

Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE trial)

DUPLICATE-ARISTOTLE

May 26, 2021

1. RCT Details

1.1 Title

Apixaban versus Warfarin in Patients with Atrial Fibrillation ([ARISTOTLE](#) trial)

1.2 Intended aim(s)

To compare the risk of stroke or systemic embolism in atrial fibrillation (AF) patients with at least 1 risk factor for stroke with apixaban versus warfarin use.

1.3 Primary endpoint for replication

The primary outcome of the study was stroke (ischemic or hemorrhage) or systemic embolism.

1.3.1 Required power for primary endpoint and noninferiority margin (if applicable)

The test was designed for noninferiority. For non-inferiority, the 95% CI should not include ≥ 1.38 to declare noninferiority and 99% CI should not include ≥ 1.44 to declare noninferiority. Assuming average follow-up period of 1.8 years and a stroke or systemic embolism rate of 1.67 per 100 subject-years, the power of the study will be 90% with 18,000 randomized patients and 448 patients with primary outcome.

1.4 Secondary endpoint for replication (assay sensitivity) and RCT finding

Major bleeding; HR = 0.69 (95% CI 0.60-0.80)

1.5 Trial estimate

HR = 0.79 (95% CI 0.66-0.95) comparing apixaban vs warfarin (Granger et al., 2011)

2. Person responsible for implementation of replication in Aetion

Ajinkya Pawar, Ph.D., Hemin Lee, MD, MPH, and Dureshahwar Jawaid, MPH implemented the study design in the Aetion Evidence Platform. They are not responsible for the validity of the design and analytic choices. All implementation steps are recorded, and the implementation history is archived in the platform.

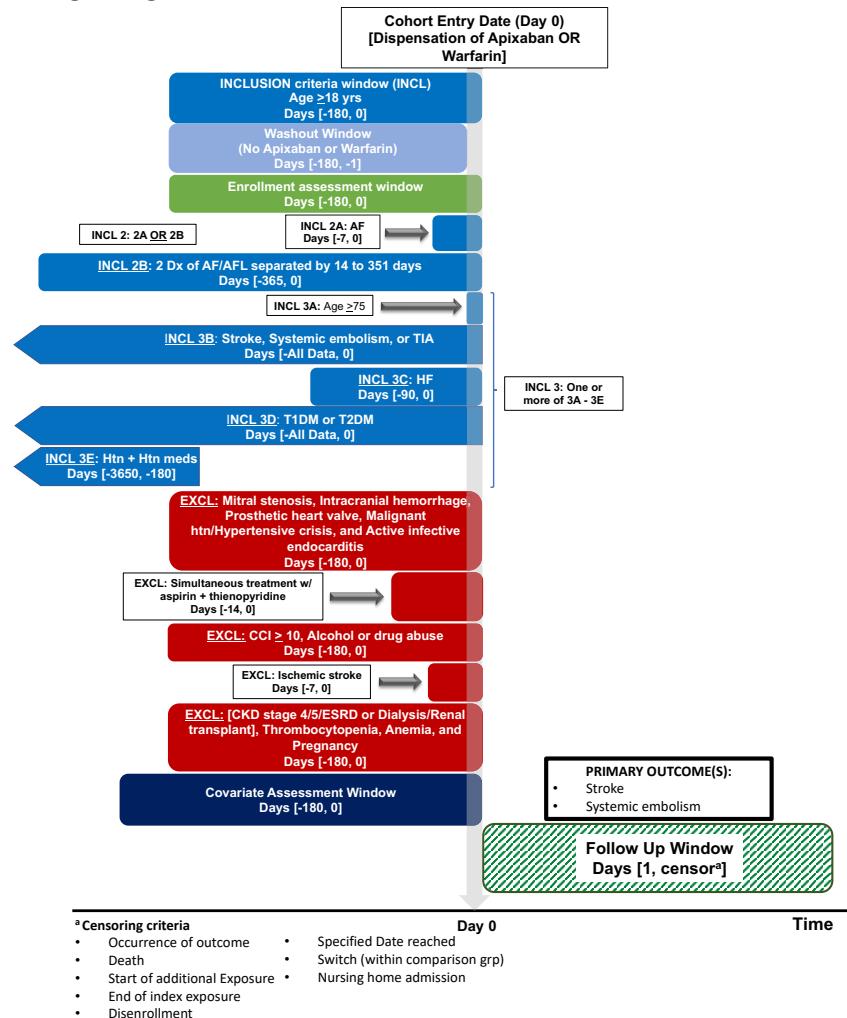
3. Data Source(s)

United/Optum, MarketScan, Medicare

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expedited review.

Design Diagram – ARISTOTLE TRIAL REPLICATION



5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score-matched, retrospective cohort study design comparing apixaban (any dose) to warfarin users. The patients will be required to have continuous enrollment during baseline period of 180 days before initiation of apixaban or warfarin (index date). We restrict the analyses to patients with a diagnosis of atrial fibrillation or atrial flutter in the 12 months prior to drug initiation along with risk factors for stroke or systemic embolism.

5.2 Important steps for cohort formation

New users (defined as no use in 180 days prior to index date) of an exposure and a comparator drug will be identified.

5.2.1 Eligible cohort entry dates

Market availability of apixaban in the U.S. started on December 28, 2012.

- For Medicare: January 01, 2013- December 31, 2017 (end of available data)
- For Marketscan: January 01, 2013- December 31, 2018 (end of available data)
- For Optum: January 01, 2013- December 31, 2019 (end of available data)

5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

5.3 Flowchart of the study cohort assembly

For apixaban vs. warfarin

	Optum		Truven		Medicare	
	Less Excluded Patients	Remaining Patients	Less Excluded Patients	Remaining Patients	Less Excluded Patients	Remaining Patients
All patients		75,894,642		200,203,908		6,886,908

Patients with claim for apixaban or warfarin	-74,955,393	939,249	-199,377,918	825,990	-2,374,503	4,512,405
Excluded due to insufficient enrollment	-87,255	851,994	-66,419	759,571	-1,340,098	3,172,307
Excluded due to prior use of warfarin	-390,759	461,235	-426,157	333,414	-1,802,129	1,370,178
Excluded due to prior use of apixaban 5mg	-250,816	210,419	-139,097	194,317	-545,919	824,259
Excluded because patient qualified in >1 exposure category	-21	210,398	-5	194,312	-51	824,208
Excluded based on missing Age	-563	209,835	0	194,312	-136	824,072
Excluded based on missing Gender	0	209,835	0	194,312	0	824,072
Inclusion 3 - Age >= 18	-82	209,753	-187	194,125	-68	824,004
Inclusion #2- Afib (Inpatient, principal) 7 days prior OR Afib or flutter (any setting, any position) 2 diagnoses separated by 14 to 351 days, measured 365 days prior to drug initiation	-86406	123,347	-96150	97,975	-275611	548,393
Inclusion #3- One or more of the 5 risk factor(s) for stroke	-2636	120,711	-2941	95,034	-5239	543,154
Excluded based on Exclusion #2- Mitral Stenosis (any position, any setting)	-320	120,391	-127	94,907	-626	542,528
Excluded based on Exclusion #3 - intracranial hemorrhage	-503	119,888	-309	94,598	-1823	540,705
Excluded based on Exclusion #4 - Prosthetic heart valve	-1916	117,972	-1004	93,594	-8562	532,143
Excluded based on Exclusion #5 - Uncontrolled hypertension	-701	117,271	-218	93,376	-1753	530,390
Excluded based on Exclusion #6 - Active infective endocarditis	-83	117,188	-43	93,333	-456	529,934
Excluded based on Exclusion #11 - Aspirin and Thienopyridine days supply overlap >7 days, measured 14 days prior to drug initiation	-10	117,178	-24	93,309	**	**
Excluded based on Exclusion #12- CCI (180 days)>=10	-5059	112,119	-1788	91,521	-6685	523,239
Excluded based on Exclusion #13- Active alcohol or drug abuse	-1381	110,738	-563	90,958	-5143	518,096
Excluded based on Exclusion #14 - Ischemic stroke (w and w/o mention of cerebral infarction)- 7 days prior	-1178	109,560	-558	90,400	-5741	512,355
Excluded based on Exclusion #15 - Severe renal impairment	-9885	99,675	-5151	85,249	-50219	462,136
Excluded based on Exclusion #17 - Thrombocytopenia	-411	99,264	-290	84,959	-2040	460,096
Excluded based on Exclusion #18 - Anemia	-933	98,331	-1034	83,925	-7386	452,710
Excluded based on Exclusion #23b - Pregnancy	-3	98,328	-9	83,916	-11	452,699
Final cohort		98,328		83,916		452,699

* Medicare database includes all patients using a novel oral anticoagulant and a subset of patients using warfarin during 2011-2017.

** = Data redacted to maintain compliance with CMS cell suppression policy

6. Variables

6.1 Exposure-related variables:

Study drug:

The study exposure of interest is initiation of apixaban. Initiation will be defined by no use of apixaban or a comparator in the prior 6 months before treatment initiation (washout period).

Comparator agents-

- Initiators of apixaban will be compared to initiators of-
 - Warfarin

6.2 Covariates:

- Age
- Sex
- Combined Comorbidity Index (CCI), measured over the baseline covariate assessment period, defined as 180 days prior to and including index date

Covariates listed above represent only a small subset of covariates that will ultimately be controlled for in the design and analysis. We use the covariates above only for initial feasibility analyses to judge whether there is likely to be sufficient overlap between treatment groups to proceed with the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and the initial power assessment and are listed in Table 1 (**Appendix B**).

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Primary Effectiveness outcomes of interest (definitions provided in **Appendix A**):

- **Primary outcome:** Stroke (hemorrhagic, ischemic) and systemic embolism
- Secondary outcomes: Individual components:
 - Hospital admission for stroke (principal diagnosis position)

- Hospital admission for systemic embolism (principal diagnosis position)

Control outcomes of interest (control outcomes only serve to assess aspects of study validity but are not further interpreted):

1. Major bleeding

6.3.2 Study follow-up

Both as-treated (AT) and intention-to-treat (ITT) analyses will be conducted with treatment defined as the index drug on the day of cohort entry. Because adherence in the real-world databases is expected to be much worse than in the trial, the AT analysis is the **primary** analysis, as it targets the relative hazard of outcomes on treatment.

For the AT analyses, the follow-up will start the day after initiation of apixaban and comparator and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest, unless otherwise specified for selected outcomes,
- The date of end of continuous registration in the database,
- End of the study period,
- Measured death event occurs,
- Nursing home admission
 - Nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on a patient, particularly on drug utilization, after admission. We will utilize this as an exclusion reason for cohorts for the same reason.
- The date of drug discontinuation, defined as the date of the last continuous treatment episode of the index drug (apixaban and comparator) plus a defined grace period (i.e., 10 days after the end of the last prescription's days' supply in main analyses).
- The date of augmentation or switching from exposure to comparator or vice versa or augmentation/switching to any other NOAC (e.g. switching from apixaban or warfarin to rivaroxaban would be a censoring event);
 - A dosage change on the index treatment does not fulfill this criterion
 - An added treatment that is not part of the exposure or comparator group does not fulfill this criterion

For the intention-to-treat (ITT) analyses, the censoring based on the augmentation/switching and treatment discontinuation will be replaced with a maximum allowed follow-up time of 365 days.

7. Initial Feasibility Analysis

Action report name:

Optum- <https://bwh-dope.aetion.com/projects/details/707/results/58231/result/0>

Marketscan- <https://bwh-dope.aetion.com/projects/details/708/results/58232/result/0>

Medicare- <https://bwh-dope.aetion.com/projects/details/709/results/58233/result/0>

Date conducted: 9/4/2020

Complete Aetion feasibility analysis using age, sex, and CCI as the only covariates and the primary endpoint (Section 6.3.1) as the outcome. No measures of association will be computed nor will incidence rates stratified by treatment group.

- Report patient characteristics by treatment group
- Report summary parameters of study population
- Report median follow-up time by treatment group
- Report reasons for censoring in the overall study population

8. Initial Power Assessment

Action report name:

For apixaban vs. warfarin

Optum- <https://bwh-dope.aetion.com/projects/details/711/results/53838/result/0>

Marketscan- <https://bwh-dope.aetion.com/projects/details/712/results/53839/result/0>

Medicare- <https://bwh-dope.aetion.com/projects/details/713/results/53840/result/0>

Date conducted: 05/12/2020

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. This outcome is used to ensure that no information on the comparative risks of the outcomes of interest are available at this stage. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 3 covariates: age, sex, and combined

comorbidity index. Power calculations are based on the formulas from Chow et al. (2008).

- Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Jessica Franklin	Date reviewed:	6/3/20
Reviewed by FDA:	Ken Quinto	Date reviewed:	6/30/20
Reasons for stopping analysis (if required):			

9. Balance Assessment

Action report name:

For apixaban vs. warfarin

Optum- <https://bwh-dope.aetion.com/projects/details/711/results/57927/result/0>

Marketscan- <https://bwh-dope.aetion.com/projects/details/712/results/57928/result/0>

Medicare- <https://bwh-dope.aetion.com/projects/details/713/results/57982/result/0>

Date conducted: 8/27/2020 (Medicare 8/30/2020)

After review of initial feasibility and power analyses, complete creation of the remaining covariates (see Table 1 below for list of covariates). Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates (excluding laboratory values, which are missing in some patients).

- Provide plot of PS distributions stratified by treatment group.

Note- Please refer to **Appendix B**.

- Report covariate balance after matching.

Note- For Table 1, please refer to **Appendix B**.

- Report reasons for censoring by treatment group.

	Overall	Referent	Exposure
Dummy Outcome	0 (0.00%)	0 (0.00%)	0 (0.00%)
Death	3,281 (1.49%)	1,664 (1.51%)	1,617 (1.47%)
Start of an additional exposure	4,890 (2.22%)	3,122 (2.83%)	1,768 (1.60%)
End of index exposure	157,724 (71.52%)	78,153 (70.88%)	79,571 (72.17%)
Specified date reached (Dec 17/Dec 18/Dec 19)	23,353 (10.59%)	10,720 (9.72%)	12,633 (11.46%)
End of patient enrollment	9,203 (4.17%)	4,146 (3.76%)	5,057 (4.59%)
Switch to other NOACs (for censoring) + nursing home admission	22,067 (10.01%)	12,454 (11.30%)	9,613 (8.72%)

- Report follow-up time by treatment group.

Median Follow-Up Time (Days) [IQR]			
Patient Group	Optum	Truven	Medicare
Overall Patient Population	98 [38-192]	98 [38-213]	98 [38-213]
Referent	98 [38-182]	98 [38-180]	98 [39-191]
Exposure	98 [38-211]	98 [38-264]	98 [38-242]

- Report overall risk of the primary outcome.

	Optum	MarketScan	Medicare	Pooled
Risk per 1,000 patients	3.61	3.6	5.64	5.06

10. Final Power Assessment

Date conducted:

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9.

All other parameters in the table should be the same as in Section 8.

- For apixaban vs. warfarin

- Pooled

Superiority Analysis		Non-inferiority Analysis	
Number of patients matched		Number of patients matched	
Reference	110,259	Reference	110,259
Exposed	110,259	Exposed	110,259
Risk per 1,000 patients	5.06	Risk per 1,000 patients	5.06
Desired HR from RCT	0.79	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.38
Number of events expected	1115.82108	Number of events expected	1115.82108
Power	0.975982555	Power	0.999686272

- Optum

Superiority Analysis		Non-inferiority Analysis	
Number of patients matched		Number of patients matched	
Reference	15,273	Reference	15,273
Exposed	15,273	Exposed	15,273
Risk per 1,000 patients	3.61	Risk per 1,000 patients	3.61
Desired HR from RCT	0.79	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.38
Number of events expected	110.27106	Number of events expected	110.27106
Power	0.235746761	Power	0.394017124

○ MarketScan

Superiority Analysis		Non-inferiority Analysis	
Number of patients matched		Number of patients matched	
Reference	14,849	Reference	14,849
Exposed	14,849	Exposed	14,849
Risk per 1,000 patients	3.6	Risk per 1,000 patients	3.60
Desired HR from RCT	0.79	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.38
Number of events expected	106.9128	Number of events expected	106.9128
Power	0.229997009	Power	0.384067948

- Medicare

Superiority Analysis		Non-inferiority Analysis	
Number of patients matched		Number of patients matched	
Reference	80,137	Reference	80,137
Exposed	80,137	Exposed	80,137
Risk per 1,000 patients	5.64	Risk per 1,000 patients	5.64
Desired HR from RCT	0.79	Assumed HR from RCT	1
Alpha (2-sided)	0.05	Alpha (2-sided)	0.05
		Non-inferiority margin	1.38
Number of events expected	903.94536	Number of events expected	903.94536
Power	0.943359069	Power	0.998023363

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Jessica Franklin	Date reviewed:	9/8/20
Reviewed by FDA:	Ken Quinto	Date reviewed:	9/29/20
Reasons for stopping analysis (if required):			

11. Study Confidence and Concerns

Deadline for voting on study confidence and listing concerns:

Date votes and concerns are summarized:

- If final feasibility and power analyses are reviewed and approved, proceed to the remaining protocol steps.
- All study team and advisory board members that review this protocol should at this stage provide their level of confidence for the

success of the RWD study in the [Google Form](#). This form also provides space for reviewers to list any concerns that they feel may contribute to a failure to replicate the findings of the RCT, including differences in study populations, poor measurement of study variables, or residual confounding. All responses will be kept confidential and individual-level results will only be shared with the individual respondent.

- After the deadline for voting has passed, provide the distribution of responses and summarize all concerns here.

12. Register study protocol on clinicalTrials.gov

Date conducted:

- Register the study on [clinicalTrials.gov](#) and upload this document.

13. Comparative Analyses

Action report name:

Date conducted:

13.1 For primary analysis:

13.2 For sensitivity analyses:

14. Requested Results

14.1 Table 1: Baseline characteristics before and after adjustment

Variable	Before adjustment			After adjustment		
	Referent	Exposure	Std. diff.	Referent	Exposure	Std. diff.
Number of patients			-			-
Age categories						
...						

14.2 Table 2: Follow-up time

Patient Group	Median Follow-Up Time (Days) [IQR]
Overall Patient Population	
Referent	
Exposure	

14.3 Table 3: Censoring events

	Overall	Referent	Exposure
Outcome			
Death			
Start of an additional exposure			
End of index exposure			
Specified date reached			
End of patient data			
End of patient enrollment			
...			

