

## Angiotensin II receptor blockers (ARBs) and manufacturing contamination

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## ORIGINAL ARTICLE

# Angiotensin II receptor blockers (ARBs) and manufacturing contamination: A retrospective National Register Study into suspected associated adverse drug reactions

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**Aims:** The aim of this study was to determine if any suspected adverse drug reactions (ADRs) observed with the use of angiotensin II receptor blockers (ARBs) could be linked to either (a) their unique respective physicochemical and pharmacological profiles and (b) the recently disclosed suspected carcinogenic manufacturing contaminants found in certain sartan drug class batches.

**Methods:** The pharmacology profiles of ARBs were data-mined from the Chemical Database of bioactive molecules with drug-like properties, European Molecular Biology Laboratory (ChEMBL). Suspected ADR data (from 01/2016–10/2022, inclusive) and prescribing rates of ARBs over a 5-year prescribing window (from 09/2016 to 08/2021, inclusive) were obtained via analysis of the United Kingdom Medicines and Healthcare products Regulatory Authority (MHRA) Yellow Card drug analysis profile and Open prescribing databases, respectively.

**Results:** The overall suspected ADRs and fatalities per 100 000 prescriptions identified across the ARBs studied were found to be different between the sartan drug class members (chi-squared test,  $P < .05$ ). There is a greater relative rate of reports for valsartan across all investigated organ classes of ADRs, than other ARBs, despite valsartan's more limited pharmacological profile and similar physicochemical properties to other sartans. The disparity in ADR reporting rates with valsartan vs other ARBs could be due to the dissimilarity in formulation excipients, patient factors and publicity surrounding batch contaminations, amongst others. Cancer-related ADRs and fatalities per 100 000 prescriptions identified across the ARBs studied are not statistically significant (chi-squared test,  $P > .05$ ) based on the datasets used over the 5-year period.

**Conclusion:** No connection between ARB pharmacology and their suspected ADRs could be found. No conclusion between sartan batch contaminations and increased suspected cancer-related ADRs was found.

**KEYWORDS**

ADRs, ARBs, contamination, polypharmacology, valsartan, Yellow Card

The authors confirm that the principal investigator for this paper is Dr Alan M. Jones.

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## 1 | INTRODUCTION

The angiotensin II receptor antagonists (angiotensin receptor blockers [ARBs]) represent a class of potent antihypertensive agents.<sup>1</sup> ARBs facilitate selective inhibition of angiotensin II by competitive antagonism of **angiotensin II type 1 (AT<sub>1</sub>) receptor**.<sup>2</sup> The renin-angiotensin-aldosterone system (RAAS) is a crucial component in the preservation of haemodynamic stability and the pathophysiology of hypertension.<sup>3,4</sup> The effector peptide of RAAS, angiotensin II, exerts its effect through interaction with the AT<sub>1</sub> receptor.<sup>5</sup> Receptor activation can mediate vasoconstriction, aldosterone release, sympathetic activation and sodium and water retention.<sup>6</sup> These processes can prompt the development of hypertension. ARBs inhibit angiotensin II AT<sub>1</sub> receptor-mediated cardiovascular effects through the displacement of angiotensin II from the AT<sub>1</sub> receptor, thus lowering blood pressure.<sup>2</sup> ARB monotherapy is proven to allow up to 50% of hypertensive patients to achieve their target blood pressure.<sup>2,7–9</sup> Furthermore, the results from landmark trials, including CLAIM Study II, conclude that ARBs are well-tolerated and effectively correspond to a reduction in blood pressure from baseline levels.<sup>8,9</sup>

There are eight ARBs clinically available in the UK, all approved by the Medicines and Healthcare products Regulatory Agency (MHRA) for hypertension: **losartan** (1994),<sup>10</sup> **valsartan** (1996),<sup>11</sup> **irbesartan** (1997),<sup>12</sup> **candesartan** (1998),<sup>13</sup> **telmisartan** (1998),<sup>14</sup> **eprosartan** (1999),<sup>15</sup> **olmesartan** (2003)<sup>16</sup> and **azilsartan** (2011).<sup>17</sup>

Adverse drug reactions (ADRs) are toxic, unintended responses to a drug or a combination of drugs and account for approximately 6–7% of hospital admissions.<sup>18</sup> The prevalence of ADRs remains a challenge in modern healthcare, leading to significant health and economic implications.<sup>19</sup> Pharmacovigilance is used to monitor drug safety during the post-marketing phase.<sup>20</sup> Spontaneous reporting of ADRs is considered a passive method of pharmacovigilance and is organised by the MHRA Yellow Card scheme in the UK.<sup>21</sup>

Understanding the pharmacology of a drug may help predict ADR prevalence as unwanted protein–drug interactions can have unintended consequences in certain patient populations.<sup>22–24</sup> Studies have assessed ARB ADRs<sup>2</sup> but the relationship between the pharmacology of ARBs and their respective ADRs has yet to be investigated. Furthermore, recent media attention regarding the detection of potential carcinogens in specific ARB products warranted an application of our technique to understand the potential relationship between ARB ADRs and the presence of a mutagenic contaminant in certain batches.

### 1.1 | Manufacturing contamination in generic sartans: a brief history

The manufacturing contamination issues with sartans appear to have begun in 2012 when one generics manufacturer (Zhejiang Huahai Pharmaceuticals [ZHP], Linhai, PRC) changed the manufacturing process of valsartan to use *N,N*-dimethylformamide (DMF) as a processing solvent.<sup>25</sup> At high temperatures, DMF decomposes to

#### What is already known about this subject

- ARBs represent a class of potent antihypertensive agents.
- The incidence of suspected ADRs in ARBs vary despite their similar mechanism of action.

#### What this study adds

- The incidence of suspected ADR reports was statistically greater with valsartan compared to other ARB comparators.
- No strong connection between the ARB pharmacology and their respective ADRs has been established.
- No connection between AZBT contamination in irbesartan and losartan and increased susceptibility to cancer-associated ADRs has been established based on spontaneous reports.
- No connection between nitrosoamine contamination in valsartan, irbesartan and losartan and increased susceptibility to cancer-associated ADRs has been established based on spontaneous reports.

