Supplemental Figures:

Supplemental figure 1: Flow diagram of cohort assembly of a 1:1 propensity score matched cohort of new users of PPI (n=20,270) and new users of H2 blockers (n=20,270)

Supplemental figure 2: Flow diagram of cohort assembly of a 1:1 propensity score matched cohort of new PPI users (n=173,321) and a control group (n=173,321)

Supplemental table 1: Association of PPI and risk of kidney outcomes in Univariate Cox regression models.

	Hazard Ratio	Confidence interval
eGFR<60 ml/min/1.73m^2	1.33	1.29-1.37
Incident chronic kidney disease	1.41	1.35-1.48
Doubling of serum creatinine	1.71	1.59-1.84
Greater than 30% decline in eGFR	1.43	1.38-1.48
ESRD	2.17	1.35-3.48
ESRD or >50% decline in eGFR	1.65	1.54-1.76

Supplemental table 2: Baseline characteristics of a 1:1 propensity score matched cohort of new users of H2 blockers (n=20,270) and new proton pump inhibitor users (n=20,270).

		H2 blockers (n=20,270)	PPI (n=20,270)	Standardized difference
Age (SD)		55.40 (12.81)	55.42 (12.60)	0.00
Baseline eGFR in ml/min/1.73m^2 (SD)		86.98 (15.88)	87.08 (15.94)	0.00
Race	White (%)	15,937 (78.62)	15,934 (78.61)	0.00
	Black (%)	3,784 (18.67)	3,778 (18.64)	0.00
	Other (%)	549 (2.71)	558 (2.75)	0.00
Sex	Male (%)	18,929 (93.38)	18,935 (93.41)	0.00
	Female (%)	1,341 (6.62)	1,335 (6.59)	0.00
Diabetes mellitus (%)		8,923 (44.02)	8,862 (43.72)	0.01
Hypertension (%)		15,814 (78.02)	15,857 (78.23)	0.01
Chronic lung disease (%)		7,951 (39.23)	7,857 (38.76)	0.01
Peripheral artery disease (%)		5,009 (24.71)	5,051 (24.92)	0.00
Cardiovascular disease (%)		8,459 (41.73)	8,430 (41.59)	0.00
Cerebrovascular disease (%)		4,596 (22.67)	4,595 (22.67)	0.00
Dementia (%)		5,058 (24.95)	5,105 (25.19)	0.01
Hyperlipidemia (%)		14,785 (72.94)	14,923 (73.62)	0.02
Hepatitis C (%)		1,198 (5.91)	1,146 (5.65)	0.01
HIV (%)		55 (0.27)	52 (0.26)	0.00
GERD (%)		3,767 (18.58)	3,759 (18.54)	0.00
Upper GI tract bleeding (%)		246 (1.21)	267 (1.32)	0.01
Ulcer disease (%)		666 (3.29)	664 (3.28)	0.00
H. Pylori infection (%)		22 (0.11)	19 (0.09)	0.01
Barrett's esophagus (%)		15 (0.07)	20 (0.10)	0.01
Achalasia (%)		1 (0.00)	3 (0.01)	0.01
Stricture (%)		33 (0.16)	43 (0.21)	0.01
Esophageal adenocarcinoma (%)		3 (0.01)	2 (0.01)	0.00

Supplemental table 3: Baseline characteristics of a 1:1 propensity score matched cohort of new users of PPI (n=173,321) and matched controls (n=173,321).

