

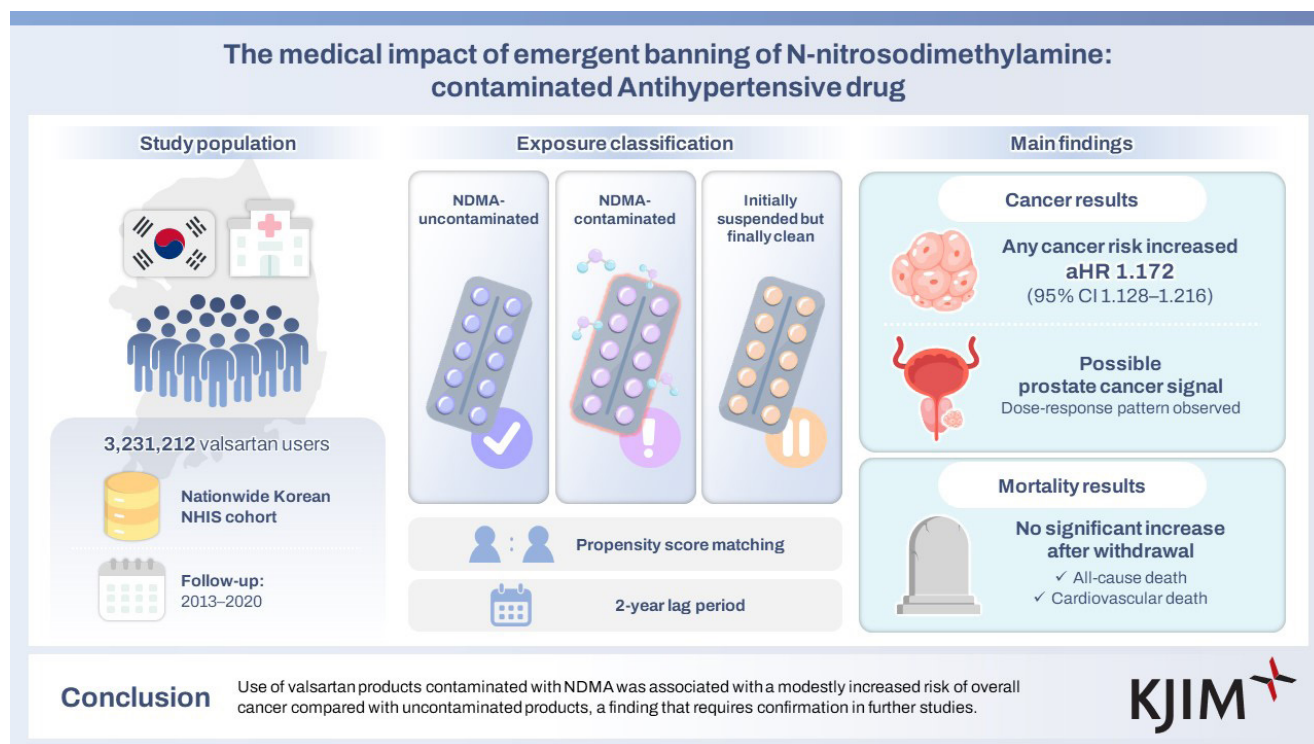


The medical impact of emergent banning of N-nitrosodimethylamine: contaminated antihypertensive drug

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Background/Aims: Concerns exist regarding the potential carcinogenic effect of N-nitrosodimethylamine (NDMA) as a contaminant of the antihypertensive medication, valsartan. This study evaluated the association of NDMA-contaminated valsartan with cancer incidence.

Methods: Nationwide longitudinal observational cohort of 3,231,212 participants from the National Health Insurance Ser-

vice of South Korea consisted and was followed up more than 7 years. We performed 1:1:1 pairwise propensity score matching (PSM) of NDMA-uncontaminated, NDMA-contaminated, and initially-suspended-but-finally confirmed as NDMA-uncontaminated valsartan user-groups. The primary outcome was any primary cancer incidence. The secondary outcome was the incidences of 12 organ-specific cancers. The risks of all-cause and cardiovascular deaths were estimated before and after the withdrawal of valsartan.

Results: Among participants (59.5 ± 13.1 yr; male, 53.5%), valsartan new users had adjusted hazard ratios and 95% confidence intervals of 1.069 (1.054–1.085) and 1.172 (1.128–1.216) for any cancer in the NDMA-exposed period (versus NDMA-unexposed) before and after PSM, respectively. Regardless of PSM, prostate cancer risk increased significantly. All-cause and cardiovascular mortality did not differ significantly with NDMA exposure before and after emergent banning.

Conclusions: Use of valsartan products contaminated with NDMA was associated with a modestly increased risk of overall cancer compared with uncontaminated products, a finding that requires confirmation in further studies.

Keywords: Valsartan; N-nitrosodimethylamine; Death; Cancer

INTRODUCTION

Pharmacological treatment of non-communicable diseases requires long-term use. Therefore, it is an existential threat that even a very small amount of carcinogen causes substantial problems through long-term accumulation. Hence, concerns about the possibility of cancer associated with antihypertensive drugs are continuously raised and resolved. Representative controversies have occurred with antihypertensive medications and overall cancers [1], angiotensin receptor blockers and lung cancer [2], nifedipine with breast and gastrointestinal tract cancers [3–5], and hydrochlorothiazide and skin cancer [6].

Recent concerns include the potential carcinogenic effect of impurities generated during manufacturing processes rather than the main drug ingredient. The European Medicines Agency withdrew medicines containing the active substance, valsartan, which was supplied by Huahai Pharmaceuticals, China, from the market in July 2018 because of contamination with N-nitrosodimethylamine (NDMA) [7]. The United States Food and Drug Administration followed this action after confirming its contamination. On July 7, 2018, the Korea Ministry of Food and Drug Safety (MFDS) immediately suspended 219 generic valsartan products potentially contaminated with NDMA, and finally withdrew 115 generic valsartan products on July 9, 2018 [8,9]. Investigations reported that Huahai Pharmaceuticals probably brought the new manufacturing process contaminating NDMA around 2012 [10]. Shortly after the withdrawal ac-

tion in 2018, Pottegård et al. [11] reported no significant increase in overall cancer (adjusted hazard ratio [aHR] 1.09, 95% confidence interval [CI] 0.85–1.41) and no dose-response relation based on the Danish health registry during 4-year interval. Gomm et al. [7], in 2021, based on German health insurance data, reported a statistically significant association between exposure to NDMA-contaminated valsartan and hepatic cancer (aHR 1.16, 95% CI 1.03–1.31); however, no association was found with the overall cancer risk during a 3-year interval. In contrast, observational study based on the French National Health Data System reported that the use of the NDMA-contaminated valsartan did not increase the overall risk of cancer, but suggested the increased risk of liver cancer and melanoma for a median follow-up of 4 years [12].

In Korea, as an immediate administrative measure, > 90% of related valsartan generic prescriptions were suspended after the government announcement. Following this decision, prescriptions of the affected products were centrally blocked through the national Drug Utilization Review system, and patients were routinely switched to NDMA-uncontaminated valsartan, creating a quasi-policy-driven natural experiment in which exposure was largely determined by regulatory action rather than individual prescribing preference [13]. Korea's health policy mandates an immediate withdrawal from the market if drugs have potential risks before confirming the substantiality of the risks. However, there may be unintended consequences of a sudden suspension of antihypertensive drugs on public health including a possibility that adherence to antihypertensive drugs

might be reduced due to fear of cancer occurrence and overall distrust of medications; regarding cancer incidence, many health checkups might be conducted due to increased health concerns of patients with an increase in prostate, thyroid and breast cancer incidence, because they are frequently diagnosed during screenings; and a possibility that cardiovascular events might increase due to a decrease in adherence to antihypertensive medications.

Therefore, this study evaluated the association of NDMA-contaminated valsartan with cancer incidence. We classified valsartan into three groups—NDMA-contaminated, NDMA-uncontaminated, and initially suspended but eventually NDMA-uncontaminated—according to the MFDS – National Health Insurance Service (NHIS) linkage, and defined exposure periods using time-dependent variables that reflect the recall-driven switching patterns. We also compared all-cause and cardiovascular deaths before and after valsartan withdrawal.

METHODS

Data source

We conducted a long-term observation analysis using nationwide claims data from the NHIS-National Health Information Database (NHID), Korea. The NHIS is a single, mandatory medical care system that covers approximately 50 million people residing in Korea. We also linked the Cause of Death Statistics by Korea Statistics to NHIS-NHID via the Microdata Integrated Service (<https://mdis.kostat.go.kr>). This study was exempted from review by the Institutional Review Board of Seoul National University Hospital (E-2103-057-1203) because of the anonymized data. Informed consent requirement was unattainable, because the NHIS-provided data were de-identified. The NHIS approved the use of the released data in 2022. This study was conducted using pre-existing cohort data, and no experiments involving live vertebrates or human subjects were performed. Therefore, separate approval for experimental protocols was not required.

Study population

We enrolled patients treated with at least one valsartan prescription between January 1, 2013 and December 31, 2020. Minimal adherence was assessed based on the number of prescription days during the 3-months period immediately

following the first observed valsartan prescription after cohort entry. Eligible patients had received a type of valsartan with prescription days $\geq 20\%$ during this initial 3-month window and were aged ≥ 30 years. The cohort entry date was set to January 1, 2013, and patients were followed up until the date of death or December 31, 2020. We excluded patients with a history of cancer before the index date and incomplete baseline characteristics.

Exposure

Valsartan was grouped into three by the NHIS as follows: NDMA-uncontaminated, NDMA-contaminated, and initially-suspended but finally confirmed as NDMA-uncontaminated valsartan (eventually NDMA-uncontaminated valsartan). In Korea, the MFDS issued an emergency suspension of 219 valsartan products on July 7, 2018, narrowing to 128 confirmed NDMA-contaminated products by July 9 after testing [9]. Concurrently, the Ministry of Health and Welfare enacted a nationwide health insurance reimbursement suspension for 125 affected products effective July 9, 08:30 via the national Drug Utilization Review system, automatically blocking prescriptions and facilitating patient switching to uncontaminated alternatives (HIRA Insurance Notice 2018-407) [13]. However, patients prescribed with “eventually NDMA-uncontaminated” valsartan received same recall messages; thus, they might show similar health behavior as the NDMA-contaminated valsartan group. Therefore, we included them in the analysis as an internal control group.

To avoid immortal time bias, valsartan was considered as a time-dependent exposure (Fig. 1). The period from January, 2013 to the first observed valsartan prescription or follow-up among patients who received NDMA-uncontaminated valsartan was defined as the NDMA-unexposed period. The follow-up time of patients who received NDMA-contaminated valsartan was grouped into the NDMA-unexposed and NDMA-exposed periods. For the eventually NDMA-uncontaminated valsartan, patients had NDMA-unexposed and eventually NDMA-uncontaminated valsartan-exposed periods.

Endpoints

The primary outcome was any primary cancer development. We also considered the incidence of 12 prevalent organ-specific cancers in Korea based on the International Classification of Diseases, 10th revision (ICD-10) codes (Supplementary Table 1). The onset date was defined as the first

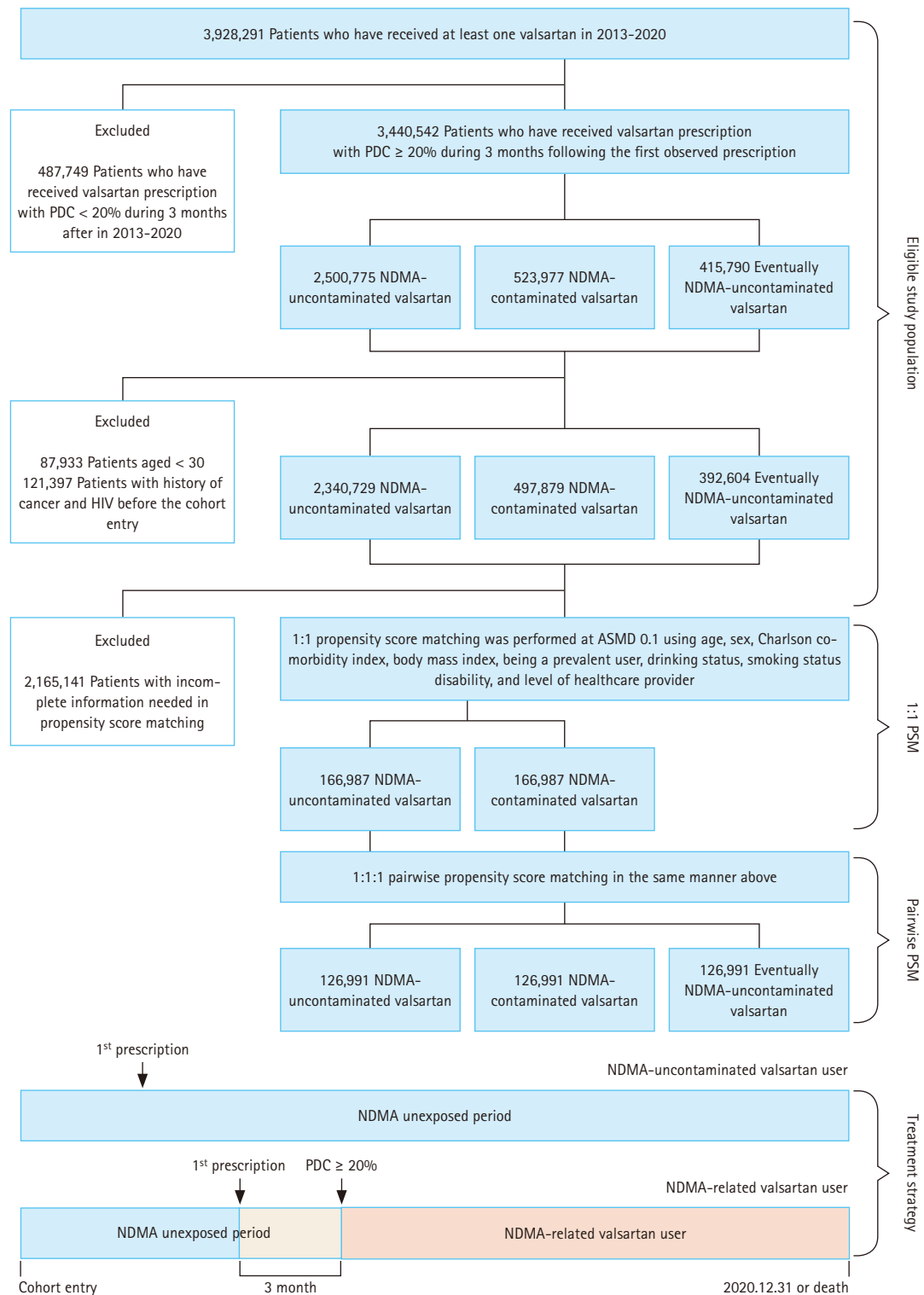


Figure 1. Flowchart of this study. PDC, prescription of days covered; NDMA, N-nitrosodimethylamine; HIV, human immunodeficiency virus; ASMD, absolute standardized mean difference; PSM, propensity score matching.

