

# Replication of the AMPLIFY Anticoagulant Trial in Healthcare Claims Data

NCT 00643201

May 25, 2021

## 1. RCT Details

This section provides a high-level overview of a **published** RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

### 1.1 Title

**Oral Apixaban for the Treatment of Acute Venous Thromboembolism ([AMPLIFY](#))**

### 1.2 Intended aim(s)

To compare the risk of symptomatic, recurrent venous thromboembolism (VTE) in patients with symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), or both for apixaban versus standard therapy of warfarin.

### 1.3 Primary endpoint for replication

The primary outcome of the study was symptomatic, recurrent VTE or death related to VTE

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

Assuming a non-inferiority margin of 1.80, it was determined that 4,094 patients would be needed to achieve 90% power to conclude noninferiority of apixaban over standard therapy at one-sided alpha level of 0.025.

### 1.5 Secondary endpoint for replication (assay sensitivity) and RCT finding

Major bleeding; RR= 0.31 (95% CI 0.17–0.55)

### 1.6 Trial estimate

RR = 0.84 (95% CI 0.60-1.18) comparing apixaban vs standard therapy (Agnelli et al., 2013)

## 2. Person responsible for implementation of replication in Aetion

Dureshahwar Jawaid, MPH implemented the study design in the Aetion Evidence Platform. She is 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)

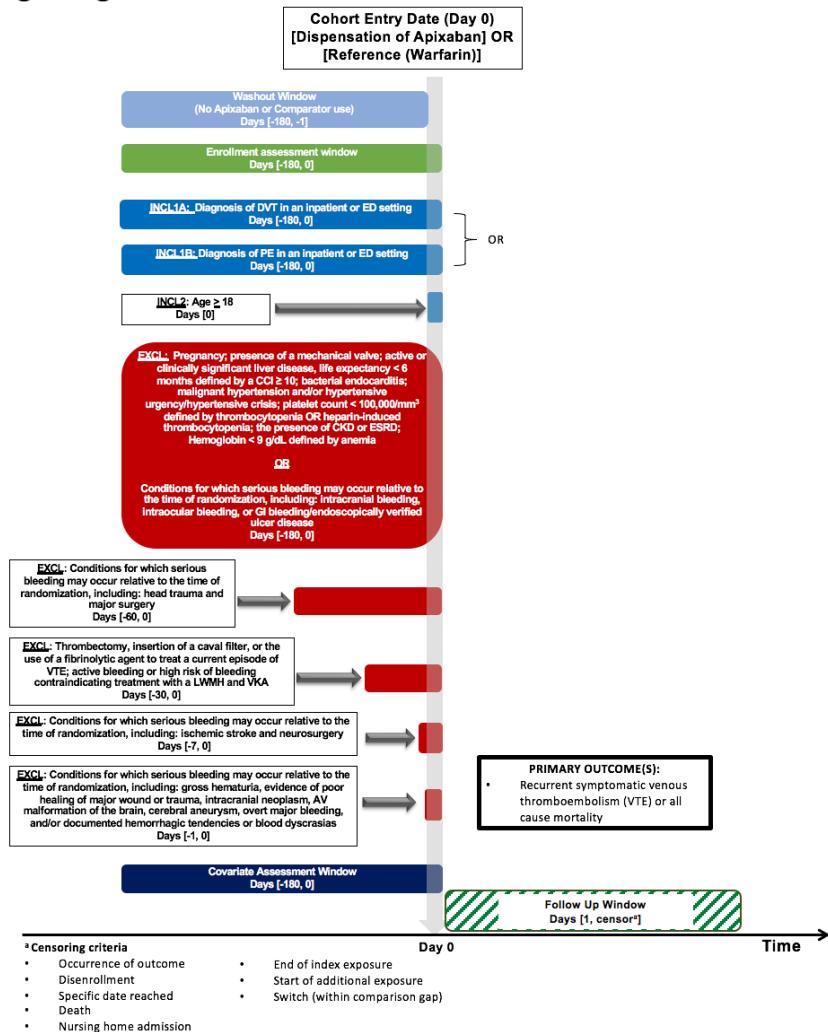
Optum, MarketScan, Medicare

#### 4. Study Design Diagram

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

Figure 1.

#### Design Diagram – AMPLIFY 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 to warfarin users. The patients will be required to have continuous enrollment during a baseline period of 180 days before initiation of apixaban or warfarin (index date). We will restrict the analyses to patients with a diagnosis of proximal DVT, PE, or both.

### 5.2 Important steps for cohort formation

New use of apixaban, exposure, and warfarin, comparator, is defined as no use of either therapy in the 180 days prior to index date.

#### 5.2.1 Eligible cohort entry dates

Market availability of apixaban in the U.S. for treatment of deep vein thrombosis and pulmonary embolism started on August 21, 2014

- For Medicare: August 21, 2014 – December 31, 2017 (end of available data)
- For Marketscan: August 21, 2014 – December 31, 2018 (end of available data)
- For Optum: August 21, 2014 – March 31, 2020 (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

|                                    | Optum                  |                    | Marketscan             |                    | Medicare               |                    |
|------------------------------------|------------------------|--------------------|------------------------|--------------------|------------------------|--------------------|
|                                    | Less Excluded Patients | Remaining Patients | Less Excluded Patients | Remaining Patients | Less Excluded Patients | Remaining Patients |
| All patients                       |                        | 77,673,639         |                        | 200,203,908        |                        | 6,886,908          |
| Did not meet cohort entry criteria | -76,868,532            | 805,107            | -<br>199,645,422       | 558,486            | -4,150,733             | 2,736,175          |

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|                                                                                                                                                                                                                                                                                                                                               |          |         |          |         |            |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|----------|---------|------------|-----------|
| Excluded due to insufficient enrollment                                                                                                                                                                                                                                                                                                       | -101,912 | 703,195 | -39,077  | 519,409 | -53,978    | 2,682,197 |
| Excluded due to prior use of referent                                                                                                                                                                                                                                                                                                         | -347,539 | 355,656 | -307,198 | 212,211 | -1,789,291 | 892,906   |
| Excluded due to prior use of exposure and because patient qualified in >1 exposure category                                                                                                                                                                                                                                                   | -254,675 | 100,981 | -137,453 | 74,763  | -554,606   | 338,300   |
| Excluded based on Age                                                                                                                                                                                                                                                                                                                         | 0        | 100,981 | 0        | 74,758  | -104       | 338,196   |
| Excluded based on Gender                                                                                                                                                                                                                                                                                                                      | 0        | 100,981 | 0        | 74,758  | 0          | 338,196   |
| Excluded based on Use of other NOACs (rivaroxaban, dabigatran, edoxaban)                                                                                                                                                                                                                                                                      | -5,094   | 95,887  | -3118    | 71,640  | -19004     | 319,192   |
| Excluded based on Inclusion # 3a - Acute Symptomatic Proximal DVT                                                                                                                                                                                                                                                                             | -82,653  | 13,234  | -60406   | 11,234  | -277,170   | 42,022    |
| Excluded based on Inclusion # 3b - Acute Symptomatic PE and based on Inclusion # 4 - Age                                                                                                                                                                                                                                                      | -4,641   | 8,593   | -2852    | 8,382   | -21,229    | 20,793    |
| Excluded based on Exclusion # 1 - pregnancy                                                                                                                                                                                                                                                                                                   | -14      | 8,579   | -42      | 8,340   | -22        | 20,771    |
| Excluded based on Exclusion # 6 - Thrombectomy, Insertion of Caval Filter, or Use of Fibrinolytic Agent                                                                                                                                                                                                                                       | -211     | 8,368   | -143     | 8,197   | -24        | 20,747    |
| Excluded based on Exclusion # 7 - Active bleeding (HAS_BLED Score >=3), based on Exclusion # 10A - Mechanical Valve, and based on Exclusion # 11.1 - Intracranial Bleeding                                                                                                                                                                    | -3,708   | 4,660   | -1447    | 6,750   | -11,558    | 9,189     |
| Excluded based on Exclusion # 11.2 - Intraocular Bleeding                                                                                                                                                                                                                                                                                     | 0        | 4,660   | 0        | 6,750   | 0          | 9,189     |
| Excluded based on Exclusion # 11.3 - Gastrointestinal Bleeding                                                                                                                                                                                                                                                                                | -12      | 4,648   | -52      | 6,698   | -78        | 9,111     |
| Excluded based on Exclusion # 11.4 - Head Trauma or Other Major Trauma                                                                                                                                                                                                                                                                        | -60      | 4,588   | -65      | 6,633   | -96        | 9,015     |
| Excluded based on Exclusion # 11.5 - Major Surgery, Exclusion # 11.6 - Ischemic Stroke, Exclusion # 11.7 – Neurosurgery, Exclusion # 11.8 - Gross Hematuria, Exclusion # 11.9 - Non - healing surgical wound, Exclusion # 11.10 - Intracranial neoplasm, arteriovenous malformation or aneurysm, and Exclusion # 11.11 - Overt Major Bleeding | -57      | 4,531   | -33      | 6,600   | -111       | 8,904     |
| Excluded based on Exclusion # 11.12 - Coagulation defects or malignant neoplasm of tissue                                                                                                                                                                                                                                                     | -36      | 4,495   | -20      | 6,580   | -33        | 8,871     |
| Excluded based on Exclusion # 12 - active liver disease                                                                                                                                                                                                                                                                                       | -133     | 4,362   | -142     | 6,438   | -226       | 8,645     |
| Excluded based on Exclusion # 13 - CCI >= 10 and based on Exclusion # 14 - Bacterial Endocarditis                                                                                                                                                                                                                                             | -39      | 4,323   | -33      | 6,405   | -28        | 8,617     |

|                                                                                                                             |     |              |     |              |      |              |
|-----------------------------------------------------------------------------------------------------------------------------|-----|--------------|-----|--------------|------|--------------|
| Excluded based on Exclusion # 15 - Uncontrolled Hypertension and based on Exclusion # 16 - thrombocytopenia                 | -26 | 4,297        | -36 | 6,369        | -78  | 8,539        |
| Excluded based on Exclusion # 17 – anemia, Exclusion # 18 - CKD/ESRD, and Exclusion # 22 - Heparin-induced thrombocytopenia | -33 | 4,264        | -31 | 6,338        | -139 | 8,400        |
| Excluded based on Exclusion # 27 - aspirin (ASA) >165 mg                                                                    | 0   | 4,264        | 0   | 6,338        | 0    | 8,400        |
| Excluded based on Exclusion # 28 - ASA plus clopidogrel or ASA plus ticlopidine                                             | 0   | 4,264        | 0   | 6,338        | 0    | 8,400        |
| <b>Final cohort</b>                                                                                                         |     | <b>4,264</b> |     | <b>6,338</b> |      | <b>8,400</b> |

## 6. Variables

### 6.1 Exposure-related variables:

#### Study drug:

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

#### Comparator:

New initiators of warfarin, defined by no use of apixaban or warfarin in the prior 6 months.

### 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:** VTE and cause-specific mortality
- **Secondary Outcome:** Individual components
  - Hospital admission for VTE (principal diagnosis position)
  - Cause-specific mortality
    - Inpatient mortality identified using discharge status codes from hospitalization for VTE

Safety outcome of interest:

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 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
- Treatment of current episode of VTE with thrombectomy, insertion of caval filter, or use of fibrinolytic agent (streptokinase, alteplase, reteplase, tenecteplase)

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:

For apixaban vs. warfarin

Optum- <https://bwh-dope.aetion.com/projects/details/1484/results/64537/result/0>

Marketscan- <https://bwh-dope.aetion.com/projects/details/1481/results/64536/result/0>

Medicare- <https://bwh-dope.aetion.com/projects/details/1483/results/64535/result/0>

Date conducted: 1/19/21

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/1484/results/64538/result/0>

Marketscan- <https://bwh-dope.aetion.com/projects/details/1481/results/64539/result/0>

Medicare- <https://bwh-dope.aetion.com/projects/details/1483/results/64540/result/0>

Date conducted: 1/19/2021

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 and FDA. Reviewers evaluate the results of the analyses described above in Sections 7 and 8, including numbers of patients, patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power. These parameters are re-evaluated and reported in the subsequent sections, after incorporating feedback and refining the protocol.
- 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: | 11/18/2020 |
| Reviewed by FDA:                             | Ken Quinto       | Date reviewed: | 11/29/2020 |
| Reasons for stopping analysis (if required): |                  |                |            |

## 9. Balance Assessment

**Action report links:**

Optum: <https://bwh-dope.aetion.com/projects/details/1484/results/64541/result/0>

Marketscan: <https://bwh-dope.aetion.com/projects/details/1481/results/64542/result/0>

Medicare: <https://bwh-dope.aetion.com/projects/details/1483/results/64543/result/0>

Date conducted: 1/19/2021

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. 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.

- 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                                                                                                                 | 67 (0.94%)     | 25 (0.70%)     | 42 (1.18%)     |
| Death                                                                                                                         | 103 (1.44%)    | 49 (1.37%)     | 54 (1.51%)     |
| Start of an additional exposure                                                                                               | 232 (3.25%)    | 175 (4.90%)    | 57 (1.60%)     |
| End of index exposure                                                                                                         | 4,701 (65.84%) | 2,202 (61.68%) | 2,499 (70.00%) |
| Specified date reached                                                                                                        | 857 (12.00%)   | 424 (11.88%)   | 433 (12.13%)   |
| End of patient enrollment                                                                                                     | 425 (5.95%)    | 198 (5.55%)    | 227 (6.36%)    |
| Switch to NOACs (for censoring) + nursing home admission + thrombectomy, insertion of caval filter, use of fibrinolytic agent | 755 (10.57%)   | 497 (13.92%)   | 258 (7.23%)    |

- Report follow-up time by treatment group.

| Median Follow-Up Time (Days) [IQR] |                 |              |             |
|------------------------------------|-----------------|--------------|-------------|
| Patient Group                      | Optum           | Marketscan   | Medicare    |
| Overall Patient Population         | 82.5 [38-174.5] | 96 [38-186]  | 74 [38-170] |
| Referent                           | 72 [37-189]     | 88 [38-171]  | 73 [38-161] |
| Exposure                           | 96.5 [38-155]   | 100 [38-195] | 78 [38-183] |

- Report overall risk of the primary outcome.

|                         | Optum | Marketscan | Medicare | Pooled |
|-------------------------|-------|------------|----------|--------|
| Risk per 1,000 patients | 12.93 | 13.13      | 14.66    | 13.74  |

## 10. Final Power Assessment

Date conducted: 12/16/20

- 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.
  - Pooled

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| <b>Non-inferiority Analysis</b> |             |
|---------------------------------|-------------|
| Number of patients matched      | 7,140       |
| Reference                       | 3,570       |
| Exposed                         | 3,570       |
| Risk per 1,000 patients         | 13.74       |
| HR from RCT                     | 0.84        |
| Alpha (2-sided)                 | 0.05        |
| Non-inferiority margin          | 1.8         |
|                                 |             |
| Number of events expected       | 98.1036     |
| Power                           | 0.965194245 |

- Optum

| <b>Non-inferiority Analysis</b> |             |
|---------------------------------|-------------|
| Number of patients matched      | 980         |
| Reference                       | 490         |
| Exposed                         | 490         |
| Risk per 1,000 patients         | 12.93       |
| HR from RCT                     | 0.84        |
| Alpha (2-sided)                 | 0.05        |
| Non-inferiority margin          | 1.8         |
|                                 |             |
| Number of events expected       | 12.6714     |
| Power                           | 0.273097221 |

○ Marketscan

| <b>Non-inferiority Analysis</b> |             |
|---------------------------------|-------------|
| Number of patients matched      | 2,762       |
| Reference                       | 1,381       |
| Exposed                         | 1,381       |
| Risk per 1,000 patients         | 13.13       |
| Assumed HR from RCT             | 0.84        |
| Alpha (2-sided)                 | 0.05        |
| Non-inferiority margin          | 1.8         |
|                                 |             |
| Number of events expected       | 36.26506    |
| Power                           | 0.631133873 |

o Medicare

| Non-inferiority Analysis   |             |
|----------------------------|-------------|
| Number of patients matched | 3,398       |
| Reference                  | 1,699       |
| Exposed                    | 1,699       |
| Risk per 1,000 patients    | 14.66       |
| Assumed HR from RCT        | 0.84        |
| Alpha (2-sided)            | 0.05        |
| Non-inferiority margin     | 1.8         |
|                            |             |
| Number of events expected  | 49.81468    |
| Power                      | 0.767185633 |

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

|                                              |              |                |            |
|----------------------------------------------|--------------|----------------|------------|
| Reviewed by PI:                              | Shirley Wang | Date reviewed: | 12/24/2020 |
| Reviewed by FDA:                             | Ken Quinto   | Date reviewed: | 01/18/2020 |
| 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](https://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

Agnelli G, Buller HR, Cohen A, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. *N Engl J Med.* 2013; 369:799-808.

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

# Appendix A

| AMPLIFY trial definitions                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Implementation in routine care                                                                                                                                                                                                                              | Please see the following Google Drive for further details or any missing information:<br><a href="https://drive.google.com/drive/folders/1WD618wrvwYIeaXzflTcuK-VCcnb6b-gV?usp=sharing">https://drive.google.com/drive/folders/1WD618wrvwYIeaXzflTcuK-VCcnb6b-gV?usp=sharing</a> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Trial details- Secondary approval, Successful NI with label change                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  | 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 ( <a href="#">link above</a> ). 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: <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5300333/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5300333/</a> |
| EXPOSURE vs. COMPARISON                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  | References/Rationale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Apixaban (dose of 10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months) verus conventional therapy (subcutaneous enoxaparin, followed by warfarin)                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  | Color coding                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| PRIMARY OUTCOME                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                             | Apixaban vs. Warfarin                                                                                                                                                                                                                                                            | Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| The primary efficacy outcome was recurrent symptomatic venous thromboembolism or death related to venous thromboembolism.                                                                                                                                                                                                                                                                                                                                                                            | Measured 1 day after drug initiation                                                                                                                                                                                                                        | Fang MC, Fan D, Sung SH, et al. Validity of Using Inpatient and Outpatient Administrative Codes to Identify Acute Venous Thromboembolism: The CVRI VTE Study. <i>Med Care</i> . 2017;55(12):e137-e143.                                                                           | Can be replicated in claims<br>Can be intermediately measured in claims                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| INCLUSION CRITERIA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  | Can't be measured in claims                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Signed Written Informed Consent                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | N/A                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                  | Can't be measured in claims but not important for the analysis                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Subjects whose index event was either unprovoked OR provoked with a risk for recurrence as described in the eligibility checklist                                                                                                                                                                                                                                                                                                                                                                    | N/A                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Either of the following:                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| • Acute symptomatic proximal deep vein thrombosis (DVT) with evidence of proximal thrombosis that involves at least the popliteal vein or a more proximal vein, demonstrated by imaging with: - compression ultrasound (CUS), including grey-scale or color-coded Doppler, OR - ascending contrast venography                                                                                                                                                                                        | Measured 180 days prior to and including day of drug initiation in any diagnosis position and in an inpatient or ED care setting<br><br><b>Deep vein thrombosis (DVT):</b><br>ICD-9 Dx: 451.xx, 453.xx<br>ICD-10 Dx: I26.xx, I80.xx, I81.xx, I82.xx, I26.xx |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| • Acute symptomatic PE with evidence of thrombosis demonstrated by imaging as follows:<br>- an intraluminal filling defect in segmental or more proximal branches on spiral computed tomography (CT) scan; or<br>- an intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or<br>- a perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scan (VPLS) | Measured 180 days prior to and including day of drug initiation in any diagnosis position and in an inpatient or ED care setting<br><br><b>Pulmonary embolism (PE):</b><br>ICD-9 Dx: 415.xx<br>ICD-10 Dx: I26.xx                                            |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Men and women, ages 18 years or greater                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Measured at day of drug initiation<br>Age $\geq 18$                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. (Additional details in <a href="#">Supplementary Appendix</a> )                                                                                                                                                                                                                                          | N/A                                                                                                                                                                                                                                                         | Criteria captured as an exclusion criteria in the Pregnancy measure                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG]) within 24 hours prior to the start of investigational product.                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| EXCLUSION CRITERIA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| WOCBP who are unwilling or unable to use an acceptable method of birth control (such as 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 avoid pregnancy for the entire study.                                                                                                                               | Measured 180 days prior to and including day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting<br><br>See 'Pregnancy' sheet for codes                                                                             |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Women who are pregnant or breastfeeding.                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Women with a positive pregnancy test on enrollment or prior to investigational product administration.                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Subjects with a provoked index event without the existence of a persistent risk factor for recurrence as described in the eligibility checklist                                                                                                                                                                                                                                                                                                                                                      | N/A                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Less than 6 months of anticoagulation planned for the most recent DVT or pulmonary embolism (PE) (index event)                                                                                                                                                                                                                                                                                                                                                                                       | N/A                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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| <p>Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current episode of venous thromboembolism (VTE).</p>                                                      | <p>Measured 30 days prior and including the day of drug initiation in any diagnosis position in an inpatient or ED care setting</p> <p><u>Thrombectomy:</u><br/>CPT codes: 37184, 37185, 37186, 37187, 37188<br/>HCPCS codes: C1757</p> <p><u>Caval filter:</u><br/>CPT codes: 37191, 37192, 37193<br/>HCPCS codes: C1880</p> <p><u>Fibrinolytic agent:</u><br/>streptokinase, alteplase, reteplase, tenecteplase</p> | <p>Components will act as both exclusion criterion and censoring events</p>                                                                                                           |  |
| <p>Active bleeding or high risk for bleeding contraindicating treatment with low-molecularweight heparin (LMWH) and a vitamin K antagonist (VKA)</p>                                                | <p>Measured 30 days prior to and including the day of drug initiation</p> <p>HAS-BLED score &gt;=3</p>                                                                                                                                                                                                                                                                                                                | <p>Major bleeding risk 5.8% per year for score 3</p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4407886/">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4407886/</a></p> |  |
| <p>Subjects with cancer who will be treated for 6 months or more with LMWH therapy</p>                                                                                                              | <p>N/A</p>                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                       |  |
| <p>Subjects with contraindications according to the local prescribing information of enoxaparin or warfarin</p>                                                                                     | <p>N/A</p>                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                       |  |
| <p>Subjects with an indication, other than VTE, intended for long-term treatment with a VKA such as:</p>                                                                                            | <p>N/A</p>                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                       |  |
| <p>Mechanical valve</p>                                                                                                                                                                             | <p>Measured 180 days prior to and including the drug initiation in any diagnosis position and in an inpatient or outpatient care setting</p> <p><u>Mechanical valve</u><br/>ICD-9 Dx: V43.3x<br/>ICD-10 Dx: Z95.2x, Z95.3x, Z95.4x<br/>ICD-9 Px: 35.0x, 35.2x, 35.3x<br/>ICD-10 Px: O2RGxxx, O2RFxxx, O2RHxxx, O2RJxxx, O2QGxxx, O2QFxxx, O2QHxxx, O2QJxxx</p>                                                        |                                                                                                                                                                                       |  |
| <p>Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism. Subjects with atrial fibrillation that appears to be associated with acute PE may participate.</p> | <p>N/A</p>                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                       |  |
| <p>Conditions for which serious bleeding may occur and the time of exclusion relative to the time of randomization:</p> <p>* 6 months</p>                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                       |  |
| <p>Intracranial bleeding</p>                                                                                                                                                                        | <p>Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient care setting</p> <p><u>Intracranial hemorrhage:</u><br/>ICD-9 Dx: 430.xx, 431.xx, 432.xx<br/>ICD-10 Dx: I60.xx, I61.xx, I62.xx</p>                                                                                                                                                               |                                                                                                                                                                                       |  |
| <p>Intraocular bleeding</p>                                                                                                                                                                         | <p>Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient care setting</p> <p><u>Vitreous hemorrhage:</u><br/>ICD-9 Dx: 379.23<br/>ICD-10 Dx: H43.1x</p> <p><u>Retinal hemorrhage:</u><br/>ICD-9 Dx: 362.81<br/>ICD-10 Dx: H35.6x, H35.73</p> <p><u>Hemophthalmos</u><br/>ICD-9 Dx: 360.43, 459.0x, 364.41<br/>ICD-10 Dx: H44.8xx</p>                      |                                                                                                                                                                                       |  |

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|                                                             | <p>Measured 180 days prior to and including day of drug initiation in any diagnosis position and in an inpatient care setting</p> <p><u>Gastrointestinal bleeding:</u></p> <p>ICD-9 Dx:<br/>531.0x gastric ulcer w/ hemorrhage,<br/>531.2x gastric ulcer w/ hemorrhage and perforation<br/>531.4x<br/>531.6x chronic / unspecified ulcer w/ hemorrhage<br/>532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x,<br/>534.0x, 534.2x, 534.4x, 534.6x, 562.0x, 562.1x, 568.8x, 569.3x, 569.8x<br/>578.x Gastrointestinal hemorrhage</p> <p>ICD-10 Dx:<br/>K25.0x, K25.2x, K25.6x, K26.0x, K26.2x, K26.4x, K26.6x, K27.0x, K27.2x, K27.4x, K27.6x,<br/>K28.0x, K28.2x, K28.4x, K28.6x, K55.21, K57.xx, K62.5x, K63.1x, K63.81, K66.1x, K92.0x,<br/>K92.1x, K92.2x</p> <p>ICD-9 Px: 44.43<br/>ICD-10 Px: 0W3PBZZ</p> |  |  |
| • 2 months                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |
| Head trauma or other major trauma                           | <p>Measured 60 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</p> <p>See 'Major Trauma' sheet for codes</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| Major surgery                                               | <p>Measured 60 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</p> <p>Major surgery selected from codes range 35.x- 84.x</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| • 1 week                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |
| - Ischemic stroke                                           | <p>Measured 7 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient care setting</p> <p><u>Ischemic stroke:</u></p> <p>ICD-9 Dx: 433.x, 434. x, 436.xx</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |  |
| - Neurosurgery                                              | <p>Measured 7 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient care setting</p> <p><u>Neurosurgery:</u></p> <p>ICD-9 Px:<br/>01.xx, 02.xx, 03.xx, 04.xx, 05.xx<br/>ICD-10 Px:<br/>00xxxx</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |  |
| • Time of randomization                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |  |
| - Gross hematuria                                           | <p>Measured 1 day prior to and including the day of drug initiation in any diagnosis position in an inpatient or outpatient care setting</p> <p><u>Gross hematuria:</u></p> <p>ICD-9 Dx: 599.71 (not 599.7x)<br/>ICD-10 Dx: R31.0</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |  |
| - Evidence of poor healing of a major wound or major trauma | <p>Measured 1 day prior and including the day of drug initiation in any diagnosis position in an inpatient or outpatient care setting</p> <p><u>Non-healing surgical wound</u></p> <p>ICD-9 Dx: 998.33<br/>ICD-10 Dx: T81.33XA</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |  |
| - Planned major surgery                                     | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |  |

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| <p>- Intracranial neoplasm, arteriovenous malformation or aneurysm</p>                                                                                                                                                                                                                                                                                                                                                                                  | <p><b>Measured 1 day prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</b></p> <p><u>Intracranial neoplasm:</u><br/>ICD-9 Dx: 239.6x, 191.xx, 225.xx<br/>ICD-10 Dx: D49.6x, C71.x, D33.0x, D33.1x, D33.2x</p> <p><u>AV malformation of brain:</u><br/>ICD-9 Dx: 747.81<br/>ICD-10 Dx: Q28.2x, Q28.3x</p> <p><u>Cerebral aneurysm</u><br/>ICD-9 Dx: 437.3x<br/>ICD-10 Dx: I67.1x</p> |  |  |
| <p>- Overt major bleeding</p>                                                                                                                                                                                                                                                                                                                                                                                                                           | <p><b>Measured 1 day prior and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</b></p> <p>See 'Major Bleeding' sheet for codes</p>                                                                                                                                                                                                                                                             |  |  |
| <p>- Documented hemorrhagic tendencies or blood dyscrasias</p>                                                                                                                                                                                                                                                                                                                                                                                          | <p><b>Measured 1 day prior and including the day of drug initiation in any diagnosis position in an inpatient or outpatient care setting</b></p> <p><u>Coagulation defects</u><br/>ICD-9 Dx: 286.x<br/>ICD-10 Dx: D65.x, D66.x, D67.xx, D68.xx, D69.xx</p> <p><u>Malignant Neoplasm Of Lymphatic And Hematopoietic Tissue</u><br/>ICD-9 Dx: 200.xx to 209.xx<br/>ICD-10 Dx: C81.xx to C96.xx</p>                                                             |  |  |
| <p>Active and clinically significant liver disease (eg, hepatorenal syndrome)</p>                                                                                                                                                                                                                                                                                                                                                                       | <p><b>Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</b></p> <p><u>Liver disease</u><br/>ICD-9 Dx:<br/>070.xx, 570.xx-573.xx<br/>456.0x-456.2x, 576.8x, 782.4x, 789.5x<br/>ICD-9 Px:<br/>39.1x, 42.91</p> <p><u>Hepatorenal syndrome</u><br/>ICD-9 Dx: 572.4<br/>ICD-10 Dx: K76.7</p>                                                                          |  |  |
| <p>Life expectancy &lt;6 months</p>                                                                                                                                                                                                                                                                                                                                                                                                                     | <p><b>Measured 180 days prior to drug initiation in any diagnosis position and in an inpatient or outpatient care setting</b></p> <p>CCI&gt;=10</p>                                                                                                                                                                                                                                                                                                          |  |  |
| <p>Bacterial endocarditis</p>                                                                                                                                                                                                                                                                                                                                                                                                                           | <p><b>Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</b></p> <p><u>Bacterial endocarditis</u><br/>ICD-9 Dx: 421.0x<br/>ICD-10 Dx: I33.0x</p>                                                                                                                                                                                                                   |  |  |
| <p>Uncontrolled hypertension: systolic blood pressure &gt;180 mm Hg or diastolic blood pressure &gt;100 mm Hg; (subjects who have a transient, higher blood pressure elevation associated with acute PE [upper limit: systolic blood pressure 200 mm Hg or diastolic blood pressure 100 mm Hg] may enter the study;) elevated blood pressure that is persistent 1-2 days after the index DVT or PE should be treated according to local guidelines.</p> | <p><b>Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</b></p> <p><u>Malignant hypertension</u><br/>ICD-9 Dx: 401.0x</p> <p><u>Hypertensive urgency/ Hypertensive crisis</u><br/>ICD-10 Dx : I16.xx</p>                                                                                                                                                          |  |  |
| <p>Platelet count &lt;100,000/mm<sup>3</sup></p>                                                                                                                                                                                                                                                                                                                                                                                                        | <p><b>Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting</b></p> <p><u>Thrombocytopenia</u><br/>ICD-9 Dx: 287.3x, 287.4x, 287.5x<br/>ICD-10 Dx: D69.3x, D69.4x, D69.5x, D69.6x</p>                                                                                                                                                                                 |  |  |

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| Hemoglobin <9 g/dL                                                                                                                                                                                                                                                                                                         | Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting<br><br><u>Anemia:</u><br>ICD-9 Dx:<br>282.x (hereditary hemolytic anemias)<br>283.x (acquired hemolytic anemias, autoimmune etc)<br>284.x (aplastic anemia and other bone marrow failure syndromes)                                                                                                                  |  |  |
| Serum creatinine >2.5 mg/dL (221 umol/L)                                                                                                                                                                                                                                                                                   | Measured 180 days prior to and including the day of drug initiation in any diagnosis position and in an inpatient or an outpatient care setting<br><br><u>CKD, ESRD:</u><br>ICD-9 Dx:<br>585.4x, 585.5x, 585.6x: CKD 4, 5, ESRD<br>586.xx: renal failure<br><br>ICD-10 Dx:<br>N19.xx<br>N18.4x Chronic kidney disease, stage 4 (severe)<br>N18.5x Chronic kidney disease, stage 5<br>N18.6x End stage renal disease<br>N18.9x Chronic kidney disease, unspecified |  |  |
| Calculated creatinine clearance <25 ml/min                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |  |
| ALT or AST >2 times upper limit of normal                                                                                                                                                                                                                                                                                  | N/A<br>(Incorporated into moderate/severe liver disease above)                                                                                                                                                                                                                                                                                                                                                                                                    |  |  |
| Total bilirubin >1.5 times upper limit of normal (unless an alternative causative factor is identified [eg, Gilbert's syndrome]).                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |  |
| Heparin-induced thrombocytopenia;                                                                                                                                                                                                                                                                                          | Measured 180 days prior to and including the day of drug initiation in any position and in an inpatient or outpatient care setting<br><br><u>Heparin induced thrombocytopenia (HIT)</u><br>ICD-9 Dx: 289.84<br>ICD-10 Dx: D75.82                                                                                                                                                                                                                                  |  |  |
| Allergic reaction to unfractionated heparin, LMWH, fondaparinux, or any VKA.                                                                                                                                                                                                                                               | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| DVT or PE treatment with more than two doses of fondaparinux or a LMWH that is labeled for once-daily dosing, or more than three doses of a LMWH that is labeled for twice-daily dosing, or continuous infusion of unfractionated heparin for more than 36 hours, before the first administration of study drug; and/or -- | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| DVT or PE treatment with more than two doses of oral VKA therapy before the first administration of study drug.                                                                                                                                                                                                            | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| Treatment with apixaban in a previous clinical trial.                                                                                                                                                                                                                                                                      | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| Subjects requiring aspirin (ASA) >165 mg/day at randomization.                                                                                                                                                                                                                                                             | Measured 1 day prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting<br><br>Aspirin (prescription only)<br>dose greater than >165 mg                                                                                                                                                                                                                                                         |  |  |
| Subjects requiring dual antiplatelet therapy (ASA plus clopidogrel or ASA plus ticlopidine) at randomization. Subjects who transition from dual antiplatelet therapy to monotherapy prior to randomization will be eligible for the trial.                                                                                 | Measured 1 day prior to and including the day of drug initiation in any diagnosis position and in an inpatient or outpatient care setting<br>(both concurrent prescription and combination products)<br>Aspirin + clopidogrel<br>or<br>Aspirin + ticlopidine                                                                                                                                                                                                      |  |  |
| Prisoners or subjects who are involuntarily incarcerated                                                                                                                                                                                                                                                                   | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness                                                                                                                                                                                                  | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| Receiving concurrent investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, eg, investigating a new dosing regimen for an approved indication)              | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study                                                                                                                                                                                     | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |
| Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol.                                                                                                                                 | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |  |

