Angioedema Events in Association with Use of Drugs that Act on the Renin-Angiotensin-Aldosterone System
Direct Test
October 2014 / v2.1

This protocol is a reduced version of the FDA Mini Sentinel protocol of July 18, 2011. The original protocol is available at:
http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Angioedema-and-RAAS_Protocol.pdf.

Patients

We propose to use a "new-user" cohort design. We will identify health plan members aged 18 years or older with a first prescription of an oral formulation of lisinopril or a beta-blocker (as either single ingredient or combination, except in combination with another drug of interest) during the time period January 01, 2010 through September 30, 2013.

We refer to the dispensing date of the first prescription as the index date. We will exclude individuals who initiated more than one drug of interest specifically on the index date. For each individual, if there is more than one new-use episode that meets the inclusion criteria, only the first episode will be used.

Note: PROMPT excludes patients with inconsistent demographic information. This cannot be turned off without changing hard coding. Aetion includes patients and uses most recently reported value. This will be a difference between analyses.

Outcome of interest

We will identify angioedema events (see Appendix A for definition).

Confounding factors

The following confounders will be considered. All variables should be measured over the 183 days prior to the index prescription, not including the index date itself. The source of diagnosis (e.g., inpatient/outpatient) and codes used for each variable are included at the end of this protocol.

The variables are:

- Age on index date (continuous)
- Age on index date, years, categorized as:
  - 18-44
  - 45-54
  - 55-64
  - ≥65
- Sex
- History of allergic reactions
- History of diabetes
- History of heart failure
- History of ischemic heart disease
- Use of NSAIDs
- Number of generic drugs (continuous)
- Number of inpatient visits (continuous)
- Number of ER visits (continuous)
- Number of ambulatory visits (continuous)
- Number of other outpatient events (continuous)

- Number of dispensed prescriptions (continuous)
- Number of other institutional stays (continuous)
- Year of cohort entry

Note: In PROMPT, number of inpatient visits, ER visits, ambulatory visits, other outpatient events, and other institutional stays are defined as the number of unique days with an encounter with the relevant place of service (POS). We will be counting events, so there may be a difference between analyses. In PROMPT, the number of inpatient and ER visits are counted from the "encounter" table in the Common Data Model; each unique day with an encounter with the relevant POS is counted where the encounter date is during the covariate assessment window and before the index date (index date - covariate assessment window <= encounter date < index date).

Follow-up

We will follow the new users from the index date until the earliest occurrence of the first angioedema outcome, initiation of another drug of interest, cessation of use of drug of interest, death, disenrollment from the health plan, end of medical benefit, or end of available data (September 30, 2013). Cessation of use occurs when a patient's days supplied appears to have been exhausted for at least 30 days (grace period 30 days, risk window 30 days).

Statistical analysis

We will calculate the incidence per 1,000 persons and incidence rate per 1,000 person-years of angioedema and the 95% confidence intervals (CIs) separately for lisinopril and beta-blockers (as a class).

We will estimate the crude hazard ratio (HR) and 95% CI of angioedema using beta -blockers as the referent group. We will fit a Cox model for lisinopril versus beta-blockers. We will fit three Cox models: crude, age/sex adjusted, and multivariate adjusted. In addition to relative rates, we will also compute rate differences for all analyses. We will replicate adjusted rate difference models via manual SAS procedures.

We will use a propensity score (PS)-stratified approach to obtain further adjusted estimates. The PS will be the probability of initiating lisinopril versus beta blocker, which will be estimated by a logistic regression model. The PS model will include the variables listed as confounding factors above.

We will fit:

1) The PS model.
2) A PS-stratified Cox model that will include an indicator variable for drug exposure as an independent variable and the PS (in deciles) as a stratification variable.
3) A 1:1 PS matched analysis using a matching caliper of 0.025.

Subgroups

We will perform the analyses for all eligible patients and for the following subgroups:

- Males
- Females
- Patients under age 65 years at index date

Sensitivity analyses

We will perform a first exposure carried forward analysis (intention-to-treat, ITT) with a fixed follow-up period of 180 days.

Appendix A: Variable Definitions

List of beta-blockers

- Acebutolol
- Atenolol
- Bisoprolol
- Carvedilol
- Labetalol
- Metoprolol
- Nebivolol
- Pindolol
- Propranolol
- Timolol

Angioedema events for exclusion

These ICD-9 codes must appear on inpatient, emergency department or ambulatory visit setting.

995.1

Angioedema events as outcome

These ICD-9 codes must appear on inpatient discharge diagnoses (any position).

995.1

History of allergic reaction

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

477.*
518.6
558.3
691.*
692.??
693.*
708.*
995.0
995.27
995.3
995.6*
995.7
V07.1
V13.81
V14.*
V15.0?
V72.7

Remove these ICD-9 codes:

692.75
692.76
692.77

History of diabetes

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

250
250.*

History of heart failure

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

402.?1
404.?1
404.?3
428.??

