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

Running title: *Abraham et al.; GI bleeding with antithrombotic therapy*

Neena S. Abraham, MD, MSCE[1,2,3]; Christine Hartman, PhD[2]; Peter Richardson PhD[2]; Diana Castillo, BA[2]; Richard L. Street Jr., PhD[2,4]; Aanand D. Naik, MD[2]

[1]Division of Gastroenterology, Dept of Medicine, Baylor College of Medicine, Houston, TX; [2]Houston VA HSR&D Center of Excellence, Michael E. DeBakey VAMC, Houston, TX; [3]Division of Gastroenterology, Mayo Clinic, Scottsdale, AZ; [4]Dept of Communications, Texas A&M University, College Station, TX

Address for Correspondence:
Neena S. Abraham MD, MSCE
Division of Gastroenterology
Mayo Clinic
Scottsdale, AZ, 85259
Tel: 480-301-6990
Fax: 480-301-8673
E-mail: abraham.neena@mayo.edu

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Abstract

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

***Methods and Results*—**Veterans ≥ 60 years prescribed anticoagulant-antiplatelet (i.e., ACAP); ASA-antiplatelet (i.e., ASAP); ASA-anticoagulant (i.e., ASAC) or triple therapy (i.e., TRIP; anticoagulant-antiplatelet-ASA) were identified from the national pharmacy database (10/01/02-09/30/08). Prescription-fill data were linked to VA and Medicare encounter files, each person-day of follow-up assessed for CAT exposure, and outcomes defined using diagnostic code algorithms derived following chart abstraction. Incidence density ratios (compared to the reference category of no CAT) and survival analysis was conducted. Among 78,133 veterans (98.6% white; mean age, 72.3 [SD 7.7]), 64% were prescribed ASAP and ACAP and 6% TRIP. Incidence of UGIE was 20.1/1000 patient-years (PY) and LGIE was 70.1/1000 PY. ASAC and TRIP were associated with highest incidence of transfusion and hospitalization. A 40% to 60% increased risk of UGIE was observed with all strategies. LGIE was 30% higher with ACAP, and transfusion increased with ASAC (HR 6.1; 95% CI: 5.2-7.1) and TRIP (HR 5.0; 95% CI: 4.2-5.8). Increased risk of hospitalization was noted with all strategies. The number needed to harm (NNH) for UGIE or LGIE ranged from 52 to 65 and 15 to 23, respectively. The NNH for hospitalization was 39 (ACAP), 34 (ASAC), 67 (ASAP) and 45 (TRIP) patients.

***Conclusions*—**Among the elderly, CAT-related LGIE and UGIE is a clinically relevant risk resulting in increased hospitalizations and transfusions.

Key words: antiplatelet drug, antithrombotic, hospitalization, patient-centered care

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Introduction

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

The burden of CAT-related GI bleeding remains largely unknown among the elderly, 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 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 measure two patient-centered outcomes (i.e., need for transfusion, and bleeding requiring hospitalization) in a national cohort of elderly patients.

Methods

Study Design and Data Sources

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We conducted a retrospective cohort study of veterans, from 10/01/02-09/30/08, using 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 (PTF), 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 using MedPAR, inpatient and outpatient files from 2002-2008, to ensure complete case ascertainment at non-VA facilities.

Study Population

Veterans aged 60 to 99 years, with a filled prescription for an anticoagulant, ASA, or antiplatelet agent were identified for cohort inclusion (**Supplemental Table 1**). The first prescription in the study period was considered the index prescription and designated t_0. Patients were followed to the end of the observation period (9/30/08) or until the end of prescription fill dates in that period of observation for the drugs of interest or until 1st occurrence of event of interest. Eligibility criteria included a history of prior VA encounters within 365 days before index prescription to ensure continuous VA enrolment. 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,

