

SUPPLEMENTARY MATERIAL

Pre- and post-diagnostic β -blocker use and lung cancer survival:

A population-based cohort study

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SUPPLEMENTARY TABLES

Supplementary Table 1. Classification of Medication Classes according to ATC codes of the Dispensings

Drug class	International Nonproprietary Name (INN)/Subclass	ATC Codes
<u>β-blockers</u>		
Any β-blocker	-	Starting with 'C07'
Selective β-blocker (according WHO/ATC coding)	Metoprolol, Atenolol, Acebutolol, Bisoprolol, Celiprolol, Esmolol, Nebivolol	C07AB Combinations: C07BB, C07CB, C07DB, C07EB, C07FB
Nonselective β-blocker (according WHO/ATC coding)	Alprenolol, Oxprenolol, Pindolol, Propranolol, Timolol, Sotalol	C07AA Combinations: C07BA, C07CA, C07DA, C07EA, C07FA
Alpha and β-blocking agents	Carvedilol, Laβlol	C07AG Combinations: C07BG, C07CG
Lipophilic character	Propranolol, Nebivolol, Carvedilol, Alprenolol, Bisoprolol, Metoprolol, Pindolol, Acebutolol, Timolol (systemic)	See single active ingredients
Hydrophilic character	Atenolol, Sotalol, Nadolol	See single active ingredients
<u>Single active ingredients (and combinations)</u>		
Metoprolol	C07AB02, C07FB02, C07CB02, C07BB02, C07BB52, C07AB52	
Bisoprolol	C07AB07, C07FB07, C07BB07, C07AB57, C09BX02	
Carvedilol	C07AG02	
Atenolol	C07AB03, C07FB03, C07CB03, C07CB53, C07BB03, C07DB01, C07AB11	
Propranolol	C07AA05, C07FA05, C07BA05	
Nebivolol	C07AB12, C07FB12, C07BB12	
Sotalol	C07AA07, C07BA07, C07AA57	
Timolol (systemic)	C07AA06, C07AA06, C07BA06, C07DA06	
Pindolol	C07AA17, C07CA17, C07AA14, C07AA03, C07CA03	
Acebutolol	C07AB04, C07BB04	
Other antihypertensive treatment	C02, C03, C04, C08, C09	
Statins	C10AA, C10BA, C10BX	
Non-steroidal anti-inflammatory drugs (NSAIDs)	M01A, M01B, N02BA, B01AC06, B01AC30, B01AC34, B01AC36, B01AC56, B01AC30	
Diabetes medication	A10	
Comparison group (medications used for same indications as β-blockers)^a	Coronary Heart Disease & Acute Myocardial Infarction	C01DA, C08, C01EB17, C01DX16, C01EB15, C01EB18, C01DX12, C10A, C10B, B01AC09A, C09B, C09C, C09D, C03A, C03B, C03C, C03D, C03E, C02D, C01A
	Congestive Heart Failure	C01B, C08D, B01AA, B01AE, B01AF, C01BG11, C01EB10
	Cardiac Arrhythmias	C09X, C02A, C02CA, C02LA, C02LB, C02LC, C02LE, C02LF, C02LG, C02LK
	Hypertension	

^a If medications are prescribed for more than one indication, they are listed only once.

Supplementary Table 2. Association between Pre-diagnostic β -blocker use and Lung Cancer Survival (Overall, by Cancer Site and Cancer Stage) when Comparing to Non-use.*