14.4 Table 4: Results from primary analyses;

Analysis	No. exposed events	No. referent events	Exposed rate	Referent rate	HR (95% CI)
Crude					
Analysis 1					
Analysis 2					
...					

HR, Hazard Ratio; CI, Confidence Interval.

14.5 Table 5: Results from secondary analyses;

15. References

Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. **page 177**

Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC. Apixaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*. 2011; 365(11):981-92.

Appendix A

#	ARISTOTLE trial definitions	Implementation in routine care	References/Rationale	Color coding
	Trial details- Primary approval, Unintended S with label change		<p>Please see the following Google Drive for further details or any missing information: https://drive.google.com/open?id=1WD618wrvwYfEaXrlTcuKVConb6b-gU</p>	Criteria
	EXPOSURE vs. COMPARISON		<p>ICD-10 codes are not listed in this document because of excel cell size limitations and excessive number of ICD-10 codes. Full ICD-10 code lists will be available in the above Google Drive Folder (link above). ICD-9 to ICD-10 code conversions were completed using a SAS macro that implements forward/backward mapping based on the CMS ICD-9 to ICD-10 mapping: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3074733/</p>	Adequate mapping in claims
	apixaban (at a dose of 5 mg twice daily) versus warfarin (target international normalized ratio, 2.0 to 3.0)	Apixaban 5mg vs warfarin		Intermediate mapping in claims
	PRIMARY OUTCOME			Poor mapping or cannot be measured in claims
	The primary outcome was ischemic or hemorrhagic stroke or systemic embolism .	<p>Measured 1 days after drug initiation in diagnosis position specified below and inpatient care setting:</p> <p>For stroke :</p> <p>Primary diagnosis position in inpatient care setting</p> <p>430.xx Subarachnoid hemorrhage (SAH) 431.xx Intracerebral hemorrhage (ICH) 433.xx Occlusion and stenosis of precerbral arteries with cerebral infarction 434.xx (excluding 434.x0) Occlusion and stenosis of cerebral arteries with cerebral infarction 436.x Acute, but ill-defined cerebrovascular events</p> <p>Systemic embolism: (inpatient, any position)</p> <p>ICD-9: 444.xx (arterial embolism) ICD-10: I74.x arterial embolism and thrombosis</p>	<p>For stroke: PPV of 85% or higher for ischemic stroke PPV ranging from 80% to 98% for hemorrhagic stroke →[Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. <i>Pharmacoepidemiology and Drug Safety</i> 2012;21 Suppl 1:100-28.] →[Tirschwell DL, Longstreth WT, Jr. Validating administrative data in stroke research. <i>Stroke: a journal of cerebral circulation</i> 2002;33:2465-70.] →[Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. <i>Pharmacoepidemiology and drug safety</i> 2008;17:20-6.]</p>	Can't be measured in claims but not important for the analysis
	INCLUSION CRITERIA			
1	Age ≥ 18 years	Measured on the day of drug initiation Age >=18 years		
2	Either of the following:			
2a	• In atrial fibrillation or atrial flutter not due to a reversible cause and documented by ECG at the time of enrollment .	<p>Measured 7 days prior to and including day of drug initiation in primary diagnosis position and inpatient care setting</p> <p>Atrial fibrillation ICD-9 diagnosis: 427.31, 427.32</p> <p>Reversible causes listed in exclusion criteria.</p>		
2b	• If not in atrial fibrillation/flutter at the time of enrollment, must have atrial fibrillation/flutter documented on two separate occasions, not due to a reversible cause at least 2 weeks apart in the 12 months prior to enrollment . Atrial fibrillation/flutter may be documented by ECG, or as an episode lasting at least one minute on a rhythm strip, Holter recording, or intracardiac electrogram (from an implanted pacemaker or defibrillator).	<p>Measured 365 days prior to and including day of drug initiation 2 diagnoses of Atrial fibrillation/flutter separated by 14 to 351 days in any diagnosis position and inpatient or outpatient care setting</p> <p>Atrial fibrillation or flutter ICD-9 diagnosis: 427.31, 427.32</p> <p>Reversible causes listed in exclusion criteria.</p>		
3	One or more of the following risk factor(s) for stroke:			
3a	• Age 75 years or older	Measured on the day of drug initiation Age >=75		
3b	• Prior stroke, TIA or systemic embolus	<p>Measured any time prior to and including day of drug initiation in diagnosis position and care setting specified below</p> <p>Stroke (inpatient care setting, primary diagnosis position)</p> <p>ICD-9 diagnosis: 430.x, 431.xx, 433.xx, 434.xx, 436.xx ICD-10 diagnosis: I63.5x, I63.6x, I63.8x, I63.9x, I65.0x, I65.1x, I65.2x, I66.0x, I66.1x, I66.2x, I66.3x, I66.8x, I66.9x</p> <p>Hemorrhagic stroke:</p> <p>ICD-9 diagnosis: 431.x</p> <p>Ischemic stroke:</p> <p>ICD-9 diagnosis: 433.x, 434.x</p> <p>Systemic embolism (inpatient care setting, any diagnosis position)</p> <p>ICD-9 diagnosis: 444.x ICD-10 diagnosis: I74.x arterial embolism and thrombosis</p> <p>TIA (inpatient or ED care setting, any diagnosis position)</p> <p>ICD-9 diagnosis: 435.xx (Transient cerebral ischemia)</p>		
3c	• Either symptomatic congestive heart failure within 3 months or left ventricular dysfunction with an LV ejection fraction (LVEF) ≤ 40% by echocardiography, radionuclide study or contrast angiography	<p>Measured 90 days prior to and including day of drug initiation in any diagnosis position and inpatient care setting</p> <p>Heart failure</p> <p>ICD-9 diagnosis: 428.x, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 ICD-10 diagnosis: I09.81, I11.0, I13.0, I13.1, I50.1x, I50.2x, I50.3x, I50.4x, I50.9</p>	<p>Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-glipizide antidiabetic drugs: population based cohort study." <i>BMJ</i> 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119</p> <p>Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." <i>Circulation</i>. 2019 Apr 8. doi:10.1161/CIRCULATIONAHA.118.039177</p>	

Appendix A

3d	• Diabetes mellitus	<p>Measured any time prior to and including day of drug initiation in any diagnosis position and any care setting</p> <p><u>Type 1, Type 2 diabetes mellitus</u> ICD-9 diagnosis: 250.x1, 250.x3, 250.x0, 250.x2 ICD-10 diagnosis: E10.x, E11.x</p>	<p>Paterno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-glipizide antidiabetic drugs: population based cohort study." <i>BMJ</i> 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119</p> <p>Paterno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." <i>Circulation</i>. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177</p>
3e	• Hypertension requiring pharmacological treatment	<p>Measured 180 days to 3650 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p><u>Hypertension</u> ICD-9 diagnosis: 401.x – 405.x ICD-10 diagnosis: I10.x – I13.x, I15.x</p> <p>Plus following medication use on the same day: (Hypertension Medications sheet) ACE/ARB/beta-blocker/Calcium channel blockers/thiazides/loop diuretics/other diuretics/other hypertensive medications</p>	<p>Paterno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-glipizide antidiabetic drugs: population based cohort study." <i>BMJ</i> 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119</p> <p>Paterno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." <i>Circulation</i>. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177</p>
4	Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the treatment period of the study or for 2 weeks after the last dose of study medication, whichever is longer, in such a manner that the risk of pregnancy is minimized.	N/A - Incorporated in the exclusion criteria.	
5	WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 48 hours prior to the start of investigational product.	N/A - Incorporated in the exclusion criteria.	
6	All subjects must provide signed written informed consent.	N/A	
EXCLUSION CRITERIA			
1	Atrial fibrillation or flutter due to reversible causes (e.g. thyrotoxicosis, pericarditis)	N/A	
2	Clinically significant (moderate or severe) mitral stenosis	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p><u>Mitral stenosis</u> ICD-9 diagnosis: 396.0x, 396.1x, 394, 746.5 ICD-10 diagnosis: I34.2x, I05.1x, I05.2x</p>	
3	Increased bleeding risk that is believed to be a contraindication to oral anticoagulation (e.g. previous intracranial hemorrhage)	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient care setting</p> <p><u>Intracranial hemorrhage</u> ICD-9 diagnosis: 430.x, 431.x, 432.x</p>	
4	Conditions other than atrial fibrillation that require chronic anticoagulation (e.g. prosthetic mechanical heart valve)	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p>ICD-9 diagnosis: V43.3x ICD-10 diagnosis: Z95.2x</p> <p>CPT procedure codes: (TAVR with prosthetic valve) 33361, 33362, 33363, 33364, 33365, 33366, 33367, 33368, 33369, 33477, 0483T, 0484T, 0569T, 0570T</p>	
5	Persistent, uncontrolled hypertension (systolic BP > 180 mm Hg, or diastolic BP > 100 mm Hg)	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or ED care setting</p> <p><u>Malignant hypertension</u> ICD-9 diagnosis: 401.0x</p> <p><u>Hypertensive urgency/Hypertensive crisis</u> ICD-10 diagnosis: I16.xx</p>	
6	Active infective endocarditis	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p><u>Endocarditis</u> ICD-9 diagnosis: 421.xx ICD-10 diagnosis: I33.xx</p>	
7	Planned major surgery	N/A	
8	Planned atrial fibrillation or flutter ablation procedure	N/A	
9	Use of an unapproved , investigational drug or device within the past 30 days	N/A	
10	Required treatment with aspirin >165 mg/day	N/A	
11	Simultaneous treatment with both aspirin and a thienopyridine (e.g., clopidogrel, ticlopidine)	<p>Measured 14 days prior to and including day of drug initiation</p> <p>Days supply overlap of >7 days of: 1) Prescription for any dose of Aspirin (Note: Unable to capture over the counter use.) AND 2) Prescription for any dose of Clopidogrel/Ticlopidine/prasugrel</p>	
12	Severe comorbid condition with life expectancy of ≤ 1 year	<p>Measured 180 days prior to and including day of drug initiation</p> <p>CCI ≥ 10</p>	

Appendix A

13	Active alcohol or drug abuse, or psychosocial reasons that make study participation impractical	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p><u>Alcohol abuse or dependence</u> ICD-9 diagnosis: 291.xx, 303.xx, 305.0x, 571.0x, 571.1x, 571.2x, 571.3x, 357.5x, 425.5x, E860.0x, V11.3x <u>Drug abuse or dependence</u> ICD-9 diagnosis: 292.xx, 304.xx, 305.2x-305.9x, 648.3x, 965.0x, 967.x, 969.x, 970.81</p>	<p>Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-glipizid antidiabetic drugs: population based cohort study." <i>BMJ</i> 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119</p> <p>Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." <i>Circulation</i>. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177</p>
14	Recent ischemic stroke (within 7 days)	<p>Measured 7 days prior to and including day of drug initiation in primary diagnosis position and inpatient care setting</p> <p><u>Ischemic stroke</u> ICD-9 diagnosis: 433.xx, 434.xx, 436.xx</p>	<p>Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-glipizid antidiabetic drugs: population based cohort study." <i>BMJ</i> 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119</p> <p>Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." <i>Circulation</i>. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177</p>
15	Severe renal insufficiency (serum creatinine > 2.5 mg/dL or a calculated creatinine clearance < 25 mL/min, See Section 6.3.2.2)	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p><u>CKD stage 4/5/ESRD</u> ICD-9 diagnosis: 585.4x, 585.5x, 585.6x ICD-10 diagnosis: N18.4x, N18.5x, N18.6x</p> <p>OR</p> <p><u>Dialysis/ Renal transplant</u> code list in sheet "Dialysis and Renal Transplant"</p>	
16	ALT or AST > 2X ULN or a Total Bilirubin \geq 1.5X ULN (unless an alternative causative factor [e.g., Gilbert's syndrome] is identified)	N/A	
17	Platelet count \leq 100,000/mm ³	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p><u>Thrombocytopenia</u> ICD-9 diagnosis: 287.3x, 287.4x, 287.5x ICD-10 diagnosis: D69.3x, D69.4x, D69.5x, D69.6x</p>	
18	Hemoglobin < 9 g/dL	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p><u>Anemia (non-deficiency/ neoplastic/chemotherapy/hemorrhagic associated)</u> ICD-9 diagnosis: 282.x, 283.x, 284.x, 285.0, 285.2 (acute posthemorrhagic anemia), 285.22 (anemia of neoplastic disease), 285.3 (antineoplastic chemotherapy induced anemia) ICD-10 diagnosis: D55 - D62, D63.0</p>	
19	Inability to comply with INR monitoring	N/A	
20	Prior randomization into an apixaban clinical study	N/A	
21	Prisoners or subjects who are involuntarily incarcerated	N/A	
22	Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness	N/A	
23	Women of child bearing potential (WOCBP) unwilling or unable to use an acceptable method to avoid pregnancy.	N/A	
23a	• WOCBP using a prohibited contraceptive method	N/A	
23b	<ul style="list-style-type: none"> WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea \geq 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL]. Even women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (e.g., vasectomy) should be considered to be of child bearing potential 	<p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and inpatient or outpatient care setting</p> <p>Codes are in the sheet "Pregnancy"</p>	
23c	• Women who are pregnant or breastfeeding		
23d	• Women with a positive pregnancy test on enrollment or prior to administration of investigational product.		

Appendix A

<u>Trial ID</u>	pNDA15
<u>Trial Name (with web links)</u>	ARISTOTLE
<u>NCT</u>	NCT00412984
<u>Therapeutic Area</u>	Cardiology/Vascular Diseases
<u>Brand Name</u>	Eliquis
<u>Generic Name</u>	apixaban
<u>Sponsor</u>	Bristol-Myers Squibb
<u>Year</u>	2012
<u>pNDA Indication</u>	For the prevention of stroke and systemic embolism resulting from nonvalvular atrial fibrillation
<u>Measurable endpoint</u>	Primary outcomes: Effectiveness: ischemic or hemorrhagic stroke or systemic embolism Safety: Major bleeding
<u>Trial finding</u>	HR 0.79; 95% CI, 0.66 to 0.95; P<0.001 for noninferiority; P = 0.01 for superiority
<u>Blinding</u>	Double-blinded
<u>No. of Patients</u>	18,201
<u>Comparator</u>	Active

Appendix A

Hypertension medication	
ACE inhibitor	Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
ARB	Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Beta blocker	Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol tartrate, metoprolol succinate, propranolol, penbutolol, pindolol, nadolol, nebivolol, sotalol, timolol
Calcium channel blocker	Diltiazem, mibepradil, verapamil, amlodipine, clevidipine, bepridil, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine
Other hypertension drugs	Doxazosin, eplerenone, prazosin, terazosin, clonidine, guanabenz, guanadrel, guanethidine, guanfacine, hydralazine, methyldopa, metyrosine, reserpine, minoxidil, aliskiren
Thiazides	Benzthiazide, chlorothiazide, chlorthalidone, cyclothiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, quinethazone, trichlormethiazide, bendroflumethiazide
Loop diuretics	Furosemide, bumetanide, torsemide, ethacrynic acid
Other diuretics	Amiloride, eplerenone, spironolactone, triamterene

Appendix A

Dialysis codes
ESRD, defined as 2 codes (either inpatient or outpatient), separated by at least 30 days
Codes include:
- ICD9 prox codes:
39.95, Hemodialysis
54.98, Peritoneal dialysis
- ICD9 dx codes:
585.5x, Chronic kidney disease, Stage V (for ESRD with no mention of dialysis)
585.6x, End stage renal disease (for ESRD with dialysis)
V56.0x, encounter for dialysis NOS
V56.8x, encounter for peritoneal dialysis
V45.1x, renal dialysis status
- CPT4 codes:
90957, 90960, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 4 or more face-to-face physician visits per month
90958, 90961, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 2-3 face-to-face physician visits per month
90959, 90962, ESRD related services monthly, for patients 12-19 and 20 years of age and older; with 1 face-to-face physician visit per month
90920, 90921, ESRD related services per full month; for patients 12-19 and twenty years of age and over
90924, 90925, ESRD related services (less than full month), per day; for patients 12-19 and twenty years of age and over
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 (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies), with single physician evaluation
90947, Dialysis procedure other than hemodialysis (eg, peritoneal dialysis, hemofiltration, or other continuous renal replacement therapies) requiring repeated physician evaluations, with or without substantial revision of dialysis prescription
90965, 90966, ESRD related services for home dialysis per full month, for patients 12-19 and 20 years of age and older
90969, 90970, ESRD related services for dialysis less than a full month of service, per day; for patients 12-19 and 20 years of age and older
90989, Dialysis training, patient, including helper where applicable, any mode, completed course
90993, Dialysis training, patient, including helper where applicable, any mode, course not completed, per training session
90999, Unlisted dialysis procedure, inpatient or outpatient
99512, Home visit for hemodialysis
- HCPCS codes:
G0257, Unscheduled or emergency dialysis treatment for ESRD patient in a hospital outpatient dept. that is not certified as an ESRD facility
G0314, G0317, ESRD related services during the course of treatment, for patients 12-19 and 20 yrs of age and over to include monitoring for the adequacy of nutrition, etc. w/4 or more physician visit per month
G0315, G0318, ESRD related services during the course of treatment, for patients 12-19 and 20 yrs of age and over to include monitoring for the adequacy of nutrition, etc. w/2 or 3 physician visit per month

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G0316, G0319, ESRD related services during the course of treatment, for patients 12-19 and 20 yrs of age and over to include monitoring for the adequacy of nutrition, etc. w/1 physician visit per month

G0322, G0323, ESRD related services for home dialysis patients per full month: for patients 12-19 and 20 yrs of age and over to include monitoring for adequacy of nutrition and etc.

