

## Appendix A: Outcome Definitions

Diseases	ICD-9-CM Diagnosis Codes	Description	ICD-10-CM Diagnosis Codes	Description
<b>Microvascular complications</b>				
<b>Retinopathy</b>				
	250.5x	Diabetes with ophthalmic manifestations	E08.3%	Diabetes mellitus due to underlying condition with ophthalmic complications
Diabetic ophthalmologic disease	362.0x	Diabetic retinopathy	E10.3%	Type 1 diabetes mellitus with ophthalmic complications
			E11.3%	Type 2 diabetes mellitus with ophthalmic complications
			E13.3%	Other specified diabetes mellitus with ophthalmic complications
Background retinopathy	362.1x	Other background retinopathy and retinal vascular changes	H35.0%	Background retinopathy and retinal vascular changes
Other non-diabetic proliferative retinopathy	362.1x	Other background retinopathy and retinal vascular changes	H35.2%	Other non-diabetic proliferative retinopathy
			H35.4%	Peripheral retinal degeneration
			H35.7%	Separation of retinal layers
			H35.8%	Other specified retinal disorders
Retinal edema	362.83	Retinal edema	H35.81%	Retinal edema
CSME	362.53	Cystoid macular degeneration	H35.35%	Cystoid macular degeneration
Other retinal disorders	362.81	Retinal hemorrhage	H35.9%	Unspecified retinal disorder
	362.82	Retinal exudates and deposits		
Proliferative diabetic	362.02	Proliferative diabetic retinopathy	H35.2%	Other non-diabetic proliferative

retinopathy		retinopathy		
			E08.35%, E10.35%, E11.35%, E13.35%	proliferative diabetic retinopathy in diabetes mellitus
Retinal detachment	361.xx	Retinal detachments and defects	H33.0%	Retinal detachments and breaks
			H33.2%	Serous retinal detachment
Blindness	369.xx	Blindness and low vision	H54.0%	Blindness, both eyes
			H54.1%	Blindness, one eye, low vision other eye
			H54.4%	Blindness, one eye
			H54.8%	Legal blindness, as defined in USA
Vitreous hemorrhage	379.23	Vitreous hemorrhage	H43.1%	Vitreous hemorrhage
<b>Nephropathy</b>				
			E08.2%	Diabetes mellitus due to underlying condition with kidney complications
Diabetic nephropathy	250.4x	Diabetes with renal manifestations	E10.2%	Type 1 diabetes mellitus with kidney complications
			E11.2%	Type 2 diabetes mellitus with kidney complications
			E13.2%	Other specified diabetes mellitus with kidney complications
Acute glomerulonephritis	580.xx	Acute glomerulonephritis	N00.%	Acute nephritic syndrome
Nephrotic syndrome	581.xx	Nephrotic syndrome	N04.%	Nephrotic syndrome
Hypertension, nephrosis	581.81	Nephrotic syndrome in diseases classified elsewhere	I12.%	Hypertensive chronic kidney disease
			I13.%	Hypertensive heart and chronic kidney disease
Chronic glomerulonephritis	582.xx	Chronic glomerulonephritis	N03.%	Chronic nephritic syndrome

Unspecified Nephritis/nephropathy	583.xx	Nephritis and nephropathy, not specified as acute or chronic	N05.%	Unspecified nephritic syndrome
Chronic kidney disease (CKD)	585.xx	Chronic kidney disease (CKD)	N18.%	Chronic kidney disease (CKD)
Renal failure	586.xx	Unspecified renal failure	N19.%	Unspecified kidney failure
Renal insufficiency	593.9x	Unspecified disorder of kidney and ureter	N28.9%	Disorder of kidney and ureter, unspecified
			N18.9%	Chronic kidney disease, unspecified
<b>Neuropathy</b>				
Diabetic neuropathy	250.6x	Diabetes with neurological manifestations	E08.4%	Diabetes mellitus due to underlying condition with neurological complications
	356.9x	Unspecified, Hereditary and idiopathic peripheral neuropathy	E10.4%	Type 1 diabetes mellitus with neurological complications
			E11.4%	Type 2 diabetes mellitus with neurological complications
			E13.4%	Other specified diabetes mellitus with neurological complications
Amyotrophy (nondiabetic)	358.1x	Myasthenic syndromes in diseases classified elsewhere	G12.21%	Amyotrophic lateral sclerosis
			G54.5%	Neuralgic amyotrophy
Cranial nerve palsy (including ophthalmic)	951.0x, 951.1x, 951.3x	Injury to oculomotor nerve; Injury to trochlear nerve; Injury to abducens nerve	G51.0%, G52.%, H49.0%, H49.1%, H49.2%	Bell's palsy; Disorders of other cranial nerves; Third [oculomotor] nerve palsy; Fourth [trochlear] nerve palsy; Sixth [abducent] nerve palsy
Mononeuropathy	354.xx	Mononeuritis of upper limb and mononeuritis multiplex	G56.%	Mononeuropathies of upper limb

