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Association of direct oral anticoagulant-proton pump inhibitor cotherapy with adverse outcomes: protocol for a population-based cohort study

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ABSTRACT

Introduction Proton pump inhibitors (PPIs) are widely used for primary and secondary prevention of upper gastrointestinal bleeding. However, there remains controversy about the overall net clinical benefit of PPIs (omeprazole, rabeprazole, pantoprazole, lansoprazole) when coprescribed with direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban). Our objective is to explore the risk of clinically relevant events, including bleeding, thromboembolic events and death, in patients prescribed DOACs while taking PPIs versus no PPI.

Methods and analysis The protocol describes a retrospective cohort study of all Ontario residents aged 66 years or older with atrial fibrillation and at least one pharmacy dispensation for a DOAC identified using linked administrative healthcare databases covering 2009–2020. Ontario drug benefit dispensation records will be used to ascertain PPI exposure during DOAC therapy. The primary outcome is a composite of clinically relevant bleeding, thrombotic events or all-cause death. A minimum of 520 patients in total with at least one of the components of the composite outcome are needed. Poisson regression with a generalised estimating equation model will be used to calculate the adjusted incidence rate difference, incidence rate ratios 95% CI, adjusting for propensity for PPI use using inverse probability of treatment weights.

Ethics and dissemination This research is exempt from REB review under section 45 of Ontario's Personal Health Information Protection Act. We will report our findings in a peer-reviewed biomedical journal and present them at conferences. The study will provide useful evidence to optimise the coprescription of DOACs and PPIs in practice.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This will be a population-based cohort study using Ontario's administrative health databases.
⇒ Exposures and covariates will be time-dependent.
⇒ As the study is limited to patients aged >66 years, we cannot generalise the results to younger patients.
⇒ As with any observational study, there is potential for residual confounding.

INTRODUCTION

Background/rationale

The direct oral anticoagulants (DOACs) refer to the factor Xa inhibitors-rivaroxaban, edoxaban, apixaban and betrixaban, and the direct thrombin inhibitor-dabigatran.[1] Before introducing DOACs within the last decade, the vitamin-K-antagonist warfarin was the only OAC used for prevention and treatment of thrombosis.[2] Proton pump inhibitors (PPIs) are H+-K+-blockers that are used to manage acid-related gastrointestinal (GI) disorders.[3] Currently, there are six PPIs available in Canada: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and dexlansoprazole. The evidence for PPIs for treating gastro-oesophageal reflux disease and GI bleeding has been used to indirectly support its concomitant use with DOACs.[4–8] In Canada, since the onset of availability of the DOACs, the proportion of total OAC prescriptions attributable to warfarin steadily decreased, from 99% in 2010 to around 10% in 2017.[9 10] According to the 2014 guidelines on AF of the Canadian Cardiovascular Society, most patients for whom an OAC is indicated should receive a DOAC rather than warfarin (strong recommendation, high-quality evidence).[11] At the same time, over 33 million prescriptions of PPIs were dispensed in Canada in 2016, and the number is increasing over time.[12] In 2018, direct factor Xa inhibitors and PPIs were among the top 10 drug classes in terms of public drug programme spending in seniors: US$316.2 million and US$180.8 million, respectively.[13]

In a recent systematic review, we showed an increased risk of bleeding in patients receiving PPI plus warfarin compared with warfarin alone (OR 1.34, 95% CI 1.22 to 1.47), likely at least partly due to residual confounding.[14] However, controversy remains about the overall net clinical benefit for the PPIs when

given with DOACs. Some studies reported no evidence of a protective effect of PPIs against dabigatran-related GI bleeding.[15 16] One large randomised trial showed that pantoprazole treatment in addition to low dose rivaroxaban did not reduce upper GI bleeding.[17] A prospective pilot study demonstrated that the use of dabigatran with PPIs reduced dabigatran plasma levels in patients with AF.[18] Similarly, it was reported that there were no significant changes found in the anticoagulant activity of factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) according to PPI exposure.[19–21] There are several reports of potential pharmacodynamic and pharmacokinetic interactions between PPIs and antithrombotic agents linked to an increase of thromboembolic event.[22–24] However, except for a lower risk of upper GI bleeding, no other clinically meaningful drug–drug interaction (DDIs) with PPIs were reported for DOACs.[25–28]

