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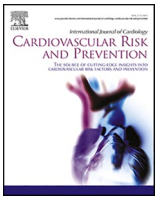

Assessment of one-year risk of ischemic stroke versus major bleeding in patients with atrial fibrillation

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ABSTRACT

Background: Patients diagnosed with atrial fibrillation (AF) are at increased risk of stroke. Several guidelines to assess the risk of ischemic stroke and major bleeding in AF patients have been published. The *CHA_2DS_2-VASc* score has been adopted widely for predicting stroke within one year of the index AF diagnosis and is used to guide the prescription of anticoagulants. Anticoagulation therapy increases the risk of bleeding and scoring systems such as *HAS-BLED* assess the risk of major bleeding in anticoagulated patients. Despite these advances, no study has examined the risks of the two outcomes simultaneously. How patients' fear of particular outcomes affects these risks also remains unknown.

Methods: We incorporated the risks of ischemic stroke and major bleeding within one year of the index AF admission as well as the fear of stroke and bleeding of each individual patient. The patients enrolled in this retrospective observational study were identified using hospital admission data from the Myocardial Infarction Data Acquisition System (MIDAS), a statewide database including all hospitalizations for cardiovascular disease in New Jersey. Probabilities of the outcomes (ischemic stroke, major bleeding, both, or neither within one year of the index AF admission) were estimated using multinomial regression with patient demographics and comorbidities (heart failure [HF], hypertension [HTN], diabetes mellitus [DM], anemia, chronic obstructive pulmonary disease [COPD], kidney disease [KD], prior stroke or transient ischemic attack [TIA]) as predictors. These estimates were used in a Deming regression to model the association of ischemic stroke and major bleeding in grouped patients. The assessment of the importance of each outcome was superimposed on the final model to arrive at a recommendation for anticoagulation therapy.

Results: The results of the Deming regression indicated a positive relationship between ischemic stroke and major bleeding (slope = 1.67, 95% confidence interval [CI] 1.37 to 1.97). Estimates of the risks of the two outcomes and the lines of best fit from Deming regression were determined. This model for risk assessment of stroke and major bleeding within one year of the index AF hospital admission combined objective data and subjective assessment of the relative fear of stroke versus bleeding by each hypothetical patient on 0–100 scale. Examples with the fears of stroke versus major bleeding being equal (50-50) and a higher fear of stroke (80–20) are presented.

Conclusions: The new model for risk assessment of ischemic stroke and major bleeding within one year of the index AF hospital admission proposed in this work used objective, empirically driven measures, and subjective assessment of the outcomes' importance for individual patients. Such models may assist physicians in their decision making regarding anticoagulation therapy.

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1. Introduction

Atrial fibrillation (AF) is commonly associated with an inceased risk of thrombus formation in the left atrium or left atrial appendage which may lead to ischemic (embolic) stroke. Risk assessment scoring systems such as *$CHADS_2$* [1] and its extension *CHA_2DS_2-VASc* [2] are widely used to help predict the one-year risk of stroke after the initial diagnosis of AF. Patients with a score above a threshold (e.g., score $\geq$2 on the 0 to 9 *CHA_2DS_2-VASc* scale) are recommended to take oral anticoagulation. Since anticoagulant and antiplatelet medications inhibit clot formation, they may increase the risk of hemorrhage. The bleeding risk in patients on oral anticoagulants can be assessed using scoring systems such as *$HEMORR_2HAGES$* and *HAS-BLED* [3]. When both stroke and bleeding scores are applied to the same patient, the risks of the two outcomes can be weighed against each other [4]. However, these scoring systems were derived independently, with data collected from different groups of patients, and using them to predict outcomes in new patients increases the uncertainty of prediction [5].

A significantly better approach is to estimate the risks of both outcomes from the same data. Using the same statistical tools and definitions of each model variable (i.e., mapping ICD-9 diagnostic codes to the same outcome and predictor variables) insures against methodology drift. In this work, a single dataset derived from a large population-based observational cohort of patients admitted with cardiovascular disease was utilized to estimate personalized risks of stroke and major bleeding in the same patients. The objective estimates derived from the data were overlaid with a subjective measure of concern of a hypothetical patient toward the two outcomes.

