SUPPLEMENTARY DATA

Supplemental Table 1. Included and Excluded RCTs from Drug Manufacturer Websites

Reference	Included (Y/N)	Reason for Exclusion
GLP-1RA		
Liraglutide/ Victoza® (Novo Nordisk)[a]		
Garber A, Henry R, Ratner R, Garcia-Hernandez PA, Rodriguez-Pattzi H, Olvera-Alvarez I, Hale PM, Zdravkovic M, Bode B, Lead Study Group: Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473-481.	Y	
Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, Zdravkovic M, During M, Matthews DR, Lead Study Group: Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32:84-90.	Y	
Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand J, Zdravkovic M, Le Thi TD, Colagiuri S, Lead-Su study group: Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabetic medicine : a journal of the British Diabetic Association 2009;26:268-278.	Y	
Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Sondergaard RE, Davies M, and the Lira-Dpp Study Group: Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010;375:1447-	Y	

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1456.		
Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, Hale PM, Zdravkovic M, Blonde L, Lead-4 Study Investigators: Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+ TZD). Diabetes Care 2009;32:1224-1230.	Y	
Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Sondergaard RE, Davies M, and the Lira-Dpp Study Group: Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010;375:1447-1456.[b]	Y	
Exenatide/ Bydureon® (Amylin)[c]		
Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K, Trautmann M: Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 2010;375:2234-2243.	Y	
Blevins T, Pullman J, Malloy J, Yan P, Taylor K, Schulteis C, Trautmann M, Porter L: DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. The Journal of clinical endocrinology and metabolism 2011;96:1301-1310.	Y	
Yki-Jarvinen H, Juurinen L, Alvarsson M, Bystedt T, Caldwell I, Davies M, Lahdenpera S, Nijpels G, Vahatalo M: Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care 2007;30:1364-1369.	N	Study designed to evaluate the initiation of exenatide in combination with insulin, not the addition of exenatide alone
DPP4		

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Sitagliptin/ Januvia® (Merck)[d]

Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP, Sitagliptin Study Group: Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes, obesity & metabolism 2007;9:194-205.	Y	
Arechavaleta R, Seck T, Chen Y, Krobot KJ, O'Neill EA, Duran L, Kaufman KD, Williams-Herman D, Goldstein BJ: Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes, obesity & metabolism 2011;13:160-168.	Y	
Barzilai N, Guo H, Mahoney EM, Caporossi S, Golm GT, Langdon RB, Williams-Herman D, Kaufman KD, Amatruda JM, Goldstein BJ, Steinberg H: Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin 2011;27:1049-1058.	N	elderly patients
Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE, Sitagliptin 036 Study Group: Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007;30:1979-1987.	N	Drug-naïve patients
Raz I, Chen Y, Wu M, Hussain S, Kaufman KD, Amatruda JM, Langdon RB, Stein PP, Alba M: Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. Curr Med Res Opin 2008;24:537-550.	N	Moderately severe type 2 diabetes (mean baseline HbA1c 9.2%)
Vilsboll T, Rosenstock J, Yki-Jarvinen H, Cefalu WT, Chen Y, Luo E, Musser B, Andryuk PJ, Ling Y, Kaufman KD, Amatruda JM, Engel SS, Katz L: Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab 2010;12:167-177.	N	Study designed to evaluate the initiation of sitagliptin in combination with insulin, not the addition of sitagliptin

