Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview

Request ID: to16_cap_mpl2r_wp008_nsdp_v02
Report Description: This report investigated the association between warfarin and gastrointestinal (GI) bleeding, with statins as the comparison exposure.
Data Source: Data from January 1, 2012 to September 30, 2015 from 14 Data Partners contributing to the Sentinel Distributed Database (SDD) were included in this report. The request package was sent to 13 Data Partners on July 12, 2016 and one Data Partner on August 30, 2016. See the Monitoring Periods tab for a list of the latest dates of available data for each Data Partner.

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.0.10

Study Design: This study used a retrospective new-user cohort design.

Exposures of Interest: The exposures of interest were new warfarin use (exposure) and new statins use (comparator), defined using National Drug Codes (NDCs) (See Appendices A and B).

Cohort Eligibility Criteria: Patients aged 18 years or older with continuous enrollment in plans with both medical and drug coverage for at least 183 days before exposure initiation, during which gaps in coverage of up to 45 days were allowed, were eligible to be included in the cohort. New use of warfarin was defined as no use of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, or combination products containing any of these drugs) or novel anticoagulants (warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban) in the previous 183 days. New use of statins was defined as no use of statins, warfarin, or novel anticoagulants in the previous 183 days. All codes were defined using NDCs (See Appendix A).

Patients were excluded from the cohort if they had evidence of the following diagnoses in the 183 days prior to exposure initiation: malignancy or blood/lymph cancer, hospice care, gastrointestinal vessel congenital anomaly, symptomatic hemophilia A carrier, artificial opening of GI tract, aplastic anemia and other bone marrow failure syndromes, coagulation defect, GI bleed, or other GI bleed. These exclusions were defined using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes (See Appendix C).

Follow-up: Follow-up time was determined by the length of the exposure episodes. Exposure episode lengths were defined using outpatient pharmacy dispensing days supplied to create a sequence of continuous exposure. Exposure episodes were considered continuous if gaps in days supplied were 14 days or less. The end date of each exposure episode was extended by 14 additional days. Follow-up began on the first day of exposure initiation and continued until the first occurrence of any of the following: 1) an outcome diagnosis; 2) a dispensing of statins or novel anticoagulants; 3) disenrollment; 4) disenrollment due to death; 5) cessation of study drug use (defined as when the days supply was exhausted for longer than 14 days without a subsequent dispensing; or 6) end of monitoring period (varies by Data Partner). Only the first valid exposure episode that occurred during the study period was included per patient.
Outcome of Interest : GI bleed was defined using ICD-9-CM diagnosis codes (see Appendix D) flagged as an incident (no GI bleed events in the 183 days prior to exposure initiation), primary diagnosis in an inpatient encounter.

Propensity Score : The following covariates were assessed during the baseline period and were included in the Propensity Score (PS): age, sex, comorbidity score, health service utilization, advanced liver disease, alcohol abuse or dependence, end state renal disease, other non-GI bleed, other GI ulcer disease or perforation, other GI diverticula or non-hemorrhagic angiodysplasia of stomach or intestine, personal history of peptic ulcer disease, renal disease, tobacco use, bariatric surgery, history of bariatric surgery, sepsis and related, shock, inflammatory bowel disease, intestinal infection, gastritis or gastroenteritis, *Helicobacter pylori* infection, obesity, antiplatelet agents and aspirin use, H2RA or sucralfate use, antibiotic combination products for *Helicobacter pylori* use, cox-2 inhibitor use, heparin use, methotrexate use, NSAID use, opioid use, respiratory opioid use, oral glucocorticoids use, PPI use, and SSRI or SNRI use (See Appendices E and F). Occurrence of these covariates was evaluated in the 183 days prior to the date of exposure initiation. The Propensity Score Matching (PSM) tool was used to calculate the PSs, identify matched cohorts based on PSs, and perform matched cohort analyses using Cox proportional hazards regression yielding hazard ratios (HRs) and 95% confidence intervals (CIs). PS calculation and matching was performed separately within each Data Partner site.

Matching: The matching ratios for the propensity score were 1:1 and 1:10. For the 1:1 matching ratio analysis, patients in the exposed and comparator cohorts were nearest neighbor matched without replacement, meaning that each comparator patient was matched one time, at most, to an exposed patient. For the 1:10 matching ratio analysis, the 1:1 matching process was repeated multiple times until there were no more potential matches left, or until all treatment patients were matched to ten comparator patients. The matching caliper was 0.01.

Effect Estimates : Cox proportional hazards regression models were used to estimate hazard ratios and corresponding 95% CIs for the following:
- Unmatched analysis, with site adjustment only
- 1:1 matched analysis stratified by matched pair and site, with adjustment for heparin
- 1:1 matched analysis stratified by site and NOT stratified by matched pair, with adjustment for heparin
- 1:10 matched analysis stratified by matched pair and site, with adjustment for heparin

See Appendix G for complete specifications for this request.

Limitations: 1) As with all observational studies, this evaluation was limited in its ability to control for all sources of potential bias. 2) The exposures, outcome, exclusions, and covariates may have been misclassified due to imperfect algorithms used to identify them.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (qf@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

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Glossary of Terms for Analyses Using Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the Sentinel Common Data Model.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). Along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

- **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
- **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
- **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
- **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
- **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Caresetting/PDX parameter.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the episode

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled” sequence.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment

Event Deduplication - specifies how events are counted by the MP algorithm: (0) 0: Counts all occurrences of an HOI during an exposure episode; (1) 1: de-duplicates occurrences of the same HOI code and code type on the same day; (2) 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Member-Years - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an exposure washout period all

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered.

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Glossary of Terms for Analyses Using Propensity Score Match (PSM) Tool*

Bias Ranking - method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which variables are selected as ranked by the Bross bias formula.

Covariate Evaluation Window - number of days before the index date to evaluate the occurrence of covariates of interest. Note: members are required to have continuous enrollment during the covariate evaluation window, regardless of the value included in the "Continuous

Covariate Grouping Indicator - a requester-defined name used to indicate how codes should be grouped to identify a single covariate.

Exposure association ranking- default method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of the relationship between confounder and exposure. This is most suitable for cases where there are fewer than 150 exposed outcomes.

High dimensional Propensity Score (hdPS) - allows for selection of empirically identified covariates in addition to and/or without predefined covariates based on the potential for confounding the exposure/outcome association under investigation.

Mahalanobis Distance- provides a measure of balance across all variables while accounting for their correlation.

Matching Caliper- maximum allowed difference in propensity scores between treatment and control patients. Options are 0.01, 0.025, and

Matching Ratio - patients in exposed and comparators are nearest neighbor matched by a 1:1 or 1:100 (up to 100) matching ratio.

Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

Number of covariates from pool of considered covariates to keep in hdPS model - The total number of covariates to keep in the hdPS model. Default value is the fewest of 1) 200; or 2) the number of initiators of the exposure of interest.

Number of covariates to consider for each claim type for inclusion in hdPS model - The number of covariates that are considered for inclusion in the hdPS model for each claim type (NDC, ICD9 diagnosis, ICD9 procedure, HCPCS, and CPT). If a value of 100 is specified in this field, then 500 covariates will be considered for inclusion (100 for each of the 5 claim types), Default value is 100.

