

Supplemental Table 1. Cardiovascular adverse event query terms by event category

Atrial fibrillation	Atrial Fibrillation, Atrial Flutter
Pericardial disease/effusion	Pericardial Disease, Pericardial Effusion, Pericardial Fibrosis, Pericardial Haemorrhage, Pericardial Rub, Pericarditis, Pericarditis Constrictive, Pleuropericarditis, Pneumopericardium
Myocardial Infarction	Acute Coronary Syndrome, Acute Myocardial Infarction, Angina Pectoris, Angina Unstable, Arteriosclerosis Coronary Artery, Coronary Angioplasty, Coronary Arterial Stent Insertion, Coronary Artery Bypass, Coronary Artery Disease, Coronary Artery Embolism, Coronary Artery Occlusion, Coronary Artery Reocclusion, Coronary Artery Restenosis, Coronary Artery Stenosis, Coronary Artery Thrombosis, Myocardial Infarction, Myocardial Ischaemia, Silent Myocardial Infarction
Ischemic Stroke	Brain Stem Infarction, Brain Stem Stroke, Cerebellar Infarction, Cerebellar Ischaemia, Cerebellar Stroke, Cerebral Artery Embolism, Cerebral Artery Occlusion, Cerebral Artery Stenosis, Cerebral Artery Thrombosis, Cerebral Infarction, Cerebral Ischaemia, Cerebrovascular Accident, Cerebrovascular Insufficiency, Embolic Cerebral Infarction, Embolic Stroke, Ischaemic Cerebral Infarction, Ischaemic Stroke, Lacunar Infarction, Lacunar Stroke, Spinal Stroke, Stroke In Evolution, Thalamic Infarction, Thrombotic Cerebral Infarction, Thrombotic Stroke, Transient Ischaemic Attack, Vertebral Artery Occlusion, Vertebral Artery Stenosis, Vertebral Artery Thrombosis, Vertebrobasilar Insufficiency
Heart Failure	Acute Left Ventricular Failure, Cardiac Dysfunction, Cardiac Failure, Cardiac Failure Acute, Cardiac Failure Congestive, Cardiogenic Shock, Cardiomyopathy, Cardiotoxicity, Cardiovascular Insufficiency, Congestive Cardiomyopathy, Diastolic Dysfunction, Dilatation Ventricular, Ischaemic Cardiomyopathy, Left Ventricular Dilatation, Left Ventricular Dysfunction, Left Ventricular Failure, Low Cardiac Output Syndrome, Myocarditis, Right Ventricular Dysfunction, Right Ventricular Failure, Stress Cardiomyopathy, Systolic Dysfunction, Ventricular Dysfunction, Ventricular Dyskinesia, Ventricular Failure, Ventricular Hypokinesia
Venous Thromboembolism	
Deep Venous Thrombosis	Deep Vein Thrombosis, Jugular Vein Thrombosis, Pelvic Venous Thrombosis, Portal Vein Thrombosis, Splenic Vein Thrombosis, Subclavian Vein Thrombosis, Vena Cava Thrombosis, Venous Thrombosis, Venous Thrombosis Limb
Pulmonary Embolism	Post Procedural Pulmonary Embolism, Pulmonary Embolism
Hypertension requiring hospitalization (this was queried separately and added to the keywords)	Blood Pressure Diastolic Increased, Blood Pressure Increased, Blood Pressure Systolic Increased, Essential Hypertension, Hypertension, Hypertensive Crisis, Hypertensive Emergency, Hypertensive Encephalopathy, Hypertensive Heart Disease, Hypertensive Urgency, Labile Blood Pressure, Labile Hypertension, Malignant Hypertension, Retinopathy Hypertensive, Systolic Hypertension, White Coat Hypertension
QT prolongation	Electrocardiogram Qt Interval Abnormal, Electrocardiogram Qt Prolonged, Torsade De Pointes
Ventricular fibrillation	Ventricular Fibrillation, Ventricular Flutter
Peripheral Vascular Disease	Aortic Stent Insertion, Arterial Occlusive Disease, Arterial Stenosis Arterial Stent Insertion, Basilar Artery Stenosis, Carotid Artery Disease, Carotid Artery Occlusion, Carotid Artery Stenosis, Carotid Artery Thrombosis, Coeliac Artery Stenosis, Mesenteric Artery Stenosis, Peripheral Arterial Occlusive Disease, Peripheral Artery Angioplasty, Peripheral Artery Bypass, Peripheral Artery Occlusion, Peripheral Artery Stenosis, Peripheral Artery Stent Insertion, Peripheral Artery Thrombosis, Peripheral Ischaemia, Peripheral Vascular Disorder, Renal Artery Stenosis, Renal Artery Stent Placement, Renal Artery Thrombosis, Superior Mesenteric Artery Syndrome, Vascular Stent Occlusion