	355.xx	Mononeuritis of lower limb and unspecified site	G57.%	Mononeuropathies of lower limb
			G58.%	Other mononeuropathies
			G59.%	Mononeuropathy in diseases classified elsewhere
Charcot's arthropathy	713.5x	Arthropathy associated with neurological disorders	E08.610, E09.610, E10.610, E11.610, E13.610	Charcot's joint in diabetes mellitus (E08, E10-E13 with .610)
			M14.6%	Charcot's joint - Excludes Charcot's joint in diabetes mellitus (E08-E13 with .610)
	357.2x	Polyneuropathy in diabetes	E08.42, E09.42, E10.42, E11.42, E13.42	polyneuropathy in diabetes mellitus (E08-E13 with .42)
			G61.%	Inflammatory polyneuropathy
Polyneuropathy			G62.%	Other and unspecified polyneuropathies
			G63.%	Polyneuropathy in diseases classified elsewhere
			G60.3%	Idiopathic progressive neuropathy
Neurogenic bladder	596.54	Neurogenic bladder NOS	N31.9%	Neuromuscular dysfunction of bladder, unspecified
	337.0x	Idiopathic peripheral autonomic neuropathy	G90.0%	Idiopathic peripheral autonomic neuropathy
Autonomic neuropathy	337.1x	Peripheral autonomic neuropathy in disorders classified elsewhere	G90.8%	Other disorders of autonomic nervous system
			G90.9%	Disorder of the autonomic nervous system, unspecified
Gastroparesis (including diabetic)	536.3x	Gastroparesis	K31.84%	Gastroparesis
	564.5	Functional diarrhea	E08.43%, E10.43%	diabetic autonomic (poly)neuropathy in

			E11.43%, E13.43%	diabetes mellitus
	458.0x	Orthostatic hypotension	I95.1%	Orthostatic hypotension
Orthostatic hypotension			I95.2%	Hypotension due to drugs
			G90.3%	Multi-system degeneration of the autonomic nervous system
<b>Macrovascular complications</b>				
<b>Cerebrovascular</b>				
Stroke - hemorrhage	430.xx	Subarachnoid hemorrhage	I60.%	Nontraumatic subarachnoid hemorrhage
	431.xx	Intracerebral hemorrhage	I61.%	Nontraumatic intracerebral hemorrhage
	432.xx	Other and unspecified intracranial hemorrhage	I62.%	Other and unspecified nontraumatic intracranial hemorrhage
Stroke - ischemic	433.xx	Occlusion and stenosis of precerebral arteries	I65.%	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
	434.xx	Occlusion of cerebral arteries	I63.%	Cerebral infarction
TIA	435.xx	Transient cerebral ischemia	G45.%	Transient cerebral ischemic attacks and related syndromes
Other cerebrovascular disease	436.xx	Acute, but ill-defined, cerebrovascular disease (excluded stroke)	I67.%	Other cerebrovascular diseases
	437.xx	Other and ill-defined cerebrovascular disease	I68.%	Cerebrovascular disorders in diseases classified elsewhere
	438.xx	Late effects of cerebrovascular disease	I69.%	Sequelae of cerebrovascular disease
			G46.%	Vascular syndromes of brain in cerebrovascular diseases
<b>Cardiovascular</b>				

