

Supplementary Table 6. The risks of any cancer and organ-specific cancers among valsartan new users before and after PSM according to the status of NDMA

PSM		Cancer	Bladder cancer			Breast cancer ^{a)}			Colorectal cancer		
			Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value
Before PSM ^{b)}	Overall	NDMA-unexposed	13,143	1.000	-	10,913	1.000	-	35,613	1.000	-
		Eventually NDMA-unexposed	1,145	0.857 (0.805–0.911)	< 0.001*	885	0.970 (0.904–1.041)	0.400	3,232	1.025 (0.988–1.064)	0.187
		NDMA-exposed	1,772	0.911 (0.866–0.960)	< 0.001*	1,287	0.909 (0.855–0.965)	0.002*	4,746	1.019 (0.987–1.052)	0.250
	6 mon exc.	NDMA-unexposed	6,070	1.000	-	4,529	1.000	-	14,530	1.000	-
		Eventually NDMA-unexposed	1,081	1.118 (1.047–1.194)	< 0.001*	831	1.312 (1.217–1.413)	< 0.001*	3,013	1.362 (1.309–1.417)	< 0.001*
		NDMA-exposed	1,674	1.142 (1.081–1.207)	< 0.001*	1,213	1.178 (1.104–1.256)	< 0.001*	4,454	1.317 (1.273–1.363)	< 0.001*
	1-year exc.	NDMA-unexposed	5,376	1.000	-	3,985	1.000	-	12,730	1.000	-
		Eventually NDMA-unexposed	923	1.027 (0.957–1.101)	0.466	727	1.239 (1.144–1.341)	< 0.001*	2,606	1.267 (1.215–1.322)	< 0.001*
		NDMA-exposed	1,489	1.082 (1.021–1.146)	0.008	1,079	1.122 (1.048–1.201)	< 0.001*	3,940	1.244 (1.200–1.290)	< 0.001*
	2-year exc. ^{d)}	NDMA-unexposed	4,056	1.000	-	2,933	1.000	-	9,406	1.000	-
		Eventually NDMA-unexposed	690	0.961 (0.887–1.043)	0.342	513	1.115 (1.015–1.226)	0.023	1,860	1.150 (1.094–1.209)	< 0.001*
		NDMA-exposed	1,124	1.013 (0.948–1.083)	0.694	758	0.997 (0.920–1.081)	0.947	2,926	1.164 (1.117–1.214)	< 0.001*
1:1 PSM ^{c)}	Overall	NDMA-unexposed	1,368	1.000	-	1,010	1.000	-	3,648	1.000	-
		NDMA-exposed	630	0.990 (0.891–1.100)	0.850	437	0.971 (0.857–1.101)	0.646	1,528	1.046 (0.978–1.119)	0.191
	6 mon exc.	NDMA-unexposed	564	1.000	-	436	1.000	-	1,339	1.000	-
		NDMA-exposed	595	1.306 (1.160–1.472)	< 0.001*	411	1.213 (1.054–1.396)	0.007	1,422	1.408 (1.303–1.521)	< 0.001*
	1-year exc.	NDMA-unexposed	512	1.000	-	389	1.000	-	1,186	1.000	-
		NDMA-exposed	537	1.227 (1.084–1.389)	0.001*	370	1.134 (0.979–1.313)	0.093	1,263	1.301 (1.199–1.411)	< 0.001*
	2-year exc. ^{d)}	NDMA-unexposed	387	1.000	-	291	1.000	-	899	1.000	-
		NDMA-exposed	416	1.166 (1.013–1.342)	0.032	263	0.971 (0.820–1.151)	0.735	948	1.189 (1.084–1.304)	< 0.001*
1:1:1 PSM ^{c)}	Overall	NDMA-unexposed	1,410	1.000	-	1,032	1.000	-	3,920	1.000	-
		Eventually NDMA-unexposed	421	1.049 (0.929–1.183)	0.440	283	1.005 (0.868–1.163)	0.946	1,000	1.049 (0.970–1.133)	0.229
		NDMA-exposed	501	1.027 (0.915–1.152)	0.653	333	0.965 (0.838–1.110)	0.613	1,235	1.050 (0.977–1.130)	0.186