# Appendix A

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| <u>Trial ID</u>                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <u>Trial Name (with web links)</u> | <a href="#">AMPLIFY</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <u>Trial Name (with pdf links)</u> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <u>NCT</u>                         | <a href="#">NCT00643201</a>                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <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>                        | 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <u>Measurable endpoint</u>         | Percentage of Participants With Symptomatic Recurrent Venous Thromboembolism [VTE] (i.e. the Composite of Recurrent Deep Vein Thrombosis [DVT] or Fatal or Non-fatal Pulmonary Embolism [PE]) Until the Intended End of Study Treatment                                                                                                                                                                                                                                  |
| <u>Exposure</u>                    | Apixaban                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <u>Comparator</u>                  | Enoxaparin, Warfarin                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <u>Population</u>                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <u>Trial finding</u>               | HR = 0.84 (95%CI 0.60–1.18)                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <u>Notes</u>                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <u>No. of Patients</u>             | 5,395                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <u>Non-inferiority margin</u>      | HR = 1.8                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <u>Assay Sens. Endpoint</u>        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <u>Assay Sens. Finding</u>         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <u>Power</u>                       | 0.90; With the use of an estimated incidence of the primary efficacy outcome of 3% at 6 months with conventional therapy and a noninferiority margin of 1.80 for the relative risk, we calculated that we would need to enroll 4094 patients for the study to have 90% power to show the noninferiority of apixaban, at a one-sided alpha level of 0.025. This sample was increased to 4816 patients to account for up to 15% of patients discontinuing treatment early. |

# Appendix A

| Title          |                                                                                           |
|----------------|-------------------------------------------------------------------------------------------|
| Major Bleeding |                                                                                           |
| ICD-9 Dx       |                                                                                           |
| 423            | HEMOPERICARDIUM                                                                           |
| 430            | SUBARACHNOID HEMORRHAGE                                                                   |
| 431            | INTRACEREBRAL HEMORRHAGE                                                                  |
| 432            | NONTRAUMATIC EXTRADURAL HEMORRHAGE                                                        |
| 432.1          | SUBDURAL HEMORRHAGE                                                                       |
| 432.9          | UNSPECIFIED INTRACRANIAL HEMORRHAGE                                                       |
| 459            | HEMORRHAGE UNSPECIFIED                                                                    |
| 531            | ACUTE GASTRIC ULCER WITH HEMORRHAGE                                                       |
| 531            | ACUTE GASTRIC ULCER WITH HEMORRHAGE WITHOUT OBSTRUCTION                                   |
| 531.01         | ACUTE GASTRIC ULCER WITH HEMORRHAGE WITH OBSTRUCTION                                      |
| 531.2          | ACUTE GASTRIC ULCER WITH HEMORRHAGE AND PERFORATION                                       |
| 531.2          | ACUTE GASTRIC ULCER WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION                   |
| 531.21         | ACUTE GASTRIC ULCER WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION                      |
| 531.4          | CHRONIC OR UNSPECIFIED GASTRIC ULCER WITH HEMORRHAGE                                      |
| 531.4          | CHRONIC OR UNSPECIFIED GASTRIC ULCER WITH HEMORRHAGE WITHOUT OBSTRUCTION                  |
| 531.41         | CHRONIC OR UNSPECIFIED GASTRIC ULCER WITH HEMORRHAGE WITH OBSTRUCTION                     |
| 531.6          | CHRONIC OR UNSPECIFIED GASTRIC ULCER WITH HEMORRHAGE AND PERFORATION                      |
| 531.6          | CHRONIC OR UNSPECIFIED GASTRIC ULCER WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION  |
| 531.61         | CHRONIC OR UNSPECIFIED GASTRIC ULCER WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION     |
| 532            | ACUTE DUODENAL ULCER WITH HEMORRHAGE                                                      |
| 532            | ACUTE DUODENAL ULCER WITH HEMORRHAGE WITHOUT OBSTRUCTION                                  |
| 532.01         | ACUTE DUODENAL ULCER WITH HEMORRHAGE WITH OBSTRUCTION                                     |
| 532.2          | ACUTE DUODENAL ULCER WITH HEMORRHAGE AND PERFORATION                                      |
| 532.2          | ACUTE DUODENAL ULCER WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION                  |
| 532.21         | ACUTE DUODENAL ULCER WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION                     |
| 532.4          | CHRONIC OR UNSPECIFIED DUODENAL ULCER WITH HEMORRHAGE                                     |
| 532.4          | CHRONIC OR UNSPECIFIED DUODENAL ULCER WITH HEMORRHAGE WITHOUT OBSTRUCTION                 |
| 532.41         | CHRONIC OR UNSPECIFIED DUODENAL ULCER WITH HEMORRHAGE WITH OBSTRUCTION                    |
| 532.6          | CHRONIC OR UNSPECIFIED DUODENAL ULCER WITH HEMORRHAGE AND PERFORATION                     |
| 532.6          | CHRONIC OR UNSPECIFIED DUODENAL ULCER WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION |
| 532.61         | CHRONIC OR UNSPECIFIED DUODENAL ULCER WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION    |

## Appendix A

|        |                                                                                                             |
|--------|-------------------------------------------------------------------------------------------------------------|
| 533    | ACUTE PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE                                                      |
| 533    | ACUTE PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE WITHOUT OBSTRUCTION                                  |
| 533.01 | ACUTE PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE WITH OBSTRUCTION                                     |
| 533.2  | ACUTE PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE AND PERFORATION                                      |
| 533.2  | ACUTE PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION                  |
| 533.21 | ACUTE PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION                     |
| 533.4  | CHRONIC OR UNSPECIFIED PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE                                     |
| 533.4  | CHRONIC OR UNSPECIFIED PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE WITHOUT OBSTRUCTION                 |
| 533.41 | CHRONIC OR UNSPECIFIED PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE WITH OBSTRUCTION                    |
| 533.6  | CHRONIC OR UNSPECIFIED PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE AND PERFORATION                     |
| 533.6  | CHRONIC OR UNSPECIFIED PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION |
| 533.61 | CHRONIC OR UNSPECIFIED PEPTIC ULCER OF UNSPECIFIED SITE WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION    |
| 534    | ACUTE GASTROJEJUNAL ULCER WITH HEMORRHAGE                                                                   |
| 534    | ACUTE GASTROJEJUNAL ULCER WITH HEMORRHAGE WITHOUT OBSTRUCTION                                               |
| 534.01 | ACUTE GASTROJEJUNAL ULCER WITH HEMORRHAGE WITH OBSTRUCTION                                                  |
| 534.2  | ACUTE GASTROJEJUNAL ULCER WITH HEMORRHAGE AND PERFORATION                                                   |
| 534.2  | ACUTE GASTROJEJUNAL ULCER WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION                               |
| 534.21 | ACUTE GASTROJEJUNAL ULCER WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION                                  |
| 534.4  | CHRONIC OR UNSPECIFIED GASTROJEJUNAL ULCER WITH HEMORRHAGE                                                  |
| 534.4  | CHRONIC OR UNSPECIFIED GASTROJEJUNAL ULCER WITH HEMORRHAGE WITHOUT OBSTRUCTION                              |
| 534.41 | CHRONIC OR UNSPECIFIED GASTROJEJUNAL ULCER WITH HEMORRHAGE WITH OBSTRUCTION                                 |
| 534.6  | CHRONIC OR UNSPECIFIED GASTROJEJUNAL ULCER WITH HEMORRHAGE AND PERFORATION                                  |
| 534.6  | CHRONIC OR UNSPECIFIED GASTROJEJUNAL ULCER WITH HEMORRHAGE AND PERFORATION WITHOUT OBSTRUCTION              |
| 534.61 | CHRONIC OR UNSPECIFIED GASTROJEJUNAL ULCER WITH HEMORRHAGE AND PERFORATION WITH OBSTRUCTION                 |
| 562.02 | DIVERTICULOSIS OF SMALL INTESTINE WITH HEMORRHAGE                                                           |
| 562.03 | DIVERTICULITIS OF SMALL INTESTINE WITH HEMORRHAGE                                                           |
| 562.12 | DIVERTICULOSIS OF COLON WITH HEMORRHAGE                                                                     |
| 562.13 | DIVERTICULITIS OF COLON WITH HEMORRHAGE                                                                     |
| 568.81 | HEMOPERITONEUM (NONTRAUMATIC                                                                                |
| 569.3  | HEMORRHAGE OF RECTUM AND ANUS                                                                               |
| 569.83 | PERFORATION OF INTESTINE                                                                                    |
| 569.85 | ANGIODYSPLASIA OF INTESTINE WITH HEMORRHAGE                                                                 |
| 569.86 | DIEULAFOY LESION (HEMORRHAGIC) OF INTESTINE                                                                 |
| 578    | HEMATEMESIS                                                                                                 |
| 578.1  | BLOOD IN STOOL                                                                                              |

## Appendix A

|                  |                                                                                      |
|------------------|--------------------------------------------------------------------------------------|
| 578.9            | HEMORRHAGE OF GASTROINTESTINAL TRACT UNSPECIFIED                                     |
| 719.1            | HEMARTHROSIS                                                                         |
| 719.1            | HEMARTHROSIS SITE UNSPECIFIED                                                        |
| 719.11           | HERARTHROSIS INVOLVING SHOULDER REGION                                               |
| 719.12           | HEMARTHROSIS INVOLVING UPPER ARM                                                     |
| 719.13           | HEMARTHROSIS INVOLVING FOREARM                                                       |
| 719.14           | HEMARTHROSIS INVOLVING HAND                                                          |
| 719.15           | HEMARTHROSIS INVOLVING PELVIC REGION AND THIGH                                       |
| 719.16           | HEMARTHROSIS INVOLVING LOWER LEG                                                     |
| 719.17           | HEMARTHROSIS INVOLVING ANKLE AND FOOT                                                |
| 719.18           | HEMARTHROSIS INVOLVING OTHER SPECIFIED SITES                                         |
| 719.19           | HEMARTHROSIS INVOLVING MULTIPLE SITES                                                |
|                  |                                                                                      |
| <b>ICD-10 Dx</b> |                                                                                      |
| I31.2            | Hemopericardium, not elsewhere classified                                            |
| I60.00           | Nontraumatic subarachnoid hemorrhage from unspecified carotid siphon and bifurcation |
| I60.01           | Nontraumatic subarachnoid hemorrhage from right carotid siphon and bifurcation       |
| I60.02           | Nontraumatic subarachnoid hemorrhage from left carotid siphon and bifurcation        |
| I60.10           | Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery         |
| I60.11           | Nontraumatic subarachnoid hemorrhage from right middle cerebral artery               |
| I60.12           | Nontraumatic subarachnoid hemorrhage from left middle cerebral artery                |
| I60.2            | Nontraumatic subarachnoid hemorrhage from anterior communicating artery              |
| I60.30           | Nontraumatic subarachnoid hemorrhage from unspecified posterior communicating artery |
| I60.31           | Nontraumatic subarachnoid hemorrhage from right posterior communicating artery       |
| I60.32           | Nontraumatic subarachnoid hemorrhage from left posterior communicating artery        |
| I60.4            | Nontraumatic subarachnoid hemorrhage from basilar artery                             |
| I60.50           | Nontraumatic subarachnoid hemorrhage from unspecified vertebral artery               |
| I60.51           | Nontraumatic subarachnoid hemorrhage from right vertebral artery                     |
| I60.52           | Nontraumatic subarachnoid hemorrhage from left vertebral artery                      |
| I60.6            | Nontraumatic subarachnoid hemorrhage from other intracranial arteries                |
| I60.7            | Nontraumatic subarachnoid hemorrhage from unspecified intracranial artery            |
| I60.8            | Other nontraumatic subarachnoid hemorrhage                                           |
| I60.9            | Nontraumatic subarachnoid hemorrhage, unspecified                                    |
| I61.0            | Nontraumatic intracerebral hemorrhage in hemisphere, subcortical                     |
| I61.1            | Nontraumatic intracerebral hemorrhage in hemisphere, cortical                        |

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|        |                                                                                             |
|--------|---------------------------------------------------------------------------------------------|
| I61.2  | Nontraumatic intracerebral hemorrhage in hemisphere, unspecified                            |
| I61.3  | Nontraumatic intracerebral hemorrhage in brain stem                                         |
| I61.4  | Nontraumatic intracerebral hemorrhage in cerebellum                                         |
| I61.5  | Nontraumatic intracerebral hemorrhage, intraventricular                                     |
| I61.6  | Nontraumatic intracerebral hemorrhage, multiple localized                                   |
| I61.8  | Other nontraumatic intracerebral hemorrhage                                                 |
| I61.9  | Nontraumatic intracerebral hemorrhage, unspecified                                          |
| I62.00 | Nontraumatic subdural hemorrhage, unspecified                                               |
| I62.01 | Nontraumatic acute subdural hemorrhage                                                      |
| I62.02 | Nontraumatic subacute subdural hemorrhage                                                   |
| I62.03 | Nontraumatic chronic subdural hemorrhage                                                    |
| I62.1  | Nontraumatic extradural hemorrhage                                                          |
| I62.9  | Nontraumatic intracranial hemorrhage, unspecified                                           |
| K25.0  | Acute gastric ulcer with hemorrhage                                                         |
| K25.2  | Acute gastric ulcer with both hemorrhage and perforation                                    |
| K25.4  | Chronic or unspecified gastric ulcer with hemorrhage                                        |
| K25.6  | Chronic or unspecified gastric ulcer with both hemorrhage and perforation                   |
| K26.0  | Acute duodenal ulcer with hemorrhage                                                        |
| K26.2  | Acute duodenal ulcer with both hemorrhage and perforation                                   |
| K26.4  | Chronic or unspecified duodenal ulcer with hemorrhage                                       |
| K26.6  | Chronic or unspecified duodenal ulcer with both hemorrhage and perforation                  |
| K27.0  | Acute peptic ulcer, site unspecified, with hemorrhage                                       |
| K27.2  | Acute peptic ulcer, site unspecified, with both hemorrhage and perforation                  |
| K27.4  | Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage                      |
| K27.6  | Chronic or unspecified peptic ulcer, site unspecified, with both hemorrhage and perforation |
| K28.0  | Acute gastrojejunal ulcer with hemorrhage                                                   |
| K28.2  | Acute gastrojejunal ulcer with both hemorrhage and perforation                              |
| K28.4  | Chronic or unspecified gastrojejunal ulcer with hemorrhage                                  |
| K28.6  | Chronic or unspecified gastrojejunal ulcer with both hemorrhage and perforation             |
| K55.21 | Angiodysplasia of colon with hemorrhage                                                     |
| K56.60 | Unspecified intestinal obstruction                                                          |
| K57.01 | Diverticulitis of small intestine with perforation and abscess with bleeding                |
| K57.11 | Diverticulosis of small intestine without perforation or abscess with bleeding              |
| K57.13 | Diverticulitis of small intestine without perforation or abscess with bleeding              |
| K57.21 | Diverticulitis of large intestine with perforation and abscess with bleeding                |

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|         |                                                                                               |
|---------|-----------------------------------------------------------------------------------------------|
| K57.31  | Diverticulosis of large intestine without perforation or abscess with bleeding                |
| K57.33  | Diverticulitis of large intestine without perforation or abscess with bleeding                |
| K57.41  | Diverticulitis of both small and large intestine with perforation and abscess with bleeding   |
| K57.51  | Diverticulosis of both small and large intestine without perforation or abscess with bleeding |
| K57.53  | Diverticulitis of both small and large intestine without perforation or abscess with bleeding |
| K57.81  | Diverticulitis of intestine, part unspecified, with perforation and abscess with bleeding     |
| K57.91  | Diverticulosis of intestine, part unspecified, without perforation or abscess with bleeding   |
| K57.93  | Diverticulitis of intestine, part unspecified, without perforation or abscess with bleeding   |
| K62.5   | Hemorrhage of anus and rectum                                                                 |
| K63.1   | Perforation of intestine (nontraumatic                                                        |
| K63.81  | Dieulafoy lesion of intestine                                                                 |
| K66.1   | Hemoperitoneum                                                                                |
| K92.0   | Hematemesis                                                                                   |
| K92.1   | Melena                                                                                        |
| K92.2   | Gastrointestinal hemorrhage, unspecified                                                      |
| M25.00  | Hemarthrosis, unspecified joint                                                               |
| M25.011 | Hemarthrosis, right shoulder                                                                  |
| M25.012 | Hemarthrosis, left shoulder                                                                   |
| M25.019 | Hemarthrosis, unspecified shoulder                                                            |
| M25.021 | Hemarthrosis, right elbow                                                                     |
| M25.022 | Hemarthrosis, left elbow                                                                      |
| M25.029 | Hemarthrosis, unspecified elbow                                                               |
| M25.031 | Hemarthrosis, right wrist                                                                     |
| M25.032 | Hemarthrosis, left wrist                                                                      |
| M25.039 | Hemarthrosis, unspecified wrist                                                               |
| M25.041 | Hemarthrosis, right hand                                                                      |
| M25.042 | Hemarthrosis, left hand                                                                       |
| M25.049 | Hemarthrosis, unspecified hand                                                                |
| M25.051 | Hemarthrosis, right hip                                                                       |
| M25.052 | Hemarthrosis, left hip                                                                        |
| M25.059 | Hemarthrosis, unspecified hip                                                                 |
| M25.061 | Hemarthrosis, right knee                                                                      |
| M25.062 | Hemarthrosis, left knee                                                                       |
| M25.069 | Hemarthrosis, unspecified knee                                                                |
| M25.071 | Hemarthrosis, right ankle                                                                     |

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|------------------------|------------------------------------------------------------------------------------------|
| M25.072                | Hemarthrosis, left ankle                                                                 |
| M25.073                | Hemarthrosis, unspecified ankle                                                          |
| M25.074                | Hemarthrosis, right foot                                                                 |
| M25.075                | Hemarthrosis, left foot                                                                  |
| M25.076                | Hemarthrosis, unspecified foot                                                           |
| M25.08                 | Hemarthrosis, other specified site                                                       |
| R58                    | Hemorrhage, not elsewhere classified                                                     |
| R31.9                  | Heaturia, unspecified in inpatient confinement                                           |
| R31.9                  | Heaturia, unspecified in inpatient confinement                                           |
| R04.2                  | Hemoptysis                                                                               |
| R04.9                  | Hemorrhage from respiratory passages, unspecified                                        |
| R04.81                 | Acute idiopathic pulmonary hemorrhage in infants                                         |
| R04.89                 | Hemorrhage from other sites in respiratory passages                                      |
| R31.0                  | Gross hematuria                                                                          |
| R31.1                  | Benign essential microscopic hematuria                                                   |
| R31.2                  | Other microscopic hematuria                                                              |
|                        |                                                                                          |
| <b>ICD-9 and 10 Px</b> |                                                                                          |
| 0W.3P8ZZ               | Control Bleeding in Gastrointestinal Tract, Via Natural or Artificial Opening Endoscopic |
| 44.43                  | ENDOSCOPIC CONTROL OF GASTRIC OR DUODENAL BLEEDING                                       |

# Appendix A

| Pregnancy              |                                                                                           |
|------------------------|-------------------------------------------------------------------------------------------|
| <b>Dx codes</b>        |                                                                                           |
| 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                                               |
| <b>Procedure codes</b> |                                                                                           |
| 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                                                              |

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- 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

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- 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 A

|                                            |                                                                                       |
|--------------------------------------------|---------------------------------------------------------------------------------------|
| <b>Title</b>                               |                                                                                       |
| Venous Thromboembolism (VTE)               |                                                                                       |
| <b>ICD-9 Dx inpatient primary position</b> |                                                                                       |
| <b>PE</b>                                  |                                                                                       |
| 415.1                                      | PULMONARY EMBOLISM AND INFARCTION                                                     |
| 415.11                                     | IATROGENIC PULMONARY EMBOLISM AND INFARCTION                                          |
| 415.19                                     | OTHER PULMONARY EMBOLISM AND INFARCTION                                               |
| <b>DVT</b>                                 |                                                                                       |
| 451.1                                      | PHLEBITIS AND THROMBOPHLEBITIS OF DEEP VEINS OF LOWER EXTREMITIES                     |
| 451.11                                     | PHLEBITIS AND THROMBOPHLEBITIS OF FEMORAL VEIN (DEEP) (SUPERFICIAL)                   |
| 451.19                                     | PHLEBITIS AND THROMBOPHLEBITIS OF OTHER                                               |
| 451.2                                      | PHLEBITIS AND THROMBOPHLEBITIS OF LOWER EXTREMITIES UNSPECIFIED                       |
| 451.81                                     | PHLEBITIS AND THROMBOPHLEBITIS OF ILIAC VEIN                                          |
| 451.9                                      | PHLEBITIS AND THROMBOPHLEBITIS OF UNSPECIFIED SITE                                    |
| 453                                        | BUDD-CHIARI SYNDROME                                                                  |
| 453.1                                      | THROMBOPHLEBITIS MIGRANS                                                              |
| 453.2                                      | EMBOLISM AND THROMBOSIS OF INFERIOR VENA CAVA                                         |
| 453.4                                      | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF DEEP VESSELS OF LOWER EXTREMITY               |
| 453.4                                      | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF UNSPECIFIED DEEP VESSELS OF LOWER EXTREMITY   |
| 453.41                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF DEEP VESSELS OF PROXIMAL LOWER EXTREMITY      |
| 453.42                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF DEEP VESSELS OF DISTAL LOWER EXTREMITY        |
| 453.5                                      | CHRONIC VENOUS EMBOLISM AND THROMBOSIS OF DEEP VESSELS OF LOWER EXTREMITY             |
| 453.5                                      | CHRONIC VENOUS EMBOLISM AND THROMBOSIS OF UNSPECIFIED DEEP VESSELS OF LOWER EXTREMITY |
| 453.51                                     | CHRONIC VENOUS EMBOLISM AND THROMBOSIS OF DEEP VESSELS OF PROXIMAL LOWER EXTREMITY    |
| 453.52                                     | CHRONIC VENOUS EMBOLISM AND THROMBOSIS OF DEEP VESSELS OF DISTAL LOWER EXTREMITY      |
| 453.8                                      | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF OTHER SPECIFIED VEINS                         |
| 453.82                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF DEEP VEINS OF UPPER EXTREMITY                 |
| 453.83                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF UPPER EXTREMITY UNSPECIFIED                   |
| 453.84                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF AXILLARY VEINS                                |
| 453.85                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF SUBCLAVIAN VEINS                              |
| 453.86                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF INTERNAL JUGULAR VEINS                        |
| 453.87                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF OTHER THORACIC VEINS                          |
| 453.89                                     | ACUTE VENOUS EMBOLISM AND THROMBOSIS OF OTHER SPECIFIED VEINS                         |

# Appendix A

|                                             |                                                                                            |
|---------------------------------------------|--------------------------------------------------------------------------------------------|
| 453.9                                       | EMBOLISM AND THROMBOSIS OF UNSPECIFIED SITE                                                |
| <b>ICD-10 Dx inpatient primary position</b> |                                                                                            |
| <b>PE</b>                                   |                                                                                            |
| I26.0                                       | Pulmonary embolism with acute cor pulmonale                                                |
| I26.01                                      | Septic pulmonary embolism with acute cor pulmonale                                         |
| I26.02                                      | Saddle embolus of pulmonary artery with acute cor pulmonale                                |
| I26.09                                      | Other pulmonary embolism with acute cor pulmonale                                          |
| I26.9                                       | Pulmonary embolism without acute cor pulmonale                                             |
| I26.99                                      | Other pulmonary embolism without acute cor pulmonale                                       |
| <b>DVT</b>                                  |                                                                                            |
| I80.1                                       | Phlebitis and thrombophlebitis of femoral vein                                             |
| I80.10                                      | Phlebitis and thrombophlebitis of unspecified femoral vein                                 |
| I80.11                                      | Phlebitis and thrombophlebitis of right femoral vein                                       |
| I80.12                                      | Phlebitis and thrombophlebitis of left femoral vein                                        |
| I80.13                                      | Phlebitis and thrombophlebitis of femoral vein, bilateral                                  |
| I80.2                                       | Phlebitis and thrombophlebitis of other and unspecified deep vessels of lower extremities  |
| I80.20                                      | Phlebitis and thrombophlebitis of unspecified deep vessels of lower extremities            |
| I80.201                                     | Phlebitis and thrombophlebitis of unspecified deep vessels of right lower extremity        |
| I80.202                                     | Phlebitis and thrombophlebitis of unspecified deep vessels of left lower extremity         |
| I80.203                                     | Phlebitis and thrombophlebitis of unspecified deep vessels of lower extremities, bilateral |
| I80.209                                     | Phlebitis and thrombophlebitis of unspecified deep vessels of unspecified lower extremity  |
| I80.21                                      | Phlebitis and thrombophlebitis of iliac vein                                               |
| I80.211                                     | Phlebitis and thrombophlebitis of right iliac vein                                         |
| I80.212                                     | Phlebitis and thrombophlebitis of left iliac vein                                          |
| I80.213                                     | Phlebitis and thrombophlebitis of iliac vein, bilateral                                    |
| I80.219                                     | Phlebitis and thrombophlebitis of unspecified iliac vein                                   |
| I80.22                                      | Phlebitis and thrombophlebitis of popliteal vein                                           |
| I80.221                                     | Phlebitis and thrombophlebitis of right popliteal vein                                     |
| I80.222                                     | Phlebitis and thrombophlebitis of left popliteal vein                                      |
| I80.223                                     | Phlebitis and thrombophlebitis of popliteal vein, bilateral                                |
| I80.229                                     | Phlebitis and thrombophlebitis of unspecified popliteal vein                               |
| I80.23                                      | Phlebitis and thrombophlebitis of tibial vein                                              |
| I80.231                                     | Phlebitis and thrombophlebitis of right tibial vein                                        |

## Appendix A

|         |                                                                                        |
|---------|----------------------------------------------------------------------------------------|
| I80.232 | Phlebitis and thrombophlebitis of left tibial vein                                     |
| I80.233 | Phlebitis and thrombophlebitis of tibial vein, bilateral                               |
| I80.239 | Phlebitis and thrombophlebitis of unspecified tibial vein                              |
| I80.29  | Phlebitis and thrombophlebitis of other deep vessels of lower extremities              |
| I80.291 | Phlebitis and thrombophlebitis of other deep vessels of right lower extremity          |
| I80.292 | Phlebitis and thrombophlebitis of other deep vessels of left lower extremity           |
| I80.293 | Phlebitis and thrombophlebitis of other deep vessels of lower extremity, bilateral     |
| I80.299 | Phlebitis and thrombophlebitis of other deep vessels of unspecified lower extremity    |
| I80.3   | Phlebitis and thrombophlebitis of lower extremities, unspecified                       |
| I80.9   | Phlebitis and thrombophlebitis of unspecified site                                     |
| I82.0   | Budd-Chiari syndrome                                                                   |
| I82.1   | Thrombophlebitis migrans                                                               |
| I80.3   | Phlebitis and thrombophlebitis of lower extremities, unspecified                       |
| I82.4   | Acute embolism and thrombosis of deep veins of lower extremity                         |
| I82.40  | Acute embolism and thrombosis of unspecified deep veins of lower extremity             |
| I82.401 | Acute embolism and thrombosis of unspecified deep veins of right lower extremity       |
| I82.402 | Acute embolism and thrombosis of unspecified deep veins of left lower extremity        |
| I82.403 | Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral  |
| I82.409 | Acute embolism and thrombosis of unspecified deep veins of unspecified lower extremity |
| I82.41  | Acute embolism and thrombosis of femoral vein                                          |
| I82.411 | Acute embolism and thrombosis of right femoral vein                                    |
| I82.412 | Acute embolism and thrombosis of left femoral vein                                     |
| I82.413 | Acute embolism and thrombosis of femoral vein, bilateral                               |
| I82.419 | Acute embolism and thrombosis of unspecified femoral vein                              |
| I82.42  | Acute embolism and thrombosis of iliac vein                                            |
| I82.421 | Acute embolism and thrombosis of right iliac vein                                      |
| I82.422 | Acute embolism and thrombosis of left iliac vein                                       |
| I82.423 | Acute embolism and thrombosis of iliac vein, bilateral                                 |
| I82.429 | Acute embolism and thrombosis of unspecified iliac vein                                |
| I82.43  | Acute embolism and thrombosis of popliteal vein                                        |
| I82.431 | Acute embolism and thrombosis of right popliteal vein                                  |
| I82.432 | Acute embolism and thrombosis of left popliteal vein                                   |
| I82.433 | Acute embolism and thrombosis of popliteal vein, bilateral                             |
| I82.439 | Acute embolism and thrombosis of unspecified popliteal vein                            |
| I82.44  | Acute embolism and thrombosis of tibial vein                                           |

## Appendix A

|         |                                                                                                 |
|---------|-------------------------------------------------------------------------------------------------|
| I82.441 | Acute embolism and thrombosis of right tibial vein                                              |
| I82.442 | Acute embolism and thrombosis of left tibial vein                                               |
| I82.443 | Acute embolism and thrombosis of tibial vein, bilateral                                         |
| I82.449 | Acute embolism and thrombosis of unspecified tibial vein                                        |
| I82.49  | Acute embolism and thrombosis of other specified deep vein of lower extremity                   |
| I82.491 | Acute embolism and thrombosis of other specified deep vein of right lower extremity             |
| I82.492 | Acute embolism and thrombosis of other specified deep vein of left lower extremity              |
| I82.493 | Acute embolism and thrombosis of other specified deep vein of lower extremity, bilateral        |
| I82.499 | Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity       |
| I82.4Y  | Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity             |
| I82.4Y1 | Acute embolism and thrombosis of unspecified deep veins of right proximal lower extremity       |
| I82.4Y2 | Acute embolism and thrombosis of unspecified deep veins of left proximal lower extremity        |
| I82.4Y3 | Acute embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral  |
| I82.4Y9 | Acute embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity |
| I82.4Z  | Acute embolism and thrombosis of unspecified deep veins of distal lower extremity               |
| I82.4Z1 | Acute embolism and thrombosis of unspecified deep veins of right distal lower extremity         |
| I82.4Z2 | Acute embolism and thrombosis of unspecified deep veins of left distal lower extremity          |
| I82.4Z3 | Acute embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral    |
| I82.4Z9 | Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity   |
| I82.5   | Chronic embolism and thrombosis of deep veins of lower extremity                                |
| I82.50  | Chronic embolism and thrombosis of unspecified deep veins of lower extremity                    |
| I82.501 | Chronic embolism and thrombosis of unspecified deep veins of right lower extremity              |
| I82.502 | Chronic embolism and thrombosis of unspecified deep veins of left lower extremity               |
| I82.503 | Chronic embolism and thrombosis of unspecified deep veins of lower extremity, bilateral         |
| I82.509 | Chronic embolism and thrombosis of unspecified deep veins of unspecified lower extremity        |
| I82.51  | Chronic embolism and thrombosis of femoral vein                                                 |
| I82.511 | Chronic embolism and thrombosis of right femoral vein                                           |
| I82.512 | Chronic embolism and thrombosis of left femoral vein                                            |
| I82.513 | Chronic embolism and thrombosis of femoral vein, bilateral                                      |
| I82.519 | Chronic embolism and thrombosis of unspecified femoral vein                                     |
| I82.52  | Chronic embolism and thrombosis of iliac vein                                                   |
| I82.521 | Chronic embolism and thrombosis of right iliac vein                                             |
| I82.522 | Chronic embolism and thrombosis of left iliac vein                                              |
| I82.523 | Chronic embolism and thrombosis of iliac vein, bilateral                                        |
| I82.529 | Chronic embolism and thrombosis of unspecified iliac vein                                       |

