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RESEARCH ARTICLE

Comparison of Adverse Drug Reaction Profiles Between Branded and Generic Cardiovascular Medications

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Abstract: ***Introduction:*** Whether generic cardiovascular (CV) drugs carry different adverse drug reaction (ADR) risks versus their branded counterparts remains debated despite strict bioequivalence regulations. ***Materials and Methods:*** We conducted a prospective, observational cohort in a tertiary-care pharmacovigilance unit enrolling adults receiving one of six CV drug classes (statins, β-blockers, ACE inhibitors/ARBs, calcium-channel blockers, antiplatelet agents, thiazide diuretics). Patients were grouped by branded vs generic label at index prescription and followed for 12 weeks. Primary outcome was any treatment-emergent ADR (TE-ADR). Secondary outcomes included serious ADR (sADR), system organ class (SOC) distribution, time-to-onset (TTO), and predictors of sADR using multivariable logistic regression. ***Results:*** Of 160 participants (49.4% branded, 50.6% generic), overall TE-ADR incidence was 24.4% branded vs 26.5% generic (risk difference +2.1%, 95% CI −8.7 to 12.9). sADR occurred in 3.8% vs 4.9% (RD +1.1%, 95% CI −4.4 to 6.6). SOC patterns were similar; myalgia dominated statins, cough with ACE inhibitors, peripheral edema with dihydropyridine CCBs, and dyspepsia with antiplatelets. Median TTO was comparable (14 vs 13 days; p=0.62). After adjustment (age, sex, comorbidity, polypharmacy, class), generics were not associated with higher sADR risk (aOR 1.07, 95% CI 0.41–2.79). Class-specific differences were nonsignificant. ***Conclusion:*** In this cohort, ADR frequency, severity, and clinical profile were comparable between branded and generic CV medications, aligning with bioequivalence and real-world safety literature.

Keywords: Generic drugs; brand-name drugs; cardiovascular agents; pharmacovigilance; adverse drug reactions; bioequivalence

INTRODUCTION

Generic substitution is central to affordable cardiovascular (CV) care, with adoption driven by stringent bioequivalence standards that aim to ensure comparable exposure and therapeutic effect to reference products.[1–3] Regulatory frameworks from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) typically require that 90% confidence intervals for generic/reference ratios of Cmax and AUC fall within 80–125%, along with quality, stability, and manufacturing controls.[1–3] While these pharmacokinetic criteria robustly predict efficacy equivalence, clinicians and patients sometimes express concern about safety and tolerability—particularly for narrow-therapeutic-index drugs or agents perceived to cause class-typical adverse effects (e.g., statin-associated myalgia, ACE inhibitor-induced cough).[4–7]

The evidence base addressing ADRs specifically—distinct from effectiveness or persistence—has grown. Population-based comparisons of branded versus generic statins, clopidogrel, β-blockers, and ACE inhibitors generally report similar clinical outcomes and discontinuation rates, with no consistent excess of serious harms attributable to generics.[5–11] Nevertheless, perceptions of reduced quality, variable excipients, and the nocebo effect can influence ADR reporting and adherence.[6,12,13] Formulation differences (color/shape) may affect recognition and pill-switch anxiety, potentially amplifying symptom attribution.[12,14] In pharmacovigilance databases, disproportionality for generics versus brands is difficult to interpret given channeling, reporting biases, and market share effects.[15,16]

In CV medicine, even small differences in ADR risk may have population-level implications, given high prevalence of long-term therapy. Statins and antiplatelets are foundational after atherosclerotic events; RAAS inhibitors, β-blockers, thiazides, and calcium-channel blockers constitute first-line antihypertensive options per contemporary guidelines.[17–19] Ensuring that generic adoption does not compromise tolerability is therefore a priority for policymakers and clinicians.

We designed a prospective observational study in a real-world, tertiary-care setting to compare ADR profiles between branded and generic CV drugs across six commonly used classes. We hypothesized non-inferiority of generics with respect to (a) overall treatment-emergent ADRs (TE-ADRs), (b) serious ADRs (sADRs), and (c) time-to-onset and SOC distribution. We further explored predictors of sADRs—including age, sex, comorbidity burden, polypharmacy, and drug class—and examined whether any class-specific interaction suggested different risk by label status. Our goal was to provide pragmatically useful evidence for clinicians considering substitution

and for formulary committees balancing cost with safety.[4,5,14,20]

MATERIAL AND METHODS

This is a Prospective, observational cohort study conducted in an academic tertiary-care pharmacovigilance unit and affiliated cardiology clinics over 12 months. The institutional ethics committee approved the protocol; all participants provided written informed consent.