Supplementary Table 6. Continued

	6 mon exc.	NDMA-unexposed	446	1.000	-	326	1.000	-	1,077	1.000	-
		Eventually NDMA-unexposed	391	1.578 (1.370–1.817)	< 0.001*	267	1.511 (1.276–1.789)	< 0.001*	927	1.629 (1.486–1.785)	< 0.001*
		NDMA-exposed	472	1.503 (1.312–1.722)	< 0.001*	310	1.368 (1.162–1.612)	< 0.001*	1,129	1.559 (1.428–1.702)	< 0.001*
	1-year exc.	NDMA-unexposed	407	1.000	-	289	1.000	-	947	1.000	-
		Eventually NDMA-unexposed	325	1.303 (1.122–1.514)	< 0.001*	231	1.332 (1.114–1.592)	0.002*	795	1.420 (1.289–1.564)	< 0.001*
		NDMA-exposed	427	1.337 (1.162–1.538)	< 0.001*	275	1.217 (1.025–1.444)	0.025	998	1.387 (1.265–1.520)	< 0.001*
	2-year exc. ^{d)}	NDMA-unexposed	311	1.000	-	214	1.000	-	721	1.000	-
		Eventually NDMA-unexposed	253	1.188 (1.004–1.406)	0.044	173	1.170 (0.955–1.434)	0.130	578	1.197 (1.072–1.337)	0.001
		NDMA-exposed	329	1.197 (1.023–1.402)	0.025	196	1.009 (0.829–1.229)	0.928	750	1.200 (1.082–1.332)	< 0.001*
PSM	Cancer	Gallbladder and etc. cancer			Kidney cancer			Liver cancer			
		Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value	
Before PSM ^{b)} Overall		NDMA-unexposed	6,968	1.000	-	6,852	1.000	-	41,439	1.000	-
		Eventually NDMA-unexposed	770	1.023 (0.948–1.104)	0.564	595	0.905 (0.830–0.986)	0.023	3,703	0.998 (0.964–1.033)	0.908
		NDMA-exposed	1,149	1.012 (0.949–1.080)	0.713	889	0.942 (0.876–1.013)	0.107	4,942	0.925 (0.897–0.954)	< 0.001*
6 mon exc.		NDMA-unexposed	3,644	1.000	-	2,943	1.000	-	17,386	1.000	-
		Eventually NDMA-unexposed	719	1.268 (1.170–1.375)	< 0.001*	551	1.199 (1.094–1.315)	< 0.001*	3,458	1.316 (1.268–1.366)	< 0.001*
		NDMA-exposed	1,073	1.214 (1.133–1.301)	< 0.001*	836	1.227 (1.135–1.327)	< 0.001*	4,636	1.187 (1.148–1.226)	< 0.001*
1-year exc.		NDMA-unexposed	3,172	1.000	-	2,593	1.000	-	15,018	1.000	-
		Eventually NDMA-unexposed	615	1.182 (1.083–1.289)	< 0.001*	480	1.127 (1.022–1.243)	0.017	2,947	1.217 (1.170–1.267)	< 0.001*
		NDMA-exposed	963	1.177 (1.094–1.266)	< 0.001*	739	1.162 (1.069–1.262)	< 0.001*	4,051	1.116 (1.077–1.156)	< 0.001*
2-year exc. ^{d)}		NDMA-unexposed	2,388	1.000	-	1,941	1.000	-	10,912	1.000	-
		Eventually NDMA-unexposed	438	1.048 (0.946–1.161)	0.371	368	1.100 (0.983–1.230)	0.096	2,051	1.085 (1.035–1.138)	< 0.001*
		NDMA-exposed	708	1.062 (0.976–1.156)	0.161	559	1.114 (1.013–1.225)	0.026	2,899	1.013 (0.972–1.056)	0.525

