Assessing post-marketing safety of authorized generic products

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Background

- **Authorized generics (AGs)**
  - AGs are a special case of generic drugs; they are brand-name products deriving US marketing approval based on the brand manufacturer's new drug application (NDA) but marketed, sold, or distributed as generic medications.
- **Negative perception bias in comparative studies of generics**
  - Generic drugs are often perceived to be less effective and safe as compared to the brand name product by patients as well as physicians (Shrank et al. Health Affairs, 2009; Shrank et al. Annals of Pharmacotherapy, 2011)
  - AGs provide a unique opportunity to unbiasedly understand the comparative effectiveness of generics versus brand products because they are essentially brand-name drugs perceived as generic drugs and therefore, a comparison of generics versus AGs is unlikely to be differentially affected by negative perceptions of generic drugs.

Objectives

- We first described utilization patterns of the three versions within first 24 months of generic availability and compared switchback rates to brand-name versions between AGs and generics
- We next compared clinical outcomes between AGs, generics, and brand-name versions of 8 pre-specified drug products

Data source and study drugs

- Health insurance claims data from OptumInsight Clinformatics (2004-2013)
- Study drugs and outcomes
  - 3 cardiovascular drugs- A composite CVD endpoint (stroke, MI, revascularizations)
  - 2 osteoporosis drugs- A composite fracture endpoint (humerus, wrist, hip, or pelvis fractures)
  - 1 diabetes drug- Initiation of insulin
  - 2 anti-depressants- Psychiatric hospitalizations