Outcome Association Ranking- method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of the relationship between confounder and the outcome. This is most suitable for

Predefined Propensity Score Matched Analysis - performed by default using the Propensity Score Match Tool. Requester-defined covariates are included along with 12 other covariates: 1. Age (continuous) 2. Sex 3. Time (monitoring period) 4. Year of Exposure 5. Comorbidity Score (calculated during requester-defined lookback) 6. Medical Utilization- number of inpatient stays (during requester-defined lookback) 7. Medical Utilization- number of institutional stays (during requester-defined lookback) 8. Medical utilization- number of emergency department visits (during requester-defined lookback) 9. Medical utilization- number of outpatient visits (during requester-defined lookback) 10. Health care utilization- number of other ambulatory encounters (e.g telemedicine, email consults during requester-defined lookback) 11. Drug utilization- number of dispensings (during requester-defined lookback) 12. Drug utilization- number of unique generics dispensed

Propensity Score Match Tool - performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts. The Propensity Score Match Tool generates tables of patient characteristics, stratified by exposure group, for the unmatched cohort and for the 1:1 matched cohort. Tables include measures of covariate balance and the Mahalanobis distance. The program also generates histograms depicting the propensity score distributions for each exposure group, separately for each Data Partner and each monitoring period, before and after matching. Figures include c-statistics. This program provides hazard ratios and 95% confidence intervals, Mantel-Haenszel rate

Query Level - Mini-Sentinel routine data queries are grouped into three distinct "levels," indicative of the level of complexity, extent of analytic adjustment, and need for repeated execution and alerting tools (i.e., prospective surveillance).

Zero Cell Correction - An indicator for whether to screen variables with a zero correction added to each cell in the confounder/outcome 2x2 table. Recommended when the number of exposed outcomes is fewer than 150.

*all terms may not be used in this report

Table 1. Cohort of New Initiators of Warfarin and Statins at Risk for Gastrointestinal Bleeding (Unmatched)

	Medical Product				Covariate Balance	
	Warfarin		Statins			
Patients (N)	141,398	100.0%	2,275,694	100.0%		
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patient Characteristics						
Mean Age (Std Dev)	61.8	14.4	58.2	11.3	3.637	0.281
18-64 Years	81,335	57.5%	1,627,759	71.5%	-14.006	-0.296
65-74 Years	28,990	20.9%	430,668	19.3%	1.657	0.041
75+ Years	31,073	22.4%	217,267	9.7%	12.703	0.351
Gender (Female)	73,546	52.0%	1,077,689	47.4%	4.657	0.093
Recorded History of:						
Combined Comorbidity Score	1.3	2.0	0.2	1.3	1.128	0.659
Advanced Liver Disease	492	0.3%	1,489	0.1%	0.283	0.062
Alcohol Abuse or Dependence	3,699	2.6%	26,686	1.2%	1.443	0.106
Bariatric Surgery	241	0.2%	1,071	0.0%	0.123	0.037
End Stage Renal Disease	1,330	0.9%	6,335	0.3%	0.662	0.085
Gastritis or Gastroenteritis	4,945	3.5%	56,015	2.5%	1.036	0.061
Helicobacter pylori Infection	254	0.2%	5,960	0.3%	-0.082	-0.018
History of Bariatric Surgery	1,626	1.1%	4,787	0.2%	0.940	0.115
History of Peptic Ulcer	472	0.3%	2,041	0.1%	0.244	0.053
Inflammatory Bowel Disease	1,452	1.0%	8,585	0.4%	0.650	0.078
Intestinal Infections	810	0.6%	7,386	0.3%	0.248	0.037
Obesity	25,195	17.8%	238,957	10.5%	7.318	0.211
Other GI Diverticula	6,004	4.2%	59,310	2.6%	1.640	0.090
Other GI Ulcer Disease	1,379	1.0%	9,109	0.4%	0.575	0.070
Other Non-GI Bleed	6,454	4.6%	54,882	2.4%	2.153	0.118
Renal Disease	13,495	9.5%	116,196	5.1%	4.438	0.171
Sepsis	4,724	3.3%	11,610	0.5%	2.831	0.207
Shock	1,651	1.2%	4,888	0.2%	0.953	0.115
Tobacco Use	22,725	16.1%	214,106	9.4%	6.663	0.201
History of Use:						
Antiplatelet Agents and Aspirin	4,191	3.0%	88,208	3.9%	-0.912	-0.050
Antibiotic Combination Products for *H. pylori*	43	0.0%	1,413	0.1%	-0.032	-0.015
Cox-2 Inhibitors	3,493	2.5%	19,619	0.9%	1.608	0.126
H2RA and Sucralfate	4,205	3.0%	49,697	2.2%	0.790	0.050
Heparins	6,893	4.9%	3,205	0.1%	4.734	0.306
Methotrexate	1,645	1.2%	12,353	0.5%	0.621	0.068
NSAIDs	24,820	17.6%	308,710	13.6%	3.988	0.110
Opioids	52,962	37.5%	459,615	20.2%	17.259	0.388
Oral Glucocorticoids	19,364	13.7%	208,211	9.1%	4.545	0.143
Ppis	21,231	15.0%	297,872	13.1%	1.926	0.055
SSRIs and SNRIs	21,836	15.4%	339,230	14.9%	0.536	0.015
Respiratory Opioids	3,491	2.5%	53,370	2.3%	0.124	0.008
Health Service Utilization Intensity:	Mean	Std Dev	Mean	Std Dev		
Mean number of ambulatory encounters	9.6	9.6	5.5	6.8	4.190	0.504
Mean number of other ambulatory encounters	3.3	5.9	1.5	3.1	1.779	0.375
Mean number of emergency room encounters	0.5	1.2	0.2	0.7	0.321	0.331
Mean number of inpatient hospital encounters	0.7	0.8	0.1	0.4	0.575	0.886
Mean number of non-acute institutional encounters	0.2	0.9	0	0.4	0.170	0.246
Mean number of filled RX	12.2	12.8	9.7	10.8	2.519	0.212
Mean number of generics	5.3	4.4	4.2	3.8	1.164	0.284
Mean number of unique drug classes	5.2	4.2	4.1	3.6	1.122	0.283

[1] Value represents standard deviation where no % follows the value

Table 2. Cohort of New Initiators of Warfarin and Statins at Risk for Gastrointestinal Bleeding (Matched 1:1 Predefined Propensity Score, Caliper = .01)