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transfusions and hospitalizations), we identified 200 patients prescribed an anticoagulant-antiplatelet (i.e., ACAP); ASA-antiplatelet (i.e., ASAP); ASA-anticoagulant (i.e., 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 ICD-9 codes in the PTF 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 [CPT], ICD-9 codes and surgical codes). We also identified patients with evidence of CPT codes for upper or lower endoscopy and/or 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 gender 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. Cases' and controls' charts were abstracted for confirmation of a CAT-related UGIE, LGIE, transfusion or inpatient hospitalization, and a diagnostic algorithm was derived to maximize positive (PPV) and negative predictive value (NPV). 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 PTF, or code 578 and 533 and a CPT code for upper endoscopy in any position. This algorithm had a PPV of 83% and NPV of 100%. The CAT-related LGIE algorithm of ICD-9 code 562 or 578 with a CPT or surgical code for

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lower GI endoscopy in any position had a PPV of 83% and a NPV of 91%. We did not include occult bleeding (ICD-9 code 792) in either algorithm, as 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 PPV of 96% and NPV of 98%. Other investigators have previously well validated the PTF for hospitalization [4]. We attributed hospitalization to the CAT-related bleeding event, if it occurred within 7 days of hospitalization encounter (i.e., 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. Using published methodology [5] exposure was defined to be 1.25 X (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," i.e., 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 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

Pharmacologic risk factors, including prescription of nonsteroidal anti-inflammatory drugs (NSAIDS), both traditional and COX-2 selective, steroids, selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors, low-molecular-weight heparin, and

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heparin overlapping with CAT prescription, were identified (**Supplemental Table 2**). We also assessed exposure to proton pump inhibitors (PPIs), statins and selective serotonin reuptake inhibitors; shown to modify GI bleeding risk [6, 7]. Models were also adjusted for demographics (age, gender, race), *Helicobacter pylori* (*H. 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 (i.e., 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 triple therapy. 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.

Analytic Methods

The chi-square test and ANOVA 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 index prescription. Incidence-density-ratios (IDR) 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, Cary, NC) PHREG procedure was used to analyze data at each UGIE, LGIE hospitalization and transfusion comparing individuals with the event to those still uncensored without the event. The Wald's Chi-Square test was used to test for significance of the influence of each independent variable.

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Hazard ratios (HR) and their 95% confidence intervals (CI) 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%-100% of his/her individual exposure time. Established methodology [12] was used to estimate NNH during the first 365 days of observation, using the equation NNH= 1/(survival probability in the control group X 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 [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), on ASAP was 632 days (SD: 495), on ASAC was 493 days (SD: 475) and TRIP was 355 days (SD: 398). The time during which cohort members were on no drugs of interest (i.e., no exposure/none) was 317 days (SD: 335). Unadjusted incidence density and IDR for each outcome of interest, during the 2.3 years of total observation, is shown in **Table 2** and are presented with the reference category of none (i.e., no CAT exposure). The overall incidence of UGIE with antithrombotic use was 20.1/1000 PY of follow-up. The greatest risk was observed with triple CAT. The overall risk of

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

Multivariate analysis (**Figures 1A, 1B, 1C and 1D**) considered risk of patients prescribed CAT for 80-90% of the exposure period (compared to 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 (HR 6.1; 95% CI: 5.2-7.1) and 5-fold higher with TRIP prescription (HR 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, compared to 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 one 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

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LGIE. The NNH for ASAC, ASAP and ACAP ranged from 15-19, 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 using Monte Carlo methodology [13] generated replicates of the original dataset assuming random and nonrandom misclassification of over-the-counter (OTC) ASA, NSAIDs or PPI. We set the drug-use indicator for each subject 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 (AHA), American College of Gastroenterology and American College of Cardiology (ACC) [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

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randomized controlled CAT trials. To our knowledge, this is the largest study investigating the GI bleeding risk associated with both the upper *and* lower GI tract, which 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 as well as 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 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 post-intervention 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 co-prescribed NSAIDs, SSRI 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 poly-pharmacy and provide concrete evidence to inform discussions between physicians and their elderly patients about medication risks and adherence.