A. Substitution rates

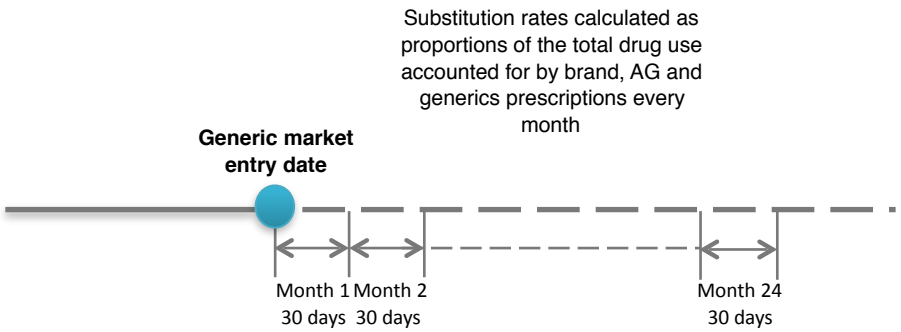
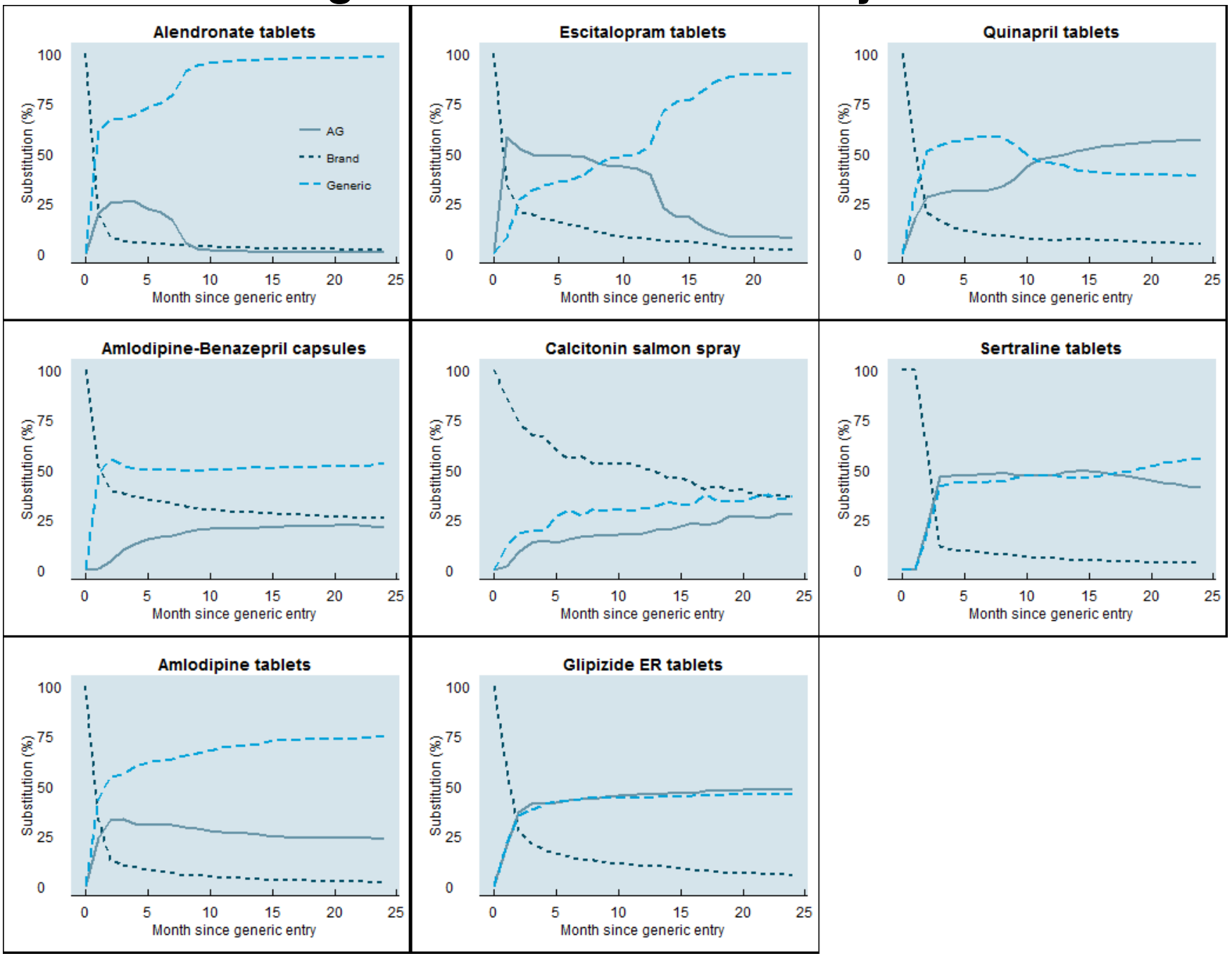
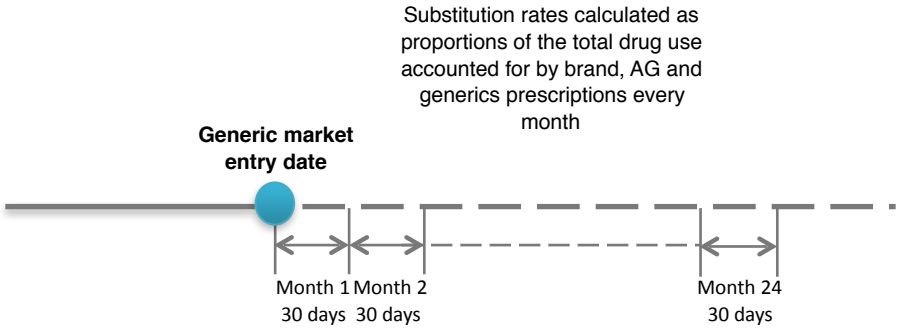


