45.3)	374 (44.7)	.86
Diabetes	409	207 (8.5)	129 (7.0)	73 (8.7)	.15
Vascular disease	1145	555 (22.8)	407 (22.2)	183 (21.9)	.83
Heart failure	184	78 (3.2)	63 (3.4)	43 (5.1)	.03
History of					
Myocardial infarction	329	171 (7.0)	104 (5.7)	54 (6.5)	.20
Thromboembolism	291	142 (5.8)	106 (5.8)	43 (5.1)	.76
$CHADS_2$ score[d]					
0-1	4264	2039 (47.8)	1546 (36.3)	679 (15.9)	.25
2	580	265 (45.7)	202 (34.8)	113 (19.5)	
3-6	272	136 (50.0)	92 (33.8)	44 (16.2)	
CHA_2DS_2-VASc score[e]					
0-1	2678	1260 (47.1)	984 (36.7)	434 (16.2)	.80
2	1030	486 (47.2)	365 (35.4)	179 (17.4)	
3-5	1284	634 (49.4)	446 (34.7)	204 (15.9)	
>5	120	59 (49.2)	42 (35.0)	19 (15.8)	
		No. (%) [95% CI] of Patients by Time to Cardioversion			
Thromboembolic complications	38	8 (0.3) [0.1-0.6]	21 (1.1) [0.7-1.6]	9 (1.1) [0.4-1.8]	.004
By sex					
Female	22	3 (0.4) [0-0.8]	13 (2.4) [1.1-3.6]	6 (2.5) [0.5-4.6]	.001
Male	16	5 (0.3) [0-0.6]	8 (0.6) [0.2-1.0]	3 (0.5) [0-1.1]	.48
By $CHADS_2$ score					
0-1	25	4 (0.2) [0-0.4]	15 (1.0) [0.5-1.5]	6 (0.9) [0.2-1.6]	.006
>1	13	4 (1.0) [0-2.0]	6 (2.0) [0.4-3.7]	3 (1.9) [0-4.1]	.50
By CHA_2DS_2-VASc score					
0-1	10	2 (0.2) [0-0.4]	4 (0.4) [0-0.8]	4 (0.9) [0-1.8]	.06
>1	28	6 (0.5) [0.1-0.9]	17 (2.0) [1.1-2.9]	5 (1.2) [0.2-2.3]	.008
By cardioversion					
First	25	5 (0.4) [0.1-0.8]	12 (1.3) [0.6-2.1]	8 (2.0) [0.6-3.3]	.01
Subsequent	13	3 (0.2) [0-0.6]	9 (0.6) [0-1.4]	1 (0.6) [0-1.9]	.046

[a] In the 2481 patients, multiple events (n = 5116) were included in the analyses.

[b] Values expressed as number (percentage) unless otherwise indicated.

[c] Bivariable comparisons between the groups were performed using the χ^2 test, the Fisher exact test, or the Wilcoxon nonparametric test.

[d] Defined as cardiac failure, hypertension, age, diabetes, and stroke (doubled).

[e] Defined as cardiac failure, hypertension, age of 75 years or older (doubled), diabetes, stroke (doubled), vascular disease, age of 65 to 74 years, and female sex.

Table 2. Multivariable Analysis of Risk Factors for Thromboembolic Complications (n=5116)

	Odds Ratio (95% CI)[a]	*P* Value
Time to cardioversion, h		
12-24 vs <12	4.0 (1.7-9.1)	.001
24-48 vs <12	3.3 (1.3-8.9)	.02
Age, y[b]	1.06 (1.03-1.09)	<.001
Female sex	2.1 (1.1-4.3)	.04
Heart failure	3.5 (1.4-8.6)	<.001
Diabetes	2.7 (1.3-5.8)	.01

[a] Multivariable logistic regression analysis with a repeated-measure model.

[b] Treated as a continuous variable without cut points.

was excluded. Procedures were divided into groups according to the time to cardioversion: less than 12 hours (group 1), 12 hours to less than 24 hours (group 2), and 24 hours to less than 48 hours (group 3).

The protocol was approved by the ethics committees of the Hospital District of Southwest Finland and the National Institute for Health and Welfare, with a waiver of informed consent. Bivariable comparisons between groups were performed with the χ^2 test, the Fisher exact test, or the Wilcoxon nonparametric test. Multivariable logistic regression analysis with a repeated-measures model was conducted to evaluate risk factors for thromboembolic complications, including comparisons between groups 2 and 1 and between groups 3 and 1.

Clinical features (age, female sex, heart failure, and diabetes) with independent predictive value for thromboembolic complications were used as covariates in the multivariate analysis based on our previous work.[4] Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc). Two-sided differences at $P < .05$ were considered significant.

