

LESS IS MORE

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

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Background: Patients with atrial fibrillation (AF) often require anticoagulation and platelet inhibition, but data are limited on the bleeding risk of combination therapy.

Methods: We performed a cohort study using nationwide registries to identify all Danish patients surviving first-time hospitalization for AF between January 1, 1997, and December 31, 2006, and their posthospital therapy of warfarin, aspirin, clopidogrel, and combinations of these drugs. Cox proportional hazards models were used to estimate risks of nonfatal and fatal bleeding.

Results: A total of 82 854 of 118 606 patients (69.9%) surviving AF hospitalization had at least 1 prescription filled for warfarin, aspirin, or clopidogrel after discharge. During mean (SD) follow-up of 3.3 (2.6) years, 13 573 patients (11.4%) experienced a nonfatal or fatal bleeding. The crude incidence rate for bleeding was high-

est for dual clopidogrel and warfarin therapy (13.9% per patient-year) and triple therapy (15.7% per patient-year). Using warfarin monotherapy as a reference, the hazard ratio (95% confidence interval) for the combined end point was 0.93 (0.88-0.98) for aspirin, 1.06 (0.87-1.29) for clopidogrel, 1.66 (1.34-2.04) for aspirin-clopidogrel, 1.83 (1.72-1.96) for warfarin-aspirin, 3.08 (2.32-3.91) for warfarin-clopidogrel, and 3.70 (2.89-4.76) for warfarin-aspirin-clopidogrel.

Conclusions: In patients with AF, all combinations of warfarin, aspirin, and clopidogrel are associated with increased risk of nonfatal and fatal bleeding. Dual warfarin and clopidogrel therapy and triple therapy carried a more than 3-fold higher risk than did warfarin monotherapy.

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MANY PATIENTS WITH atrial fibrillation (AF) require long-term oral anticoagulation with vitamin K antagonists.¹ Patients with AF often have coexisting vascular disease, such as ischemic heart disease, and, thus, an indication for platelet inhibitor therapy. Because platelet inhibitor therapy in patients with AF provides less protection against thromboembolic events than does regular oral anticoagulation therapy,^{2,3} the physician may choose to combine aspirin or clopidogrel with a standard anticoagulant or even to use triple therapy with aspirin, clopidogrel, and an oral anticoagulant.^{1,4} The safety of this approach is poorly documented and represents a major therapeutic dilemma. No studies address dual therapy with an oral anticoagulant and clopidogrel, and studies addressing triple therapy are small and lack documentation for the duration of treatment. Consequently, estimates of

risk vary significantly.⁵⁻¹¹ Because undocumented combinations are endorsed in current international guidelines and expert statements for the treatment of AF,^{1,12} it is imperative that better estimates of safety are provided in terms of the risk of bleeding complications. Thus, in the present study, we examined a nationwide cohort of 118 606 patients with AF discharged from hospitals in Denmark between January 1, 1997, and December 31, 2006, to analyze the risk of hospitalization or death due to bleeding after treatment with warfarin, aspirin, clopidogrel, and combinations of these drugs.

METHODS

DATABASES

All Danish citizens have a unique personal registration number that enables cross-linkage of nationwide data concerning hospitalizations, drug use, and death. Since 1978, the Danish National Patient Registry has registered all hospi-

tal admissions in Denmark. Each admission is registered with 1 primary and, if appropriate, 1 or more secondary diagnoses using the *International Classification of Diseases, 10th Revision (ICD-10)*. The Danish Register of Medicinal Product Statistics holds information regarding all prescriptions (according to the international Anatomical Therapeutic Chemical [ATC] codes) filled in Denmark since 1995. The registry also includes information about the date of dispensation and the strength and quantity of the drug dispensed. All pharmacies are required by Danish legislation to provide information that ensures complete and accurate registration.^{13,14} The National Causes of Death Register contains data concerning immediate, contributory, and underlying causes of death classified using *ICD-10*. Vital status can be obtained from the Central Population Register, which records all deaths within 14 days.

STUDY POPULATION

All patients 30 years or older discharged from hospitals between January 1, 1997, and December 31, 2006, with a first-time primary or secondary diagnosis of AF (*ICD-10* code I48) were included. The diagnosis of AF has been validated in the Danish National Patient Registry with a positive predictive value of 99%.¹⁵ A more detailed description of patient selection has been provided elsewhere.¹⁶

COMORBIDITIES

Comorbidities were defined from co-diagnoses at discharge for the index AF and from admissions 1 year before the index AF admission, as done by Rasmussen et al.¹⁷ Comorbidity diagnoses (*ICD-10* codes) were ischemic heart disease (I20-I25) (including acute myocardial infarction [I21]), heart failure (I50), valvular heart disease (I34-I37), hypertension (I10-I15), ischemic stroke (I63-I66, I69.3, and I69.4), systemic embolism (I26 and I74), diabetes (E10-E14), acute and chronic renal failure (N17-N19 and R34), liver disease (K70-K77, R16, and R17), and malignancy (C00-C97).