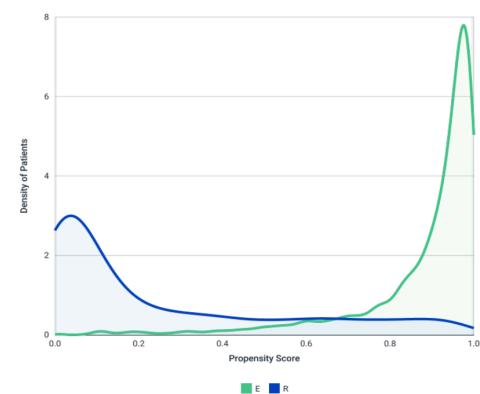
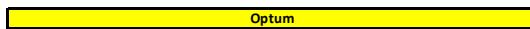
## Appendix A

|         |                                                                                                   |
|---------|---------------------------------------------------------------------------------------------------|
| I82.53  | Chronic embolism and thrombosis of popliteal vein                                                 |
| I82.531 | Chronic embolism and thrombosis of right popliteal vein                                           |
| I82.532 | Chronic embolism and thrombosis of left popliteal vein                                            |
| I82.533 | Chronic embolism and thrombosis of popliteal vein, bilateral                                      |
| I82.539 | Chronic embolism and thrombosis of unspecified popliteal vein                                     |
| I82.54  | Chronic embolism and thrombosis of tibial vein                                                    |
| I82.541 | Chronic embolism and thrombosis of right tibial vein                                              |
| I82.542 | Chronic embolism and thrombosis of left tibial vein                                               |
| I82.543 | Chronic embolism and thrombosis of tibial vein, bilateral                                         |
| I82.549 | Chronic embolism and thrombosis of unspecified tibial vein                                        |
| I82.59  | Chronic embolism and thrombosis of other specified deep vein of lower extremity                   |
| I82.591 | Chronic embolism and thrombosis of other specified deep vein of right lower extremity             |
| I82.592 | Chronic embolism and thrombosis of other specified deep vein of left lower extremity              |
| I82.593 | Chronic embolism and thrombosis of other specified deep vein of lower extremity, bilateral        |
| I82.599 | Chronic embolism and thrombosis of other specified deep vein of unspecified lower extremity       |
| I82.5Y  | Chronic embolism and thrombosis of unspecified deep veins of proximal lower extremity             |
| I82.5Y1 | Chronic embolism and thrombosis of unspecified deep veins of right proximal lower extremity       |
| I82.5Y2 | Chronic embolism and thrombosis of unspecified deep veins of left proximal lower extremity        |
| I82.5Y3 | Chronic embolism and thrombosis of unspecified deep veins of proximal lower extremity, bilateral  |
| I82.5Y9 | Chronic embolism and thrombosis of unspecified deep veins of unspecified proximal lower extremity |
| I82.5Z  | Chronic embolism and thrombosis of unspecified deep veins of distal lower extremity               |
| I82.5Z1 | Chronic embolism and thrombosis of unspecified deep veins of right distal lower extremity         |
| I82.5Z2 | Chronic embolism and thrombosis of unspecified deep veins of left distal lower extremity          |
| I82.5Z3 | Chronic embolism and thrombosis of unspecified deep veins of distal lower extremity, bilateral    |
| I82.5Z9 | Chronic embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity   |
| I82.6   | Acute embolism and thrombosis of veins of upper extremity                                         |
| I82.60  | Acute embolism and thrombosis of unspecified veins of upper extremity                             |
| I82.601 | Acute embolism and thrombosis of unspecified veins of right upper extremity                       |
| I82.602 | Acute embolism and thrombosis of unspecified veins of left upper extremity                        |
| I82.603 | Acute embolism and thrombosis of unspecified veins of upper extremity, bilateral                  |
| I82.609 | Acute embolism and thrombosis of unspecified veins of unspecified upper extremity                 |
| I82.62  | Acute embolism and thrombosis of deep veins of upper extremity                                    |
| I82.621 | Acute embolism and thrombosis of deep veins of right upper extremity                              |
| I82.622 | Acute embolism and thrombosis of deep veins of left upper extremity                               |
| I82.623 | Acute embolism and thrombosis of deep veins of upper extremity, bilateral                         |

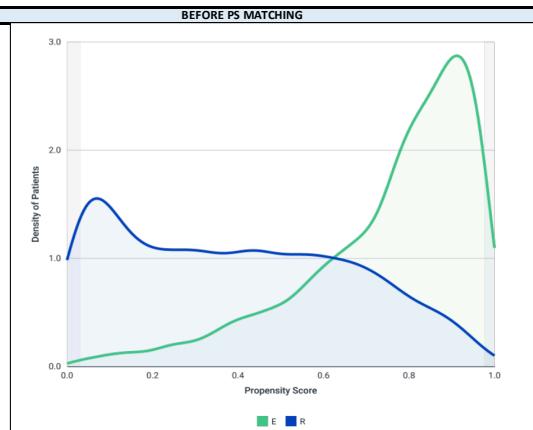
## Appendix A

|         |                                                                            |
|---------|----------------------------------------------------------------------------|
| I82.629 | Acute embolism and thrombosis of deep veins of unspecified upper extremity |
| I82.890 | Acute embolism and thrombosis of other specified veins                     |
| I82.90  | Acute embolism and thrombosis of unspecified vein                          |
| I82.A1  | Acute embolism and thrombosis of axillary vein                             |
| I82.A11 | Acute embolism and thrombosis of right axillary vein                       |
| I82.A12 | Acute embolism and thrombosis of left axillary vein                        |
| I82.A13 | Acute embolism and thrombosis of axillary vein, bilateral                  |
| I82.A19 | Acute embolism and thrombosis of unspecified axillary vein                 |
| I82.B1  | Acute embolism and thrombosis of subclavian vein                           |
| I82.B11 | Acute embolism and thrombosis of right subclavian vein                     |
| I82.B12 | Acute embolism and thrombosis of left subclavian vein                      |
| I82.B13 | Acute embolism and thrombosis of subclavian vein, bilateral                |
| I82.B19 | Acute embolism and thrombosis of unspecified subclavian vein               |
| I82.C1  | Acute embolism and thrombosis of internal jugular vein                     |
| I82.C11 | Acute embolism and thrombosis of right internal jugular vein               |
| I82.C12 | Acute embolism and thrombosis of left internal jugular vein                |
| I82.C13 | Acute embolism and thrombosis of internal jugular vein, bilateral          |
| I82.C19 | Acute embolism and thrombosis of unspecified internal jugular vein         |

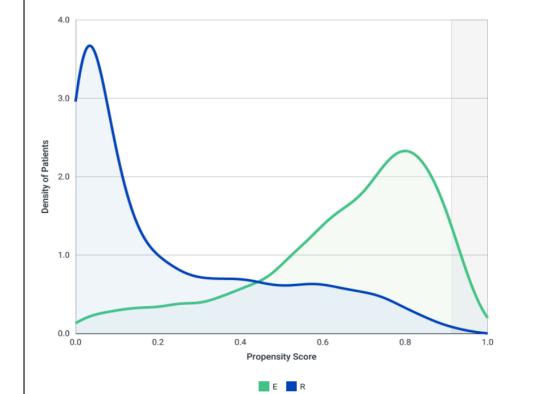
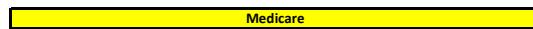
# Appendix B



The c-statistics for the propensity score model, pre-matching was 0.938. The postmatching c-statistic was 0.684.

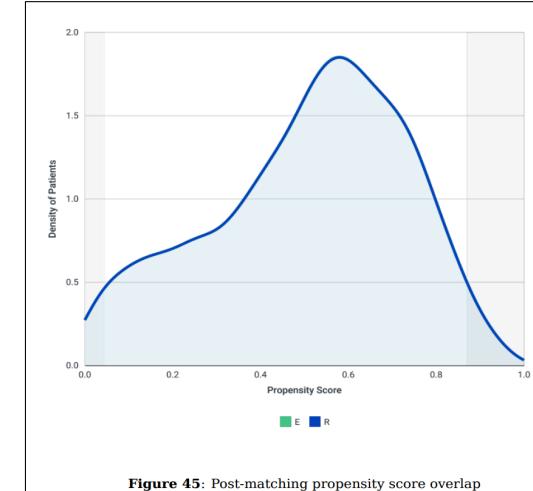
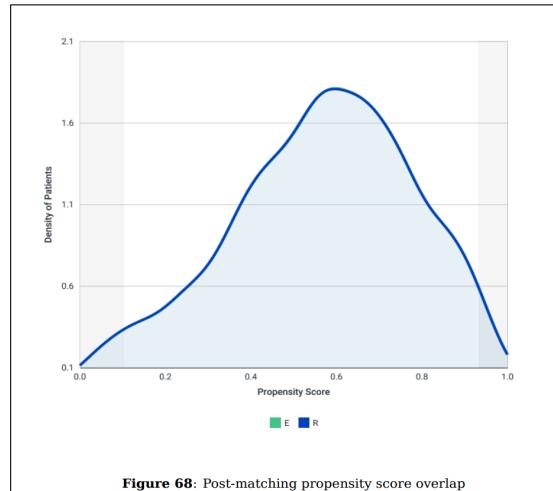
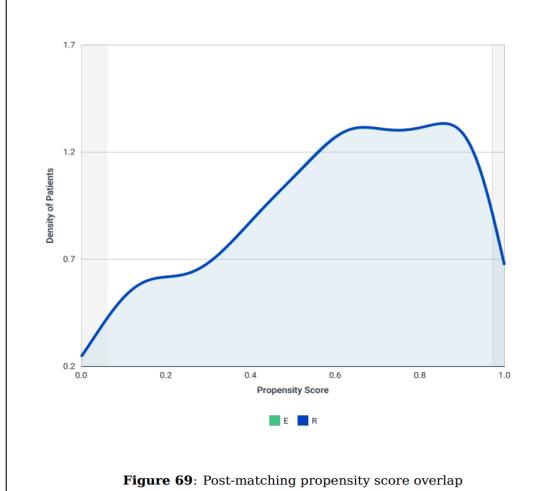


The c-statistics for the propensity score model, pre-matching was 0.848. The postmatching c-statistic was 0.572.



The c-statistics for the propensity score model, pre-matching was 0.874. The postmatching c-statistic was 0.566.

AFTER PS MATCHING



# Appendix B

| Variable                                                                           | Unmatched            |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
|------------------------------------------------------------------------------------|----------------------|---------------------|-----------|----------------------|---------------------|-----------|----------------------|-------------------|-----------|----------------------|---------------------|-----------|
|                                                                                    | Optum                |                     |           | MarketScan           |                     |           | Medicare             |                   |           | POOLED               |                     |           |
|                                                                                    | Reference - Warfarin | Exposure - Apixaban | St. Diff. | Reference - Warfarin | Exposure - Apixaban | St. Diff. | Reference - Warfarin | posure - Apixaban | St. Diff. | Reference - Warfarin | Exposure - Apixaban | St. Diff. |
| Number of patients                                                                 | 1,472                | 2,783               |           | 2,464                | 3,874               |           | 4,983                | 3,406             |           | 8,919                | 10,063              |           |
| Age                                                                                |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...mean (sd)                                                                       | 56.64 (14.48)        | 56.04 (14.74)       | 0.04      | 51.80 (12.29)        | 50.99 (12.53)       | 0.07      | 62.86 (14.56)        | 63.42 (13.81)     | -0.04     | 58.78 (13.96)        | 56.59 (13.60)       | 0.16      |
| Age categories without zero category                                               |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...18 - 54; n (%)                                                                  | 605 (41.1%)          | 1,207 (43.4%)       | -0.05     | 1,318 (53.5%)        | 2,133 (55.1%)       | -0.03     | 1,326 (26.6%)        | 852 (25.0%)       | 0.04      | 3,249 (36.4%)        | 4192 (41.7%)        | -0.11     |
| ...55 - 64; n (%)                                                                  | 500 (34.0%)          | 878 (31.5%)         | 0.05      | 989 (40.1%)          | 1,531 (39.5%)       | 0.01      | 1,364 (27.4%)        | 856 (25.1%)       | 0.05      | 2,853 (32.0%)        | 3,265 (32.4%)       | -0.01     |
| ...65 - 74; n (%)                                                                  | 185 (12.6%)          | 398 (14.3%)         | -0.05     | 86 (3.5%)            | 118 (3.0%)          | 0.03      | 1,233 (24.7%)        | 998 (29.3%)       | -0.10     | 1,504 (16.9%)        | 1,514 (15.0%)       | 0.05      |
| ...>75; n (%)                                                                      | 182 (12.4%)          | 300 (10.8%)         | 0.05      | 71 (2.9%)            | 92 (2.4%)           | 0.03      | 1,060 (21.3%)        | 700 (20.6%)       | 0.02      | 1,313 (14.7%)        | 1,092 (10.9%)       | 0.11      |
| Gender without zero category- United                                               |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...Males; n (%)                                                                    | 747 (50.7%)          | 1,386 (49.8%)       | 0.02      | 1,324 (53.7%)        | 1,972 (50.9%)       | 0.06      | 2,339 (46.9%)        | 1,571 (46.1%)     | 0.02      | 4,410 (49.4%)        | 4,929 (49.0%)       | 0.01      |
| ...Females; n (%)                                                                  | 725 (49.3%)          | 1,397 (50.2%)       | -0.02     | 1,140 (46.3%)        | 1,902 (49.1%)       | -0.06     | 2,644 (53.1%)        | 1,835 (53.9%)     | -0.02     | 4,509 (50.6%)        | 5,134 (51.0%)       | -0.01     |
| Race                                                                               |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...White; n (%)                                                                    |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...Black; n (%)                                                                    |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...Asian; n (%)                                                                    |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...Hispanic; n (%)                                                                 |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...North American Native; n (%)                                                    |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...Other/Unknown; n (%)                                                            |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| Region without zero category- United v3 (lumping missing&other category with West) |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| ...Northeast; n (%)                                                                | 156 (10.6%)          | 262 (9.4%)          | 0.04      | 452 (18.3%)          | 622 (16.1%)         | 0.06      | 1,000 (20.1%)        | 644 (18.9%)       | 0.03      | 1608 (18.0%)         | 1,528 (15.2%)       | 0.08      |
| ...South; n (%)                                                                    | 414 (28.1%)          | 1,333 (47.9%)       | -0.42     | 749 (30.4%)          | 869 (22.4%)         | 0.18      | 1,368 (27.5%)        | 1,425 (41.8%)     | -0.30     | 2,531 (28.4%)        | 3,627 (36.0%)       | -0.16     |
| ...Midwest; n (%)                                                                  | 503 (34.2%)          | 658 (23.6%)         | 0.24      | 802 (32.5%)          | 1,978 (51.1%)       | -0.38     | 1,556 (31.2%)        | 795 (23.3%)       | 0.18      | 2,861 (32.1%)        | 3,431 (34.1%)       | -0.04     |
| ...West; n (%)                                                                     | 399 (27.1%)          | 530 (19.0%)         | 0.19      | 456 (18.5%)          | 394 (10.2%)         | 0.24      | 1,059 (21.3%)        | 542 (15.9%)       | 0.14      | 1,914 (21.5%)        | 1,466 (14.6%)       | 0.18      |
| ...Unknown+missing; n (%)                                                          | N/A                  | N/A                 | #VALUE!   | ** (0.2%)            | ** (0.3%)           | -0.02     | N/A                  | N/A               | #VALUE!   | ** (0.2%)            | ** (0.3%)           | -0.02     |
| CV Covariates                                                                      |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| Ischemic heart disease; n (%)                                                      | 226 (15.4%)          | 459 (16.5%)         | -0.03     | 305 (12.4%)          | 499 (12.9%)         | -0.02     | 968 (19.4%)          | 714 (21.0%)       | -0.04     | 1,499 (16.8%)        | 1,672 (16.6%)       | 0.01      |
| Acute MI; n (%)                                                                    | 67 (4.6%)            | 123 (4.4%)          | 0.01      | 106 (4.3%)           | 169 (4.4%)          | 0.00      | 210 (4.2%)           | 168 (4.9%)        | -0.03     | 383 (4.3%)           | 460 (4.6%)          | -0.01     |
| ACS/unstable angina; n (%)                                                         | 40 (2.7%)            | 99 (3.6%)           | -0.05     | 71 (2.9%)            | 129 (3.3%)          | -0.02     | 178 (3.6%)           | 131 (3.8%)        | -0.01     | 289 (3.2%)           | 359 (3.6%)          | -0.02     |
| Old MI; n (%)                                                                      | 36 (2.4%)            | 72 (2.6%)           | -0.01     | 31 (1.3%)            | 47 (1.2%)           | 0.01      | 269 (5.4%)           | 171 (5.0%)        | 0.02      | 336 (3.8%)           | 290 (2.9%)          | 0.05      |
| Stable angina; n (%)                                                               | 19 (1.3%)            | 70 (2.5%)           | -0.09     | 27 (1.1%)            | 82 (2.1%)           | -0.08     | 92 (1.8%)            | 81 (2.4%)         | -0.04     | 138 (1.5%)           | 233 (2.3%)          | -0.06     |
| Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%)  | 137 (9.3%)           | 278 (10.0%)         | -0.02     | 165 (6.7%)           | 260 (6.7%)          | 0.00      | 683 (13.7%)          | 516 (15.1%)       | -0.04     | 985 (11.0%)          | 1,054 (10.5%)       | 0.02      |
| Other atherosclerosis with ICD10 v2 Copy; n (%)                                    | ** (0.5%)            | 12 (0.4%)           | 0.01      | 12 (0.5%)            | ** (0.2%)           | 0.05      | 38 (0.8%)            | 18 (0.5%)         | 0.04      | #VALUE!              | #VALUE!             | #VALUE!   |
| Previous cardiac procedure (CABG or PCTA or Stent) v4; n (%)                       | ** (0.3%)            | ** (0.1%)           | 0.04      | ** (0.2%)            | 21 (0.5%)           | -0.05     | 20 (0.4%)            | 13 (0.4%)         | 0.00      | #VALUE!              | #VALUE!             | #VALUE!   |
| History of CABG or PCTA; n (%)                                                     | 40 (2.7%)            | 66 (2.4%)           | 0.02      | 19 (0.8%)            | 32 (0.8%)           | 0.00      | 226 (4.5%)           | 165 (4.8%)        | -0.01     | 285 (3.2%)           | 263 (2.6%)          | 0.04      |
| Any stroke; n (%)                                                                  | ** (0.7%)            | 37 (1.3%)           | -0.06     | 25 (1.0%)            | 34 (0.9%)           | 0.01      | 158 (3.2%)           | 103 (3.0%)        | 0.01      | #VALUE!              | 174 (1.7%)          | #VALUE!   |
| Ischemic stroke (w and w/o mention of cerebral infarction); n (%)                  | ** (0.7%)            | 37 (1.3%)           | -0.06     | 25 (1.0%)            | 33 (0.9%)           | 0.01      | 146 (2.9%)           | 100 (2.9%)        | 0.00      | #VALUE!              | 170 (1.7%)          | #VALUE!   |
| Hemorrhagic stroke; n (%)                                                          | 0 (0.0%)             | ** (0.1%)           | -0.04     | 0 (0.0%)             | ** (0.0%)           | #DIV/0!   | 12 (0.2%)            | ** (0.1%)         | 0.03      | 012 (0.1%)           | #VALUE!             | #VALUE!   |
| TIA; n (%)                                                                         | ** (0.3%)            | ** (0.4%)           | -0.02     | ** (0.3%)            | 12 (0.3%)           | 0.00      | 44 (0.9%)            | 19 (0.6%)         | 0.03      | #VALUE!              | #VALUE!             | #VALUE!   |
| Other cerebrovascular disease; n (%)                                               | ** (0.7%)            | 15 (0.5%)           | 0.03      | 20 (0.8%)            | 22 (0.6%)           | 0.02      | 72 (1.4%)            | 53 (1.6%)         | -0.02     | #VALUE!              | 90 (0.9%)           | #VALUE!   |
| Cerebrovascular procedure; n (%)                                                   | 0 (0.0%)             | 0 (0.0%)            | #DIV/0!   | 0 (0.0%)             | 0 (0.0%)            | #DIV/0!   | ** (0.0%)            | ** (0.0%)         | #DIV/0!   | #VALUE!              | #VALUE!             | #VALUE!   |
| Heart failure (CHF); n (%)                                                         | 145 (9.9%)           | 273 (9.8%)          | 0.00      | 197 (8.0%)           | 326 (8.4%)          | -0.01     | 805 (16.2%)          | 506 (14.9%)       | 0.04      | 1147 (12.9%)         | 1,105 (11.0%)       | 0.06      |
| Peripheral Vascular Disease (PVD) or PVD Surgery v2; n (%)                         | 52 (3.5%)            | 92 (3.3%)           | 0.01      | 65 (2.6%)            | 67 (1.7%)           | 0.06      | 315 (6.3%)           | 206 (6.0%)        | 0.01      | 432 (4.8%)           | 365 (3.6%)          | 0.06      |
| Atrial fibrillation; n (%)                                                         | 104 (7.1%)           | 173 (6.2%)          | 0.04      | 131 (5.3%)           | 247 (6.4%)          | -0.05     | 503 (10.1%)          | 309 (9.1%)        | 0.03      | 738 (8.3%)           | 729 (7.3%)          | 0.04      |
| Other cardiac dysrhythmia; n (%)                                                   | 263 (17.9%)          | 433 (15.6%)         | 0.06      | 409 (16.6%)          | 635 (16.4%)         | 0.01      | 1,028 (20.6%)        | 668 (19.6%)       | 0.02      | 1,736 (17.3%)        | 1,736 (17.3%)       | 0.05      |
| Cardiac conduction disorders; n (%)                                                | 94 (6.4%)            | 176 (6.3%)          | 0.00      | 136 (5.5%)           | 169 (4.4%)          | 0.05      | 366 (7.3%)           | 234 (6.9%)        | 0.02      | 596 (6.7%)           | 579 (5.8%)          | 0.04      |
| Other CVD; n (%)                                                                   | 396 (26.9%)          | 811 (29.1%)         | -0.05     | 579 (23.5%)          | 1,035 (26.7%)       | -0.07     | 1,178 (23.6%)        | 852 (25.0%)       | -0.03     | 2,153 (24.1%)        | 2,698 (26.8%)       | -0.06     |
| Diabetes-related complications                                                     |                      |                     |           |                      |                     |           |                      |                   |           |                      |                     |           |
| Occurrence of Diabetic Neuropathy v2 Copy; n (%)                                   | 31 (2.1%)            | 123 (4.4%)          | -0.13     | 46 (1.9%)            | 74 (1.9%)           | 0.00      | 291 (5.8%)           | 154 (4.5%)        | 0.06      | 368 (4.1%)           | 351 (3.5%)          | 0.03      |
| Occurrence of diabetic nephropathy V3 with ICD10 Copy; n (%)                       | 21 (1.4%)            | 51 (1.8%)           | -0.03     | 34 (1.4%)            | 37 (1.0%)           | 0.04      | 110 (2.2%)           | 51 (1.5%)         | 0.05      | 165 (1.8%)           | 139 (1.4%)          | 0.03      |
| Hypoglycemia v2; n (%)                                                             | ** (0.4%)            | ** (0.1%)           | 0.06      | ** (0.3%)            | ** (0.1%)           | 0.04      | 131 (2.6%)           | 83 (2.4%)         | 0.01      | #VALUE!              | #VALUE!             | #VALUE!   |
| Hyperglycemia; n (%)                                                               | 131 (8.9%)           | 230 (8.3%)          | 0.02      | 117 (4.7%)           | 208 (5.4%)          | -0.03     | 452 (9.1%)           | 301 (8.8%)        | 0.01      | 700 (7.8%)           | 739 (7.3%)          | 0.02      |
| Diabetic ketoacidosis; n (%)                                                       | ** (0.3%)            | 16 (0.6%)           | -0.04     | ** (0.3%)            | 19 (0.5%)           | -0.03     | 27 (0.5%)            | 15 (0.4%)         | 0.01      | #VALUE!              | 50 (0.5%)           | #VALUE!   |
| Hypertension: 1 inpatient or 2 outpatient claims within 365 days; n (%)            | 588 (39.9%)          | 996 (35.8%)         | 0.08      | 974 (39.5%)          | 1,599 (41.3%)       | -0.04     | 2,258 (45.3%)        | 1,402 (41.2%)     | 0.08      | 3,820 (42.8%)        | 3,997 (39.7%)       | 0.06      |
| Hyperlipidemia v2; n (%)                                                           | 508 (34.5%)          | 964 (34.6%)         | 0.00      | 705 (28.6%)          | 1,203 (31.1%)       | -0.05     | 1,995 (40.0%)        | 1,423 (41.8%)     | -0.04     | 3,208 (36.0%)        | 3,590 (35.7%)       | 0.01      |
| Edema; n (%)                                                                       | 243 (16.5%)          | 444 (16.0%)         | 0.01      | 335 (13.6%)          | 550 (14.2%)         | -0.02     | 789 (15.8%)          | 506 (14.9%)       | 0.02      | 1,367 (15.3%)        | 1,500 (14.9%)       | 0.01      |
| Renal Dysfunction (non-diabetic) v2; n (%)                                         | 213 (14.5%)          | 407 (14.6%)         | 0.00      | 307 (12.5%)          | 486 (12.5%)         | 0.00      | 916 (18.4%)          | 580 (17.0%)       | 0.04      | 1,436 (16.1%)        | 1,473 (14.6%)       | 0.04      |
| Occurrence of acute renal disease v2; n (%)                                        | 86 (5.8%)            | 202 (7.3%)          | -0.06     | 159 (6.5%)           | 265 (6.8%)          | -0.01     | 513 (10.3%)          | 284 (8.3%)        | 0.07      | 758 (8.5%)           | 751 (7.5%)          | 0.04      |
| Occurrence of chronic renal insufficiency; n (%)                                   | 87 (5.9%)            | 124 (4.5%)          | 0.06      | 84 (3.4%)            | 113 (2.9%)          | 0.03      | 359 (7.2%)           | 197 (5.8%)        | 0.06      | 530 (5.9%)           | 434 (4.3%)          | 0.07      |