There is a concern that the use of PPIs may reduce the efficacy of DOACs due to alteration of gastric pH as an acidic environment is required for the dissolution of DOACs; the increase in gastric pH induced by PPIs might affect the solubility and absorption of some of the DOACs (ie, dabigatran and rivaroxaban).[29] In the RE-LY trial, concomitant use of PPIs reduced dabigatran exposure by 15%, but no significant impact on efficacy outcomes was observed.[30] A pilot RCT reported that a 2-week period of PPI withdrawal leads to a significant increase in dabigatran trough and peak plasma levels in patients with AF.[31]

It is important for clinicians to know whether there are clinically relevant effects of the interaction between PPIs and DOACs when they are coprescribed. Several studies have considered the effects of cotherapy on GI bleeding.[7 32 33] However, none explicitly investigate the effects of concomitant PPIs on the key clinical outcomes (ie, clinically relevant GI bleeding, thromboembolic events or death) simultaneously in DOAC-treated patients.

Objectives

The objective of the study is to examine the risk of thromboembolic events, clinically relevant bleeding, and all-cause death in patients concomitantly prescribed DOACs and PPIs.

Our research question is: Among patients receiving DOACs for any indication, does concomitant PPI prescription alter the event rate for the composite outcome (thromboembolic events, clinically relevant bleeding events and death), compared with not taking PPIs?

METHODS AND ANALYSIS

Study design and data sources

Our study is a population-based cohort study of administrative healthcare data in Ontario, Canada's most populous province. The databases that will be used are listed in table 1.

We will use Ontario's administrative health databases, which are linked at the person-level using a coded version of the Ontario health insurance number. Prescription drug claims will be identified using the Ontario Drug Benefit Database, which contains comprehensive records of prescriptions dispensed to all Ontarians aged 65 years or older. The Canadian Institute for Health Information (CIHI) Discharge Abstract Database captures diagnostic and procedural information about hospital admissions. The Ontario Health Insurance Plan Registered Persons Database contains demographic and mortality data. OHIP physician claims data will be used to identify physicians' services. Researchers routinely use these databases to study the clinical consequences of DDIs.[34 35] International Classification of Diseases, 9th Revision, Clinical Modification codes and International Classification of Diseases, 10th Revision, Clinical Modification codes will be used to capture the clinical diagnoses associated with healthcare encounters (see table 1 and online supplemental appendix). The planned start and end dates for the study are 1 November 2021 and 31 December 2022, respectively.

Study population

Ontario residents aged 66 years or older who are newly dispensed a DOAC (dabigatran, rivaroxaban, edoxaban, or apixaban) from 1 January 2009 to 31 March 2020 will be included. As prescription drug information is available for all adults from their 65th birthday in Ontario, our inclusion of individuals aged 66 years or older will allow for a 1-year lookback period for existing medications. We will exclude patients with a missing or invalid provincial health insurance number, missing age or sex, and prescription for multiple DOACs at entry. Patients will be censored on death, hospitalisation for bleeding or thrombosis, discontinuation of DOAC, switch to other than the entry DOAC, loss of health insurance or the end of the study period (31 March 2020), whichever occurs first. A study flow diagram is provided in figure 1.

Patient and public involvement

Patients were involved in an initial research priority setting focus group study.

Main exposures

We will create a DOAC cohort (the control cohort) and a DOAC-PPI cotherapy cohort (the exposure cohort). Drug exposure with doses will be determined from records of dispensation. Exposure to DOACs and PPIs will be treated as time-varying variables. The drug exposure period will be defined according to the combination of the date the prescription is filled and the prescription duration (days supplied).