WARFARIN AND PLATELET INHIBITOR THERAPY

The Danish Register of Medicinal Product Statistics was used to identify all prescriptions filled for warfarin (ATC code B01AA03), aspirin (ATC code B01AC06), and clopidogrel (ATC code B01AC04). For each dispensed prescription, the daily dose used was estimated from the average dosage in up to 7 consecutive prescriptions. On the basis of these estimates, we calculated whether patients had tablets available at any point in time. This method allowed exposure status and dosages to change.^{18,19} Previous antithrombotic treatment was defined as prescriptions filled for warfarin, aspirin, or clopidogrel within 90 days before hospitalization. Of the antithrombotic therapies examined, aspirin was the only drug that could be bought over-the-counter. Patients undergoing persistent aspirin treatment, however, usually receive aspirin with a prescription to collect financial reimbursement, as documented by the high use in this study and in others of patients with ischemic heart disease.²⁰ We included only aspirin claimed by prescription in this analysis. In addition to warfarin, phenprocoumon can also be prescribed in Denmark. To ensure that these results were not affected by unmeasured phenprocoumon exposure, patients receiving phenprocoumon after hospital discharge (n=4882) were excluded from the study.

EXPOSURE GROUPS

Seven exposure groups were defined: monotherapy with warfarin, aspirin, and clopidogrel; dual therapy with warfarin-

aspirin, warfarin-clopidogrel, and aspirin-clopidogrel; and triple therapy with warfarin-aspirin-clopidogrel. Nonexposure was classified as no treatment.

CONCOMITANT MEDICAL THERAPY

Prescriptions filled for renin-angiotensin system inhibitors (ATC code C09A); antiarrhythmics, including β -blockers (ATC code C07), calcium channel blockers (ATC code C08), digoxin (ATC code C01A), amiodarone (ATC code C01BD01), and class IC antiarrhythmics (ATC code C01BC); statins (ATC code C10AA); nonsteroidal anti-inflammatory drugs (ATC code M01A); and proton pump inhibitors (ATC code A02BC) within 90 days of hospital discharge were identified and were classified as concomitant medical therapy.

END POINTS

The primary end point was bleeding. Bleeding was defined as an admission to a Danish hospital, excluding emergency department visits, with a bleeding diagnosis (primary or secondary), a nonfatal bleeding episode, or a diagnosis of bleeding as the cause of death reported in the National Causes of Death Register (a fatal bleeding episode). Bleedings were divided into 4 groups according to organ systems, and only the most frequently used bleeding diagnoses were included: gastrointestinal bleedings (*ICD-10* codes K25.0, K25.4, K26.0, K26.4, K27.0, K28.0, K92.0, K92.1, and K92.2), intracranial bleedings (*ICD-10* codes I60, I61, I62, I69.0, I69.1, I69.2, S06.4, S06.5, and S06.6), urinary tract bleedings (*ICD-10* codes N02 and R31), and airway bleedings (*ICD-10* codes J94.2 and R04). The secondary end point was ischemic stroke, defined as admission to a Danish hospital with a nonfatal ischemic or unspecified stroke diagnosis (*ICD-10* codes I63 and I64, primary or secondary) or a diagnosis of ischemic or unspecified stroke as the cause of death reported in the National Causes of Death Register (fatal ischemic stroke). Finally, the effect of a nonfatal bleeding episode on the risk of all-cause mortality was estimated.

STATISTICAL ANALYSIS

Baseline variables and patient characteristics for each drug exposure group are presented as percentages or as means with standard deviations. Crude incidence rates, calculated as percentages of events per patient-year, and relative risk ratios were assessed for the combined end point of nonfatal or fatal bleedings. The unadjusted numbers needed to harm were estimated as the number needed to harm per year exposed. Adjusted risks of nonfatal and fatal bleeding and ischemic stroke were analyzed using Cox proportional hazards regression models, including the exposure groups as time-dependent covariates in the models, ensuring that patients were considered at risk only when they received therapy. The models allowed patients to switch from one exposure group to another. Warfarin monotherapy was used as a reference. The models were adjusted for the following baseline characteristics: age, sex, year of index AF admission, comorbidities, and concomitant medical treatment. The risk of death after a nonfatal bleeding episode was analyzed in a separate Cox model where nonfatal bleeding was included as a time-varying variable; patients were counted in the nonbleeding group until the date of bleeding and thereafter were included in the bleeding group. Model assumptions were tested for linearity and lack of interactions and were found valid. Patients were observed until the first bleeding event and were censored when dying of causes