# Appendix B

|                                                                |             |               |       |               |               |       |               |               |         |              |              |         |
|----------------------------------------------------------------|-------------|---------------|-------|---------------|---------------|-------|---------------|---------------|---------|--------------|--------------|---------|
| Chronic kidney disease v2; n (%)                               | 80 (5.4%)   | 116 (4.2%)    | 0.06  | 76 (3.1%)     | 102 (2.6%)    | 0.03  | 345 (6.9%)    | 189 (5.5%)    | 0.06    | 501 (5.6%)   | 407 (4.0%)   | 0.07    |
| CKD Stage 3-4; n (%)                                           | 48 (3.3%)   | 90 (3.2%)     | 0.01  | 56 (2.3%)     | 75 (1.9%)     | 0.03  | 249 (5.0%)    | 143 (4.2%)    | 0.04    | 353 (4.0%)   | 308 (3.1%)   | 0.05    |
| Occurrence of hypertensive nephropathy; n (%)                  | 41 (2.8%)   | 51 (1.8%)     | 0.07  | 53 (2.2%)     | 69 (1.8%)     | 0.03  | 213 (4.3%)    | 98 (2.9%)     | 0.08    | 307 (3.4%)   | 218 (2.2%)   | 0.07    |
| Occurrence of miscellaneous renal insufficiency v2; n (%)      | 92 (6.2%)   | 163 (5.9%)    | 0.01  | 132 (5.4%)    | 192 (5.0%)    | 0.02  | 326 (6.5%)    | 229 (6.7%)    | -0.01   | 550 (6.2%)   | 584 (5.8%)   | 0.02    |
| <b>Other Covariates</b>                                        |             |               |       |               |               |       |               |               |         |              |              |         |
| Liver disease; n (%)                                           | ** (0.5%)   | ** (0.1%)     | 0.07  | 0 (0.0%)      | ** (0.1%)     | -0.04 | 28 (0.6%)     | ** (0.2%)     | 0.06    | #VALUE!      | #VALUE!      | #VALUE! |
| Osteoarthritis; n (%)                                          | 283 (19.2%) | 553 (19.9%)   | -0.02 | 397 (16.1%)   | 570 (14.7%)   | 0.04  | 1,164 (23.4%) | 836 (24.5%)   | -0.03   | 1844 (20.7%) | 1959 (19.5%) | 0.03    |
| Other arthritis, arthropathies and musculoskeletal pain; n (%) | 868 (59.0%) | 1,587 (57.0%) | 0.04  | 1,414 (57.4%) | 2,100 (54.2%) | 0.06  | 2,917 (58.5%) | 1,938 (56.9%) | 0.03    | 5199 (58.3%) | 5625 (55.9%) | 0.05    |
| Dorsopathies; n (%)                                            | 440 (29.9%) | 894 (32.1%)   | -0.05 | 634 (25.7%)   | 995 (25.7%)   | 0.00  | 1,702 (34.2%) | 1,139 (33.4%) | 0.02    | 2776 (31.1%) | 3028 (30.1%) | 0.02    |
| Fractures; n (%)                                               | 62 (4.2%)   | 99 (3.6%)     | 0.03  | 78 (3.2%)     | 114 (2.9%)    | 0.02  | 347 (7.0%)    | 227 (6.7%)    | 0.01    | 487 (5.5%)   | 440 (4.4%)   | 0.05    |
| Falls v2; n (%)                                                | 88 (6.0%)   | 140 (5.0%)    | 0.04  | 47 (1.9%)     | 98 (2.5%)     | -0.04 | 241 (4.8%)    | 124 (3.6%)    | 0.06    | 376 (4.2%)   | 362 (3.6%)   | 0.03    |
| Osteoporosis; n (%)                                            | 66 (4.5%)   | 115 (4.1%)    | 0.02  | 53 (2.2%)     | 68 (1.8%)     | 0.03  | 400 (8.0%)    | 306 (9.0%)    | -0.04   | 519 (5.8%)   | 489 (4.9%)   | 0.04    |
| Depression; n (%)                                              | 286 (19.4%) | 455 (16.3%)   | 0.08  | 334 (13.6%)   | 495 (12.8%)   | 0.02  | 1,352 (27.1%) | 888 (26.1%)   | 0.02    | 1972 (22.1%) | 1838 (18.3%) | 0.09    |
| Anxiety; n (%)                                                 | 305 (20.7%) | 617 (22.2%)   | -0.04 | 407 (16.5%)   | 699 (18.0%)   | -0.04 | 1,372 (27.5%) | 959 (28.2%)   | -0.02   | 2084 (23.4%) | 2275 (22.6%) | 0.02    |
| Sleep_Disorder; n (%)                                          | 74 (5.0%)   | 81 (2.9%)     | 0.11  | 196 (8.0%)    | 109 (2.8%)    | 0.23  | 376 (7.5%)    | 105 (3.1%)    | 0.20    | 646 (7.2%)   | 295 (2.9%)   | 0.20    |
| Dementia; n (%)                                                | 73 (5.0%)   | 136 (4.9%)    | 0.00  | 49 (2.0%)     | 70 (1.8%)     | 0.01  | 577 (11.6%)   | 375 (11.0%)   | 0.02    | 699 (7.8%)   | 581 (5.8%)   | 0.08    |
| Delirium; n (%)                                                | 34 (2.3%)   | 80 (2.9%)     | -0.04 | 42 (1.7%)     | 55 (1.4%)     | 0.02  | 345 (6.9%)    | 203 (6.0%)    | 0.04    | 421 (4.7%)   | 338 (3.4%)   | 0.07    |
| Psychosis; n (%)                                               | 25 (1.7%)   | 51 (1.8%)     | -0.01 | 25 (1.0%)     | 37 (1.0%)     | 0.00  | 418 (8.4%)    | 305 (9.0%)    | -0.02   | 468 (5.2%)   | 393 (3.9%)   | 0.06    |
| Obesity; n (%)                                                 | 561 (38.1%) | 974 (35.0%)   | 0.06  | 869 (35.3%)   | 1,303 (33.6%) | 0.04  | 1,465 (29.4%) | 837 (24.6%)   | 0.11    | 2895 (32.5%) | 3114 (30.9%) | 0.03    |
| Overweight; n (%)                                              | 64 (4.3%)   | 193 (6.9%)    | -0.11 | 74 (3.0%)     | 212 (5.5%)    | -0.12 | 175 (3.5%)    | 165 (4.8%)    | -0.07   | 313 (3.5%)   | 570 (5.7%)   | -0.11   |
| Smoking; n (%)                                                 | 538 (36.5%) | 1,004 (36.1%) | 0.01  | 444 (18.0%)   | 742 (19.2%)   | -0.03 | 2,380 (47.8%) | 1,651 (48.5%) | -0.01   | 3362 (37.7%) | 3397 (33.8%) | 0.08    |
| Alcohol abuse or dependence; n (%)                             | 25 (1.7%)   | 56 (2.0%)     | -0.02 | 33 (1.3%)     | 45 (1.2%)     | 0.01  | 102 (2.0%)    | 80 (2.3%)     | -0.02   | 160 (1.8%)   | 181 (1.8%)   | 0.00    |
| Drug abuse or dependence; n (%)                                | 75 (5.1%)   | 163 (5.9%)    | -0.04 | 50 (2.0%)     | 87 (2.2%)     | -0.01 | 319 (6.4%)    | 228 (6.7%)    | -0.01   | 444 (5.0%)   | 478 (4.8%)   | 0.01    |
| COPD; n (%)                                                    | 256 (17.4%) | 430 (15.5%)   | 0.05  | 219 (8.9%)    | 306 (7.9%)    | 0.04  | 1,312 (26.3%) | 902 (26.5%)   | 0.00    | 1787 (20.0%) | 1638 (16.3%) | 0.10    |
| Asthma; n (%)                                                  | 203 (13.8%) | 348 (12.5%)   | 0.04  | 284 (11.5%)   | 441 (11.4%)   | 0.00  | 773 (15.5%)   | 484 (14.2%)   | 0.04    | 1260 (14.1%) | 1273 (12.7%) | 0.04    |
| Obstructive sleep apnea; n (%)                                 | 261 (17.7%) | 405 (14.6%)   | 0.08  | 375 (15.2%)   | 538 (13.9%)   | 0.04  | 748 (15.0%)   | 465 (13.7%)   | 0.04    | 1384 (15.5%) | 1408 (14.0%) | 0.04    |
| Pneumonia; n (%)                                               | 258 (17.5%) | 513 (18.4%)   | -0.02 | 363 (14.7%)   | 651 (16.8%)   | -0.06 | 1,074 (21.6%) | 748 (22.0%)   | -0.01   | 1695 (19.0%) | 1912 (19.0%) | 0.00    |
| <b>Other Medications</b>                                       |             |               |       |               |               |       |               |               |         |              |              |         |
| Use of ACE inhibitors; n (%)                                   | 223 (15.1%) | 334 (12.0%)   | 0.09  | 392 (15.9%)   | 614 (15.8%)   | 0.00  | 751 (15.1%)   | 437 (12.8%)   | 0.07    | 1366 (15.3%) | 1385 (13.8%) | 0.04    |
| Use of ARBs; n (%)                                             | 94 (6.4%)   | 200 (7.2%)    | -0.03 | 218 (8.8%)    | 364 (9.4%)    | -0.02 | 233 (4.7%)    | 163 (4.8%)    | 0.00    | 545 (6.1%)   | 727 (7.2%)   | -0.04   |
| Use of Loop Diuretics - United; n (%)                          | 117 (7.9%)  | 190 (6.8%)    | 0.04  | 166 (6.7%)    | 232 (6.0%)    | 0.03  | 677 (13.6%)   | 383 (11.2%)   | 0.07    | 960 (10.8%)  | 805 (8.0%)   | 0.10    |
| Use of other diuretics-United; n (%)                           | 34 (2.3%)   | 60 (2.2%)     | 0.01  | 52 (2.1%)     | 78 (2.0%)     | 0.01  | 138 (2.8%)    | 74 (2.2%)     | 0.04    | 224 (2.5%)   | 212 (2.1%)   | 0.03    |
| Use of nitrates-United; n (%)                                  | 20 (1.4%)   | 42 (1.5%)     | -0.01 | 33 (1.3%)     | 43 (1.1%)     | 0.02  | 158 (3.2%)    | 123 (3.6%)    | -0.02   | 211 (2.4%)   | 208 (2.1%)   | 0.02    |
| Use of other hypertension drugs; n (%)                         | 33 (2.2%)   | 69 (2.5%)     | -0.02 | 65 (2.6%)     | 89 (2.3%)     | 0.02  | 235 (4.7%)    | 147 (4.3%)    | 0.02    | 333 (3.7%)   | 305 (3.0%)   | 0.04    |
| Use of Anti-arrhythmics; n (%)                                 | 16 (1.1%)   | 34 (1.2%)     | -0.01 | 25 (1.0%)     | 59 (1.5%)     | -0.05 | 57 (1.1%)     | 53 (1.6%)     | -0.04   | 98 (1.1%)    | 146 (1.5%)   | -0.04   |
| Use of COPD/asthma meds- United; n (%)                         | 243 (16.5%) | 463 (16.6%)   | 0.00  | 359 (14.6%)   | 635 (16.4%)   | -0.05 | 1,077 (21.6%) | 815 (23.9%)   | -0.05   | 1679 (18.8%) | 1913 (19.0%) | -0.01   |
| Use of statins; n (%)                                          | 288 (19.6%) | 557 (20.0%)   | -0.01 | 459 (18.6%)   | 739 (19.1%)   | -0.01 | 1,330 (26.7%) | 935 (27.5%)   | -0.02   | 2077 (23.3%) | 2231 (22.2%) | 0.03    |
| Use of other lipid-lowering drugs; n (%)                       | 47 (3.2%)   | 95 (3.4%)     | -0.01 | 94 (3.8%)     | 153 (3.9%)    | -0.01 | 236 (4.7%)    | 155 (4.6%)    | 0.00    | 377 (4.2%)   | 403 (4.0%)   | 0.01    |
| Use of antiplatelet agents; n (%)                              | 24 (1.6%)   | 43 (1.5%)     | 0.01  | 53 (2.2%)     | 92 (2.4%)     | -0.01 | 235 (4.7%)    | 161 (4.7%)    | 0.00    | 312 (3.5%)   | 296 (2.9%)   | 0.03    |
| Use of heparin and other low-molecular weight heparins; n (%)  | 840 (57.1%) | 122 (4.4%)    | 1.39  | ** (0.1%)     | ** (0.0%)     | 0.04  | 2,098 (42.1%) | 154 (4.5%)    | 0.99    | #VALUE!      | #VALUE!      | #VALUE! |
| Use of NSAIDs; n (%)                                           | 156 (10.6%) | 344 (12.4%)   | -0.06 | 348 (14.1%)   | 620 (16.0%)   | -0.05 | 542 (10.9%)   | 385 (11.3%)   | -0.01   | 1046 (11.7%) | 1349 (13.4%) | -0.05   |
| Use of opioids- United; n (%)                                  | 589 (40.0%) | 1,111 (39.9%) | 0.00  | 1,127 (45.7%) | 1,713 (44.2%) | 0.03  | 2,163 (43.4%) | 1,464 (43.0%) | 0.01    | 3879 (43.5%) | 4288 (42.6%) | 0.02    |
| Use of antidepressants; n (%)                                  | 385 (26.2%) | 715 (25.7%)   | 0.01  | 560 (22.7%)   | 915 (23.6%)   | -0.02 | 1,907 (38.3%) | 1,309 (38.4%) | 0.00    | 2852 (32.0%) | 2939 (29.2%) | 0.06    |
| Use of antipsychotics; n (%)                                   | 69 (4.7%)   | 147 (5.3%)    | -0.03 | 94 (3.8%)     | 144 (3.7%)    | 0.01  | 763 (15.3%)   | 544 (16.0%)   | -0.02   | 926 (10.4%)  | 835 (8.3%)   | 0.07    |
| <b>Labs</b>                                                    |             |               |       |               |               |       |               |               |         |              |              |         |
| Lab values- HbA1c (%) v3; n (%)                                | 129 (8.8%)  | 284 (10.2%)   | -0.05 | ** (0.4%)     | 35 (0.9%)     | -0.06 | N/A           | N/A           | #VALUE! | #VALUE!      | 319 (4.8%)   | #VALUE! |
| Lab values- HbA1c (%) (within 3 months) v3; n (%)              | 75 (5.1%)   | 179 (6.4%)    | -0.06 | ** (0.3%)     | 23 (0.6%)     | -0.04 | N/A           | N/A           | #VALUE! | #VALUE!      | 202 (3.0%)   | #VALUE! |
| Lab values- HbA1c (%) (within 6 months) v3; n (%)              | 129 (8.8%)  | 284 (10.2%)   | -0.05 | ** (0.4%)     | 35 (0.9%)     | -0.06 | N/A           | N/A           | #VALUE! | #VALUE!      | 319 (4.8%)   | #VALUE! |
| Lab values- BNP; n (%)                                         | 22 (1.5%)   | 37 (1.3%)     | 0.02  | 0 (0.0%)      | ** (0.2%)     | -0.06 | N/A           | N/A           | #VALUE! | 022 (0.6%)   | #VALUE!      | #VALUE! |
| Lab values- BNP (within 3 months); n (%)                       | 21 (1.4%)   | 35 (1.3%)     | 0.01  | 0 (0.0%)      | ** (0.2%)     | -0.06 | N/A           | N/A           | #VALUE! | 021 (0.5%)   | #VALUE!      | #VALUE! |
| Lab values- BNP (within 6 months); n (%)                       | 22 (1.5%)   | 37 (1.3%)     | 0.02  | 0 (0.0%)      | ** (0.2%)     | -0.06 | N/A           | N/A           | #VALUE! | 022 (0.6%)   | #VALUE!      | #VALUE! |
| Lab values- BUN (mg/dl); n (%)                                 | 290 (19.7%) | 642 (23.1%)   | -0.08 | 18 (0.7%)     | 49 (1.3%)     | -0.06 | N/A           | N/A           | #VALUE! | 308 (7.8%)   | 691 (10.4%)  | -0.09   |
| Lab values- BUN (mg/dl) (within 3 months); n (%)               | 203 (13.8%) | 452 (16.6%)   | -0.07 | ** (0.4%)     | 32 (0.8%)     | -0.05 | N/A           | N/A           | #VALUE! | 484 (7.3%)   | #VALUE!      | #VALUE! |
| Lab values- BUN (mg/dl) (within 6 months); n (%)               | 290 (19.7%) | 642 (23.1%)   | -0.08 | 18 (0.7%)     | 49 (1.3%)     | -0.06 | N/A           | N/A           | #VALUE! | 308 (7.8%)   | 691 (10.4%)  | -0.09   |
| Lab values- Creatinine (mg/dl); v2; n (%)                      | 297 (20.2%) | 679 (24.4%)   | -0.10 | 20 (0.8%)     | 52 (1.3%)     | -0.05 | N/A           | N/A           | #VALUE! | 317 (8.1%)   | 731 (11.0%)  | -0.10   |
| Lab values- Creatinine (mg/dl) (within 3 months) v2; n (%)     | 206 (14.0%) | 483 (17.4%)   | -0.09 | 12 (0.5%)     | 34 (0.9%)     | -0.05 | N/A           | N/A           | #VALUE! | 218 (5.5%)   | 517 (7.8%)   | -0.09   |
| Lab values- Creatinine (mg/dl) (within 6 months) v2; n (%)     | 297 (20.2%) | 679 (24.4%)   | -0.10 | 20 (0.8%)     | 52 (1.3%)     | -0.05 | N/A           | N/A           | #VALUE! | 317 (8.1%)   | 731 (11.0%)  | -0.10   |
| Lab values- HDL level (mg/dl); n (%)                           | 164 (11.1%) | 376 (13.5%)   | -0.07 | 12 (0.5%)     | 37 (1.0%)     | -0.06 | N/A           | N/A           | #VALUE! | 176 (4.5%)   | 413 (6.2%)   | -0.08   |
| Lab values- HDL level (mg/dl) (within 3 months); n (%)         | 90 (6.1%)   | 211 (7.6%)    | -0.06 | ** (0.3%)     | 23 (0.6%)     | -0.04 | N/A           | N/A           | #VALUE! | 234 (3.5%)   | #VALUE!      | #VALUE! |
| Lab values- HDL level (mg/dl) (within 6 months); n (%)         | 164 (11.1%) | 376 (13.5%)   | -0.07 | 12 (0.5%)     | 37 (1.0%)     | -0.06 | N/A           | N/A           | #VALUE! | 176 (4.5%)   | 413 (6.2%)   | -0.08   |
| Lab values- LDL level (mg/dl); v2; n (%)                       | 167 (11.3%) | 387 (13.9%)   | -0.08 | 13 (0.5%)     | 37 (1.0%)     | -0.06 | N/A           | N/A           | #VALUE! | 180 (4.6%)   | 424 (6.4%)   | -0.08   |

# Appendix B

|                                                                             |                 |                 |       |                       |                   |         |             |             |                  |                 |             |         |  |
|-----------------------------------------------------------------------------|-----------------|-----------------|-------|-----------------------|-------------------|---------|-------------|-------------|------------------|-----------------|-------------|---------|--|
| Lab values- LDL level (mg/dl) (within 3 months) v2; n (%)                   | 91 (6.2%)       | 217 (7.8%)      | -0.06 | ** (0.3%)             | 24 (0.6%)         | -0.04   | N/A         | N/A         | #VALUE!          | #VALUE!         | 241 (3.6%)  | #VALUE! |  |
| Lab values- LDL level (mg/dl) (within 6 months) v2; n (%)                   | 167 (11.3%)     | 387 (13.9%)     | -0.08 | 13 (0.5%)             | 37 (1.0%)         | -0.06   | N/A         | N/A         | #VALUE!          | 180 (4.6%)      | 424 (6.4%)  | -0.08   |  |
| Lab values- NT-proBNP; n (%)                                                | ** (0.6%)       | ** (0.2%)       | 0.06  | 0 (0.0%)              | 0 (0.0%)          | #DIV/0! | N/A         | N/A         | #VALUE!          | #VALUE!         | #VALUE!     | #VALUE! |  |
| Lab values- NT-proBNP (within 3 months); n (%)                              | ** (0.5%)       | ** (0.1%)       | 0.07  | 0 (0.0%)              | 0 (0.0%)          | #DIV/0! | N/A         | N/A         | #VALUE!          | #VALUE!         | #VALUE!     | -       |  |
| Lab values- NT-proBNP (within 6 months); n (%)                              | ** (0.6%)       | ** (0.2%)       | 0.06  | 0 (0.0%)              | 0 (0.0%)          | #DIV/0! | N/A         | N/A         | #VALUE!          | #VALUE!         | #VALUE!     | -       |  |
| Lab values- Total cholesterol (mg/dl) v2; n (%)                             | 169 (11.5%)     | 386 (13.9%)     | -0.07 | ** (0.4%)             | 38 (1.0%)         | -0.07   | N/A         | N/A         | #VALUE!          | #VALUE!         | 424 (6.4%)  | #VALUE! |  |
| Lab values- Total cholesterol (mg/dl) (within 3 months) v2; n (%)           | 92 (6.2%)       | 215 (7.7%)      | -0.06 | ** (0.3%)             | 24 (0.6%)         | -0.04   | N/A         | N/A         | #VALUE!          | #VALUE!         | 239 (3.6%)  | #VALUE! |  |
| Lab values- Total cholesterol (mg/dl) (within 6 months) v2; n (%)           | 169 (11.5%)     | 386 (13.9%)     | -0.07 | ** (0.4%)             | 38 (1.0%)         | -0.07   | N/A         | N/A         | #VALUE!          | #VALUE!         | 424 (6.4%)  | #VALUE! |  |
| Lab values- Triglyceride level (mg/dl); n (%)                               | 167 (11.3%)     | 382 (13.7%)     | -0.07 | 12 (0.5%)             | 36 (0.9%)         | -0.05   | N/A         | N/A         | #VALUE!          | 179 (4.5%)      | 418 (6.3%)  | -0.08   |  |
| Lab values- Triglyceride level (mg/dl) (within 3 months); n (%)             | 90 (6.1%)       | 212 (7.6%)      | -0.06 | ** (0.3%)             | 22 (0.6%)         | -0.04   | N/A         | N/A         | #VALUE!          | #VALUE!         | 234 (3.5%)  | #VALUE! |  |
| Lab values- Triglyceride level (mg/dl) (within 6 months); n (%)             | 167 (11.3%)     | 382 (13.7%)     | -0.07 | 12 (0.5%)             | 36 (0.9%)         | -0.05   | N/A         | N/A         | #VALUE!          | 179 (4.5%)      | 418 (6.3%)  | -0.08   |  |
| Lab result number- HbA1c (%) mean (only 2 to 20 included) v4                | 129             | 283             |       | 11                    | 35                |         | N/A         | N/A         | 140              | 318             |             |         |  |
| ...mean (sd)                                                                | 6.38 (1.65)     | 6.67 (1.84)     | -0.17 | 7.09 (1.28)           | 7.19 (1.62)       | -0.07   | N/A         | N/A         | 6.44 (1.63)      | 6.73 (1.82)     | -0.17       |         |  |
| ...Missing; n (%)                                                           | 1,343 (91.2%)   | 2,500 (89.8%)   | 0.05  | 2,453 (99.6%)         | 3,839 (99.1%)     | 0.06    | N/A         | N/A         | 3,796 (96.4%)    | 6,339 (95.2%)   | 0.06        |         |  |
| Lab result number- BNP mean v2                                              | 22              | 37              |       | -                     | 6                 |         | N/A         | N/A         | 22               | 43              |             |         |  |
| ...mean (sd)                                                                | 188.71 (481.48) | 211.85 (716.09) | -0.04 | - (-)                 | 821.82 (1,746.63) | #VALUE! | N/A         | N/A         | #VALUE!          | 296.96 (918.07) | #VALUE!     |         |  |
| ...Missing; n (%)                                                           | 1,450 (98.5%)   | 2,746 (98.7%)   | -0.02 | 2,464 (100.0%)        | 3,868 (99.8%)     | 0.06    | N/A         | N/A         | 3,914 (99.4%)    | 6,614 (99.4%)   | 0.00        |         |  |
| Lab result number- BUN (mg/dl) mean v2                                      | 290             | 642             |       | 18                    | 49                |         | N/A         | N/A         | 308              | 691             |             |         |  |
| ...mean (sd)                                                                | 14.97 (5.67)    | 14.75 (4.93)    | 0.04  | 11,126.96 (35,122.84) | 14.95 (5.16)      | 0.45    | N/A         | N/A         | 664.37 (8292.09) | 14.76 (4.95)    | 0.11        |         |  |
| ...Missing; n (%)                                                           | 1,182 (80.3%)   | 2,141 (76.9%)   | 0.08  | 2,446 (99.3%)         | 3,825 (98.7%)     | 0.06    | N/A         | N/A         | 3,628 (92.2%)    | 5,966 (89.6%)   | 0.09        |         |  |
| Lab result number- Creatinine (mg/dl) mean (only 0.1 to 15 included) v3     | 292             | 674             |       | 18                    | 52                |         | N/A         | N/A         | 310              | 726             |             |         |  |
| ...mean (sd)                                                                | 0.91 (0.29)     | 0.92 (0.23)     | -0.04 | 1.05 (0.31)           | 0.95 (0.19)       | 0.39    | N/A         | N/A         | 0.92 (0.29)      | 0.92 (0.23)     | 0.00        |         |  |
| ...Missing; n (%)                                                           | 1,180 (80.2%)   | 2,109 (75.8%)   | 0.11  | 2,446 (99.3%)         | 3,822 (98.7%)     | 0.06    | N/A         | N/A         | 3,626 (92.1%)    | 5,931 (89.1%)   | 0.10        |         |  |
| Lab result number- HDL level (mg/dl) mean (only <5000 included) v2          | 164             | 376             |       | 11                    | 37                |         | N/A         | N/A         | 175              | 413             |             |         |  |
| ...mean (sd)                                                                | 54.89 (18.99)   | 49.89 (16.20)   | 0.28  | 48.00 (11.92)         | 42.95 (12.24)     | 0.42    | N/A         | N/A         | 54.46 (18.71)    | 49.27 (15.91)   | 0.30        |         |  |
| ...Missing; n (%)                                                           | 1,308 (88.9%)   | 2,407 (86.5%)   | 0.07  | 2,453 (99.6%)         | 3,837 (99.0%)     | 0.07    | N/A         | N/A         | 3,761 (95.6%)    | 6,244 (93.8%)   | 0.08        |         |  |
| Lab result number- LDL level (mg/dl) mean (only <5000 included) v2          | 164             | 385             |       | 11                    | 34                |         | N/A         | N/A         | 175              | 419             |             |         |  |
| ...mean (sd)                                                                | 108.72 (37.92)  | 112.46 (39.24)  | -0.10 | 92.09 (39.78)         | 94.24 (30.60)     | -0.06   | N/A         | N/A         | 107.67 (38.14)   | 110.98 (38.67)  | -0.09       |         |  |
| ...Missing; n (%)                                                           | 1,308 (88.9%)   | 2,398 (86.2%)   | 0.08  | 2,453 (99.6%)         | 3,840 (99.1%)     | 0.06    | N/A         | N/A         | 3,761 (95.6%)    | 6,238 (93.7%)   | 0.08        |         |  |
| Lab result number- Total cholesterol (mg/dl) mean (only <5000 included) v2  | 169             | 386             |       | 10                    | 38                |         | N/A         | N/A         | 179              | 424             |             |         |  |
| ...mean (sd)                                                                | 191.79 (42.02)  | 191.77 (43.11)  | 0.00  | 176.40 (28.15)        | 173.63 (53.27)    | 0.07    | N/A         | N/A         | 190.93 (41.54)   | 190.14 (44.15)  | 0.02        |         |  |
| ...Missing; n (%)                                                           | 1,303 (88.5%)   | 2,397 (86.1%)   | 0.07  | 2,454 (99.6%)         | 3,836 (99.0%)     | 0.07    | N/A         | N/A         | 3,757 (95.5%)    | 6,233 (93.6%)   | 0.08        |         |  |
| Lab result number- Triglyceride level (mg/dl) mean (only <5000 included) v2 | 167             | 382             |       | 11                    | 36                |         | N/A         | N/A         | 178              | 418             |             |         |  |
| ...mean (sd)                                                                | 132.55 (72.17)  | 147.15 (76.74)  | -0.20 | 163.09 (137.89)       | 220.01 (535.52)   | -0.15   | N/A         | N/A         | 134.44 (77.63)   | 153.43 (172.03) | -0.14       |         |  |
| ...Missing; n (%)                                                           | 1,305 (88.7%)   | 2,401 (86.3%)   | 0.07  | 2,453 (99.6%)         | 3,838 (99.1%)     | 0.06    | N/A         | N/A         | 3,758 (95.5%)    | 6,239 (93.7%)   | 0.08        |         |  |
| Lab result number- Hemoglobin mean (only >0 included)                       | 255             | 568             |       | 13                    | 41                |         | N/A         | N/A         | 268              | 609             |             |         |  |
| ...mean (sd)                                                                | 13.68 (1.85)    | 13.90 (1.82)    | -0.12 | 18,472.91 (45,243.58) | 14.22 (1.44)      | 0.58    | N/A         | N/A         | 909.09 (9627.75) | 13.92 (1.80)    | 0.13        |         |  |
| ...Missing; n (%)                                                           | 1,217 (82.7%)   | 2,215 (79.6%)   | 0.08  | 2,451 (99.5%)         | 3,833 (98.9%)     | 0.07    | N/A         | N/A         | 3,668 (93.2%)    | 6,048 (90.9%)   | 0.09        |         |  |
| Lab result number- Serum sodium mean (only >90 and <190 included)           | 283             | 641             |       | 16                    | 50                |         | N/A         | N/A         | 299              | 691             |             |         |  |
| ...mean (sd)                                                                | 140.35 (2.52)   | 140.27 (2.65)   | 0.03  | 138.74 (3.71)         | 139.42 (2.77)     | -0.21   | N/A         | N/A         | 140.26 (2.60)    | 140.21 (2.66)   | 0.02        |         |  |
| ...Missing; n (%)                                                           | 1,189 (80.8%)   | 2,142 (77.0%)   | 0.09  | 2,448 (99.4%)         | 3,824 (98.7%)     | 0.07    | N/A         | N/A         | 3,637 (92.4%)    | 5,966 (89.6%)   | 0.10        |         |  |
| Lab result number- Albumin mean (only >0 and <=10 included)                 | 254             | 602             |       | 14                    | 41                |         | N/A         | N/A         | 268              | 643             |             |         |  |
| ...mean (sd)                                                                | 4.05 (0.45)     | 4.16 (0.37)     | -0.27 | 4.10 (0.28)           | 4.09 (0.41)       | 0.03    | N/A         | N/A         | 4.05 (0.44)      | 4.16 (0.37)     | -0.27       |         |  |
| ...Missing; n (%)                                                           | 1,218 (82.7%)   | 2,181 (78.4%)   | 0.11  | 2,450 (99.4%)         | 3,833 (98.9%)     | 0.05    | N/A         | N/A         | 3,668 (93.2%)    | 6,014 (90.3%)   | 0.11        |         |  |
| Lab result number- Glucose (fasting or random) mean (only 10-1000 included) | 282             | 638             |       | 17                    | 52                |         | N/A         | N/A         | 299              | 690             |             |         |  |
| ...mean (sd)                                                                | 107.08 (33.93)  | 111.43 (45.57)  | -0.11 | 140.46 (83.78)        | 142.00 (79.78)    | -0.02   | N/A         | N/A         | 108.98 (38.37)   | 113.73 (48.97)  | -0.11       |         |  |
| ...Missing; n (%)                                                           | 1,190 (80.8%)   | 2,145 (77.1%)   | 0.09  | 2,447 (99.3%)         | 3,822 (98.7%)     | 0.06    | N/A         | N/A         | 3,637 (92.4%)    | 5,967 (89.6%)   | 0.10        |         |  |
| Lab result number- Potassium mean (only 1-7 included)                       | 294             | 667             |       | 17                    | 48                |         | N/A         | N/A         | 311              | 715             |             |         |  |
| ...mean (sd)                                                                | 4.33 (0.42)     | 4.36 (0.38)     | -0.07 | 4.36 (0.54)           | 4.28 (0.39)       | 0.17    | N/A         | N/A         | 4.33 (0.43)      | 4.35 (0.38)     | -0.05       |         |  |
| ...Missing; n (%)                                                           | 1,178 (80.0%)   | 2,116 (76.0%)   | 0.10  | 2,447 (99.3%)         | 3,826 (98.8%)     | 0.05    | N/A         | N/A         | 3,625 (92.1%)    | 5,942 (89.3%)   | 0.10        |         |  |
| <b>Comorbidity Scores</b>                                                   |                 |                 |       |                       |                   |         |             |             |                  |                 |             |         |  |
| Combined comorbidity score, 365 days Copy                                   |                 |                 |       |                       |                   |         |             |             |                  |                 |             |         |  |
| ...mean (sd)                                                                | 3.18 (2.27)     | 3.34 (2.24)     | -0.07 | 2.50 (2.14)           | 2.91 (2.13)       | -0.19   | 3.69 (2.64) | 3.77 (2.52) | -0.03            | 3.28 (2.45)     | 3.32 (2.30) | -0.02   |  |

