
Article:
Batty, JA orcid.org/0000-0003-4102-5418 and Hall, M (2023) Trends in ACEi and ARB expenditure: Compelling case for competition in generic drug markets. International Journal of Cardiology, 370. pp. 419-420. ISSN 0167-5273

https://doi.org/10.1016/j.ijcard.2022.11.027

Editorial

Trends in ACEi and ARB expenditure: a compelling case for competition in generic drug markets

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) inhibit the renin-angiotensin-aldosterone system (RAAS). The RAAS is an elegant cascade of vasoactive peptides that orchestrates key homeostatic processes[1]. In response to hypotension, hypo-osmolality or beta-adrenergic stimulation, the kidneys secrete renin, which cleaves circulating angiotensinogen to angiotensin I. Angiotensin converting enzyme (ACE) catalyses the conversion of angiotensin I into angiotensin II and hydrolyses bradykinin. Angiotensin II acts on AT_1 receptors in the arterioles, kidney, adrenal cortex, and brain to stimulate vasoconstriction, sodium reabsorption and thirst; synergistically increasing blood pressure. Overactivity of the RAAS leads to deleterious cardiac remodelling after myocardial infarction and is central to the pathophysiology of hypertension, heart failure, diabetes mellitus and chronic kidney disease. As such, the development of drugs that inhibit the RAAS was a major strategic priority for pharmaceutical companies in the second half of the 20^{th} century.

Following observations that inhibition of ACE led to reductions in blood pressure, the prototypical oral ACEi – captopril – was approved as an antihypertensive agent in 1981. Through a series of placebo-controlled randomised trials, ACEis were proven to reduce adverse outcomes across a number of cardiovascular disease states. However, the use of ACEis in some patients was limited by bradykinin-mediated side effects, including cough and angioedema. This encouraged the development of direct-acting, selective AT_1 receptor blockers (ARBs). The first agent of this class – losartan – was approved in 1995. ARBs demonstrated non-inferiority to ACEis in clinical endpoints, with a better side-effect profile.

Although initially protected by pharmaceutical patents and sold as branded products by their developers, generic forms of ACEis became available in 2000, followed a decade later by generic ARBs. These generic forms are therapeutically equivalent to the original formulations but can be produced by any manufacturer, creating competition and typically resulting in lower prices. However, this is not always the case: manufacturer consolidation, closed distribution systems, raw material shortages and stringent manufacturing standards (in addition to specific cases of alleged price fixing) mean that generic drugs are not always low in cost[2]. The ACEi and ARB classes remain among the most widely prescribed in the United States (US)[3]. As the number of people for whom treatment with these agents is indicated is expected to increase as a result of the global demographic transition towards population ageing and multimorbidity, evaluating secular trends in ACEi and ARB expenditure is highly relevant.

Previously, Bian *et al* reported ACEi and ARB utilisation and expenditure in the US Medicaid programs, from 1991 to 2008[4]. Medicaid provides healthcare coverage for low-income adults, children, pregnant women, older adults and people with disabilities. After adjustment for inflation, the introduction of generic formulations of ACEis led to a 59.2% reduction in the cost of ACEi reimbursements. Over the same period, the cost of branded ARBs increased by 51.7%. Remarkably, this study noted the persistence of branded ACEi use despite the availability of bioequivalent, cheaper, generic alternatives. Overall, by maximising the prescription of generic products, Bian *et al* suggested potential cost savings to Medicaid of up to $142.3 million (of a total ACEi/ARB-related expenditure of $309.8 million, in 2008).

In this issue of IJC, Almadfaa *et al* present contemporary follow-up to the work by Bian *et al*, and evaluate ACEi and ARB prescriptions and expenditure patterns in the US Medicaid programs, from 1991 to 2021[5]. Using open access Medicaid pharmacy data, the authors make a number of important observations. Firstly, the improved availability and utilisation of generic formulations has led to a dramatic fall in the overall cost of these drug classes. However, counterintuitively, branded ARB utilisation and expenditure has risen markedly in recent years. This likely reflects the impact of the PARADIGM-HF study, which demonstrated the superiority of the combination of an ARB (valsartan) with a novel neprilysin inhibitor (sacubitril) over an ACEi (enalapril), in reducing mortality in heart failure[6]. This formulation remains on-patent for the foreseeable future. Secondly, the authors report a significant drop-off in utilisation of generic ACEi and ARBs during 2019 and 2020. Although now refuted by empirical data[7], there was speculation early in the COVID-19 pandemic that ACEis and ARBs may be harmful in patients with COVID-19 infection[8]. Concurrently, a number of generic ARBs were recalled due to the presence of carcinogenic nitrosamine impurities[9]. Although these factors may have impacted negatively on ACEi and ARB prescribing, huge increases in the average prices of branded agents were seen during this period, as brought to light by Almadfaa and colleagues.

