Comparative Effectiveness and Safety of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) in Older Adults with Type 2 Diabetes

Medicare Fee-for-Service Claims Database, 20% Random Sample, 2007-2019

December 29, 2021

This protocol has been finalized and submitted to the ENCePP registry prior to establishing the described cohorts (i.e., without knowledge of ultimate results). The research team has worked extensively with Medicare data for projects related to diabetes and cardiovascular outcomes.

1. BACKGROUND:

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used blood pressure lowering drugs which work by inhibiting the renin-angiotensin system (1). ACEIs and ARBs are equally recommended as first-line therapy to treat hypertension in multiple guidelines (2017 American College of Cardiology/American Heart Association and the 2018 European Society of Cardiology/European Society of Hypertension guidelines) (1,2). Nevertheless, which drug class is more effective in preventing clinically relevant cardiovascular outcomes and mortality overall or in specific subpopulations is still not clear. (3)

There are several head-to-head trials assessing the relative effectiveness of these two drug classes (4-9) on various endpoints in subgroups of patients. However, the available evidence is limited by small sample size (4-5) and in the context of impact on MACE in type 2 diabetes the data are limited to the ONTARGET trial (9). In non-diabetic populations, the ELITE II showed ARBs were associated with an increased risk of sudden death among those with heart failure (hazard ratio, HR 1.30, 95% CI 1.00 to 1.69) during a median follow-up of 555 days (7). The OPTIMAAL trial showed that ARBs are associated with an increased risk of cardiovascular death among post MI patients (relative risk, RR, 1.17, 95% CI 1.01 to 1.34) during an average follow-up of 2.7 years (8). However, the ONTARGET trial in which about one-third of participants had T2DM showed no differences (9).

On the other hand, real-world evidence is conflicting as well. An observational study using REACH registry data suggested ARBs are associated with a 10% lower rate of cardiovascular events (HR 0.90, 95% CI 0.86 to 0.95) and overall mortality (HR 0.89, 95% Cl 0.82 to 0.97) compared to ACEIs during a 4-year follow-up (10). A recent multinational cohort study involving 2,297,881 ACEIs initiators and 673,938 ARBs initiators from 8 databases suggested ARBs do not differ significantly in effectiveness compared with ACEIs (11). However, this study is limited by lack of mortality data and did not look at subpopulation with conditions like heart failure, chronic kidney disease, etc. Therefore, it is necessary to perform a high-quality real-world study to assess the comparative effectiveness of ACEIs to ARBs. More than one-third of the adults with diabetes are currently aged 65 years or older (12), and both ACEIs and ARBs are recommended as first line therapy in type 2 diabetes with hypertension (13). Thus, to reduce bias and achieve better baseline comparability in real-world study (14), we propose to assess the comparative effectiveness of ACEIs to ARBs in older adults with type 2 diabetes.

2. OBJECTIVES

Our specific aims are:

1. To estimate absolute and relative rate and risk of in cardiovascular outcomes and all-cause mortality in Medicare beneficiaries with type 2 diabetes (T2D) initiating ACEIs or ARBs.

2. To identify subgroups of Medicare beneficiaries with T2D that are more likely to benefit from ACEI's or ARBs to prevent cardiovascular outcomes and all-cause mortality using machine learning-based heterogeneous treatment effect analysis.

3. STUDY DESIGNS

We will implement an active-comparator, new-user (ACNU) design. The new user component aims to eliminate time-related biases by restricting the analysis to patients under observation at the start of the treatment (mimicking an intervention). The active comparator component will help to balance the baseline risk of cardiovascular outcomes between comparison groups, and provides indirect control for diabetes and hypertension severity. Therefore, such a design can be used to examine the CV risk associated with initiating ACEIs versus ARBs.

4. DATA SOURCES

- Medicare Fee-for-Service (FFS) Database (Parts A, B, and D), 20% random sample, 2007-2019

5. STUDY POPULATION

1. Medicare FFS enrollees ≥65 years of age with T2D having continuous coverage in fee-for-service Medicare plans A (inpatient services), B (physician and outpatient services) and D (prescription drugs)
2. The base population for the analysis will consist of all beneficiaries with ≥1 prescription dispensing claim for ACEI or ARB between January 01, 2007, and December 30, 2019.

We will assess the comparative effectiveness and safety of ACEIs and ARBs in patients with T2D as ACEIs or ARBs are recommended first and/or second-line therapy in such population. We will require 2 claims of diagnosis of T2D or 1 claims of diagnosis of T2D plus pharmacy claims for diabetes medication. Type 2 diabetes diagnosis is identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision (ICD-10-CM) diagnosis and procedure codes, as shown in **Table 1**.
Table 1. Diagnosis to identify T2D.

Diagnosis	ICD-9	ICD-10
type 2 diabetes	250.*0, 250.*2	E11.***

Table 2. Diabetes medications to identify T2D.

Class	generic drug name
DPP4i	Sitagliptin, Saxagliptin, Linagliptin, Alogliptin, Vildagliptin, etc.
GLP1RA	Exenatide, Exenatide extended release, Liraglutide, Dulaglutide, Albiglutide
Sulfonylureas	glyburide, glipizide, glimepiride, gliclazide
Thiazolidinediones	pioglitazone, rosiglitazone
SGLT2i	Canagliflozin, Dapagliflozin, Empagliflozin
Insulin	Rapid-acting: insulin aspart, Insulin glulisine, and insulin lispro; Regular or short-acting insulin: Human Regular Intermediate-acting insulin: NPH Long-acting: degludec, detemir, and glargine Ultra long-acting: glargine U-300

DPP4i, Dipeptidyl peptidase 4 inhibitors; GLP1RA, Glucagon-like peptide 1 receptor agonists; SGLT2i, Sodium/glucose cotransporter-2 inhibitors

We will exclude the following patients:

1) To ensure new use of either ACEIs or ARBs, we will exclude all individuals who do not have at least **12 months** of continuous enrollment (inpatient, outpatient, and prescription coverage) in the appropriate insurance database prior to the first prescription dispensing claim (12-month baseline period), during which no use of any of the study drug classes compared is detected.

