Supplementary Figure 1: Cohort Selection

4,140,390 serum creatinine tests with an associated urine ACR in the past 12 months

3,172 creatinine tests excluded due to an invalid IKN, missing gender or date of birth, death prior to index date or associated with a non-Ontario resident

4,137,218 creatinine tests associated with a valid health number and Ontario residency

1,864,329 creatinine tests excluded:
<40 years of age (n=276,539)
Index date > March 31st, 2009 (n=1,582,793)
Kidney transplant recipient (n=2,923)
Evidence of a history of dialysis prior to the index date (n=2,074)

2,272,889 creatinine tests meeting inclusion criteria

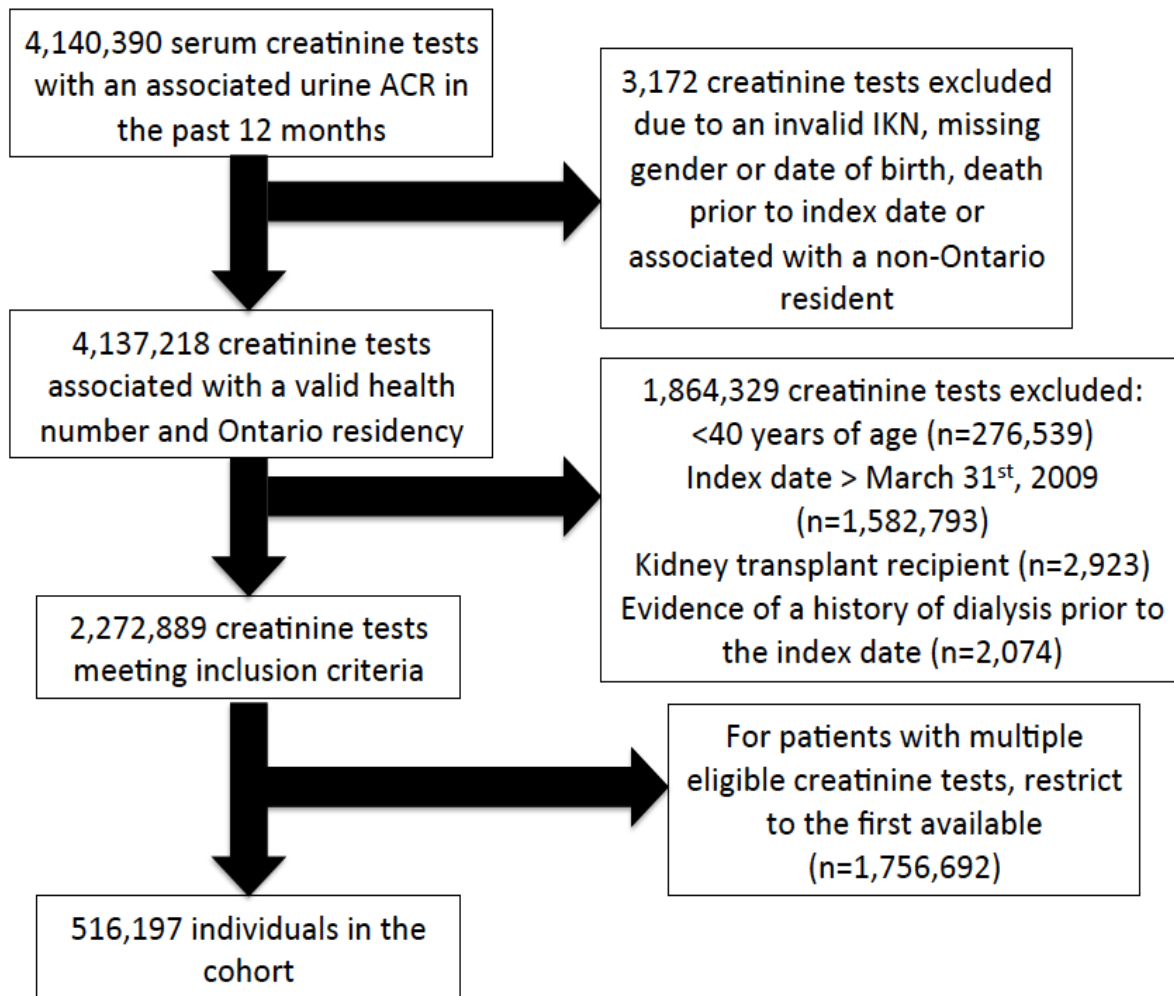For patients with multiple eligible creatinine tests, restrict to the first available (n=1,756,692)

