BMJ Open

Effects of the July 2018 worldwide valsartan recall and shortage on global trends in antihypertensive medication use: a time-series analysis in 83 countries

Yuna Choi,[1] Araniy Santhireswaran,[1] Cherry Chu,[2] Katie J Suda,[3] Inma Hernandez,[4] Jared W Magnani ,[3] Mina Tadrous [1,2]

To cite: Choi Y, Santhireswaran A, Chu C, *et al*. Effects of the July 2018 worldwide valsartan recall and shortage on global trends in antihypertensive medication use: a time-series analysis in 83 countries. *BMJ Open* 2023;**13**:e068233. doi:10.1136/bmjopen-2022-068233

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068233).

Received 14 September 2022
Accepted 16 January 2023

For numbered affiliations see end of article.

Correspondence to
Dr Mina Tadrous;
mina.tadrous@utoronto.ca

ABSTRACT

Objectives This study aims to examine the effects of the July 2018 worldwide valsartan recall and shortage on global trends of antihypertensive medication use in 83 countries.

Methods A time-series analysis of monthly purchases of valsartan, other angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) across 83 countries from January 2017 to July 2020 was conducted using the IQVIA MIDAS database. Trends in outcomes were investigated globally and by economic level (developed vs developing economies). The valsartan recall's impact on antihypertensive use was assessed with interventional autoregressive integrated moving average modelling.

Results Global valsartan utilisation trends decreased significantly by 15.7% (−61 166 515 SU; p<0.0001), while global purchases of other ARBs increased by 44.8% (+958 069 420 SU; p=0.8523) and ACEIs increased by 1.6% (+44 106 747 SU; p=0.1102). Of the 32 developed countries, 20 (62.5%) showed a decline in 1-month percentage change in valsartan purchases, whereas only 10 out of 33 developing countries (30.3%) experienced a decrease in valsartan purchases. Mean 1-month, 3-month and 6-month percentage changes for developed countries were −1.2%, −9.3% and −12.2%, respectively, while the changes for developing countries were 25.0%, 7.3% and −1.2%.

Conclusions Global valsartan purchases substantially decreased post-recall, highlighting the far-reaching impacts of drug shortages. Opposing utilisation trends by economic level raise concerns of potential distribution of contaminated medications from developed countries to developing countries. Concerted actions for equitable global access to quality medications and mitigation of drug shortages are needed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our data set included a large number of countries and an extensive observational period of validated data from IQVIA MIDAS to provide a holistic analysis of this global issue.
⇒ A shortcoming of IQVIA-MIDAS data is the limited data on low-income, developing economies, where inequality gaps in drug access are greatest.
⇒ This study underestimates the full scope of the shortage in terms of total units since this analysis did not include valsartan combination products due to variability across countries.
⇒ Another limitation is the lack of prescription-level data, which prevents assessment of patient-level consumption and discontinuation, patient-switching to alternatives and pharmacy-level recalls.

INTRODUCTION

Valsartan, an angiotensin II receptor clocker (ARB), is a medication commonly used for the treatment of hypertension and heart failure.[1 2] On 5 July 2018, the European Medicines Agency (EMA) issued a recall of all medicines containing valsartan supplied by Zhejiang Huahai Pharmaceuticals, following the detection of an impurity, N-nitrosodimethylamine (NDMA).[1] NDMA is a probable carcinogen associated with liver toxicity and the occurrence of many forms of cancer.[3] The NDMA impurity is believed to have originated from unreported changes to Huahai's valsartan manufacturing process introduced in 2012.[1 4] Immediately following the EMA's announcement, Novartis, a customer of Huahai, voluntarily recalled over 2300 batches of valsartan products sent to 23 countries to protect users from the potentially carcinogenic contamination.[2] More than 23 countries across North America and Asia also issued valsartan recalls, and on 13 July 2018, the Food and Drug Administration issued a delayed recall compared with other countries.[2 5]

Recalls intend to protect the public from potentially harmful drug products. However,

despite its intentions, any disruption in drug manufacturing can lead to global drug shortages with detrimental effects on patient health outcomes and healthcare costs.[6–8] Evaluating the global impact of the valsartan recall is essential to understanding the varying effects of drug shortages on international healthcare systems and economies and provides a case example of the effects of disruption in drug access.[9] However, assessment of worldwide effects in response to the recall has been limited with previous studies focusing on the changes in valsartan use at the national or regional level.[10–12] This study aims to investigate the effects of the July 2018 valsartan recall and subsequent shortage on global utilisation trends of valsartan, ARBs and angiotensin-converting enzyme inhibitors (ACEIs) across 83 countries overall, and based on their economic development status.

METHODS

Study design and data source

An interrupted time-series analysis of global antihypertensive medication use between January 2017 and July 2020 was conducted. Monthly purchasing data of valsartan, ARBs excluding valsartan and ACEIs in 65 countries and 2 regional groups (Central America (n=6 countries) and French West Africa (n=12 countries)) between July 2014 and September 2020 were obtained from IQVIA MIDAS (Multinational Integrated Data Analysis System) (online supplemental appendix A table A1).[13] Venezuela was excluded from analysis due to hyperinflation. Purchasing data are expressed in standardised units (SU), which represents a single tablet/capsule for all antihypertensive medications being studied.[13–15] IQVIA-MIDAS covers 89.5% of all community-based and hospital-based pharmacy purchases of registered products.[16–18] Further database validation is included in online supplemental appendix B.

All available purchases of ARBs and ACEIs, including brands and generics, were extracted. MIDAS dataset organises medicines based on the Anatomic Therapeutic Chemical (ATC) classification system by WHO and identifies drugs based on their 3rd level ATC classification codes.[19] Only antihypertensives only single-entity ARBs and ACEIs are included to minimise differences between countries and various products that may not be consistent across global markets. IQVIA-MIDAS supplies aggregated data and contains no patient-level or facility-level information. Hence, this study did not require review by the institutional ethics board.

