Paper RE06

Early Detection of Adverse Events Associated with Antihypertensive Medications: A Real-World Evidence Study Using FAERS Data

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ABSTRACT

Real-world evidence (RWE) is increasingly recognized as a vital complement to clinical trials, offering insights into drug safety, effectiveness, and outcomes in routine clinical practice. Its relevance is especially pronounced in pharmacovigilance, where traditional trials may lack the scale or duration to detect rare or long-term adverse events. Leveraging RWE from the FDA Adverse Event Reporting System (FAERS), this study evaluates the safety of five commonly prescribed antihypertensives-amlodipine, losartan, atenolol, enalapril, and hydrochlorothiazide between 2018 and 2023. Disproportionality analysis using Proportional Reporting Ratio (PRR) and Reporting Odds Ratio (ROR) identified notable drug–event associations, including Foetal Disorder with losartan, and Sensitisation with atenolol and Gingival Hypertrophy with amlodipine. These findings align with known safety profiles and demonstrate how large-scale RWE datasets like FAERS can uncover meaningful safety signals, enhancing regulatory oversight and clinical decision-making in real-world settings.

INTRODUCTION

Randomized controlled trials (RCTs) remain the gold standard for establishing drug efficacy and initial safety; however, their ability to detect rare, delayed, or population-specific adverse events is inherently limited by restricted sample sizes, controlled settings, and relatively short follow-up durations. As a result, post-marketing surveillance plays a critical role in understanding real-world drug safety across diverse patient populations.

Real-world evidence (RWE) leverages routinely collected healthcare data, including spontaneous adverse event reporting systems, electronic health records, and claims databases, to evaluate medication use and outcomes in routine clinical practice. RWE has gained increasing importance across multiple therapeutic areas such as cardiology, oncology, endocrinology, and infectious diseases, where long-term treatment and heterogeneous patient characteristics are common.

Antihypertensive medications represent an ideal therapeutic class for RWE-based safety evaluations due to their widespread and chronic use among patients with multiple comorbidities. Even infrequent adverse events can have substantial public health implications when exposure is large. This study aims to assess post-marketing safety signals associated with five commonly prescribed antihypertensive agents using FAERS data, highlighting the role of disproportionality analysis in early safety signal detection.

DATA SOURCE

FAERS is a publicly available spontaneous reporting system maintained by the U.S. Food and Drug Administration to support post-marketing safety surveillance. The database contains individual case safety reports submitted by healthcare professionals, consumers, and pharmaceutical manufacturers worldwide. Each report may include patient demographics, suspected and concomitant drugs, reported adverse events, indications, outcomes, and therapy dates.

For this analysis, all quarterly FAERS datasets released between January 2018 and December 2023 were obtained from the FDA website. The analysis utilized data from the Demographics (DEMO), Drug (DRUG), Reaction (REAC), Indication (INDI), Outcome (OUTC), and Therapy Dates (THER) tables. FAERS data are de-identified and publicly accessible, enabling secondary analyses without patient-level identifiers.

DATA PREPARATION

Data preparation was conducted using SAS to ensure accurate case identification and to minimize duplicate reporting. FAERS follows a version-based reporting structure, where multiple versions of a case may exist as additional information becomes available. To ensure consistency, only the most recent version of each case was retained based on the combination of CASEID and the highest CASEVERSION value from the DEMO dataset.

Drug records were standardized using the active ingredient field (PROD_AI) to identify reports involving amlodipine, losartan, atenolol, enalapril, and hydrochlorothiazide. Only drugs classified as Primary Suspect (ROLE_COD = 'PS')

were included to reduce confounding from concomitant therapies.

The DRUG and REAC datasets were merged using PRIMARYID, and duplicate drug–event combinations were removed so that each case contributed only once to a given drug–event pair. Non-clinical adverse event terms, such as medication errors or product use issues, were excluded. Additionally, drug–event pairs reported in fewer than three cases were filtered out to improve the stability of disproportionality metrics.