Supplementary Table 6. Continued

1:1 PSM ^{d)}	Overall	NDMA-unexposed	707	1.000	-	675	1.000	-	4,256	1.000	-	
		NDMA-exposed	358	0.996 (0.867–1.145)	0.959	311	1.007 (0.867–1.170)	0.923	1,693	0.981 (0.921–1.045)	0.552	
	6 mon exc.	NDMA-unexposed	365	1.000	-	276	1.000	-	1,623	1.000	-	
		NDMA-exposed	337	1.191 (1.021–1.388)	0.026	294	1.368 (1.154–1.623)	< 0.001*	1,569	1.311 (1.219–1.409)	< 0.001*	
	1-year exc.	NDMA-unexposed	322	1.000	-	244	1.000	-	1,401	1.000	-	
		NDMA-exposed	310	1.176 (1.002–1.380)	0.047	254	1.230 (1.028–1.473)	0.024	1,366	1.199 (1.111–1.294)	< 0.001*	
	2-year exc. ^{d)}	NDMA-unexposed	247	1.000	-	184	1.000	-	1,020	1.000	-	
		NDMA-exposed	228	1.039 (0.866–1.247)	0.683	205	1.243 (1.016–1.521)	0.035	991	1.079 (0.988–1.179)	0.092	
	1:1:1 PSM ^{d)}	Overall	NDMA-unexposed	692	1.000	-	744	1.000	-	4,620	1.000	-
			Eventually NDMA-unexposed	248	1.062 (0.906–1.244)	0.459	200	0.953 (0.803–1.133)	0.587	1,230	1.097 (1.022–1.177)	0.010
6 mon exc.		NDMA-exposed	273	0.951 (0.815–1.111)	0.530	251	0.973 (0.828–1.143)	0.740	1,390	1.004 (0.938–1.075)	0.905	
		NDMA-unexposed	296	1.000	-	223	1.000	-	1,313	1.000	-	
1-year exc.		Eventually NDMA-unexposed	229	1.393 (1.165–1.666)	< 0.001*	186	1.518 (1.240–1.858)	< 0.001*	1,125	1.686 (1.551–1.833)	< 0.001*	
		NDMA-exposed	255	1.224 (1.028–1.458)	0.023	236	1.514 (1.250–1.835)	< 0.001*	1,273	1.499 (1.381–1.626)	< 0.001*	
2-year exc. ^{d)}		NDMA-unexposed	262	1.000	-	198	1.000	-	1,124	1.000	-	
		Eventually NDMA-unexposed	201	1.288 (1.066–1.555)	0.009	160	1.319 (1.066–1.633)	0.011	964	1.478 (1.352–1.615)	< 0.001*	
			NDMA-exposed	237	1.183 (0.987–1.418)	0.069	203	1.304 (1.066–1.595)	0.010	1,111	1.327 (1.218–1.445)	< 0.001*
			NDMA-unexposed	205	1.000	-	146	1.000	-	826	1.000	-
	Eventually NDMA-unexposed		140	1.013 (0.815–1.259)	0.911	129	1.319 (1.038–1.676)	0.024	666	1.193 (1.076–1.323)	< 0.001*	
		NDMA-exposed	172	0.955 (0.777–1.172)	0.657	163	1.285 (1.025–1.612)	0.030	801	1.110 (1.006–1.225)	0.038	
PSM	Cancer	Lung cancer			Pancreatic cancer			Prostate cancer ^{a)}				
		Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value		
Before PSM ^{b)}	Overall	NDMA-unexposed	27,856	1.000	-	21,872	1.000	-	55,614	1.000	-	
		Eventually NDMA-unexposed	2,823	0.968 (0.930–1.007)	0.105	2,137	0.942 (0.900–0.985)	0.010	4,934	0.936 (0.908–0.964)	< 0.001*	
		NDMA-exposed	4,122	0.948 (0.916–0.981)	0.002*	3,235	0.970 (0.934–1.008)	0.121	7,497	1.012 (0.987–1.038)	0.351	

