WORK PLAN – DATA EXTRACTION AND DATA ANALYSIS

Project: Association between angiotensin converting enzyme inhibitor or angiotensin receptor blocker use and COVID-19 severity and mortality among US Veterans

NCT number: Not yet assigned

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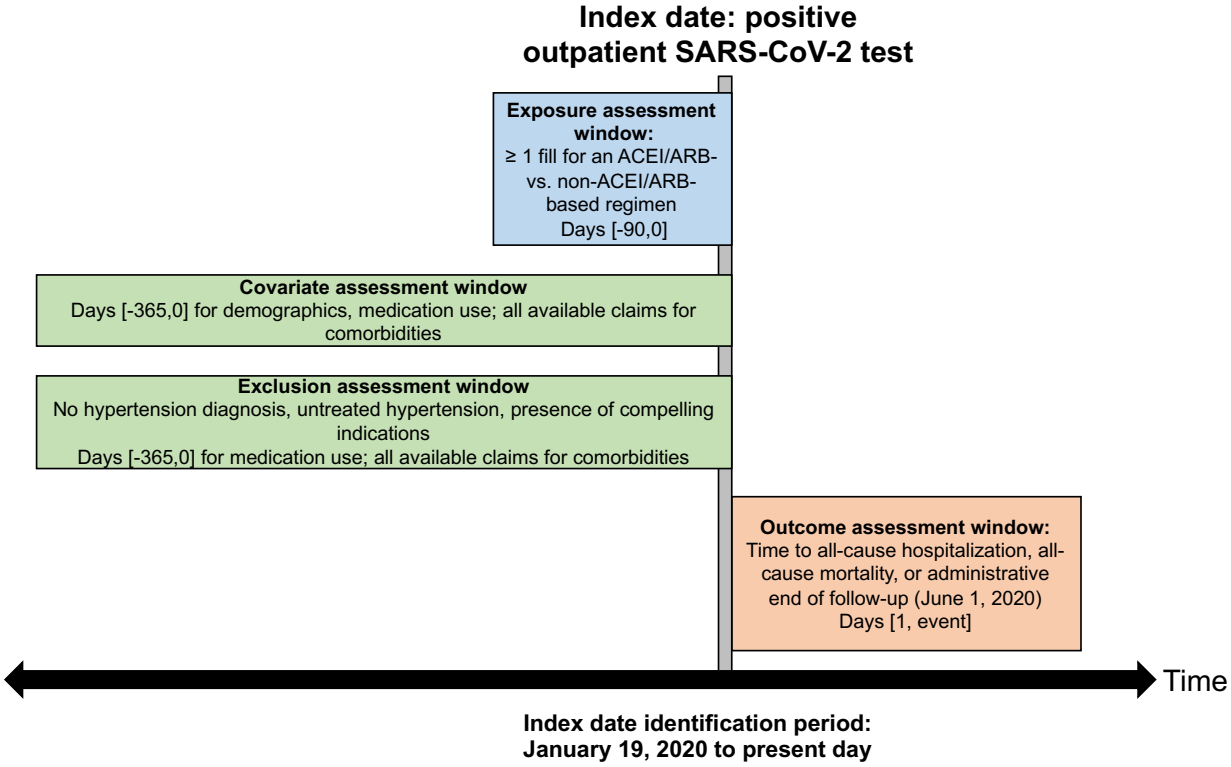
AIM 1

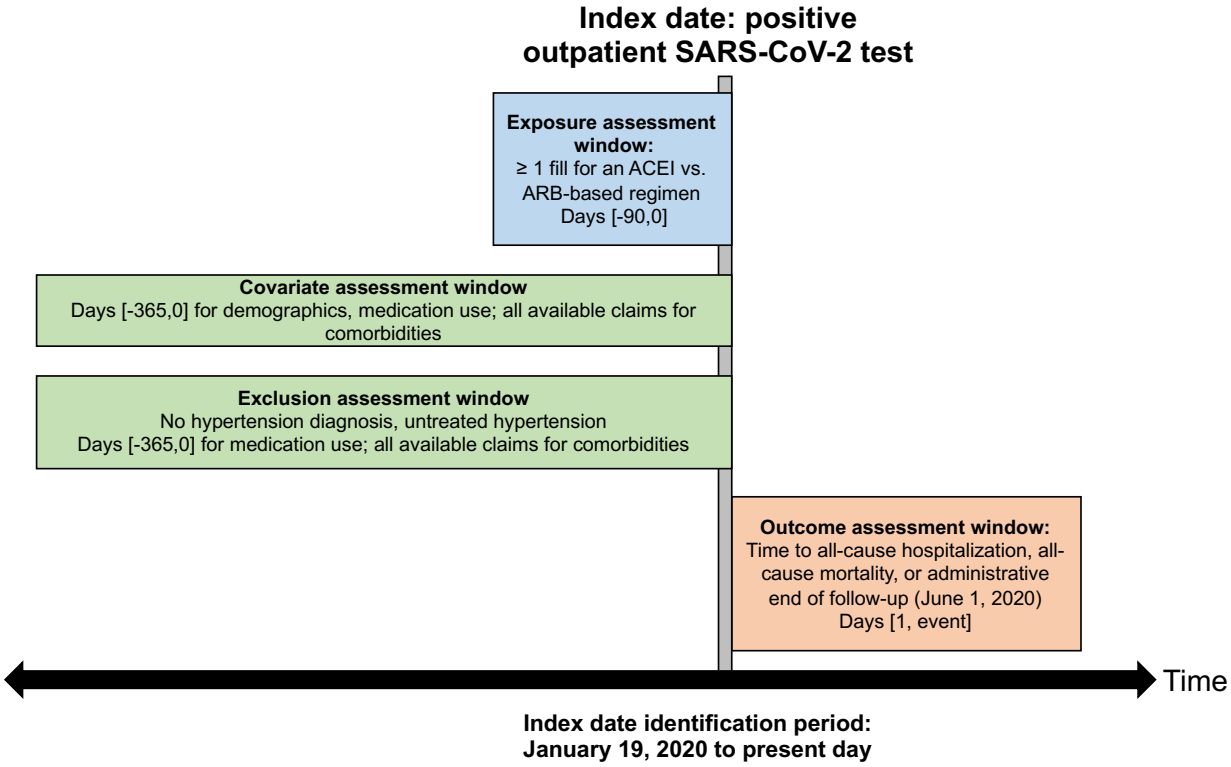
Study Schema

Aim 1.1: Among Veterans with treated hypertension and without compelling indications* who test positive for SARS-CoV-2, compare all-cause hospitalization and all-cause mortality rates between current users of a range of doses of ACEI/ARB- vs. non-ACEI/ARB-based regimens.



*Diabetes, chronic kidney disease, heart failure, coronary heart disease, and history of stroke.

Aim 1.2: Among Veterans with treated hypertension who test positive for SARS-CoV-2, compare all-cause hospitalization and all-cause mortality rates between current users of a range of doses of ACEI- vs. ARB-based regimens.



Cohort Creation

We will create two separate, analysis-ready datasets to carry out the analyses for Aims 1.1 and 1.2.

1. Aim 1 Cohort Creation
    1.1. Please identify all Veterans who have a positive laboratory test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between January 19, 2020 to present-day using the official VA definition in the COVID-19 domain (see Appendix A). The date of the positive test will be denoted as the index date.
    1.2. Restrict the cohort to Veterans *without* a hospitalization in the 7 days prior to the index date to narrow the cohort to Veterans who were tested in the outpatient setting.
    1.3. Restrict the cohort to Veterans who had ≥1 inpatient or any outpatient encounter in each of the two, six-month periods during the 365 days prior to the index date.
    1.4. Restrict the cohort to Veterans *without* data inconsistencies (test patients, not Veterans, multiple death dates in data, or not alive on index date).
    1.5. Restrict the cohort to Veterans with a diagnosis of hypertension at any point prior to their index date (see Appendix B for definition of hypertension).
    1.6. Restrict the cohort to Veterans who have an outpatient pharmacy fill in 90 days prior to the index date for any antihypertensive medication (see Appendix E).
    1.7. Cohort creation specific for Aim 1.1
        1.7.1. Follow steps 1.1 through 1.6 above.
        1.7.2. Restrict the analysis to Veterans who do not have a history of diabetes, stroke, chronic kidney disease, heart failure with reduced ejection fraction, or coronary heart disease (see Appendix B for definitions of these conditions).
        1.7.3. Categorize Veterans according to current antihypertensive medication use as in steps 1.7.3.1 and 1.7.3.2 below. The groups should be mutually exclusive.
            1.7.3.1. Identify and categorize Veterans who have a pharmacy fill for an angiotensin converting enzyme inhibitor (ACEI) **or** angiotensin receptor blocker (ARB; see Appendix E) within the 90 days prior to the index date. These Veterans will be categorized as Veterans with current use of "ACEI/ARB-based regimens". Veterans included in this group may have fills for non-ACEI/ARB medications but must also have a fill for an ACEI or an ARB. For each Veteran, please create variables to indicate the use of these non-ACEI/ARB medication classes in the dataset.

1.7.3.2. Identify Veterans who have a pharmacy fill an antihypertensive medication class *other than* an ACEI or an ARB AND do not have a fill for an ACEI or an ARB (see Appendix E) within the 90 days prior to the index date. These Veterans will be categorized as Veterans with current use of "non-ACEI/ARB-based regimens". Veterans included in this group may have fills for multiple non-ACEI/ARB medications. For each Veteran's regimen, please create variables to indicate the use of all medication classes in the dataset.

1.7.4. Please provide a flow chart with the number of Veterans retained and excluded during steps 1.1 through 1.7.3.2. See Figure 1.

1.8. Cohort creation specific for Aim 1.2

1.8.1. Follow steps 1.1 through 1.6 above.

1.8.2. Exclude Veterans who do not have a pharmacy fill for an ACEI or ARB within the 90 days prior to the index date (see Appendix E).

1.8.3. Exclude Veterans who have a pharmacy fill for both an ACEI and an ARB within the 90 days prior to the index date.

1.8.4. Identify and categorize Veterans who have a pharmacy fill for ACEI within the 90 days prior to the index date. These Veterans will be categorized as "ACEI users". Veterans included in this group may have fills for non-ACEI medications (other than ACEIs) but must also have a fill for an ACEI. For each Veteran, please create variables to indicate the use of these non-ACEI medication classes in the dataset.

1.8.5. Identify and categorize Veterans who have a pharmacy fill for an ARB within the 90 days prior to the index date. These Veterans will be categorized as "ARB users". Veterans included in this group may have fills for non-ARB medications (other than ARBs) but must also have a fill for an ARB. For each Veteran, please create variables to indicate the use of these non-ARB medication classes in the dataset.

1.8.6. Please provide a flow chart with the number of Veterans retained and excluded during steps 1.1 through 1.6, then 1.8.1 through 1.8.5. See Figure 3.

Data Management

1. The data management will be conducted using VINCI. Consistency will be followed for the name and levels for variables created for Veterans in each data set. The steps below describe the data management for Veterans who are included in the aim 1.1 cohort (ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimen) and the aim 1.2 cohort (ACEI users vs. ARB users). Baseline covariates will be created as listed in Appendix B. Please produce separate analyses ready datasets for aims 1.1 and 1.2.
2. Please report the percent missingness of each variable in each cohort, separately.
3. For each cohort, create a single variable indicating to which medication exposure group the Veteran has been assigned.
    a. Aim 1.1: “ACEI/ARB-based regimen cohort” and “non-ACEI/ARB-based regimen cohort”
    b. Aim 1.2: “ACEI user cohort” and “ARB user cohort”.
4. For each Veteran, identify the occurrence of the primary and secondary outcomes.
5. For each observation, identify the time to occurrence or censoring of the primary and secondary outcomes in days, separately.
6. For secondary analyses within each cohort (see statistical analysis section):
    a. The main exposure will be re-defined using alternative exposure definitions, and patients will be re-categorized according to these new definitions (see Appendix C). The primary analysis will be repeated.
    b. A variable identifying the occurrence of negative control outcomes will be created.
    c. A variable identifying the time to occurrence or censoring of negative control outcomes in days will be created.

Statistical analysis

Aim 1.1

1. Calculate baseline patient characteristics (Appendix B) for users of ACEI/ARB-based regimens and non-ACEI/ARB-based regimens, separately. Populate Table 1, left panel ("before weighting").
2. Generate propensity scores (PS) for being a user of an ACEI/ARB-based regimen vs. a non-ACEI/ARB-based regimen using generalized boosted regression models as a function of all baseline covariates.[1,2] The algorithm should minimize standardized mean differences in covariates between exposure groups in the PS-weighted population.[3] Generate Supplemental Figure S1, which shows the distribution of PSs among Veterans who are hospitalized for COVID-19 between the ACEI/ARB-based regimen vs. non-ACEI/ARB-based regimen cohorts.
3. Use the final PS generated in step 2 to calculate each study-eligible Veteran's matching weight.
4. Verify covariate balance in the matching weighted population using the Kolmogorov-Smirnov metric[4,5] and calculate absolute standardized mean differences. Populate Table 1, right panel ("after weighting"). Generate Supplemental Figure S2.
5. Primary analysis: Apply matching-weighted Cox regression with Poissonization[6] to estimate the causal marginal hazard ratio comparing the primary outcome (time to all-cause hospitalization or all-cause mortality) and secondary outcomes as appropriate between medication exposure groups (ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens). Populate Table 2 and generate Figure 2.
6. Perform bootstrap resampling[7] to generate 95% confidence intervals using 2-sided alpha = 0.025 for the primary outcome and 2-sided alpha = 0.05 for the secondary outcomes.
7. Secondary analyses:
    a. Re-run steps 5 and 6 as follows and populate Supplemental Table S1:
        i. Unadjusted (i.e., "Crude" analysis, Cox regression with no covariate adjustment)
        ii. Multivariable-adjusted (Cox regression with Poissonization with adjustment for all covariates included in the estimation of the PS),
        iii. PS adjusted (Cox regression with Poissonization with PS used as a covariate in the model, adjusted for deciles of the PS),
        iv. PS stratification (Cox regression with Poissonization within strata of deciles of the PS to estimate stratum-specific estimates of treatment

effect. Produce and report a pooled estimate [not stratum-specific] across stratum to estimate an overall treatment effect via the method of Imbens[8]).

v. PS matching (Cox regression with Poissonization within a 1:1 PS matched (greedy algorithm, nearest neighbor matching with a caliper size equal to 0.2 of the standard deviation of the logit of the PS without replacement).

vi. Inverse probability of treatment weighting (IPTW) (Weighted Cox regression with Poissonization using stabilized, traditional IPTW with truncation at 99th percentile).

vii. Subgroup analyses. The PS and matching weights will need to be reproduced within each subgroup for each subgroup analysis. Populate Supplemental Table S2 with results of all subgroup analyses.

1. Stratify the population by the total number of antihypertensive medications in the regimen (i.e., 1, 2, 3, ≥4). Repeat primary analysis within these strata (i.e., Steps 5 and 6 above only).
2. Create subgroups of the population by age (<40, 40 to <50, 50 to <60, 60 to <70 and ≥70 years), sex (male and female), race-ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian), and body mass index (<18.5 kg/m^2, 18.5-<25 kg/m^2 , 25-<30 kg/m^2 , and ≥30 kg/m^2). Repeat primary analysis within each subgroup (i.e., Steps 5 and 6 above only).
3. Stratify the population by tertiles of Modified Therapeutic Intensity Score of the medication defining the main exposure. Repeat the primary analysis within each tertile (i.e., Steps 5 and 6 above only).

viii. Sensitivity analysis varying the exposure definition. The PS and matching weights will need to be reproduced within each group under each alternative definition. Populate Supplemental Table S3 with results.

1. Re-define the primary exposure according to the alterative definitions listed in Appendix C. The alternative definition will only apply to the primary exposure of interest. For example, if a patient is taking an ACEI and a calcium channel blocker, the definition will only be applied to the ACEI. For the non-ACEI/ARB-based

regimen group, the alternative definition must hold true for at least one of the medications in the regimen.

2. Re-categorize Veterans into exposure groups based on each definition.
3. Recalculate primary and secondary outcomes under each alternative exposure definition (i.e., Steps 5 and 6 above only).

8. Secondary analyses:
    a. Repeat the primary analysis (i.e., Step 5 only) for all negative control outcomes, separately. See Appendix D for definitions of negative control outcomes. Populate Supplemental Table S4.
    b. Perform methods described by Vanderweele[9] to describe the value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away the observed treatment-outcome association and generate Supplemental Figure S3.
    c. Perform negative control calibration on the estimates generated in the primary analysis to adjust for residual bias using the control outcome calibration approach by Tchetgen Tchetgen.[10]

Aim 1.2

1. Calculate baseline patient characteristics (Appendix B) for ACEI users and ARB users, separately. Populate Table 3, left panel ("before weighting").
2. Generate PS for being a user of an ACEI vs. an ARB using generalized boosted regression models as a function of baseline covariates.[1,2] The algorithm should minimize standardized mean differences in covariates between exposure groups in the PS-weighted population.[3] Generate Supplemental Figure S4, which shows the distribution of PSs among outpatient Veterans who are hospitalized for COVID-19 between the ACEI users vs. ARB users.
3. Use the final PS generated in step 2 to calculate each study-eligible Veteran's matching weight.
4. Verify covariate balance in the matching weighted population using the Kolmogorov-Smirnov metric[4,5] and calculate absolute standardized mean differences. Populate Table 3, right panel ("after weighting"). Generate Supplemental Figure S5.
5. Primary analysis: Apply matching-weighted Cox regression with Poissonization[6] to estimate the causal marginal hazard ratio comparing the primary outcome (time to all-

cause hospitalization or all-cause mortality) and secondary outcomes as appropriate between medication exposure groups (ACEI users vs. ARB users). Populate Table 4 and generate Figure 4.

6. Perform bootstrap resampling[7] to generate 95% confidence intervals using 2-sided alpha = 0.025 for the primary outcome and 2-sided alpha = 0.05 for the secondary outcomes.
7. Secondary analyses:
    a. Re-run steps 5 and 6 as follows and populate Supplemental Table S5:
        i. Unadjusted (i.e., "Crude" analysis, Poisson regression with no covariate adjustment)
        ii. Multivariable-adjusted (Cox regression with Poissonization with adjustment for all covariates included in the estimation of the PS),
        iii. PS adjusted (Cox regression with Poissonization with PS used as a covariate in the model, adjusted for deciles of the PS),
        iv. PS stratification (Cox regression with Poissonization within strata of PS to estimate stratum-specific estimates of treatment effect. Produce and report a pooled estimate [not stratum-specific] across stratum to estimate an overall treatment effect via the method of Imbens[8]).
        v. PS matching (Cox regression with Poissonization within a 1:1 PS matched (greedy algorithm, nearest neighbor matching with a caliper size equal to 0.2 of the standard deviation of the logit of the PS without replacement).
        vi. Inverse propensity treatment weighting (IPTW) (Weighted Cox regression with Poissonization using stabilized, traditional IPTW with truncation at 99th percentile).
        vii. Subgroup analyses. The PS and matching weights will need to be reproduced within each subgroup for each subgroup analysis. Populate Supplemental Table S6 with results of all subgroup analyses.
            1. Stratify the population by the total number of antihypertensive medications in the regimen (i.e., 1, 2, 3, ≥4). Repeat primary analysis within these strata (i.e., Steps 5 and 6 above only).
            2. Create subgroups of the population by age (<40, 40 to <50, 50 to <60, 60 to <70 and ≥70 years), sex (male and female), race-ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian), and body mass index (<18.5 kg/m^2, 18.5-<25 kg/m^2 , 25-

<30 kg/m^2 , and ≥30 kg/m^2). Repeat primary analysis within each subgroup (i.e., Steps 5 and 6 above only).

3. Stratify the population by tertiles of Modified Therapeutic Intensity Score of the medication defining the main exposure. Repeat the primary analysis within each tertile (i.e., Steps 5 and 6 above only).

viii. Sensitivity analysis varying the exposure definition. The PS and matching weights will need to be reproduced within each group under each alternative definition. Populate Supplemental Table S7 with results.

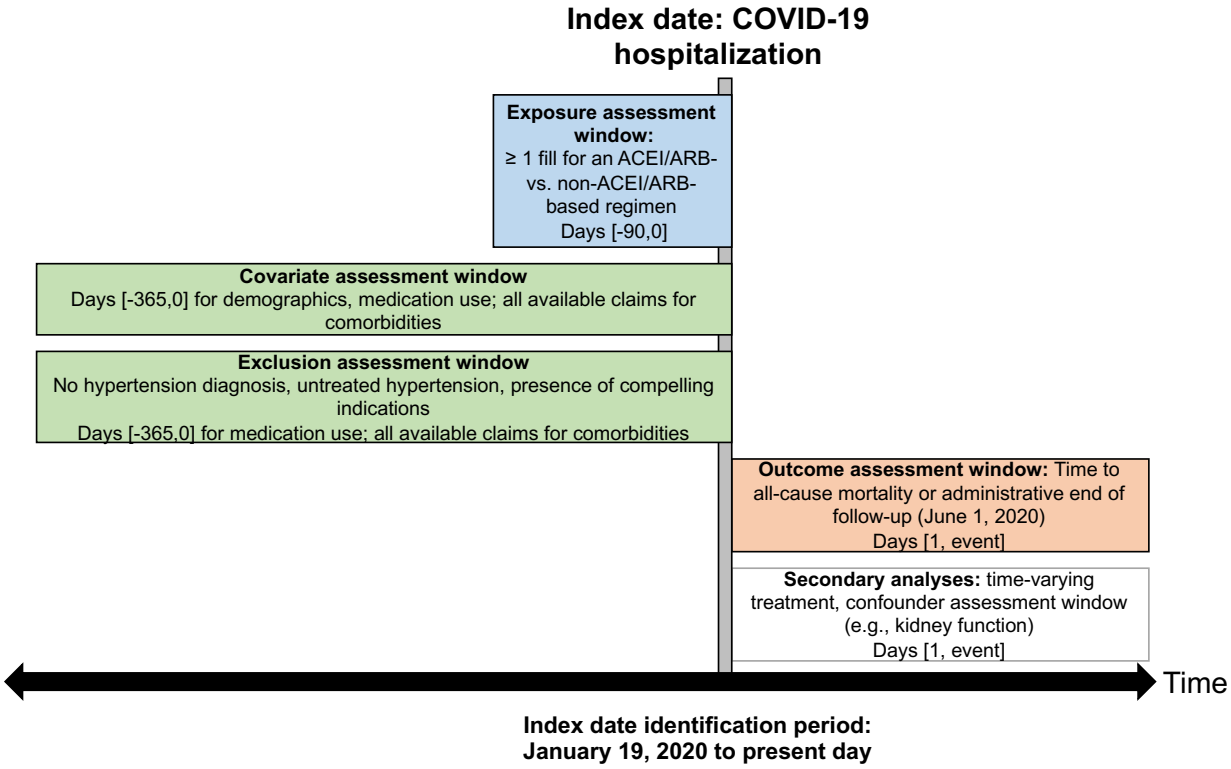
1. Re-define the primary exposure according to the alterative definitions listed in Appendix C. The alternative definition will only apply to the primary exposure of interest. For example, if a patient is taking an ACEI and a calcium channel blocker, the definition will only be applied to the ACEI. For the non-ACEI/ARB-based regimen group, the alternative definition must hold true for at least one of the medications in the regimen.
2. Re-categorize Veterans into exposure groups based on each definition.
3. Recalculate primary and secondary outcomes under each alternative exposure definition (i.e., Steps 5 and 6 above only).

