Risk of Lower and Upper Gastrointestinal Bleeding, Transfusions, and Hospitalizations With Complex Antithrombotic Therapy in Elderly Patients

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Background—Complex antithrombotic therapy (CAT) prescribed to elderly patients increases the risk of gastrointestinal bleeding. We quantified upper (UGIE) and lower gastrointestinal (LGIE) events, transfusions, and hospitalizations in a national cohort of elderly veterans prescribed CAT.

Methods and Results—Veterans ≥60 years of age prescribed anticoagulant-antiplatelet, aspirin (ASA)-antiplatelet, ASA-anticoagulant, or triple therapy (ie, TRIP, anticoagulant-antiplatelet-ASA) were identified from the national pharmacy database (October 1, 2002 to September 30, 2008). Prescription-fill data were linked to Veteran Affairs and Medicare encounter files, each person-day of follow-up was assessed for CAT exposure, and outcomes were defined by using diagnostic code algorithms derived following chart abstraction. Incidence density ratios (compared with the reference category of no CAT) and survival analysis was conducted. Among 78 133 veterans (98.6% white; mean age, 72.3 [standard deviation 7.7]), 64% were prescribed ASA-antiplatelet and anticoagulant-antiplatelet and 6% were prescribed TRIP. The incidence of UGIE was 20.1/1000 patient-years, and the incidence of LGIE was 70.1/1000 patient-years. ASA-anticoagulant and TRIP were associated with the highest incidence of transfusion and hospitalization. A 40% to 60% increased risk of UGIE was observed with all strategies. LGIE was 30% higher with anticoagulant-antiplatelet, and transfusion increased with ASA-anticoagulant (hazard ratio, 6.1; 95% confidence interval, 5.2–7.1) and TRIP (hazard ratio, 5.0; 95% confidence interval, 4.2–5.8). Increased risk of hospitalization was noted with all strategies. The number needed to harm for UGIE or LGIE ranged from 52 to 65 and 15 to 23, respectively. The number needed to harm for hospitalization was 39 (anticoagulant-antiplatelet), 34 (ASA-anticoagulant), 67 (ASA-antiplatelet), and 45 (TRIP) patients.

Conclusions—Among elderly patients, CAT-related LGIE and UGIE are clinically relevant risks resulting in increased hospitalizations and transfusions. **(*Circulation*. 2013;128:1869-1877.)**

Key words: antiplatelet agents ■ antithrombotic agents ■ assessment, patient outcome ■ blood component transfusion ■ hospitalization

Over 700 000 Americans have cerebrovascular disease, 13 million have coronary artery disease, and 12 million have peripheral arterial disease.[1] These conditions often coexist,[2] resulting in the prescription of multiple antithrombotic medications, including anticoagulants (ie, warfarin) and antiplatelet agents (ie, ticlopidine, clopidogrel, or aspirin [ASA]). When prescribed in dual or triple combinations, these regimens are considered complex antithrombotic therapies (CATs). Their efficacy in preventing secondary cardiac events must be balanced with their increased risk of gastrointestinal (GI) bleeding (ie, upper gastrointestinal events [UGIEs], including ulcer bleeding and perforation and obstruction; and lower gastrointestinal events [LGIEs], including diverticular bleeding, hemorrhoidal bleeding, and bleeding from polyps and other vascular lesions).

Clinical Perspective on p 1877

The burden of CAT-related GI bleeding remains largely unknown among elderly patients, an emerging population of patients systematically excluded from pivotal CAT trials. The best evidence would come from a double-blind, randomized, controlled trial with multiple arms that assesses GI bleeding as the outcome of interest. However, this would be unethical, given the known GI bleeding risk factor of advanced age.[3] To quantify the risk of CAT-related GI bleeding, we examined

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Received March 26, 2013; accepted August 28, 2013.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.004747/-/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.004747**

UGIE and LGIE risk and associated transfusions and hospitalizations in a national cohort of elderly patients. Our goal was to quantify the real-life number needed to harm (NNH) associated with CAT-related GI bleeding and to measure 2 patient-centered outcomes (ie, need for transfusion and bleeding requiring hospitalization) in a national cohort of elderly patients.

Methods

Study Design and Data Sources

We conducted a retrospective cohort study of veterans, from October 1 2002 to September 30, 2008, with the use of national administrative data from 176 Department of Veteran Affairs (VA) facilities in the United States. The Baylor College of Medicine Institutional Review Board, Houston, TX, approved the research protocol. Patient prescriptions were identified from the DSS National Data Extracts, accessed from the Austin Automation Center of the VA, which provided key prescription-fill data, including facility, dates of fill, days' supply, and total quantity of drug dispensed. Inpatient data were obtained from the Patient Treatment File, outpatient data were obtained from the Outpatient Clinic File, and the VA Vital Status File was used to capture deaths reported by the Beneficiary Identification and Record Locator Subsystem, Medicare Vital Status file, and Death Master File as compiled by the Social Security Administration. Each individual's Medicare records were also examined by using MedPAR, inpatient and outpatient files from 2002 to 2008, to ensure complete case ascertainment at non-VA facilities.

Study Population

Veterans 60 to 99 years of age, with a filled prescription for an anticoagulant, ASA, or antiplatelet agent, were identified for cohort inclusion (Table I in the online-only Data Supplement). The first prescription in the study period was considered the index prescription and designated as t_0. Patients were followed to the end of the observation period (September 30, 2008) or until the end of prescription-fill dates in that period of observation for the drugs of interest or until first occurrence of an event of interest. Eligibility criteria included a history of previous VA encounters within 365 days before the index prescription to ensure continuous VA enrollment. Veterans prescribed drugs of interest in the 180 days before the index prescription date were excluded to ensure a true incident cohort.