2. Methods

This study was conducted utilizing the Myocardial Infarction Data Acquisition System data repository (MIDAS-DR, RWJMS IRB Pro 2013003225) [6]. MIDAS is a statewide database that includes hospital discharge data (UB82/UB92) of all patients discharged from all non-federal acute care hospitals in New Jersey, including longitudinal follow-up for up to 30 years. MIDAS contains socio-demographic and clinical data on patients who were discharged with the diagnosis of acute myocardial infarction (since 1986), other CVD diagnoses (e.g., stroke, heart failure, pulmonary embolism; since 1995), and all records of hospitalizations involving invasive cardiac procedures, such as cardiac catheterization, percutaneous coronary intervention [PCI], and coronary artery bypass graft [CABG] surgery since 1986. It has been expanded to include all discharge records (regardless of diagnoses) from all non-federal acute care hospitals in New Jersey since 1995. The discharge information is combined with death certificate registration data to enable the determination of long-term vital status of all patients in MIDAS (97% sensitivity). MIDAS records contain information on patient diagnoses and procedures as specified by the International Classification of Diseases Version 9 (ICD-9) [7].

2.1. Study dataset

The data for this study was derived from MIDAS and included records of 58,088 patients admitted to NJ hospitals with AF for the first time between 2000 and 2014. Admission records between 1995 and 2015 were retained in the data to guarantee at least 5 years of lookback for existing conditions and one year of follow-up for outcomes for all patients included in the study. ICD-9 diagnoses codes were mapped to outcomes and covariates as shown in Tables A.1 and A.2 using the R package *icd* [8]. Patients with records of acute and subacute endocarditis, chronic rheumatic pericarditis, diseases of aortic valve, diseases of mitral and aortic valves, diseases of mitral valve, diseases of other endocardial structures, operations on valves and septa of heart, operations on valves and septa of heart, organ or tissue replaced by other means, organ or tissue replaced by transplant, other diseases of endocardium, other rheumatic heart disease, and atrial flutter were excluded (Table A1).

2.2. Statistical analysis

Statistical analyses were performed with R 4.0.3 software [9]. The outcomes of ischemic stroke and major bleeding were combined into a single variable with levels corresponding to stroke only, major bleeding only, stroke and major bleeding, or neither of the outcomes within one year of the index AF admission. Thirty risk factors were considered in relation to the outcomes and eleven were chosen via a stepwise variable selection procedure for multinomial logistic regression. The final model included the following predictors: sex, race (White, Black, other), age ($<$65, 65 to 74, and $\geq$75 years), and indicators for diagnoses of HF, HTN, DM, anemia, COPD, KD, stroke, and TIA prior to or during the index AF admission.

Given the combinations of risk factors, the estimated risks and standard errors of the combined outcome were obtained from a multinomial logistic regression model. These estimates were log-transformed and modeled using Deming regression. The latter is an errors-in-variables statistical model that accounts for errors in observations of both the risk factors and outcomes [10]. For each combination of the risk factors, the number of observations was used as the weight in the model. Deming regression produced the line of best fit for the risk estimates. The resulting model was combined with a hypothetical patient's assessment of fear of each outcome (stroke or major bleeding) to produce decision graphs. The dots in the green region of the graphs represented the subgroups of patients to be recommended for anticoagulation therapy. The regions were adjusted based on the hypothetical patient's fears of each outcome as expressed on a 100-point scale. The fear scores for stroke and major bleeding must add up to 100 (as shown by examples below). The higher score stands for higher level of fear for the outcome. The full algorithm is represented schematically in Figure A1.

3. Results

The results from the Deming regression indicated a positive, statistically significant relationship between stroke and major bleeding risks (slope = 1.67, 95% CI 1.37 to 1.97). The estimate of 1.67 means that for every additional unit increase of $\log_2$ risk of major bleeding (per 10,000 patients) there is a 1.67 unit increase in $\log_2$ risk of stroke (per 10,000 patients) within 1 year of the index AF admission. Thus, if the major bleeding risk is doubled, then the risk of stroke is more than tripled ($2^{1.67} = 3.18$). The estimates of risks of the outcomes and the line of best fit from Deming regression are shown in Fig. 1A and B on logarithmic and linear scales, respectively.