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		alone
Chan JC, Scott R, Arjona Ferreira JC, Sheng D, Gonzalez E, Davies MJ, Stein PP, Kaufman KD, Amatruda JM, Williams-Herman D: Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes Obes Metab 2008;10:545-555.	N	Patients with renal insufficiency
Arjona Ferreira JC, Marre M, Barzilai N, Guo H, Golm GT, Sisk CM, Kaufman KD, Goldstein BJ: Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes and moderate-to-severe chronic renal insufficiency. Diabetes Care 2013;36:1067-1073.	N	Patients with renal insufficiency
Arjona Ferreira JC, Corry D, Mogensen CE, Sloan L, Xu L, Golm GT, Gonzalez EJ, Davies MJ, Kaufman KD, Goldstein BJ: Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis 2013;61:579-587.	N	Patients with renal insufficiency
Saxagliptin/ Onglyza® (AstraZeneca)[e]		
DeFronzo RA, Hissa MN, Garber AJ, Gross JL, Duan RY, Ravichandran S, Chen RS, Saxagliptin 014 Study Group: The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. Diabetes Care 2009;32:1649-1655.	Y	
Göke B, Gallwitz B, Eriksson J, Hellqvist Å, Gause-Nilsson I: Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. International journal of clinical practice 2010;64:1619-1631.	Y	
Jadzinsky M, Pfutzner A, Paz-Pacheco E, Xu Z, Allen E, Chen R, C. V. Investigators: Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. Diabetes Obes Metab 2009;11:611-622.	N	Drug naïve patients (not previously treated with any type 2 diabetes medications)

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Nowicki M, Rychlik I, Haller H, Warren ML, Suchower L, Gause-Nilsson I, D. C. Investigators: Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. Diabetes Obes Metab 2011;13:523-532.	N	Patients with renal impairment

Caption:

Abbreviations: HbA1c = glycated hemoglobin; N = no; Y = yes.

Notes:

[a] The website https://www.victozapro.com/ was last searched in August 2016.

[b] Data from both the liraglutide and sitagliptin arms in this study were included in the current analyses.

[c] The website https://www.bydureonhcp.com/ was last searched August 2016.

[d] The website https://www.merckconnect.com/januvia/overview.html was last searched August 2016.

[e] The website https://www.onglyza-hcp.com/ was last searched August 2016.

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SUPPLEMENTARY DATA

Supplemental Table 2. Diagnosis Codes

Diagnosis	ICD-9-CM
Study inclusion criteria	
Type 2 Diabetes	250.x0, 250.x2
Study exclusion criteria	
Type 1 Diabetes	250.x1, 250.x3
Secondary Diabetes	249.x
Gestational Diabetes	648.8
Dementia	290.x, 294.1, 331.2
Hemiplegia	334.1, 342.x, 343.x, 344.0– 344.6, 344.9
Metastatic Solid Tumor	196.x–199.x
Liver Disease	456.0–456.2, 572.2–572.8
AIDS	042.x–044.x
Malignancy	140.x–172.x, 174.x–195.8, 200.x–208.x, 238.6

Caption:

Abbreviations: AIDS = acquired immune deficiency syndrome; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

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SUPPLEMENTARY DATA

Supplemental Table 3. Data extracted from included RCTs

Drug Class	RCT, author	Drug	Dosage	Follow-up (weeks)	Baseline HbA1c, %	Change of HbA1c, %	Age (mean years)	Use of advanced therapy prior to randomization[a], %	White, %	Male, %	Number of Patients
GLP-1RA	Garber et al. (28)	Liraglutide	1.2 mg	52	8.30	-0.84	53.7	36	80	47	246
			1.8 mg	52	8.30	-1.14	52.0	35	75	49	251
	Nauck et al. (20)	Liraglutide	0.6 mg	26	8.4	-0.70	56.0	71	84	62	242
			1.2 mg	26	8.30	-1.00	57.0	68	88	54	240
			1.8 mg	26	8.40	-1.00	57.0	70	88	59	242
	Marre et al. (25)	Liraglutide	0.6 mg	26	8.4	-0.60	55.7	70	N/A	54	233
			1.2 mg	26	8.50	-1.08	57.7	69	N/A	45	228
			1.8 mg	26	8.50	-1.13	55.6	73	N/A	53	234
	Pratley et al. (19)	Liraglutide	1.2 mg	26	8.40	-1.24	55.9	0	82	52	225
			1.8 mg	26	8.40	-1.50	55.0	0	87	52	221
	Zinman et al. (29)	Liraglutide	1.2 mg	26	8.50	-1.50	55.0	84	81	57	178
			1.8 mg	26	8.60	-1.50	55.0	84	83	51	178
	Diamant	Exenatide	2 mg	26	8.30	-1.50	58.0	30	82	52	228