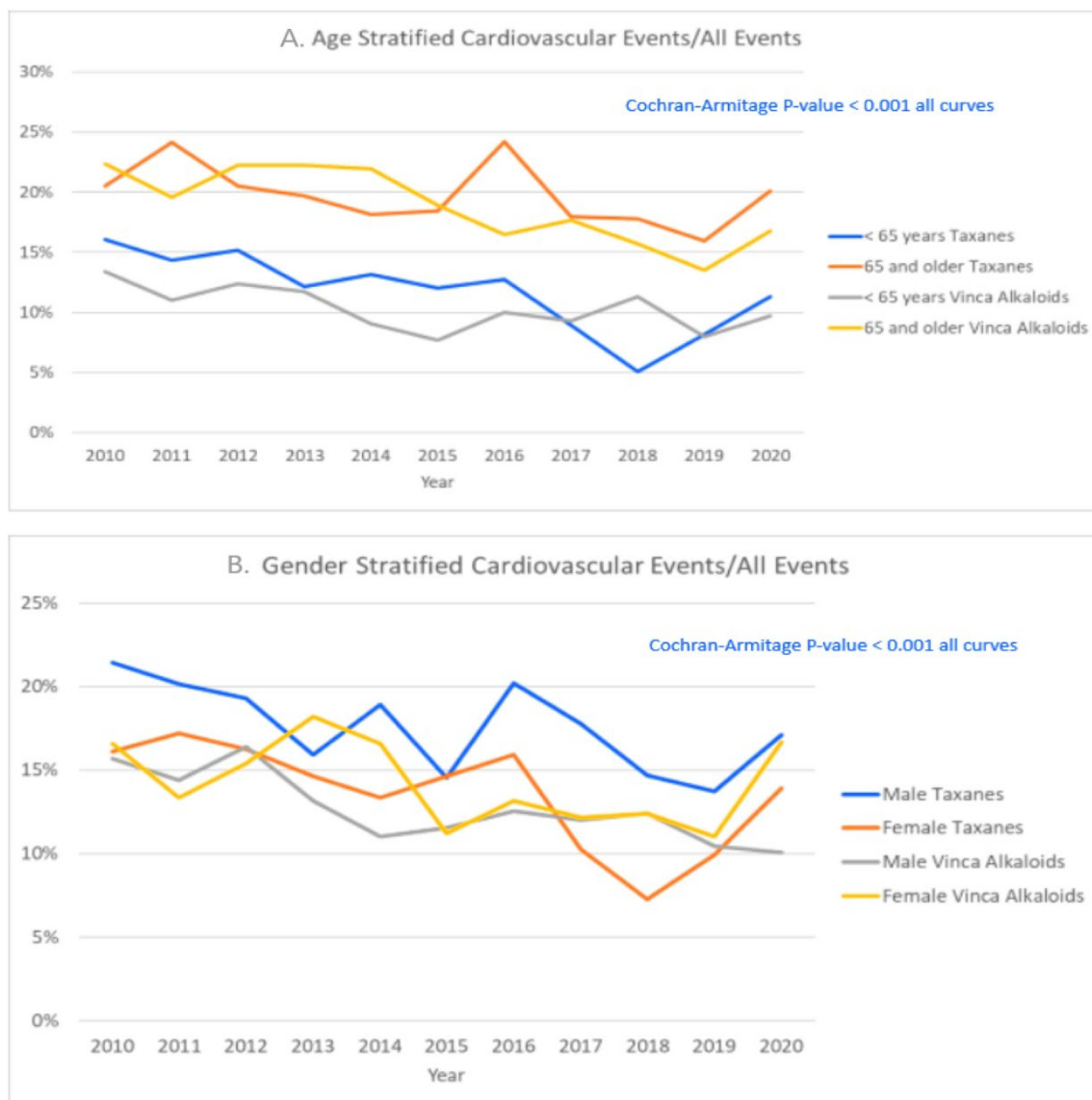
Supplemental Table 2. Specific cardiovascular adverse event reporting with Combination (any-4) vs. Monotherapy from 2010-2020.