8. Secondary analyses:
   a. Repeat the primary analysis for all negative control outcomes, separately. See Appendix D for definitions of negative control outcomes. Populate Supplemental Table S8.
   b. Perform methods described by Vanderweele[9] to describe the value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away the observed treatment-outcome association and generate Supplemental Figure S6.
   c. Perform negative control calibration on the estimates generated in the primary analysis to adjust for residual bias using the control outcome calibration approach by Tchetgen Tchetgen.[10]

AIM 2

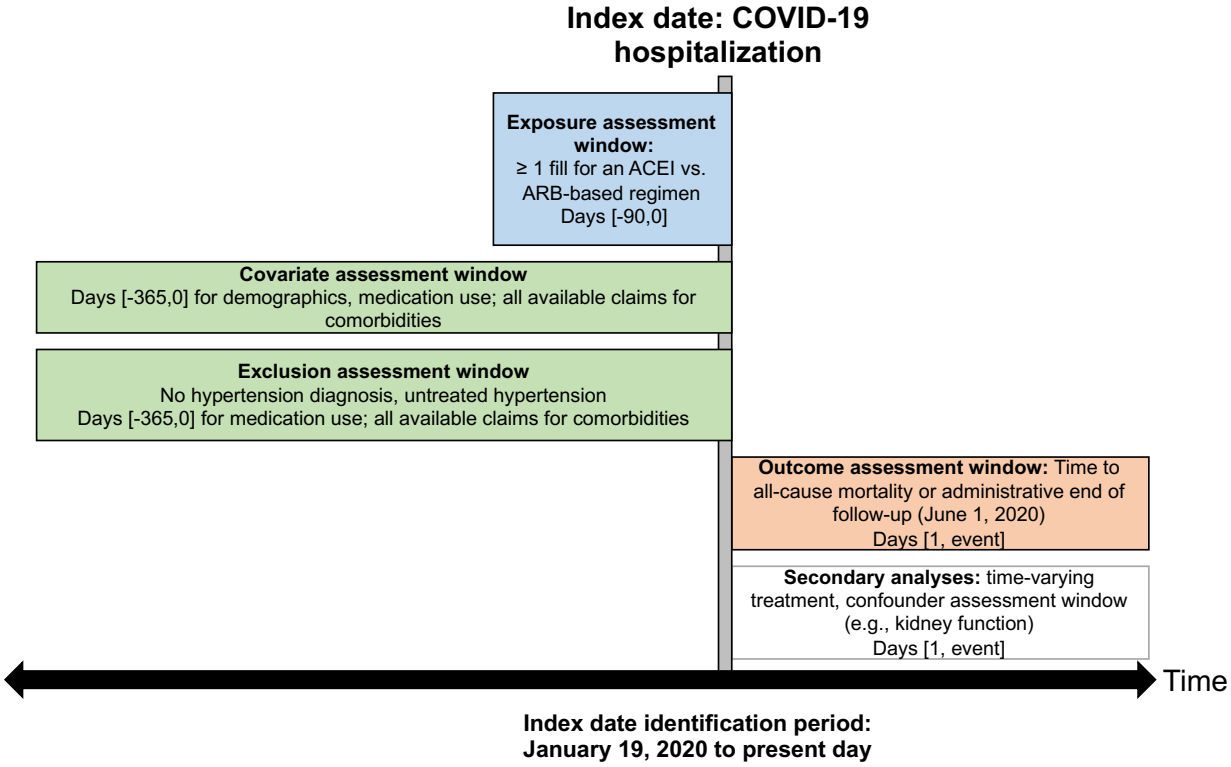
Study Schema:

Aim 2.1: Among Veterans with treated hypertension and without compelling indications* who are hospitalized for COVID-19, compare all-cause mortality rates between current users of a range of doses of ACEI/ARB- vs. non-ACEI/ARB-based regimens.



*Diabetes, chronic kidney disease, heart failure, coronary heart disease, and history of stroke.

Aim 2.2: Among Veterans with treated hypertension who are hospitalized for COVID-19, compare all-cause mortality rates between current users of a range of doses of ACEI- vs. ARB-based regimens.



Cohort Creation

We will create two separate, analysis-ready datasets to carry out the analyses for Aims 2.1 and 2.2.

2. Aim 2 Cohort Creation
    2.1. Please identify all Veterans who have a hospitalization for COVID-19 between January 19, 2020 to present-day (see Appendix G for definition of COVID-19-related hospitalization). The admit date of hospitalization will be denoted as the index date.
    2.2. Restrict the cohort to Veterans who had ≥1 inpatient or any outpatient encounter in each of the two, six-month periods during the 365 days prior to the index date.
    2.3. Restrict the cohort to Veterans *without* data inconsistencies (test patients, not Veterans, multiple death dates in data, or not alive on index date).
    2.4. Restrict the cohort to Veterans with a diagnosis of hypertension at any point prior to their index date (see Appendix B for definition of hypertension).
    2.5. Restrict the cohort to Veterans who have an outpatient pharmacy fill in 90 days prior to the index date for any antihypertensive medication (see Appendix F).
    2.6. Cohort creation specific for Aim 2.1
        2.6.1. Follow steps 2.1 through 2.5 above.
        2.6.2. Restrict the analysis to Veterans who do not have a history of diabetes, stroke, chronic kidney disease, heart failure with reduced ejection fraction, or coronary heart disease (see Appendix B for definitions of these conditions).
        2.6.3. Categorize Veterans according to antihypertensive medication use as in steps 2.6.3.1 and 2.6.3.2 below. The groups should be mutually exclusive.
            2.6.3.1. Identify and categorize Veterans who have a pharmacy fill for an angiotensin converting enzyme inhibitor (ACEI) **or** angiotensin receptor blocker (ARB; see Appendix F) within the 90 days prior to the index date. These Veterans will be categorized as Veterans with current use of "ACEI/ARB-based regimens". Veterans included in this group may have fills for non-ACEI/ARB medications but must also have a fill for an ACEI or an ARB. For each Veteran, please create variables to indicate the use of these non-ACEI/ARB medication classes in the dataset.
            2.6.3.2. Identify Veterans who have a pharmacy fill an antihypertensive medication class other than an ACEI or an ARB AND do not have a fill for an ACEI or an ARB (see Appendix F) within the 90 days prior to the index date. These

Veterans will be categorized as Veterans with current use of "non-ACEI/ARB-based regimens". Veterans included in this group may have fills for multiple non-ACEI/ARB medications. For each Veteran's regimen, please create variables to indicate the use of all medication classes in the dataset.

2.6.4. Please provide a flow chart with the number of Veterans retained and excluded during steps 2.1 through 2.6.3.2. See Figure 5.

2.7. Cohort creation specific for Aim 2.2

2.7.1. Follow steps 2.1 through 2.5 above.

2.7.2. Exclude Veterans who do not have a pharmacy fill for an ACEI or ARB within the 90 days prior to the index date (see Appendix F).

2.7.3. Exclude Veterans who have a pharmacy fill for both an ACEI and an ARB within the 90 days prior to the index date.

2.7.4. Identify and categorize Veterans who have a pharmacy fill for ACEI within the 90 days prior to the index date. These Veterans will be categorized as "ACEI users". Veterans included in this group may have fills for non-ACEI medications (other than ACEIs) but must also have a fill for an ACEI. For each Veteran, please create variables to indicate the use of these non-ACEI medication classes in the dataset.

2.7.5. Identify and categorize Veterans who have a pharmacy fill for an ARB within the 90 days prior to the index date. These Veterans will be categorized as "ARB users". Veterans included in this group may have fills for non-ARB medications (other than ARBs) but must also have a fill for an ARB. For each Veteran, please create variables to indicate the use of these non-ARB medication classes in the dataset.

2.7.6. Please provide a flow chart with the number of Veterans retained and excluded during steps 2.1 through 2.5, then 2.7.1 through 2.7.5. See Figure 7.

Data Management

7. The data management will be conducted using VINCI. Consistency will be followed for the name and levels for variables created for Veterans in each data set. The steps below describe the data management for Veterans who are included in the aim 1.1 cohort (ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimen) and the aim 1.2 cohort (ACEI users vs. ARB users). Baseline covariates will be created as listed in Appendix B. Please produce separate analyses ready datasets for aims 2.1 and 2.2.
8. Separate analyses ready datasets for aims 2.1 and 2.2 will be created.
9. The percent missingness of each variable will be reported in each cohort, separately.
10. For each cohort, a single variable indicating to which medication exposure group the Veteran has been assigned will be created.
    a. Aim 2.1: “ACEI/ARB-based regimen cohort” and “non-ACEI/ARB-based regimen cohort”
    b. Aim 2.2: “ACEI user cohort” and “ARB user cohort”.
11. For each Veteran, the occurrence of the primary and secondary outcomes will be identified.
12. For each observation, the time to occurrence or censoring of the primary and secondary outcomes in days will be identified, separately.
13. For secondary analyses within each cohort (see statistical analysis section):
    a. The main exposure will be re-defined using alternative exposure definitions, and patients will be re-categorized according to these new definitions (see Appendix H).The primary analysis will be repeated.
    b. A variable identifying the occurrence of negative control outcomes will be created.
    c. A variable identifying the time to occurrence or censoring of negative control outcomes in days will be created.
    d. A variable for each time-varying covariate as listed in Appendix J will be created.
14. For the “leave-out-an-essential-ingredient” negative control sensitivity analysis, a separate cohort Aims 2.1 and 2.2 will be created with the following modifications:
    a. Change the index-date identification period from “January 19, 2020 to present-day” to January 1, 2016, to December 31, 2018.
    b. Change step 1.1 to: All Veterans who have a hospitalization for bacterial pneumonia will be identified (see Appendix H for definition of pneumonia hospitalization). The admit date of the hospitalization will be denoted as the index date.
        i. For Veterans with more than one eligible bacterial pneumonia hospitalization, the first hospitalization will be used.
    c. Label this cohort: “leave-out-an-essential-ingredient negative control sensitivity analysis”

Statistical analysis

Aim 2.1

1. Calculate baseline patient characteristics (Appendix B) for users of ACEI/ARB-based regimens and non-ACEI/ARB-based regimens, separately. Populate Table 5, left panel ("before weighting").
2. Generate propensity scores (PS) for being a user of an ACEI/ARB-based regimen vs. a non-ACEI/ARB-based regimen using generalized boosted regression models as a function of all baseline covariates.[1,2] The algorithm should minimize standardized mean differences in covariates between exposure groups in the PS-weighted population.[3] Generate Supplemental Figure S7, which shows the distribution of PSs among Veterans who are hospitalized for COVID-19 between the ACEI/ARB-based regimen vs. non-ACEI/ARB-based regimen cohorts.
3. Use the final PS generated in step 2 to calculate each study-eligible Veteran's matching weight.
4. Verify covariate balance in the matching weighted population using the Kolmogorov-Smirnov metric[4,5] and calculate absolute standardized mean differences. Populate Table 5, right panel ("after weighting"). Generate Supplemental Figure S8.
5. Primary analysis: Apply matching-weighted Cox regression with Poissonization[6] to estimate the causal marginal hazard ratio comparing the primary outcome (time to all-cause mortality) and secondary outcomes as appropriate between medication exposure groups (ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens). Populate Table 6 and generate Figure 6.
6. Perform bootstrap resampling[7] to generate 95% confidence intervals using 2-sided alpha = 0.05 for the primary and secondary outcomes.
7. Secondary analyses:
    a. Re-run steps 5 and 6 as follows and populate Supplemental Table S9:
        i. Unadjusted (i.e., "Crude" analysis, Poisson regression with no covariate adjustment)
        ii. Multivariable-adjusted (Cox regression with Poissonization with adjustment for all covariates included in the estimation of the PS),
        iii. PS adjusted (Cox regression with Poissonization with PS used as a covariate in the model, adjusted for deciles of the PS),

iv. PS stratification (Cox regression with Poissonization within strata of deciles of the PS to estimate stratum-specific estimates of treatment effect. Produce and report a pooled estimate [not stratum-specific] across stratum to estimate an overall treatment effect via the method of Imbens[8]).

v. PS matching (Cox regression with Poissonization within a 1:1 PS matched (greedy algorithm, nearest neighbor matching with a caliper size equal to 0.2 of the standard deviation of the logit of the PS without replacement).

vi. Inverse probability of treatment weighting (IPTW) (Weighted cox regression with Poissonization using stabilized, traditional IPTW with truncation at 99th percentile)

vii. Subgroup analyses. The PS and matching weights will need to be reproduced within each subgroup for each subgroup analysis. Populate Supplemental Table S10 with results of all subgroup analyses.

    1. Stratify the population by the total number of antihypertensive medications in the regimen (i.e., 1, 2, 3, ≥4). Repeat primary analysis within these strata (i.e., Steps 5 and 6 above only).
    2. Create subgroups of the population by age (<40, 40 to <50, 50 to <60, 60 to <70 and ≥70 years), sex (male and female), race-ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian), and body mass index (<18.5 kg/m^2, 18.5-<25 kg/m^2 , 25-<30 kg/m^2 , and ≥30 kg/m^2). Repeat primary analysis within each subgroup (i.e., Steps 5 and 6 above only).
    3. Stratify the population by tertiles of Modified Therapeutic Intensity Score of the medication defining the main exposure. Repeat the primary analysis within each tertile (i.e., Steps 5 and 6 above only).

viii. Sensitivity analysis varying the exposure definition. The PS and matching weights will need to be reproduced within each group under each alternative definition. Populate Supplemental Table S11 with results.

    1. Re-define the primary exposure according to the alterative definitions listed in Appendix H. The alternative definition will only apply to the primary exposure of interest. For example, if a patient

is taking an ACEI and a calcium channel blocker, the definition will only be applied to the ACEI. For the non-ACEI/ARB-based regimen group, the alternative definition must hold true for at least one of the medications in the regimen.

2. Re-categorize Veterans into exposure groups based on each definition.
3. Recalculate primary and secondary outcomes under each alternative exposure definition (i.e., Steps 5 and 6 above only).

8. Secondary analyses:
    a. Repeat the primary analysis for all negative control outcomes, separately. See Appendix I for definitions of negative control outcomes. Populate Supplemental Table S12.
    b. Perform methods described by Vanderweele[9] to describe the value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away the observed treatment-outcome association and generate Supplemental Figure S9.
    c. Perform negative control calibration on the estimates generated in the primary analysis to adjust for residual bias using the control outcome calibration approach by Tchetgen Tchetgen.[10]
    d. Leave-out-an-essential-ingredient negative control sensitivity analysis:
        i. This analysis will require one additional step.
        ii. First, generate a PS for being in the COVID-19 cohort vs. non-COVID-19 cohort.
        iii. Perform PS matching to match each COVID-19 veteran with a non-COVID-19 Veteran using a 1:1 PS matching (greedy algorithm, nearest neighbor matching with a caliper size equal to 0.2 of the standard deviation of the logit of the PS without replacement).
        iv. Next, repeat steps 2-6 above to estimate the association of the main medication exposure with the study outcomes. Repeat the primary analysis in this matching weighted cohort. Populate Supplemental Table S13.

Aim 2.2

1. Calculate baseline patient characteristics (Appendix B) for ACEI users and ARB users, separately. Populate Table 7, left panel ("before weighting").
2. Generate PS for being a user of an ACEI vs. an ARB using generalized boosted regression models as a function of baseline covariates.[1,2] The algorithm should minimize standardized mean differences in covariates between exposure groups in the PS-weighted population.[3] Generate Supplemental Figure S10, which shows the distribution of PSs among outpatient Veterans who are hospitalized for COVID-19 between the ACEI users vs. ARB users.
3. Use the final PS generated in step 2 to calculate each study-eligible Veteran's matching weight.
4. Verify covariate Verify covariate balance in the matching weighted population using the Kolmogorov-Smirnov metric[4,5] and calculate absolute standardized mean differences. Populate Table 7, right panel ("after weighting"). Generate Supplemental Figure S11.
5. Primary analysis: Apply matching-weighted Cox regression with Poissonization[6] to estimate the causal marginal hazard ratio comparing the primary outcome (time to all-cause mortality) and secondary outcomes as appropriate between medication exposure groups (ACEI users vs. ARB users). Populate Table 8 and generate Figure 8.
6. Perform bootstrap resampling[7] to generate 95% confidence intervals using 2-sided alpha = 0.05 for the primary and secondary outcomes.
7. Secondary analyses:
    a. Re-run steps 5 and 6 as follows and populate Supplemental Table S14:
        i. Unadjusted (i.e., "Crude" analysis, Cox regression with Poissonization[6] with no covariate adjustment)
        ii. Multivariable-adjusted (Cox regression with Poissonization[6] with adjustment for all covariates included in the estimation of the PS),
        iii. Propensity-score adjusted (Cox regression with Poissonization[6] with PS used as a covariate in the model, adjusted for deciles of the PS),
        iv. PS stratification (Cox regression with Poissonization[6] within strata of PS to estimate stratum-specific estimates of treatment effect. Produce and report a pooled estimate [not stratum-specific] across stratum to estimate an overall treatment effect via the method of Imbens[8]).
        v. PS matching (Cox regression with Poissonization[6] within a 1:1 PS matched (greedy algorithm, nearest neighbor matching with a caliper size

equal to 0.2 of the standard deviation of the logit of the PS without replacement).

vi. IPTW (Weighted Cox regression with Poissonization[6] using stabilized, traditional IPTW with truncation at 99th percentile)

vii. Subgroup analyses. The PS and matching weights will need to be reproduced within each subgroup for each subgroup analysis. Populate Supplemental Table S15 with results of all subgroup analyses.

1. Stratify the population by the total number of antihypertensive medications in the regimen (i.e., 1, 2, 3, ≥4). Repeat primary analysis within these strata (i.e., Steps 5 and 6 above only).
2. Create subgroups of the population by age (<40, 40 to <50, 50 to <60, 60 to <70 and ≥70 years), sex (male and female), race-ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian), and body mass index (<18.5 kg/m^2, 18.5-<25 kg/m^2 , 25-<30 kg/m^2 , and ≥30 kg/m^2). Repeat primary analysis within each subgroup (i.e., Steps 5 and 6 above only).
3. Stratify the population by tertiles of Modified Therapeutic Intensity Score of the medication defining the main exposure. Repeat the primary analysis within each tertile (i.e., Steps 5 and 6 above only).

viii. Sensitivity analysis varying the exposure definition. The PS and matching weights will need to be reproduced within each group under each alternative definition. Populate Supplemental Table S16 with results.

1. Re-define the primary exposure according to the alterative definitions listed in Appendix H. The alternative definition will only apply to the primary exposure of interest. For example, if a patient is taking an ACEI and a calcium channel blocker, the definition will only be applied to the ACEI. For the non-ACEI/ARB-based regimen group, the alternative definition must hold true for at least one of the medications in the regimen.
2. Re-categorize Veterans into exposure groups based on each definition.
3. Recalculate primary and secondary outcomes under each alternative exposure definition (i.e., Steps 5 and 6 above only).

8. Secondary analyses:
    a. Repeat the primary analysis for all negative control outcomes, separately. See Appendix I for definitions of negative control outcomes. Populate Supplemental Table S17.
    b. Perform methods described by Vanderweele[9] to describe the value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away the observed treatment-outcome association and generate Supplemental Figure S12.
    c. Perform negative control calibration on the estimates generated in the primary analysis to adjust for residual bias using the control outcome calibration approach by Tchetgen Tchetgen.[10]
    d. Leave-out-an-essential-ingredient negative control sensitivity analysis:
        i. This analysis will require one additional step.
        ii. First, generate a PS for being in the COVID-19 cohort vs. non-COVID-19 cohort.
        iii. Perform PS matching to match each COVID-19 veteran with a non-COVID-19 Veteran using a 1:1 PS matching (greedy algorithm, nearest neighbor matching with a caliper size equal to 0.2 of the standard deviation of the logit of the PS without replacement).
        iv. Next, repeat steps 2-6 above to estimate the association of the main mediation exposure with the study outcomes. Repeat the primary analysis in this matching weighted cohort. Populate Supplemental Table S18.

Proposed Tables and Figures

Aim 1.1 Main Tables

Table 1: Baseline characteristics of Veterans with treated hypertension without compelling indications for an ACEI or ARB who have a positive outpatient SARS-CoV-2 test and are taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 1.1), before and after propensity score weighting.

	Before weighting				After weighting		
Patient characteristics	**Total (n = xxxx)**	**ACEI/ARB-based regimen (n = xxxx)**	**Non-ACEI/ARB-based regimen (n = xxxx)**	**ASMD**	**ACEI/ARB-based regimen (n = xxxx)**	**Non-ACEI/ARB-based regimen (n = xxxx)**	**ASMD**
Demographics							
Age (years)							
Mean (SD)							
<40							
40 to <50							
50 to <60							
60 to <70							
≥70							
Female sex							
Race-ethnicity/ethnicity							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Asian American							
Other							
Median area-level income							
<$25,000							
$25,000 - $49,999							
$50,000 - $74,999							
≥$75,000							
Commercial health insurance							
Priority group status							
1							
2 through 8							
VISN Region							
Northeast							
Southeast							

Continental Pacific Current smoker	
Vitals and laboratory measurements Body mass index, kg/m^2 Mean (SD) Underweight (<18.5) Normal weight (18.5 - <25) Overweight (25 - <30) Obese (≥30) Systolic BP, mm Hg Mean (SD) < 130 130 - 139 140 - 159 ≥ 160 Diastolic BP, mm Hg Mean (SD) < 80 80 - 89 90 - 99 ≥ 100 Total cholesterol, mg/dL LDL-C, mg/dL HDL-C, mg/dL Triglycerides, mg/dL Hemoglobin A1c, % Serum potassium, mEq/L Serum creatinine, mg/dL eGFR, mL/min/1.73m^2	
Comorbidities Peripheral artery disease History of renal transplant Atrial fibrillation Chronic obstructive pulmonary disease	

Asthma Depression Charlson Comorbidity Index, mean (SD)	
Antihypertensive Medication ACEI ARB CCB Thiazide diuretic Alpha-blocker Beta-blocker Centrally-acting Direct vasodilator Direct renin inhibitor Aldosterone receptor antagonist Loop diuretic Potassium-sparing diuretic Total number of antihypertensive medications in regimen, median (IQR) One Two Three Four or more mTIS of antihypertensive regimen, median (IQR)	
Other medication use Current statin use Current aspirin use	

Numbers in table are number (column %) or mean (standard deviation) unless otherwise specified.

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; ASMD: absolute standardized mean difference; BP: blood pressure; CCB: calcium channel blocker; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SD: standard deviation

Modified Therapeutic Intensity Score is a standardized measure to measure regimen intensity calculated as $\Sigma_1^n \frac{Prescribed\ Dose}{ACC/AHA\ 2017\ Maximum\ Dose}$ where n is the number of antihypertensive medications.[11,12]

Table 2: Incidence rates and hazard ratios for all-cause hospitalization and all-cause mortality among SARS-CoV-2 positive outpatient Veterans taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 1.1) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Primary Outcome				
All-cause hospitalization or all-cause mortality				
Secondary Outcomes				
All-cause hospitalization				
All-cause mortality				
ICU admission				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IQR: interquartile range; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2				

Aim 1.1 Supplemental Tables

Supplemental Table S1: Incidence rates and hazard ratios for all-cause hospitalization and all-cause mortality among SARS-CoV-2 positive outpatient Veterans taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 1.1) overall, by covariate adjustment strategy.

Outcome	ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)	Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)	Hazard Ratio (95% CI)	p-value
All-cause hospitalization or all-cause mortality				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
Secondary Outcomes				
All-cause hospitalization				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
All-cause mortality				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
ICU admission				
Crude				

Multivariable-adjusted Propensity score as covariate Propensity score stratification Propensity score matching IPTW Matching weight adjusted
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S2: Incidence rates and hazard ratios for all-cause hospitalization and all-cause mortality among SARS-CoV-2 positive outpatient Veterans taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 1.1) in subgroups, matching weight adjusted.