diagnosis of any or organ-specific cancers. To evaluate the safety, all-cause and cardiovascular death were considered as secondary outcomes. We divided the year 2018 from January 1 to July 6 (before withdrawal) and July 7 to December 31 (after withdrawal) to compare the incidence of safety outcomes. The ICD-10 codes of fatal cardiovascular events included hypertensive disease (I10–I16), ischemic heart disease (I20–I25), myocarditis/cardiomyopathy (I40–I43), arrhythmias/heart failure (I46–I52), cerebrovascular disease (I60–I69), and aortic aneurysm (I70–I73).

Statistical analysis

To address potential confounding effects, we performed propensity score matching (PSM) using nearest method to match participants in three groups. Matching was based on age, sex, body mass index, Charlson comorbidity index (CCI), prevalent user of antihypertensive medication, drinking status, smoking status, presence of disability, and level of healthcare provider from primary to tertiary hospitals (Supplementary Table 2). Using these variables, propensity scores were generated and the eventually NDMA-contaminated valsartan group was matched to each of the NDMA-uncontaminated valsartan and NDMA-contaminated valsartan (Fig. 1). Matching performance was validated by achieving an absolute standardized mean difference < 10% (Supplementary Table 2).

We compared participants' baseline characteristics before and after PSM by using an analysis of variance (ANOVA) or Welch's ANOVA for continuous variables and a χ^2 test for categorical variables. Crude incidence rates (IRs) and their 95% CIs were estimated under the assumption that each event follows the Poisson distribution. To focus on new-user design, we isolated valsartan new users and time-dependent Cox models were used to estimate aHRs considering age, sex, CCI, and the year of the first observed valsartan prescription. The dose-response relationship was evaluated using the same model. We replicated all these analyses including valsartan prevalent users, considering being a prevalent user as a confounder. We pre-specified a 2-year lag period for the primary analysis to account for reverse causation and potential diagnostic delay, and conducted the analysis after excluding patients with events within 2 years of the first observed valsartan prescription. For the secondary outcome, the risk of all-cause death was estimated among valsartan new users, and cardiovascular death was assessed using a cause-specific competing risk model.

We performed sensitivity analyses using different lag periods (no lag, 6 months, and 1 year), and the Akaike information criterion (AIC) was used to evaluate the robustness across models. Furthermore, three sensitivity analyses were implemented to account for key factors: (i) analysis stratified by prostate cancer aged ≤ 65 or > 65 years old; (ii) analyses excluding patients diagnosed with any cancer during the first year of follow-up; (iii) analyses including only patients who received valsartan prescriptions since 2015.

The significance level for all statistical analyses was set at 0.05. To account for multiple comparisons, the Bonferroni correction was applied. Given that any cancer and 12 types of cancers were examined, $p < 0.004$ was considered the corrected significant threshold. Statistical analysis was performed using SAS Enterprise Guide (version 7.13; SAS Institute), R software (version 4.1.3; R project), and Rex (version 3.5.3; RexSoft).

RESULTS

Baseline characteristics

NDMA-uncontaminated (including original) and NDMA-contaminated valsartan were used from the study onset (January 1, 2013), while the eventually NDMA-uncontaminated valsartan was first claimed in September 2013. All prescriptions of valsartan invariably decreased after July, 2018, while those for NDMA-contaminated valsartan were totally eliminated. For the eventually NDMA-uncontaminated valsartan, although the temporary withdrawal was dismissed two days after initial suspension, the claim amount decreased in July–October, 2018, but maintained at the end of study period (December 31, 2020) (Supplementary Fig. 1).

We identified 3,231,212 participants who received at least one tablet of valsartan, satisfying minimal adherence to prescription. Table 1 shows the baseline characteristics of the entire cohort and by valsartan groups. Compared with the NDMA-uncontaminated group, the NDMA-contaminated and eventually NDMA-uncontaminated valsartan groups reported hypertensive medication history less. In contrast, patients in the NDMA-uncontaminated valsartan group had higher comorbidity (high CCI) and were more likely to be treated in secondary and tertiary hospitals.

All covariates before PSM differed according to the valsartan group. After 1:1 PSM, 166,987 users of NDMA-contaminated valsartan and 166,987 users of NDMA-uncontami-

Table 1. Baseline characteristics of study population before propensity score matching

Characteristic	Total (n = 3,231,212)	Original valsartan (n = 2,340,729)	Eventually NDMA- uncontaminated valsartan (n = 392,604)	NDMA- contaminated valsartan (n = 497,879)	p value
Age (yr)	59.5 ± 13.1	59.6 ± 13.1	58.4 ± 13.0	60.2 ± 13.0	< 0.001 ^{b)}
Sex					
Male	1,729,185 (53.5)	1,251,572 (53.5)	220,216 (56.1)	257,397 (51.7)	< 0.001
Female	1,502,027 (46.5)	1,089,157 (46.5)	172,388 (43.9)	240,482 (48.3)	
CCI					< 0.001
0	1,117,080 (34.6)	795,896 (34.0)	152,286 (38.8)	168,898 (33.9)	
1	811,326 (25.1)	585,361 (25.0)	98,847 (25.2)	127,118 (25.5)	
2	545,323 (16.9)	396,944 (17.0)	62,529 (15.9)	85,850 (17.2)	
≥ 3	757,483 (23.4)	562,528 (24.0)	78,942 (20.1)	116,013 (23.2)	
Being a prevalent user					< 0.001
No	2,580,766 (79.9)	1,726,616 (73.8)	392,548 (99.9)	461,599 (92.7)	
Yes	650,446 (20.1)	614,110 (26.2)	56 (0.1)	36,280 (7.3)	
Drinking status					< 0.001 ^{c)}
No	580,727 (18.0)	423,135 (18.1)	64,843 (16.5)	92,749 (18.6)	
Yes	525,191 (16.3)	377,406 (16.1)	67,279 (17.1)	80,506 (16.2)	
Missing	2,125,294 (65.8)	1,540,188 (65.8)	260,482 (66.4)	324,624 (65.2)	
Disability					< 0.001
No	366,137 (11.3)	266,799 (11.4)	41,883 (10.7)	57,455 (11.5)	
Yes	2,865,075 (88.7)	2,073,930 (88.6)	350,721 (89.3)	440,424 (88.5)	
Level of healthcare provider					< 0.001 ^{c)}
Tertiary	275,395 (8.5)	272,014 (11.6)	680 (0.2)	2,701 (0.5)	
Secondary	777,139 (24.1)	636,297 (27.2)	59,218 (15.1)	81,624 (16.4)	
Primary	1,966,594 (60.9)	1,313,803 (56.1)	297,279 (75.7)	355,512 (71.4)	
Healthcare center	185,545 (5.7)	100,059 (4.3)	31,432 (8.0)	54,063 (10.9)	
Others ^{a)}	24,665 (0.8)	17,128 (0.7)	3,749 (1.0)	3,788 (0.8)	
Missing	1,874 (0.1)	1,428 (0.1)	255 (0.1)	191 (0.1)	

Values are presented as mean ± standard deviation or number (%).

NDMA, N-nitrosodimethylamine; CCI, Charlson comorbidity index.

^{a)}Others' healthcare providers included dentistry, psychiatry, and oriental medicine.

^{b)}Welch's t-test was performed for unequal population variances.

^{c)}Chi-square test was performed including missing value.

nated valsartan users were identified (Supplementary Table 3). Next, we performed 1:1:1 pairwise-PSM for the comparison of the three groups (Supplementary Table 4). After this process, 126,991 users were matched in each group: NDMA-contaminated valsartan, eventually NDMA-uncontaminated valsartan, and NDMA-uncontaminated valsartan. The baseline characteristics between these valsartan groups were moderated after PSM (Supplementary Table 3, 4). The

flow diagram of the study is presented in Figure 1. Before PSM, the mean follow-up years (standard deviation) of each exposure group were 7.2 (1.9), 7.1 (1.7), and 7.2 (1.6) for the NDMA-uncontaminated, NDMA-contaminated, and eventually NDMA-uncontaminated valsartan groups, respectively.

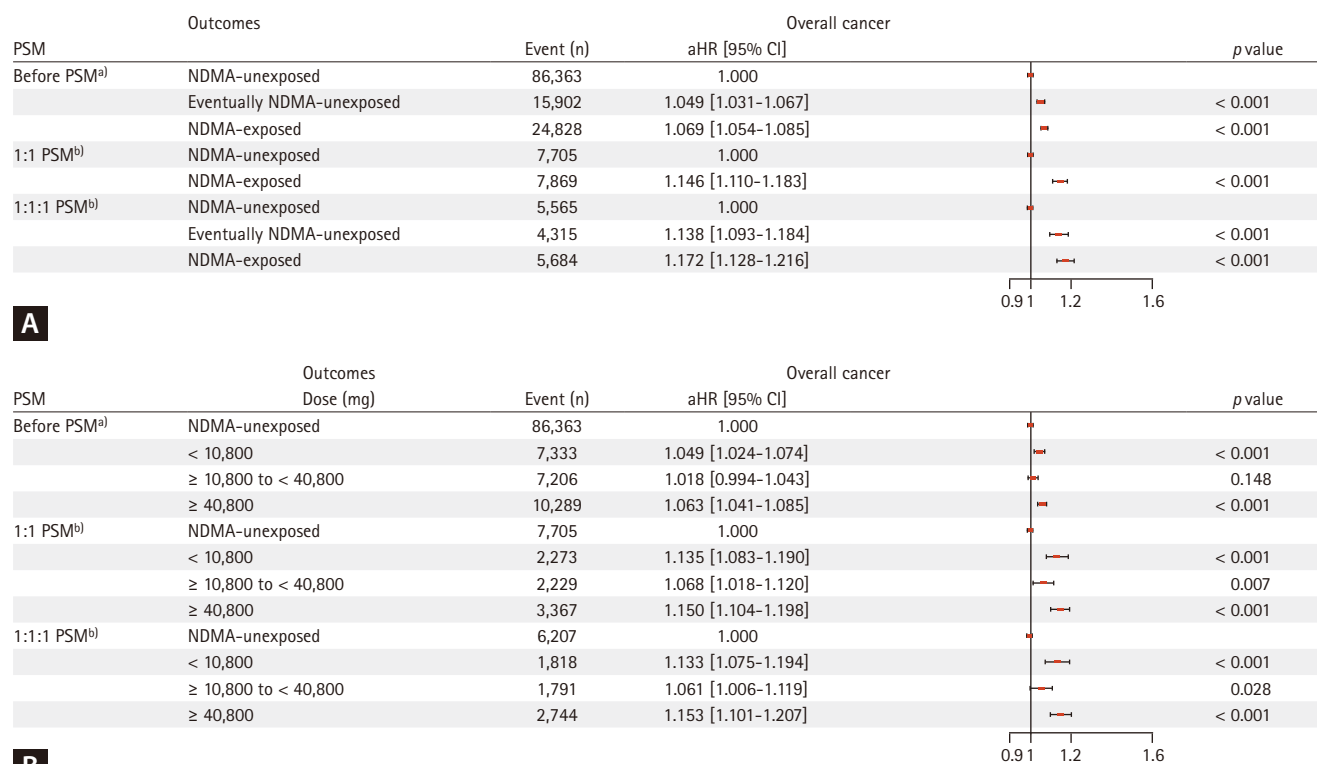


Figure 2. (A) The risks of any cancer and (B) the dose-response relationship among valsartan new users. All the results were estimated excluding patients with the events within 2 years after the first observed valsartan prescription. aHR, adjusted hazard ratio; CI, confidence interval; PSM, propensity score matching; NDMA, N-nitrosodimethylamine. ^{a)}All hazard ratios before PSM were adjusted for age, sex, Charlson's comorbidity index, and the year of the first observed valsartan prescription. ^{b)}All hazard ratios after PSM were adjusted for age, sex, and the year of the first observed valsartan prescription. *Statistically significances at the threshold using Bonferroni correction for 13 tests ($p < 0.005$).