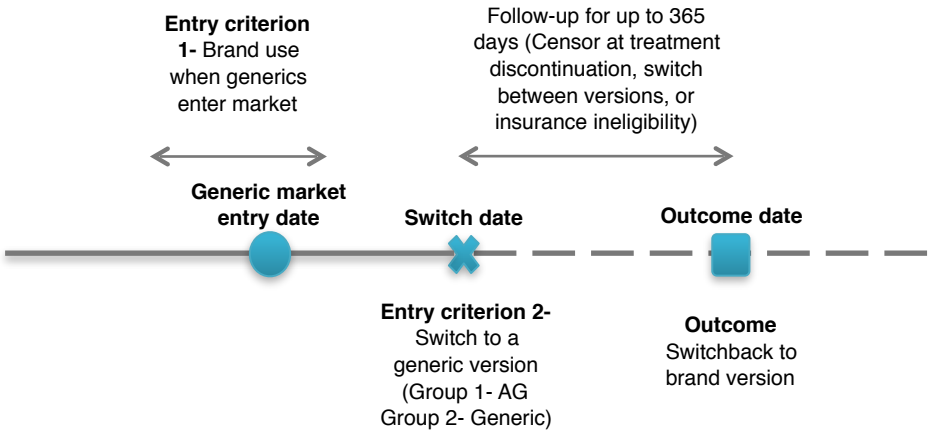
Figure 2- Substitution analysis



A. Substitution rates



B. Switchback rates



Switchback analysis

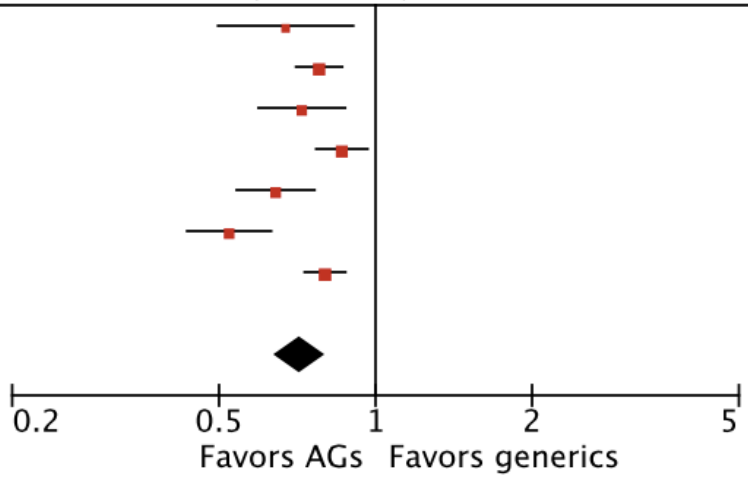
- A Cox proportional hazards (PH) regression model that adjusted for basic demographics (age, gender, and calendar year) gave hazard ratios (HR) and 95% confidence intervals for brand switchbacks comparing AG and generic groups
- To derive summary effect estimates across the 8 included drug products, we conducted random effects meta-analysis to pool effect estimates for each comparison in the switchback analysis

Figure 3- Switchback analysis

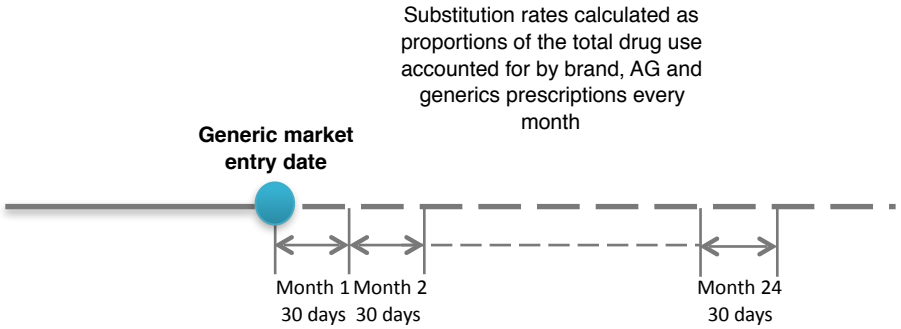
Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI
Alendronate tablets	8.4%	0.67 [0.50, 0.91]
Amlodipine tablets	17.3%	0.78 [0.70, 0.86]
Amlodipine-benazepril capsules	12.8%	0.72 [0.60, 0.87]
Escitalopram tablets	16.8%	0.86 [0.77, 0.97]
Glipizide ER tablets	13.8%	0.64 [0.54, 0.76]
Quinapril tablets	13.1%	0.52 [0.43, 0.63]
Sertraline tablets	17.9%	0.80 [0.73, 0.88]
Total (95% CI)	**100.0%**	**0.72 [0.64, 0.81]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 26.15$, df = 6 (P = 0.0002); $I^2 = 77\%$

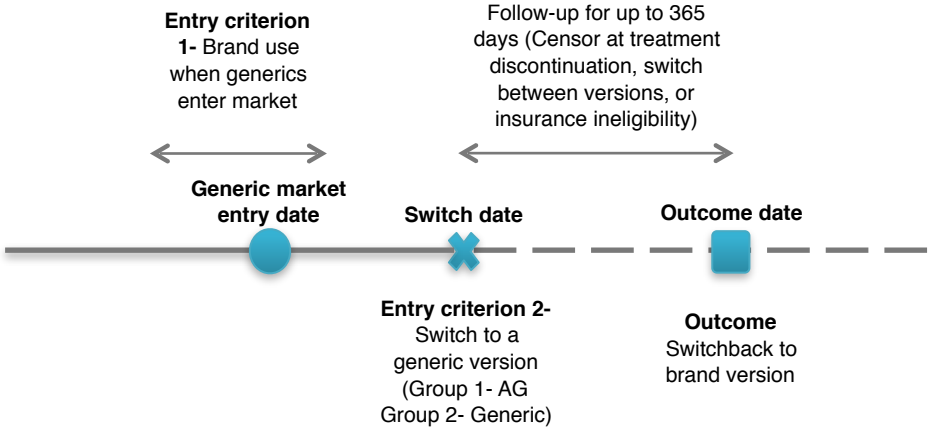
Test for overall effect: Z = 5.67 (P < 0.00001)



