

Supplemental Figure legends

Supplemental Figure 1: Propensity score diagnostics. 1a) Distribution of propensity scores in the PPI and H2 blockers groups in the original cohort. 1b) Distribution of propensity scores in the PPI and H2 blockers groups in the pseudo cohort after inverse probability of treatment weighting. 1c) Standardized differences before and after inverse probability of treatment weighting in select comorbidities. A positive difference indicates higher proportion (or mean) in the PPI group. Standardized difference rows are presented in descending order of difference in the original cohort. GERD, gastroesophageal reflux disease; ACE/ARB, Angiotensin converting enzyme inhibitors / Angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drugs.

Supplemental Figure 2: Kaplan-Meier curves of PPI and H2 blockers groups

Supplemental table 1: Summary of target trial protocol, and strategy adopted for emulating the trial

Protocol Components	Description in Target Trial Protocol	Our Strategy
Eligibility criteria	New users of PPIs or H2 blockers between July 2002 and June 2004	Select cohort participants that received a PPIs or H2 blockers prescription between July 2002 and June 2004, and have no prior history of prescriptions for these medications in VA data.
Treatment strategy	Use PPIs as only acid suppressant	Select those whose first recorded acid suppressant prescription is PPIs. Exclude those who, within 180 days of this first prescription, used H2 blockers or were prescribed a supply of ≤ 90 days of PPIs.
Control strategy	Use H2 blockers as only acid suppressant	Select those whose first recorded acid suppressant prescription is a H2 blocker. Exclude those who, within 180 days of this first prescription, used PPI or were prescribed a supply of ≤ 90 days of H2 blockers.
Assignment procedures	Participants will be randomly assigned to treatment or control strategies at the time of enrollment and will be notified of the group they are in.	Apply inverse probability of treatment weighting based on high dimensional propensity score to reduce the probability of assignment based on measured characteristics. Apply an instrumental variable approach to reduce probability of assignment based on unmeasured characteristics. Only pre-treatment information will be used.
Follow-up	Follow-up begins 180 days after group assignment. Follow for 10 years, or when death occurs	Exclude those who die within 180 days after their first recorded prescription. Follow participants for 10 years or until there is a record of death in the National Death Index (NDI).
Outcome	All-cause mortality and cause specific mortality	Cause of mortality will be determined by recorded underlying cause of death in the NDI (ICD-10).
Causal contrasts of interest	Intention-to-treat effect	Fix participants' group assignment based on first recorded treatment for the entire duration of follow-up.
Analysis plan	Estimate the intention-to-treat effect via comparison of all cause and cause-specific survival probabilities at 10 years among individuals assigned to PPI or H2 blockers groups.	Fine and Gray models will be used to estimate survival probability at 10 years.

Supplemental table 2: PPI and H2 blockers initial prescriptions

Medication	Formula	Pill format (mg)	Times per day	N (%)	
PPIs	Lansoprazole	15	1	1047 (0.66)	
		30	1	9652 (6.12)	
		30	2	810 (0.51)	
	Omeprazole	20	1	34149 (21.66)	
		20	2	5773 (3.66)	
	Rabeprazole	20	1	92650 (58.78)	
		20	2	13250 (8.41)	
Other PPIs				294 (0.19)	
H2 blockers	Cimetidine	300	1	109 (0.19)	
		300	2	101 (0.18)	
		400	1	275 (0.48)	
		400	2	579 (1.02)	
	Ranitidine	150	1	8225 (14.47)	
			2	42349 (74.50)	
		300	1	1819 (3.20)	
			2	3156 (5.55)	
	Other H2 blockers				229 (0.40)

Supplemental table 3: Results from time-varying analyses of PPI exposure

Cause of death	ICD-10 cause of death	Fine and Gray HR (95% CI)
Death	Any	1.07 (1.04, 1.10)
Disease of the circulatory system	I00-I99	1.03 (1.01, 1.05)
Neoplasms	C00-D49	1.30 (1.27, 1.33)
Disease of the genitourinary system	N00-N99	1.20 (1.12, 1.28)
Infectious and parasitic diseases	A00-B99	1.41 (1.31, 1.52)

Exposure was defined as time varying ever exposure to PPI.
Results are provided as hazard ratios with 95% confidence intervals in Fine and Gray models.