We will identify a period of continuous DOAC use for each patient, beginning with the first pharmacy claim for a DOAC following the patient's 66th birthday (index date). Our definition of continuous use is a subsequent prescription within 1.5 times the days supplied of the previous DOAC prescription, using a minimum grace period of 30 days. The risk of DOAC-related bleeding,

Table 1 Description of the Ontario databases to be used in the study

Name of database	Database description
1. Ontario Drug Benefit (ODB) Plan Database	Records of dispensed outpatient prescriptions paid for by the provincial government. The ODB formulary includes a wide range of routine outpatient medications, including the prescription drugs of interest to this study.
2. Canadian Institute for Health Information–Discharge Abstract Database (CIHI-DAD)	The CIHI-DAD collects diagnostic, and procedural variables for each admission to a hospital in Ontario. Coding of primary and secondary diagnoses and inpatient procedures uses the 10th version of the Canadian Modified International Classification of Diseases (ICD-10 CA) for all diagnoses after 2002.
3. Canadian Institute for Health Information-National Ambulatory Care Reporting System (CIHI-NACRS)	The NACRS is compiled by the Canadian Institute for Health Information (CIHI) and contains administrative, clinical (diagnoses and procedures), demographic, and administrative information for all patient visits made to hospital-based and community-based ambulatory care centres (emergency departments, day surgery units, haemodialysis units, and cancer care clinics) in Ontario.
4. Ontario Health Insurance Plan (OHIP) Claims History Database	Claims for physician services paid for by the provincial government. It includes a fee code for each service and a diagnosis code for the condition representing the main reason for each service
5. Ontario Registered Persons Database (RPDB)	The RPDB captures information regarding Ontarians' sex, date of birth, postal code and vital status.
6. Ontario Mental Health Reporting System (OMHRS)	The OMHRS analyzes and reports on information submitted to CIHI about all individuals receiving hospital-based adult mental health services in Ontario.
7. Same Day Surgery Database (SDS)	The SDS summarises information about same day surgery encounters. Each record contains the procedures undergone as well as clinical information about the individual. The clinical information follows the ICD coding scheme (ICD-9 before 2002 and ICD-10 from 2002 onwards).
8. Corporate Provider Database (CPDB)	This database contains addresses, registration and programme eligibility information (eg, contracts such as primary care group) about individual healthcare providers, such as physicians.
9. ICES Physician Database (IPDB)	The IPDB contains information about physicians practicing in Ontario. The IPDB includes demographic information about each physician (ie, age, sex), practice location, physician specialty, services provided, where each physician was trained and year of graduation.
10. Ontario Census Area Profiles (CENSUS)	Ontario-level demographic and statistical data on individuals and households.
11. Postal Code Conversion File (PCCF)	Links postal codes with Census-based area-level variables such as neighbourhood income quintiles and urban/rural residence.
12. Ontario Asthma Database (ASTHMA)	ASTHMA contains all Ontario asthma patients identified since 1991.
13. Ontario Congestive Heart Failure Database (CHF)	The CHF database contains all Ontarians with CHF identified since 1991.
14. Ontario Chronic Obstructive Pulmonary Disease Database (COPD)	COPD contains all Ontario COPD patients identified since 1991.
15. Ontario Hypertension Database (HYPER)	HYPER contains all Ontario hypertension patients identified since 1991.
16. Ontario Dementia Database (DEMENTIA)	The Ontario Dementia Dataset is composed of all Ontario persons who have been identified with Alzheimer's and related dementias in ICES data holdings between the ages of 40–110 years.
17. Ontario Crohn's and Colitis Cohort Database (OCCC)	OCCC includes all Ontario patients who were identified with Crohn's disease or Ulcerative Colitis from the ages of 0–105 years.
18. Ontario Diabetes Database (ODD)	The ODD is a population-based disease registry constructed using a validated algorithm based on hospitalisations and physician visits to identify individuals with physician-diagnosed diabetes mellitus in Ontario.
19. Ontario Rheumatoid Arthritis Database (ORAD)	ORAD contains data on all Ontario rheumatoid arthritis patients identified since 1991.
20. Ontario Cancer Registry (OCR)	Patient demographics, cancer diagnosis details and death information.

thromboembolic events or death will be captured only while patients are taking the index DOAC. Thus, all study analyses will be restricted to periods of anticoagulant treatment during follow-up, defined as the interval from the date the prescription was filled through 1 day after the end of the days of supply, representing approximately two half-lives of the DOACs.