Chart-Validation Study

To ensure accurate case ascertainment of outcomes of interest (CAT-related UGIE, LGIE, transfusions, and hospitalizations), we identified 200 patients prescribed an anticoagulant-antiplatelet (ACAP), ASA-antiplatelet (ASAP), ASA-anticoagulant (ASAC) therapy, or anticoagulant-antiplatelet-ASA (TRIP) for at least 7 days at the Houston VA in the first 6 months of 2003. We identified 66 potential cases of CAT-related bleeding by the presence of *International Classification of Diseases, Ninth Revision* (ICD-9) codes in the Patient Treatment File for gastric (531), duodenal (532), peptic (533), or gastrojejunal ulcer (534); ulceration/perforation of the intestine (569.82 and 569.83); GI hemorrhage (578); diverticulosis (562); occult blood (792) and transfusion (procedural codes [*Current Procedural Terminology*], ICD-9 codes and surgical codes). We also identified patients with evidence of Current Procedural Terminology codes for upper or lower endoscopy and ICD-9 codes for surgical endoscopy or surgical GI bleeding (diagnostic or hemostatic) procedures.

A test sample was created by matching each potential case by age and sex to 134 potential controls prescribed a CAT regimen during the same period, but without a bleeding-related diagnostic or procedure code. A full list of administrative codes used in the chart-validation study is available from the authors. The charts of cases and controls were abstracted for confirmation of a CAT-related UGIE, LGIE, transfusion, or inpatient hospitalization, and a diagnostic algorithm was derived to maximize positive and negative predictive values. These algorithms were then validated in a second independent sample of 100 patients from the last 6 months of 2003.

Outcomes of Interest

Our final diagnostic case-ascertainment algorithm defined CAT-related UGIE as the presence of an ICD-9 code 531, 532, 534, and 569 in any position of the Patient Treatment File, or code 578 and 533 and a Current Procedural Terminology code for upper endoscopy in any position. This algorithm had a positive predictive value of 83% and negative predictive value of 100%. The CAT-related LGIE algorithm of ICD-9 code 562 or 578 with a Current Procedural Terminology or surgical code for lower GI endoscopy in any position had a positive predictive value of 83% and a negative predictive value of 91%. We did not include occult bleeding (ICD-9 code 792) in either algorithm, because we could not ascertain the source of the bleeding reliably during primary chart abstraction of the test or validation samples. The diagnostic codes for transfusion had a positive predictive value of 96% and negative predictive value of 98%. Other investigators have previously well validated the Patient Treatment File for hospitalization.[4] We attributed hospitalization to the CAT-related bleeding event, if it occurred within 7 days of hospitalization encounter (ie, ensuring a tight temporal window).

Assessment of Drug Exposure

Prescription-fill data were assessed on a day-by-day basis; an individual exposure period started at t_0 and ended with final termination of days' supply. With the use of published methodology,[5] exposure was defined to be 1.25×(number of days supplied) to extend exposure by a conservative grace period during which pharmacologically induced GI bleeding may occur. An individual would be considered off the CAT regimen, ie, time periods with no exposure, when that individual's longitudinal prescription-fill data did not demonstrate prescription of the drugs of interest. Each person-day of follow-up within the exposure period was assessed for the presence of ACAP, ASAP, ASAC, TRIP (defined by overlapping prescriptions of 5 days or more for each drug of interest), or none. Exposure to CAT strategies and other pharmacological risk factors was considered in a time-varying pattern, assessed for each individual, creating a unique record for each interval for each distinct pattern of prescription-fill data.

Potential Risk Factors and Confounding Variables

Pharmacological risk factors, including prescription of nonsteroidal anti-inflammatory drugs (NSAIDS), both traditional and cyclooxygenase-2 selective, steroids, selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors, low-molecular-weight heparin, and heparin overlapping with CAT prescription, were identified (Table II in the online-only Data Supplement). We also assessed exposure to proton pump inhibitors (PPIs), statins, and SSRIs, shown to modify GI bleeding risk.[6,7] Models were also adjusted for demographics (age, sex, race), *Helicobacter pylori* infection (using our previously validated algorithm),[8] and a time-dependent Elixhauser comorbidity Index score[9] (Table 1). Unadjusted analyses were used to assess patient characteristics that might be associated with a greater likelihood of being prescribed a particular prescription strategy (ie, confounding by indication); prescription of a PPI or triple therapy were associated with unique patient characteristics that influenced outcomes in unadjusted analyses. Thus, a propensity score[10] was calculated to estimate the conditional probability of a patient being prescribed a PPI or TRIP. Survival analyses were then stratified by propensity score quintiles to adjust for bias when estimating treatment effects,[11] and treatment effect was assessed within each stratum.