Similar 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 prior studies evaluating LGIE have found that LGIE is more common than UGIE (74% vs. 26%, p=0.012) in patients taking dual antiplatelet therapy [22] and associated with more severe bleeding (35.4% vs. 55.1%, p=0.03) as defined by hemodynamic instability and 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 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 pharmacoepidemiologic 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 to that in gap periods (i.e., no exposure). Thus, patients were not artificially matched to controls; their periods of CAT exposure were compared to 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 (RR= 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 40-60% increased risk of UGIE and 10-20% increased risk of LGIE with ASAP,

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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 (i.e., ACAP, the risk of UGIE and LGIE hovered around 30-40% 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 may simply reflect the baseline risk of bleeding in an elderly, highly comorbid elderly 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 OTC ASA, PPI and NSAIDs and addressed this by examining random and nonrandom misclassification of exposure to these, 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 OTC ASA, NSAID, or PPI exposure.

Our study is limited by the accuracy of exposure and outcome ascertainment using administrative data. We have minimized this by validating both the pharmacy-fill data and

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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 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 vs. other). To further minimize the impact of under-ascertainment, 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. Lastly, our sample was predominantly male veterans, which may limit generalizability to nonveterans. We do not believe this is significant, as male gender is a known risk factor for atherosclerosis; and GI bleeding-risk is not gender 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 ACC/AHA guidelines do not recommend dual antiplatelet therapy in patients with stable chronic CAD and no recent acute coronary syndrome (<12 months) but do recommend it in post-PCI 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 the EXCELLENT and PRODIGY trials have both recently shown that 6-month dual antiplatelet therapy is sufficient in most patients at low risk of restenosis following implantation of drug-eluting stents

[34, 35]. Future work is required to quantify the GI risk-cardioprotective benefit ratios among the elderly for both short- and long-term secondary cardioprevention medication management strategies. Furthermore, the use of patient-oriented outcomes such as bleeding-related hospitalization and need for transfusion is important for quantifying risk-benefit ratios in a manner that is salient to older, morbid patients.

Our study demonstrates 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 elders by minimizing time on CAT and ensuring that prescription occurs within the context of safer prescribing habits, as outlined by concerned GI and cardiology societies [20].

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Conflict of Interest Disclosures: None.

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Table 1. Baseline characteristics of cohort (N=78,133), as stratified by CAT prescription strategy at index prescription

Characteristic	CAT Prescription Strategy				p-value
	ACAP (n=10,769)	ASAC (n=22,897)	ASAP (n=39,496)	TRIP (n=4,971)	
Average age (SD)	74.1 (7.2)	72.5 (8.0)	72.2 (8.1)	71.2 (8.0)	
60-69 years (%)	27%	39%	40%	45%	
70-79 years (%)	47%	39%	38%	37%	<0.0001
≥80 years (%)	26%	23%	22%	18%	
Male (%)	99.0%	98%	99%	99%	0.0002
Race/Ethnicity					
White (%)	40%	64%	52%	71%	
Black (%)	2%	11%	8%	10%	<0.0001
Hispanic (%)	1%	3%	5%	5%	
Other/Unknown	56%	23%	35%	14%	
Comorbidity					
Elixhauser 0-1 (%)	18%	15%	24%	15%	<0.0001
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 (%)	41%	41%	41%	44%	0.0012

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

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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)

*Where the incidence density represents a measure of the instantaneous rate of development of the outcome of interest given 1000 person-years (PY) of exposure.