Data analysis

Monthly purchases of antihypertensives (valsartan, ARBs, ACEIs) were analysed in a global context and by economic development level. Total global purchases were calculated using data from 83 countries. Countries were then stratified based on the 2019 United Nations Conference

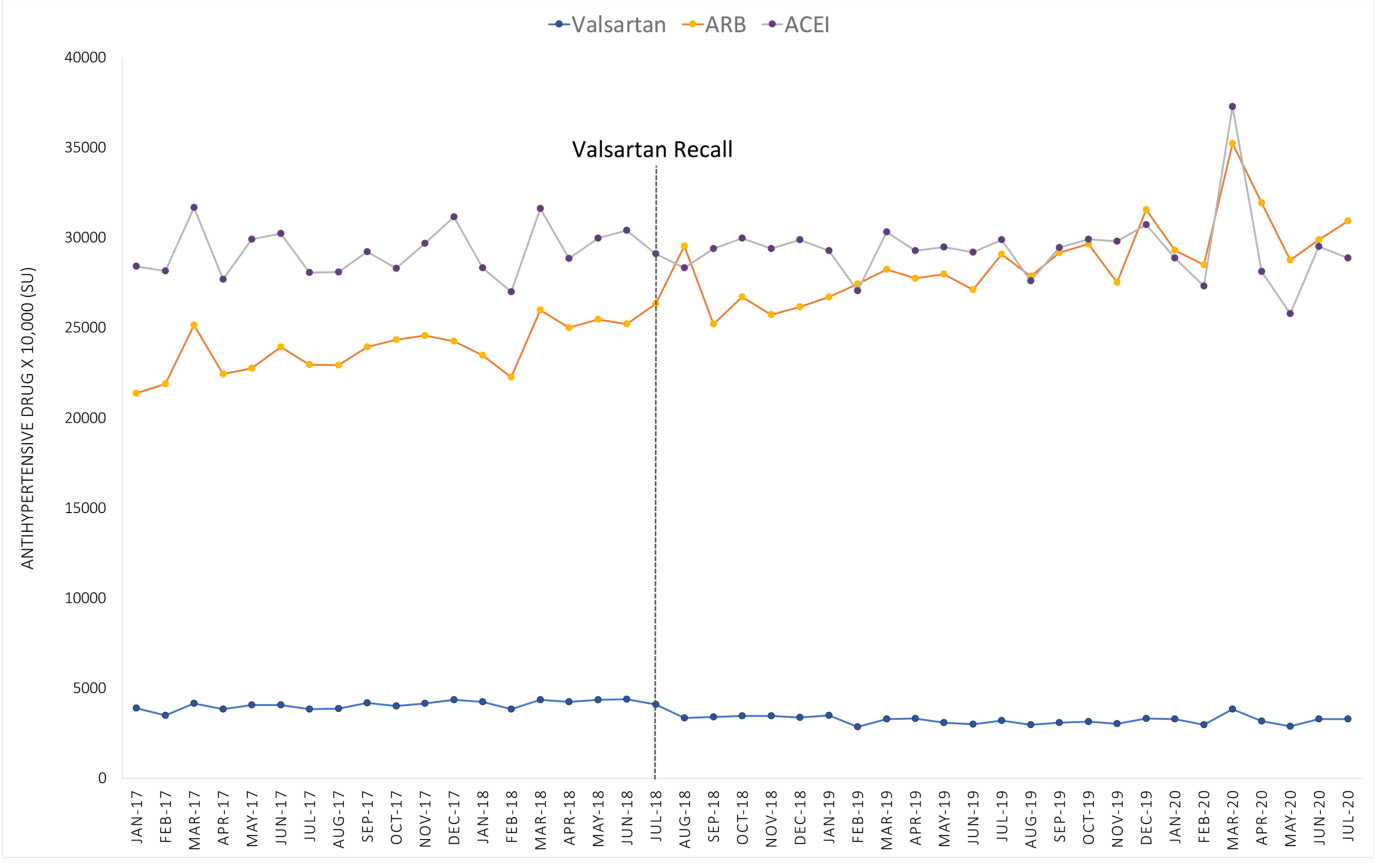

Figure 1 Global trends in monthly purchases of valsartan, non-valsartan ARBs and ACEIs between Jan 2017 and July 2020 in 83 countries. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

on Trade and Development's classification of economic development status.[13 20] Sixty-five countries were classified into two groups: 'developed economies' (n=32) and 'developing economies' (n=33), which included economies in transition. Regional groups were excluded from economic analysis since they included multiple countries of different economic levels. Changes in valsartan, ARB and ACE inhibitor purchases were measured between July and August 2018, globally and by economic level, to determine changes in utilisation immediately after the recall. Country-level differences in valsartan purchases were quantified as percentage changes comparing pre-recall to post-recall periods for each country. Total monthly valsartan purchases over 1-month, 3-month and 6-month periods from July 2018 were compared with the same periods in 2017. Quarterly and biannual totals were compared on a year-over-year basis to account for seasonal fluctuations.

Statistical analyses

Interventional-autoregressive integrated moving average (ARIMA) modelling was used to evaluate the statistical significance of the valsartan recall on global trends in antihypertensive use. ARIMA models assess time-series trends while accounting for seasonality and autocorrelation, which are common in drug utilisation.[21–23] Stationarity of the data was judged through multiple methods: the augmented Dickey-Fuller test, analysis of the autocorrelation function (ACF) and partial ACF plots, and optimisation of the SD of the series. In the case of non-stationarity, first-differencing was applied to the series to achieve stationarity. A step intervention function was used to analyse immediate changes in valsartan sale trends due to the recall.[24] We expected a delayed impact of the recall on ARB and ACEI purchases, therefore a ramp function was used to fit these models. The appropriate order of autoregressive and/or moving average terms to incorporate in the model was derived from the ACF and partial ACF plots of the differenced series. Model-fit was determined using the Ljung-Box test for white noise in order to analyse the residuals, and comparison of information criteria such as the Akaike Information Criterion.[24] P values less than 0.05 were considered statistically significant. All analyses were performed on SAS V.9.4.