G0326, G0327, ESRD related services for home dialysis (less than full month), per day; for patients 12-19 and 20 yrs of age and over

S9335, Home therapy, hemodialysis; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing services coded separately), per diem

S9339, Home therapy, peritoneal dialysis, administrative services, care coordination and all necessary supplies and equipment, per diem

OR

Kidney transplant, defined as either 1 inpatient or 1 outpatient code

Codes include:

-ICD9 dx codes:

V42.0x, Kidney transplant status

996.81 Complications of transplanted kidney

-ICD9 prox codes:

55.6x, Transplant of kidney (Exclude 55.61)

CPT4 codes:

Appendix A

Pregnancy
Dx codes
650 NORMAL DELIVERY
660 OBSTRUCTED LABOR
661 ABNORMALITY OF FORCES OF LABOR
662 LONG LABOR
663 UMBILICAL CORD COMPLICATIONS DURING LABOR AND DELIVERY
664 TRAUMA TO PERINEUM AND VULVA DURING DELIVERY
665 OTHER OBSTETRICAL TRAUMA
667 RETAINED PLACENTA OR MEMBRANES WITHOUT HEMORRHAGE
668 COMPLICATIONS OF THE ADMINISTRATION OF ANESTHETIC OR OTHER SEDATION IN LABOR AND DELIVERY
669.94 UNSPECIFIED COMPLICATION OF LABOR AND DELIVERY POSTPARTUM CONDITION OR COMPLICATION
V24 POSTPARTUM CARE AND EXAMINATION
V24.0 POSTPARTUM CARE AND EXAMINATION IMMEDIATELY AFTER DELIVERY
V24.1 POSTPARTUM CARE AND EXAMINATION OF LACTATING MOTHER
V24.2 ROUTINE POSTPARTUM FOLLOW
V27 OUTCOME OF DELIVERY
V27.0 MOTHER WITH SINGLE LIVEBORN
V27.1 MOTHER WITH SINGLE STILLBORN
V27.2 MOTHER WITH TWINS BOTH LIVEBORN
V27.3 MOTHER WITH TWINS ONE LIVEBORN AND ONE STILLBORN
V27.4 MOTHER WITH TWINS BOTH STILLBORN
V27.5 MOTHER WITH OTHER MULTIPLE BIRTH ALL LIVEBORN
V27.6 MOTHER WITH OTHER MULTIPLE BIRTH SOME LIVEBORN
V27.7 MOTHER WITH OTHER MULTIPLE BIRTH ALL STILLBORN
V27.9 MOTHER WITH UNSPECIFIED OUTCOME OF DELIVERY
Procedure codes
72.0 LOW FORCEPS OPERATION
72.1 LOW FORCEPS OPERATION WITH EPISIOTOMY
72.2 MID FORCEPS OPERATION
72.21 MID FORCEPS OPERATION WITH EPISIOTOMY
72.29 OTHER MID FORCEPS OPERATION
72.3 HIGH FORCEPS OPERATION
72.31 HIGH FORCEPS OPERATION WITH EPISIOTOMY
72.39 OTHER HIGH FORCEPS OPERATION

Appendix A

- 72.4 FORCEPS ROTATION OF FETAL HEAD
- 72.5 BREECH EXTRACTION
- 72.51 PARTIAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
- 72.52 OTHER PARTIAL BREECH EXTRACTION
- 72.53 TOTAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
- 72.54 OTHER TOTAL BREECH EXTRACTION
- 72.6 FORCEPS APPLICATION TO AFTERCOMING HEAD
- 72.7 VACUUM EXTRACTION
- 72.71 VACUUM EXTRACTION WITH EPISIOTOMY
- 72.79 OTHER VACUUM EXTRACTION
- 72.8 OTHER SPECIFIED INSTRUMENTAL DELIVERY
- 72.9 UNSPECIFIED INSTRUMENTAL DELIVERY
- 73.0 ARTIFICIAL RUPTURE OF MEMBRANES
- 73.01 INDUCTION OF LABOR BY ARTIFICIAL RUPTURE OF MEMBRANES
- 73.09 OTHER ARTIFICIAL RUPTURE OF MEMBRANES
- 73.1 OTHER SURGICAL INDUCTION OF LABOR
- 73.2 INTERNAL AND COMBINED VERSION AND EXTRACTION
- 73.21 INTERNAL AND COMBINED VERSION WITHOUT EXTRACTION
- 73.22 INTERNAL AND COMBINED VERSION WITH EXTRACTION
- 73.3 FAILED FORCEPS
- 73.4 MEDICAL INDUCTION OF LABOR
- 73.5 MANUALLY ASSISTED DELIVERY
- 73.51 MANUAL ROTATION OF FETAL HEAD
- 73.59 OTHER MANUALLY ASSISTED DELIVERY
- 73.6 EPISIOTOMY
- 73.8 OPERATIONS ON FETUS TO FACILITATE DELIVERY
- 73.9 OTHER OPERATIONS ASSISTING DELIVERY
- 73.91 EXTERNAL VERSION ASSISTING DELIVERY
- 73.92 REPLACEMENT OF PROLAPSED UMBILICAL CORD
- 73.93 INCISION OF CERVIX TO ASSIST DELIVERY
- 73.94 PUBIOTOMY TO ASSIST DELIVERY
- 73.99 OTHER OPERATIONS ASSISTING DELIVERY
- 74.0 CLASSICAL CESAREAN SECTION
- 74.1 LOW CERVICAL CESAREAN SECTION
- 74.2 EXTRAPERITONEAL CESAREAN SECTION

Appendix A

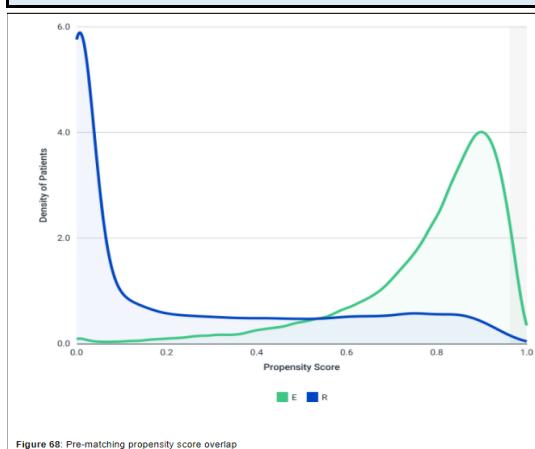
- 74.3 REMOVAL OF EXTRATUBAL ECTOPIC PREGNANCY
- 74.4 CESAREAN SECTION OF OTHER SPECIFIED TYPE
- 74.9 CESAREAN SECTION OF UNSPECIFIED TYPE
- 74.91 HYSTEROTOMY TO TERMINATE PREGNANCY
- 74.99 OTHER CESAREAN SECTION OF UNSPECIFIED TYPE
- 75.4 MANUAL REMOVAL OF RETAINED PLACENTA
- 75.5 REPAIR OF CURRENT OBSTETRIC LACERATION OF UTERUS
- 75.6 REPAIR OF OTHER CURRENT OBSTETRIC LACERATION
- 75.7 MANUAL EXPLORATION OF UTERINE CAVITY, POSTPARTUM
- 75.9 OTHER OBSTETRIC OPERATIONS

Appendix B: Apixaban vs Warfarin

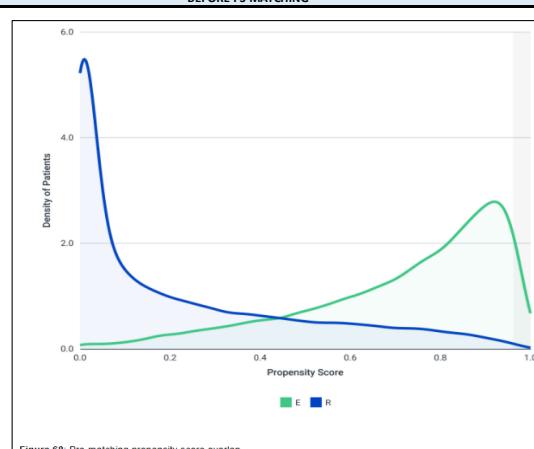
Optum

MarketScan

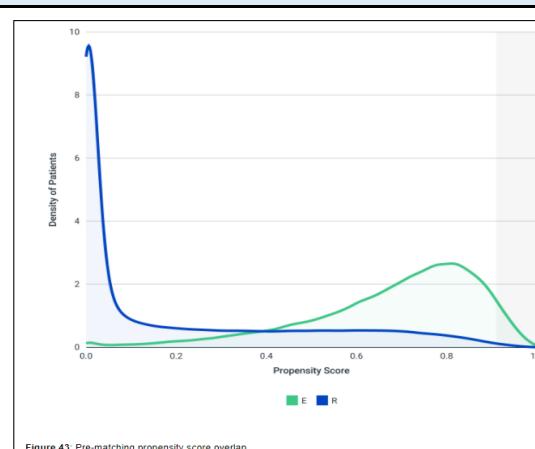
Medicare



The c-statistics for the propensity score model, pre-matching was 0.911. The post-matching c-statistic was 0.547.



The c-statistics for the propensity score model, pre-matching was 0.904. The post-matching c-statistic was 0.54.



The c-statistics for the propensity score model, pre-matching was 0.901. The post-matching c-statistic was 0.531.

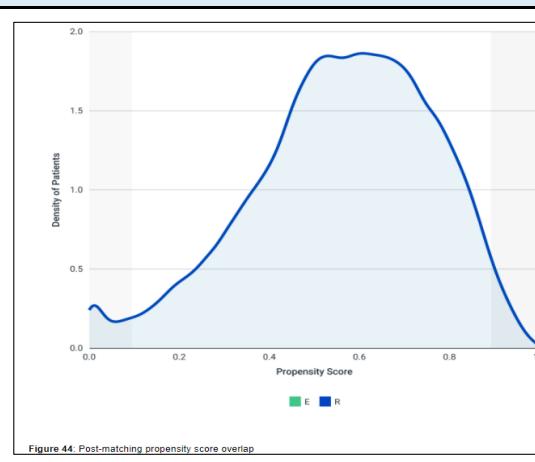
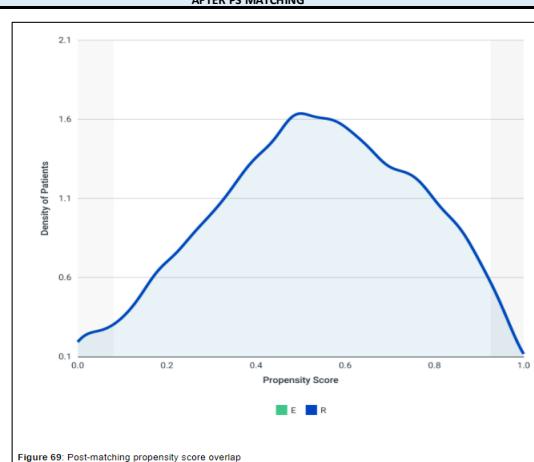
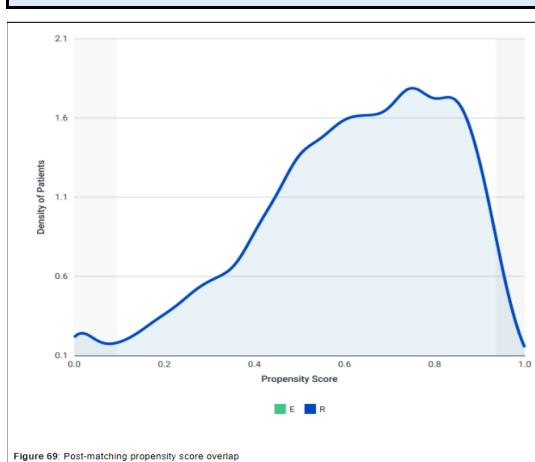