516,197 individuals in the cohort

Supplementary Table 1 (total cohort): Risk of hemorrhage by eGFR and urine albumin-to-creatinine ratio†

			Albuminuria categories (mg/g)		
			<30	**30-300**	**>300**
Chronic Kidney Disease Stage by eGFR categories	**≥90**	Number of hemorrhage events	859	289	67
		Cumulative incidence % (95% CI)	0.5 (0.4, 0.5)	0.9 (0.8, 1.0)	1.3 (1.0, 1.7)
		Incidence rate per 1,000 person-years (95% CI)	1.6 (1.5, 1.7)	3.1 (2.7, 3.4)	4.5 (3.6, 5.8)
		Unadjusted RR (95% CI)	referent	1.9 (1.6, 2.2)	2.8 (2.2, 3.6)
		Adjusted RR[a] (95% CI)	referent	1.6 (1.4, 1.8)	2.3 (1.8, 2.9)
	60-<90	Number of hemorrhage events	1694	699	202
		Cumulative incidence % (95% CI)	0.9 (0.9, 0.9)	2.0 (1.8, 2.1)	3.1 (2.6, 3.5)
		Incidence rate per 1,000 person-years (95% CI)	3.1 (2.9, 3.2)	6.7 (6.2, 7.2)	10.7 (9.3, 12.2)
		Unadjusted RR (95% CI)	1.9 (1.7, 2.0)	4.1 (3.7, 4.5)	6.4 (5.5, 7.4)
		Adjusted RR[a] (95% CI)	1.0 (0.9, 1.1)	1.6 (1.4, 1.8)	2.5 (2.2, 3.0)
	45-<60	Number of hemorrhage events	618	323	144
		Cumulative incidence % (95% CI)	2.1 (1.9, 2.2)	3.0 (2.6, 3.3)	4.2 (3.5, 4.9)
		Incidence rate per 1,000 person-years (95% CI)	7.1 (6.6, 7.7)	10.4 (9.4, 11.6)	15.0 (12.7, 17.6)
		Unadjusted RR (95% CI)	4.3 (3.9, 4.8)	6.2 (5.4, 7.0)	8.8 (7.4, 10.4)
		Adjusted RR[a] (95% CI)	1.4 (1.2, 1.6)	1.7 (1.4, 1.9)	2.6 (2.2, 3.2)
	30-<45	Number of hemorrhage events	341	326	157
		Cumulative incidence % (95% CI)	3.3 (2.9, 3.6)	5.0 (4.4, 5.5)	5.3 (4.5, 6.1)
		Incidence rate per 1,000 person-years (95% CI)	11.4 (10.3, 12.7)	18.2 (16.3, 20.2)	19.3 (16.5, 22.5)
		Unadjusted RR (95% CI)	6.8 (6.0, 7.6)	10.3 (9.1, 11.7)	10.9 (9.3, 12.9)
		Adjusted RR[a] (95% CI)	1.7 (1.5, 2.0)	2.3 (2.0, 2.6)	2.8 (2.3, 3.3)
	15-<30	Number of hemorrhage events	101	135	139
		Cumulative incidence % (95% CI)	4.6 (3.7, 5.5)	5.6 (4.7, 6.5)	7.7 (6.4, 8.9)

		Incidence rate per 1,000 person-years (95% CI)	17.1 (14.1, 20.8)	21.6 (18.3, 25.5)	29.5 (25.0, 34.7)
		Unadjusted RR (95% CI)	9.6 (7.8, 11.7)	11.7 (9.8, 13.9)	15.9 (13.4, 18.9)
		Adjusted RR[a] (95% CI)	1.9 (1.5, 2.4)	2.4 (1.9, 2.9)	3.7 (3.0, 4.5)
	<15	Number of hemorrhage events	6	17	36
		Cumulative incidence % (95% CI)	7.1 (1.6, 12.5)	8.2 (4.5, 12.0)	10.1 (7.0, 13.2)
		Incidence rate per 1,000 person-years (95% CI)	29.3 (13.3, 64.4)	35.1 (22.0, 56.0)	42.4 (30.9, 58.5)
		Unadjusted RR (95% CI)	14.7 (6.8, 31.8)	17.1 (10.8, 27.1)	21.0 (15.3, 28.9)
		Adjusted RR[a] (95% CI)	3.0 (1.3, 6.6)	3.5 (2.2, 5.6)	5.5 (3.9, 7.6)

Supplementary Table 2 (age>=66): Risk of hemorrhage by eGFR and urine albumin-to-creatinine ratio†