PPI cotherapy will be defined as the period during which gastroprotective effects are most plausible, defined as the interval from filling the prescription (or index date) through the end of the dispensed days of supply. No cotherapy will be defined as person-days with no filled PPI prescription during the observational window.

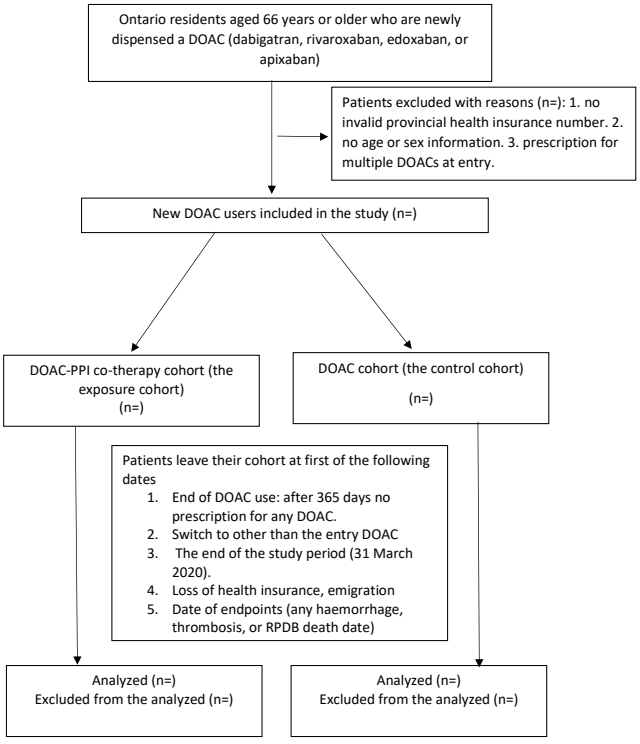

Figure 1 Study flow diagram. DOAC, direct oral anticoagulant; PPI, proton pump inhibitor; RPDB, Ontario Registered Persons Database.

Main outcomes

The primary outcome will be a composite of clinically relevant bleeding, thrombotic events or all-cause death. The diagnosis and procedure codes used to define the outcomes can be found in online supplemental appendix. Thrombotic events are defined as any thromboembolic event, including myocardial infarction (MI), systemic embolism, ischaemic stroke, deep vein thrombosis and pulmonary embolism as captured in hospital discharge abstracts (DAD) or emergency department records (National Ambulatory Care Reporting System (NACRS)). Clinically relevant bleeding is defined as hospitalisation with a most responsible diagnosis, or an emergency department visit with a primary diagnosis of any bleeding. Secondary outcomes include the individual members of the composite primary outcome measure, emergency department visits for the primary outcome, and hospitalisation for the primary outcome. Outcomes will be measured through the records for the hospitalisations and emergency visits registered in the relevant databases after the index date.

Sample size

We will include up to 26 covariates in the final multivariable Poisson regression models and a minimum of 520 patients (26 covariates×20) with at least one of the components of the composite outcome (ie, clinically relevant bleeding, thromboembolic events or death).[36] To our knowledge, there have been no studies examining rates of the composite outcome of clinically relevant bleeding, thromboembolic events or death for patients taking DOACs precisely as we have defined them here. Regarding the feasibility of the sample size, a recent Ontario study showed that 128 273 patients (average 14 252 annually) initiated anticoagulation with a DOAC from 2009 to 2017, and 10.5% were reported to have suffered at least one of the composite outcome (ie, clinically relevant bleedings, thromboembolic events and death).[37] If the percentage of cotherapy with PPIs is around 35% as reported by Ray *et al*,[7] our cotherapy cohort numbers could reach 5000 annually. During the 10-year observational windows, there should be approximately 5250 patients with at least one component event of the composite outcome.