Myocardial infarction (acute)	410.xx	Acute myocardial infarction	121.%	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
			122.%	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
			123.%	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period)
Other acute IHD	411.xx	Other acute and subacute forms of ischemic heart disease	124.%	Other acute ischemic heart diseases
Old myocardial infarction	412.xx	Old myocardial infarction	125.2%	Old myocardial infarction
Angina pectoris	413.xx	Angina pectoris	120.%	Angina pectoris
Other chronic IHD	414.xx	Other forms of chronic ischemic heart disease	125.%	Chronic ischemic heart disease
Atherosclerosis	440.xx	Atherosclerosis	170.%	Atherosclerosis
Aortic aneurysm/dissection	441.xx	Aortic aneurysm and dissection	171.%	Aortic aneurysm and dissection
Other aneurysm	442.xx	Other aneurysm	172.%	Other aneurysm
Arterial embolism and thrombosis	444.xx	Arterial embolism and thrombosis	174.%	Arterial embolism and thrombosis
Atheroembolism	445.xx	Atheroembolism	175.%	Atheroembolism
Ventricular fibrillation	427.4x	Ventricular fibrillation and flutter	149.0%	Ventricular fibrillation and flutter
Atrial fibrillation	427.3x	Atrial fibrillation and flutter	148.%	Atrial fibrillation and flutter
Heart failure	428.xx	Heart failure	150.%	Heart failure
Cardiovascular disease, unspecified	429.2x	Cardiovascular disease, unspecified	169.9%	Sequelae of unspecified cerebrovascular diseases

Peripheral vascular disease				
Diabetic PVD	249.7x	Secondary diabetes mellitus with peripheral circulatory disorders		
	250.7x	Diabetes with peripheral circulatory disorders	E08.5%, E10.5%, E11.5%, E13.5%	Diabetes mellitus with circulatory complications
Other PVD	443.xx	Other peripheral vascular disease	I73.%	Other peripheral vascular diseases
Other disorders of arteries and arterioles	447.xx	Other disorders of arteries and arterioles	I77.%	Other disorders of arteries and arterioles
Gangrene/Ulcer				
Gangrene in diabetes mellitus	250.7x	Diabetes with peripheral circulatory disorders (gangrene)	E08.52%	Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy with gangrene
	249.7x	Secondary diabetes mellitus with peripheral circulatory disorders (diabetic gangrene)	E10.52%	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
			E11.52%	Type 2 diabetes mellitus with diabetic peripheral angiopathy with gangrene
			E13.52%	Other specified diabetes mellitus with diabetic peripheral angiopathy with gangrene
Foot ulcer	250.8x	Diabetes with other specified manifestations (any associated ulceration)	E08.621	Diabetes mellitus due to underlying condition with foot ulcer
	249.8x	Secondary diabetes mellitus with other specified manifestations ( any associated ulceration)	E10.621	Type 1 diabetes mellitus with foot ulcer
E11.621			Type 2 diabetes mellitus with foot ulcer	

			E13.621	Other specified diabetes mellitus with foot ulcer
			L89.5%	Pressure ulcer of ankle
			L89.6%	Pressure ulcer of heel
Ulcer of lower limbs	707.1x	Ulcer of lower limbs, except pressure ulcer	L97.%	Non-pressure chronic ulcer of lower limb, not elsewhere classified
Gas gangrene	040.xx		A48.0%	Other bacterial diseases, not elsewhere classified, Gas gangrene
Foot wound	892.1x	Open wound of foot except toe(s) alone, complicated	S91.%	Open wound of ankle, foot and toes
Gangrene (not diabetic)	785.4x	Gangrene	I96.%	Gangrene, not elsewhere classified (excluded gangrene in diabetes mellitus)

CSME: cystoid macular edema/degeneration; NOS, not otherwise specified; TIA, transient ischemic attack; IHD, ischemic heart disease; ASCVD, atherosclerotic cardiovascular disease; PVD, peripheral vascular disease; LE, lower extremity.