	Medical Product				Covariate Balance	
	Warfarin		Statins			
Patients (N)	137,418	97.2%	137,418	6.0%		
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patient Characteristics						
Mean Age (Std Dev)	61.9	14.4	62.8	12.2	-0.993	-0.075
18-64 Years	79,023	58%	78,668	57.2%	0.258	0.005
65-74 Years	28,104	21%	30,606	22.7%	-1.855	-0.045
75+ Years	30,291	22.5%	28,144	20.9%	1.592	0.039
Gender (Female)	70,864	51.6%	69,859	50.8%	0.731	0.015
Recorded History of:						
Combined Comorbidity Score	1.3	2.0	1.4	2.2	-0.124	-0.059
Advanced Liver Disease	473	0.3%	443	0.3%	0.022	0.004
Alcohol Abuse or Dependence	3,547	2.6%	3,966	2.9%	-0.305	-0.019
Bariatric Surgery	224	0.2%	188	0.1%	0.026	0.007
End Stage Renal Disease	1,296	0.9%	1,336	1.0%	-0.029	-0.003
Gastritis or Gastroenteritis	4,773	3.5%	4,781	3.5%	-0.006	0.000
Helicobacter pylori Infection	247	0.2%	255	0.2%	-0.006	-0.001
History of Bariatric Surgery	1,459	1.1%	1,344	1.0%	0.084	0.008
History of Peptic Ulcer	435	0.3%	476	0.3%	-0.030	-0.005
Inflammatory Bowel Disease	1,379	1.0%	1,368	1.0%	0.008	0.001
Intestinal Infections	793	0.6%	822	0.6%	-0.021	-0.003
Obesity	23,944	17.4%	25,264	18.4%	-0.961	-0.025
Other GI Diverticula	5,760	4.2%	6,024	4.4%	-0.192	-0.009
Other GI Ulcer Disease	1,337	1.0%	1,334	1.0%	0.002	0.000
Other Non-GI Bleed	6,186	4.5%	6,379	4.6%	-0.140	-0.007
Renal Disease	13,036	9.5%	13,899	10.1%	-0.628	-0.021
Sepsis	4,490	3.3%	4,141	3.0%	0.254	0.015
Shock	1,584	1.2%	1,617	1.2%	-0.024	-0.002
Tobacco Use	21,673	15.8%	24,655	17.9%	-2.170	-0.058
History of Use:						
Antiplatelet Agents and Aspirin	4,145	3.0%	4,760	3.5%	-0.448	-0.025
Antibiotic Combination Products for *H. pylori*	43	0.0%	44	0.0%	-0.001	0.000
Cox-2 Inhibitors	3,353	2.4%	3,514	2.6%	-0.117	-0.008
H2RA and Sucralfate	4,025	2.9%	4,022	2.9%	0.002	0.000
Heparins	6,037	4.4%	2,510	1.8%	2.567	0.148
Methotrexate	1,572	1.1%	1,706	1.2%	-0.098	-0.009
NSAIDs	23,897	17.4%	24,444	17.8%	-0.398	-0.010
Opioids	50,689	36.9%	53,446	38.9%	-2.006	-0.041
Oral Glucocorticoids	18,762	13.7%	19,443	14.1%	-0.496	-0.014
Ppis	20,491	14.9%	20,768	15.1%	-0.202	-0.006
SSRIs and SNRIs	21,118	15.4%	20,796	15.1%	0.234	0.007
Respiratory Opioids	3,383	2.5%	3,462	2.5%	-0.057	-0.004
Health Service Utilization Intensity:	Mean	Std Dev	Mean	Std Dev		
Mean number of ambulatory encounters	9.6	9.6	9.9	12.2	-0.287	-0.026
Mean number of other ambulatory encounters	3.1	5.7	3.1	5.9	0.020	0.004
Mean number of emergency room encounters	0.5	1.2	0.6	1.2	-0.044	-0.037
Mean number of inpatient hospital encounters	0.7	0.8	0.7	0.9	-0.014	-0.016
Mean number of non-acute institutional encounters	0.2	0.9	0.2	0.9	0.015	0.018
Mean number of filled RX	12.2	12.8	12.4	13.4	-0.260	-0.020
Mean number of generics	5.3	4.4	5.4	4.7	-0.104	-0.023
Mean number of unique drug classes	5.2	4.2	5.3	4.5	-0.079	-0.018

[1] Value represents standard deviation where no % follows the value

Table 3. Cohort of New Initiators of Warfarin and Statins at Risk for Gastrointestinal Bleeding (Matched 1:10 Predefined Propensity Score, Caliper = .01)

	Medical Product				Covariate Balance	
	Warfarin		Statins			
Patients (N)	137,418	97.2%	786,569	34.6%		
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patient Characteristics						
Mean Age (Std Dev)	61.9	14.4	62.8	12.2	-0.971	-0.073
18-64 Years	79,023	58%	78,883	57.4%	0.102	0.002
65-74 Years	28,104	21%	30,425	22.6%	-1.721	-0.043
75+ Years	30,291	22.5%	28,110	20.8%	1.618	0.041
Gender (Female)	70,864	51.6%	69,855	50.8%	0.734	0.015
Recorded History of:						
Combined Comorbidity Score	1.3	2.0	1.4	2.2	-0.125	-0.059
Advanced Liver Disease	473	0.3%	422	0.3%	0.037	0.007
Alcohol Abuse or Dependence	3,547	2.6%	3,982	2.9%	-0.316	-0.019
Bariatric Surgery	224	0.2%	203	0.1%	0.015	0.004
End Stage Renal Disease	1,296	0.9%	1,329	1.0%	-0.024	-0.002
Gastritis or Gastroenteritis	4,773	3.5%	4,805	3.5%	-0.023	-0.001
Helicobacter pylori Infection	247	0.2%	257	0.2%	-0.007	-0.002
History of Bariatric Surgery	1,459	1.1%	1,353	1.0%	0.077	0.008
History of Peptic Ulcer	435	0.3%	456	0.3%	-0.015	-0.003
Inflammatory Bowel Disease	1,379	1.0%	1,394	1.0%	-0.011	-0.001
Intestinal Infections	793	0.6%	802	0.6%	-0.007	-0.001
Obesity	23,944	17.4%	25,249	18.4%	-0.950	-0.025
Other GI Diverticula	5,760	4.2%	5,973	4.3%	-0.155	-0.008
Other GI Ulcer Disease	1,337	1.0%	1,303	0.9%	0.025	0.003
Other Non-GI Bleed	6,186	4.5%	6,293	4.6%	-0.078	-0.004
Renal Disease	13,036	9.5%	13,828	10.1%	-0.576	-0.020
Sepsis	4,490	3.3%	4,100	3.0%	0.284	0.016
Shock	1,584	1.2%	1,636	1.2%	-0.038	-0.003
Tobacco Use	21,673	15.8%	24,828	18.1%	-2.296	-0.062
History of Use:						
Antiplatelet Agents and Aspirin	4,145	3.0%	4,813	3.5%	-0.486	-0.027
Antibiotic Combination Products for *H. pylori*	43	0.0%	42	0.0%	0.000	0.000
Cox-2 Inhibitors	3,353	2.4%	3,511	2.6%	-0.115	-0.007
H2RA and Sucralfate	4,025	2.9%	4,064	3.0%	-0.028	-0.002
Heparins	6,037	4.4%	2,514	1.8%	2.564	0.148
Methotrexate	1,572	1.1%	1,706	1.2%	-0.097	-0.009
NSAIDs	23,897	17.4%	24,709	18.0%	-0.591	-0.016
Opioids	50,689	36.9%	53,663	39.1%	-2.164	-0.045
Oral Glucocorticoids	18,762	13.7%	19,659	14.3%	-0.652	-0.019
Ppis	20,491	14.9%	20,680	15.0%	-0.138	-0.004
SSRIs and SNRIs	21,118	15.4%	20,888	15.2%	0.167	0.005
Respiratory Opioids	3,383	2.5%	3,452	2.5%	-0.051	-0.003
Health Service Utilization Intensity:	Mean	Std Dev	Mean	Std Dev		
Mean number of ambulatory encounters	9.6	9.6	9.9	12.3	-0.275	-0.025
Mean number of other ambulatory encounters	3.1	5.7	3.1	5.9	0.022	0.004
Mean number of emergency room encounters	0.5	1.2	0.6	1.2	-0.043	-0.037
Mean number of inpatient hospital encounters	0.7	0.8	0.7	0.9	-0.013	-0.015
Mean number of non-acute institutional encounters	0.2	0.9	0.2	0.9	0.014	0.017
Mean number of filled RX	12.2	12.8	12.5	13.5	-0.313	-0.024
Mean number of generics	5.3	4.4	5.4	4.7	-0.114	-0.025
Mean number of unique drug classes	5.2	4.2	5.3	4.5	-0.089	-0.020

