

Incident Thromboembolism in the Aorta and the Renal, Mesenteric, Pelvic, and Extremity Arteries After Discharge From the Hospital With a Diagnosis of Atrial Fibrillation

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Background: The impact of atrial fibrillation (AF) on risk of peripheral arterial thromboembolism is unknown.

Methods: We analyzed the risk of thromboembolism (embolus and/or thrombosis) in the aorta and the renal, mesenteric, pelvic, and extremity arteries in a cohort of patients discharged from the hospital with an incident diagnosis of AF relative to the risk of thromboembolism in these vessels in the Danish population. In a random sample of half of the Danish population, 14917 men and 14945 women aged 50 to 89 years were identified in the Danish National Hospital Discharge Register with a diagnosis of AF from January 1, 1980, through December 31, 1993. Patients were followed up from diagnosis of AF in the Danish National Hospital Discharge Register and the Causes of Death Register until the first diagno-

sis of a thromboembolic event, death, or the end of 1993. Risk of a thromboembolic event relative to the risk in the Danish population was analyzed by means of Poisson regression modeling.

Results: Patients with a hospital diagnosis of AF had an increased risk of thromboembolic events in the aorta and the renal, mesenteric, pelvic, and extremity arteries (relative risk, 4.0 [95% confidence interval, 3.5-4.6] in men; and relative risk, 5.7 [95% confidence interval, 5.1-6.3] in women) compared with the Danish population.

Conclusion: A hospital diagnosis of AF is an important risk factor for peripheral arterial thromboembolic complications.

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IT IS WELL documented that patients with atrial fibrillation (AF) have an increased risk of cerebrovascular thromboembolism.¹⁻¹⁰ The incidence of peripheral arterial thromboembolic events (ie, thromboembolic events outside the cerebral and coronary artery systems) in patients with AF is lower than the incidence of stroke.¹¹ The main reason for this may be that most of the cerebral arteries are functional end arteries, whereas occlusion of many other arteries may not lead to clinical manifestations because of protection from collateral circulation. Clinical articles on series of patients with peripheral thromboembolism report that 30% to 80% of patients with acute peripheral thromboembolic events have AF.¹²⁻³⁷ This indicates that AF is the most important risk factor for peripheral thromboembolism. We have found no reports on estimates of risk of peripheral arterial thromboembolism in patients with AF. Therefore, the purpose of this article was to analyze the risk of thromboembolism in the aorta and the renal,

mesenteric, pelvic, and extremity arteries in patients discharged from the hospital with an incident diagnosis of AF relative to the risk of thromboembolism in the same vascular beds in the Danish population.

RESULTS

DEMOGRAPHIC AND CLINICAL DATA

The cohort of patients with an incident hospital discharge diagnosis of AF and no previous discharge diagnosis of peripheral arterial thromboembolism from January 1, 1980, through December 31, 1993, consisted of 29862 individuals (14917 men and 14945 women) aged 50 to 89 years.

The proportions of previous or concomitant hospital discharge diagnoses of hypertension; diabetes; ischemic heart disease, with or without myocardial infarction; congestive heart failure; stroke; mitral valve disease; aortic valve disease; and peripheral atherosclerosis are shown in **Table 1**.

MATERIALS AND METHODS

STUDY POPULATION

The general health and hospital care systems in Denmark are noncharge and nonprofit systems that are financed through taxes. The cohort of patients with AF was found within a nearly 50% random sample (all persons with 1 of 15 randomly selected birthdays a month) from the Danish population. Patients were included in the cohort if they were discharged from the hospital from January 1, 1980, through December 31, 1993, with an incident diagnosis of AF and had no history or presence of a peripheral thromboembolism (including emboli as well as thromboses) in the Danish National Hospital Discharge Register. Registrations with modification codes *not found* or *under observation for* were excluded. Patients whose conditions solely were diagnosed in outpatient clinics were not included in the present cohort. To avoid inclusion of prevalent cases, patients who had received a diagnosis of AF or peripheral thromboembolism in the Danish National Discharge Register from January 1, 1977, through December 31, 1979, were excluded. The month and year of the first registration (ie, incidence) of AF was registered, along with registration of age and sex. Previous (from 1977) or simultaneous diagnosis in the Danish National Hospital Discharge Register of diseases disposing to AF³⁸⁻⁴⁰ or peripheral thromboembolism were recorded, eg, hypertension; diabetes; ischemic heart disease, with or without acute myocardial infarction; congestive heart failure; stroke; mitral valve disease; aortic valve disease; and peripheral atherosclerosis.

