WEB MATERIAL

Cardiotoxicity of Use of Sequential Aromatase Inhibitors in Women With Breast Cancer

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Web Table 1. ICD-9 and ICD-10 Diagnostic Codes for Cardiovascular Outcomes

Study Outcome	ICD-9 Diagnosis Codes	ICD-10 Diagnosis Codes
Myocardial infarction	410x	I21x
Ischemic stroke	433x, 434x, 436x	I63x, I64x
Congestive heart failure	428x	I50x
Cardiovascular mortality	390x-398x, 401x-405x, 410x-417x, 420x-429x (excluding 427.5), 430x-438x, 440x-447x	I00x-I77x excluding I46.9

ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*.

Web Table 2. Cohort Entry Year of Patients Who Switch to Aromatase Inhibitors and those Who Continue on Tamoxifen, United Kingdom, 1998–2016

Year of Cohort Entry	Aromatase Inhibitors (*n* = 1,962)		Tamoxifen (*n* = 3,874)	
	No.	%	No.	%
1998–2002	167	8.5	693	17.9
2003–2007	963	49.1	1,665	43.0
2008–2012	677	34.5	1,098	28.3
2013–2016	155	7.9	418	10.8

Web Table 3. Baseline Characteristics of Women Diagnosed with Breast Cancer and Stratified by Treatment (Switch with Aromatase Inhibitors or Continuous Tamoxifen) Before Matching on Propensity Scores, United Kingdom, 1998–2016

Characteristic	AIs (*n* = 2,145)		Tamoxifen (*n* = 150,673)		SD
	No.	%	No.	%	
Age, years[a]	68.2 (10.7)		68.5 (11.1)		0.03
Body mass index[b]					
≤ 24.9	795	37.1	55,648	36.9	0.00
25.0-29.9	707	33.0	47,264	31.4	0.03
≥30.0	474	22.1	34,456	22.9	0.02
Unknown	169	7.9	13,305	8.8	0.03
Townsend deprivation score					
Quintile 1	569	26.5	38,877	25.8	0.02
Quintile 2	598	27.9	40,516	26.9	0.02
Quintile 3	446	20.8	33,354	22.1	0.03
Quintile 4	365	17.0	25,541	17.0	0.00
Quintile 5	167	7.8	12,358	8.2	0.02
Unknown	0	0.0	27	0.0	0.02
Ethnicity					
Caucasian	2,040	95.1	142,506	94.6	0.02
Other	47	2.2	2,758	1.8	0.03
Unknown	58	2.7	5,409	3.6	0.05
Smoking status					
Current	312	14.6	20,863	13.9	0.02
Past	537	25.0	33,679	22.4	0.06
Never	1,224	57.1	88,367	58.7	0.03
Unknown	72	3.4	7,764	5.2	0.09
Comorbidities					
Alcohol-related disorders	124	5.8	8,668	5.8	0.00
Myocardial infarction	42	2.0	2,652	1.8	0.01
Stroke or transient ischemic attack	77	3.6	4,865	3.2	0.02
Heart failure	74	3.4	4,367	2.9	0.03
Peripheral vascular disease	50	2.3	2,787	1.9	0.03
Venous thromboembolism	208	9.7	9,928	6.6	0.11
COPD	104	4.8	6,632	4.4	0.02
Chronic kidney disease	140	6.5	10,319	6.9	0.01
Other cancers	574	26.8	31,291	20.8	0.14
Non-breast cancer surgery	530	24.7	34,286	22.8	0.05
Anticoagulants					
Vitamin K antagonists	98	4.6	3,557	2.4	0.12
Direct oral anticoagulants	[c]	[c]	14	0.0	0.02
Heparin	21	1.0	544	0.4	0.08