# Appendix B

|                                                                                            |               |               |         |               |               |         |               |               |           |               |               |         |
|--------------------------------------------------------------------------------------------|---------------|---------------|---------|---------------|---------------|---------|---------------|---------------|-----------|---------------|---------------|---------|
| Non-Frailty; n (%)                                                                         | 607 (41.2%)   | 1,297 (46.6%) | -0.11   | 986 (40.0%)   | 1,622 (41.9%) | -0.04   | 219 (4.4%)    | 103 (3.0%)    | 0.07      | 1,812 (20.3%) | 3,022 (30.0%) | -0.22   |
| Frailty Score (mean): Empirical Version 365 days, v2                                       |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.17 (0.06)   | 0.17 (0.06)   | 0.00    | 0.16 (0.05)   | 0.15 (0.05)   | 0.20    | 0.10 (0.08)   | 0.09 (0.07)   | 0.13      | 0.13 (0.07)   | 0.14 (0.06)   | -0.15   |
| <b>Healthcare Utilization</b>                                                              |               |               |         |               |               |         |               |               |           |               |               |         |
| Any hospitalization; n (%)                                                                 | 1,342 (91.2%) | 2,517 (90.4%) | 0.03    | 2,456 (99.7%) | 3,872 (99.9%) | -0.04   | 4,571 (91.7%) | 2,940 (86.3%) | 0.17      | 8,369 (93.8%) | 9,329 (92.7%) | 0.04    |
| Any hospitalization within prior 30 days; n (%)                                            | 1,218 (82.7%) | 2,064 (74.2%) | 0.21    | 2,325 (94.4%) | 3,266 (84.3%) | 0.33    | 3,605 (72.3%) | 2,224 (65.3%) | 0.15      | 7148 (80.1%)  | 7554 (75.1%)  | 0.12    |
| Any hospitalization during prior 31-180 days; n (%)                                        | 210 (14.3%)   | 596 (21.4%)   | -0.19   | 279 (11.3%)   | 830 (21.4%)   | -0.28   | 1,509 (30.3%) | 1,094 (32.1%) | -0.04     | 1998 (22.4%)  | 2520 (25.0%)  | -0.06   |
| Internal medicine/family medicine visits; n (%)                                            | 1,258 (85.5%) | 2,349 (84.4%) | 0.03    | 1,907 (77.4%) | 3,135 (80.9%) | -0.09   | 4,700 (94.3%) | 3,253 (85.5%) | -0.05     | 7865 (88.2%)  | 8737 (86.8%)  | 0.04    |
| Internal medicine/family medicine visits (30 days prior); n (%)                            | 1,116 (75.8%) | 1,989 (71.5%) | 0.10    | 1,366 (55.4%) | 2,291 (59.1%) | -0.07   | 4,141 (83.1%) | 2,772 (81.4%) | 0.04      | 6623 (74.3%)  | 7052 (70.1%)  | 0.09    |
| Internal medicine/family medicine visits (31 to 180 days prior); n (%)                     | 789 (53.6%)   | 1,532 (50.5%) | -0.03   | 1,473 (59.8%) | 2,428 (62.7%) | -0.06   | 3,375 (67.7%) | 2,384 (70.0%) | -0.05     | 5637 (63.2%)  | 6344 (63.0%)  | 0.00    |
| Cardiologist visit; n (%)                                                                  | 1,070 (72.7%) | 2,090 (75.1%) | -0.05   | 635 (25.8%)   | 1,120 (28.9%) | -0.07   | 3,481 (69.9%) | 2,461 (72.3%) | -0.05     | 5186 (58.1%)  | 5671 (56.4%)  | 0.03    |
| Number of Cardiologist visits (30 days prior); n (%)                                       | 938 (63.7%)   | 1,782 (64.0%) | -0.01   | 430 (17.5%)   | 779 (20.1%)   | -0.07   | 2,604 (52.3%) | 1,815 (53.3%) | -0.02     | 3972 (44.5%)  | 4376 (43.5%)  | 0.02    |
| Number of Cardiologist visits (31 to 180 days prior); n (%)                                | 283 (19.2%)   | 629 (22.6%)   | -0.08   | 286 (11.6%)   | 527 (13.6%)   | -0.06   | 1,509 (30.3%) | 1,143 (33.6%) | -0.07     | 2078 (23.3%)  | 2299 (22.8%)  | 0.01    |
| Electrocardiogram v2; n (%)                                                                | 1,212 (82.3%) | 2,366 (85.0%) | -0.07   | 1,173 (47.6%) | 1,921 (49.6%) | -0.04   | 4,197 (84.2%) | 2,949 (86.6%) | -0.07     | 6582 (73.8%)  | 7236 (71.9%)  | 0.04    |
| Use of glucose test strips; n (%)                                                          | 12 (0.8%)     | 29 (1.0%)     | -0.02   | 28 (1.1%)     | 41 (1.1%)     | 0.00    | 79 (1.6%)     | 49 (1.4%)     | 0.02      | 119 (1.3%)    | 119 (1.2%)    | 0.01    |
| Dialysis; n (%)                                                                            | 0 (0.0%)      | ** (0.0%)     | #DIV/0! | ** (0.1%)     | ** (0.0%)     | 0.04    | ** (0.1%)     | ** (0.1%)     | 0.00      | #VALUE!       | #VALUE!       | #VALUE! |
| number of different/distinct medication prescriptions                                      |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 7.51 (5.02)   | 7.40 (5.43)   | 0.02    | 7.83 (4.96)   | 7.62 (5.35)   | 0.04    | 9.24 (6.13)   | 9.03 (6.18)   | 0.03      | 8.56 (5.65)   | 8.04 (5.67)   | 0.00    |
| Number of Hospitalizations                                                                 |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 1.06 (0.59)   | 1.04 (0.59)   | 0.03    | 1.15 (0.49)   | 1.15 (0.46)   | 0.00    | 1.26 (0.90)   | 1.19 (0.91)   | 0.08      | 1.20 (0.76)   | 1.13 (0.68)   | 0.00    |
| Number of hospital days                                                                    |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 4.88 (4.21)   | 3.69 (3.93)   | 0.29    | 5.81 (5.06)   | 4.29 (4.36)   | 0.32    | 5.63 (6.19)   | 4.42 (5.91)   | 0.20      | 5.56 (5.60)   | 4.17 (4.84)   | 0.00    |
| Number of Emergency Department (ED) visits v3                                              |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 1.67 (2.14)   | 1.71 (2.26)   | -0.02   | 3.11 (4.52)   | 3.36 (5.17)   | -0.05   | 2.65 (5.20)   | 2.69 (4.62)   | -0.01     | 2.62 (4.64)   | 2.68 (4.35)   | 0.00    |
| Number of Office visits                                                                    |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 4.43 (4.31)   | 4.96 (4.44)   | -0.12   | 4.45 (4.21)   | 5.00 (4.89)   | -0.12   | 9.79 (12.11)  | 11.14 (13.34) | -0.11     | 7.43 (9.48)   | 7.07 (8.65)   | 0.00    |
| Number of internal medicine/family medicine visits                                         |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 8.44 (11.38)  | 8.11 (12.98)  | 0.03    | 5.17 (8.34)   | 5.69 (9.30)   | -0.06   | 11.97 (12.82) | 10.87 (11.70) | 0.09      | 9.51 (11.51)  | 8.11 (11.23)  | 0.00    |
| Number of Cardiologist visits                                                              |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 2.25 (3.08)   | 2.58 (3.92)   | -0.09   | 0.63 (1.78)   | 0.78 (2.35)   | -0.07   | 2.57 (4.11)   | 2.71 (4.05)   | -0.03     | 1.98 (3.45)   | 1.93 (3.45)   | 0.00    |
| Number of electrocardiograms received v2                                                   |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 1.88 (1.87)   | 2.01 (1.96)   | -0.07   | 0.85 (1.27)   | 0.91 (1.37)   | -0.05   | 2.23 (2.51)   | 2.36 (2.62)   | -0.05     | 1.79 (2.13)   | 1.70 (2.03)   | 0.00    |
| Number of HbA1c tests ordered                                                              |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.24 (0.56)   | 0.27 (0.59)   | -0.05   | 0.20 (0.49)   | 0.22 (0.53)   | -0.04   | 0.29 (0.63)   | 0.29 (0.62)   | 0.00      | 0.26 (0.58)   | 0.26 (0.58)   | 0.00    |
| Number of glucose tests ordered                                                            |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.10 (0.52)   | 0.17 (0.82)   | -0.10   | 0.11 (0.91)   | 0.11 (0.52)   | 0.00    | 0.16 (0.58)   | 0.17 (0.72)   | -0.02     | 0.14 (0.68)   | 0.15 (0.68)   | 0.00    |
| Number of lipid tests ordered                                                              |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.35 (0.62)   | 0.37 (0.64)   | -0.03   | 0.35 (0.72)   | 0.36 (0.90)   | -0.01   | 0.34 (0.65)   | 0.40 (0.65)   | -0.09     | 0.34 (0.67)   | 0.38 (0.75)   | 0.00    |
| Total N distinct ICD9/ICD10 diagnoses at the 3rd digit level Copy                          |               |               |         |               |               |         |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 10.10 (11.60) | 10.98 (12.08) | -0.07   | 8.83 (10.24)  | 10.70 (10.19) | -0.18   | 15.68 (15.31) | 15.80 (15.08) | -0.01     | 12.87 (13.50) | 12.50 (12.54) | 0.00    |
| <b>For PS</b>                                                                              |               |               |         |               |               |         |               |               |           |               |               |         |
| Hemorrhagic stroke+Other cerebrovascular disease+Cerebrovascular procedure (for PS); n (%) | ** (0.7%)     | 17 (0.6%)     | 0.01    | 20 (0.8%)     | 23 (0.6%)     | 0.02    | 78 (1.6%)     | 54 (1.6%)     | 0.00      | #VALUE!       | 94 (0.9%)     | #VALUE! |
| immobilization; n (%)                                                                      | 37 (2.5%)     | 73 (2.6%)     | #DIV/0! | 52 (2.1%)     | 75 (1.9%)     | #DIV/0! | 2.01 (1.68)   | 1.45 (1.21)   | 52 (2.1%) | 75 (1.9%)     | 0.21          |         |
| Occurrence of creatinine tests ordered (for PS); n (%)                                     | 82 (5.6%)     | 194 (7.0%)    | -0.06   | 147 (6.0%)    | 199 (5.1%)    | 0.04    | 430 (8.6%)    | 286 (8.4%)    | 0.01      | 659 (7.4%)    | 679 (6.7%)    | 0.03    |
| Occurrence of BUN tests ordered (for PS); n (%)                                            | 33 (2.2%)     | 81 (2.9%)     | -0.04   | 76 (3.1%)     | 103 (2.7%)    | 0.02    | 225 (4.5%)    | 151 (4.4%)    | 0.00      | 334 (3.7%)    | 335 (3.3%)    | 0.02    |
| Occurrence of chronic renal insufficiency w/o CKD (for PS); v2; n (%)                      | 18 (1.2%)     | 13 (0.5%)     | 0.08    | 23 (0.9%)     | 16 (0.4%)     | 0.06    | 102 (2.0%)    | 32 (0.9%)     | 0.09      | 143 (1.6%)    | 61 (0.6%)     | 0.10    |
| Chronic kidney disease Stage 1-2 (for PS); n (%)                                           | 27 (1.8%)     | 28 (1.0%)     | 0.07    | 18 (0.7%)     | 29 (0.7%)     | 0.00    | 0             | 0             | #VALUE!   | #VALUE!       | #VALUE!       |         |
| Chronic kidney disease Stage 3-6 (for PS); n (%)                                           | 48 (3.3%)     | 90 (3.2%)     | 0.01    | 56 (2.3%)     | 75 (1.9%)     | 0.03    | 249 (5.0%)    | 143 (4.2%)    | 0.04      | 353 (4.0%)    | 308 (3.1%)    | 0.05    |
| Acute kidney injury; n (%)                                                                 | 86 (5.8%)     | 204 (7.3%)    | #DIV/0! | 159 (6.5%)    | 264 (6.8%)    | #DIV/0! | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!   | 159 (6.5%)    | 264 (6.8%)    | 0.37    |
| Bladder stones+Kidney stones (for PS); n (%)                                               | 58 (3.9%)     | 111 (4.0%)    | -0.01   | 69 (2.8%)     | 118 (3.0%)    | -0.01   | 177 (3.6%)    | 117 (3.4%)    | 0.01      | 304 (3.4%)    | 346 (3.4%)    | 0.00    |
| Alcohol abuse or dependence+Drug abuse or dependence (for PS); n (%)                       | 93 (6.3%)     | 210 (7.5%)    | -0.05   | 77 (3.1%)     | 126 (3.3%)    | -0.01   | 387 (7.8%)    | 279 (8.2%)    | -0.01     | 557 (6.2%)    | 615 (6.1%)    | 0.00    |
| Other atherosclerosis+Cardiac conduction disorders+Other CVD (for PS); v2 Copy; n (%)      | 459 (31.2%)   | 916 (32.9%)   | -0.04   | 670 (27.2%)   | 1,136 (29.3%) | -0.05   | 1,423 (28.6%) | 1,010 (29.7%) | -0.02     | 2552 (28.6%)  | 3062 (30.4%)  | -0.04   |

# Appendix B

|                                                                                   |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
|-----------------------------------------------------------------------------------|---------------------|---------------------|-------------|---------------------|---------------------|---------------|-----------------|-----------------|--------------|-------------------|-------------------|---------|---------|------|
| Previous cardiac procedure (CABG or PTCA or Stent) +                              |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| History of CABG or PTCA (for PS) ; n (%)                                          | 44 (3.0%)           | 67 (2.4%)           | 0.04        | 24 (1.0%)           | 41 (1.1%)           | -0.01         | 236 (4.7%)      | 166 (4.9%)      | -0.01        | 304 (3.4%)        | 274 (2.7%)        | 0.04    |         |      |
| Diabetes with complication; n (%)                                                 | 61 (4.1%)           | 193 (6.9%)          | #DIV/0!     | 96 (3.9%)           | 139 (3.6%)          | #DIV/0!       | 240 (4.8%)      | 165 (4.8%)      | #DIV/0!      | 96 (3.9%)         | 139 (3.6%)        | 0.28    |         |      |
| Delirium + Psychosis (for PS); n (%)                                              | 56 (3.8%)           | 123 (4.4%)          | -0.03       | 58 (2.4%)           | 88 (2.3%)           | 0.01          | 681 (13.7%)     | 456 (13.4%)     | 0.01         | 795 (8.9%)        | 667 (6.6%)        | 0.09    |         |      |
| Any use of Meglitinides (for PS); n (%)                                           | 0 (0.0%)            | ** (0.1%)           | -0.04       | ** (0.1%)           | ** (0.0%)           | 0.04          | ** (0.0%)       | ** (0.0%)       | #DIV/0!      | #VALUE!           | #VALUE!           | #VALUE! | #VALUE! |      |
| Any use of AGIs (for PS); n (%)                                                   | ** (0.1%)           | ** (0.0%)           | 0.04        | ** (0.0%)           | ** (0.0%)           | #DIV/0!       | ** (0.0%)       | 0 (0.0%)        | #DIV/0!      | #VALUE!           | #VALUE!           | #VALUE! | #VALUE! |      |
| CKD stage 3-6 + dialysis (for PS); n (%)                                          | 48 (3.3%)           | 93 (3.3%)           | 0.00        | 58 (2.4%)           | 77 (2.0%)           | 0.03          | 251 (5.0%)      | 147 (4.3%)      | 0.03         | 357 (4.0%)        | 317 (3.2%)        | 0.04    |         |      |
| Use of thiazide-United; n (%)                                                     | 80 (5.4%)           | 111 (4.0%)          | 0.07        | 144 (5.8%)          | 218 (5.6%)          | 0.01          | 218 (4.4%)      | 132 (3.9%)      | 0.03         | 442 (5.0%)        | 461 (4.6%)        | 0.02    |         |      |
| Use of beta blockers; n (%)                                                       | 204 (13.9%)         | 361 (13.0%)         | 0.03        | 391 (15.9%)         | 629 (16.2%)         | -0.01         | 933 (18.7%)     | 556 (16.3%)     | 0.06         | 1528 (17.1%)      | 1546 (15.4%)      | 0.05    |         |      |
| Use of calcium channel blockers; n (%)                                            | 151 (10.3%)         | 283 (10.2%)         | 0.00        | 280 (11.4%)         | 463 (12.0%)         | -0.02         | 507 (10.2%)     | 305 (9.0%)      | 0.04         | 938 (10.5%)       | 1051 (10.4%)      | 0.00    |         |      |
| All antidiabetic medications except Insulin; n (%)                                | 146 (9.9%)          | 299 (10.7%)         | -0.03       | 259 (10.5%)         | 426 (11.1%)         | -0.02         | 620 (12.4%)     | 405 (11.9%)     | 0.02         | 1025 (11.5%)      | 1130 (11.2%)      | 0.01    |         |      |
| DM Medications -Insulin Copy; n (%)                                               | 48 (3.3%)           | 111 (4.0%)          | -0.04       | 112 (4.5%)          | 147 (3.8%)          | 0.04          | 247 (5.0%)      | 149 (4.4%)      | 0.03         | 407 (4.6%)        | 407 (4.0%)        | 0.03    |         |      |
| Use of Low Intensity Statins; n (%)                                               | 169 (11.5%)         | 283 (10.2%)         | 0.04        | 245 (9.9%)          | 375 (9.7%)          | 0.01          | 788 (15.8%)     | 546 (16.0%)     | -0.01        | 1202 (13.5%)      | 1204 (12.0%)      | 0.04    |         |      |
| Use of High Intensity Statins; n (%)                                              | 127 (8.6%)          | 281 (10.1%)         | -0.05       | 216 (8.8%)          | 380 (9.8%)          | -0.03         | 562 (11.3%)     | 417 (12.2%)     | -0.03        | 905 (10.1%)       | 1078 (10.7%)      | -0.02   |         |      |
| Malignant hypertension; n (%)                                                     | ** (0.6%)           | ** (0.1%)           | 0.08        | 317 (12.9%)         | 101 (2.6%)          | 0.39          | 517 (10.4%)     | 93 (2.7%)       | 0.32         | #VALUE!           | #VALUE!           | #VALUE! |         |      |
| Cardiovascular stress test; n (%)                                                 | ** (0.7%)           | 12 (0.4%)           | 0.04        | 12 (0.5%)           | 26 (0.7%)           | -0.03         | 73 (1.5%)       | 60 (1.8%)       | -0.02        | #VALUE!           | 98 (1.0%)         | #VALUE! |         |      |
| Echocardiogram; n (%)                                                             | 909 (61.8%)         | 1,927 (69.2%)       | -0.16       | 1,573 (63.8%)       | 2,714 (70.1%)       | -0.13         | 2,941 (59.0%)   | 2,092 (61.4%)   | -0.05        | 5423 (60.8%)      | 6733 (66.9%)      | -0.13   |         |      |
| Number of BNP tests                                                               |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 0.14 (0.44)         | 0.19 (0.52)         | -0.10       | 0.13 (0.44)         | 0.17 (0.48)         | -0.09         | 0.20 (0.56)     | 0.23 (0.56)     | -0.05        | 0.17 (0.51)       | 0.20 (0.52)       | -0.06   |         |      |
| Number of Cardiac biomarkers tests (tropnin, CK-MBs, Myoglobin, CPK)              |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 0.45 (1.21)         | 0.61 (1.57)         | -0.11       | 0.42 (1.08)         | 0.50 (1.30)         | -0.07         | 0.41 (0.85)     | 0.49 (1.00)     | -0.09        | 0.42 (0.98)       | 0.53 (1.29)       | 0.00    |         |      |
| Number of Ambulatory Blood pressure monitoring tests                              |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 0.00 (0.00)         | 0.00 (0.03)         | 0.00        | 0.00 (0.03)         | 0.00 (0.02)         | 0.00          | 0.00 (0.00)     | 0.00 (0.00)     | #DIV/0!      | 0.00 (0.02)       | 0.00 (0.02)       | 0.00    |         |      |
| N of days on antihypertensive medications during baseline                         |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 37.98 (65.20)       | 35.77 (64.02)       | 0.03        | 43.81 (70.14)       | 45.02 (70.00)       | -0.02         | 41.02 (66.36)   | 38.28 (65.03)   | 0.04         | 41.29 (67.24)     | 40.18 (66.72)     | 0.00    |         |      |
| N of days in database anytime prior                                               |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 1,695.95 (1,337.57) | 1,675.11 (1,387.51) | 0.02        | 2,110.22 (1,479.65) | 2,106.29 (1,554.62) | 0.00          | 650.58 (464.01) | 703.17 (394.05) | -0.12        | 1226.36 (1010.09) | 1512.13 (1231.02) | 0.00    |         |      |
| Mean Copay for per prescription cost (charges in U.S. \$) (180-1 day prior)       |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 22.40 (42.74)       | 20.39 (46.66)       | 0.04        | 11.68 (20.56)       | 11.08 (17.18)       | 0.03          | 110.93 (145.27) | 119.78 (325.16) | -0.04        | 68.90 (110.50)    | 50.45 (191.05)    | 0.00    |         |      |
| ...Missing; n (%)                                                                 | 215 (14.6%)         | 305 (11.0%)         | 0.11        | 296 (12.0%)         | 380 (9.8%)          | 0.07          | 595 (11.9%)     | 349 (10.2%)     | 0.05         | 1106 (12.4%)      | 1034 (10.3%)      | 0.07    |         |      |
| Colonoscopy; n (%)                                                                | 45 (3.1%)           | 102 (3.7%)          | -0.03       | 109 (4.4%)          | 148 (3.8%)          | 0.03          | 131 (2.6%)      | 105 (3.1%)      | -0.03        | 285 (3.2%)        | 355 (5.8%)        | -0.02   |         |      |
| Fecal occult blood (FOB) test; n (%)                                              | 44 (3.0%)           | 53 (1.9%)           | 0.07        | 81 (3.3%)           | 117 (3.0%)          | 0.02          | 93 (1.9%)       | 83 (2.4%)       | -0.03        | 218 (2.4%)        | 253 (2.5%)        | -0.01   |         |      |
| Flu vaccine; n (%)                                                                | 180 (12.2%)         | 385 (13.8%)         | -0.05       | 243 (9.9%)          | 376 (9.7%)          | 0.01          | 1,351 (27.1%)   | 881 (25.9%)     | 0.03         | 1774 (19.9%)      | 1642 (16.3%)      | 0.09    |         |      |
| Mammogram; n (%)                                                                  | 139 (9.4%)          | 279 (10.0%)         | -0.02       | 228 (9.3%)          | 382 (9.9%)          | -0.02         | 437 (8.8%)      | 313 (9.2%)      | -0.01        | 804 (9.0%)        | 974 (9.7%)        | -0.02   |         |      |
| Pap smear; n (%)                                                                  | 81 (5.5%)           | 152 (5.5%)          | 0.00        | 165 (6.7%)          | 307 (7.9%)          | -0.05         | 164 (3.3%)      | 120 (3.5%)      | -0.01        | 410 (4.6%)        | 579 (5.8%)        | -0.05   |         |      |
| Pneumonia vaccine; n (%)                                                          | 254 (17.3%)         | 595 (21.4%)         | -0.10       | 250 (10.1%)         | 504 (13.0%)         | -0.09         | 1,373 (27.6%)   | 1,063 (31.2%)   | -0.08        | 1877 (21.0%)      | 2162 (21.5%)      | -0.01   |         |      |
| PSA test or Prostate exam for DRE; n (%)                                          | 117 (7.9%)          | 283 (10.2%)         | -0.08       | 225 (9.1%)          | 381 (8.9%)          | -0.02         | 379 (7.6%)      | 313 (9.2%)      | -0.06        | 721 (8.1%)        | 977 (9.7%)        | -0.06   |         |      |
| Bone mineral density; n (%)                                                       | 28 (1.9%)           | 66 (2.4%)           | -0.03       | 29 (1.2%)           | 55 (1.4%)           | -0.02         | 133 (2.7%)      | 136 (4.0%)      | -0.07        | 190 (2.1%)        | 257 (2.6%)        | -0.03   |         |      |
| Use of CNS stimulants; n (%)                                                      | 15 (1.0%)           | 43 (1.5%)           | -0.05       | 19 (0.8%)           | 67 (1.7%)           | -0.08         | 40 (0.8%)       | 28 (0.8%)       | 0.00         | 74 (0.8%)         | 138 (1.4%)        | -0.06   |         |      |
| Use of estrogens, progestins, androgens; n (%)                                    | 151 (10.3%)         | 309 (11.1%)         | -0.03       | 284 (11.5%)         | 637 (16.4%)         | -0.14         | 220 (4.4%)      | 183 (5.4%)      | -0.05        | 655 (7.3%)        | 1129 (11.2%)      | 0.13    | 0.13    | 0.13 |
| Use of Angiogenesis inhibitors; n (%)                                             | ** (0.1%)           | ** (0.0%)           | 0.04        | ** (0.0%)           | ** (0.1%)           | -0.04         | ** (0.1%)       | ** (0.1%)       | 0.00         | #VALUE!           | #VALUE!           | #VALUE! |         |      |
| Use of Oral Immunosuppressants; n (%)                                             | ** (0.1%)           | ** (0.2%)           | -0.03       | 13 (0.5%)           | ** (0.3%)           | 0.03          | 12 (0.2%)       | ** (0.2%)       | 0.00         | #VALUE!           | #VALUE!           | #VALUE! |         |      |
| Use of fondaparinux or Bivalirudin; n (%)                                         | ** (0.2%)           | ** (0.1%)           | 0.03        | 13 (0.5%)           | ** (0.1%)           | 0.07          | ** (0.2%)       | ** (0.1%)       | 0.03         | #VALUE!           | #VALUE!           | #VALUE! |         |      |
| Use of other direct thrombin inhibitors (lepirudin, desirudin, argatroban); n (%) | 0 (0.0%)            | 0 (0.0%)            | #DIV/0!     | 0 (0.0%)            | #DIV/0!             | 0 (0.0%)      | 0 (0.0%)        | 0 (0.0%)        | #DIV/0!      | 0 (0.0%)          | 0 (0.0%)          | #DIV/0! |         |      |
| Use of Ticagrelor ON CED; n (%)                                                   | 0 (0.0%)            | 0 (0.0%)            | #DIV/0!     | ** (0.0%)           | ** (0.1%)           | -0.04         | ** (0.0%)       | ** (0.1%)       | -0.04        | #VALUE!           | #VALUE!           | #VALUE! |         |      |
| Use of Ticagrelor; n (%)                                                          | 0 (0.0%)            | 0 (0.0%)            | #DIV/0!     | ** (0.0%)           | ** (0.1%)           | -0.04         | ** (0.0%)       | ** (0.3%)       | -0.08        | #VALUE!           | #VALUE!           | #VALUE! |         |      |
| Number of D-dimer tests                                                           |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 0.18 (0.45)         | 0.20 (0.47)         | -0.04       | 0.16 (0.42)         | 0.19 (0.48)         | -0.07         | 0.18 (0.44)     | 0.22 (0.50)     | -0.08        | 0.17 (0.44)       | 0.20 (0.48)       | 0.00    |         |      |
| Number of CRP, high-sensitivity CRP tests                                         |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 0.09 (0.43)         | 0.12 (0.59)         | -0.06       | 0.09 (0.39)         | 0.11 (0.56)         | -0.04         | 0.12 (0.54)     | 0.15 (0.58)     | -0.05        | 0.11 (0.49)       | 0.13 (0.58)       | 0.00    |         |      |
| Number of PT or aPTT tests                                                        |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 1.08 (2.54)         | 0.67 (1.47)         | 0.20        | 0.97 (2.49)         | 0.63 (1.48)         | 0.17          | 1.27 (2.98)     | 0.42 (0.90)     | 0.39         | 1.16 (2.78)       | 0.57 (1.31)       | 0.00    |         |      |
| Number of Bleeding time tests                                                     |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 0.00 (0.00)         | 0.00 (0.00)         | #DIV/0!     | 0.00 (0.02)         | 0.00 (0.00)         | 0.00          | 0.00 (0.00)     | 0.00 (0.00)     | #DIV/0!      | 0.00 (0.01)       | 0.00 (0.00)       | 0.00    |         |      |
| HAS-BLED Score (ICD-9 and ICD-10), 180 days                                       |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 2.01 (0.69)         | 1.99 (0.71)         | 0.03        | 1.88 (0.70)         | 1.88 (0.68)         | 0.00          | 2.34 (0.79)     | 2.36 (0.77)     | -0.03        | 2.16 (0.75)       | 2.07 (0.72)       | 0.00    |         |      |
| N of Generic name drugs                                                           |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 13.81 (14.14)       | 12.17 (14.72)       | 0.11        | 11.84 (10.98)       | 10.94 (11.84)       | 0.08          | 18.87 (18.89)   | 17.63 (18.34)   | 0.07         | 16.09 (16.30)     | 13.54 (15.09)     | 0.00    |         |      |
| N of Brand name drugs                                                             |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| ...mean (sd)                                                                      | 1.91 (3.43)         | 3.26 (4.17)         | -0.35       | 2.10 (3.31)         | 3.10 (3.40)         | -0.30         | 3.01 (5.24)     | 4.06 (5.03)     | -0.20        | 2.58 (4.51)       | 3.47 (4.22)       | 0.00    |         |      |
| Use of clopidogrel; n (%)                                                         | 12 (0.8%)           | ** (0.3%)           | 0.07        | 18 (0.7%)           | 16 (0.4%)           | 0.04          | 175 (3.5%)      | 113 (3.3%)      | 0.01         | 205 (2.3%)        | #VALUE!           | #VALUE! |         |      |
| Systemic embolism; n (%)                                                          | 28 (1.9%)           | 47 (1.7%)           | 0.02        | 52 (2.1%)           | 73 (1.9%)           | 0.01          | 76 (1.5%)       | 58 (1.7%)       | -0.02        | 156 (1.7%)        | 178 (1.8%)        | -0.01   |         |      |
| DVT; n (%)                                                                        | 861 (58.5%)         | 1,392 (50.0%)       | 0.17        | 1,610 (65.3%)       | 1,981 (51.1%)       | 0.29          | 2,794 (56.1%)   | 1,519 (44.6%)   | 0.23         | 5265 (59.0%)      | 4892 (48.6%)      | 0.21    |         |      |
| Post-thrombotic syndrome; n (%)                                                   | 0 (0.0%)            | ** (0.1%)           | #DIV/0!     | ** (0.1%)           | ** (0.2%)           | #DIV/0!       | 131 (2.6%)      | 41 (1.2%)       | #DIV/0!      | ** (0.1%)         | ** (0.2%)         | 0.04    |         |      |
| PE; n (%)                                                                         | 1,472 (100.0%)      | 2,783 (100.0%)      | #DIV/0!     | 2,457 (99.7%)       | 3,874 (100.0%)      | -0.08         | 4,964 (99.6%)   | 3,400 (99.8%)   | -0.04        | 8893 (99.7%)      | 10057 (99.9%)     | -0.04   |         |      |
| Coagulation defects; n (%)                                                        | 28 (1.9%)           | 42 (1.5%)           | #DIV/0!     | 83 (3.4%)           | 99 (2.6%)           | #DIV/0!       | 0               | 0               | #DIV/0!      | 83 (3.4%)         | 99 (2.6%)         | 0.27    |         |      |
| Diabetes: 1 inpatient or 2 outpatient claims within 183 days; n (%)               |                     |                     |             |                     |                     |               |                 |                 |              |                   |                   |         |         |      |
| 217 (14.7%)                                                                       | 446 (16.0%)         | -0.04               | 383 (15.5%) | 574 (14.8%)         | 0.02                | 1,134 (22.8%) | 694 (20.4%)     | 0.06            | 1734 (19.4%) | 1714 (17.0%)      | 0.06              |         |         |      |

# Appendix B

|                                                                                                       |               |               |               |               |               |         |               |               |               |               |               |         |
|-------------------------------------------------------------------------------------------------------|---------------|---------------|---------------|---------------|---------------|---------|---------------|---------------|---------------|---------------|---------------|---------|
| Intracranial or retroperitoneal hemorrhage: 1 inpatient or 2 outpatient claims within 183 days; n (%) | ** (0.2%)     | ** (0.2%)     | 0.00          | ** (0.1%)     | ** (0.1%)     | 0.00    | 17 (0.3%)     | ** (0.2%)     | 0.02          | #VALUE!       | #VALUE!       | #VALUE! |
| Peptic Ulcer Disease; n (%)                                                                           | 372 (25.3%)   | 669 (24.0%)   | 0.03          | 442 (17.9%)   | 777 (20.1%)   | -0.06   | 1,545 (31.0%) | 1,080 (31.7%) | -0.02         | 2359 (26.4%)  | 2526 (25.1%)  | 0.03    |
| Upper GI bleed; n (%)                                                                                 | ** (0.2%)     | ** (0.1%)     | 0.03          | ** (0.1%)     | ** (0.1%)     | 0.00    | ** (0.1%)     | ** (0.3%)     | -0.04         | #VALUE!       | #VALUE!       | #VALUE! |
| Lower/ unspecified GI bleed; n (%)                                                                    | 17 (1.2%)     | 32 (1.1%)     | 0.01          | 38 (1.5%)     | 38 (1.0%)     | 0.05    | 59 (1.2%)     | 36 (1.1%)     | 0.01          | 114 (1.3%)    | 106 (1.1%)    | 0.02    |
| Urogenital bleed; n (%)                                                                               | 41 (2.8%)     | 77 (2.8%)     | 0.00          | 75 (3.0%)     | 115 (3.0%)    | 0.00    | 137 (2.7%)    | 92 (2.7%)     | 0.00          | 253 (2.8%)    | 284 (2.8%)    | 0.00    |
| Other bleeds; n (%)                                                                                   | 49 (3.3%)     | 103 (3.7%)    | -0.02         | 96 (3.9%)     | 144 (3.7%)    | 0.01    | 196 (3.9%)    | 114 (3.3%)    | 0.03          | 341 (3.8%)    | 361 (3.6%)    | 0.01    |
| Prior cancer; n (%)                                                                                   | 194 (13.2%)   | 447 (16.1%)   | -0.08         | 279 (11.3%)   | 511 (13.2%)   | -0.06   | 901 (18.1%)   | 751 (22.0%)   | -0.10         | 1,374 (15.4%) | 1,709 (17.0%) | -0.04   |
| Antibiotics; n (%)                                                                                    | 633 (43.0%)   | 1,313 (47.2%) | #DIV/0!       | 1,127 (45.7%) | 1,866 (48.2%) | #DIV/0! | 899 (18.0%)   | 523 (15.4%)   | #DIV/0!       | 1,127 (45.7%) | 1,866 (48.2%) | 1.30    |
| Aspirin; n (%)                                                                                        | ** (0.6%)     | 15 (0.5%)     | 0.01          | 24 (1.0%)     | 50 (1.3%)     | -0.03   | ** (0.1%)     | ** (0.2%)     | -0.03         | #VALUE!       | #VALUE!       | #VALUE! |
| Aspirin/dipyridamole; n (%)                                                                           | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!       | 0 (0.0%)      | ** (0.0%)     | #DIV/0! | ** (0.0%)     | ** (0.1%)     | -0.04         | #VALUE!       | #VALUE!       | #VALUE! |
| Other antiplatelet agents; n (%)                                                                      | ** (0.1%)     | ** (0.1%)     | 0.00          | ** (0.1%)     | ** (0.1%)     | 0.00    | 13 (0.3%)     | ** (0.2%)     | 0.02          | #VALUE!       | #VALUE!       | #VALUE! |
| PGP inhibitors; n (%)                                                                                 | 290 (19.7%)   | 590 (21.2%)   | -0.04         | 512 (20.8%)   | 842 (21.7%)   | -0.02   | 1,127 (22.6%) | 834 (24.5%)   | -0.04         | 1,929 (21.6%) | 2,266 (22.5%) | -0.02   |
| Other gastroprotective agents; n (%)                                                                  | 14 (1.0%)     | 38 (1.4%)     | -0.04         | 22 (0.9%)     | 51 (1.3%)     | -0.04   | 94 (1.9%)     | 57 (1.7%)     | 0.02          | 130 (1.5%)    | 146 (1.5%)    | 0.00    |
| Number of lipid tests ordered                                                                         |               |               |               |               |               |         |               |               |               |               |               |         |
| ...mean (sd)                                                                                          | 0.35 (0.62)   | 0.37 (0.64)   | -0.03         | 0.35 (0.72)   | 0.36 (0.90)   | -0.01   | 0.36 (0.72)   | 0.42 (0.70)   | -0.08         | 0.36 (0.70)   | 0.38 (0.77)   | 0.00    |
| Proton pump inhibitor; n (%)                                                                          | 265 (18.0%)   | 493 (17.7%)   | 0.01          | 416 (16.9%)   | 666 (17.2%)   | -0.01   | 1,416 (28.4%) | 947 (27.8%)   | 0.01          | 2,097 (23.5%) | 2,106 (20.9%) | 0.06    |
| H2 receptor antagonist; n (%)                                                                         | 48 (3.3%)     | 74 (2.7%)     | 0.04          | 91 (3.7%)     | 127 (3.3%)    | 0.02    | 348 (7.0%)    | 249 (7.3%)    | -0.01         | 487 (5.5%)    | 450 (4.5%)    | 0.05    |
| Vitamin K therapy; n (%)                                                                              | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!       | ** (0.0%)     | ** (0.0%)     | #DIV/0! | ** (0.0%)     | 0 (0.0%)      | #DIV/0!       | #VALUE!       | #VALUE!       | #VALUE! |
| Number of INR (prothrombin) tests ordered                                                             |               |               |               |               |               |         |               |               |               |               |               |         |
| ...mean (sd)                                                                                          | 0.84 (2.15)   | 0.35 (0.80)   | 0.30          | 0.76 (2.07)   | 0.39 (0.86)   | 0.23    | 1.24 (2.96)   | 0.40 (0.86)   | 0.39          | 1.04 (2.62)   | 0.38 (0.84)   | 0.00    |
| Treating prescriber - Cardiologist; n (%)                                                             | 950 (64.5%)   | 1,803 (64.8%) | -0.01         | 1,503 (61.0%) | 2,341 (60.4%) | 0.01    | 2,604 (52.3%) | 1,815 (53.3%) | -0.02         | 5,057 (56.7%) | 5,959 (59.2%) | -0.05   |
| Treating prescriber - Primary Care Physician; n (%)                                                   | 1,278 (86.8%) | 2,280 (81.9%) | 0.14          | 1,112 (45.1%) | 1,672 (43.2%) | 0.04    | 1,906 (38.3%) | 1,293 (38.0%) | 0.01          | 4,296 (48.2%) | 5,245 (52.1%) | -0.08   |
| Treating prescriber - Other; n (%)                                                                    | 1,449 (98.4%) | 2,693 (96.8%) | 0.10          | 2,303 (93.5%) | 3,562 (91.9%) | 0.06    | 4,710 (94.5%) | 3,212 (94.3%) | 0.01          | 8,462 (94.9%) | 9,467 (94.1%) | 0.04    |
| Alpha blockers; n (%)                                                                                 | 73 (5.0%)     | 146 (5.2%)    | -0.01         | 95 (3.9%)     | 155 (4.0%)    | -0.01   | 373 (7.5%)    | 278 (8.2%)    | -0.03         | 541 (6.1%)    | 579 (5.8%)    | 0.01    |
| CHADS2 VASc score, 180 days, V                                                                        |               |               |               |               |               |         |               |               |               |               |               |         |
| ...mean (sd)                                                                                          | 1.73 (1.38)   | 1.29 (1.12)   | 0.35          | 1.73 (1.43)   | 1.08 (1.06)   | 0.52    | 2.01 (1.68)   | 1.45 (1.21)   | 0.38          | 1.89 (1.57)   | 1.26 (1.13)   | 0.00    |
| Use of Prasugrel; n (%)                                                                               | 0 (0.0%)      | ** (0.1%)     | -0.04         | 0 (0.0%)      | ** (0.1%)     | -0.04   | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!       | 0 (0.0%)      | #VALUE!       | #VALUE! |
| Use of Loop Diuretics+other diuretics+other hypertension drugs; n (%)                                 |               |               |               |               |               |         |               |               |               |               |               |         |
| Commercial vs Medicare Advantage- BusinessType                                                        | 154 (10.5%)   | 275 (9.9%)    | 0.02          | 241 (9.8%)    | 344 (8.9%)    | 0.03    | 899 (18.0%)   | 523 (15.4%)   | 0.07          | 1,294 (14.5%) | 1,142 (11.3%) | 0.10    |
| Code - CORRECT ONE - OPTUM                                                                            |               |               |               |               |               |         |               |               |               |               |               |         |
| ...Commercial; n (%)                                                                                  | 0,857 (58.2%) | 1,657 (59.5%) | -0.03         | 0,177 (7.2%)  | 224 (5.8%)    | 0.06    | -             | -             | #VALUE!       | #VALUE!       | 1,881 (28.3%) | #VALUE! |
| ...Medicare Advantage; n (%)                                                                          | 0,615 (41.8%) | 1,126 (40.5%) | 0.03          | 2,287 (92.8%) | 3,650 (94.2%) | -0.06   | -             | -             | #VALUE!       | #VALUE!       | 4,776 (71.7%) | #VALUE! |
| Commercial vs Medicare Advantage- BusinessType                                                        |               |               |               |               |               |         |               |               |               |               |               |         |
| Code                                                                                                  |               |               |               |               |               |         |               |               |               |               |               |         |
| ...COM = COMMERCIAL; n (%)                                                                            | 857 (58.2%)   | 1,657 (59.5%) | -0.03         | -             | -             | -       | -             | -             | #VALUE!       | 857 (58.2%)   | 1,657 (59.5%) | -0.03   |
| ...MCR = MEDICARE; n (%)                                                                              | 615 (41.8%)   | 1,126 (40.5%) | 0.03          | -             | -             | -       | -             | -             | #VALUE!       | 615 (41.8%)   | 1,126 (40.5%) | 0.03    |
| ...MCD = MEDICAL; n (%)                                                                               | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!       | -             | -             | -       | -             | -             | #VALUE!       | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| ...NONE = NO BUSINESS LINE CODE (added in 2015); n (%)                                                | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!       | -             | -             | -       | -             | -             | #VALUE!       | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| ...UNK = UNKNOWN (added in 2015); n (%)                                                               | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!       | -             | -             | -       | -             | -             | #VALUE!       | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| Commercial vs Medicare Advantage- Data Type                                                           |               |               |               |               |               |         |               |               |               |               |               |         |
| ...1 - For Service; n (%)                                                                             | -             | -             | 2,058 (83.5%) | 3,291 (85.0%) | -0.04         | -       | -             | -             | 2,058 (83.5%) | 3,291 (85.0%) | -0.04         |         |
| ...2 - Encounter; n (%)                                                                               | -             | -             | 229 (9.3%)    | 359 (9.3%)    | 0.00          | -       | -             | -             | 229 (9.3%)    | 359 (9.3%)    | 0.00          |         |
| ...3 - Medicare; n (%)                                                                                | -             | -             | 157 (6.4%)    | 204 (5.3%)    | 0.05          | -       | -             | -             | 157 (6.4%)    | 204 (5.3%)    | 0.05          |         |
| ...4 - MedicareEncounter; n (%)                                                                       | -             | -             | 20 (0.8%)     | 20 (0.5%)     | 0.04          | -       | -             | -             | 20 (0.8%)     | 20 (0.5%)     | 0.04          |         |
| Metropolitan Statistical Area - Urban (any MSA) vs Rural (non-MSA)                                    |               |               |               |               |               |         |               |               |               | 0             | 0             | 0.00    |
| ...Urban; n (%)                                                                                       | -             | -             | 1,819 (73.8%) | 2,639 (68.1%) | 0.13          | -       | -             | -             | 1,819 (73.8%) | 2,639 (68.1%) | 0.13          |         |
| ...Rural; n (%)                                                                                       | -             | -             | 197 (8.0%)    | 483 (12.5%)   | -0.15         | -       | -             | -             | 197 (8.0%)    | 483 (12.5%)   | -0.15         |         |
| ...Unknown/Missing; n (%)                                                                             | -             | -             | 448 (18.2%)   | 752 (19.4%)   | -0.03         | -       | -             | -             | 448 (18.2%)   | 752 (19.4%)   | -0.03         |         |