β -blocker/ subgroup	All eligible patients (N=6172)					Propensity score matched cohort (N=2874)				
	N	Events	HR ^a	95% CI	P	N	Events	HR ^b	95% CI	P
No β-blocker										
Total	4735	4120	1.00	Ref.	/	1437	1280	1.00	Ref.	/
Stage I	713	414	1.00	Ref.	/	229	143	1.00	Ref.	/
Stage II	266	171	1.00	Ref.	/	80	63	1.00	Ref.	/
Stage III	1348	1229	1.00	Ref.	/	412	384	1.00	Ref.	/
Stage IV	1907	1847	1.00	Ref.	/	538	525	1.00	Ref.	/
NSCLC	3458	2919	1.00	Ref.	/	1014	879	1.00	Ref.	/
SCLC	814	773	1.00	Ref.	/	249	240	1.00	Ref.	/
Any β-blocker										
Total	1437	1265	0.99	0.92-1.07	0.8114	1437	1265	1.00	0.93-1.09	0.9325
Stage I	239	152	1.06	0.84-1.33	0.6261	239	152	1.03	0.82-1.29	0.8139
Stage II	79	65	1.03	0.70-1.52	0.8629	79	65	0.99	0.69-1.42	0.9631
Stage III	411	366	0.86	0.75-0.98	0.0278	411	366	0.92	0.79-1.06	0.2540
Stage IV	549	539	1.08	0.96-1.21	0.2125	549	539	1.11	0.99-1.25	0.0797
NSCLC	1027	883	0.98	0.90-1.07	0.7142	1027	883	0.99	0.90-1.09	0.7871
SCLC	252	239	1.13	0.95-1.34	0.1541	252	239	1.14	0.95-1.36	0.1493
Selective β-blocker										
Total	1278	1122	0.98	0.91-1.05	0.5515	1278	1122	0.97	0.90-1.06	0.5212
Stage I	215	139	1.12	0.89-1.41	0.3208	215	139	1.08	0.86-1.37	0.5098
Stage II	69	56	0.97	0.65-1.47	0.8989	69	56	0.96	0.66-1.41	0.8543
Stage III	368	327	0.85	0.74-0.98	0.0277	368	327	0.90	0.77-1.04	0.1556
Stage IV	484	474	1.07	0.95-1.21	0.2395	484	474	1.07	0.95-1.21	0.2447
NSCLC	909	781	0.99	0.91-1.09	0.8636	909	781	0.98	0.88-1.08	0.6280
SCLC	229	216	1.09	0.91-1.30	0.3482	229	216	1.04	0.87-1.25	0.6517
Nonselective β-blocker										
Total	178	162	1.08	0.92-1.27	0.3488	178	162	1.19	1.01-1.41	0.0398
Stage I	26	15	0.81	0.47-1.40	0.4516	26	15	0.84	0.48-1.47	0.5350
Stage II	10	9	1.25	0.60-2.58	0.5520	10	9	1.11	0.59-2.06	0.7536
Stage III	53	49	0.99	0.73-1.33	0.9409	53	49	1.22	0.90-1.65	0.2015
Stage IV	70	70	1.00	0.79-1.28	0.9759	70	70	1.14	0.91-1.43	0.2498
NSCLC	131	115	0.98	0.81-1.19	0.8428	131	115	1.09	0.90-1.33	0.3745
SCLC	25	25	1.22	0.81-1.84	0.3461	25	25	1.67	1.16-2.40	0.0062
Hydrophilic β-blocker										
Total	349	307	0.87	0.77-0.98	0.0256	349	307	0.98	0.87-1.10	0.7142
Stage I	55	40	1.23	0.87-1.73	0.2442	55	40	1.36	0.95-1.95	0.0884
Stage II	25	23	1.04	0.63-1.70	0.8849	25	23	1.26	0.80-1.99	0.3124
Stage III	89	73	0.72	0.56-0.92	0.0084	89	73	0.82	0.63-1.08	0.1643
Stage IV	134	132	0.90	0.75-1.09	0.2841	134	132	1.01	0.85-1.22	0.8814
NSCLC	234	203	0.92	0.80-1.07	0.2961	234	203	1.01	0.87-1.17	0.9306
SCLC	67	63	0.94	0.71-1.23	0.6312	67	63	1.06	0.80-1.40	0.6802
Lipophilic β-blocker										
Total	1073	943	1.06	0.98-1.14	0.1669	1073	943	1.01	0.93-1.10	0.8280
Stage I	184	111	0.94	0.74-1.21	0.6467	184	111	0.88	0.70-1.110	0.2814
Stage II	53	41	0.98	0.65-1.47	0.9163	53	41	0.83	0.56-1.21	0.3335
Stage III	320	291	0.95	0.82-1.10	0.4936	320	291	1.00	0.86-1.16	0.9998
Stage IV	405	397	1.15	1.01-1.30	0.0294	405	397	1.11	0.98-1.26	0.0929