Patient and public involvement

None.

RESULTS

Global trends

Valsartan

Across the study period (January 2017 to July 2020), global purchases of valsartan decreased by 15.7% from 390 657 161 SU to 329 490 646 SU (difference=−61 166 515) (figure 1). Overall consumption sharply declined in developed economies (−30.0%) from 223 587 043 SU to 156 567 837 SU (difference=−67 019 206), while developing economies showed an increase (+3.5%) from 166 580 668 SU to 172 375 551 SU (difference=+5 794 883) (figure 2). The changes in monthly purchases were statistically significant globally (p<0.0001) and by economic

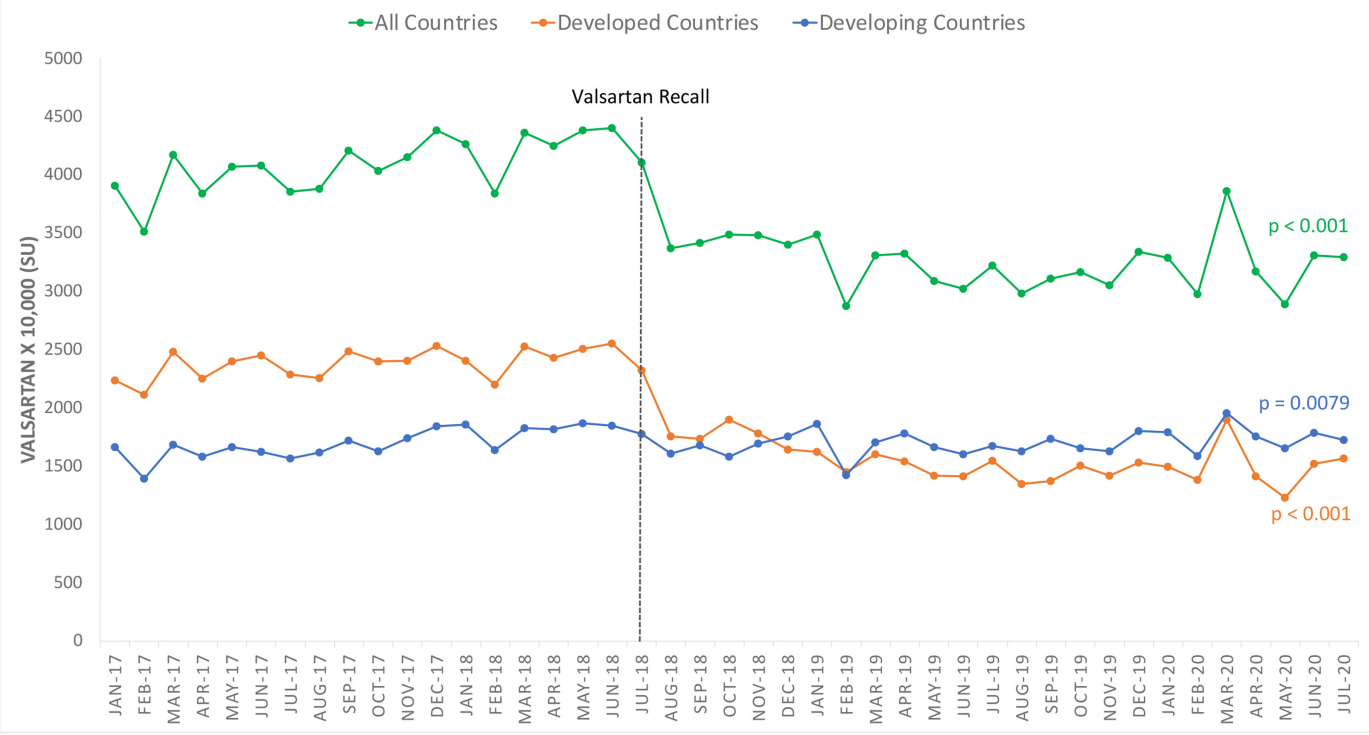

Figure 2 Global trends in monthly purchases of valsartan between January 2017 and July 2020 in 83 countries and by economic development status (developed: 32 countries; developing: 33 countries).

Table 1 Changes in antihypertensive purchases between January 2017 and July 2020

Drugs/drug classes	January 2017–July 2020 (%)	P value	July 2018–August 2018 (%)
Valsartan	−15.7	<0.0001	−17.9
Developed countries	−30.0	<0.0001	−24.4
Developing countries	+3.5	0.0079	−9.5
ARBs excluding valsartan*	+44.8	0.8532	+12.2
Developed countries	+37.6	0.1186	−3.5
Developing countries	+50.8	0.5875	+24.3
ACE inhibitors*	+1.6	0.1102	−2.7
Developed countries	+3.3	0.0003	−3.3
Developing countries	−0.7	0.4343	−1.8

*P value derived from ramp intervention function on time series.
†P value derived from step intervention function on time series.
ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

level (developed: p<0.0001, developing: p=0.0079) (table 1). Monthly valsartan purchases decreased by 17.9% (−73 567 639 SU) globally from July to August 2018. Specifically, developed countries showed a decline of 24.4% (−56 616 235 SU), whereas developing economies only observed a decrease of 9.5% (−16 868 364 SU).

Per cent changes of post-recall valsartan utilisation compared with pre-recall utilisation based on economic status, initially decreased in developed economies and increased in developing economies. 1-month and 3-month per cent changes in valsartan purchases were −1.2% and −9.3% for developed economies, but 25.0% and 7.3% for developing economies. Though developed economies previously showed greater pre-recall valsartan purchases over their developing counterparts, their valsartan use progressively diminished, eventually falling below developing economies by December 2018. Therefore, a clear shift in patterns of use between developed and developing economies is evident.