		Control (n=173,321)	PPI (n=173,321)	Standardized difference
Age (SD)		57.03 (12.71)	56.85 (11.85)	0.00
Baseline eGFR in ml/min/1.73m^2 (SD)		86.57 (16.02)	86.56 (15.67)	0.00
Race	White	136,827 (78.94)	137,174 (79.14)	0.00
	Black	32,440 (18.72)	32,018 (18.47)	0.01
	Other	4,054 (2.34)	4,129 (2.38)	0.00
Sex	Male	161,294 (93.06)	161,259 (93.04)	0.00
	Female	12,027 (6.94)	12,062 (6.96)	0.00
Diabetes mellitus (%)		71,342 (41.16)	72,309 (41.72)	0.01
Hypertension (%)		136,355 (78.67)	136,782 (78.92)	0.01
Chronic lung disease (%)		66,505 (38.37)	66,955 (38.63)	0.01
Peripheral artery disease (%)		29,766 (17.17)	31,311 (18.07)	0.02
Cardiovascular disease (%)		71,435 (41.22)	71,807 (41.43)	0.00
Cerebrovascular disease (%)		25,049 (14.45)	26,457 (15.26)	0.02
Dementia (%)		30,874 (17.81)	32,380 (18.68)	0.02
Hyperlipidemia (%)		126,572 (73.03)	127,463 (73.54)	0.01
Hepatitis C (%)		15,321 (8.84)	14,892 (8.59)	0.01
HIV (%)		714 (0.41)	678 (0.39)	0.00
GERD (%)		88,721 (51.19)	86,804 (50.08)	0.02
Upper GI tract bleeding (%)		7,459 (4.30)	7,898 (4.56)	0.01
Ulcer disease (%)		23,984 (13.84)	26,228 (15.13)	0.04
H. Pylori infection (%)		3,329 (1.92)	4,052 (2.34)	0.03
Barrett's esophagus (%)		1,981 (1.14)	3,207 (1.85)	0.06
Achalasia (%)		201 (0.12)	214 (0.12)	0.00
Stricture (%)		1,893 (1.09)	2,299 (1.33)	0.02
Esophageal adenocarcinoma (%)		251 (0.14)	291 (0.17)	0.01

Supplemental table 4: Risk of renal events in models additionally adjusted for number of eGFR measurements prior to cohort entry.

Outcome		H2 blockers (n=20,270)	PPI (n=173,321)
eGFR measurement	Average number of eGFR measurement (SD)	4.72 (5.73)	6.93 (7.21)
Incident eGFR<60 ml/min/1.73m^2	Hazard Ratio (Confidence interval)	1	1.18 (1.15, 1.22)
Incident chronic kidney disease	Hazard Ratio (Confidence interval)	1	1.24 (1.19, 1.30)
Doubling of serum creatinine	Hazard Ratio (Confidence interval)	1	1.52 (1.41, 1.64)
Greater than 30% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.28 (1.24, 1.33)
End stage renal disease	Hazard Ratio (Confidence interval)	1	1.89 (1.17, 3.06)
End stage renal disease or >50% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.45 (1.36, 1.55)
Hazard Ratios were obtained from Cox models adjusted for number of eGFR measurement, baseline eGFR, age, race, gender, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma			

Supplemental table 5a: Risk of renal events in models additionally adjusted for use of NSAIDs prior to cohort entry.

Outcome		H2 blockers (n=20,270)	PPI (n=173,321)
NSAIDs	Number of patients with NSAIDs (%)	8,697 (42.91)	89,999 (51.93)
Incident eGFR<60 ml/min/1.73m^2	Hazard Ratio (Confidence interval)	1	1.22 (1.18, 1.26)
Incident chronic kidney disease	Hazard Ratio (Confidence interval)	1	1.28 (1.22, 1.34)
Doubling of serum creatinine	Hazard Ratio (Confidence interval)	1	1.53 (1.42, 1.65)
Greater than 30% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.32 (1.27, 1.36)
End stage renal disease	Hazard Ratio (Confidence interval)	1	1.99 (1.23, 3.23)
End stage renal disease or >50% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.47 (1.38, 1.57)

Hazard Ratios were obtained from Cox models adjusted for use of NSAIDs, baseline eGFR, age, race, gender, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
NSAIDs exposure was defined as use of any NSAIDs for 30 days or more before cohort entry.

Supplemental table 5b: Risk of renal events in models additionally adjusted for use of NSAIDs after cohort entry.