ANALYSIS APPROACH

Disproportionality analysis was performed using established pharmacovigilance methodologies to identify potential drug–adverse event safety signals within the FAERS database. For each drug–adverse event (AE) pair, a 2×2 contingency table was constructed, comparing the reporting frequency of a specific AE for the drug of interest against the reporting frequency of the same AE for all other drugs in the database. This approach enables the assessment of whether an AE is reported disproportionately more often for a particular drug relative to the background reporting pattern.

The Proportional Reporting Ratio (PRR) was calculated to quantify the relative reporting proportion of an adverse event for a given drug compared with all other drugs. PRR provides an intuitive measure of disproportionality by comparing the proportion of reports for a specific AE among all reports for the drug of interest to the corresponding proportion among reports for other drugs.

In parallel, the Reporting Odds Ratio (ROR) was computed as the odds of reporting a specific adverse event for the drug of interest relative to the odds of reporting the same event for all other drugs. The ROR offers a complementary measure of disproportionality and allows for the derivation of confidence intervals, supporting the assessment of statistical uncertainty around the observed association.

To evaluate the statistical strength of the observed associations, the chi-square statistic was applied to each contingency table. The chi-square test assesses whether the observed reporting pattern for a drug–AE pair deviates significantly from what would be expected under the assumption of independence between drug exposure and adverse event occurrence.

A drug–AE combination was considered a potential safety signal if it met all predefined criteria commonly used in pharmacovigilance practice: PRR ≥ 2, ROR > 1 with the lower bound of the 95% confidence interval exceeding 1, chi-square ≥ 4, and a minimum of three reported cases. Applying multiple complementary criteria ensured that identified signals reflected both statistical robustness and meaningful disproportional reporting, thereby reducing the likelihood of spurious associations.

RESULTS

The analysis identified multiple statistically significant safety signals across all five antihypertensive agents evaluated using FAERS data. Amlodipine demonstrated strong disproportionality signals, with prominent associations related to gingival, musculoskeletal, and hemodynamic adverse events, reflecting its known pharmacologic effects as a calcium channel blocker.

For losartan, the analysis revealed notable signals involving fetal and congenital conditions, as well as hypersensitivity-related reactions, consistent with established safety considerations for angiotensin receptor blockers, particularly in specific patient populations.

Atenolol showed marked disproportional reporting for neurological and cardiovascular-related adverse events, including sensitisation and conditions associated with altered cerebral and cardiac function, aligning with beta-blocker pharmacology.

In the case of enalapril, safety signals were observed for cardiovascular, hematologic, and edema-related events, consistent with the known adverse effect profile of angiotensin-converting enzyme inhibitors. Hydrochlorothiazide demonstrated significant signals related to dermatologic, gastrointestinal, oncologic, and electrolyte-related adverse events, reflecting recognized risks associated with thiazide diuretics.

Across all evaluated drugs, PRR, ROR, and chi-square statistics were concordant, supporting the robustness of the detected associations. Overall, the identified safety signals were largely consistent with established pharmacologic mechanisms, underscoring the value of FAERS-based real-world evidence in identifying clinically relevant adverse event patterns in routine clinical practice.

DISCUSSION

This study highlights the utility of FAERS as a real-world data source for early detection of adverse events associated with widely used antihypertensive medications. The observed consistency between detected signals and known pharmacologic mechanisms supports the validity of disproportionality analysis as a core pharmacovigilance tool.

Given the chronic use of anti-hypertensive therapies and the diversity of treated populations, ongoing safety monitoring is essential. RWE-based analyses can complement traditional clinical trials by providing timely insights into safety risks that may not be apparent during pre-approval development.

The results underscore the importance of integrating real-world safety data into routine pharmacovigilance practices to support informed regulatory decision-making and optimize patient safety.

CONCLUSION

This paper demonstrates the practical application of FAERS-based real-world evidence for early detection of adverse events associated with commonly prescribed antihypertensive medications. Through structured data preparation and SAS-driven disproportionality analysis, known safety signals were successfully identified, reinforcing the value of RWE in post-marketing pharmacovigilance. The approach described in this paper can be readily adapted to other drug classes and therapeutic areas to support ongoing safety monitoring activities.

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