β -blocker/ subgroup	All eligible patients (N=6172)					Propensity score matched cohort (N=2874)				
	N	Events	HR ^a	95% CI	P	N	Events	HR ^b	95% CI	P
NSCLC	782	669	1.03	0.93-1.13	0.6013	782	669	0.98	0.89-1.09	0.7449
SCLC	181	172	1.14	0.95-1.38	0.1696	181	172	1.08	0.89-1.30	0.4499

Abbreviations: ATC=Anatomical Therapeutic Chemical Code, CI=Confidence interval, HR=Hazard ratio, NSAIDs=Non-steroidal anti-inflammatory drugs, NSCLC=Non-small cell lung cancer, PY=Person-years, SCLC=Small cell lung cancer

^a Hazard ratio from the Cox proportional hazard model β -blocker use four months prior diagnosis; adjusted for age, sex, year of diagnosis, socio-economic status, comorbidities (cardiovascular, hypertension, cerebrovascular, lung, diabetes), treatment (surgery, chemotherapy, radiotherapy, radiotherapy aimed at metastasis), best supportive care, stage, histology (NSCLC, SCLC, Other), previous cancer, time-dependent use of NSAIDs, statins, antihypertensive (other than β -blocker) and diabetes medication after diagnosis and number of distinct ATC classes prescribed during four months prior to diagnosis. Stratification factors were omitted from the stratified models.

^b Hazard ratio from the Cox proportional hazard model for β -blocker use four months prior diagnosis; adjusted for time-dependent use of NSAIDs, statins, antihypertensive (other than β -blocker) and diabetes medication.

Supplementary Table 3. Association between Post-diagnostic β -blocker use and Lung Cancer Survival (Overall, by Histological Subtype and Cancer Stage) when Comparing to Non-use.*