Outcome		H2 blockers (n=20,270)	PPI (n=173,321)
Incident eGFR<60 ml/min/1.73m^2	Number of patients with NSAIDs (%)	6,272 (30.94)	44,236 (25.52)
	Hazard Ratio (Confidence interval)	1	1.22 (1.18, 1.26)
Incident chronic kidney disease	Number of patients with NSAIDs (%)	6,329 (31.22)	44,487 (25.67)
	Hazard Ratio (Confidence interval)	1	1.28 (1.23, 1.34)
Doubling of serum creatinine	Number of patients with NSAIDs (%)	6,417 (31.66)	44,994 (25.96)
	Hazard Ratio (Confidence interval)	1	1.52 (1.41, 1.64)
Greater than 30% decline in eGFR	Number of patients with NSAIDs (%)	6,346 (31.31)	44,622 (25.75)
	Hazard Ratio (Confidence interval)	1	1.32 (1.28, 1.36)
End stage renal disease	Number of patients with NSAIDs (%)	6,434 (31.74)	45,078 (26.01)
	Hazard Ratio (Confidence interval)	1	1.94 (1.20, 3.14)
End stage renal disease or >50% decline in eGFR	Number of patients with NSAIDs (%)	6,412 (31.63)	44,969 (25.95)
	Hazard Ratio (Confidence interval)	1	1.47 (1.37, 1.57)

Hazard Ratios were obtained from Cox models adjusted for use of NSAIDs, baseline eGFR, age, race, gender, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
NSAIDs exposure was defined as use of any NSAIDs for 30 days or more after cohort entry.

Supplemental table 6: Risk of renal events in a subcohort of patients where data on baseline microalbumin/creatinine ratio was available (n=29,059).

Outcome		H2 blockers (n=2,322)	PPI (n=26,737)
Microalbumin /creatinine ratio (mg/g)	<20 (%)	1,734 (74.68)	19,587 (73.26)
	20-300 (%)	539 (23.21)	6,547 (24.49)
	>300 (%)	49 (2.11)	603 (2.26)
Incident eGFR<60 ml/min/1.73m^2	Hazard Ratio (Confidence interval)	1	1.22 (1.13, 1.32)
Incident chronic kidney disease	Hazard Ratio (Confidence interval)	1	1.33 (1.21, 1.47)
Doubling of serum creatinine	Hazard Ratio (Confidence interval)	1	1.43 (1.20, 1.71)
Greater than 30% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.34 (1.24, 1.46)
End stage renal disease	Hazard Ratio (Confidence interval)	1	2.82 (0.88, 8.98)
End stage renal disease or >50% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.36 (1.17, 1.59)
Hazard Ratios were obtained from Cox models adjusted for microalbumin/creatinine ratio, baseline eGFR, age, race, gender, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma Microalbumin/creatinine ratio in mg/g was categorized as <20, 20-300, and >300.			

Supplemental table 7: Risk of renal events in models additionally adjusted for baseline serum bicarbonate (n=174,322)

Outcome		H2 blockers (n=17,561)	PPI (n=156,761)
Carbon dioxide (MEQ/L)	Average carbon dioxide (SD)	26.96 (2.95)	27.02 (2.94)
Incident eGFR<60 ml/min/1.73m^2	Hazard Ratio (Confidence interval)	1	1.22 (1.18, 1.26)
Incident chronic kidney disease	Hazard Ratio (Confidence interval)	1	1.28 (1.22, 1.35)
Doubling of serum creatinine	Hazard Ratio (Confidence interval)	1	1.56 (1.44, 1.68)
Greater than 30% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.32 (1.27, 1.37)
End stage renal disease	Hazard Ratio (Confidence interval)	1	2.20 (1.28, 3.79)
End stage renal disease or >50% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.49 (1.38, 1.60)
Hazard Ratios were obtained from Cox models adjusted for carbon dioxide, baseline eGFR, age, race, gender, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma Serum bicarbonate in MEG/L was treated as a continuous variable.			

Supplemental table 8a: Risk of renal events in models additionally adjusted for use of ACE or ARB

Outcome		H2 blockers (n=20,270)	PPI (n=173,321)
ACE/ARB	Number of patients with ACEI/ARB (%)	6,086 (30.02)	68,890 (39.75)
Incident eGFR<60 ml/min/1.73m^2	Hazard Ratio (Confidence interval)	1	1.21 (1.17, 1.24)
Incident chronic kidney disease	Hazard Ratio (Confidence interval)	1	1.26 (1.21, 1.32)
Doubling of serum creatinine	Hazard Ratio (Confidence interval)	1	1.51 (1.40, 1.63)
Greater than 30% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.31 (1.27, 1.35)
End stage renal disease	Hazard Ratio (Confidence interval)	1	1.90 (1.18, 3.08)
End stage renal disease or >50% decline in eGFR	Hazard Ratio (Confidence interval)	1	1.45 (1.36, 1.55)
Hazard Ratios were obtained from Cox models adjusted for use of ACE/ARB, baseline eGFR, age, race, gender, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma ACE or ARB exposure was defined as use of either for 30 days or more before cohort entry.			