[1] Value represents standard deviation where no % follows the value

Table 4: Effect Estimates for Gastrointestinal Bleeding by Analysis Type

Medical Product	Number of New Users	Person Years at Risk	Average Person Days at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1000 Person Years	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person Years	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Warfarin	141,398	51,449.25	132.90	0.36	813	15.802	5.75	13.30	4.60	5.94 (5.49, 6.43)	<.0001
Statins	2,275,694	1,043,272.07	167.45	0.46	2610	2.502	1.15				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	137,418	26,481.61	70.39	0.19	553	20.882	4.02	12.95	2.50	2.78 (2.36, 3.28)	<.0001
Statins	137,418	26,481.61	70.39	0.19	210	7.930	1.53				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model NOT Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	137,418	50,333.94	133.79	0.37	802	15.934	5.84	9.42	2.47	2.22 (1.97, 2.49)	<.0001
Statins	137,418	71,090.12	188.95	0.52	463	6.513	3.37				
1:10 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	137,418	39,165.19	104.10	0.29	664	16.954	4.83	12.41	3.95	3.10 (2.76, 3.49)	<.0001
Statins	786,569	152,685.78	70.90	0.19	694	4.545	0.88				

Sentinel

Table 5: Effect Estimates for Gastrointestinal Bleeding by Analysis Type and Age Group

Medical Product	Number of New Users	Person Years at Risk	Average Person Days at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1000 Person Years	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person Years	Risk Difference per 1000 New Users	Hazard Ratio (95% CI)	Wald P-Value
Ages 18-64 Years											
Unmatched Analysis (Site-adjusted only)											
Warfarin	81,335	26,913.53	120.86	0.33	229	8.509	2.82	7.34	2.32	6.97 (6.01, 8.08)	<.0001
Statins	1,627,759	687,497.08	154.27	0.42	803	1.168	0.49				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	78,134	14,093.20	65.88	0.18	169	11.992	2.16	8.02	1.45	3.35 (2.43, 4.63)	<.0001
Statins	78,134	14,093.20	65.88	0.18	56	3.974	0.72				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model NOT Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	78,134	25,928.31	121.21	0.33	225	8.678	2.88	5.39	1.32	2.29 (1.83, 2.86)	<.0001
Statins	78,134	37,096.16	173.41	0.47	122	3.289	1.56				
1:10 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	78,134	20,462.56	95.66	0.26	199	9.725	2.55	7.60	2.16	4.01 (3.21, 5.02)	<.0001
Statins	462,928	83,429.82	65.83	0.18	177	2.122	0.38				
Ages 65-74 Years											
Unmatched Analysis (Site-adjusted only)											
Warfarin	28,990	10,631.85	133.95	0.37	204	19.188	7.04	15.77	5.16	5.59 (4.79, 6.53)	<.0001
Statins	430,668	236,403.44	200.49	0.55	807	3.414	1.87				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	27,992	5,701.41	74.39	0.20	128	22.451	4.57	12.98	2.64	2.46 (1.78, 3.41)	<.0001
Statins	27,992	5,701.41	74.39	0.20	54	9.471	1.93				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model NOT Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	27,992	10,401.04	135.72	0.37	200	19.229	7.14	12.02	2.82	2.38 (1.89, 3.00)	<.0001
Statins	27,992	16,790.23	219.09	0.60	121	7.207	4.32				
1:10 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	27,992	8,523.63	111.22	0.30	164	19.241	5.86	13.85	4.73	3.03 (2.42, 3.80)	<.0001
Statins	164,565	34,344.14	76.23	0.21	185	5.387	1.12				

Ages 75+ Years											
Unmatched Analysis (Site-adjusted only)											
Warfarin	31,073	13,903.87	163.43	0.45	380	27.331	12.23	18.95	7.63	3.29 (2.92, 3.71)	<.0001
Statins	217,267	119,371.55	200.68	0.55	1,000	8.377	4.60				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	30,426	6,633.15	79.63	0.22	238	35.880	7.82	20.50	4.47	2.31 (1.83, 2.92)	<.0001
Statins	30,426	6,633.15	79.63	0.22	102	15.377	3.35				
1:1 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model NOT Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	30,426	13,705.77	164.53	0.45	377	27.507	12.39	13.68	4.63	1.87 (1.59, 2.20)	<.0001
Statins	30,426	17,071.51	204.94	0.56	236	13.824	7.76				
1:10 Matched Predefined PS Analysis; Caliper=0.01 (Cox Model Stratified by Matched Pair and Adjusted for Heparin Use)											
Warfarin	30,426	10,109.75	121.36	0.33	309	30.565	10.16	19.89	7.74	2.54 (2.16, 2.99)	<.0001
Statins	151,415	34,285.05	82.70	0.23	366	10.675	2.42				

Note: Subgroup re-matching was not limited to members who were matched in the full analysis.

Appendix A. Generic and Brand Names Used to Define Warfarin and Novel Anticoagulants in this Request

Brand Name	Generic Name
Coumadin	WARFARIN SODIUM
warfarin	WARFARIN SODIUM
Jantoven	WARFARIN SODIUM
Eliquis	APIXABAN
Pradaxa	DABIGATRAN ETEXILATE MESYLATE
Xarelto	RIVAROXABAN
Savaysa	EDOXABAN TOSYLATE

Appendix B. Generic and Brands Names Used to Define Statins in this Request

Brand Name	Generic Name
Pravachol	PRAVASTATIN SODIUM
Juvisync	SITAGLIPTIN PHOSPHATE/SIMVASTATIN
Zocor	SIMVASTATIN
Mevacor	LOVASTATIN
Caduet	AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM
Lipitor	ATORVASTATIN CALCIUM
Advicor	NIACIN/LOVASTATIN
Simcor	NIACIN/SIMVASTATIN
Lescol	FLUVASTATIN SODIUM
Lescol XL	FLUVASTATIN SODIUM
lovastatin	LOVASTATIN
pravastatin	PRAVASTATIN SODIUM
simvastatin	SIMVASTATIN
fluvastatin	FLUVASTATIN SODIUM
atorvastatin	ATORVASTATIN CALCIUM
Crestor	ROSUVASTATIN CALCIUM
amlodipine-atorvastatin	AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM
Vytorin 10-40	EZETIMIBE/SIMVASTATIN
Vytorin 10-20	EZETIMIBE/SIMVASTATIN
Vytorin 10-10	EZETIMIBE/SIMVASTATIN
Vytorin 10-80	EZETIMIBE/SIMVASTATIN
Altoprev	LOVASTATIN
Liptruzet	EZETIMIBE/ATORVASTATIN CALCIUM

Appendix C. International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes Used to Define Exclusions in this Request

Code	Code Type	Description
140	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
141	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
142	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
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238	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
239	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
230.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
231.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
232.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
233.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
234.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
235.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
236.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
237.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
238.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
239.*	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
230.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
231.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
232.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
233.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
234.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
235.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
236.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
237.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
238.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
239.**	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
273.0	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
273.3	ICD-9 CM Diagnosis	Malignancy or blood/lymph cancer
S9126	ICD-9 CM Diagnosis	Hospice care
747.61	ICD-9 CM Diagnosis	Gastrointestinal vessel congenital anomaly
V83.02	ICD-9 CM Diagnosis	Sympotomatic hemophilia A carrier
V44.0	ICD-9 CM Diagnosis	Artificial opening of GI tract
V44.1	ICD-9 CM Diagnosis	Artificial opening of GI tract
V44.2	ICD-9 CM Diagnosis	Artificial opening of GI tract
V44.3	ICD-9 CM Diagnosis	Artificial opening of GI tract
V44.4	ICD-9 CM Diagnosis	Artificial opening of GI tract
284	ICD-9 CM Diagnosis	Aplastic anemia and other bone marrow failure syndromes
284.*	ICD-9 CM Diagnosis	Aplastic anemia and other bone marrow failure syndromes
284.**	ICD-9 CM Diagnosis	Aplastic anemia and other bone marrow failure syndromes
286	ICD-9 CM Diagnosis	Coagulation defects
286.*	ICD-9 CM Diagnosis	Coagulation defects
286.**	ICD-9 CM Diagnosis	Coagulation defects
535.71	ICD-9 CM Diagnosis	Other GI Bleed
530.21	ICD-9 CM Diagnosis	GI Bleed
531.0	ICD-9 CM Diagnosis	GI Bleed
531.0*	ICD-9 CM Diagnosis	GI Bleed
531.1	ICD-9 CM Diagnosis	GI Bleed
531.1*	ICD-9 CM Diagnosis	GI Bleed
531.2	ICD-9 CM Diagnosis	GI Bleed
531.2*	ICD-9 CM Diagnosis	GI Bleed
531.4	ICD-9 CM Diagnosis	GI Bleed
531.4*	ICD-9 CM Diagnosis	GI Bleed
531.6	ICD-9 CM Diagnosis	GI Bleed
531.6*	ICD-9 CM Diagnosis	GI Bleed
532.0	ICD-9 CM Diagnosis	GI Bleed
532.0*	ICD-9 CM Diagnosis	GI Bleed
532.1	ICD-9 CM Diagnosis	GI Bleed