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

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

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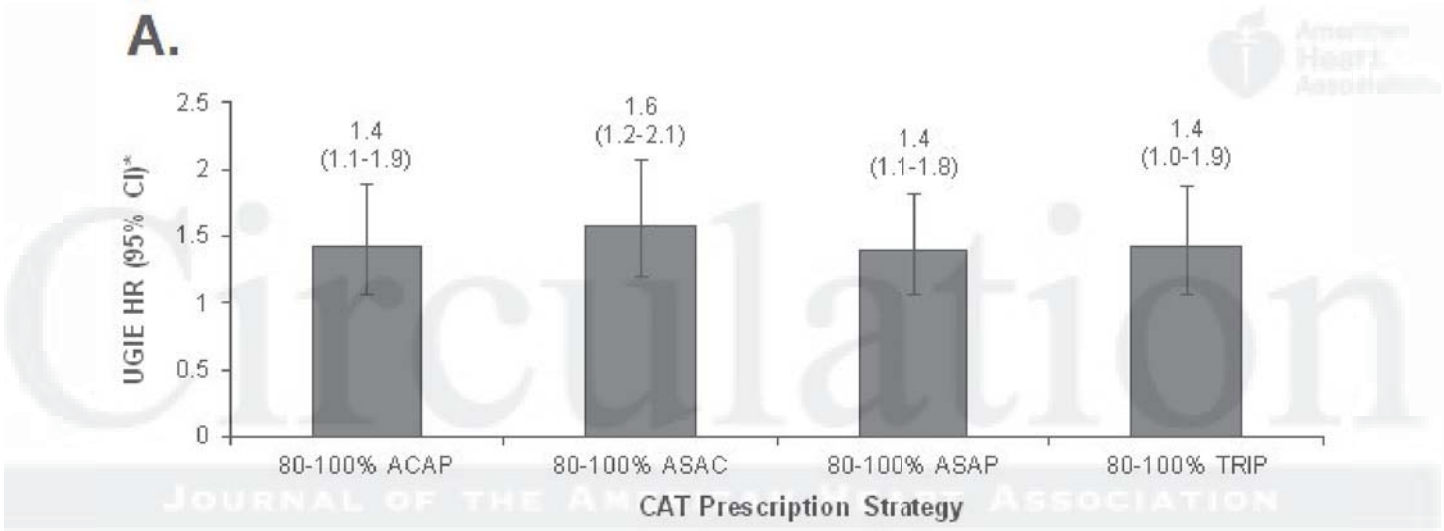
Table 3. 1-year number needed to harm (NNH) for patients who spend 80-100% time on CAT

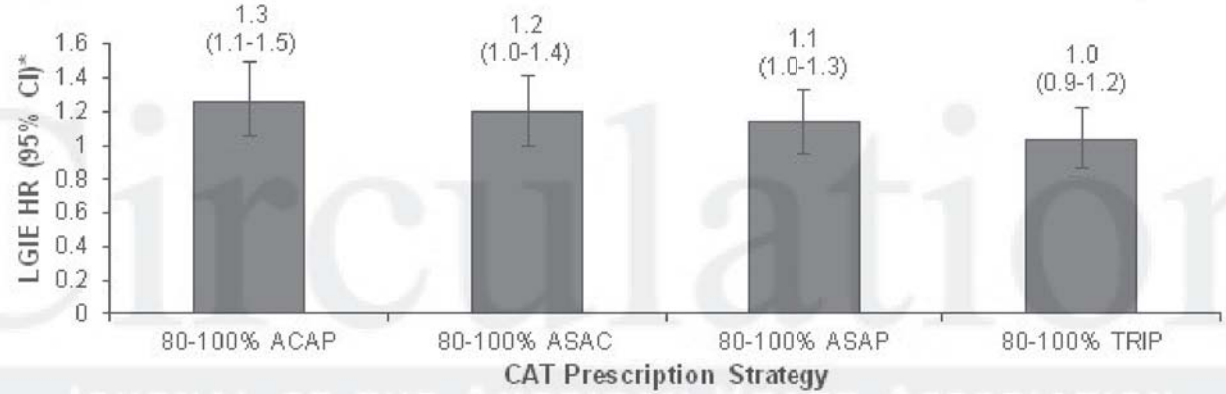
1-Year NNH*	ACAP	ASAC	ASAP	TRIP
UGIE NNH (95% CI)	65 (24-379)	56 (22-231)	93 (34-544)	52 (20-210)
LGIE NNH (95% CI)	19 (11-37)	15 (9-30)	18 (10-37)	23 (13-49)
Transfusion NNH (95% CI)	43 (21-128)	16 (9-31)	51 (24-182)	25 (14-50)
Hospitalization NNH (95% CI)	39 (18-121)	34 (16-89)	67 (30-214)	45 (21-126)

