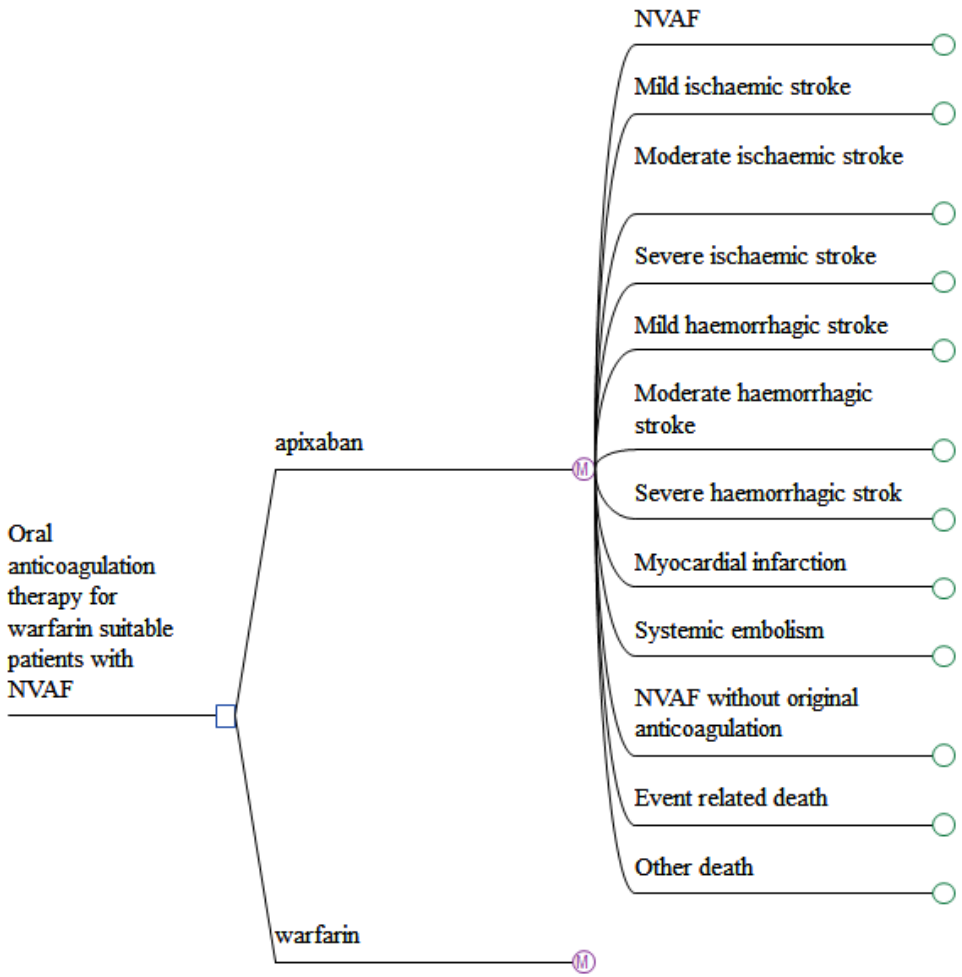
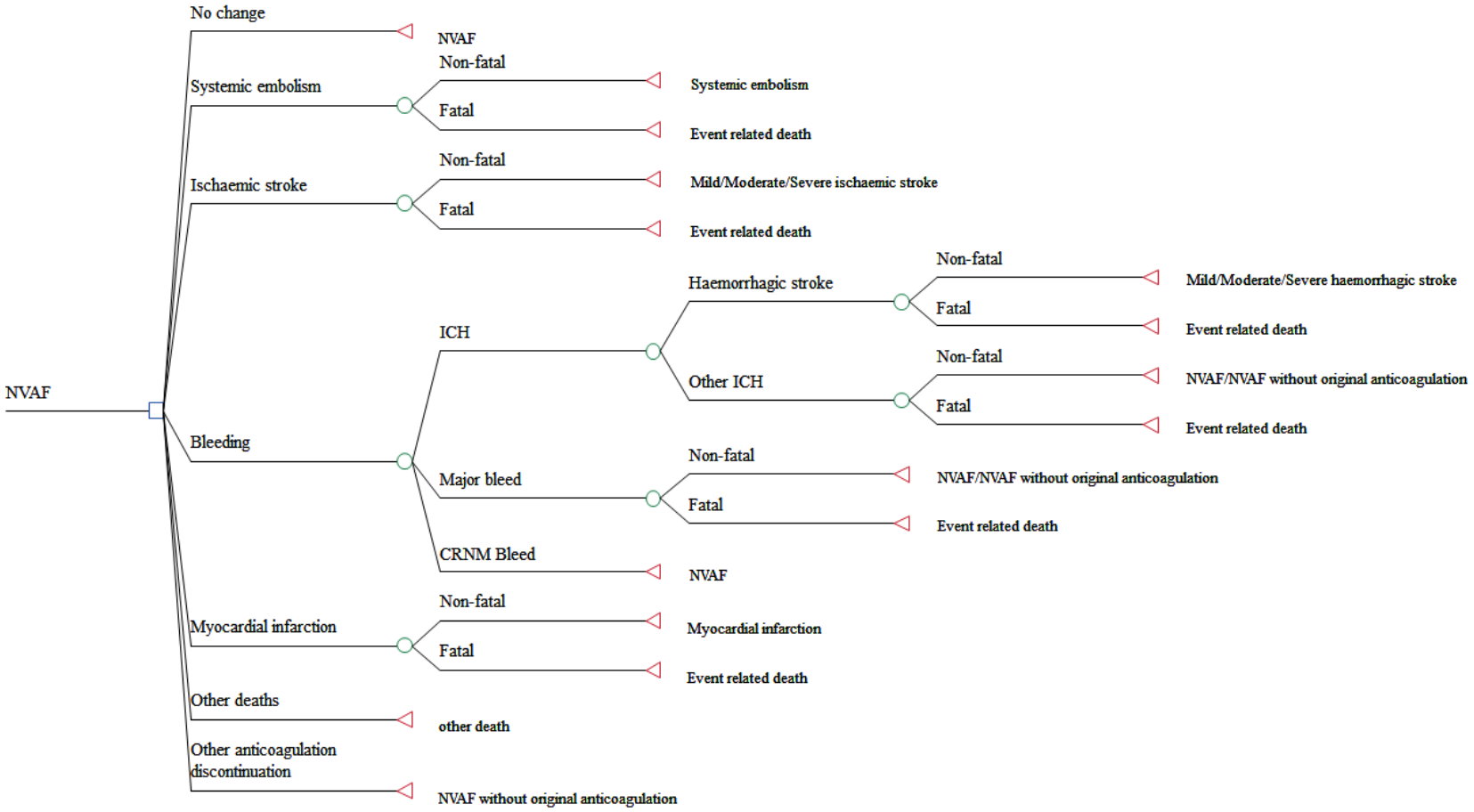
Supporting information