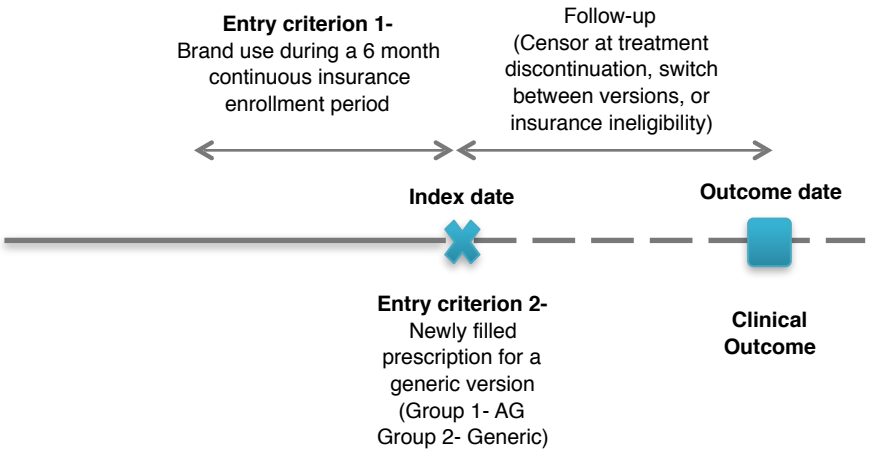
A. Substitution rates



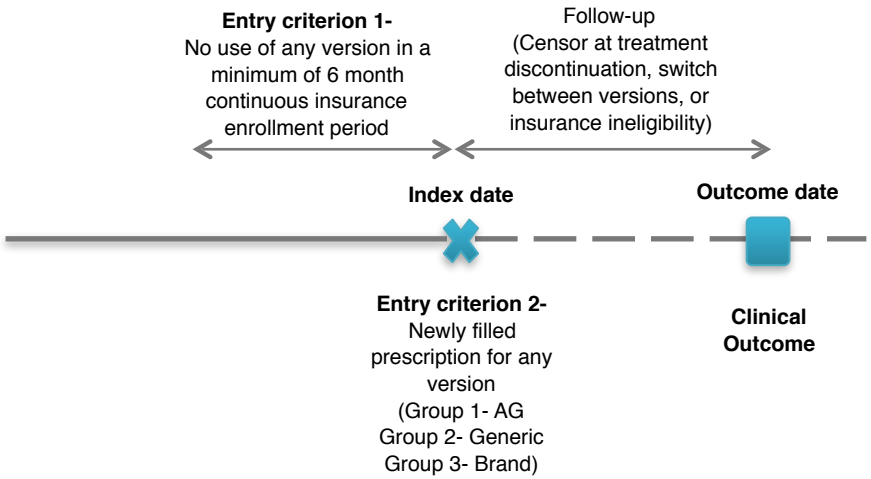
B. Switchback rates



C. Clinical outcomes (among AG or generic switchers)



D. Clinical outcomes (among brand, AG, or generic initiators)



Statistical analysis

- For the comparative effectiveness analyses, propensity score (PS) based methods were used for rigorous confounding adjustment
- PSs were calculated as the predicted probability of initiating the exposure group of interest (AGs in the AG versus generic and AG versus brand comparisons, Generics in the generic versus brand comparison) conditional upon patient covariate constellations
- After calculating the PS, 1:1 matching procedure within a caliper of 0.025 of the PS was implemented for each comparison
- In the matched cohorts, Cox PH models were used to derive the adjusted effect estimates in each comparison
- To derive summary effect estimates across the 8 included drug products, we conducted random effects meta-analysis to pool effect estimates for each comparison in the switchback analysis