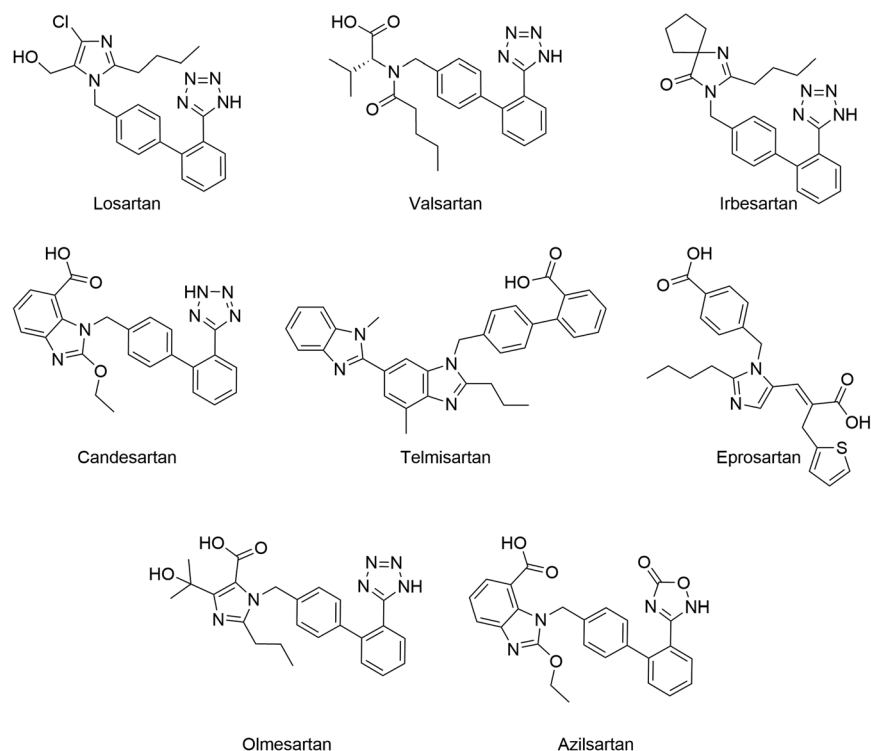
carbon monoxide and dimethylamine. Dimethylamine can in turn react with another reagent used in the synthesis of valsartan, sodium nitrite, to form *N*-nitroso-*N*-dimethylamine (NDMA, Figure 1). It was not until 2018 that European and American medical authorities initiated recalls of certain batches due to the detection of NDMA (and *N*-nitroso-*N*-diethylamine [NDEA]) contaminants initially. The story is further complicated by the fact that generic manufacturing is a low-margin operation and there are multiple suppliers who have made slight and different changes to the synthesis, purification and processing of valsartan-containing medications and related ARBs (especially losartan and irbesartan) with a view to improving the efficiency and cost of manufacture. Thus between 2012 and 2018, NDMA contamination of valsartan batches from ZHP was likely but the levels are unknown. However, not all generic valsartan was made by ZHP, thus the disparate range of recalls of products from national regulatory bodies.

At the time of writing, contamination is not an ARB class issue, affecting only certain batches of valsartan, losartan and irbesartan, and most likely when the original approved process chemistry had been modified.<sup>26</sup> Four recalls of sartan batches have been issued by the UK's MHRA (November 2018 [valsartan], January 2019 [irbesartan], June 2021 [irbesartan and losartan], and August 2021 [(irbesartan)].<sup>27</sup>

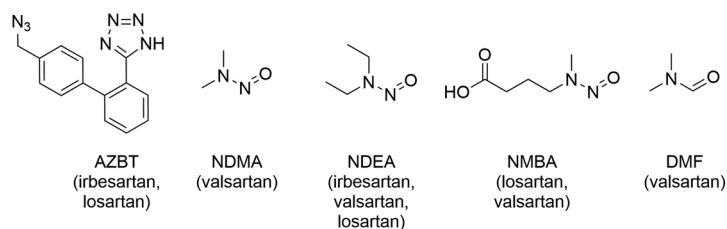
The issue with nitrosoamine contamination (such as NDMA and others, see Figure 1), referred to as a probable carcinogen, is not just confined to sartans; indeed, pioglitazone, ranitidine, metformin and

**FIGURE 1** The chemical structures of ARB drugs used in this study and batch impurities detected in certain ARB containing products

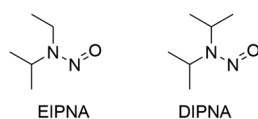
#### Sartans



#### Known Batch Contaminants (found in certain batches of ARBs in parentheses)



#### Possible Nitrosoamine Contaminants



**TABLE 1** Current temporary limits on contaminants

Contaminant	FDA	EMA	MHRA (UK)
NDMA	96 ng/day	96 ng/day (0.32–3.00 ppm per ARB)	—
NDEA	26.5 ng/day	26.5 ng/day (0.082–0.82 ppm per ARB)	—
DMF	8 000 000 ng/day	—	—
AZBT (losartan)	—	—	33 ppm
AZBT (irbesartan)	—	—	66 ppm

others have emerged.<sup>28</sup> To demonstrate the scale of the problem, in 2019 alone there were 139 valsartan, 57 losartan and 16 irbesartan recalls. More recently, the identification of the possible mutagen 5-(4'-(azidomethyl)-[1,1'-biphenyl]-2-yl)-1H-tetrazole (AZBT) (Figure 1) resulted in the recall of 31 batches of irbesartan-containing products and two batches of losartan-containing products by the

MHRA (UK) in June 2021.<sup>29</sup> Since the initial discovery of nitrosoamine contamination, a ratcheting up of regulations on permissible levels of nitrosoamine impurities has taken place, leading to further recalls.<sup>30–32</sup> Thus, there are three distinct types of contamination we need to consider with the sartan drug class: AZBT, nitrosoamines and DMF solvent (Figure 1 and Table 1).

## 1.2 | What we know about the patient consequences of contamination

A German national study, after the 30 recalls of valsartan-containing products in 2018, demonstrated a 64% decrease in valsartan usage and a 57% uptick in alternative ARB medications.<sup>33</sup> Losartan prescribing made up the shortfall in managing hypertension of patients previously on valsartan in other studies.<sup>34</sup>

A Canadian retrospective national study, from the latest recall (9 July 2018) showed no pronounced cancer risk in the patient population.<sup>35</sup> A Danish national study showed no marked increase in cancer risk with the contaminated valsartan batches. This encouraging result is tempered by the fact that valsartan batches were described as probably, possibly or unlikely to contain nitrosoamine contaminants, highlighting the lack of definitive data on contamination and who took what and when.<sup>36</sup> Another study found no association with NDMA contaminated valsartan batches and overall risk of cancer. However, slightly increased risk of hepatic cancer was noted.<sup>37</sup>

## 1.3 | Aims

First, this research aims to discover whether there is a potential link between the unique pharmacological activity of ARBs and their respective suspected ADR profiles.

Second, this research aims to identify whether there is a link between nitrosoamine and AZBT contamination in certain batches of sartans, with cancer-related ADRs compared to non-contaminated ARB comparators.