S1 Fig. Schematic representation of Markov model.



S2 Fig. Health states transitions from NVAF.



S1 Table. Base-case and sensitivity analyses inputs for clinical events, deaths, post-event treatment and anticoagulation management.

Variables	Apixaban			Warfarin		
	Base-case	**Range**	**References**	**Base-case**	**Range**	**References**
Risk of clinical events						
Ischaemic Stroke (IS)						
Risk of IS (Rate/100 PYs)	0.98	0.56-1.51	Secondary analysis of ARISTOTLE data	1.09	0.86-1.32	[1]
Risk adjustment factor for IS per decade	1.40	0.80-2.16	[2]	1.40	0.80-2.16	[2]
Risk of recurrent IS	4.10	3.41-4.91	[3]	4.10	3.41-4.91	[3]
Intracranial Haemorrhage(ICH)						
Risk of ICH (Rate/100 PYs)	0.33	0.15-0.51	[1]	0.80	0.35-1.87	[1]
Risk adjustment factor for ICH per decade	1.97	1.79-2.16	[4]	1.97	1.79-2.16	[4]
Risk of recurrent haemorrhagic stroke	3.00	2.02-4.46	[3]	3.00	2.02-4.46	[3]
Proportion of haemorrhagic strokes (HS) among ICHs	0.77	0.65-0.87	Secondary analysis of ARISTOTLE data	0.64	0.44-0.70	Secondary analysis of ARISTOTLE data
Other major bleeds						
Risk of other major bleeds (Rate/100 PYs)	1.79	1.02-2.77	[1]	2.27	1.30-3.51	[1]
Risk adjustment factor for other major bleeds per decade	1.97	1.79-2.16	[4]	1.97	1.79-2.16	[4]
Proportion of GI bleeds among other major bleeds	0.38	0.32-0.44	Assumption (same distribution as observed in ARISTOTLE [1])	0.50	-	CDARS
Clinically relevant non major bleeds (CRNB)						
Risk of CRNB (Rate/100 PYs)	2.08	1.19-3.22	Secondary analysis of ARISTOTLE data	3.00	2.59-3.45	Secondary analysis of ARISTOTLE data
Risk adjustment factor for CRNB	1.97	1.79-2.16	[4]	1.97	1.79-2.16	[4]