Table 1. Baseline Characteristics of the Study Cohort

Characteristic	Treatment Group							
	Total ^a	Warfarin Monotherapy	Aspirin Monotherapy	Clopidogrel Monotherapy	Clopidogrel + Aspirin	Warfarin + Aspirin	Warfarin + Clopidogrel	Warfarin + Aspirin + Clopidogrel
Patients, total No. (%)	118 606 (100)	50 919 (42.9)	47 541 (40.1)	3717 (3.1)	2859 (2.4)	18 345 (15.5)	1430 (1.2)	1261 (1.1)
Age, mean (SD), y	73.7 (12.3)	70.3 (10.7)	74.7 (11.4)	72.6 (10.2)	72.1 (10.3)	70.8 (10.0)	70.2 (8.9)	69.9 (9.2)
Female sex, No. (%)	56 421 (47.6)	20 491 (40.2)	23 147 (48.7)	1488 (40.0)	1076 (37.6)	7228 (39.4)	430 (30.1)	358 (28.4)
Male sex, No. (%)	62 185 (52.4)	30 428 (59.8)	24 394 (51.3)	2229 (60.0)	1783 (62.4)	11 117 (60.6)	1000 (69.9)	903 (71.6)
Comorbidities, No. (%)								
Acute myocardial infarction	7301 (6.2)	2206 (4.3)	3963 (8.3)	1220 (32.8)	1045 (36.5)	1495 (8.2)	380 (26.6)	378 (30.0)
Ischemic heart disease	19 273 (16.2)	7275 (14.3)	9808 (20.6)	1629 (43.8)	1214 (42.5)	3988 (21.7)	613 (42.9)	485 (38.5)
Heart failure	21 784 (18.4)	8681 (17.1)	8739 (18.3)	730 (19.6)	542 (19.0)	3294 (18.0)	288 (20.1)	232 (18.4)
Valvular heart disease	5607 (4.7)	3218 (4.7)	2318 (4.9)	174 (4.7)	148 (5.2)	1264 (6.9)	96 (6.7)	76 (6.0)
Hypertension	18 385 (15.5)	9905 (17.5)	8158 (17.2)	890 (23.9)	688 (24.1)	3515 (19.2)	319 (22.3)	260 (20.6)
Ischemic stroke	8825 (7.4)	3512 (7.4)	3624 (7.4)	299 (8.0)	154 (5.4)	1316 (7.2)	88 (6.2)	54 (4.3)
Systemic embolism	1519 (1.3)	9846 (1.9)	456 (1.0)	24 (0.7)	22 (0.8)	296 (1.6)	15 (1.1)	16 (1.3)
Diabetes	9966 (8.4)	3898 (7.7)	4249 (8.9)	463 (12.5)	370 (12.9)	1590 (8.7)	174 (12.2)	143 (11.3)
Liver disease	568 (0.5)	122 (0.2)	146 (0.3)	9 (0.2)	4 (0.1)	34 (0.2)	3 (0.2)	3 (0.2)
Renal failure	2871 (2.4)	745 (1.5)	900 (1.9)	134 (3.6)	82 (2.8)	248 (1.4)	27 (1.9)	22 (1.7)
Malignancy	1476 (1.2)	269 (0.5)	366 (0.8)	17 (0.5)	20 (0.7)	74 (0.4)	3 (0.2)	4 (0.3)
Bleeding	4075 (3.4)	905 (1.8)	1299 (2.7)	144 (3.9)	69 (2.4)	281 (1.5)	23 (1.6)	22 (1.7)
Anemia	3914 (3.3)	737 (1.4)	1311 (2.8)	132 (3.6)	73 (2.6)	269 (1.5)	25 (1.8)	16 (1.3)
Concomitant therapy, No. (%)								
RAS inhibitors ^b	31 388 (26.5)	17 604 (34.6)	14 368 (30.2)	1579 (42.5)	1263 (44.2)	7169 (39.1)	690 (48.3)	620 (49.2)
Antiarrhythmics ^c	91 099 (76.8)	44 421 (87.2)	39 953 (84.0)	3212 (86.4)	2515 (88.0)	16 339 (89.1)	1295 (90.6)	1145 (90.8)
Statins	14 027 (11.6)	7548 (14.8)	7518 (15.8)	1583 (42.6)	1306 (45.7)	4162 (22.7)	658 (46.0)	600 (47.6)
NSAIDs	11 600 (9.8)	4528 (8.9)	5185 (10.9)	389 (10.5)	300 (10.5)	1727 (9.4)	139 (9.7)	115 (9.1)
PPIs	16 041 (13.5)	5349 (10.5)	6367 (13.4)	889 (23.9)	563 (19.7)	1945 (10.6)	264 (18.5)	182 (14.4)
Previous antithrombotic treatment, No. (%)								
Warfarin	15 193 (12.8)	12 753 (25.1)	4313 (9.1)	314 (8.5)	236 (8.3)	3624 (19.8)	320 (22.4)	265 (21.0)
Aspirin	19 788 (16.7)	7431 (14.6)	13 356 (28.1)	891 (24.0)	896 (31.3)	5171 (28.2)	310 (21.7)	359 (28.5)
Clopidogrel	1390 (1.0)	512 (1.0)	713 (1.5)	607 (16.3)	369 (12.9)	274 (1.5)	209 (14.6)	130 (10.3)

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; RAS, renin-angiotensin system.

^aThe total population is not equal to the sum of patients in the treatment groups because patients were allowed to cross over between groups.

^bThe RAS inhibitors comprise angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and renin inhibitors.

^cThe antiarrhythmics comprise β-blockers, calcium channel blockers, digoxin, amiodarone, and class 1C antiarrhythmics.

other than the prespecified end points or when passing the end of the observational period (December 31, 2006). All statistical calculations were performed using a software package (SAS version 9.1.4 for Windows; SAS Institute Inc, Cary, North Carolina).

SENSITIVITY ANALYSES

To ensure the robustness of the present findings, 4 sensitivity analyses were performed: 2 Cox proportional hazards analyses of nonfatal and fatal bleeding including patients with AF (1) from the most recent calendar years (2004-2006) and (2) with a codiagnosis of ischemic heart disease, including myocardial infarction, and 2 stratified propensity analyses in which patients in each exposure group were (3) stratified into tertiles according to their propensity for experiencing a bleeding and (4) stratified for being exposed to warfarin monotherapy as first exposure.