## Appendix B: Definitions of Comorbidities

Comorbidities	ICD-9	ICD-10
Mental illness (substance abuse, schizophrenia, depression, other mental disorders)	291.0-292.9, 295.0-295.9, 296.0-296.9, 300.4, 301.12, 303.0-305.9, 308.0, 309.0, 309.1, 309.28, 309.81, 311	F11-F20, F30, F31, F32, F39, F341, F43, F329
Any cardiovascular disease	390-459	I00-I99
Hypertension	401-405	I10-I13, I15
Coronary artery disease	410-414	I20-I25
Angina	411, 413	I20, I24
MI	410	I21
Congestive heart failure (CHF)	398.91, 428	I0981, I50
Peripheral vascular disease	443	I73, I77, I798
Other cardiovascular diseases	390-459 (excluding 401-405, 410-414, 428, 398.91, 394-397, 424, 443)	I00-I99 (excluding I10-I13, I15, I20-I25, I0981, I50, I73, I77, I798)
Tobacco	305.1, V15.82, 649.0	F17200, Z87891, O9933
Obesity	278	E66
Hyperlipidemia	272.0-272.4	E780 - E785
Renal disease	250.4, 590, 593, 791.0	E1121, E1129, E1165, N110, N28, R803, R809

## Appendix C: Medication category

### 1. Anti-hyperglycemia

#### 1.1. Oral medication

- 1.1.1. Alpha-Glucosidase Inhibitors: Acarbose, Miglitol
- 1.1.2. Biguanides: Metformin
- 1.1.3. DPP-4: Alogliptin, Linagliptin, Saxagliptin, Sitagliptin
- 1.1.4. Glucagon-Like Peptides: Albiglutide, Dulaglutide, Exenatide, Liraglutide
- 1.1.5. Meglitinides: Nateglinide, Repaglinide
- 1.1.6. SGLT2 Inhibitors: Dapagliflozin, Canagliflozin, Empagliflozin
- 1.1.7. Sulfonylureas: Glimepiride, Gliclazide, Glipizide, Glyburide, Chlorpropamide, Tolazamide, Tolbutamide
- 1.1.8. Thiazolidinediones: Rosiglitazone, Pioglitazone

#### 1.2. Insulin

- 1.2.1. Short-acting: Regular (R)
- 1.2.2. Rapid-acting: Insulin aspart, Insulin glulisine, Insulin lispro
- 1.2.3. Intermediate-acting: Insulin isophane
- 1.2.4. Long-acting: Insulin detemir, Insulin glargine

### 2. Anti-Hypertension

#### 2.1. Diuretics:

- 2.1.1. Diuretics: Chlorthalidone, Chlorothiazide, Furosemide, Hydrochlorothiazide, Indapamide, Metolazone
- 2.1.2. Potassium-sparing diuretics: Amiloride hydrochloride, Spironolactone, Triamterene
- 2.1.3. Loop diuretic: Bumetanide

- 2.2. Beta-blocker: Acebutolol, Atenolol, Betaxolol, Bisoprolol fumarate, Carteolol hydrochloride, Metoprolol tartrate, Metoprolol succinate, Nadolol, Penbutolol