Due to CMS cell suppression policy, all values less than 11 are denoted with \*\*

# Appendix B

| PS-matched                                                                        |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
|-----------------------------------------------------------------------------------|----------------------|---------------------|-----------|----------------------|---------------------|-----------|----------------------|---------------------|-----------|----------------------|---------------------|-----------|
|                                                                                   | Optum                |                     |           | MarketScan           |                     |           | Medicare             |                     |           | POOLED               |                     |           |
| Variable                                                                          | Reference - Warfarin | Exposure - Apixaban | St. Diff. | Reference - Warfarin | Exposure - Apixaban | St. Diff. | Reference - Warfarin | Exposure - Apixaban | St. Diff. | Reference - Warfarin | Exposure - Apixaban | St. Diff. |
| Number of patients                                                                | 490                  | 490                 |           | 1,381                | 1,381               |           | 1,699                | 1,699               |           | 3,570                | 3,570               |           |
| Age                                                                               |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| ...mean (sd)                                                                      | 57.18 (14.30)        | 57.47 (14.12)       | -0.02     | 51.78 (12.29)        | 51.77 (12.07)       | 0.00      | 62.91 (14.58)        | 62.87 (14.01)       | 0.00      | 57.82 (13.70)        | 57.83 (13.31)       | 0.00      |
| Age categories without zero category                                              |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| ...18 - 54; n (%)                                                                 | 201 (41.0%)          | 184 (37.6%)         | 0.07      | 726 (52.6%)          | 748 (54.2%)         | -0.03     | 449 (26.4%)          | 453 (26.7%)         | -0.01     | 1,376 (38.5%)        | 1,385 (38.8%)       | -0.01     |
| ...55 - 64; n (%)                                                                 | 167 (34.1%)          | 170 (34.7%)         | -0.01     | 568 (41.1%)          | 547 (39.6%)         | 0.03      | 494 (29.1%)          | 475 (28.0%)         | 0.02      | 1,229 (34.4%)        | 1,192 (33.4%)       | 0.02      |
| ...65 - 74; n (%)                                                                 | 54 (11.0%)           | 87 (17.8%)          | -0.19     | 53 (3.8%)            | 48 (3.5%)           | 0.02      | 383 (22.5%)          | 427 (25.1%)         | -0.06     | 490 (13.7%)          | 562 (15.7%)         | -0.06     |
| ...>75; n (%)                                                                     | 68 (13.9%)           | 49 (10.0%)          | 0.12      | 34 (2.5%)            | 38 (2.8%)           | -0.02     | 373 (22.0%)          | 344 (20.2%)         | 0.04      | 475 (13.3%)          | 431 (12.1%)         | 0.04      |
| Gender without zero category- United                                              |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| ...Males; n (%)                                                                   | 240 (49.0%)          | 229 (46.7%)         | 0.05      | 727 (52.6%)          | 709 (51.3%)         | 0.03      | 786 (46.3%)          | 781 (46.0%)         | 0.01      | 1,753 (49.1%)        | 1,719 (48.2%)       | 0.02      |
| ...Females; n (%)                                                                 | 250 (51.0%)          | 261 (53.3%)         | -0.05     | 654 (47.4%)          | 672 (48.7%)         | -0.03     | 913 (53.7%)          | 918 (54.0%)         | -0.01     | 1,817 (50.9%)        | 1,851 (51.8%)       | -0.02     |
| Race                                                                              |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| ...White; n (%)                                                                   |                      |                     |           |                      |                     |           | 1,373 (80.8%)        | 1,381 (81.3%)       |           | 1,373 (80.8%)        | 1,381 (81.3%)       | 0.00      |
| ...Black; n (%)                                                                   |                      |                     |           |                      |                     |           | 247 (14.5%)          | 240 (14.1%)         |           | 247 (14.5%)          | 240 (14.1%)         | 0.00      |
| ...Asian; n (%)                                                                   |                      |                     |           |                      |                     |           | ** (0.5%)            | ** (0.4%)           |           | ** (0.5%)            | ** (0.4%)           | 0.00      |
| ...Hispanic; n (%)                                                                |                      |                     |           |                      |                     |           | 34 (2.0%)            | 33 (1.9%)           |           | 34 (2.0%)            | 33 (1.9%)           | 0.00      |
| ...North American Native; n (%)                                                   |                      |                     |           |                      |                     |           | ** (0.4%)            | ** (0.6%)           |           | ** (0.4%)            | ** (0.6%)           | 0.00      |
| ...Other/Unknown; n (%)                                                           |                      |                     |           |                      |                     |           | 29 (1.7%)            | 28 (1.6%)           |           | 29 (1.7%)            | 28 (1.6%)           | 0.00      |
| Region without zero category- United                                              |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| v3 (lumping missing+other category)                                               |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| ...Northeast; n (%)                                                               | 59 (12.0%)           | 66 (13.5%)          | -0.04     | 246 (17.8%)          | 232 (16.8%)         | 0.03      | 345 (20.3%)          | 339 (20.0%)         | 0.01      | 650 (18.2%)          | 637 (17.8%)         | 0.01      |
| ...South; n (%)                                                                   | 191 (39.0%)          | 187 (38.2%)         | 0.02      | 387 (28.0%)          | 397 (28.7%)         | -0.02     | 609 (35.8%)          | 608 (35.8%)         | 0.00      | 1,187 (33.2%)        | 1,192 (33.4%)       | 0.00      |
| ...Midwest; n (%)                                                                 | 137 (28.0%)          | 136 (27.8%)         | 0.00      | 527 (38.2%)          | 526 (38.1%)         | 0.00      | 442 (26.0%)          | 468 (27.5%)         | -0.03     | 1,106 (31.0%)        | 1,130 (31.7%)       | -0.02     |
| ...West; n (%)                                                                    | 103 (21.0%)          | 101 (20.6%)         | 0.01      | 218 (15.8%)          | 223 (16.1%)         | -0.01     | 303 (17.8%)          | 284 (16.7%)         | 0.03      | 624 (17.5%)          | 608 (17.0%)         | 0.01      |
| ...Unknown+missing; n (%)                                                         | N/A                  | N/A                 | #VALUE!   | ** (0.2%)            | ** (0.2%)           | 0.00      | N/A                  | N/A                 | #VALUE!   | ** (0.2%)            | ** (0.2%)           | 0.00      |
| CV Covariates                                                                     |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| Ischemic heart disease; n (%)                                                     | 90 (18.4%)           | 93 (19.0%)          | -0.02     | 186 (13.5%)          | 158 (11.4%)         | 0.06      | 373 (22.0%)          | 375 (22.1%)         | 0.00      | 649 (18.2%)          | 626 (17.5%)         | 0.02      |
| Acute MI; n (%)                                                                   | 23 (4.7%)            | 25 (5.1%)           | -0.02     | 64 (4.6%)            | 59 (4.3%)           | 0.01      | 81 (4.8%)            | 84 (4.9%)           | 0.00      | 168 (4.7%)           | 168 (4.7%)          | 0.00      |
| ACS/unstable angina; n (%)                                                        | 18 (3.7%)            | 17 (3.5%)           | 0.01      | 44 (3.2%)            | 35 (2.5%)           | 0.04      | 74 (4.4%)            | 69 (4.1%)           | 0.01      | 136 (3.8%)           | 121 (3.4%)          | 0.02      |
| Old MI; n (%)                                                                     | 18 (3.7%)            | 13 (2.7%)           | 0.06      | 16 (1.2%)            | 12 (0.9%)           | 0.03      | 89 (5.2%)            | 97 (5.7%)           | -0.02     | 123 (3.4%)           | 122 (3.4%)          | 0.00      |
| Stable angina; n (%)                                                              | ** (1.4%)            | ** (1.0%)           | 0.04      | 19 (1.4%)            | 16 (1.2%)           | 0.02      | 42 (2.5%)            | 43 (2.5%)           | 0.00      | #VALUE!              | #VALUE!             | #VALUE!   |
| Coronary atherosclerosis and other forms of chronic ischemic heart disease; n (%) | 62 (12.7%)           | 58 (11.8%)          | 0.03      | 104 (7.5%)           | 90 (6.5%)           | 0.04      | 266 (15.7%)          | 271 (16.0%)         | -0.01     | 432 (12.1%)          | 419 (11.7%)         | 0.01      |
| Other atherosclerosis with ICD10 v2                                               |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| Copy; n (%)                                                                       | ** (0.4%)            | ** (0.6%)           | -0.03     | ** (0.4%)            | ** (0.3%)           | 0.02      | 12 (0.7%)            | ** (0.6%)           | 0.01      | #VALUE!              | #VALUE!             | #VALUE!   |
| Previous cardiac procedure (CABG or PTCa or Stent) v4; n (%)                      | ** (0.4%)            | 0 (0.0%)            | 0.09      | ** (0.3%)            | ** (0.7%)           | -0.06     | ** (0.6%)            | ** (0.4%)           | 0.03      | #VALUE!              | #VALUE!             | #VALUE!   |
| History of CABG or PTCa; n (%)                                                    | 20 (4.1%)            | 14 (2.9%)           | 0.07      | ** (0.8%)            | ** (0.4%)           | 0.05      | 87 (5.1%)            | 96 (5.7%)           | -0.03     | #VALUE!              | #VALUE!             | #VALUE!   |
| Any stroke; n (%)                                                                 | ** (1.6%)            | ** (1.0%)           | 0.05      | 13 (0.9%)            | ** (0.8%)           | 0.01      | 58 (3.4%)            | 58 (3.4%)           | 0.00      | #VALUE!              | #VALUE!             | #VALUE!   |
| Ischemic stroke (w and w/o mention of cerebral infarction); n (%)                 | ** (1.6%)            | ** (1.0%)           | 0.05      | 13 (0.9%)            | ** (0.8%)           | 0.01      | 54 (3.2%)            | 56 (3.3%)           | -0.01     | #VALUE!              | #VALUE!             | #VALUE!   |
| Hemorrhagic stroke; n (%)                                                         | 0 (0.0%)             | 0 (0.0%)            | #DIV/0!   | 0 (0.0%)             | 0 (0.0%)            | #DIV/0!   | ** (0.2%)            | ** (0.1%)           | 0.03      | #VALUE!              | #VALUE!             | #VALUE!   |
| TIA; n (%)                                                                        | ** (0.4%)            | ** (0.4%)           | 0.00      | ** (0.2%)            | ** (0.2%)           | 0.00      | ** (0.6%)            | 13 (0.8%)           | -0.02     | #VALUE!              | #VALUE!             | #VALUE!   |
| Other cerebrovascular disease; n (%)                                              | ** (1.4%)            | ** (1.2%)           | 0.02      | ** (0.8%)            | ** (0.8%)           | 0.00      | 28 (1.6%)            | 30 (1.8%)           | -0.02     | #VALUE!              | #VALUE!             | #VALUE!   |
| Cerebrovascular procedure; n (%)                                                  | 0 (0.0%)             | 0 (0.0%)            | #DIV/0!   | 0 (0.0%)             | 0 (0.0%)            | #DIV/0!   | ** (0.1%)            | 0 (0.0%)            | 0.04      | #VALUE!              | 0 (0.0%)            | #VALUE!   |
| Heart failure (CHF); n (%)                                                        | 52 (10.6%)           | 53 (10.8%)          | -0.01     | 114 (8.3%)           | 115 (8.3%)          | 0.00      | 285 (16.8%)          | 304 (17.9%)         | -0.03     | 451 (12.6%)          | 472 (13.2%)         | -0.02     |
| Peripheral Vascular Disease (PVD) or PVD                                          |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| Surgery v2; n (%)                                                                 | 16 (3.3%)            | 15 (3.1%)           | 0.01      | 31 (2.2%)            | 32 (2.3%)           | -0.01     | 116 (6.5%)           | 111 (6.5%)          | 0.01      | 163 (4.6%)           | 158 (4.4%)          | 0.01      |
| Atrial fibrillation; n (%)                                                        | 36 (7.3%)            | 36 (7.3%)           | 0.00      | 90 (6.5%)            | 84 (6.1%)           | 0.02      | 178 (10.5%)          | 180 (10.6%)         | 0.00      | 304 (8.5%)           | 300 (8.4%)          | 0.00      |
| Other cardiac dysrhythmia; n (%)                                                  | 90 (18.4%)           | 90 (18.4%)          | 0.00      | 241 (17.5%)          | 234 (16.9%)         | 0.02      | 365 (21.5%)          | 379 (22.3%)         | -0.02     | 696 (19.5%)          | 703 (19.7%)         | -0.01     |
| Cardiac conduction disorders; n (%)                                               | 28 (5.7%)            | 28 (5.7%)           | 0.00      | 87 (6.3%)            | 68 (4.9%)           | 0.06      | 126 (7.4%)           | 127 (7.5%)          | 0.00      | 241 (6.8%)           | 223 (6.2%)          | 0.02      |
| Other CVD; n (%)                                                                  | 137 (28.0%)          | 132 (26.9%)         | 0.02      | 332 (24.0%)          | 359 (26.0%)         | -0.05     | 420 (24.7%)          | 450 (26.5%)         | -0.04     | 889 (24.9%)          | 941 (26.4%)         | -0.03     |
| Diabetes-related complications                                                    |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| Occurrence of Diabetic Neuropathy v2                                              |                      |                     |           |                      |                     |           |                      |                     |           |                      |                     |           |
| Copy; n (%)                                                                       | 18 (3.7%)            | 24 (4.9%)           | -0.06     | 26 (1.9%)            | 25 (1.8%)           | 0.01      | 100 (5.9%)           | 99 (5.8%)           | 0.00      | 144 (4.0%)           | 148 (4.1%)          | -0.01     |
| Occurrence of diabetic nephropathy V3 with ICD10 Copy; n (%)                      | 13 (2.7%)            | ** (1.2%)           | 0.11      | 18 (1.3%)            | 14 (1.0%)           | 0.03      | 47 (2.8%)            | 31 (1.8%)           | 0.07      | 78 (2.2%)            | #VALUE!             | #VALUE!   |
| Hypoglycemia v2; n (%)                                                            | ** (0.6%)            | ** (0.2%)           | 0.06      | ** (0.1%)            | 0.03                | 0.01      | 51 (3.0%)            | 44 (2.6%)           | 0.02      | #VALUE!              | #VALUE!             | #VALUE!   |
| Hyperglycemia; n (%)                                                              | 53 (10.8%)           | 41 (8.4%)           | 0.08      | 76 (5.5%)            | 80 (5.8%)           | -0.01     | 151 (8.9%)           | 158 (9.3%)          | -0.01     | 280 (7.8%)           | 279 (7.8%)          | 0.00      |
| Diabetic ketoacidosis; n (%)                                                      | ** (0.6%)            | ** (0.4%)           | 0.03      | ** (0.1%)            | ** (0.7%)           | -0.10     | ** (0.4%)            | ** (0.4%)           | 0.00      | #VALUE!              | #VALUE!             | #VALUE!   |
| Hypertension: 1 inpatient or 2 outpatient claims within 365 days; n (%)           | 207 (42.2%)          | 210 (42.9%)         | -0.01     | 553 (40.0%)          | 564 (40.8%)         | -0.02     | 775 (45.6%)          | 782 (46.0%)         | -0.01     | 1,535 (43.0%)        | 1,556 (43.6%)       | -0.01     |
| Hyperlipidemia v2; n (%)                                                          | 172 (35.1%)          | 171 (34.9%)         | 0.00      | 419 (30.3%)          | 405 (29.3%)         | 0.02      | 709 (41.7%)          | 710 (41.8%)         | 0.00      | 1,300 (36.4%)        | 1,286 (36.0%)       | 0.01      |
| Edema; n (%)                                                                      | 92 (18.8%)           | 74 (15.1%)          | 0.10      | 194 (14.0%)          | 188 (13.6%)         | 0.01      | 279 (16.4%)          | 281 (16.5%)         | 0.00      | 565 (15.8%)          | 543 (15.2%)         | 0.02      |
| Renal Dysfunction (non-diabetic) v2; n (%)                                        | 76 (15.5%)           | 80 (16.3%)          | -0.02     | 188 (13.6%)          | 179 (13.0%)         | 0.02      | 297 (17.5%)          | 334 (19.7%)         | -0.06     | 561 (15.7%)          | 593 (16.6%)         | -0.02     |
| Occurrence of acute renal disease v2; n (%)                                       | 36 (7.3%)            | 43 (8.8%)           | -0.06     | 97 (7.0%)            | 98 (7.1%)           | 0.00      | 166 (9.8%)           | 183 (10.8%)         | -0.03     | 299 (8.4%)           | 324 (9.1%)          | -0.02     |
| Occurrence of chronic renal insufficiency; n (%)                                  | 27 (5.5%)            | 25 (5.1%)           | 0.02      | 44 (3.2%)            | 32 (2.3%)           | 0.06      | 109 (6.4%)           | 128 (7.5%)          | -0.04     | 180 (5.0%)           | 185 (5.2%)          | -0.01     |

# Appendix B

|                                                                |             |             |       |             |             |         |             |             |         |              |              |         |
|----------------------------------------------------------------|-------------|-------------|-------|-------------|-------------|---------|-------------|-------------|---------|--------------|--------------|---------|
| Chronic kidney disease v2; n (%)                               | 24 (4.9%)   | 23 (4.7%)   | 0.01  | 41 (3.0%)   | 29 (2.1%)   | 0.06    | 105 (6.2%)  | 124 (7.3%)  | -0.04   | 170 (4.8%)   | 176 (4.9%)   | 0.00    |
| CKD Stage 3-4; n (%)                                           | 16 (3.3%)   | 15 (3.1%)   | 0.01  | 34 (2.5%)   | 23 (1.7%)   | 0.06    | 79 (4.6%)   | 92 (5.4%)   | -0.04   | 129 (3.6%)   | 130 (3.6%)   | 0.00    |
| Occurrence of hypertensive nephropathy; n (%)                  | 15 (3.1%)   | 17 (3.5%)   | -0.02 | 30 (2.2%)   | 21 (1.5%)   | 0.05    | 63 (3.7%)   | 73 (4.3%)   | -0.03   | 108 (3.0%)   | 111 (3.1%)   | -0.01   |
| Occurrence of miscellaneous renal insufficiency v2; n (%)      | 31 (6.3%)   | 34 (6.9%)   | -0.02 | 88 (6.4%)   | 77 (5.6%)   | 0.03    | 109 (6.4%)  | 117 (6.9%)  | -0.02   | 228 (6.4%)   | 228 (6.4%)   | 0.00    |
| <b>Other Covariates</b>                                        |             |             |       |             |             |         |             |             |         |              |              |         |
| Liver disease; n (%)                                           | ** (0.4%)   | 0 (0.0%)    | 0.09  | 0 (0.0%)    | 0 (0.0%)    | #DIV/0! | ** (0.4%)   | ** (0.3%)   | 0.02    | #VALUE!      | #VALUE!      | #VALUE! |
| Osteoarthritis; n (%)                                          | 104 (21.2%) | 112 (22.9%) | -0.04 | 226 (16.4%) | 233 (16.9%) | -0.01   | 436 (25.7%) | 414 (24.4%) | 0.03    | 766 (21.5%)  | 759 (21.3%)  | 0.00    |
| Other arthritis, arthropathies and musculoskeletal pain; n (%) | 282 (57.6%) | 277 (56.5%) | 0.02  | 771 (55.8%) | 760 (55.0%) | 0.02    | 997 (58.7%) | 996 (58.6%) | 0.00    | 2050 (57.4%) | 2033 (56.9%) | 0.01    |
| Dorsopathies; n (%)                                            | 154 (31.4%) | 165 (33.7%) | -0.05 | 368 (26.6%) | 358 (25.9%) | 0.02    | 589 (34.7%) | 579 (34.1%) | 0.01    | 1111 (31.1%) | 1102 (30.9%) | 0.00    |
| Fractures; n (%)                                               | 26 (5.3%)   | 28 (5.7%)   | -0.02 | 40 (2.9%)   | 47 (3.4%)   | -0.03   | 123 (7.2%)  | 135 (7.9%)  | -0.03   | 189 (5.3%)   | 210 (5.9%)   | -0.03   |
| Falls v2; n (%)                                                | 33 (6.7%)   | 38 (7.8%)   | -0.04 | 29 (2.1%)   | 26 (1.9%)   | 0.01    | 88 (5.2%)   | 89 (5.2%)   | 0.00    | 150 (4.2%)   | 153 (4.3%)   | 0.00    |
| Osteoporosis; n (%)                                            | 19 (3.9%)   | 23 (4.7%)   | -0.04 | 31 (2.2%)   | 28 (2.0%)   | 0.01    | 147 (8.7%)  | 146 (8.6%)  | 0.00    | 197 (5.5%)   | 197 (5.5%)   | 0.00    |
| Depression; n (%)                                              | 100 (20.4%) | 96 (19.6%)  | 0.02  | 188 (13.6%) | 196 (14.2%) | -0.02   | 479 (28.2%) | 471 (27.7%) | 0.01    | 767 (21.5%)  | 763 (21.4%)  | 0.00    |
| Anxiety; n (%)                                                 | 113 (23.1%) | 116 (23.7%) | -0.01 | 236 (17.1%) | 250 (18.1%) | -0.03   | 483 (28.4%) | 481 (28.3%) | 0.00    | 832 (23.3%)  | 847 (23.7%)  | -0.01   |
| Sleep_Disorder; n (%)                                          | 21 (4.3%)   | 25 (5.1%)   | -0.04 | 64 (4.6%)   | 66 (4.8%)   | -0.01   | 83 (4.9%)   | 80 (4.7%)   | 0.01    | 168 (4.7%)   | 171 (4.8%)   | 0.00    |
| Dementia; n (%)                                                | 26 (5.3%)   | 29 (5.9%)   | -0.03 | 27 (2.0%)   | 33 (2.4%)   | -0.03   | 207 (12.2%) | 218 (12.8%) | -0.02   | 260 (7.3%)   | 280 (7.8%)   | -0.02   |
| Delirium; n (%)                                                | 16 (3.3%)   | 16 (3.3%)   | 0.00  | 21 (1.5%)   | 23 (1.7%)   | -0.02   | 137 (8.1%)  | 136 (8.0%)  | 0.00    | 174 (4.9%)   | 175 (4.9%)   | 0.00    |
| Psychosis; n (%)                                               | ** (1.8%)   | 12 (2.4%)   | -0.04 | 15 (1.1%)   | 13 (0.9%)   | 0.02    | 154 (9.1%)  | 160 (9.4%)  | -0.01   | #VALUE!      | 185 (5.2%)   | #VALUE! |
| Obesity; n (%)                                                 | 188 (38.4%) | 193 (39.4%) | -0.02 | 502 (36.4%) | 507 (36.7%) | -0.01   | 472 (27.8%) | 483 (28.4%) | -0.01   | 1162 (32.5%) | 1183 (33.1%) | -0.01   |
| Overweight; n (%)                                              | 23 (4.7%)   | 27 (5.5%)   | -0.04 | 49 (3.5%)   | 57 (4.1%)   | -0.03   | 70 (4.1%)   | 63 (3.7%)   | 0.02    | 142 (4.0%)   | 147 (4.1%)   | -0.01   |
| Smoking; n (%)                                                 | 192 (39.2%) | 196 (40.0%) | -0.02 | 255 (18.5%) | 250 (18.1%) | 0.01    | 829 (48.8%) | 826 (48.6%) | 0.00    | 1276 (35.7%) | 1272 (35.6%) | 0.00    |
| Alcohol abuse or dependence; n (%)                             | ** (2.0%)   | ** (1.6%)   | 0.03  | 18 (1.3%)   | 16 (1.2%)   | 0.01    | 39 (2.3%)   | 38 (2.2%)   | 0.01    | #VALUE!      | #VALUE!      | #VALUE! |
| Drug abuse or dependence; n (%)                                | 26 (5.3%)   | 29 (5.9%)   | -0.03 | 29 (2.1%)   | 35 (2.5%)   | -0.03   | 131 (7.7%)  | 118 (6.9%)  | 0.03    | 186 (5.2%)   | 182 (5.1%)   | 0.00    |
| COPD; n (%)                                                    | 92 (18.8%)  | 97 (19.8%)  | -0.03 | 122 (8.8%)  | 129 (9.3%)  | -0.02   | 482 (28.4%) | 481 (28.3%) | 0.00    | 696 (19.5%)  | 707 (19.8%)  | -0.01   |
| Asthma; n (%)                                                  | 68 (13.9%)  | 63 (12.9%)  | 0.03  | 160 (11.6%) | 163 (11.8%) | -0.01   | 251 (14.8%) | 263 (15.5%) | -0.02   | 479 (13.4%)  | 489 (13.7%)  | -0.01   |
| Obstructive sleep apnea; n (%)                                 | 90 (18.4%)  | 95 (19.4%)  | -0.03 | 215 (15.6%) | 212 (15.4%) | 0.01    | 255 (15.0%) | 258 (15.2%) | -0.01   | 560 (15.7%)  | 565 (15.8%)  | 0.00    |
| Pneumonia; n (%)                                               | 89 (18.2%)  | 87 (17.8%)  | 0.01  | 217 (15.7%) | 229 (16.6%) | -0.02   | 417 (24.5%) | 403 (23.7%) | 0.02    | 723 (20.3%)  | 719 (20.1%)  | 0.00    |
| <b>Other Medications</b>                                       |             |             |       |             |             |         |             |             |         |              |              |         |
| Use of ACE inhibitors; n (%)                                   | 75 (15.3%)  | 70 (14.3%)  | 0.03  | 220 (15.9%) | 222 (16.1%) | -0.01   | 266 (15.7%) | 261 (15.4%) | 0.01    | 561 (15.7%)  | 553 (15.5%)  | 0.01    |
| Use of ARBs; n (%)                                             | 34 (6.9%)   | 42 (8.6%)   | -0.06 | 124 (9.0%)  | 132 (9.6%)  | -0.02   | 84 (4.9%)   | 79 (4.6%)   | 0.01    | 242 (6.8%)   | 253 (7.1%)   | -0.01   |
| Use of Loop Diuretics - United; n (%)                          | 47 (9.6%)   | 49 (10.0%)  | -0.01 | 94 (6.8%)   | 94 (6.8%)   | 0.00    | 236 (13.9%) | 243 (14.3%) | -0.01   | 377 (10.6%)  | 386 (10.8%)  | -0.01   |
| Use of other diuretics-United; n (%)                           | 18 (3.7%)   | 13 (2.7%)   | 0.06  | 30 (2.2%)   | 22 (1.6%)   | 0.04    | 47 (2.8%)   | 53 (3.1%)   | -0.02   | 95 (2.7%)    | 88 (2.5%)    | 0.01    |
| Use of nitrates-United; n (%)                                  | ** (1.6%)   | ** (1.2%)   | 0.03  | 20 (1.4%)   | 19 (1.4%)   | 0.00    | 65 (3.8%)   | 63 (3.7%)   | 0.01    | #VALUE!      | #VALUE!      | #VALUE! |
| Use of other hypertension drugs; n (%)                         | 14 (2.9%)   | 16 (3.3%)   | -0.02 | 37 (2.7%)   | 41 (3.0%)   | -0.02   | 85 (5.0%)   | 92 (5.4%)   | -0.02   | 136 (3.8%)   | 149 (4.2%)   | -0.02   |
| Use of Anti-arrhythmics; n (%)                                 | ** (1.4%)   | ** (1.8%)   | -0.03 | 18 (1.3%)   | 21 (1.5%)   | -0.02   | 24 (1.4%)   | 31 (1.8%)   | -0.03   | #VALUE!      | #VALUE!      | #VALUE! |
| Use of COPD/asthma meds- United; n (%)                         | 91 (18.6%)  | 87 (17.8%)  | 0.02  | 203 (14.7%) | 255 (18.5%) | -0.10   | 398 (23.4%) | 389 (22.9%) | 0.01    | 692 (19.4%)  | 731 (20.5%)  | -0.03   |
| Use of statins; n (%)                                          | 111 (22.7%) | 111 (22.7%) | 0.00  | 261 (18.9%) | 259 (18.8%) | 0.00    | 468 (27.5%) | 468 (27.5%) | 0.00    | 840 (23.5%)  | 838 (23.5%)  | 0.00    |
| Use of other lipid-lowering drugs; n (%)                       | 20 (4.1%)   | 18 (3.7%)   | 0.02  | 52 (3.8%)   | 48 (3.5%)   | 0.02    | 77 (4.5%)   | 78 (4.6%)   | 0.00    | 149 (4.2%)   | 144 (4.0%)   | 0.01    |
| Use of antiplatelet agents; n (%)                              | ** (1.6%)   | ** (2.0%)   | -0.03 | 26 (1.9%)   | 31 (2.2%)   | -0.02   | 95 (5.6%)   | 81 (4.8%)   | 0.04    | #VALUE!      | #VALUE!      | #VALUE! |
| Use of heparin and other low-molecular weight heparins; n (%)  | 95 (19.4%)  | 101 (20.6%) | -0.03 | 1 (0.1%)    | 0 (0.0%)    | 0.04    | 156 (9.2%)  | 153 (9.0%)  | 0.01    | 252 (7.1%)   | 254 (7.1%)   | 0.00    |
| Use of NSAIDs; n (%)                                           | 47 (9.6%)   | 55 (11.2%)  | -0.05 | 205 (14.8%) | 209 (15.1%) | -0.01   | 203 (11.9%) | 193 (11.4%) | 0.02    | 457 (12.7%)  | 457 (12.8%)  | 0.00    |
| Use of opioido- United; n (%)                                  | 199 (40.6%) | 193 (39.4%) | 0.02  | 631 (45.7%) | 622 (45.0%) | 0.01    | 740 (43.6%) | 718 (42.3%) | 0.03    | 1570 (44.0%) | 1533 (42.9%) | 0.02    |
| Use of antidepressants; n (%)                                  | 137 (28.0%) | 135 (27.6%) | 0.01  | 322 (23.3%) | 338 (24.5%) | -0.03   | 683 (40.2%) | 671 (39.5%) | 0.01    | 1142 (32.0%) | 1144 (32.0%) | 0.00    |
| Use of antipsychotics; n (%)                                   | 27 (5.5%)   | 32 (6.5%)   | -0.04 | 58 (4.2%)   | 57 (4.1%)   | 0.01    | 285 (16.8%) | 287 (16.9%) | 0.00    | 370 (10.4%)  | 376 (10.5%)  | 0.00    |
| <b>Labs</b>                                                    |             |             |       |             |             |         |             |             |         |              |              |         |
| Lab values- HbA1c (%) v3; n (%)                                | 52 (10.6%)  | 49 (10.0%)  | 0.02  | ** (0.2%)   | 21 (1.5%)   | -0.14   | N/A         | N/A         | #VALUE! | #VALUE!      | 070 (3.7%)   | #VALUE! |
| Lab values- HbA1c (%) (within 3 months)                        | 28 (5.7%)   | 29 (5.9%)   | -0.01 | ** (0.1%)   | 12 (0.9%)   | -0.11   | N/A         | N/A         | #VALUE! | #VALUE!      | 041 (2.2%)   | #VALUE! |
| Lab values- HbA1c (%) (within 6 months)                        | 52 (10.6%)  | 49 (10.0%)  | 0.02  | ** (0.2%)   | 21 (1.5%)   | -0.14   | N/A         | N/A         | #VALUE! | #VALUE!      | 070 (3.7%)   | #VALUE! |
| Lab values- BNP; n (%)                                         | ** (1.0%)   | ** (2.0%)   | -0.08 | 0 (0.0%)    | ** (0.2%)   | -0.06   | N/A         | N/A         | #VALUE! | #VALUE!      | #VALUE!      | #VALUE! |
| Lab values- BNP (within 3 months); n (%)                       | ** (1.0%)   | ** (2.0%)   | -0.08 | 0 (0.0%)    | ** (0.2%)   | -0.06   | N/A         | N/A         | #VALUE! | #VALUE!      | #VALUE!      | #VALUE! |
| Lab values- BNP (within 6 months); n (%)                       | ** (1.0%)   | ** (2.0%)   | -0.08 | 0 (0.0%)    | ** (0.2%)   | -0.06   | N/A         | N/A         | #VALUE! | #VALUE!      | #VALUE!      | #VALUE! |
| Lab values- BUN (mg/dl); n (%)                                 | 107 (21.8%) | 107 (21.8%) | 0.00  | ** (0.8%)   | 21 (1.5%)   | -0.07   | N/A         | N/A         | #VALUE! | #VALUE!      | 128 (6.8%)   | #VALUE! |
| Lab values- BUN (mg/dl) (within 3 months); n (%)               | 72 (14.7%)  | 80 (16.3%)  | -0.04 | ** (0.4%)   | 12 (0.9%)   | -0.06   | N/A         | N/A         | #VALUE! | #VALUE!      | 092 (4.9%)   | #VALUE! |
| Lab values- BUN (mg/dl) (within 6 months); n (%)               | 107 (21.8%) | 107 (21.8%) | 0.00  | ** (0.8%)   | 21 (1.5%)   | -0.07   | N/A         | N/A         | #VALUE! | #VALUE!      | 128 (6.8%)   | #VALUE! |
| Lab values- Creatinine (mg/dl) v2; n (%)                       | 109 (22.2%) | 115 (23.5%) | -0.03 | ** (0.8%)   | 23 (1.7%)   | -0.08   | N/A         | N/A         | #VALUE! | #VALUE!      | 138 (7.4%)   | #VALUE! |
| Lab values- Creatinine (mg/dl) (within 3 months); v2; n (%)    | 73 (14.9%)  | 87 (17.8%)  | -0.08 | ** (0.4%)   | 13 (0.9%)   | -0.06   | N/A         | N/A         | #VALUE! | #VALUE!      | 100 (5.3%)   | #VALUE! |
| Lab values- Creatinine (mg/dl) (within 6 months); v2; n (%)    | 109 (22.2%) | 115 (23.5%) | -0.03 | ** (0.8%)   | 23 (1.7%)   | -0.08   | N/A         | N/A         | #VALUE! | #VALUE!      | 138 (7.4%)   | #VALUE! |
| Lab values- HDL level (mg/dl); n (%)                           | 58 (11.8%)  | 66 (13.5%)  | -0.05 | ** (0.4%)   | 20 (1.4%)   | -0.11   | N/A         | N/A         | #VALUE! | #VALUE!      | 086 (4.6%)   | #VALUE! |
| Lab values- HDL level (mg/dl) (within 3 months); n (%)         | 34 (6.9%)   | 42 (8.6%)   | -0.06 | ** (0.1%)   | ** (0.8%)   | -0.10   | N/A         | N/A         | #VALUE! | #VALUE!      | #VALUE!      | #VALUE! |
| Lab values- HDL level (mg/dl) (within 6 months); n (%)         | 58 (11.8%)  | 66 (13.5%)  | -0.05 | ** (0.4%)   | 20 (1.4%)   | -0.11   | N/A         | N/A         | #VALUE! | #VALUE!      | 086 (4.6%)   | #VALUE! |
| Lab values- LDL level (mg/dl); n (%)                           | 59 (12.0%)  | 69 (14.1%)  | -0.06 | ** (0.4%)   | 19 (1.4%)   | -0.11   | N/A         | N/A         | #VALUE! | #VALUE!      | 088 (4.7%)   | #VALUE! |