Table 1: Unmatched

Variable	Unmatched								St. Diff.				
	Optum	Truven		Medicare		POOLED							
Reference	46,518	Apixaban (any dose)	51,684	Reference	Warfarin	Apixaban (any dose)	174,898	Reference	Warfarin	Apixaban (any dose)	370,862	263,296	
Number of patients				47,096	36,714	277,248	370,862						
Age													
...mean (sd)	75.30 (8.70)	74.09 (8.49)	74.33 (11.29)	69.50 (12.30)	77.78 (9.41)	77.33 (8.13)	77.04 (8.86)	75.60 (9.09)			0.16		
...older (10%)	77.00 (70.00, 82.00)	75.00 (68.00, 81.00)	76.00 (66.00, 83.00)	69.00 (60.00, 79.00)	78.00 (72.00, 84.00)	77.00 (72.00, 83.00)							
Age categories without zero category													
...18 - 54; n (%)	1,093 (2.3%)	1,861 (3.6%)	2,201 (4.7%)	3,698 (10.1%)	2,803 (1.0%)	1,281 (0.7%)	6,097 (1.6%)	6,840 (2.6%)			-0.01		
...55 - 64; n (%)	4,064 (8.7%)	5,668 (11.0%)	8,470 (18.0%)	11,308 (30.3%)	8,161 (2.9%)	4,224 (2.4%)	20,695 (5.6%)	21,200 (8.1%)			-0.01		
...65 - 74; n (%)	13,880 (29.2%)	16,773 (32.5%)	10,436 (22.2%)	7,808 (21.3%)	83,745 (30.2%)	59,633 (34.1%)	108,061 (29.1%)	84,214 (32.0%)			-0.01		
...>75; n (%)	27,481 (59.1%)	27,382 (53.0%)	25,989 (55.2%)	13,900 (37.9%)	182,539 (65.8%)	109,760 (62.8%)	236,009 (63.6%)	151,042 (57.4%)			0.01		
Gender without zero category- United													
...Male; n (%)	25,508 (54.8%)	25,542 (49.4%)	26,865 (57.0%)	20,513 (55.9%)	15,230 (48.8%)	76,603 (43.8%)	187,603 (50.6%)	122,658 (46.6%)			0.01		
...Female; n (%)	21,010 (45.2%)	26,142 (50.6%)	20,231 (43.0%)	16,201 (44.1%)	14,218 (51.2%)	98,295 (56.2%)	181,259 (49.4%)	140,638 (53.4%)			-0.01		
Race without zero category													
...White; n (%)	N/A	N/A	N/A	N/A	259,440 (93.6%)	162,140 (92.7%)	259,440 (93.6%)	162,140 (92.7%)			#REF!		
...Black; n (%)	N/A	N/A	N/A	N/A	8,892 (3.2%)	5,772 (3.3%)	8,892 (3.2%)	5,772 (3.3%)			0.00		
...Asian; n (%)	N/A	N/A	N/A	N/A	2,208 (0.8%)	1,884 (1.1%)	2,208 (0.8%)	1,884 (1.1%)			0.00		
...Hispanic; n (%)	N/A	N/A	N/A	N/A	2,251 (0.8%)	1,567 (0.9%)	2,251 (0.8%)	1,567 (0.9%)			0.00		
...North American Native; n (%)	N/A	N/A	N/A	N/A	773 (0.3%)	394 (0.2%)	773 (0.3%)	394 (0.2%)			0.00		
...Other/Unknown; n (%)	N/A	N/A	N/A	N/A	3,684 (1.3%)	3,141 (1.8%)	3,684 (1.3%)	3,141 (1.8%)			0.00		
Region without zero category- United v3 (Jumping missing/other category with West)													
...Northeast; n (%)	6,849 (14.7%)	6,040 (11.7%)	11,511 (24.4%)	7,944 (21.6%)	62,468 (22.5%)	32,667 (18.7%)	80,828 (21.8%)	46,651 (17.7%)			0.01		
...South; n (%)	15,118 (32.5%)	23,275 (45.0%)	15,235 (32.3%)	9,410 (25.6%)	95,216 (34.3%)	77,615 (44.4%)	125,569 (33.9%)	110,300 (41.9%)			-0.01		
...Midwest; n (%)	10,705 (23.0%)	10,011 (19.4%)	12,823 (27.2%)	14,967 (40.8%)	73,735 (26.6%)	36,209 (20.7%)	97,263 (26.2%)	61,187 (23.2%)			0.01		
...West; n (%)	13,846 (29.8%)	12,358 (23.9%)	7,324 (15.6%)	4,225 (11.5%)	45,829 (16.5%)	28,407 (16.2%)	66,999 (18.1%)	44,990 (17.1%)			0.00		
...Unknown/missing; n (%)	N/A	203 (0.4%)	168 (0.5%)	N/A	N/A	203 (0.4%)	N/A	168 (0.5%)			0.00		
Calendar Time by day (March 29, 2013 to CED)													
...mean (sd)	1,024,531 (739.16)	1,652,151 (790.60)	535,68 (509.15)	1,132,76 (552.83)	3,905 (1.4%)	2,792 (1.6%)	3,115.82 (318.51)	2336.89 (329.48)			2.40		
...median (IQR)	943,000 (551.00)	1,757,00 (1,289.00)	2,132,00 (389.00)	121,000,838.00	148,00 (58,00, 1,587.00)	8,444 (3.0%)	4,048 (2.3%)						
CV Covariates													
Ischemic heart disease; n (%)	15,366 (33.0%)	18,835 (36.4%)	15,378 (32.7%)	12,189 (33.2%)	85,977 (31.0%)	61,345 (35.1%)	116,721 (31.5%)	92,369 (35.1%)			-0.01		
Acute MI; n (%)	1,062 (2.3%)	1,788 (3.5%)	1,106 (2.3%)	1,178 (3.2%)	5,202 (1.9%)	4,915 (2.8%)	7,370 (2.0%)	7,882 (3.0%)			-0.01		
ACS/unstable angina; n (%)	996 (2.1%)	1,822 (3.5%)	1,029 (2.2%)	1,272 (3.5%)	5,178 (1.9%)	5,389 (3.1%)	7,203 (1.9%)	8,487 (3.2%)			-0.01		
Old MI; n (%)	2,154 (4.6%)	3,103 (6.0%)	1,390 (3.0%)	1,228 (3.3%)	12,481 (4.5%)	9,804 (5.6%)	16,025 (4.3%)	14,135 (5.4%)			0.00		
Stroke; n (%)	1,906 (4.1%)	3,373 (6.5%)	1,430 (3.0%)	1,709 (4.7%)	7,700 (2.8%)	7,682 (4.5%)	11,036 (3.0%)	12,944 (4.9%)			-0.01		
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	14,190 (30.5%)	16,844 (32.6%)	14,344 (30.5%)	10,912 (29.7%)	80,277 (29.0%)	55,930 (32.0%)	108,811 (29.3%)	83,686 (31.8%)			0.00		
Other atherosclerosis with CD10 v2 Copy; n (%)	640 (1.4%)	482 (0.9%)	767 (1.6%)	353 (1.0%)	80,277 (29.0%)	55,930 (32.0%)	108,811 (29.3%)	83,686 (31.8%)			2,672 (1.0%)	0.00	
Previous cardiac procedure (CABG or PTCA or Stent)													
v4; n (%)	466 (1.0%)	590 (1.1%)	582 (1.2%)	378 (1.0%)	2,737 (1.0%)	1,850 (1.1%)	3,785 (1.0%)	2,818 (1.1%)			0.00		
History of CABG or PTCA; n (%)	3,408 (7.3%)	5,202 (10.1%)	1,986 (4.2%)	1,679 (4.6%)	21,847 (7.9%)	17,991 (10.3%)	27,241 (7.3%)	24,872 (9.4%)			-0.01		
Any stent; n (%)	3,889 (8.4%)	5,294 (10.2%)	4,154 (8.8%)	3,107 (8.5%)	22,265 (8.0%)	17,801 (9.6%)	30,308 (8.2%)	25,202 (9.6%)			0.00		
Ischemic stroke w/ or w/o mention of cerebral infarction; n (%)	3,868 (8.3%)	5,274 (10.2%)	4,139 (8.8%)	3,089 (8.4%)	22,171 (8.0%)	15,733 (9.6%)	30,178 (8.1%)	25,090 (9.5%)			0.00		
Hemorrhagic stroke; n (%)	39 (0.1%)	43 (0.1%)	33 (0.1%)	29 (0.1%)	140 (0.1%)	110 (0.1%)	212 (0.1%)	182 (0.1%)			0.00		
TIA; n (%)	1,324 (2.8%)	2,160 (4.2%)	1,325 (2.8%)	1,405 (3.8%)	6,957 (2.5%)	6,574 (3.8%)	9,606 (2.6%)	10,339 (3.9%)			-0.01		
Other cerebrovascular disease; n (%)	1,133 (2.4%)	1,895 (3.7%)	1,082 (2.3%)	1,018 (2.8%)	6,167 (2.2%)	5,465 (3.1%)	8,382 (2.3%)	8,378 (3.2%)			-0.01		
Left effects of cerebrovascular disease; n (%)	1,203 (2.6%)	1,446 (2.8%)	1,059 (2.2%)	660 (1.6%)	6,565 (2.4%)	4,464 (2.6%)	8,827 (2.4%)	6,570 (2.5%)			0.00		
Cerebrovascular procedure; n (%)	36 (0.1%)	74 (0.1%)	40 (0.1%)	37 (0.1%)	272 (0.1%)	239 (0.1%)	348 (0.1%)	350 (0.1%)			0.00		
Hippocampal infarct (HIF); n (%)	11,451 (24.6%)	13,056 (25.3%)	10,527 (22.4%)	7,845 (21.4%)	20,750 (20.8%)	17,398 (21.7%)	79,728 (21.5%)	58,899 (22.4%)			0.00		
Hippocampal Vascular Disease (PVD) or PVD Surgery v2; n (%)											2,053 (0.8%)	0.00	
Diabetic retinopathy; n (%)	4,031 (8.7%)	4,250 (8.3%)	3,753 (8.0%)	2,213 (6.0%)	22,154 (8.0%)	11,347 (6.0%)	29,938 (8.1%)	19,850 (7.5%)			0.00		
Atrial fibrillation; n (%)	44,976 (96.7%)	50,504 (97.7%)	36,062 (98.1%)	258,810 (93.3%)	162,538 (92.9%)	438,806 (94.1%)	249,068 (94.6%)				0.00		
Other cardiac dysrhythmia; n (%)	28,564 (61.4%)	46,297 (89.6%)	18,736 (39.8%)	27,343 (74.5%)	128,350 (46.3%)	124,814 (71.4%)	175,650 (47.4%)	198,454 (75.4%)			-0.04		
Cardiac conduction disorders; n (%)	3,879 (8.3%)	6,455 (12.5%)	3,318 (7.0%)	3,652 (9.5%)	18,316 (6.6%)	16,705 (6.6%)	25,513 (6.6%)	26,812 (10.2%)			-0.01		
Other CVD; n (%)	15,662 (33.7%)	21,521 (41.6%)	15,575 (31.1%)	14,236 (38.8%)	74,638 (26.9%)	58,184 (33.3%)	105,875 (28.5%)	93,941 (35.7%)			-0.01		
Diabetes-related complications													
Diabetic retinopathy; n (%)	618 (1.3%)	532 (1.0%)	530 (1.1%)	251 (0.7%)	2,648 (1.0%)	1,270 (0.7%)	3,796 (1.0%)	2,053 (0.8%)			0.00		
Diabetes with other ophthalmic manifestations; n (%)											0.00		
Retinal detachment, vitreous hemorrhage; n (%)	70 (0.2%)	105 (0.2%)	394 (0.8%)	152 (0.4%)	1,768 (0.6%)	753 (0.4%)	2,232 (0.6%)	1,010 (0.4%)			0.00		
Retinal detachment, vitreous hemorrhage, retinectomy; n (%)	46 (0.1%)	38 (0.1%)	54 (0.1%)	32 (0.1%)	278 (0.1%)	132 (0.1%)	378 (0.1%)	202 (0.1%)			0.00		
Retinal laser coagulation therapy; n (%)	36 (0.1%)	42 (0.1%)	55 (0.1%)	21 (0.1%)	331 (0.1%)	169 (0.1%)	416 (0.1%)	416 (0.1%)			#VALUE!		
Occurrence of Diabetic Neuropathy v2 Copy; n (%)	2,516 (5.4%)	2,284 (4.4%)	2,055 (4.4%)	1,237 (3.4%)	10,444 (3.8%)	5,519 (2.9%)	15,015 (4.0%)	9,040 (3.4%)			0.00		
Diabetic neuropathy; n (%)											#VALUE!		
Diabetic neuropathy v2; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			0.00		
Diabetic neuropathy v2; n (%)	262 (0.8%)	145 (0.3%)	522 (1.1%)	168 (0.5%)	2,539 (1.2%)	1,249 (1.3%)	4,424 (1.7%)	2,662 (0.9%)			0.00		
Hyperglycemia; n (%)	2,214 (4.8%)	3,478 (6.7%)	1,225 (2.6%)	1,520 (4.1%)	14,278 (5.1%)	12,139 (6.9%)	17,715 (4.8%)	17,137 (6.5%)			-0.01		
Disorders of fluid electrolyte and acid-base balance; n (%)													
Diabetic ketoacidosis; n (%)	3,947 (8.5%)	6,950 (13.4%)	3,246 (6.9%)	3,753 (10.2%)	20,433 (7.4%)	9,603 (9.3%)	27,626 (7.4%)	20,306 (7.7%)			0.00		
Hyperosmolar hyperglycemic nonketotic syndrome (HHS); n (%)	38 (0.1%)	27 (0.1%)	48 (0.1%)	28 (0.1%)	26,016 (0.1%)	14,020 (0.1%)	352 (0.1%)	197 (0.1%)			0.00		
Diabetes mellitus without mention of complications; n (%)											0.00		
Hypertension: 1 inpatient or 2 outpatient claims within 365 days; n (%)	12,418 (26.7%)	11,942 (23.1%)	12,169 (25.8%)	8,307 (22.6%)	72,769 (26.2%)	39,895 (22.8%)	97,356 (26.3%)	60,144 (22.8%)			0.01		
Hypertension v2; n (%)	38,202 (82.1%)	31,513 (61.0%)	22,282 (47.3%)	30,224 (82.3%)	240,781 (86.8%)	156,352 (89.4%)	31,340 (84.7%)	231,515 (87.9%)			0.00		
Hypertension v2; n (%)	26,248 (56.4%)	5,000 (1.0%)	4,232 (0.8%)	3,423 (0.8%)	22,434 (0.8%)	15,113 (0.8%)	31,340 (0.8%)	24,776 (0.8%)			0.00		
Renal dysfunction (non-diabetic); n (%)	33 (0.1%)	33 (0.1%)	36 (0.1%)	16 (0.0%)	140 (0.1%)	91 (0.1%)	146 (0.1%)	140 (0.1%)			#VALUE!		
Occurrence of acute renal disease v2; n (%)	27 (0.1%)	23 (0.1%)	31 (0.1%)	13 (0.0%)	102 (0.0%)	74 (0.0%)	**	**			#VALUE!		
Occurrence of chronic renal insufficiency; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			#VALUE!		
Chronic kidney disease v2; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			#VALUE!		
CKD Stage 3-4; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			#VALUE!		
Occurrence of hypertensive nephropathy; n (%)	0												

Table 1: Unmatched

Linagliptin; n (%)	76 (0.2%)	128 (0.2%)	125 (0.3%)	106 (0.3%)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	#VALUE!	#VALUE!	#VALUE!
Saxagliptin; n (%)	130 (0.3%)	115 (0.2%)	164 (0.3%)	76 (0.2%)	0	0	#VALUE!	#VALUE!	#VALUE!
Sitagliptin; n (%)	519 (1.1%)	513 (1.0%)	1,048 (2.2%)	603 (1.6%)	0.08 (0.40)	0.10 (0.44)	1,567 (0.4%)	1116 (0.4%)	0.00
Concomitant initiation or current use of 2nd Generation AGIs; n (%)	2,811 (6.0%)	2,013 (3.9%)	2,878 (6.1%)	1,524 (4.2%)	222 (0.1%)	87 (0.0%)	5,911 (1.6%)	3,624 (1.4%)	0.00
Concomitant initiation or current use of AGIs; n (%)	22 (0.0%)	20 (0.0%)	20 (0.0%)	20 (0.1%)	85 (0.0%)	59 (0.0%)	127 (0.0%)	99 (0.0%)	#DIV/0!
Concomitant initiation or current use of Glitazones; n (%)	296 (0.6%)	383 (0.7%)	394 (0.8%)	295 (0.8%)	10,008 (3.6%)	4,508 (2.6%)	10,698 (2.9%)	5,186 (2.0%)	0.01
Concomitant initiation or current use of Insulin; n (%)	175 (0.4%)	313 (0.6%)	295 (0.6%)	325 (0.9%)	75 (0.0%)	24 (0.0%)	#VALUE!	#VALUE!	#VALUE!
Concomitant initiation or current use of Meglitinides; n (%)	1,335 (2.9%)	1,061 (2.1%)	1,855 (3.9%)	943 (2.6%)	5,097 (1.8%)	1,483 (0.8%)	8,287 (2.2%)	3,487 (1.3%)	0.01
Concomitant initiation or current use of Metformin; n (%)	41 (0.1%)	46 (0.1%)	147 (0.3%)	61 (0.2%)	0	0	#VALUE!	#VALUE!	#VALUE!
Use of 2nd Generation Sulfonylureas; n (%)	5,447 (11.7%)	5,502 (10.6%)	5,060 (10.7%)	3,953 (10.8%)	0.09 (0.06)	0.08 (0.06)	10,507 (2.8%)	9,455 (3.6%)	0.00
Pat use of 2nd Generation Sulfonylureas; n (%)	536 (1.2%)	437 (0.8%)	638 (1.4%)	322 (0.9%)	**	**	#VALUE!	#VALUE!	#VALUE!
Pat use of AGIs Copy; n (%)	**	**	17 (0.0%)	**	**	**	#VALUE!	#VALUE!	#VALUE!
Pat use of Glitazones Copy; n (%)	90 (0.2%)	80 (0.2%)	100 (0.2%)	78 (0.2%)	40 (0.0%)	19 (0.0%)	#VALUE!	#VALUE!	#VALUE!
Pat use of GLP-1 Receptor Agonists; n (%)	96 (0.2%)	119 (0.2%)	113 (0.3%)	122 (0.3%)	**	**	#VALUE!	#VALUE!	#VALUE!
Pat use of Insulin Copy; n (%)	593 (1.3%)	410 (0.8%)	630 (1.3%)	324 (0.9%)	42 (0.0%)	21 (0.0%)	1,246 (3.0%)	755 (0.3%)	0.00
Pat use of Meglitinides Copy; n (%)	26 (0.1%)	12 (0.0%)	40 (0.1%)	23 (0.1%)	0	0	#VALUE!	#VALUE!	#VALUE!
Pat use of Metformin (Final) Copy; n (%)	1,078 (2.3%)	1,158 (2.2%)	1,073 (2.3%)	959 (2.6%)	365.00 (0.00)	365.00 (0.00)	2,516 (0.7%)	2,482 (0.9%)	0.00
Other Medications									
Use of ACE Inhibitors; n (%)	16,031 (34.5%)	16,348 (31.6%)	15,709 (33.4%)	11,934 (32.5%)	94,664 (34.1%)	55,262 (31.6%)	126,404 (34.1%)	83,544 (31.7%)	0.00
Use of ARBs; n (%)	9,327 (20.1%)	12,884 (24.9%)	9,485 (25.8%)	10,532 (22.4%)	48,704 (21.2%)	44,745 (25.6%)	75,563 (21.2%)	67,114 (25.5%)	0.01
Use of Beta-blockers; United; n (%)	13,550 (29.1%)	12,517 (24.2%)	14,343 (30.6%)	8,029 (21.9%)	88,519 (30.1%)	46,121 (26.4%)	116,773 (30.1%)	66,680 (25.3%)	0.01
Use of Fibrates; United; n (%)	2,891 (6.3%)	2,865 (5.7%)	3,117 (7.1%)	2,950 (7.5%)	35,939 (8.6%)	9,440 (5.7%)	25,457 (8.6%)	14,300 (5.5%)	0.01
Use of Inotropes; United; n (%)	3,113 (6.7%)	3,399 (6.6%)	3,604 (7.7%)	2,376 (6.5%)	23,060 (8.3%)	18,512 (6.3%)	29,777 (8.0%)	20,300 (7.7%)	0.00
Use of Hyper tension drugs; n (%)	3,138 (6.7%)	3,262 (6.3%)	3,277 (7.0%)	2,136 (5.8%)	19,290 (7.0%)	11,843 (6.8%)	25,705 (6.5%)	17,241 (6.5%)	0.00
Use of digoxin; United; n (%)	7,261 (15.6%)	3,915 (7.6%)	8,724 (18.5%)	3,451 (9.4%)	48,844 (17.6%)	17,770 (10.2%)	64,829 (17.5%)	25,337 (9.5%)	0.02
Use of Anti-arrhythmics; n (%)	7,019 (15.1%)	11,603 (22.4%)	8,401 (17.8%)	9,912 (27.0%)	43,026 (15.5%)	41,098 (23.5%)	58,446 (15.8%)	62,633 (23.8%)	0.02
Use of COPD/asthma meds; United; n (%)	7,511 (16.1%)	10,113 (19.6%)	8,597 (18.3%)	7,219 (19.7%)	50,139 (18.1%)	36,786 (21.0%)	66,247 (17.9%)	54,118 (20.6%)	0.01
Use of statins; n (%)	25,912 (55.7%)	28,245 (54.6%)	26,335 (55.9%)	19,285 (52.5%)	156,203 (56.3%)	97,740 (55.9%)	208,450 (56.2%)	145,270 (55.2%)	0.00
Use of other; n (%)	2,792 (0.6%)	2,670 (0.5%)	4,079 (8.7%)	2,525 (6.9%)	19,312 (7.0%)	11,016 (1.3%)	26,183 (7.1%)	16,206 (6.2%)	0.00
Use of nonsteroidal agents; n (%)	3,472 (7.5%)	5,766 (11.2%)	4,580 (9.7%)	4,623 (12.6%)	23,628 (8.5%)	22,256 (12.7%)	31,680 (8.5%)	32,645 (12.4%)	0.01
Use of oral anticoagulants; Dabigatran, Rivaroxaban, Apixaban, Warfarin; n (%)	46,518 (100.0%)	51,684 (100.0%)	47,096 (100.0%)	36,714 (100.0%)	277,248 (100.0%)	174,898 (100.0%)	370,862 (100.0%)	263,296 (100.0%)	0.00
Use of heparin and other low-molecular weight heparins; n (%)	1,826 (3.9%)	262 (0.5%)	17 (0.0%)	9 (0.0%)	11,736 (4.2%)	1,025 (0.6%)	13,579 (3.7%)	1,296 (0.5%)	0.02
Use of NSAIDs; n (%)	3,545 (7.6%)	6,273 (12.1%)	3,897 (8.3%)	4,968 (13.5%)	23,704 (8.0%)	22,086 (12.6%)	31,146 (8.4%)	33,327 (12.7%)	0.01
Use of oral corticosteroids; n (%)	8,810 (18.1%)	11,399 (22.1%)	8,644 (18.4%)	7,663 (20.9%)	55,726 (20.1%)	40,611 (23.2%)	72,780 (19.6%)	59,673 (22.7%)	0.01
Use of bisphosphonates; United; n (%)	1,626 (3.5%)	1,754 (4.4%)	1,385 (2.9%)	849 (2.3%)	9,601 (3.5%)	5,599 (4.9%)	12,612 (3.4%)	8,502 (3.2%)	0.00
Use of statins; United; n (%)	11,255 (24.6%)	12,555 (27.4%)	12,511 (24.6%)	8,800 (24.5%)	44,255 (24.6%)	35,839 (24.5%)	46,900 (24.5%)	46,899 (24.5%)	0.00
Use of anti-depressants; n (%)	9,146 (19.7%)	11,418 (22.1%)	8,850 (18.8%)	8,738 (20.1%)	40,236 (21.7%)	40,727 (23.3%)	78,021 (21.0%)	59,533 (22.5%)	0.00
Use of anti-psychotics; n (%)	720 (1.5%)	918 (1.8%)	680 (1.4%)	531 (1.4%)	5,996 (2.2%)	4,070 (3.7%)	7,396 (2.0%)	5,519 (2.3%)	0.00
Use of anti-coagulants; n (%)	5,473 (11.8%)	6,369 (12.3%)	4,883 (10.4%)	3,637 (9.9%)	34,654 (12.5%)	22,276 (12.7%)	45,010 (12.5%)	32,282 (12.3%)	0.00
Use of lithium; United; n (%)	38 (0.1%)	39 (0.1%)	29 (0.1%)	29 (0.1%)	200 (0.1%)	173 (0.1%)	267 (0.1%)	240 (0.1%)	0.00
Use of Benzo; United; n (%)	5,108 (11.0%)	6,832 (13.2%)	5,792 (12.3%)	4,959 (13.5%)	36,471 (13.2%)	27,284 (15.6%)	47,377 (12.8%)	39,075 (14.8%)	-0.01
Use of anxiolytic/sedatives; United; n (%)	2,139 (4.6%)	2,540 (6.4%)	2,857 (6.1%)	2,470 (6.7%)	16,581 (6.0%)	11,562 (6.6%)	21,577 (5.8%)	16,572 (6.3%)	0.00
Use of dementia meds; United; n (%)	1,633 (3.5%)	1,682 (3.9%)	1,713 (3.6%)	1,885 (2.4%)	12,226 (4.4%)	7,476 (4.3%)	15,572 (4.2%)	10,043 (3.8%)	0.00
Use of anti-parkinsonian; United; n (%)	1,231 (2.6%)	1,449 (2.8%)	1,232 (2.6%)	836 (2.3%)	8,890 (3.2%)	5,5878 (4.9%)	11,153 (3.1%)	8,163 (3.1%)	0.00
Use of anti-psychotics; n (%)	**	**	**	**	**	**	**	**	#VALUE!
Any use of 1st generation sulfonylureas; n (%)	0 (0.0%)	0 (0.0%)	**	**	18 (0.0%)	12 (0.0%)	#VALUE!	#VALUE!	0.00
Entresto (sacubitril/valsartan); n (%)	142 (0.3%)	387 (0.7%)	51 (0.1%)	139 (0.4%)	9,353 (3.4%)	6,025 (0.4%)	9,546 (2.6%)	6,551 (2.5%)	0.00
Initiation as monotherapy; n (%)	**	**	**	**	585 (0.2%)	519 (0.3%)	#VALUE!	#VALUE!	#VALUE!
Dual therapy with metformin v4 (latest based on Action's suggestion)- not adding to P5; n (%)	22 (0.0%)	69 (0.1%)	29 (0.1%)	67 (0.2%)	#REF!	#REF!	#REF!	#REF!	#REF!
Lab values									
Lab values-HbA1c (HbA1c); n (%)	5,987 (12.9%)	8,246 (16.0%)	614 (1.3%)	450 (1.2%)	N/A	N/A	6,601 (7.4%)	8,699 (12.9%)	-0.01
Lab values-HbA1c (HbA1c) (within 3 months); n (%)	3,745 (8.1%)	5,104 (9.9%)	409 (0.9%)	311 (0.8%)	N/A	N/A	4,154 (4.4%)	5,415 (6.1%)	0.01
Lab values-HbA1c (HbA1c) (within 6 months); n (%)	5,987 (12.9%)	8,246 (16.0%)	614 (1.3%)	450 (1.2%)	N/A	N/A	6,601 (7.1%)	8,696 (9.8%)	0.01
Lab values-BNP; n (%)	745 (1.6%)	999 (1.9%)	670 (1.4%)	670 (1.4%)	N/A	N/A	812 (0.9%)	1,051 (1.2%)	0.00
Lab values-BNP (within 3 months); n (%)	450 (1.0%)	709 (1.4%)	47 (0.1%)	40 (0.1%)	N/A	N/A	497 (0.5%)	749 (0.8%)	0.00
Lab values-BNP (within 6 months); n (%)	745 (1.6%)	999 (1.9%)	670 (1.4%)	670 (1.4%)	N/A	N/A	812 (0.9%)	1,051 (1.2%)	0.00
Lab values-BUN (mg/dl); n (%)	12,115 (26.0%)	16,732 (32.4%)	734 (1.6%)	690 (1.9%)	N/A	N/A	12,849 (3.7%)	17,422 (19.7%)	-0.01
Lab values-BUN (mg/dl) (within 3 months); n (%)	7,935 (17.1%)	11,391 (22.0%)	495 (1.1%)	494 (1.3%)	N/A	N/A	8,430 (9.0%)	11,885 (13.4%)	-0.01
Lab values-BUN (mg/dl) (within 6 months); n (%)	12,115 (26.0%)	16,732 (32.4%)	734 (1.6%)	690 (1.9%)	N/A	N/A	12,849 (3.7%)	17,422 (19.7%)	-0.01
Lab values-Creatinine (mg/dl); n (%)	12,356 (26.6%)	17,327 (33.5%)	755 (1.6%)	724 (2.0%)	N/A	N/A	13,111 (4.0%)	18,051 (20.4%)	-0.02
Lab values-HDL level (mg/dl) (within 3 months); n (%)	8,846 (17.4%)	12,327 (22.2%)	545 (1.2%)	454 (1.2%)	N/A	N/A	8,826 (9.5%)	11,967 (13.5%)	-0.01
Lab values-LDL level (mg/dl); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	5,310 (5.7%)	7,138 (8.1%)	-0.01
Lab values-HDL level (mg/dl) (within 6 months); n (%)	8,841 (18.0%)	11,485 (22.2%)	545 (1.2%)	482 (1.3%)	N/A	N/A	8,826 (9.5%)	11,967 (13.5%)	-0.01
Lab values-LDL level (mg/dl); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	9,482 (10.1%)	12,559 (14.2%)	-0.01
Lab values-LDL level (mg/dl) (within 3 months); n (%)	5,236 (11.3%)	7,197 (13.9%)	412 (0.9%)	312 (0.8%)	N/A	N/A	5,648 (6.0%)	7,505 (8.5%)	-0.01
Lab values-Creatinine (mg/dl) (within 6 months); n (%)	8,846 (23.0%)	11,865 (23.0%)	510 (1.1%)	511 (1.4%)	N/A	N/A	8,600 (9.2%)	12,376 (14.0%)	-0.01
Lab values-Creatinine (mg/dl) (within 3 months); n (%)	12,356 (26.6%)	17,327 (33.5%)	755 (1.6%)	724 (2.0%)	N/A	N/A	13,111 (4.0%)	18,051 (20.4%)	-0.02
Lab values-HDL level (mg/dl); n (%)	8,841 (18.0%)	11,485 (22.2%)	545 (1.2%)	482 (1.3%)	N/A	N/A	8,826 (9.5%)	11,967 (13.5%)	-0.01
Lab values-LDL level (mg/dl); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	9,482 (10.1%)	12,559 (14.2%)	-0.01
Lab values-LDL level (mg/dl) (within 3 months); n (%)	5,236 (11.3%)	7,197 (13.9%)	412 (0.9%)	312 (0.8%)	N/A	N/A	5,648 (6.0%)	7,505 (8.5%)	-0.01
Lab values-Total cholesterol (mg/dl); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	9,064 (9.7%)	12,205 (13.8%)	-0.01
Lab values-Total cholesterol (mg/dl) (within 3 months); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	9,064 (9.7%)	12,205 (13.8%)	-0.01
Lab values-Triglyceride level (mg/dl); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	9,064 (9.7%)	12,205 (13.8%)	-0.01
Lab values-Triglyceride level (mg/dl) (within 3 months); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	9,064 (9.7%)	12,205 (13.8%)	-0.01
Lab values-Triglyceride level (mg/dl) (within 6 months); n (%)	8,846 (19.0%)	12,078 (23.4%)	636 (1.4%)	481 (1.3%)	N/A	N/A	9,064 (9.7%)	12,205 (13.8%)	-0.01
Lab result number-Creatinine (mg/dl) mean (only to 15 included); v3	0.09 (0.20)	0.95 (0.23)	1.01 (0.28)	0.97 (0.23)	N/A	N/A	1.00 (0.27)	0.96 (0.23)	0.16
...mean (d)	6.50 (1.17)	6.23 (1.06)	7.03 (1.38)	6.79 (1.44)	N/A	N/A	6.77 (1.28)	6.48 (1.23)	0.25
...median (IQR)	6.20 (5.80, 6.90)	6.00 (5.60, 6.60)	6.68 (6.10, 7.60)	6.40 (5.90, 7.20)	N/A	N/A	6.45 (6.00, 7.00)	6.20 (5.80, 6.60)	0.25
...Missing; n (%)	40,583 (87.2%)	43,466 (84.1%)	46,544 (98.8%)	36,271 (98.8%)	N/A	N/A	87,127 (93.1%)	79,737 (90.2%)	0.00
Lab result number-BNP mean v2	302.74 (0.43-46)	318.02 (487.53)	425.66 (678.07)	473.61 (790.82)	N/A	N/A	364.58 (455.54)	382.64 (631.44)	-0.03
...mean (d)	195.00 (103.00, 347.00)	193.80 (98.90, 363.00)	207.00 (80.00, 445.00)	180.50 (110.50, 418.00)	N/A	N/A	258.43 (668.44)	354.70 (799.28)	-0.01
...median (