Table 1. Baseline Characteristics of Cohort (n=78 133), as Stratified by CAT Prescription Strategy at Index Prescription

	CAT Prescription Strategy				
Characteristic	ACAP (n=10 769)	ASAC (n=22 897)	ASAP (n=39 496)	TRIP (n=4971)	*P* Value
Average age, y (SD)	74.1 (7.2)	72.5 (8.0)	72.2 (8.1)	71.2 (8.0)	<0.0001
60–69 y, %	27	39	40	45	
70–79 y, %	47	39	38	37	
≥80 y, %	26	23	22	18	
Male, %	99.0	98	99	99	0.0002
Race/ethnicity, %					<0.0001
White	40	64	52	71	
Black	2	11	8	10	
Hispanic	1	3	5	5	
Other/Unknown	56	23	35	14	
Comorbidity, %					<0.0001
Elixhauser 0–1	18	15	24	15	
Elixhauser ≥2	82	85	76	85	
PPI use, %	32	39	35	49	<0.0001
NSAID/Coxib use, %	7	12	12	12	<0.0001
Steroid use, %	4	7	3	6	<0.0001
Statin use, %	69	60	71	82	<0.0001
SSRI use, %	12	15	15	15	<0.0001
History of UGIE, %	12	12	11	11	0.0004
History of GERD, %	34	30	33	32	<0.0001
H pylori, %	1	1	1	1	0.103
History of CVA, %	18	14	17	14	<0.0001
History of MI, %	20	11	22	42	<0.0001
History of IHD, %	84	65	80	90	<0.0001
Hypertension, %	90	90	88	88	<0.0001
Atrial fibrillation, %	59	54	11	25	<0.0001
PCI/CABG, %	30	6	23	19	<0.0001
Diabetes mellitus, %	41	41	41	44	0.0012

ACAP indicates combination anticoagulant and antiplatelet therapy; ASAC, combination aspirin and anticoagulant therapy; ASAP, combination aspirin and antiplatelet therapy; CAT, complex antithrombotic therapy; coxib, cyclooxygenase-2 selective inhibitors; CVA, cerebrovascular accident (stroke); GERD, gastroesophageal reflux disease; IHD, ischemic heart disease; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PCI/CABG, percutaneous coronary intervention/coronary arterial bypass graft; PPI, proton pump inhibitor; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; TRIP, triple therapy of aspirin, antiplatelet and anticoagulant agents; and UGIE, upper gastrointestinal event.

Analytic Methods

The χ^2 test and analysis of variance were used to test for differences in demographic and clinical characteristics among subgroups. The incidence density (number of events/person-years of follow-up) of UGIE, LGIE hospitalization, and transfusion was calculated for 2.3 years following the index prescription. Incidence density ratios allowed comparison of rates among CAT exposure subgroups, including the reference category of none. Cox proportional hazards models were constructed censoring patients for end of follow-up period without event, last day of CAT exposure, or death. The Statistical Analysis System version 9.1 (SAS Institute, NC) PHREG procedure was used to analyze data at each UGIE, LGIE hospitalization, and transfusion comparing individuals with the event with those still uncensored without the event. The Wald χ^2 test was used to test for the significance of the influence of each independent variable. Hazard ratios and their 95% confidence intervals (CIs) were calculated. The magnitude of GI bleeding risk was also quantified by the NNH associated for each CAT prescription of interest, assuming the patient had been prescribed the regimen for at least 80% to 100% of his/her individual exposure time. Established methodology[12] was used to estimate NNH during the first 365 days of observation by using the equation NNH=1/(survival probability in the control group × hazard ratio comparing the treatment groups − survival probability in the control group).

Results

The study population included 78 133 veterans (98.6% white; mean age, 72.3 [standard deviation (SD) 7.7]) prescribed dual or triple CAT (Table 1); 64% had been prescribed an antiplatelet-based strategy (ASAP and ACAP), and 6% had been prescribed TRIP. Baseline characteristics are described in Table 1. There were no significant differences among CAT strategies with regard to history of UGIE or gastroesophageal reflux disease, and concomitant NSAID prescription overall ranged from 7% to 34%. The prevalence of *H pylori* infection was also similar among subgroups (*P*=0.103).

The mean duration of follow-up time for cohort members was 838 days (SD, 548 days) or 2.3 years. The mean duration of time on ACAP was 548 days (SD, 488), the mean duration of time on ASAP was 632 days (SD, 495), the mean duration of time on ASAC was 493 days (SD, 475), and the mean duration of time on TRIP was 355 days (SD, 398). The time during which cohort members were on no drugs of interest (ie, no exposure/none) was 317 days (SD, 335). The unadjusted incidence density and incidence density ratio for each outcome of interest, during the 2.3 years of total observation, are shown in Table 2 and are presented with the reference category of none (ie, no CAT exposure). The overall incidence of UGIE with antithrombotic use was 20.1/1000 person-years of follow-up. The greatest risk was observed with triple CAT.

Table 2. Incidence Density Rates and Incidence Density Ratios of Outcomes of Interest (n=78 133)