	Matching weight adjusted				
Subgroup	**ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**	**$P_{interaction}$**
Age, years					
<40					
40 to <50					
50 to <60					
60 to <70					
≥70					
Sex					
Male					
Female					
Race-ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Asian American					
Body mass index, kg/m^2					
Underweight (<18.5)					
Normal weight (18.5 - <25)					
Overweight (25 - <30)					
Obese (≥30)					
Antihypertensive medications being taken					
One					
Two					
Three					
Four or more					
Tertile of mTIS					
T1 (mTIS x-x)					
T2 (mTIS x-x)					

T3 (mTIS x-x)
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval;
Modified Therapeutic Intensity Score is a standardized measure calculated as $\boldsymbol{\Sigma_1^n} \frac{\boldsymbol{Prescribed\ Dose}}{\boldsymbol{ACC/AHA\ 2017\ Maximum\ Dose}}$ where n is the number of antihypertensive medications.[11,12] For the purposes of this table, the mTIS represents the Modified Therapeutic Intensity Score of the specified drug in the regimen, not the patients entire medication regimen. For example, a patient on lisinopril 20 mg daily would have a mTIS for lisinopril of 20/40 = 0.5.

Supplemental Table S3: Incidence rates and hazard ratios for the primary and secondary outcomes among SARS-CoV-2 positive outpatient Veterans taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 1.1) overall, by varying the definition of the primary medication exposure.

	Matching weight adjusted			
Outcome	**ACEI/ARB-based regimen N event/N exposed (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen N event/N exposed (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
All-cause hospitalization or all-cause mortality				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
Secondary Outcomes				
All-cause hospitalization				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
All-cause mortality				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				

ICU admission 1 pharmacy fill in previous 90 days (primary analysis) 2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date*
* Defined as: prescription dispensed before the index date with a days' supply that met or exceeded the index date. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; EHR: electronic health record; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S4: One or more inpatient encounter for negative control outcomes among SARS-CoV-2 positive outpatient Veterans taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 1.1) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Severe gastrointestinal bleeding				
Urinary tract infection				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019				

Aim 1.2 Main Tables

Table 3: Baseline characteristics of Veterans with treated hypertension who have a positive outpatient SARS-CoV-2 test and are taking ACEI vs. ARB based regimens (Aim 1.2), before and after propensity score weighting.

	Before weighting				After weighting		
Patient characteristics	**Total (n = xxxx)**	**ACEI users (n = xxxx)**	**ARB users (n = xxxx)**	**ASMD**	**ACEI users (n = xxxx)**	**ARB users (n = xxxx)**	**ASMD**
Demographics							
Age (years)							
Mean (SD)							
<40							
40 to <50							
50 to <60							
60 to <70							
≥70							
Female sex							
Race-ethnicity/ethnicity							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Asian American							
Other							
Median area-level income							
<$25,000							
$25,000 - $49,999							
$50,000 - $74,999							
≥$75,000							
Commercial health insurance							
Priority group status							
1							
2 through 8							
VISN Region							
Northeast							
Southeast							
Continental							
Pacific							

Current smoker	
Vitals and laboratory measurements	
Body mass index, kg/m^2	
Mean (SD)	
Underweight (<18.5)	
Normal weight (18.5 - <25)	
Overweight (25 - <30)	
Obese (≥30)	
Systolic BP, mm Hg	
Mean (SD)	
< 130	
130 - 139	
140 - 159	
≥ 160	
Diastolic BP, mm Hg	
Mean (SD)	
< 80	
80 - 89	
90 - 99	
≥ 100	
Total cholesterol, mg/dL	
LDL-C, mg/dL	
HDL-C, mg/dL	
Triglycerides, mg/dL	
Hemoglobin A1c, %	
Serum potassium, mEq/L	
Serum creatinine, mg/dL	
eGFR, mL/min/1.73m^2	
Comorbidities	
Diabetes	
Chronic kidney disease	
Heart failure with reduced ejection fraction	
Coronary heart disease	
History of stroke	
Peripheral artery disease	

History of renal transplant Atrial fibrillation Chronic obstructive pulmonary disease Asthma Depression Charlson Comorbidity Index	
Antihypertensive Medication ACEI ARB CCB Thiazide diuretic Alpha-blocker Beta-blocker Centrally-acting Direct vasodilator Direct renin inhibitor Aldosterone receptor antagonist Loop diuretic Potassium-sparing diuretic Total number of antihypertensive medications in regimen One Two Three Four or more mTIS of antihypertensive regimen, median (IQR)	
Other medication use Current statin use Current aspirin use	
Numbers in table are number (column %) or mean (standard deviation) unless otherwise specified. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; ASMD: absolute standardized mean difference; BP: blood pressure; CCB: calcium channel blocker; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SD: standard deviation	

Table 4: Incidence rates and hazard ratios for all-cause hospitalization and all-cause mortality among SARS-CoV-2 positive outpatient Veterans taking an ACEI vs. ARB based regimens (Aim 1.2) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI users (n = xxxx) N (Rate per 100 person years)**	**ARB users (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Primary Outcome				
All-cause hospitalization or all-cause mortality				
Secondary Outcomes				
All-cause hospitalization				
All-cause mortality				
ICU admission				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IQR: interquartile range;				

Aim 1.2 Supplemental Tables

Supplemental Table S5: Incidence rates and hazard ratios for all-cause hospitalization and all-cause mortality among SARS-CoV-2 positive outpatient Veterans taking an ACEI vs. ARB based regimens (Aim 1.2) overall, by covariate adjustment strategy.

Outcome	ACEI user (n = xxxx) N (Rate per 100 person years)	ARB user (n = xxxx) N (Rate per 100 person years)	Hazard Ratio (95% CI)	p-value
All-cause hospitalization or all-cause mortality				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
Secondary Outcomes				
All-cause hospitalization				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
All-cause mortality				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
ICU admission				
Crude				
Multivariable-adjusted				

Propensity score as covariate Propensity score stratification Propensity score matching IPTW Matching weight adjusted
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S6: Incidence rates and hazard ratios for all-cause hospitalization and all-cause mortality among SARS-CoV-2 positive outpatient Veterans taking an ACEI vs. ARB based regimens (Aim 1.2) in subgroups, matching weight adjusted.

	Matching weight adjusted				
Subgroup	**ACEI user (n = xxxx) N (Rate per 100 person years)**	**ARB user (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**	**$P_{interaction}$**
Age, years					
<40					
40 to <50					
50 to <60					
60 to <70					
≥70					
Sex					
Male					
Female					
Race-ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Asian American					
Body mass index, kg/m^2					
Underweight (<18.5)					
Normal weight (18.5 - <25)					
Overweight (25 - <30)					
Obese (≥30)					
Antihypertensive medications being taken					
One					
Two					
Three					
Four or more					
Tertile of mTIS					
T1 (mTIS x-x)					
T2 (mTIS x-x)					
T3 (mTIS x-x)					

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Modified Therapeutic Intensity Score is a standardized measure calculated as $\boldsymbol{\Sigma_1^n} \frac{\boldsymbol{Prescribed\ Dose}}{\boldsymbol{ACC/AHA\ 2017\ Maximum\ Dose}}$ where n is the number of antihypertensive medications.[11,12] For the purposes of this table, the mTIS represents the Modified Therapeutic Intensity Score of the specified drug in the regimen, not the patients entire medication regimen. For example, a patient on lisinopril 20 mg daily would have a mTIS for lisinopril of 20/40 = 0.5.

Supplemental Table S7: Incidence rates and hazard ratios for the primary and secondary outcomes among SARS-CoV-2 positive outpatient Veterans taking an ACEI vs. ARB based regimens (Aim 1.2) overall, by varying the definition of the primary medication exposure.

	Matching weight adjusted			
Outcome	**ACEI user N event/N exposed (Rate per 100 person years)**	**ARB user N event/N exposed (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
All-cause hospitalization or all-cause mortality				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
Secondary Outcomes				
All-cause hospitalization				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
All-cause mortality				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				

ICU admission 1 pharmacy fill in previous 90 days (primary analysis) 2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date*
* Defined as: prescription dispensed before the index date with a days' supply that met or exceeded the index date. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; EHR: electronic health record; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S8: One or more inpatient encounter for negative control outcomes among SARS-CoV-2 positive outpatient Veterans taking an ACEI vs. an ARB based regimen (Aim 1.2) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI users (n = xxxx) N (Rate per 100 person years)**	**ARB users (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Severe gastrointestinal bleeding				
Urinary tract infection				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019				

Aim 1.1 Main Figures

Figure 1: Flowchart

Editable from: https://drive.google.com/file/d/1DHhWPAe9VxUXFrSbvQjbtoFxdarIlmv4/view?usp=sharing

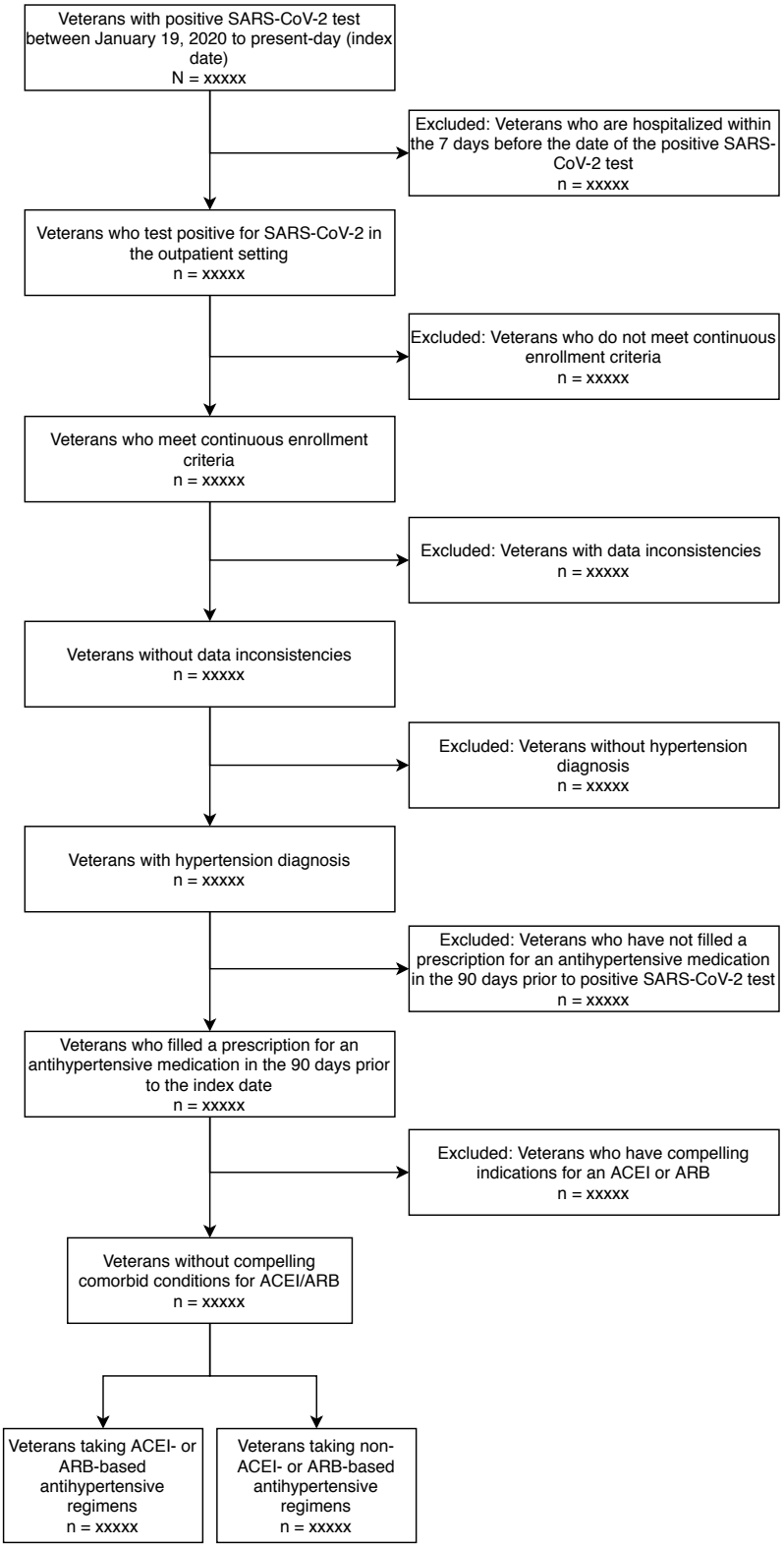
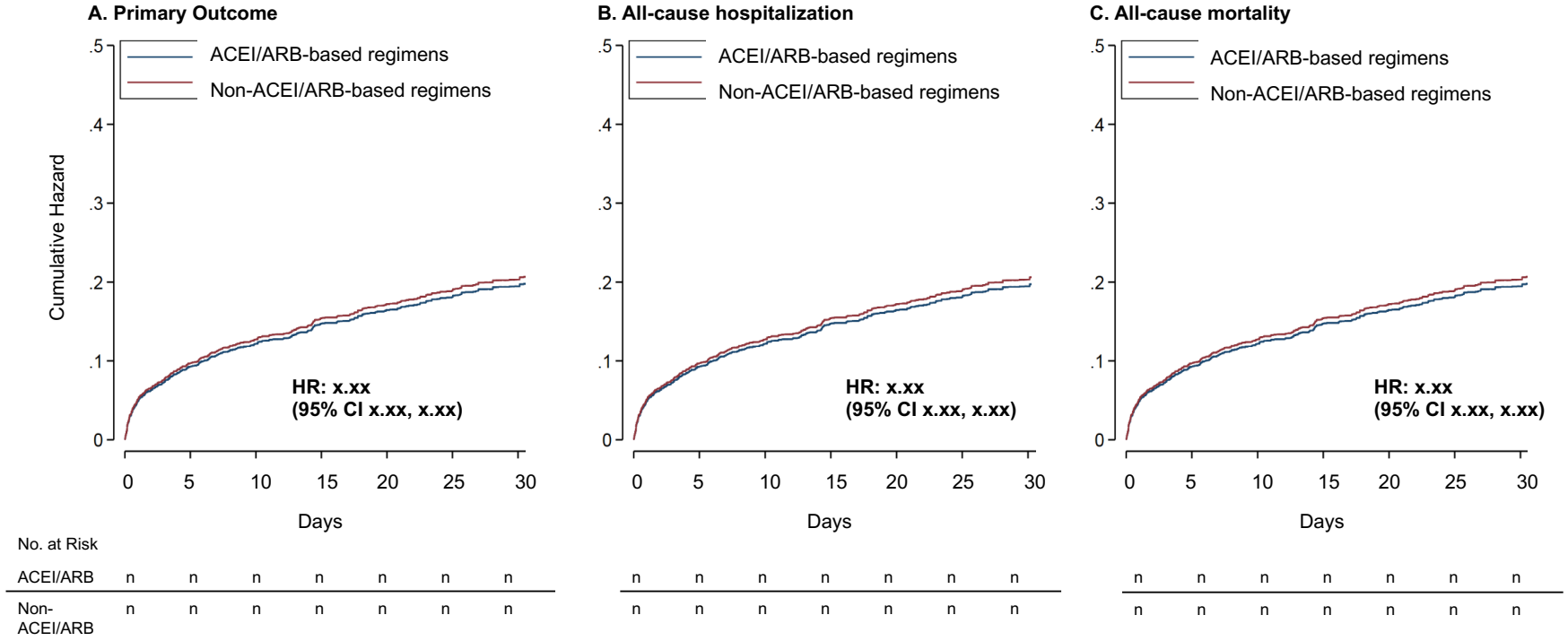
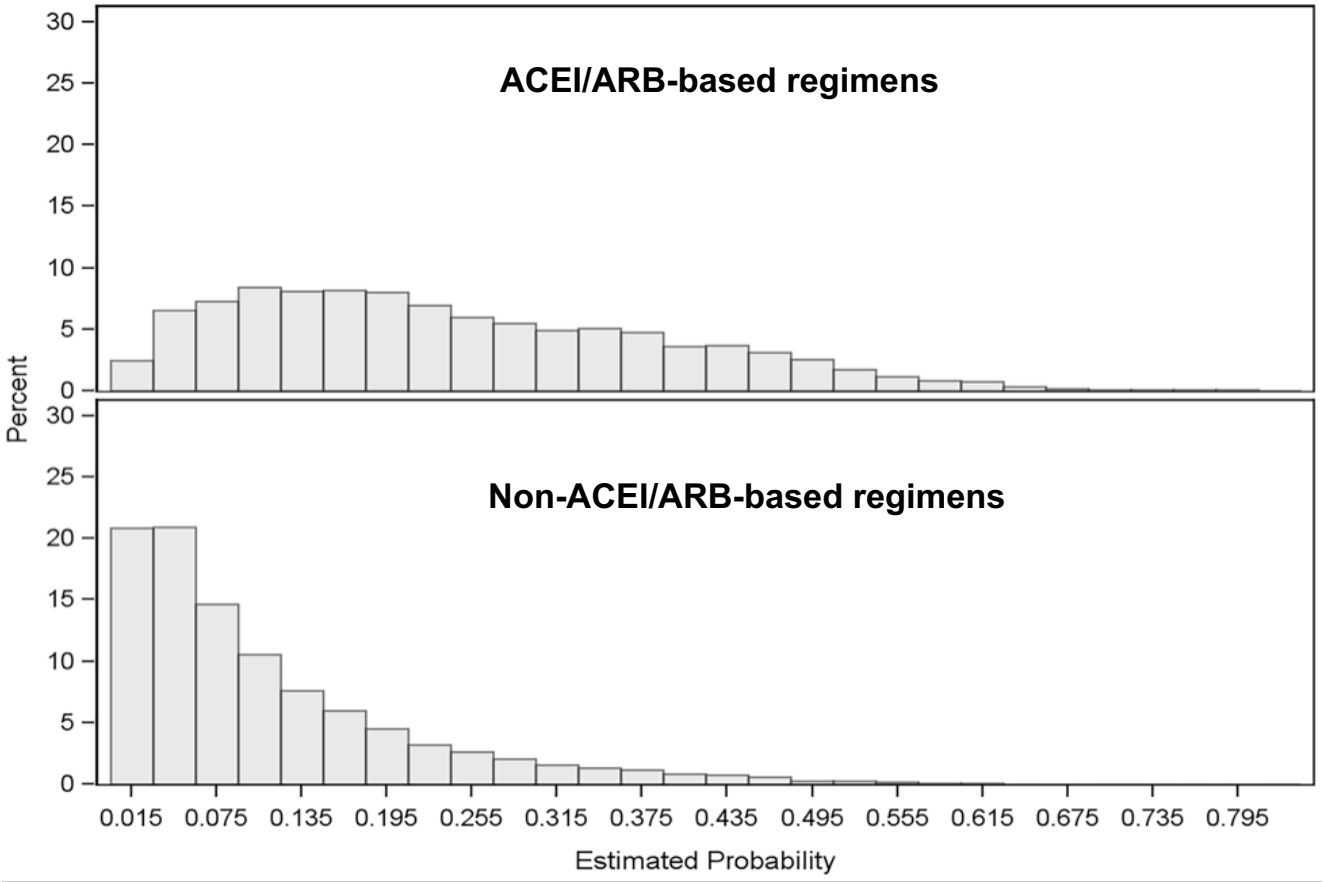


Figure 2: Matching weight-adjusted cumulative hazard curves (ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens) for experiencing all-cause hospitalization or mortality among outpatient Veterans who are SARS-CoV-2 positive.



Aim 1.1 Supplemental Figures

Supplemental Figure S1: Distribution of propensity scores among outpatient Veterans who are SARS-CoV-2 positive between the ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimen cohorts.



Supplemental Figure S2: Characteristic balance before and after propensity score weighting among outpatient Veterans who are SARS-CoV-2 positive between the ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens cohorts.

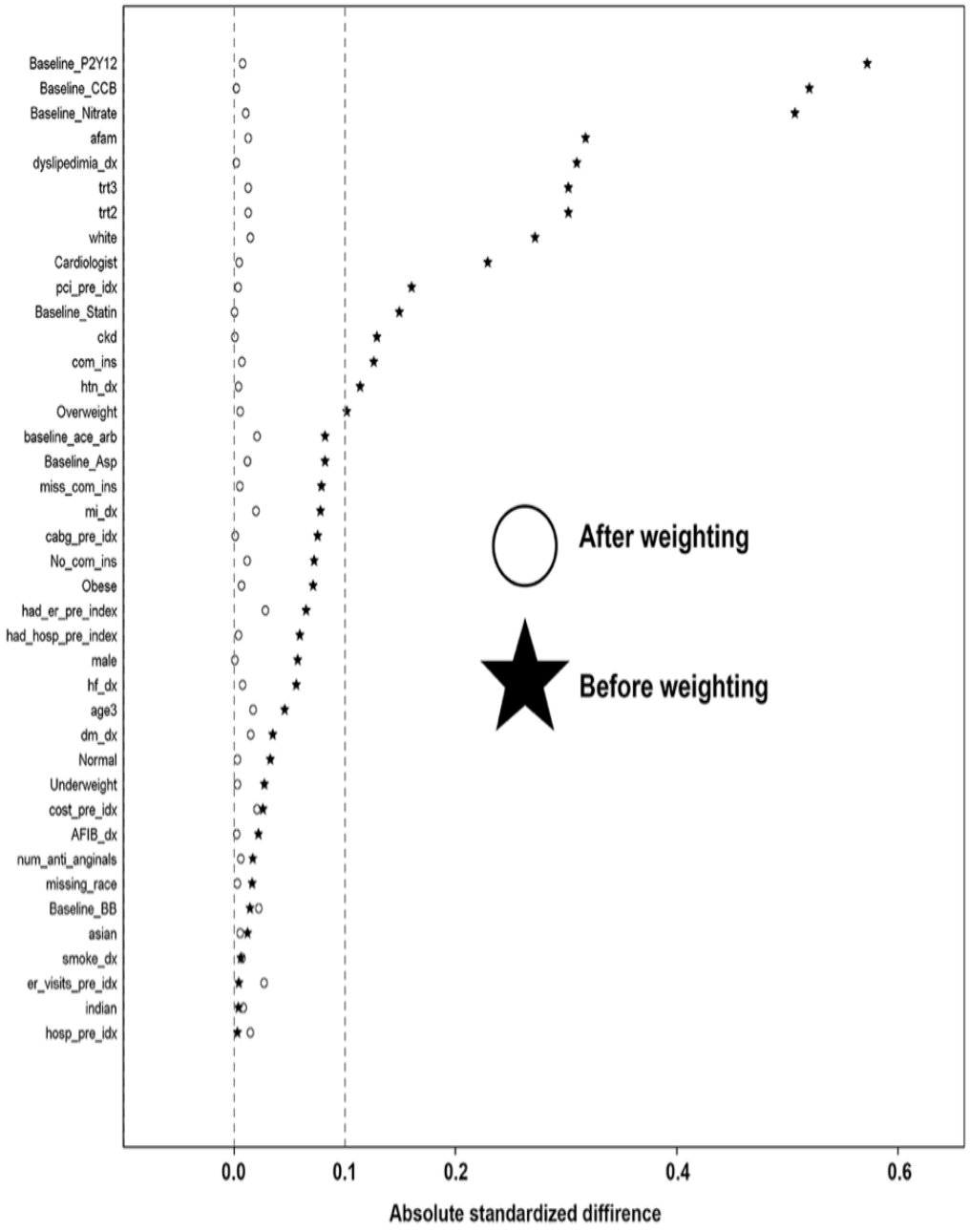
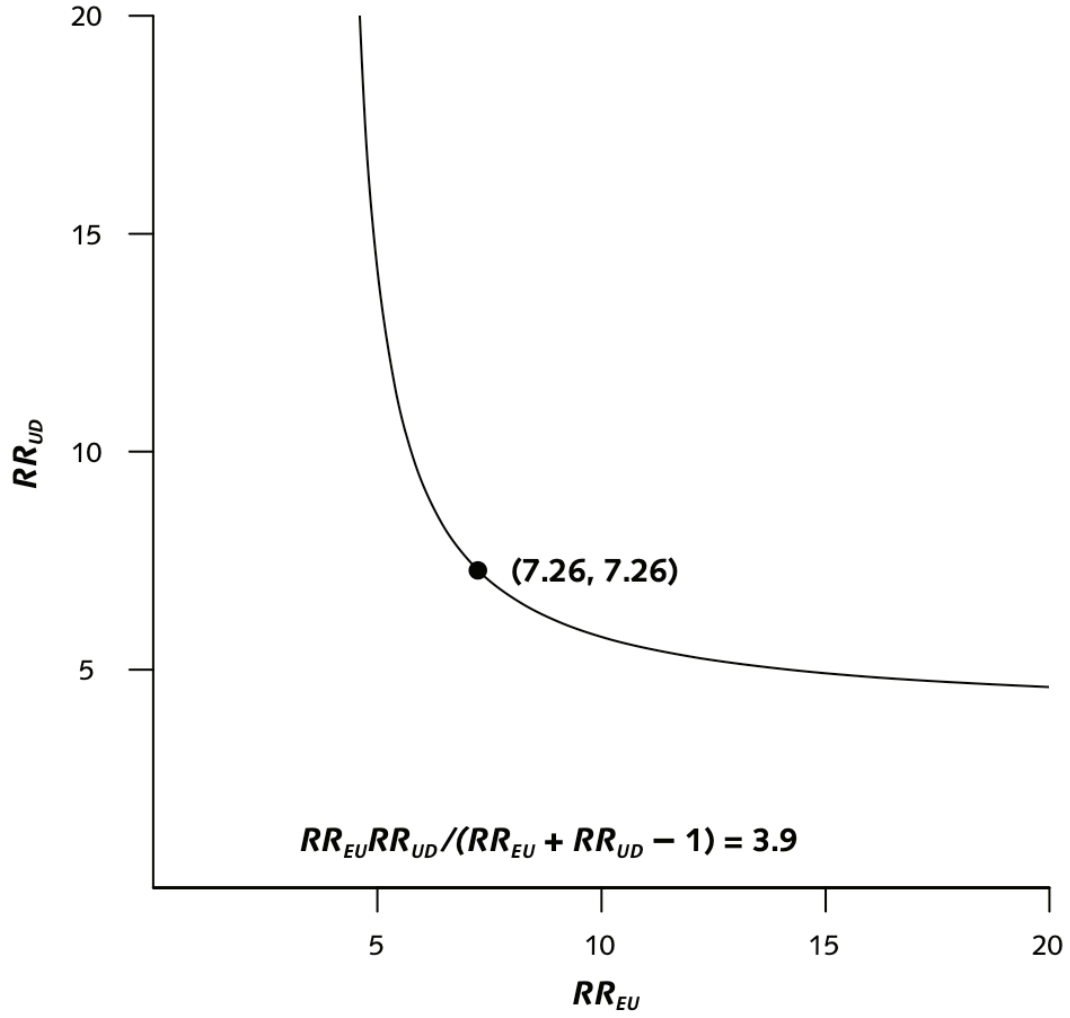


*Figure will be updated with covariates on left using the same list from Table 1.