Participants: Adults (≥18 years) initiating or switching to a single index CV agent from one of six classes: statins, β-blockers, ACE inhibitors or ARBs, dihydropyridine calcium-channel blockers (CCBs), antiplatelet agents (aspirin, clopidogrel), or thiazide diuretics. Patients were allocated to branded or generic exposure groups based on the label of the index product dispensed.

Inclusion criteria:

1. New start or brand↔generic switch for an eligible agent; 2) anticipated therapy duration ≥12 weeks; 3) ability to complete follow-up and symptom diaries.

Exclusion criteria:

1. Known hypersensitivity to the index agent/class; 2) current participation in an interventional trial; 3) end-stage renal disease on dialysis or Child-Pugh C hepatic disease; 4) pregnancy or lactation; 5) documented nonadherence at baseline screening; 6) combination products where the brand/generic status could not be attributed to a single active ingredient.

Outcomes and definitions:

Primary outcome: any treatment-emergent ADR (TE-ADR) during 12-week follow-up, assessed at 2, 6, and 12 weeks by structured interview and diary review, and coded by MedDRA SOC/PT. Severity was graded per CTCAE v5.0; serious ADRs (sADRs) were those resulting in hospitalization, life-threat, disability, or death. Causality used WHO-UMC criteria (possible/probable/certain). Secondary outcomes: SOC distribution, time-to-onset (TTO), drug interruption, and class-specific TE-ADR rates.

Sample size: Assuming a TE-ADR rate of 25% with brands and a non-inferiority margin of 10 percentage points for generics, 160 participants (1:1 groups) provide ≈80% power (α=0.05) to exclude a difference greater than the margin using a Wald-type confidence interval for risk difference.

Covariates: Age, sex, BMI, Charlson comorbidity index, baseline eGFR, number of concomitant medications, smoking status, and drug class. Polypharmacy was defined as ≥5 concomitant chronic medications.

Statistical analysis: Categorical variables were compared with χ^2 or Fisher's exact test; continuous variables with t-test or Wilcoxon rank-sum as appropriate. Kaplan–Meier methods summarized TTO with log-rank comparison. Multivariable logistic regression estimated adjusted odds ratios (aORs) for sADR, including prespecified covariates; an interaction term (class × label) explored class-specific effects. Two-sided $p<0.05$ was considered significant. Analyses were performed with standard statistical software.

RESULTS AND OBSERVATIONS:

Table 1. Baseline characteristics (N=160)

Characteristic	Branded (n=79)	Generic (n=81)	p-value
Age, years (mean ± SD)	58.9 ± 10.7	59.6 ± 11.2	0.69
Female sex	32 (40.5%)	33 (40.7%)	0.98
BMI, kg/m²	26.8 ± 4.1	27.1 ± 4.3	0.62
Charlson index ≥3	21 (26.6%)	23 (28.4%)	0.80
Polypharmacy (≥5 meds)	29 (36.7%)	31 (38.3%)	0.84
eGFR <60 mL/min/1.73m²	14 (17.7%)	16 (19.8%)	0.73
Current smoker	11 (13.9%)	12 (14.8%)	0.88
Index class: statin	21 (26.6%)	22 (27.2%)	0.93
β-blocker	13 (16.5%)	14 (17.3%)	
ACEi/ARB	15 (19.0%)	16 (19.8%)	
DHP-CCB	12 (15.2%)	12 (14.8%)	
Antiplatelet	11 (13.9%)	12 (14.8%)	
Thiazide diuretic	7 (8.9%)	5 (6.2%)	

In table 1, the mean age is similar (58.9 ± 10.7 years for Branded vs. 59.6 ± 11.2 years for Generic, p=0.69), indicating no significant difference. Both groups have nearly identical proportions of females (40.5% vs. 40.7%, p=0.98), showing no sex-based differences. Body Mass Index is comparable (26.8 ± 4.1 kg/m² vs. 27.1 ± 4.3 kg/m², p=0.62), suggesting similar body composition. This measures comorbidity burden, with 26.6% (Branded) and 28.4% (Generic) having a score

≥3 (p=0.80), indicating similar levels of chronic illness. 36.7% (Branded) and 38.3% (Generic) take ≥5 medications (p=0.84), showing comparable medication burdens. This indicates reduced kidney function, present in 17.7% (Branded) and 19.8% (Generic, p=0.73), with no significant difference. Smoking rates are nearly identical (13.9% vs. 14.8%, p=0.88).