# Appendix B

|                                                                             |                |                   |       |                       |                     |         |             |             |                    |                |                  |         |
|-----------------------------------------------------------------------------|----------------|-------------------|-------|-----------------------|---------------------|---------|-------------|-------------|--------------------|----------------|------------------|---------|
| Lab values- LDL level (mg/dl) (within 3 months) v2; n (%)                   | 34 (6.9%)      | 43 (8.8%)         | -0.07 | ** (0.2%)             | ** (0.8%)           | -0.09   | N/A         | N/A         | #VALUE!            | #VALUE!        | #VALUE!          | #VALUE! |
| Lab values- LDL level (mg/dl) (within 6 months) v2; n (%)                   | 59 (12.0%)     | 69 (14.1%)        | -0.06 | ** (0.4%)             | 19 (1.4%)           | -0.11   | N/A         | N/A         | #VALUE!            | #VALUE!        | 088 (4.7%)       | #VALUE! |
| Lab values- NT-proBNP; n (%)                                                | ** (0.8%)      | 0 (0.0%)          | 0.13  | 0 (0.0%)              | 0 (0.0%)            | #DIV/0! | N/A         | N/A         | #VALUE!            | #VALUE!        | 0 (0.0%)         | #VALUE! |
| Lab values- NT-proBNP (within 3 months); n (%)                              | ** (0.8%)      | 0 (0.0%)          | 0.13  | 0 (0.0%)              | 0 (0.0%)            | #DIV/0! | N/A         | N/A         | #VALUE!            | #VALUE!        | 0 (0.0%)         | -       |
| Lab values- NT-proBNP (within 6 months); n (%)                              | ** (0.8%)      | 0 (0.0%)          | 0.13  | 0 (0.0%)              | 0 (0.0%)            | #DIV/0! | N/A         | N/A         | #VALUE!            | #VALUE!        | 0 (0.0%)         | -       |
| Lab values- Total cholesterol (mg/dl) v2; n (%)                             | 60 (12.2%)     | 69 (14.1%)        | -0.06 | ** (0.3%)             | 20 (1.4%)           | -0.12   | N/A         | N/A         | #VALUE!            | #VALUE!        | 089 (4.8%)       | #VALUE! |
| Lab values- Total cholesterol (mg/dl) (within 3 months) v2; n (%)           | 35 (7.1%)      | 43 (8.8%)         | -0.06 | ** (0.1%)             | ** (0.8%)           | -0.10   | N/A         | N/A         | #VALUE!            | #VALUE!        | #VALUE!          | #VALUE! |
| Lab values- Total cholesterol (mg/dl) (within 6 months) v2; n (%)           | 60 (12.2%)     | 69 (14.1%)        | -0.06 | ** (0.3%)             | 20 (1.4%)           | -0.12   | N/A         | N/A         | #VALUE!            | #VALUE!        | 089 (4.8%)       | #VALUE! |
| Lab values- Triglyceride level (mg/dl); n (%)                               | 60 (12.2%)     | 68 (13.9%)        | -0.05 | ** (0.4%)             | 19 (1.4%)           | -0.11   | N/A         | N/A         | #VALUE!            | #VALUE!        | 087 (4.6%)       | #VALUE! |
| Lab values- Triglyceride level (mg/dl) (within 3 months); n (%)             | 35 (7.1%)      | 43 (8.8%)         | -0.06 | ** (0.1%)             | ** (0.8%)           | -0.10   | N/A         | N/A         | #VALUE!            | #VALUE!        | #VALUE!          | #VALUE! |
| Lab values- Triglyceride level (mg/dl) (within 6 months); n (%)             | 60 (12.2%)     | 68 (13.9%)        | -0.05 | ** (0.4%)             | 19 (1.4%)           | -0.11   | N/A         | N/A         | #VALUE!            | #VALUE!        | 087 (4.6%)       | #VALUE! |
| Lab result number- HbA1c (%) mean (only 2 to 20 included) v4                | 52             | 49                | 3     | 21                    |                     |         | N/A         | N/A         | 55                 | 70             |                  |         |
| ...mean (sd)                                                                | 6.43 (1.98)    | 6.63 (1.68)       | -0.11 | 7.47 (1.98)           | 6.61 (1.26)         | 0.52    | N/A         | N/A         | 6.49 (2.00)        | 6.62 (1.58)    | -0.07            |         |
| ...Missing; n (%)                                                           | 438 (89.4%)    | 441 (90.0%)       | 0.02  | 1,378 (99.8%)         | 1,360 (98.5%)       | 0.14    | N/A         | N/A         | 1,816 (97.1%)      | 1,801 (96.3%)  | 0.04             |         |
| Lab result number- BNP mean v2                                              | 5              | 10                | -     | 3                     |                     |         | N/A         | N/A         | 5                  | 13             |                  |         |
| ...mean (sd)                                                                | 82.32 (68.33)  | 593.05 (1,341.63) | -0.54 | - (-)                 | 1,474.33 (2,513.81) | #VALUE! | N/A         | N/A         | #VALUE!            | #VALUE!        | 796.42 (1698.18) | #VALUE! |
| ...Missing; n (%)                                                           | 485 (99.0%)    | 480 (98.0%)       | 0.08  | 1,381 (100.0%)        | 1,378 (99.8%)       | 0.06    | N/A         | N/A         | 1,866 (99.7%)      | 1,858 (99.3%)  | 0.06             |         |
| Lab result number- BUN (mg/dl) mean v2                                      | 107            | 107               | 11    | 21                    |                     |         | N/A         | N/A         | 118                | 128            |                  |         |
| ...mean (sd)                                                                | 14.59 (4.94)   | 14.77 (5.11)      | -0.04 | 18,197.88 (44,223.54) | 14.28 (4.67)        | 0.58    | N/A         | N/A         | 1709.64 (1304.81)  | 14.69 (5.06)   | 0.18             |         |
| ...Missing; n (%)                                                           | 383 (78.2%)    | 383 (78.2%)       | 0.00  | 1,370 (99.2%)         | 1,360 (98.5%)       | 0.07    | N/A         | N/A         | 1,753 (93.7%)      | 1,743 (93.2%)  | 0.02             |         |
| Lab result number- Creatinine (mg/dl) mean (only 0.1 to 15 included) v3     | 109            | 115               | 9     | 23                    |                     |         | N/A         | N/A         | 118                | 138            |                  |         |
| ...mean (sd)                                                                | 0.89 (0.22)    | 0.90 (0.23)       | -0.04 | 1.02 (0.21)           | 0.94 (0.18)         | 0.41    | N/A         | N/A         | 0.90 (0.22)        | 0.91 (0.22)    | -0.05            |         |
| ...Missing; n (%)                                                           | 381 (77.8%)    | 375 (76.5%)       | 0.03  | 1,372 (99.3%)         | 1,358 (98.3%)       | 0.09    | N/A         | N/A         | 1,753 (93.7%)      | 1,733 (92.6%)  | 0.04             |         |
| Lab result number- HDL level (mg/dl) mean (only <5000 included) v2          | 58             | 66                | 4     | 20                    |                     |         | N/A         | N/A         | 62                 | 86             |                  |         |
| ...mean (sd)                                                                | 53.28 (16.01)  | 51.19 (15.56)     | 0.13  | 43.75 (16.07)         | 45.90 (14.63)       | -0.14   | N/A         | N/A         | 52.67 (16.15)      | 49.96 (15.45)  | 0.17             |         |
| ...Missing; n (%)                                                           | 432 (88.2%)    | 424 (86.5%)       | 0.05  | 1,377 (99.7%)         | 1,361 (98.6%)       | 0.12    | N/A         | N/A         | 1,809 (96.7%)      | 1,785 (95.4%)  | 0.07             |         |
| Lab result number- LDL level (mg/dl) mean (only <5000 included) v2          | 58             | 68                | 4     | 17                    |                     |         | N/A         | N/A         | 62                 | 85             |                  |         |
| ...mean (sd)                                                                | 113.22 (39.81) | 110.23 (37.87)    | 0.08  | 80.50 (59.31)         | 88.47 (23.32)       | -0.18   | N/A         | N/A         | 111.11 (41.35)     | 105.88 (35.75) | 0.14             |         |
| ...Missing; n (%)                                                           | 432 (88.2%)    | 422 (86.1%)       | 0.06  | 1,377 (99.7%)         | 1,364 (98.8%)       | 0.10    | N/A         | N/A         | 1,809 (96.7%)      | 1,786 (95.5%)  | 0.06             |         |
| Lab result number- Total cholesterol (mg/dl) mean (only <5000 included) v2  | 60             | 69                | 3     | 20                    |                     |         | N/A         | N/A         | 63                 | 89             |                  |         |
| ...mean (sd)                                                                | 193.95 (42.54) | 190.48 (38.93)    | 0.09  | 186.67 (41.79)        | 161.78 (32.05)      | 0.67    | N/A         | N/A         | 193.60 (42.87)     | 184.03 (37.75) | 0.24             |         |
| ...Missing; n (%)                                                           | 430 (87.8%)    | 421 (85.9%)       | 0.06  | 1,378 (99.8%)         | 1,361 (98.6%)       | 0.14    | N/A         | N/A         | 1,808 (96.6%)      | 1,782 (95.2%)  | 0.07             |         |
| Lab result number- Triglyceride level (mg/dl) mean (only <5000 included) v2 | 60             | 68                | 4     | 19                    |                     |         | N/A         | N/A         | 64                 | 87             |                  |         |
| ...mean (sd)                                                                | 139.10 (84.71) | 141.70 (80.32)    | -0.03 | 248.00 (206.07)       | 124.68 (70.13)      | 0.80    | N/A         | N/A         | 145.91 (95.02)     | 137.98 (78.74) | 0.09             |         |
| ...Missing; n (%)                                                           | 430 (87.8%)    | 422 (86.1%)       | 0.05  | 1,377 (99.7%)         | 1,362 (98.6%)       | 0.12    | N/A         | N/A         | 1,807 (96.6%)      | 1,784 (95.4%)  | 0.06             |         |
| Lab result number- Hemoglobin mean (only >0 included)                       | 83             | 97                | 6     | 17                    |                     |         | N/A         | N/A         | 89                 | 114            |                  |         |
| ...mean (sd)                                                                | 13.73 (1.94)   | 13.73 (1.83)      | 0.00  | 40,008.30 (62,283.25) | 14.48 (1.45)        | 0.91    | N/A         | N/A         | 2709.99 (15017.83) | 13.84 (1.79)   | 0.25             |         |
| ...Missing; n (%)                                                           | 407 (83.1%)    | 393 (80.2%)       | 0.07  | 1,375 (99.6%)         | 1,364 (98.8%)       | 0.09    | N/A         | N/A         | 1,782 (95.2%)      | 1,757 (93.9%)  | 0.06             |         |
| Lab result number- Serum sodium mean (only >90 and <190 included)           | 103            | 102               | 9     | 22                    |                     |         | N/A         | N/A         | 112                | 124            |                  |         |
| ...mean (sd)                                                                | 140.36 (2.80)  | 140.11 (2.59)     | 0.09  | 137.64 (4.57)         | 140.09 (1.89)       | -0.70   | N/A         | N/A         | 140.14 (2.98)      | 140.11 (2.49)  | 0.01             |         |
| ...Missing; n (%)                                                           | 387 (79.0%)    | 388 (79.2%)       | 0.00  | 1,372 (99.3%)         | 1,359 (98.4%)       | 0.08    | N/A         | N/A         | 1,759 (94.0%)      | 1,747 (93.4%)  | 0.02             |         |
| Lab result number- Albumin mean (only >0 and <=10 included)                 | 95             | 100               | 8     | 16                    |                     |         | N/A         | N/A         | 103                | 116            |                  |         |
| ...mean (sd)                                                                | 4.08 (0.41)    | 4.08 (0.40)       | 0.00  | 4.00 (0.32)           | 4.16 (0.48)         | -0.39   | N/A         | N/A         | 4.07 (0.41)        | 4.09 (0.41)    | -0.05            |         |
| ...Missing; n (%)                                                           | 395 (80.6%)    | 390 (79.6%)       | 0.03  | 1,373 (99.4%)         | 1,365 (98.8%)       | 0.06    | N/A         | N/A         | 1,768 (94.5%)      | 1,755 (93.8%)  | 0.03             |         |
| Lab result number- Glucose (fasting or random) mean (only 10-1000 included) | 103            | 103               | 9     | 23                    |                     |         | N/A         | N/A         | 112                | 126            |                  |         |
| ...mean (sd)                                                                | 112.05 (46.57) | 108.13 (37.41)    | 0.09  | 166.42 (108.75)       | 131.56 (58.94)      | 0.40    | N/A         | N/A         | 116.42 (53.83)     | 112.41 (42.21) | 0.08             |         |
| ...Missing; n (%)                                                           | 387 (79.0%)    | 387 (79.0%)       | 0.00  | 1,372 (99.3%)         | 1,358 (98.3%)       | 0.09    | N/A         | N/A         | 1,759 (94.0%)      | 1,745 (93.3%)  | 0.03             |         |
| Lab result number- Potassium mean (only 1-7 included)                       | 107            | 112               | 9     | 20                    |                     |         | N/A         | N/A         | 116                | 132            |                  |         |
| ...mean (sd)                                                                | 4.34 (0.42)    | 4.34 (0.40)       | 0.00  | 4.37 (0.55)           | 4.37 (0.40)         | 0.00    | N/A         | N/A         | 4.34 (0.43)        | 4.34 (0.40)    | 0.00             |         |
| ...Missing; n (%)                                                           | 383 (78.2%)    | 378 (77.1%)       | 0.03  | 1,372 (99.3%)         | 1,361 (98.6%)       | 0.07    | N/A         | N/A         | 1,755 (93.8%)      | 1,739 (92.9%)  | 0.04             |         |
| <b>Comorbidity Scores</b>                                                   |                |                   |       |                       |                     |         |             |             |                    |                |                  |         |
| CCI (180 days)- ICD9 and ICD10 v2                                           |                |                   |       |                       |                     |         |             |             |                    |                |                  |         |
| ...mean (sd)                                                                | 3.51 (2.21)    | 3.71 (2.52)       | -0.08 | 2.89 (2.11)           | 2.83 (2.17)         | 0.03    | 3.97 (2.69) | 4.05 (2.67) | -0.03              | 3.49 (2.42)    | 3.53 (2.47)      | -0.02   |

# Appendix B

|                                                                                            |               |               |           |               |               |           |               |               |           |               |               |         |
|--------------------------------------------------------------------------------------------|---------------|---------------|-----------|---------------|---------------|-----------|---------------|---------------|-----------|---------------|---------------|---------|
| Non-Frailty; n (%)                                                                         | 206 (42.0%)   | 210 (42.9%)   | -0.02     | 581 (42.1%)   | 583 (42.2%)   | 0.00      | 57 (3.4%)     | 47 (2.8%)     | 0.03      | 844 (23.6%)   | 840 (23.5%)   | 0.00    |
| Frailty Score (mean): Empirical Version<br>365 days, v2                                    |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.18 (0.06)   | 0.18 (0.06)   | 0.00      | 0.15 (0.05)   | 0.15 (0.05)   | 0.00      | 0.10 (0.07)   | 0.10 (0.08)   | 0.00      | 0.13 (0.06)   | 0.13 (0.07)   | 0.00    |
| Healthcare Utilization                                                                     |               |               |           |               |               |           |               |               |           |               |               |         |
| Any hospitalization; n (%)                                                                 | 438 (89.4%)   | 453 (92.4%)   | -0.10     | 1,379 (99.9%) | 1,380 (99.9%) | 0.00      | 1,564 (92.1%) | 1,555 (91.5%) | 0.02      | 3,381 (94.7%) | 3,388 (94.9%) | -0.01   |
| Any hospitalization within prior 30 days; n (%)                                            | 374 (76.3%)   | 364 (74.3%)   | 0.05      | 1,287 (93.2%) | 1,302 (94.3%) | -0.05     | 1,204 (70.9%) | 1,229 (72.3%) | -0.03     | 2865 (80.3%)  | 2895 (81.1%)  | -0.02   |
| Any hospitalization during prior 31-180 days; n (%)                                        | 101 (20.6%)   | 121 (24.7%)   | -0.10     | 185 (13.4%)   | 166 (12.0%)   | 0.04      | 565 (33.3%)   | 546 (32.1%)   | 0.03      | 851 (23.8%)   | 833 (23.3%)   | 0.01    |
| Internal medicine/family medicine visits; n (%)                                            | 427 (87.1%)   | 427 (87.1%)   | 0.00      | 1,079 (78.1%) | 1,090 (78.9%) | -0.02     | 1,606 (94.5%) | 1,626 (95.7%) | -0.06     | 3112 (87.2%)  | 3143 (88.0%)  | -0.02   |
| Internal medicine/family medicine visits (30 days prior); n (%)                            | 361 (73.7%)   | 360 (73.5%)   | 0.00      | 753 (54.5%)   | 821 (59.4%)   | -0.10     | 1,399 (82.3%) | 1,402 (82.5%) | -0.01     | 2513 (70.4%)  | 2583 (72.4%)  | -0.04   |
| Internal medicine/family medicine visits (31 to 180 days prior); n (%)                     | 294 (60.0%)   | 294 (60.0%)   | 0.00      | 855 (61.9%)   | 817 (59.2%)   | 0.06      | 1,184 (69.7%) | 1,140 (67.1%) | 0.06      | 2333 (65.4%)  | 2251 (63.1%)  | 0.05    |
| Cardiologist visit; n (%)                                                                  | 352 (71.8%)   | 365 (74.5%)   | -0.06     | 393 (28.5%)   | 375 (27.2%)   | 0.03      | 1,203 (70.8%) | 1,213 (71.4%) | -0.01     | 1948 (54.6%)  | 1953 (54.7%)  | 0.00    |
| Number of Cardiologist visits (30 days prior); n (%)                                       | 297 (60.6%)   | 308 (62.9%)   | -0.05     | 271 (19.6%)   | 270 (19.6%)   | 0.00      | 880 (51.8%)   | 902 (53.1%)   | -0.03     | 1448 (40.6%)  | 1480 (41.5%)  | -0.02   |
| Number of Cardiologist visits (31 to 180 days prior); n (%)                                | 111 (22.7%)   | 123 (25.1%)   | -0.06     | 173 (12.5%)   | 165 (11.9%)   | 0.02      | 558 (32.8%)   | 563 (33.1%)   | -0.01     | 842 (23.6%)   | 851 (23.8%)   | 0.00    |
| Electrocardiogram v2; n (%)                                                                | 401 (81.8%)   | 415 (84.7%)   | -0.08     | 694 (50.3%)   | 691 (50.0%)   | 0.01      | 1,449 (85.3%) | 1,442 (84.9%) | 0.01      | 2544 (71.3%)  | 2548 (71.4%)  | 0.00    |
| Use of glucose test strips; n (%)                                                          | ** (1.2%)     | ** (1.4%)     | -0.02     | 19 (1.4%)     | ** (0.8%)     | 0.06      | 31 (1.8%)     | 29 (1.7%)     | 0.01      | #VALUE!       | #VALUE!       | #VALUE! |
| Dialysis; n (%)                                                                            | 0 (0.0%)      | ** (0.2%)     | -0.06     | 0 (0.0%)      | ** (0.1%)     | -0.04     | ** (0.1%)     | ** (0.1%)     | 0.00      | #VALUE!       | #VALUE!       | #VALUE! |
| number of different/distinct medication prescriptions                                      |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 7.88 (5.51)   | 8.00 (5.83)   | -0.02     | 7.89 (4.81)   | 8.01 (5.76)   | -0.02     | 9.33 (6.22)   | 9.31 (6.22)   | 0.00      | 8.57 (5.62)   | 8.63 (5.99)   | -0.01   |
| Number of Hospitalizations                                                                 |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 1.11 (0.72)   | 1.08 (0.56)   | 0.05      | 1.17 (0.48)   | 1.16 (0.49)   | 0.02      | 1.30 (0.93)   | 1.29 (0.93)   | 0.01      | 1.22 (0.76)   | 1.21 (0.74)   | 0.01    |
| Number of hospital days                                                                    |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 5.44 (4.46)   | 5.11 (7.06)   | 0.06      | 5.43 (4.09)   | 5.28 (6.21)   | 0.03      | 5.85 (5.04)   | 5.73 (7.43)   | 0.02      | 5.63 (4.61)   | 5.47 (6.93)   | 0.03    |
| Number of Emergency Department (ED) visits v3                                              |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 1.79 (2.37)   | 1.82 (2.21)   | -0.01     | 3.20 (5.17)   | 3.17 (4.44)   | 0.01      | 2.70 (7.14)   | 2.73 (4.23)   | -0.01     | 2.77 (5.95)   | 2.78 (4.10)   | 0.00    |
| Number of Office visits                                                                    |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 5.01 (4.71)   | 5.03 (4.44)   | 0.00      | 4.72 (4.41)   | 4.77 (5.34)   | -0.01     | 10.37 (13.98) | 10.07 (11.65) | 0.02      | 7.45 (10.18)  | 7.33 (8.85)   | 0.01    |
| Number of internal medicine/family medicine visits                                         |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 10.16 (13.90) | 9.39 (12.98)  | 0.06      | 5.30 (7.34)   | 5.51 (8.85)   | -0.03     | 12.46 (13.83) | 11.04 (12.11) | 0.11      | 9.37 (11.76)  | 8.67 (11.10)  | 0.06    |
| Number of Cardiologist visits                                                              |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 2.58 (3.80)   | 2.62 (3.94)   | -0.01     | 0.71 (1.95)   | 0.70 (1.90)   | 0.01      | 2.81 (4.52)   | 2.89 (4.25)   | -0.02     | 1.97 (3.63)   | 2.01 (3.48)   | -0.01   |
| Number of electrocardiograms received v2                                                   |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 1.98 (2.00)   | 2.10 (2.02)   | -0.06     | 0.90 (1.31)   | 0.92 (1.37)   | -0.01     | 2.31 (2.51)   | 2.35 (2.54)   | -0.02     | 1.72 (2.05)   | 1.76 (2.09)   | -0.02   |
| Number of HbA1c tests ordered                                                              |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.28 (0.63)   | 0.29 (0.64)   | -0.02     | 0.22 (0.51)   | 0.22 (0.55)   | 0.00      | 0.29 (0.62)   | 0.29 (0.60)   | 0.00      | 0.26 (0.58)   | 0.26 (0.59)   | 0.00    |
| Number of glucose tests ordered                                                            |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.14 (0.62)   | 0.17 (0.73)   | -0.04     | 0.13 (1.17)   | 0.13 (0.60)   | 0.00      | 0.15 (0.60)   | 0.17 (0.60)   | -0.03     | 0.14 (0.87)   | 0.15 (0.62)   | -0.01   |
| Number of lipid tests ordered                                                              |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 0.37 (0.62)   | 0.39 (0.74)   | -0.03     | 0.38 (0.72)   | 0.36 (0.66)   | 0.03      | 0.36 (0.65)   | 0.37 (0.64)   | -0.02     | 0.37 (0.67)   | 0.37 (0.66)   | 0.00    |
| Total N distinct ICD9/ICD10 diagnoses at the 3rd digit level Copy                          |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 12.13 (12.97) | 12.28 (12.70) | -0.01     | 10.37 (10.13) | 10.29 (10.87) | 0.01      | 17.46 (15.46) | 17.28 (15.89) | 0.01      | 13.99 (13.29) | 13.89 (13.71) | 0.01    |
| For PS                                                                                     |               |               |           |               |               |           |               |               |           |               |               |         |
| Hemorrhagic stroke+Other cerebrovascular disease+Cerebrovascular procedure (for PS); n (%) |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | ** (1.4%)     | ** (1.2%)     | 0.02      | 11 (0.8%)     | 11 (0.8%)     | 0.00      | 31 (1.8%)     | 31 (1.8%)     | 0.00      | #VALUE!       | #VALUE!       | #VALUE! |
| Major trauma potentially causing prolonged hospitalization (for PS); n (%)                 |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 16 (3.3%)     | #DIV/0!       | 31 (2.2%) | 33 (2.4%)     | #DIV/0!       | 92 (5.4%) | 92 (5.4%)     | #DIV/0!       | 31 (2.2%) | 33 (2.4%)     | -0.01         |         |
| Occurrence of creatinine tests ordered (for PS); n (%)                                     |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 30 (6.1%)     | 30 (6.1%)     | 0.00      | 80 (5.8%)     | 72 (5.2%)     | 0.03      | 129 (7.6%)    | 151 (8.9%)    | -0.05     | 239 (6.7%)    | 253 (7.1%)    | -0.02   |
| Occurrence of BUN tests ordered (for PS); n (%)                                            |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 13 (2.7%)     | 15 (3.1%)     | -0.02     | 36 (2.6%)     | 42 (3.0%)     | -0.02     | 63 (3.7%)     | 81 (4.8%)     | -0.05     | 112 (3.1%)    | 138 (3.9%)    | -0.04   |
| Occurrence of chronic renal insufficiency w/o CKD (for PS); n (%)                          |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | ** (1.0%)     | ** (0.6%)     | 0.04      | ** (0.5%)     | ** (0.5%)     | 0.00      | 18 (1.1%)     | 26 (1.5%)     | -0.04     | #VALUE!       | #VALUE!       | #VALUE! |
| Chronic kidney disease Stage 1-2 (for PS); n (%)                                           |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | ** (1.4%)     | ** (1.6%)     | -0.02     | ** (0.7%)     | ** (0.4%)     | 0.04      | 28 (1.6%)     | 27 (1.6%)     | 0.00      | #VALUE!       | #VALUE!       | #VALUE! |
| Chronic kidney disease Stage 3-6 (for PS); n (%)                                           |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 16 (3.3%)     | 15 (3.1%)     | 0.01      | 34 (2.5%)     | 23 (1.7%)     | 0.06      | 79 (4.6%)     | 92 (5.4%)     | -0.04     | 129 (3.6%)    | 130 (3.6%)    | 0.00    |
| Acute kidney injury; n (%)                                                                 |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 38 (7.8%)     | 43 (8.8%)     | #DIV/0!   | 99 (7.2%)     | 98 (7.1%)     | #DIV/0!   | 168 (9.9%)    | 184 (10.8%)   | #DIV/0!   | 99 (7.2%)     | 98 (7.1%)     | 0.00    |
| Bladder stones+Kidney stones (for PS); n (%)                                               |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 21 (4.3%)     | 19 (3.9%)     | 0.02      | 39 (2.8%)     | 49 (3.5%)     | -0.04     | 62 (3.6%)     | 64 (3.8%)     | -0.01     | 122 (3.4%)    | 132 (3.7%)    | -0.02   |
| Alcohol abuse or dependence+Drug abuse or dependence (for PS); n (%)                       |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 33 (6.7%)     | 36 (7.3%)     | -0.02     | 46 (3.3%)     | 49 (3.5%)     | -0.01     | 156 (9.2%)    | 145 (8.5%)    | 0.02      | 235 (6.6%)    | 230 (6.4%)    | 0.01    |
| Other atherosclerosis+Cardiac conduction disorders+Other CVD (for PS) v2 Copy; n (%)       |               |               |           |               |               |           |               |               |           |               |               |         |
| ...mean (sd)                                                                               | 155 (31.6%)   | 149 (30.4%)   | 0.03      | 394 (28.5%)   | 402 (29.1%)   | -0.01     | 500 (29.4%)   | 539 (31.7%)   | -0.05     | 1049 (29.4%)  | 1090 (30.5%)  | -0.02   |