Non-valsartan ARBs

Overall utilisation trends of non-valsartan ARBs were similar globally and by economic level. A 44.8% (+957 069 420 SU) increase in global ARB purchases was observed, where developed economies experienced an increase of 37.6% (+365 442 234 SU) and developing economies of 50.8% (+588 972 714 SU) (figure 3). In August 2018, global ARB purchases increased by 12.2% (+322 018 679 SU), and accordingly developing economies observed a 24.3% (+361 605 323 SU) increase, while developed economies

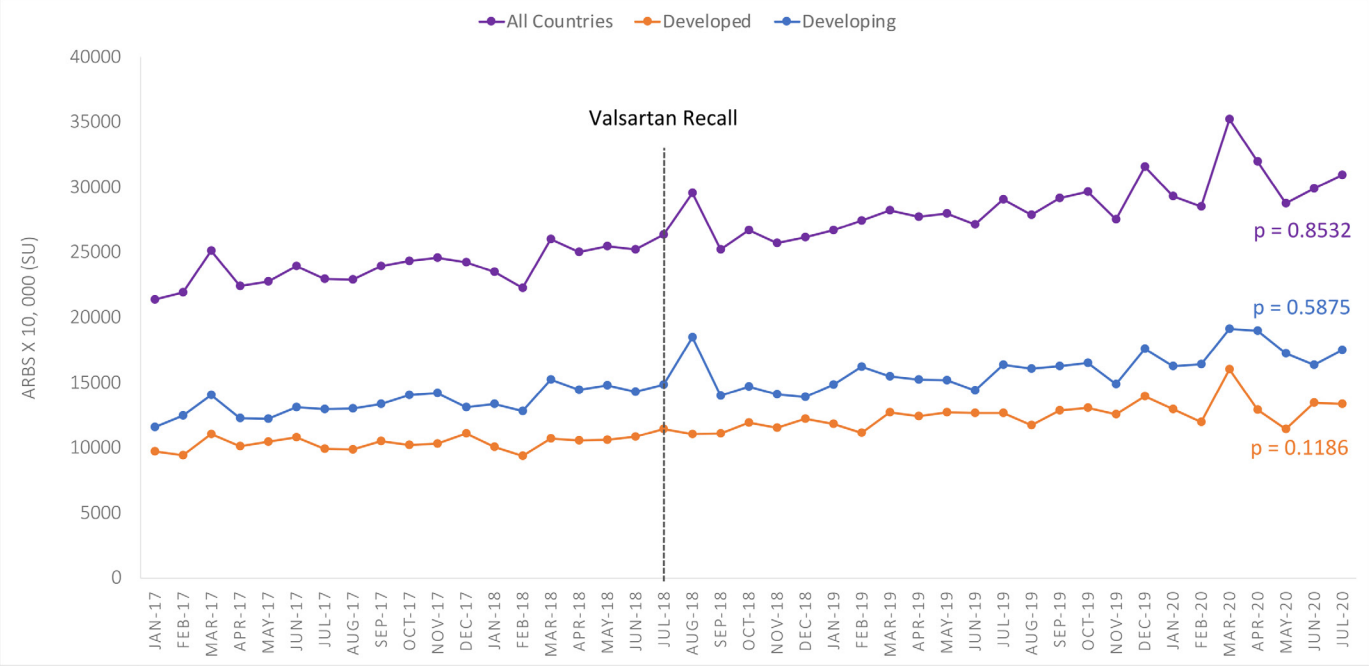

Figure 3 Global trends in monthly purchases of ARBs between January 2017 and July 2020 in 83 countries and by economic development status (developed: 32 countries; developing: 33 countries). ARB, angiotensin II receptor blocker.