Incidence of primary cancers

The crude IRs (case per 1,000 person-years) of any cancer and their 95% CIs before and after PSM among valsartan new users were as follows: 20.62 (20.54–20.70) and 19.91 (19.63–20.20) for NDMA-uncontaminated valsartan; 19.43 (19.28–19.58) and 19.73 (19.44–20.01) for NDMA-contaminated valsartan; and 17.50 (17.35–17.65) and 18.27 (18.00–18.54) for eventually NDMA-uncontaminated valsartan, respectively (Supplementary Table 5). Particularly, the IRs per 1,000 person-years (95% CIs) of prostate cancer before PSM were 6.58 (6.52–6.64) for NDMA-uncontaminated valsartan, 5.51 (5.40–5.62) for eventually NDMA-uncontaminated valsartan, and 6.71 (6.59–6.83) for NDMA-contaminated valsartan. After PSM, the corresponding IRs (95% CIs) were 6.72 (6.51–6.93), 6.06 (5.87–6.27), and 6.90 (6.69–7.12), respectively.

The aHRs of any cancer and 12 organ-specific cancers in valsartan new users, as well as in the original population, were

estimated according to different lag criteria (6 months and 1 and 2 years) (Supplementary Table 6, 7). For each clinical outcome, the lowest AICs were detected when participants who experienced events within 2 years were excluded. The risks (95% CIs) of any cancer during the NDMA-exposed period (compared to those for the NDMA-unexposed) among valsartan new user were as follows: 1.069 (95% CI 1.054–1.085) before PSM, 1.146 (1.110–1.183) after 1:1 PSM; and 1.172 (1.128–1.216) after 1:1:1 PSM (Fig. 2A). Similar trends were observed in the original population, with risks of 1.098 (1.084–1.113) before PSM, 1.146 (1.113–1.180) after 1:1 PSM, and 1.172 (1.129–1.217) after 1:1:1 PSM (Supplementary Table 7). However, increases in any cancer risk in both populations were also observed during the eventually NDMA-unexposed period, a biologically implausible finding.

In analyses of 12 organ-specific cancers, prostate, stomach, and pancreatic cancers showed significantly increased

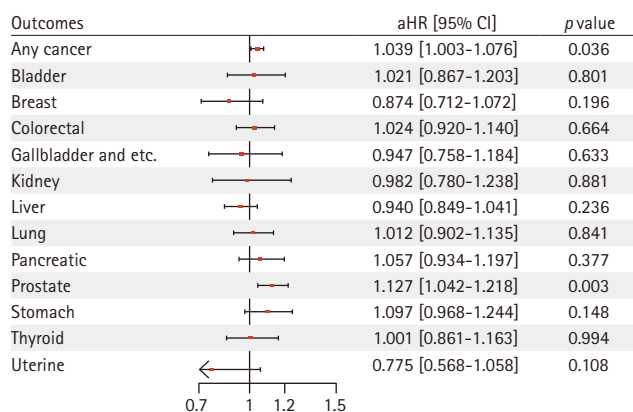


Figure 3. The risks of 12 prevalent organ-specific cancers in Korea according to NDMA-contaminated valsartan. Analyses of risks in NDMA-contaminated valsartan compared to eventually NDMA-uncontaminated valsartan. All the results were estimated excluding patients with the events within 2 years after the first observed valsartan prescription. All hazard ratios after PSM were adjusted for age, sex, and the year of the first observed valsartan prescription. aHR, adjusted hazard ratio; CI, confidence interval; NDMA, N-nitrosodimethylamine; PSM, propensity score matching.

risk during the NDMA-exposed period regardless of PSM. Notably, no increased risk was observed during the eventually NDMA-uncontaminated period after PSM (Supplementary Table 6 for valsartan new users; Supplementary Table 7 for original population). Colorectal cancer also showed a significantly increased risk during the NDMA-exposed period regardless of PSM. However, these cancers showed an increased risk during the eventually NDMA-uncontaminated period after 1:1:1 PSM, possibly suggesting the false-positive association (Supplementary Table 6).

To further investigate, we evaluated the dose-response relationship for organ-specific cancers with statistically significant differences (Fig. 2B, Supplementary Table 8). The aHR for any cancer was significant at the highest dose levels, regardless of PSMs among valsartan new users, as was for prostate cancer. Colorectal cancer showed dose-response relationships after 1:1 PSM, but pancreatic cancer did not 1:1:1 PSM. Stomach cancer showed no dose-response relationship under either PSMs.

In the comparison between NDMA-contaminated valsartan and eventually NDMA-uncontaminated valsartan, we found equivalent results although statistical significance is marginal in any cancer (Fig. 3). Overall, the risks of most organ-specific cancers were increased during the NDMA-contaminated period, compared to eventually NDMA-uncontaminated valsartan period.

Next, we conducted sensitivity analyses for valsartan new users under three scenarios. First, subgroup analyses of prostate cancer revealed consistent risk trends across age group (Supplementary Table 9). Second, in another sensitivity analysis excluding patients with any cancer during the first year of follow-up, prostate cancer risks and dose-response relationships remained similar (Supplementary Table 10, 11). Third, when including patients who received valsartan since 2015, clinical significance was observed only for any cancer, although the trend was similar (Supplementary Table 12, 13).

Risks of all-cause and cardiovascular death before and after immediate banning

The crude all-cause and cardiovascular death rates (case per 1,000 person-years) among valsartan new users were evaluated before and after the immediate ban on NDMA-contaminated valsartan (Supplementary Table 14). No significant difference in the risks of all-cause or cardiovascular deaths was observed before and after the ban (July 7, 2018) among valsartan new users exposed to NDMA ($p = 0.225$ for all-cause death; $p = 0.418$ for cardiovascular death; Table 2). These findings remained consistent after 1:1:1 pairwise PSM, with $p = 0.337$ and $p \geq 0.999$, respectively (Table 2).

DISCUSSION

In this nationwide cohort study, we observed an increased risk of any cancer associated with the use of NDMA-contaminated valsartan products. In analysis of 12 prevalent cancer outcomes, prostate cancer consistently showed an increased risk during the NDMA-exposed period with evidence of a dose-response pattern, whereas no excess risk was observed in the eventually NDMA-uncontaminated group after PSM, supporting a potential prostate-specific signal. In contrast, there was no evidence that the risks of all-cause and cardiovascular deaths increased after emergent banning. Although NDMA-contaminated valsartan is no longer on the market, the issue of impurities in antihypertensive drugs continues, including recent azide (azidomethyl-biphenyl-tetrazole) issue associated with the angiotensin type 1 receptor antagonist class, namely “sartan” [14], and the results of this study can offer valuable evidence for determining future health policy stance.

The principal strength of this study was the use of a

Table 2. Comparison of risks of all-cause and cardiovascular deaths before and after July 7, 2018 in South Korea

PSM	Death	All-cause			Cardiovascular		
		Df	Wald chi-square	p value	Df	Wald chi-square	p value
Before	$H_0: \beta_{\text{NDMA-contaminated}} \text{Jan 1-Jul 6} = \beta_{\text{NDMA-contaminated}} \text{Jul 7-Dec 31} \ \& \ \beta_{\text{Finally NDMA-uncontaminated}} \text{Jan 1-Jul 6} = \beta_{\text{Eventually NDMA-uncontaminated}} \text{Jul 7-Dec 31}$	2	2.985	0.225	2	1.745	0.418
	Contrasts (Jan 1-Jul 6 vs. Jul 7-Dec 31)						
	$H_0: \beta_{\text{NDMA-contaminated}} \text{Jan 1-Jul 6} = \beta_{\text{NDMA-contaminated}} \text{Jul 7-Dec 31}$	1	2.298	0.130	1	0.295	0.587
	$H_0: \beta_{\text{Finally NDMA-uncontaminated}} \text{Jan 1-Jul 6} = \beta_{\text{Eventually NDMA-uncontaminated}} \text{Jul 7-Dec 31}$	1	0.708	0.400	1	1.444	0.230
After 1:1:1	$H_0: \beta_{\text{NDMA-contaminated}} \text{Jan 1-Jul 6} = \beta_{\text{NDMA-contaminated}} \text{Jul 7-Dec 31} \ \& \ \beta_{\text{Finally NDMA-uncontaminated}} \text{Jan 1-Jul 6} = \beta_{\text{Eventually NDMA-uncontaminated}} \text{Jul 7-Dec 31}$	2	2.174	0.337	2	0.000	≥ 0.999
	Contrasts (Jan 1-Jul 6 vs. Jul 7-Dec 31)						
	$H_0: \beta_{\text{NDMA-contaminated}} \text{Jan 1-Jul 6} = \beta_{\text{NDMA-contaminated}} \text{Jul 7-Dec 31}$	1	0.798	0.372	1	0.000	0.998
	$H_0: \beta_{\text{Finally NDMA-uncontaminated}} \text{Jan 1-Jul 6} = \beta_{\text{Finally NDMA-uncontaminated}} \text{Jul 7-Dec 31}$	1	1.743	0.187	1	0.000	0.999

PSM, propensity score matching; Df, degree of freedom; NDMA, N-nitrosodimethylamine; Jan, January; Jul, July; Dec, December.

high-quality nationwide registry, without selection bias. Because the NHIS in Korea is a single, mandatory medical care system, this study enabled the collection of > 3 million patients' data for > 7 years. Additionally, as confirmed by the MFDS, we could provide the three valsartan categories from the NHIS. In particular, patients prescribed with "eventually NDMA-uncontaminated" valsartan had a high possibility of the same reaction as the NDMA-contaminated valsartan group. In principle, the Korean NHIS-NHID claim data do not allow the search for product names (only generic names can be searched) to prevent commercial use. However, with the 3-year's efforts (2020 to 2022), the Korean NHIS accepted that it was a study for public purposes, and offered the data classified into three groups, not according to the individual brand names. Therefore, we minimized possible bias in four ways; by increasing the lag period after exposure, performing PSM, establishing dose-response relationship, and identifying no significant association in the eventually NDMA-uncontaminated valsartan group as an internal control. Lastly, in Korea, the National Plan for Cancer Control was implemented in 1996 and all cancer patients were benefited of reduced insurance rate regarding cancer treatment, which resulted in the near complete and correct registration (98.3%) of all cancers in the Korea National Cancer Inci-

dence Database [15].

The International Agency for Research on Cancer classified NDMA as "probably carcinogenic to humans" owing to limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies [16]. NDMA is suspected to exert both localized and systemic carcinogenic effects due to the induction of DNA-damaging metabolites in the liver and gastrointestinal tract [17]. Furthermore, tumors in the gastrointestinal tract, lungs, and liver have been observed in animal studies [18]. Gastrointestinal tract tumors and uterine cancer (but not prostate cancer) showed possible association, which were all observed in animal experiment. Among the individual cancer sites evaluated in our study, prostate cancer most consistently met the a priori criteria of statistical significance, internal control contrast, and dose-response pattern, although causal inference remains limited. Although the association between prostate cancer and NDMA has not been reported previously, it is possible that urinary excretion of the carcinogenic substances cause prostate cancer [19]. According to an animal experimental study, if patients with a body weight of 70 kg and an average body surface area take the highest dose of valsartan (320 mg/day) containing the highest observed level of NDMA (20.19 μg) over a 6-year period, 126 cases of cancer

per 100,000 people might occur [20], which is about double our overall estimation. The European Medicines Agency estimated that there could be one extra case of cancer for every 5,000 patients exposed to contaminated valsartan at the highest dose [21]. Therefore, it is not surprising that the patients with NDMA-contaminated valsartan group showed higher cancer incidence in this large-number, long term follow-up data.

The results of this study might be compared with those of the French group in many aspects [12]. The subjects of this study were about 5 years younger than those in the French study and had a higher proportion of patients without a history of previous hypertension medication use. However, there is a possibility that the proportion of high-risk patients (23% of CCI ³ 3) could be higher, and the rates of alcohol consumption and smoking were also higher compared with those enrolled in French study. In the case of the study population, the number of subjects in this study was 3.2 million, twice the number of the French study's 1.5 million. However, the number of patients in the NDMA-contaminated valsartan group was more than twice in the French group. This difference is attributed to the relatively small price difference between the off-patent original valsartan drug and the generic valsartan in Korea, leading to a higher market share for the original valsartan [22]. Regarding the duration of follow-up observation, this study was slightly longer, but still not considerably long. However, considering the distribution period from the market release to the banning of NDMA-contaminated drugs, it can be considered as the maximum duration possible. In the French study, there was no difference in the overall cancer risk, whereas in this study, the overall cancer risks were higher in both eventually NDMA-uncontaminated valsartan and NDMA-contaminated valsartan groups. There might be several explanations. First, the elevated cancer risk observed in the eventually NDMA-uncontaminated valsartan group is unlikely to represent an effect of NDMA exposure, and may instead reflect residual confounding related to generic drug selection, which could not be fully captured in claims data. Second, the overall cancer IR, more exactly detection rate, in this study (17.50–20.62 per 1,000 people) was higher than that in the French study (12.93–13.09 per 1,000 people) (Supplementary Table 5). This higher detection rate in Korea might be the Korean Cancer Registration Act, increasing insurance coverage regarding cancer treatment, which resulted in the near complete and correct registration (98.3%) of all cancers in

the Korea National Cancer Incidence Database [15]. Therefore, it is possible that these differences in early detection rates might detect significant risk that could not be identified in smaller, more symptomatic cohorts with shorter follow-up. Although the NDMA-contaminated valsartan group showed a significantly higher overall cancer risk compared with the eventually NDMA-uncontaminated group, part of this excess may reflect recall-related surveillance and residual confounding; nevertheless, the association remained statistically significant even under conservative assumptions. Indeed, similar finding of abrupt increase in reporting of neoplasms associated with valsartan after medication recall regardless of NDMA contamination was reported [23]. However, our data showed that the overall cancer risk is still significantly higher even considering the possible false-positive rate. Regarding individual cancers, the French study showed a higher risk of liver cancer and melanoma, but this study did not show a significant increase of them. Melanoma is the most common tumor in Western countries, but its frequency is very low in East-Asian countries [24], hence it was not analyzed in this study's evaluation of the top 12 prevalent cancers in Korea. On the other hand, in the case of liver cancer, the majority causes are hepatitis B (74%) and C (9%) viral related, while toxin-related cases are very rare in Korea [25]. If NDMA acted as a carcinogenesis enhancer, there could make a significantly higher risk in the prevalent liver cancer in Korea. However, this study did not find such an effect, suggesting that NDMA is more likely to function as a direct carcinogen rather than a carcinogenesis enhancing function. In contrast to the French study, which found no difference, this study identified a significant association with prostate cancer. While there is no clear reason for this, such as ethnic/social differences in the cases of melanoma and liver cancer, the higher incidence (early detection) rates of these two tumors might contribute to the significant differences, otherwise not detected analysis of symptomatic patients during the limited 4-year follow-up period cases. Despite the several differences between two studies, we think that both studies add more value when together than alone in that they have confirmed that cancer issue with NDMA-contaminated valsartan is not a hypothetical threat, but is actually likely to increase cancer incidence.