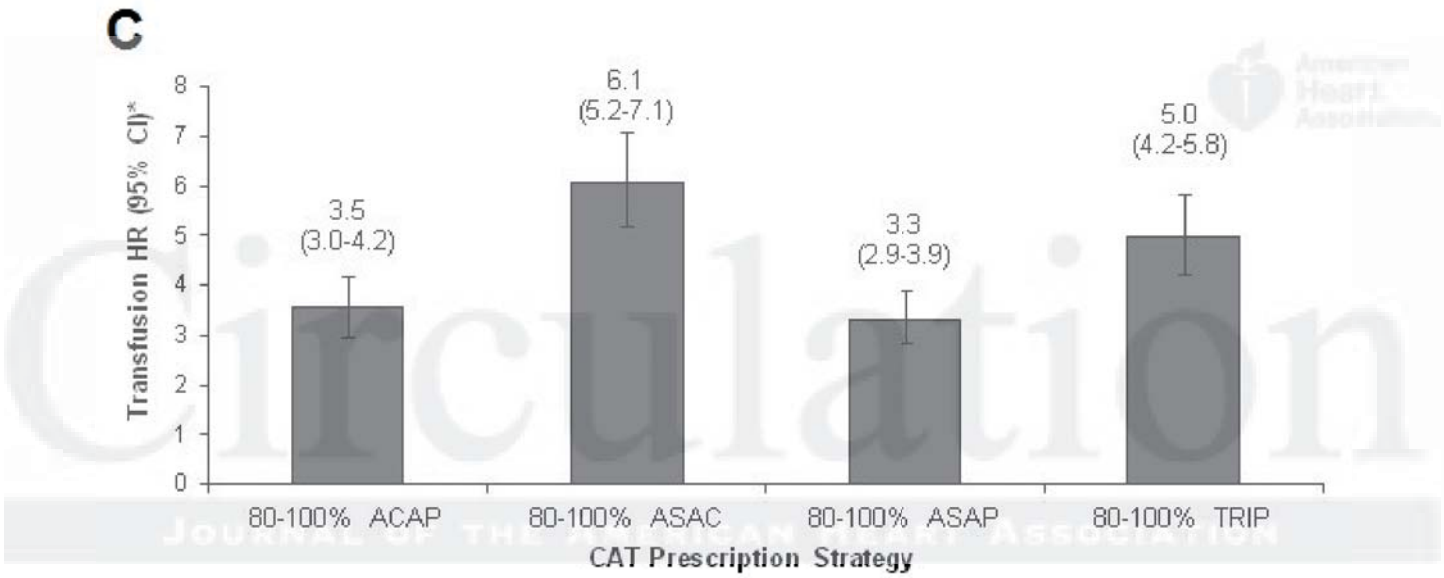
*Treatment group consists of patients who spend at least 80% of time on CAT strategy. Comparison group are patients who spend at least 80% of time without therapy.
Where CAT= complex antithrombotic therapy; UGIE= upper gastrointestinal event; LGIE= lower gastrointestinal event; NNH= number needed to harm; CI= confidence interval; ACAP= combination anticoagulant and antiplatelet therapy; ASAC= combination aspirin and anticoagulant therapy; ASAP= combination aspirin and antiplatelet therapy; TRIP= triple therapy of aspirin, antiplatelet and anticoagulant agents.

