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

Morten L. Hansen, MD, PhD; Rikke Sorensen, MD; Mette T. Clausen, MSc Pharm; Marie Louise Fog-Petersen, MSc Pharm; Jakob Raunso, MD; Niels Gadsoell, MD, DMSc; Gunnar H. Gislason, MD, PhD; Fredrik Folke, MD; Soren S. Andersen, MD; Tina K. Schramm, MD; Steen Z. Abildstrom, MD, PhD; Henrik E. Poulsen, MD, DMSc; Lars Kober, MD, DMSc; Christian Torp-Pedersen, MD, DMSc

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.4,5 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. 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%. A more detailed description of patient selection has been provided elsewhere.

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. Comorbidity diagnoses (ICD-10 codes) were ischemic heart disease (I00-I09, I20-I25) (including acute myocardial infarction [I21]), heart failure (I50), valvular heart disease (I34-I37), hypertension (I10-I15), ischemic stroke (I63, I65, I66, I68, 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. 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. 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-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 D08), digoxin (ATC code C01A), amiodarone (ATC code C01BD01), and class 1C 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 diagnosis of 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.
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
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).
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. However, most trial participants are carefully selected and mainly include prevalent users of warfarin. Because most major bleeds occur early in the course of anticoagulation, enrollment of longtime users of warfarin will result in lower estimates of bleeding. This bias was illustrated in an inception cohort study 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%. We found a comparable overall risk of bleeding in patients receiving either warfarin or aspirin monotherapy.
clopidogrel monotherapy was in-
monotherapy, similar to the present findings.31 Further-
found to have a risk of bleeding similar to that of aspirin 
ment with clopidogrel monotherapy has previously been 
tered over aspirin for the prevention of ischemic stroke. Treat-
comparable bleeding risk but superiority of warfarin 
patients receiving triple therapy. These combinations also 
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-

This analysis confirmed that aspirin monotherapy is a risk 
factor for gastrointestinal bleeding in particular.20 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 per-
ception that this therapy is less risky for bleeding com-
pared with oral anticoagulant therapy.1,2 The present re-
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. Treat-
ment 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 Further-
more, we found that clopidogrel monotherapy was in-

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aspirin Monotherapy</th>
<th>Clopidogrel Monotherapy</th>
<th>Aspirin + Clopidogrel</th>
<th>Warfarin + Aspirin</th>
<th>Warfarin + Clopidogrel</th>
<th>Warfarin+ Aspirin+ Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal bleeding</td>
<td>0.84 (0.80-0.89)</td>
<td>0.94 (0.76-1.16)</td>
<td>1.64 (1.33-2.03)</td>
<td>1.77 (1.66-1.90)</td>
<td>3.16 (2.47-4.03)</td>
<td>3.93 (3.05-5.05)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>1.37 (1.13-1.65)</td>
<td>2.22 (1.30-3.77)</td>
<td>1.16 (0.43-3.15)</td>
<td>1.96 (1.50-2.57)</td>
<td>2.45 (0.78-7.70)</td>
<td>1.11 (0.16-7.94)</td>
</tr>
<tr>
<td>Fatal or nonfatal bleeding</td>
<td>0.93 (0.88-0.98)</td>
<td>1.06 (0.87-1.29)</td>
<td>1.66 (1.34-2.04)</td>
<td>1.83 (1.72-1.96)</td>
<td>3.08 (2.32-3.91)</td>
<td>3.70 (2.89-4.76)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.78 (0.68-0.89)</td>
<td>1.24 (0.78-1.97)</td>
<td>0.39 (0.12-1.21)</td>
<td>1.44 (1.19-1.73)</td>
<td>1.32 (0.49-3.53)</td>
<td>1.36 (1.30-1.42)</td>
</tr>
<tr>
<td>Airway bleeding</td>
<td>0.55 (0.50-0.61)</td>
<td>0.63 (0.39-1.01)</td>
<td>1.49 (1.02-2.19)</td>
<td>1.57 (1.37-1.79)</td>
<td>4.81 (3.42-6.75)</td>
<td>4.94 (3.40-7.19)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.28 (1.17-1.41)</td>
<td>1.18 (0.84-1.67)</td>
<td>2.60 (1.67-5.80)</td>
<td>2.30 (2.93-6.60)</td>
<td>3.46 (2.19-5.46)</td>
<td>5.38 (3.48-8.32)</td>
</tr>
<tr>
<td>Urinary tract bleeding</td>
<td>0.84 (0.76-0.94)</td>
<td>1.12 (0.75-1.67)</td>
<td>1.52 (0.99-2.34)</td>
<td>1.57 (1.37-1.79)</td>
<td>1.75 (0.94-3.27)</td>
<td>2.12 (1.13-3.97)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

Figure 3. Hazard ratios (HRs) for the risk of nonfatal (n=12 191) 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.

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 studies34-35 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 trials32,33 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.

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.
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. 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-
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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Correspondence: Morten L. Hansen, MD, PhD, Department of Cardiology, Copenhagen University Hospital Gentofte, Niels Andersens Vej 65 2900, Hellerup, Copenhagen, Denmark (mlh@heart.dk).

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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