History of ischemic heart disease

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

410
410.*
411
411.*
412
412.*
413
413.*
414
414.*

Generic drugs for NSAID use

Drugs for NSAID use should be any drug containing the following single generic drug ingredients. NSAIDs used in combinations will not be considered.

- Aspirin
- Celecoxib
- Diclofenac potassium
- Diclofenac sodium
- Diflunisal
- Etodolac
- Fenoprofen calcium
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Ketorolac tromethamine
- Ketoprofen
- Meclofenamate sodium
- Meloxicam
- Nabumetone
- Naproxen
- Naproxen sodium
- Oxaprozin

- Piroxicam
- Rofecoxib
- Salsalate
- Sulindac
- Tolmetin sodium
- Valdecoxib

Angioedema Events in Association with Use of Drugs that Act on the Renin-Angiotensin-Aldosterone System
Direct Test
October 2014 / v2.1

This protocol is a reduced version of the FDA Mini Sentinel protocol of July 18, 2011. The original protocol is available at:
http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Angioedema-and-RAAS_Protocol.pdf.

Patients

We propose to use a "new-user" cohort design. We will identify health plan members aged 18 years or older with a first prescription of an oral formulation of lisinopril or a beta-blocker (as either single ingredient or combination, except in combination with another drug of interest) during the time period January 01, 2010 through September 30, 2013.

We refer to the dispensing date of the first prescription as the index date. We will require eligible individuals to meet all of the following criteria during the 183-day period prior to the index date: 1) continuous health plan enrollment, pharmacy and medical benefit; 2) no prescription of any of the drugs of interest; and 3) no diagnosis of angioedema (see Appendix) in the 183 days prior to the index date, but not including the index date itself. We will exclude individuals who initiated more than one drug of interest on the index date. For each individual, if there is more than one new-use episode that meets the inclusion criteria, only the first episode will be used.

Note: PROMPT excludes patients with inconsistent demographic information. This cannot be turned off without changing hard coding. Aetion includes patients and uses most recently reported value. This will be a difference between analyses.

Outcome of interest

We will identify angioedema events (see Appendix A for definition).

Confounding factors

The following confounders will be considered. All variables should be measured over the 183 days prior to the index prescription, not including the index date itself. The source of diagnosis (e.g., inpatient/outpatient) and codes used for each variable are included at the end of this protocol.

The variables are:

- Age on index date (continuous)
- Age on index date, years, categorized as:
  - 18-44
  - 45-54
  - 55-64
  - ≥65
- Sex
- History of allergic reactions
- History of diabetes
- History of heart failure
- History of ischemic heart disease
- Use of NSAIDs
- Number of generic drugs (continuous)

- Number of inpatient visits (continuous)
- Number of ER visits (continuous)
- Number of ambulatory visits (continuous)
- Number of other outpatient events (continuous)
- Number of dispensed prescriptions (continuous)
- Number of other institutional stays (continuous)
- Year of cohort entry

Note: In PROMPT, number of inpatient visits, ER visits, ambulatory visits, other outpatient events, and other institutional stays are defined as the number of unique days with an encounter with the relevant place of service (POS). We will be counting events, so there may be a difference between analyses. In PROMPT, the number of inpatient and ER visits are counted from the "encounter" table in the Common Data Model; each unique day with an encounter with the relevant POS is counted where the encounter date is during the covariate assessment window and before the index date (index date - covariate assessment window <= encounter date < index date).

Follow-up

We will follow the new users from the index date until the earliest occurrence of the first angioedema outcome, initiation of another drug of interest, cessation of use of drug of interest, death, disenrollment from the health plan, end of medical benefit, or end of available data (September 30, 2013). Cessation of use occurs when a patient's days supplied appears to have been exhausted for at least 30 days (grace period 30 days, risk window 30 days).

Statistical analysis

We will calculate the incidence per 1,000 persons and incidence rate per 1,000 person-years of angioedema and the 95% confidence intervals (CIs) separately for lisinopril and beta-blockers (as a class).

We will estimate the crude hazard ratio (HR) and 95% CI of angioedema using beta -blockers as the referent group. We will fit a Cox model for lisinopril versus beta-blockers. We will fit three Cox models: crude, age/sex adjusted, and multivariate adjusted. In addition to relative rates, we will also compute rate differences for all analyses. We will replicate adjusted rate difference models via manual SAS procedures.

We will use a propensity score (PS)-stratified approach to obtain further adjusted estimates. The PS will be the probability of initiating lisinopril versus beta blocker, which will be estimated by a logistic regression model. The PS model will include the variables listed as confounding factors above.

We will fit:

1) The PS model.
2) A PS-stratified Cox model that will include an indicator variable for drug exposure as an independent variable and the PS (in deciles) as a stratification variable.
3) A 1:1 PS matched analysis using a matching caliper of 0.025.