532.1*	ICD-9 CM Diagnosis	GI Bleed
532.2	ICD-9 CM Diagnosis	GI Bleed
532.2*	ICD-9 CM Diagnosis	GI Bleed
532.4	ICD-9 CM Diagnosis	GI Bleed
532.4*	ICD-9 CM Diagnosis	GI Bleed
532.6	ICD-9 CM Diagnosis	GI Bleed
532.6*	ICD-9 CM Diagnosis	GI Bleed
533.1	ICD-9 CM Diagnosis	GI Bleed
533.1*	ICD-9 CM Diagnosis	GI Bleed
533.2	ICD-9 CM Diagnosis	GI Bleed
533.2*	ICD-9 CM Diagnosis	GI Bleed
533.4	ICD-9 CM Diagnosis	GI Bleed
533.4*	ICD-9 CM Diagnosis	GI Bleed
533.6	ICD-9 CM Diagnosis	GI Bleed
533.6*	ICD-9 CM Diagnosis	GI Bleed
534.0	ICD-9 CM Diagnosis	GI Bleed
534.0*	ICD-9 CM Diagnosis	GI Bleed
534.1	ICD-9 CM Diagnosis	GI Bleed
534.1*	ICD-9 CM Diagnosis	GI Bleed
534.2	ICD-9 CM Diagnosis	GI Bleed
534.2*	ICD-9 CM Diagnosis	GI Bleed
534.4	ICD-9 CM Diagnosis	GI Bleed
534.4*	ICD-9 CM Diagnosis	GI Bleed
534.6	ICD-9 CM Diagnosis	GI Bleed
534.6*	ICD-9 CM Diagnosis	GI Bleed
535.01	ICD-9 CM Diagnosis	GI Bleed
535.11	ICD-9 CM Diagnosis	GI Bleed
535.21	ICD-9 CM Diagnosis	GI Bleed
535.31	ICD-9 CM Diagnosis	GI Bleed
535.41	ICD-9 CM Diagnosis	GI Bleed
535.51	ICD-9 CM Diagnosis	GI Bleed
535.61	ICD-9 CM Diagnosis	GI Bleed
537.83	ICD-9 CM Diagnosis	GI Bleed
537.84	ICD-9 CM Diagnosis	GI Bleed
562.02	ICD-9 CM Diagnosis	GI Bleed
562.03	ICD-9 CM Diagnosis	GI Bleed
562.12	ICD-9 CM Diagnosis	GI Bleed
562.13	ICD-9 CM Diagnosis	GI Bleed
569.86	ICD-9 CM Diagnosis	GI Bleed
456.0	ICD-9 CM Diagnosis	GI Bleed
456.20	ICD-9 CM Diagnosis	GI Bleed
530.7	ICD-9 CM Diagnosis	GI Bleed
530.82	ICD-9 CM Diagnosis	GI Bleed
455.2	ICD-9 CM Diagnosis	GI Bleed
455.5	ICD-9 CM Diagnosis	GI Bleed
455.8	ICD-9 CM Diagnosis	GI Bleed
568.81	ICD-9 CM Diagnosis	GI Bleed
569.3	ICD-9 CM Diagnosis	GI Bleed
533.0	ICD-9 CM Diagnosis	GI Bleed
533.0*	ICD-9 CM Diagnosis	GI Bleed
569.85	ICD-9 CM Diagnosis	GI Bleed
578	ICD-9 CM Diagnosis	GI Bleed
578.*	ICD-9 CM Diagnosis	GI Bleed

Appendix D. International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes Used to Define Gastrointestinal Bleeding in this Request

Code	Code Type
455.2	ICD-9 CM Diagnosis
455.5	ICD-9 CM Diagnosis
455.8	ICD-9 CM Diagnosis
456.0	ICD-9 CM Diagnosis
456.20	ICD-9 CM Diagnosis
530.21	ICD-9 CM Diagnosis
530.7	ICD-9 CM Diagnosis
530.82	ICD-9 CM Diagnosis
531.0	ICD-9 CM Diagnosis
531.1	ICD-9 CM Diagnosis
531.2	ICD-9 CM Diagnosis
531.4	ICD-9 CM Diagnosis
531.6	ICD-9 CM Diagnosis
532.0	ICD-9 CM Diagnosis
532.1	ICD-9 CM Diagnosis
532.2	ICD-9 CM Diagnosis
532.4	ICD-9 CM Diagnosis
532.6	ICD-9 CM Diagnosis
533.0	ICD-9 CM Diagnosis
533.1	ICD-9 CM Diagnosis
533.2	ICD-9 CM Diagnosis
533.4	ICD-9 CM Diagnosis
533.6	ICD-9 CM Diagnosis
534.0	ICD-9 CM Diagnosis
534.1	ICD-9 CM Diagnosis
534.2	ICD-9 CM Diagnosis
534.4	ICD-9 CM Diagnosis
534.6	ICD-9 CM Diagnosis
535.01	ICD-9 CM Diagnosis
535.11	ICD-9 CM Diagnosis
535.21	ICD-9 CM Diagnosis
535.31	ICD-9 CM Diagnosis
535.41	ICD-9 CM Diagnosis
535.51	ICD-9 CM Diagnosis
535.61	ICD-9 CM Diagnosis
537.83	ICD-9 CM Diagnosis
537.84	ICD-9 CM Diagnosis
562.02	ICD-9 CM Diagnosis
562.03	ICD-9 CM Diagnosis
562.12	ICD-9 CM Diagnosis
562.13	ICD-9 CM Diagnosis
568.81	ICD-9 CM Diagnosis
569.3	ICD-9 CM Diagnosis
569.85	ICD-9 CM Diagnosis
569.86	ICD-9 CM Diagnosis
578.0	ICD-9 CM Diagnosis
578	ICD-9 CM Diagnosis
531.0*	ICD-9 CM Diagnosis
531.1*	ICD-9 CM Diagnosis
531.2*	ICD-9 CM Diagnosis
531.4*	ICD-9 CM Diagnosis

531.6*	ICD-9 CM Diagnosis
532.0*	ICD-9 CM Diagnosis
532.1*	ICD-9 CM Diagnosis
532.2*	ICD-9 CM Diagnosis
532.4*	ICD-9 CM Diagnosis
532.6*	ICD-9 CM Diagnosis
533.0*	ICD-9 CM Diagnosis
533.1*	ICD-9 CM Diagnosis
533.2*	ICD-9 CM Diagnosis
533.4*	ICD-9 CM Diagnosis
533.6*	ICD-9 CM Diagnosis
534.0*	ICD-9 CM Diagnosis
534.1*	ICD-9 CM Diagnosis
534.2*	ICD-9 CM Diagnosis
534.4*	ICD-9 CM Diagnosis
534.6*	ICD-9 CM Diagnosis
578.*	ICD-9 CM Diagnosis