Data on the incidence of a hospital diagnosis of AF in the Danish population from January 1, 1980, through December 31, 1993, have been published elsewhere⁴¹ together with outcome data, such as total and cardiovascular mortality⁴¹ and stroke.¹⁰

FOLLOW-UP

Patients were followed up in the Danish National Hospital Discharge Register and the Causes of Death Register from diagnosis of AF until the first diagnosis of a thromboembolic event (ie, embolus or thrombosis), death, or the end of 1993. Follow-up used the personal identification number, a 10-digit code that is a unique identification of every person with an address in Denmark at any time since April 1968. Follow-up ended at the end of 1993 because of a change in the World Health Organization International Classification of Diseases (ICD) that occurred in Denmark in 1994. Diseases were coded by the medical staff in the discharging hospital according to *International Classification of Diseases, Eighth Revision (ICD-8)* codes.⁴² Cause of death was coded by the Danish National Board of Health according to World Health Organization standards on the basis of causes of death noted in death certificates, which were filled in by physicians in the hospital, in general practice, or in forensic medicine.

The definitions of diseases and causes of death by ICD-8 codes for the present analysis are available from the authors.

Persons who died within the same month as the incident AF diagnosis (n=2580) were excluded from the analysis.

STATISTICAL METHODS

Sex-, age- and calendar-year-specific incidence rates of peripheral thromboembolism in the population were calculated by dividing the number of incident cases in the population sample by the corresponding person-years in the 50% sample from the Danish population. Person-years at risk for a peripheral arterial thromboembolism for the AF cohort was calculated for each sex in 5-year age groups and for 3 calendar periods: 1980-1984, 1985-1989, and 1990-1993. The observed number of peripheral thromboembolic events was compared with that expected for the cohort. The expected number of peripheral thromboembolic events was calculated by multiplying person-years at risk by the corresponding sex-, age-, and calendar-year-specific incident peripheral thromboembolic event rates in the Danish population. The crude relative risk (RR) (the ratio between the observed and expected number of outcomes) and the excess number and excess risk (the difference between the observed and expected number of outcomes, and the difference divided by the person-years at risk, respectively) were calculated for each 10-year age group in men and women. A more consistent variation in RR than in excess risk was seen across ages and sex. Therefore, analysis of risk variation has been used, giving a multiplicative rather than an additive risk model.

The RR of *peripheral thromboembolism*, defined as the observed divided by expected number of peripheral thromboembolic events, was analyzed separately for men and women by means of Poisson regression models.⁴³ In such log-linear or multiplicative regression models, the observed number is considered to be Poisson-distributed. The logarithm of the expected number of peripheral thromboembolic events was used as an offset variable (ie, a constant in the log-linear regression model), and the covariates (ie, age and calendar time at AF diagnosis, time since diagnosis, and status of earlier or concomitant diseases) were multiplicative factors in the model. For each of the covariates (except age), 1 of the categories was chosen as the reference, and the reported estimated values for the other categories can be interpreted as RRs compared with this reference category, standardized for the other factors in the model. For the covariates describing previous diseases, the group with no previous disease was the reference category. This illustrates relative changes in risk for the cohort relative to the population rates. The interpretation of an estimated age value is the RR for the cohort at the reference category of covariates compared with the Danish population for the specific age group.

Poisson regression models were fitted using PROC GENMOD in SAS statistical software (SAS Version 6.12; SAS Institute Inc, Cary, NC).

For men in the AF cohort, the crude peripheral thromboembolism rates in the age intervals 50 to 59, 60 to 69, 70 to 79, and 80 to 89 years were 3, 4, 6, and 4 per 1000 person-years, respectively. In women, the rates in

the same age intervals were 2, 5, 8, and 10 per 1000 person-years, respectively.

Six hundred twenty-one persons had events of peripheral arterial thromboembolism. The distribution of

Table 1. Demographic and Clinical Data for Persons in the Danish Atrial Fibrillation Cohort, 1980-1993*

Characteristic	Men (n = 14 917)	Women (n = 14 945)
Age at atrial fibrillation diagnosis, y		
50-59	11.5	4.7
60-69	27.3	16.6
70-79	39.5	40.2
80-89	21.8	38.5
History and/or presence of		
Hypertension	16.6	19.8
Diabetes	9.3	11.2
Ischemic heart disease		
With myocardial infarction	19.7	10.8
Without myocardial infarction	29.4	33.5
Congestive heart failure	33.1	31.2
Stroke	9.9	10.6
Mitral valve disease	1.9	3.5
Aortic valve disease	2.0	2.4
Peripheral atherosclerosis	4.4	3.5

*Persons with no history or presence of thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries. Data are given as percentages. Because of rounding, percentages may not all total 100.

events in the body were: 7% in the aorta, 2% in the renal artery, 29% in the mesenteric arteries, 9% in the pelvic arteries, and 61% in the upper and lower extremities. Some patients had events in more than 1 site at the same time.