Supplemental Figure S3: Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away an observed treatment-outcome risk ratio of RR = x.x. (Aim 1.1)



Aim 1.2 Main Figures

Figure 3: Flowchart

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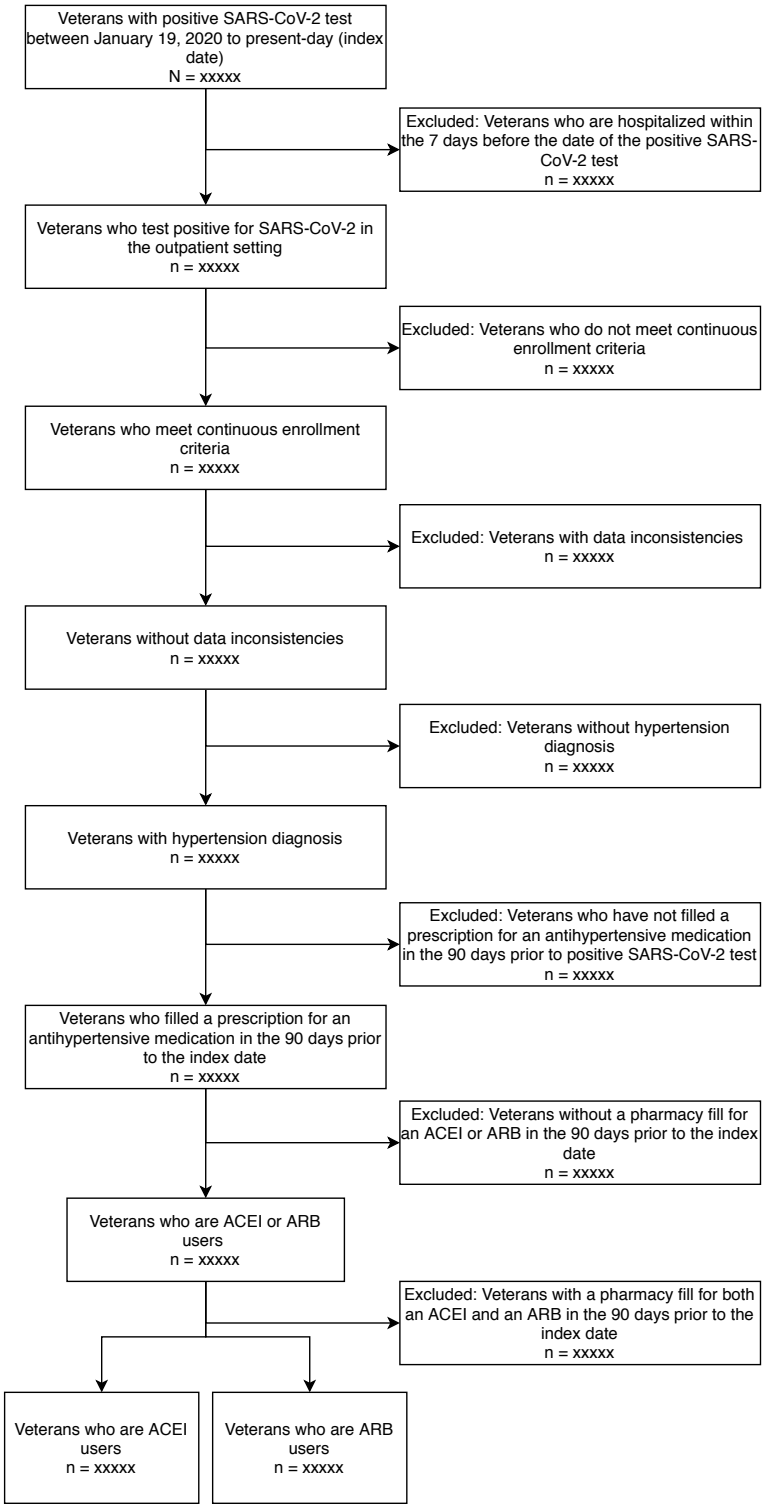
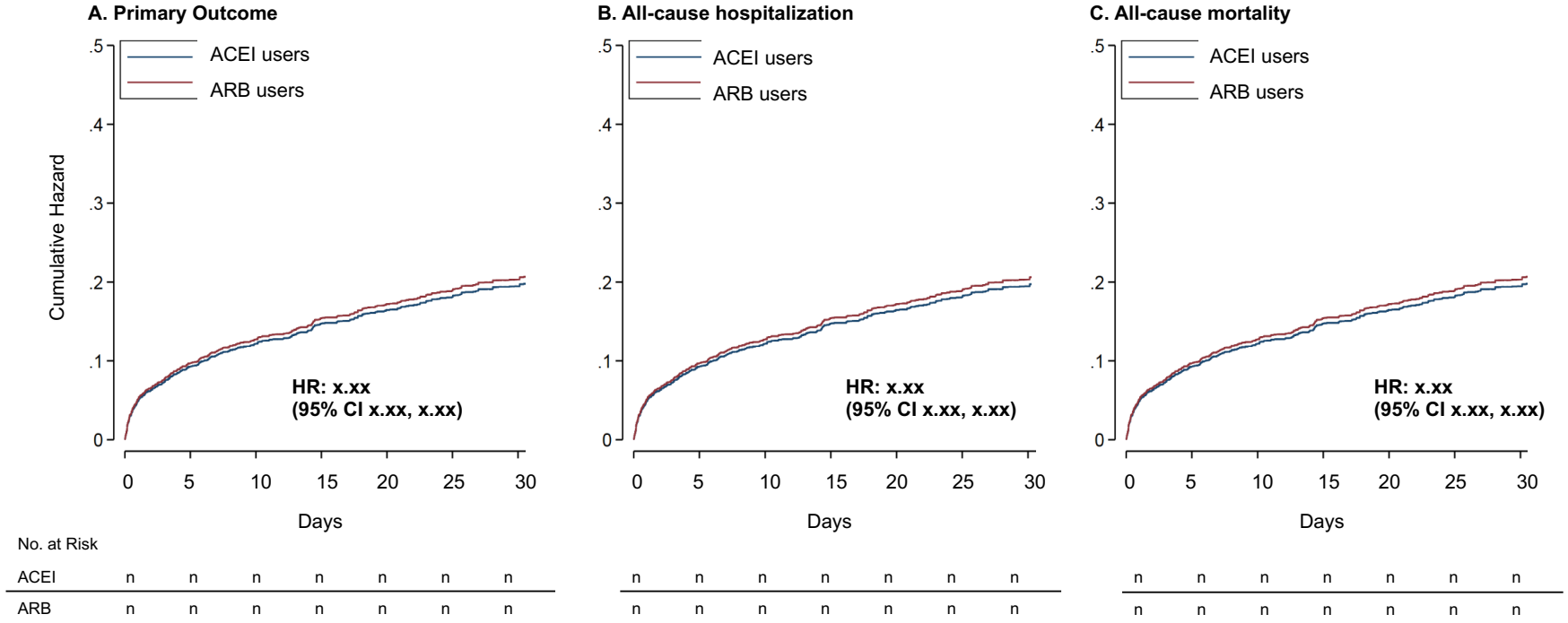
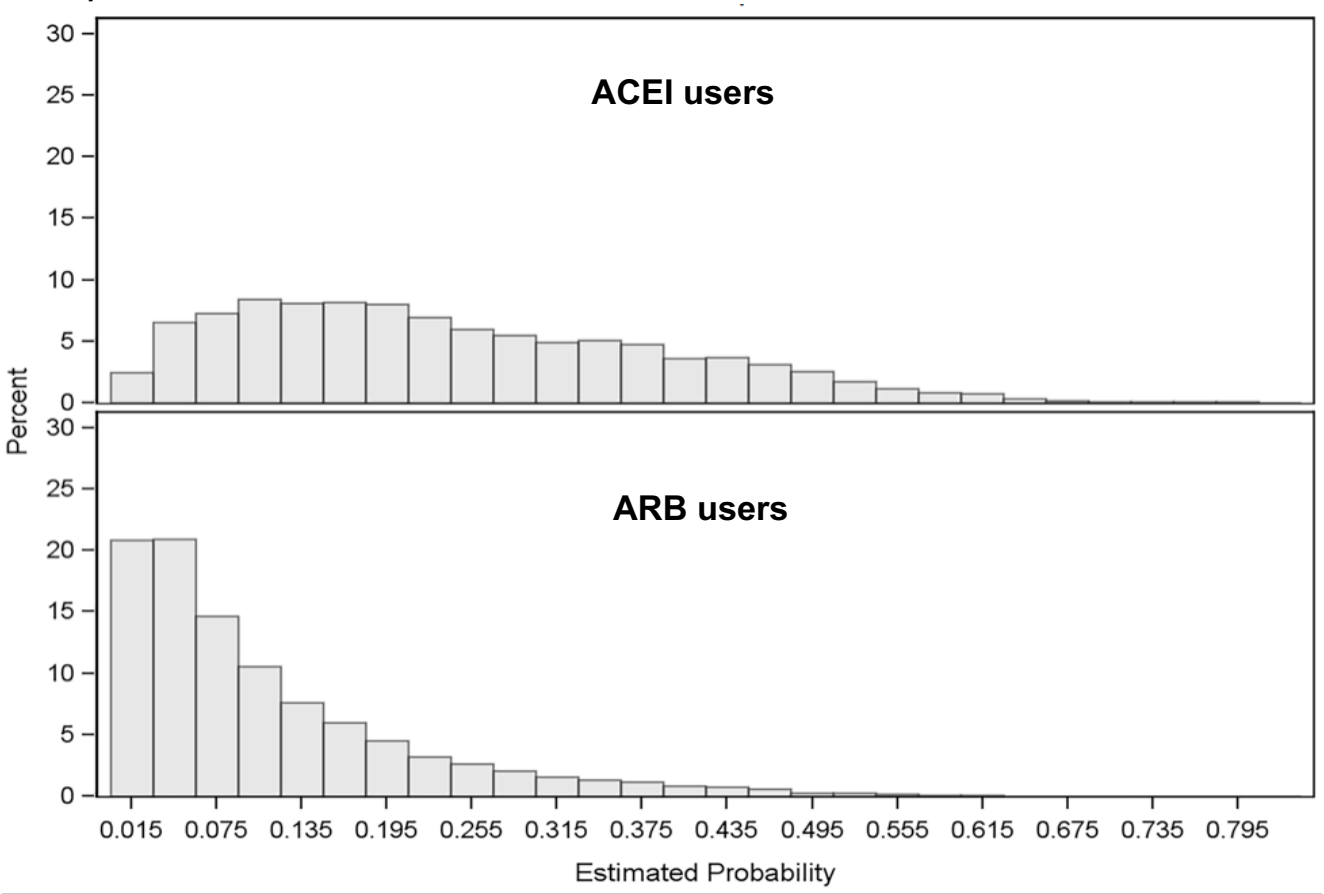


Figure 4: Matching weight-adjusted cumulative hazard curves (ACEI users vs. ARB users) for experiencing all-cause hospitalization or all-cause mortality among outpatient Veterans who are SARS-CoV-2 positive.



Aim 1.2 Supplemental Figures

Supplemental Figure S4: Distribution of propensity scores among outpatient Veterans who are SARS-CoV-2 positive between ACEI users vs. ARB users.



Supplemental Figure S5: Characteristic balance before and after propensity score weighting among outpatient Veterans who are SARS-CoV-2 positive between the ACEI users vs. ARB users.

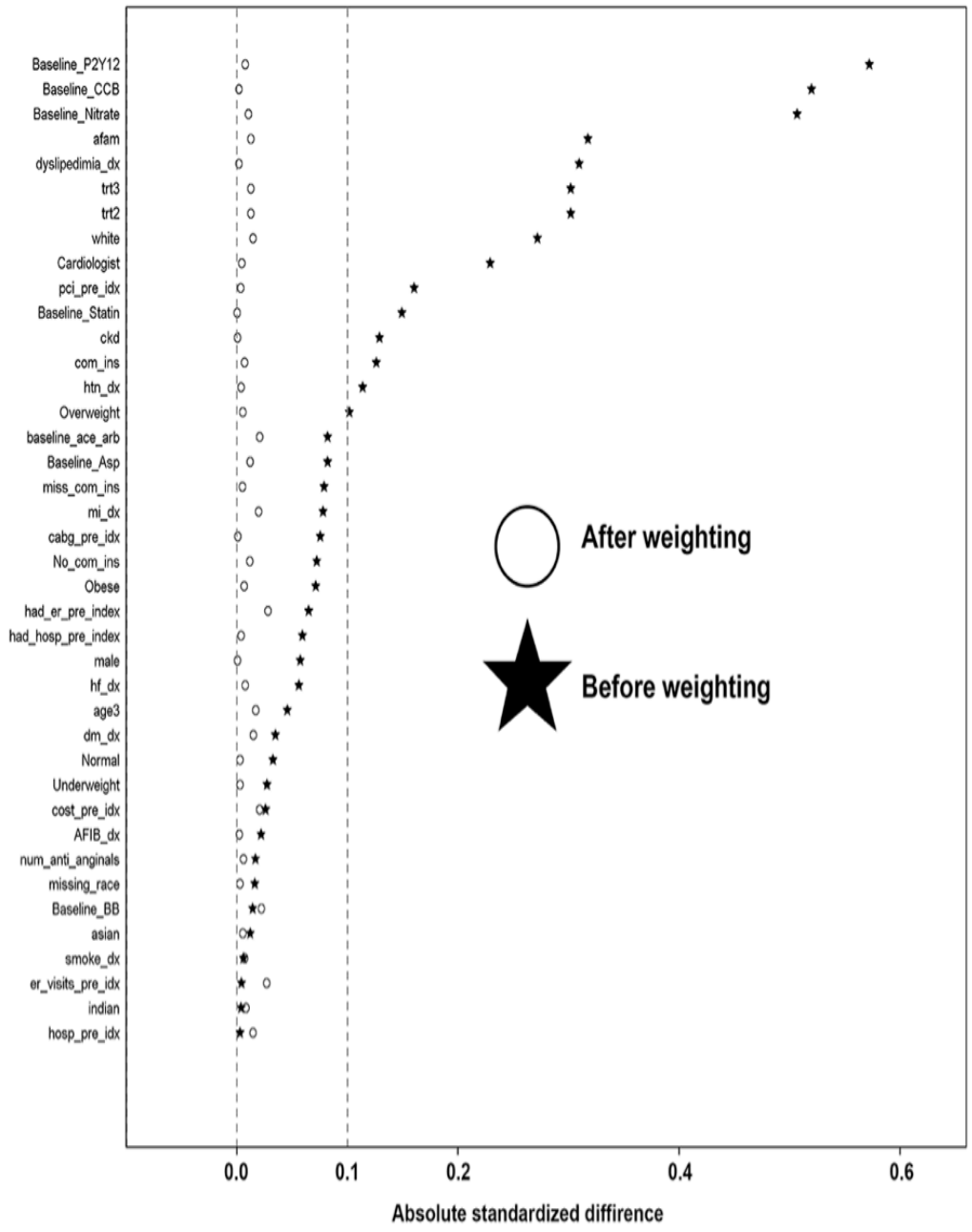
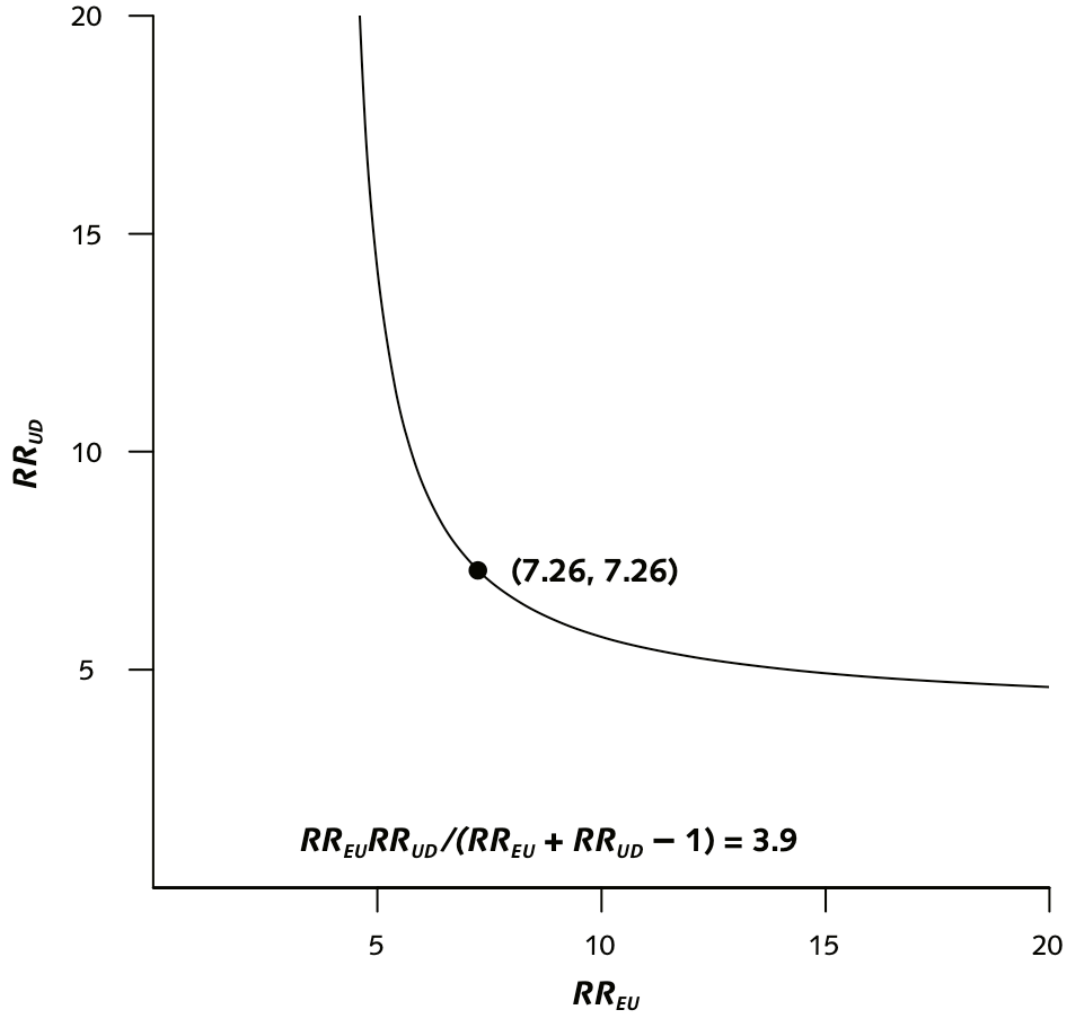


*Figure will be updated with covariates on left using the same list from Table 1.

Supplemental Figure S6: Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away an observed treatment-outcome risk ratio of RR = x.x. (Aim 1.2)



Aim 2.1 Main Tables

Table 5: Baseline characteristics of Veterans with hypertension without compelling indications for an ACEI or ARB hospitalized with COVID-19 and are taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 2.1), before and after propensity score weighting.

	Before weighting				After weighting		
Patient characteristics	**Total (n = xxxx)**	**ACEI/ARB-based regimen (n = xxxx)**	**Non-ACEI/ARB-based regimen (n = xxxx)**	**ASMD**	**ACEI/ARB-based regimen (n = xxxx)**	**Non-ACEI/ARB-based regimen (n = xxxx)**	**ASMD**
Demographics							
Age (years)							
Mean (SD)							
<40							
40 to <50							
50 to <60							
60 to <70							
≥70							
Female sex							
Race-ethnicity/ethnicity							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Asian American							
Other							
Current smoker							
Vitals and laboratory measurements							
Body mass index, kg/m^2							
Mean (SD)							
Underweight (<18.5)							
Normal weight (18.5 - <25)							
Overweight (25 - <30)							
Obese (≥30)							
Systolic BP, mm Hg							
Mean (SD)							
< 130							
130 - 139							

140 - 159 ≥ 160 Diastolic BP, mm Hg Mean (SD) < 80 80 - 89 90 - 99 ≥ 100 Total cholesterol, mg/dL LDL-C, mg/dL HDL-C, mg/dL Triglycerides, mg/dL Hemoglobin A1c, % Serum potassium, mEq/L Serum creatinine, mg/dL eGFR, mL/min/1.73m^2	
Comorbidities Peripheral artery disease History of renal transplant Atrial fibrillation Chronic obstructive pulmonary disease Asthma Depression Charlson Comorbidity Index, mean (SD)	
Antihypertensive Medication ACEI ARB CCB Thiazide diuretic Alpha-blocker Beta-blocker Centrally-acting Direct vasodilator Direct renin inhibitor	

Aldosterone receptor antagonist Loop diuretic Potassium-sparing diuretic Total number of antihypertensive medications in regimen, median (IQR) One Two Three Four or more mTIS of antihypertensive regimen, median (IQR)	
Other medication use Current statin use Current aspirin use	

Numbers in table are number (column %) or mean (standard deviation) unless otherwise specified.