Prostate cancer is not a frequently studied tumor in animal experiments, which limits the direct investigation of the mechanisms linking NDMA to prostate cancer. However, several studies have demonstrated associations between

N-nitroso compounds, including NDMA, and prostate cancer. For instance, N-nitroso compounds have been shown to possess carcinogenic potential and are implicated in prostate cancer development [26,27]. Taken together with our prostate cancer findings, these data support biological plausibility for a potential NDMA-related effect, but the magnitude and causal nature of this association require further confirmation. These findings suggest that while the specific mechanism remains unclear, the potential relationship warrants further investigation.

When the results of clinical or basic research are applied to the real-world, it is not uncommon to observe an adverse effect from well-intentioned health behavior. After an alert by the European Medicines Agency and an urgent banning announcement by Korean MFDS, there were many patients' complaints and anxieties. Physicians raised concerns that adherence to antihypertensive drugs might be reduced by immaterial cancer risk, resulting in increased cardiovascular events. Indeed, in Canada, immediate increase in emergency department visits for hypertension and a delayed increase and hospitalizations for stroke/transient ischemic attack following the recall [28]. However, the findings of this study did not show an increase in all-cause or cardiovascular deaths in the NDMA-contaminated or eventually NDMA-uncontaminated valsartan group, among whom adherence to cardiovascular medication might be reduced due to fear and distrust. To provide a clearer perspective on alternative angiotensin receptor blockers available in Korea and their relative usage, we have summarized this information in Supplementary Table 15, highlighting the potential impact of the NDMA-related restrictions on the prescription patterns during the study period. The valsartan recall incident highlights Korea's excessive number of generic drugs, approved through a lenient "co-development and commissioned bio-equivalence" system. Unlike other countries, this system has led to quality control challenges and insufficient regulatory oversight, emphasizing the need for stricter approval processes and policies ensuring formularies include at least two similar class drugs for continuity and safety. Current regulatory frameworks set NDMA acceptable-intake limits to correspond to an excess lifetime cancer risk of ~1 case per 100,000 exposed individuals. Our modest relative risk elevation (aHR 1.07–1.17) is directionally compatible with these projections but cannot be directly equated with lifetime risk given the observational design and finite exposure duration.

Limitations

The current study has several limitations. First, in real-world research, there are several confounding factors, which makes it difficult to draw a definitive conclusion beyond hypotheses generation. However, research evaluating the impact of carcinogens, including medications for chronic non-communicable diseases, is virtually impossible to conduct randomized clinical studies for ethical reasons as well as the very small incidence of cancer, demanding long-term follow-up of many patients. Therefore, it might be an inherent limitation that only observational studies such as this study can be conducted. Above all, because regulations on drugs containing NDMA have become stricter and the possibility of marketability in the future is further reduced, research on the clinical significance of NDMA contaminants in the antihypertensive drug might be more difficult in the future. The unique advantage of this study is the presence of patients treated with "eventually NDMA-uncontaminated" valsartan. Although the overall duration of the suspension of this group was only 3 days from July 7 to July 9, 2018, the claim amount was continuously decreased, which raised the possibility that they showed the same reaction as the NDMA-contaminated valsartan group. Therefore, we evaluated the incidence of cancer, cardiovascular death and overall death in this group as an internal control group, similar to the "placebo" group of clinical trials. We believe that the existence of this group could compensate for the many limitations of observational research. Second, despite good covariates balance after PSM, residual confounding from unmeasured factors, including cancer screening behaviors, socioeconomic status, selection of generic products by hospital type/region rather than cost, and changes in health-care utilization following the valsartan recall, cannot be fully eliminated. Third, we did not account for treatment switching/persistence. Although Supplementary Figure 1 shows eventually NDMA-uncontaminated valsartan maintained substantial post-recall use despite brief suspension and re-approval, any switching may alter healthcare utilization/cancer surveillance, causing non-differential misclassification biasing toward null. Fourth, incidental cancer diagnosis might have increased due to increased health examinations because of health concerns of patients and screening intensity, which may cause surveillance bias. The number of health examinations in each group could not be estimated because health examinations were not reimbursed by the NHIS, thus records were unavailable in the claim data. Al-

though we adopted an active-comparator new-user design, and adjusted for healthcare utilization proxies, differential cancer surveillance across exposure groups cannot be fully excluded. Prostate cancer detection is particularly susceptible to surveillance bias, as it relies heavily on prostate specific antigen (PSA) testing and opportunistic screening rather than symptomatic presentation. Following the valsartan recall, differential increases in healthcare utilization among affected patients may have led to intensified prostate cancer screening, disproportionately influencing observed IRs in our NDMA-exposed groups. While our active-comparator design and adjustment for healthcare utilization proxies mitigate this concern to some extent, we interpret prostate cancer findings with additional caution, recognizing that differential PSA testing and heightened clinical attention post-recall may contribute to the observed association beyond any true NDMA effect. However, the incidence of thyroid or breast cancer was not significantly increased in NDMA-contaminated valsartan group, reducing the possibility of bias. Fifth, we only evaluated the incidence of cardiovascular and all-cause deaths, and other soft endpoints, such as angina, coronary revascularization, nonfatal myocardial infarction, or heart failure hospitalization were not evaluated. This was because the diagnostic accuracy of these soft endpoints based on the claim data only was very low. However, we could not exclude the possibility that the nonfatal cardiovascular event was actually increased due to decreased adherence to medical treatment. Sixth, this study did not differentiate between original and generic drugs, which may contain different contaminants. Additionally, we could not account for other medications or potential substances within the drugs that may influence the outcomes. These factors represent important limitations of our study. Finally, our study focused on the relative risk associated with higher cumulative doses of NDMA-contaminated valsartan, which cannot be directly translated into public health impacts. Precise dose exposure over time may be influenced by factors such as prescription adherence and patient behavior. Nonetheless, our findings align with biological understanding that cumulative exposure can amplify the carcinogenic risk, emphasizing the importance of monitoring cumulative exposure in clinical practice.

Conclusion

We demonstrated that the use of NDMA-contaminated valsartan products was associated with an increased risk

of overall cancer, with prostate cancer showing a possible unfavorable association. However, there was no evidence that all-cause and cardiovascular deaths increased following emergent banning of possible NDMA-contaminated valsartan products, which support the health policy of the emergent action to potentially hazardous drugs. Nonetheless, these findings should be interpreted with caution given the several limitations and further validations are needed to confirm these findings.

KEY MESSAGE

1. The use of NDMA-contaminated valsartan products was associated with an increased risk of any cancer.
2. Findings from the analysis of 12 prevalent cancer outcomes suggest a possible unfavorable association between exposure to NDMA and prostate cancer, regardless of PSM.
3. There was no evidence that the risks of all-cause and cardiovascular deaths increased after emergent banning.

REFERENCES

1. Copland E, Canoy D, Nazarzadeh M, et al. Antihypertensive treatment and risk of cancer: an individual participant data meta-analysis. *Lancet Oncol* 2021;22:558-570.
2. Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol* 2010;11:627-636.
3. Wright CM, Moorin RE, Chowdhury EK, et al. Calcium channel blockers and breast cancer incidence: an updated systematic review and meta-analysis of the evidence. *Cancer Epidemiol* 2017;50(Pt A):113-124.
4. Jonas M, Goldbourt U, Boyko V, Mandelzweig L, Behar S, Reicher-Reiss H. Nifedipine and cancer mortality: ten-year follow-up of 2607 patients after acute myocardial infarction. *Cardiovasc Drugs Ther* 1998;12:177-181.
5. Pahor M, Guralnik JM, Salive ME, Corti MC, Carbonin P, Havlik RJ. Do calcium channel blockers increase the risk of cancer? *Am J Hypertens* 1996;9:695-699.
6. Pottegård A, Pedersen SA, Schmidt SAJ, Hölmich LR, Friis S,

- Gaist D. Association of hydrochlorothiazide use and risk of malignant melanoma. *JAMA Intern Med* 2018;178:1120-1122.
7. Gomm W, Röthlein C, Schüssel K, et al. N-nitrosodimethylamine-contaminated valsartan and the risk of cancer—a longitudinal cohort study based on German Health Insurance Data. *Dtsch Arztebl Int* 2021;118:357-362.
8. Park B. Issues on carcinogen contaminated antihypertensive drugs and constructing drug safety management system. *J Korean Med Assoc* 2019;62:182-185.
9. Safety KMoFaD. Immediate suspension of 219 valsartan products using potentially NDMA-contaminated API. Korea Institute of Drug Safety & Risk Management, 2018.
10. Lowe D. The Sartan Contamination Story. Washington DC: Science, c2019 [cited 2026 Jan 14]. Available from: <https://blogs.sciencemag.org/pipeline/archives/2019/01/04/the-sartan-contamination-story>.
11. Pottegård A, Kristensen KB, Ernst MT, Johansen NB, Quaratarolo P, Hallas J. Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study. *BMJ* 2018;362:k3851.
12. Mansouri I, Botton J, Semenzato L, Haddy N, Zureik M. N-nitrosodimethylamine-contaminated valsartan and risk of cancer: a nationwide study of 1.4 million valsartan users. *J Am Heart Assoc* 2022;11:e8067.
13. Notice HI. HIRA Insurance Notice 2018-407. Health Insurance Review & Assessment Service, 2018.
14. Salim H, Jones AM. Angiotensin II receptor blockers (ARBs) and manufacturing contamination: a retrospective National Register Study into suspected associated adverse drug reactions. *Br J Clin Pharmacol* 2022;88:4812-4827.
15. Kang MJ, Jung KW, Bang SH, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2020. *Cancer Res Treat* 2023;55:385-399.
16. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: an updating of IARC Monographs Volumes 1-42. Lyon: International Agency for Research on Cancer, 1987.
17. Tricker AR, Preussmann R. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. *Mutat Res* 1991;259:277-289.
18. Lijinsky W, Reuber MD. Carcinogenesis in rats by nitrosodimethylamine and other nitrosomethylalkylamines at low doses. *Cancer Lett* 1984;22:83-88.
19. Brendler SY, Tompa A, Hutter KF, Preussmann R, Pool-Zobel BL. In vivo and in vitro genotoxicity of several N-nitrosamines in extrahepatic tissues of the rat. *Carcinogenesis* 1992;13:2435-2441.
20. Li K, Ricker K, Tsai FC, et al. Estimated cancer risks associated with nitrosamine contamination in commonly used medications. *Int J Environ Res Public Health* 2021;18:9465.
21. European Medicines Agency. Update on review of recalled valsartan medicines: preliminary assessment of possible risk to patients. Amsterdam: European Medicines Agency, c2018 [cited 2026 Jan 14]. Available from: <https://www.ema.europa.eu/en/news/update-review-recalled-valsartan-medicines-preliminary-assessment-possible-risk-patients>.
22. Kim DS, Shin J, Chung J. Analysis of the Korean generic medicine market: Factors affecting the market share of generic medicines. *Clin Transl Sci* 2022;15:433-441.
23. Al-Kindi SG, Oliveira GH. Abrupt increase in reporting of neoplasms associated with valsartan after medication recall. *Circ Cardiovasc Qual Outcomes* 2019;12:e005536.
24. Oh CM, Cho H, Won YJ, et al. Nationwide trends in the incidence of melanoma and non-melanoma skin cancers from 1999 to 2014 in South Korea. *Cancer Res Treat* 2018;50:729-737.
25. Jang W, Lee HW, Lee JS, et al. Clinical characteristics and prognosis of Korean patients with hepatocellular carcinoma with respect to etiology. *J Liver Cancer* 2022;22:158-166.
26. Sinha R, Park Y, Graubard BI, et al. Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. *Am J Epidemiol* 2009;170:1165-1177.
27. Burke AJ, McAuliffe JD, Natoni A, Ridge S, Sullivan FJ, Glynn SA. Chronic nitric oxide exposure induces prostate cell carcinogenesis, involving genetic instability and a pro-tumorigenic secretory phenotype. *Nitric Oxide* 2022;127:44-53.
28. Jackevicius CA, Krumholz HM, Chong A, et al. Population impact of generic valsartan recall. *Circulation* 2020;141:411-413.