Variables	Apixaban			Warfarin		
	Base-case	**Range**	**References**	**Base-case**	**Range**	**References**
per decade						
Myocardial infarction (MI)						
Risk of MI for (Rate/100 PYs)	0.53	0.30-0.82	[1]	0.61	0.45-0.80	[1]
Risk adjustment factor for MI per decade	1.30	-	[5]	1.30	-	[5]
Other cardiovascular (CV) hospitalisation						
Risk of other CV hospitalisation for apixaban (Rate/100 PYs)	10.46	5.98-16.71	Assumption*	10.46	5.98-16.71	Assumption*
Systematic Embolism (SE)						
Risk of SE (Rate/100 PYs)	0.09	0.05-0.14	[1]	0.10	0.05-0.20	Assumption
Death						
Case fatality rate (CFR, %)						
CFR of IS	18%	11-26%	Secondary analysis of AVERROES and ARISTOTLE	15%	9-22%	Secondary analysis of AVERROES and ARISTOTLE
CFR of HS	35%	20-52%	Secondary analysis of AVERROES and ARISTOTLE	53%	41-65%	Secondary analysis of AVERROES and ARISTOTLE
CFR of other ICH	13%	6-22%	Secondary analysis of AVERROES and ARISTOTLE	13%	6-22%	Secondary analysis of AVERROES and ARISTOTLE
CFR of GI bleeds	1%	0-2%	Assumption (same rate as that of warfarin estimated from CDARS)	1%	0-2%	CDARS
CFR of SE	9%	2-21%	ARISTOTLE Case Study Report	9%	2-21%	ARISTOTLE Case Study Report
CFR of MI for females	16%	9-24%	Assumption (same rate as that of warfarin estimated from CDARS)	16%	9-24%	CDARS
CFR of MI for males	14%	8-21%	Assumption (same rate as that of	14%	8-21%	CDARS

Variables	Apixaban			Warfarin		
	Base-case	**Range**	**References**	**Base-case**	**Range**	**References**
			warfarin estimated from CDARS)			
Mortality						
Background mortality risk	1	-	Assumption	1	-	Assumption
Additional mortality risk adjustment for AF	1.34	1.20-1.53	[6]	1.34	1.20-1.53	[6]
Additional mortality risk adjustment for mild ischaemic stroke	3.18	1.42-4.94	[7-9]	3.18	1.42-4.94	[7-9]
Additional mortality risk adjustment for moderate ischaemic stroke	5.84	4.08-7.60	[7-9]	5.84	4.08-7.60	[7-9]
Additional mortality risk adjustment for severe ischaemic stroke	15.75	13.99-17.51	[7-9]	15.75	13.99-17.51	[7-9]
Additional mortality risk adjustment for mild haemorrhagic stroke	3.18	1.82-4.92	[7-9]	3.18	1.82-4.92	[7-9]
Additional mortality risk adjustment for moderate haemorrhagic stroke	5.84	3.34-9.03	[7-9]	5.84	3.34-9.03	[7-9]
Additional mortality risk adjustment for severe haemorrhagic stroke	15.75	9.00-24.35	[7-9]	15.75	9.00-24.35	[7-9]
Additional mortality risk adjustment for SE	1.34	1.20-3.18	Assumption	1.34	1.20-3.18	Assumption
Additional mortality risk adjustment for MI females	4.16	3.44-5.03	[10]	4.16	3.44-5.03	[10]
Additional mortality risk adjustment for MI males	2.56	2.27-2.88	[10]	2.56	2.27-2.88	[10]
Death rate in different treatment arm (same as trial period)						
Rate of death (Rate/100 PYs)	3.08	2.50-3.72	Secondary analysis of ARISTOTLE data	3.34	2.71-4.04	Secondary analysis of ARISTOTLE data