Table 1: Unmatched

...Missing: n (%)	36,095 (77.6%)	37,242 (72.1%)	46,570 (98.9%)	36,184 (98.6%)	N/A	N/A			
Lab result number-Glucose(fasting or random) mean (only 10-1000 included)									
...mean	110.98 (35.59)	108.13 (31.46)	129.63 (47.03)	126.66 (44.91)	N/A	N/A	120.36 (41.74)	115.83 (37.63)	0.11
...median [IQR]	101.00 (92.00, 118.00)	100.00 ([91.67, 114.00])	116.50 ([97.50, 148.00])	113.00 (98.00, 140.00)	N/A	N/A			
...Missing: n (%)	34,922 (75.1%)	35,423 (68.5%)	46,441 (98.6%)	36,039 (98.2%)	N/A	N/A			
Lab result number-Potassium mean (only 1-7 included)									
...mean [sd]	4.35 (0.43)	4.39 (0.42)	4.34 (0.42)	4.37 (0.42)	N/A	N/A	4.34 (0.43)	4.38 (0.42)	-0.09
...median [IQR]	4.32 (4.10, 4.60)	4.40 ([4.10, 4.65])	4.30 ([4.10, 4.60])	4.35 ([4.10, 4.60])	N/A	N/A			
...Missing: n (%)	34,273 (73.7%)	34,566 (66.9%)	46,398 (98.5%)	36,047 (98.2%)	N/A	N/A			
Comorbidity Scores									
Comorbidity-C90 and CD10 v2									
...mean	3.31 (1.80)	3.52 (1.80)	3.03 (1.71)	3.16 (1.63)	2.07 (1.92)	2.18 (2.00)	3.17 (1.76)	3.37 (1.73)	-0.11
...median [IQR]	3.00 (2.00, 4.00)	3.00 ([2.00, 5.00])	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	2.00 (0.00, 3.00)	2.00 (1.00, 3.00)			
Frality Score: Qualitative Version 365 days as Categories, v1									
...0; n (%)	14,245 (30.6%)	28,483 (55.1%)	4,407 (9.4%)	13,475 (36.7%)	277,248 (100.0%)	174,898 (100.0%)	295,900 (79.8%)	216,856 (82.4%)	0.00
...1 to 2; n (%)	16,218 (34.9%)	16,697 (32.3%)	19,912 (42.3%)	13,626 (37.1%)	0 (0.0%)	0 (0.0%)	36,139 (9.7%)	30,323 (11.5%)	-0.01
...3 or more; n (%)	16,055 (34.5%)	6,504 (12.6%)	22,768 (48.3%)	9,613 (26.2%)	0 (0.0%)	0 (0.0%)	38,823 (10.5%)	16,117 (6.1%)	0.02
Frality Score: Empirical Version 365 days as Categories, v3									
...<0.1298; n (%)	4,465 (9.6%)	5,291 (10.2%)	4,016 (8.5%)	3,794 (10.3%)	221,855 (80.0%)	143,801 (82.2%)	230,336 (62.1%)	152,886 (58.1%)	0.01
...0.1298 - 0.1631167; n (%)	13,374 (28.8%)	14,905 (28.8%)	12,572 (26.7%)	10,993 (29.9%)	23,931 (8.6%)	14,240 (8.1%)	49,881 (13.5%)	40,138 (15.2%)	0.00
...>0.1631167; n (%)	28,679 (61.7%)	31,488 (60.9%)	30,504 (64.8%)	21,927 (59.7%)	31,462 (11.3%)	16,857 (9.6%)	90,645 (24.4%)	70,722 (26.7%)	0.00
Non-Frality; n (%)	25,223 (54.2%)	29,309 (56.7%)	23,478 (49.9%)	18,490 (50.4%)	5,444 (2.0%)	3,205 (1.8%)	54,145 (14.6%)	51,004 (19.4%)	-0.01
Frality Score (mean): Qualitative Version 365 days, v1									
...mean [sd]	2.1 (2.29)	0.97 (1.59)	2.84 (2.14)	1.65 (1.91)	51 (0.0%)	23 (0.0%)	2.48 (2.22)	1.25 (1.73)	0.62
...median [IQR]	2.00 (0.00, 3.00)	0.00 ([0.00, 1.00])	2.00 (1.00, 4.00)	1.00 (0.00, 3.00)	**	0 (0.0%)			
Frality Score (mean): Empirical Version 365 days, v2									
...mean [sd]	0.19 (0.06)	0.19 (0.06)	0.18 (0.06)	0.18 (0.05)	12.09 ([7.08, 19.38])	10.59 ([5.75, 17.41])	0.18 (0.06)	0.19 (0.06)	-0.17
...median [IQR]	0.18 ([0.15, 0.21])	0.17 ([0.15, 0.21])	0.17 ([0.14, 0.20])	0.17 ([0.14, 0.20])	#REF!	#REF!			
Healthcare Utilization									
Any hospitalization (n)	8,809 (18.9%)	15,564 (30.1%)	11,202 (23.8%)	12,977 (35.3%)	63,143 (22.8%)	60,091 (34.4%)	83,154 (22.4%)	88,632 (33.7%)	-0.02
Any hospitalization during prior 30 days; n (%)	5,453 (12.7%)	9,233 (18.1%)	6,631 (14.4%)	8,475 (23.1%)	36,365 (24.5%)	35,076 (25.5%)	49,414 (21.7%)	53,570 (23.3%)	-0.02
Any hospitalization during prior 31-180 days; n (%)	3,999 (8.8%)	7,277 (14.1%)	5,230 (11.1%)	5,128 (14.0%)	29,055 (14.0%)	29,055 (14.0%)	48,663 (13.8%)	45,477 (15.3%)	-0.01
Endocrinologist Visit; n (%)	1,287 (2.8%)	1,520 (3.0%)	1,484 (3.2%)	1,290 (3.5%)	10,807 (0.9%)	7,100 (0.1%)	13,578 (3.7%)	9,919 (3.8%)	0.00
Endocrinologist Visit (30 days prior); n (%)	378 (0.8%)	470 (1.0%)	414 (1.1%)	116,999 (42.2%)	106,590 (61.2%)	117,847 (61.8%)	107,891 (41.0%)	102,100 (41.6%)	-0.02
Endocrinologist Visit (31 to 180 days prior); n (%)	1,086 (2.3%)	1,231 (2.4%)	1,269 (2.7%)	1,066 (2.9%)	163,170 (58.9%)	107,358 (61.4%)	165,525 (44.6%)	109,655 (41.6%)	0.00
Internal medicine/family medicine visits (30 days prior); n (%)	40,302 (86.6%)	45,027 (87.1%)	37,672 (80.0%)	30,010 (81.8%)	28,150 (82.3%)	148,191 (84.7%)	306,125 (82.5%)	223,228 (84.8%)	0.00
Internal medicine/family medicine visits (30 days prior); v2; n (%)	25,580 (55.8%)	27,969 (54.1%)	22,966 (48.8%)	18,628 (50.7%)	**	**	#VALUE!	#VALUE!	#VALUE!
Internal medicine/family medicine visits (31 to 180 days prior); v2; n (%)	37,369 (80.3%)	40,783 (78.9%)	34,952 (74.2%)	26,875 (73.2%)	0	0	#VALUE!	#VALUE!	#VALUE!
Cardiologist visit; n (%)	31,404 (67.5%)	43,792 (84.7%)	25,898 (55.0%)	25,364 (61.5%)	199,955 (72.1%)	148,611 (65.0%)	257,257 (69.4%)	217,767 (82.7%)	0.02
Number of Cardiologist visits (30 days prior); n (%)	18,721 (40.2%)	32,136 (62.2%)	14,126 (30.0%)	19,025 (51.8%)	138,538 (50.0%)	89,178 (51.0%)	171,385 (46.2%)	140,339 (53.3%)	-0.01
Number of Cardiologist visits (31 to 180 days prior); n (%)	25,239 (54.3%)	31,683 (61.3%)	21,920 (46.5%)	18,451 (50.3%)	208,192 (75.5%)	132,225 (75.6%)	255,351 (68.8%)	182,359 (69.3%)	0.00
Electrocardiogram (21); n (%)	25,997 (55.9%)	41,720 (80.7%)	26,827 (57.0%)	23,295 (73.6%)	168,037 (60.6%)	145,748 (83.3%)	220,861 (59.6%)	216,703 (82.3%)	-0.03
Diagnosis; n (%)	**	**	0 (0.0%)	0 (0.0%)	**	**	#VALUE!	#VALUE!	#VALUE!
Number of CT Copy; n (%)	37,301 (80.2%)	43,095 (83.4%)	37,454 (79.5%)	30,197 (82.4%)	53,264 (19.2%)	28,431 (16.3%)	126,019 (34.4%)	101,723 (38.6%)	-0.01
N antidiabetic drugs at index date v3 Copy									
...mean [sd]	0.23 (0.58)	0.20 (0.56)	0.26 (0.64)	0.23 (0.61)	0.24 (0.59)	0.20 (0.55)	0.24 (0.60)	0.20 (0.56)	0.07
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])			
number of different/distinct medication prescriptions									
...mean [sd]	8.79 (4.31)	9.43 (4.56)	9.29 (4.50)	9.54 (4.63)	9.19 (4.28)	9.79 (4.53)	9.15 (4.31)	9.68 (4.55)	-0.12
...median [IQR]	8.00 ([6.00, 11.00])	9.00 ([6.00, 12.00])	9.00 ([6.00, 12.00])	9.00 ([6.00, 12.00])	9.00 ([6.00, 12.00])	9.00 ([7.00, 12.00])			
Number of Hospitalizations									
...mean [sd]	0.23 (0.52)	0.35 (0.60)	0.27 (0.53)	0.39 (0.57)	0.29 (0.61)	0.43 (0.69)	0.28 (0.59)	0.41 (0.66)	-0.21
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 1.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 1.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 1.00])			
Number of hospital days									
...mean [sd]	1.26 (4.08)	1.73 (3.09)	1.58 (4.59)	1.73 (3.80)	1.72 (5.06)	2.25 (5.28)	1.64 (4.89)	2.08 (4.88)	-0.09
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 2.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])			
Number of Emergency Department (ED) visits v3									
...mean [sd]	0.59 (1.33)	0.88 (1.63)	0.44 (1.86)	0.81 (2.41)	0.76 (1.63)	1.02 (1.82)	0.70 (1.63)	0.96 (1.88)	-0.15
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 1.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 2.00])			
Number of Office visits									
...mean [sd]	5.81 (4.53)	5.95 (4.05)	6.57 (5.23)	6.08 (4.28)	14.12 (13.27)	14.44 (12.71)	12.12 (11.73)	11.41 (10.63)	0.06
...median [IQR]	5.00 ([3.00, 8.00])	5.00 ([3.00, 9.00])	5.00 ([3.00, 9.00])	5.00 ([3.00, 8.00])	11.00 ([5.00, 19.00])	11.00 ([6.00, 18.00])			
Number of Endocrinologist visits									
...mean [sd]	0.10 (0.93)	0.10 (0.92)	0.12 (1.03)	0.12 (1.01)	0.17 (1.42)	0.17 (1.44)	0.15 (1.32)	0.15 (1.30)	0.00
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])			
Number of Internal medicine/family medicine visits									
...mean [sd]	10.66 (13.33)	9.539 (12.68)	8.16 ([11.92])	7.22 (10.73)	8.63 (10.80)	8.05 (8.86)	8.82 (11.29)	8.24 (10.59)	0.05
...median [IQR]	7.00 ([2.00, 15.00])	6.00 ([2.00, 12.00])	4.00 ([1.00, 11.00])	4.00 ([1.00, 9.00])	5.00 ([1.00, 12.00])	5.00 ([2.00, 11.00])			
Number of Cardiologist visits									
...mean [sd]	4.51 (6.33)	6.12 (8.43)	3.39 (5.69)	4.21 (5.48)	5.3 (7.47)	6.15 (6.94)	4.97 (7.13)	5.87 (6.66)	-0.13
...median [IQR]	2.00 ([0.00, 6.00])	4.00 ([2.00, 9.00])	1.00 ([0.00, 4.00])	2.00 ([0.00, 6.00])	3.00 ([0.00, 7.00])	4.00 ([2.00, 8.00])			
Number of electrocardiograms received v2									
...mean [sd]	1.52 (2.38)	2.68 (8.89)	1.35 (1.98)	2.31 (2.43)	1.59 (2.19)	2.66 (2.59)	1.55 (2.19)	2.62 (2.63)	-0.44
...median [IQR]	1.00 ([0.00, 2.00])	2.00 ([1.00, 4.00])	1.00 ([0.00, 2.00])	2.00 ([0.00, 3.00])	1.00 ([0.00, 2.00])	2.00 ([1.00, 4.00])			
Number of laboratory tests ordered									
...mean [sd]	0.38 (0.69)	0.39 (0.67)	0.20 (0.53)	0.23 (0.55)	0.38 (0.70)	0.37 (0.68)	0.36 (0.68)	0.35 (0.66)	0.01
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 1.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 1.00])	0.00 ([0.00, 1.00])			
Number of glucose tests ordered									
...mean [sd]	0.14 (1.31)	0.17 (0.72)	0.12 (0.69)	0.13 (0.75)	0.12 (0.56)	0.12 (0.57)	0.12 (0.71)	0.13 (0.94)	-0.01
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])			
Number of lipid tests ordered									
...mean [sd]	0.59 (0.81)	0.64 (0.79)	0.31 (0.79)	0.42 (0.91)	0.61 (0.74)	0.66 (0.75)	0.57 (0.76)	0.62 (0.78)	-0.06
...median [IQR]	0.00 ([0.00, 1.00])	0.00 ([0.00, 1.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 1.00])	0.00 ([0.00, 1.00])			
Number of tests for microalbuminuria									
...mean [sd]	0.19 (0.63)	0.18 (0.60)	0.09 (0.44)	0.10 (0.43)	0.11 (0.40)	0.10 (0.40)	0.12 (0.44)	0.12 (0.44)	0.00
...median [IQR]	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])	0.00 ([0.00, 0.00])			
Total N-district IC90/CD10 diagnoses at the 3rd digit level Copy									
...mean [sd]	6.46 (8.68)	11.88 (10.69)	3.40 (6.52)	7.07 (8.23)	6.76 (6.97)	11.41 (11.56)	6.30 (9.21)	10.90 (10.98)	-0.45
...median [IQR]	4.00 ([0.00, 10.00])	10.00 ([4.00, 17.00])	0.00 ([0.00, 4.00])	5.00 ([0.00, 11.00])	3.00 ([0.00, 10.00])	9.00 ([1.00, 17.00])			
For PS									
Hemorrhagic stroke-Other cerebrovascular disease/Stroke procedure (for PS); n (%)	1,191 (2.6%)	1,971 (3.8%)	1,132 (2.4%)	1,054 (2.9%)	267 (0.1%)	225 (0.1%)	2,590 (0.7%)	3,250 (1.2%)	-0.01
Occurrence of creatinine tests ordered (for PS); n (%)	2,569 (5.5%)	3,140 (6.1%)	2,388 (5.1%)	1,798 (4.9%)	12,740 (4.6%)				