			Albuminuria categories (mg/g)		
			<30	**3-300**	**>300**
Chronic Kidney Disease Stage by GFR categories	**≥90**	Number of hemorrhage events	174	77	21
		Cumulative incidence % (95% CI)	1.4 (1.2, 1.6)	2.2 (1.7, 2.7)	4.1 (2.4, 5.8)
		Incidence rate per 1,000 person-years (95% CI)	4.6 (4.0, 5.4)	7.7 (6.2, 9.6)	14.5 (9.5, 22.2)
		Unadjusted RR (95% CI)	referent	1.6 (1.3, 2.1)	3.0 (1.9, 4.7)
		Adjusted RRa (95% CI)	referent	1.5 (1.2, 2.0)	2.5 (1.6, 4.0)
	60-<90	Number of hemorrhage events	1258	552	139
		Cumulative incidence % (95% CI)	1.6 (1.5, 1.7)	2.7 (2.4, 2.9)	4.4 (3.7, 5.2)
		Incidence rate per 1,000 person-years (95% CI)	5.4 (5.1, 5.7)	9.2 (8.5, 10.0)	15.9 (13.5, 18.8)
		Unadjusted RR (95% CI)	1.2 (1.0, 1.4)	2.0 (1.6, 2.3)	3.3 (2.6, 4.1)
		Adjusted RRa (95% CI)	0.9 (0.8, 1.1)	1.3 (1.1, 1.5)	2.0 (1.6, 2.6)
	45-<60	Number of hemorrhage events	559	282	108
		Cumulative incidence % (95% CI)	2.5 (2.2, 2.7)	3.3 (2.9, 3.7)	4.9 (4.0, 5.8)
		Incidence rate per 1,000 person-years (95% CI)	8.5 (7.8, 9.2)	11.7 (10.4, 13.1)	17.9 (14.8, 21.5)
		Unadjusted RR (95% CI)	1.8 (1.5, 2.1)	2.4 (2.0, 2.9)	3.6 (2.9, 4.6)
		Adjusted RRa (95% CI)	1.2 (1.0, 1.4)	1.3 (1.1, 1.6)	2.0 (1.6, 2.5)
	30-<45	Number of hemorrhage events	317	305	124
		Cumulative incidence % (95% CI)	3.4 (3.1, 3.8)	5.5 (4.9, 6.0)	6.1 (5.1, 7.1)
		Incidence rate per 1,000 person-years (95% CI)	12.2 (10.9, 13.6)	20.2 (18.0, 22.5)	22.9 (19.3, 27.3)
		Unadjusted RR (95% CI)	2.5 (2.1, 3.0)	4.0 (3.3, 4.8)	4.5 (3.6, 5.6)
		Adjusted RRa (95% CI)	1.4 (1.2, 1.7)	1.9 (1.6, 2.4)	2.2 (1.7, 2.8)
	15-	Number of hemorrhage events	94	125	108

	<30	Cumulative incidence % (95% CI)	4.7 (3.8, 5.6)	6.0 (5.0, 7.1)	8.5 (7.0, 10.0)
		Incidence rate per 1,000 person-years (95% CI)	17.5 (14.3, 21.4)	23.6 (19.8, 28.0)	33.9 (28.2, 40.8)
		Unadjusted RR (95% CI)	3.5 (2.7, 4.4)	4.5 (3.6, 5.6)	6.3 (5.0, 7.9)
		Adjusted RRa (95% CI)	1.6 (1.2, 2.0)	2.0 (1.6, 2.5)	2.8 (2.2, 3.6)
	<15	Number of hemorrhage events	≤5	15	28
		Cumulative incidence % (95% CI)	≤6.4 (1.0, 11.8)	9.3 (4.8, 13.8)	12.3 (8.1, 16.6)
		Incidence rate per 1,000 person-years (95% CI)	≤26.5 (11.1, 62.9)	42.0 (25.6, 68.9)	56.5 (39.4, 81.0)
		Unadjusted RR (95% CI)	≤4.7 (2.0, 11.2)	6.9 (4.1, 11.4)	9.1 (6.2, 13.2)
		Adjusted RRa (95% CI)	2.2 (0.9, 5.2)	2.9 (1.7, 4.9)	4.4 (3.0, 6.5)

[a]Adjusted for age (per year), sex, income quintile (lowest referent), ischemic stroke, myocardial infarction, coronary artery disease, coronary revascularization, deep venous thrombosis, atrial fibrillation, hypertension, congestive heart failure, diabetes, prior hemorrhage, residential status and year of index date (2002 referent), proton pump inhibitor use, anticoagulant use, and antiplatelet use.