Variables	Apixaban			Warfarin		
	Base-case	**Range**	**References**	**Base-case**	**Range**	**References**
Anticoagulation treatment choice post events						
Post ICH (% of switch treatment, aspirin as 2nd line treatment)	44%	31-57%	[11]	44%	31-57%	[11]
Post GI bleeding (% of switch treatment, aspirin as 2nd line treatment	25%	1-69%	[12]	29%	3-69%	CDARS
Post non-ICH and non-GI bleeding (% of switch treatment, aspirin as 2nd line treatment	25%	-	[12]	20%	-	CDARS
Post IS (% of no changes)	100%	-	Expert opinion	100%	-	Assumption
Post SE (% of no changes)	100%	-	Expert opinion	100%	-	Expert opinion
Risk for aspirin as 2nd line treatment (Rate/100 PYs)						
Risk for IS	3.45	1.97-5.34	Secondary data analysis of AVERROES	3.45	1.97-5.34	Secondary data analysis of AVERROES
Risk of ICH	0.32	0.18-0.50	Secondary data analysis of AVERROES	0.32	0.18-0.50	Secondary data analysis of AVERROES
Risk of other major bleeds	0.89	0.51-1.37	Secondary data analysis of AVERROES	0.89	0.51-1.37	Secondary data analysis of AVERROES
Risk of CRNMB	2.94	1.68-4.54	Secondary data analysis of AVERROES	2.94	1.68-4.54	Secondary data analysis of AVERROES
Risk of MI	1.11	0.63-1.72	Secondary data analysis of AVERROES	1.11	0.63-1.72	Secondary data analysis of AVERROES
Risk of other CV hospitalisation	13.57	7.76-20.98	Secondary data analysis of AVERROES	13.57	7.76-20.98	Secondary data analysis of AVERROES
Anticoagulation management						
Patients experiencing dyspepsia	1.67%	-	ARISTOTLE Case	0.41%	-	CDARS

Variables	Apixaban			Warfarin		
	Base-case	Range	References	Base-case	Range	References
whilst on treatment (%)			Study Report			
Patients requiring annual renal monitoring whilst on treatment (%)	0	0-100%	Assumption based on Secondary analysis of ARISTOTLE data	29.65%	-	CDARS

Footnote: * rate for apixaban taken from the AVERROES, assume same rate for warfarin;

Abbreviations: ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES：Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CDARS：Clinical Data Analysis and Reporting System of Hong Kong

S2 Table. Base-case and sensitivity analyses inputs for utility and cost

Variables	Basecase	Ranges	References
Utility			
Utility of AF	0.76	0.74-0.77	[13]
Utility of mild ischaemic stroke	0.62	0.56-0.67	[14]
Utility of moderate ischaemic stroke	0.56	0.51-0.62	[14]
Utility of severe ischaemic stroke	0.51	0.46-0.57	[14]
Utility of mild haemorrhagic stroke	0.62	0.56-0.67	[14]
Utility of moderate haemorrhagic stroke	0.56	0.51-0.62	[14]
Utility of severe haemorrhagic stroke	0.51	0.46-0.57	[14]
Utility of SE	0.63	0.59-0.66	[14]
Utility decrement of MI	0.61	0.57-0.65	[14]
Utility decrement of other ICH	0.15	0.08-0.24	[14]
Utility decrement of other major bleed	0.15	0.08-0.24	[14]
Utility decrement of CRNMB	0.06	0.03-0.10	[14]
Utility decrement of other CV hospitalisation	0.13	0.08-0.18	[14]
Utility decrement while on aspirin (2^{nd} line treatment)	0	-	[15]
Utility decrement while on warfarin	0.01	0-0.08	[15]
Utility decrement while on apixaban	0	-	Assumption
Utility decrement while on aspirin (2^{nd} line)	0	-	[15]