Subgroups

We will perform the analyses for all eligible patients and for the following subgroups:

- Males
- Females
- Patients under age 65 years at index date

Sensitivity analyses

We will perform a first exposure carried forward analysis (intention-to-treat, ITT) with a fixed follow-up period of 180 days.

Appendix A: Variable Definitions

List of beta-blockers

- Acebutolol
- Atenolol
- Bisoprolol
- Carvedilol
- Labetalol
- Metoprolol
- Nebivolol
- Pindolol
- Propranolol
- Timolol

Angioedema events for exclusion

These ICD-9 codes must appear on inpatient, emergency department or ambulatory visit setting.

995.1

Angioedema events as outcome

These ICD-9 codes must appear on inpatient discharge diagnoses (any position).

995.1

History of allergic reaction

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

477.*
518.6
558.3
691.*
692.??
693.*
708.*
995.0
995.27
995.3
995.6*
995.7
V07.1
V13.81
V14.*
V15.0?
V72.7

Remove these ICD-9 codes:

692.75
692.76
692.77

History of diabetes

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

250
250.*

History of heart failure

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

402.?1
404.?1
404.?3
428.??

History of ischemic heart disease

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

410
410.*
411
411.*
412
412.*
413
413.*
414
414.*

Generic drugs for NSAID use

Drugs for NSAID use should be any drug containing the following single generic drug ingredients. NSAIDs used in combinations will not be considered.

- Aspirin
- Celecoxib
- Diclofenac potassium
- Diclofenac sodium
- Diflunisal
- Etodolac
- Fenoprofen calcium
- Flurbiprofen
- Ibuprofen
- Indomethacin
- Ketorolac tromethamine
- Ketoprofen
- Meclofenamate sodium
- Meloxicam
- Nabumetone
- Naproxen
- Naproxen sodium
- Oxaprozin

- Piroxicam
- Rofecoxib
- Salsalate
- Sulindac
- Tolmetin sodium
- Valdecoxib

Celecoxib versus Non-selective NSAIDs (ns-NSAIDs) and the Outcome of Gastrointestinal (GI) Bleed
Direct Test
November 2014 / v1.2

Patients

We propose to use a "new-user" cohort design. We will identify health plan members aged 18 years or older with a first prescription of an oral formulation of celecoxib or a non-selective NSAID (identified via NDC codes) during the time period January 1, 2010 through September 30, 2013.

We refer to the dispensing date of the first prescription as the index date. We will require eligible individuals to meet all of the following criteria during the 180-day period prior to the index date: 1) continuous health plan enrollment, pharmacy and medical benefit; and 2) no prescription of any of the drugs of interest. We will exclude individuals who initiated more than one drug of interest on the index date. For each individual, if there is more than one new-use episode that meets the inclusion criteria, only the first episode will be used.

Note: PROMPT excludes patients with inconsistent demographic information. This cannot be turned off without changing hard coding. Aetion includes patients and uses most recently reported value. This will be a difference between analyses.

Outcome of interest

We will identify gastrointestinal bleed (GI) events (see Appendix A for definition).

Confounding factors

The following confounders will be considered. All variables should be measured over the 180 days prior to the index prescription, not including the index date itself. The source of diagnosis (e.g., inpatient/outpatient) and codes used for each variable are included at the end of this protocol.

The variables are:

- Age on index date (continuous)
- Age on index date, years, categorized as:
    - 18-44
    - 45-54
    - 55-64
    - ≥65
- Sex
- History of angina
- History of congestive heart failure
- History of diabetes
- History of gastrointestinal bleed
- History of hypertension
- History of ischemic heart disease
- History of peptic ulcer disease
- History of rheumatoid arthritis
- History of osteoarthritis
- Use of a statin
- Use of warfarin
- Use of clopidogrel
- Use of PPI or H2 Blocker
- Number of generic drugs (continuous)

- Number of inpatient visits (continuous)
- Number of ER visits (continuous)
- Number of ambulatory visits (Mini-Sentinel "AV") (continuous)
- Number of other outpatient events (Mini-Sentinel "OA") (continuous)
- Number of dispensed prescriptions (continuous)
- Number of other institutional stays (Mini-Sentinel "IS") (continuous)
- Year of cohort entry

Note: In PROMPT, number of inpatient visits, ER visits, ambulatory visits, other outpatient events, and other institutional stays are defined as the number of unique days with an encounter with the relevant place of service (POS). We will be counting events. This will be a difference between analyses. In PROMPT, the number of inpatient and ER visits are counted from the "encounter" table in the Common Data Model; each unique day with an encounter with the relevant POS is counted where: index date - covariate assessment window <= encounter date < index date.

Follow-up

We will follow the new users from the index date until the earliest occurrence of the first GI bleed, initiation of another drug of interest, cessation of use of drug of interest, death, disenrollment from the health plan, end of medical benefit, or end of available data (September 30, 2013). Cessation of use occurs when a patient's days supplied appears to have been exhausted for at least 30 days (grace period 30 days, risk window 30 days).