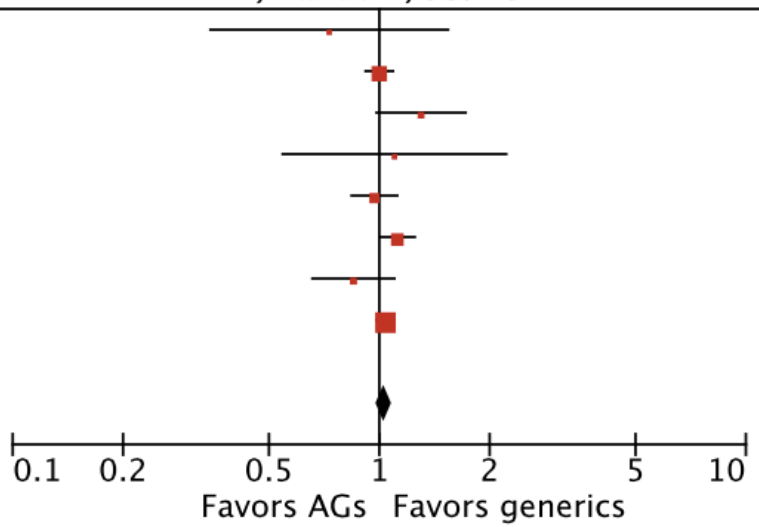
Figure 4- Clinical outcomes comparison- authorized generics versus generics

A. Initiators comparison

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI
Alendronate tablets	0.5%	0.73 [0.35, 1.54]
Amlodipine tablets	24.3%	1.00 [0.92, 1.09]
Amlodipine-benazepril capsules	3.6%	1.30 [0.98, 1.72]
Calcitonin salmon nasal spray	0.6%	1.10 [0.55, 2.22]
Escitalopram tablets	11.8%	0.97 [0.84, 1.12]
Glipizide ER tablets	17.8%	1.12 [1.00, 1.25]
Quinapril tablets	4.3%	0.85 [0.66, 1.10]
Sertraline tablets	37.0%	1.04 [0.98, 1.10]
Total (95% CI)	**100.0%**	**1.03 [0.98, 1.09]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.06$, df = 7 (P = 0.25); $I^2 = 23\%$

Test for overall effect: Z = 1.16 (P = 0.25)



B. Switchers comparison

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI
Alendronate tablets	2.4%	1.19 [0.73, 1.93]
Amlodipine tablets	46.9%	1.03 [0.92, 1.15]
Amlodipine-benazepril capsules	3.7%	1.20 [0.81, 1.78]
Calcitonin salmon nasal spray	0.2%	2.13 [0.39, 11.67]
Escitalopram tablets	6.7%	0.86 [0.64, 1.15]
Glipizide ER tablets	2.3%	1.22 [0.74, 2.00]
Quinapril tablets	16.8%	1.09 [0.91, 1.31]
Sertraline tablets	20.9%	1.17 [0.99, 1.38]
Total (95% CI)	**100.0%**	**1.07 [0.99, 1.15]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.21$, df = 7 (P = 0.63); $I^2 = 0\%$

Test for overall effect: Z = 1.77 (P = 0.08)

