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Review article

Direct oral anticoagulant and antiplatelet combination therapy: Hemorrhagic events in coronary artery stent recipients

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ABSTRACT

Direct oral anticoagulant (DOAC) use is growing as monotherapy and combined with platelet inhibitors. The safety of such combination therapy, especially in comparison to regimens including warfarin, in real world populations remains uncertain. We investigated hemorrhage associated with DOAC and antiplatelet combination therapy in a cohort of elderly coronary artery stent recipients. We employed Medicare data 2010–2013 for a 40% random sample of beneficiaries enrolled in inpatient, outpatient and prescription benefits. We used Cox proportional hazards models to examine the association of the combination anticoagulant (DOAC or warfarin) plus antiplatelets with major hemorrhage events (upper gastrointestinal or intracranial) in the 12 months following stent placement. We identified 70,900 stent recipients. 14.4% had atrial fibrillation (AF) diagnosis preoperatively. Among the 24.5 million observation days, exposure distribution was: 73.8% antiplatelets only, 4.7% antiplatelets plus warfarin, 0.6% antiplatelets plus DOAC, 2.2% warfarin only, 0.3% DOAC only and 18.4% no observed antiplatelets or anticoagulant. Overall, 8,029 patients (11.3%) experienced major hemorrhage. Among AF patients, compared to antiplatelets only, DOAC plus antiplatelets was associated with increased hemorrhage risk (HR, 1.94; 95%CI, 1.48–2.54); warfarin plus antiplatelets conferred comparable bleed risk (HR, 1.69; 95%CI, 1.47–1.94). In the non-AF group, compared to antiplatelets alone, combination DOAC plus antiplatelets (HR, 3.09; 95%CI, 2.15–4.46), and warfarin plus antiplatelets (HR, 2.21; 95%CI, 1.97–2.48) conferred greater bleed risk. Among elderly coronary artery stent recipients with AF, the two drug combinations, DOAC plus antiplatelets and warfarin plus antiplatelets, were associated with similarly increased risk of major hemorrhage compared to antiplatelets alone.

1. Introduction

Since their 2010 market introduction, direct oral anticoagulants (DOACs) have grown in popularity [4–6,12,19,21]. They address the unpredictable bioavailability, and requisite laboratory monitoring that make warfarin use challenging and inconvenient [21]. The use of DOACs has seen rapid growth in atrial fibrillation (AF) patients, and in patients with acute coronary syndromes (ACS) [4–6,12,19,21]. In patients with multiple comorbidities [14] who undergo coronary artery stenting, DOACs are increasingly used in combination with antiplatelets [2,3,17,18,22]. The safety of this regimen and its association with hemorrhagic events remains uncertain.

Randomized trials have investigated the safety of DOAC plus antiplatelet therapy in patients with ACS [2,3,17,18,22]. All phase II trials[2,3,18,22] have demonstrated a definite increase in bleeding with the combination therapy in comparison to antiplatelet treatment alone. A phase III study [3] with apixaban, in high-risk ACS patients, was terminated prematurely due to increased bleeding, without evidence for decreased major cardiovascular events. In contrast, a phase III study [17] of rivaroxaban in ACS patients showed significant reductions in the composite endpoint of death, myocardial infarction, and stroke, but an increased rate of major bleeding. Safety examined in the context of these carefully controlled clinical trials, in select populations, is not always apparent when such products are used in real-world settings [7]. No prior investigation explores the relative safety of the combined use of anticoagulant and antiplatelet treatment option in a large cohort from the community. The increasing use of DOACs especially in combination with antiplatelets, in our aging population, makes

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relative safety in real world settings especially important to clinicians.

To examine safety of DOAC and antiplatelet combination therapy outside of the clinical trial setting, we studied a cohort of Medicare patients undergoing cardiac stenting and examined major hemorrhagic events associated with receipt of medication combinations (antiplatelets plus DOAC or antiplatelets plus warfarin). Our models used time-varying exposure to reflect real-world prescription fill patterns; we controlled for diverse patient characteristics and comorbidities and stratified on atrial fibrillation diagnosis at time of stent placement.

2. Methods

2.1. Data and cohort

Using a 40% random sample of the Medicare beneficiaries enrolled in fee-for-service Medicare Parts A (inpatient), B (outpatient) and D (prescription) coverage, residing in the U.S., we identified a cohort of patients receiving inpatient coronary artery stents in 2010–2012 (Table S1). The year 2010 was selected as the baseline year because DOACs appeared on the market in 2010. Each patient's first stent episode between 2010 and 2012 served as the index stent episode. Patients dying within 30 days of the index stent episode were excluded. Patients not enrolled Medicare Part D or not using prescription benefits (i.e. no prescription fill record) in the 120 days preceding index stent were also excluded. We also excluded cancer patients because of their potentially complicated anticoagulation profile.

