

Supplementary Online Content

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eFigure 1. Consort Diagram

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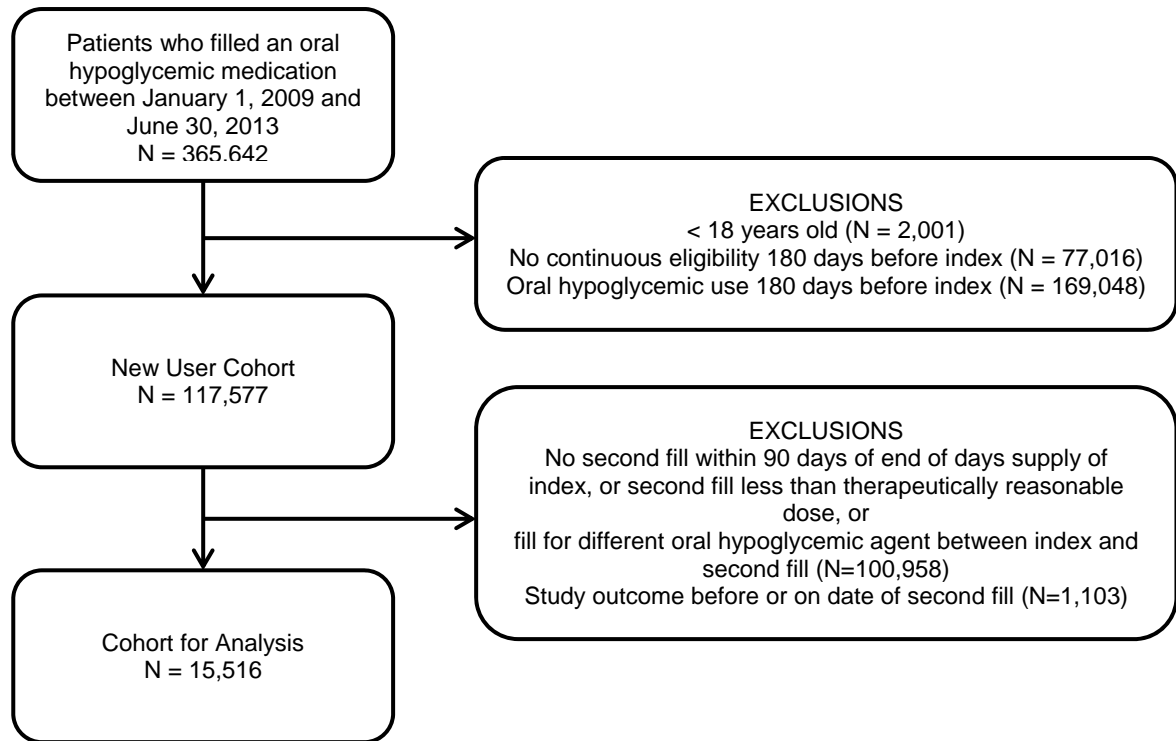
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This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Consort Diagram



eTable 1. Oral Glucose-Lowering Agents

Drug Class	Drug name	Index Drug
Alpha-glucosidase inhibitor	Acarbose	
	Miglitol	
Biguanide	Metformin hcl	x
Combination	Glipizide/metformin hcl	
	Glyburide, micronized/metformin hcl	
	Glyburide/metformin hcl	
	Metformin/amino acids comb. #7/herbal comb.#125/choline	
	Metformin/caffeine/amino acids#7/herbal comb#125/choline bit	
	Pioglitazone hcl/metformin hcl	
	Pioglitazone/glimepiride	
	Repaglinide/metformin hcl	
	Rosiglitazone maleate/glimepiride	
	Rosiglitazone maleate/metformin hcl	
	Sitagliptin phosphate/metformin hcl	
	Sitagliptin/simvastatin	
	Linagliptin/metformin	
Saxagliptin/metformin		
DPP-4 inhibitor	Sitagliptin phosphate	x
	Linagliptin	x
	Saxagliptin	x
GLP-1 receptor agonist	Exenatide	
	Liraglutide	
Meglitinide	Nateglinide	
	Repaglinide	
Pramlintide	Pramlintide acetate	
Sulfonylurea	Acetohexamide	x
	Chlorpropamide	x
	Glimepiride	x
	Glipizide	x
	Glyburide	x
	Glyburide,micronized	x
	Tolazamide	x
	Tolbutamide	x
Thiazolidinedione	Pioglitazone hcl	x
	Rosiglitazone maleate	x

eTable 2. Multivariable Time-Varying Models: Primary Therapy Intensification and Secondary Clinical Outcomes^a