## 2 | METHODS

### 2.1 | Chemical properties and pharmacology

The Electronic Medicine Compendium (EMC)<sup>38</sup> and Chemical Database of bioactive molecules with drug-like properties, European Molecular Biology Laboratory (ChEMBL) database<sup>39</sup> were used to determine the physicochemical properties and pharmacology of all eight ARBs. The  $pIC_{50}$  was calculated using the median  $AT_1$  receptor  $IC_{50}$  of each drug and is calculated as follows:  $pIC_{50} = -\log_{10}[IC_{50}]$ . The  $IC_{50}$  is a quantitative measure that indicates the concentration of drug needed to inhibit a biological component by 50%. The lipophilic ligand efficiency (LLE) was determined using  $LLE = pIC_{50} - \log_{10}P$ .  $\log_{10}P$  is the experimentally measured partition coefficient of a substance between organic and aqueous environments in its neutral form and  $\log_{10}P$  the calculated partition coefficient. The LLE combines both potency and lipophilicity and assesses the binding energy of the drug to its target, excluding nonspecific interactions.<sup>40–42</sup> Thus, an LLE value of less than five can correlate to an increased risk of toxicity.<sup>43</sup> The criteria for blood-brain barrier (BBB) penetration are as follows; molecular weight (MW) < 450 Da; <6 hydrogen bond donors (HBD); <2

hydrogen bond acceptors (HBA); neutral or basic drug molecule (defined by  $pK_a$ ); topological polar surface area ( $tPSA$ ) < 90 Å;  $\log_{10}D$  at pH 7.4 is in the range 1–3 and has low affinity to efflux p-glycoprotein mechanism.<sup>42</sup>  $pK_a$  is the  $-\log_{10}K_a$ , where  $K_a$  is the acid dissociation constant and  $\log_{10}D^{7.4}$  (distribution coefficient is the partition coefficient for an ionised compound) was calculated from the respective  $\log_{10}P$ ,  $pK_a$  and pH values.  $\log_{10}D^{7.4}$  gives an indication of the distribution between aqueous and organic phase at pH = 7.4 and indicates the lipophilicity of the molecule in an ionised state.  $tPSA$  considers the polar atoms on the surface of the molecule. The  $C_{max}$  peak serum concentration of the ARBs were calculated from European Medicines Agency (EMA) data in ng/mL to standardised nM.<sup>44–46</sup>

Non-listed physicochemical and pharmacological parameters on the EMC and ChEMBL databases were extracted from literature database searches of each drug name + pharmacokinetic search terms using Springer Link, NCBI and ScienceDirect.<sup>44–52</sup>

### 2.2 | Target affinity

The ChEMBL database was used to collect quantitative measurements between each ARB and a human protein target.<sup>39</sup> Azilsartan and olmesartan bioactivity data were obtained from *Bos taurus* proteins as human targets were not listed. ARB data were curated and compared using median  $IC_{50}$  values. The median  $IC_{50}$  value is less influenced by outlier values and to reduce the reproducibility/reliability issue of selecting a single  $IC_{50}$  value. A threshold of 10  $\mu M$  was used to exclude biologically inconsequential interactions.

### 2.3 | Prescribing data

The OpenPrescribing database provides all prescribing data in England across National Health Service (NHS) primary care practices (accessed on 11 November 2021).<sup>53,54</sup> Each ARB was filtered by its licensed formulations and available strength. The prescription numbers for each drug strength between September 2016 and August 2021 were extracted and subsequently combined. The value obtained provided an estimate of the total number of prescriptions of each ARB dispensed over the past 5 years (see Figure S1 in the Supporting Information).

### 2.4 | Adverse drug reactions

Suspected ADR data on ARBs were curated from the MHRA Yellow Card Interactive Drug Analysis Profile web portal.<sup>55</sup> Reports submitted from January 2016 to October 2021 were extracted. Eprosartan's last ADR data point was in 2017, thereby producing minimal ADR reports required for standardisation. Therefore, eprosartan was excluded from ADR extraction and further discussion (see inclusion/exclusion criteria, Table 2).

**TABLE 2** Inclusion and exclusion criteria

Inclusion	Exclusion
5-year data window	Outside this period
Pharmacology data availability for AT <sub>1</sub> and others	Non-homosapien target for off-targets
Prescribing data availability	<100 000 prescriptions during the period
ADR data availability for the 5-year period	Incomplete/partial ADR data availability
Licensed ARB in the UK	Not a licensed ARB in the UK

Significant ADRs were selected and assessed. The selection criteria included a high prevalence of ADRs within a particular organ class (above an ADR baseline level, which was approximately 10% of total ADRs) or a visible difference in ADRs across the ARBs (independent of baseline).

Importantly, cancer-related ADRs were also selected for analysis within this study to determine whether generic manufacturing contamination in certain sartan-containing products increased cancer-associated ADRs compared to other ARBs.

To enable standardisation and comparison of the raw data, the ADR reports were divided by 100 000 prescriptions (Rx).

Azilsartan is the most recently licensed ARB in the UK and significantly less prescribed (see Figure S1 in the Supporting Information). As azilsartan had fewer than 100 000 prescriptions over the past 5 years, it was not possible to standardise the data obtained. Therefore, azilsartan was also excluded from ADR data collection and further discussion.

## 2.5 | Statistical analysis

Chi-squared tests (Excel for Microsoft 365) were performed on the standardised ADR/100000 Rx data to determine whether the differences between suspected ADRs and ARBs were statistically significant. A *p*-value of <.05 was set for statistical significance (Figure S2 in the Supporting Information).

## 2.6 | Ethical approval

This study used non-identifiable data freely available in the public domain. Thus, the study was exempt from ethical approval.

## 2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.<sup>56,57</sup>

## 3 | RESULTS

### 3.1 | Chemical properties and pharmacokinetics

Azilsartan, candesartan and olmesartan are formulated as prodrugs (azilsartan medoxomil, candesartan cilexetil and olmesartan medoxomil, respectively).<sup>38</sup> Results are given for active drugs only as prodrugs have minimal or no efficacy (Table 3).<sup>2</sup> Valsartan is the only ARB with multiple licensed formulations (tablets, capsules and oral solutions).<sup>58</sup> Results included in Table 3 are given for the tablet formulation unless otherwise stated.

Properties of ARBs concerning AT<sub>1</sub> inhibition (*p*IC<sub>50</sub>, *clog*<sub>10</sub>P and LLE) are summarised in Table 3. Among the ARBs, telmisartan is the most lipophilic compound (*clog*<sub>10</sub>P = 6.13) and demonstrated the greatest potency at the AT<sub>1</sub> receptor (*p*IC<sub>50</sub> = 9). Most ARBs had an LLE value below 5, apart from olmesartan (5.93).