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	et al. (26)	QW									
	Blevins et al. (27)	Exenatide QW	2 mg	24	8.50	-1.60	56.0	57	63	60	129
DPP-4	Nauck et al. (20)	Sitagliptin	100 mg	52	7.50	-0.67	56.8	34	74	57	382
	Arechaval eta et al. (32)	Sitagliptin	100 mg	30	7.50	-0.47	56.3	0	58	55	443
	DeFronzo et al. (31)	Saxagliptin	2.5 mg	24	8.10	-0.59	54.7	0	80	43	186
		Saxagliptin	5 mg	24	8.10	-0.69	54.7	0	83	54	186
		Saxagliptin	10 mg	24	8.00	-0.58	54.2	0	80	53	180
	Göke et al. (33)	Saxagliptin	5 mg	52	7.46	-0.74	57.5	0	82	50	293
	Pratley et al. (19)	Sitagliptin	100 mg	26	8.50	-0.90	55.0	0	91	55	219

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SUPPLEMENTARY DATA

Caption:

Sources of all RCTs are listed in **Supplemental Table 1**. Last observation carried forward (LOCF) was reported in all trials, except Göke et al. (33) which removed from their analysis patients who received supplemental diabetes medications (e.g. rescue).

Abbreviations: DPP4 = dipeptidyl peptidase 4; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; mg = milligrams; N/A = not available; RCT = randomized controlled trial; QW = once weekly.

Notes:

[a] Use of advanced therapy prior to randomization is defined as 100% minus the percent of patients who were only on metformin monotherapy.

[b] Two low dose (0.6 mg) liraglutide treatment arms were excluded.

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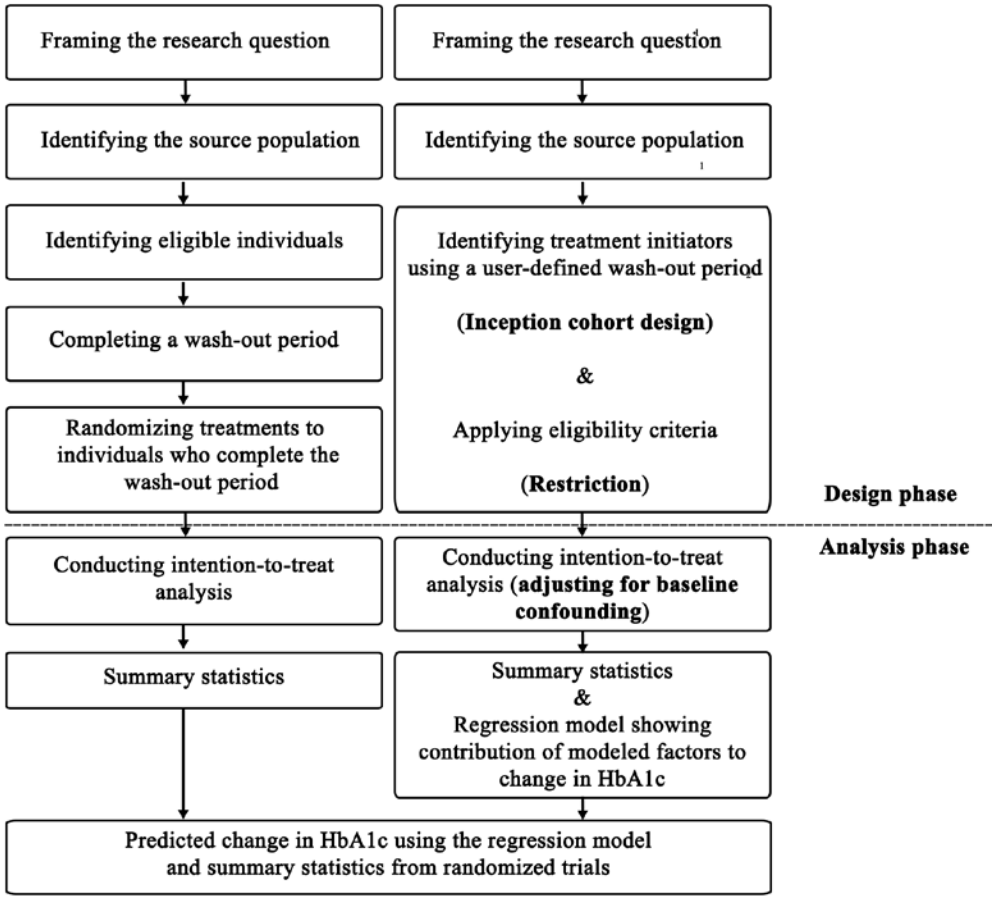
SUPPLEMENTARY DATA