Table 2. Treatment-emergent ADRs by class (12-week incidence)

Class	Branded TE-ADR n/N (%)	Generic TE-ADR n/N (%)	Risk difference (pp)
Statins	5/21 (23.8)	6/22 (27.3)	+3.5
β-blockers	3/13 (23.1)	3/14 (21.4)	−1.7
ACEi/ARB	4/15 (26.7)	5/16 (31.3)	+4.6
DHP-CCB	3/12 (25.0)	3/12 (25.0)	0.0
Antiplatelets	3/11 (27.3)	3/12 (25.0)	−2.3
Thiazides	1/7 (14.3)	1/5 (20.0)	+5.7
Overall	**19/79 (24.1)**	**21/81 (25.9)**	**+1.8**

In table 2, Statins: Branded: 5/21 (23.8%), Generic: 6/22 (27.3%), Risk difference: +3.5 pp. Generic statins have a slightly higher TE-ADR rate. β-blockers: Branded: 3/13 (23.1%), Generic: 3/14 (21.4%), Risk difference: −1.7 pp. Branded β-blockers have a slightly higher TE-ADR rate. ACEi/ARB: Branded: 4/15 (26.7%), Generic: 5/16 (31.3%), Risk difference: +4.6 pp. Generic ACEi/ARBs have a higher TE-ADR rate. DHP-CCB (dihydropyridine calcium channel blockers): Branded: 3/12 (25.0%), Generic: 3/12 (25.0%), Risk difference: 0.0 pp. Both groups have identical TE-ADR rates. Antiplatelets: Branded: 3/11 (27.3%), Generic: 3/12 (25.0%), Risk difference: −2.3 pp. Branded antiplatelets have a slightly higher TE-ADR rate. Thiazides: Branded: 1/7 (14.3%), Generic: 1/5 (20.0%), Risk difference: +5.7 pp. Generic thiazides have a higher TE-ADR rate. Overall: Branded: 19/79 (24.1%), Generic: 21/81 (25.9%), Risk difference: +1.8 pp. Across all drug classes, Generic medications have a slightly higher TE-ADR rate.

Table 3. Severity and management of ADRs

Outcome	Branded (n=79)	Generic (n=81)	p-value
Any TE-ADR	19 (24.1%)	21 (25.9%)	0.79
CTCAE grade 1–2	16 (20.3%)	17 (21.0%)	0.92
Serious ADR (sADR)	3 (3.8%)	4 (4.9%)	0.72
Drug interruption	6 (7.6%)	7 (8.6%)	0.82
Hospitalization due to ADR	1 (1.3%)	1 (1.2%)	0.97

In table 3, Any TE-ADR: 19 (24.1%) in the Branded group vs. 21 (25.9%) in the Generic group (p=0.79). The rates of any TE-ADR are similar, with a slightly higher incidence in the Generic group. CTCAE Grade 1–2 (mild to moderate ADRs, based on Common Terminology Criteria for Adverse Events): 16 (20.3%) in Branded vs. 17 (21.0%) in Generic (p=0.92). Mild to moderate ADRs are nearly identical between groups. Serious ADR (sADR): 3 (3.8%) in Branded vs. 4 (4.9%) in Generic (p=0.72). Serious ADRs are slightly more frequent in the Generic group but remain rare in both. Drug Interruption: 6 (7.6%) in Branded vs. 7 (8.6%) in Generic (p=0.82). The need to interrupt medication due to ADRs is comparable. Hospitalization due to ADR: 1 (1.3%) in Branded vs. 1 (1.2%) in Generic (p=0.97). Hospitalizations are rare and virtually identical.

Table 4. MedDRA SOC pattern among TE-ADRs (top categories)

SOC	Branded n (%) of TE-ADRs	Generic n (%) of TE-ADRs
Musculoskeletal & connective tissue (e.g., myalgia—statins)	6 (31.6%)	7 (33.3%)
Respiratory (e.g., ACEi cough)	4 (21.1%)	5 (23.8%)
Gastrointestinal (e.g., dyspepsia/bloating—antiplatelets, CCB)	4 (21.1%)	4 (19.0%)
General disorders (fatigue)	3 (15.8%)	3 (14.3%)
Nervous system (dizziness/headache)	2 (10.5%)	2 (9.5%)

In table 4, Musculoskeletal & Connective Tissue (e.g., myalgia—statins)**:** Branded: 6/19 (31.6%), Generic: 7/21 (33.3%). This is the most common SOC for TE-ADRs in both groups, with slightly higher prevalence in the Generic group. Myalgia is often associated with statins. Respiratory (e.g., ACEi cough)**:** Branded: 4/19 (21.1%), Generic: 5/21 (23.8%). Respiratory ADRs, such as cough linked to ACE inhibitors, are slightly more frequent in the Generic group. Gastrointestinal (e.g., dyspepsia/bloating—antiplatelets, CCB**)**: Branded: 4/19 (21.1%), Generic: 4/21 (19.0%). Gastrointestinal ADRs are slightly more common in the Branded group. General Disorders (fatigue): Branded: 3/19

(15.8%), Generic: 3/21 (14.3%). Fatigue is equally distributed and less frequent in both groups. Nervous System (dizziness/headache): Branded: 2/19 (10.5%), Generic: 2/21 (9.5%). Nervous system ADRs are the least common and similarly rare in both groups.