6. EXPOSURE

Exposure will be defined by at least **two** same-drug class prescription dispensing claims of either an ACEI or an ARB between January 1, 2007, and December 31, 2019, identified using National Drug Codes (NDCs). The second prescription will serve as the index date for the analysis. Patients will be required to fill a second prescription of the same drug within (days' supply + 90 days) of index date. This is to increase the probability that the new users are actually started on the therapy. Patients without a qualifying second prescription of the same drug class dispensed will be enumerated in both cohorts. ACEIs and ARBs alone are shown in the Table below. The Anatomical Therapeutic Chemical (ATC) codes and their combination products are shown in **Supplemental Table 1**.

Table 3. ACEI and ARB products.

ACEIs	ARBs
benazepril (Lotensin) **captopril** (Capoten) **enalapril** (Vasotec) ***fosinopril** (Monopril) ***lisinopril** (Prinivil, Zestril) ***perindopril** (Aceon) ***quinapril** (Accupril) **ramipril** (Altace) ***trandolapril** (Mavik)	**eprosartan** (Tevetan) ***irbesartan** (Avapro) **losartan** (Cozaar) ***olmesartan** (Benicar) ***telmisartan** (Micardis) ***valsartan** (Diovan)

*long-acting

7. OUTCOMES

We will identify outcomes using prior published algorithms that have been shown to have high reported specificity (93-98%) or positive predictive value (>95%)(15, 16-18, 19, 20). The primary outcomes are

(i) Hospitalization of Heart failure (HHF)

(ii) composite endpoint of inpatient myocardial infarction (MI), inpatient stroke or all-cause mortality (Major Cardiovascular Events, MACE outcome)

(iii) the composite of MACE plus HHF.

(iv) All-cause mortality

Secondary outcomes include individual components of the MACE outcome (non-fatal MI, stroke, and HHF), and MACE plus invasive cardiac procedures (stents, revascularization, bypass surgery). We will assume death as a competing event for these cardiovascular outcomes (details below). Since cardiovascular deaths account for approximately 70% of diabetes related deaths in adults aged 65 years or older, we will use all-cause mortality as a proxy for cardiovascular mortality.(21)

All outcomes will be identified in inpatient setting with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision (ICD-10-CM) diagnosis and procedure codes, in primary or secondary positions (**Supplemental Table 2-4**). We will identify invasive cardiac procedures using standardized coding systems: Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) (**Supplemental Table 5**). To prevent bias due to changes in coding practices (ICD-9-CM to ICD-10-CM transition after Oct 2015), we will assess trends in outcome codes over calendar time using various outcome definition algorithms following approaches outlined in literature (22). Date of mortality will be ascertained from the Medicare Master Beneficiary Summary File (MBSF): National Death Index (NDI) segment. Over 99% of dates of death reported in the MBSF have been validated using death certificate data according to the Research Data Assistance Center (ResDAC)(23).

As both ACEIs and ARBs increase creatinine and hence reduce eGFR initially but actually improves renal function, we will assess end stage renal disease (ESRD) and dialysis as safety outcome. An ESRD complication

will be identified based on ICD-9 codes 27650, 27651, 27652, 2767, 27669,40403, 40413,40493, 5184, 514, 4281, and 428x and ICD-10 codes E860, E861, E869, E875, E8770, E8779, I132, J810, J811, and I50x. A dialysis will be identified by CPT codes 90935, 90937, 90945, and 90947 and ICD 9 codes V45.1, V56.0, V56.1, 39.95, 54.98 and ICD10 codes Z99.2, Z49.31, Z49.01, Z49.02, Z49.31, Z49.32 (**Supplemental Table 6**).

For each outcome, we will exclude patients who experienced that outcome before ACEI or ARB initiation.

8. COVARIATES

We will identify potential confounders using ICD-9/10-CM diagnosis and procedure codes, HCPCS and CPT codes during the 1-year baseline period, identifying conditions at high risk of cardiovascular morbidity and mortality: demographics, diabetes complications and proxies of diabetes severity (oral antihyperglycemic medications including DPP4i, SGLT2i, GLP1RA, sulfonylureas, and thiazolidinediones, short and long-term insulin, number of hyperglycemia diagnosis, number of non-insulin antihyperglycemic prescriptions, foot ulcers, hypoglycemia, retinopathy, neuropathy and nephropathy), cardiovascular disorders and proxies of cardiovascular severity, chronic comorbid disorders, Charlson/Elixhauser combined comorbidity scores, proxies of frailty (durable medical equipment claims, disability or chronic debilitating conditions), socioeconomic status indicators (low income subsidy), codes for smoking, obesity or bariatric surgery, markers of healthy user bias (influenza vaccination, lipid tests), blood pressure medications including calcium channel blocker (CCB), diuretics, thiazides, thiazide-like diuretics (loop diuretics aldosterone antagonists and other type of diuretics), lipid lowering medications including statins and fenofibrates, chronic disease medications use, and measures of healthcare utilization. All covariates are shown in **Supplemental Table 7**.