Appendix E. International Classification of Diseases, Ninth Revision, Clinical Modification Diagnosis Codes Used to Define Diagnosis and Procedure Covariates in this Request

Covariate	Code	Code Type
AdvancedLiverDisease	456.0	ICD9-CM Diagnosis
AdvancedLiverDisease	456.0*	ICD9-CM Diagnosis
AdvancedLiverDisease	456.1	ICD9-CM Diagnosis
AdvancedLiverDisease	456.1*	ICD9-CM Diagnosis
AdvancedLiverDisease	456.2	ICD9-CM Diagnosis
AdvancedLiverDisease	456.2*	ICD9-CM Diagnosis
AdvancedLiverDisease	572.2	ICD9-CM Diagnosis
AdvancedLiverDisease	572.2*	ICD9-CM Diagnosis
AdvancedLiverDisease	572.3	ICD9-CM Diagnosis
AdvancedLiverDisease	572.3*	ICD9-CM Diagnosis
AdvancedLiverDisease	572.4	ICD9-CM Diagnosis
AdvancedLiverDisease	572.4*	ICD9-CM Diagnosis
AdvancedLiverDisease	572.8	ICD9-CM Diagnosis
AdvancedLiverDisease	572.8*	ICD9-CM Diagnosis
AlcoholAbuseorDependence	V11.3	ICD9-CM Diagnosis
AlcoholAbuseorDependence	291.0	ICD9-CM Diagnosis
AlcoholAbuseorDependence	291.1	ICD9-CM Diagnosis
AlcoholAbuseorDependence	291.2	ICD9-CM Diagnosis
AlcoholAbuseorDependence	291.3	ICD9-CM Diagnosis
AlcoholAbuseorDependence	291.5	ICD9-CM Diagnosis
AlcoholAbuseorDependence	291.8*	ICD9-CM Diagnosis
AlcoholAbuseorDependence	291.9	ICD9-CM Diagnosis
AlcoholAbuseorDependence	303.0*	ICD9-CM Diagnosis
AlcoholAbuseorDependence	303.9*	ICD9-CM Diagnosis
AlcoholAbuseorDependence	305.0*	ICD9-CM Diagnosis
AlcoholAbuseorDependence	357.5	ICD9-CM Diagnosis
AlcoholAbuseorDependence	425.5	ICD9-CM Diagnosis
AlcoholAbuseorDependence	535.3*	ICD9-CM Diagnosis
AlcoholAbuseorDependence	571.0	ICD9-CM Diagnosis
AlcoholAbuseorDependence	571.1	ICD9-CM Diagnosis
AlcoholAbuseorDependence	571.2	ICD9-CM Diagnosis
AlcoholAbuseorDependence	571.3	ICD9-CM Diagnosis
AlcoholAbuseorDependence	980.0	ICD9-CM Diagnosis
EndStageRenalDisease	585.6	ICD9-CM Diagnosis
EndStageRenalDisease	585.6*	ICD9-CM Diagnosis
OtherNonGIBleed	423.0	ICD9-CM Diagnosis
OtherNonGIBleed	459.0	ICD9-CM Diagnosis
OtherNonGIBleed	599.7	ICD9-CM Diagnosis
OtherNonGIBleed	599.7*	ICD9-CM Diagnosis
OtherNonGIBleed	719.1	ICD9-CM Diagnosis
OtherNonGIBleed	719.1*	ICD9-CM Diagnosis
OtherNonGIBleed	784.7	ICD9-CM Diagnosis
OtherNonGIBleed	784.8	ICD9-CM Diagnosis
OtherNonGIBleed	786.3	ICD9-CM Diagnosis
OtherNonGIBleed	786.3*	ICD9-CM Diagnosis
OtherGIUlcerDisease	530.20	ICD9-CM Diagnosis
OtherGIUlcerDisease	531.3	ICD9-CM Diagnosis
OtherGIUlcerDisease	531.3*	ICD9-CM Diagnosis
OtherGIUlcerDisease	531.5	ICD9-CM Diagnosis
OtherGIUlcerDisease	531.5*	ICD9-CM Diagnosis

OtherGIUlcerDisease	531.7	ICD9-CM Diagnosis
OtherGIUlcerDisease	531.7*	ICD9-CM Diagnosis
OtherGIUlcerDisease	531.9	ICD9-CM Diagnosis
OtherGIUlcerDisease	531.9*	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.3	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.3*	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.5	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.5*	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.7	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.7*	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.9	ICD9-CM Diagnosis
OtherGIUlcerDisease	532.9*	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.3	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.3*	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.5	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.5*	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.7	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.7*	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.9	ICD9-CM Diagnosis
OtherGIUlcerDisease	533.9*	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.3	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.3*	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.5	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.5*	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.7	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.7*	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.9	ICD9-CM Diagnosis
OtherGIUlcerDisease	534.9*	ICD9-CM Diagnosis
OtherGIUlcerDisease	569.41	ICD9-CM Diagnosis
OtherGIUlcerDisease	569.82	ICD9-CM Diagnosis
OtherGIUlcerDisease	569.83	ICD9-CM Diagnosis
OtherGIDiverticula	562.00	ICD9-CM Diagnosis
OtherGIDiverticula	562.01	ICD9-CM Diagnosis
OtherGIDiverticula	562.10	ICD9-CM Diagnosis
OtherGIDiverticula	562.11	ICD9-CM Diagnosis
OtherGIDiverticula	569.84	ICD9-CM Diagnosis
HistoryofPepticUlcer	V12.71	ICD9-CM Diagnosis
RenalDisease	582	ICD9-CM Diagnosis
RenalDisease	582.*	ICD9-CM Diagnosis
RenalDisease	582.**	ICD9-CM Diagnosis
RenalDisease	583	ICD9-CM Diagnosis
RenalDisease	583.*	ICD9-CM Diagnosis
RenalDisease	583.**	ICD9-CM Diagnosis
RenalDisease	585.1	ICD9-CM Diagnosis
RenalDisease	585.1*	ICD9-CM Diagnosis
RenalDisease	585.2	ICD9-CM Diagnosis
RenalDisease	585.2*	ICD9-CM Diagnosis
RenalDisease	585.3	ICD9-CM Diagnosis
RenalDisease	585.3*	ICD9-CM Diagnosis
RenalDisease	585.4	ICD9-CM Diagnosis
RenalDisease	585.4*	ICD9-CM Diagnosis
RenalDisease	585.5	ICD9-CM Diagnosis
RenalDisease	585.5*	ICD9-CM Diagnosis
RenalDisease	585.9	ICD9-CM Diagnosis
RenalDisease	585.9*	ICD9-CM Diagnosis