ETHICS

The Danish Data Protection Agency approved this study, and data were made available at the individual level such that specific individuals could not be identified. For this reason, retrospective register studies do not require ethical approval in Denmark.

RESULTS

BASELINE CHARACTERISTICS

Of 126 837 patients admitted to a Danish hospital with first-time AF between January 1, 1997, and December 31, 2006, 118 606 (93.5%) were alive at discharge and were included in this study. Mean (SD) follow-up was 3.3 (2.6) years. After discharge, 82 854 patients (69.9%) had at least 1 prescription filled for warfarin, aspirin, clopidogrel, or combinations of these drugs. A detailed description of the baseline characteristics of the treatment groups is given in **Table 1**. Patients treated with aspirin monotherapy were older and more often female than were patients in the other treatment groups. Clopidogrel therapy was mainly administered in patients with a codiagnosis of myocardial infarction or ischemic heart disease. Warfarin and aspirin monotherapy and dual therapy were associated with long-term therapy, whereas the other treatment regimens were used for shorter periods (**Table 2**).

NONFATAL AND FATAL BLEEDING

This combined end point occurred in 13 573 patients (11.4%), with 12 191 (10.3%) experiencing nonfatal

Table 2. Characteristics and Risk of Bleeding Associated With Single, Dual, and Triple Antithrombotic Treatment After Atrial Fibrillation Hospitalization

Variable	Dosage, Median, mg	Duration of Treatment, Median (Range, 5-95 percentile), d	Treatment Duration/Period of Observation, Median (Range)	Bleedings, No.	Exposure Time, Patient-years	Incidence Rate, % per Patient-year, Unadjusted 95% CI	Relative Risk Increase, (Unadjusted 95% CI)	NNH per Year, Unadjusted, (Unadjusted 95% CI)
Warfarin monotherapy	5 (3.5-6.5)	391 (106-1036)	0.58 (0.15-0.93)	3642	93 492	3.9	1 [Reference]	1 [Reference]
Aspirin monotherapy	75 (75-150)	323 (98-861)	0.42 (0.11-0.80)	2694	72 146	3.7	0.96 (0.95-0.96)	217 (151-388)
Clopidogrel monotherapy	75 (75-75)	75 (26-213)	0.10 (0.02-0.35)	105	1865	5.6	1.45 (1.22-1.66)	619 (288-4102)
Clopidogrel + aspirin	NA	99 (34-263)	0.14 (0.04-0.37)	94	1264	7.4	1.91 (1.59-2.21)	28 (20-48)
Warfarin + aspirin	NA	198 (74-496)	0.22 (0.06-0.60)	1209	17 712	6.9	1.75 (1.71-1.79)	34 (30-39)
Warfarin + clopidogrel	NA	64 (27-154)	0.08 (0.02-0.23)	69	496	13.9	3.57 (2.88-4.22)	10 (8-14)
Warfarin + clopidogrel + aspirin	NA	83 (28-180)	0.09 (0.03-0.24)	64	408	15.7	4.03 (3.22-4.78)	8 (7-12)
No treatment	NA	NA	NA	2959	140 800	2.8	NA	NA
Total	NA	NA	NA	13 573	450 143	3.0	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; NNH, number needed to harm.

Table 3. Number and Crude Incidence Rate of Bleeding Events Associated With Single, Dual, and Triple Antithrombotic Treatment After Atrial Fibrillation Hospitalization

Variable	Events, No.	Incidence Rate, Unadjusted, % per Patient-year						
		Warfarin Monotherapy	Aspirin Monotherapy	Clopidogrel Monotherapy	Aspirin + Clopidogrel	Warfarin + Aspirin	Warfarin + Clopidogrel	Warfarin + Aspirin + Clopidogrel
Nonfatal bleeding	12 192	3.6	3.3	4.8	7.0	6.4	13.3	15.4
Fatal bleeding	1381	0.2	0.4	0.8	0.6	0.4	0.6	0.2
Fatal and nonfatal bleeding	13 573	3.9	3.7	5.6	7.4	6.8	13.9	15.7
Intracranial bleeding	2154	0.6	0.5	1.0	0.2	0.8	0.8	1.0
Airway bleeding	3185	1.3	0.7	1.0	2.2	2.3	7.1	7.1
Gastrointestinal bleeding	4637	0.9	1.5	1.9	3.1	2.1	3.8	5.1
Urinary tract bleeding	3051	1.0	0.9	1.3	1.7	1.6	2.0	2.4

bleeding and 1381 (1.2%) fatal bleeding. Most bleeding events were gastrointestinal; the anatomical distribution of bleeding is given in **Table 3**. The crude incidence rate of combined nonfatal and fatal bleeding was highest in the initial period after discharge and was unaffected by previous warfarin treatment (**Figure 1**).

TIME TRENDS

Between January 1, 1997, and December 31, 2006, the proportion of patients with AF who had a prescription filled for warfarin, aspirin, or clopidogrel within 90 days of discharge increased from 21.4% to 44.8%, from 16.9% to 33.0%, and from 0% to 5.0%, respectively. The crude incidence rate of the combined end point of bleeding within 180 days of discharge increased from 4.7% to 9.0% per patient-year (**Figure 2**). For patients receiving warfarin monotherapy within 90 days of discharge, the bleeding rate correspondingly increased from 5.1% to 6.3% per patient-year.