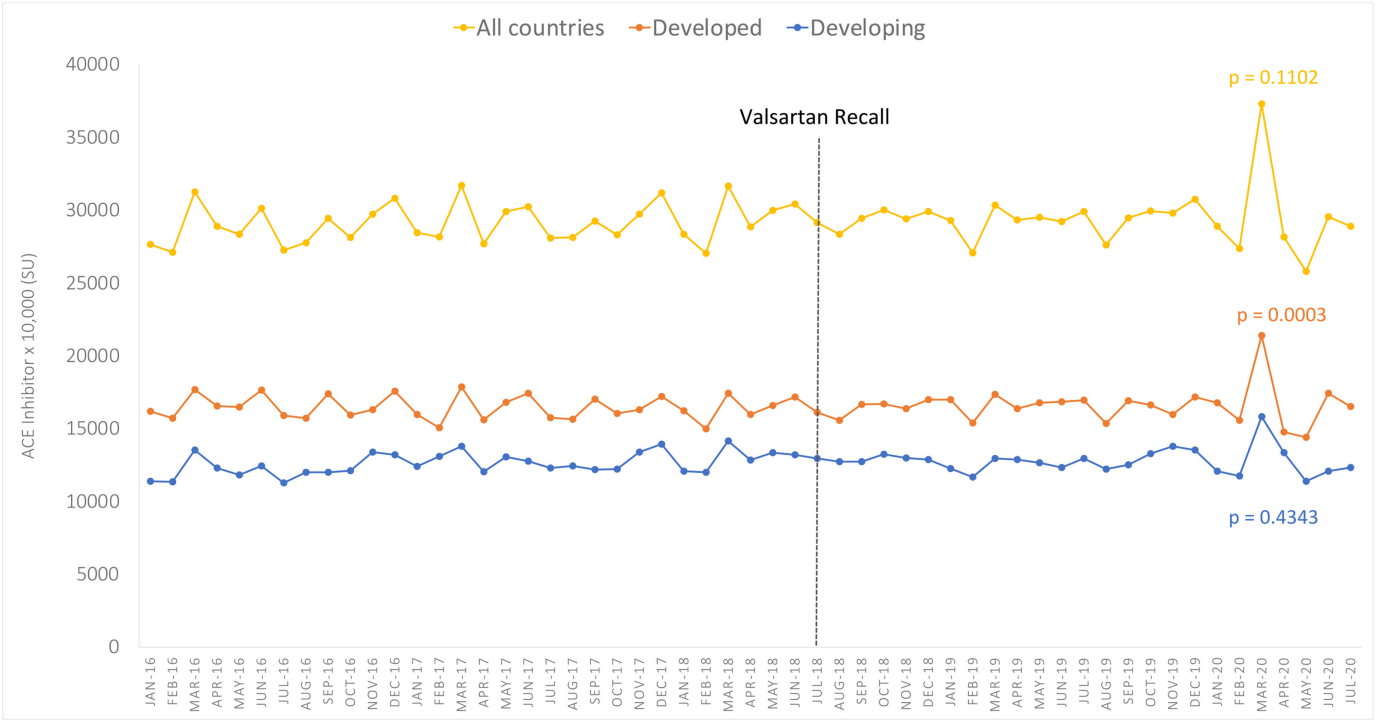

Figure 4 Global trends in monthly purchases of ACE inhibitors in January 2017 to July 2020 in 83 countries and by economic development status (developed: 32 countries; developing: 33 countries). ACE, angiotensin-converting enzyme.

showed a 3.5% (−39 589 891 SU) decrease. Throughout the study period, developing economies showed greater changes in ARB purchases than developed economies, as opposed to valsartan and ACEI purchases. In March 2020, all ARB purchases amplified with a 44.8% (+673 060 174 SU) global surge compared with February 2020 (developed: 33.5% (+402 562 483 SU), developing: 16.3% (+268 581 702 SU)). However, there was no significant impact on ARB use in response to the valsartan recall (table 1).

Angiotensin-converting enzyme inhibitors

ACEI consumption did not change substantially after the valsartan recall (figure 4). Global ACEI purchases increased by 1.6% (+44 106 747 SU) (developed: 3.3% (+52 199 501 SU), developing: −0.7% (−8 685 338 SU)) across the study period. Monthly ACEI purchases decreased by 2.7% (−77 063 592 SU) in August 2018. Utilisation trends in ACEI were statistically significant for developed economies (p=0.0003), but not globally (p=0.1102) or for developing economies (p=0.4343) (table 1). ACEI purchases also increased in March 2020 (global: 36.4% (+996 274 287 SU), developed: 37.5% (+583 516 420 SU), developing: 35.0% (+410 212 368 SU)).

Trends in valsartan sales by country

In July 2018, 20 out of 32 (62.5%) developed economies had reductions in 1 month (July–Aug) valsartan purchases relative to July 2017 (figure 5A). The largest decreases were observed in Czech Republic (−74.5%), Austria (−72.9%) and Norway (−52.2%) (online supplemental appendix A table A2). The countries with developed economies with the greatest increases in purchases were Finland (169.1%), Ireland (75.2%) and Estonia (41.1%) (online supplemental appendix A table A3). Of the 12 developed economies that experienced increased 1-month per cent change, 9 countries had sustained growths of valsartan purchases indicated by 6-month per cent changes. In July 2018, 23 out of 33 (70%) countries with developing economies showed increased 1-month valsartan purchases (figure 5B). The largest increases were in Kazakhstan (487.3%), Thailand (99.4%) and South Korea (85.7%), and the greatest reductions were in Peru (−89.9%), Pakistan (−61.1%) and Puerto Rico (−45.4%).

For developed economies, the 3-month and 6-month per cent changes showed gradually declining trends (figure 5A) (online supplemental appendix A table A2). For developing economies, increased purchases were observed in 21 countries for the 3-month period and 18 countries for the 6-month period (online supplemental appendix A table A3). On average, the 1-month per cent change was −1.2% in developed economies but +25.04% for developing economies (online supplemental appendix C figure C1). The 3-month and the 6-month changes in total valsartan purchases in developed economies were −9.3% and −12.2%, respectively, and +7.3% and −1.2%, respectively, in developing economies (online supplemental appendix C figures C2 and C3).

DISCUSSION

Global valsartan utilisation significantly dropped after the valsartan recall, and results revealed divergence in