# Appendix B

|                                                                                                 |              |             |                     |                     |                |                     |                     |               |                 |                 |              |                   |                   |             |
|-------------------------------------------------------------------------------------------------|--------------|-------------|---------------------|---------------------|----------------|---------------------|---------------------|---------------|-----------------|-----------------|--------------|-------------------|-------------------|-------------|
| Previous cardiac procedure (CABG or PCTA or Stent) + History of CABG or PCTA (for PS) v3; n (%) | 22 (4.5%)    | 14 (2.9%)   | 0.08                | 14 (1.0%)           | 13 (0.9%)      | 0.01                | 91 (5.4%)           | 96 (5.7%)     | -0.01           | 127 (3.6%)      | 123 (3.4%)   | 0.01              |                   |             |
| Diabetes with complication; n (%)                                                               | 35 (7.1%)    | 32 (6.5%)   | #DIV/0!             | 53 (3.8%)           | 50 (3.6%)      | #DIV/0!             | 156 (9.2%)          | 167 (9.8%)    | #DIV/0!         | 53 (3.8%)       | 50 (3.6%)    | 0.01              |                   |             |
| Delirium + Psychosis (for PS); n (%)                                                            | 23 (4.7%)    | 26 (5.3%)   | -0.03               | 30 (2.2%)           | 33 (2.4%)      | -0.01               | 263 (15.5%)         | 262 (15.4%)   | 0.00            | 316 (8.9%)      | 321 (9.0%)   | 0.00              |                   |             |
| Any use of Meglitinides (for PS); n (%)                                                         | 0 (0.0%)     | ** (0.2%)   | -0.06               | ** (0.1%)           | ** (0.1%)      | 0.00                | 0 (0.0%)            | 0 (0.0%)      | #DIV/0!         | #VALUE!         | #VALUE!      | #VALUE!           |                   |             |
| Any use of AGIs (for PS); n (%)                                                                 | 0 (0.0%)     | 0 (0.0%)    | #DIV/0!             | ** (0.1%)           | 0 (0.0%)       | 0.04                | 0 (0.0%)            | 0 (0.0%)      | #DIV/0!         | 0 (0.0%)        | 0 (0.0%)     | #VALUE!           |                   |             |
| CKD stage 3-6 + dialysis (for PS); n (%)                                                        | 16 (3.3%)    | 17 (3.5%)   | -0.01               | 34 (2.5%)           | 25 (1.8%)      | 0.05                | 80 (4.7%)           | 94 (5.5%)     | -0.04           | 130 (3.6%)      | 136 (3.8%)   | -0.01             |                   |             |
| Use of thiazide; n (%)                                                                          | 22 (4.5%)    | 23 (4.7%)   | -0.01               | 79 (5.7%)           | 88 (6.4%)      | -0.03               | 79 (4.6%)           | 82 (4.8%)     | -0.01           | 180 (5.0%)      | 193 (5.4%)   | -0.02             |                   |             |
| Use of beta blockers; n (%)                                                                     | 75 (15.3%)   | 66 (13.5%)  | 0.05                | 231 (16.7%)         | 218 (15.8%)    | 0.02                | 331 (19.5%)         | 328 (19.3%)   | 0.01            | 637 (17.8%)     | 612 (17.1%)  | 0.02              |                   |             |
| Use of calcium channel blockers; n (%)                                                          | 55 (11.2%)   | 56 (11.4%)  | -0.01               | 170 (12.3%)         | 169 (12.2%)    | 0.00                | 194 (11.4%)         | 179 (10.5%)   | 0.03            | 419 (11.7%)     | 404 (11.3%)  | 0.01              |                   |             |
| All antidiabetic medications except Insul                                                       | 57 (11.6%)   | 62 (12.7%)  | -0.03               | 149 (10.8%)         | 158 (11.4%)    | -0.02               | 207 (12.2%)         | 219 (12.9%)   | -0.02           | 413 (11.6%)     | 439 (12.3%)  | -0.02             |                   |             |
| DM Medications -Insulin Copy; n (%)                                                             | 23 (4.7%)    | 27 (5.5%)   | -0.04               | 59 (4.3%)           | 49 (3.5%)      | 0.04                | 80 (4.7%)           | 91 (5.4%)     | -0.03           | 162 (4.5%)      | 167 (4.7%)   | -0.01             |                   |             |
| Use of Low Intensity Statins; n (%)                                                             | 61 (12.4%)   | 63 (12.9%)  | -0.02               | 136 (9.8%)          | 132 (9.6%)     | 0.01                | 283 (16.7%)         | 277 (16.3%)   | 0.01            | 480 (13.4%)     | 472 (13.2%)  | 0.01              |                   |             |
| Use of High Intensity Statins; n (%)                                                            | 51 (10.4%)   | 51 (10.4%)  | 0.00                | 127 (9.2%)          | 132 (9.6%)     | -0.01               | 195 (11.5%)         | 204 (12.0%)   | -0.02           | 373 (10.4%)     | 387 (10.8%)  | -0.01             |                   |             |
| Malignant hypertension; n (%)                                                                   | ** (0.2%)    | ** (0.2%)   | 0.00                | 76 (5.5%)           | 85 (6.2%)      | -0.03               | 82 (4.8%)           | 73 (4.3%)     | 0.02            | #VALUE!         | #VALUE!      | #VALUE!           |                   |             |
| Cardiovascular stress test; n (%)                                                               | ** (1.0%)    | ** (0.4%)   | 0.07                | ** (0.6%)           | ** (0.7%)      | -0.01               | 21 (1.2%)           | 26 (1.5%)     | -0.03           | #VALUE!         | #VALUE!      | #VALUE!           |                   |             |
| Echocardiogram; n (%)                                                                           | 298 (60.8%)  | 349 (71.2%) | -0.22               | 910 (65.9%)         | 960 (69.5%)    | -0.08               | 1,040 (61.2%)       | 1,058 (62.3%) | -0.02           | 2248 (63.0%)    | 2367 (66.3%) | -0.07             |                   |             |
| Number of BNP tests                                                                             | ...mean (sd) |             | 0.17 (0.51)         | 0.22 (0.59)         | -0.09          | 0.15 (0.47)         | 0.17 (0.49)         | -0.04         | 0.17 (0.51)     | 0.22 (0.53)     | -0.10        | 0.16 (0.49)       | 0.20 (0.52)       | 0.00        |
| Number of Cardiac biomarkers tests (tropnin, CK-MBs, Myoglobin, CPK)                            | ...mean (sd) |             | 0.46 (1.22)         | 0.73 (1.68)         | -0.18          | 0.44 (1.13)         | 0.54 (1.46)         | -0.08         | 0.39 (0.80)     | 0.46 (0.96)     | -0.08        | 0.42 (1.00)       | 0.53 (1.28)       | 0.00        |
| Number of Ambulatory Blood pressure monitoring tests                                            | ...mean (sd) |             | 0.00 (0.00)         | 0.00 (0.06)         | 0.00           | 0.00 (0.04)         | 0.00 (0.03)         | 0.00          | 0.00 (0.00)     | 0.00 (0.00)     | #DIV/0!      | 0.00 (0.02)       | 0.00 (0.03)       | 0.00        |
| N of days on antihypertensive medications during baseline                                       | ...mean (sd) |             | 41.64 (66.76)       | 40.37 (67.11)       | 0.02           | 45.23 (70.39)       | 45.62 (70.62)       | -0.01         | 41.49 (66.16)   | 43.81 (67.50)   | -0.03        | 42.96 (67.91)     | 44.04 (68.67)     | 0.00        |
| N of days in database anytime prior                                                             | ...mean (sd) |             | 1,631.36 (1,356.14) | 1,568.20 (1,247.77) | 0.05           | 2,203.52 (1,550.45) | 2,092.63 (1,508.64) | 0.07          | 720.02 (502.47) | 681.78 (392.54) | 0.08         | 1418.98 (1141.20) | 1349.21 (1080.43) | 0.00        |
| Mean Copay for per prescription cost (charges in U.S. \$) (180-1 day prior)                     | ...mean (sd) |             | 22.31 (49.02)       | 22.88 (47.07)       | -0.01          | 11.22 (16.38)       | 10.92 (16.98)       | 0.02          | 111.13 (120.49) | 117.56 (187.51) | -0.04        | 60.29 (85.70)     | 63.31 (130.97)    | 0.00        |
| ...Missing; n (%)                                                                               | 57 (11.6%)   |             | 59 (12.0%)          | -0.01               | 156 (11.3%)    | 155 (11.2%)         | 0.00                | 182 (10.7%)   | 179 (10.5%)     | 0.01            | 395 (11.1%)  | 393 (11.0%)       | 0.00              |             |
| Colonoscopy; n (%)                                                                              | 17 (3.5%)    |             | 20 (4.1%)           | -0.03               | 55 (4.0%)      | 50 (3.6%)           | 0.02                | 47 (2.8%)     | 47 (2.8%)       | 0.00            | 119 (3.3%)   | 117 (3.3%)        | 0.00              |             |
| Fecal occult blood (FOB) test; n (%)                                                            | 14 (2.9%)    |             | 14 (2.9%)           | 0.00                | 47 (3.4%)      | 45 (3.3%)           | 0.01                | 33 (1.9%)     | 43 (2.5%)       | -0.04           | 94 (2.6%)    | 102 (2.9%)        | -0.02             |             |
| Flu vaccine; n (%)                                                                              | 62 (12.7%)   |             | 57 (11.6%)          | 0.03                | 142 (10.3%)    | 144 (10.4%)         | 0.00                | 440 (25.9%)   | 432 (25.4%)     | 0.01            | 644 (18.0%)  | 633 (17.7%)       | 0.01              |             |
| Mammogram; n (%)                                                                                | 43 (8.8%)    |             | 49 (10.0%)          | -0.04               | 138 (10.0%)    | 152 (11.0%)         | -0.03               | 152 (8.9%)    | 138 (8.1%)      | 0.03            | 333 (9.3%)   | 339 (9.5%)        | -0.01             |             |
| Pap smear; n (%)                                                                                | 26 (5.3%)    |             | 23 (4.7%)           | 0.03                | 98 (7.1%)      | 106 (7.7%)          | -0.02               | 48 (2.8%)     | 54 (3.2%)       | -0.02           | 172 (4.8%)   | 183 (5.1%)        | -0.01             |             |
| Pneumonia vaccine; n (%)                                                                        | 94 (19.2%)   |             | 85 (17.3%)          | 0.05                | 179 (13.0%)    | 178 (12.9%)         | 0.00                | 506 (29.8%)   | 501 (29.5%)     | 0.01            | 779 (21.8%)  | 764 (21.4%)       | 0.01              |             |
| PSA test or Prostate exam for DRE; n (%)                                                        | 42 (8.6%)    |             | 39 (8.0%)           | 0.02                | 132 (9.6%)     | 132 (9.6%)          | 0.00                | 134 (7.9%)    | 122 (7.2%)      | 0.03            | 308 (8.6%)   | 293 (8.2%)        | 0.01              |             |
| Bone mineral density; n (%)                                                                     | ** (1.8%)    |             | 15 (3.1%)           | -0.08               | 20 (1.4%)      | 21 (1.5%)           | -0.01               | 39 (2.3%)     | 42 (2.5%)       | -0.01           | #VALUE!      | 78 (2.2%)         | #VALUE!           |             |
| Use of CNS stimulants; n (%)                                                                    | ** (1.8%)    |             | ** (1.8%)           | -0.02               | ** (0.5%)      | 26 (1.5%)           | -0.13               | ** (0.6%)     | ** (0.6%)       | 0.00            | #VALUE!      | #VALUE!           | #VALUE!           |             |
| Use of estrogens, progestins, androgens; r                                                      | 48 (9.8%)    |             | 42 (8.6%)           | 0.04                | 175 (12.7%)    | 176 (12.7%)         | 0.00                | 62 (3.6%)     | 65 (3.8%)       | -0.01           | 285 (8.0%)   | 283 (7.9%)        | 0.00              |             |
| Use of Angiogenesis inhibitors; n (%)                                                           | 0 (0.0%)     |             | ** (0.2%)           | -0.06               | ** (0.1%)      | ** (0.1%)           | 0.00                | ** (0.1%)     | ** (0.2%)       | -0.03           | #VALUE!      | #VALUE!           | #VALUE!           |             |
| Use of Oral Immunosuppressants; n (%)                                                           | ** (0.2%)    |             | ** (0.2%)           | 0.00                | ** (0.4%)      | ** (0.2%)           | 0.04                | ** (0.2%)     | ** (0.2%)       | 0.00            | #VALUE!      | #VALUE!           | #VALUE!           |             |
| Use of fondaparinux or Bivalirudin; n (%)                                                       | 0 (0.0%)     |             | 0 (0.0%)            | #DIV/0!             | ** (0.1%)      | ** (0.1%)           | 0.00                | ** (0.2%)     | ** (0.1%)       | 0.03            | #VALUE!      | #VALUE!           | #VALUE!           |             |
| Use of other direct thrombin inhibitors (I                                                      | 0 (0.0%)     |             | 0 (0.0%)            | #DIV/0!             | 0 (0.0%)       | #DIV/0!             | 0 (0.0%)            | 0 (0.0%)      | #DIV/0!         | 0 (0.0%)        | 0 (0.0%)     | #DIV/0!           | 0 (0.0%)          | #DIV/0!     |
| Use of Ticagrelor ON CED; n (%)                                                                 | 0 (0.0%)     |             | 0 (0.0%)            | #DIV/0!             | ** (0.1%)      | 0 (0.0%)            | 0.04                | 0 (0.0%)      | ** (0.1%)       | -0.04           | #VALUE!      | #VALUE!           | #VALUE!           |             |
| Use of Ticagrelor; n (%)                                                                        | 0 (0.0%)     |             | 0 (0.0%)            | #DIV/0!             | ** (0.1%)      | ** (0.1%)           | 0.00                | 0 (0.0%)      | ** (0.2%)       | -0.06           | #VALUE!      | #VALUE!           | #VALUE!           |             |
| Number of D-dimer tests                                                                         | ...mean (sd) |             | 0.19 (0.44)         | 0.19 (0.45)         | 0.00           | 0.17 (0.44)         | 0.18 (0.45)         | -0.02         | 0.19 (0.45)     | 0.18 (0.43)     | 0.02         | 0.18 (0.44)       | 0.18 (0.44)       | 0.00        |
| Number of CRP, high-sensitivity CRP tests                                                       | ...mean (sd) |             | 0.13 (0.58)         | 0.14 (0.77)         | -0.01          | 0.10 (0.45)         | 0.09 (0.49)         | 0.02          | 0.13 (0.59)     | 0.13 (0.57)     | 0.00         | 0.12 (0.54)       | 0.12 (0.57)       | 0.00        |
| Number of PT or aPTT tests                                                                      | ...mean (sd) |             | 1.03 (2.16)         | 1.03 (2.17)         | 0.00           | 0.85 (2.00)         | 0.81 (1.96)         | 0.02          | 0.53 (1.12)     | 0.52 (1.10)     | 0.01         | 0.72 (1.67)       | 0.70 (1.65)       | 0.00        |
| Number of Bleeding time tests                                                                   | ...mean (sd) |             | 0.00 (0.00)         | 0.00 (0.00)         | #DIV/0!        | 0.00 (0.00)         | 0.00 (0.00)         | #DIV/0!       | 0.00 (0.00)     | #DIV/0!         | 0.00 (0.00)  | 0.00 (0.00)       | #DIV/0!           | 0.00 (0.00) |
| HAS-BLED Score (ICD-9 and ICD-10), 180 days                                                     | ...mean (sd) |             | 2.06 (0.69)         | 2.07 (0.63)         | -0.02          | 1.90 (0.70)         | 1.90 (0.68)         | 0.00          | 2.38 (0.81)     | 2.39 (0.78)     | -0.01        | 2.15 (0.75)       | 2.16 (0.72)       | 0.00        |
| N of Generic name drugs                                                                         | ...mean (sd) |             | 14.39 (14.69)       | 14.42 (16.73)       | 0.00           | 11.78 (10.46)       | 12.02 (13.21)       | -0.02         | 19.11 (18.82)   | 19.05 (19.03)   | 0.00         | 15.63 (15.51)     | 15.70 (16.68)     | 0.00        |
| N of Brand name drugs                                                                           | ...mean (sd) |             | 2.59 (4.40)         | 2.63 (2.88)         | -0.01          | 2.47 (3.76)         | 2.53 (2.57)         | -0.02         | 3.47 (5.81)     | 3.51 (3.78)     | -0.01        | 2.96 (4.92)       | 3.01 (3.24)       | 0.00        |
| Use of clopidogrel; n (%)                                                                       | ** (0.6%)    |             | ** (0.8%)           | -0.02               | ** (0.5%)      | ** (0.5%)           | 0.00                | 68 (4.0%)     | 62 (3.6%)       | 0.02            | #VALUE!      | #VALUE!           | #VALUE!           |             |
| Systemic embolism; n (%)                                                                        | ** (1.8%)    |             | 12 (2.4%)           | -0.04               | 26 (1.9%)      | 28 (2.0%)           | -0.01               | 29 (1.7%)     | 29 (1.7%)       | 0.00            | #VALUE!      | 69 (1.9%)         | #VALUE!           |             |
| DVT; n (%)                                                                                      | 257 (52.4%)  |             | 248 (50.6%)         | 0.04                | 757 (54.8%)    | 739 (53.5%)         | 0.03                | 824 (48.5%)   | 849 (50.0%)     | -0.03           | 1838 (51.5%) | 1836 (51.4%)      | 0.00              |             |
| Post-thrombotic syndrome; n (%)                                                                 | 0 (0.0%)     |             | 0 (0.0%)            | #DIV/0!             | ** (0.1%)      | ** (0.1%)           | #DIV/0!             | ** (0.2%)     | ** (0.1%)       | #DIV/0!         | ** (0.1%)    | ** (0.1%)         | 0.00              |             |
| PE; n (%)                                                                                       | 490 (100.0%) |             | 490 (100.0%)        | #DIV/0!             | 1,381 (100.0%) | 1,381 (100.0%)      | #DIV/0!             | 1,692 (99.6%) | 1,695 (99.8%)   | -0.04           | 3563 (99.8%) | 3566 (99.9%)      | -0.03             |             |
| Coagulation defects; n (%)                                                                      | ** (1.6%)    |             | ** (2.2%)           | #DIV/0!             | 35 (2.5%)      | 40 (2.9%)           | #DIV/0!             | 28 (1.6%)     | 32 (1.9%)       | 35 (2.5%)       | 40 (2.9%)    | -0.02             |                   |             |
| Diabetes: 1 inpatient or 2 outpatient clai                                                      | 86 (17.6%)   |             | 90 (18.4%)          | -0.02               | 212 (15.4%)    | 210 (15.2%)         | 0.01                | 371 (21.8%)   | 407 (24.0%)     | -0.05           | 669 (18.7%)  | 707 (19.8%)       | -0.03             |             |

# Appendix B

|                                                                            |               |             |             |               |               |         |               |               |             |               |               |         |
|----------------------------------------------------------------------------|---------------|-------------|-------------|---------------|---------------|---------|---------------|---------------|-------------|---------------|---------------|---------|
| Intracranial or retroperitoneal hemorrhha                                  | ** (0.4%)     | ** (0.4%)   | 0.00        | ** (0.1%)     | ** (0.1%)     | 0.00    | ** (0.3%)     | ** (0.2%)     | 0.02        | #VALUE!       | #VALUE!       | #VALUE! |
| Peptic Ulcer Disease; n (%)                                                | 134 (27.3%)   | 140 (28.6%) | -0.03       | 257 (18.6%)   | 268 (19.4%)   | -0.02   | 534 (31.4%)   | 545 (32.1%)   | -0.02       | 925 (25.9%)   | 953 (26.7%)   | -0.02   |
| Upper GI bleed; n (%)                                                      | 0 (0.0%)      | 0 (0.0%)    | #DIV/0!     | ** (0.1%)     | ** (0.1%)     | 0.00    | ** (0.2%)     | ** (0.1%)     | 0.03        | #VALUE!       | #VALUE!       | #VALUE! |
| Lower/ unspecified GI bleed; n (%)                                         | ** (1.6%)     | ** (1.4%)   | 0.02        | 22 (1.6%)     | 20 (1.4%)     | 0.02    | 19 (1.1%)     | 20 (1.2%)     | -0.01       | #VALUE!       | #VALUE!       | #VALUE! |
| Urogenital bleed; n (%)                                                    | ** (1.8%)     | 12 (2.4%)   | -0.04       | 48 (3.5%)     | 41 (3.0%)     | 0.03    | 37 (2.2%)     | 48 (2.8%)     | -0.04       | #VALUE!       | 101 (2.8%)    | #VALUE! |
| Other bleeds; n (%)                                                        | 18 (3.7%)     | 18 (3.7%)   | 0.00        | 55 (4.0%)     | 53 (3.8%)     | 0.01    | 70 (4.1%)     | 63 (3.7%)     | 0.02        | 143 (4.0%)    | 134 (3.8%)    | 0.01    |
| Prior cancer; n (%)                                                        | 78 (15.9%)    | 79 (16.1%)  | -0.01       | 174 (12.6%)   | 176 (12.7%)   | 0.00    | 349 (20.5%)   | 334 (19.7%)   | 0.02        | 601 (16.8%)   | 589 (16.5%)   | 0.01    |
| Antibiotics; n (%)                                                         | 234 (47.8%)   | 235 (48.0%) | #DIV/0!     | 664 (48.1%)   | 671 (48.6%)   | #DIV/0! | 857 (50.4%)   | 853 (50.2%)   | #DIV/0!     | 664 (48.1%)   | 671 (48.6%)   | -0.01   |
| Aspirin; n (%)                                                             | ** (0.4%)     | ** (0.6%)   | -0.03       | 14 (1.0%)     | 19 (1.4%)     | -0.04   | ** (0.2%)     | ** (0.1%)     | 0.03        | #VALUE!       | #VALUE!       | #VALUE! |
| Aspirin/dipyridamole; n (%)                                                | 0 (0.0%)      | 0 (0.0%)    | #DIV/0!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! | ** (0.1%)     | ** (0.1%)     | 0.00        | #VALUE!       | #VALUE!       | #VALUE! |
| Other antiplatelet agents; n (%)                                           | ** (0.2%)     | 0 (0.0%)    | 0.06        | ** (0.1%)     | ** (0.1%)     | 0.00    | ** (0.4%)     | ** (0.3%)     | 0.02        | #VALUE!       | #VALUE!       | #VALUE! |
| PGP inhibitors; n (%)                                                      | 103 (21.0%)   | 92 (18.8%)  | 0.06        | 306 (22.2%)   | 316 (22.9%)   | -0.02   | 410 (24.1%)   | 404 (23.8%)   | 0.01        | 819 (22.9%)   | 812 (22.7%)   | 0.00    |
| Other gastroprotective agents; n (%)                                       | ** (1.0%)     | ** (0.6%)   | 0.04        | 14 (1.0%)     | 13 (0.9%)     | 0.01    | 35 (2.1%)     | 26 (1.5%)     | 0.05        | #VALUE!       | #VALUE!       | #VALUE! |
| Number of lipid tests ordered                                              |               |             |             |               |               |         |               |               |             |               |               |         |
| ...mean (sd)                                                               | 0.37 (0.62)   | 0.39 (0.74) | -0.03       | 0.38 (0.72)   | 0.36 (0.66)   | 0.03    | 0.37 (0.69)   | 0.38 (0.68)   | -0.01       | 0.37 (0.69)   | 0.37 (0.68)   | 0.00    |
| Proton pump inhibitor; n (%)                                               | 94 (19.2%)    | 105 (21.4%) | -0.05       | 232 (16.8%)   | 225 (16.3%)   | 0.01    | 494 (29.1%)   | 490 (28.8%)   | 0.01        | 820 (23.0%)   | 820 (23.0%)   | 0.00    |
| H2 receptor antagonist; n (%)                                              | 15 (3.1%)     | 21 (4.3%)   | -0.06       | 47 (3.4%)     | 49 (3.5%)     | -0.01   | 128 (7.5%)    | 139 (8.2%)    | -0.03       | 190 (5.3%)    | 209 (5.9%)    | -0.03   |
| Vitamin K therapy; n (%)                                                   | 0 (0.0%)      | 0 (0.0%)    | #DIV/0!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| Number of INR (prothrombin) tests ordered                                  |               |             |             |               |               |         |               |               |             |               |               |         |
| ...mean (sd)                                                               | 0.80 (1.89)   | 0.53 (1.24) | 0.17        | 0.68 (1.73)   | 0.50 (1.11)   | 0.12    | 0.51 (1.10)   | 0.49 (1.06)   | 0.02        | 0.62 (1.49)   | 0.50 (1.11)   | 0.00    |
| Treating prescriber - Cardiologist; n (%)                                  | 299 (61.0%)   | 313 (63.9%) | -0.06       | 871 (63.1%)   | 868 (62.9%)   | 0.00    | 880 (51.8%)   | 902 (53.1%)   | -0.03       | 2050 (57.4%)  | 2083 (58.3%)  | -0.02   |
| Treating prescriber - Primary Care Physician                               | 415 (84.7%)   | 407 (83.1%) | 0.04        | 600 (43.4%)   | 636 (46.3%)   | -0.05   | 642 (37.8%)   | 637 (37.5%)   | 0.01        | 1657 (46.4%)  | 1680 (47.1%)  | -0.01   |
| Treating prescriber - Other; n (%)                                         | 474 (96.7%)   | 476 (97.1%) | -0.02       | 1,287 (93.2%) | 1,288 (93.3%) | 0.00    | 1,613 (94.9%) | 1,617 (95.2%) | -0.01       | 3374 (94.5%)  | 3381 (94.7%)  | -0.01   |
| Alpha blockers; n (%)                                                      | 30 (6.1%)     | 21 (4.3%)   | 0.08        | 54 (3.9%)     | 56 (4.1%)     | -0.01   | 123 (7.2%)    | 125 (7.4%)    | -0.01       | 207 (5.8%)    | 202 (5.7%)    | 0.00    |
| CHA2DS2 VASc score, 180 days, V                                            |               |             |             |               |               |         |               |               |             |               |               |         |
| ...mean (sd)                                                               | 1.49 (1.21)   | 1.52 (1.17) | -0.03       | 1.24 (1.16)   | 1.25 (1.21)   | -0.01   | 1.55 (1.37)   | 1.56 (1.36)   | -0.01       | 1.42 (1.27)   | 1.43 (1.28)   | 0.00    |
| Use of Prasugrel; n (%)                                                    | 0 (0.0%)      | 0 (0.0%)    | #DIV/0!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! | 0 (0.0%)      | 0 (0.0%)      | #DIV/0!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| Use of Loop Diuretics+other diuretics+tot                                  | 66 (13.5%)    | 66 (13.5%)  | 0.00        | 138 (10.0%)   | 139 (10.1%)   | 0.00    | 312 (18.4%)   | 334 (19.7%)   | -0.03       | 516 (14.5%)   | 539 (15.1%)   | -0.02   |
| Commercial vs Medicare Advantage- Business Type Code - CORRECT ONE - OPTUM |               |             |             |               |               |         | 0             | 0             |             |               |               |         |
| ...Commercial; n (%)                                                       | 260 (53.1%)   | 249 (50.8%) | 0.05        | #VALUE!       | #VALUE!       | #VALUE! | -             | -             | #VALUE!     | #VALUE!       | #VALUE!       | #VALUE! |
| ...Medicare Advantage; n (%)                                               | 0,230 (46.9%) | 241 (49.2%) | -0.05       | 1287 (93.2%)  | 1285 (93.0%)  | 0.01    | -             | -             | #VALUE!     | #VALUE!       | 1,526 (81.6%) | #VALUE! |
| Commercial vs Medicare Advantage- Business Type Code                       |               |             |             |               |               |         |               |               |             |               |               |         |
| ...COM = COMMERCIAL; n (%)                                                 | 260 (53.1%)   | 249 (50.8%) | 0.05        | -             | -             | #VALUE! | -             | -             | #VALUE!     | 260 (53.1%)   | 249 (50.8%)   | 0.05    |
| ...MCR = MEDICARE; n (%)                                                   | 230 (46.9%)   | 241 (49.2%) | -0.05       | -             | -             | #VALUE! | -             | -             | #VALUE!     | 230 (46.9%)   | 241 (49.2%)   | -0.05   |
| ...MCD = MEDICAIID; n (%)                                                  | 0 (0.0%)      | 0 (0.0%)    | #DIV/0!     | -             | -             | #VALUE! | -             | -             | #VALUE!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| ...NONE = NO BUSINESS LINE CODE (added                                     | 0 (0.0%)      | 0 (0.0%)    | #DIV/0!     | -             | -             | #VALUE! | -             | -             | #VALUE!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| ...UNK = UNKNOWN (added in 2015); n (%)                                    | 0 (0.0%)      | 0 (0.0%)    | #DIV/0!     | -             | -             | #VALUE! | -             | -             | #VALUE!     | 0 (0.0%)      | 0 (0.0%)      | #DIV/0! |
| Commercial vs Medicare Advantage- Data                                     |               |             |             |               |               |         |               |               |             |               |               |         |
| ...1 - Fee For Service; n (%)                                              | -             | -           | -           | 0             | 0             | -       | -             | -             | -           | 1,156 (83.7%) | 1,156 (83.7%) | 0.00    |
| ...2 - Encounter; n (%)                                                    | -             | -           | -           | 1,156 (83.7%) | 1,158 (83.9%) | -       | -             | -             | -           | 131 (9.5%)    | 127 (9.2%)    | 0.00    |
| ...3 - Medicare; n (%)                                                     | -             | -           | -           | 131 (9.5%)    | 127 (9.2%)    | -       | -             | -             | -           | 85 (6.2%)     | 86 (6.2%)     | 0.00    |
| ...4 - Medicare Encounter; n (%)                                           | -             | -           | -           | 85 (6.2%)     | 86 (6.2%)     | -       | -             | -             | -           | ** (0.7%)     | ** (0.7%)     | 0.00    |
| Metropolitan Statistical Area - Urban (any MSA) vs Rural (non-MSA)         |               |             |             |               |               |         | 0             | 0             |             |               |               |         |
| ...Urban; n (%)                                                            | -             | -           | 998 (72.3%) | 993 (71.9%)   | -             | -       | -             | -             | 998 (72.3%) | 993 (71.9%)   | 0.00          |         |
| ...Rural; n (%)                                                            | -             | -           | 151 (10.9%) | 153 (11.1%)   | -             | -       | -             | -             | 151 (10.9%) | 153 (11.1%)   | 0.00          |         |
| ...Unknown/Missing; n (%)                                                  | -             | -           | 232 (16.8%) | 235 (17.0%)   | -             | -       | -             | -             | 232 (16.8%) | 235 (17.0%)   | 0.00          |         |