WARFARIN, ASPIRIN, CLOPIDOGREL, OR COMBINATIONS OF THESE DRUGS AND RISK OF BLEEDING AND ISCHEMIC STROKE

For each treatment exposure, crude incidence rates (Table 3) and Cox proportional hazards analysis

(**Table 4** and **Figure 3**) of nonfatal and fatal bleeding are given. Using warfarin monotherapy as a reference, risk increased with the number of antithrombotic agents used. Exposure to triple therapy increased the risk more than 3-fold for nonfatal and fatal bleeding (hazard ratio [HR] for bleeding, 3.70; 95% confidence interval [CI], 2.89-4.76) (Figure 3 and Table 4). Except for gastrointestinal bleeding, aspirin monotherapy was associated with a lower risk of bleeding than was warfarin monotherapy. For those receiving clopidogrel monotherapy, the risk of bleeding was comparable with that of warfarin monotherapy. The risk of nonfatal and fatal bleeding was significantly lower in patients not receiving treatment (HR, 0.83; 95% CI, 0.79-0.86). Cox proportional hazards analysis of nonfatal and fatal ischemic stroke showed no benefit of combination therapy (**Figure 4**).

BLEEDINGS AND RISK OF ALL-CAUSE MORTALITY

Increased risk of death was found using Cox proportional hazards analysis in patients experiencing a nonfatal bleeding episode with an HR of 2.45 (95% CI, 2.37-2.57).

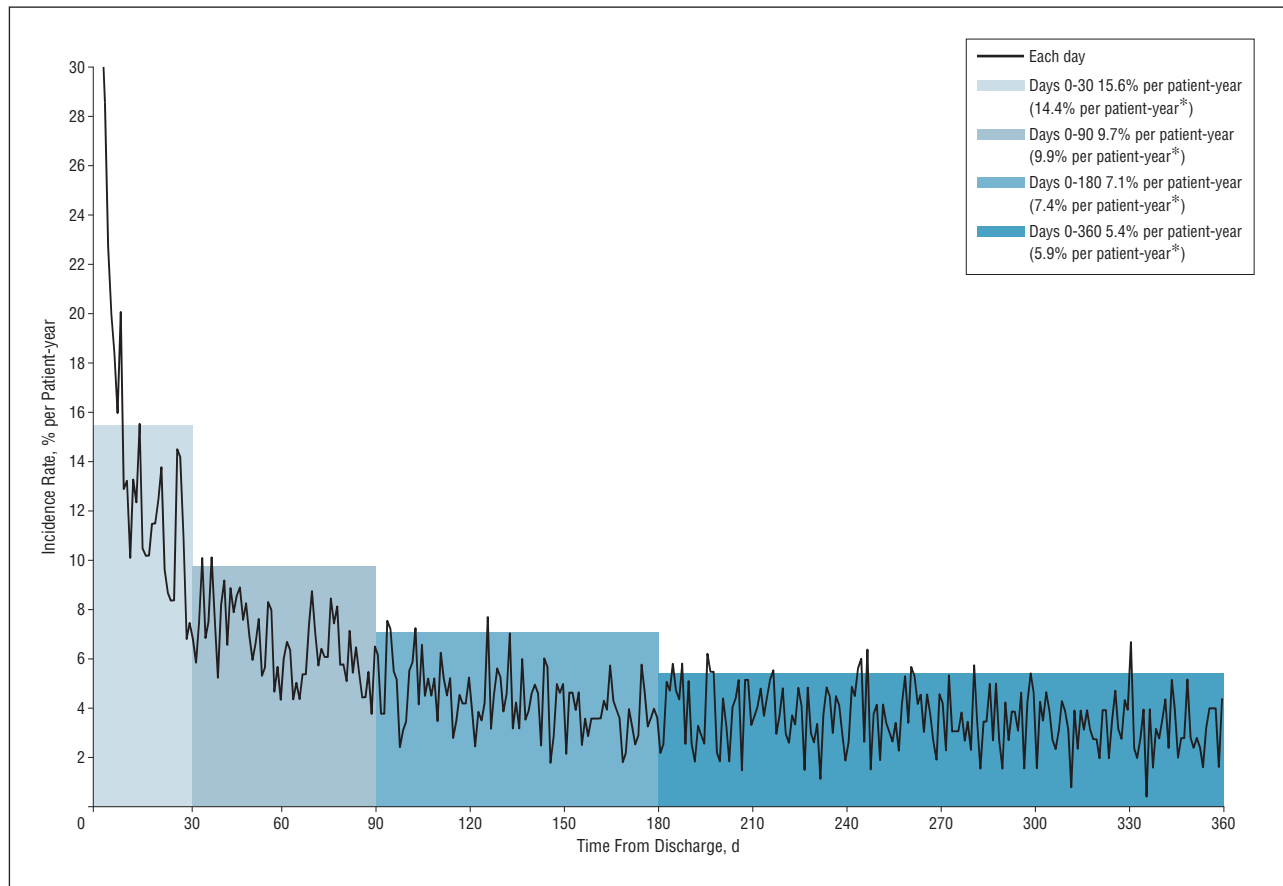


Figure 1. Crude incidence rates of nonfatal and fatal bleeding each day and within 0 to 30, 0 to 90, 0 to 180, and 0 to 360 days after hospital discharge for atrial fibrillation. *Patients receiving warfarin before the index atrial fibrillation hospitalization.

