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Incidence, Source, Determinants, and Prognostic Impact of Major Bleeding in Outpatients With Stable Coronary Artery Disease

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ABSTRACT

BACKGROUND Although there is evidence that patients who experience major bleeding after an acute coronary event are at higher risk of death in the months after the event, the incidence and impact on outcome of bleeding beyond 1 year of follow-up in patients with stable coronary artery disease (CAD) are largely unknown.

OBJECTIVES The goal of this study was to assess the incidence, source, determinants, and prognostic impact of major bleeding in stable CAD.

METHODS We prospectively included 4,184 consecutive CAD outpatients who were free from any myocardial infarction (MI) or coronary revascularization for >1 year at inclusion. Follow-up was performed at 2 years, with major bleeding defined as a type ≥3 bleed using the Bleeding Academic Research Consortium (BARC) definition.

RESULTS There were 51 major bleeding events during follow-up (0.6%/year). Most events were BARC type 3a bleeds with 12 fatal bleeds (type 5). In most cases (54.9%), the site of bleeding was gastrointestinal. Major bleeding was significantly associated with mortality (adjusted hazard ratio: 2.89; 95% confidence intervals: 1.73 to 4.83; $p < 0.0001$). The increased risk of bleeding associated with vitamin K antagonist (VKA) treatment was particularly evident when VKA was combined with an antiplatelet therapy (APT). In contrast, the risk of cardiovascular death, MI, or nonhemorrhagic stroke did not differ in patients who received VKA + APT versus patients on VKA alone.

CONCLUSIONS In patients with stable CAD (i.e., >1 year, with no acute events), major bleeding events are rare, but such events are an independent predictor of death. When oral anticoagulation is required, concomitant APT should not be prescribed in the absence of a recent cardiovascular event. (J Am Coll Cardiol 2014;64:1430–6) © 2014 by the American College of Cardiology Foundation.

Bleeding has emerged as an important outcome in patients with coronary artery disease (CAD). There is evidence that patients who experience major bleeding when presenting with acute coronary syndrome or who are undergoing percutaneous coronary intervention are at a higher risk of death in the following months (1–5). Several mechanisms explain the deleterious effects of major bleeding, including the cessation of antithrombotic therapies, which induces an increased risk of acute stent thrombosis, myocardial infarction (MI), and cardiovascular death, blood transfusion, the prevalence of comorbidities in patients who bleed, and the deleterious effect of anemia (6–8). In contrast, there are

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limited data on the incidence, source, and prognostic impact of bleeding beyond 1 year of follow-up (i.e., in patients with stable CAD). However, these patients, who may be very long past or who may never have sustained an acute event, constitute the majority of CAD patients in the outpatient setting. We therefore designed the present study to assess the importance of bleeding and its impact on outcomes in patients with stable CAD who are at least 1 year past any coronary events (any MI or revascularization procedure).

SEE PAGE 1437

METHODS

POPULATION. The CORONOR (Suivi d'une cohorte de patients COROnariens stables en region NORd-Pas-de-Calais) study was a prospective multicenter study that enrolled 4,184 consecutive outpatients with stable CAD (9). Patients were prospectively included between February 1, 2010 and April 30, 2011 by 50 cardiologists. The cardiologists were selected on the basis of geographic distribution to provide a representative sample of the area's current cardiology practices in public universities, public institutions, and private centers. To be eligible for the CORONOR study, each patient had to fulfill the inclusion criteria. There were no exclusion criteria. This study was approved by the French medical data protection committee CCTIRS (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé) and authorized by the Commission nationale de l'informatique et des libertés for the treatment of personal health data. All patients consented to the study after being informed in writing of the study's objectives and treatment of data, as well as of their rights to object, of access, and of rectification.

INCLUSION CRITERIA OF THE CORONOR STUDY. Patients were categorized with stable CAD if they had documented CAD and were free from any MI and/or any coronary revascularization (either percutaneous coronary intervention or coronary artery bypass graft surgery) for at least 1 year at inclusion. Documented CAD was defined as all patients with a history of MI, history of coronary revascularization, and/or the presence of a coronary stenosis >50% on a coronary angiogram. To represent the real-life spectrum of stable CAD, patients with other cardiovascular or noncardiovascular illnesses or comorbidities were not excluded from the study.

STUDY DESIGN. Data collection. At the initial visit, attending physicians prospectively completed the case record forms, which contained information regarding demographic and clinical characteristics of the patients, including usual cardiovascular risk factors and treatments. During the outpatient visit, the investigators reviewed the patients' current drug treatment and entered all prescribed drugs on the case record form.

Objective, follow-up, definitions, and endpoints. The objectives of this analysis were to assess the incidence, source, determinants, and prognostic impact of major bleeding in patients with stable CAD. A 2-year clinical follow-up was performed at outpatient visits or by contacting the general practitioner. We collected data on death, MI, stroke, and major bleeding. All clinical events were adjudicated blindly by 2 investigators, or by 3 investigators in case of disagreement, according to pre-specified definitions. The cause of death was determined after a detailed review of the circumstances of death and was classified as cardiovascular or noncardiovascular. Deaths from unknown causes were considered cardiovascular. Bleeding events were classified using the Bleeding Academic Research Consortium (BARC) definition (10). Information on BARC type 1 and 2 bleeds was not available in our registry. Although not in the BARC definitions, for the purpose of this study, we arbitrarily defined major bleeding as all BARC type ≥3 events. To assess ischemic risk, a composite endpoint was defined as cardiovascular death, MI, or nonhemorrhagic stroke.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as absolute numbers and percents. We used the chi-square test or the Fisher exact test for the comparison of categorical variables and the Student unpaired *t* test for the comparison of continuous variables as appropriate. Cumulative event rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard analyses were performed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). For each variable, the proportional hazards assumption was tested visually using Kaplan-Meier curves and by examining a plot of -ln [-ln(survival time)] against the ln(time). In addition, the proportional hazard was assessed and satisfied by including an interaction time-dependent term in the multivariable Cox regression analysis. All statistical analyses were performed using STATA 9.2 software (STATA Corporation, College Station, Texas). Statistical significance was assumed at p value <0.05.

RESULTS

The baseline characteristics of the patients included in the CORONOR study have been reported previously

ABBREVIATIONS AND ACRONYMS

APT = antiplatelet therapy
BARC = Bleeding Academic Research Consortium
CAD = coronary artery disease
CIs = confidence intervals
eGFR = estimated glomerular filtration rate
HR = hazard ratio
MI = myocardial infarction
VKA = vitamin K antagonist