Exposure Category	Events (n)	PY of Follow-Up	Incidence Density* (95% CI)	Incidence Density Ratio† (95% CI)
Outcome: UGIE				
None	100	5253	19.0 (15.5–23.2)	Reference
ACAP	377	20 703	18.2 (16.4–20.1)	1.0 (0.9–1.0)
ASAC	849	36 295	23.4 (21.8–25.0)	1.2 (1.1–1.4)
ASAP	1337	76 205	17.5 (16.6–18.5)	0.9 (0.9–1.0)
TRIP	354	12 845	27.6 (24.8–30.6)	1.4 (1.3–1.7)
Anticoagulant monotherapy	204	8541	23.9 (20.7–27.4)	1.3 (1.2–1.4)
Antiplatelet monotherapy	165	8280	19.9 (17.0–23.2)	1.0 (1.0–1.1)
Aspirin monotherapy	226	11 201	20.2 (17.6–23.0)	1.1 (1.0–1.1)
Outcome: LGIE				
None	268	4651	57.6 (50.9–65.0)	Reference
ACAP	1471	18 987	77.5 (73.6–81.5)	1.3 (1.3–1.4)
ASAC	2471	33 591	73.6 (70.7–76.5)	1.3 (1.2–1.4)
ASAP	4766	70 808	67.3 (65.4–69.3)	1.2 (1.1–1.2)
TRIP	871	11 782	73.9 (69.1–79.0)	1.3 (1.2–1.4)
Anticoagulant monotherapy	546	7407	73.7 (67.7–80.2)	1.3 (1.2–1.4)
Antiplatelet monotherapy	474	7359	64.4 (58.7–70.5)	1.1 (1.1–1.2)
Aspirin monotherapy	660	9929	66.5 (61.5–71.7)	1.2 (1.1–1.2)
Outcome: transfusion				
None	262	4696	55.8 (49.2–63.0)	Reference
ACAP	917	20 423	44.9 (42.0–47.9)	0.7 (0.6–0.8)
ASAC	3333	34 065	97.8 (94.6–101.2)	1.6 (1.5–1.8)
ASAP	2613	74 115	35.3 (33.9–36.6)	0.6 (0.5–0.7)
TRIP	1339	11 317	118.3 (112.1–124.8)	2.1 (1.8–2.4)
Anticoagulant monotherapy	671	7532	89.1 (82.5–96.1)	1.6 (1.4–1.7)
Antiplatelet monotherapy	306	7815	36.2 (34.9–43.8)	0.7 (0.7–0.8)
Aspirin monotherapy	635	9819	64.7 (59.7–69.9)	1.2 (1.1–1.2)
Outcome: hospitalization				
None	171	5059	33.8 (28.9–39.3)	Reference
ACAP	688	20 313	33.9 (31.4–36.5)	1.0 (1.0-1.0)
ASAC	1438	35 590	40.4 (38.3–42.5)	1.2 (1.1–1.3)
ASAP	2195	75 255	29.2 (28.0–30.4)	0.9 (0.8–0.9)
TRIP	556	12 498	44.5 (40.9–48.3)	1.3 (1.2–1.4)
Anticoagulant monotherapy	336	8175	41.1 (36.8–45.7)	1.2 (1.1–1.3)
Antiplatelet monotherapy	257	8097	31.7 (28.0–35.9)	0.9 (0.9–1.0)
Aspirin monotherapy	399	10 795	37.0 (33.4–40.8)	1.3 (1.2–1.4)

ACAP indicates combination anticoagulant and antiplatelet therapy; ASAC, combination aspirin and anticoagulant therapy; ASAP, combination aspirin and antiplatelet therapy; CAT, complex antithrombotic therapy; CI, confidence interval; LGIE, lower gastrointestinal event; PY, person-years; TRIP, triple therapy of aspirin, antiplatelet and anticoagulant agents; and UGIE, upper gastrointestinal event.

*Where the incidence density represents a measure of the instantaneous rate of development of the outcome of interest given 1000 PY of exposure.

†Incidence density ratio given the reference category of no CAT exposure.

The overall risk of lower GI bleeding was 70.1/1000 person-years, with greatest risk seen with ACAP and TRIP. Patients prescribed ASAC and TRIP had the greatest incidence of transfusion and hospitalization. The incidence density ratio compared each incidence density with no CAT exposure and was stable in most cases. It did increase with each CAT strategy, with the exception of when the incidence density of the none category for that outcome (ie, transfusion, hospitalization) exceeded that of a specific CAT prescription strata. In these CAT strata, the incidence density ratio appeared falsely protective; however, the 95% CI overlap suggested no significant difference.

Multivariate analysis (Figure) considered the risk of patients prescribed CAT for 80% to 90% of the exposure period (in comparison with periods with no CAT exposure) and adjusted for demographic characteristics, Elixhauser comorbidity score, prescription channeling, geographic location, VA priority group, clinical risk factors, and multiple time-dependent pharmacological covariates, including concurrent NSAID, steroid, PPI, statin, and SSRI use. These models revealed a 40% to 60% increased risk of UGIE with all CAT strategies. Among patients prescribed ACAP there was a 30% increase in LGIE. The risk of transfusion was increased 6-fold with ASAC prescription (hazard ratio, 6.1; 95% CI, 5.2–7.1) and