† Categories of estimated glomerular filtration rate and albumin-to-creatinine ratio based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) nomenclature which classifies adults into four categories by chronic kidney disease prognosis (low, moderate, high or very high risk). Color coding represents the KDIGO chronic kidney disease risk group, low risk green, moderate risk yellow, high risk orange, and very high risk red. ACR determined by a random spot urine to creatinine ratio.

‡ In accordance with ICES privacy policies, cell sizes less than or equal to five cannot be reported.

Abbreviations: eGFR, estimated glomerular filtration rate; RR, relative risk; CI, confidence interval.

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Supplementary Table 3: Effect modification of the association of urine albumin to creatinine ratio with hemorrhage

Urine ACR (mg/g)	Adjusted RR (95% CI) of all cause hemorrhage												
	Age (years)			Diabetes		History of hemorrhage		Atrial fibrillation		Ischemic stroke		Anticoagulant use[b]	
	40 to <66	66 to 80	>80	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
<30	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent	Referent
30-300	1.76 (1.58, 1.97)	1.40 (1.29, 1.53)	1.27 (1.13, 1.43)	1.46 (1.36, 1.57)	1.47 (1.34, 1.62)	1.56 (1.31, 1.86)	1.46 (1.37, 1.55)	1.30 (1.10, 1.55)	1.48 (1.40, 1.58)	1.44 (1.11, 1.86)	1.47 (1.38, 1.56)	1.30 (1.11, 1.52)	1.35 (1.25, 1.45)
>300	2.96 (2.54, 3.45)	1.96 (1.73, 2.21)	1.80 (1.52, 2.13)	2.07 (1.87, 2.29)	2.35 (2.03, 2.71)	1.46 (1.13, 1.90)	2.29 (2.10, 2.50)	1.71 (1.36, 2.17)	2.23 (2.04, 2.44)	1.52 (1.06, 2.18)	2.21 (2.03, 2.41)	1.30 (1.02, 1.64)	2.05 (1.84, 2.29)
P value for the interaction term	P<.0001			P=0.25		P<.0001		P=0.003		P=0.005		P=0.0001	

[a]Adjusted for age (per year), sex, income quintile (lowest referent), ischemic stroke, myocardial infarction, coronary artery disease, coronary revascularization, deep venous thrombosis, atrial fibrillation, hypertension, congestive heart failure, diabetes, prior hemorrhage, residential status and year of index date (2002 referent), eGFR (≥90 ml/min/1.73 m2 as the referent).
[b]Also adjusted for anticoagulant, antiplatelet and proton pump inhibitor use (analysis restricted to individuals ≥66 years of age).
Abbreviations: ACR, albumin to creatinine ratio; RR, relative risk; CI, confidence interval

Appendix 1

Table S1: STROBE Statement

	Item No.	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods – setting and design
Setting	5	Describe the setting, locations and relevant dates, including periods of recruitment, exposure, follow-up and data collection	Methods – setting and design; data sources
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods – Patients; Appendices
		(b) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if	Methods – outcomes; appendices

		applicable	
Data sources/ Measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods – data sources; appendices
Bias	9	Describe any efforts to address potential sources of bias	Methods – statistical analysis; Discussion
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine subgroups and interactions	Methods
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	
Results			
Participants	13	(a) Report numbers of individuals at each stage of study – e.g. numbers potentially eligible, examined for eligibilty, confirmed eligible, included in the study, completing follow-up, and analysed	Results; Supplementary Fig 1
		(b) Give reasons for non-participation at each stage	Results

		(c) Consider use of a flow diagram	Supplementary Fig 1
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Results
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (e.g. average and total amount)	Results
Outcome data	15	Report numbers of outcome events or summary measures over time	Results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results
		(b) Report category boundaries when continuous variables were categorized	Results
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results
Other analyses	17	Report other analyses done – e.g. analyses of subgroups and interactions, and sensitivity analyses	Results
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuus both direction and magnitude of any potential bias	Discussion

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Gerneralisability	21	Discuss the gerneralisability (external validity) of the study results	Discussion
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Acknowledgments