Statistical analysis

We will calculate the incidence per 1,000 persons and incidence rate per 1,000 person-years of GI bleed and the 95% confidence intervals (CIs) separately for celecoxib and ns-NSAIDs.

We will estimate the crude hazard ratio (HR) and 95% CI of GI bleed using ns-NSAIDs as the referent group. We will fit a Cox model for celecoxib versus ns-NSAIDs. We will fit three Cox models: crude, age/sex adjusted, and multivariate adjusted. In addition to relative rates, we will also compute rate differences for all analyses. We will replicate adjusted rate difference models via manual SAS procedures.

We will use a propensity score (PS)-stratified approach to obtain further adjusted estimates. The PS will be the probability of initiating celecoxib versus an ns-NSAID, which will be estimated by a logistic regression model. The PS model will include the variables listed as confounding factors above.

We will fit:

1) The PS model.
2) A PS-stratified Cox model that will include an indicator variable for drug exposure as an independent variable and the PS (in deciles) as a stratification variable.
3) A 1:1 PS matched analysis using a matching caliper of 0.025.

Sensitivity analyses

We will perform a first exposure carried forward analysis (intention-to-treat, ITT) with a fixed follow-up period of 180 days.

Appendix A: Variable Definitions

Drugs for celecoxib use

File "DT3 celecoxib_ndc.txt" contains NDC codes for oral celecoxib.

Drugs for ns-NSAID use

File "DT3 nsnaid_ndc.txt" contains NDC codes for the following oral non-selective NSAID agents:

- Aspirin
- Diclofenac Epolamine
- Diclofenac Potassium
- Diclofenac Sodium
- Diclofenac Submicronized
- Diflunisal
- Etodolac
- Fenoprofen Calcium
- Flurbiprofen
- Flurbiprofen Sodium
- Ibuprofen
- Indomethacin
- Indomethacin Sodium
- Ketoprofen
- Ketoprofen, Micronized
- Ketorolac Tromethamine
- Meclofenamate Sodium
- Meloxicam
- Nabumetone
- Nabumetone, Micronized
- Naproxen
- Naproxen Sodium
- Oxaprozin
- Piroxicam
- Salsalate
- Sulindac
- Tolmetin Sodium

Gastrointestinal bleed outcome

These ICD-9 codes must appear in the an inpatient diagnosis field.

531.0
531.1
531.2
531.4
531.5
531.6
532.0
532.1
532.2
532.4
532.5

532.6
533.0
533.1
533.2
533.4
533.5
533.6
534.0
534.1
534.2
534.4
534.5
534.6
569.3
569.41
569.8
578.0
578.1
578.9

History of angina

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

413
413.*

History of congestive heart failure

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

402.?1
404.?1
404.?3
428.??

History of diabetes

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

250
250.*

History of gastrointestinal bleed

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

531.0
531.1
531.2
531.4
531.5
531.6
532.0

532.1
532.2
532.4
532.5
532.6
533.0
533.1
533.2
533.4
533.5
533.6
534.0
534.1
534.2
534.4
534.5
534.6
569.3
569.41
569.8
578.0
578.1
578.9

History of hypertension

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

401
401.0
401.1
401.9
402
402.0
402.00
402.01
402.1
402.10
402.11
402.9
402.90
402.91
403
403.0
403.00
403.01
403.1
403.10
403.11
403.9
403.90
403.91
404
404.0

404.00
404.01
404.02
404.03
404.1
404.10
404.11
404.12
404.13
404.9
404.90
404.91
404.92
405
405.0
405.01
405.09
405.1
405.11
405.19
405.9
405.91
405.99
437.2

History of ischemic heart disease

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

410
410.*
411
411.*
412
412.*
413
413.*
414
414.*

History of peptic ulcer disease

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

532
532.*
533
533.*

History of rheumatoid arthritis

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

714.0

714.2

History of osteoarthritis

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

715
715.*

Use of a statin

Drug use with generic drug name of the following:

- Atorvastatin
- Fluvastatin
- Lovastatin
- Pitavastatin
- Pravastatin
- Rosuvastatin
- Simvastatin

Use of warfarin

Drug use with generic drug name of "WARFARIN SODIUM".

Use of clopidogrel

Drug use with generic drug name of "CLOPIDOGREL BISULFATE".

Use of PPI or H2 blocker

Drug use with generic drug name of the following:

- Nizatidine
- Omeprazole
- Famotidine
- Pantoprazole Sodium
- Cimetidine Hcl
- Lansoprazole
- Rabeprazole Sodium
- Cimetidine
- Famotidine/Calcium Carbonate/Magnesium Hydroxide
- Ranitidine Hcl
- Esomeprazole Magnesium
- Omeprazole/Sodium Bicarbonate
- Omeprazole Magnesium
- Esomeprazole Strontium
- Dexlansoprazole

High versus Low Intensity Statins and the Outcome of Hospitalization for Acute Coronary Syndrome
Direct Test
December 2014 / v1

Patients

We propose to use a "new-user" cohort design. We will identify health plan members aged 18 years or older with a first prescription of a high or low intensity statin (identified via NDC codes) during the time period January 1, 2010 through September 30, 2013.