Characteristic	AIs (*n* = 2,145)		Tamoxifen (*n* = 150,673)		SD
	No.	%	No.	%	
Antidepressants					
SSRIs	228	10.6	14,598	9.7	0.03
SNRIs	52	2.4	2,199	1.5	0.07
Tricyclic antidepressants	247	11.5	14,568	9.7	0.06
Other	23	1.1	1,535	1.0	0.01
Antidiabetic drugs					
Metformin	104	4.8	7,102	4.7	0.01
Sulfonylureas	60	2.8	4,281	2.8	0.00
Thiazolidinediones	18	0.8	808	0.5	0.04
Incretin-based drugs	[c]	[c]	418	0.3	0.04
Insulin	26	1.2	1,861	1.2	0.00
Other	[c]	[c]	93	0.1	0.01
Antihypertensive drugs					
Diuretics	600	28.0	44,380	29.5	0.03
Beta-blockers	409	19.1	27,963	18.6	0.01
Calcium channel blockers	348	16.2	23,758	15.8	0.01
ACE inhibitors	343	16.0	24,035	16.0	0.00
Angiotensin II receptor blockers	156	7.3	10,800	7.2	0.00
Other	129	6.0	7,452	5.0	0.05
Other drugs					
Bisphosphonates	106	4.9	7,670	5.1	0.01
NSAIDs	365	17.0	24,156	16.0	0.03
Opioids	599	27.9	37,909	25.2	0.06
Acetylsalicylic acid	344	16.0	22,933	15.2	0.02
Non-ASA antiplatelets	36	1.7	2,272	1.5	0.01
Statins	396	18.5	25,651	17.0	0.04
Hormone replacement therapy	120	5.6	6,979	4.6	0.04
Breast-cancer related variables					
Chemotherapy	330	15.4	16,390	10.9	0.13
Radiation therapy	414	19.3	28,561	19.0	0.01
Breast cancer surgery	1,777	82.8	131,641	87.4	0.13
Time since diagnosis, months[a]	22.2 (16.2)		22.5 (17.3)		0.02
Duration of previous tamoxifen use, months[a]	19.0 (15.6)		19.7 (16.9)		0.04

Abbreviations: ACE, angiotensin converting enzyme; AIs, aromatase inhibitors; ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standardized difference; SNRIs, serotonin and noradrenaline reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors

a. Values are expressed as mean (standard deviation)

b. Weight (kg)/height (m^2)

c. Cells with less than five observations are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink

Web Table 4. Number of Patients at Risk Since Time from Treatment Initiation Stratified by Cardiovascular Outcome and Treatment

Outcome	Treatment	Patients at Risk					
		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Myocardial infarction	Aromatase inhibitors	1,962	1,189	822	516	261	98
	Tamoxifen	3,874	2,447	1,503	808	396	84
Ischemic stroke	Aromatase inhibitors	1,962	1,188	824	517	264	99
	Tamoxifen	3,874	2,447	1,501	807	395	83
Heart failure	Aromatase inhibitors	1,962	1,191	824	517	264	98
	Tamoxifen	3,874	2,446	1,503	810	396	84
Cardiovascular mortality	Aromatase inhibitors	1,962	1,191	825	519	264	99
	Tamoxifen	3,874	2,447	1,501	807	395	83

Web Table 5. Risk of Major Adverse Cardiovascular Events (MACE)[a] When Comparing Aromatase Inhibitors Switchers Versus Continuing Tamoxifen in Women with Breast Cancer, United Kingdom, 1998–2016

Exposure	No. of Events	Person-Years	Incidence Rate [b]		HR [c]	
			IR	95% CI	HR	95% CI
Tamoxifen	55	7,114	7.7	5.8, 10.1	1.00	Referent
Aromatase inhibitors	46	3,809	12.1	8.8, 16.1	1.47	0.98, 2.18

a. MACE includes nonfatal myocardial infarction, nonfatal stroke, and cardiovascular mortality.
b. Per 1,000 person-years.
c. Hazard ratio obtained from matched population.

Web Table 6. Risk of Myocardial Infarction, Ischemic Stroke, Heart Failure, and Cardiovascular Mortality When Comparing Aromatase Inhibitors Switchers versus Continuing Tamoxifen in Women with Breast Cancer When Stratifying by Duration of Previous Tamoxifen Use, United Kingdom, 1998–2016