Table 5. Time-to-onset (days) of first TE-ADR

Measure	Branded	Generic	p-value
Median (IQR)	14 (7–28)	13 (7–27)	0.62
≤7 days	6 (31.6%)	7 (33.3%)	0.88
8–28 days	9 (47.4%)	10 (47.6%)	0.99
>28 days	4 (21.1%)	4 (19.0%)	0.85

In table 5, Time Intervals for TE-ADR Onset: **≤7 days**: Branded: 6/19 (31.6%), Generic: 7/21 (33.3%), p=0.88. **8–28 days**: Branded: 9/19 (47.4%), Generic: 10/21 (47.6%), p=0.99. **>28 days**: Branded: 4/19 (21.1%), Generic: 4/21 (19.0%), p=0.85.

Table 6. Predictors of serious ADR (multivariable logistic regression)

Predictor	Adjusted OR	95% CI	p-value
Generic (vs branded)	1.07	0.41–2.79	0.88
Age ≥65 years	1.89	0.72–4.95	0.20
Female sex	1.14	0.45–2.90	0.78
Charlson index ≥3	2.41	0.92–6.35	0.07
Polypharmacy (≥5 meds)	2.76	1.02–7.47	0.046
Statin (ref all others)	0.92	0.30–2.82	0.89

In table 6, The lack of a significant difference (OR=1.07, p=0.88) aligns with previous tables showing similar TE-ADR rates (24.1% vs. 25.9%), severity, SOC distribution, and time to onset. This reinforces that Generic and Branded medications have comparable safety profiles. The significant association (OR=2.76, p=0.046) highlights polypharmacy as a key risk factor for TE-ADRs, consistent with clinical knowledge that multiple medications increase the risk of drug interactions and adverse effects. Clinicians should closely monitor patients on ≥5 medications. The near-significant association (OR=2.41, p=0.07) suggests that patients with higher comorbidity burdens may be at increased risk for TE-ADRs, warranting further investigation in larger studies. These factors do not appear to significantly influence TE-ADR risk in this study, though the wide CIs suggest limited power to detect effects.

DISCUSSION

In this prospective, real-world cohort spanning six CV drug classes, generic products exhibited TE-ADR and sADR rates comparable to branded products across multiple dimensions—frequency, SOC distribution, severity, management (interruptions, hospitalizations), and TTO. These findings align with regulatory expectations from bioequivalence frameworks and with observational literature reporting no clinically meaningful safety disadvantage for generic CV agents.[1–5,8–11]

Our class-level patterns mirrored well-described adverse-effect signatures: myalgia with statins, cough with ACE inhibitors, edema with dihydropyridine CCBs, and GI effects with antiplatelets.[7–11] Equivalence of patterns between branded and generic arms suggests excipient and formulation differences did not materially alter tolerability at a population level. Although our study was not powered for narrow-therapeutic-index drugs, it is notable that the adjusted risk of sADR did not differ by label, and polypharmacy—not brand/generic status—emerged as the salient predictor of serious events, echoing pharmacovigilance analyses linking medication count to harm.[15,21]

Concerns about generics often reflect perceptual factors and nocebo phenomena rather than pharmacological differences.[12,13] Interventions that maintain pill appearance and provide anticipatory counseling during brand↔generic switches may mitigate symptom attribution and improve persistence.[12,14] Our neutral TTO curves and similar interruption rates are consistent with this interpretation. Moreover, policy analyses show that generic substitution improves access and adherence by lowering out-of-pocket cost, with downstream benefits for CV outcomes—provided safety and effectiveness are maintained.[4,22–24]

Strengths include prospective design, standardized ADR ascertainment with MedDRA coding and WHO-UMC causality, and prespecified adjustment for confounders. Limitations include modest sample size (possible type II error for small class-specific differences), single-region recruitment, and 12-week follow-up that may miss very late events (e.g., rare hepatotoxicity). We also did not assay plasma concentrations; however, bioequivalence is adjudicated at the regulatory level, and our pragmatic focus was clinical safety. Finally, we did not stratify by manufacturer; future multicenter studies could incorporate lot/manufacturer-level random effects.

Implications: For formularies and clinicians, these data support generic substitution as a safe strategy for common CV agents. Pharmacovigilance programs should prioritize high-risk contexts (polypharmacy, multimorbidity) rather than brand status per se and incorporate communication strategies to reduce nocebo-driven discontinuation.[12,13,21,24]

CONCLUSION

Across six major cardiovascular drug classes, branded and generic products demonstrated comparable adverse drug reaction profiles in frequency, severity, onset, and clinical impact. Safety surveillance should focus on patient-level risk factors—especially polypharmacy—rather than label status. These findings support policies promoting generic use to enhance access without compromising safety.

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