β -blocker/ subgroup	All eligible patients (N=6172)					Propensity score matched cohort (N=2874)				
	PY	Events	HR ^a	95% CI	P	PY	Events	HR ^b	95% CI	P
No β-blocker										
Total	7738	3800	1.00	Ref.	/	1944	1132	1.00	Ref.	/
Stage I	2575	349	1.00	Ref.	/	652	113	1.00	Ref.	/
Stage II	773	155	1.00	Ref.	/	170	58	1.00	Ref.	/
Stage III	1975	1107	1.00	Ref.	/	489	329	1.00	Ref.	/
Stage IV	1677	1766	1.00	Ref.	/	392	488	1.00	Ref.	/
NSCLC	6525	2678	1.00	Ref.	/	1483	880	1.00	Ref.	/
SCLC	950	723	1.00	Ref.	/	237	240	1.00	Ref.	/
Any β-blocker										
Total	3453	1585	1.09	1.02-1.17	0.0148	2855	1413	1.03	0.95-1.12	0.4430
Stage I	1375	217	1.08	0.88-1.33	0.4492	1111	182	1.01	0.79-1.28	0.9429
Stage II	336	81	1.06	0.75-1.49	0.7560	226	70	0.99	0.69-1.42	0.9510
Stage III	908	488	1.00	0.88-1.14	0.9990	777	421	0.96	0.83-1.12	0.6061
Stage IV	474	620	1.13	1.02-1.26	0.0257	440	576	1.11	0.99-1.25	0.0851
NSCLC	2824	1124	1.08	0.99-1.17	0.0835	2295	985	0.99	0.90-1.09	0.8799
SCLC	312	289	1.26	1.07-1.48	0.0057	286	268	1.22	1.02-1.46	0.0279
Selective β-blocker										
Total	3079	1404	1.08	1.00-1.16	0.0379	2569	1260	1.01	0.93-1.09	0.8848
Stage I	1204	192	1.15	0.94-1.42	0.1834	978	164	1.07	0.84-1.35	0.5886
Stage II	297	73	1.13	0.79-1.62	0.5152	200	63	1.03	0.71-1.50	0.8807
Stage III	817	439	1.01	0.88-1.14	0.9365	707	382	0.96	0.82-1.12	0.5941
Stage IV	422	542	1.13	1.01-1.26	0.0370	395	508	1.07	0.95-1.20	0.2967
NSCLC	2490	995	1.10	1.01-1.19	0.0321	2040	882	1.00	0.91-1.11	0.9492
SCLC	293	258	1.19	1.01-1.41	0.0425	268	239	1.09	0.91-1.30	0.3626
Nonselective β-blocker										
Total	519	241	1.17	1.02-1.33	0.0226	400	205	1.21	1.04-1.41	0.0143
Stage I	218	34	0.97	0.68-1.39	0.8748	164	25	0.96	0.64-1.45	0.8496
Stage II	53	15	1.36	0.76-2.44	0.2956	32	12	1.26	0.71-2.25	0.4346
Stage III	150	80	1.08	0.86-1.37	0.5123	123	67	1.18	0.90-1.55	0.2311
Stage IV	60	87	1.04	0.84-1.30	0.7074	51	76	1.18	0.95-1.45	0.1296
NSCLC	455	175	1.06	0.90-1.23	0.4941	354	143	1.08	0.90-1.28	0.4204
SCLC	28	39	1.33	0.95-1.85	0.0930	24	35	1.76	1.29-2.38	0.0003
Hydrophilic β-blocker										
Total	895	383	0.93	0.84-1.04	0.2035	743	342	1.00	0.89-1.12	0.9450
Stage I	288	56	1.19	0.89-1.60	0.2314	232	48	1.34	0.98-1.83	0.0670
Stage II	103	28	1.01	0.64-1.59	0.9661	60	24	1.32	0.84-2.09	0.2295
Stage III	237	103	0.83	0.68-1.03	0.0902	210	89	0.88	0.68-1.14	0.3226
Stage IV	116	149	0.94	0.79-1.12	0.4660	106	136	1.02	0.86-1.23	0.7873
NSCLC	674	261	0.97	0.85-1.11	0.6525	542	227	1.01	0.87-1.16	0.9239
SCLC	89	74	1.02	0.79-1.31	0.9008	84	69	1.11	0.85-1.45	0.4569
Lipophilic β-blocker										
Total	2733	1228	1.15	1.07-1.24	0.0002	2246	1092	1.03	0.95-1.12	0.4779
Stage I	1154	169	0.99	0.80-1.22	0.9111	924	142	0.89	0.71-1.13	0.3376
Stage II	250	59	1.21	0.84-1.73	0.3084	169	49	0.88	0.61-1.28	0.5169
Stage III	729	400	1.09	0.96-1.24	0.1979	619	345	1.04	0.89-1.21	0.6046
Stage IV	358	465	1.19	1.06-1.33	0.0041	336	435	1.10	0.97-1.24	0.1435

β -blocker/ subgroup	All eligible patients (N=6172)					Propensity score matched cohort (N=2874)				
	PY	Events	HR ^a	95% CI	P	PY	Events	HR ^b	95% CI	P
NSCLC	2287	883	1.12	1.03-1.22	0.0112	1849	773	0.99	0.90-1.09	0.8658
SCLC	234	217	1.23	1.04-1.47	0.0171	214	201	1.14	0.95-1.38	0.1530

Abbreviations: ATC=Anatomical Therapeutic Chemical Code, CI=Confidence interval, HR=Hazard ratio, NSAIDs=Non-steroidal anti-inflammatory drugs, NSCLC=Non-small cell lung cancer, PY=Person-years, SCLC=Small cell lung cancer

^a Hazard ratio from the Cox proportional hazard model for time-dependent β -blocker use; adjusted for age, sex, year of diagnosis, socio-economic status, comorbidities (cardiovascular, hypertension, cerebrovascular, lung, diabetes), treatment (surgery, chemotherapy, radiotherapy, radiotherapy aimed at metastasis), best supportive care, stage, histology (NSCLC, SCLC, Other), previous cancer, time-dependent use of NSAIDs, statins, antihypertensive (other than β -blocker) and diabetes medication after diagnosis and number of distinct ATC classes prescribed during four months prior to diagnosis. Stratification factors were omitted from the stratified models.