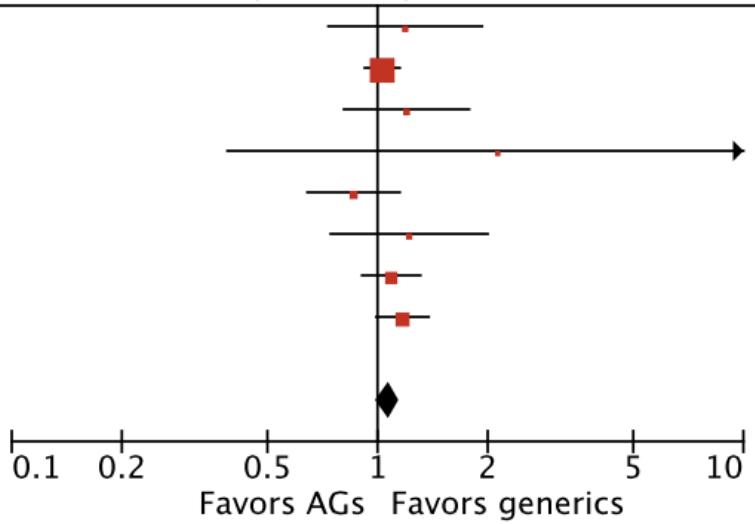


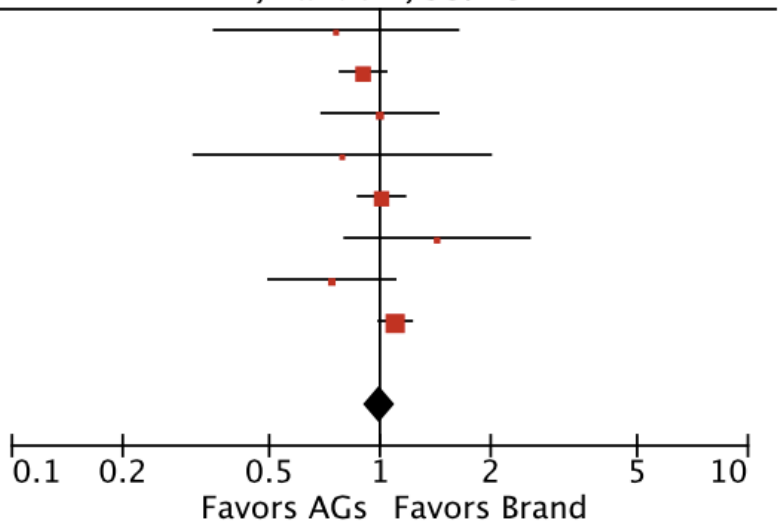
Figure 5- Clinical outcomes comparisons for brand-name products

A. AG versus Brand-name initiators

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI
Alendronate tablets	1.6%	0.76 [0.35, 1.63]
Amlodipine tablets	24.8%	0.90 [0.78, 1.04]
Amlodipine-benazepril capsules	6.4%	1.00 [0.69, 1.44]
Calcitonin salmon nasal spray	1.1%	0.79 [0.31, 2.00]
Escitalopram tablets	24.3%	1.01 [0.87, 1.17]
Glipizide ER tablets	2.7%	1.43 [0.80, 2.55]
Quinapril tablets	5.5%	0.74 [0.50, 1.10]
Sertraline tablets	33.5%	1.10 [0.99, 1.22]
Total (95% CI)	**100.0%**	**0.99 [0.90, 1.10]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.61$, df = 7 (P = 0.21); $I^2 = 27\%$

Test for overall effect: Z = 0.11 (P = 0.91)

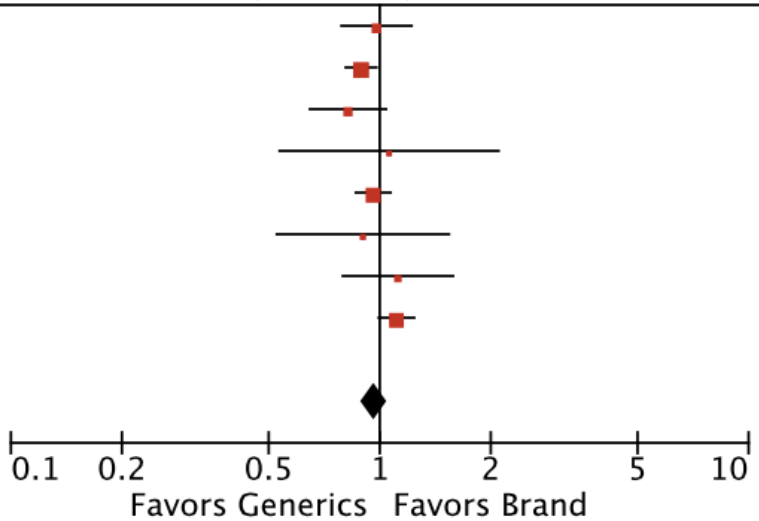


B. Generics versus Brand-name initiators

Study or Subgroup	Weight	Hazard Ratio IV, Random, 95% CI
Alendronate tablets	10.5%	0.98 [0.79, 1.22]
Amlodipine tablets	25.3%	0.89 [0.81, 0.98]
Amlodipine-benazepril capsules	9.3%	0.82 [0.65, 1.04]
Calcitonin salmon nasal spray	1.4%	1.06 [0.54, 2.10]
Escitalopram tablets	23.2%	0.96 [0.86, 1.07]
Glipizide ER tablets	2.3%	0.90 [0.53, 1.54]
Quinapril tablets	5.1%	1.12 [0.79, 1.58]
Sertraline tablets	22.8%	1.11 [0.99, 1.24]
Total (95% CI)	**100.0%**	**0.97 [0.89, 1.05]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.53$, df = 7 (P = 0.12); $I^2 = 39\%$

Test for overall effect: Z = 0.74 (P = 0.46)



Summary

- AG use was associated with significantly lower brand-switchbacks compared with generics, which may be attributable to similar pill characteristics such as color, shape, and size between AGs and brands
- No significant differences were noted in clinical outcomes across the three versions
- This study adds to mounting evidence that generics are associated with clinical benefit comparable to brand-name products

Study Team

- Rishi Desai
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- Justin Bohn
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