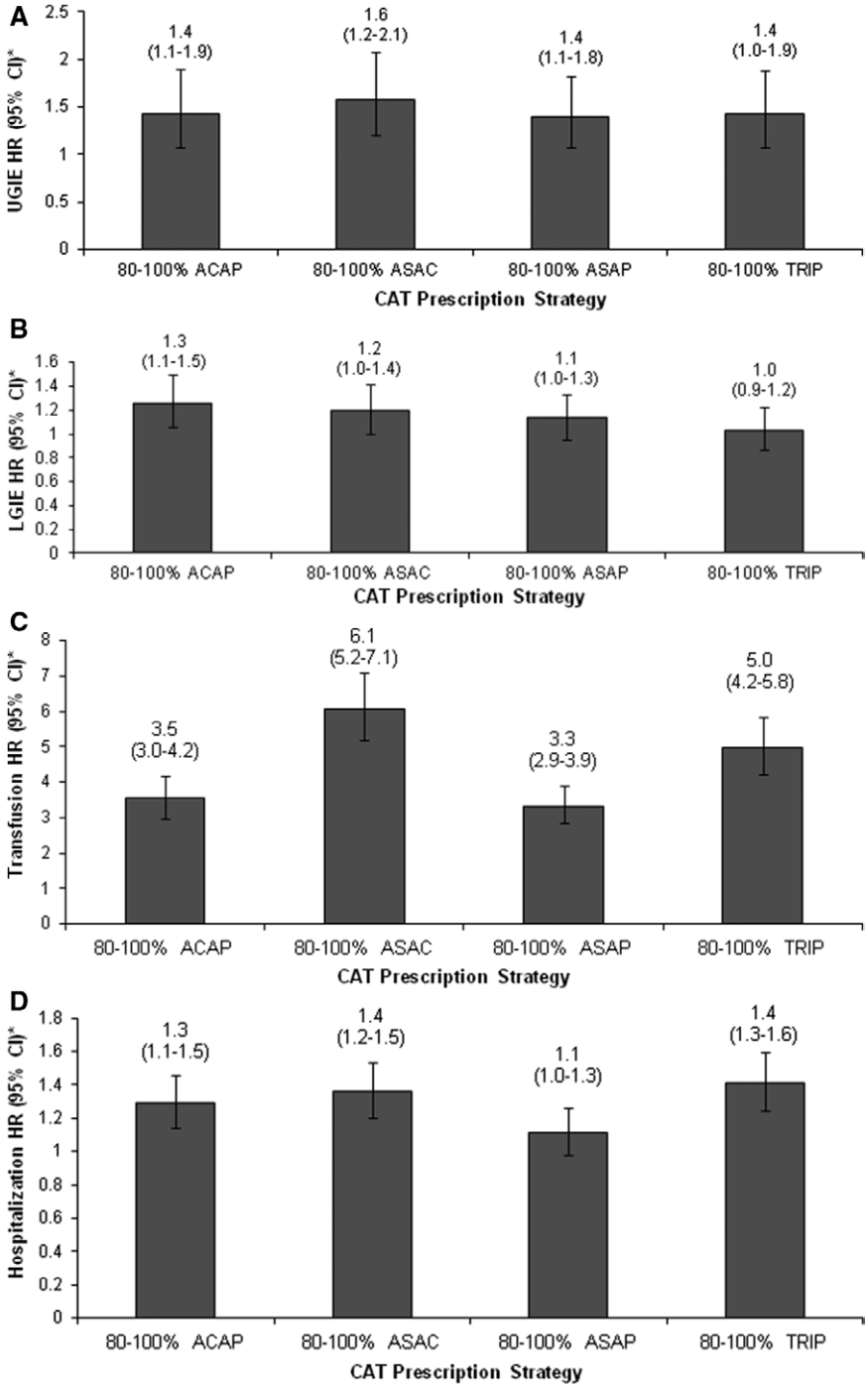

Figure. Adjusted cumulative percentage of time on CAT prescription strategy and risk of UGIE (**A**), LGIE (**B**), transfusions (**C**), and hospitalizations (**D**). *Where comparison group is 0% on therapy. All multivariate analyses adjusted for demographic characteristics, Elixhauser comorbidity, prescription channeling, geographic location, priority group, clinical risk factors, and multiple time-dependent pharmacological covariates including NSAIDs, steroids, PPI, statins, and SSRI. ACAP indicates combination anticoagulant and antiplatelet therapy; ASAC, combination aspirin and anticoagulant therapy; ASAP, combination aspirin and antiplatelet therapy; CAT, complex antithrombotic therapy; CI, confidence interval; HR, hazard ratio; LGIE, lower gastrointestinal event; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitor; TRIP, triple therapy of aspirin, antiplatelet, and anticoagulant agents; and UGIE, upper gastrointestinal event.

5-fold higher with TRIP prescription (hazard ratio, 5.0; 95% CI, 4.2–5.8). The increased risk of hospitalization associated with all strategies ranged from 10% with ASAP to 40% with ASAC and TRIP in comparison with periods with no CAT exposure.

The NNH was calculated in the first 365 days following index prescription to report the number of patients needed to be treated with a particular drug strategy to incur 1 additional outcome of interest (Table 3). As few as 52 patients (95% CI, 20–210) prescribed TRIP, 56 patients prescribed ASAC (95% CI, 22–231), and 65 patients prescribed ACAP (95% CI, 24–379) would result in 1 additional UGIE. Far fewer patients were required to generate an additional LGIE. The NNH for ASAC, ASAP, and ACAP ranged from 15 to 19, respectively. The LGIE NNH for TRIP was slightly greater at 23. As few as 16 patients prescribed ASAC resulted in an additional transfusion risk; risk of transfusion was least among patients prescribed ASAP. Table 3 demonstrates the frequency of expected hospitalizations associated with the prescriptions of interest. The NNH to incur 1 additional GI bleeding-related hospitalization was 39, 34, 67, and 45 patients for ACAP, ASAC, ASAP, and TRIP, respectively (Table 3).

Sensitivity Analyses

A 1-way threshold sensitivity analysis with the use of Monte Carlo methodology[13] generated replicates of the original data set assuming random and nonrandom misclassification of over-the-counter ASA, NSAIDs, or PPI. We set the drug-use indicator for each patient at 10%, 25%, and 50% misclassification for each drug and examined the impact of variation on CAT-related bleeding risk. The results for our outcomes of interest did not meaningfully change in magnitude or direction of effect (data not shown), confirming the robustness of our initial models.