Covariates

The potential confounders include patient demographics at cohort entry date (age, sex, urban/rural residence (Ontario Registered Persons Database (RPDB) rural variable) and socioeconomic status (income quintiles: census-based median neighbourhood (dissemination area) income quintile)), indications (AF, thromboembolism, valve replacement/repair comorbidities, hip or knee replacement), Charlson Comorbidity Index, comorbidities (MI, congestive heart failure, peripheral vascular disease, ischaemic stroke, transient ischaemic attack, dementia, chronic pulmonary disease, anaemia, kidney diseases and hepatic diseases), components of HAS-B_ED score (hypertension, abnormal kidney or liver function, stroke, bleeding history and alcohol use)), CHADS2-VASc Score for AF stroke risk, and prior relevant medications (warfarin (yes/no) within 100 days preceding the index date, former PPIs cotherapy consisted of person-days for patients who filled a PPI prescription in the past year, but whose days of supply ended prior to lookback period and, thus, should not benefit from cotherapy.

The potential mediators of the proposed covariates during the following-up period include prescription aspirin (time-varying covariable), antiplatelet agents (time-varying covariable), nonsteroidal anti-inflammatory drugs (NSAIDs) (time-varying covariable), statins (yes/no), antimicrobials (yes/no), histamine H2 receptor antagonists (cimetidine, famotidine, nizatidine, sucralfate and ranitidine) (yes/no) and selective serotonin receptor inhibitors (SSRIs) (yes/no). Detailed information on covariates is provided in online supplemental appendix.

Bias

To control for confounding, we will include covariables mentioned above in the model to adjust the results. Furthermore, time-varying exposures will help address potential time-varying confounding.[38] For instance, the doses of our primary exposures (DOACS and PPIs) and prescription of other drugs that may affect outcome risk (eg, NSAIDs and antiplatelet agents) will be captured in a time-varying fashion on a day-to-day

basis, and time-dependent Poisson regression models will be used. However, one of the key limitations of any observational study is the risk of residual confounding, even after all potential adjustments are made. In addition, any missing data will be dealt with by multiple imputation should observations be missing in more than 10% of cases.[39]

Data collection

The lookback windows include (1) 365 days for defining new DOAC use, (2) 100 days for other related drugs, (3) 180 days to 3 years for disease comorbidities and derived indices and (4) as per the diagnosis dates in ICES-derive chronic disease cohorts.

Baseline data collection will include age at cohort entry, sex, key medical comorbidities (see online supplemental appendix), previous GI bleeding history, indications for DOAC, the name of DOAC and PPIs, the first prescription date of DOAC (index date), information for covariates, patients who transfer to other DOAC during the observational window and the type and date of each outcome.

Data analysis

As this is a population-based study, we will include all eligible Ontario residents. We will compare baseline characteristics of exposures and controls using standardised differences. We will compute a set of stabilised inverse probability of treatment (IPT) weight to account for differences in the baseline characteristics (online supplemental appendix) between the two cohorts.[40] First, the IPT weights will be obtained by fitting a logistic regression model with the primary outcome and the DOACs and PPIs cotherapy as independent variables. Next, we will apply IPT weights and assessed balance between the two cohorts by calculating weighted standardised differences, which express the difference of means or prevalence between the two cohorts as a proportion of the pooled SD, with standardised differences above 0.10 considered potentially meaningful. The time-dependent Poisson regression model will then be used to estimate the adjusted incidence of the target outcomes according to both exposure cohort and control cohort with all available covariates using the weighted sample[41] and IPT weight adjusted incidence rate ratios and 95% CIs will be obtained. The criterion for statistical significance will be set at alpha=0.05. All statistical analyses will be performed at ICES using SAS V.9.4 (SAS Institute).

Sensitivity analysis will be performed (1) by excluding patients who did not maintain their original DOAC use assignments during their follow-up and (2) by excluding patients who re-entered the cohort. Subgroup analysis will be performed according to the different DOACs, PPIs and indications, respectively, if sample size and power permit.

ETHICS AND DISSEMINATION

This research is exempt from REB review as the data used in the project is authorised under section 45 of Ontario's Personal Health Information Protection Act. The data will be analysed at ICES (www.ices.on.ca) in linked, anonymised form. On completion, the results of this population-based study will be submitted to a peer-reviewed biomedical journal for publication and presented at several conferences.