The prediction intervals for stroke risk from the Deming regression model were used to construct the areas reflecting the level of concern, or fear, of a patient toward each outcome (stroke or major bleeding). The regression line corresponded to the state of equivalence (equal fear of

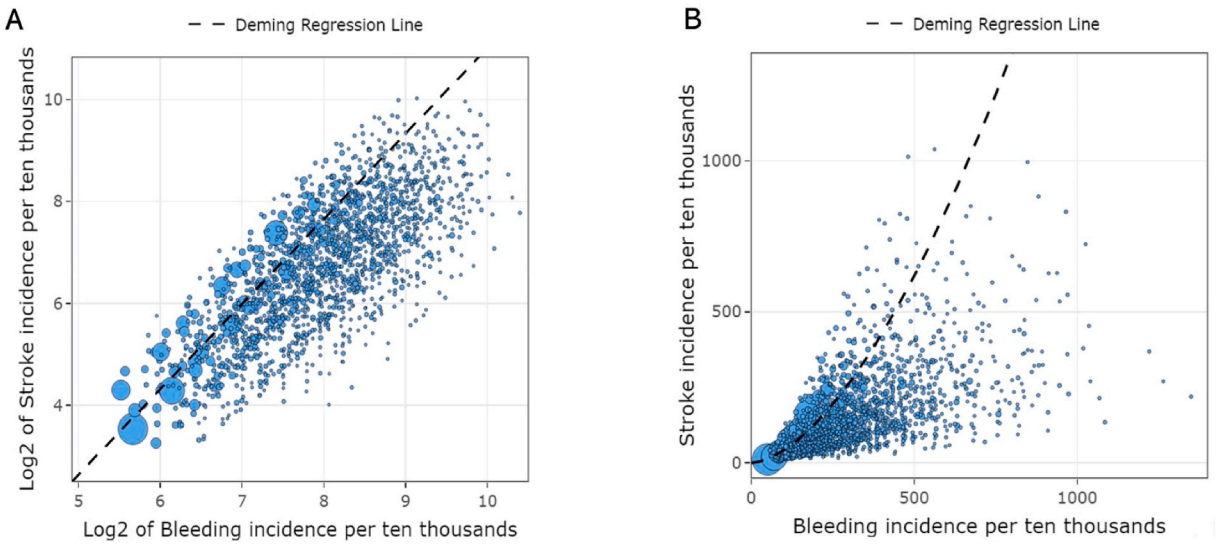

Fig. 1. Stroke versus major bleeding estimates from multinomial regression model and Deming regression line of best fit on log-log (A) and linear (B) scales. The size of the dots is proportional to the number of patients with a particular combination of risk factors.