The properties associated with the probability of BBB penetration are demonstrated in Table 3 and Figure S3 in the Supporting Information. Azilsartan and telmisartan failed to meet the MW requirement: telmisartan was the heaviest drug (514.63 Da). All ARBs are acidic and therefore do not meet the neutral/basic requirement. Irbesartan and telmisartan met the requirement of <sup>t</sup>PSA < 90 Å (87.13 and 72.94, respectively). All ARBs met the <6 HBD requirement, but failed to meet the <2 HBA requirements. Only losartan met the *log*<sub>10</sub>D<sub>7.4</sub> requirement (2.82). Azilsartan, eprosartan and olmesartan demonstrated a low affinity to the efflux *p*-glycoprotein mechanism. In summary, the risk of BBB penetration is similar across all ARBs (2–3 out of 7). Eprosartan, irbesartan, losartan and olmesartan shared the greatest risk of BBB penetration (3 out of 7).

The pharmacokinetic properties of the ARBs are summarised in Table 3. Telmisartan had a *t*<sub>1/2</sub> > 20 h, as opposed to losartan which had the shortest (*t*<sub>1/2</sub> ~ 2 h) although both are dosed o.d. Telmisartan has the highest volume of distribution, at 500 L, which is reflected by its high *clog*<sub>10</sub>P. Most ARBs undergo CYP metabolism, excluding eprosartan, olmesartan and telmisartan.

### 3.2 | Target affinity

The pharmacology profiles of the ARBs are shown in Table 4. Telmisartan was most potent towards the AT<sub>1</sub> receptor (1 nM). Azilsartan and olmesartan were least potent towards the AT<sub>1</sub> receptor (420 nM) but bioactivity is obtained from *bos taurus*. Losartan was least potent towards the AT<sub>1</sub> receptor in *homosapiens*. Generally, ARBs demonstrated unique pharmacological profiles with minimal biologically relevant inhibition of targets other than the intended AT<sub>1</sub> receptor. Losartan and telmisartan appeared to be least selective, possessing the greatest number of potentially biologically relevant interactions (*n* = 2).

The pharmacological activity included potentially biologically relevant inhibition of receptors other than AT<sub>1</sub> (based on each drug's respective *C*<sub>max</sub>). Telmisartan was highly potent towards the

TABLE 3 Physicochemical, blood–brain barrier, pharmacokinetic and pharmacological properties of the eight ARBs

Variable	Azilsartan <sup>a</sup>	Candesartan <sup>a</sup>	Eprosartan	Irbesartan	Losartan	Olmesartan <sup>a</sup>	Telmisartan	Valsartan
<b>Molecular obesity and on-target efficiency metrics</b>								
clog <sub>10</sub> P	5.92	4.68	3.75	5.39	4.06	2.16	6.13	4.59
pIC <sub>50</sub>	6.38	7.97	8.33	7.96	7.79	8.09	9	8.57
LLE	0.46	3.29	4.58	2.57	3.73	5.93	2.87	3.98
<b>Blood–brain barrier penetrant properties</b>								
MW (Da)	456.46	440.46	424.52	428.54	422.92	446.51	514.63	435.53
pK <sub>a</sub>	Acid: 3.39	Acid: 3.44	Acid: 3.47	Acid: 5.85	Acid: 4.26	Acid: 0.89	Acid: 3.62	Acid: 4.00
<sup>t</sup> PSA <sub>A</sub> (Å)	123.5	118.81	92.42	87.13	92.51	129.81	72.94	112.07
HB acceptors	8	7	5	5	6	7	5	5
HB donors	2	2	2	1	2	3	1	2
clog <sub>10</sub> D <sub>7.4</sub>	0.3	−0.3	0.06	4.23	2.82	−1	4.86	0.08
P-glycoprotein substrate	No	Yes	No	Yes	Yes	No	Yes	Yes
No. of BBB requirements met	2	2	3	3	3	3	2	2
<b>Pharmacokinetics</b>								
Bioavailability (%F)	60%	14%	13%	60–80%	33%	25.60%	50%	23% (39% oral)
Half-life (h)	11	9	5–9	11–15	2	10–15	>20	6
T <sub>max</sub> (h)	1.5–3	3–4	1–2	1.5–2	1	2	0.5–1	2–4 (1–2 oral)
C <sub>max</sub> (nM)	12 000	227	2945	7701	591	1064	544	4592
CYP metabolism	Yes: CYP2C9	Yes: CYP2C9	No	Yes: CYP2C9	Yes: CYP2C9, CYP3A4	No	No	Minimal: CYP 2C9
Renal excretion	42%	33%	7%	20%	35%	10–16%	<1%	13%
Volume of distribution (L)	16	0.1	13	53–93	34	16–29 IV	500	17 (i.v.)
Clearance (L/h)	0.138 (R)	0.02 (P), 0.01 (R)	7.8 (P)	0.18–0.21 (R)	36 (P), 4.44 (R),	1.3 (P), 0.5–0.7 (R)	60 (P)	2 (P), 0.62 (R)
PPB	>99%	>99%	98%	96%	≥99%	99.7%	>99.5%	94–97%
Dosing	OD (40 mg) to OD (80 mg)	OD (8 mg), to OD (32 mg)	OD (600 mg)	OD (150 mg), to OD (300 mg)	OD (50 mg), to OD (100 mg)	OD (10 mg), to OD (40 mg)	OD (20–40 mg), to OD (80 mg)	OD (80 mg), to OD (320 mg)

(IV), intravenous formulation; (P), plasma; (R) renal; clog<sub>10</sub>D<sub>7.4</sub>, calculated log<sub>10</sub>D at pH 7.4; clog<sub>10</sub>P, calculated log<sub>10</sub>P; HB, hydrogen bond; MW, molecular weight; LLE, lipophilic ligand efficiency; pK<sub>a</sub>, acid dissociation constant; PPB, plasma protein binding; C<sub>max</sub>, peak serum concentration; T<sub>max</sub>, time taken to reach C<sub>max</sub>; <sup>t</sup>PSA, total polar surface area.

<sup>a</sup>Figures given for active drug only.