Outcome	Duration of Previous Tamoxifen Use	Exposure	No. of Events	Person-Years	Incidence Rate [a]		HR [b]	
					IR	95% CI	HR	95% CI
Myocardial infarction	≤1year	Tamoxifen	9	3,613	2.5	1.1, 4.7	1.00	Referent
		Aromatase inhibitors	11	1,876	5.9	2.9, 10.5	2.00	0.81, 4.93
	>1year	Tamoxifen	5	3,513	1.4	0.5, 3.3	1.00	Referent
		Aromatase inhibitors	7	1,944	3.6	1.5, 7.4	2.29	0.72, 7.27
Ischemic stroke	≤1year	Tamoxifen	13	3,614	3.6	1.9, 6.2	1.00	Referent
		Aromatase inhibitors	11	1,874	5.9	2.9, 10.5	1.46	0.65, 3.29
	>1year	Tamoxifen	9	3,507	2.6	1.2, 4.9	1.00	Referent
		Aromatase inhibitors	8	1,957	4.1	1.8, 8.1	1.45	0.56, 3.77
Heart failure	≤1year	Tamoxifen	5	3,616	1.4	0.5, 3.2	1.00	Referent
		Aromatase inhibitors	9	1,878	4.8	2.2, 9.1	3.16	1.05, 9.51
	>1year	Tamoxifen	9	3,512	2.6	1.2, 4.9	1.00	Referent
		Aromatase inhibitors	[c]	[c]	2.0	0.6, 5.2	0.73	0.22, 2.38
Cardiovascular mortality	≤1year	Tamoxifen	22	3,619	6.1	3.8, 9.2	1.00	Referent
		Aromatase Inhibitors	11	1,882	5.8	2.9, 10.5	0.83	0.40, 1.76
	>1year	Tamoxifen	14	3,515	4.0	2.2, 6.7	1.00	Referent
		Aromatase inhibitors	8	1,961	4.1	1.8, 8.1	0.96	0.40, 2.29

a. Per 1,000 person-years

b. Hazard ratio obtained from matched population

c. Cells with less than five observations are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink

Web Table 7. Risk of Myocardial Infarction, Ischemic Stroke, Heart Failure, and Cardiovascular Mortality When Comparing Aromatase Inhibitors Switchers versus Continuing Tamoxifen in Women with Breast Cancer Using Inverse Probability of Censoring Weighting for Discontinuation, Switch, and Mortality, United Kingdom, 1998–2016

Outcome	No. of Events	Person-Years	Incidence Rate [a]		HR [b]	
			IR	95% CI	HR	95% CI
Myocardial infarction						
Tamoxifen	14	7,126	2.0	1.1, 3.3	1.00	Referent
Aromatase inhibitors	18	3,820	4.7	2.8, 7.5	1.95	0.91, 4.17
Ischemic stroke						
Tamoxifen	22	7,120	3.1	1.9, 4.7	1.00	Referent
Aromatase inhibitors	19	3,831	5.0	3.0, 7.7	1.82	0.94, 3.52
Heart failure						
Tamoxifen	14	7,128	2.0	1.1, 3.3	1.00	Referent
Aromatase inhibitors	13	3,835	3.4	1.8, 5.8	1.77	0.77, 4.07
Cardiovascular mortality						
Tamoxifen	36	7,134	5.0	3.5, 7.0	1.00	Referent
Aromatase Inhibitors	19	3,843	4.9	3.0, 7.7	0.98	0.52, 1.84

Abbreviation: CI, confidence interval; HR, Hazard ratio

a. Per 1,000 person-years

b. Hazard ratio obtained from matched population

Web Table 8. Risk of Myocardial Infarction, Ischemic Stroke, Heart Failure, and Cardiovascular Mortality When Comparing Aromatase Inhibitors Switchers Versus Continuing Tamoxifen in Women with Breast Cancer Using 60-day Grace Period, United Kingdom, 1998–2016

Outcome	No. of Events	Person-Years	Incidence Rate [a]		HR [b]	
			IR	95% CI	HR	95% CI
Myocardial infarction						
Tamoxifen	32	15,091	2.1	1.5, 3.0	1.00	Referent
Aromatase inhibitors	26	7,742	3.4	2.2, 4.9	1.59	0.95, 2.68
Ischemic stroke						
Tamoxifen	56	15,075	3.7	2.8, 4.8	1.00	Referent
Aromatase inhibitors	30	7,748	3.9	2.6, 5.5	1.07	0.68, 1.66
Heart failure						
Tamoxifen	39	15,069	2.6	1.8, 3.5	1.00	Referent
Aromatase inhibitors	31	7,766	4.0	2.7, 5.7	1.54	0.96, 2.48
Cardiovascular mortality						
Tamoxifen	90	15,144	5.9	4.8, 7.3	1.00	Referent
Aromatase Inhibitors	35	7,791	4.5	3.1, 6.3	0.77	0.52, 1.13