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Credit authorship contributions

Juhee Ahn: investigation, data curation, formal analysis, writing - orig-

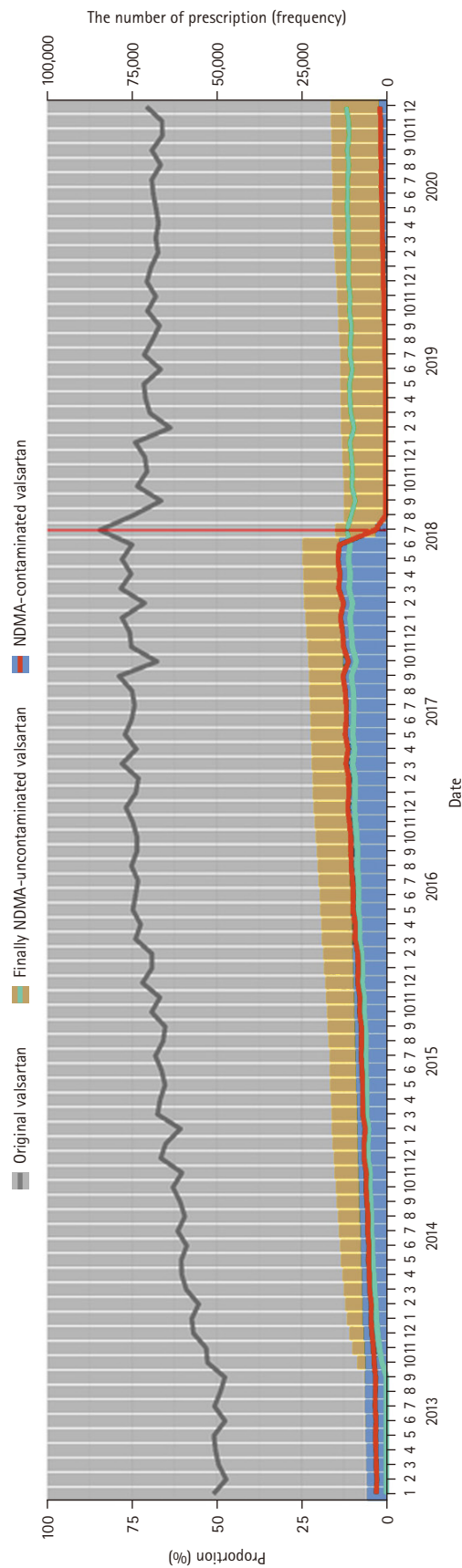
inal draft; Sungho Won: conceptualization, methodology, data curation, formal analysis, writing - original draft; Jong-Heon Park: conceptualization, resources, supervision; Hae-Young Lee: conceptualization, methodology, resources, investigation, data curation, formal analysis, validation, software, writing - original draft, writing - review & editing, visualization, supervision, project administration, funding acquisition

Conflicts of interest

The authors disclose no conflicts.

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Supplementary Figure 1. Monthly prescription trend of valsartan in 2013–2020. The red line presents the potentially estimated NDMA-contaminated valsartan, according to the Ministry of Food and Drug Safety in Korea. The red line presents the number of tablets while color bars indicate the proportion for each group, among all valsartan prescriptions. NDMA, N-nitrosodimethylamine.

Supplementary Table 1. Definition of cancers according to ICD-10 codes

Code	Definition
C00–C96	Any cancer
C67	Bladder
C50	Breast
C18, C19, C20	Colorectal
C23, C24	Gallbladder and etc.
C64	Kidney
C22	Liver
C33, C34	Lung
C25	Pancreatic
C61	Prostate
C16	Stomach
C73	Thyroid
C54, C55	Uterine

ICD-10, International Classification of Diseases, 10th revision.

Supplementary Table 2. Absolute standardized mean differences after propensity score matching

	1:1 matching	1:1:1 matching		
	NDMA-contaminated valsartan vs. original valsartan	Eventually NDMA-uncontaminated valsartan vs. original valsartan	NDMA-contaminated valsartan vs. original valsartan	Eventually NDMA-uncontaminated valsartan vs. NDMA-contaminated valsartan
Age	0.009	0.020	0.003	0.022
Sex	0.000	0.000	0.000	0.000
BMI	0.011	0.019	0.021	0.039
CCI	0.028	0.029	0.000	0.029
Being a prevalent user	0.000	0.000	0.000	0.001
Drinking status	0.010	0.006	0.013	0.019
Smoking status	0.000	0.024	0.024	0.000
Disability	0.033	0.008	0.012	0.003
Level of healthcare provider	0.000	0.036	0.000	0.036

NDMA, N-nitrosodimethylamine; BMI, body mass index; CCI, Charlson comorbidity index.

Supplementary Table 3. Baseline characteristics of study population after 1:1 propensity score matching

Characteristic	Total (n = 333,974)	Original valsartan (n = 166,987)	NDMA-contained valsartan (n = 166,987)	p value
Age (yr)	59.2 ± 11.8	59.2 ± 11.7	59.1 ± 11.8	0.008 ^{b)}
Sex				> 0.999
Male	186,118 (55.7)	93,059 (55.7)	93,059 (55.7)	
Female	147,856 (44.3)	73,928 (44.3)	73,928 (44.3)	
BMI (kg/m ²)	25.2 ± 3.2	25.2 ± 3.1	25.3 ± 3.3	0.002 ^{b)}
CCI				0.046
0	104,918 (31.4)	52,366 (31.4)	52,552 (31.5)	
1	91,772 (27.5)	46,017 (27.6)	45,755 (27.4)	
2	60,815 (18.2)	30,149 (18.1)	30,666 (18.4)	
≥ 3	76,469 (22.9)	38,455 (23.0)	38,014 (22.8)	
Being a prevalent user				> 0.999
No	308,628 (92.4)	154,314 (92.4)	154,314 (92.4)	
Yes	25,346 (7.6)	12,673 (7.6)	12,673 (7.6)	
Drinking status				0.005
No	177,969 (53.3)	88,577 (53.0)	89,392 (53.5)	
Yes	156,005 (46.7)	78,410 (47.0)	77,595 (46.5)	
Smoking status				0.006
Current	76,836 (23.0)	38,038 (22.8)	38,798 (23.2)	
Ever	59,463 (17.8)	29,743 (17.8)	29,720 (17.8)	
Never	197,675 (59.2)	99,206 (59.4)	98,469 (59.0)	
Disability				< 0.001
No	300,461 (90.0)	151,058 (90.5)	15,929 (9.5)	
Yes	33,513 (10.0)	149,403 (89.5)	17,584 (10.5)	
Level of healthcare provider				> 0.999
Tertiary	1,844 (0.6)	922 (0.6)	922 (0.6)	
Secondary	51,010 (15.3)	25,505 (15.3)	25,505 (15.3)	
Primary	242,030 (72.5)	121,015 (72.5)	121,015 (72.5)	
Healthcare center	37,224 (11.2)	18,612 (11.2)	18,612 (11.2)	
Others ^{a)}	1,866 (0.6)	933 (0.6)	933 (0.6)	
Follow-up duration (yr)		8.0 [0]	4.4 [2.9]	< 0.001 ^{b)}

Values are presented as mean ± standard deviation, number (%), or median [interquartile range].

NDMA, N-nitrosodimethylamine; BMI, body mass index; CCI, Charlson comorbidity index.

^{a)}Others' healthcare providers included dentistry, psychiatry, and oriental medicine.

^{b)}Welch's t-test was performed for unequal population variances.

Supplementary Table 4. Baseline characteristics of study population after 1:1:1 propensity score matching

Characteristic	Total (n = 380,973)	Original valsartan (n = 126,991)	Eventually NDMA- uncontaminated valsartan (n = 126,991)	NDMA-contained valsartan (n = 126,991)	p value
Age (yr)	57.9 ± 11.8	57.9 ± 11.7	57.7 ± 11.9	58.0 ± 11.8	< 0.001 ^{b)}
Sex					> 0.999
Male	228,288 (59.9)	76,096 (59.9)	76,096 (59.9)	76,096 (59.9)	
Female	152,685 (40.1)	50,895 (40.1)	50,895 (40.1)	50,895 (40.1)	
BMI (kg/m ²)	25.4 ± 3.3	25.4 ± 3.2	25.5 ± 3.4	25.4 ± 3.3	< 0.001 ^{b)}
CCI					0.187
0	133,761 (35.11)	44,495 (35.0)	44,946 (35.4)	44,320 (34.9)	
1	104,516 (27.4)	34,931 (27.5)	34,639 (27.3)	34,946 (27.5)	
2	66,106 (17.4)	21,960 (17.3)	22,058 (17.4)	22,088 (17.4)	
≥ 3	76,590 (20.1)	25,605 (20.2)	25,348 (20.0)	25,637 (20.2)	
Being a prevalent user					> 0.999
No	380,892 (99.9)	126,964 (99.9)	126,964 (99.9)	126,964 (99.9)	
Yes	81 (0.1)	27 (0.1)	27 (0.1)	27 (0.1)	
Drinking status					< 0.001
No	188,911 (49.6)	62,813 (49.5)	62,443 (49.2)	63,655 (50.1)	
Yes	192,062 (50.4)	64,178 (50.5)	64,548 (50.8)	63,336 (49.9)	
Smoking status					0.172
Current	98,508 (25.9)	32,705 (25.8)	33,125 (26.1)	32,678 (25.7)	
Ever	71,287 (18.7)	23,778 (18.7)	23,595 (18.6)	23,914 (18.8)	
Never	211,178 (55.4)	70,508 (55.5)	70,271 (55.3)	70,399 (55.4)	
Disability					0.009
No	343,782 (90.2)	114,850 (90.4)	114,525 (90.2)	114,407 (90.1)	
Yes	37,191 (9.8)	12,141 (9.6)	12,466 (9.8)	12,584 (9.9)	
Level of healthcare provider					0.177
Tertiary	580 (0.2)	193 (0.2)	194 (0.2)	193 (0.2)	
Secondary	52,941 (13.9)	17,541 (13.8)	17,859 (14.1)	17,541 (13.8)	
Primary	292,578 (76.8)	97,731 (77.0)	97,116 (76.5)	97,731 (77.0)	
Healthcare center	32,295 (8.5)	10,672 (8.4)	10,951 (8.6)	10,672 (8.4)	
Others ^{a)}	2,579 (0.7)	854 (0.7)	871 (0.7)	854 (0.7)	
Follow-up duration (yr)		8.0 [0]	3.5 [3.4]	4.2 [2.7]	< 0.001 ^{b)}

NDMA, N-nitrosodimethylamine; BMI, body mass index; CCI, Charlson comorbidity index; ANOVA, analysis of variance.

^{a)}Others' healthcare providers included dentistry, psychiatry, and oriental medicine.

^{b)}Welch's ANOVA was performed for unequal population variances.

Supplementary Table 5. The number of any cancer and each organ-specific cancer among valsartan new users before and after PSM

Cancer	PSM	Before			After 1:1:1 matching		
		Original (n = 1,726,619)	Eventually NDMA- uncontaminated (n = 392,548)	NDMA- contaminated (n = 461,599)	Original (n = 126,964)	Eventually NDMA- uncontaminated (n = 126,964)	NDMA- contaminated (n = 126,964)
Any cancer	Event	258,328	50,956	65,571	18,625	17,265	18,480
	Absolute risk	0.150	0.130	0.142	-	-	-
	IR (95% CI) ^{a)}	20.62 (20.54–20.70)	17.50 (17.35–17.65)	19.43 (19.28–19.58)	19.91 (19.63–20.20)	18.27 (18.00–18.54)	19.73 (19.44–20.01)
Bladder	Event	11,264	2,075	2,721	798	739	795
	Absolute risk	0.007	0.005	0.006	-	-	-
	IR (95% CI) ^{a)}	0.84 (0.83–0.86)	0.67 (0.65–0.70)	0.76 (0.73–0.79)	0.80 (0.75–0.86)	0.74 (0.69–0.79)	0.80 (0.74–0.85)
Breast	Event	9,269	1,697	2,119	573	540	535
	Absolute risk	0.012	0.010	0.010	-	-	-
	IR (95% CI) ^{a)}	1.51 (1.48–1.54)	1.26 (1.20–1.32)	1.24 (1.19–1.29)	1.44 (1.32–1.56)	1.35 (1.24–1.47)	1.34 (1.23–1.46)
Colorectal	Event	29,424	6,210	7,958	2,044	1,996	2,115
	Absolute risk	0.017	0.016	0.017	-	-	-
	IR (95% CI) ^{a)}	2.21 (2.19–2.24)	2.03 (1.98–2.08)	2.23 (2.18–2.28)	2.06 (1.97–2.15)	2.00 (1.92–2.09)	2.13 (2.04–2.22)
Gallbladder and etc.	Event	6,078	1,222	1,587	462	383	368
	Absolute risk	0.004	0.003	0.003	-	-	-
	IR (95% CI) ^{a)}	0.45 (0.44–0.47)	0.40 (0.38–0.42)	0.44 (0.42–0.46)	0.46 (0.42–0.51)	0.38 (0.34–0.42)	0.37 (0.33–0.41)
Kidney	Event	5,830	1,104	1,402	406	386	403
	Absolute risk	0.003	0.003	0.003	-	-	-
	IR (95% CI) ^{a)}	0.44 (0.42–0.45)	0.36 (0.34–0.38)	0.39 (0.37–0.41)	0.41 (0.37–0.45)	0.39 (0.35–0.43)	0.40 (0.37–0.44)
Liver	Event	34,582	7,084	8,419	2,507	2,394	2,340
	Absolute risk	0.020	0.018	0.018	-	-	-
	IR (95% CI) ^{a)}	2.60 (2.58–2.63)	2.32 (2.26–2.37)	2.36 (2.31–2.41)	2.53 (2.43–2.63)	2.41 (2.31–2.50)	2.36 (2.27–2.46)
Lung	Event	24,127	4,560	6,114	1,670	1,453	1,629
	Absolute risk	0.014	0.012	0.013	-	-	-
	IR (95% CI) ^{a)}	1.81 (1.79–1.83)	1.49 (1.44–1.53)	1.71 (1.67–1.75)	1.68 (1.60–1.76)	1.45 (1.38–1.53)	1.64 (1.56–1.72)
Pancreatic	Event	18,641	3,659	4,944	1,378	1,276	1,467
	Absolute risk	0.011	0.009	0.011	-	-	-
	IR (95% CI) ^{a)}	1.40 (1.38–1.42)	1.19 (1.15–1.23)	1.38 (1.34–1.42)	1.38 (1.31–1.46)	1.28 (1.21–1.35)	1.47 (1.40–1.55)
Prostate	Event	46,423	9,351	12,271	3,928	3,568	4,033
	Absolute risk	0.050	0.042	0.051	-	-	-
	IR (95% CI) ^{a)}	6.58 (6.52–6.64)	5.51 (5.40–5.62)	6.71 (6.59–6.83)	6.72 (6.51–6.93)	6.06 (5.87–6.27)	6.90 (6.69–7.12)
Stomach	Event	20,212	4,155	5,475	1,515	1,384	1,515
	Absolute risk	0.012	0.011	0.012	-	-	-
	IR (95% CI) ^{a)}	1.52 (1.50–1.54)	1.35 (1.31–1.40)	1.53 (1.49–1.57)	1.52 (1.45–1.60)	1.39 (1.31–1.46)	1.52 (1.45–1.60)
Thyroid	Event	16,554	3,221	4,003	1,204	1,170	1,208
	Absolute risk	0.010	0.008	0.009	-	-	-
	IR (95% CI) ^{a)}	1.24 (1.22–1.26)	1.05 (1.01–1.09)	1.12 (1.08–1.15)	1.21 (1.14–1.28)	1.17 (1.10–1.24)	1.21 (1.15–1.28)
Uterine	Event	3,262	663	828	195	203	192
	Absolute risk	0.004	0.004	0.004	-	-	-
	IR (95% CI) ^{a)}	0.53 (0.51–0.55)	0.49 (0.46–0.53)	0.48 (0.45–0.52)	0.49 (0.42–0.56)	0.50 (0.44–0.58)	0.48 (0.41–0.55)