SENSITIVITY ANALYSES

Results of the 4 sensitivity analyses are given in **Table 5**. All the analyses showed consistent results, indicating the robustness of the findings.

COMMENT

The present study demonstrated that in patients with AF, the risk of bleeding increased in proportion to the number of antithrombotic agents used. Most important, patients receiving dual therapy with warfarin and clopidogrel and those receiving triple therapy with warfarin, aspirin, and clopidogrel had a more than 3-fold higher risk of bleeding than did patients treated solely with warfarin. The importance of this finding was highlighted by a significantly increased risk of death after a nonfatal bleeding episode and a nonbeneficial effect in terms of preventing ischemic stroke.

MONOTHERAPIES

The rate of nonfatal and fatal bleedings of 3.9% per patient-year for warfarin monotherapy in the present study is higher than the reported rates of major bleeding in randomized clinical trials.²¹⁻²⁵ However, most trial participants are carefully selected and mainly include prevalent users of warfarin. Because most major bleeds occur

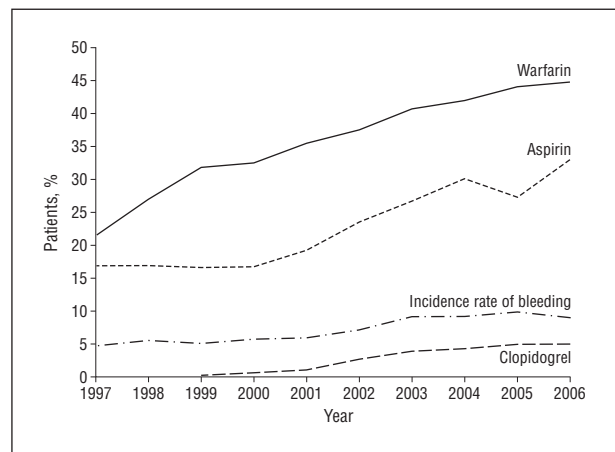


Figure 2. Proportion of patients with atrial fibrillation who had a prescription filled for warfarin, aspirin, or clopidogrel within 90 days of hospital discharge and the crude incidence rate of nonfatal and fatal bleeding (in percentage per patient-year) within 180 days of discharge.

early in the course of anticoagulation, enrollment of long-time users of warfarin will result in lower estimates of bleeding.^{26,27} This bias was illustrated in an inception cohort study²⁸ of elderly patients with AF who had newly started warfarin therapy. In these patients, the rate of major bleeding during the first year was 7%.²⁸

We found a comparable overall risk of bleeding in patients receiving either warfarin or aspirin monotherapy.

Table 4. Hazard Ratios From the Cox Regression Analysis of Risk of Bleeding Using Warfarin Monotherapy as a Reference

Variable	Hazard Ratio (95% CI)					
	Aspirin Monotherapy	Clopidogrel Monotherapy	Aspirin + Clopidogrel	Warfarin + Aspirin	Warfarin + Clopidogrel	Warfarin + Aspirin + Clopidogrel
Nonfatal bleeding	0.84 (0.80-0.89)	0.94 (0.76-1.16)	1.64 (1.33-2.03)	1.77 (1.66-1.90)	3.16 (2.47-4.03)	3.93 (3.05-5.05)
Fatal bleeding	1.37 (1.13-1.65)	2.22 (1.30-3.77)	1.16 (0.43-3.15)	1.96 (1.50-2.57)	2.45 (0.78-7.70)	1.11 (0.16-7.94)
Fatal or nonfatal bleeding	0.93 (0.88-0.98)	1.06 (0.87-1.29)	1.66 (1.34-2.04)	1.83 (1.72-1.96)	3.08 (2.32-3.91)	3.70 (2.89-4.76)
Intracranial bleeding	0.78 (0.68-0.89)	1.24 (0.78-1.97)	0.39 (0.12-1.21)	1.44 (1.19-1.73)	1.32 (0.49-3.53)	1.36 (1.30-1.42)
Airway bleeding	0.55 (0.50-0.61)	0.63 (0.39-1.01)	1.49 (1.02-2.19)	1.57 (1.37-1.79)	4.81 (3.42-6.75)	4.94 (3.40-7.19)
Gastrointestinal bleeding	1.28 (1.17-1.41)	1.18 (0.84-1.67)	2.60 (1.87-3.60)	2.30 (2.03-2.60)	3.46 (2.19-5.46)	5.38 (3.48-8.32)
Urinary tract bleeding	0.84 (0.76-0.94)	1.12 (0.75-1.67)	1.52 (0.99-2.34)	1.57 (1.37-1.79)	1.75 (0.94-3.27)	2.12 (1.13-3.97)

Abbreviation: CI, confidence interval.

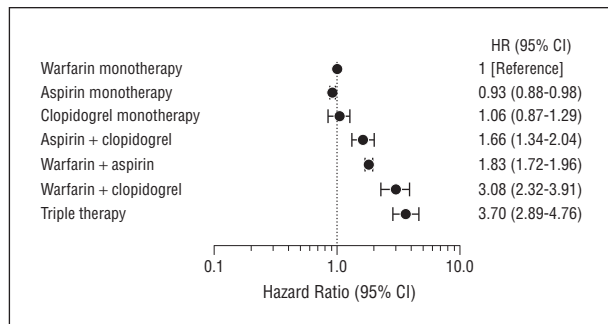


Figure 3. Hazard ratios (HRs) for the risk of nonfatal (n=12191) and fatal (n=1381) bleeding associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs. CI indicates confidence interval.