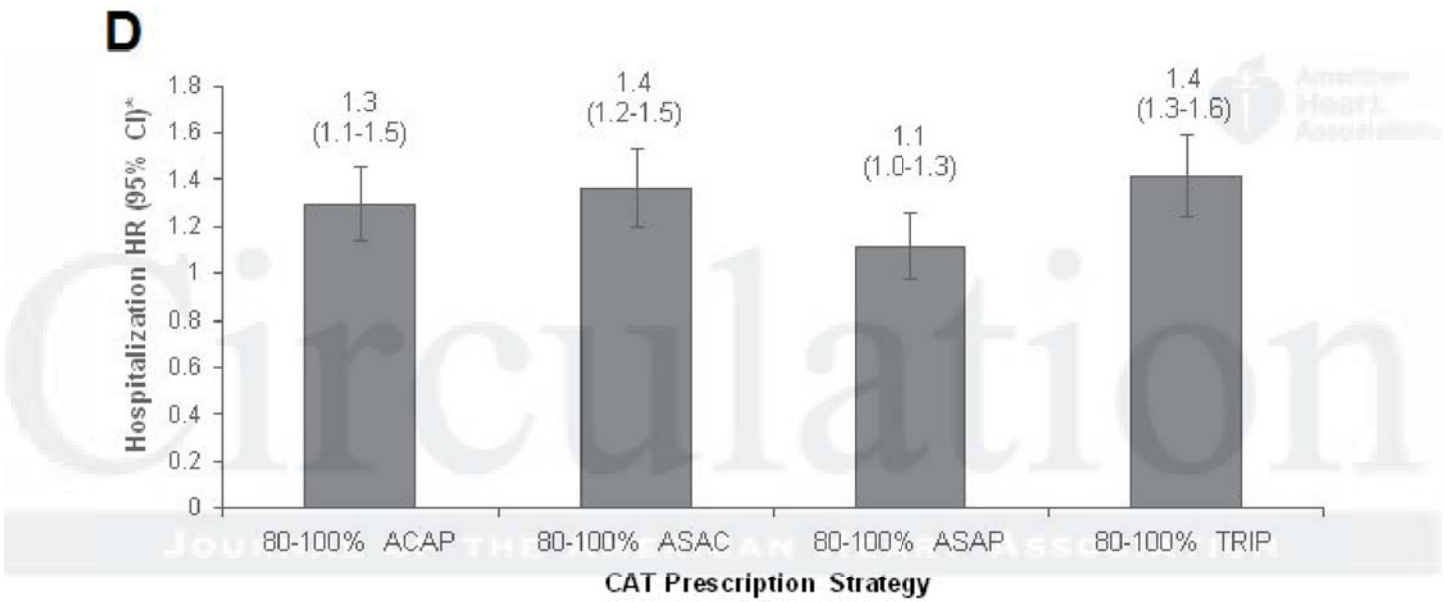
Figure Legend:

Figure 1. Adjusted cumulative percent time on CAT prescription strategy and risk of UGIE (Panel A), LGIE (Panel B), transfusions (Panel C) and hospitalizations (Panel D). *Where comparison group is 0% on therapy. All multivariate analyses adjusted for demographic characteristics, Elixhauser co-morbidity, prescription channeling, geographic location, priority group, clinical risk factors, and multiple time-dependent pharmacological covariates including NSAIDs, steroids, PPI, statins, and SSRI. Where CAT= complex antithrombotic therapy; UGIE= upper gastrointestinal event; LGIE= lower gastrointestinal event; HR= hazard ratio; CI= confidence interval; ACAP= combination anticoagulant and antiplatelet therapy; ASAC= combination aspirin and anticoagulant therapy; ASAP= combination aspirin and antiplatelet therapy; TRIP= triple therapy of aspirin, antiplatelet and anticoagulant agents.









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

Neena S. Abraham, Christine Hartman, Peter Richardson, Diana Castillo, Richard L. Street, Jr. and Aanand D. Naik

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Antithrombotic prescriptions

Antithrombotic Type	Description
Anticoagulant	
Low molecular weight heparin	Anagrelide
	Ardeparin
	Dalteparin
	Danaparoidna
	Enoxaparin
	Fondaparinux
	Tinzaparin
Coumadin	Dicumarol
	Warfarin
Heparin	Heparin
Direct thrombin inhibitor	Argatroban
	Bivalirudin
	Lepirudin
Other	Anisindione
Aspirin	
Salicylate	Aspirin

Antiplatelet	
Thienopyridine	Clopidogrel
	Dipyridamole
	Ticlopidine
Glycoprotein IIb/IIIa inhibitor	Abciximab
	Eptifibatide
	Tirofiban