The major strengths of this study by Almadfaa *et al* are the scale of their data (including 548 million prescriptions) and the 31-year follow up period. However, the analysis of Medicaid pharmacy data is limited by the lack of an accurate population denominator, on account of continual enrolment changes as a result of changes to legislation (e.g., the Medicare Prescription Drug Plans [Part D] in 2006). By performing direct standardisation to a reference population and reporting age- and sex-adjusted prescription rates per 100,000 enrolees, it would have been possible to suppress artefactual trends in prescription rates observed as a consequence of ever-changing enrolment, and emphasise changes due

to differences in prescribing behaviour. Furthermore, only prescription-level data were available, precluding any inference regarding individual indications, dosing patterns or medication adherence.

In summary, despite four decades since their introduction, ACEis and ARBs remain a cornerstone in the management of cardiovascular disease. The trends reported by Almadfaa *et al* in this issue of IJC provide a compelling case for the existence of a competitive, regulated market of bio-equivalent, generic drugs[10]. Combined with strategies that encourage the prescription of generic formulations over their branded counterparts, this ensures that drugs remain affordable to healthcare systems and available to patients. Future work – in collaboration with health economists – should seek to identify determinants of generic prescribing behaviour and must lead to behavioural, legislative and regulatory interventions that may further improve the global affordability of these important agents.

[975 / 1,000 words, 10 / 10 references]

References

[1] Mentz RJ, Bakris GL, Waeber B, McMurray JJV, Gheorghiade M, Ruilope LM, et al. The past, present and future of renin–angiotensin aldosterone system inhibition. International Journal of Cardiology. 2013;167:1677-87.

[2] Frank RG, McGuire TG, Nason I. The Evolution of Supply and Demand in Markets for Generic Drugs. Milbank Q. 2021;99:828-52.

[3] Fuentes AV, Pineda MD, Venkata KCN. Comprehension of Top 200 Prescribed Drugs in the US as a Resource for Pharmacy Teaching, Training and Practice. Pharmacy (Basel). 2018;6.

[4] Bian B, Kelton CM, Guo JJ, Wigle PR. ACE Inhibitor and ARB utilization and expenditures in the Medicaid fee-for-service program from 1991 to 2008. J Manag Care Pharm. 2010;16:671-9.

[5] Almadfaa RO, Wigle PR, Hincapie AL, Guo JJ. The utilization, expenditure, and price of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the US Medicaid programs: Trends over a 31 year period. International Journal of Cardiology. 2022.

[6] McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. New England Journal of Medicine. 2014;371:993-1004.

[7] Fernando ME, Drovandi A, Golledge J. Meta-analysis of the association between angiotensin pathway inhibitors and COVID-19 severity and mortality. Systematic Reviews. 2021;10:243.

[8] Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020;38:781-2.

[9] Shephard EA, Nawarskas JJ. Nitrosamine Impurities in Angiotensin Receptor Blockers. Cardiol Rev. 2020;28:262-5.

[10] R.O. Almadfaa, P.R. Wigle, A.L. Hincapie, J.J. Guo. The utilization, expenditure, and price of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the US Medicaid programs: trends over a 31 year period. International Journal of Cardiology. 2022.

Declaration of Competing Interest

The authors (JB and MH) report no relationships that could be construed as a conflict of interest.

Author Agreement Form – International Journal of Cardiology

Manuscript Title: Trends in ACEi and ARB expenditure: a compelling case for competition in generic drug markets

List of all Authors: Jonathan A Batty and Marlous Hall

Corresponding Author: Jonathan Batty

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the International Journal of Cardiology.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: “The authors report no relationships that could be construed as a conflict of interest”.