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Contributors AH and MW obtained the funding and developed the study idea. MW, AH and MP designed the study. MW obtained data permissions and research ethics approvals. LTh, DS, LTa and LM contributed to the study design, methodology and analysis plan. AH and DS provided clinical guidance, AH developed the outcome data sets and MP provided expertise in large administrative health databases housed at ICES in designing the study. MW drafted the initial manuscript, and all authors critiqued the protocol manuscript. All authors approved the attached manuscript for publication and are accountable for all aspects of the work.

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Patient and public involvement Patients were involved in a prior research priority-setting focus group study that led to this study design.

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REFERENCES

1 Chaudhary R, Sharma T, Garg J, *et al*. Direct oral anticoagulants: a review on the current role and scope of reversal agents. *J Thromb Thrombolysis* 2020;49:271–86.
2 Sterne JA, Bodalia PN, Bryden PA, *et al*. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. *Health Technol Assess* 2017;21:1–386.
3 Savarino V, Marabotto E, Zentilin P, *et al*. Proton pump inhibitors: use and misuse in the clinical setting. *Expert Rev Clin Pharmacol* 2018;11:1123–34.
4 Burnett AE, Mahan CE, Vazquez SR, *et al*. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTe treatment. *J Thromb Thrombolysis* 2016;41:206–32.
5 Chan EW, Lau WCY, Leung WK, *et al*. Prevention of Dabigatran-Related gastrointestinal bleeding with gastroprotective agents: a population-based study. *Gastroenterology* 2015;149:586–95.
6 O'Dea D, Whetteckey J, Ting N. A prospective, randomized, open-label study to evaluate two management strategies for gastrointestinal symptoms in patients newly on treatment with dabigatran. *Cardiol Ther* 2016;5:187–201.
7 Ray WA, Chung CP, Murray KT, *et al*. Association of oral anticoagulants and proton pump inhibitor Cotherapy with hospitalization for upper gastrointestinal tract bleeding. *JAMA* 2018;320:2221–30.
8 Tang B, Xiao S. Logistic regression analysis of risk factors for upper gastrointestinal bleeding induced by PCI in combination with double antiplatelet therapy for STEMI patients. *Acta Gastroenterol Belg* 2020;83:245–8.
9 Weitz JI, Semchuk W, Turpie AGG, *et al*. Trends in prescribing oral anticoagulants in Canada, 2008-2014. *Clin Ther* 2015;37:2506–14.
10 Perreault S, de Denus S, White-Guay B, *et al*. Oral anticoagulant prescription trends, profile use, and determinants of adherence in patients with atrial fibrillation. *Pharmacotherapy* 2020;40:40–54.
11 Verma A, Cairns JA, Mitchell LB, *et al*. 2014 focused update of the Canadian cardiovascular Society guidelines for the management of atrial fibrillation. *Can J Cardiol* 2014;30:1114–30.
12 Summary Safety Review - Proton Pump Inhibitors (PPIs) - Assessing the risk of a type of skin reaction [Subacute Cutaneous Lupus Erythematosus (SCLE)], 2017. Available: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/proton-pump-inhibitors-assessing-risk-type-skin-reaction.html [Accessed 10 Sep 2020].
13 Lee K, Jani T, Cheng R, *et al*. Prescribed drug spending in Canada, 2019: a focus on public drug programs. *Healthc Q* 2020;23:10–12.
14 Wang M, Zeraatkar D, Obeda M. Drug–drug interactions with warfarin: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2021.
15 Bang CS, Joo MK, Kim B-W, *et al*. The role of acid suppressants in the prevention of anticoagulant-related gastrointestinal bleeding: a systematic review and meta-analysis. *Gut Liver* 2020;14:57–66.
16 Nantsupawat T, Soontrapa S, Nantsupawat N, *et al*. Risk factors and prevention of dabigatran-related gastrointestinal bleeding in patients with atrial fibrillation. *J Arrhythm* 2018;34:30–5.