Supplemental Table 2. Pharmacologic co-variates

Drug Type	Drug Name
Anticoagulant	
Pain relievers/salicylates	Acetaminophen
	Choline magnesium trisalicylate
	Codeine
	Dihydrocodeine
	Disalycilate
	Hydrocodone
	Magnesium
	Opium
	Oxycodone
	Pentazocine
	Pravigard
	Propoxyphene
	Salsalate
Non-Aspirin NSAID	Dichlorodifluoromethane
	Diclofenac
	Diflunisal
	Difluprednate
	Diphenhydramine
	Doxapram
	Etodolac

	Fenoprofen
	Flurbiprofen
	Ibuprofen
	Indomethacin
	Ketoprofen
	Ketorolac
	Meclofenamate
	Meclofenamic acid
	Meloxicam
	Nabumetone
	Naproxen
	Oxaprozin
	Oxycodone
	Phenylbutazone
	Phenylbutyrate
	Piroxicam
	Sulindac
	Tolmetin
Coxib	Celecoxib
	Rofecoxib
	Valdecoxib
H2RA	Cimetidine
	Famotidine

	Nizatidine
	Ranitidine
PPI	Dexlansoprazole
	Esomeprazole
	Lansoprazole
	Omeprazole
	Pantoprazole
	Rabeprazole
Prostaglandin	Misoprostol
Anticoagulant	Anisindione
	Ardeparin
	Dalteparin
	Danaparoid
	Enoxaparin
	Fondaparinux
	Tinzaparin
	Dicumarol
	Phenprocoumon
	Warfarin
	Heparin
	Argatroban
	Bivalirudin
	Lepirudin

Antiplatelet	Clopidogrel
	Ticlopidine
	Abciximab
	Eptifibatide
	Tirofiban
	Prasugrel
	Aspirin
	Dipyridamole
Steroid	Adrenocorticotropin
	Betamethasone
	Budesonide
	Corticosteroids
	Corticosterone
	Corticotropin
	Cortisone
	Cosyntropin
	Desoxycorticosterne
	Desoxycorticosterone
	Dexamethasone
	Dextroamphetamine
	Diphenhydramine
	Entocort
	Fludrocortisone

	Hydrocortisone
	Hydroxycorticosteroids
	Hydroxycorticosterone
	Hydroxyzine
	Lisdexamfetamine
	Methylprednisolone
	Niacinamide
	Prednisoline
	Prednisolone
	Prednisone
	Pulmicort
	Triamcinolone
	Triamcnlne
Statin	Atorvastatin
	Cerivastatin
	Cladribine
	Ezetimibe
	Fluvastatin
	Lovastatin
	Pitavastatin
	Pravastatin
	Rosuvastatin
	Simvastatin

	Somatostatin
Antianginal	Amylase
	Chlordiazepoxide
	Erythrityl
	Hydralazine
	Hydroxyzine
	Isosorbide
	Lubraseptic
	Mannitol
	Meprobamate
	Niacin
	Nitrate
	Nitrazine
	Nitroglycerin
	Pentaerythritol
	Phenobarbital
	Ranolazine
	Sodium
Calcium Channel Blocker	Afeditab
	Amlodipine
	Bepridil
	Caduet
	Cardizem

	Clevidepine
	Diltiazem
	Enalapril
	Felodipine
	Isradipine
	Mibefradil
	Nicardipine
	Nifedipine
	Nimodipine
	Nisoldipine
	Telmisartan
	Trandolapril
	Verapamil
Antibiotics	Ciprofloxacin
	Furazolidone
	Acetazolamide
	Amoxicillin
	Ampicillin
	Tamoxifen
	Bismuth
	Metronidazole
	Tinidazole
	Clarithromycin

	Amphotericin
	Tetracycline
	Rifabutin
	Levofloxacin
	Bismuth
	Helidac
Peripheral artery treatment	Adenosine
	Ambrisentan
	Amrinone
	Bosentan
	Cilostazol
	Flosequinan
	Fluosol
	Inamrinone
	Indomethacin
	Midodrine
	Milrinone
	Nesiritide
	Pentoxifylline
	Phenobarbital
	Regadenoson
	Treprostinil
Acetaminophen/Pain relievers	Acetaminophen