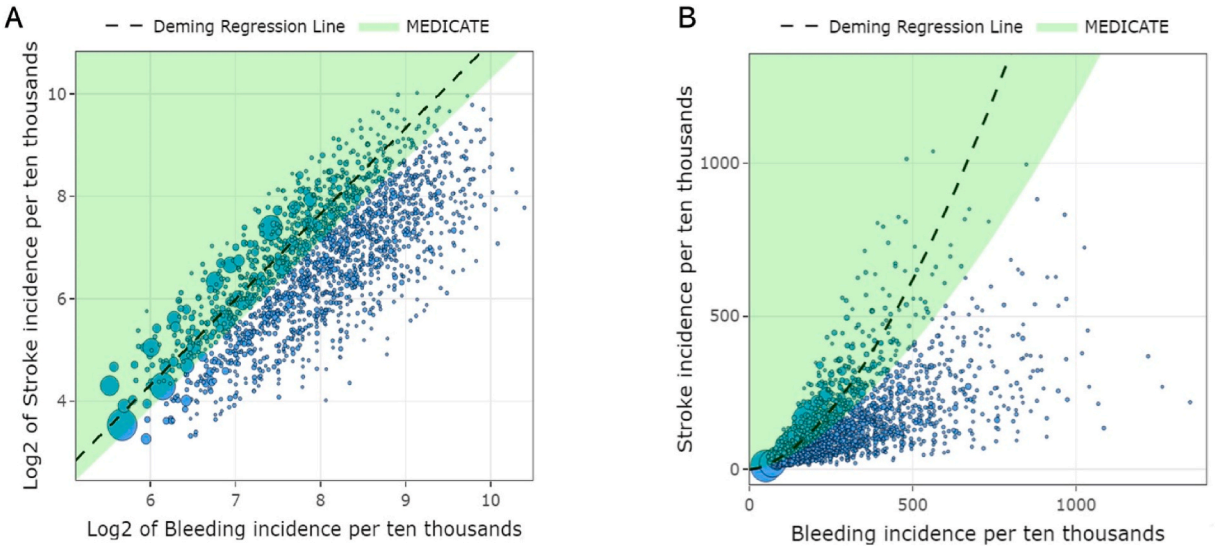

Fig. 2. Fear scores of 80–20 for stroke versus major bleeding, respectively. The points correspond to patients grouped by the risk factors, with the size of the points proportional to the number of patients in each group. Groups of patients inside the green area are recommended to pursue anticoagulation therapy.

the two outcomes) while the green area covered the patient groups that were potential candidates for anticoagulation therapy. If a patient belonged to a group represented by a point in the green region, the algorithm would recommend anticoagulation therapy (Fig. 2).

Since in practice the recommendations will be given to one patient at the time, it is more relevant to visualize the results by plotting a single point that represents the group to which the patient belongs. For example, the risks of stroke and major bleeding for a 79-year-old White female previously diagnosed with HF, HTN, and COPD were estimated to be 2.0% and 2.8% respectively by the model. The group to which the patient belonged was therefore represented by a single point on the graph, with the risk of major bleeding on the X-axis, and the risk of ischemic stroke on the Y-axis. If the patient was equally concerned about having a stroke and a major bleeding (or if she was equivocal), the fear scores would be expressed as 50-50. On the graph this would correspond to the regression line. The area above the regression line (area highlighted in green) would represent the region where anticoagulation would be recommended. If, on the other hand, the patient was more

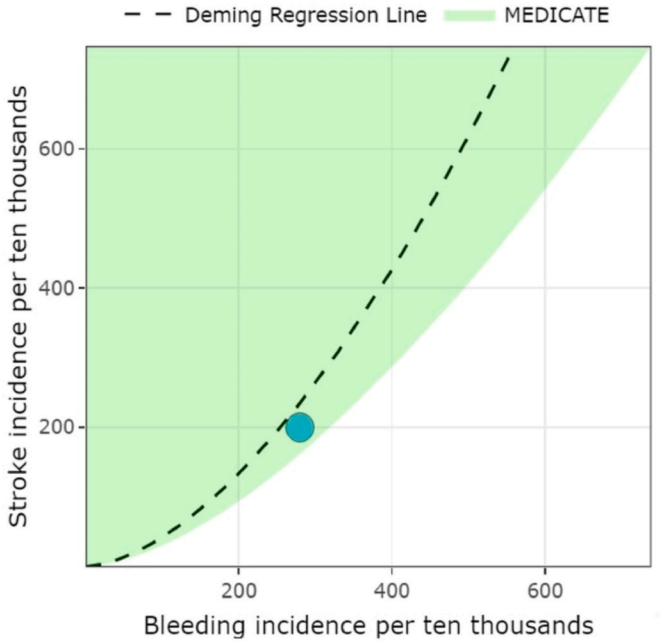

Fig. 3. Predicted risks of stroke (2.0%) and major bleeding (2.8%) for a 79-year-old White female previously diagnosed with HF, HTN, and COPD are represented by the point on the graph. The green area corresponds to the outcomes fear scores of 80–20 for ischemic stroke vs. major bleeding respectively. Since the point is withing the green area, the algorithm's recommendation for this patient is for anticoagulation therapy.

fearful of having an ischemic stroke than a bleeding event, she could express it as 80-20 scores for ischemic stroke versus major bleeding respectively. Compared to the previous scenario (50-50), the fear scores of 80–20 would increase the region where anticoagulation would be recommended (i.e., the green area in Fig. 3), and therefore more likely for the patient to be advised to initiate therapy.

4. Discussion

In this study of patients with hospitalization for AF, we developed a novel approach to predict the risk of stroke and/or major bleeding within one year of index AF admission. The impetus for this work was to develop a clinical prediction rule to help guide the decision to recommend anticoagulation therapy for these patients. Predictions were based on personalized risks derived through models based on the MIDAS data repository, a statewide database that includes virtually all hospitalizations for cardiovascular disease in New Jersey. The estimated probabilities for each group of patients (i.e., patients with the same combinations of demographic parameters and comorbidities) were then used as inputs to a Deming regression framework to model the risk of stroke versus the risk of major bleeding. The models indicated a strong association of the two outcomes (slope = 1.67, 95% CI 1.37 to 1.97).