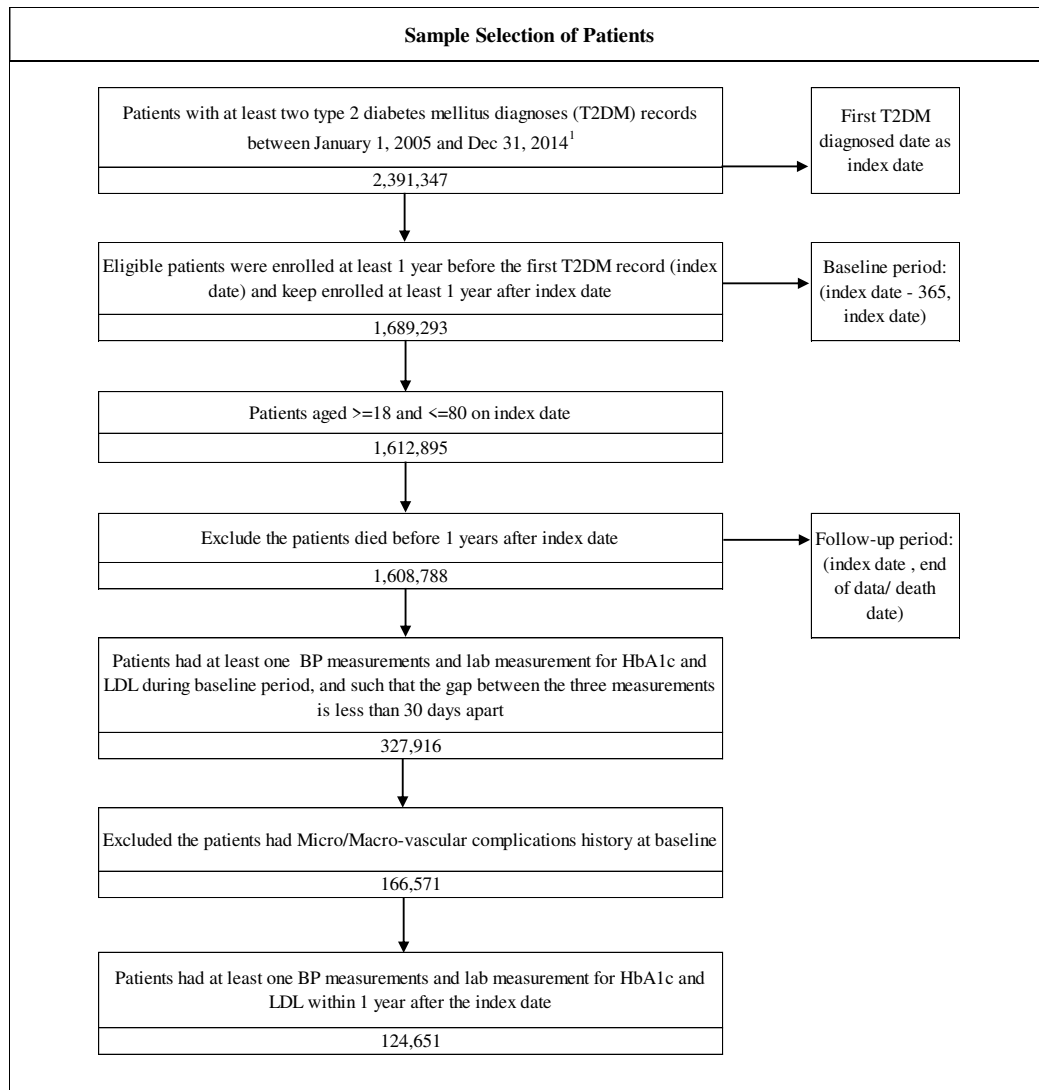
sulfate, Penbutolol sulfate, Pindolol, Propranolol hydrochloride, Solotol hydrochloride, Timolol maleate

- 2.3. ACE inhibitors: Benazepril hydrochloride, Captopril, Enalapril maleate, Fosinopril sodium, Lisinopril, Moexipril, Perindopril, Quinapril hydrochloride, Ramipril, Trandolapril
- 2.4. Angiotensin II receptor blockers: Candesartan, Eprosartan mesylate, Irbesartan, Losartan potassium, Telmisartan, Valsartan
- 2.5. Calcium channel blockers: Amlodipine besylate, Bepridil, Diltiazem hydrochloride, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil hydrochloride
- 2.6. Alpha blockers: Doxazosin mesylate, Prazosin hydrochloride, Terazosin hydrochloride
- 2.7. Alpha-2 Receptor Agonist: Methyldopa
- 2.8. Central agonists: Alpha methyldopa, Clonidine hydrochloride, Guanabenz acetate, Guanfacine hydrochloride
- 2.9. Peripheral adrenergic inhibitors: Guanadrel, Guanethidine monosulfate, Reserpine
- 2.10. Blood vessel dilators (vasodilators): Hydralazine hydrochloride, Minoxidil

### 3. Lipid Lowering Medication

- 3.1. Statins: Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin Calcium, Simvastatin
- 3.2. Niacin: Omega-3 Fatty Acid Ethyl Esters, Marine-Derived Omega-3 Polyunsaturated Fatty Acids
- 3.3. Bile-acid resins: Cholestyramine, Colestipol, Colesevelam Hcl
- 3.4. Fibric acid derivatives: Gemfibrozil, Fenofibrate, Clofibrate
- 3.5. Cholesterol absorption inhibitors