Events (Reporting odds ratio [95% confidence interval]; N)	Taxanes monotherapy (N)	Taxanes + Any of the 4 agents	p-value	Vinca Alkaloids monotherapy (N)	Vinca Alkaloids + Any of the 4 agents	p-value
Hypertension requiring hospitalization	Ref (866)	0.90 [0.82 – 0.99] (1,830)	0.02	Ref (267)	0.73 [0.63 – 0.85] (536)	<0.0001
Heart failure	Ref (626)	0.26 [0.23 – 0.29] (852)	<0.0001	Ref (252)	0.66 [0.57 – 0.77] (553)	<0.0001
Atrial fibrillation	Ref (668)	0.64 [0.55 – 0.74] (283)	<0.0001	Ref (178)	0.92 [0.75 – 1.12] (264)	0.40
Venous thromboembolism	Ref (1,290)	1.98 [0.93 – 1.04] (461)	0.18	Ref (286)	0.87 [0.75 – 1.01] (426)	0.07
Arterial vascular event*	Ref (1,086)	0.94 [0.83 – 1.08] (317)	0.37	Ref (222)	0.97 [0.81 – 1.16] (292)	0.75
Myocardial infarction	Ref (630)	0.84 [0.71 – 1.00] (192)	0.05	Ref (131)	1.08 [0.88 – 1.31] (191)	0.47
Stroke	Ref (483)	0.98 [0.78 – 1.23] (133)	0.86	Ref (94)	0.99 [0.74 – 1.32] (102)	0.95
QT prolongation	Ref (412)	1.25 [1.00 – 1.55] (112)	0.05	Ref (69)	0.78 [0.58 – 1.05] (126)	0.11
Ventricular fibrillation	Ref (365)	1.20 [0.96 – 1.52] (97)	0.12	Ref (59)	0.98 [0.54 – 1.01] (115)	0.06
Peripheral vascular disease	Ref (115)	2.43 [1.35 – 4.39] (11)	0.003	Ref (16)	0.86 [0.48 – 1.55] (29)	0.62
<p>The odds ratio for cardiovascular adverse event reporting (adjusted for age, gender, year of reporting, reporting source, need for hospitalization, mortality) is shown as compared to any of the combinations.</p> <p>*Arterial vascular events include myocardial infarction or ischemic stroke. It is plausible that both events may have been reported in 1 adverse event report.</p> <p>OR, odds ratio; CI, confidence interval.</p>						