Deming regression has been used widely in pediatric and adult cardiology with satisfactory results [11–13]. However, an additional component representing patients' personal assessment of the relative importance of the outcomes (a subjective measure) was used to adjust the risk estimates and to provide guidance to physicians regarding the recommendation of anticoagulation therapy to patients. This approach is in line with the personalized medicine paradigm [14] and provides an avenue for patients to exert more influence on issues directly affecting their well-being.

In a recently published case vignette [15], three medical experts discussed argument for and against continuing anticoagulation therapy in a 74-year-old male after ablation. Considering relatively high risk of

Table 1
Patient demographic characteristics, diagnosis, and procedures, and outcomes (on or before index AF admission).

Patient characteristics	Number (%) (n = 58,058)
Demographic characteristics	
Age (years)	
Mean (SD)	66.9 (16.0)
<65	23,757 (40.9%)
65-74	12,864 (22.1%)
≥75	21,467 (37.0%)
Female sex	27,372 (47.1%)
Race	
White	47,829 (82.3%)
Black	4,680 (8.1%)
Other	5,579 (9.6%)
Ethnicity	
Hispanic	4,228 (7.3%)
Non-Hispanic	47,154 (81.2%)
Unknown	6,706 (11.5%)
Obesity	8,042 (13.8%)
Diagnosis	
Coronary heart disease	
Acute myocardial infarction	2,656 (4.6%)
Atherosclerosis	1,236 (2.1%)
Cardiac dysrhythmias (except AF and atrial flutter)	10,313 (17.8%)
Cardiomyopathy	3,632 (6.3%)
Heart failure	10,377 (17.9%)
Hypertension	39,064 (67.2%)
Dyslipidemia	22,595 (38.9%)
Other peripheral vascular diseases	2,292 (3.9%)
Cerebrovascular disease	
Cerebrovascular disease	1,517 (2.6%)
Ischemic Stroke	1,495 (2.6%)
Transient ischemic attack	1,633 (2.8%)
Chronic disease	
Anemia	9,085 (15.6%)
Chronic liver disease and cirrhosis	798 (1.4%)
Chronic obstructive pulmonary disease	11,076 (19.1%)
Diabetes	11,872 (20.4%)
Hyperthyroidism	1,247 (2.1%)
Hypothyroidism	6,415 (11.0%)
Kidney disease	5,152 (8.9%)
Obstructive sleep apnea	2,306 (4.0%)
Gastrointestinal bleeding	1,025(1.8%)
Pulmonary embolism	673 (1.2%)
Procedures	
Pacemaker	879 (1.5%)
Coronary artery bypass graft	740 (1.3%)
Percutaneous coronary intervention	2,504 (4.3%)
Ablation	697 (1.2%)
Outcomes	
Stroke only within 1 year of index AF admission	459 (0.8%)
Major bleeding only within 1 year of index AF admission	855 (1.5%)
Stroke and major bleeding within 1 year of index AF admission	47 (0.1%)

stroke before the ablation (CHA_2DS_2VASc score of 2 but becoming 3 in a year, when the patient turns 75) and relatively low risk of major bleeding (HAS-BLEED score of 2), one expert recommended continuing anticoagulation while another recommended to discontinue the therapy 2 months after a successful ablation, arguing that the risk of stroke in patients with no atrial fibrillation are significantly lower compared to atrial fibrillation patients with the same risk factors. The importance of considering the patient's preferences regarding the outcomes was highlighted.

A limitation of this study is the absence of medication and laboratory data in MIDAS, including information about anticoagulation therapy. Differences in the use of anticoagulation could influence the outcomes as patients with the same comorbidity profile could potentially have different outcomes based on background medical therapy within one year of index AF admission. Examination of the extent to which medication use improves the prediction of stroke and bleeding events will be a topic of future study. Likewise, laboratory data could also further stratify patients and help to explain the outcomes. The use of the left atrial appendage occlusion and other invasive methods are beyond the scope of this work [11,12]. In addition, combinations of antithrombotic therapy (e.g., single antiplatelet versus triple therapy) have been studied [13], but are outside the scope of this study. A randomized trial designed to guide anticoagulation strategy would help to validate and generalize the method.