PSM, propensity score matching; NDMA, N-Nitrosodimethylamine; IR, incidence rate; CI, confidence interval.

^{a)}Incidence rate per 1,000 person-years is calculated for each valsartan group and clinical outcome.

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)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	Overall	13,143	1.000	-	10,913	1.000	-	35,613	1.000	-
	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
	Eventually NDMA-unexposed	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-exposed	6,070	1.000	-	4,529	1.000	-	14,530	1.000	-
	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*
	Eventually NDMA-unexposed	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-exposed	5,376	1.000	-	3,985	1.000	-	12,730	1.000	-
	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*
	Eventually NDMA-unexposed	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-exposed	4,056	1.000	-	2,933	1.000	-	9,406	1.000	-
	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*
	Eventually NDMA-unexposed	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	1,368	1.000	-	1,010	1.000	-	3,648	1.000	-
	NDMA-unexposed	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
	NDMA-exposed	564	1.000	-	436	1.000	-	1,339	1.000	-
6 mon exc.	NDMA-unexposed	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*
	NDMA-exposed	512	1.000	-	389	1.000	-	1,186	1.000	-
	Eventually NDMA-unexposed	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*
1-year exc.	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*
	Eventually NDMA-unexposed	1,410	1.000	-	1,032	1.000	-	3,920	1.000	-
2-year exc ^{d)}	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
	Eventually NDMA-unexposed	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*

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*
1-year exc.	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*
	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)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	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 ^{c)}	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 ^{c)}	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
		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
	6 mon exc.	NDMA-unexposed	296	1,000	-	223	1,000	-	1,313	1,000	-
		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*
	1-year exc.	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*
	2-year exc. ^{d)}	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			p value	Pancreatic cancer			p value	Prostate cancer ^{a)}	
		Event	aHR (95% CI)	Event		aHR (95% CI)	Event	aHR (95% CI)		Event	p value
		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	0.010	4,934	0.936 (0.908–0.964)
Before PSM ^{b)}	Overall	NDMA-unexposed	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*
1-year exc.	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*
	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*
2-year exc. ^{d)}	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*
	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
1:1 PSM ^{c)}	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*
	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)}	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
6 mon exc.	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
	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

PSM	Cancer	Stomach cancer			Thyroid cancer			Uterine cancer ^{a)}		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	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*
6 mon exc.	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
1-year 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*
2-year exc. ^{d)} NDMA-unexposed	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
1:1 PSM ^{c)}	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
6 mon exc.	NDMA-unexposed	2,651	1.000	-	2,207	1.000	-	332	1.000	-
	Eventually NDMA-unexposed	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
	NDMA-exposed	1,054	1.000	-	748	1.000	-	146	1.000	-
1-year exc.	NDMA-unexposed	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
	Eventually 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	NDMA-unexposed	688	1.000	-	483	1.000	-	99	1.000	-
	Eventually NDMA-unexposed	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
	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 ($p < 0.004$).

Supplementary Table 7. The risks of any cancer and organ-specific cancers in original population before and after PSM according to the status of NDMA

PSM	Cancer	Any cancer			Bladder cancer			Breast cancer ^{a)}		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	Overall	410,341	1.000	-	17,768	1.000	-	14,354	1.000	-
	NDMA-unexposed	27,566	0.975 (0.963–0.988)	< 0.001*	1,146	0.868 (0.817–0.924)	< 0.001*	885	0.985 (0.918–1.056)	0.667
	Eventually NDMA-unexposed	46,234	0.984 (0.974–0.993)	0.001	2,021	0.921 (0.879–0.966)	0.001*	1,455	0.910 (0.861–0.963)	0.001*
	6 mon exc. NDMA-unexposed	225,149	1.000	-	10,293	1.000	-	7,626	1.000	-
1-year exc.	Overall	25,709	1.348 (1.330–1.366)	< 0.001*	1,082	1.206 (1.130–1.287)	< 0.001*	831	1.428 (1.325–1.538)	< 0.001*
	NDMA-unexposed	43,789	1.277 (1.264–1.291)	< 0.001*	1,915	1.181 (1.123–1.242)	< 0.001*	1,378	1.211 (1.141–1.284)	< 0.001*
	Eventually NDMA-unexposed	22,439	1.000	-	9,399	1.000	-	6,867	1.000	-
	2-year exc. ^{d)}	2,606	1.241 (1.223–1.259)	< 0.001*	924	1.105 (1.030–1.185)	0.005	727	1.334 (1.232–1.444)	< 0.001*
1:1 PSM ^{c)}	Overall	3,430	1.098 (1.084–1.113)	< 0.001*	1,320	1.036 (0.975–1.100)	0.255	880	1.005 (0.934–1.081)	0.896
	NDMA-unexposed	34,300	1.000	-	1,477	1.000	-	1,094	1.000	-
	6 mon exc. NDMA-unexposed	16,250	1.025 (1.004–1.047)	0.018	708	0.961 (0.871–1.061)	0.433	499	0.964 (0.858–1.084)	0.541
	1-year exc. NDMA-unexposed	14,313	1.343 (1.311–1.376)	< 0.001*	671	1.261 (1.128–1.409)	< 0.001*	472	1.211 (1.063–1.379)	0.004
1:1:1 PSM ^{c)}	Overall	12,311	1.000	-	604	1.000	-	458	1.000	-
	NDMA-unexposed	12,620	1.261 (1.229–1.293)	< 0.001*	610	1.188 (1.059–1.333)	0.003*	429	1.145 (1.000–1.311)	0.051
	6 mon exc. NDMA-unexposed	9,206	1.000	-	473	1.000	-	346	1.000	-
	1-year exc. NDMA-unexposed	9,364	1.146 (1.113–1.180)	< 0.001*	476	1.097 (0.964–1.248)	0.159	309	0.974 (0.833–1.138)	0.737
1:1:1 PSM ^{c)}	Overall	33,635	1.000	-	1,410	1.000	-	1,032	1.000	-
	Eventually NDMA-unexposed	9,266	1.032 (1.006–1.058)	0.017	421	1.049 (0.929–1.183)	0.440	283	1.005 (0.868–1.163)	0.946
1:1:1 PSM ^{c)}	Overall	11,481	1.040 (1.016–1.066)	0.001	501	1.027 (0.915–1.152)	0.653	333	0.965 (0.838–1.110)	0.613
	NDMA-unexposed	11,481	1.040 (1.016–1.066)	0.001	501	1.027 (0.915–1.152)	0.653	333	0.965 (0.838–1.110)	0.613

Supplementary Table 7. Continued

PSM	Cancer	Colorectal cancer			Gallbladder and etc. cancer			Kidney cancer		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	6 mon exc. NDMA-unexposed	9,006	1.000	-	446	1.000	-	326	1.000	-
	Eventually NDMA-unexposed	7,518	1.548 (1.499–1.598)	< 0.001*	391	1.578 (1.370–1.817)	< 0.001*	267	1.511 (1.276–1.789)	< 0.001*
	1-year exc. NDMA-unexposed	9,251	1.520 (1.475–1.567)	< 0.001*	472	1.503 (1.312–1.722)	< 0.001*	310	1.368 (1.162–1.612)	< 0.001*
	Eventually NDMA-unexposed	7,702	1.000	-	407	1.000	-	289	1.000	-
	2-year exc. ^{d)} NDMA-unexposed	8,022	1.371 (1.327–1.416)	< 0.001*	427	1.337 (1.162–1.538)	< 0.001*	275	1.217 (1.025–1.444)	0.025
	Eventually NDMA-unexposed	5,568	1.000	-	311	1.000	-	214	1.000	-
	1-year exc. NDMA-unexposed	6,308	1.365 (1.319–1.412)	< 0.001*	325	1.303 (1.122–1.514)	< 0.001*	231	1.332 (1.114–1.592)	0.002*
	Eventually NDMA-unexposed	4,317	1.138 (1.093–1.184)	< 0.001*	253	1.188 (1.004–1.406)	0.044	173	1.170 (0.955–1.434)	0.130
	2-year exc. ^{d)} NDMA-unexposed	5,689	1.172 (1.129–1.217)	< 0.001*	329	1.197 (1.023–1.402)	0.025	196	1.009 (0.829–1.229)	0.928
	Eventually NDMA-unexposed	4,780	1.000	-	9,725	1.000	-	9,322	1.000	-
Before PSM ^{b)}	6 mon exc. NDMA-unexposed	5,437	1.032 (1.003–1.063)	0.032	1,304	1.024 (0.964–1.087)	0.447	993	0.930 (0.869–0.995)	0.036
	Eventually NDMA-unexposed	25,211	1.000	-	6,129	1.000	-	5,123	1.000	-
	1-year exc. NDMA-unexposed	3,014	1.504 (1.446–1.565)	< 0.001*	719	1.365 (1.260–1.480)	< 0.001*	551	1.291 (1.179–1.415)	< 0.001*
	Eventually NDMA-unexposed	5,121	1.375 (1.333–1.418)	< 0.001*	1,224	1.247 (1.171–1.329)	< 0.001*	937	1.236 (1.150–1.328)	< 0.001*
	2-year exc. ^{d)} NDMA-unexposed	22,439	1.000	-	5,492	1.000	-	4,629	1.000	-
	Eventually NDMA-unexposed	2,606	1.374 (1.318–1.434)	< 0.001*	615	1.259 (1.154–1.373)	< 0.001*	480	1.198 (1.087–1.321)	< 0.001*
	1-year exc. NDMA-unexposed	4,558	1.295 (1.253–1.339)	< 0.001*	1,104	1.203 (1.126–1.286)	< 0.001*	833	1.165 (1.080–1.257)	< 0.001*
	Eventually NDMA-unexposed	17,421	1.000	-	4,384	1.000	-	3,698	1.000	-
	2-year exc. ^{d)} NDMA-unexposed	1,860	1.203 (1.144–1.264)	< 0.001*	438	1.092 (0.986–1.209)	0.091	368	1.138 (1.018–1.272)	0.023
	Eventually NDMA-unexposed	3,430	1.184 (1.140–1.230)	< 0.001*	829	1.079 (1.000–1.165)	0.050	644	1.099 (1.008–1.198)	0.032
1:1 PSM ^{c)}	Overall	3,920	1.000	-	762	1.000	-	720	1.000	-
	NDMA-unexposed	1,764	1.043 (0.979–1.110)	0.191	402	0.987 (0.865–1.125)	0.840	343	0.992 (0.861–1.144)	0.916