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; ASMD: absolute standardized mean difference; BP: blood pressure; CCB: calcium channel blocker; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SD: standard deviation

Modified Therapeutic Intensity Score is a standardized measure to measure regimen intensity calculated as $\Sigma_1^n \frac{Prescribed\ Dose}{ACC/AHA\ 2017\ Maximum\ Dose}$ where n is the number of antihypertensive medications.[11,12]

Table 6: Incidence rates and hazard ratios for the primary and secondary outcomes among Veterans hospitalized for COVID-19 taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 2.1) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Primary Outcome				
All-cause mortality				
Secondary Outcomes				
Duration of hospitalization, days, median (IQR)				
ICU admission				
Dialysis				
Mechanical ventilation				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IQR: interquartile range; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2				

Aim 2.1 Supplemental Tables

Supplemental Table S9: Incidence rates and hazard ratios for the primary and secondary outcomes among Veterans hospitalized for COVID-19 taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 2.1) overall, by covariate adjustment strategy

Outcome	ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)	Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)	Hazard Ratio (95% CI)	p-value
All-cause mortality				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
Secondary Outcomes				
Duration of hospitalization, days, median (IQR)				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
ICU admission				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
Dialysis				
Crude				

Multivariable-adjusted
Propensity score as covariate
Propensity score stratification
Propensity score matching
IPTW
Matching weight adjusted
Mechanical ventilation
Crude
Multivariable-adjusted
Propensity score as covariate
Propensity score stratification
Propensity score matching
IPTW
Matching weight adjusted
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S10: Incidence rates and hazard ratios for all-cause mortality among Veterans hospitalized for COVID-19 taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 2.1) in subgroups, matching weight adjusted.

	Matching weight adjusted				
Subgroup	**ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**	**$P_{interaction}$**
Age, years					
<40					
40 to <50					
50 to <60					
60 to <70					
≥70					
Sex					
Male					
Female					
Race-ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Asian American					
Body mass index, kg/m^2					
Underweight (<18.5)					
Normal weight (18.5 - <25)					
Overweight (25 - <30)					
Obese (≥30)					
Antihypertensive medications being taken					
One					
Two					
Three					
Four or more					
Tertile of mTIS					
T1 (mTIS x-x)					
T2 (mTIS x-x)					
T3 (mTIS x-x)					

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval;
Modified Therapeutic Intensity Score is a standardized measure calculated as $\Sigma_1^n \frac{Prescribed\ Dose}{ACC/AHA\ 2017\ Maximum\ Dose}$ where n is the number of antihypertensive medications.[11,12] For the purposes of this table, the mTIS represents the Modified Therapeutic Intensity Score of the specified drug in the regimen, not the patients entire medication regimen. For example, a patient on lisinopril 20 mg daily would have a mTIS for lisinopril of 20/40 = 0.5.

Supplemental Table S11: Incidence rates and hazard ratios for the primary and secondary outcomes among Veterans hospitalized for COVID-19 taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 2.1) overall, by varying the definition of the primary medication exposure.

	Matching weight adjusted			
Outcome	**ACEI/ARB-based regimen N event/N exposed (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen N event/N exposed (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
All-cause mortality				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
1 pharmacy fill in the previous 90 days and medication continued during hospitalization				
Secondary Outcomes				
Duration of hospitalization, days, median (IQR)				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
1 pharmacy fill in the previous 90 days and medication continued during hospitalization				
ICU admission				

1 pharmacy fill in previous 90 days (primary analysis) 2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date* 1 pharmacy fill in the previous 90 days and medication continued during hospitalization
Dialysis 1 pharmacy fill in previous 90 days (primary analysis) 2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date* 1 pharmacy fill in the previous 90 days and medication continued during hospitalization
Mechanical ventilation 1 pharmacy fill in previous 90 days (primary analysis) 2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date* 1 pharmacy fill in the previous 90 days and medication continued during hospitalization
* Defined as: prescription dispensed before the index date with a days' supply that met or exceeded the index date.

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; EHR: electronic health record; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S12: One or more inpatient encounter negative control outcomes among Veterans hospitalized for COVID-19 taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 2.1) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Severe gastrointestinal bleeding				
Urinary tract infection				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019				

Supplemental Table S13: All-cause mortality among Veterans hospitalized for bacterial pneumonia vs. COVID-19 taking ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens (Aim 2.1) overall, propensity matching weight adjusted. [Leave-out-essential ingredient negative control analysis]

	Matching weight adjusted				
	ACEI/ARB-based regimen		Non-ACEI/ARB-based regimen		HR (95% CI) for treatment arm within hospitalized cohort
Cohort	**N event/no event**	**Hazard Ratio (95% CI)**	**N event/no event**	**Hazard Ratio (95% CI)**	
Hospitalized for bacterial pneumonia	xx/xxxx	1.0 (reference)	xx/xxxx	HR (95% CI) p=0.xx	HR (95% CI) p=0.xx
Hospitalized for COVID-19	xx/xxxx	HR (95% CI) p=0.xx	xx/xxxx	HR (95% CI) p=0.xx	HR (95% CI) p=0.xx

Measure of interaction on additive scale: Relative excess risk due to interaction (RERI) (95% CI): x.xx (x.xx to x.xx), p=0.xx

Measure of interaction on multiplicative scale: ratio of hazard ratios (95% CI) = x.xx (x.xx to x.xx), p=0.xx

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; HR: hazard ratio

Aim 2.2 Main Tables

Table 7: Baseline characteristics of Veterans with treated hypertension who are hospitalized for COVID-19 and taking ACEI vs. ARB-based regimens (Aim 2.2), before and after propensity score weighting.

	Before weighting				After weighting		
Patient characteristics	**Total (n = xxxx)**	**ACEI users (n = xxxx)**	**ARB users (n = xxxx)**	**ASMD**	**ACEI users (n = xxxx)**	**ARB users (n = xxxx)**	**ASMD**
Demographics							
Age (years)							
Mean (SD)							
<40							
40 to <50							
50 to <60							
60 to <70							
≥70							
Female sex							
Race-ethnicity/ethnicity							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Asian American							
Other							
Median area-level income							
<$25,000							
$25,000 - $49,999							
$50,000 - $74,999							
≥$75,000							
Commercial health insurance							
Priority group status							
1							
2 through 8							
VISN Region							
Northeast							
Southeast							
Continental							
Pacific							

Current smoker	
Vitals and laboratory measurements	
Body mass index, kg/m^2	
Mean (SD)	
Underweight (<18.5)	
Normal weight (18.5 - <25)	
Overweight (25 - <30)	
Obese (≥30)	
Systolic BP, mm Hg	
Mean (SD)	
< 130	
130 - 139	
140 - 159	
≥ 160	
Diastolic BP, mm Hg	
Mean (SD)	
< 80	
80 - 89	
90 - 99	
≥ 100	
Total cholesterol, mg/dL	
LDL-C, mg/dL	
HDL-C, mg/dL	
Triglycerides, mg/dL	
Hemoglobin A1c, %	
Serum potassium, mEq/L	
Serum creatinine, mg/dL	
eGFR, mL/min/1.73m^2	
Comorbidities	
Diabetes	
Chronic kidney disease	
Heart failure with reduced ejection fraction	
Coronary heart disease	
History of stroke	
Peripheral artery disease	

History of renal transplant Atrial fibrillation Chronic obstructive pulmonary disease Asthma Depression Charlson Comorbidity Index	
Antihypertensive Medication ACEI ARB CCB Thiazide diuretic Alpha-blocker Beta-blocker Centrally-acting Direct vasodilator Direct renin inhibitor Aldosterone receptor antagonist Loop diuretic Potassium-sparing diuretic Total number of antihypertensive medications in regimen One Two Three Four or more mTIS of antihypertensive regimen, median (IQR)	
Other medication use Current statin use Current aspirin use	
Numbers in table are number (column %) or mean (standard deviation) unless otherwise specified. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; ASMD: absolute standardized mean difference; BP: blood pressure; CCB: calcium channel blocker; eGFR: estimated glomerular filtration rate; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SD: standard deviation	

Table 8: Incidence rates and hazard ratios for the primary and secondary outcomes among Veterans hospitalized for COVID-19 taking an ACEI vs. an ARB based regimen (Aim 2.2) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI users (n = xxxx) N (Rate per 100 person years)**	**ARB users (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Primary Outcome				
All-cause mortality				
Secondary Outcomes				
Duration of hospitalization, days, median (IQR)				
ICU admission				
Dialysis				
Mechanical ventilation				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IQR: interquartile range;				

Aim 2.2 Supplemental Tables

Supplemental Table S14: Incidence rates and hazard ratios for the primary and secondary outcomes among Veterans hospitalized for COVID-19 taking an ACEI vs. an ARB based regimen (Aim 2.2) overall, by covariate adjustment strategy

Outcome	ACEI user (n = xxxx) N (Rate per 100 person years)	ARB user (n = xxxx) N (Rate per 100 person years)	Hazard Ratio (95% CI)	p-value
All-cause mortality				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
Secondary Outcomes				
Duration of hospitalization, days, median (IQR)				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
ICU admission				
Crude				
Multivariable-adjusted				
Propensity score as covariate				
Propensity score stratification				
Propensity score matching				
IPTW				
Matching weight adjusted				
Dialysis				
Crude				
Multivariable-adjusted				

Propensity score as covariate Propensity score stratification Propensity score matching IPTW Matching weight adjusted Mechanical ventilation Crude Multivariable-adjusted Propensity score as covariate Propensity score stratification Propensity score matching IPTW Matching weight adjusted
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S15: Incidence rates and hazard ratios for all-cause hospitalization Veterans hospitalized for COVID-19 taking an ACEI vs. ARB based regimens (Aim 1.2) in subgroups, matching weight adjusted.

	Matching weight adjusted				
Subgroup	**ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Non-ACEI/ARB-based regimen (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**	**$P_{interaction}$**
Age, years					
<40					
40 to <50					
50 to <60					
60 to <70					
≥70					
Sex					
Male					
Female					
Race-ethnicity					
Non-Hispanic White					
Non-Hispanic Black					
Hispanic					
Asian American					
Body mass index, kg/m^2					
Underweight (<18.5)					
Normal weight (18.5 - <25)					
Overweight (25 - <30)					
Obese (≥30)					
Antihypertensive medications being taken					
One					
Two					
Three					
Four or more					
Tertile of mTIS					
T1 (mTIS x-x)					
T2 (mTIS x-x)					
T3 (mTIS x-x)					

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Modified Therapeutic Intensity Score is a standardized measure calculated as $\boldsymbol{\Sigma_1^n} \frac{\boldsymbol{Prescribed\ Dose}}{\boldsymbol{ACC/AHA\ 2017\ Maximum\ Dose}}$ where n is the number of antihypertensive medications.[11,12] For the purposes of this table, the mTIS represents the Modified Therapeutic Intensity Score of the specified drug in the regimen, not the patients entire medication regimen. For example, a patient on lisinopril 20 mg daily would have a mTIS for lisinopril of 20/40 = 0.5.

Supplemental Table S16: Incidence rates and hazard ratios for the primary and secondary outcomes among Veterans hospitalized for COVID-19 taking an ACEI vs. ARB (Aim 2.2) overall, by varying the definition of the primary medication exposure.				
	Matching weight adjusted			
Outcome	**ACEI users N event/N exposed (Rate per 100 person years)**	**ARB users N event/N exposed (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
All-cause mortality				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
1 pharmacy fill in the previous 90 days and medication continued during hospitalization				
Secondary Outcomes				
Duration of hospitalization, days, median (IQR)				
1 pharmacy fill in previous 90 days (primary analysis)				
2 pharmacy fills in the previous 180 days				
1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days				
Medication on-hand at index date*				
1 pharmacy fill in the previous 90 days and medication continued during hospitalization				
ICU admission				
1 pharmacy fill in previous 90 days (primary analysis)				

2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date* 1 pharmacy fill in the previous 90 days and medication continued during hospitalization Dialysis 1 pharmacy fill in previous 90 days (primary analysis) 2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date* 1 pharmacy fill in the previous 90 days and medication continued during hospitalization Mechanical ventilation 1 pharmacy fill in previous 90 days (primary analysis) 2 pharmacy fills in the previous 180 days 1 pharmacy fill in the previous 90 days and 3 consecutive pharmacy fills in the previous 365 days Medication on-hand at index date* 1 pharmacy fill in the previous 90 days and medication continued during hospitalization
* Defined as: prescription dispensed before the index date with a days' supply that met or exceeded the index date. ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; EHR: electronic health record; ICU: intensive care unit; IPTW: inverse propensity treatment weighting; IQR: interquartile range

Supplemental Table S17: One or more inpatient encounter for negative control outcomes among Veterans hospitalized for COVID-19 taking an ACEI vs. an ARB based regimen (Aim 2.2) overall, matching weight adjusted.				
	Matching weight adjusted			
Outcome	**ACEI users (n = xxxx) N (Rate per 100 person years)**	**ARB users (n = xxxx) N (Rate per 100 person years)**	**Hazard Ratio (95% CI)**	**p-value**
Severe gastrointestinal bleeding				
Urinary tract infection				
ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019				

Supplemental Table S18: All-cause mortality among Veterans hospitalized for bacterial pneumonia vs. COVID-19 taking ACEI vs. ARB (Aim 2.2) overall, propensity matching weight adjusted. [Leave-out-essential ingredient negative control analysis]

	Matching weight adjusted				
	ACEI users		ARB users		HR (95% CI) for treatment arm within hospitalized cohort
Cohort	**N event/no event**	**Hazard Ratio (95% CI)**	**N event/no event**	**Hazard Ratio (95% CI)**	
Hospitalized for bacterial pneumonia	xx/xxxx	1.0 (reference)	xx/xxxx	HR (95% CI) p=0.xx	HR (95% CI) p=0.xx
Hospitalized for COVID-19	xx/xxxx	HR (95% CI) p=0.xx	xx/xxxx	HR (95% CI) p=0.xx	HR (95% CI) p=0.xx

Measure of interaction on additive scale: Relative excess risk due to interaction (RERI) (95% CI): x.xx (x.xx to x.xx), p=0.xx

Measure of interaction on multiplicative scale: ratio of hazard ratios (95% CI) = x.xx (x.xx to x.xx), p=0.xx

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin-II receptor blocker; CI: confidence interval; COVID-19: Coronavirus Disease 2019; HR: hazard ratio

Aim 2.1 Main Figures

Figure 5: Flowchart

Editable from: https://drive.google.com/file/d/1XrXGdGJ2Xg39r6ne47xUpF9NozVMfgg_/view?usp=sharing

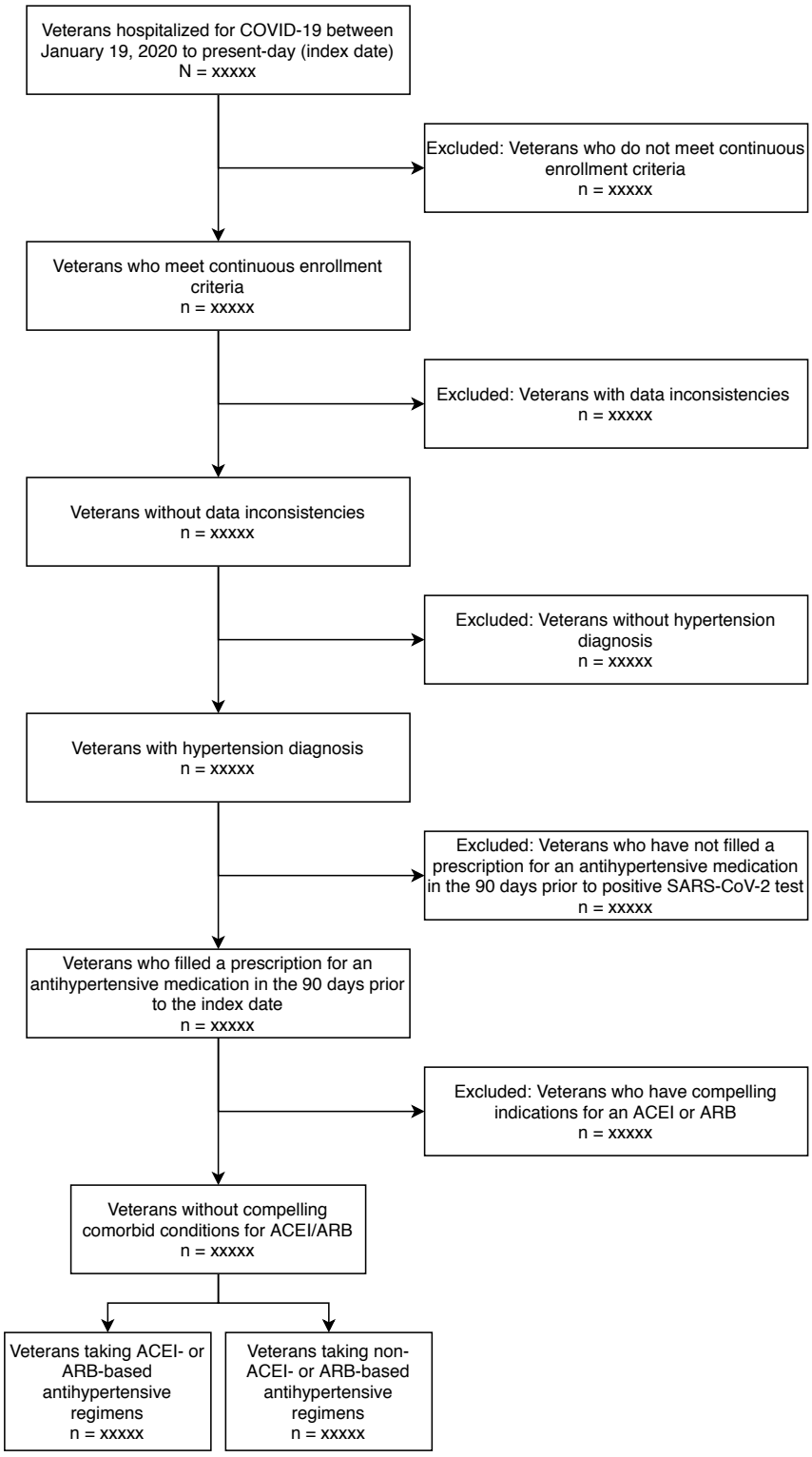
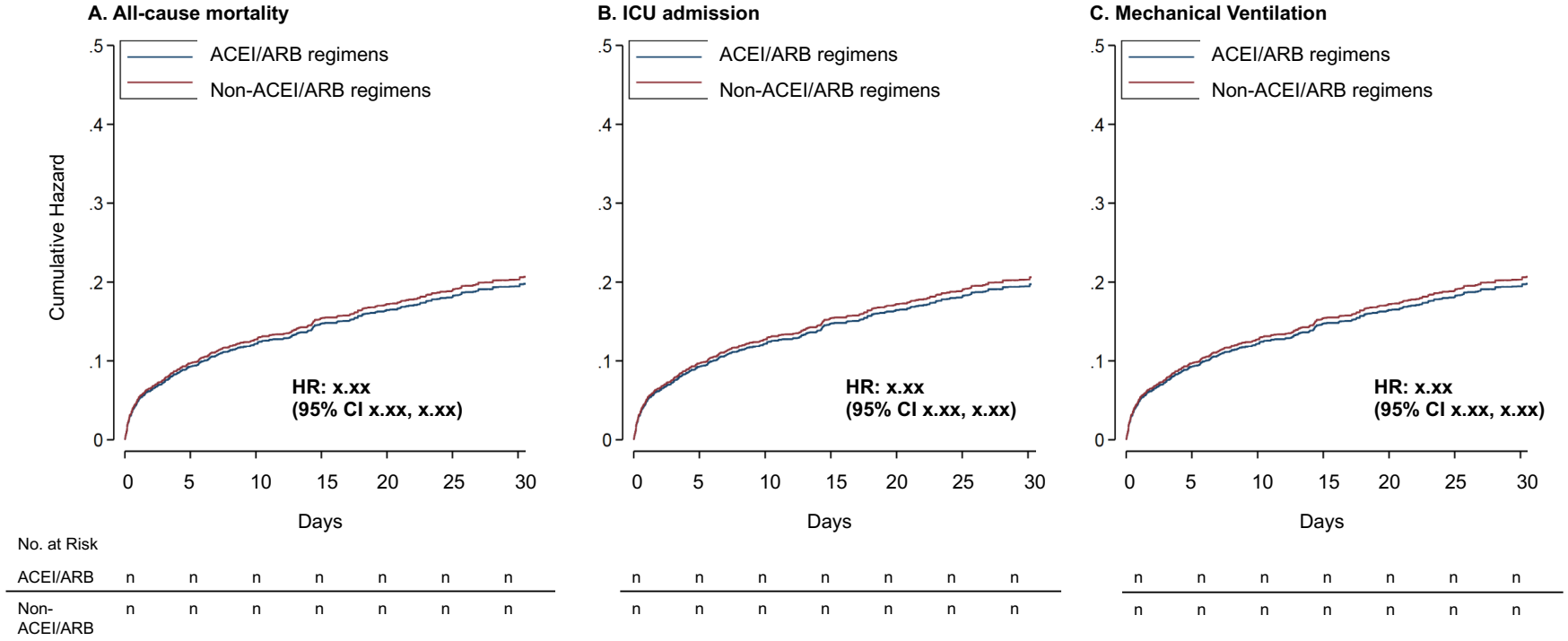
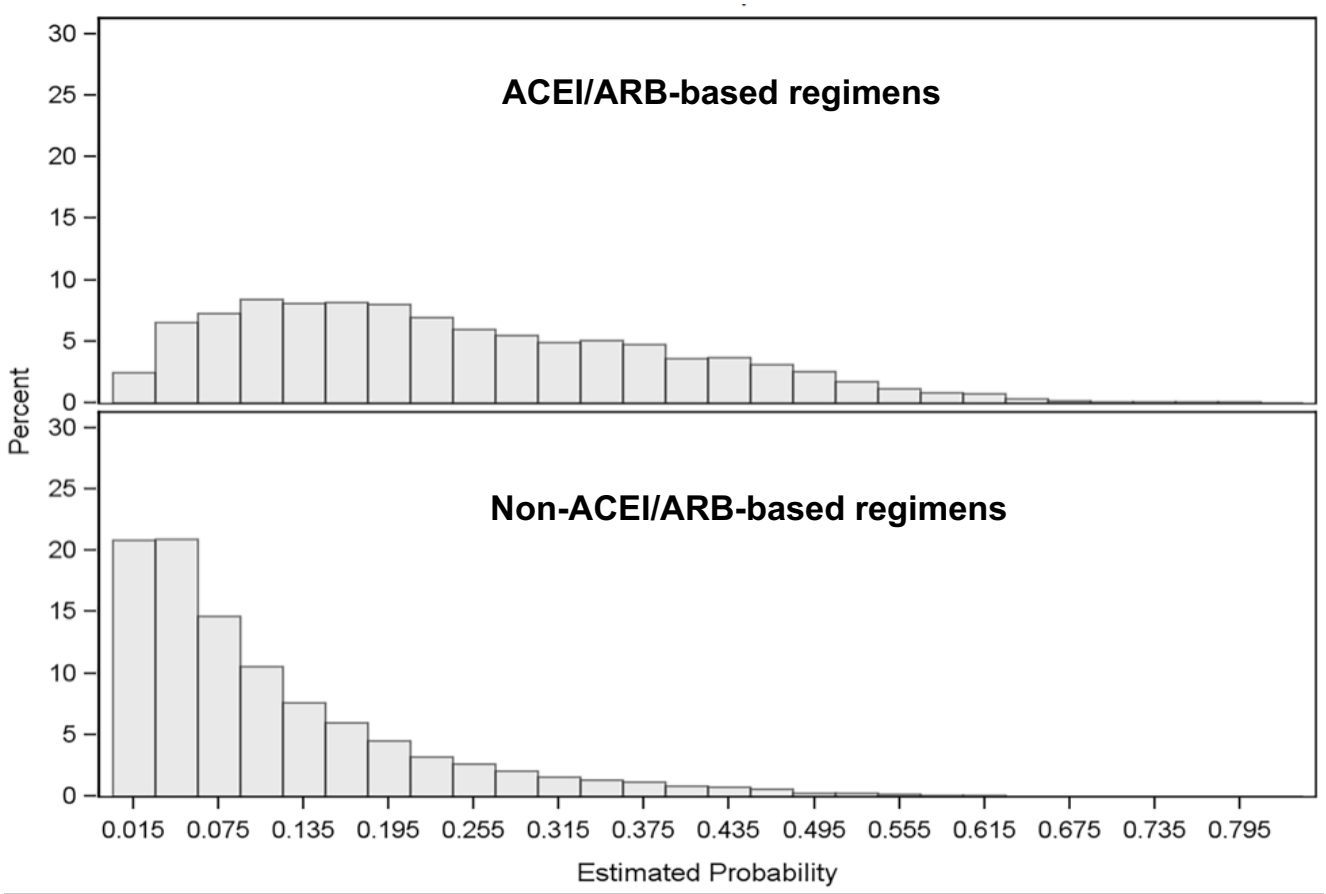


Figure 6: Matching weight-adjusted cumulative hazard curves (ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens) for experiencing all-cause mortality among outpatient Veterans who are hospitalized for COVID-19.