Index Drug Class	Metformin	DPP-4 inhibitor		Sulfonylurea		Thiazolidinedione	
		≤1 year	> 1 year	≤1 year	> 1 year	≤1 year	> 1 year
Primary Outcome							
Treatment intensification: second oral agent or insulin	REF	1.54 (1.39, 1.72) [*]	2.06 (1.69, 2.51) [*]	1.66 (1.54, 1.78) [*]	1.76 (1.51, 2.06) [*]	1.50 (1.31, 1.71) [*]	2.08 (1.66, 2.60) [‡]
Treatment intensification: second oral agent	REF	1.59 (1.42, 1.77) [*]	2.19 (1.79, 2.67) [*]	1.64 (1.52, 1.77) [*]	1.71 (1.45, 2.00) [*]	1.51 (1.32, 1.73) [*]	2.08 (1.66, 2.62) [‡]
Treatment intensification: insulin	REF	1.16 (0.87, 1.56)	1.86 (1.28, 2.69) ^{**}	1.70 (1.43, 2.03) [*]	1.79 (1.38, 2.33) [*]	1.37 (0.97, 1.92)	1.02 (0.61, 1.71)
Secondary Outcome							
Diabetes-related ED visit	REF	1.06 (0.79, 1.43)	0.96 (0.58, 1.59)	1.18 (0.97, 1.45)	1.38 (1.00, 1.91)	1.18 (0.82, 1.70)	1.42 (0.83, 2.41)
Composite cardiovascular outcome	REF	1.04 (0.88, 1.23)	0.81 (0.59, 1.11)	1.23 (1.09, 1.38) ^{**}	0.90 (0.71, 1.15)	1.11 (0.90, 1.37)	0.86 (0.58, 1.27)
Congestive heart failure	REF	1.22 (1.06, 1.39) ^{**}	0.91 (0.72, 1.13)	1.25 (1.15, 1.37) [*]	1.02 (0.88, 1.18)	1.17 (0.98, 1.39)	0.89 (0.68, 1.17)

^aAdjusted for age, sex, index copayment, race, income, education, comorbidity, number of medications, number of physician visits, number of hospitalizations, combined comorbidity score, propensity score; ^{*}Significant at p<.0001; ^{**}Significant at p=.005

eTable 3. Multivariable Models, Sensitivity Analyses^a

Index Drug Class	Metformin	DPP-4 inhibitor	Sulfonylurea	Thiazolidinedione
<i>SENSITIVITY ANALYSIS 1: Diabetes Diagnosis Prior to Initiation</i>				
<i>Primary Outcome</i>				
Therapy intensification: second oral agent or insulin	REF	1.65 (1.45, 1.87) [*]	1.49 (1.36, 1.63) [*]	1.63 (1.40, 1.90) [*]
Therapy intensification: second oral agent	REF	1.72 (1.51, 1.96) [*]	1.48 (1.35, 1.63) [*]	1.66 (1.42, 1.94) [*]
Therapy intensification: insulin	REF	1.33 (0.99, 1.80)	1.43 (1.17, 1.74) ^{**}	1.20 (0.83, 1.74)
<i>Secondary Outcome</i>				
Diabetes-related ED visit	REF	0.85 (0.62, 1.18)	1.18 (0.96, 1.46)	1.18 (0.81, 1.72)
Composite cardiovascular outcome	REF	0.97 (0.80, 1.16)	1.16 (1.02, 1.32)	1.04 (0.82, 1.31)
Congestive heart failure	REF	0.97 (0.83, 1.13)	1.13 (1.02, 1.25)	1.03 (0.86, 1.25)
<i>SENSITIVITY ANALYSIS 2: No Prior Cardiovascular Disease</i>				
Composite cardiovascular outcome	REF	1.04 (0.83, 1.29)	1.11 (0.96, 1.28)	0.97 (0.74, 1.26)
Composite cardiovascular outcome without revascularization	REF	1.04 (0.83, 1.29)	1.11 (0.96, 1.28)	0.97 (0.75, 1.26)
Congestive heart failure	REF	1.15 (1.01, 1.30)	1.18 (1.09, 1.28) [*]	1.08 (0.93, 1.26)
<i>SENSITIVITY ANALYSIS 3: Index Medication on Hand at Intensification</i>				
Therapy intensification: second oral agent or insulin	REF	1.38 (1.22, 1.56) [*]	1.65 (1.53, 1.79) [*]	1.53 (1.32, 1.77) [*]
Therapy intensification: second oral agent	REF	1.42 (1.25, 1.61) [*]	1.66 (1.53, 1.80) [*]	1.57 (1.35, 1.83) [*]