Supplementary Table 7. Continued

6 mon exc. NDMA-unexposed	1,568	1,000	-	412	1,000	-	319	1,000	-
NDMA-exposed	1,647	1.403 (1.306–1.508)	< 0.001*	380	1.183 (1.025–1.366)	0.022	326	1.336 (1.138–1.568)	< 0.001*
1-year exc. NDMA-unexposed	1,399	1,000	-	368	1,000	-	284	1,000	-
NDMA-exposed	1,474	1.305 (1.211–1.407)	< 0.001*	349	1.155 (0.994–1.342)	0.060	282	1.199 (1.013–1.419)	0.035
2-year exc. ^{d)} NDMA-unexposed	1,069	1,000	-	290	1,000	-	216	1,000	-
NDMA-exposed	1,117	1.182 (1.086–1.287)	< 0.001*	261	1.007 (0.850–1.192)	0.938	231	1.208 (1.001–1.458)	0.049
1:1:1 PSM ^{c)} Overall NDMA-unexposed	3,920	1,000	-	692	1,000	-	744	1,000	-
Eventually NDMA-unexposed	1,000	1.049 (0.970–1.133)	0.229	248	1.062 (0.906–1.244)	0.459	200	0.953 (0.803–1.133)	0.587
NDMA-exposed	1,236	1.051 (0.977–1.131)	0.178	273	0.951 (0.815–1.111)	0.530	251	0.973 (0.828–1.143)	0.740
6 mon exc. NDMA-unexposed	1,077	1,000	-	296	1,000	-	223	1,000	-
Eventually NDMA-unexposed	927	1.629 (1.486–1.785)	< 0.001*	229	1.393 (1.165–1.666)	< 0.001*	186	1.518 (1.240–1.858)	< 0.001*
NDMA-exposed	1,130	1.561 (1.430–1.704)	< 0.001*	255	1.224 (1.028–1.458)	0.023	236	1.514 (1.250–1.835)	< 0.001*
1-year exc. NDMA-unexposed	947	1,000	-	262	1,000	-	198	1,000	-
Eventually NDMA-unexposed	795	1.420 (1.289–1.565)	< 0.001*	201	1.288 (1.066–1.555)	0.009	160	1.319 (1.066–1.633)	0.011
NDMA-exposed	999	1.389 (1.267–1.522)	< 0.001*	237	1.183 (0.987–1.418)	0.069	203	1.304 (1.066–1.595)	0.010
2-year exc. ^{d)} NDMA-unexposed	721	1,000	-	205	1,000	-	146	1,000	-
Eventually NDMA-unexposed	578	1.198 (1.072–1.338)	0.001	140	1.013 (0.815–1.259)	0.911	129	1.319 (1.038–1.676)	0.024
NDMA-exposed	751	1.203 (1.084–1.334)	< 0.001*	172	0.955 (0.777–1.172)	0.657	163	1.285 (1.025–1.612)	0.030
PSM	Cancer	Liver cancer			Lung cancer			Pancreatic cancer	
	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)} Overall NDMA-unexposed	54,593	1,000	-	38,101	1,000	-	29,789	1,000	-
Eventually NDMA-unexposed	3,703	1.027 (0.992–1.063)	0.135	2,824	1.002 (0.963–1.042)	0.933	2,137	0.959 (0.916–1.003)	0.068
NDMA-exposed	5,638	0.954 (0.927–0.981)	0.001	4,718	0.979 (0.949–1.010)	0.191	3,630	0.973 (0.939–1.008)	0.132
6 mon exc. NDMA-unexposed	28,856	1,000	-	22,900	1,000	-	17,804	1,000	-
Eventually NDMA-unexposed	3,458	1.453 (1.400–1.507)	< 0.001*	2,643	1.360 (1.304–1.418)	< 0.001*	2,002	1.283 (1.223–1.346)	< 0.001*
NDMA-exposed	5,299	1.259 (1.221–1.297)	< 0.001*	4,491	1.258 (1.217–1.300)	< 0.001*	3,444	1.224 (1.179–1.271)	< 0.001*

Supplementary Table 7. Continued

1-year exc. NDMA-unexposed	25,439	1,000	-	20,495	1,000	-	16,035	1,000	-
Eventually NDMA-unexposed	2,947	1,321 (1.270–1.374)	< 0.001*	2,296	1,269 (1.213–1.327)	< 0.001*	1,769	1,215 (1.154–1.278)	< 0.001*
NDMA-exposed	4,657	1,179 (1.141–1.217)	< 0.001*	3,970	1,187 (1.146–1.229)	< 0.001*	3,053	1,154 (1.109–1.201)	< 0.001*
2-year exc. ^{d)} NDMA-unexposed	19,512	1,000	-	16,122	1,000	-	12,923	1,000	-
Eventually NDMA-unexposed	2,051	1,142 (1.089–1.197)	< 0.001*	2,991	1,135 (1.076–1.196)	< 0.001*	1,298	1,095 (1.032–1.162)	0.003*
1:1 PSM ^{c)} NDMA-exposed	3,406	1,058 (1.019–1.098)	0.003*	1,655	1,091 (1.048–1.136)	< 0.001*	2,331	1,061 (1.014–1.111)	0.010
NDMA-unexposed	4,541	1,000	-	2,989	1,000	-	2,518	1,000	-
6 mon exc. NDMA-unexposed	1,951	0.988 (0.931–1.047)	0.677	1,595	1,041 (0.974–1.112)	0.236	1,347	1,062 (0.987–1.142)	0.105
NDMA-exposed	1,872	1,000	-	1,493	1,000	-	1,193	1,000	-
1-year exc. NDMA-unexposed	1,820	1.318 (1.233–1.410)	< 0.001*	1,515	1.348 (1.252–1.452)	< 0.001*	1,262	1.363 (1.255–1.479)	< 0.001*
NDMA-exposed	1,638	1,000	-	1,321	1,000	-	1,052	1,000	-
2-year exc. ^{d)} NDMA-unexposed	1,596	1.209 (1.127–1.298)	< 0.001*	1,330	1.247 (1.153–1.348)	< 0.001*	1,111	1.252 (1.148–1.364)	< 0.001*
NDMA-exposed	1,216	1,000	-	1,009	1,000	-	827	1,000	-
1:1:1 PSM ^{c)} NDMA-exposed	1,185	1.091 (1.006–1.183)	0.035	997	1.120 (1.025–1.224)	0.012	850	1.135 (1.030–1.250)	0.011
NDMA-unexposed	4,621	1,000	-	2,770	1,000	-	2,428	1,000	-
Eventually NDMA-unexposed	1,230	1.097 (1.022–1.177)	0.010	879	1.022 (0.941–1.111)	0.606	724	1.011 (0.923–1.108)	0.813
NDMA-exposed	1,390	1.004 (0.938–1.075)	0.914	1,104	1.043 (0.964–1.127)	0.295	971	1.102 (1.013–1.199)	0.023
6 mon exc. NDMA-unexposed	1,314	1,000	-	1,028	1,000	-	820	1,000	-
Eventually NDMA-unexposed	1,125	1.685 (1.550–1.832)	< 0.001*	821	1.484 (1.349–1.632)	< 0.001*	667	1.507 (1.355–1.677)	< 0.001*
NDMA-exposed	1,273	1.498 (1.381–1.625)	< 0.001*	1,037	1.479 (1.351–1.619)	< 0.001*	907	1.609 (1.457–1.777)	< 0.001*
1-year exc. NDMA-unexposed	1,125	1,000	-	899	1,000	-	714	1,000	-
Eventually NDMA-unexposed	964	1.477 (1.352–1.614)	< 0.001*	711	1.333 (1.205–1.474)	< 0.001*	578	1.342 (1.199–1.501)	< 0.001*
NDMA-exposed	1,111	1.326 (1.217–1.444)	< 0.001*	898	1.312 (1.193–1.444)	< 0.001*	790	1.424 (1.283–1.581)	< 0.001*
2-year exc. ^{d)} NDMA-unexposed	827	1,000	-	676	1,000	-	553	1,000	-
Eventually NDMA-unexposed	666	1.192 (1.075–1.322)	< 0.001*	508	1.115 (0.993–1.253)	0.066	428	1.150 (1.012–1.307)	0.032
NDMA-exposed	801	1.109 (1.005–1.224)	0.040	650	1.098 (0.985–1.225)	0.093	582	1.207 (1.072–1.358)	0.002*

Supplementary Table 7. Continued

PSM	Cancer	Prostate cancer ^{a)}			Stomach cancer			Thyroid cancer		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	Overall	75,234	1.000	-	32,955	1.000	-	25,606	1.000	-
	NDMA-unexposed	4,934	0.948 (0.920–0.976)	< 0.001*	2,237	1.071 (1.024–1.119)	0.003*	1,439	0.918 (0.870–0.970)	0.002*
	Eventually NDMA-unexposed	8,570	1.024 (1.000–1.048)	0.045	3,852	1.067 (1.031–1.104)	< 0.001*	2,387	0.917 (0.878–0.958)	< 0.001*
	6 mon exc. NDMA-unexposed	41,112	1.000	-	17,975	1.000	-	11,950	1.000	-
1-year exc.	Overall	4,618	1.313 (1.272–1.356)	< 0.001*	2,067	1.478 (1.409–1.550)	< 0.001*	1,335	1.358 (1.281–1.440)	< 0.001*
	NDMA-unexposed	8,149	1.342 (1.310–1.376)	< 0.001*	3,627	1.393 (1.343–1.445)	< 0.001*	2,237	1.262 (1.204–1.322)	< 0.001*
	Eventually NDMA-unexposed	36,959	1.000	-	15,901	1.000	-	10,512	1.000	-
	2-year exc ^{d)}	3,965	1.204 (1.164–1.246)	< 0.001*	1,789	1.364 (1.297–1.436)	< 0.001*	1,152	1.235 (1.159–1.315)	< 0.001*
1:1 PSM ^{c)}	Overall	7,281	1.275 (1.243–1.308)	< 0.001*	3,191	1.312 (1.261–1.364)	< 0.001*	1,988	1.184 (1.127–1.244)	< 0.001*
	NDMA-unexposed	29,353	1.000	-	12,218	1.000	-	8,247	1.000	-
	Eventually NDMA-unexposed	2,855	1.066 (1.024–1.109)	0.002*	1,235	1.168 (1.099–1.242)	< 0.001*	830	1.087 (1.009–1.170)	0.027
	2-year exc ^{d)}	5,455	1.159 (1.125–1.194)	< 0.001*	2,337	1.182 (1.129–1.237)	< 0.001*	1,496	1.076 (1.017–1.149)	0.011
6 mon exc.	Overall	7,127	1.000	-	2,841	1.000	-	2,347	1.000	-
	NDMA-unexposed	3,373	1.030 (0.985–1.078)	0.195	1,328	1.053 (0.980–1.132)	0.159	900	0.924 (0.847–1.007)	0.071
	Eventually NDMA-unexposed	2,991	1.000	-	1,216	1.000	-	855	1.000	-
	2-year exc ^{d)}	3,111	1.352 (1.283–1.424)	< 0.001*	1,242	1.397 (1.287–1.516)	< 0.001*	847	1.285 (1.164–1.419)	< 0.001*
1:1:1 PSM ^{c)}	Overall	2,651	1.000	-	1,075	1.000	-	747	1.000	-
	NDMA-unexposed	2,785	1.275 (1.207–1.346)	< 0.001*	1,106	1.315 (1.206–1.433)	< 0.001*	756	1.200 (1.082–1.332)	< 0.001*
	Eventually NDMA-unexposed	2,057	1.000	-	815	1.000	-	562	1.000	-
	2-year exc ^{d)}	2,059	1.118 (1.051–1.190)	< 0.001*	835	1.194 (1.083–1.317)	< 0.001*	565	1.100 (0.977–1.239)	0.114
1:1:1 PSM ^{c)}	Overall	7,153	1.000	-	2,726	1.000	-	2,417	1.000	-
	NDMA-unexposed	1,877	0.974 (0.921–1.030)	0.354	754	1.096 (1.002–1.199)	0.044	528	0.967 (0.870–1.075)	0.536
	Eventually NDMA-unexposed	2,501	1.054 (1.001–1.110)	0.047	935	1.097 (1.008–1.193)	0.032	637	0.951 (0.861–1.051)	0.325
	2-year exc ^{d)}	2,501	1.054 (1.001–1.110)	0.047	935	1.097 (1.008–1.193)	0.032	637	0.951 (0.861–1.051)	0.325

Supplementary Table 7. Continued

PSM	Cancer	Uterine cancer ^{a)}									
		Event	aHR (95% CI)	p value							
Before PSM ^{b)}	Overall	NDMA-unexposed	4,793	1.000	-						
	6 mon exc.	Eventually NDMA-unexposed	355	0.933 (0.835–1.042)	0.220						
		NDMA-exposed	648	1.004 (0.922–1.093)	0.933						
		NDMA-unexposed	2,789	1.000	-						
		Eventually NDMA-unexposed	339	1.263 (1.125–1.419)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	619	1.264 (1.155–1.383)	< 0.001*						
		NDMA-unexposed	2,527	1.000	-						
		Eventually NDMA-unexposed	301	1.198 (1.059–1.355)	0.004						
		NDMA-exposed	558	1.206 (1.109–1.326)	< 0.001*						
		Eventually NDMA-unexposed	2,053	1.000	-						
2-year exc.	2-year exc.	NDMA-exposed	235	1.175 (1.022–1.350)	0.023						
		NDMA-unexposed	425	1.132 (1.017–1.261)	0.023						
		Eventually NDMA-unexposed	425	1.132 (1.017–1.261)	0.023						
		NDMA-exposed	425	1.132 (1.017–1.261)	0.023						
		Eventually NDMA-unexposed	425	1.132 (1.017–1.261)	0.023						
1-year exc.	1-year exc.	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
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6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
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6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
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		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
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1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
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2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
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6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
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1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-exposed	2,078	1.000	-						
		NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		Eventually NDMA-unexposed	1,669	1.466 (1.371–1.567)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
1-year exc.	1-year exc.	NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		NDMA-unexposed	1,818	1.000	-						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
		NDMA-exposed	2,239	1.553 (1.459–1.654)	< 0.001*						
		Eventually NDMA-unexposed	1,412	1.282 (1.194–1.377)	< 0.001*						
2-year exc. ^{d)}	2-year exc. ^{d)}	NDMA-exposed	1,993	1.416 (1.326–1.512)	< 0.001*						
		NDMA-unexposed	1,374	1.000	-						
		Eventually NDMA-unexposed	987	1.052 (0.969–1.143)	0.229						
		NDMA-exposed	1,422	1.178 (1.093–1.270)	< 0.001*						
		Eventually NDMA-unexposed	1,422	1.178 (1.093–1.270)	< 0.001*						
6 mon exc.	6 mon exc.	NDMA-ex									