Variables	Basecase	Ranges	References
Utility decrement of dyspepsia	0.2	-	[16, 17]
Utility decrement of renal monitoring	0	-	Assumption
Utility decrement associated with age	0.00029	-	[14]
Cost			
Daily drug acquisition cost (USD/day)			
Apixaban	2.21	1.77-2.65	Local market price
Aspirin (2nd line)	0.13	0.13-0.16	Local market price
Warfarin	0.19	0.19-0.23	Local market price
Cost of anticoagulation management, monitoring and routine care			
Frequency of INR monitoring of warfarin (number/month)	1.0	-	CDARS
Cost of INR monitoring (USD/visit)	19.35	16.19-23.12	[18]
Annual cost of routine care visits due to dyspepsia (USD/patient)	7	-	CDARS, [18]
Cost of routine care visits due to renal monitoring (USD/patient-year)	19	-	CDARS, [18]
Acute Event cost (USD/episode)			
Mild ischaemic stroke*	11,715	9,372-14,059	CDARS, [18]
Moderate ischaemic stroke*	11,013	8,810-13,215	CDARS, [18]
Severe ischaemic stroke*	24,251	19,401-29,101	CDARS, [18]
Fatal ischaemic stroke*	15,582	12,466-18,698	CDARS, [18]
Mild haemorrhagic stroke*	10,992	8,794-13,190	CDARS, [18]
Moderate haemorrhagic stroke*	10,332	8,266-12,398	CDARS, [18]
Severe haemorrhagic stroke*	22,753	18,202-27,304	CDARS, [18]
Fatal haemorrhagic stroke*	14,619	11,695-17,543	CDARS, [18]
Systemic embolism	10,809	8,647-12,971	CDARS, [18]
Other ICH	4816	3,853-5,779	[19]
GI Bleeds	7367	5,894-8,840	CDARS, [18]
Non-ICH and non-GI bleeding	4469	3,575-5,363	CDARS, [18]
CRNM Bleeds	4348	3,478-5,218	CDARS, [18]
Myocardial infarction	7790	6,232-9,348	CDARS, [18]
Other CV Hospitalisation	5254	4,203-6,305	CDARS, [18]
Long-term maintenance cost (USD/month, lifetime)			
Mild ischaemic stroke	250	200-300	Assumption†
Moderate ischaemic stroke	271	217-325	Assumption†
Severe ischaemic stroke	766	613-919	Assumption†
Mild haemorrhagic stroke	234	187-281	Assumption†
Moderate haemorrhagic stroke	254	203-305	Assumption†

Variables	Basecase	Ranges	References
Severe haemorrhagic stroke	719	575-863	Assumption†
Systemic embolism	230	184-276	Assumption†
Myocardial infarction	25	20-30	Assumption‡

Footnote: *stroke distribution assumed to be the same as the ARISTOTLE trial (secondary analysis); † long-term maintenance cost considered resource use in hospital, primary care, healthcare contacts and utilisation of social services; ‡ long-term maintenance cost considered medication cost including ACE inhibitors, beta blockers and statins.

Abbreviations: ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CDARS: Clinical Data Analysis and Reporting System of Hong Kong

S3 Table. The ICD-9 codes (diagnosis codes unless other specified) used in this study.

ICD-9 codes	Descriptions
Atrial fibrillation	
427.3	Atrial fibrillation and flutter
Valvular heart diseases/replacement or hyperthyroidism	
242	Thyrotoxicosis with or without goitre
394.0	Mitral stenosis
Procedures	
35.20	Open And Other Replacement Of Unspecified Heart Valve
35.22	Open And Other Replacement Of Aortic Valve
35.24	Open And Other Replacement Of Mitral Valve
35.26	Open And Other Replacement Of Pulmonary Valve
35.28	Open And Other Replacement Of Tricuspid Valve
Congestive Heart Failure	
398.91	Rheumatic heart failure (congestive)
402.01	Malignant hypertensive heart disease with heart failure
402.11	Benign hypertensive heart disease with heart failure
402.91	Unspecified hypertensive heart disease with heart failure