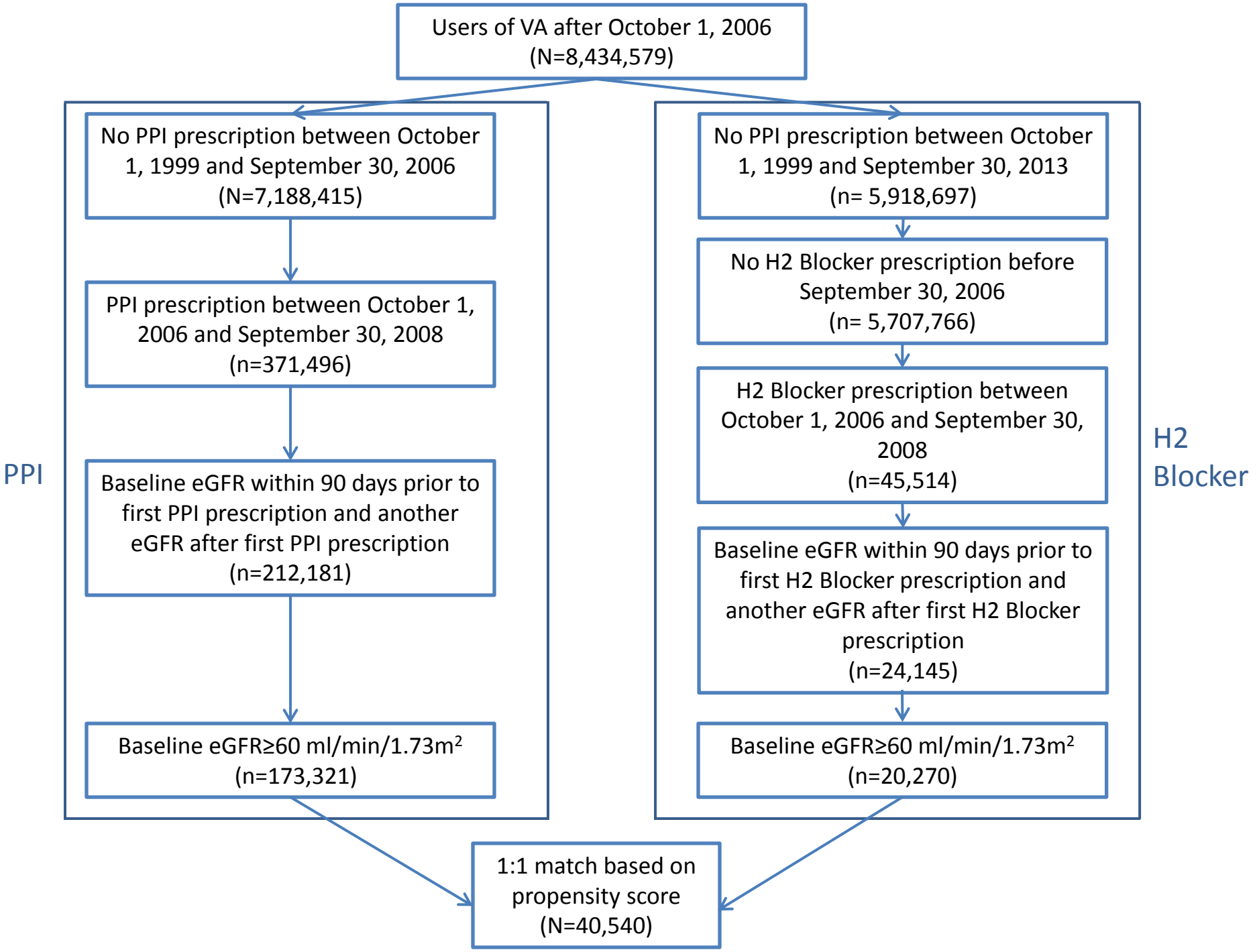
Supplemental table 8b: Risk of renal events in models additionally adjusted for for use of ACE or ARB after cohort entry.