9. STASTICAL ANALYSES

We will estimate propensity scores (PS), the probability of ACEIs initiation vs. ARBs, conditional on baseline covariates using logistic regression. We will control measured confounding by inverse probability of treatment weighting (IPTW) by assigning weights of 1/PS and 1/(1-PS) multiplied by the marginal proportion of ACEIs and ARBs initiators to ACEIs and ARBs cohorts, respectively.(23, 25) This creates pseudopopulations in which each exposure arm has the same distribution of covariates as the overall population and therefore all measured covariates are balanced across treatment cohorts. We will assess balance in covariate distributions by requiring absolute standardized mean differences (SMD) less than 0.1.(26)

We will account for potential informative censoring due to loss to follow-up (treatment discontinuation in as-treated analyses, and insurance disenrollment in intention-to-treat analyses), using inverse probability of censoring weights (IPCW) (27). First, we will predict the probability of not dropping out, i.e., probability of not getting censored (PC), at each quintile of the follow-up time, conditional on baseline covariates (similar to those used in IPTW) and we will pool these probabilities over the follow-up duration using pooled linear logistic regression. We then will assign weights of 1/PC for every study subject, multiplied by the proportion of patients not lost to follow-up to reduce variance (27). The final weight is IPTW multiplied by IPCW to account for baseline confounding as well as potential informative censoring due to lost follow-up.

We will estimate 2-year risks of outcomes of interest, risk differences (RD) and ratios (RR) for ACEIs vs. ARBs after weighting by IPTW and IPCW. Confidence intervals will be derived from 2.5^{th} and 97.5^{th} percentiles of estimates from 500 bootstrap resamples of the study population (random resampling with replacement). When estimating risks of cardiovascular outcomes in older Medicare patients, censoring those who died prior to having the outcome of interest, as commonly done in survival analyses, could bias the risks.(27, 28) To avoid this, we will use Aalen Johansen (AJ) estimators to estimate risks. We first will estimate the overall survival function for 2 years and the hazard function for each event type (outcome of interest as well as death) in a population weighted by IPTW and IPCW. We then will multiply the hazard function of the outcome of interest at each event time by the overall survival at the previous time point to obtain the AJ estimators. This estimator treats death as a

competing risk, by setting the risk of patients to 0 after death.(29)

For comparison, we will also estimate RD and RR by linear and log binomial regression models respectively, instead of AJ estimators, after applying IPTW and IPCW and confidence intervals are derived by robust variance estimators. We will treat death as a censoring event and therefore not assume a zero risk for the outcome of interest after death in such analyses. We will also report cumulative risk curves as a function of the follow-up time (adjusted for baseline confounding and informative censoring) for each analytic comparison of interest.

10. SENSITIVITY ANALYSES

We will conduct several sensitivity analyses to assess the robustness of our claims-based algorithms of outcomes: (i) we will exclude each of the following conditions from baseline cardiovascular disease (CVD) definition – peripheral arterial disease, non-specific angina/ischemic heart disease and cardiomyopathy; (ii) we will limit all codes for baseline CVD/heart failure (HF) conditions to inpatient settings only to increase the specificity of codes; (iii) we will vary our outcome definitions for HF by including rheumatic and hypertensive HF codes in addition to the primary congestive HF codes; (iv) we will vary our stroke definition by limiting to codes for ischemic stroke only; (v) we will include cardiovascular revascularization procédures (stents, bypass, primary coronary intervention) to MACE outcome definitions ; (vi) for each outcome, we will **include** patients who experienced that outcome before ACEI or ARB initiation.

To account for the carry-over effect in as-treated analysis, we will follow outcomes continued 30, 60, and 90 days (latency period), respectively, after treatment was changed or stopped.

We will also allow time varying covariates in censoring weight models by including codes for hyperglycemia (ketoacidosis, uncontrolled diabetes or hyperosmolar non-ketosis) and any hospitalization in 3-monthly periods prior to the interval when treatment discontinuation or switching occurred. We will extend the follow-up to all-available years (1, 3, 4, and maximum 5 years) and estimated the hazard ratios using competing risk-adjusted Fine and Gray Cox models, truncating the weights at 1 and 99% to deal with large weights associated with long-term follow-up, as suggested by Cole and Hernan (2018). We will exclude earlier ACEI agents (captopril) from analyses, and also compared the most commonly used agent in each class and compared long-acting ACEIs vs. long-acting ARBs. In order to assess the potential for differential detection bias, we evaluated the proportions of health seeking behaviors (flu shots, lipid tests) during the first 6 months following drug initiation among ACEIs versus ARBs initiators.

11. SUBGROUP ANALYSIS

1. Subgroup analysis in predefined subpopulation.

First, we will also perform analyses looking at one factor at a time in the following subgroups: (i) age ≤ 75 years vs age > 75 years; (ii) HF vs no HF; (iii) major atherosclerotic CVD (MI, ischemic heart disease, stroke, cerebrovascular diseases, cardiovascular revascularization procedures, peripheral arterial diseases and revascularization) vs no major atherosclerotic CVD; (iv) hypertension (ICD-9-CM codes 401.x, 402.x, 403.x, 404.x, or 405.x and/or ICD-10 codes I10.x, I11.x, I12.x, I13.x, or I15.x) vs no hypertension; (v) on insulin vs not on insulin; We will identify these predefined factors using ICD-9-CM, ICD-10-CM, CPT, and HCPCS codes following claims data-based algorithms from prior validation studies (**Supplemental Table 8**) (15-18).

Second, we will identify non-overlapping subgroups based on two factors, i.e., HF and major atherosclerotic CVD during the 12 months prior to drug initiation: (i) no history of HF or CVD; (ii) history of HF but no CVD; (iii) history of CVD but no HF; and (iv) history of both HF and CVD.

2. Subgroup analysis using machine learning methods to assess heterogeneous treatment effect (HTE) and discover complex interactions between treatment and covariates.