Discussion

Secondary cardioprotection trials[14–19] reveal an absolute benefit of CAT ranging from ≈0.6% to 16.5%. However, this benefit must be balanced against the risk of GI bleeding. An expert consensus published jointly by the American Heart Association, the American College of Gastroenterology, and the American College of Cardiology[20] highlighted the GI risk of dual and triple antithrombotic drug combinations, the magnitude of which remained poorly characterized in an effectiveness setting. This study quantifies the GI bleeding risk of mono, dual, and triple antithrombotic therapies, highlighting the real-life burden associated with commonly prescribed CAT strategies among older adults, individuals previously excluded from randomized, controlled CAT trials. To our knowledge, this is the largest study to investigate the GI bleeding risk associated with both the upper and lower GI tract that also quantifies that risk as patient-centered outcomes: need for blood transfusion and bleed-related hospitalization. This real-world sample of elderly, comorbid patients demonstrated the substantial risk for lower and upper GI bleeding following complex antithrombotic therapy and the high rate of hospitalization and need for transfusions associated with these GI bleeding events.

The average age of our population (72.5 years) reflects the rapidly growing cohort of elderly cardiovascular patients and mirrors the increased use of interventional cardiology and modern surgical management of atherosclerotic disease among elderly Americans (≥70 years). Frequently, more complex pharmacological regimens are recommended to treat a postintervention population, reflected (in our study) in a much higher proportion of TRIP therapy in those ≥70 years than anticipated. These individuals were also more likely to be coprescribed NSAIDs, SSRIs, and steroids, further increasing their risk of GI bleeding events. The incidence-density, multivariate-analysis, and NNH data help quantify the real-life risk of elderly patients prescribed CAT; the NNH to incur an additional LGIE was as low as 15 with ASAC and 23 with TRIP. An additional UGIE occurred after 52 patients were prescribed TRIP, and after 56 patients were prescribed ASAC. The NNH of transfusion risk was in the range of 16 to 51 patients, and the number of patients required to incur 1 additional bleed-related hospitalization was as low as 34 (with ASAC) to 67 (with ASAP). These results should give pause to the routine use of CAT therapy in elderly patients burdened by polypharmacy and provide concrete evidence to inform discussions between physicians and their elderly patients about medication risks and adherence.

Similarly to our study, Grove et al[21] highlighted GI adverse events associated with clopidogrel in a nationwide Dutch population-based cohort. Their results suggested an NNH ranging from 33 to 58 patients. Unlike the Dutch cohort, ours was older, sicker, and larger, with 78 133 members. The few previous studies evaluating LGIE have found that LGIE is more common than UGIE (74% versus 26%, P=0.012) in patients taking dual-antiplatelet therapy[22] and associated

Table 3. One-Year Number Needed to Harm (NNH) for Patients Who Spend 80% to 100% Time on CAT

1-Year NNH*	ACAP	ASAC	ASAP	TRIP
UGIE NNH (95% CI)	65 (24–379)	56 (22–231)	93 (34–544)	52 (20–210)
LGIE NNH (95% CI)	19 (11–37)	15 (9–30)	18 (10–37)	23 (13–49)
Transfusion NNH (95% CI)	43 (21–128)	16 (9–31)	51 (24–182)	25 (14–50)
Hospitalization NNH (95% CI)	39 (18–121)	34 (16–89)	67 (30–214)	45 (21–126)

ACAP indicates combination anticoagulant and antiplatelet therapy; ASAC, combination aspirin and anticoagulant therapy; ASAP, combination aspirin and antiplatelet therapy; CAT, complex antithrombotic therapy; CI, confidence interval; LGIE, lower gastrointestinal event; NNH, number needed to harm; TRIP, triple therapy of aspirin, antiplatelet and anticoagulant agents; and UGIE, upper gastrointestinal event.

*Treatment group consists of patients who spend at least 80% of time on CAT strategy. Comparison groups are patients who spend at least 80% of time without therapy.

with more severe bleeding (35.4% versus 55.1%, P=0.03) as defined by hemodynamic instability and the need for transfusion.[23] Our data extend this literature by quantifying the risk of UGIE, LGIE, and bleeding-related transfusions and hospitalizations associated with antiplatelets, and presents these data in the context of the way antiplatelet drugs are prescribed in this country, in dual and triple combinations, including ASA and anticoagulants.

Our studies also differ by methodology. Rather than perform a case-control study, we chose a rigorous pharmacoepidemiological method of capturing each cohort member's exposure time to prescriptions of interest on a day-by-day basis and compared the associated risk of individual exposure time with that in gap periods (ie, no exposure). Thus, patients were not artificially matched to controls; their periods of CAT exposure were compared with periods off CAT within the same high-risk cohort. This more realistically reflects the real-life experience and natural history of CAT exposure risk in a highly vulnerable, comorbid, elderly cardiovascular population.[24,25]

NSAIDs such as low-dose ASA increase the risk of major bleeding ≈2-fold over placebo (relative risk, 1.71; 95% CI, 1.41–2.08)[26] and cause both UGIE and LGIE bleeding by direct injury to GI mucosa, causing ulceration and erosions, and via platelet thromboxane A2 production, which can exacerbate luminal bleeding from GI abnormalities, including vascular lesions, diverticulosis, and hemorrhoids.[27–29] ASA injury as the likely inciting factor is supported by our data, which demonstrate a 40% to 60% increased risk of UGIE and 10% to 20% increased risk of LGIE with ASAP, ASAC, and TRIP. Antithrombotic agents, including the thienopyridine P2Y12 platelet inhibitors (clopidogrel, prasugrel, ticagrelor), and anticoagulant agents such as Coumadin are not thought to independently cause GI mucosal injury; but they exacerbate bleeding from existing mucosal breaks or injury.[3,30] Among patients in whom an ASA prescription was not recorded (ie, ACAP), the risk of UGIE and LGIE hovered at ≈30% to 40% over baseline, in keeping with the range of an ASA bleed. This may represent bleeding associated with surreptitious ASA or NSAID use, placing both the upper and lower GI tract at risk, or undocumented *H pylori* infection with injury in the upper GI tract, or it may simply reflect the baseline risk of bleeding in an elderly, highly comorbid cardiovascular population.