TABLE 4 The target selectivity profile of the eight ARBs (Median IC<sub>50</sub> values in nM)

	Azilsartan	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
<b>G protein-coupled receptor</b>								
Angiotensin II type 1a receptor	420 nM					420 nM		
Type-1 angiotensin II receptor		11 nM	5 nM	11 nM	16 nM		1 nM	3 nM
Angiotensin II type 2 receptor					10 000 nM		0.33 nM	
<b>Kinases</b>								
Adenosine A3 receptor		1220 nM						
Alpha-2b adrenergic receptor		3843 nM						
Beta-3 adrenergic receptor		4300 nM						
Epidermal growth factor receptor erbB1		3277 nM						
Receptor protein-tyrosine kinase erbB-2		5947 nM						
<b>Transporters</b>								
Bile salt export pump			134 000 nM	7310 nM	9265 nM		16 200 nM	82 035 nM
Bile acid transporter				30 000 nM				
Canalicular multispecific organic anion transporter 1			57 900 nM				>133 000 nM	>133 000 nM
Canalicular multispecific organic anion transporter 2			6650 nM	21 100 nM			60 000 nM	>133 000 nM
Multidrug resistance-associated protein 4			>133 000 nM	83 200 nM			36 000 nM	>133 000 nM
Multidrug and toxin extrusion protein 1				>500 000 nM	>250 000 nM		17 900 nM	
<b>Enzymes</b>								
Norepinephrine transporter		3065 nM						
Solute carrier organic anion transporter family member 1B1					288 nM		1862 nM	
Solute carrier organic anion transporter family member 1B3					1148 nM		1259 nM	
Thromboxane-A synthase		3059 nM						
Thiosulfate sulfurtransferase		>100 000 nM						
Neprilysin			> 10 000 nM					
Angiotensin-converting enzyme			19 nM					
Cytochrome P450 2 J2						>50 000 nM	540 nM	
Cytochrome P450 2C9		3000 nM			2882 nM		4780 nM	
Cytochrome P450 3A4		9000 nM					> 50 000 nM	
Cytochrome P450 1A2							> 50 000 nM	

(Continues)



TABLE 4 (Continued)

	Azilsartan	Candesartan	Eprosartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan
Cytochrome P450 2C19							> 50 000 nM	
Cytochrome P450 2D6							> 50 000 nM	
HERG				194 984 nM				
Peroxisome proliferator-activated receptor alpha							> 10 000 nM	
Peroxisome proliferator-activated receptor delta							> 10 000 nM	
Peroxisome proliferator-activated receptor gamma							12 200 nM	
Platelet glycoprotein VI (GPVI)					11 000 nM			
<b>Membrane glycoproteins</b>								
<b>C<sub>max</sub></b>								
	Unknown	No inhibition (>10 000 nM)	< 10 000 nM	< 1000 nM	< 100 nM	< 10 nM.		

**angiotensin II type 2 (AT<sub>2</sub>) receptor** (0.33 nM), whereas other ARBs demonstrated weak or no interaction. Telmisartan also showed **cytochrome P450 CYP 2J2** inhibition (540 nM). Losartan had a distinct enzymatic pharmacology profile and showed a unique inhibition to angiotensin-converting enzyme (ACE) at significant efficacy (19 nM). Losartan also showed inhibition of the solute carrier organic anion transporter family member 1B1 (**SLCO1B1**) at 288 nM. Lastly, irbesartan showed inhibition to the bile salt export pump (**BSEP**), at 7310 nM. Losartan and telmisartan exhibited more promiscuous profiles.

### 3.3 | Total general ADRs and fatalities

The number of UK prescriptions between 2016 and 2021 concerning the six ARBs studied is summarised in Table 5. The prescription rates between ARBs differed; losartan had the highest (50072423) followed by candesartan (34716351), irbesartan (9000312), olmesartan (2159448), valsartan (1986541) and telmisartan (1625888).

The number of reported suspected ADRs and fatalities between 2016 and 2021 associated with the six ARBs studied are summarised in Table 5. The following ADR trend was established: valsartan had the highest number of reported ADRs per 100 000 Rx (117.09) followed by telmisartan (5.35), irbesartan (4.97), olmesartan (4.08), candesartan (3.46) and losartan (2.92). The discrepancy in reported ADRs between ARBs resulted in a statistically significant *P*-value of <.05. Valsartan also had the highest reported suspected fatalities per 100 000 Rx (3.17). Irbesartan and olmesartan had no reported suspected fatalities associated with usage. Figures S4 and S5 in the Supporting Information represent the standardised data of suspected ADR and fatalities, respectively.

### 3.4 | Gastrointestinal ADRs and fatalities

Valsartan had the most suspected gastrointestinal ADRs at 11.88 per 100 000 Rx (Table 5). All ARBs had no reported GI-associated fatalities associated with usage within the investigated period. Moreover, valsartan had the highest number of reports of diarrhoea, nausea and vomiting ADR (3.88 and 2.97 per 100 000 Rx, respectively).

### 3.5 | General disorders and administration site ADRs and fatalities

Valsartan had the highest number of ADRs associated with general disorders and administration, at 13.94 per 100 000 Rx (Table 5). Valsartan had the highest number of fatalities per 100 000 Rx (1.26), followed by telmisartan (0.06), candesartan (0.01) and losartan (0.002). Valsartan also had the highest suspected rate of fatigue and malaise per 100 000 Rx (3.17 and 1.76, respectively).

**TABLE 5** Summary of the reported suspected ADRs within the UK associated with the six studied ARBs. The numbers in brackets are reported ADRs per 100 000 prescriptions. *P*-values are obtained by chi-squared analysis performed on all the six studied ARBs