17 Moayyedi P, Eikelboom JW, Bosch J, *et al*. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2019;157:403–12.
18 Bolek T, Samoš M, Stančiaková L, *et al*. The impact of proton pump inhibition on dabigatran levels in patients with atrial fibrillation. *Am J Ther* 2019;26:e308–13.
19 Bolek T, Samoš M, Škorňová I, *et al*. Does proton pump inhibition change the on-treatment anti-Xa activity in xabans-treated patients with atrial fibrillation? A pilot study. *J Thromb Thrombolysis* 2019;47:140–5.
20 Moayyedi P, Eikelboom JW, Bosch J, *et al*. Safety of proton pump inhibitors based on a large, Multi-Year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 2019;157:682–91.
21 Moore KT, Plotnikov AN, Thyssen A, *et al*. Effect of multiple doses of omeprazole on the pharmacokinetics, pharmacodynamics, and safety of a single dose of rivaroxaban. *J Cardiovasc Pharmacol* 2011;58:581–8.
22 Gilard M, Arnaud B, Cornily J-C, *et al*. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (omeprazole clopidogrel aspirin) study. *J Am Coll Cardiol* 2008;51:256–60.
23 O'Donoghue ML, Braunwald E, Antman EM, *et al*. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009;374:989–97.
24 Muldowney JAS, Benge CD. Combination therapy with clopidogrel and proton-pump inhibitors. *Lancet* 2010;375:27–8.
25 Hutchaleelaha A, Lambing J, Romanko K. Effect of a proton pump inhibitor or an antacid on pharmacokinetics of Betrixaban, a novel oral factor Xa inhibitor: 1389928. *Clin Pharmacol Drug Dev* 2012;1.
26 Giugliano RP, Ruff CT, Braunwald E, *et al*. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–104.
27 The Hokusai-VTE Investigators*et al*. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406–15.
28 Upreti VV, Song Y, Wang J, *et al*. Effect of famotidine on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. *Clin Pharmacol* 2013;5:59.
29 Ogawa R, Echizen H. Drug-Drug interaction profiles of proton pump inhibitors. *Clin Pharmacokinet* 2010;49:509–33.
30 Liesenfeld K-H, Lehr T, Dansirikul C, *et al*. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. *J Thromb Haemost* 2011;9:2168–75.
31 Schnierer M, Samoš M, Bolek T, *et al*. The effect of proton pump inhibitor withdrawal on dabigatran etexilate plasma levels in patients with atrial fibrillation: a washout study. *J Cardiovasc Pharmacol* 2020;75:333–5.
32 Lee S-R, Kwon S, Choi E-K, *et al*. Proton pump inhibitor Co-Therapy in patients with atrial fibrillation treated with oral anticoagulants and a prior history of upper gastrointestinal tract bleeding. *Cardiovasc Drugs Ther* 2021;117.
33 Lee H-J, Kim H-K, Kim B-S, *et al*. Risk of upper gastrointestinal bleeding in patients on oral anticoagulant and proton pump inhibitor co-therapy. *PLoS One* 2021;16:e0253310–e10.
34 Wright AJ, Gomes T, Mamdani MM, *et al*. The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers. *CMAJ* 2011;183:303–7.
35 Juurlink DN, Gomes T, Ko DT, *et al*. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *Can Med Assoc J* 2009;180:713–8.
36 Ogundimu EO, Altman DG, Collins GS. Adequate sample size for developing prediction models is not simply related to events per variable. *J Clin Epidemiol* 2016;76:175–82.
37 Durand M, Schnitzer ME, Pang M, *et al*. Comparative effectiveness and safety of direct oral anticoagulants versus vitamin K antagonists in nonvalvular atrial fibrillation: a Canadian multicentre observational cohort study. *CMAJ Open* 2020;8:E877–86.
38 Mansournia MA, Etminan M, Danaei G, *et al*. Handling time varying confounding in observational research. *BMJ* 2017;359:j4587.
39 Pedersen AB, Mikkelsen EM, Cronin-Fenton D, *et al*. Missing data and multiple imputation in clinical epidemiological research. *Clin Epidemiol* 2017;9:157–66.
40 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661–79.
41 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.