We will use the iterative causal forest (iCF) algorithm developed by Wang et al. to identify subgroups with HTE (30,31). As absolute risk is the recommend measure for treatment effect in subgroups (32) and our iCF algorithm relied on causal forest (CF) which may not handle survival outcomes well (although CF have been extended to assess right-censored survival data, i.e., causal survival forest (33) most recently), we will assess treatment effect by the 2-year risk difference for cardiovascular outcomes between the ACEIs and ARBs groups ($\Delta Y = \overline{Y}_{treated} - \overline{Y}_{untreated}$) using initial treatment analysis (not censor for treatment changes) over a fixed 2-year follow-up period. We required all patients to enter the cohort no later than Dec 31, 2017, to increase the probably for a 2-year follow-up period. Our new-user cohort will include a small portion (<10%) that will be censored during follow-up as they lost part A or B of Medicare coverage during follow-up, which was adjusted by inverse probability censoring weight (IPCW). Death was treated as a competing risk by setting the risk for HHF after death to 0.

To increase reproducibility, we will increase the iteration number incrementally from 500 to 10,000. We will tune leaf size to obtain a depth = 4, 3, and 2 forests, and grew each CF with 200 trees. If iCF identified heterogeneous subgroups, in each group, we will first calculate the PS by logistic regression to adjust for confounding, then assessed subgroup-specific treatment effects (i.e., conditional average treatment effect, CATE) by risk difference applying IPTW multiplied by IPCW.

To compare results with iCF, we also implemented other machine learning methods to identify subgroups/interactions between treatment and covariates, including logistic regression with LASSO penalty (34), aVirtualTwin (35), and FindIt (36).

All computation interaction/subgroup identification will be conducted in R software (version 3.6). R codes for iCF are available at https://github.com/tianshengwang. In Medicare, data management and estimation of subgroup specific treatment effects will be carried out in SAS, version 9.4.

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APPENDIX

Supplemental Table 1. ACEIs and ARBs alone/combination and their ATC codes.

ATC code	Drug
C09AA07	benazepril
C09BA07	benazepril and diuretics
C09AA01	captopril
C09BA01	captopril and diuretics
C09AA02	enalapril
C09BA02	enalapril and diuretics
C09BB02	enalapril and lercanidipine
C09BB06	enalapril and nitrendipine
C09AA09	fosinopril
C09BA09	fosinopril and diuretics
C09AA03	lisinopril
C09BB03	lisinopril and amlodipine
C09BA03	lisinopril and diuretics
C10BX07	rosuvastatin, amlodipine and lisinopril
C09AA13	moexipril
C09BA13	moexipril and diuretics
C09AA06	quinapril
C09BA06	quinapril and diuretics
C10BX06	atorvastatin, acetylsalicylic acid and ramipril
C10BX18	atorvastatin, amlodipine and ramipril
C09AA05	ramipril
C09BB07	ramipril and amlodipine
C09BX05	ramipril and bisoprolol
C09BA05	ramipril and diuretics
C09BB05	ramipril and felodipine
C09BX03	ramipril, amlodipine and hydrochlorothiazide
C10BX17	rosuvastatin and ramipril
C10BX04	simvastatin, acetylsalicylic acid and ramipril
C09AA10	trandolapril
C09BB10	trandolapril and verapamil
C10BX10	rosuvastatin and valsartan
C09CA03	valsartan
C09DX02	valsartan and aliskiren
C09DB01	valsartan and amlodipine
C09DA03	valsartan and diuretics
C09DB08	valsartan and lercanidipine
C09DX05	valsartan and nebivolol
C09DX04	valsartan and sacubitril

C09DX01	valsartan, amlodipine and hydrochlorothiazide
C09CA01	losartan
C09DB06	losartan and amlodipine
C09DA01	losartan and diuretics
C09CA04	irbesartan
C09DB05	irbesartan and amlodipine
C09DA04	irbesartan and diuretics
C09DX07	irbesartan, amlodipine and hydrochlorothiazide

Supplemental Table 2. Cardiovascular conditions and codes used to define outcomes of interest

Condition	ICD-9-CM Codes	ICD-10-CM codes	Positions	Setting	Accuracy of codes (Validation study)
Myocardial infarction	410.xx	I20.xx, I21.xx	Primary or secondary	Inpatient	Specificity >93%; Sensitivity >86% [McCormick, 2014] PPV >94% [Kiyota 2004]
Cerebrovascular diseases or stroke	430.xx, 431.xx, 433.xx, 434.xx, 436.xx	I60.xx, I61.xx, I63.xx-I67.xx, I69.xxx	Primary or secondary	Inpatient	PPV 76%, sensitivity 68% [Jones, 2014] Specificity >95%, Sensitivity >82% [McCormick, 2015]
Heart failure (primary definition)	428.xx	I09.9, I11.0, I50.x	Primary or secondary	Inpatient	Specificity: 99%, [Birman-Deych, 2005], PPV 93% [Ezekowitz, 2008], sensitivity = 80.0% (67.0 - 90.0); specificity = 97.8% (93.8 - 99.6); PPV: 93.6% [So, 2006]
Heart failure (secondary definition)	428.xx, 398.91, 402.x1, 402.x3, 404.x1, 404.x3	I09.9, I11.0, I50.x	Primary or secondary	Inpatient	Specificity: 99%, [Birman-Deych, 2005], PPV 93% [Ezekowitz, 2008], sensitivity = 80.0% (67.0 - 90.0); specificity = 97.8% (93.8 - 99.6); PPV: 93.6% [So, 2006]

Supplemental Table 3. Codes used to define primary outcome of heart failure hospitalization