2.2. Exposure

We used the Medicare Part D Prescription Drug Event file (PDE) to identify prescription fills prior to and following index stent episode. Pre-index prescription fills were used to ascertain prescription supply prior to stent. For each day in the observation period, following index stent receipt, a warfarin, DOAC (dabigatran, rivoroxaban), or antiplatelets exposure category was assigned to each patient for each day based on fill date and days supply dispensed. For each patient, exposure was allowed to vary over time based on prescription fill events. Exposure was assumed to begin on the date of the prescription fill event; overlapping supplies were carried forward (e.g. a 90 day supply filled 80 days after a previous 90 day supply resulted in a 10 day supply carried forward). Patients were considered to have stopped medication use if no repeat fill occurred after 120% of days supply had elapsed (e.g. no repeat fill within 108 of a 90 day fill was classified as discontinuation of the medication 108 days after last observed fill). Prescription fill events occurring in the 120 days prior to stent receipt were carried forward following index stent hospitalization when supply was sufficient to cover post discharge days. We assumed no consumption of home medication supply for the full length of index and subsequent hospitalizations; and we assumed medication use resumed after discharge.

2.3. Outcome

The primary outcome of interest was major hemorrhagic events (upper gastrointestinal and intracranial), identified from the Emergency Room visit or on an inpatient claim. Hemorrhages were classified as upper gastrointestinal, intracranial (traumatic, non-traumatic), and other (Table S1). Hemorrhages in the first 30 days after stenting were considered periprocedural morbidity and were conservatively excluded. In sensitivity analysis we additionally considered this time period as seven or 14 days. The direction and magnitude of observed associations in these sensitivity analyses were similar to those of the main analysis; these analyses are not reported further.

2.4. Covariates

From index episode (up to 10 diagnosis codes), patients were stratified based on their atrial fibrillation (AF) status (*International Classification of Disease* (ICD-9) diagnostic code 427.31). Covariates included in the models were age, gender, race (categorized as Black, Hispanic, and other based on Medicare denominator file variable), Medicare Part D low income subsidy (a marker for income 150% or less of federal poverty level, dichotomized), [1] and index drug-eluting stent placement (versus bare metal). The following comorbidities, present at the time of the index episode were also included: chronic obstructive lung disease and/or tobacco use (combined as "tobacco exposure" proxy variable), diabetes mellitus, hypertension, myocardial infarction, ischemic stroke, acute coronary syndrome (ACS), congestive heart failure, chronic kidney disease, end-stage renal disease, peripheral vascular disease, liver disease, alcoholism, mechanical heart valve, long-term anticoagulation, pulmonary embolism/deep vein thrombosis, and hypercoagulable state (Table S1).

In addition, models adjusted for other time-varying drug exposure during observation due to their possible contribution to bleed risk: antibiotics, proton pump inhibitors, cyclooxygenase-2 (COX-2) inhibitors, oral glucocorticoids and prescription non-selective non-steroidal anti-inflammatories (NSAIDs).

We calculated bleed risk for each patient using the claims based "Anticoagulation and Risk Factors in Atrial Fibrillation" (ATRIA) score [9] for the index episode; this is reported in Table 1 as a baseline characteristic but we did not include this score in the models, because we used other covariates listed above (due to the significant overlap).

2.5. Statistical analysis

The main analysis modeled primary outcome on current treatment (a time-dependent exposure) adjusted for the covariates listed above, using a Cox proportional hazards model. Data were structured as follows. The unit of analysis was a person day until death, first bleed event, disenrollment from fee for service Medicare Parts A, B or D coverage or end of 12-months post index observation time. The dependent variable was the major hemorrhagic event, and the exposure of interest was medication receipt status (DOAC only, warfarin only, DOAC plus antiplatelets, warfarin plus antiplatelets, or none of the above; antiplatelet receipt only was the reference exposure category).

Pre-specified subgroup analyses were run, stratifying on AF diagnosis status (at time of index (stent placement) hospitalization). In addition, the models were repeated for the individual components of the primary outcome, specifically: upper gastrointestinal hemorrhage and intracranial hemorrhage. We also repeated the analyses including the "other hemorrhage" category in the composite hemorrhage outcome. Finally, the main analyses were repeating separating clopidogrel (dominant anti-platelet) from all other anti-coagulants.

All probability values were the result of two sided tests and the level of statistical significance was set at 0.05. SAS 9.4 (SAS Institute, Cary, North Carolina) was used for analysis. This study was approved by the Dartmouth Committee for Protection of Human Subjects.

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