Table 1: Matched

Variable	PS-matched								St. Diff.
	Optum		Truven		Medicare		POOLED		
Reference	15273	15273	Reference	14849	Apixaban (any dose)	14849	Reference	80137	Exposure - DPP4i
Number of patients								80137	110,259
Age									
...mean (sd)	74.79 (8.86)	74.64 (9.26)	72.66 (11.86)	72.78 (11.72)	77.10 (8.28)	77.01 (8.32)	76.18 (8.92)	76.11 (8.98)	0.01
...sd (se)	76.00 (70.00, 82.00)	75.00 (69.00, 82.00)	74.00 (63.00, 82.00)	74.00 (64.00, 82.00)	77.00 (71.00, 83.00)	77.00 (71.00, 83.00)			
Age categories without zero category									
...18 - 54; n (%)	412 (2.7%)	489 (3.2%)	1,005 (6.8%)	900 (6.1%)	736 (0.9%)	812 (1.0%)	2,153 (2.0%)	2,201 (2.0%)	0.00
...55 - 64; n (%)	1,359 (8.9%)	1,466 (9.6%)	3,129 (21.1%)	3,175 (21.4%)	2,397 (3.0%)	2,427 (3.0%)	6,885 (6.2%)	7,068 (6.4%)	0.00
...65 - 74; n (%)	4,944 (32.4%)	4,931 (32.3%)	3,428 (23.1%)	3,533 (23.8%)	27,342 (34.1%)	27,427 (34.2%)	35,714 (32.4%)	35,891 (32.6%)	0.00
...≥75; n (%)	8,558 (56.0%)	8,387 (54.9%)	7,287 (49.1%)	7,241 (48.8%)	49,662 (62.0%)	49,473 (61.7%)	65,507 (59.4%)	65,099 (59.0%)	0.00
Gender without zero category - United									
...Male; n (%)	7,950 (52.1%)	7,963 (52.1%)	8,187 (55.1%)	8,226 (55.4%)	36,474 (45.5%)	36,464 (45.5%)	52,611 (47.7%)	52,653 (47.8%)	0.00
...Female; n (%)	7,323 (47.9%)	7,310 (47.9%)	6,682 (44.9%)	6,623 (44.6%)	43,663 (54.5%)	43,673 (54.5%)	57,648 (52.3%)	57,606 (52.2%)	0.00
Race without zero category									
...White; n (%)	N/A	N/A	N/A	N/A	74,275 (92.7%)	74,299 (92.7%)	74,275 (92.7%)	74,299 (92.7%)	#REF!
...Black; n (%)	N/A	N/A	N/A	N/A	2,826 (3.5%)	2,833 (3.5%)	2,826 (3.5%)	2,833 (3.5%)	0.00
...Asian; n (%)	N/A	N/A	N/A	N/A	788 (1.0%)	762 (1.0%)	788 (1.0%)	762 (1.0%)	0.00
...Hispanic; n (%)	N/A	N/A	N/A	N/A	723 (0.9%)	776 (1.0%)	723 (0.9%)	776 (1.0%)	0.00
...North American Native; n (%)	N/A	N/A	N/A	N/A	253 (0.3%)	238 (0.3%)	253 (0.3%)	238 (0.3%)	0.00
...Other/Unknown; n (%)	N/A	N/A	N/A	N/A	1,272 (1.6%)	1,229 (1.5%)	1,272 (1.6%)	1,229 (1.5%)	0.00
Region without zero category - United v3 (Jumping missing/other category with West)									
...Northeast; n (%)	2,074 (13.6%)	2,058 (13.5%)	3,638 (24.5%)	3,629 (24.4%)	15,635 (19.5%)	15,661 (19.5%)	21,347 (19.4%)	21,348 (19.4%)	0.00
...South; n (%)	5,550 (36.3%)	5,501 (36.0%)	4,451 (30.0%)	4,448 (30.0%)	30,844 (38.5%)	30,914 (38.6%)	40,845 (37.0%)	40,863 (37.1%)	0.00
...Midwest; n (%)	3,239 (21.2%)	3,229 (21.1%)	4,806 (32.4%)	4,766 (32.1%)	20,032 (25.0%)	20,032 (25.0%)	27,937 (25.3%)	28,027 (25.4%)	0.00
...West; n (%)	4,410 (28.9%)	4,485 (29.4%)	1,883 (12.7%)	1,933 (13.0%)	13,766 (17.2%)	13,530 (16.9%)	20,059 (18.2%)	19,948 (18.1%)	0.00
...Unknown/missing; n (%)	N/A	N/A	71 (0.5%)	73 (0.5%)	N/A	N/A	71 (0.5%)	73 (0.5%)	0.00
Calendar Time by day (March 29, 2013 to CED)									
...mean (sd)	1,346.50 (640.11)	1,295.54 (647.77)	850.64 (519.69)	831.37 (525.46)	365.00 (0.00)	365.00 (0.00)	566.36 (305.17)	556.71 (308.71)	0.03
...median (IQR)	376.00 (83.00, 1,868.50)	308.00 (75.00, 1,820.00)	784.00 (436.00, 2,118.00)	753.00 (410.00, 1,197.00)	365.00 (365.00, 365.00)	365.00 (365.00, 365.00)			
CV Covariates									
Ischemic heart disease; n (%)	5,440 (35.6%)	5,555 (36.4%)	5,202 (35.0%)	5,293 (35.6%)	27,989 (34.9%)	28,209 (35.2%)	38,631 (35.5%)	39,057 (35.4%)	0.00
Acute MI; n (%)	525 (3.4%)	542 (3.5%)	510 (3.4%)	494 (3.3%)	2,314 (2.9%)	2,362 (2.9%)	3,349 (3.0%)	3,398 (3.1%)	0.00
ACS/unstable angina; n (%)	486 (3.2%)	497 (3.3%)	490 (3.3%)	475 (3.2%)	2,388 (3.0%)	2,389 (3.0%)	3,364 (3.1%)	3,361 (3.0%)	0.00
Old MI; n (%)	875 (5.7%)	830 (5.4%)	522 (3.5%)	532 (3.6%)	4,574 (5.7%)	4,707 (5.9%)	5,971 (5.4%)	6,069 (5.5%)	0.00
Stroke; n (%)	863 (5.7%)	855 (5.6%)	624 (4.2%)	593 (4.0%)	3,262 (4.1%)	3,335 (4.2%)	4,749 (4.3%)	4,783 (4.3%)	0.00
Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)	4,999 (32.7%)	4,972 (32.6%)	4,830 (32.4%)	4,809 (32.4%)	25,708 (32.1%)	25,961 (32.4%)	35,537 (32.2%)	35,742 (32.4%)	0.00
Other atherosclerosis with CD10 v2 Copy; n (%)	201 (1.3%)	164 (1.1%)	198 (1.3%)	197 (1.3%)	984 (1.2%)	977 (1.2%)	1,383 (1.3%)	1,338 (1.2%)	0.00
Previous cardiac procedure (CABG or PTCA or Stent)									
v4; n (%)	280 (1.8%)	137 (0.9%)	316 (2.1%)	171 (1.2%)	1,502 (1.9%)	818 (1.0%)	2,098 (1.9%)	1,126 (1.0%)	0.01
History of CABG or PTCA; n (%)	1,401 (9.2%)	1,435 (9.5%)	718 (4.8%)	802 (5.4%)	8,095 (10.1%)	8,580 (10.7%)	10,214 (9.3%)	10,817 (9.8%)	0.00
Any stent; n (%)	1,429 (9.4%)	1,424 (9.3%)	1,356 (9.1%)	1,370 (9.2%)	7,131 (8.9%)	7,238 (8.9%)	9,916 (9.0%)	10,032 (9.1%)	0.00
Ischemic stroke w/ or w/o mention of cerebral infarction; n (%)	1,416 (9.3%)	1,418 (9.3%)	1,352 (9.1%)	1,365 (9.2%)	7,092 (8.9%)	7,200 (8.0%)	9,860 (8.8%)	9,982 (9.1%)	0.00
Hemorrhagic stroke; n (%)	21 (0.1%)	**	11 (0.1%)	13 (0.1%)	59 (0.1%)	62 (0.1%)	99 (0.1%)	101 (0.1%)	#VALUE!
TIA; n (%)	561 (3.7%)	562 (3.7%)	514 (3.5%)	510 (3.4%)	2,620 (3.0%)	2,699 (3.4%)	3,695 (3.4%)	3,771 (3.4%)	0.00
Other cerebrovascular disease; n (%)	471 (3.1%)	470 (3.1%)	409 (2.8%)	409 (2.8%)	2,032 (2.9%)	2,287 (3.0%)	3,183 (2.9%)	3,166 (2.9%)	0.00
Left effects of cerebrovascular disease; n (%)	433 (2.8%)	425 (2.8%)	321 (2.2%)	335 (2.3%)	2,165 (2.7%)	2,209 (2.8%)	2,919 (2.6%)	2,969 (2.7%)	0.00
Cerebrovascular procedure; n (%)	14 (0.1%)	17 (0.1%)	13 (0.1%)	16 (0.1%)	103 (0.1%)	99 (0.1%)	130 (0.1%)	132 (0.1%)	0.00
Hospitalization for CHF; n (%)	4,026 (26.4%)	4,076 (26.7%)	3,528 (21.8%)	3,512 (23.7%)	18,310 (22.8%)	18,437 (23.0%)	25,864 (23.3%)	26,025 (23.6%)	0.00
Hospital Peripheral Vascular Disease (PVD) or PVD Surgery v2; n (%)									
n (%)	1,343 (8.8%)	1,384 (9.1%)	1,142 (7.7%)	1,102 (7.4%)	6,437 (8.0%)	6,456 (8.0%)	8,922 (8.1%)	8,952 (8.1%)	0.00
Atrial fibrillation; n (%)	14,720 (96.4%)	14,426 (97.2%)	14,375 (96.5%)	14,269 (97.2%)	74,268 (92.7%)	74,269 (92.7%)	103,417 (93.8%)	103,363 (93.7%)	0.00
Other cardiac dysrhythmia; n (%)	11,951 (78.2%)	11,531 (75.5%)	8,702 (58.6%)	8,479 (57.1%)	49,385 (61.6%)	48,611 (60.7%)	70,038 (63.5%)	68,621 (62.2%)	0.00
Cardiac conduction disorders; n (%)	1,633 (10.7%)	1,697 (11.1%)	1,347 (9.1%)	1,372 (9.2%)	7,098 (8.9%)	7,032 (8.8%)	10,078 (9.1%)	10,101 (9.2%)	0.00
Other CVD; n (%)	5,937 (38.9%)	5,926 (38.8%)	5,818 (39.1%)	5,710 (38.5%)	25,840 (32.2%)	25,851 (32.3%)	37,590 (34.1%)	37,487 (34.0%)	0.00
Diabetes-related complications									
Diabetic retinopathy; n (%)									
Diabetes with other ophthalmic manifestations; n (%)	179 (1.2%)	165 (1.1%)	125 (0.8%)	134 (0.9%)	686 (0.9%)	724 (0.9%)	990 (0.9%)	1,023 (0.9%)	0.00
Retinal detachment; n (%)	29 (0.2%)	25 (0.2%)	92 (0.6%)	93 (0.6%)	420 (0.5%)	437 (0.5%)	541 (0.5%)	555 (0.5%)	0.00
Retinal detachment, vitreous hemorrhage; n (%)									
Retiretinal membrane; n (%)	15 (0.1%)	14 (0.1%)	16 (0.1%)	15 (0.1%)	58 (0.1%)	66 (0.1%)	889 (0.1%)	995 (0.1%)	0.00
Retinal laser coagulation therapy; n (%)	**	12 (0.1%)	13 (0.1%)	12 (0.1%)	85 (0.1%)	90 (0.1%)	#VALUE!	114 (0.1%)	#VALUE!
Occurrence of Diabetic Neuropathy v2 Copy; n (%)	763 (5.0%)	784 (5.1%)	557 (3.8%)	568 (3.8%)	2,858 (3.6%)	2,971 (3.7%)	4,178 (3.8%)	4,322 (3.9%)	0.00
Occurrence of Diabetic nephropathy V3 with CD10									
CD10 v2 Copy; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!
Hypertension v2; n (%)	76 (0.5%)	80 (0.5%)	128 (0.9%)	103 (0.7%)	1,106 (1.4%)	1,192 (1.4%)	1,210 (1.2%)	1,284 (1.2%)	0.00
Hypoglycemia; n (%)	862 (5.6%)	903 (5.9%)	505 (3.4%)	496 (3.3%)	5,184 (6.5%)	4,951 (6.2%)	6,555 (5.9%)	6,350 (5.8%)	0.00
Disorders of fluid electrolyte and acid-base balance; n (%)									
Diabetic ketoacidosis; n (%)	1,693 (11.1%)	1,852 (12.1%)	1,339 (9.0%)	1,402 (9.4%)	6,132 (7.7%)	5,838 (7.3%)	9,164 (8.3%)	9,092 (8.2%)	0.00
Diabetic ketoacidosis; n (%)	**	13 (0.1%)	14 (0.1%)	11 (0.1%)	69 (0.1%)	80 (0.1%)	#VALUE!	104 (0.1%)	#VALUE!
Hyperosmolar hyperglycemic nonketotic syndrome (HHS); n (%)	18 (0.1%)	15 (0.1%)	16 (0.1%)	**	71 (0.1%)	74 (0.1%)	105 (0.1%)	#VALUE!	#VALUE!
Diabetes mellitus without mention of complications; n (%)									
n (%)	3,809 (24.9%)	3,816 (25.0%)	3,576 (24.1%)	3,582 (24.1%)	20,010 (25.0%)	20,230 (25.2%)	27,395 (24.8%)	27,628 (25.1%)	0.00
Within 365 days; n (%)	13,001 (85.1%)	12,934 (84.7%)	11,752 (79.1%)	11,730 (79.0%)	71,353 (89.0%)	71,353 (89.0%)	96,163 (87.7%)	96,017 (87.1%)	0.00
Hyperglycemia v2; n (%)	9,005 (59.0%)	7,798 (52.5%)	7,774 (52.4%)	41,925 (33.3%)	70,869 (38.0%)	71,404 (32.8%)	104,000 (33.3%)	103,437 (33.5%)	0.00
Diabetes mellitus v2; n (%)	1,843 (12.1%)	1,485 (10.0%)	1,405 (7.6%)	1,405 (7.6%)	7,090 (5.1%)	7,090 (5.1%)	9,074 (5.1%)	9,074 (5.1%)	0.00
Renal dysfunction (non-diabetic) v2; n (%)	15 (0.1%)	**	12 (0.1%)	55 (0.1%)	49 (0.1%)	49 (0.1%)	#VALUE!	#VALUE!	#VALUE!
Occurrence of acute renal disease v2; n (%)	12 (0.1%)	**	11 (0.1%)	46 (0.1%)	42 (0.1%)	42 (0.1%)	#VALUE!	#VALUE!	#VALUE!
Occurrence of chronic renal insufficiency; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!
Chronic kidney disease v2; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!
CKD Stage 3-4; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!
Occurrence of hypertensive nephropathy; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	#VALUE!
Occurrence of miscellaneous renal insufficiency v2; n (%)	**	**	**	**	6 (0.0%)	6 (0.0%)	#VALUE!	#VALUE!	#VALUE!
Glaucoma or cataracts v2; n (%)	2,873 (18.8%)	3,064 (20.1%)	2,941 (19.8%)	2,840 (19.2%)	16,717 (20.9%)	16,763 (20.6%)	22,641 (20.5%)	22,768 (20.6%)	0.00
Cellulitis or abscess of face; n (%)	294 (1.9%)	198 (1.3%)	195 (1.3%)	1108 (1.4%)	1,212 (1.5%)	1,270 (1.4%)	1,770 (1.5%)	1,770 (1.5%)	0.00
Foot ulcer; n (%)	322 (2.1%)	323 (2.1%)	345 (2.3%)	304 (2.0%)	1,810 (2.3%)	1,795 (2.2%)	2,477 (2.2%)	2,422 (2.2%)	0.00
Bladder stones; n (%)	18 (0.1%)	27 (0.2%)	19 (0.1%)	32 (0.2%)	79 (0.1%)	105 (0.1%)	116 (0.1%)	164 (0.1%)	0.00
Kidney stones; n (%)	222 (1.5%)	225 (1.5%)	253 (1.7%)	275 (1.9%)	1,205 (1.5%)	1,230 (1.5%)	1,680 (1.5%)	1,730 (1.6%)	0.00
Urinary tract infection (UTI); n (%)	1,543 (10.1%)	1,671 (10.9%)	1,230 (8.3%)	1,255 (8.5%)	10,192 (12.7%)	10,461 (13.1%)	12,965 (11.8%)	13,387 (12.1%)	0.00
Urinary tract infection; n (%)	4,469 (29.3%)</								