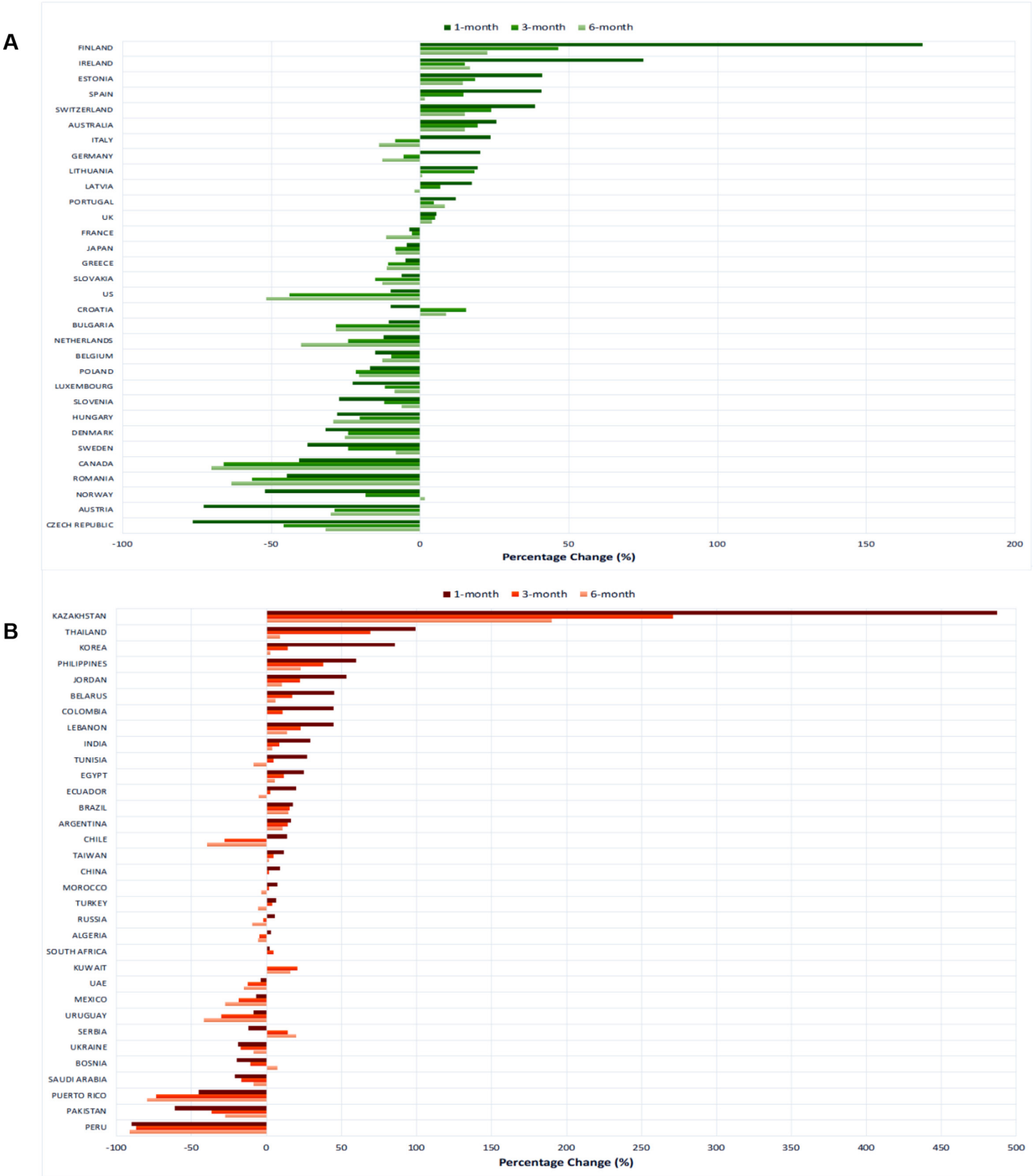

Figure 5 Country-level percentage changes (%) in valsartan purchases in 32 developed countries (A), 33 developing countries (B): total % change over 1 month (July 2017 vs July 2018), 3 months (July–Sep 2017 vs July–Sep 2018) and 6 months (July–Dec 2017 vs July–Dec 2018).

valsartan purchasing across economic levels. Importantly, developed economies exhibited a significant decrease in valsartan use after the global recall, while developing economies showed slightly increased valsartan use. The reduction in global valsartan purchases demonstrates the far-reaching global impacts due to the globalisation of drug supply chains and in turn their increased vulnerability to disruptions. Moreover, the opposing trends in

valsartan utilisation by economic level indicate the disproportionate burden of drug shortages on developing economies as well as the potential for contaminated drugs from developed economies being discarded in developing economies. Inequality in drug utilisation across economies may be inevitable during shortages, leaving developing economies to face the brunt of this burden (online supplemental appendix D).

This study highlights the global implications of multinational drug manufacturing processes that previous studies have attributed to globalisation.[25] The valsartan recall triggered declining trends in valsartan purchases globally and in developed economies, with increased usage of non-valsartan ARB. Gradual recalls as health authorities updated the affected lots and as other manufacturers in China and India detected similar impurities in late 2018, may also account for the lack of recuperation in valsartan use.[26 27] With globalisation of drug manufacturing favouring outsourcing to developing countries with cheaper costs and higher production efficiency, China accounts for 40% of global active pharmaceutical ingredient manufacturing and plays a leading role as the sole-source for many medications.[28] Yet, this high concentration exacerbates the risks of supply chain disturbances and drug shortages.[29–31] Although many studies have discussed issues stemming from global manufacturing and drug shortages, little is understood about the causes to the complexity and opaqueness of global supply chains.[8 9 28 32 33] The increase in uncertainty behind shortages is concerning—for example, the causes behind USA drug shortages in 2020 were 51% unknown,[34] suggesting the lack of transparency in the pharmaceutical industry.

Trends in valsartan purchases were dissimilar across economies, demonstrating the gaps in access to medicine and use. Differences can be due to variations in country-level response to drug recalls and shortages, which is strongly linked to economic development.[9 32 33] The mild decrease in developed economies can be attributed to their greater stability and resilience of drug supply chains. Developing economies experienced a 25.0% increase in valsartan use, whereas developed economies showed a 1.22% decrease over 1 month after the recall. The larger increasing trend for non-valsartan ARBs in developing economies is concerning, since generic irbesartan and losartan were also recalled globally in 2018 and 2019.[26 27] The drastic increase in developing economies may alarmingly suggest the use of potentially contaminated drugs that were discarded by countries with developed economies. Developing economies often use inexpensive drugs when pressures of cost and unavailability of medicines are high. Substandard and falsified medications account for 25% of medicine consumed in low/middle-income countries, explaining the increase in valsartan use in developing economies.[35]

The causes of drug shortages are multifactorial[10] and require considerations of economic level, healthcare system management and generic market share of each country.[32] Reasons may include differences in medicine procurement (regional vs fragmented), national pharmaceutical market, domestic manufacturing and legislation for pharmaceutical industries. While recalls and shortages pervade globally, discrepancies in national regulatory policies and actions can widen the gap among countries. Efforts by regulatory agencies to protect drug supply chains are especially important, as pharmaceutical regulations vary across countries. As implementation depends on national authorities,[36] ineffective regulations and weak enforcement capacities in one nation may corrupt the global supply chain.[37] Irrespective of the cause, drug shortages result in global impacts with acute and chronic consequences.