Supplemental Figure 1. Conceptual Framework for Comparing Randomized Trial and Real-world Data



Legend:

Adapted from: Toh S, Manson JE. An analytic framework for aligning observational and randomized trial data: Application to postmenopausal hormone therapy and coronary heart disease. *Stat Biosci.* Nov 01 2013;5(2). Abbreviations: HbA1c = glycated hemoglobin.

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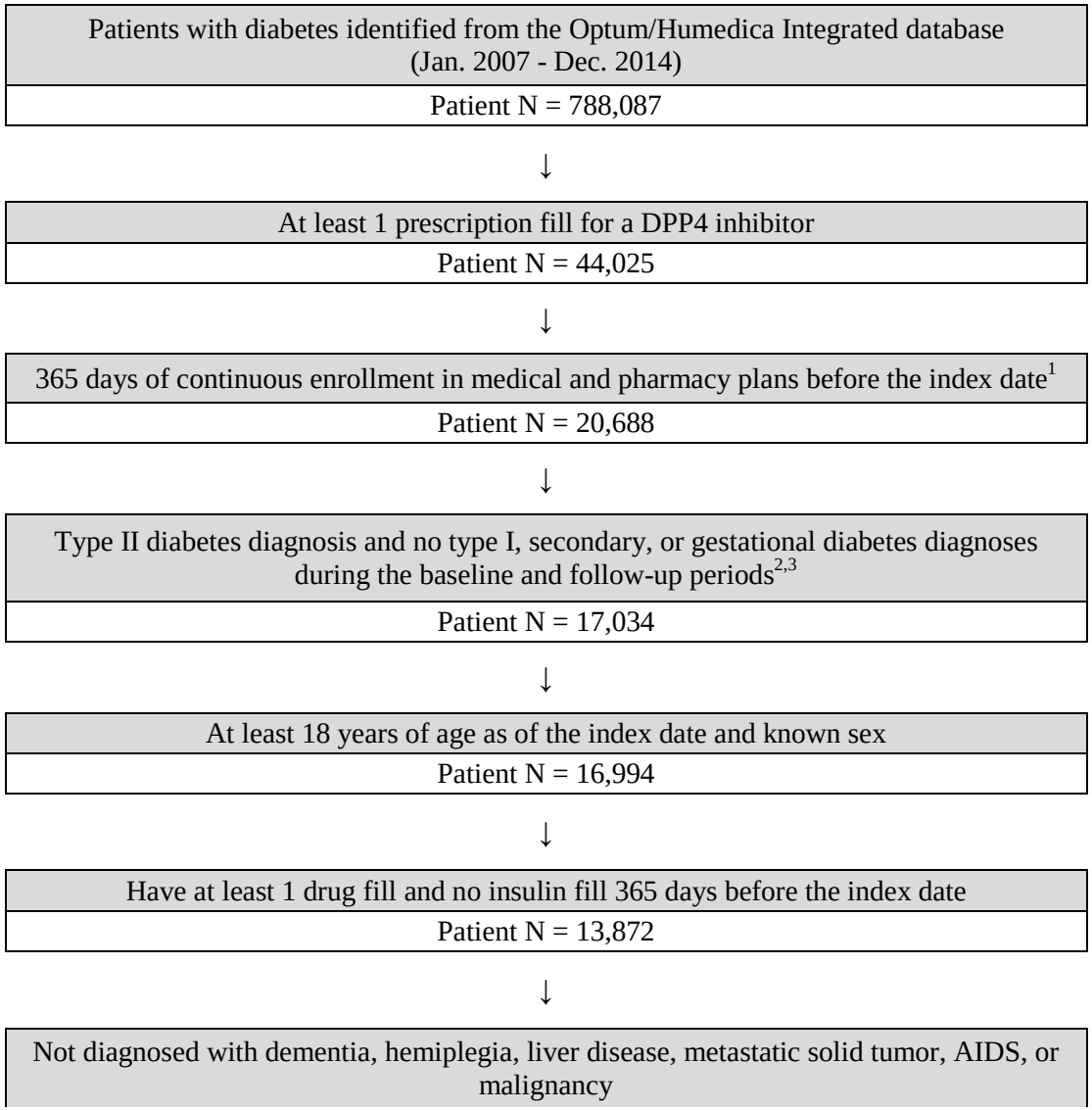
SUPPLEMENTARY DATA