Table 1: Matched

Linagliptin; n (%)	32 (0.2%)	23 (0.2%)	45 (0.3%)	51 (0.3%)	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	#VALUE!	#VALUE!	#VALUE!
Saxagliptin; n (%)	41 (0.3%)	37 (0.2%)	49 (0.3%)	40 (0.3%)	0	0	#VALUE!	#VALUE!	#VALUE!
Sitagliptin; n (%)	149 (1.0%)	158 (1.0%)	296 (2.0%)	241 (1.6%)	0.09 [0.42]	0.09 [0.42]	#VALUE!	399 (0.4%)	#VALUE!
Concomitant initiation or current use of 2nd Generation AGIs; n (%)	801 (5.2%)	721 (4.7%)	768 (5.2%)	753 (5.1%)	529 (0.7%)	381 (0.5%)	2,098 (1.9%)	1,855 (1.7%)	0.00
Concomitant initiation or current use of AGIs; n (%)	**	**	**	14 (0.1%)	0 (0.0%)	**	#VALUE!	#VALUE!	#VALUE!
Concomitant initiation or current use of Glitazones; n (%)	89 (0.6%)	132 (0.9%)	115 (0.8%)	140 (0.9%)	43 (0.1%)	48 (0.1%)	247 (0.2%)	320 (0.3%)	0.00
Concomitant initiation or current use of Insulin; n (%)	58 (0.4%)	70 (0.5%)	101 (0.7%)	122 (0.8%)	27 (0.0%)	17 (0.0%)	186 (0.2%)	209 (0.2%)	0.00
Concomitant initiation or current use of Metformin; n (%)	370 (2.4%)	402 (2.6%)	485 (3.3%)	483 (3.3%)	0	0	#VALUE!	#VALUE!	#VALUE!
Metformin; n (%)	15 (0.1%)	15 (0.1%)	39 (0.3%)	30 (0.2%)	19 (0.0%)	16 (0.0%)	0.73 (0.1%)	0.61 (0.1%)	0.00
Concomitant initiation or current use of Metformin; n (%)	1,747 (11.4%)	1,811 (11.9%)	1,584 (10.7%)	1,650 (11.1%)	1,019 (1.3%)	824 (1.0%)	4,350 (3.3%)	4,285 (3.3%)	0.00
Part use of 2nd Generation SUs; n (%)	167 (1.1%)	183 (1.2%)	160 (1.1%)	165 (1.1%)	**	12 (0.0%)	#VALUE!	360 (0.3%)	#VALUE!
Part use of AGIs; n (%)	**	**	**	0 (0.0%)	0 (0.0%)	#VALUE!	#VALUE!	#VALUE!	#VALUE!
Part use of Glip; n (%)	28 (0.2%)	34 (0.2%)	30 (0.2%)	37 (0.2%)	**	**	#VALUE!	#VALUE!	#VALUE!
Part use of GLP-1 RA; n (%)	31 (0.2%)	31 (0.2%)	43 (0.3%)	42 (0.3%)	**	**	#VALUE!	#VALUE!	#VALUE!
Part use of Insulin; n (%)	165 (1.1%)	172 (1.1%)	165 (1.1%)	174 (1.2%)	**	**	#VALUE!	#VALUE!	#VALUE!
Part use of Meglitinides; n (%)	5 (0.0%)	5 (0.0%)	12 (0.1%)	13 (0.1%)	**	**	#VALUE!	#VALUE!	#VALUE!
Part use of Metformin (final); n (%)	390 (2.6%)	386 (2.5%)	382 (2.6%)	405 (2.7%)	**	**	#VALUE!	#VALUE!	#VALUE!
Other Medication									
Use of ACE Inhibitors; n (%)	5,108 (33.4%)	5,185 (33.9%)	4,931 (32.2%)	4,911 (33.1%)	26,746 (33.4%)	26,769 (33.4%)	36,785 (33.4%)	36,865 (33.4%)	0.00
Use of ARBs; n (%)	3,359 (22.0%)	3,277 (21.5%)	3,611 (24.3%)	3,632 (24.5%)	18,865 (23.5%)	18,827 (23.5%)	25,838 (23.4%)	25,736 (23.3%)	0.00
Use of Beta-blockers; United; n (%)	4,256 (28.0%)	4,204 (28.0%)	4,099 (27.6%)	3,973 (26.6%)	23,860 (23.5%)	23,819 (23.5%)	31,770 (28.8%)	31,770 (28.8%)	0.00
Use of fibrat; n (%)	916 (6.0%)	954 (6.2%)	937 (6.0%)	937 (6.0%)	1,712 (1.5%)	1,694 (1.5%)	6,876 (6.3%)	6,876 (6.3%)	0.00
Use of statins; United; n (%)	1,096 (7.0%)	1,033 (7.0%)	1,163 (7.8%)	1,081 (7.3%)	7,236 (6.0%)	6,935 (6.0%)	9,039 (8.2%)	9,039 (8.2%)	0.00
Use of other hypertension drugs; n (%)	987 (6.5%)	1,075 (7.0%)	944 (6.4%)	1,009 (6.8%)	5,421 (6.8%)	5,527 (7.4%)	7,352 (6.7%)	8,011 (7.3%)	0.00
Use of digoxin; United; n (%)	1,982 (13.0%)	1,340 (8.8%)	2,364 (15.9%)	1,677 (11.3%)	11,421 (14.3%)	8,950 (11.2%)	15,767 (4.3%)	11,967 (10.9%)	0.01
Use of Anti-arrhythmics; n (%)	2,830 (18.5%)	2,881 (18.9%)	3,408 (23.0%)	3,334 (22.5%)	16,013 (20.0%)	16,120 (20.1%)	22,251 (20.2%)	22,335 (20.3%)	0.00
Use of COPD/asthma meds; United; n (%)	2,680 (17.5%)	2,826 (18.5%)	2,911 (19.6%)	16,177 (20.3%)	21,289 (19.8%)	21,289 (19.8%)	21,914 (19.9%)	21,914 (19.9%)	0.00
Use of statins; n (%)	8,379 (54.9%)	8,384 (54.9%)	8,068 (54.3%)	8,166 (54.7%)	44,642 (55.7%)	44,673 (55.7%)	61,089 (55.4%)	61,183 (55.5%)	0.00
Use of other; n (%)	807 (5.3%)	809 (5.3%)	1,122 (7.6%)	1,135 (7.6%)	4,999 (6.2%)	5,066 (6.3%)	6,928 (6.3%)	7,010 (6.4%)	0.00
Use of oral contraceptives; n (%)	1,518 (9.9%)	1,535 (10.1%)	1,870 (12.6%)	1,810 (12.2%)	9,611 (12.0%)	9,781 (12.2%)	12,999 (11.8%)	13,126 (11.9%)	0.00
Use of oral anticoagulants; Dabigatran, Rivaroxaban, Apixaban, Warfarin); n (%)	15,273 (100.0%)	15,273 (100.0%)	14,849 (100.0%)	14,849 (100.0%)	80,137 (100.0%)	80,137 (100.0%)	110,259 (100.0%)	110,259 (100.0%)	0.00
Use of heparin and other low-molecular weight heparins; n (%)	201 (1.3%)	246 (1.6%)	**	**	838 (1.0%)	1,007 (1.3%)	#VALUE!	#VALUE!	#VALUE!
Use of NSAIDs; n (%)	1,595 (10.4%)	1,554 (10.2%)	1,662 (11.2%)	1,661 (11.2%)	9,357 (11.1%)	9,421 (11.8%)	12,614 (11.4%)	12,636 (11.5%)	0.00
Use of oral corticosteroids; n (%)	3,107 (20.0%)	3,092 (20.2%)	2,955 (19.9%)	2,974 (20.0%)	17,909 (23.3%)	17,955 (22.4%)	23,971 (21.7%)	24,021 (21.8%)	0.00
Use of bisphosphonates; United; n (%)	525 (3.4%)	526 (3.4%)	365 (2.5%)	355 (2.4%)	2,725 (3.4%)	2,741 (3.4%)	3,615 (3.3%)	3,622 (3.3%)	0.00
Use of statins; United; n (%)	3,699 (24.0%)	3,750 (24.0%)	3,919 (25.0%)	3,919 (25.0%)	22,236 (24.0%)	22,236 (24.0%)	26,220 (23.9%)	26,220 (23.9%)	0.00
Use of anti-depressants; n (%)	3,382 (22.0%)	3,379 (21.1%)	3,016 (20.3%)	3,005 (20.3%)	19,919 (23.7%)	19,236 (24.0%)	25,370 (23.0%)	25,370 (23.0%)	0.00
Use of anti-psychotics; n (%)	280 (1.8%)	281 (1.8%)	244 (1.6%)	243 (1.6%)	1,983 (1.5%)	2,058 (1.6%)	2,507 (2.3%)	2,584 (2.3%)	0.00
Use of anti-coagulants; n (%)	1,932 (12.6%)	1,991 (13.0%)	1,587 (10.7%)	1,608 (10.8%)	10,833 (13.5%)	10,990 (13.7%)	14,326 (13.0%)	14,389 (13.2%)	0.00
Use of lithium; United; n (%)	12 (0.1%)	13 (0.1%)	16 (0.1%)	11 (0.1%)	59 (0.1%)	86 (0.1%)	110 (0.1%)	110 (0.1%)	0.00
Use of Benzos; United; n (%)	1,886 (12.3%)	1,904 (12.5%)	2,009 (13.5%)	1,965 (13.2%)	12,174 (15.2%)	12,263 (15.3%)	16,089 (14.6%)	16,132 (14.6%)	0.00
Use of anxiolytic/sedatives; United; n (%)	699 (4.6%)	770 (5.0%)	952 (6.4%)	662 (6.5%)	5,173 (6.5%)	5,258 (6.6%)	6,824 (6.3%)	6,990 (6.3%)	0.00
Use of dementia; United; n (%)	533 (3.5%)	499 (3.3%)	491 (3.3%)	495 (3.3%)	3,443 (4.3%)	3,510 (4.4%)	4,467 (4.1%)	4,504 (4.1%)	0.00
Use of anti-parkinsonian; United; n (%)	444 (2.9%)	450 (2.9%)	401 (2.7%)	389 (2.6%)	2,817 (3.5%)	2,844 (3.3%)	3,652 (3.3%)	3,683 (3.3%)	0.00
Use of anti-psychotics; n (%)	0 (0.0%)	0 (0.0%)	**	**	**	**	#VALUE!	#VALUE!	#VALUE!
Any use of 1st generation sulfonylureas; n (%)	0 (0.0%)	0 (0.0%)	**	**	**	**	#VALUE!	#VALUE!	#VALUE!
Entresto (sacubitril/valsartan); n (%)	65 (0.4%)	74 (0.5%)	35 (0.2%)	20 (0.1%)	99 (0.1%)	114 (0.1%)	199 (0.2%)	209 (0.2%)	0.00
Initiation as monotherapy; n (%)	0 (0.0%)	2 (0.0%)	**	**	**	**	#VALUE!	#VALUE!	#VALUE!
Dual therapy with metformin v4 (latest based on Action's suggestion)- not adding to P5; n (%)	**	**	**	13 (0.1%)	13 (0.1%)	194 (0.2%)	203 (0.3%)	#VALUE!	#VALUE!
Lab									
Lab values- HbA1c (HbA1c); n (%)	2,202 (14.4%)	2,238 (14.7%)	173 (1.2%)	142 (1.0%)	N/A	N/A	2,375 (14.3%)	2,380 (14.3%)	0.00
Lab values- HbA1c (HbA1c) within 3 months; v2; n (%)	1,417 (9.3%)	1,426 (9.4%)	111 (0.7%)	97 (0.7%)	N/A	N/A	1,528 (5.1%)	1,533 (5.1%)	0.00
Lab values- HbA1c (HbA1c) within 6 months; v2; n (%)	2,202 (14.4%)	2,238 (14.7%)	173 (1.2%)	142 (1.0%)	N/A	N/A	2,375 (14.3%)	2,380 (14.3%)	0.00
Lab values- BNP; n (%)	266 (1.7%)	324 (2.1%)	37 (0.2%)	22 (0.1%)	N/A	N/A	303 (1.0%)	346 (1.1%)	0.00
Lab values- BNP; within 3 months; n (%)	177 (1.2%)	226 (1.5%)	27 (0.2%)	19 (0.1%)	N/A	N/A	204 (0.7%)	245 (0.8%)	0.00
Lab values- BNP; within 6 months; n (%)	266 (1.7%)	324 (2.1%)	37 (0.2%)	22 (0.1%)	N/A	N/A	303 (1.0%)	346 (1.1%)	0.00
Lab values- BUN (mg/dl); n (%)	3,435 (28.4%)	4,694 (30.7%)	258 (1.7%)	231 (1.6%)	N/A	N/A	4,603 (15.3%)	4,925 (16.4%)	0.00
Lab values- BUN (mg/dl) within 3 months; n (%)	2,953 (19.3%)	3,245 (21.2%)	181 (1.2%)	155 (1.0%)	N/A	N/A	3,134 (10.4%)	3,400 (11.3%)	0.00
Lab values- BUN (mg/dl) within 6 months; n (%)	3,435 (28.4%)	4,694 (30.7%)	258 (1.7%)	231 (1.6%)	N/A	N/A	4,603 (15.3%)	4,925 (16.4%)	0.00
Lab values- Creatinine (mg/dl); v2; n (%)	4,447 (29.1%)	4,846 (31.7%)	273 (1.8%)	237 (1.6%)	N/A	N/A	4,720 (15.7%)	5,083 (16.9%)	0.00
Lab values- Creatinine (mg/dl); v2; n (%)	3,016 (19.7%)	3,373 (22.1%)	191 (1.3%)	157 (1.1%)	N/A	N/A	3,207 (10.6%)	3,530 (11.7%)	0.00
Lab values- Creatinine (mg/dl) within 6 months; v2; n (%)	4,447 (29.1%)	4,846 (31.7%)	273 (1.8%)	237 (1.6%)	N/A	N/A	4,720 (15.7%)	5,083 (16.9%)	0.00
Lab values- HDL level (mg/dl); n (%)	2,935 (19.2%)	3,065 (20.1%)	175 (1.2%)	140 (0.9%)	N/A	N/A	3,110 (10.3%)	3,205 (10.6%)	0.00
Lab values- LDL level (mg/dl); v2; n (%)	3,142 (20.6%)	3,273 (21.4%)	192 (1.3%)	139 (0.9%)	N/A	N/A	3,207 (10.6%)	3,330 (11.7%)	0.00
Lab values- LDL level (mg/dl); within 3 months; n (%)	3,142 (20.6%)	3,273 (21.4%)	192 (1.3%)	139 (0.9%)	N/A	N/A	3,207 (10.6%)	3,330 (11.7%)	0.00
Lab values- LDL level (mg/dl); within 6 months; n (%)	3,142 (20.6%)	3,273 (21.4%)	192 (1.3%)	139 (0.9%)	N/A	N/A	3,207 (10.6%)	3,330 (11.7%)	0.00
Lab values- LDL level (mg/dl); v2; n (%)	1,887 (12.4%)	1,978 (13.0%)	114 (0.8%)	82 (0.6%)	N/A	N/A	2,001 (6.6%)	2,060 (6.8%)	0.00
Lab values- LDL cholesterol (mg/dl); within 6 months; v2; n (%)	3,142 (20.6%)	3,273 (21.4%)	192 (1.3%)	139 (0.9%)	N/A	N/A	3,334 (11.1%)	3,412 (11.3%)	0.00
Lab values- NT-proBNP; n (%)	42 (0.3%)	61 (0.4%)	**	**	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
Lab values- NT-proBNP; within 3 months; n (%)	34 (0.2%)	44 (0.3%)	**	**	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
Lab values- NT-proBNP; within 6 months; n (%)	42 (0.3%)	61 (0.4%)	**	**	N/A	N/A	#VALUE!	#VALUE!	#VALUE!
Lab values- Total cholesterol (mg/dl); v2; n (%)	3,012 (19.7%)	3,125 (20.5%)	174 (1.2%)	137 (0.9%)	N/A	N/A	3,186 (10.6%)	3,262 (10.8%)	0.00
Lab values- Triglyceride level (mg/dl); n (%)	2,951 (11.6%)	1,870 (12.2%)	98 (0.7%)	80 (0.5%)	N/A	N/A	1,869 (6.6%)	1,950 (6.5%)	0.00
Lab values- Triglyceride level (mg/dl); within 3 months; n (%)	2,951 (19.3%)	3,091 (20.2%)	171 (1.2%)	139 (0.9%)	N/A	N/A	3,122 (10.4%)	3,230 (10.7%)	0.00
Lab values- Triglyceride level (mg/dl); within 6 months; n (%)	2,951 (19.3%)	3,091 (20.2%)	171 (1.2%)	139 (0.9%)	N/A	N/A	3,122 (10.4%)	3,230 (10.7%)	0.00
Lab values- Triglyceride level (mg/dl); within 3 months; v2; n (%)	1,805 (11.8%)	1,886 (12.3%)	97 (0.7%)	79 (0.5%)	N/A	N/A	1,902 (6.3%)	1,965 (6.5%)	0.00
Lab values- Triglyceride level (mg/dl); within 6 months; v2; n (%)	1,805 (11.8%)	1,886 (12.3%)	97 (0.7%)	79 (0.5%)	N/A	N/A	1,902 (6.3%)	1,965 (6.5%)	0.00
Lab values- Triglyceride level (mg/dl); v2; n (%)	18,016 (20%)	86,98 (13,695.52)	18,61 (6.49)	18,61 (6.49)	N/A	N/A	438,02 (9615.95)	18,31 (6.44)	0.06
Lab values- Triglyceride level (mg/dl); v2; n (%)	0.97 (0.25)	0.97 (0.23)	0.97 (0.24)	1.00 (0.25)	N/A	N/A	0.97 (0.25)	0.98 (0.24)	-0.04
Lab values- Triglyceride level (mg/dl); v2; n (%)	0.94 (0.80, 1.10)	0.94 (0.81, 1.09)	0.94 (0.80, 1.08)	0.98 (0.85, 1.13)	N/A	N/A	0.94 (0.80, 1.10)	0.98 (0.85, 1.13)	0.00
Lab result number- HDL level (mg/dl) mean (only to 15 included); v3	10,928 (71.16%)	10,470 (68.6%)	14,582 (98.2%)	14,618 (98.4%)	N/A	N/A	14,616 (44.66)	16,311 (40.94)	0.04
Lab result number- LDL level (mg/dl) mean (only to 15 included); v2	51.89 (16.24)	52.65 (17.24)	45.20 (16.08)	45.00 (13.88)	N/A	N/A	48.59 (16.16)	48.88 (15.67)	-0.02
Lab result number- LDL level (mg/dl) mean (only to 15 included); v2	49,50 (41.00, 60.25)	50,00 (41.00, 62.00)	43,25 (35.88, 52.20)	44,00 (35.12, 52.75)	N/A	N/A	44,61 (58.40)	519,16 (833.97)	-0.15
Lab result number- LDL level (mg/dl) mean (only to 15 included); v2	12,338 (80.8%)	12,208 (79.9%)	14,675 (98.9%)	14,709 (99.1%)	N/A	N/A	13,727 (92.1%)	13,751 (92.1%)	0.00
Lab result number- Total cholesterol (mg									