Limitations of our data must be acknowledged. Members of our cohort were still at risk of GI bleeding–related outcomes during gap periods of nonexposure to CAT therapy, likely explained by the significant overall comorbidity of these patients and residual confounding insufficiently addressed by propensity scores and consideration of prescription channeling. In observational studies, selection bias and residual confounding cannot be entirely excluded. Furthermore, the observational nature of the study can support only associations of risk and cannot speak to causality. We anticipated our inability to capture over-the-counter ASA, PPI, and NSAIDs and addressed this by examining random and nonrandom misclassification of exposure to these by using a 1-way threshold sensitivity analysis of worse-case scenarios, assuming 10%, 25%, and 50% misclassification among patients of higher socioeconomic status (priority group 8 or top quintile income-level zip code). Our data demonstrate robust outcome estimates, even assuming 50% underreporting of over-the-counter ASA, NSAID, or PPI exposure.

Our study is limited by the accuracy of exposure and outcome ascertainment with the use of administrative data. We have minimized this by validating both the pharmacy-fill data and methodology for ascertainment of outcomes of interest. When veterans enroll in the VA, they are assigned a priority group, based on service-connected and other disability, income, and special considerations.[31] High-priority veterans have a service-connected condition and an income less than an annual threshold established by the VA, and they tend to obtain all their care at VA facilities.[32] Low-priority veterans have higher socioeconomic status and may be more likely to be treated at non-VA facilities. Thus, the Cox proportional models were stratified by priority-group level (low priority versus other). To further minimize the impact of underascertainment, we restricted our cohort to regular VA users who are more likely to be treated at a VA facility. As with any study that uses prescription-fill data as the source of exposure, we can only assess prescription fill, not actual use of the drug, but this, again, is a limitation of any observational study that uses pharmacy-fill data and not unique to our study. Last, our sample comprised predominantly male veterans, which may limit generalizability to nonveterans. We do not believe this is significant, because male sex is a known risk factor for atherosclerosis, and GI bleeding risk is not sex specific. Thus, our cohort is likely an ideal high-risk cohort for examination of CAT-related GI bleeding epidemiology.

Our data should serve as a caution to prescribing physicians and encourage vigilance in prescribing CAT beyond the necessary therapeutic window. Current American College of Cardiology/American Heart Association guidelines do not recommend dual-antiplatelet therapy in patients with stable chronic coronary artery disease and no recent acute coronary syndrome (<12 months), but they do recommend it in post-percutaneous coronary intervention patients with a drug-eluting stent. Even among the latter, recommendations for chronic CAT (ASAP, TRIP) beyond 12 months are unjustified in most.[33] These recommendations may change, as trials have recently shown that 6-month dual-antiplatelet therapy is sufficient in most patients at low risk of restenosis following the implantation of drug-eluting stents.[34,35] Future work is required to quantify the GI risk–cardioprotective benefit ratios among elderly patients for both short- and long-term secondary cardioprevention medication management strategies. Furthermore, the use of patient-oriented outcomes such as bleeding-related hospitalization and the need for transfusion is important for quantifying risk–benefit ratios in a manner that is salient to older, morbid patients.

Our study demonstrates that CAT prescription is associated with a clinically significant risk of UGIE, LGIE, and bleed-related transfusion and hospitalization. These data are important to consider when counseling elderly patients regarding the potential risk-benefit of CAT prescription strategies and further highlight the importance of risk stratification and risk modification of vulnerable elderly patients by minimizing the time on CAT and ensuring that prescription occurs within the context of safer prescribing habits, as outlined by concerned GI and cardiology societies.[20]

Acknowledgments

Abstract presented at Digestive Diseases Week 2012, San Diego, California May 19-22, 2012. Dr Abraham is the guarantor of the paper. Dr Abraham conceived, designed, and conducted the study, acquired necessary funding, interpreted the data, prepared the manuscript, and had final approval of this research. Drs Hartman and Richardson provided analytic support in programming, statistical analysis, and interpretation of results. D. Castillo, and Drs Naik, Street, Hartman, and Richardson assisted Dr Abraham in preparation of the manuscript.

Sources of Funding

Dr Abraham was supported by a Merit Review Award from the Department of Veterans Affairs (IIR08-028) and an American Gastroenterological Association-Sucampo-ASP Designated Research Scholar Award in Geriatric Gastroenterology. This material is also the result of work supported with resources and the use of facilities at the Houston VA HSR&D Center of Excellence, Houston Veterans Affairs Medical Center (HFP90-020). None of the funding agencies played a role in the design and conduct of the study, analysis and interpretation of the data, or preparation and approval of the manuscript. The views expressed are those of the authors and do not necessarily reflect those of the Department of Veterans Affairs, the US government, or Baylor College of Medicine.

Disclosures

None.