	Candesartan	Irbesartan	Losartan	Olmesartan	Telmisartan	Valsartan	<i>P</i> values
Total prescriptions	34 716 351	9 000 312	50 072 423	2 159 448	1 625 888	1 986 541	
Total ADRs	1201 (3.46)	447 (4.97)	1464 (2.92)	88 (4.08)	87 (5.35)	2326 (117.09)	<.05
Fatalities	5 (0.01)	0 (0)	3 (0.01)	0 (0)	1 (0.06)	63 (3.17)	<.05
Gastrointestinal disorders							
Total ADRs	102 (0.29)	47 (0.52)	129 (0.26)	27 (1.25)	2 (0.12)	236 (11.88)	<.05
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
<i>Diarrhoea (excl. infective)</i>	21 (0.06)	6 (0.07)	14 (0.03)	3 (0.14)	1 (0.06)	77 (3.88)	<.05
<i>Nausea/vomiting</i>	21 (0.06)	13 (0.14)	29 (0.06)	2 (0.09)	0 (0)	59 (2.97)	<.05
General disorders and administration site							
Total ADRs	170 (0.49)	58 (0.64)	198 (0.40)	8 (0.37)	17 (1.05)	277 (13.94)	<.05
Fatalities	2 (0.01)	0 (0)	1 (0.002)	0 (0)	1 (0.06)	25 (1.26)	0.32
<i>Fatigue</i>	29 (0.08)	5 (0.06)	24 (0.05)	2 (0.09)	0 (0)	63 (3.17)	<.05
<i>Malaise</i>	26 (0.07)	11 (0.12)	23 (0.05)	0 (0)	1 (0.06)	35 (1.76)	0.22
Musculoskeletal and connective tissue disorders							
Total ADRs	85 (0.24)	23 (0.26)	117 (0.23)	9 (0.42)	5 (0.31)	79 (3.98)	<.05
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
Neoplasms benign malignant and unspecified (incl. cysts and polyps)							
Total ADRs	4 (0.01)	4 (0.04)	5 (0.01)	0 (0)	1 (0.06)	14 (0.70)	0.73
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.25)	0.94
Nervous system disorders							
Total ADRs	167 (0.48)	45 (0.50)	197 (0.39)	10 (0.46)	2 (0.12)	260 (13.09)	<.05
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.05)	1
<i>Dizziness</i>	47 (0.14)	12 (0.13)	54 (0.11)	3 (0.14)	1 (0.06)	99 (4.98)	<.05
Psychiatric disorders							
Total ADRs	73 (0.21)	26 (0.29)	87 (0.17)	8 (0.37)	2 (0.12)	70 (3.52)	<.05
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.05)	1
Investigations							
Total ADRs	39 (0.11)	21(0.23)	55 (0.11)	0 (0)	10 (0.62)	256 (12.89)	<.05
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	–
<i>Cardiac and vascular investigations (excl. enzyme test)</i>	19 (0.05)	10 (0.11)	21 (0.04)	0 (0)	8 (0.49)	74 (3.72)	<.05
Cardiac disorders							
Total ADRs	31 (0.09)	15 (0.17)	47 (0.09)	0 (0)	2 (0.12)	137 (6.90)	<.05
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	23 (1.16)	0.33

### 3.6 | Nervous/psychiatric ADRs and fatalities

Nervous-system-associated ADRs followed the general ADR and fatalities reporting trend, with valsartan having the highest rate of ADRs and fatalities per 100 000 Rx (13.09, 0.05) (Table 5). The major reported nervous system ADR was dizziness. The highest reports of dizziness were associated with valsartan, olmesartan and candesartan, irbesartan, losartan and telmisartan in descending order.

Valsartan obtained the highest number of psychiatric-related ADRs per 100 000 Rx, at 3.52. Valsartan was the only ARB to have

usage associated with a psychiatric-linked fatality (0.05 per 100 000 Rx) within the investigated time.

### 3.7 | Neoplasms, benign, malignant and unspecified

Valsartan had the greatest number of ADRs per 100 000 Rx linked to neoplasms (0.70) followed by telmisartan (0.06), irbesartan (0.04), losartan and candesartan (0.01) (Table 5). Valsartan was the

only ARB to have fatalities associated with neoplasms (0.25 per 100 000 Rx) within the investigated period. Olmesartan had no reported reactions.

### 3.8 | Miscellaneous ADRs and fatalities

Valsartan had the highest number of ADRs linked to musculoskeletal and connective tissue disorders, at 3.98 per 100 000 Rx (Table 5).

Valsartan had the most suspected investigation-related ADRs at 12.89 per 100 000 Rx (Table 5). Notably, valsartan had high reports of cardiac and vascular investigations associated with usage (3.72 per 100 000 Rx). Olmesartan had no reported suspected ADRs.

Valsartan exhibited the most suspected cancer (neoplasm) ADRs compared to other ARBs (6.90 per 100 000 Rx) (Table 5). These ADR levels corroborate within the cardiac-disorder-associated fatality figures, at 1.16 per 100 000 Rx followed by the remaining ARBs, with no reported fatalities.

## 4 | DISCUSSION

Inspection of Table 4 reveals that most target inhibition is clinically unachievable (based on each drug's respective  $C_{max}$ ) unless drug accumulation transpires.<sup>22</sup> Indeed, only irbesartan and valsartan have the propensity to accumulate<sup>38</sup> but accumulation is limited and unlikely to reach the values required for the proposed inhibition to have a pronounced biological consequence. The remaining ARBs have no evidence of clinically relevant accumulation over time.<sup>38</sup> Thus, the findings indicate that ARBs generally have a limited pharmacology profile.

Based on the chemical properties concerning on-target efficiency (Table 3), it is difficult to predict which ARB would have the greatest pharmacology profile. The relationship between molecular promiscuity (the ability of a molecule to interact with multiple targets) and toxicity is well known.<sup>22</sup> Physicochemical properties such as high lipophilicity and MW have been suggested to correlate with higher promiscuity.<sup>59,60</sup> This is evident with telmisartan which showed greater potentially biologically relevant inhibitory activities (Table 4).

### 4.1 | Total ADRs and fatalities

Valsartan demonstrates a similar physicochemical profile to most of the ARB class (Table 3) with virtually no biologically relevant interactions, excluding AT<sub>1</sub> (Table 4). However, the research found that valsartan had statistically higher reported ADRs and fatalities per 100 000 Rx compared to the remaining ARBs (Table 5).

The disparity in ADR reporting rates with valsartan vs other ARBs could be due to the dissimilarity in the pharmaceutical excipients present in valsartan compared to other ARB comparators. The findings reveal that all ARBs had reported cases of ADRs related to the

gastrointestinal system, with valsartan having significantly higher reports. The exclusive presence of the excipient, sodium lauryl sulfate (SLS) in valsartan capsules may provide a rationale behind the reporting rate differences.<sup>61</sup> OpenPrescribing data showed a higher prescribing of the capsule forms (88% of all items dispensed) over both tablet and oral formulations. Investigations have shown that SLS has the propensity to trigger stomach irritation.<sup>62–64</sup> SLS is unique to valsartan capsules, so may contribute to the suspected gastrointestinal ADRs. Nevertheless, ADRs concerning SLS in pharmaceutical formulations are more associated with topical formulations.<sup>64</sup> Therefore, further clinical trials are required to establish whether there is a distinctive link between excipient in oral formulations and suspected ADRs reported.

Another rationale behind the variation in ADR reporting rates with valsartan vs comparable ARBs may be purely related to the comorbidities and concomitant drug use associated with valsartan. According to the National Institute for Health and Care Excellence (NICE) guidelines,<sup>65</sup> valsartan (alongside, candesartan and losartan) is one of the very few ARBs recommended to patients with comorbidities such as diabetes with hypertension. It is presumed that patients with comorbidities are likely to engage with polypharmacy. Studies illustrate that ADR risk increases disproportionately with a plethora of drugs administered.<sup>66,67</sup> Patients may become susceptible to drug–drug interactions and potentially generate ADRs associated with the concomitant use. Guidance stating the preferential ARB for management in comorbid conditions is unavailable. However, treatment for certain conditions is unique to valsartan, including the management of left ventricular systolic dysfunction after a recent MI.<sup>58</sup> The prevalence of comorbidities in patients and the choice of ARB may explain the difference in ADR reporting rate.