RenalDisease	586	ICD9-CM Diagnosis
RenalDisease	588	ICD9-CM Diagnosis
RenalDisease	588.*	ICD9-CM Diagnosis
RenalDisease	588.**	ICD9-CM Diagnosis
TobaccoUse	305.1	ICD9-CM Diagnosis
TobaccoUse	305.1*	ICD9-CM Diagnosis
TobaccoUse	649.0	ICD9-CM Diagnosis
TobaccoUse	649.0*	ICD9-CM Diagnosis
TobaccoUse	989.84	ICD9-CM Diagnosis
TobaccoUse	V15.82	ICD9-CM Diagnosis
TobaccoUse	83887	HCPCS Procedure
TobaccoUse	99406	HCPCS Procedure
TobaccoUse	99407	HCPCS Procedure
TobaccoUse	1034F	HCPCS Procedure
TobaccoUse	1035F	HCPCS Procedure
TobaccoUse	4000F	HCPCS Procedure
TobaccoUse	4001F	HCPCS Procedure
TobaccoUse	4004F	HCPCS Procedure
TobaccoUse	C9801	HCPCS Procedure
TobaccoUse	C9802	HCPCS Procedure
TobaccoUse	G0375	HCPCS Procedure
TobaccoUse	G0376	HCPCS Procedure
TobaccoUse	G0436	HCPCS Procedure
TobaccoUse	G0437	HCPCS Procedure
TobaccoUse	G8093	HCPCS Procedure
TobaccoUse	G8094	HCPCS Procedure
TobaccoUse	G8402	HCPCS Procedure
TobaccoUse	G8403	HCPCS Procedure
TobaccoUse	G8453	HCPCS Procedure
TobaccoUse	G8454	HCPCS Procedure
TobaccoUse	G8455	HCPCS Procedure
TobaccoUse	G8456	HCPCS Procedure
TobaccoUse	G8688	HCPCS Procedure
TobaccoUse	G9016	HCPCS Procedure
TobaccoUse	S4990	HCPCS Procedure
TobaccoUse	S4991	HCPCS Procedure
TobaccoUse	S4995	HCPCS Procedure
TobaccoUse	S9075	HCPCS Procedure
TobaccoUse	S9453	HCPCS Procedure
BariatricSurgery	43644	CPT Procedure
BariatricSurgery	43645	CPT Procedure
BariatricSurgery	43800	CPT Procedure
BariatricSurgery	43801	CPT Procedure
BariatricSurgery	43802	CPT Procedure
BariatricSurgery	43803	CPT Procedure
BariatricSurgery	43804	CPT Procedure
BariatricSurgery	43805	CPT Procedure
BariatricSurgery	43806	CPT Procedure
BariatricSurgery	43807	CPT Procedure
BariatricSurgery	43808	CPT Procedure
BariatricSurgery	43809	CPT Procedure
BariatricSurgery	43810	CPT Procedure
BariatricSurgery	43811	CPT Procedure
BariatricSurgery	43812	CPT Procedure
BariatricSurgery	43813	CPT Procedure

BariatricSurgery	43814	CPT Procedure
BariatricSurgery	43815	CPT Procedure
BariatricSurgery	43816	CPT Procedure
BariatricSurgery	43817	CPT Procedure
BariatricSurgery	43818	CPT Procedure
BariatricSurgery	43819	CPT Procedure
BariatricSurgery	43820	CPT Procedure
BariatricSurgery	43821	CPT Procedure
BariatricSurgery	43822	CPT Procedure
BariatricSurgery	43823	CPT Procedure
BariatricSurgery	43824	CPT Procedure
BariatricSurgery	43825	CPT Procedure
BariatricSurgery	43826	CPT Procedure
BariatricSurgery	43827	CPT Procedure
BariatricSurgery	43828	CPT Procedure
BariatricSurgery	43829	CPT Procedure
BariatricSurgery	43830	CPT Procedure
BariatricSurgery	43831	CPT Procedure
BariatricSurgery	43832	CPT Procedure
BariatricSurgery	43833	CPT Procedure
BariatricSurgery	43834	CPT Procedure
BariatricSurgery	43835	CPT Procedure
BariatricSurgery	43836	CPT Procedure
BariatricSurgery	43837	CPT Procedure
BariatricSurgery	43838	CPT Procedure
BariatricSurgery	43839	CPT Procedure
BariatricSurgery	43840	CPT Procedure
BariatricSurgery	43841	CPT Procedure
BariatricSurgery	43842	CPT Procedure
BariatricSurgery	43843	CPT Procedure
BariatricSurgery	43844	CPT Procedure
BariatricSurgery	43845	CPT Procedure
BariatricSurgery	43846	CPT Procedure
BariatricSurgery	43847	CPT Procedure
BariatricSurgery	43848	CPT Procedure
BariatricSurgery	43849	CPT Procedure
BariatricSurgery	43850	CPT Procedure
BariatricSurgery	43851	CPT Procedure
BariatricSurgery	43852	CPT Procedure
BariatricSurgery	43853	CPT Procedure
BariatricSurgery	43854	CPT Procedure
BariatricSurgery	43855	CPT Procedure
BariatricSurgery	43856	CPT Procedure
BariatricSurgery	43857	CPT Procedure
BariatricSurgery	43858	CPT Procedure
BariatricSurgery	43859	CPT Procedure
BariatricSurgery	43860	CPT Procedure
BariatricSurgery	43861	CPT Procedure
BariatricSurgery	43862	CPT Procedure
BariatricSurgery	43863	CPT Procedure
BariatricSurgery	43864	CPT Procedure
BariatricSurgery	43865	CPT Procedure
BariatricSurgery	43866	CPT Procedure
BariatricSurgery	43867	CPT Procedure
BariatricSurgery	43868	CPT Procedure

BariatricSurgery	43869	CPT Procedure
BariatricSurgery	43870	CPT Procedure
BariatricSurgery	43871	CPT Procedure
BariatricSurgery	43872	CPT Procedure
BariatricSurgery	43873	CPT Procedure
BariatricSurgery	43874	CPT Procedure
BariatricSurgery	43875	CPT Procedure
BariatricSurgery	43876	CPT Procedure
BariatricSurgery	43877	CPT Procedure
BariatricSurgery	43878	CPT Procedure
BariatricSurgery	43879	CPT Procedure
BariatricSurgery	43880	CPT Procedure
BariatricSurgery	43881	CPT Procedure
BariatricSurgery	49570	CPT Procedure
BariatricSurgery	49571	CPT Procedure
BariatricSurgery	49572	CPT Procedure
BariatricSurgery	49573	CPT Procedure
BariatricSurgery	49574	CPT Procedure
BariatricSurgery	49575	CPT Procedure
BariatricSurgery	S2083	HCPCS Procedure
BariatricSurgery	S2213	HCPCS Procedure
HistoryofBariatricSurgery	V45.86	ICD9-CM Diagnosis
Sepsis	003.1	ICD9-CM Diagnosis
Sepsis	020.2	ICD9-CM Diagnosis
Sepsis	022.3	ICD9-CM Diagnosis
Sepsis	036.2	ICD9-CM Diagnosis
Sepsis	038	ICD9-CM Diagnosis
Sepsis	038.*	ICD9-CM Diagnosis
Sepsis	038.**	ICD9-CM Diagnosis
Sepsis	054.5	ICD9-CM Diagnosis
Sepsis	449	ICD9-CM Diagnosis
Sepsis	785.52	ICD9-CM Diagnosis
Sepsis	790.7	ICD9-CM Diagnosis
Sepsis	995.91	ICD9-CM Diagnosis
Sepsis	995.92	ICD9-CM Diagnosis
Shock	785.5	ICD9-CM Diagnosis
Shock	785.5*	ICD9-CM Diagnosis
InflammatoryBowelDisease	555	ICD9-CM Diagnosis
InflammatoryBowelDisease	555.*	ICD9-CM Diagnosis
InflammatoryBowelDisease	556	ICD9-CM Diagnosis
InflammatoryBowelDisease	556.*	ICD9-CM Diagnosis
IntestinalInfections	001	ICD9-CM Diagnosis
IntestinalInfections	001.*	ICD9-CM Diagnosis
IntestinalInfections	002	ICD9-CM Diagnosis
IntestinalInfections	002.*	ICD9-CM Diagnosis
IntestinalInfections	003.0	ICD9-CM Diagnosis
IntestinalInfections	003.20	ICD9-CM Diagnosis
IntestinalInfections	003.29	ICD9-CM Diagnosis
IntestinalInfections	003.8	ICD9-CM Diagnosis
IntestinalInfections	003.9	ICD9-CM Diagnosis
IntestinalInfections	004	ICD9-CM Diagnosis
IntestinalInfections	004.*	ICD9-CM Diagnosis
IntestinalInfections	005	ICD9-CM Diagnosis
IntestinalInfections	005.*	ICD9-CM Diagnosis
IntestinalInfections	006	ICD9-CM Diagnosis