We refer to the dispensing date of the first prescription as the index date. We will require eligible individuals to meet all of the following criteria during the 180-day period prior to the index date: 1) continuous health plan enrollment, pharmacy and medical benefit; 2) no prescription of any of the drugs of interest; and 3) no hospitalizations for acute coronary syndrome (outcome; see Appendix A). We will exclude individuals who initiated more than one drug of interest on the index date. For each individual, if there is more than one new-use episode that meets the inclusion criteria, only the first episode will be used.

Note: PROMPT excludes patients with inconsistent demographic information. This cannot be turned off without changing hard coding. Aetion includes patients and uses most recently reported value. This will be a difference between analyses.

Outcome of interest

We will identify hospitalizations for acute coronary syndrome (ACS; see Appendix A for definition).

Confounding factors

The following confounders will be considered. All variables should be measured over the 180 days prior to the index prescription, not including the index date itself. The source of diagnosis (e.g., inpatient/outpatient) and codes used for each variable are included at the end of this protocol.

The variables are:

- Age on index date (continuous)
- Age on index date, years, categorized as:
    - 18-44
    - 45-54
    - 55-64
    - ≥65
- Sex
- History of congestive heart failure
- History of diabetes
- History of hypertension
- History of MI
- History of other ischemic heart disease
- History of atrial fibrillation
- History of cardiovascular system symptoms
- History of chest pain
- History of conduction disorders
- History of stroke or TIA
- History of peripheral vascular disease
- History of depression
- History of disorders of lipid metabolism

- History of postsurgical aortocoronary bypass
- Number of generic drugs (continuous)
- Number of inpatient visits (continuous)
- Number of ER visits (continuous)
- Number of ambulatory visits (Mini-Sentinel "AV"; see Appendix B) (continuous)
- Number of other outpatient events (Mini-Sentinel "OA"; see Appendix B) (continuous)
- Number of dispensed prescriptions (continuous)
- Number of other institutional stays (Mini-Sentinel "IS"; see Appendix B) (continuous)
- Year of cohort entry

Note: In PROMPT, number of inpatient visits, ER visits, ambulatory visits, other outpatient events, and other institutional stays are defined as the number of unique days with an encounter with the relevant place of service (POS). We will be counting events. This will be a difference between analyses. In PROMPT, the number of inpatient and ER visits are counted from the "encounter" table in the Common Data Model; each unique day with an encounter with the relevant POS is counted where: the encounter date is during the covariate assessment period and before the index date (index date - covariate assessment window <= encounter date < index date).

Follow-up

We will follow the new users from the index date until the earliest occurrence of the first hospitalization for ACS, initiation of another drug of interest, cessation of use of drug of interest, death, disenrollment from the health plan, end of medical benefit, or end of available data (September 30, 2013). Cessation of use occurs when a patient's days supplied appears to have been exhausted for at least 30 days (grace period 30 days, risk window 30 days).

Statistical analysis

We will calculate the incidence per 1,000 persons and incidence rate per 1,000 person-years of hospitalization for ACS and the 95% confidence intervals (CIs) separately for high and low-intensity statins.

We will estimate the crude hazard ratio (HR) and 95% CI of hospitalization for ACS using low-intensity statins as the referent group. We will fit a Cox model for high-intensity versus low-intensity statins. We will fit three Cox models: crude, age/sex adjusted, and multivariate adjusted. In addition to relative rates, we will also compute rate differences for all analyses. We will replicate adjusted rate difference models via manual SAS procedures.

We will use a propensity score (PS)-stratified approach to obtain further adjusted estimates. The PS will be the probability of initiating a high-intensity versus low-intensity statin, which will be estimated by a logistic regression model. The PS model will include the variables listed as confounding factors above.

We will fit:

1) The PS model.
2) A PS-stratified Cox model that will include an indicator variable for drug exposure as an independent variable and the PS (in deciles) as a stratification variable.
3) A 1:1 PS matched analysis using a matching caliper of 0.025.

Subgroups

We will perform the analyses for all eligible patients and for the following subgroups:

- Males
- Females
- Patients under age 65 years at index date

Sensitivity analyses

We will perform a first exposure carried forward analysis (intention-to-treat, ITT) with a fixed follow-up period of 180 days.