Code type	Codes	Description
ICD-9-CM diagnosis	428	Heart Failure
ICD-9-CM diagnosis	4280	Congestive heart Failure not otherwise specified (NOS)
ICD-9-CM diagnosis	4281	Left Heart Failure
ICD-9-CM diagnosis	42820	Systolic Heart Failure NOS
ICD-9-CM diagnosis	42821	Acute Systolic Heart Failure
ICD-9-CM diagnosis	42822	Chronic Systolic Heart Failure
ICD-9-CM diagnosis	42823	Acute on Chronic Systolic Heart Failure
ICD-9-CM diagnosis	42830	Diastolic Heart Failure NOS
ICD-9-CM diagnosis	42831	Acute Diastolic Heart Failure
ICD-9-CM diagnosis	42832	Chronic Diastolic Heart Failure
ICD-9-CM diagnosis	42833	Acute on Chronic Diastolic Heart Failure
ICD-9-CM diagnosis	42840	Systolic/Diastolic Heart Failure NOS
ICD-9-CM diagnosis	42841	Acute Systolic/Diastolic Heart Failure
ICD-9-CM diagnosis	42842	Chronic Systolic/Diastolic Heart Failure
ICD-9-CM diagnosis	42843	Acute/Chronic Systolic/Diastolic Heart Failure
ICD-9-CM diagnosis	4289	Heart Failure NOS
ICD-10-CM diagnosis	I50	Heart Failure
ICD-10-CM diagnosis	I501	Left ventricular Failure
ICD-10-CM diagnosis	I502	Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5020	Unspecified Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5021	Acute Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5022	Chronic Systolic (congestive) heart Failure
ICD-10-CM diagnosis	I5023	Acute on chronic Systolic (congestive) heart failure
ICD-10-CM diagnosis	I503	Diastolic (congestive) heart Failure
ICD-10-CM diagnosis	I5030	Unspecified diastolic (congestive) heart Failure
ICD-10-CM diagnosis	I5031	Acute diastolic (congestive) heart Failure
ICD-10-CM diagnosis	I5032	Chronic diastolic (congestive) heart Failure
ICD-10-CM diagnosis	I5033	Acute on chronic diastolic (congestive) heart failure
ICD-10-CM diagnosis	I504	Combined systolic and diastolic (congestive) heart failure
ICD-10-CM diagnosis	I5040	Unspecific combined systolic and diastolic (congestive)
ICD-10-CM diagnosis	I5041	Acute combined systolic and diastolic (congestive)
ICD-10-CM diagnosis	I5042	Chronic combined systolic and diastolic heart fail
ICD-10-CM diagnosis	I5043	Acute on chronic combined systolic and diastolic heart failure
ICD-10-CM diagnosis	I509	Heart failure, unspecified

Supplemental Table 4. Codes used to define myocardial infarction outcomes

Code	Code type	Description
41000	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) anterolateral, unspecified
41001	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) anterolateral, initial
41002	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) anterolateral, subsequent
41010	ICD-9-CM diagnosis	AMI anterior wall, unspecified
41011	ICD-9-CM diagnosis	AMI anterior wall, initial
41012	ICD-9-CM diagnosis	AMI anterior wall, subsequent
41020	ICD-9-CM diagnosis	AMI inferolateral, unspecified
41021	ICD-9-CM diagnosis	Acute myocardial infarction (AMI) inferolateral, initial
41022	ICD-9-CM diagnosis	AMI inferolateral, subsequent
41030	ICD-9-CM diagnosis	AMI inferoposterial, unspecified
41031	ICD-9-CM diagnosis	AMI inferoposterial, initial
41032	ICD-9-CM diagnosis	AMI inferoposterial, subsequent
41040	ICD-9-CM diagnosis	AMI inferior wall, unspecified
41041	ICD-9-CM diagnosis	AMI inferior wall, initial
41042	ICD-9-CM diagnosis	AMI INFERIOR WALL, subsequent
41050	ICD-9-CM diagnosis	AMI lateral, unspecified
41051	ICD-9-CM diagnosis	AMI lateral, initial
41052	ICD-9-CM diagnosis	AMI LATERAL NEC, subsequent
41060	ICD-9-CM diagnosis	True posterior wall infarction episode of care unspecified
41061	ICD-9-CM diagnosis	True posterior wall infarction; initial episode of care
41062	ICD-9-CM diagnosis	True posterior wall infarction; subsequent episode of care
41070	ICD-9-CM diagnosis	Subendocardial infarction, episode of care unspecified
41071	ICD-9-CM diagnosis	Subendocardial infarction, initial episode of care
41072	ICD-9-CM diagnosis	Subendocardial infarction, subsequent episode of care
41080	ICD-9-CM diagnosis	Of other specified sites, episode of care unspecified
41081	ICD-9-CM diagnosis	Of other specified sites, initial episode of care
41082	ICD-9-CM diagnosis	Of other specified sites, subsequent episode of care
41090	ICD-9-CM diagnosis	Unspecified site, episode of care unspecified
41091	ICD-9-CM diagnosis	Unspecified site, initial episode of care
41092	ICD-9-CM diagnosis	Unspecified site, subsequent episode of care
I21	ICD-10-CM diagnosis	STEMI & NSTEMI
I210	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of anterior wall
I2101	ICD-10-CM diagnosis	STEMI involving left main coronary artery
I2102	ICD-10-CM diagnosis	STEMI involving left anterior descending coronary artery
I2109	ICD-10-CM diagnosis	STEMI involving other coronary artery of anterior wall
I211	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of inferior wall
I2111	ICD-10-CM diagnosis	STEMI involving right coronary artery
I2119	ICD-10-CM diagnosis	STEMI involving other coronary artery of inferior wall
I212	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of other sites
I2121	ICD-10-CM diagnosis	STEMI involving left circumflex coronary artery