^aAdjusted for age, sex, index copayment, race, income, education, comorbidity, number of medications, number of physician visits, number of hospitalizations, combined comorbidity score, propensity score; ^{*}Significant at p<.0001; ^{**}Significant at p=.005

eTable 4. Multivariable Models: Primary Therapy Intensification Outcome^a

Variables	Therapy intensification: second oral agent or insulin	Therapy intensification: second oral agent	Therapy intensification: insulin
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Index Drug Class			
Metformin	REF	REF	REF
DPP-4 inhibitor	1.62 (1.47, 1.79) [*]	1.68 (1.52, 1.87) [*]	1.35 (1.06, 1.74)
Sulfonylurea	1.68 (1.57, 1.79) [*]	1.65 (1.54, 1.77) [*]	1.73 (1.49, 2.00) [*]
Thiazolidinedione	1.61 (1.43, 1.80) [*]	1.62 (1.44, 1.83) [*]	1.24 (0.93, 1.67)
Age (ref=<55)			
Age 55 - 64	1.01 (0.95, 1.09)	1.03 (0.95, 1.10)	0.91 (0.77, 1.08)
Age 65+	0.82 (0.74, 0.92) ^{**}	0.81 (0.72, 0.92) ^{**}	0.96 (0.74, 1.25)
Sex	1.13 (1.06, 1.20) [*]	1.14 (1.07, 1.21) [*]	1.05 (0.91, 1.20)
Index out-of-pocket spend (\$)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Median income in zip (ref=<\$50,000)			
\$50,000 - \$99,999	1.04 (0.97, 1.12)	1.04 (0.96, 1.12)	0.88 (0.74, 1.03)
\$100,000+	0.92 (0.80, 1.06)	0.97 (0.84, 1.12)	0.57 (0.40, 0.81) ^{**}
Percent black in zip	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)
Percent with high school education or greater in zip	0.99 (0.99, 1.00) [*]	0.99 (0.99, 1.00) [*]	1.00 (0.99, 1.00)
Comorbidity			
Chronic Kidney Disease	0.98 (0.82, 1.17)	0.98 (0.81, 1.18)	1.11 (0.76, 1.60)
Coronary Artery Disease	1.03 (0.92, 1.16)	0.99 (0.88, 1.12)	1.28 (1.01, 1.63)
Ischemic stroke	0.96 (0.75, 1.23)	0.98 (0.75, 1.27)	0.95 (0.57, 1.58)
Congestive Heart Failure	0.94 (0.74, 1.20)	0.90 (0.69, 1.18)	1.09 (0.70, 1.69)
Asthma or COPD	1.03 (0.90, 1.16)	1.08 (0.95, 1.24)	0.93 (0.71, 1.21)
Depression	1.03 (0.89, 1.18)	1.04 (0.90, 1.21)	1.06 (0.79, 1.44)
Hypertension	1.08 (1.01, 1.16) ^{**}	1.09 (1.01, 1.17) ^{**}	0.96 (0.82, 1.12)
Atrial fibrillation	0.91 (0.71, 1.15)	0.99 (0.77, 1.27)	0.62 (0.36, 1.08)
Number of unique medications	0.98 (0.97, 0.99) [*]	0.98 (0.97, 0.99) [*]	1.00 (0.98, 1.02)
Number of physician visits	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	1.01 (1.00, 1.02)
Number of hospitalizations	1.08 (0.97, 1.20)	1.04 (0.93, 1.17)	1.27 (1.05, 1.53)
Combined comorbidity score	0.98 (0.95, 1.02)	0.95 (0.92, 0.99)	1.09 (1.01, 1.17) [*]