Supplementary Table 7. Continued

1:1 PSM ^{c)}	Overall	NDMA-unexposed	358	1.000	-
		NDMA-exposed	202	0.983 (0.814–1.187)	0.859
	6 mon exc.	NDMA-unexposed	168	1.000	-
		NDMA-exposed	194	1.344 (1.086–1.663)	0.007
	1-year exc.	NDMA-unexposed	146	1.000	-
		NDMA-exposed	183	1.406 (1.125–1.757)	0.003*
	2-year exc.	NDMA-unexposed	119	1.000	-
		NDMA-exposed	139	1.244 (0.970–1.594)	0.085
1:1:1 PSM ^{c)}	Overall	NDMA-unexposed	351	1.000	-
		Eventually NDMA-unexposed	108	0.903 (0.714–1.142)	0.395
		NDMA-exposed	132	0.882 (0.706–1.103)	0.272
	6 mon exc.	NDMA-unexposed	110	1.000	-
		Eventually NDMA-unexposed	104	1.532 (1.162–2.020)	0.002*
		NDMA-exposed	126	1.418 (1.088–1.849)	0.010
	1-year exc.	NDMA-unexposed	92	1.000	-
		Eventually NDMA-unexposed	96	1.607 (1.199–2.154)	0.001
		NDMA-exposed	120	1.517 (1.148–2.006)	0.003*
	2-year exc.	NDMA-unexposed	73	1.000	-
		Eventually NDMA-unexposed	79	1.530 (1.109–2.112)	0.010
		NDMA-exposed	82	1.197 (0.870–1.648)	0.270

PSM, propensity score matching; NDMA, N-nitrosodimethylamine; aHR, adjusted hazard ratio; CI, confidence interval; 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, being a prevalent user, and the year of the first observed valsartan prescription.

^{c)}All hazard ratios after PSM were adjusted for age, sex, being a prevalent user, 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 ($p < 0.004$).

Supplementary Table 8. The risks of any cancer and significant organ-specific cancers in valsartan new users before and after PSM according to NDMA-contaminated valsartan doses

PSM	Colorectal cancer			Pancreatic cancer			Prostate cancer ^{a)}			Stomach cancer		
	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	2-year exc.	NDMA-unexposed (mg)					15,521	1.000	-			
		< 10,800					1,336	1.097 (1.037–1.160)	0.001*			
		10,800–40,760					1,365	1.104 (1.044–1.167)	< 0.001*			
		40,800–525,120					1,937	1.126 (1.074–1.181)	< 0.001*			
1:1 PSM ^{c)}	2-year exc.	NDMA-unexposed (mg)		899	1.000	-	1,723	1.000	-	688	1.000	-
		< 10,800		261	1.117 (0.973–1.283)	0.117	490	1.102 (0.996–1.218)	0.060	234	1.355 (1.167–1.572)	< 0.001*
		10,800–40,760		269	1.103 (0.961–1.266)	0.161	495	1.052 (0.951–1.163)	0.330	176	0.996 (0.843–1.177)	0.965
		40,800–525,120		418	1.240 (1.102–1.395)	< 0.001*	764	1.151 (1.056–1.255)	0.001*	290	1.163 (1.011–1.337)	0.034
1:1:1 PSM ^{d)}	2-year exc.	NDMA-unexposed (mg)					560	1.000	-	551	1.000	-
		< 10,800					169	1.149 (0.966–1.365)	0.116	403	1.093 (0.978–1.221)	0.118
		10,800–40,760					178	1.150 (0.969–1.364)	0.109	420	1.071 (0.959–1.195)	0.224
		40,800–525,120					239	1.120 (0.960–1.307)	0.150	658	1.178 (1.072–1.294)	< 0.001*

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

^{a)}All analyses for prostate cancer were performed limited to men.

^{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.

*Statistically significances at the threshold using Bonferroni correction for 5 tests ($p < 0.01$).

Supplementary Table 9. Subgroup analyses in patients with prostate cancer in valsartan new users according to age

Age (yr)		Eventually NDMA-unexposed	NDMA-exposed	Age NDMA interaction term	
		aHR (95% CI)	aHR (95% CI)	Wald χ^2	p value
Before PSM	≤ 65	0.979 (0.929–1.032)	1.110 (1.063–1.160)	2.080	0.353
	> 65	1.076 (1.011–1.145)	1.166 (1.108–1.226)		
1:1 PSM	≤ 65	-	1.124 (1.031–1.226)	0.310	0.578
	> 65	-	1.162 (1.044–1.293)		
1:1:1 PSM	≤ 65	1.065 (0.960–1.181)	1.176 (1.070–1.294)	0.433	0.805
	> 65	1.037 (0.904–1.190)	1.208 (1.068–1.368)		

NDMA, N-nitrosodimethylamine; aHR, adjusted hazard ratio; CI, confidence interval; PSM, propensity score matching.
 This analysis was performed excluding patients with events with 2 years after the first observed valsartan prescription.

Supplementary Table 10. The risks of any cancer and prostate cancer in valsartan new users excluding patients with any cancer during the first year of follow-up

PSM	Cancer	All cancer			Prostate cancer ^{a)}		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	NDMA-unexposed	86,363	1.000	-	15,521	1.000	-
	Eventually NDMA-unexposed	15,902	1.049 (1.031–1.067)	< 0.001	2,855	1.019 (0.979–1.060)	0.364
	NDMA-exposed	24,828	1.069 (1.054–1.085)	< 0.001	4,638	1.132 (1.095–1.170)	< 0.001
1:1 PSM ^{c)}	NDMA-unexposed	7,705	1.000	-	1,703	1.000	-
	NDMA-exposed	7,869	1.146 (1.110–1.183)	< 0.001	1,714	1.125 (1.051–1.204)	< 0.001
1:1:1 PSM ^{c)}	NDMA-unexposed	5,565	1.000	-	1,342	1.000	-
	Eventually NDMA-unexposed	4,315	1.138 (1.093–1.184)	< 0.001	950	1.038 (0.954–1.129)	0.386
	NDMA-exposed	5,684	1.172 (1.128–1.216)	< 0.001	1,374	1.168 (1.082–1.261)	< 0.001

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

This analysis was performed excluding patients with events with 2 years after the first observed valsartan prescription.

^{a)}All analyses for prostate cancer were performed limited to men.

^{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.

Supplementary Table 11. The risks of any cancer and prostate cancer in valsartan new users excluding patients with any cancer during the first year of follow-up according to NDMA-contaminated valsartan doses

PSM		All cancer			Prostate cancer ^{a)}		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	NDMA-unexposed (mg)	86,363	1.000	-	15,521	1.000	-
	< 10,800	7,333	1.049 (1.024–1.074)	< 0.001	1,336	1.096 (1.036–1.159)	0.001
	10,800–40,760	7,206	1.018 (0.994–1.043)	0.148	1,365	1.101 (1.041–1.164)	< 0.001
	40,800–525,120	10,289	1.063 (1.041–1.085)	< 0.001	1,937	1.121 (1.069–1.176)	< 0.001
1:1 PSM ^{c)}	NDMA-unexposed (mg)	7,705	1.000	-	1,703	1.000	-
	< 10,800	2,273	1.135 (1.083–1.190)	< 0.001	484	1.105 (0.998–1.223)	0.054
	10,800–40,760	2,229	1.067 (1.018–1.120)	0.007	482	1.038 (0.937–1.150)	0.474
	40,800–525,120	3,367	1.150 (1.104–1.198)	< 0.001	748	1.142 (1.046–1.246)	0.003
1:1:1 PSM ^{c)}	NDMA-unexposed (mg)	6,207	1.000	-	1,412	1.000	-
	< 10,800	1,818	1.133 (1.075–1.194)	< 0.001	397	1.094 (0.978–1.224)	0.114
	10,800–40,760	1,791	1.061 (1.006–1.119)	0.028	410	1.058 (0.947–1.183)	0.317
	40,800–525,120	2,744	1.153 (1.101–1.207)	< 0.001	642	1.164 (1.059–1.280)	0.002

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

This analysis was performed excluding patients with events with 2 years after the first observed valsartan prescription.

^{a)}All analyses for prostate cancer were performed limited to men.

^{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.

Supplementary Table 12. The risks of any cancer and prostate cancer in valsartan new users observed since 2015

PSM	Cancer	All cancer			Prostate cancer ^{a)}		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	NDMA-unexposed	37,103	1.000	-	6,537	1.000	-
	Eventually NDMA-unexposed	8,474	1.015 (0.992–1.040)	0.206	1,505	1.016 (0.960–1.074)	0.586
	NDMA-exposed	13,356	1.045 (1.025–1.066)	< 0.001	2,438	1.115 (1.064–1.168)	< 0.001
1:1 PSM ^{c)}	NDMA-unexposed	2,278	1.000	-	520	1.000	-
	NDMA-exposed	2,807	1.143 (1.081–1.208)	< 0.001	591	1.052 (0.934–1.185)	0.401
1:1:1 PSM ^{c)}	NDMA-unexposed	1,286	1.000	-	318	1.000	-
	Eventually NDMA-unexposed	1,146	1.150 (1.062–1.246)	< 0.001	264	1.070 (0.909–1.261)	0.416
	NDMA-exposed	1,644	1.216 (1.129–1.309)	< 0.001	377	1.115 (0.959–1.297)	0.156

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

This analysis was performed excluding patients with events with 2 years after the first observed valsartan prescription.

^{a)}All analyses for prostate cancer were performed limited to men.

^{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.

Supplementary Table 13. The risks of any cancer and prostate cancer in valsartan new user observed since 2015 according to NDMA-contaminated valsartan doses

PSM		All cancer			Prostate cancer ^{a)}		
		Event	aHR (95% CI)	p value	Event	aHR (95% CI)	p value
Before PSM ^{b)}	NDMA-unexposed (mg)	37,103	1.000	-	6,537	1.000	-
	< 10,800	4,120	1.056 (1.029–1.083)	< 0.001	712	1.108 (1.026–1.198)	0.009
	10,800–40,760	4,146	1.106 (1.079–1.134)	< 0.001	775	1.116 (1.036–1.204)	0.004
	40,800–525,120	5,090	0.985 (0.959–1.011)	0.247	951	1.076 (1.005–1.152)	0.036
1:1 PSM ^{c)}	NDMA-unexposed (mg)	2,278	1.000	-	520	1.000	-
	< 10,800	890	1.237 (1.145–1.337)	< 0.001	176	1.089 (0.918–1.293)	0.327
	10,800–40,760	836	1.068 (0.985–1.158)	0.111	185	1.014 (0.855–1.203)	0.871
	40,800–525,120	1,081	1.091 (1.014–1.174)	0.020	230	1.021 (0.872–1.195)	0.800
1:1:1 PSM ^{c)}	NDMA-unexposed (mg)	1,832	1.000	-	435	1.000	-
	< 10,800	716	1.233 (1.131–1.345)	< 0.001	152	1.116 (0.927–1.343)	0.245
	10,800–40,760	679	1.065 (0.973–1.164)	0.171	154	1.004 (0.833–1.210)	0.966
	40,800–525,120	896	1.119 (1.032–1.214)	0.007	198	1.031 (0.870–1.223)	0.723

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

This analysis was performed excluding patients with events with 2 years after the first observed valsartan prescription.

^{a)}All analyses for prostate cancer were performed limited to men.

^{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.

Supplementary Table 14. The number of all-cause and cardiovascular death in valsartan new users in 2018

Death	PSM	From January 1, 2018 to July 6, 2018			From July 7, 2018 to December 31, 2018		
		Original	Eventually NDMA-uncontaminated	NDMA-contaminated	Original	Eventually NDMA-uncontaminated	NDMA-contaminated
All-cause	Event	12,800	2,132	3,907	12,388	2,207	3,690
	IR (95% CI) ^{a)}	15.77 (15.49–16.04)	11.29 (10.81–11.77)	17.94 (17.38–18.51)	16.03 (15.75–16.31)	12.27 (11.76–12.79)	17.80 (17.23–18.38)
Cardiovascular	Event	3,358	517	966	3,147	497	924
	IR (95% CI) ^{a)}	4.14 (4.00–4.28)	2.74 (2.51–2.98)	4.44 (4.16–4.72)	4.07 (3.93–4.22)	2.76 (2.53–3.02)	4.46 (4.17–4.75)

PSM, propensity score matching; NDMA, N-nitrosodimethylamine; IR, incidence rate; CI, confidence interval.

^{a)}Incidence rate per 1,000 person-years is calculated for each valsartan group and clinical outcome.

Supplementary Table 15. Tables of angiotensin receptor blockers available in Korea

Name of angiotensin receptor blocker	Initial daily dose (mg)	Target dose in clinical trials (mg)	No. of doses per day
Candesartan	4	12–32	1
Eprosartan	300	600	1
Losartan	50	100	1–2
Valsartan	40–80	160–320	1
Irbesartan	75	300	1
Telmisartan	20–40	40–120	1
Fimasartan	20–60	60–120	1
Azilsartan	10–20	20–40	1