I2129	ICD-10-CM diagnosis	STEMI involving other sites
I213	ICD-10-CM diagnosis	ST elevation (STEMI) myocardial infarction of Unspecified site
I214	ICD-10-CM diagnosis	ST elevation (NSTEMI) myocardial infarction
I22	ICD-10-CM diagnosis	Subsequent STEMI & NSTEMI
I220	ICD-10-CM diagnosis	Subsequent STEMI of anterior wall
I221	ICD-10-CM diagnosis	Subsequent STEMI of inferior wall
I222	ICD-10-CM diagnosis	ST elevation (NSTEMI) myocardial infarction
I228	ICD-10-CM diagnosis	Subsequent STEMI of sites
I229	ICD-10-CM diagnosis	Subsequent STEMI of Unspecified site

Supplemental Table 5. Codes used to define invasive cardiac revascularization and bypass procedures

Codes	Description	Code type
92920	Angioplasty, single vessel	CPT
92921	Angioplasty, additional branch	CPT
92924	Atherectomy, single vessel	CPT
92925	Atherectomy, additional branch	CPT
92928	Stent, single vessel	CPT
92929	Stent, additional branch	CPT
92933	Atherectomy + stent, single vessel	CPT
92934	Atherectomy + stent, additional branch	CPT
92937	PCI of or through bypass, any method(s)	CPT
92938	PCI of or through bypass, additional branch	CPT
92941	PCI of acute MI, all interventions, single vessel	CPT
92943	PCI of chronic total occlusion, any method(s)	CPT
92944	PCI of chronic total occlusion, additional branch	CPT
92973	Percutaneous coronary thrombectomy, mechanical	CPT
92975	Thrombolysis, coronary, by intracoronary infusion	CPT
92977	Thrombolysis, coronary, by intravenous infusion	CPT
33508	Endoscopy, surgical, including video-assisted harvest of vein(s) for coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT
33510	Coronary artery bypass, vein only; single coronary venous graft	CPT
33511	Coronary artery bypass, vein only; 2 coronary venous grafts	CPT
33512	Coronary artery bypass, vein only; 3 coronary venous grafts	CPT
33513	Coronary artery bypass, vein only; 4 coronary venous grafts	CPT
33514	Coronary artery bypass, vein only; 5 coronary venous grafts	CPT
33516	Coronary artery bypass, vein only; 6 or more coronary venous grafts	CPT
33517	Coronary artery bypass, using venous graft(s) and arterial graft(s); single vein graft (list separately in addition to code for primary procedure)	CPT
33518	Coronary artery bypass, using venous graft(s) and arterial graft(s); 2 venous grafts (list separately in addition to code for primary procedure)	CPT
33519	Coronary artery bypass, using venous graft(s) and arterial graft(s); 3 venous grafts (list separately in addition to code for primary procedure)	CPT
33520	Coronary Artery Bypass, Nonautogenous Graft (eg, Synthetic or Cadaver); Single Graft	CPT
33521	Coronary artery bypass, using venous graft(s) and arterial graft(s); 4 venous grafts (list separately in addition to code for primary procedure)	CPT
33522	Coronary artery bypass, using venous graft(s) and arterial graft(s); 5 venous grafts (list separately in addition to code for primary procedure)	CPT
33523	Coronary artery bypass, using venous graft(s) and arterial graft(s); 6 or more venous grafts (list separately in addition to code for primary procedure)	CPT
33525	Coronary Artery Bypass, Nonautogenous Graft (eg, Synthetic or Cadaver); Two Coronary Grafts	CPT
33528	Coronary Artery Bypass, Nonautogenous Graft (eg, Synthetic or Cadaver); Three Or More Coronary Grafts	CPT

33530	Reoperation, coronary artery bypass procedure or valve procedure, more than 1 month after original operation (List separately in addition to code for primary procedure)	CPT
33533	Coronary artery bypass, using arterial graft(s); single arterial graft	CPT
33534	Coronary artery bypass, using arterial graft(s); 2 coronary arterial grafts	CPT
33535	Coronary artery bypass, using arterial graft(s); 3 coronary arterial grafts	CPT
33536	Coronary artery bypass, using arterial graft(s); 4 or more coronary arterial grafts	CPT
35600	Harvest of upper extremity artery, 1 segment, for coronary artery bypass procedure (list separately in addition to code for primary procedure)	CPT
33572	Coronary endarterectomy, open, any method, of left anterior descending, circumflex, or right coronary artery performed in conjunction with coronary artery bypass graft procedure, each vessel (List separately in addition to primary procedure)	CPT
00566	Anesthesia for direct coronary artery bypass grafting; without pump oxygenator	CPT
00567	Anesthesia for direct coronary artery bypass grafting; with pump oxygenator	CPT
35500	Harvest of upper extremity vein, 1 segment, for lower extremity or coronary artery bypass procedure (List separately in addition to code for primary procedure)	CPT
4110F	Internal mammary artery graft performed for primary, isolated coronary artery bypass graft procedure (CABG)	CPT
C9600	Drug eluting stent, single vessel	HCPCS
C9601	Drug eluting stent, additional branch	HCPCS
C9602	Atherectomy + drug eluting stent, single vessel	HCPCS
C9603	Atherectomy + drug eluting stent, additional branch	HCPCS
C9604	PCI of or through bypass, any method(s), with drug-eluting stent	HCPCS
C9605	PCI of or through bypass, any method(s), with drug-eluting stent, additional branch	HCPCS
C9606	PCI of acute MI, all interventions, with drug-eluting stent, single vessel	HCPCS
C9607	PCI of chronic total occlusion, any method(s), with drug-eluting stent	HCPCS
C9608	PCI of chronic total occlusion, any method(s), with drug-eluting stent, additional branch	HCPCS
G8497	All quality actions for the applicable measures in the coronary artery bypass graft (CABG) measures group have been performed for this patient	HCPCS
S2208	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using single arterial and venous graft(s), single venous graft	HCPCS
S2207	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using venous graft only, single coronary venous graft	HCPCS
S2209	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using two arterial grafts and single venous graft	HCPCS
S2205	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using arterial graft(s), single coronary arterial graft	HCPCS
S2206	Minimally invasive direct coronary artery bypass surgery involving mini-thoracotomy or mini-sternotomy surgery, performed under direct vision; using arterial graft(s), two coronary arterial grafts	HCPCS