5. Conclusions

The strengths of the study include the population-based nature of the cohort that affords greater generalizability of the findings. Since the MIDAS cohort is derived from population-level data, the findings are least affected by selection bias. We attempted to derive the personalized risks through a parsimonious model, retaining predictions based on simple and clinically relevant predictors. This approach is transparent and straightforward to apply in a clinical setting. We are also developing a web-based implementation of this model (web application using R Shiny technology). We hope to undertake efforts to evaluate the utility of the prediction rule in other diverse geographic settings.(see Table 1)

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Credit authorship contribution statement (equal contribution)

Davit Sargsyan: Conceptualization, project administration, writing, formal analysis, review and editing. **Javier Cabrera**: Conceptualization, writing, formal analysis, review and editing. **Yajie Duan**: Conceptualization, writing, formal analysis, review and editing. **Cande Ananth**: Conceptualization, writing, review and editing. **William J. Kostis**: Conceptualization, writing, review and editing. **John B. Kostis**: Conceptualization, project administration, writing, review and editing.

Declaration of competing interest

All authors declare: no support from any organization for the submitted work; no financial relationships with any organizadutions that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Appendix

Table A.1
Exclusions

Comorbidity	ICD-9
Acute and subacute endocarditis	421.0; 421.1; 421.9
Chronic rheumatic pericarditis	393
Diseases of aortic valve	395.0; 395.1; 395.2; 395.9
Diseases of mitral and aortic valves	396.0; 396.1; 396.2; 396.3; 396.8; 396.9
Diseases of mitral valve	394.0; 394.1; 394.2; 394.9
Diseases of other endocardial structures	397.0; 397.1; 397.9
Operations on valves and septa of heart	350.0; 350.1; 350.2; 350.3; 350.4; 350.5; 350.6; 350.7; 350.8; 350.9; 351.0; 351.1; 351.2; 351.3; 351.4; 352.0; 352.1; 352.2; 352.3; 352.4; 352.5; 352.6; 352.7; 352.8
Organ or tissue replaced by other means	V43.21; V43.22; V43.3; V43.4; V43.89
Organ or tissue replaced by transplant	V42.0; V42.1; V42.2; V42.6; V42.7; V42.81; V42.82; V42.83; V42.84; V42.89
Other diseases of endocardium	424.0; 424.1; 424.2
Other rheumatic heart disease	398.0; 398.90; 398.91; 398.99
Atrial flutter	427.32