Supplemental Figure 2. Selection of Real-World Patients with Type II Diabetes who Initiated a DPP4 Inhibitor



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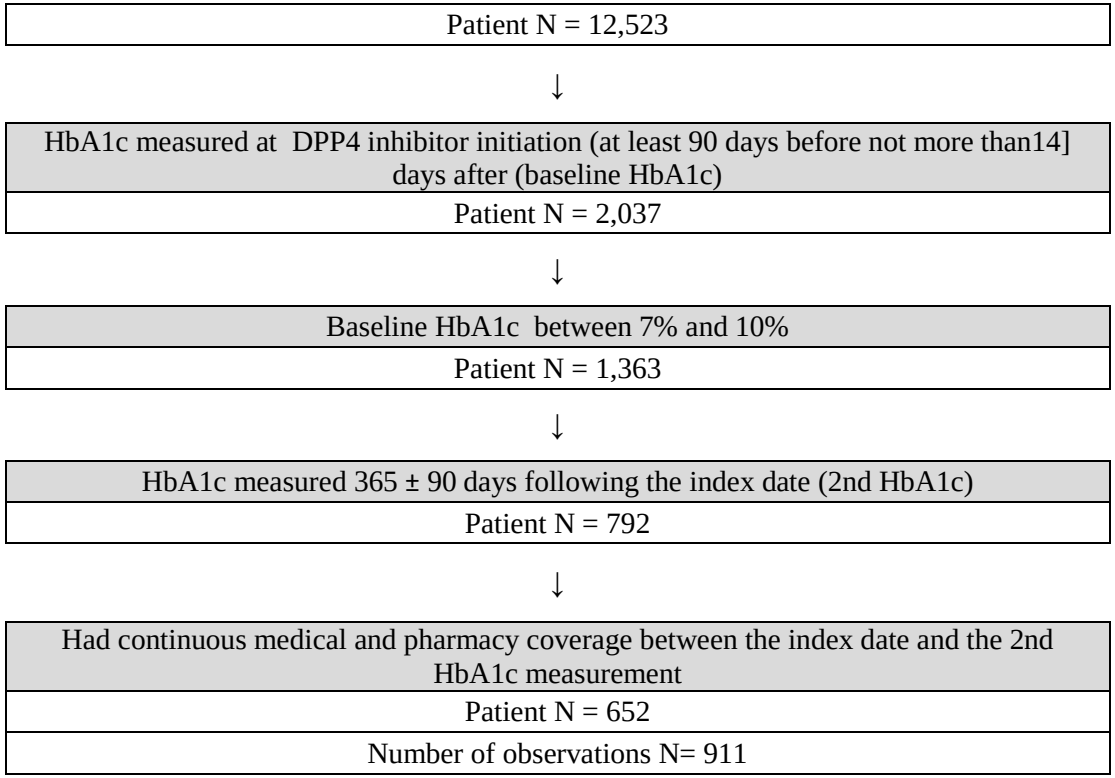
SUPPLEMENTARY DATA