Appendix A: Variable Definitions

Drugs for high intensity statin use

The file "DT4 ndc_high.txt" contains NDC codes for:

- Atorvastatin > 10 mg
- Lovastatin > 40 mg
- Rosuvastatin > 5 mg
- Simvastatin > 40 mg
- Pitavastatin > 1 mg

Drugs for low intensity statin use

The file "DT4 ndc_low.txt" contains NDC codes for:

- Atorvastatin ≤ 10 mg
- Fluvastatin
- Lovastatin ≤ 40 mg
- Pravastatin
- Rosuvastatin ≤ 5 mg
- Simvastatin ≤ 40 mg
- Pitavastatin ≤ 1 mg

Hospitalization for acute coronary syndrome outcome

These ICD-9 codes must appear in the primary inpatient diagnosis field.

410.?0
410.?1
411
411.*
413
413.*

History of congestive heart failure

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

402.?1
404.?1
404.?3
428*

History of diabetes

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

250
250.*

History of hypertension

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

401*
402*
403*
404*
405*
437.2

History of MI

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

410
410.*

History of other ischemic heart disease

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

411
411.*
412
412.*
413
413.*
414
414.*

History of atrial fibrillation

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

427.31

History of cardiovascular system symptoms

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

785*

History of chest pain

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

786.5*

History of conduction disorders

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

426*

History of stroke or TIA

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

430*
431*
433.?1
434*
435*
436*

Remove these ICD-9 codes:

434.x0 (i.e., 434.00, 434.10, 434.90)

History of peripheral vascular disease

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

- 040.0 - GAS GANGRENE
- 250.7 - DIABETES WITH PERIPHERAL CIRCULATORY DISORDERS
- 250.70 - DIABETES WITH PERIPHERAL CIRCULATORY DISORDERS TYPE II OR UNSPECIFIED TYPE NOT STATED AS UNCONTROLLED
- 250.71 - DIABETES WITH PERIPHERAL CIRCULATORY DISORDERS TYPE I [JUVENILE TYPE] NOT STATED AS UNCONTROLLED
- 250.72 - DIABETES WITH PERIPHERAL CIRCULATORY DISORDERS TYPE II OR UNSPECIFIED TYPE UNCONTROLLED
- 250.73 - DIABETES WITH PERIPHERAL CIRCULATORY DISORDERS TYPE I [JUVENILE TYPE] UNCONTROLLED
- 442.3 - ANEURYSM OF ARTERY OF LOWER EXTREMITY
- 443.81 - PERIPHERAL ANGIOPATHY IN DISEASES CLASSIFIED ELSEWHERE
- 443.9 - PERIPHERAL VASCULAR DISEASE UNSPECIFIED
- 444.22 - ARTERIAL EMBOLISM AND THROMBOSIS OF LOWER EXTREMITY
- 707.1 - ULCER OF LOWER LIMB EXCEPT PRESSURE ULCER
- 707.10 - UNSPECIFIED ULCER OF LOWER LIMB
- 707.11 - ULCER OF THIGH
- 707.12 - ULCER OF CALF
- 707.13 - ULCER OF ANKLE
- 707.14 - ULCER OF HEEL AND MIDFOOT
- 707.15 - ULCER OF OTHER PART OF FOOT
- 707.19 - ULCER OF OTHER PART OF LOWER LIMB
- 785.4 - GANGRENE
- 892.1 - OPEN WOUND OF FOOT EXCEPT TOE(S) ALONE COMPLICATED

History of depression

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

296.2
296.2*
296.3
296.3*
309.0
309.0*

309.1
309.1*
311

History of disorders of lipid metabolism

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

272
272.*

History of postsurgical aortocoronary bypass

These ICD-9 codes may appear in any diagnosis field (inpatient, outpatient or otherwise).

V45.81

Comparative effectiveness of percutaneous coronary interventions (PTCA) versus coronary artery bypass grafting (CABG) on cardiac events in the subsequent 12 months

Direct Test Protocol
January 2015

This protocol is based on:
Centers for Medicare and Medicaid Services (CMS) Linkable 2008–2010 Medicare Data Entrepreneurs' Synthetic Public Use File (DE-SynPUF) user manual, 15 January 2013; Appendix B-I, a CER example

Patients
We propose to use a cohort design. We will identify health plan members with PTCA or CABG in an inpatient setting within the time period 01 January 2009 through 31 December 2009 regardless of prior exposure (and treating each exposure period individually). The first INP event with either PTCA or CABG will be defined as the index event; patients with multiple exposure events on the same cohort entry date will be excluded. The admission date of this index event will be defined as the index admission date while the discharge date of this index event will be defined as the index discharge date. We will require eligible individuals to have at least 12 months (365 days) of continuous pharmacy and medical benefits prior to the index event.

Outcome of interest
International Classification of Diseases, Ninth Edition (ICD-9) diagnosis, ICD-9 procedure, Diagnosis-related group (DRG), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes, in any position unless otherwise specified, will be used to identify outcomes of interest and confounding factors.