Supplementary Table 6. Continued

	6 mon exc.	NDMA-unexposed	13,675	1.000	-	10,661	1.000	-	23,781	1.000	-
		Eventually NDMA-unexposed	2,642	1.252 (1.201–1.306)	< 0.001*	2,002	1.194 (1.138–1.253)	< 0.001*	4,618	1.208 (1.170–1.247)	< 0.001*
		NDMA-exposed	3,916	1.207 (1.164–1.252)	< 0.001*	3,060	1.197 (1.149–1.247)	< 0.001*	7,121	1.290 (1.255–1.325)	< 0.001*
	1-year exc.	NDMA-unexposed	11,928	1.000	-	9,367	1.000	-	20,828	1.000	-
		Eventually NDMA-unexposed	2,295	1.181 (1.129–1.236)	< 0.001*	1,769	1.143 (1.086–1.203)	< 0.001*	3,965	1.122 (1.084–1.161)	< 0.001*
		NDMA-exposed	3,433	1.139 (1.096–1.184)	< 0.001*	2,694	1.132 (1.084–1.182)	< 0.001*	6,318	1.228 (1.194–1.264)	< 0.001*
	2-year exc. ^{d)}	NDMA-unexposed	8,838	1.000	-	7,084	1.000	-	15,521	1.000	-
		Eventually NDMA-unexposed	1,654	1.084 (1.028–1.142)	0.003*	1,298	1.053 (0.992–1.117)	0.091	2,855	1.022 (0.982–1.064)	0.290
		NDMA-exposed	2,530	1.058 (1.012–1.106)	0.013	2,017	1.053 (1.001–1.106)	0.044	4,638	1.135 (1.098–1.173)	< 0.001*
1:1 PSM ^{c)}	Overall	NDMA-unexposed	2,790	1.000	-	2,341	1.000	-	6,621	1.000	-
		NDMA-exposed	1,399	1.029 (0.959–1.105)	0.422	1,193	1.076 (0.995–1.163)	0.065	2,953	1.042 (0.992–1.094)	0.099
	6 mon exc.	NDMA-unexposed	1,308	1.000	-	1,041	1.000	-	2,569	1.000	-
		NDMA-exposed	1,323	1.342 (1.240–1.453)	< 0.001*	1,110	1.378 (1.262–1.505)	< 0.001*	2,706	1.365 (1.290–1.443)	< 0.001*
	1-year exc.	NDMA-unexposed	1,141	1.000	-	910	1.000	-	2,255	1.000	-
		NDMA-exposed	1,149	1.237 (1.138–1.346)	< 0.001*	967	1.252 (1.141–1.373)	< 0.001*	2,412	1.288 (1.215–1.366)	< 0.001*
	2-year exc. ^{d)}	NDMA-unexposed	855	1.000	-	700	1.000	-	1,723	1.000	-
		NDMA-exposed	838	1.103 (1.001–1.214)	0.047	723	1.135 (1.022–1.262)	0.018	1,749	1.132 (1.058–1.211)	< 0.001*
1:1:1 PSM ^{c)}	Overall	NDMA-unexposed	2,770	1.000	-	2,427	1.000	-	7,152	1.000	-
		Eventually NDMA-unexposed	879	1.022 (0.941–1.111)	0.604	724	1.012 (0.923–1.109)	0.801	1,877	0.974 (0.921–1.031)	0.363
		NDMA-exposed	1,103	1.042 (0.963–1.126)	0.305	970	1.102 (1.013–1.199)	0.024	2,500	1.054 (1.001–1.110)	0.046
	6 mon exc.	NDMA-unexposed	1,028	1.000	-	820	1.000	-	2,077	1.000	-
		Eventually NDMA-unexposed	821	1.484 (1.349–1.632)	< 0.001*	667	1.507 (1.355–1.677)	< 0.001*	1,669	1.467 (1.372–1.568)	< 0.001*
		NDMA-exposed	1,036	1.477 (1.350–1.617)	< 0.001*	906	1.607 (1.455–1.775)	< 0.001*	2,238	1.553 (1.459–1.654)	< 0.001*
	1-year exc.	NDMA-unexposed	899	1.000	-	714	1.000	-	1,817	1.000	-
		Eventually NDMA-unexposed	711	1.333 (1.205–1.474)	< 0.001*	578	1.342 (1.199–1.501)	< 0.001*	1,412	1.283 (1.195–1.378)	< 0.001*
		NDMA-exposed	897	1.311 (1.192–1.442)	< 0.001*	789	1.422 (1.281–1.579)	< 0.001*	1,992	1.416 (1.326–1.512)	< 0.001*