Notes:

1. The index date is the earliest prescription fill date for a DPP4-containing diabetes medication.
2. Baseline is the 365-day period prior to the index date. Patients are followed up until the 2nd HbA1c reading, measured 365 ± 90 days following the index date.
3. Diabetes diagnoses based on ICD-9-CM diagnosis codes: 250.x0 and 250.x2 (type II), 250.x1 and 250.x3 (type I), 249.xx (secondary), 648.8 (gestational).

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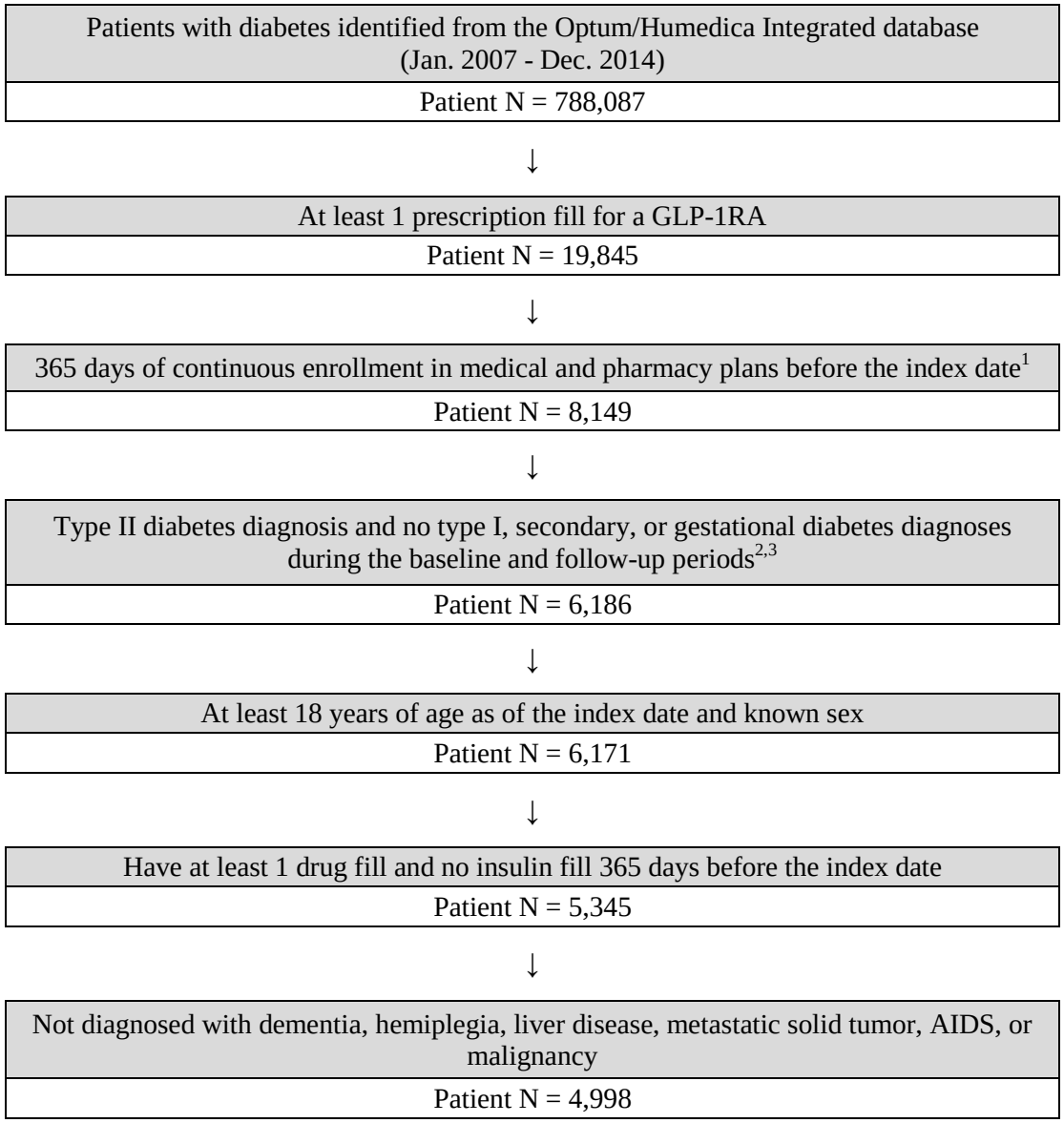
SUPPLEMENTARY DATA

