Effect of Cost and Formulation on Persistence and Adherence to Initial Metformin Therapy for Type 2 Diabetes

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Patients taking metformin adhere to their prescribed regimen, on average, about 65% of the time (1,2). Given metformin's central role in type 2 diabetes management, optimizing adherence is important. Common causes of nonadherence include cost and side effects. Metformin is inexpensive but causes gastrointestinal side effects in up to 25% of patients (2). Extended-release (ER) formulations reduce side effects but may cost more, and they have not been clearly shown to improve adherence in routine practice (3). As a result, although it is common practice to change from immediate release (IR) formulations to ER once patients develop side effects, there is not a consensus on whether ER formulations should routinely be used when metformin is first prescribed (3). We undertook a retrospective cohort study of how cost and initial choice of formulation affect adherence and persistence to metformin.

The study used merged de-identified claims data from commercial insurance carriers in the U.S. from 1 January 2012 to 31 December 2016 (4). A cohort was identified of patients age 18 years or older who filled an initial 30-day prescription for metformin monotherapy with a baseline type 2 diabetes diagnosis, at least 1 year of baseline and follow-up data, and no prior antidiabetes drug use. Baseline covariates included age, sex, insurance type, comorbidities, medications, median income at the 5-digit ZIP code level, and total and out-of-pocket (OOP) cost of the initial metformin prescription as well as its formulation (ER or IR) and dose.

The primary outcome, "persistence," was defined as at least one metformin prescription claim during the 6–12 month window after the initial prescription. Secondary outcomes were "adherence," the percentage of days for which the patient had filled sufficient prescriptions to be taking metformin as prescribed, and "adequate adherence," defined as adherence of 80% or more, both during the 1st year of follow-up (5). Univariate statistics and logistic and linear regression were used to describe covariates, outcomes, and their association. The Weill Cornell Medical College Institutional Review Board ruled this research exempt.

The final study population was 81,406 individuals, of whom 78% had commercial insurance, 19% had Medicare Advantage, and 2.5% were dual-eligible for Medicare and Medicaid. The population was 46% female. Twenty-eight percent were age 45–54 years, 31% were 55–64, and 16% were 65–74. Rates of major comorbidities ranged from 0.4% for dementia to 6.4% for diabetes complications.

Metformin prescription costs were low, with median total cost for the first prescription of $5 (interquartile range [IQR] 4–8) and median OOP cost of $4 (IQR 3–7). Nearly all metformin prescriptions (99%) were generic. Brand prescriptions were associated with higher median total ($305) and OOP cost ($55). Twenty-six percent of initial prescriptions were for ER metformin, which compared with IR had higher median total ($6 vs. $5) and OOP cost ($5 vs. $4) ($P < 0.01$ for all differences).

Persistence was higher with ER metformin than with IR metformin (75% vs. 73%), as was adherence (62% vs. 59%) and adequate adherence (42% vs. 37%). This relationship was consistent after stratification by prescription OOP cost. In multivariable logistic regression including adjustment for cost, dose, demographics, and comorbidities, the odds ratio (OR) for persistence was higher for ER formulations (OR 1.14 [95% CI 1.10–1.18], $P < 0.001$) (Table 1). The adjusted relationship between persistence and cost was nonlinear, with the highest persistence in the lowest cost quartile and lower relative persistence in all higher cost quartiles (OR range 0.81–0.95, $P < 0.001$ for all contrasts). Results of multivariable modeling for the other outcomes were comparable, as were results of sensitivity analyses.

This analysis found that, despite slightly higher cost, initial use of ER metformin was associated with better adherence. This study is consistent with prior publications but is the first to show this effect after adjustment for key covariates including cost and dose (2). While

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Table 1—Results of multivariable logistic regression with persistence as a binary outcome.

Baseline variable	OR	95% CI lower bound	95% CI upper bound
Commercial insurance	Ref		
Dual eligible	1.08	0.96	1.20
Medicare Advantage	1.12	1.06	1.18
Female sex	0.91	0.88	0.94
Age (years)			
18–34	0.56	0.52	0.61
35–44	0.76	0.71	0.81
45–54	0.94	0.89	1.10
55–64	1.04	0.98	1.10
65–74	Ref		
75–84	0.81	0.75	0.87
≥85	0.67	0.58	0.79
Year			
2013	Ref		
2014	1.03	0.99	1.07
2015	1.03	1.00	1.07
MI	0.93	0.84	1.04
CHF	0.84	0.77	0.90
PVD	0.94	0.87	1.01
Stroke	0.97	0.91	1.04
Dementia	1.11	0.86	1.42
Diabetes complications	0.95	0.89	1.01
Liver disease	0.93	0.87	1.00
Renal disease	0.80	0.73	0.89
Cancer	1.01	0.94	1.09
Baseline prescription drug use			
1–3 drug classes	Ref		
4 drug classes	1.06	1.01	1.11
5–6 drug classes	1.07	1.03	1.12
>6 drug classes	1.05	1.01	1.10
ZIP code median income			
≤$42,000	Ref		
$42,000 to $54,000	1.06	1.02	1.11
$54,000 to $72,000	1.12	1.07	1.17
>$72,000	1.14	1.08	1.19
ZIP code demographics			
Majority percentage white	1.08	1.02	1.15
Majority percentage black	1.01	0.93	1.09
Metformin formulation			
IR	Ref		
ER	1.14	1.10	1.18
Metformin pills daily			
1 pill	Ref		
2 pills	1.08	0.99	1.18
>2 pills	1.13	1.01	1.27
Metformin daily dose			
≤500 mg	Ref		
501–1,000 mg	0.99	0.90	1.08
>1,000 mg	0.96	0.86	1.06
Metformin prescription cost (OOP)			
<$2.65	Ref		
$2.65–$4.07	0.87	0.84	0.91
$4.07–$7.15	0.95	0.91	1.00
>$7.15	0.81	0.77	0.85

CHF, congestive heart failure; MI, myocardial infarction; PVD, peripheral vascular disease; Ref, reference.

modest, the association between ER metformin and improved adherence (equating to a 2.5% absolute increase in adherence and a 13% relative increase in persistence) is meaningful if it is causal. For perspective, a program that lowered copays for medication and provider visits as well as providing access to wellness coaching improved metformin adherence by 5% (1).

We believe these findings provide the strongest evidence to date that routine initial use of ER metformin is a simple intervention that may improve adherence. This is consistent with cost-effectiveness analyses suggesting that routine use of ER metformin could be cost-saving (5). However, these data only provide preliminary evidence for such a causal claim. Prospective studies of efforts to improve adherence to diabetes medications should evaluate use of ER metformin as a potentially important component.

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