In men and women, the observed vs expected numbers of peripheral thromboembolic events were 232 vs 57.3 and 389 vs 68.6 during 48660.0 and 51007.8 years at risk, respectively (**Table 2**). Thus, the crude RR of a peripheral thromboembolic event was 4.0 (95% confidence interval, 3.5-4.6) for men and 5.7 (95% confidence interval, 5.1-6.3) for women compared with the Danish population. Nearly half of the excess events occurred in patients aged 70 to 79 years (Table 2).

RISK FACTORS FOR PERIPHERAL ARTERIAL THROMBOEMBOLISM

Risk factors for peripheral arterial thromboembolism in the AF cohort are shown in **Table 3**. At the reference category for the other risk factors (ie, the second year after AF diagnosis and no history or presence of concomitant diseases), patients aged 60 to 69 years had a 4.0-fold (men) and 6.8-fold (women) increase in RR of peripheral thromboembolism compared with the Danish population. The RR of thromboembolism diminished with increasing age. Men and women aged 80 to 89 years had a 1.9- and 3.2-fold increase in relative thromboembolic risk, respectively.

The highest risk of peripheral arterial thromboembolism was seen during the first year after incident AF diagnosis; thereafter, the thromboembolic risk declined (Table 3).

In both men and women, a higher RR of peripheral thromboembolism was present in patients with diagnoses of peripheral atherosclerosis, acute myocardial infarction, and stroke. In men, a higher thromboembolic risk was also present in diabetic patients with

AF. In women, a higher thromboembolic risk was also seen in patients with hypertension or congestive heart failure.

COMMENT

We have documented that a hospital diagnosis of AF is associated with a 4.0-fold (men) and 5.7-fold (women) increase in RR of incident peripheral arterial thromboembolism compared with the Danish population.

Peripheral atherosclerosis was a significant risk factor for thromboembolism in both men and women. There may be more than 1 possible pathophysiological mechanism. First, distant lodgment of embolic material may take place at a distally located atherosclerotic plaque formation, causing total obstruction of the blood flow. Second, the embolic material may originate from the fibrillating atrium or from a ruptured plaque proximal to the site of the acute occlusion. Third, localized thrombus formation may have caused some cases of thromboembolism. Fourth, AF per se activates the coagulation system⁴⁴⁻⁴⁷; this may facilitate local thrombus formation in case of a plaque rupture.

A history of myocardial infarction was associated with a moderately increased risk of peripheral thromboembolism in men and women. The mechanism may be formation of a mural thrombus in the infarction zone with subsequent embolization, or the myocardial infarction may be caused by embolization from the fibrillating atrium to a coronary artery and thus indicates a risk of embolization from the fibrillating atrium. Finally, if the myocardial infarction was caused by plaque rupture, the patient has demonstrated a capability of plaque rupture and local thrombus formation. This capability may also be present in the peripheral vascular system.

A history of stroke was a risk factor for thromboembolism in both men and women. However, a history of stroke did not attain statistical significance in women. We believe that if we had had a larger cohort of patients with AF, a history of stroke also would have shown statistical significance in women.

Diabetes was a significant risk factor for peripheral thromboembolism in men but not in women. The ICD-8 coding system does not differentiate between type 1 and type 2 diabetes mellitus before 1986. One possible explanation for the significance of diabetes in men may be a preponderance of type 2 diabetes in men, since type 2 diabetes is associated with more widespread atherosclerosis than type 1. This is in accord with men having a higher incidence rate of type 2 diabetes than women in Denmark.

Hypertension and heart failure were risk factors for a thromboembolic event in women but not in men. The present series included a limited number of thromboembolic events. It is possible that the dissimilarities observed in the risk factors for thromboembolic events in men and women originated from significance by chance, or that misclassification of hypertension and congestive heart failure may have introduced bias. However, we have no reason to believe that misclassification of hypertension and congestive heart failure should depend on sex.