IntestinalInfections	006.*	ICD9-CM Diagnosis
IntestinalInfections	007	ICD9-CM Diagnosis
IntestinalInfections	007.*	ICD9-CM Diagnosis
IntestinalInfections	008	ICD9-CM Diagnosis
IntestinalInfections	008.*	ICD9-CM Diagnosis
IntestinalInfections	009	ICD9-CM Diagnosis
IntestinalInfections	009.*	ICD9-CM Diagnosis
IntestinalInfections	021.1	ICD9-CM Diagnosis
IntestinalInfections	022.2	ICD9-CM Diagnosis
GastritisGastroenteritis	535.00	ICD9-CM Diagnosis
GastritisGastroenteritis	535.10	ICD9-CM Diagnosis
GastritisGastroenteritis	535.20	ICD9-CM Diagnosis
GastritisGastroenteritis	535.30	ICD9-CM Diagnosis
GastritisGastroenteritis	535.40	ICD9-CM Diagnosis
GastritisGastroenteritis	535.50	ICD9-CM Diagnosis
GastritisGastroenteritis	535.60	ICD9-CM Diagnosis
GastritisGastroenteritis	535.70	ICD9-CM Diagnosis
GastritisGastroenteritis	558	ICD9-CM Diagnosis
GastritisGastroenteritis	558.*	ICD9-CM Diagnosis
GastritisGastroenteritis	558.**	ICD9-CM Diagnosis
HelicobacterPylori	041.86	ICD9-CM Diagnosis
Obesity	278.00	ICD9-CM Diagnosis
Obesity	278.01	ICD9-CM Diagnosis
Obesity	278.03	ICD9-CM Diagnosis
Obesity	V85.3	ICD9-CM Diagnosis
Obesity	V85.3*	ICD9-CM Diagnosis
Obesity	V85.4	ICD9-CM Diagnosis
Obesity	V85.4*	ICD9-CM Diagnosis

Appendix G: Specifications for Request ID to16_cap_mpl2r_wp008_nsdp_v02

The Applied Surveillance Core requested use of the Cohort Identification and Descriptive Analysis (CIDA) Tool, version 2.0.10, with Propensity Score Matching (PSM) to investigate gastrointestinal (GI) bleeding following new use of warfarin compared with statins. This is a re-run of request to16_cap_mpl2r_nsdp_v02 with updated covariate, outcome, and exclusion code lists.

Query Period 1/1/2012 - 9/30/2015
Age Groups 18-64, 65-74, 75+
Coverage Requirement Medical and Drug Coverage
Enrollment Requirement 183 days
Enrollment Gap 45 days
Covariates for Subgroup Analyses Age
Additional Covariates Heparin Use

	Run 1		Run 2	
	Exposure	**Comparator**	**Exposure**	**Comparator**
Drug/Exposure				
Incident exposure	Warfarin	Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, or combination products containing any of these drugs)	Warfarin	Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, or combination products containing any of these drugs)
Incident w/ respect to:	Warfarin, statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, or combination products containing any of these drugs) or novel anticoagulants (apixaban, dabigatran, rivaroxaban, or edoxaban)	Statins, warfarin, or novel anticoagulants (apixaban, dabigatran, rivaroxaban, or edoxaban)	Warfarin, statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, or combination products containing any of these drugs) or novel anticoagulants (apixaban, dabigatran, rivaroxaban, or edoxaban)	Statins, warfarin, or novel anticoagulants (apixaban, dabigatran, rivaroxaban, or edoxaban)
Washout (days)	0 to 183 days before exposure	0 to 183 days before exposure	0 to 183 days before exposure	0 to 183 days before exposure
Cohort Definition	01	01	01	01
Episode Gap	14	14	14	14
Exposure Extension Period	14	14	14	14
Min Episode Duration	0	0	0	0
Min Days Supplied	0	0	0	0
Truncate at Death	Yes	Yes	Yes	Yes
Episode Truncation by Incident Exposure	Yes	Yes	Yes	Yes
Condition Criteria				
Pre-Existing Condition	Malignancy or blood/lymph cancer, Hospice care, Gastrointestinal vessel congenital anomaly, Symptomatic hemophilia A carrier, Artificial opening of GI tract, Aplastic anemia & other bone marrow failure syndromes, Coagulation defects, GI Bleed, and Other GI Bleed	Malignancy or blood/lymph cancer, Hospice care, Gastrointestinal vessel congenital anomaly, Sympotomatic hemophilia A carrier, Artificial opening of GI tract, Aplastic anemia & other bone marrow failure syndromes, Coagulation defects, GI Bleed, and Other GI Bleed	Malignancy or blood/lymph cancer, Hospice care, Gastrointestinal vessel congenital anomaly, Symptomatic hemophilia A carrier, Artificial opening of GI tract, Aplastic anemia & other bone marrow failure syndromes, Coagulation defects, GI Bleed, and Other GI Bleed	Malignancy or blood/lymph cancer, Hospice care, Gastrointestinal vessel congenital anomaly, Sympotomatic hemophilia A carrier, Artificial opening of GI tract, Aplastic anemia & other bone marrow failure syndromes, Coagulation defects, GI Bleed, and Other GI Bleed
Include or Exclude	Exclude	Exclude	Exclude	Exclude
Lookback Start	-183	-183	-183	-183
Lookback End	-1	-1	-1	-1
Care Setting/ PDX	Any	Any	Any	Any
Event/Outcome				
Event/ Outcome	GI Bleed	GI Bleed	GI Bleed	GI Bleed
Care Setting/PDX	Principal inpatient diagnosis	Principal inpatient diagnosis	Principal inpatient diagnosis	Principal inpatient diagnosis
Incident w/ respect to:	GI Bleed	GI Bleed	GI Bleed	GI Bleed
Incident With Respect to Care Setting/PDX	Principal inpatient diagnosis	Principal inpatient diagnosis	Principal inpatient diagnosis	Principal inpatient diagnosis
Washout (days)	183	183	183	183
Event De-duplication	2	2	2	2
Blackout Period	0	0	0	0
Evaluation Window	-183	-183	-183	-183
Perform HDPS Analysis	No	No	No	No
Matching Ratio	1:1	1:1	1:many	1:many
Matching Caliper Settings	0.010	0.010	0.010	0.010

Appendix H. Date of Latest Available Data as of September 30, 2015 for Each Data Partner in this Request

Data Partner (Masked)	Monitoring Period
1	January 1, 2012- September 30, 2015
2	January 1, 2012- April 30, 2015
3	January 1, 2012- October 31, 2014
4	January 1, 2012- June 30, 2015
5	January 1, 2012- February 28, 2015
6	January 1, 2012- July 31, 2014
7	January 1, 2012- June 30, 2012
8	January 1, 2012- July 31, 2015
9	January 1, 2012- September 30, 2015
10	January 1, 2012- September 30, 2015
11	January 1, 2012- September 30, 2015
12	January 1, 2012- September 30, 2015
13	January 1, 2012- June 30, 2015
14	January 1, 2012- December 31, 2014