	Actifed
	Apap
	Codeine
	Hydrocodone
	Meperidine
	Oxycodone
	Pentazocine
	Propoxyphene
Antiarrythmics	Adenosine
	Amiodarone
	Bretylium
	Disopyramide
	Dofetilide
	Dronedarone
	Encainide
	Flecainide
	Ibutilide
	Ibytilide
	Lidocaine
	Mexiletine
	Moricizine
	Procain
	Procainamide

	Procaine
	Propafenone
	Quinidine
	Rythmol
	Tocainide
ACE Inhibitors	Benazepril
	Captopril
	Enalapril
	Enalaprilat
	Fosinopril
	Lisinopril
	Moexipril
	Perindopril
	Quinapril
	Ramipril
	Trandolapril
Alpha Blockers	Alfuzosin
	Doxazosin
	Prazosin
	Silodosin
	Tamsulosin
	Terazosin
	Uroxatral

Beta Blockers	Acebutolol
	Atenolol
	Betaxolol
	Bisoprolol
	Brevibloc
	Carteolol
	Carvedilol
	Esmolol
	Labetalol
	Metoprolol
	Nadolol
	Nebivolol
	Penbutolol
	Pindolol
	Propranolol
	Sotalol
	Timolol
Digitalis	Deslanoside
	Digitalis
	Digitoxin
	Digoxin
Loop Diuretics	Bumetanide
	Ethacrynate

	Ethacrynic
	Furosemide
	Torsemide
Other Diuretics	Acetazolamide
	Amiloride
	Bendroflumethiazide
	Benzthiazide
	Chlorothiazide
	Chlorthalidone
	Cyclothiazide
	Dichlorphenamide
	Eplerenone
	Hctz
	Hydrochlorothiazide
	Hydrochlrothiazide12
	Hydroflumethiazide
	Indapamide
	Inspra
	Mannitol
	Methazolamide
	Methyclothiazide
	Metolazone
	Polythiazide

	Quinethazone
	Spironolactone
	Triamterene
	Trichlormethiazide
	Urea
Antihypertensives	Aliskiren
	Alseroxylon
	Amlodipine
	Atenol
	Atenolol
	Benazepril
	Bendroflumethiazide
	Benicar
	Bisopro
	Bisoprolol
	Candesartan
	Captopril
	Chlorothiazide
	Chlorthalidone
	Clonidine
	Cryptenamine
	Deserpidine
	Diazoxide

Enalapril

Eprosartan

Flumethiazide

Fosinopril

Guanabenz

Guanadrel

Guanethidine

Guanfacine

Hctz

Hydralazine

Hydrochlorothiazide

Hydroflumethiazide

Irbesartan

Losartan

Lotrel

Mecamylamine

Methyclothiazide

Methyldopa

Methyldopate

Metyrosine

Micardis

Minoxidil

Olmesartan

	Pargyline
	Paroxetine
	Polythiazide
	Quinethazone
	Rauwolfia
	Rescinnamine
	Reserpine
	Sildenafil
	Sodium
	Tadalafil
	Telmisartan
	Tevetin
	Trandola
	Trimethaphan
	Valsartan
Other Antilipemic Agents	Altoprev
	Atorvastatin
	Clofibrate
	Colesevelam
	Colestipol
	Crestor
	Dextrothyroxine
	Ezetimibe

	Fenofibrate
	Fenofibric
	Fluvastatin
	Gemfibrozil
	Glycine
	Lovastatin
	Niacin
	Omacor
	Omega
	Pravastatin
	Probucol
	Simvastatin
	Tricor
	Vit
	Vytorin
	Zetia
	Zocor
Antidepressants	Amitriptyline
	Amoxapine
	Benactyzine
	Clomipramine
	Desipramine
	Donepezil

Doxepin
Duloxetine
Ergoloid
Galantamine
Imipramine
Isocarboxazid
Maprotiline
Memantine
Milnacipran
Nefazodone
Nortriptyline
Phenelzine
Protriptyline
Selegiline
Sodium
Tacrine
Tranylcypromine
Trazodone
Trimipramine