Abbreviation: CI, confidence interval; HR, Hazard ratio

a. Per 1,000 person-years

b. Hazard ratio obtained from matched population

Web Table 9. Risk of Myocardial Infarction, Ischemic Stroke, Heart Failure, and Cardiovascular Mortality When Comparing Aromatase Inhibitors Switchers Versus Continuing Tamoxifen in Women with Breast Cancer Using 90-day Exposure Lag, United Kingdom, 1998–2016

Outcome	No. of Events	Person-Years	Incidence Rate [a]		HR [b]	
			IR	95% CI	HR	95% CI
Myocardial infarction	12	6,199	1.9	0.8, 3.0	1.00	Referent
Tamoxifen	17	3,371	5.0	2.6, 7.4	2.24	1.05, 4.80
Aromatase inhibitors						
Ischemic stroke	20	6,195	3.2	1.8, 4.6	1.00	Referent
Tamoxifen	15	3,388	4.4	2.2, 6.7	1.34	0.68, 2.63
Aromatase inhibitors						
Heart failure	14	6,198	2.3	1.1, 3.4	1.00	Referent
Tamoxifen	11	3,387	3.2	1.3, 5.2	1.41	0.63, 3.13
Aromatase inhibitors						
Cardiovascular mortality						
Tamoxifen	33	6,203	5.3	3.5, 7.1	1.00	Referent
Aromatase Inhibitors	16	3,394	4.7	2.4, 7.0	0.78	0.41, 1.43

a. Per 1,000 person-years

b. Hazard ratio obtained from matched population

c. Patients who were lost to follow-up, discontinued or switched treatment, or died before end of lag period were censored (AI=1,653, tam=3,527)

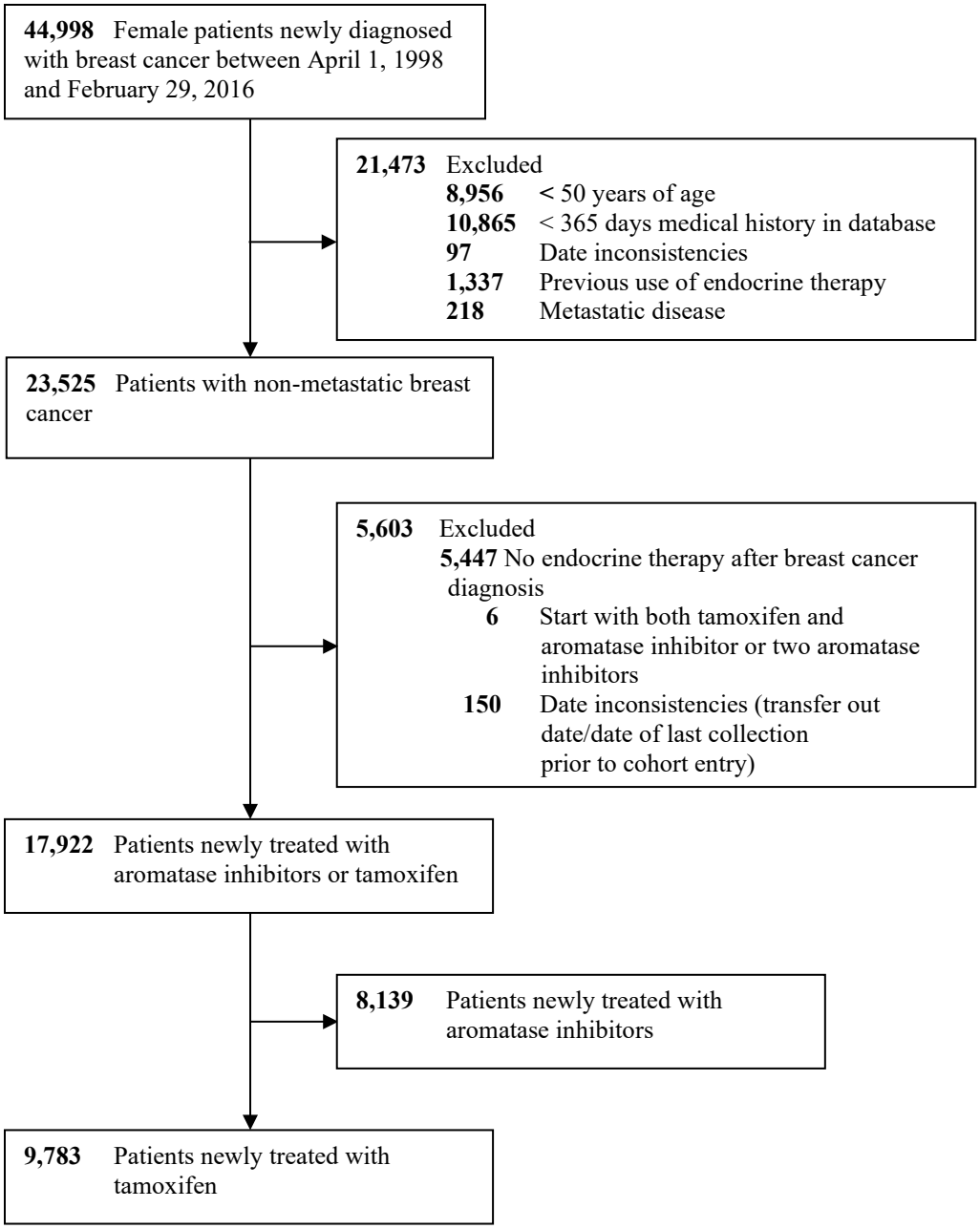
Web Table 10. Risk of Myocardial Infarction, Ischemic Stroke, Heart Failure, and Cardiovascular Mortality When Comparing Aromatase Inhibitors Switchers versus Continuing Tamoxifen in Women with Breast Cancer When Adjusting for Calendar Time in Outcome Model, United Kingdom, 1998–2016