Global impacts of the valsartan shortage highlight the urgent need for a coordinated system that ensures drug access for all patients. Although extensive measures for drug shortage mitigation are placed in the USA and European countries, they are scarce in developing economies, thus preventing a complete understanding of the underlying mechanisms of ongoing shortages. Even more, with the pharmaceutical industry and political power deeply entangled, achieving equitable global access to medications is complex.[38] Therefore, research to identify the priorities of international stakeholders and unpredictable risks within the multinational stages of supply chains is critical to preventing disruptions. Harmonised action and communication with cross-national collaboration for a globalised response has been recommended by numerous organisations and studies to prevent drug shortages.[9 32 38 39] With in-depth knowledge and specific mitigation strategies, we will be able to navigate the unpredictability of current global drug supply chains and respond to their disruptions. Moreover, ARBs have been associated with increased cancer risk even prior to the 2018 NMDA contamination. Several other ARBs including irbesartan and losartan have also been recalled due to carcinogenic impurities.[40 41] However, the extent of these recalls was not as broad as the valsartan recall and therefore we focused on the valsartan recall and its impact on utilisation of related ARBs for the purpose of this study. Although, future research should further study the relationship between cumulative exposure to ARBs and cancer risk to better understand their implications for patient drug use and safety.

Our study has several limitations that warrant discussion. First, IQVIA-MIDAS data on low-income, developing economies, where inequality gaps in drug access are greatest, are limited.[9] Second, this analysis did not include valsartan combination products due to variability across countries. Because combination products were a part of the recall,[25 27] this study underestimates the full scope of the shortage in terms of total units. Another limitation is the lack of prescription-level data, which prevents assessment of patient-level consumption and discontinuation, patient-switching to alternatives and pharmacy-level recalls.

CONCLUSION

Drug shortages have grown as a global threat in frequency, intensity and duration. Importantly, the major vulnerability of global supply chains to disruptions caused by drug manufacturing and quality issues is highlighted by steep, persistent decreases in global valsartan purchases. The unequal impacts of drug recalls and subsequent shortages across countries and especially economic levels emphasise the need for multisector collaboration at both national and international levels. Unified action with shared goals to safeguard adequate supplies of medications for all populations is essential. Future research in creating sustainability and resilience through various modalities is necessary to prevent further burden on the healthcare system.

Author affiliations
[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada
[2]Women's College Hospital, Toronto, Ontario, Canada
[3]Center for Health Equity Research and Promotion, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA
[4]University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, California, USA

Twitter Jared W Magnani @jared_w_magnani and Mina Tadrous @mina__T

Contributors All authors contributed to the study design, curation and interpretation of data, and drafting and revising the manuscript. MT was the guarantor and was responsible for the conceptualisation and project administration of the study. MT, CC, KJS, IH and JWM were responsible for project supervision. YC led the methodology and formal analysis, while AS and YC took lead roles in writing the original manuscript draft. All authors have validated all data and conclusions made, approved the final manuscript and are accountable for all aspects of this study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data presented in this manuscript are contained within the figures and tables in the manuscript, no further data will be shared.

ORCID iDs
Jared W Magnani http://orcid.org/0000-0002-5075-3604
Mina Tadrous http://orcid.org/0000-0003-1911-6129

REFERENCES

1 EMA. EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity. European Medicines Agency; 2018. Available: https://www.ema.europa.eu/en/news/ema-reviewing-medicines-containing-valsartan-zhejiang-huahai-following-detection-impurity-some [Accessed 11 Feb 2022].
2 Farrukh MJ, Tariq MH, Malik O, *et al*. Valsartan recall: global regulatory overview and future challenges. *Ther Adv Drug Saf* 2019;10:2042098618823458.
3 Toxicological profile for N-nitrosodimethylamine (NDMA). CDC. Available: https://www.atsdr.cdc.gov/toxprofiles/tp141-c1.pdf [Accessed 21 Jan 2022].
4 EMA. Sartans art 31. Europa.eu. Available: https://www.ema.europa.eu/en/documents/variation-report/angiotensin-ii-receptor-antagonists-sartans-article-31-referral-chmp-assessment-report_en.pdf [Accessed 12 Feb 2022].
5 Office of the Commissioner. FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity. U.S. Food and Drug Administration; 2018. Available: https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity [Accessed 12 Mar 2022].
6 Institute CD, HOWE Institute. Assessing canada's drug shortage problem [Internet]. Available: https://www.cdhowe.org/sites/default/files/2021-12/Commentary_515.pdf [Accessed 4 Mar 2022].
7 *Assessing relationships between drug shortages in the United States and other countries*. RAND Corporation, 2021.
8 Ventola CL. The drug shortage crisis in the united states: causes, impact, and management strategies. *P T* 2011;36:740–57. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278171/
9 Shukar S, Zahoor F, Hayat K, *et al*. Drug shortage: causes, impact, and mitigation strategies. *Front Pharmacol* 2021;12:693426.
10 Fenna J, Chu C, Hassan R, *et al*. Extent of a valsartan drug shortage and its effect on antihypertensive drug use in the canadian population: a national cross-sectional study. *CMAJ Open* 2021;9:E1128–33.
11 Rudolph UM, Enners S, Kieble M, *et al*. Impact of angiotensin receptor blocker product recalls on antihypertensive prescribing in germany. *J Hum Hypertens* 2021;35:903–11.
12 Jackevicius CA, Krumholz HM, Chong A, *et al*. Population impact of generic valsartan recall. *Circulation* 2020;141:411–3.
13 IQVIA. Global medicines use in 2020. 2015. Available: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-medicines-use-in-2020 [Accessed 24 Feb 2022].
14 IQVIA. ACTS 2019. Available: https://www.iqvia.com/ publications/acts-2019-33rd-edition-quality-assurance-report-of-iqvia [Accessed 10 Mar 2022].
15 IQVIA. ACTS 2018. Available: https://www.iqvia.com/-/media/iqvia/pdfs/library/publications/acts-2018-32nd-edition.pd [Accessed 10 Mar 2022].
16 Zeitouny S, Suda KJ, Mitsantisuk K, *et al*. Mapping global trends in vaccine sales before and during the first wave of the COVID-19 pandemic: a cross-sectional time-series analysis. *BMJ Glob Health* 2021;6
17 Yan VKC, Blais JE, Li X, *et al*. Trends in cardiovascular medicine use in 65 middle- and high-income countries. *J Am Coll Cardiol* 2021;77:1021–3.
18 Blais JE, Wei Y, Yap KKW, *et al*. Trends in lipid-modifying agent use in 83 countries. *Atherosclerosis* 2021;328:44–51.
19 WHOCC. WHOCC - ATC/DDD index. Whocc.no. Available: https://www.whocc.no/atc_ddd_index/ [Accessed 21 Mar 2022].
20 United Nations Conference on Trade and Development (UNCTAD). World economic situation and prospects 2019. Available: https://unctad.org/system/files/official-document/wesp2019_en.pdf [Accessed 20 Jan 2022].
21 Schaffer AL, Dobbins TA, Pearson S-A. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol* 2021;21:58.
22 Jandoc R, Burden AM, Mamdani M, *et al*. Interrupted time series analysis in drug utilization research is increasing: systematic review and recommendations. *J Clin Epidemiol* 2015;68:950–6.
23 Li L, Cuerden MS, Liu B, *et al*. Three statistical approaches for assessment of intervention effects: a primer for practitioners. *Risk Manag Healthc Policy* 2021;14:757–70.
24 Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA)