We will define cardiac events as any occurrence of angina, heart failure, ischemic heart disease, or cardiac arrest (see Appendix for codes) in any setting (inpatient, outpatient, or medical services [via carrier files]) during the 12 months (365 days) after the index discharge date.

Confounding factors
The following confounders will be considered. All variables will be measured over the 12 months (365 days) prior to the index admission date and defined as at least one code regardless of setting (inpatient, outpatient, or medical services [via carrier files]; see Appendix for codes).

The variables are:

- Demographics
    - Gender (male, female)
    - Race (white, black, other/hispanic)
    - Age on index event date (continuous)
        - Age group (<70, 70-79, 80+ years)
- Comorbidities
    - High cholesterol
    - Hypertension
    - Previous ischemic heart disease
    - Diabetes
- Outcomes: cardiac events
    - Angina pectoris
    - Heart failure
    - Ischemic heart disease

- Angina pectoris, heart failure, ischemic heart disease, or cardiac arrest

Note: Codes for CAD and depression were also included in the literature, but neither were reported in the example results and have therefore been skipped in this test protocol.

Follow-up

Follow-up will begin on the day following the index discharge date and continue until the earliest of death, insurance disenrollment, claim for a cardiac event, end of data (31 December 2010), or crossover exposure.

Statistical analysis

We will report counts and proportions for bivariate analyses of intervention (PTCA or CABG) and demographics, comorbidities, and outcomes. We will estimate odds ratios (ORs) and standard errors (SEs) for heart failure as an outcome of the intervention (PTCA or CABG) conditioning on demographics, comorbidities, and outcomes using a multivariate logistic regression model.

Appendix

Definition of diseases or intervention

Variable of interest	ICD-9 diagnosis codes	ICD-9 procedure codes	DRG	HCPCS
CABG (INP setting only)		36.1*, 36.2*	106, 107, 109, 547-550	33510-33514, 33516-33519, 33521-33523, 33533-33536, 35600, 33572, S2205-S2209
PTCA (INP setting only)		00.66, 36.06, 36.07, 36.09	516, 517, 526, 527, 555-558	33140, 92980-92982, 92984, 92995, 92996
Angina pectoris	413			
Heart failure	398.91, 402.01, 402.11, 402.91, 428.0*-428.9*, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93			
Ischemic heart disease	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.10, 414.11, 414.12, 414.19, 414.2, 414.3, 414.8, 414.9	00.66, 36.01, 36.02, 36.03, 36.04, 36.05, 36.06, 36.07, 36.09, 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.2, 36.31, 36.32 Note: Not available in carrier claims.		33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536, 33542, 33545, 33548, 92975, 92977, 92980, 92982, 92995, 33140, 33141
Cardiac arrest	427.5*			
Hypertension	401.1*, 401.9*, 401.0*			
Diabetes	249.*, 250.*, 357.2, 362.01, 362.02, 366.41		637-639	
High cholesterol	272.0*			

Total inpatient expenditures in 2008 among beneficiaries who had at least one inpatient claim in 2008

Direct Test Protocol
January 2015

This protocol is based on:
Centers for Medicare and Medicaid Services (CMS) Linkable 2008–2010 Medicare Data Entrepreneurs' Synthetic Public Use File (DE-SynPUF) user manual, 15 January 2013; Appendix B-II, an HSR example

Patients

We propose to use a cohort design. We will identify health plan members with at least one inpatient claim and continuous pharmacy and medical benefits within the time period 01 January 2008 through 31 December 2008. The first INP event in 2008 will be defined as the index event, regardless of prior exposure (and treating each exposure period individually).

Outcome of interest

International Classification of Diseases, Ninth Edition (ICD-9) diagnosis, ICD-9 procedure, Healthcare Common Procedure Coding System (HCPCS) codes, in any position unless otherwise specified, will be used to identify outcomes of interest and confounding factors.

We will define total inpatient expenditures in 2008 as the sum of all inpatient annual Medicare reimbursement amounts, inpatient annual beneficiary responsibility amounts, and inpatient annual primary payer reimbursement amounts after and including the index date.

Confounding factors

The following confounders will be considered. All variables will be measured within the time period 01 January 2008 through 31 December 2008, regardless of setting (inpatient, outpatient, or medical services [via carrier files]; see Appendix for codes) unless otherwise specified.

The variables are:

- Demographics
  - Gender (male, female)
  - Race (white, black, other/Hispanic)
- Chronic conditions (no, yes)
  - Alzheimer or related disorders or senile dementia
  - Heart failure
  - Chronic kidney disease
  - Cancer, comprising female breast, colorectal, prostate, or lung
  - Chronic obstructive pulmonary disease (COPD)
  - Depression
  - Diabetes
  - Ischemic heart disease
  - Osteoporosis
  - Rheumatoid arthritis or osteoarthritis (RA/OA)
  - Stroke/Transient ischemic attack

Follow-up

Follow-up will begin on the index date and continue until 31 December 2008.