^b Hazard ratio from the Cox proportional hazard model for time-dependent β -blocker use; adjusted for time-dependent use of NSAIDs, statins, antihypertensive (other than β -blocker) and diabetes medication.

Supplementary Table 4. Association between Post-diagnostic Cumulative Dose and Cumulative Duration of β -blocker use and Overall Lung Cancer Survival (Overall, by β -receptor Affinity and Pharmacokinetic Characteristics) when Comparing to Non-use.*

β -blocker/Exposure	All eligible patients (N=6172)					Propensity score matched cohort (N=2874)				
	PY	Events	HR ^a	95% CI	P	PY	Events	HR ^b	95% CI	P
Any β-blocker										
0 DDDs	7555	3778	1.00	Ref.	/	1864	1123	1.00	Ref.	/
>0 - 365 DDDs	2047	1223	1.08	1.00-1.16	0.0542	1625	1093	1.04	0.95-1.13	0.4214
366+ DDDs	1077	251	0.98	0.85-1.13	0.7492	962	232	0.98	0.84-1.15	0.8337
Trend (180 DDDs)			1.00	0.97-1.02	0.7726			0.99	0.97-1.02	0.4667
0 months	7738	3800	1.00	Ref.	/	1944	1132	1.00	Ref.	/
1-12 months	1799	1178	1.14	1.05-1.23	0.0014	1410	1047	1.08	0.98-1.18	0.1197
13-24 months	627	213	0.94	0.83-1.07	0.3658	543	193	0.92	0.79-1.07	0.2698
25-36 months	375	103	0.97	0.79-1.20	0.8120	331	96	0.94	0.74-1.20	0.6430
> 36 months	652	91	1.28	1.04-1.57	0.0224	571	77	1.06	0.80-1.39	0.6932
Trend (12 months)			1.04	1.01-1.08	0.0124			1.01	0.97-1.05	0.7977
Selective β-blockers										
0 DDDs	7908	3948	1.00	Ref.	/	2129	1268	1.00	Ref.	/
>0 - 365 DDDs	1822	1089	1.07	1.00-1.16	0.0665	1475	981	1.01	0.93-1.1	0.8052
366+ DDDs	966	218	0.95	0.81-1.10	0.4750	853	201	0.95	0.8-1.11	0.4966
Trend (180 DDDs)			0.99	0.97-1.02	0.5299			0.99	0.96-1.01	0.3173
0 months	8112	3981	1.00	Ref.	/	2230	1285	1.00	Ref.	/
1-12 months	1585	1037	1.14	1.05-1.23	0.0017	1267	927	1.05	0.96-1.16	0.2808
13-24 months	567	191	0.89	0.77-1.02	0.0820	496	176	0.86	0.73-1.00	0.0514
25-36 months	340	90	0.98	0.79-1.21	0.8301	297	85	0.98	0.76-1.25	0.8462
> 36 months	587	86	1.27	1.02-1.57	0.0306	509	72	1.10	0.84-1.44	0.5024
Trend (12 months)			1.04	1.00-1.08	0.0286			1.00	0.96-1.04	0.9009
Nonselective β-blockers										
0 DDDs	1022	5032	1.00	Ref.	/	4104	2260	1.00	Ref.	/
>0 - 365 DDDs	350	198	1.20	1.04-1.39	0.0131	244	168	1.29	1.10-1.52	0.0018
366+ DDDs	115	25	0.83	0.56-1.23	0.3542	112	23	0.86	0.61-1.22	0.4004
Trend (180 DDDs)			1.02	0.97-1.07	0.5301			1.01	0.96-1.06	0.6810
0 months	1067	5144	1.00	Ref.	/	4399	2340	1.00	Ref.	/
1-12 months	345	204	1.19	1.02-1.38	0.0260	250	175	1.28	1.09-1.51	0.0033
13-24 months	78	20	1.12	0.83-1.52	0.4680	56	15	1.16	0.83-1.63	0.3842
25-36 months	40	13	1.05	0.58-1.90	0.8803	37	11	1.00	0.57-1.77	0.9886
> 36 months	57	4	1.12	0.56-2.27	0.7476	57	4	0.64	0.32-1.28	0.2109
Trend (12 months)			1.07	0.99-1.15	0.1056			1.03	0.95-1.13	0.4535
Hydrophilic β-blockers										
0 DDDs	9861	4882	1.00	Ref.	/	3774	2118	1.00	Ref.	/
>0 - 365 DDDs	569	318	1.01	0.90-1.13	0.8772	431	281	1.06	0.93-1.20	0.3682
366+ DDDs	250	52	0.63	0.47-0.83	0.0010	245	49	0.79	0.60-1.04	0.0946
Trend (180 DDDs)			0.95	0.92-0.99	0.0262			0.99	0.95-1.03	0.6129
0 months	1029	5002	1.00	Ref.	/	4056	2203	1.00	Ref.	/
1-12 months	520	303	1.00	0.88-1.14	0.9609	407	271	1.03	0.90-1.18	0.6307
13-24 months	149	43	0.82	0.65-1.04	0.0996	122	38	0.98	0.76-1.26	0.8487
25-36 months	98	23	0.76	0.50-1.17	0.2129	88	20	0.86	0.56-1.33	0.5013
> 36 months	128	14	0.78	0.51-1.18	0.2368	127	13	0.80	0.49-1.30	0.3742