Outcome	No. of Events	Person-Years	Incidence Rate [a]		HR [b]	
			IR	95% CI	HR	95% CI
Myocardial infarction						
Tamoxifen	14	7,126	2.0	1.1, 3.3	1.00	Referent
Aromatase inhibitors	18	3,820	4.7	2.8, 7.5	2.03	0.99, 4.17
Ischemic stroke						
Tamoxifen	22	7,120	3.1	1.9, 4.7	1.00	Referent
Aromatase inhibitors	19	3,831	5.0	3.0, 7.7	1.67	0.89, 3.11
Heart failure						
Tamoxifen	14	7,128	2.0	1.1, 3.3	1.00	Referent
Aromatase inhibitors	13	3,835	3.4	1.8, 5.8	1.80	0.83, 3.89
Cardiovascular mortality						
Tamoxifen	36	7,134	5.0	3.5, 7.0	1.00	Referent
Aromatase Inhibitors	19	3,843	4.9	3.0, 7.7	0.86	0.49, 1.54

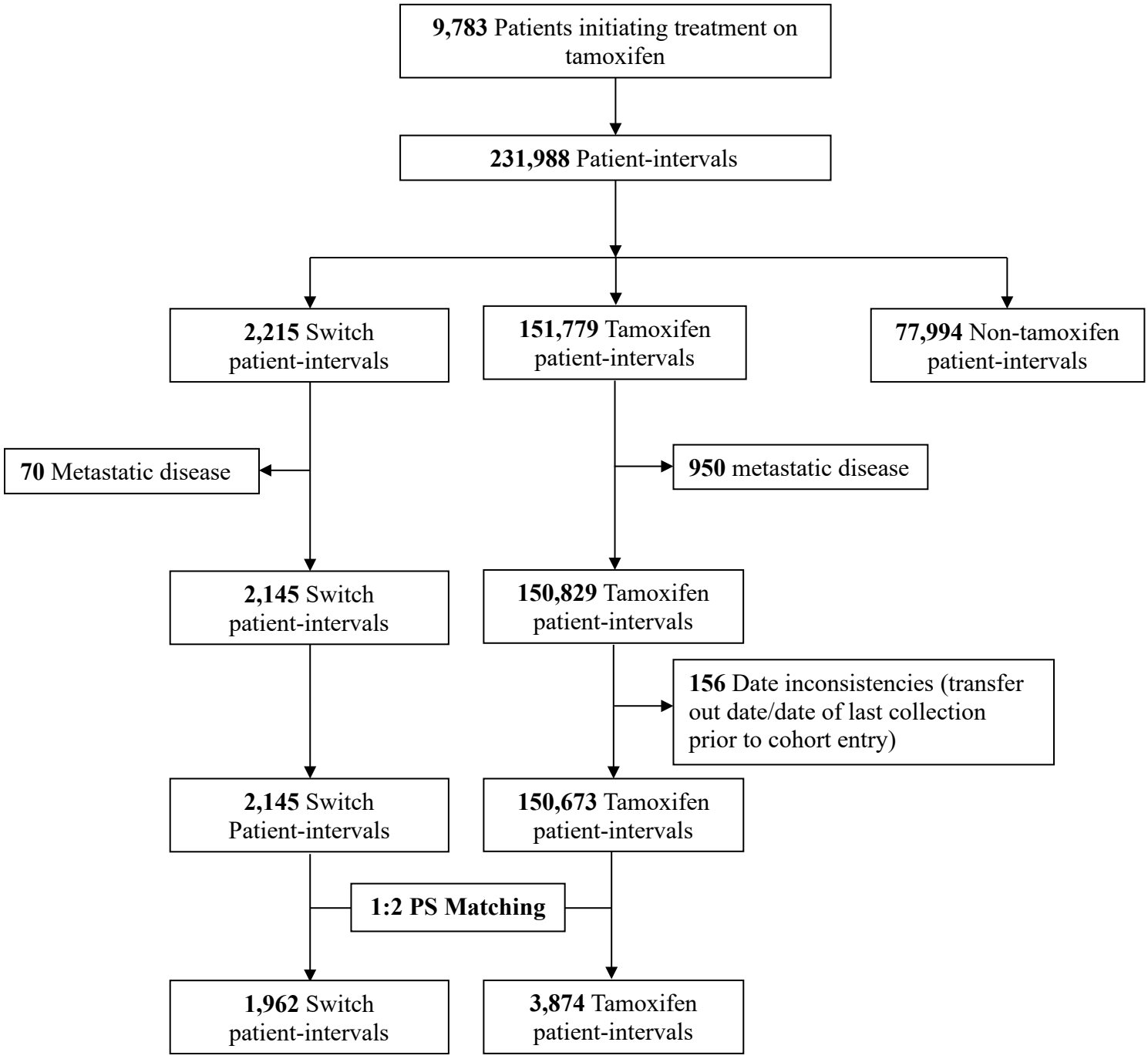
a. Per 1,000 person-years

b. Hazard ratio obtained from matched population

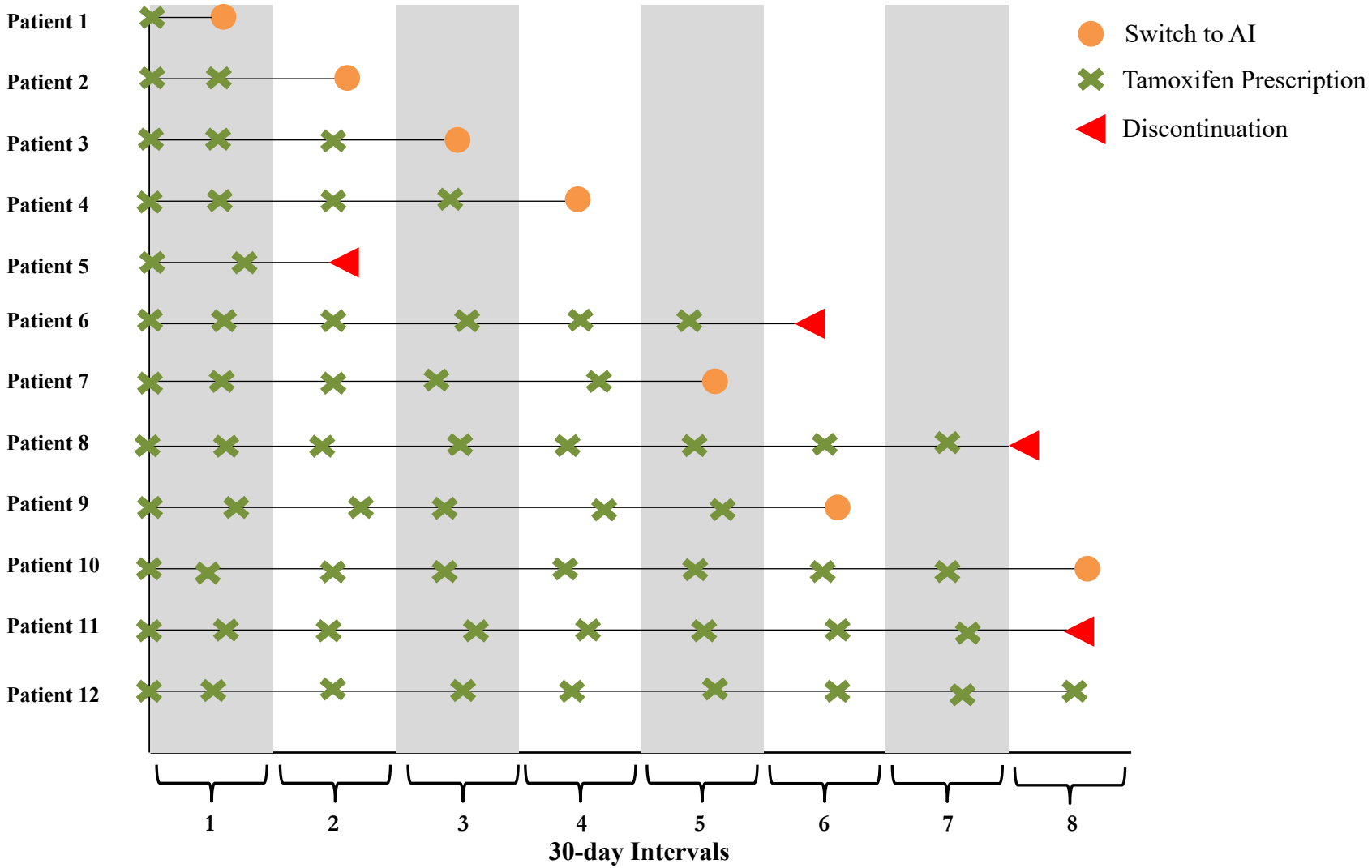
Web Figure 1. Flow Diagram of Study Population Depicting Selection of Women with Diagnosis of Breast Cancer Initiating Treatment on Tamoxifen, United Kingdom, 1998–2016