Aim 2.1 Supplemental Figures

Supplemental Figure S7: Distribution of propensity scores among outpatient Veterans who are hospitalized for COVID-19 between the ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimen cohorts.



Supplemental Figure S8: Characteristic balance before and after propensity score weighting among outpatient Veterans who are hospitalized for COVID-19 between the ACEI/ARB-based regimens vs. non-ACEI/ARB-based regimens cohorts.

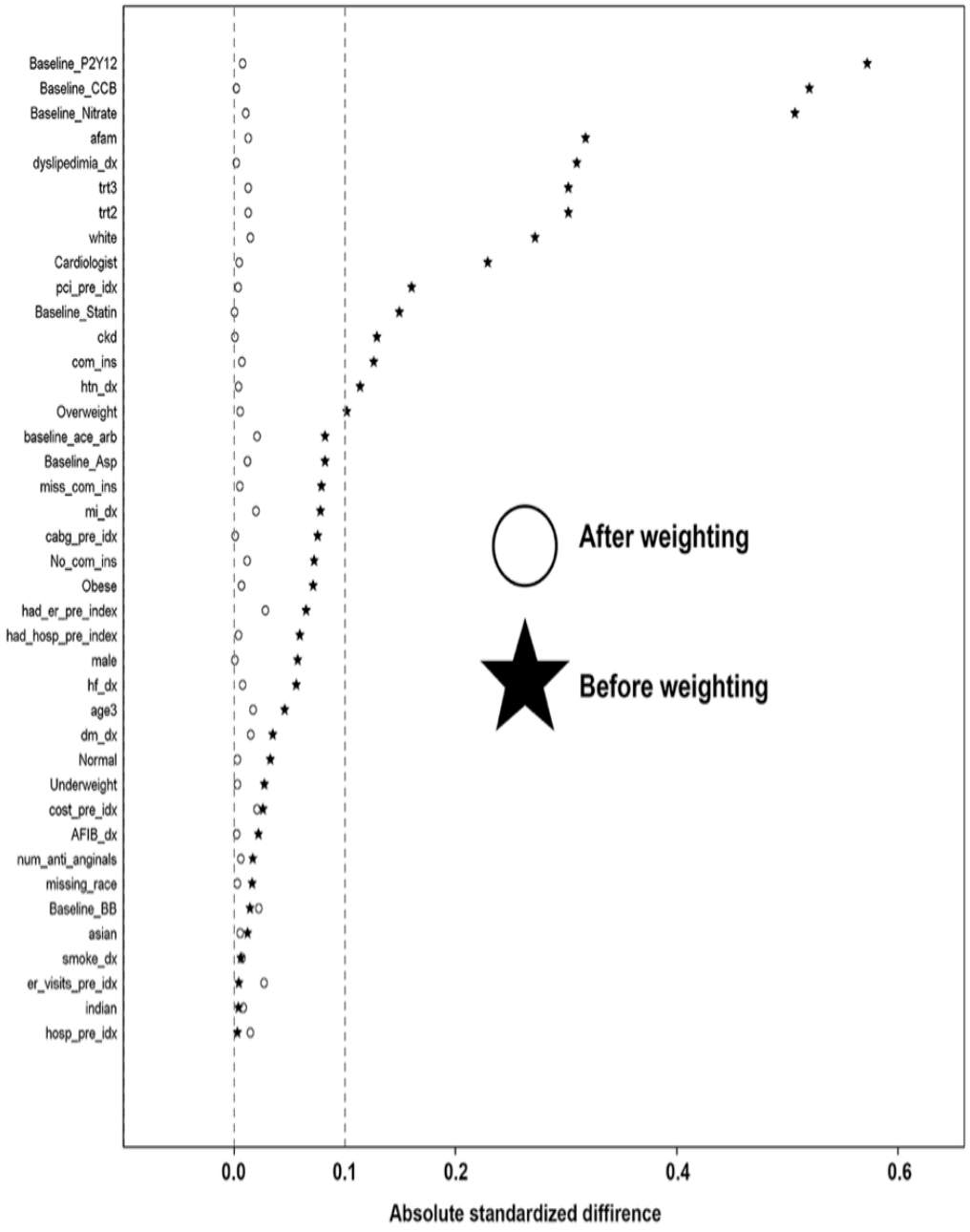
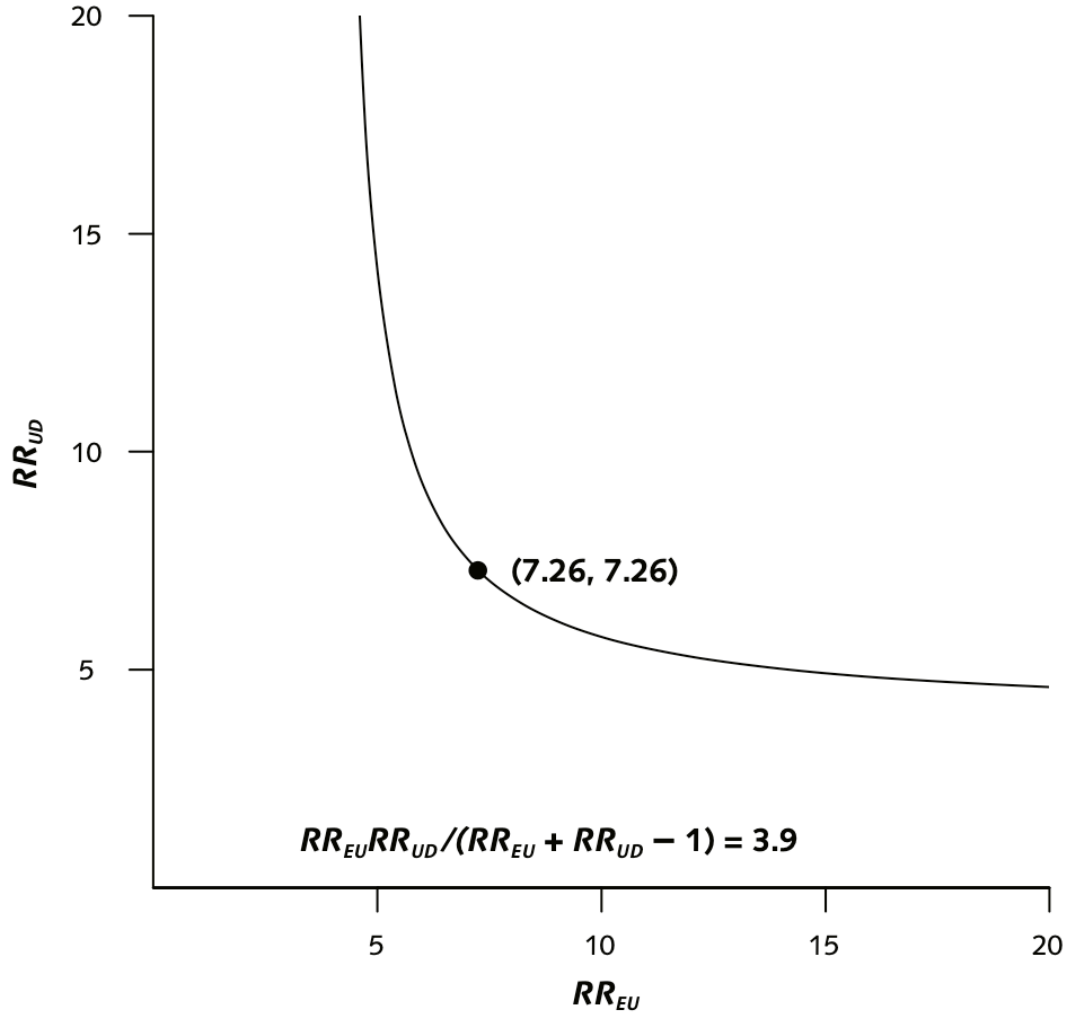


*Figure will be updated with covariates on left using the same list from Table 1.

Supplemental Figure S9: Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away an observed treatment-outcome risk ratio of RR = x.x. (Aim 2.1)



Aim 2.2 Main Figures

Figure 7: Flowchart

Editable from: https://drive.google.com/file/d/12g7r7OEd6vecy5NzUFUB4eSD73JAeOEA/view?usp=sharing

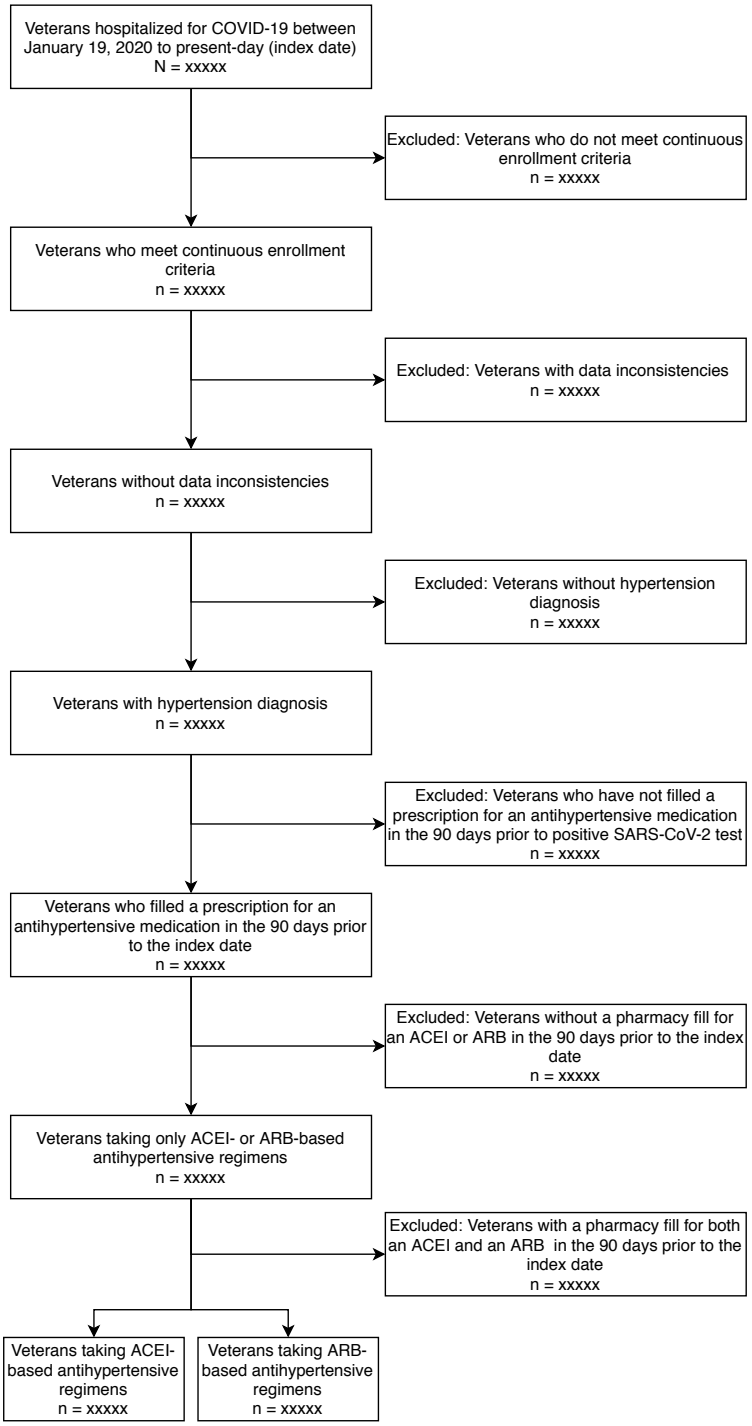
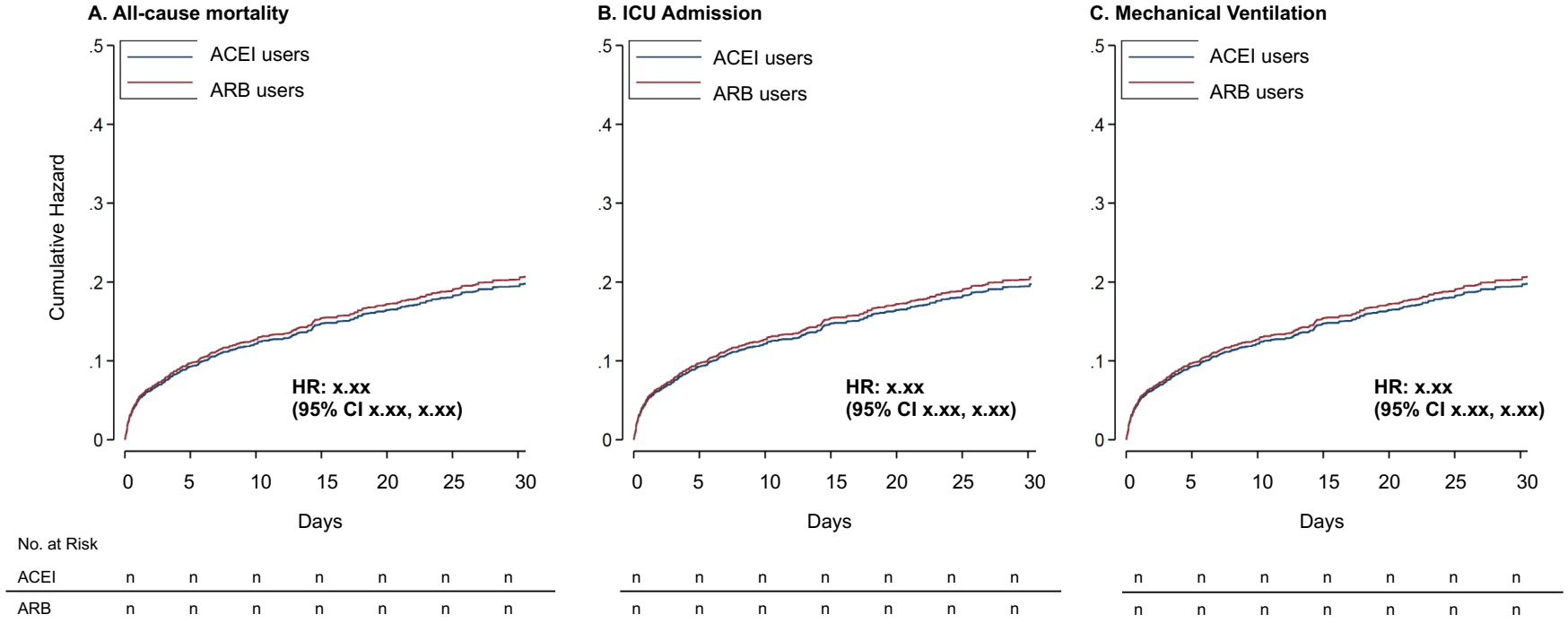
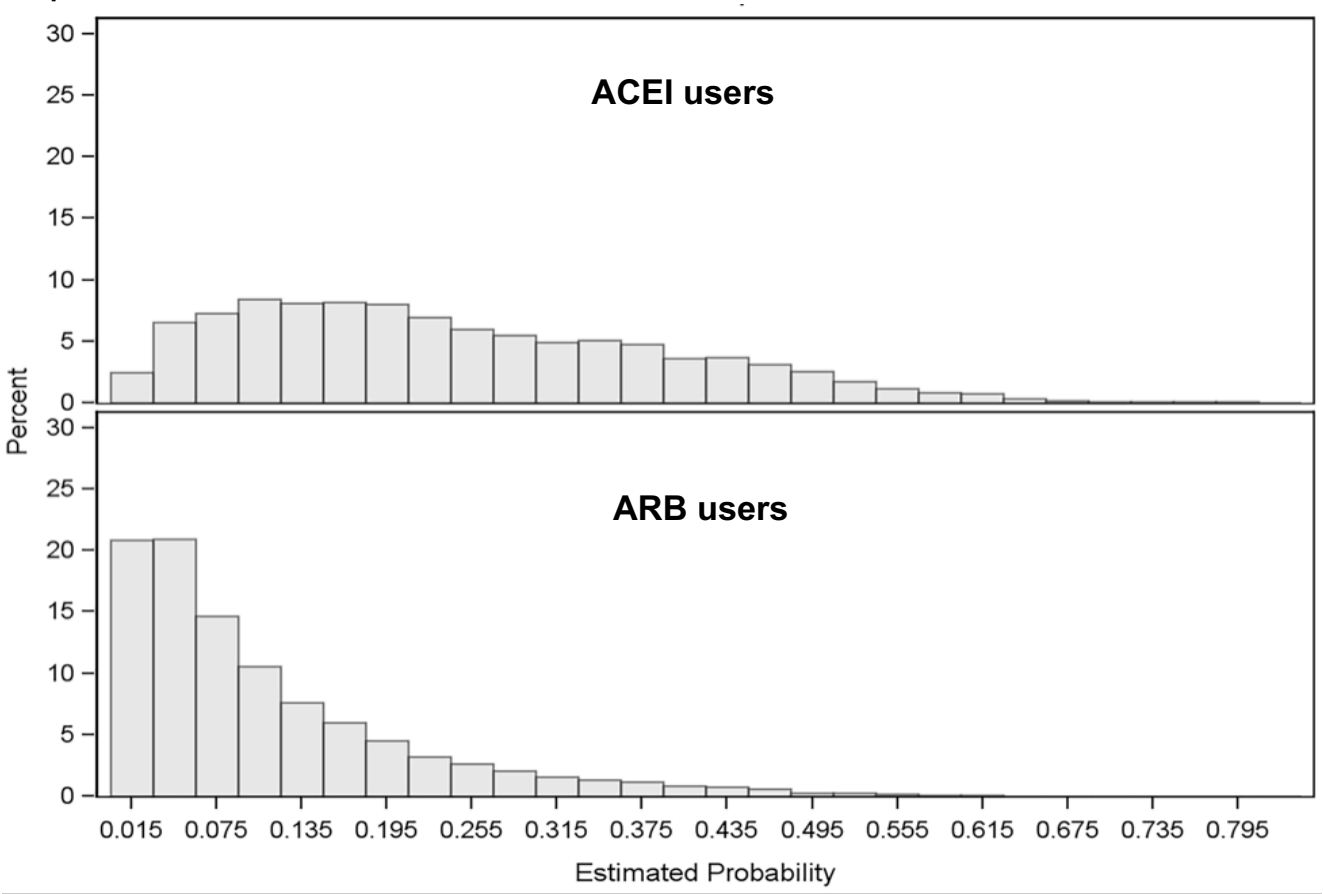


Figure 8: Matching weight-adjusted cumulative hazard curves (ACEI users vs. ARB users) for experiencing all-cause mortality among outpatient Veterans who are hospitalized for COVID-19.



Aim 2.2 Supplemental Figures

Supplemental Figure S10: Distribution of propensity scores among outpatient Veterans who are hospitalized for COVID-19 between ACEI users vs. ARB users.



Supplemental Figure S11: Characteristic balance before and after propensity score weighting among outpatient Veterans who are hospitalized for COVID-19 between the ACEI users vs. ARB users.