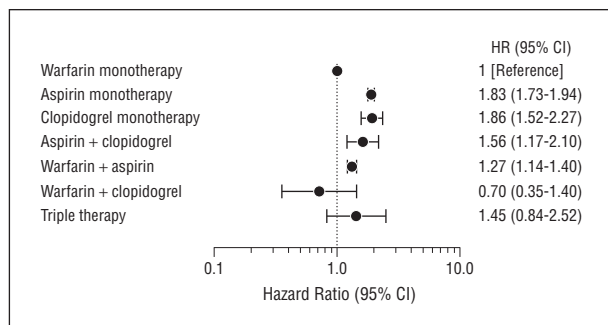


Figure 4. Hazard ratios (HRs) for the risk of nonfatal (n=9785) and fatal (n=3537) ischemic stroke associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs. CI indicates confidence interval.

This analysis confirmed that aspirin monotherapy is a risk factor for gastrointestinal bleeding in particular.²⁹ In the present study, increasing age favored the use of aspirin monotherapy. Patients with AF considered at high risk for bleeding are often prescribed aspirin with the perception that this therapy is less risky for bleeding compared with oral anticoagulant therapy.^{1,2} The present results support those of another recent study³⁰ that found a comparable bleeding risk but superiority of warfarin over aspirin for the prevention of ischemic stroke. Treatment with clopidogrel monotherapy has previously been found to have a risk of bleeding similar to that of aspirin monotherapy, similar to the present findings.³¹ Furthermore, we found that clopidogrel monotherapy was in-

ferior to warfarin monotherapy in the prevention of ischemic stroke. Thus, this challenges a common practice favoring either aspirin or clopidogrel over warfarin in certain populations due to the misconception that this would provide better safety for patients.

COMBINATION THERAPIES

The appropriateness of combination therapy in patients with AF and a dual indication for oral anticoagulation and platelet inhibitor therapy is unresolved. Observational studies^{32,33} have confirmed the conventional wisdom that combined warfarin and a platelet inhibitor is a risk factor for serious bleeding complications. The studies were limited due to insufficient patient numbers to estimate the risk associated with specific platelet inhibitors combined with oral anticoagulation plus lack of the information to track actual medication use at the time of the bleeding episode.

Combined aspirin and warfarin therapy was frequently used in the present cohort (15.5%). For these patients, the risk of bleeding was almost twice as high as that for patients receiving warfarin monotherapy. This commonly used treatment practice raises safety concerns, particularly because the present study and the clinical trials³⁴⁻³⁶ testing the efficacy of either low- or normal-intensity oral anticoagulation, combined with platelet inhibitors for the prevention of stroke, did not show superiority over traditional anticoagulant monotherapy. Most recently, a meta-analysis³⁷ highlighted the increased bleeding risk associated with the concurrent use of an oral anticoagulant and aspirin. In the present study, dual aspirin and clopidogrel therapy was associated with an increased risk of bleeding and ischemic stroke, respectively, compared with warfarin monotherapy. Dual aspirin and clopidogrel therapy has been found to be beneficial only in patients with AF unsuitable for warfarin treatment, and there is an increase in the risk of bleeding complications, in agreement with the present study.^{3,38}

We found the highest risk of bleeding in patients receiving dual warfarin and clopidogrel therapy and in patients receiving triple therapy. These combinations also did not add efficacy for the prevention of ischemic stroke. To our knowledge, the safety of combined warfarin and clopidogrel has not been addressed previously. Two ob-

Table 5. Sensitivity Analyses of the Risk of Combined Fatal and Nonfatal Bleeding Using Warfarin Monotherapy as a Reference

Variable	Aspirin Monotherapy	Clopidogrel Monotherapy	Aspirin + Clopidogrel	Warfarin + Aspirin	Warfarin + Clopidogrel	Warfarin + Aspirin + Clopidogrel
Cox regression analysis						
Atrial fibrillation and IHD ^a	1.29 (1.18-1.41)	1.29 (0.94-1.79)	2.65 (1.93-3.64)	2.24 (1.99-2.53)	3.27 (2.07-5.16)	5.10 (3.30-7.89)
Late period (2004-2006)	0.97 (0.85-1.10)	0.94 (0.65-1.35)	1.68 (1.21-2.33)	1.91 (1.66-2.20)	3.09 (2.06-4.65)	3.57 (2.40-5.31)
Propensity score						
Stratified for bleeding ^b	0.95 (0.90-1.00)	1.08 (0.85-1.27)	1.73 (1.40-2.13)	1.85 (1.73-1.98)	3.16 (2.48-4.02)	3.84 (2.99-4.93)
Stratified for warfarin monotherapy ^c	0.94 (0.89-0.99)	1.04 (0.89-0.99)	1.65 (1.34-2.04)	1.83 (1.72-1.96)	3.07 (2.41-3.91)	3.65 (2.84-4.69)

Abbreviation: IHD, ischemic heart disease.

^aAtrial fibrillation and a codiagnosis of IHD including acute myocardial infarction.

^bC statistic=0.61.