G8159	Patient documented to have received coronary artery bypass graft without use of internal mammary artery	HCPCS
G8158	Patient documented to have received coronary artery bypass graft with use of internal mammary artery	HCPCS
G8171	Patient with isolated coronary artery bypass graft not documented to have been discharged on aspirin or clopidogrel	HCPCS
G8170	Patient with isolated coronary artery bypass graft documented to have been discharged on aspirin or clopidogrel	HCPCS
G8164	Patient with isolated coronary artery bypass graft documented to have prolonged intubation	HCPCS
G8161	Patient with isolated coronary artery bypass graft documented to have received pre-operative beta-blockade	HCPCS
G8166	Patient with isolated coronary artery bypass graft documented to have required surgical re-exploration	HCPCS
G8162	Patient with isolated coronary artery bypass graft not documented to have received preoperative beta-blockade	HCPCS
G8165	Patient with isolated coronary artery bypass graft not documented to have prolonged intubation	HCPCS
G8167	Patient with isolated coronary artery bypass graft did not require surgical re-exploration	HCPCS
36.03	Open chest coronary artery angioplasty	ICD-9-CM procedure
36.04	Intracoronary artery thrombolytic infusion	ICD-9-CM procedure
36.06	Insertion of non-drug-eluting coronary artery stent(s)	ICD-9-CM procedure
36.07	Insertion of drug-eluting coronary artery stent(s)	ICD-9-CM procedure
36.09	other coronary angioplasty - Other removal of coronary artery obstruction	ICD-9-CM procedure
36.10	Aortocoronary bypass for heart revascularization, not otherwise specified	ICD-9-CM procedure
36.11	(Aorto)coronary bypass of one coronary artery	ICD-9-CM procedure
36.12	(Aorto)coronary bypass of two coronary arteries	ICD-9-CM procedure
36.13	(Aorto)coronary bypass of three coronary arteries	ICD-9-CM procedure
36.14	(Aorto)coronary bypass of four or more coronary arteries	ICD-9-CM procedure
36.15	Single internal mammary-coronary artery bypass	ICD-9-CM procedure
36.16	Double internal mammary-coronary artery bypass	ICD-9-CM procedure
36.17	Abdominal - coronary artery bypass	ICD-9-CM procedure
36.19	Other bypass anastomosis for heart revascularization	ICD-9-CM procedure
36.2	Heart revascularization by arterial implant	ICD-9-CM procedure
36.31	Open chest transmyocardial revascularization	ICD-9-CM procedure
36.32	Other transmyocardial revascularization	ICD-9-CM procedure

36.33	Endoscopic transmyocardial revascularization	ICD-9-CM procedure
36.34	Percutaneous transmyocardial revascularization	ICD-9-CM procedure
36.39	Other heart revascularization	ICD-9-CM procedure
00.66	Percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy	ICD-9-CM procedure
0210xxx	Bypass Coronary Artery, One Artery	ICD-10-CM procedure
0211xxx	Bypass Coronary Artery, Two Arteries	ICD-10-CM procedure
0212xxx	Bypass Coronary Artery, Three Arteries	ICD-10-CM procedure
0213xxx	Bypass Coronary Artery, Four or More Arteries	ICD-10-CM procedure

Supplemental Table 6. Codes used to define dialysis.

Codes	Codes	Description
ICD-9-CM diagnosis	**ICD-10-CM diagnosis**	
V45.1	V45.1	Renal dialysis status
V56.0	Z49.31	Extracorporeal dialysis
V56.1	Z49.01	Fitting and adjustment of extracorporeal dialysis catheter
V56.2	Z49.02	Fitting and adjustment of peritoneal dialysis catheter
V56.31	Z49.31	Encounter for adequacy testing for hemodialysis
V56.31	Z49.32	Encounter for adequacy testing for peritoneal dialysis
ICD-9-CM procedure	**ICD-10-CM procedure**	
39.95	5A1D70Z, 5A1D80Z, 5A1D90Z	Hemodialysis
54.98	E1M39Z	Peritoneal dialysis
	CPT	
	90935	Hemodialysis procedure with single physician evaluation
	90937	Hemodialysis procedure requiring repeated evaluation(s) with or without substantial revision of dialysis prescription
	90945	Dialysis procedure other than hemodialysis with single physician evaluation
	90947	Procedure other than hemodialysis requiring repeated physician evaluations, with or without substantial revision of dialysis prescription
	Revenue center	
	0800	Inpatient renal dialysis, general classification
	0801	Inpatient hemodialysis
	0802	Inpatient peritoneal (Non-CAPD)
	0803	Inpatient continuous ambulatory peritoneal dialysis (CAPD)
	0804	Inpatient continuous cycling peritoneal dialysis (CCPD)
	0809	Other inpatient dialysis

Supplemental Table 7. All baseline covariates.