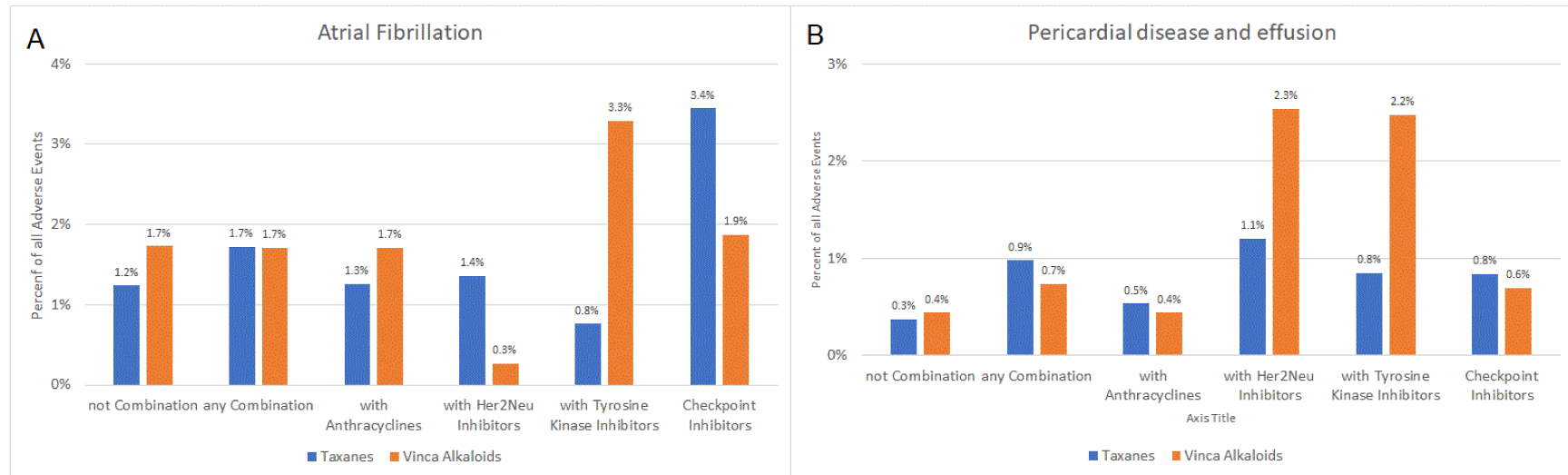
Supplemental Table 3. Adjusted reporting odds ratio of hypertension reporting hospitalization, heart failure, atrial fibrillation, and venous thromboembolism reporting in Combination (any-4) vs. Monotherapy from 2010-2020 in United States, and 3-European countries

Events (Reporting odds ratio [95% confidence interval])	United States					
	Taxanes monotherapy	Taxanes + Any of the 4 agents	p-value	Vinca Alkaloids monotherapy	Vinca Alkaloids + Any of the 4 agents	p-value
Hypertension requiring hospitalization	Ref	0.79 [0.65 – 0.95]	0.01	Ref	0.47 [0.30 – 0.76]	0.002
Heart failure	Ref	0.29 [0.22 – 0.38]	<0.0001	Ref	0.55 [0.34 – 0.89]	0.02
Atrial fibrillation	Ref	0.94 [0.69 – 1.28]	0.68	Ref	0.61 [0.35 – 1.07]	0.08
Venous thromboembolism	Ref	0.78 [0.61 – 0.98]	0.04	Ref	0.81 [0.55 – 1.19]	0.27
	Europe (France, Germany, and Italy)					
Hypertension requiring hospitalization	Ref	0.85 [0.72 – 0.99]	0.04	Ref	0.61 [0.46 – 0.80]	0.0003
Heart failure	Ref	0.27 [0.22 – 0.32]	<0.0001	Ref	0.50 [0.38 – 0.66]	<0.0001
Atrial fibrillation	Ref	0.47 [0.37 – 0.61]	<0.0001	Ref	0.51 [0.35 – 0.74]	0.001
Venous thromboembolism	Ref	0.98 [0.78 – 1.23]	0.89	Ref	0.83 [0.62 – 1.11]	0.20

Supplemental Figure 1: Trends of reported cardiovascular events among all reported events for Taxanes and vinca alkaloids from 2010 to 2020 (A) stratified by age and (B) stratified by gender



Supplemental Figure 2A: Proportion of patients with reported atrial fibrillation and **(2B)** pericardial disease and effusion among all reported events stratified based on use of type of combination with either taxanes or vinca alkaloids from 2010 to 2020. Refer to table 1 and 2 to see the total number of reported events to know the denominator for these events.



Supplemental Figure 3A: Proportion of patients with reported venous thromboembolism, (2B) myocardial infarction, (2C) ischemic stroke, and (2D) other cardiac therapies among all reported events stratified based on use of type of combination with either taxanes or vinca alkaloids from 2010 to 2020. Refer to table 1 and 2 to see the total number of reported events to know the denominator for these events. PVD = peripheral vascular disease, QTP = QT prolongation, VF = ventricular fibrillation