^aAdditionally adjusted for propensity score; ^{*} Significant at p<.0001; ^{**} Significant at p=.005

eTable 5. Multivariable Models: Secondary Clinical Outcome^a

Variables	Diabetes-related ED visit	Composite cardiovascular outcome	Congestive Heart Failure
	HR (95%CI)	HR (95%CI)	HR (95%CI)
Index Drug Class			
Metformin	REF	REF	REF
DPP-4 inhibitor	1.04 (0.79, 1.36)	0.99 (0.85, 1.16)	1.13 (1.00, 1.28)
Sulfonylurea	1.23 (1.04, 1.46)	1.16 (1.04, 1.29)	1.19 (1.10, 1.28)*
Thiazolidinedione	1.24 (0.91, 1.70)	1.05 (0.87, 1.27)	1.08 (0.93, 1.26)
Age (ref=<55)			
Age 55 - 64	0.71 (0.59, 0.86)**	1.60 (1.43, 1.79)*	0.87 (0.80, 0.95)**
Age 65+	0.75 (0.56, 1.00)	1.51 (1.28, 1.77)*	0.90 (0.79, 1.02)
Sex	1.12 (0.96, 1.30)	1.45 (1.32, 1.60)*	0.92 (0.86, 0.98)
Index out-of-pocket spend (\$)	1.00 (0.99, 1.00)	1.00 (0.99, 1.00)**	1.00 (1.00, 1.00)
Median Income (ZIP)(ref=<\$50,000)			
\$50,000 - \$99,999	1.02 (0.84, 1.23)	0.99 (0.89, 1.11)	0.98 (0.90, 1.07)
\$100,000+	1.02 (0.71, 1.46)	1.01 (0.82, 1.24)	0.95 (0.82, 1.11)
Percent non-Hispanic black (ZIP)	1.01 (1.00, 1.01)*	1.00 (1.00, 1.00)	1.01 (1.00, 1.01)*
Percent ≥ HS education (ZIP)	1.00 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Comorbidity			
Chronic Kidney Disease	0.95 (0.66, 1.37)	0.85 (0.69, 1.04)	0.95 (0.79, 1.14)
Coronary Artery Disease	0.97 (0.76, 1.25)	8.34 (7.49, 9.29)*	1.21 (1.07, 1.36)**
Ischemic stroke	1.30 (0.86, 1.96)	2.37 (1.97, 2.85)*	1.17 (0.94, 1.44)
Congestive Heart Failure	1.16 (0.78, 1.71)	2.49 (2.09, 2.98)*	1.10 (0.90, 1.35)
Asthma or COPD	1.40 (1.10, 1.78)	1.25 (1.08, 1.45)**	1.33 (1.19, 1.49)*
Depression	1.45 (1.11, 1.90)	1.06 (0.87, 1.29)	1.16 (1.02, 1.32)
Hypertension	1.57 (1.32, 1.86)*	1.72 (1.54, 1.92)*	1.41 (1.30, 1.52)*
Atrial fibrillation	1.28 (0.86, 1.89)	1.06 (0.88, 1.29)	1.15 (0.94, 1.41)
Number of unique medications	1.03 (1.01, 1.05)	1.03 (1.02, 1.04)*	1.03 (1.02, 1.04)*
Number of physician visits	1.02 (1.01, 1.03)*	1.00 (1.00, 1.01)	1.02 (1.02, 1.02)*
Number of hospitalizations	1.52 (1.30, 1.76)*	1.08 (0.98, 1.19)	1.28 (1.18, 1.40)*
Combined comorbidity score	1.05 (0.98, 1.12)	1.02 (0.98, 1.06)	1.12 (1.08, 1.15)*

^aAdditionally adjusted for propensity score; * Significant at p<.0001; ** Significant at p=.005

eTable 6. Specific Sulfonylurea and Thiazolidinedione Agents and Cardiovascular Outcomes

Index drug generic	Index N	Composite cardiovascular outcome (N)	Percent
Glimepiride (SFU)	1447	263	18.2
Glipizide (SFU)	1393	254	18.2
Glyburide (SFU)	728	107	14.7
Tolazamide (SFU)	1	0	0
Tolbutamide (SFU)	1	0	0
Pioglitazone (TZD)	910	143	15.7
Rosiglitazone (TZD)	38	7	18.4