β -blocker/Exposure	All eligible patients (N=6172)					Propensity score matched cohort (N=2874)				
	PY	Events	HR ^a	95% CI	P	PY	Events	HR ^b	95% CI	P
Trend (12 months)			0.95	0.89-1.01	0.0925			0.98	0.92-1.04	0.5307
<u>Lipophilic β-blockers</u>										
0 DDDs	8247	4133	1.00	Ref.	/	2444	1442	1.00	Ref.	/
>0 - 365 DDDs	1650	946	1.12	1.04-1.21	0.0046	1322	848	1.02	0.94-1.12	0.6032
366+ DDDs	809	179	1.08	0.92-1.27	0.3432	701	163	0.98	0.82-1.16	0.7953
Trend (180 DDDs)			1.02	0.99-1.04	0.2409			0.99	0.96-1.02	0.4521
0 months	8458	4157	1.00	Ref.	/	2553	1453	1.00	Ref.	/
1-12 months	1428	912	1.20	1.11-1.30	<0.0001	1121	807	1.08	0.98-1.19	0.1045
13-24 months	512	167	0.95	0.83-1.10	0.5219	446	154	0.88	0.75-1.03	0.1001
25-36 months	298	76	1.03	0.82-1.29	0.8077	256	70	0.95	0.74-1.23	0.7136
> 36 months	495	73	1.50	1.20-1.89	0.0004	423	61	1.13	0.86-1.48	0.3833
Trend (12 months)			1.08	1.04-1.12	0.0001			1.01	0.97-1.06	0.5823

Abbreviations: ATC=Anatomical Therapeutic Chemical Code, CI=Confidence interval, HR=Hazard ratio, NSAIDs=Non-steroidal anti-inflammatory drugs, PY=Person-years

^a Hazard ratio from the Cox proportional hazard model; adjusted for age, sex, year of diagnosis, socio-economic status, comorbidities (cardiovascular, hypertension, cerebrovascular, lung, diabetes), treatment (surgery, chemotherapy, radiotherapy, radiotherapy aimed at metastasis), best supportive care, stage, histology (NSCLC, SCLC, Other), previous cancer, time-dependent use of NSAIDs, statins, antihypertensive (other than β -blocker) and diabetes medication after diagnosis and number of distinct ATC classes prescribed during four months prior to diagnosis. Stratification factors were omitted from the stratified models.

^b Hazard ratio from the Cox proportional hazard model for time-dependent β -blocker use; adjusted for time-dependent use of NSAIDs, statins, antihypertensive (other than β -blocker) and diabetes medication.