Supplementary Table 6. Continued

2-year exc. ^{d)} NDMA-unexposed			676	1.000	-	553	1.000	-	1,373	1.000	-
Eventually NDMA-unexposed			508	1.115 (0.993–1.253)	0.066	428	1.150 (1.012–1.307)	0.032	987	1.053 (0.969–1.144)	0.222
NDMA-exposed			649	1.096 (0.983–1.223)	0.099	581	1.204 (1.070–1.356)	0.002*	1,421	1.178 (1.093–1.270)	< 0.001*
PSM	Cancer	Stomach cancer				Thyroid cancer			Uterine cancer ^{a)}		
		Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value	Event	aHR (95% CI)	<i>p</i> value	
Before PSM ^{b)}	Overall	NDMA-unexposed	24,266	1.000	-	20,200	1.000	-	3,812	1.000	-
		Eventually NDMA-unexposed	2,236	1.043 (0.998–1.091)	0.062	1,439	0.903 (0.855–0.954)	< 0.001*	355	0.915 (0.819–1.023)	0.118
		NDMA-exposed	3,340	1.047 (1.008–1.088)	0.017	2,139	0.908 (0.867–0.952)	< 0.001*	586	0.978 (0.894–1.071)	0.633
6 mon exc.		NDMA-unexposed	10,378	1.000	-	7,367	1.000	-	1,881	1.000	-
		Eventually NDMA-unexposed	2,066	1.341 (1.278–1.407)	< 0.001*	1,335	1.224 (1.154–1.299)	< 0.001*	339	1.191 (1.060–1.339)	0.003
		NDMA-exposed	3,132	1.331 (1.278–1.386)	< 0.001*	2,000	1.196 (1.138–1.258)	< 0.001*	557	1.210 (1.099–1.332)	< 0.001*
1-year exc.		NDMA-unexposed	8,991	1.000	-	6,433	1.000	-	1,675	1.000	-
		Eventually NDMA-unexposed	1,788	1.259 (1.196–1.325)	< 0.001*	1,152	1.145 (1.075–1.220)	< 0.001*	301	1.143 (1.010–1.293)	0.034
		NDMA-exposed	2,734	1.255 (1.202–1.311)	< 0.001*	1,776	1.141 (1.081–1.203)	< 0.001*	500	1.162 (1.051–1.286)	0.004
2-year exc. ^{d)}		NDMA-unexposed	6,529	1.000	-	4,826	1.000	-	1,289	1.000	-
		Eventually NDMA-unexposed	1,234	1.114 (1.048–1.184)	< 0.001*	830	1.043 (0.969–1.123)	0.264	235	1.139 (0.990–1.310)	0.068
		NDMA-exposed	1,974	1.155 (1.097–1.215)	< 0.001*	1,323	1.064 (1.001–1.131)	0.048	370	1.092 (0.972–1.227)	0.138
1:1 PSM ^{d)}	Overall	NDMA-unexposed	2,651	1.000	-	2,207	1.000	-	332	1.000	-
		NDMA-exposed	1,140	1.044 (0.966–1.128)	0.276	806	0.934 (0.852–1.023)	0.143	176	0.973 (0.795–1.191)	0.794
6 mon exc.		NDMA-unexposed	1,054	1.000	-	748	1.000	-	146	1.000	-
		NDMA-exposed	1,062	1.390 (1.272–1.518)	< 0.001*	756	1.287 (1.158–1.430)	< 0.001*	168	1.349 (1.072–1.698)	0.011
1-year exc.		NDMA-unexposed	921	1.000	-	653	1.000	-	126	1.000	-
		NDMA-exposed	933	1.292 (1.177–1.419)	< 0.001*	676	1.209 (1.082–1.351)	< 0.001*	157	1.407 (1.105–1.790)	0.006
2-year exc. ^{d)}		NDMA-unexposed	688	1.000	-	483	1.000	-	99	1.000	-
		NDMA-exposed	700	1.198 (1.077–1.334)	< 0.001*	497	1.116 (0.982–1.268)	0.092	114	1.220 (0.928–1.604)	0.154