Table 1: Matched

...Missing; n (%)	11,535 (75.5%)	11,360 (74.4%)	14,655 (98.7%)	14,686 (98.9%)	N/A	N/A			
Lab result number-Glucose (fasting or random) mean (only 10-1000 included)					N/A	N/A	119.31 (40.26)	120.79 (44.36)	-0.03
...mean	110.11 (33.77)	110.43 (36.05)	128.77 (45.98)	131.44 (51.52)	N/A	N/A			
...median [IQR]	101.00 (92.00, 117.00)	101.00 (92.00, 116.00)	115.00 (97.00, 147.75)	116.25 (97.83, 143.31)	N/A	N/A			
...Missing; n (%)	11,123 (72.8%)	10,823 (70.9%)	14,590 (98.3%)	14,639 (98.6%)	N/A	N/A			
Lab result number-Potassium mean (only 1-7 included)					N/A	N/A			
...mean [sd]	4.36 (0.44)	4.39 (0.43)	4.32 (0.41)	4.37 (0.40)	N/A	N/A	4.34 (0.43)	4.38 (0.42)	-0.09
...median [IQR]	4.35 (4.10, 4.60)	4.40 (4.10, 4.65)	4.30 (4.10, 4.57)	4.40 (4.10, 4.60)	N/A	N/A			
...Missing; n (%)	10,855 (71.1%)	10,470 (68.6%)	14,593 (98.3%)	14,632 (98.5%)	N/A	N/A			
Comorbidity Scores									
Comorbidity-C90 and CD10 v2									
...mean	3.50 (1.86)	3.50 (1.84)	3.22 (1.73)	3.20 (1.71)	2.20 (2.00)	2.22 (2.02)	3.36 (1.80)	3.35 (1.78)	0.01
...median [IQR]	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)			
Frailty Score: Qualitative Version 365 days as Categories, v1									
...0; n (%)	6,480 (42.4%)	5,808 (38.0%)	2,847 (19.2%)	2,765 (18.6%)	80,137 (100.0%)	80,137 (100.0%)	89,464 (81.1%)	88,710 (80.5%)	0.00
...1 to 2; n (%)	4,987 (32.7%)	5,444 (35.6%)	5,982 (40.3%)	6,121 (41.2%)	0 (0.0%)	0 (0.0%)	10,969 (9.9%)	11,565 (10.5%)	0.00
...3 or more; n (%)	3,806 (24.9%)	4,021 (26.3%)	6,020 (40.5%)	5,963 (40.2%)	0 (0.0%)	0 (0.0%)	9,826 (8.8%)	9,984 (9.1%)	0.00
Frailty Score: Empirical Version 365 days as Categories, v3									
...<0.12908; n (%)	1,344 (8.8%)	1,533 (10.0%)	1,237 (8.3%)	1,288 (8.7%)	63,958 (79.8%)	63,584 (79.3%)	66,539 (60.3%)	66,405 (60.2%)	0.00
...0.12908 - 0.1631167; n (%)	4,185 (27.4%)	4,252 (27.8%)	4,009 (27.0%)	4,061 (27.3%)	7,169 (8.9%)	7,168 (8.9%)	15,363 (13.9%)	15,481 (14.0%)	0.00
...>0.1631167; n (%)	9,744 (63.8%)	9,488 (62.1%)	9,603 (64.7%)	9,500 (64.0%)	9,910 (11.2%)	9,385 (11.7%)	28,357 (25.7%)	28,373 (25.7%)	0.00
Non-Frailty; n (%)	8,075 (52.9%)	8,222 (53.8%)	7,317 (49.3%)	7,321 (49.3%)	1,831 (2.3%)	1,475 (1.8%)	17,223 (15.6%)	17,018 (15.4%)	0.00
Frailty Score (mean): Qualitative Version 365 days, v1									
...mean [sd]	1.62 (2.14)	1.69 (2.07)	2.40 (2.09)	2.39 (2.08)	0.09 (0.06)	0.09 (0.06)	2.00 (2.12)	2.04 (2.07)	-0.02
Frailty Score (mean): Empirical Version 365 days, v2									
...mean [sd]	0.19 (0.06)	0.19 (0.06)	0.18 (0.05)	0.18 (0.05)	13.79 (10.60)	13.94 (11.23)	0.19 (0.06)	0.19 (0.06)	0.00
...median [IQR]	0.18 (0.15, 0.22)	0.18 (0.15, 0.22)	0.17 (0.15, 0.21)	0.17 (0.15, 0.21)	11.48 (6.52, 18.58)	11.41 (6.24, 18.92)			
Healthcare Utilization									
Any hospitalization (n)									
...Any hospitalization during prior 30 days; n (%)	2,655 (16.4%)	2,680 (16.8%)	3,263 (22.0%)	3,266 (22.0%)	17,754 (20.2%)	17,754 (20.2%)	23,682 (22.7%)	23,695 (22.7%)	0.00
...Any hospitalization during prior 31-180 days; n (%)	1,771 (11.1%)	1,800 (11.5%)	1,943 (12.1%)	1,961 (12.1%)	11,795 (14.0%)	11,795 (14.0%)	15,568 (14.2%)	15,568 (14.2%)	0.00
Endocrinologist Visit; n (%)	423 (2.8%)	422 (2.8%)	485 (3.2%)	480 (3.2%)	3,239 (4.0%)	3,111 (3.9%)	4,337 (3.8%)	4,013 (3.6%)	0.00
Endocrinologist Visit (30 days prior); n (%)	121 (0.8%)	130 (0.9%)	169 (1.1%)	151 (1.0%)	956 (1.2%)	936 (1.2%)	1,246 (1.1%)	1,207 (1.1%)	0.00
Endocrinologist Visit (31 to 180 days prior); n (%)	357 (2.3%)	341 (2.2%)	394 (2.7%)	399 (2.7%)	2,719 (3.4%)	2,622 (3.3%)	3,362 (3.0%)	3,362 (3.0%)	0.00
Internal medicine/family medicine visits (30 days prior); n (%)	13,081 (85.6%)	13,272 (86.9%)	12,120 (81.6%)	11,913 (80.2%)	66,414 (82.9%)	67,563 (84.3%)	91,615 (83.1%)	92,748 (84.1%)	0.00
Internal medicine/family medicine visits (30 days prior); v2; n (%)	8,371 (54.8%)	8,426 (55.2%)	7,582 (51.1%)	7,465 (50.3%)	42,114 (52.6%)	41,751 (52.1%)	58,067 (52.7%)	57,642 (52.3%)	0.00
Internal medicine/family medicine visits (31 to 180 days prior); v2; n (%)	11,810 (77.3%)	11,921 (78.1%)	11,016 (74.2%)	10,766 (72.5%)	58,410 (72.9%)	59,572 (74.3%)	81,236 (73.7%)	82,259 (74.6%)	0.00
Cardiologist visit; n (%)	11,538 (7.5%)	12,060 (7.9%)	9,253 (6.2%)	9,102 (6.1%)	63,820 (7.9%)	66,537 (8.0%)	84,711 (7.6%)	87,708 (7.9%)	0.00
Number of Cardiologist visits (30 days prior); n (%)	8,214 (53.8%)	8,242 (54.0%)	6,208 (41.8%)	6,079 (40.5%)	46,109 (57.5%)	46,119 (57.6%)	60,531 (54.9%)	60,440 (54.8%)	0.00
Number of Cardiologist visits (31 to 180 days prior); n (%)	8,453 (53.5%)	8,712 (57.0%)	7,212 (48.6%)	6,953 (46.8%)	46,069 (57.5%)	47,552 (59.3%)	61,734 (56.6%)	63,217 (57.3%)	0.00
Electrocardiogram (2; n (%)	10,536 (69.0%)	11,542 (75.6%)	10,205 (68.7%)	11,063 (70.5%)	60,573 (75.6%)	64,303 (80.2%)	81,314 (73.7%)	86,508 (78.8%)	-0.01
Diagnosis; n (%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**	**	**	**	**
Number of CT Scan; n (%)	12,399 (81.2%)	12,421 (81.3%)	12,023 (81.0%)	11,989 (80.7%)	14,760 (18.4%)	14,638 (18.3%)	39,182 (15.5%)	39,048 (15.4%)	0.00
N antidiabetic drugs at index date v3 Copy									
...mean [sd]	0.22 (0.56)	0.22 (0.58)	0.24 (0.62)	0.24 (0.63)	0.23 (0.58)	0.22 (0.57)	0.23 (0.58)	0.22 (0.58)	0.02
...median [IQR]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)			
number of different/distinct medication prescriptions									
...mean [sd]	9.21 (4.49)	9.27 (4.57)	9.70 (4.58)	9.69 (4.72)	9.75 (4.49)	9.84 (4.55)	9.67 (4.50)	9.74 (4.58)	-0.02
...median [IQR]	9.00 (6.00, 12.00)	9.00 (6.00, 12.00)	9.00 (6.00, 12.00)	9.00 (6.00, 12.00)	9.00 (7.00, 12.00)	9.00 (7.00, 12.00)			
Number of Hospitalizations									
...mean [sd]	0.33 (0.61)	0.33 (0.57)	0.38 (0.59)	0.38 (0.58)	0.43 (0.70)	0.43 (0.70)	0.41 (0.67)	0.41 (0.67)	0.00
...median [IQR]	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)			
Number of hospital days									
...mean [sd]	1.71 (4.11)	1.72 (4.67)	1.94 (3.92)	1.92 (4.82)	2.42 (5.05)	2.41 (6.24)	2.26 (4.79)	2.25 (5.87)	0.00
...median [IQR]	0.00 (0.00, 2.00)	0.00 (0.00, 3.00)	0.00 (0.00, 3.00)	0.00 (0.00, 3.00)	0.00 (0.00, 3.00)	0.00 (0.00, 3.00)			
Number of Emergency Department (ED) visits v3									
...mean [sd]	0.75 (1.46)	0.76 (1.44)	0.67 (2.44)	0.69 (2.09)	0.96 (1.92)	1.00 (1.88)	0.89 (1.94)	0.93 (1.86)	-0.02
...median [IQR]	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)			
Number of Office visits									
...mean [sd]	5.55 (4.15)	5.59 (5.91)	6.05 (4.59)	5.98 (4.28)	13.20 (12.77)	13.26 (11.74)	11.18 (11.12)	11.22 (10.24)	0.00
...median [IQR]	5.00 (3.00, 8.00)	5.00 (3.00, 7.00)	5.00 (3.00, 8.00)	5.00 (3.00, 8.00)	10.00 (5.00, 17.00)	10.00 (6.00, 17.00)			
Number of Endocrinologist visits									
...mean [sd]	0.09 (0.86)	0.09 (0.88)	0.12 (1.05)	0.10 (0.95)	0.16 (1.33)	0.16 (1.33)	0.14 (1.24)	0.14 (1.23)	0.00
...median [IQR]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)			
Number of Internal medicine/family medicine visits									
...mean [sd]	9.28 (12.23)	9.34 (12.11)	7.57 (11.65)	7.44 (11.28)	7.89 (8.77)	7.90 (8.87)	8.04 (10.41)	8.04 (10.40)	0.00
...median [IQR]	6.00 (2.00, 12.00)	6.00 (2.00, 12.00)	4.00 (1.00, 9.00)	4.00 (1.00, 9.00)	5.00 (1.00, 11.00)	5.00 (2.00, 11.00)			
Number of Cardiologist visits									
...mean [sd]	5.17 (6.51)	5.26 (7.88)	3.57 (5.21)	3.55 (5.23)	5.65 (7.11)	5.72 (6.54)	5.30 (6.80)	5.36 (6.29)	-0.01
...median [IQR]	3.00 (1.00, 7.00)	4.00 (1.00, 8.00)	2.00 (0.00, 5.00)	2.00 (0.00, 5.00)	3.00 (1.00, 8.00)	4.00 (1.00, 8.00)			
Number of electrocardiograms received v2									
...mean [sd]	2.16 (2.89)	2.23 (2.51)	1.90 (2.42)	1.89 (2.05)	2.32 (2.61)	2.36 (2.40)	2.24 (2.63)	2.28 (2.37)	-0.02
...median [IQR]	1.00 (0.00, 3.00)	2.00 (1.00, 3.00)	1.00 (0.00, 3.00)	1.00 (0.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)			
Number of laboratory tests ordered									
...mean [sd]	0.36 (0.67)	0.37 (0.66)	0.19 (0.50)	0.19 (0.50)	0.38 (0.68)	0.38 (0.68)	0.35 (0.66)	0.35 (0.66)	0.00
...median [IQR]	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)			
Number of creatinine tests ordered									
...mean [sd]	0.07 (0.36)	0.07 (0.37)	0.06 (0.34)	0.06 (0.33)	0.10 (0.42)	0.10 (0.40)	0.09 (0.40)	0.09 (0.39)	0.00
...median [IQR]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)			
Number of BUN tests ordered									
...mean [sd]	0.04 (0.26)	0.04 (0.27)	0.04 (0.25)	0.04 (0.27)	0.06 (0.32)	0.06 (0.30)	0.05 (0.30)	0.05 (0.29)	0.00
...median [IQR]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)			
Number of Tests for microalbuminuria									
...mean [sd]	0.18 (0.62)	0.17 (0.59)	0.08 (0.40)	0.08 (0.40)	0.11 (0.40)	0.11 (0.40)	0.12 (0.44)	0.11 (0.43)	0.02
...median [IQR]	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)			
Total N-district IC90/CD10 diagnoses at the 3rd digit level Copy									
...mean [sd]	9.31 (10.15)	9.08 (10.16)	5.28 (7.97)	5.18 (7.95)	9.65 (11.24)	9.65 (11.37)	9.01 (10.71)	8.97 (10.81)	0.00
...median [IQR]	7.00 (0.00, 14.00)	6.00 (0.00, 14.00)	2.00 (0.00, 7.00)	1.00 (0.00, 7.00)	6.00 (0.00, 15.00)	6.00 (0.00, 15.00)			
For PS									
Hemorrhagic stroke/Other cerebrovascular disease/Procedure (for PS); n (%)	498 (3.3%)	488 (3.2%)	421 (2.8%)	426 (2.9%)	2,424 (3.0%)	3,343 (3.0%)	3,324 (3.0%)		0.00
Occurrence of creatinine tests ordered (for PS); n (%)	843 (5.5%)	852 (5.6%)	705 (4.7%)	700 (4.7%)	6,314 (7.9%)	6,358 (7.9%)	7,862 (7.1%)	7,910 (7.2%)	0.00
Occurrence of BUN tests ordered (for PS); n (%)	448 (2.9%)	467 (3.1%)	406 (2.7%)	414 (2.8%)	3,672 (4.6%)	3,754 (4.7%)	4,526 (4.1%)	4,635 (4.2%)	0.00
Occurrence of chronic renal insufficiency w/o CKD (for PS); n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	ID/IV/!
Chronic kidney disease Stage 1-2 (for PS); n (%)	0 (0.0%)								