Results | Of 2481 patients with acute AF, 5116 successful cardioversions were performed without anticoagulation. The mean age was 61.0 (SD, 12.4) years, 1638 were female (32.0%), and 2434 had more than 1 risk factor for stroke (47.6%). Thirty-eight thromboembolic events occurred in 38 patients (0.7%; 95% CI, 0.5%-1.0%); 31 were strokes. The incidence of thromboembolic complications increased from 0.3% in group 1 to 1.1% in group 3 ($P = .004$, **Table 1**).

The incidence of thromboembolic complications according to the time to cardioversion in subgroups is presented in Table 1. In multivariable logistic regression analysis (**Table 2**), time to cardioversion longer than 12 hours was an independent predictor for thromboembolic complications (odds ratio of 4.0 [95% CI, 1.7-9.1] between groups 2 and 1 [$P = .001$]; odds ratio of 3.3 [95% CI, 1.3-8.9] between groups 3 and 1 [$P = .02$]).

Discussion | Stroke is the most serious complication of AF. After the recommended 3 weeks of therapeutic anticoagulation, the stroke risk in elective cardioversion of AF ranges from 0.3% to 0.8%.[1] In our study, the risk of thromboembolic complications was 0.7% when cardioversion was performed without anticoagulation within 48 hours of AF onset.

However, we found that a delay to cardioversion of 12 hours or longer from symptom onset was associated with a greater risk of thromboembolic complications (1.1%). When the duration of AF was less than 12 hours, the risk of thromboembolism was low (0.3%) without anticoagulation. The main limitation of this retrospective study lies on the verification of AF duration based on real-life evaluation in the emergency department.

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COMMENT & RESPONSE

Risk and Benefits of Screening Mammography

To the Editor One of the major conclusions of the recent article by Drs Pace and Keating[1] was that "The net benefit of screening depends greatly on baseline breast cancer risk, which should be incorporated into screening decisions." This seems logical, but I do not believe there is evidence that it is true.

The primary reason screening mammography is so controversial is because the most important outcome is mortality, and only 8 old randomized trials have used mortality as an outcome. Recent trials testing new modalities such as ultrasound or magnetic resonance imaging in high-risk groups have used rate of breast cancer detection as an outcome.[2,3] These trials cannot distinguish between detection of potentially lethal cancers and overdiagnosis of indolent, harmless cancers.

It seems clear that screening women at high risk results in a higher rate of cancer detection, but breast cancer biology is complex, and it cannot be assumed that the mortality benefit would be proportional. For example, patients with *BRCA1* mutations have a high risk of triple-negative cancers, which are not amenable to early detection with mammography and are frequently found as interval cancers.[4] This group might not benefit proportionally. Alternatively, the Gail model is heavily weighted toward predicting risk of hormonally driven tumors. Screening these women might detect a large number of small, indolent luminal A cancers that would increase the rate of overdiagnosis but not necessarily reduce mortality.

There are no data to estimate the degree of benefit that any high-risk group may derive from mammography. Women at high risk may have other options for prevention. One of the greatest harms of mammography, one not mentioned in the article,[1] is that it may encourage overreliance for protection on a technique that may or may not be effective.

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In Reply We agree with Dr Lannin that the evidence of the benefits of mammography in women at higher risk for breast cancer is limited. None of the randomized trials of mammography screening specifically assessed if the mortality benefits of mammography differed for higher-risk groups, such as women with a family history of breast cancer or women with dense breasts, compared with women at lower risk. However, these trials did allow assessment of the modifying effect of age, one of the most important risk factors for breast cancer. Results from meta-analyses suggest that the relative risk reduction is greater for 60- to 70-year-old women than for younger women, as shown in Table 1 of the article.

Furthermore, because the absolute risk of breast cancer and breast cancer death is higher among women at higher risk, even if the relative risk reduction is similar, the absolute risk reduction will be greater, and thus the number of deaths averted through screening will be higher—as it is for 50-year-old vs 40-year-old women, for example. Although it is plausible that the relative risk reduction could be less among some women at higher risk, whether because of more aggressive disease less amenable to mammographic detection or more indolent disease less likely to cause death, tumors in higher-risk women are likely to be heterogeneous, and some other women at higher risk may experience greater relative risk reduction from mammography screening. It therefore seems unlikely that across all women at higher risk, the relative risk reduction would be lower than for women at average risk. Thus, as described above, we expect the absolute risk reduction to be higher among women at higher risk overall than among women at average risk. We want to underscore, however, that our discussion of women at high risk does not generalize to women with genetic cancer syndromes, who may benefit from other screening and prevention strategies.

The risk-benefit ratio of screening also depends on the likelihood of harms, such as false-positive results and overdiagnosis. It is equally difficult to generalize about the risk of these harms among women who are at higher vs lower risk for breast cancer for reasons other than age. Some studies show that women with dense breasts[1] or a positive family history[2] have a higher risk of false-positive results. Less evidence is available about whether breast cancer risk might modify the likelihood of overdiagnosis. Without clear evidence that the harms of mammography are uniformly greater among women at higher risk, given greater absolute risk reductions, we conclude that the risk-benefit ratio of screening is likely to be higher among women at higher risk than among those at lower risk.