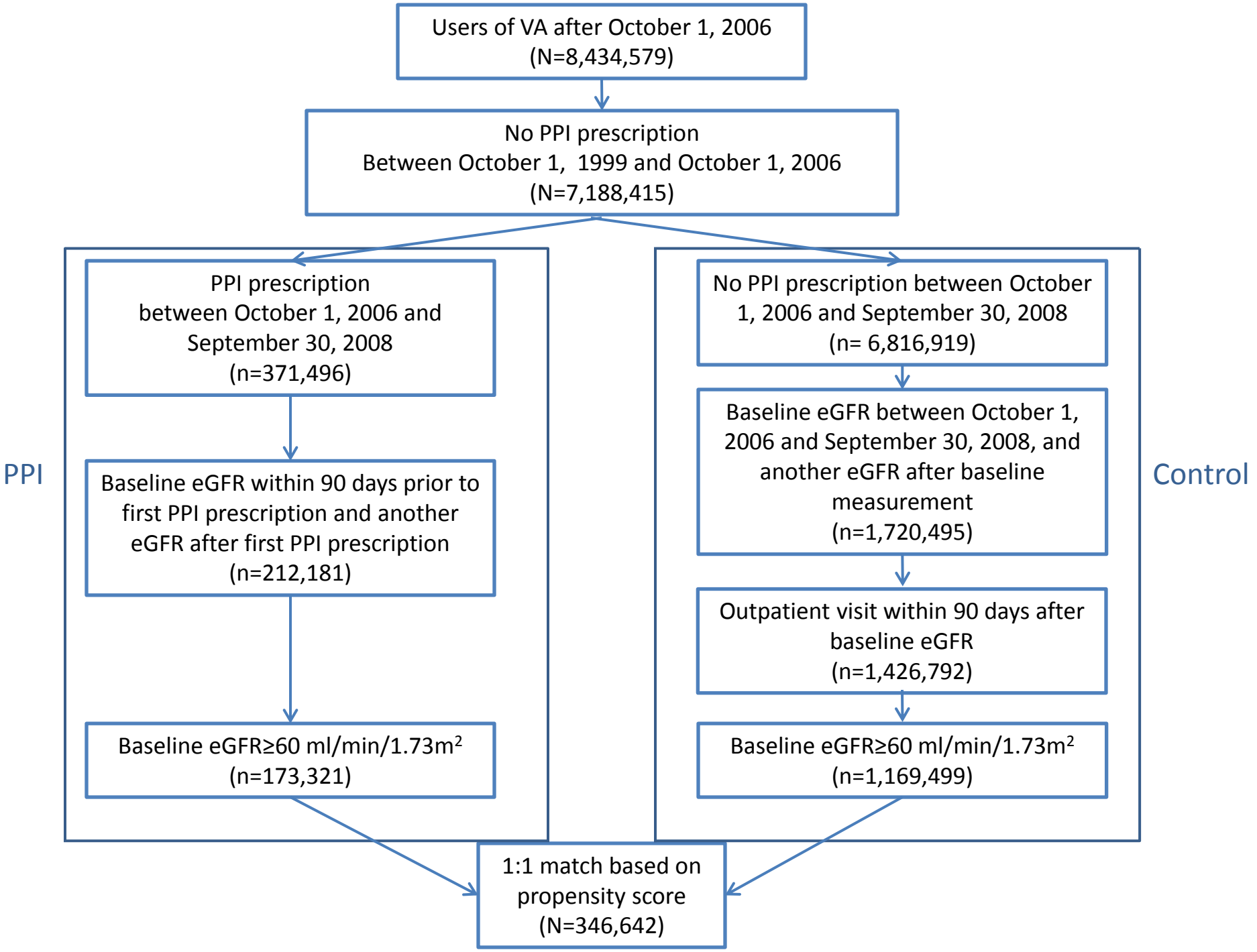
Outcome		H2 blockers (n=20,270)	PPI (n=173,321)
Incident eGFR<60 ml/min/1.73m^2	Number of patients with ACE/ARB (%)	8,633 (42.59)	81,679 (47.13)
	Hazard Ratio (Confidence interval)	1	1.22 (1.18, 1.26)
Incident chronic kidney disease	Number of patients with ACE/ARB (%)	8,773 (43.28)	83,278 (48.05)
	Hazard Ratio (Confidence interval)	1	1.29 (1.23, 1.34)
Doubling of serum creatinine	Number of patients with ACE/ARB (%)	9,013 (44.46)	86,027 (49.63)
	Hazard Ratio (Confidence interval)	1	1.53 (1.42, 1.65)
Greater than 30% decline in eGFR	Number of patients with ACE/ARB (%)	8,801 (43.42)	83,564 (48.21)
	Hazard Ratio (Confidence interval)	1	1.32 (1.28, 1.37)
End stage renal disease	Number of patients with ACE/ARB (%)	9,050 (44.65)	86,785 (50.07)
	Hazard Ratio (Confidence interval)	1	1.96 (1.21, 3.17)
End stage renal disease or >50% decline in eGFR	Number of patients with ACE/ARB (%)	9,000 (44.40)	85,866 (49.54)
	Hazard Ratio (Confidence interval)	1	1.47 (1.38, 1.57)