models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol* 2021;21:58.
25 Ifpma.org. The globalisation of the pharmaceutical industry. Available: https://www.ifpma.org/wp-content/uploads/2016/11/The-Globalisation-of-the-Pharmaceutical-Industry-Monograph.pdf [Accessed 1 Apr 2022].
26 Health. Expansion of recall of valsartan drugs to include additional lots, as a precaution. Canada.ca; 2021. Available: https://recalls-rappels.canada.ca/en/alert-recall/expansion-recall-valsartan-drugs-include-additional-lots-precaution [Accessed 22 Mar 2022].
27 Center for Drug Evaluation, Research. FDA updates & press on ARB recalls: valsartan, losartan and irbesartan. U.S. FDA; 2021. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan [Accessed 22 Mar 2022].
28 Marriott W, Center M. Identifying the root causes of drug shortages and finding enduring solutions. Duke.edu; 2018. Available: https://healthpolicy.duke.edu/sites/default/files/2020-02/presentation_slides__0.pdf [Accessed 12 Mar 2022].
29 Woo J, Wolfgang S, Batista H. The effect of globalization of drug manufacturing, production, and sourcing and challenges for american drug safety. *Clin Pharmacol Ther* 2008;83:494–7.
30 Alexandra Harney BH. Toxin at heart of drug recall shows holes in medical safety net. Reuters. Available: https://www.reuters.com/article/us-health-pharmaceuticals-china-insight [Accessed 21 Mar 2022].
31 Colon C, Brännström Å, Rovenskaya E, *et al*. Fragmentation of production amplifies systemic risks from extreme events in supply-chain networks. *PLoS One* 2020;15:e0244196.
32 Acosta A, Vanegas EP, Rovira J, *et al*. Medicine shortages: gaps between countries and global perspectives. *Front Pharmacol* 2019;10:763.
33 Badreldin HA, Atallah B. Global drug shortages due to COVID-19: impact on patient care and mitigation strategies. *Res Social Adm Pharm* 2021;17:1946–9.
34 Pppmag.com. An update on the state of drug shortages: July 2021 - pharmacypurchasing & products magazine. Available: https://www.pppmag.com/article/2764 [Accessed 1 Apr 2022].
35 Kohler J, Martinez M, Petkov M, *et al*. Corruption in the pharmaceutical sector: diagnosing the challenges. World Health Organization; 2016. Available: https://www.transparency.org.uk/sites/default/files/pdf/publications/29-06-2016-Corruption_In_The_Pharmaceutical_Sector_Web-2.pdf [Accessed 25 Mar 2022].
36 Lybecker K. Pharmaceutical counterfeiting: endangering public health, society and the economy. Fraser Institute; 2018. Available: https://www.fraserinstitute.org/sites/default/files/pharmaceutical-counterfeiting-endangering-public-health-society-and-the-economy.pdf [Accessed 28 Mar 2022].
37 Christian L, Collins L, Kiatgrajai M, *et al*. The problem of substandard medicines in developing countries. WISC; 2012. Available: https://lafollette.wisc.edu/images/publications/workshops/2012-medicines.pdf [Accessed 28 Mar 2022].
38 Access to medicines: making market forces serve the poor. WHO. Available: https://www.who.int/publications/10-year-review/chapter-medicines.pdf [Accessed 1 Mar 2022].
39 Drug Shortages Canada. Multi-stakeholder steering committee on drug shortages multi-stakeholder toolkit. 2017. Available: https://www.drugshortagescanada.ca/files/MSSC_Tool kit_2017.pdf [Accessed 28 Feb 2022].
40 Sipahi I, Debanne SM, Rowland DY, *et al*. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol* 2010;11:627–36.
41 Sipahi I. Risk of cancer with angiotensin-receptor blockers increases with increasing cumulative exposure: meta-regression analysis of randomized trials. *PLoS One* 2022;17:e0263461.