Supplemental Figure 3. Selection of Real-World Patients with Type II Diabetes who Initiated a GLP-1RA



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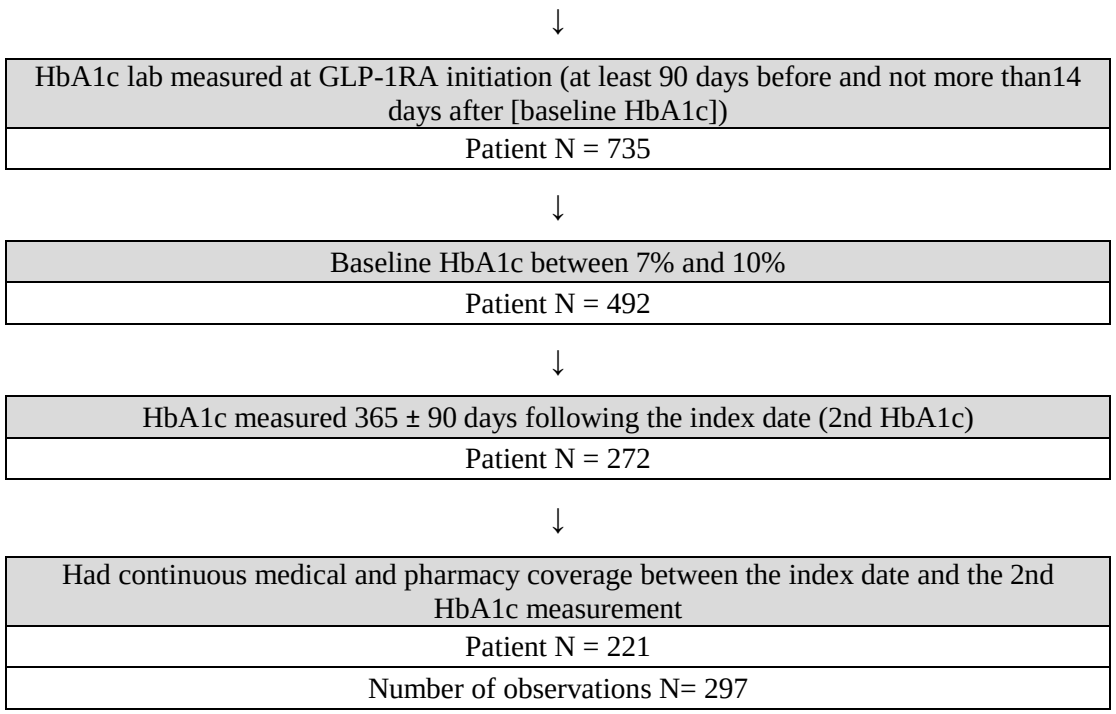
SUPPLEMENTARY DATA



Notes:

1. The index date is the earliest prescription fill date for a GLP-1 agonist-containing diabetes medication.
2. Baseline is the 365-day period prior to the index date. Patients are followed up until the 2nd HbA1c reading, measured 365 ± 90 days following the index date.
3. Diabetes diagnoses based on ICD-9-CM diagnosis codes: 250.x0 and 250.x2 (type II), 250.x1 and 250.x3 (type I), 249.xx (secondary), 648.8 (gestational).

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