404.01	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.03	Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease
404.11	Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.13	Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease
404.91	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
404.93	Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end stage renal disease
428	Heart failure

Hypertension

401	Essential hypertension
402	Hypertensive heart disease
403	Hypertensive chronic kidney disease
404	Hypertensive heart and chronic kidney disease
405	Secondary hypertension
437.2	Hypertensive encephalopathy

Diabetes

250	Diabetes mellitus

Ischaemic stroke

433.01	Occlusion and stenosis of basilar artery with cerebral infarction
433.11	Occlusion and stenosis of carotid artery with cerebral infarction
433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction

433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434	Occlusion of cerebral arteries
436	Acute, but ill-defined, cerebrovascular disease
437.0	Cerebral atherosclerosis
437.1	Other generalized ischaemic cerebrovascular disease

Transient ischaemic attack

435	Transient cerebral ischaemia

Systemic embolism

444	Arterial embolism and thrombosis
445	Atheroembolism

Myocardial infarction

410	Acute myocardial infarction

Intracranial haemorrhage (haemorrhagic stroke)

430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
432	Other and unspecified intracranial haemorrhage

Non-intracranial haemorrhage

Gastrointestinal bleeding

455.2	Internal haemorrhoids with other complication
455.5	External haemorrhoids with other complication
455.8	Unspecified haemorrhoids with other complication
456.0	Oesophageal varices with bleeding
456.2	Oesophageal varices in diseases classified elsewhere
530.7	Mallory—Weiss syndrome
530.8	Oesophageal disorder nec
531.0	Acute gastric ulcer with haemorrhage
531.2	Acute gastric ulcer with haemorrhage and perforation, without mention of obstruction
531.4	Chronic or unspecified gastric ulcer with haemorrhage
531.6	Chronic or unspecified gastric ulcer with haemorrhage and perforation
532.0	Acute duodenal ulcer with haemorrhage
532.2	Acute duodenal ulcer with haemorrhage and perforation
532.4	Chronic or unspecified duodenal ulcer with haemorrhage
532.6	Chronic or unspecified duodenal ulcer with haemorrhage and perforation

533.0	Acute peptic ulcer of unspecified site with haemorrhage
533.2	Acute peptic ulcer of unspecified site with haemorrhage and perforation
533.4	Chronic or unspecified peptic ulcer of unspecified site with haemorrhage
533.6	Chronic or unspecified peptic ulcer of unspecified site with haemorrhage and perforation
534.0	Acute gastrojejunal ulcer with haemorrhage
534.2	Acute gastrojejunal ulcer with haemorrhage and perforation, without mention of obstruction
534.4	Chronic or unspecified gastrojejunal ulcer with haemorrhage
534.6	Chronic or unspecified gastrojejunal ulcer with haemorrhage and perforation
535.01	Acute gastritis, with haemorrhage
535.11	Atrophic gastritis, with haemorrhage
535.21	Gastric mucosal hypertrophy, with haemorrhage
535.31	Alcoholic gastritis, with haemorrhage
535.41	Other specified gastritis, with haemorrhage
535.51	Unspecified gastritis and gastroduodenitis, with haemorrhage
535.61	Duodenitis, with haemorrhage
535.71	Eosinophilic gastritis, with haemorrhage
537.8	Gastroduodenal dis nec
562.02	Diverticula sm intestine w haemorrhage
562.03	Diverticulitis sm intestine w haemorrhage
562.12	Diverticula of colon w haemorrhage
562.13	Diverticulitis of colon w haemorrhage
568.81	Hemoperitoneum
569.3	Rectal and anal haemorrhage
569.85	Angiodysplasia with hem nec
578	Gastrointest haemorr

Other sites

423.0	Hemopericardium
459.0	Haemorrhage NOS
593.81	Renal vascular disorder
599.7	Haematuria
623.8	Noninflam dis vagina nec
626.2	Excessive menstruation
626.6	Metrorrhagia
719.1	Hemarthrosis
784.7	Epistaxis
784.8	Haemorrhage from throat
786.3	Haemoptysis

S1 File. Supplemental references

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