	Overall population		
Characteristic	**ACEIs, N= (%)**	**ARBs, N= (%)**	**ASDM**
Demographic characteristics			
Age†, mean (SD)			
Race			
Whites			
African Americans			
Others			
Sex†, Males			
Low-income subsidy, mean (SD)			
Measures of DM severity/complications			
Diabetes retinopathy			
Diabetes nephropathy			
Diabetes neuropathy			
Diabetes circulatory complications†			
Number of antihyperglycemic drugs			
0			
1			
2			
3			
4+			
Number of hyperglycemia diagnoses			
0			
1			

2			
3			
4+			
Hypoglycemia			
Foot ulcers			
Cardiovascular disorders			
Baseline CVD			
Coronary artery disease			
Angina			
Myocardial infarction†			
Cardiac revascularization or bypass			
Atherosclerosis†			
Ischemic heart diseases			
Cerebrovascular diseases			
Cardiomyopathy			
Congestive heart failure†			
Congestive heart failure or cardiomyopathy†			
Peripheral vascular diseases†			
Atrial fibrillation†			
Arrhythmia disorders†			
Cardiac arrest			
Defibrillator			
Comorbid conditions			
Anemia			

Alcohol disorders			
Asthma†			
Brain injury			
Cancer (except for non-melanoma skin)			
Chronic lung disorders			
CKD (stage 1-3)†			
Coagulopathy			
Connective tissue disorders			
Dementia			
Deficiency anemia			
Depression†			
Difficulty walking†			
Dyslipidemia			
Endocrine disorders†			
Edema†			
Electrolytes disorders†			
HIV			
Hematological disorders			
Hypertension			
Hypotension			
Immune disorders			
Metabolic disorders			
Metastatic cancers			
Mild liver disorders			

Moderate liver disorders			
Nutritional disorders			
Nervous system disorders			
Paraplegia			
Parkinsonism			
Pneumonia†			
Psychosis			
Pulmonary circulation disorders			
Rehabilitation			
Renal disorders†			
Rheumatic disorders			
Smoking and smoking cessation†			
Thromboembolism			
Valvular disorders†			
Weight loss			
Durable medical equipment claims			
Ambulance†			
Hospital beds			
Home oxygen†			
Wheelchairs			
History of medications use			
Metformin†			
Short acting insulin†			
Long-acting insulin			

Thiazolidinediones			
Meglitinide			
Sulfonylurea			
DPP-4i†			
Immunosuppressive drugs			
Steroids			
CCB			
BB			
NSAIDS			
Aspirin†			
Oral contraceptives			
Estrogen			
Loop diuretics†			
Other diuretics			
Statin			
Fenofibrates			
Number of antihypertensive drugs			
Measures of healthcare utilization			
N of HbA1C tests			
0			
1			
2			
3			
4			

≥ 5			
N of flu shots			
0			
1			
2			
≥ 3			
N of lipid tests			
0			
1			
2			
3			
≥ 4			
N of hospital admissions			
0			
1			
≥ 2			
Days of hospitalization			
0			
1			
≥ 2			
N of emergency room visits			
0			
1			
2			

≥ 3			
N of emergency room visits due to DM			
0			
1			
≥ 2			
N of outpatient visits			
0			
1			
2			
3			
4			
≥ 5			
N of outpatient visits due to DM			

Supplemental Table 8. Cardiovascular conditions and codes used to define baseline subgroups of interest

Condition	ICD-9-CM Codes	ICD-10-CM codes	HCPCS/ CPT codes	Subgroup	Accuracy of codes (Validation study)
MI	410.xx	I20.xx, I21.xx		CVD	Specificity >93%; Sensitivity >86% [McCormick, 2014] PPV >94% [Kiyota 2004]
Cerebrovascular diseases	430.xx, 431.xx, 433.xx, 434.xx, 436.xx, 437.xx, 438.xx	I60.xx, I61.xx, I63.xx-I67.xx, I69.xxx		CVD	PPV 76%, sensitivity 68% [Jones, 2014] Specificity >95%, Sensitivity >82% [McCormick, 2015]
Ischemic heart diseases	411.xx, 414.xx	I24.xxx, I25.xxx		CVD	Specificity 96%, PPV 96%, Sensitivity 57% [Birman-Deych, 2005]
Angina	413.0, 413.9	I20.0, I20.8, I20.9		CVD	
Atherosclerosis	440.xx, 441.xx	I70.xx, I71.xx		CVD	
Peripheral vascular diseases	443.9, 249.70, 249.71, 250.70, 250.71, 250.72, 250.73	I739, E115.x, E105.x, E085.x, E095.x, E135.x	27295, 27590, 27591, 27592, 27594, 27596, 27598,27599,27880, 27881, 27882, 27888, 27889, 28800, 28805,	CVD	Community-based sample: Specificity: 92.0 (86.1 to 95.9), Sensitivity: 38.7 (27.6 to 50.6) Vascular laboratory sample:

	28810, 28820, 28825, 35221, 35226, 35256, 35286, 35302, 35303, 35304, 35305, 35306, 35331, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35452, 35454, 35456, 35459, 35470, 35472, 35473, 35474, 35480, 35481, 35482, 35483, 35485, 35490, 35491, 35492, 35493, 35495, 35500, 35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35583, 35585, 35587, 35621, 35623, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681, 35682, 35700, 35875, 35876, 35879, 35881, 35883, 35884, 35903	Specificity: 89.3 (88.6 to 90.0), Sensitivity: 76.9 (76.2 to 77.6) [Fan et al., 2013]

Heart failure	428.xx, 398.91, 402.x1, 402.x3, 404.x1, 404.x3	I09.9, I11.0, I50.x	CHF	Specificity: 99%, [Birman-Deych, 2005], PPV 93% [Ezekowitz, 2008], sensitivity = 80.0% (67.0 - 90.0); specificity = 97.8% (93.8 - 99.6); PPV: 93.6% [Go, 2006]
Cardiomyopathy	425.xx	I42.xx, I43.xx	CHF	