Table 2. Crude Risk Measures of Thromboembolic Events for Persons in the Danish Atrial Fibrillation Cohort, 1980-1993*

Age at Atrial Fibrillation Diagnosis, y	Person-years at Risk	No. of Peripheral Thromboembolic Events		Standardized Morbidity Ratio, O/E	Excess Thromboembolic Events		
		O	E		No., O - E	Rate (O - E), per 1000 PYRS	%†
Men							
50-59	8174.0	27	4.6	5.9	22.4	2.7	12.8
60-69	15 771.5	66	14.8	4.5	51.2	3.2	29.3
70-79	17 397.7	107	24.4	4.4	82.6	4.8	47.3
80-89	7316.8	32	13.4	2.4	18.6	2.5	10.7
50-89	48 660.0	232	57.3	4.0	174.7	3.6	100.0
Women							
50-59	3722.3	8	1.5	5.3	6.5	1.7	2.0
60-69	11 317.2	61	7.6	8.0	53.4	4.7	16.7
70-79	21 538.3	175	27.5	6.4	147.5	6.8	46.0
80-89	14 430.0	145	32.1	4.5	112.9	7.8	35.2
50-89	51 007.8	389	68.6	5.7	320.4	6.3	100.0

*O indicates observed; E, expected; and PYRS, person-years at risk.
 †Because of rounding, percentages may not all total 100.

It is, therefore, most likely that the observed differences between men and women derive from residual confounding. We had no information on potentially confounding factors, such as the type of AF (ie, paroxysmal, persistent, or permanent), family history of AF, social class, exercise habits, smoking status, cholesterol level, body mass index, severity of comorbidity, and medication, including coumarin therapy.

The ICD-8 coding does not differentiate between an embolus and a thrombosis as the cause of an acute arterial occlusion; however, this is not a serious limitation. First, 81% of acute peripheral arterial occlusions are embolic.²³ Second, in the presence of AF, it can be assumed that an even higher proportion of acute vascular occlusion is caused by embolization. Third, in surgery or during autopsy, it often may be impossible to differentiate between embolization and/or thrombus formation, especially when differentiating between acute and acute on chronic limb ischemia.⁴⁸

Randomized trials have documented that coumarin therapy reduces the risk of stroke in patients with AF by 68%.⁴⁹ A randomized trial to demonstrate the effect of coumarin therapy on risk of peripheral thromboembolism in patients with AF will never be performed, because it would be deemed unethical to randomize patients with AF to placebo treatment.

We believe that coumarin therapy is effective in preventing peripheral arterial thromboembolism in patients with AF. Indirect evidence for this comes from the fact that heart valve disease was not associated with an increased risk of peripheral thromboembolism in the present cohort. This may be caused by the widespread use of coumarin derivatives in patients with heart valve disease with or without AF.

Besides an increased risk of thromboembolic cerebrovascular events, patients with AF also have an increased risk of peripheral arterial embolism. We advocate that this also should be taken into account when considering anticoagulation therapy in patients with AF.

Table 3. Risk Factors for Thromboembolism for Persons in the Atrial Fibrillation Cohort (1980-1993) vs the Danish Population*

Characteristic	RR (95%CI)†	
	Men	Women
Age at atrial fibrillation diagnosis, y		
50-59	6.0 (3.7-9.7)	4.3 (2.0-9.4)
60-69	4.0 (2.7-6.0)	6.8 (4.8-9.7)
70-79	3.7 (2.5-5.3)	4.9 (3.6-6.5)
80-89	1.9 (1.2-3.0)	3.2 (2.3-4.3)
Time since atrial fibrillation diagnosis, y		
<1	1.2 (0.8-1.6)	1.3 (1.0-1.7)
1-<2‡	1	1
2-4	0.7 (0.5-1.0)	0.9 (0.7-1.2)
≥5	0.7 (0.5-1.1)	0.8 (0.6-1.1)
History and/or presence of at baseline§		
Hypertension	0.9 (0.6-1.2)	1.5 (1.2-1.9)
Diabetes	1.8 (1.2-2.6)	1.2 (0.9-1.6)
Ischemic heart disease		
With myocardial infarction	1.4 (1.0-2.0)	1.4 (1.0-1.9)
Without myocardial infarction	1.3 (1.0-1.8)	1.1 (0.8-1.3)
Stroke	1.5 (1.0-2.3)	1.2 (0.9-1.7)
Congestive heart failure	1.0 (0.7-1.3)	1.4 (1.2-1.8)
Mitral valve disease	0.9 (0.3-2.8)	0.8 (0.4-1.7)
Aortic valve disease	1.2 (0.4-3.4)	0.5 (0.1-1.4)
Peripheral atherosclerosis	2.6 (1.6-4.1)	2.8 (1.9-4.2)

*For thromboembolism in the aorta and the renal, mesenteric, pelvic, and extremity arteries.

†Risk estimates are adjusted for other factors in the table. RR indicates relative risk; CI, confidence interval.

‡Reference period.

§Relative risk to no disease.

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