^cC statistic=0.77.

servational studies^{6,39} reported that efficacy outcome is comparable with triple therapy. Other studies with predominantly patients with AF addressing the issue of bleeding complications associated with triple antithrombotic therapy were small single-center studies that lacked information on treatment duration and actual use of triple therapy at the time of the bleeding episode. Accordingly, triple therapy was associated with a variable cumulative incidence of major bleeding that ranged from 1.4% to 21.6%. Recently, a review by Rubboli et al¹² addressed the issue of optimal antithrombotic treatment in patients with AF and an indication for oral anticoagulant therapy after percutaneous coronary intervention. The authors concluded that triple therapy is highly effective and specifically superior to dual platelet inhibitor therapy and oral anticoagulation therapy combined with aspirin. At the same time, they recognized that triple therapy has a poor safety profile; the reported cumulative incidence of major bleeding is 5% soon after percutaneous coronary intervention, increasing to more than 10% for longer treatment duration.

STRENGTHS AND LIMITATIONS OF THE STUDY

The present study covers the entire cohort of Danish patients discharged from the hospital with a diagnosis of AF between January 1, 1997, and December 31, 2006, independent of race, socioeconomic status, age, or participation in health insurance programs, thus minimizing the risk of selection bias. The main limitation is inherent from the observational nature of the study. We included AF that led to hospitalization and, thus, might have assembled a sicker population more prone to bleeding. Therefore, it could be difficult to extend these results to the wider community. However, a recent Danish community-based study⁴⁰ showed that 94% of all patients diagnosed as having AF were seen in the hospital, suggesting that the present findings could be extrapolated to most patients with AF. Furthermore, we did not have any information on whether the individual cases of AF were paroxysmal, persistent, or permanent or might have been triggered by a single episode of acute illness; these are factors that could dictate the uses of a specific treatment. We had no knowledge of the factors influencing the decision by physicians to prescribe different

combinations of antithrombotic medications, although monotherapy or perceived safe combinations of drugs most likely were prescribed to patients considered at increased risk for bleeding. Confounding by indication would, therefore, probably affect the results conservatively. Also, the determination of treatment was based on filled prescriptions from pharmacies. The exact relationship between prescription fills and actual treatment may vary and could dilute the results. Another important limitation is the lack of information on the international normalized ratio in patients receiving warfarin.^{41,42} We did not have the clinical information to determine the severity of the bleeding episode, but by using a bleeding definition based on readmission to a hospital with a bleeding diagnosis, we presume that this event constitutes severe bleeding because it is clinically serious enough to warrant hospitalization. Finally, we could not identify bleeding episodes not causing hospitalization or death. Thus, these results could underestimate the accurate risk associated with therapy.

IMPLICATIONS

This study documents that combinations of anticoagulation and platelet inhibitor therapy are associated with a substantial increased risk of bleeding in patients with AF. Particularly, dual warfarin and clopidogrel therapy and triple therapy had poor safety profiles. The importance of avoiding bleeding was emphasized owing to an increased risk of death after a nonfatal bleeding episode and a nonbeneficial effect in terms of preventing ischemic stroke. When indications exist for anticoagulant therapy and platelet inhibitor therapy, the benefit of combining treatments has not been demonstrated. Consequently, combination therapy should be carefully considered and should be given only for a short time when treatments are mandatory.

CONCLUSIONS

Combinations of warfarin, aspirin, and clopidogrel are frequently used in patients with AF. In real-life circumstances, combination therapy is associated with a much higher risk of severe bleeding than previously recog-

nized. Particularly, dual warfarin and clopidogrel therapy and triple therapy were associated with a more than 3-fold higher risk of nonfatal and fatal bleeding than was warfarin monotherapy. These results stress that appropriate selection of patients for these therapies is important and that physicians should consider the expected benefits and risks carefully before prescribing combination therapy.

Editor's Note

This study reports bleeding risks in a large observational cohort of over 118 000 Danish patients with atrial fibrillation and more than 3 years of follow-up. They find that adding clopidogrel or aspirin to warfarin monotherapy greatly increases the fatal and nonfatal bleeding risk while showing no benefit to prevention of ischemic stroke. This demonstration of no benefit from a frequently used dual and triple anticoagulant combination and significant harms places this article in our Less Is More classification.

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Author Contributions: Dr Hansen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Hansen, Gadsbøll, Gislason, and Torp-Pedersen. *Acquisition of data:* Hansen, Clausen, Fog-Petersen, and Torp-Pedersen. *Analysis and interpretation of data:* Hansen, Clausen, Fog-Petersen, Raunso, Gadsbøll, Gislason, Folke, Andersen, Poulsen, Køber, and Torp-Pedersen. *Drafting of the manuscript:* Hansen, Clausen, Fog-Petersen, Gadsbøll, and Torp-Pedersen. *Critical revision of the manuscript for important intellectual content:* Sørensen, Raunso, Gadsbøll, Gislason, Folke, Andersen, Schramm, Abildstrøm, Poulsen, Køber, and Torp-Pedersen. *Statistical analysis:* Hansen, Gislason, Køber, and Torp-Pedersen. *Obtained funding:* Torp-Pedersen. *Administrative, technical, and material support:* Torp-Pedersen. *Study supervision:* Clausen, Gadsbøll, Gislason, Folke, Schramm, Abildstrøm, Poulsen, Køber, and Torp-Pedersen.

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Space management in Haiti.

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