### 4.2 | Nervous/psychiatric ADRs and fatalities

Results depicted in Table 5 show that ADRs related to the nervous system are prevalent across all ARBs, decreasing from valsartan > irbesartan > candesartan > olmesartan > losartan > telmisartan. Studies suggest that physicochemical properties including MW, HB and lipophilicity are critical to BBB penetration.<sup>68,69</sup> The dissimilarity in physicochemical properties may explain the differences in reports. Lipid solubility is preferential for drug delivery across the BBB but may not guarantee adequate BBB penetration.<sup>70</sup>

The BBB predictions in Table 3 differ from published evidence of ARB BBB penetration. Sequential studies conclude that candesartan and telmisartan are the most effective ARBs at BBB penetration and even show efficacy in dose-dependent reductions in dementia incidence.<sup>71–73</sup>

Generally, lipid-soluble drugs have a large volume of distribution, thereby generating a higher tendency to partition out of the plasma and enter extravascular compartments.<sup>74,75</sup> The decreased drug serum concentration reduces the amount of drug presented to the BBB.<sup>75</sup> The greater lipophilicity and distribution observed in telmisartan may explain its reduced number of ADR reports.

Psychiatric suspected ADR reports were also prevalent across all ARBs. However, a definitive link between the pharmacology profiles and observed ADR could not be concluded.

### 4.3 | Neoplasms, benign, malignant and unspecified

As the pharmacology profiles of ARBs are similar, manufacturing contamination may be observable in suspected ADR reporting. As a note of caution, a study investigating the trends in ARB-associated neoplasm ADRs illustrates how drug recalls may inadvertently increase ADR reporting. Al-Kindi and Oliveira identified that the percentage of ADR reporting of valsartan compared to ARB comparators increased from 5.3% pre-recall to 23.4% post-recall.<sup>76</sup> The study concluded that the increase in the reporting of valsartan-associated cancers was biologically implausible and was likely associated with public apprehension following the media coverage.<sup>76</sup>

Trends were established via the Food and Drug Administration Adverse Events Reporting System (FAERS) but, the observed phenomenon may remain true within the UK. Data analysis from the Yellow Card Interactive Drug Analysis profile shows a steep and transient rise in ADR reporting of valsartan-associated cancers post-recall as reports increased from one to six between 2017 and 2018 and later declined.<sup>55</sup>

We found no statistical differences in reporting rates between irbesartan or losartan and other non-contaminated ARBs such as candesartan (Figure S2 in the Supporting Information) concerning cancer-related ADRs.

Therefore, no potential relationship can be drawn between the AZBT mutagenic contamination in irbesartan or losartan and increased susceptibility to cancer-associated ADRs. However, the exposed batches were only recently removed from the market during the most recent study year (2021).<sup>29</sup> However, this gives insight into longer term nitrosoamine contamination of irbesartan and losartan usage and at this stage no strong association with cancer prevalence. An increase in neoplasm ADRs reporting associated with losartan and irbesartan use may occur in the future as seen with valsartan. Therefore, caution should be exercised, and further investigation performed.

The results show that valsartan obtained more reported cases of cancer-related ADRs than other ARBs and the highest reported rate of fatalities. This may be due to decreases in prescribing following recalls and the longer time frame (2012–2018) when contamination of batches went undetected with nitrosoamines.

### 4.4 | Biologically relevant inhibition of non-AT<sub>1</sub> targets

After valsartan, olmesartan had the second most observed gastrointestinal ADRs. Olmesartan is associated with gastrointestinal symptoms resembling sprue-like enteropathy.<sup>77,78</sup> Studies have revealed

that this may be indicative of a class effect of ARBs.<sup>79–81</sup> The mechanistic rationale for this ADR is elusive but may be related to AT<sub>2</sub> receptor activation by angiotensin II.<sup>79,80</sup> AT<sub>1</sub> and AT<sub>2</sub> receptors are expressed throughout the gastrointestinal system. Evidence suggests that AT<sub>2</sub> receptors promote apoptosis of enterocytes.<sup>79</sup> ARBs predominantly have a high affinity for AT<sub>1</sub> receptors, which can lead to receptor saturation. Circulating angiotensin II can bind to unopposed AT<sub>2</sub> receptors, thus inducing receptor overstimulation, intestinal cell apoptosis and villous atrophy.<sup>79,80</sup> Telmisartan shows unique inhibition of the AT<sub>2</sub> receptor (IC<sub>50</sub> = 0.33 nM vs C<sub>max</sub> of 544 nM) (Table 4). Therefore, telmisartan may potentially be associated with reduced occurrence of enteropathy through telmisartan-induced inhibition of AT<sub>2</sub> receptor activity and further investigation is required.

Drug-induced liver injury can be mediated via BSEP inhibition. BSEP inhibitors facilitate the reduction of biliary bile salt leakage and bile flow.<sup>82</sup> Persistent BSEP inhibition may lead to bile salt accumulation within hepatocytes and, subsequently, the generation of acquired clinical cholestasis.<sup>82,83</sup> Our results indicate that irbesartan has a distinctive inhibition of BSEP (Table 4) and is supported by data reported by previous studies (irbesartan IC<sub>50</sub> = 17 µM).<sup>84</sup> Thus, amongst the ARBs, we predict that irbesartan may be associated with greater hepatobiliary disorders.

After valsartan, telmisartan obtained the second most reported ADRs and fatalities (5.35 and 0.06 per 100 000 Rx, respectively). Our results demonstrate that telmisartan exhibited a potent inhibitory effect towards CYP 2 J2 (Table 4), which correlates with the findings from similar studies.<sup>85,86</sup> CYP 2 J2 is involved in phase I metabolism.<sup>87</sup> Enzyme inhibition results in decreased metabolism of competing substrates. CYP P<sub>450</sub> isoenzymes are not believed to be involved in telmisartan metabolism; however,<sup>88</sup> patients taking concomitant CYP 2 J2-metabolised drugs may be predisposed to telmisartan-induced drug interactions. Inhibition of the CYP isoenzyme may elevate serum levels of the unmetabolised entity and induce exaggerated therapeutic or adverse effects.<sup>89</sup> Likewise, drugs that require biotransformation for activity may experience therapeutic failure leading to worsening of the disease.<sup>90</sup> Telmisartan-induced-CYP 2 J2 inhibition may explain why telmisartan had the second-highest reported ADRs and fatalities following standardisation.