Statistical analysis

We will report counts and proportions for univariate analyses of total inpatient expenditures, demographics, and chronic conditions. We will estimate coefficient estimates and standard errors (SEs) for total inpatient expenditure modeled on demographics and chronic conditions using a generalized linear model (GLM) with the gamma family and log link.

Appendix

Definition of chronic conditions

Note: Codes were not provided within the example text and were therefore assumed to be identical to those listed for the same conditions in the CMS Linkable 2008-2010 Medicare DE-SynPUF Codebook.

Variable of interest	ICD-9 diagnosis codes	ICD-9 procedure codes	HCPCS
Alzheimer or related disorders or senile dementia	(at least one code in any position or setting) 331.0*, 331.1*, 331.2*, 331.7*, 290.0*, 290.1*, 290.20, 290.21, 290.3*, 290.40, 290.41, 290.42, 290.43, 294.0*, 294.1*, 294.8*		
Heart failure	(at least one code in any position or setting) 398.91, 402.01, 402.11, 402.91, 428.*, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93		
Chronic kidney disease	(at least one code in any position in the INP setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one year apart) 016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4*, 189.0*, 189.9*, 223.0*, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4*, 274.1*, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1*, 442.1*, 572.4*, 580.0*, 580.4*, 580.81, 580.89, 580.9*, 581.0*, 581.1*, 581.2*, 581.3*, 581.81, 581.89, 581.9*, 582.0*, 582.1*, 582.2*, 582.4*, 582.81, 582.89, 582.9*, 583.0*, 583.1*, 583.2*, 583.4*, 583.6*, 583.7*, 583.81, 583.89, 583.9*, 584.5*, 584.6*, 584.7*, 584.8*, 584.9*, 585.*, 585.1*, 585.2*, 585.3*, 585.4*, 585.5*, 585.6*, 585.9*, 586, 587, 588.0*, 588.1*, 588.81, 588.89, 588.9*, 591.*, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4*		
Cancer, female breast	(at least one code in any position in the INP setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one year apart) 174.0*, 174.1*, 174.2*, 174.3*, 174.4*, 174.5*, 174.6*, 174.8*, 174.9*, 233.0*		
Cancer, colorectal	(at least one code in any position in the INP setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one year apart) 154.0*, 154.1*, 153.0*, 153.1*, 153.2*, 153.3*, 153.4*, 153.5*, 153.6*, 153.7*, 153.8*, 153.9, 230.3*, 230.4*		
Cancer, prostate	(at least one code in any position in the INP setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one year apart) 185.*, 233.4*		
Cancer, lung	(at least one code in any position in the INP		

	setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one year apart) 162.0*, 162.2*, 162.3*, 162.4*, 162.5*, 162.8*, 162.9*, 231.2*		
Chronic obstructive pulmonary disease (COPD)	(at least one code in any position in the INP setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one year apart) 491.0*, 491.1*, 491.20, 491.21, 491.22, 491.8*, 491.9*, 492.0*, 492.8*, 494.0*, 494.1*, 496.*		
Depression	(at least one code in any position or setting) 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0*, 300.4*, 309.1*, 311.*		
Diabetes	(at least one code in any position in the INP setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one year apart) 249.*, 250.*, 357.2*, 362.01, 362.02, 366.41		
Ischemic heart disease	(at least one code in any position or setting) 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0*, 411.1*, 411.81, 411.89, 412.*, 413.0*, 413.1*, 413.9*, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.10, 414.11, 414.12, 414.19, 414.2*, 414.3*, 414.8*, 414.9*	00.66, 36.01, 36.02, 36.03, 36.04, 36.05, 36.06, 36.07, 36.09, 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19, 36.2, 36.31, 36.32 Note: Not available in carrier claims.	33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33533, 33534, 33535, 33536, 33542, 33545, 33548, 92975, 92977, 92980, 92982, 92995, 33140, 33141
Osteoporosis	(at least one code in any position or setting) 733.00, 733.01, 733.02, 733.03, 733.09		
Rheumatoid arthritis or osteoarthritis (RA/OA)	(at least two codes in any position or setting within one year apart) 714.0*, 714.1*, 714.2*, 714.30, 714.31, 714.32, 714.33, 715.00, 715.04, 715.09, 715.10, 715.11, 715.12, 715.13, 715.14, 715.15, 715.16, 715.17, 715.18, 715.20, 715.21, 715.22, 715.23, 715.24, 715.25, 715.26, 715.27, 715.28, 715.30, 715.31, 715.32, 715.33, 715.34, 715.35, 715.36, 715.37, 715.38, 715.80, 715.89, 715.90, 715.98		
Stroke/Transient ischemic attack	(at least one code in any position in the INP setting, OR at least two codes in any position in the non-INP setting [i.e., OUT or OV] within one		

	year apart) 430.*, 431.*, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0*, 435.1*, 435.3*, 435.8*, 435.9*, 436.*, 997.02		