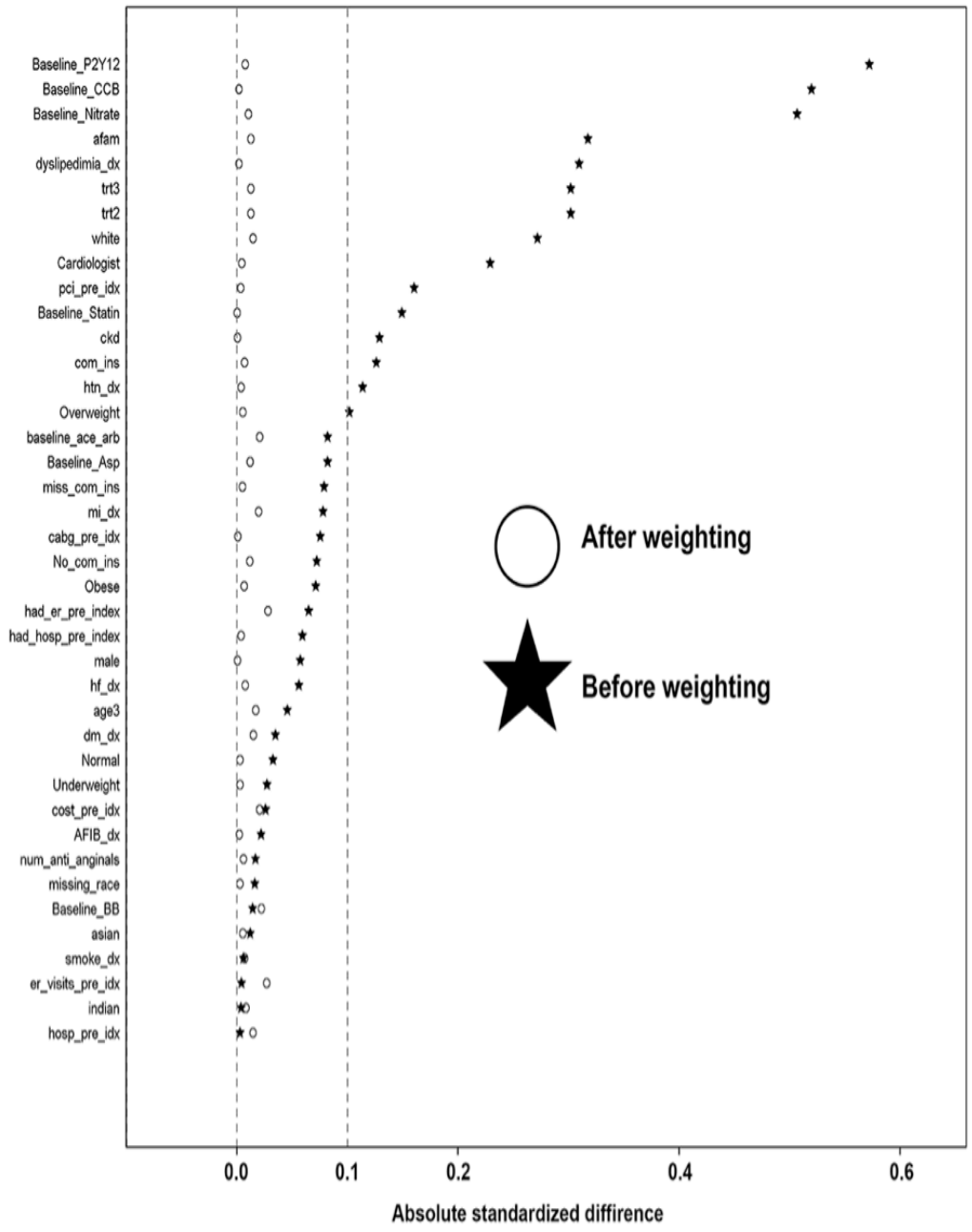
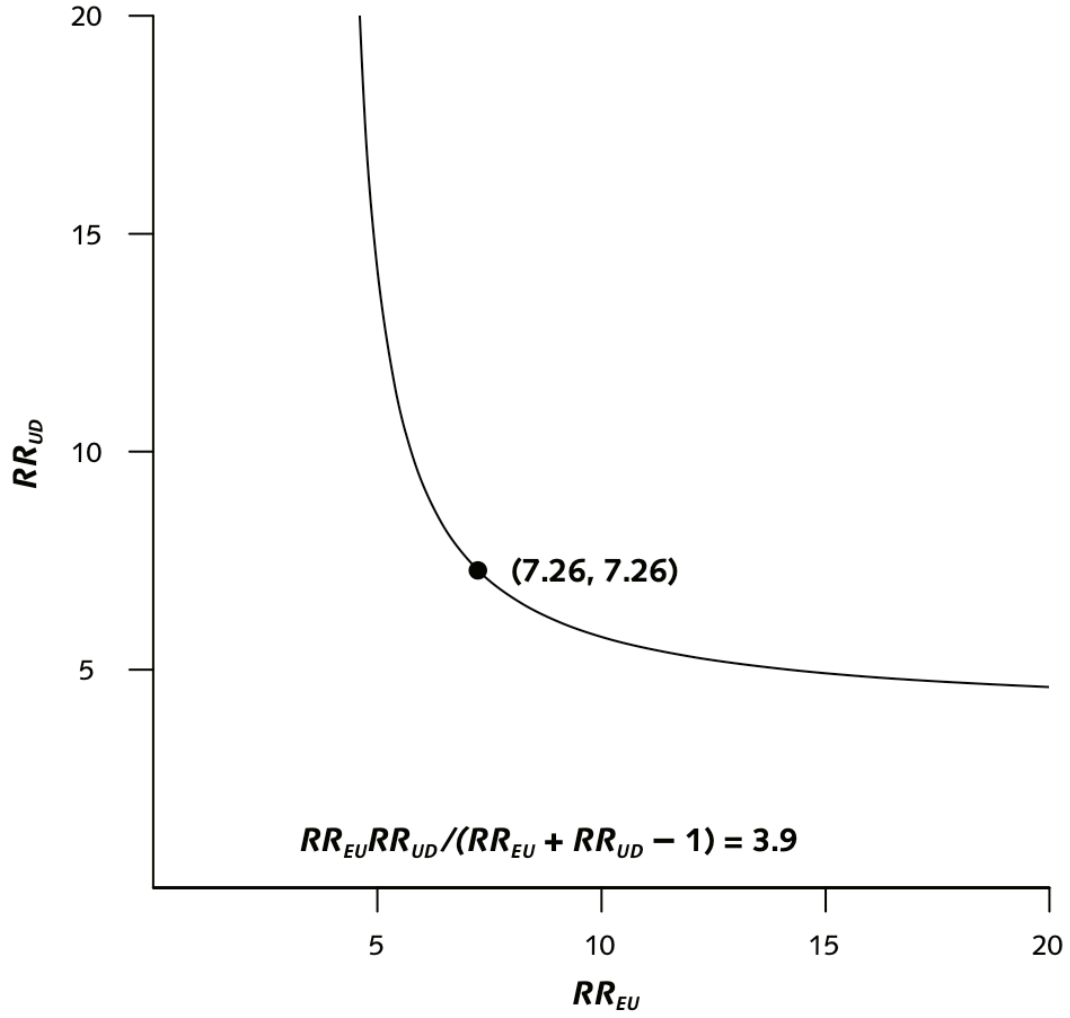


*Figure will be updated with covariates on left using the same list from Table 1.

Supplemental Figure S12: Value of the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the treatment and outcome to fully explain away an observed treatment-outcome risk ratio of RR = x.x. (Aim 2.2)



Appendix A: Variables used to define study population (Aim 1).

Variable	Definition
Index date	Date of the positive SARS-CoV-2 test.
SARS-CoV-2 positive test	Veterans with a positive SARS-CoV-2 test between January 19, 2020, to present-day will be identified using the VA's official SARS-CoV-2 phenotype definition, which incorporates testing external to the VA. Patients identified as "VA confirmed" and "VA probable" will be categorized as SARS-CoV-2 positive.
SARS-CoV-2 positive outpatients	Veterans with a positive SARS-CoV-2 test will be identified as above. Then, to capture outpatients who have been tested, patients will be excluded if they have been hospitalized within the 7 days before the date of the positive test.
Hypertension	Any of the following using all available claims prior to the index date: (a) ICD-9 codes: a. At least 1 inpatient claim with a discharge ICD-9 diagnosis (any position) of 401.x, 403.0x, 403.1x, 403.9x. b. ≥2 outpatient claims with an ICD-9 diagnosis code of 401.x, 403.0x, 403.1x, 403.9x in any position at least 30 days apart (b) ICD-10 codes: a. 1 inpatient claim with an ICD-10 discharge diagnosis code of I10, I12.0, I12.9 in any discharge diagnosis position b. ≥2 outpatient claims with an ICD-10 diagnosis code of I10, I12.0, I12.9 in any position at least 30 days apart
Treated hypertension	Having hypertension, as defined above, and currently taking antihypertensive medication, as defined as a pharmacy fill for an antihypertensive medication within 90 days prior to the index date (see Appendix E for list of medication classes).
Compelling indication for ACEI or ARB	Individuals with diabetes, stroke, chronic kidney disease, heart failure with reduced ejection fraction, or coronary heart disease as defined in Appendix B will be excluded from the population for Aim 1.1.

Appendix B. Variables used to define baseline covariates (Aim 1).

Variable	Definition
Age	Age of Veterans calculated on the index date based on the date of birth.
Sex	Male or female
Race-ethnicity	Non-Hispanic Black, Non-Hispanic White, Hispanic, Asian, and Other/Missing
Area level income	Using ZIP and FIPS codes based on data obtained from the American Community Survey. The variable ZCTA was matched to ZIP code in the American Community Survey. If ZCTA and ZIP did not match, then FIPS code (county level) from the American Community Survey was used.
Veterans Integrated Service Network	Defined by receipt of care in one of the 23 VISNs. Will be categorized into 4 regions after data query: Northeast, Southeast, Continental, and Pacific according to the VA regional offices map.[13] The Northeast region is comprised of VISNs 1, 2, 4, 5, 10, and 12. The Southeast region is comprised of VISNs 5, 6, 7, 8, 9, and 16. The Continental region is comprised of VISNs 15, 17, 18, 19, and 23. Finally, the Pacific region is comprised of VISNs 20, 21, and 22.
Current Smoking	Any of the following within one year prior to the index date: (a) ICD-9 codes: a. ≥1 hospitalization with a discharge diagnosis code of tobacco use (ICD-9 CM diagnosis code of 305.1, 649.0x, 989.84, or V15.82) in any discharge position b. ≥1 physician evaluation and management visit with a diagnosis code of tobacco use (ICD-9-CM diagnosis code of 305.1, 649.0x, 989.84, or V15.82) in any discharge position (b) ICD-19 codes: a. ≥1 hospitalization with a discharge diagnosis code of tobacco use (ICD-10 CM diagnosis code of F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291, or Z87.891) in any discharge position b. ≥1 outpatient visit with a diagnosis code of tobacco use (ICD-10 CM diagnosis code of F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291, or Z87.891) in any discharge position (c) ≥1 hospitalization with a discharge diagnosis code or physician evaluation and management visit of tobacco use with a CPT code of 99406, 99407, G0436, G0437, G9016, S9453, S4995, G9276, G9458, 1034F, 4004F, 4001F (d) ≥1 pharmacy claim for nicotine or varenicline.
Insurance type	Coded as government (Medicare, Medicaid), private (all insurance external to Medicare/Medicaid), none, and unknown.
Priority group status	Coded as 1 through 9 or multiple.
Height	Veteran's height (in m) on the index date or the date closest to the index date during the one-year pre-index period. Retain values that are within 3 standard deviations of the mean of all heights for the cohort. For Veterans without observations within 3 standard deviations of the mean, other values will be accepted as valid if for height, there are at least 2 identical observations. Otherwise, code as missing.
Weight	Veteran's weight (in kg) on the index date or the date closest to the index date during the one-year pre-index period. Retain values that are within 3 standard deviations of the mean of all weights for the cohort. For Veterans without observations within 3 standard deviations of the mean, other values will be accepted as valid if for weight, there are at least 2 observations within 5 pounds. Otherwise, code as missing.
Body mass index	The patient's body mass index on or closest to the index date during the one-year pre-index period. Height and weight measurements do not need to be on the same day. This variable will be calculated from height and weight observations as weight (in kilograms) divided by height (in meters, squared).

Systolic blood pressure	Most recent proximal SBP value corresponding to an outpatient encounter in cardiology, renal, and primary care settings in the one-year pre-index period (including the index date). SBP values will be dropped if any of the following was true: Missing value (either SBP or DBP), systolic less than diastolic, systolic >300 mm Hg, and systolic <60 mm Hg.
Diastolic blood pressure	Most recent proximal DBP value corresponding to an outpatient encounter in cardiology, renal, and primary care settings in the one-year pre-index period (including the index date). DBP values will be dropped if any of the following was true: Missing value (either SBP or DBP), diastolic greater than systolic, diastolic <30 mm Hg, and or diastolic >180 mm Hg.
Heart rate	Most recent proximal heart rate/pulse value corresponding to an outpatient encounter in the one-year pre-index period (including the index date).
Total cholesterol	The total cholesterol value closest to the index date in the one-year pre-index period. Defined using OMOP's mapping where LOINC is '2093-3'.
HDL-C level	The HDL-C value closest to the index date in the one-year pre-index period. Defined using OMOP's mapping where LOINC is '2085-9'.
LDL-C level	The LDL-C value closest to the index date in the one-year pre-index period. Defined using OMOP's mapping where LOINC is '13457-7','18262-6','2089-1','2574-2','9346-8'.
Triglyceride level	The triglyceride value closest to the index date in the one-year pre-index period. Defined using OMOP's mapping where LOINC is '2571-8'.
Hemoglobin A1c	The glycated hemoglobin (i.e., "hemoglobin A1c") value closest to the index date in the one-year pre-index period. Defined using OMOP's mapping where LOINC is '4548-4'.
Serum creatinine	The serum creatinine value closest to the index date in the one-year pre-index period. Defined using OMOP's mapping where LOINC is '33914-3'.
Estimated glomerular filtration rate	The estimated glomerular filtration rate closest to the index date in the one-year pre-index period. The VA calculates eGFR using the Modified Diet in Renal Disease equation.[14]
Serum potassium	The serum potassium value closest to the index date in the one-year pre-index period. Defined using OMOP's mapping where LOINC is '6298-4', '2823-3'.
Diabetes	Any of the following using all available claims prior to the index date: (a) ICD-9 codes: a. At least 1 inpatient claim with a discharge ICD-9 diagnosis (any position) of 250.xx, 357.2, 362.0x, or 366.41. b. At least 2 carrier claims, carrier line or outpatient claims with ICD-9 diagnoses (any position) of 250.xx, 357.2, 362.0x, or 366.41, linked to an ambulatory physician evaluation and management claim, with the 2 claims occurring at least 7 days apart. (b) ICD-10 codes: a. At least 1 inpatient claim with a discharge ICD-10 diagnosis (any position) of 'E0836', 'E08.42', 'E09.36', 'E09.42', 'E10.10', 'E10.11', 'E10.29', 'E10.311', 'E10.319', 'E10.36', 'E10.39', 'E10.40', 'E10.42', 'E10.51', 'E10.618', 'E10.620', 'E10.621', 'E10.622', 'E10.628', 'E10.630', 'E10.638', 'E10.641', 'E10.649', 'E10.65', 'E10.69', 'E10.8', 'E10.9', 'E11.00', 'E11.01', 'E11.29', 'E11.311', 'E11.319', 'E11.329', 'E11.339', 'E11.349', 'E11.359', 'E11.36', 'E11.39', 'E11.40', 'E11.42', 'E11.51', 'E11.618', 'E11.620', 'E11.621', 'E11.622', 'E11.628', 'E11.630', 'E11.638', 'E11.641', 'E11.649', 'E11.65', 'E11.69', 'E11.8', 'E11.9', 'E13.10', 'E13.36', 'E13.42'.

	b. At least 2 carrier claims, carrier line or outpatient claims with ICD-10 diagnoses (any position) of 'E0836', 'E08.42', 'E09.36', 'E09.42', 'E10.10', 'E10.11', 'E10.29', 'E10.311', 'E10.319', 'E10.36', 'E10.39', 'E10.40', 'E10.42', 'E10.51', 'E10.618', 'E10.620', 'E10.621', 'E10.622', 'E10.628', 'E10.630', 'E10.638', 'E10.641', 'E10.649', 'E10.65', 'E10.69', 'E10.8', 'E10.9', 'E11.00', 'E11.01', 'E11.29', 'E11.311', 'E11.319', 'E11.329', 'E11.339', 'E11.349', 'E11.359', 'E11.36', 'E11.39', 'E11.40', 'E11.42', 'E11.51', 'E11.618', 'E11.620', 'E11.621', 'E11.622', 'E11.628', 'E11.630', 'E11.638', 'E11.641', 'E11.649', 'E11.65', 'E11.69', 'E11.8', 'E11.9', 'E13.10', 'E13.36', 'E13.42', linked to an ambulatory physician evaluation and management claim, with the 2 claims occurring at least 7 days apart. (c) At least 1 pharmacy claim for an oral antidiabetic drug fill or insulin.
Chronic kidney disease [15,16]	Any of the following using all available claims prior to the index date: (c) ICD-9 codes: a. At least 1 inpatient claim with a discharge ICD-9 diagnosis (any position) of 250.xx, 357.2, 362.0x, or 366.41. b. At least 2 carrier claims, carrier line or outpatient claims with ICD-9 diagnoses (any position) of 250.xx, 357.2, 362.0x, or 366.41, linked to an ambulatory physician evaluation and management claim, with the 2 claims occurring at least 7 days apart. (d) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code of chronic kidney disease (ICD-10 diagnosis code of 'A18.11', 'A52.75', 'C6.49', 'C6.89', 'D30.00', 'D41.00', 'D41.20', 'D59.3', 'E10.21', 'E10.29', 'E11.21', 'E11.29', 'E74.8', 'I12.0', 'I129', 'I13.0', 'I13.10', 'I13.11', 'I13.2', I70.1', 'I72.2', 'K76.7', 'M10.30', 'N00.3', 'N00.8', 'N00.9', 'N01.3', 'N02.2', 'N03.2', 'N03.3', 'N03.5', 'N03.8', 'N03.9', 'N04.0', 'N04.3', 'N04.4', 'N04.8', 'N04.9', 'N05.2', 'N05.5', 'N05.8', 'N05.9', 'N08.x', 'N13.30', 'N17.0', 'N17.1', 'N17.2', 'N17.8', 'N17.9', 'N18.1', 'N18.2', 'N18.3', 'N18.4', 'N18.5', 'N18.6', 'N18.9', 'N19.x', 'N25.0', 'N25.1', 'N25.81', 'N25.89', 'N25.9', 'N26.9','Q61.02', 'Q61.19', 'Q61.2', 'Q61.3', 'Q61.4', 'Q61.5', 'Q61.8', 'Q62.10', 'Q62.11', 'Q62.12', 'Q62.31', 'Q62.39', 'R94.4') in any discharge diagnosis position. b. ≥1 physician evaluation and management visit with a diagnosis code of chronic kidney disease (ICD-10-CM diagnosis code of 'A18.11', 'A52.75', 'C6.49', 'C6.89', 'D30.00', 'D41.00', 'D41.20', 'D59.3', 'E10.21', 'E10.29', 'E11.21', 'E11.29', 'E74.8', 'I12.0', 'I129', 'I13.0', 'I13.10', 'I13.11', 'I13.2', I70.1', 'I72.2', 'K76.7', 'M10.30', 'N00.3', 'N00.8', 'N00.9', 'N01.3', 'N02.2', 'N03.2', 'N03.3', 'N03.5', 'N03.8', 'N03.9', 'N04.0', 'N04.3', 'N04.4', 'N04.8', 'N04.9', 'N05.2', 'N05.5', 'N05.8', 'N05.9', 'N08.x', 'N13.30', 'N17.0', 'N17.1', 'N17.2', 'N17.8', 'N17.9', 'N18.1', 'N18.2', 'N18.3', 'N18.4', 'N18.5', 'N18.6', 'N18.9', 'N19.x', 'N25.0', 'N25.1', 'N25.81', 'N25.89', 'N25.9', 'N26.9','Q61.02', 'Q61.19', 'Q61.2', 'Q61.3', 'Q61.4', 'Q61.5', 'Q61.8', 'Q62.10', 'Q62.11', 'Q62.12', 'Q62.31', 'Q62.39', 'R94.4') in any position. (e) Estimated glomerular filtration rate of <60 mL/min/1.73m^2. The eGFR reading used is the most recent within the one-year pre-index period. To account for data/reading errors, only eGFR values between 0 and 250 will be considered.
Heart failure with reduced ejection fraction	Defined as left ventricular ejection fraction (LVEF) value <=40% in the one-year pre-index period. If no LVEF measurement is available, then we will look for the presence of one of the following using all available claims before the index date: following ICD-10 codes indicating systolic heart failure using all available claims prior to the index date: (a) ICD-9 codes: a. ≥ 1 inpatient claim with ICD-10 diagnoses (any position) of '428.0x', '428.1x', '428.2x', '428.4x' or

	b. ≥ 2 outpatient or carrier claims on separate calendar days with ICD-10 diagnoses (any position) of '428.0x', '428.1x', '428.2x', '428.4x' (b) ICD-10 codes: a. ≥ 1 inpatient claim with ICD-10 diagnoses (any position) of 'I50.1', 'I50.2x', 'I50.4x', 'I50.9', or b. ≥ 2 outpatient or carrier claims on separate calendar days with ICD-10 diagnoses (any position) of 'I50.1', 'I50.2x', 'I50.4x', 'I50.9' (c) At least one prescription for Entresto® (sacubitril/valsartan) in the prior 90 days.
History of CHD [17]	Any of the following using all available claims prior to the index date: (a) ICD-9 codes: a. At least 1 inpatient claim with a discharge ICD-9 diagnosis (any position) of 410.xx-414.xx, V45.81 or V45.82. b. At least 2 carrier claims, carrier line or outpatient claims with ICD-9 diagnoses (any position) of 410.xx-414.xx, V45.81 or V45.82. (b) ICD-10 codes: a. An inpatient claim diagnosis codes of I20.0, I21.xx, I22.xx, I24.0, I24.8, I24.9, I25.10, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1 or Z9861. b. An outpatient or carrier file claim, linked to E&M code, with diagnosis codes of codes I20.0, I21.xx, I22.xx, I24.0, I24.8, I24.9, I25.10, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.3, I25.41, I25.42, Z95.1 or Z98.61. Veterans who met the definition of a prior coronary revascularization, as defined below, will be also considered to have a history of CHD.
Prior coronary revascularization	Defined by ≥ 1 inpatient or outpatient procedure with a current procedure terminology (CPT) code for coronary revascularization (33510-33519, 33521-33523, 33530, 33533-33536, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, and 92944), an ICD-9 procedure code of 00.66, 36.0, 36.01-36.19, 36.2, or an ICD-10 procedure code starting with any of the following 4 digits: 0210, 0211, 0212, 0213, 0270, 0271, 0272, 0273, 02C0, 02C1, 02C2, 02C3, 3E07 using all available claims prior to the index date. In addition to having 1 inpatient or outpatient procedure, Veterans are required to meet at least 1 of the following criteria: a) Have no inpatient claims with a diagnosis code for acute myocardial infarction (ICD9 codes 410.x0 or 410.x1 or ICD10 codes I21.xx or I22.xx) within 60 days prior to the procedure. b) Have primary discharge diagnosis code for non-elective CHD-related hospitalization prior to the index date (arrhythmia [ICD-9 diagnosis code of 427.xx, except 427.5 or ICD-10 diagnosis code of I47.1, I47.2, I47.9, I48.91, I48.92, I49.01, I49.02, I49.1, I49.3, I49.40, I49.49, I49.5, I49.8, I49.9, R00.1], cardiac arrest [ICD-9 diagnosis code of 427.5 or ICD-10 diagnosis code of I46.9], heart failure [ICD-9 diagnosis code of 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x or ICD-10 diagnosis code of I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9], and unstable angina [ICD-9 diagnosis code of 411.xx or ICD-10 diagnosis code of I20.0, I24.0, I24.1, I24.8]).
History of Stroke[18]	Any of the following using all available claims prior to the index date: (a) ICD-9 codes:

	a. ≥1 inpatient claim with a discharge ICD-9 diagnosis (primary or secondary position) of 433.x1 or 434.x1. b. ≥1 outpatient or carrier claim with ICD-9 diagnoses (any position) of 433.x1 or 434.x1, linked by CLAIM_ID to an ambulatory physician evaluation and management claim. c. ≥1 claim with ICD-9 diagnoses (any position) of 433.x1 or 434.x1 in other file types (Home Health Agency [HHA], durable medical equipment [DME], Hospice, SNF). (b) ICD-10 codes: a. ≥1 inpatient ICD-10 diagnosis (primary or secondary position) I63.xx b. ≥1 outpatient or carrier claim with ICD-10 diagnoses (any position) of I63.xx linked by CLAIM_ID to an ambulatory physician evaluation and management claim c. ≥1 claim with ICD-10 diagnoses (any position) of I63.xx in other file types (Home Health Agency [HHA], durable medical equipment [DME], Hospice, SNF). d. ≥ 1 inpatient ICD-10 procedure code in ('03CH0ZZ', '03CH4ZZ', '03CJ0ZZ', '03CJ4ZZ', '03CK0ZZ', '03CK4ZZ', '03CL0ZZ', '03CL4ZZ', '03CM0ZZ', '03CM4ZZ', '03CN0ZZ', '03CN4ZZ', '03RH07Z', '03RH0JZ', '03RH0KZ', '03RH47Z', '03RH4JZ', '03RH4KZ', '03RJ07Z', '03RJ0JZ', '03RJ0KZ', '03RJ47Z', '03RJ4JZ', '03RJ4KZ', '03RK07Z', '03RK0JZ', '03RK0KZ', '03RK47Z', '03RK4JZ', '03RK4KZ', '03RL07Z', '03RL0JZ', '03RL0KZ', '03RL47Z', '03RL4JZ', '03RL4KZ', '03RM07Z', '03RM0JZ', '03RM0KZ', '03RM47Z', '03RM4JZ', '03RM4KZ', '03RN07Z', '03RN0JZ', '03RN0KZ', '03RN47Z', '03RN4JZ', '03RN4KZ') (c) CPT codes: a. ≥1 inpatient or outpatient claim with a CPT code for carotid revascularization (35301, 35390, 37215, 37216, 0005T, 0075T, or 0076).
History of PAD	Any of the following using all available claims prior to the index date: (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code of peripheral vascular disease (ICD-9-CM diagnosis codes 440.20-440.24, 440.31, 444.2, 443.9, or 444.81) in any position, or b. ≥2 physician evaluation and management outpatient or carrier claims with an ICD-9-CM diagnosis code of peripheral vascular disease on separate days, or c. ≥1 inpatient, outpatient or carrier claim with a CPT code 37205 or 75962. (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code of peripheral vascular disease (ICD-10-CM diagnosis codes 'I70.209', 'I70.219, 'I70.229', 'I70.25', 'I70.269', 'I70.499', 'I73.9') or b. ≥2 physician evaluation and management outpatient or carrier claims with an ICD-10-CM diagnosis code of peripheral vascular disease on separate days, or (c) ≥1 inpatient, outpatient or carrier claim with a CPT code 37205 or 75962.
History of ASCVD	Defined by a history of CHD, cerebrovascular disease, or peripheral artery disease, as defined above.
History of renal transplant	Any of the following using all available claims prior to the index date: (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code V42.0 in any position, or

	b. ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code V42.0 (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code Z94.0 in any position, or b. ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code Z94.0.
Atrial fibrillation[19]	Any of the following using all available claims prior to the index date: (c) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code 427.31 in any position, or b. ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code 427.31 (d) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code of I48.0, I48.2, I48.91 in any position, or ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code I48.0, I48.2, I48.91.
Chronic obstructive pulmonary disease[20]	Any of the following using all available claims prior to the index date: (e) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code 491-492 or 496 in any position, or b. ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code 491-492 or 496 (f) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code of J41-J44 in any position, or (a) ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code J41-J44
Asthma[21]	Any of the following using all available claims prior to the index date: (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code 493 in any position, or b. ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code 493 (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code of J45 in any position, or (a) ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code J45
History of depression[22]	Any of the following using all available claims prior to the index date: (a) ICD-9 codes: a. ≥1 inpatient claim with a discharge diagnosis code 296.2, 296.3, 296.5, 300.4, 309.x, 311 in any position, or b. ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code 296.2, 296.3, 296.5, 300.4, 309.x, 311 (b) ICD-10 codes: a. ≥1 inpatient claim with a discharge diagnosis code of F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2in any position, or (a) ≥2 physician evaluation and management outpatient or carrier claims with a diagnosis code F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2