## Appendix D: Flow Chart of Sample Selection



### Appendix E: A1C Targets of intensive and standard glycemc control groups in major RCTs

	Intensive treatment	Standard treatment
UKPDS-33	7% -> 7%	7.9%
UKPDS-34	7% ->7.4%	8%
ACCORD	Target at 6.0% 8.1% -> 6.4% (3.5 yrs follow-up) 8.1% -> 7.2% (5 yrs follow-up)	7.5% 7.6%
ADVANCE	Target at 6.5% 7.5% -> 6.5%	7.3%
STENO-2	8.4% -> 7.9%	8.8% -> 9.0% (received intensive treatment at 2 <sup>nd</sup> stage)
VADT	9.4% -> 6.9%	9.4% -> 8.4%
ORIGIN	6.4% -> 6.5%	6.2%
ADDITION-Europe	Target at <7%	Routine care

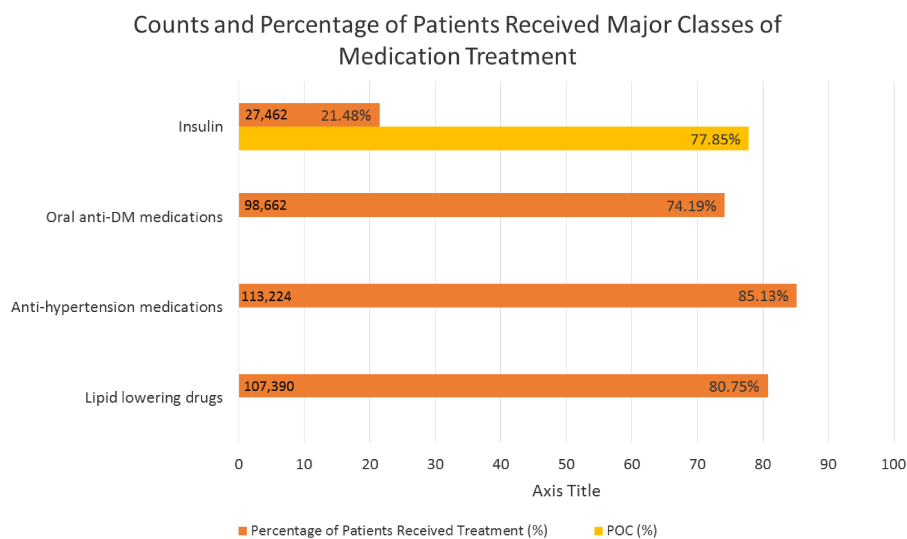
## Appendix F: Medication usage and Prevalence of Clinical Outcomes in follow-up period

### Medication usage

In the follow-up period, 21.48% of patients (27,462) were identified as insulin users and the average percentage of coverage was 77.85%, while 74.19% (98,662) used at least one oral anti-diabetic medication. 85.13% (113,224) of patients had received anti-hypertension medication and 80.75% (107,390) had had lipid lowering drugs.

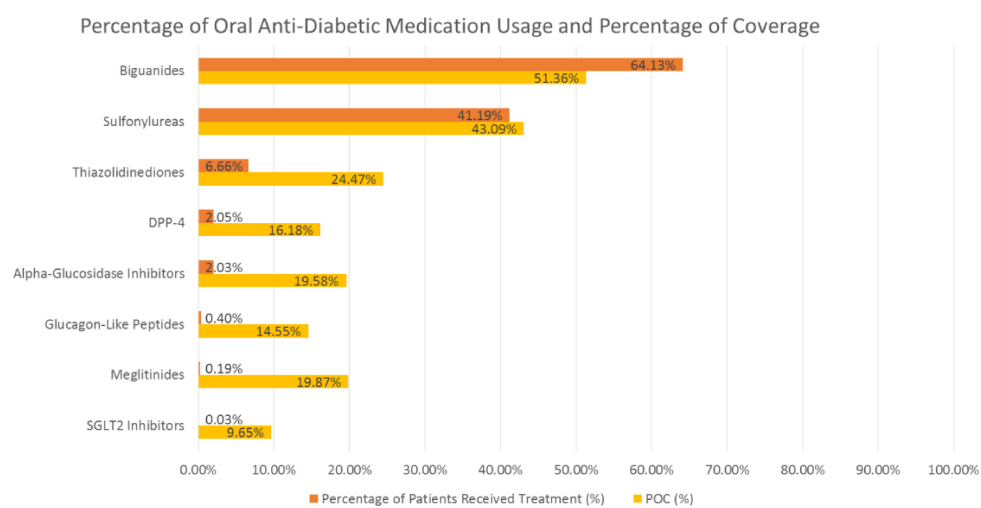
(Figure 1)