CYP 2 J2 is well known to metabolise several other drugs such as astemizole, terfenadine, danazol<sup>91</sup> and potentially both telmisartan and flunarizine.<sup>85</sup> Inhibition of CYP 2 J2 with telmisartan (and other drugs) is likely to have cardioprotective effects including on inflammatory and vasodilation pathways via the arachidonic acid to epoxyeicosatrienoic acid pathway.<sup>92</sup>

Our findings show that losartan has inhibitory effects on SLCO1B1 (Table 4). The SLCO1B1 gene encodes for the organic anion transporter 1B1 (OATP1B1), which mediates the sinusoidal uptake of a variety of xenobiotics.<sup>93</sup> Co-administration of SLCO1B1 inhibitors, such as losartan, may prevent OATP1B1-mediated transport. Inhibition of transporter may elevate the serum exposure to OATP1B1 substrates and increase the risk of ADRs.<sup>94</sup> As losartan is an inhibitor of SLCO1B1, it may be associated with OATP1B1-inhibition-related

ADRs. Similarly, to rifampicin, inhibition of OATP1B1 transporters with losartan may lead to drug–drug interactions (DDIs).<sup>95</sup>

Losartan shows potent inhibitory effects towards ACE ( $IC_{50} = 19$  nM vs  $C_{max}$  of 591 nM) (Table 4). ACE is a pivotal component of the RAAS and is involved in the conversion of angiotensin-I to angiotensin-II.<sup>96</sup> Inhibition of ACE results in the reduced production of angiotensin-II, thereby lowering blood pressure. This activity is exploited by the antihypertensive ACE inhibitors. Dry cough is a symptom commonly associated with ACE inhibitors, although the pathogenesis remains controversial.<sup>97</sup> The degradation of bradykinin and substance P by ACE and their subsequent accumulation within the respiratory tract by ACE inhibitors remains a possible mediator to the development of ACE-inhibitor-induced cough.<sup>97,98</sup> An increase in bradykinin is suggested to evoke sensitisation of airway sensory nerves triggering cough symptoms.<sup>98,99</sup> The mechanistic differences of ARBs prevent them from interfering with ACE activity.<sup>97,98</sup> Losartan shows a unique inhibition of ACE and may have a greater frequency of cough-related ADRs. However, cough association with ARBs has been shown to be a confounding and not causal.<sup>100</sup>

## 5 | LIMITATIONS

Quantitative measurements concerning the  $IC_{50}$  values against human proteins were not provided for all targets on ChEMBL. Therefore, conclusions on the drug interactions with other target families cannot be made. Azilsartan and olmesartan bioactivity data were obtained from non-human targets, which may lead to the under- or over-estimation of inhibition in human targets.

Reported ADRs were obtained through the MHRA Yellow Card Scheme Interactive Drug Analysis Profiles. Spontaneous reporting schemes have several inherent weaknesses, specifically under-reporting. The estimated rate of under-reporting is said to range from 6 to 100%; thus,<sup>101</sup> underestimation of any given ADR may be encountered.

Additional factors can influence reporting: ADR publicity,<sup>102</sup> the length of time on the market and novelty of the drug. Such factors can make comparisons between drugs difficult, particularly when small numbers are involved. Furthermore, the Yellow Card Interactive Drug Analysis Profile provides reports irrespective of comorbidities, concomitant drug use, genetics, drug strength and formulation.

When considering the neoplasm (cancer) risk profile, that may be due to manufacturing contamination, several disparate factors require to be noted:

1. Nitrosoamine-contaminated generic sartans have been on the market since 2012. Small but chronic doses of a potential carcinogenic impurity (e.g., NDMA) may take many years to appear (potentially beyond the 5-year timeframe of this study).
2. Information on whether patients in the UK (or elsewhere) were exposed to specific contaminated or non-contaminated batches is

not available. Thus, a conclusion on cancer risk remains speculative in this study and others.

3. The most recent AZBT contamination led to recalls during the final months of this study, so is unlikely to have led to an uptick in cancer reports at this stage.
4. Media coverage can have a large influence on reporting, for example the nocebo case of statin-associated muscle symptoms.<sup>103</sup>
5. Candesartan, losartan and valsartan are also approved and recommended for chronic heart failure (CHF). Comorbidities and, hence, polypharmacy is frequent in these elderly patient populations and morbidity (hospitalisation) and mortality is high.

Conclusions concerning the safety and risk of a medicine cannot be generated based solely on the information provided in the Drug Analysis Profile,<sup>104</sup> only signal hypothesis generation. In addition, reporters do not have to prove causality to report a suspected ADR, only suspicion is required. Therefore, many suspected ADRs reported may not be linked to the drug.

## 6 | CONCLUSIONS

ARBs are effective antihypertensive agents applied to ameliorate negative effects on the cardiovascular system. This research has uncovered the suspected ADR rates for the ARB class. Additionally, we performed a detailed analysis of the pharmacology and physico-chemical properties of ARBs. The discrepancy between the chemical properties and pharmacology between ARBs was minimal, yet valsartan had statistically more reports of ADRs and fatalities. The limited valsartan pharmacological activity identified has made it difficult to establish a link between the pharmacology and suspected ADRs. However, this study has opened new avenues of research to dismiss any potential contributory factors. Investigation into the impact of comorbidity, concomitant drug use, or genetic variations on ADR profile may determine whether patient differences can statistically lead to variations in ADR frequency. Evaluation of the incidence of ADRs obtained by the sacubitril/valsartan formulation, Entresto™,<sup>105</sup> compared to other combined ARBs, may discover whether a high level of ADRs transpires with all valsartan–drug combinations.

The results for valsartan might have been caused by both an increased reporting frequency of suspected ADR (due to high media coverage and patient/health care professional awareness) and a significantly decreased prescribing frequency after the first recalls in July 2018 accompanied by an increased prescribing frequency for other ARBs.

Lastly, our findings indicate that there is currently insufficient information to link batch contamination and increased susceptibility to cancer-associated ADRs in valsartan, irbesartan and losartan-containing products, respectively, during the period of this study.



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## COMPETING INTERESTS

The authors have no conflicts of interest to declare.

## CONTRIBUTORS

H.S. carried out the data acquisition and analysis and interpretation and drafted the manuscript. A.M.J. conceived and designed the study including analysis and interpretation of data for the work and supervised, drafted and revised the manuscript. All authors gave final approval to the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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## SUPPORTING INFORMATION

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