References

1. Vallurupalli NG, Goldhaber SZ. Gastrointestinal complications of dual antiplatelet therapy. *Circulation*. 2006;113:e655–e658.
2. Ness J, Aronow WS. Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. *J Am Geriatr Soc*. 1999;47:1255–1256.
3. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, Furberg CD, Johnson DA, Kahi CJ, Laine L, Mahaffey KW, Quigley EM, Scheiman J, Sperling LS, Tomaselli GF; ACCF/ACG/AHA. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;122:2619–2633.
4. Page WF, Mahan CM, Kang HK. Vital status ascertainment through the files of the Department of Veterans Affairs and the Social Security Administration. *Ann Epidemiol*. 1996;6:102–109.
5. Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am J Gastroenterol*. 2008;103:872–882.
6. Abraham NS, Hartman C, Castillo D, Richardson P, Smalley W. Effectiveness of national provider prescription of PPI gastroprotection among elderly NSAID users. *Am J Gastroenterol*. 2008;103:323–332.
7. Lanas A, Bajador E, Serrano P, Fuentes J, Carreño S, Guardia J, Sanz M, Montoro M, Sáinz R. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. *N Engl J Med*. 2000;343:834–839.
8. Thirumurthi S, Desilva R, Castillo DL, Richardson P, Abraham NS. Identification of Helicobacter pylori infected patients, using administrative data. *Aliment Pharmacol Ther*. 2008;28:1309–1316.
9. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36:8–27.
10. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med*. 1997;127(8 pt 2):757–763.
11. Newgard CD, Hedges JR, Arthur M, Mullins RJ. Advanced statistics: the propensity score–a method for estimating treatment effect in observational research. *Acad Emerg Med*. 2004;11:953–961.
12. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ*. 1999;319:1492–1495.
13. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med*. 1991;10:585–598.
14. Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: organization to assess strategies for ischemic syndromes (OASIS) pilot study results. *Circulation*. 1998;98:1064–1070.
15. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–39.
16. Cohen M, Adams PC, Parry G, Xiong J, Chamberlain D, Wieczorek I, Fox KA, Chesebro JH, Strain J, Keller C. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users. Primary end points analysis from the ATACS trial. Antithrombotic Therapy in Acute Coronary Syndromes Research Group. *Circulation*. 1994;89:81–88.
17. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331–7.
18. van Es RF, Jonker JJ, Verheugt FW, Deckers JW, Grobbee DE. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. *Lancet*. 2002;360:109–13.
19. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.
20. Bhatt DL, Scheiman J, Abraham NS, Antman EM, Chan FK, Furberg CD, Johnson DA, Mahaffey KW, Quigley EM. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation*. 2008;118:1894–909.
21. Grove EL, Würtz M, Schwarz P, Jørgensen NR, Vestergaard P. Gastrointestinal events with clopidogrel: a nationwide population-based cohort study. *J Gen Intern Med*. 2013;28:216–222.
22. Casado Arroyo R, Polo-Tomas M, Roncalés MP, Scheiman J, Lanas A. Lower GI bleeding is more common than upper among patients on dual antiplatelet therapy: long-term follow-up of a cohort of patients commonly using PPI co-therapy. *Heart*. 2012;98:718–723.
23. Hashash JG, Shamseddeen W, Skoury A, Aoun N, Barada K. Gross lower gastrointestinal bleeding in patients on anticoagulant and/or antiplatelet therapy: endoscopic findings, management, and clinical outcomes. *J Clin Gastroenterol*. 2009;43:36–42.
24. Abraham NS, El-Serag HB, Hartman C, Richardson P, Deswal A. Cyclooxygenase-2 selectivity of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction and cerebrovascular accident. *Aliment Pharmacol Ther*. 2007;25:913–924.
25. Abraham NS, Castillo DL, Hartman C. National mortality following upper gastrointestinal or cardiovascular events in older veterans with recent NSAID use. *Aliment Pharmacol Ther*. 2008;28:97–106.
26. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med*. 2006;119:624–638.
27. Cryer B. Reducing the gastrointestinal risks of low-dose aspirin. *Gastroenterology*. 2010;138:30–33.
28. Laine L, Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, Yu Q, Bombardier C. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology*. 2003;124:288–292.
29. Laine L. Review article: gastrointestinal bleeding with low-dose aspirin - what's the risk? *Aliment Pharmacol Ther*. 2006;24:897–908.
30. Abraham NS. Prescribing proton pump inhibitor and clopidogrel together: current state of recommendations. *Curr Opin Gastroenterol*. 2011;27:558–564.
31. Shen Y, Hendricks A, Zhang S, Kazis LE. VHA enrollees' health care coverage and use of care. *Med Care Res Rev*. 2003;60:253–267.
32. Hynes DM, Koelling K, Stroupe K, Arnold N, Mallin K, Sohn MW, Weaver FM, Manheim L, Kok L. Veterans' access to and use of Medicare and Veterans Affairs health care. *Med Care*. 2007;45:214–223.
33. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60:645–681.

34. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation*. 2012;125:505–513.

35. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fuca G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R, Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation*. 2012;125:2015–26.

CLINICAL PERSPECTIVE

This retrospective cohort analysis of >78 000 US veterans 60 to 99 years of age prescribed complex antithrombotic therapy (aspirin, antiplatelet, and anticoagulant in dual and triple combinations) between October 2002 and September 2009 highlights the real-life risk of upper and lower gastrointestinal bleeding associated with these regimens. The magnitude of risk is quantified as the number needed to harm for upper and lower gastrointestinal bleeding, and by quantifying 2 additional patient-centered outcomes, the need for transfusion and bleeding requiring hospitalization. This study demonstrates the real-world reality of antithrombotic bleeding in a national population of elderly, comorbid, cardiac patients. These data are important to consider when counseling elderly patients regarding the potential risk-benefit of dual and triple antithrombotic regimens, further highlighting the importance of risk stratification and risk modification of elderly patients, and minimizing the time on dual and triple antithrombotic regimens.

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