Figure 1: Prescription Rates of Major Classes of Medication Treatments and Percentage of Coverage of Insulin



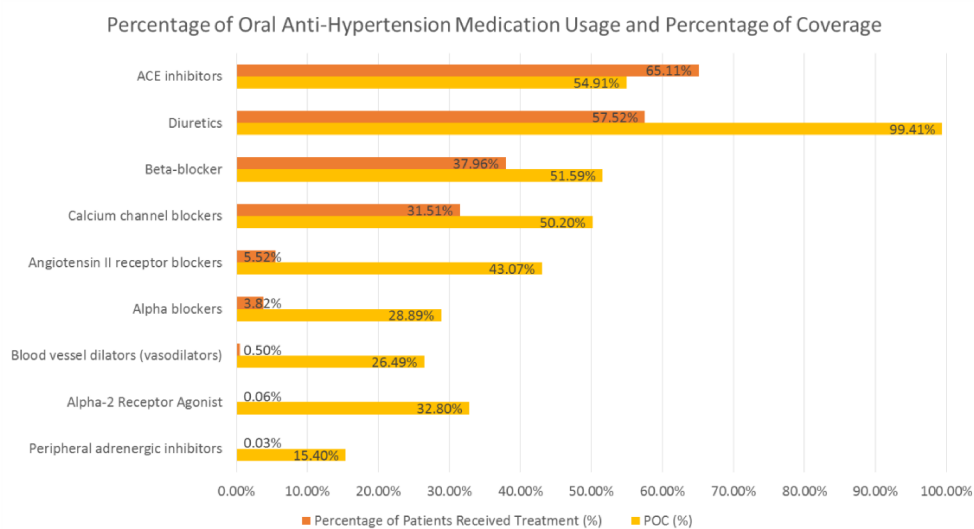
This figure (**Figure 2**) was shown the ranking the oral anti-diabetic medication use rate. The biguanides was most widely used (64.13%) and patients who received biguanides were covered 51.35% time of follow-up period averagely. Sulfonylureas and thiazolidinedione were the second and third frequently used anti-diabetic medications. 41.19% and 6.66% of patients were prescribed and covered 43.09% and 24.47% of follow-up period respectively. Only about 2% patients used DPP-4 and Alpha-Glucosidase Inhibitors, while the less than 1% patients were prescribed Glucagon-Like Peptides agonists, meglitinides and SGLT2 Inhibitors.

Figure 2: Prescription Rates of Classes of Anti-Diabetic Medication and Percentages of Coverage



ACE Inhibitors, Diuretics, Beta-blocker and Calcium channel blockers were top 4 most frequently used anti-hypertension medications, which were used among 65.11%, 57.52%, 37.96% and 31.51% respectively. The percentage of coverage of patients who have ever been prescribed Diuretics reached 99.41%, while all the other three drug were between 50.20% and 54.91%. Small percentage of patients used Angiotensin II receptor blockers or Alpha blockers, which were 5.52% and 3.82% respectively. And less than 1% patients were prescribed blood vessel dilators, Alpha-2 receptor agonist and or peripheral adrenergic inhibitors (0.50%, 0.06%, and 0.03% respectively). (**Figure 3**)