Charlson Comorbidity Index[23]	Continuous variable to represent chronic disease burden. Calculated according to methods described in Quan et al (incorporates Elixhauser and Deyo comorbidities).
Current statin use	Defined as one or more pharmacy fills for a statin in the 90 days prior to each Veteran's index date (atorvastatin, rosuvastatin, simvastatin, fluvastatin, pitavastatin, pravastatin, or lovastatin).
Current aspirin use	Defined as one or more pharmacy fills for aspirin in the 90 days prior to each Veteran's index date.
Antihypertensive medication daily dose	Calculated for each antihypertensive medication being taken. Described as milligrams of drug taken per day. We will first parse the dosage value then use the quantity and days supplied variables to inform the parsed dose value (if partial or multiple pills are being taken per day, for example).
Antihypertensive Modified Therapeutic Intensity Score	Continuous variable calculated for each antihypertensive medication being taken. Calculated using the most proximal prescription dispensed in the pre-index period using the daily dose as calculated above, divided by the maximum daily dose per the 2017 ACC/AHA blood pressure guideline. See Appendix F.

Appendix C: Variables used to define main exposures (Aim 1).

Variable	Definition
Antihypertensive – non-ACEI or ARB-based regimen (Aim 1.1)	Defined as one or more pharmacy fills for an oral non-ACEI or ARB medications in the 90 days (± 14 days) prior to each Veteran's index date and categorized by class as aldosterone receptor antagonist, beta-blocker, calcium channel blocker, centrally-acting drug, direct arterial vasodilator, direct renin inhibitor, thiazide diuretic, loop diuretic, and potassium sparing diuretic. See Appendix E for specific drug names within each class. Exclude non-oral products.
Antihypertensive – ACEI/ARB-based regimen (Aim 1.1)	Defined as one or more pharmacy fills for an oral ACEI or an ARB in the 90 days (± 14 days) prior to each Veteran's index date. See Appendix E for specific drug names within each class. Exclude non-oral products. Exclude sacubitril/valsartan (Brand name: Entresto®) from ARB exposures.
Antihypertensive – ACEI (Aim 1.2)	Defined as one or more pharmacy fills for an oral ACEI in the 90 days (± 14 days) prior to each Veteran's index date. See Appendix E for specific drug names within each class. Exclude non-oral products.
Antihypertensive – ARB (Aim 1.2)	Defined as one or more pharmacy fills for an oral ARB in the 90 days (± 14 days) prior to each Veteran's index date. See Appendix E for specific drug names within each class. Exclude non-oral products. Exclude sacubitril/valsartan (Brand name: Entresto®) from ARB exposures.
Antihypertensive medication daily dose	Calculated for each antihypertensive medication being taken. Described as milligrams of drug taken per day. We will first parse the dosage value then use the quantity and days supplied variables to inform the parsed dose value (if partial or multiple pills are being taken per day, for example).
Antihypertensive Modified Therapeutic Intensity Score	Continuous variable calculated for each antihypertensive medication being taken. Calculated using the most proximal prescription dispensed in the pre-index period using the daily dose as calculated above, divided by the maximum daily dose per the 2017 ACC/AHA blood pressure guideline. See Appendix F.
Number of antihypertensive medication fills	Calculated for each antihypertensive medication being taken. Number of antihypertensive medication fills in the most proximal 12 months prior each Veteran's index date. Used only in a sensitivity analysis.
Alternative exposure definition 1	Used for a sensitivity analysis. Described as a dichotomous variable (yes=1; no=0). Calculated as "yes" if the patient had two pharmacy fills for the primary exposure of interest in the 180 (± 14 days) days prior to the index date. The pharmacy fills do not have to be consecutive.
Alternative exposure definition 2	Used for a sensitivity analysis. Described as a dichotomous variable (yes=1; no=0). Calculated as "yes" if the patient had 1 pharmacy fill in the 90 days (± 14 days) prior to the index date for the primary exposure of interest and 3 consecutive pharmacy fills for the primary exposure of interest in the one year (± 14 days) prior to the index date. A "consecutive" fill is defined as pharmacy fills with less than 30 days of gap in days' supply between the fills.
Alternative exposure definition 3	Used for a sensitivity analysis. Described as a dichotomous variable (yes=1; no=0). Calculated as "yes" if a prescription for the primary exposure of interest was dispensed before the index date with a days' supply that met or exceeded the index date. Calculated as "no" if prescription was dispensed before the index date with a days' supply that did not meet or exceed the index date.

Appendix D: Variables used to define outcomes (Aim 1).

Variable	Definition
Primary Outcomes	
All-cause hospitalization	A binary variable indicating the occurrence of one or more all-cause hospitalization(s) during the post index period.
Time to all-cause hospitalization	Integer number of days from index date to first all-cause hospitalization (inpatient claim/encounter) post the index date.
All-cause mortality	A binary variable indicating all-cause mortality during the post index period.
Time to all-cause mortality	Integer number of days from index date to all-cause mortality post the index date.
Primary composite outcome	Composite of time to all-cause hospitalization or all-cause mortality.
Secondary Outcomes	
ICU admission	A binary variable indicating admission to an intensive care unit during the first hospitalization post-index date.
Negative Control Outcomes	
Severe gastrointestinal bleeding[24]	Occurrence of any of the following codes associated with a hospital (inpatient) encounter post-index date: (a) ICD-10 code in any position for K25-K28, K92.2, AND (b) CPT code 78278, 7424.x, 7425.x, 74260, 435.xx, 436.xx, 440.xx, 44120, 446.xx
Urinary tract infection	Presence of a positive urine culture, defined as urine culture with at least one organism with a quantitative count of $>10^5$ CFU/mL of any of the following uropathogens: Escherichia coli, Pseudomonas aeruginosa, Enterococcus spp., Klebsiella spp., Enterobacter spp., Proteus spp., Citrobacter spp., Providentia spp., Morganella spp., Serratia spp., Candida spp. during the hospitalization post-index date (including the index date) OR Presence of the ICD10 codes N10, N30, N39, A41.9 using all available claims post the index date.

Appendix E: List of Antihypertensive Medications by Class

Antihypertensive medication class	Medication Name
Angiotensin converting enzyme inhibitor	benazepril
	captopril
	enalapril
	fosinopril
	lisinopril
	moexipril
	perindopril
	quinapril
	ramipril
	trandolapril
Angiotensin-II receptor blocker	azilsartan
	candesartan
	eprosartan
	irbesartan
	losartan
	olmesartan
	telmisartan
	valsartan*
Alpha-blocker	doxazosin
	prazosin
	terazosin
Beta-blocker	acebutolol
	nebivolol
	atenolol
	betaxolol
	bisoprolol
	metoprolol
	pindolol

	penbutolol
	carvedilol
	labetalol
	nadolol
	propranolol
	timolol
Calcium channel blocker	amlodipine
	felodipine
	isradipine
	nicardipine
	nifedipine
	nisoldipine
	diltiazem
	verapamil
Centrally-acting	clonidine
	guanabenz
	guanfacine
	methyldopa
	reserpine
Direct vasodilators	hydralazine
	minoxidil
Direct renin inhibitor	aliskiren
Aldosterone receptor antagonist	spironolactone
	eplerenone
Loop diuretic	bumetanide
	ethacrynic acid
	furosemide
	torsemide
Potassium-sparing diuretic	amiloride
	triamterene
Thiazide diuretic	bendroflumethiazide

	chlorothiazide chlorthalidone hydrochlorothiazide indapamide metolazone
*Excluding sacubitril/valsartan products.	

Appendix F: Calculation of Modified Therapeutic Intensity Score

For each antihypertensive medication being taken for each patient, a Modified Therapeutic Intensity Score will be calculated as the $\frac{\textit{Prescribed Dose}}{\textit{ACC/AHA 2017 Maximum Dose}}$.[11,12] The maximum dose will be defined using the table below based on the 2017 ACC/AHA blood pressure guideline.[25] If a drug was not listed in the 2017 ACC/AHA guideline, then the max dose as listed in the Food and Drug Administration-approved manufacturer labeling will be used.

Each medication's mTIS can be summed for a total regimen mTIS score, calculated as $\Sigma_1^n \frac{\textit{Prescribed Dose}}{\textit{ACC/AHA 2017 Maximum Dose}}$ where n is the number of antihypertensive medications.

Example: a patient on lisinopril 20 mg daily would have a mTIS for lisinopril of 20/40 = 0.5.

Table. Complete List of Antihypertensive Medications Used During SPRINT

Medication Name	Medication Class	Maximum Daily Dose
benazepril	ACEI	40
captopril	ACEI	150
enalapril	ACEI	40
fosinopril	ACEI	40
lisinopril	ACEI	40
moexipril	ACEI	30
perindopril	ACEI	16
quinapril	ACEI	80
ramipril	ACEI	20
trandolapril	ACEI	4
doxazosin	Alpha Blocker	16
prazosin	Alpha Blocker	20
terazosin	Alpha Blocker	20
azilsartan	Angiotensin II Receptor Blocker	80
candesartan	Angiotensin II Receptor Blocker	32
eprosartan	Angiotensin II Receptor Blocker	800
irbesartan	Angiotensin II Receptor Blocker	300
losartan	Angiotensin II Receptor Blocker	100
olmesartan	Angiotensin II Receptor Blocker	40
telmisartan	Angiotensin II Receptor Blocker	80
valsartan	Angiotensin II Receptor Blocker	320
acebutolol	Beta Blocker	800
nebivolol	Beta Blocker	40
atenolol	Beta Blocker	100

betaxolol	Beta Blocker	20
bisoprolol	Beta Blocker	10
metoprolol	Beta Blocker	200
pindolol	Beta Blocker	60
penbutolol	Beta Blocker	40
carvedilol	Beta Blocker	50
labetalol	Beta Blocker	800
nadolol	Beta Blocker	120
propranolol	Beta Blocker	160
timolol	Beta Blocker	60
amlodipine	Calcium Channel Blocker	10
felodipine	Calcium Channel Blocker	10
isradipine	Calcium Channel Blocker	10
nicardipine	Calcium Channel Blocker	120
nifedipine	Calcium Channel Blocker	90
nisoldipine	Calcium Channel Blocker	34
diltiazem	Calcium Channel Blocker	360
verapamil	Calcium Channel Blocker	360
clonidine	Central Alpha-2 Agonists and Other Centrally Acting Drugs	Oral 0.8 Patch 0.3/wk
guanabenz	Central Alpha-2 Agonists and Other Centrally Acting Drugs	64
guanfacine	Central Alpha-2 Agonists and Other Centrally Acting Drugs	2
methyldopa	Central Alpha-2 Agonists and Other Centrally Acting Drugs	1000
reserpine	Central Alpha-2 Agonists and Other Centrally Acting Drugs	.25
hydralazine	Direct Arterial Vasodilators	200
minoxidil	Direct Arterial Vasodilators	100
aliskiren	Direct Renin Inhibitor	300
eplerenone	Aldosterone receptor antagonist	100
spironolactone	Aldosterone receptor antagonist	100
bumetanide	Loop diuretic	2
ethacrynic acid	Loop diuretic	100
furosemide	Loop diuretic	80
torsemide	Loop diuretic	10
amiloride	Potassium-sparing diuretic	10
triamterene	Potassium-sparing diuretic	100
bendroflumethiazide	Thiazide diuretic	5
chlorothiazide	Thiazide diuretic	2000
chlorthalidone	Thiazide diuretic	25
hctz	Thiazide diuretic	50
indapamide	Thiazide diuretic	2.5

metolazone	Thiazide diuretic	5

Appendix G: Variables used to define study population (Aim 2).

Variable	Definition
Index date	Admit date of the COVID-19 related hospitalization.
SARS-CoV-2 positive test	Veterans with a positive SARS-CoV-2 test between January 19, 2020, to present-day will be identified using the VA's official SARS-CoV-2 phenotype definition, which incorporates testing external to the VA. Patients identified as "VA confirmed" and "VA probable" will be categorized as SARS-CoV-2 positive.
COVID-19 related hospitalization	Hospitalization within 7 days before or 14 days after SARS-CoV-2 positive test (defined above). If a patient has more than one hospitalization in this timeframe, the one closest to the SARS-CoV-2 positive test will be selected as the index date.
Hypertension	Any of the following using all available claims prior to the index date: (f) ICD-9 codes: a. At least 1 inpatient claim with a discharge ICD-9 diagnosis (any position) of 401.x, 403.0x, 403.1x, 403.9x. b. ≥2 outpatient claims with an ICD-9 diagnosis code of 401.x, 403.0x, 403.1x, 403.9x in any position at least 30 days apart (g) ICD-10 codes: a. 1 inpatient claim with an ICD-10 discharge diagnosis code of I10, I12.0, I12.9 in any discharge diagnosis position b. ≥2 outpatient claims with an ICD-10 diagnosis code of I10, I12.0, I12.9 in any position at least 30 days apart
Treated hypertension	Having hypertension, as defined above, and currently taking antihypertensive medication, as defined as a pharmacy fill for an antihypertensive medication within 90 days prior to the index date (see Appendix E for list of medication classes).
Compelling indication for ACEI or ARB	Individuals with diabetes, stroke, chronic kidney disease, heart failure with reduced ejection fraction, or coronary heart disease as defined in Appendix B will be excluded from the population for Aim 2.1.
Hospitalized for pneumonia not due to COVID-19	Patients will be identified who are hospitalized (i.e., an inpatient encounter) with an ICD-10 code of J13-J18 in any position. Used for a sensitivity analysis only.

Appendix H: Variables used to define main exposures (Aim 2).

Variable	Definition
Antihypertensive – non-ACEI or ARB-based regimen (Aim 2.1)	Defined as one or more pharmacy fills for an oral non-ACEI or ARB medications in the 90 days (± 14 days) prior to each Veteran's index date and categorized by class as aldosterone receptor antagonist, beta-blocker, calcium channel blocker, centrally-acting drug, direct arterial vasodilator, direct renin inhibitor, thiazide diuretic, loop diuretic, and potassium sparing diuretic. See Appendix E for specific drug names within each class. Exclude non-oral products.
Antihypertensive – ACEI/ARB-based regimen (Aim 2.1)	Defined as one or more pharmacy fills for an oral ACEI or an ARB in the 90 days (± 14 days) prior to each Veteran's index date. See Appendix E for specific drug names within each class. Exclude non-oral products. Exclude sacubitril/valsartan (Brand name: Entresto®) from ARB exposures.
Antihypertensive – ACEI- based regimen (Aim 2.2)	Defined as one or more pharmacy fills for an oral ACEI in the 90 days (± 14 days) prior to each Veteran's index date. See Appendix E for specific drug names within each class. Exclude non-oral products.
Antihypertensive – ARB-based regimen (Aim 2.2)	Defined as one or more pharmacy fills for an oral ARB in the 90 days (± 14 days) prior to each Veteran's index date. See Appendix E for specific drug names within each class. Exclude non-oral products. Exclude sacubitril/valsartan (Brand name: Entresto®) from ARB exposures.
Antihypertensive medication daily dose	Calculated for each antihypertensive medication being taken. Described as milligrams of drug taken per day. We will first parse the dosage value then use the quantity and days supplied variables to inform the parsed dose value (if partial or multiple pills are being taken per day, for example).
Antihypertensive Modified Therapeutic Intensity Score	Continuous variable calculated for each antihypertensive medication being taken. Calculated using the most proximal prescription dispensed in the pre-index period using the daily dose as calculated above, divided by the maximum daily dose per the 2017 ACC/AHA blood pressure guideline. See Appendix F.
Number of antihypertensive medication fills	Calculated for each antihypertensive medication being taken. Number of antihypertensive medication fills in the most proximal 12 months prior each Veteran's index date. Used only in a sensitivity analysis.
Alternative exposure definition 1	Used for a sensitivity analysis. Described as a dichotomous variable (yes=1; no=0). Calculated as "yes" if the patient had two pharmacy fills for the primary exposure of interest in the 180 (± 14 days) days prior to the index date. The pharmacy fills do not have to be consecutive.
Alternative exposure definition 2	Used for a sensitivity analysis. Described as a dichotomous variable (yes=1; no=0). Calculated as "yes" if the patient had 1 pharmacy fill in the 90 days (± 14 days) prior to the index date for the primary exposure of interest and 3 consecutive pharmacy fills for the primary exposure of interest in the one year (± 14 days) prior to the index date. A "consecutive" fill is defined as pharmacy fills with less than 30 days of gap in days' supply between the fills.
Alternative exposure definition 3	Used for a sensitivity analysis. Described as a dichotomous variable (yes=1; no=0). Calculated as "yes" if a prescription for the primary exposure of interest was dispensed before the index date with a days' supply that met or exceeded the index date. Calculated as "no" if prescription was dispensed before the index date with a days' supply that did not meet or exceed the index date.
Alternative exposure definition 4	Used for a sensitivity analysis. Described as a dichotomous variable (yes=1; no=0). Calculated as "yes" if the patient had 1 pharmacy fill in the 90 days prior to the index date and at least one medication administration for the same antihypertensive medication post the index date (including the index date).

Appendix I: Variables used to define outcomes (Aim 2).

Variable	Definition
Primary Outcomes	
All-cause mortality	A binary variable indicating all-cause mortality during the post index period.
Time to all-cause mortality	Integer number of days from index date to all-cause mortality post the index date.
Secondary Outcomes	
Duration of hospitalization	Integer number of days of the inpatient claim post-index date, inclusive of admit and discharge dates.
ICU admission	A binary variable indicating admission to an intensive care unit during the first hospitalization post-index date.
Dialysis	A binary variable indicating occurrence of dialysis post-index date, inclusive of admit and discharge dates.
Mechanical ventilation	Occurrence of any of the following codes associated with a hospital (inpatient) encounter post-index date (including the index date): (a) ICD-10 codes: J95.850, Z99.1x, T88.4x (b) Current Procedural Terminology: 31500 (c) ICD-10 procedure codes: 5A19054, 5A0945Z, 5A1935Z, 5A1955Z, 5A0935Z (d) Order for intubation placed in the electronic health record (e) Inpatient medication administration of a paralytic agent (succinylcholine, cisatracurium, or rocuronium)
Negative Control Outcomes	
Severe gastrointestinal bleeding[24]	Occurrence of any of the following codes associated with a hospital (inpatient) encounter post-index date: (c) ICD-10 code in any position for K25-K28, K92.2, AND (d) CPT code 78278, 7424.x, 7425.x, 74260, 435.xx, 436.xx, 440.xx, 44120, 446.xx
Urinary tract infection	Presence of a positive urine culture, defined as urine culture with at least one organism with a quantitative count of $>10^5$ CFU/mL of any of the following uropathogens: Escherichia coli, Pseudomonas aeruginosa, Enterococcus spp., Klebsiella spp., Enterobacter spp., Proteus spp., Citrobacter spp., Providentia spp., Morganella spp., Serratia spp., Candida spp. during the hospitalization post-index date (including the index date) OR Presence of the ICD10 codes N10, N30, N39, A41.9 using all available claims post the index date.

Appendix J: Variables used to define time-varying covariates (Aim 2).

Variable	Definition
Systolic blood pressure	Each systolic blood pressure value post-index date (including the index date) will be collected where the measure date falls between the admit and discharge dates (admit and discharge dates included). SBP values will be dropped if any of the following was true: Missing value, systolic less than diastolic, systolic >300 mm Hg, and systolic <60 mm Hg.
Heart rate	Each heart rate measurement value post-index date (including the index date) will be collected where the measure date falls between the admit and discharge dates (admit and discharge dates included). HR values will be dropped if missing.
Estimated glomerular filtration rate	Each eGFR recorded where the measure date falls between the admit and discharge dates (admit and discharge dates included). If multiple values for 1 day exist, they will be averaged to create 1 value for that day. If no value exists for a day, use last observation measured. The VA calculates eGFR using the Modified Diet in Renal Disease equation.[14]
Serum potassium	Each daily serum potassium value where the measure date falls between the admit and discharge dates (admit and discharge dates included) will be collected and reported as daily values. If multiple values for 1 day exist, they will be averaged to create 1 value for that day. If no value exists for a day, use the last observation measured. Defined using OMOP's mapping where LOINC is '6298-4', '2823-3'.
Daily administration of antihypertensive medication regimen	Calculated for each antihypertensive medication from the baseline regimen. Described as a dichotomous variable (yes=1; no=0) for each day. Calculated as "yes" if at least one medication administration for the antihypertensive medication occurred during the hospitalization day (including the index date). Calculated as "no" if no medication administration occurred for the antihypertensive medication during the hospitalization day (including the index date).
Daily administration of pressor/inotrope	Daily administration of norepinephrine, phenylephrine, dopamine, vasopressin, epinephrine, milrinone, dobutamine, angiotensin II, or midodrine. Described as a dichotomous variable (yes=1; no=0) for each day. Calculated as "yes" if at least one medication administration for the medication occurred during the hospitalization day (including the index date). Calculated as "no" if no medication administration occurred for the antihypertensive medication during the hospitalization day (including the index date).

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