Hazard Ratios were obtained from Cox models adjusted for use of ACE/ARB, baseline eGFR, age, race, gender, diabetes mellitus, hypertension, cardiovascular disease, peripheral artery disease, cerebrovascular disease, chronic lung disease, hepatitis C, HIV, dementia, GERD, upper GI tract bleeding, ulcer disease, H. Pylori infection, Barrett's esophagus, achalasia, stricture and esophageal adenocarcinoma
ACE or ARB exposure was defined as use of either for 30 days or more after cohort entry.

Supplemental table 9. Distribution of PPI and H2 blockers use

PPI*	N (%)
Omeprazole	170,898 (98.60)
Pantoprazole	1,677 (0.97)
Lansoprazole	457 (0.26)
Rabeprazole	186 (0.11)
Esomeprazole	103 (0.06)
*PPI that a patient received as their first PPI prescription	
H2 blockers*	N (%)
Ranitidine	19,847 (97.91)
Cimetidine	281 (1.39)
Famotidine	142 (0.70)
*H2 blockers that a patient received as their first H2 blockers prescription	


Users of VA after October 1, 2006
(N=8,434,579)
PPI
No PPI prescription between October 1, 1999 and September 30, 2006
(N=7,188,415)
PPI prescription between October 1, 2006 and September 30, 2008
(n=371,496)
Baseline eGFR within 90 days prior to first PPI prescription and another eGFR after first PPI prescription
(n=212,181)
Baseline eGFR≥60 ml/min/1.73m2
(n=173,321)
H2 Blocker
No PPI prescription between October 1, 1999 and September 30, 2013
(n= 5,918,697)
No H2 Blocker prescription before September 30, 2006
(n= 5,707,766)
H2 Blocker prescription between October 1, 2006 and September 30, 2008
(n=45,514)
Baseline eGFR within 90 days prior to first H2 Blocker prescription and another eGFR after first H2 Blocker prescription
(n=24,145)
Baseline eGFR≥60 ml/min/1.73m2
(n=20,270)
1:1 match based on propensity score
(N=40,540)


Users of VA after October 1, 2006
(N=8,434,579)
No PPI prescription
Between October 1, 1999 and October 1, 2006
(N=7,188,415)
PPI
PPI prescription
between October 1, 2006 and
September 30, 2008
(n=371,496)
Baseline eGFR within 90 days prior to
first PPI prescription and another
eGFR after first PPI prescription
(n=212,181)
Baseline eGFR≥60 ml/min/1.73m2
(n=173,321)
Control
No PPI prescription between October
1, 2006 and September 30, 2008
(n= 6,816,919)
Baseline eGFR between October 1,
2006 and September 30, 2008, and
another eGFR after baseline
measurement
(n=1,720,495)
Outpatient visit within 90 days after
baseline eGFR
(n=1,426,792)
Baseline eGFR≥60 ml/min/1.73m2
(n=1,169,499)
1:1 match based on
propensity score
(N=346,642)