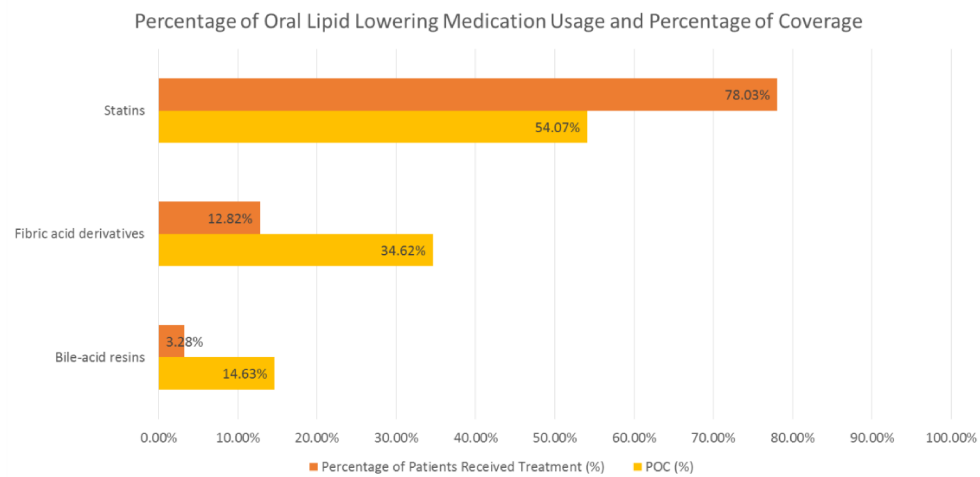
Figure 3: Prescription Rates of Classes of Anti-Hypertension Medications and Percentages of Coverage





78.03% of patients used statins and the treatment covered 54.07% of follow-up period. And 12.82% and 3.28% of patients used fibric acid derivatives and bile-acid resins as lipid lowering medication and were covered by the treatment 34.62% and 14.63% time of whole follow-up period respectively. (Figure 4)

Figure 4: Prescription Rates of Classes of Lipid Lowering Medications and Percentages of Coverage



## Prevalence of Clinical Outcomes

Out of total 124,651 patients, 43,890 (35.21%) patients had at least one microvascular complication during the follow-up period, which included 12,615 (10.12%) retinopathy, 8,863 (7.11%) nephropathy, and 32,833 (26.34%) neuropathy. 10.68% of patients had the first diagnosis of microvascular complication at the first year after index date, while 6.34% happened at second year, 4.66% at third year, and 13.54% happened after 3-year of post-index.

Out of 124,651 patients, 40,798 (32.73%) patients had at least one macrovascular complication during the follow-up period, which included 25,504 (20.46%) patients with CAD, 13,138(10.54%) patients with cerebrovascular disease, 12,066 (9.68%) patients with PVD, and 8239 (6.61%) AAE. 10.78% of total patients had the first diagnosis of macrovascular complication at the first year after index date, while 5.55% happened at second year, 4.17% at third year, and 12.24% happened after 3- year of post-index.

During the whole follow-up period, 22,524 patients died (18.07%). Patients died at the first year of post-index have been excluded from this study. 2456 (1.97%) patients were found died at the second year after index date, while 2630 (2.11%) death occurred at the third year of post-index, and 17,439 (13.99%) patients died after three years of post-index. (**Table 1**)

Table 1: Prevalence of Clinical Outcomes and the Proportions of First Event Occurrence Year

	Whole follow-up period		1-year Post-index		2-year Post-index		3-year Post-index		>3-year Post-index	
	n	%	n	%	n	%	n	%	n	%
<b>N=124651</b>										
<b>Microvascular Complications</b>	43890	35.21%	13313	10.68%	7903	6.34%	5809	4.66%	16878	13.54%
<b>Retinopathy</b>	12615	10.12%	4276	3.43%	2306	1.85%	1683	1.35%	4350	3.49%
<b>Nephropathy</b>	8863	7.11%	3041	2.44%	1633	1.31%	1147	0.92%	3041	2.44%
<b>Neuropathy</b>	32833	26.34%	10346	8.30%	6046	4.85%	4325	3.47%	12116	9.72%
<b>Macrovascular Complications</b>	40798	32.73%	13437	10.78%	6918	5.55%	5198	4.17%	15257	12.24%
<b>CAD</b>	25504	20.46%	9685	7.77%	4363	3.50%	3129	2.51%	8327	6.68%
<b>Cerebrovascular disease</b>	13138	10.54%	4575	3.67%	2194	1.76%	1658	1.33%	4712	3.78%
<b>PVD</b>	12066	9.68%	4450	3.57%	2082	1.67%	1458	1.17%	4076	3.27%
<b>AAE</b>	8239	6.61%	2879	2.31%	1433	1.15%	1060	0.85%	2879	2.31%
<b>Death</b>	22524	18.07%	n/a	n/a	2456	1.97%	2630	2.11%	17439	13.99%

\*Follow-up time= 1st diagnosed date-index date; Years of follow-up was rounded up