Appendix 2: Coding definitions for demographic and co-morbid conditions

Characteristic	Database	Codes
Age, Sex, Income, Rural	RPDB	
Prior Hemorrhage	CIHI-DAD	Subarachnoid hemorrhage ICD9: 430 ICD10: I600, I601, I602, I603, I604, I605, I606, I607, I609 Intracerebral hemorrhage ICD9: 431 ICD10: I61 Other non-traumatic intracranial hemorrhage ICD9: 432 ICD10: I62 Upper gastrointestinal ICD9: 5307, 5310, 5312, 5314, 5316, 5320, 5322, 5324, 5326, 5330, 5332, 5334, 5336, 5340, 5342, 5344, 5346, 5780, 5781 ICD10: I850, I9820, I983, K2210, K2211, K2212, K2214, K2216, K226, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K3180, K31811, K6380, K920, K921 Lower gastrointestinal ICD9: 5693, 5789 ICD10: K5520, K625, K922
Diabetes Mellitus	CIHI-DAD/OHIP	ICD9: 250 ICD10: E10, E11, E12, E13, E14 OHIP diagnosis code: 250 OHIP fee code: Q040, K029, K030, K045, K046
Hypertension	CIHI-DAD/OHIP	ICD9: 401, 402, 403, 404, 405 ICD10: I10, I11, I12, I13, I15 OHIP diagnosis code: 401, 402, 403
Congestive Heart Failure	CIHI-DAD	ICD9: 425, 5184, 514, 428 ICD10: I500, I501, I509, I255, J81 CCP: 4961, 4962, 4963, 4964 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR

		OHIP fee codes: R701, R702, Z429 OHIP diagnosis code: 428
Coronary Artery Disease	CIHI-DAD	ICD9: 412, 410 ICD10: I21, I22, Z955, T822 CCI: 1IJ50, 1IJ76 CCP: 4801, 4802, 4803, 4804, 4805, 481, 482, 483 OHIP fee code: "R741", R742, R743, G298, E646, E651, E652, E654, E655, Z434, Z448 OHIP diagnosis code: 410, 412
Prior Gastrointestinal Endoscopy	OHIP	Oesophagus OHIP: Z515, Z399, Z400, E696, E702, E690, E795, E770, E692, E698, E703, E799, E695, E797, E798, E629 Stomach OHIP fee code: Z527, Z547, Z528, E674, E675 Intestines OHIP fee code: Z560, Z749, E629, Z584, Z512, E747, Z514, Z555, E740, E741, E747, E705, Z580, Z497, Z496 Rectum OHIP fee code: Z535, Z536, Z592, E746, E641, E797
Coronary Revascularization	CIHI-DAD/OHIP	CCP: 481, 482, 483, 480 CCI: 1IJ50, 1IJ26, 1IJ27, 1IJ57, 1IJ76 OHIP fee code: R741, R742, R743, E651, E652, E654, E646, G298, Z434, G262

Abbreviations: RPDB, Registered Persons Database; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; OHIP, Ontario Health Insurance Plan; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; CCI, Canadian Classification of Interventions

Appendix 2: Outcome Definitions

Outcome	Codes	Validity
Major Hemorrhage	<u>Upper Gastrointestinal</u> **ICD9:** 530.7, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 578.0, 578.1 **ICD10:** I85.0, I98.20, I98.3, K22.10, K22.11, K22.12, K22.14, K22.16, K22.6, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80, K31.811, K63.80, K92.0, K92.1 <u>Lower Gastrointestinal</u> **ICD9**: 569.3, 578.9 **ICD10**: K55.20, K62.5, K92.2 <u>Intracerebral</u> **ICD9**: 431 **ICD10:** I61 <u>Subarachnoid</u> **ICD9**: 430 **ICD10**: I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.9 <u>Other non-traumatic intracranial</u> **ICD9:** 432 **ICD10**:I62	ICD9 Sensitivity: 94% (CI 91 to 96) Specificity: 83% (CI 78 to 87) Arnason et al. 2006 Package

Abbreviations: ICD, International Classification of Diseases.

Note: Codes may appear at any time during a patient's admission (and may not necessarily be their most responsible diagnosis).

Appendix 3: Druglist

DRUG NAME

Anticoagulant Agents:

Acenocoumarol

Danaparoid sodium

Enoxaparin sodium

Fondaparinux sodium

Heparin

Lepirudin

Nadroparin calc

Rivaroxaban

Tinzaparin sodium

Warfarin

Antiplatelet Agents:

Dipyridamole

Acetylsalicylic acid & dipyridamole

Ticlopidine hcl

Clopidogrel

Prasugrel hcl

Acetylsalicylic acid

Proton Pump Inhibitor Agents:

Amoxicillin trihydrate & clarithromycin & lansoprazole

Esomeprazole magnesium

Lansoprazole

Omeprazole

Pantoprazole

Rabeprazole