Web Figure 2. Flow Diagram Depicting Selection of Patients Switching to Aromatase Inhibitors Who Were Matched with Patients Who Continued Tamoxifen Treatment, United Kingdom, 1998–2016

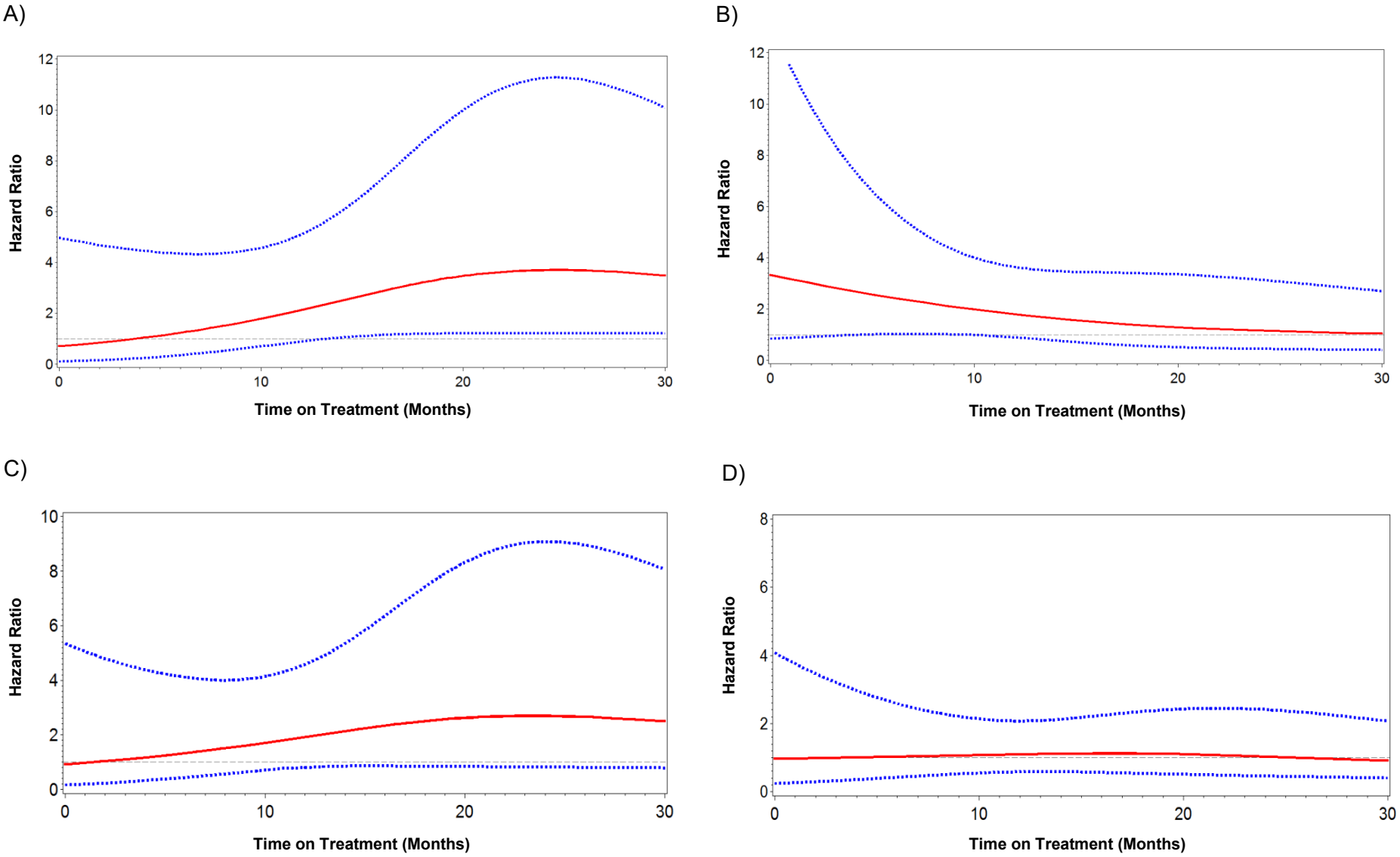


Web Figure 3. Schematic of Prevalent New-User Design Depicting Matching of Patients Switching to Aromatase Inhibitors with Patients Continuing Tamoxifen Treatment



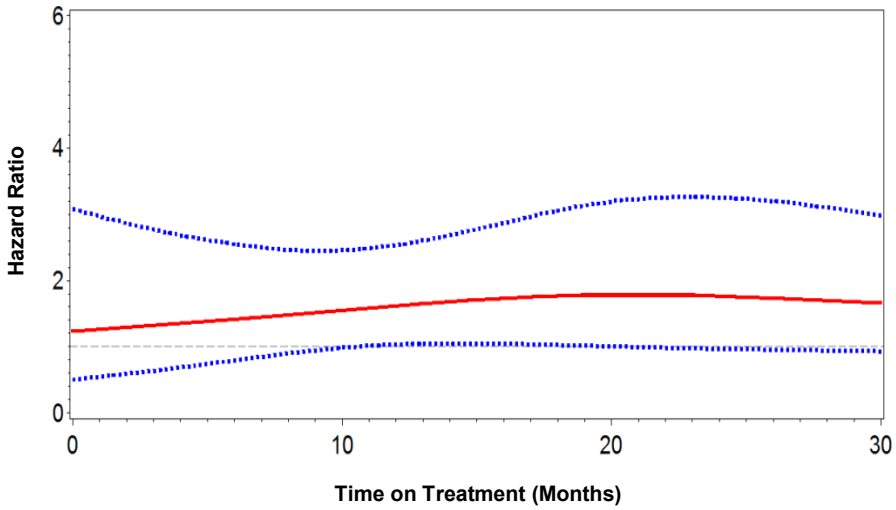
At each 30-day interval, patients who switched to aromatase inhibitors (AIs) were identified (exposed group). In each interval, a patient who switched to AIs was matched to two distinct patients who continued on tamoxifen therapy and received a tamoxifen prescription in the interval. Patients in a given interval were matched based on time-conditional propensity scores using nearest neighbor matching without replacement with a caliper of 0.2 standard deviation of the logit of the propensity score.

Web Figure 4. Restricted Cubic Spline of the Hazard Ratio for Myocardial Infarction (Panel A), Ischemic Stroke (Panel B), Heart Failure (Panel C), and Cardiovascular Mortality (Panel D) as a Function of Time on Treatment When Comparing Patients Switching to Aromatase Inhibitors with Patients Continuing Tamoxifen Treatment, United Kingdom, 1998–2016



Web Figure 5. Restricted Cubic Spline of the Hazard Ratio for Major Adverse Cardiovascular Events (MACE) as a Function of Time on Treatment (Panel A) and Duration of Previous Tamoxifen Treatment (Panel B) When Comparing Patients Switching to Aromatase Inhibitors with Patients Continuing Tamoxifen Treatment, United Kingdom, 1998–2016

A)



B)