Supplementary Table 6. Continued

1:1:1 PSM ^{c)} Overall	NDMA-unexposed	2,726	1.000	-	2,417	1.000	-	351	1.000	-
	Eventually NDMA-unexposed	753	1.095 (1.001–1.198)	0.048	528	0.967 (0.870–1.075)	0.536	108	0.905 (0.715–1.145)	0.407
	NDMA-exposed	935	1.097 (1.008–1.193)	0.032	637	0.951 (0.861–1.051)	0.325	131	0.878 (0.702–1.098)	0.253
6 mon exc.	NDMA-unexposed	823	1.000	-	598	1.000	-	110	1.000	-
	Eventually NDMA-unexposed	683	1.647 (1.482–1.831)	< 0.001*	485	1.526 (1.346–1.729)	< 0.001*	104	1.535 (1.165–2.024)	0.002*
	NDMA-exposed	871	1.649 (1.491–1.823)	< 0.001*	583	1.439 (1.275–1.623)	< 0.001*	125	1.409 (1.080–1.839)	0.011
1-year exc.	NDMA-unexposed	723	1.000	-	517	1.000	-	92	1.000	-
	Eventually NDMA-unexposed	588	1.441 (1.288–1.611)	< 0.001*	417	1.355 (1.186–1.548)	< 0.001*	96	1.611 (1.202–2.159)	0.001*
	NDMA-exposed	760	1.450 (1.305–1.611)	< 0.001*	521	1.313 (1.157–1.490)	< 0.001*	119	1.507 (1.139–1.994)	0.004
2-year exc. ^{d)}	NDMA-unexposed	548	1.000	-	377	1.000	-	73	1.000	-
	Eventually NDMA-unexposed	416	1.179 (1.036–1.342)	0.012	298	1.170 (1.003–1.365)	0.045	79	1.533 (1.111–2.116)	0.009
	NDMA-exposed	567	1.247 (1.107–1.406)	< 0.001*	382	1.151 (0.996–1.330)	0.057	81	1.184 (0.859–1.631)	0.302

PSM, propensity score matching; aHR, adjusted hazard ratio; CI, confidence interval; NDMA, N-nitrosodimethylamine; mon, month; exc., excluded.

^{a)}All analyses for prostate, breast or uterine cancers were performed limited to men or women.

^{b)}All hazard ratios before PSM were adjusted for age, sex, Charlson comorbidity index, and the year of the first observed valsartan prescription.

^{c)}All hazard ratios after PSM were adjusted for age, sex, and the year of the first observed valsartan prescription.

^{d)}Each model has the lowest Akaike information criterion.

*Statistically significances at the threshold using Bonferroni correction for 13 tests ($p < 0.004$).