Table A.2
Comorbidities

Comorbidity	ICD-9
Atrial Fibrillation (main condition)	427.31
AMI	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
Anemia	280.0; 280.1; 280.8; 280.9; 281.0; 281.1; 281.2; 281.3; 281.4; 281.8; 281.9; 282.0; 282.1; 282.2; 282.3; 282.40; 282.41; 282.42; 282.43; 282.44; 282.45; 282.46; 282.47; 282.49; 282.5; 282.60; 282.61; 282.62; 282.63; 282.64; 282.68; 282.69; 282.7; 282.8; 282.9; 283.0; 283.10; 283.11; 283.19; 283.2; 283.9; 284.01; 284.09; 284.11; 284.12; 284.19; 284.2; 284.81; 284.89; 284.9; 285.0; 285.1; 285.21; 285.22; 285.29; 285.3; 285.8; 285.9
Atherosclerosis	440.0; 440.1; 440.20; 440.21; 440.22; 440.23; 440.24; 440.29; 440.30; 440.31; 440.32; 440.4; 440.8; 440.9
Cardiac dysrhythmias (except AF)	427.0; 427.1; 427.2; 427.41; 427.42; 427.5; 427.60; 427.61; 427.69; 427.81; 427.89; 427.9
Chronic liver disease and cirrhosis	571.0; 571.1; 571.2; 571.3; 571.40; 571.41; 571.42; 571.49; 571.5; 571.6; 571.8; 571.9; 571.0; 571.1; 571.2; 571.3; 571.40; 571.41; 571.42; 571.49; 571.5; 571.6; 571.8; 571.9
Cardiomyopathy	425.0; 425.11; 425.18; 425.2; 425.3; 425.4; 425.5; 425.7; 425.8; 425.9
COPD	490; 491.0; 491.1; 491.20; 491.21; 491.22; 491.8; 491.9; 492.0; 492.8; 493.00; 493.01; 493.02; 493.10; 493.11; 493.12; 493.20; 493.21; 493.22; 493.81; 493.82; 493.90; 493.91; 493.92; 494.0; 494.1; 495.0; 495.1; 495.2; 495.3; 495.4; 495.5; 495.6; 495.7; 495.8; 495.9; 496
Cerebrovascular disease	433.00; 433.10; 433.20; 433.30; 433.80; 433.90
Diabetes	250.00; 250.01; 250.02; 250.03; 250.10; 250.11; 250.12; 250.13; 250.20; 250.21; 250.22; 250.23; 250.30; 250.31; 250.32; 250.33; 250.40; 250.41; 250.42; 250.43; 250.50; 250.51; 250.52; 250.53; 250.60; 250.61; 250.62; 250.63; 250.70; 250.71; 250.72; 250.73; 250.80; 250.81; 250.82; 250.83; 250.90; 250.91; 250.92; 250.93
GI bleeding	456.0; 459.0; 562.03; 562.03; 562.12; 562.12; 562.12; 562.13; 562.13; 562.13; 562.13; 562.13; 569.3; 569.85
HF	428.0; 428.1; 428.20; 428.21; 428.22; 428.23; 428.30; 428.31; 428.32; 428.33; 428.40; 428.41; 428.42; 428.43; 428.9
Hypertension	401.0; 401.1; 401.9; 402.00; 402.10; 402.90; 403.00; 403.01; 403.10; 403.11; 403.90; 403.91; 404.00; 404.01; 404.02; 404.03; 404.10; 404.11; 404.12; 404.13; 404.90; 404.91; 404.92; 404.93; 405.01; 405.09; 405.11; 405.19; 405.91; 405.99
Hyperthyroidism	242.00; 242.01; 242.10; 242.11; 242.20; 242.21; 242.30; 242.31; 242.40; 242.41; 242.80; 242.81; 242.90; 242.91
Hypothyroidism	243; 244.0; 244.1; 244.2; 244.3; 244.8; 244.9
Intracranial bleeding	430; 430; 430; 430; 430; 430; 430; 430; 430; 431; 431; 431; 431; 431; 431; 431; 431; 432.0; 432.1; 432.1; 432.1; 432.1; 432.9; 852.01; 852.02; 852.06; 852.21; 852.22; 852.26
ICD	V45.02
Kidney disease	584.5; 584.6; 584.7; 584.8; 584.9; 585.1; 585.2; 585.3; 585.4; 585.5; 585.6; 585.9
Dyslipidemia	272.0; 272.1; 272.2; 272.3; 272.4; 272.5; 272.6; 272.7; 272.8; 272.9
Obesity	278.00; 278.01; 278.02; 278.03; 278.1; 278.2; 278.3; 278.4; 278.8
Other peripheral vascular diseases	443.0; 443.1; 443.21; 443.22; 443.23; 443.24; 443.29; 443.81; 443.82; 443.89; 443.9
Intravascular vitreous hemorrhage, hemoperitoneum, hemarthrosis, cardiac tamponade, intramuscular with compartment syndrome, hematuria, nontraumatic hematoma of soft tissue	379.23; 379.23; 379.23; 379.23; 568.81; 719.10; 719.11; 719.11; 719.12; 719.16; 719.16; 719.17; 423.3; 729.72; 729.72; 729.72; 599.70; 599.71; 729.92
Pacemaker	V45.01
Pulmonary embolism	415.0; 415.0; 415.0; 415.12; 415.12; 415.13; 415.13; 415.19; 415.19
Obstructive sleep apnea	327.23
Spinal hematoma	336
Ischemic Stroke	433.01; 433.11; 433.21; 433.31; 433.81; 433.91; 434.01; 434.11; 434.91
Thyroiditis	245.0; 245.1; 245.2; 245.3; 245.4; 245.8; 245.9
TIA	435.0; 435.1; 435.2; 435.3; 435.8; 435.9
Trauma	958.2; 958.90; 958.91; 958.92; 958.92

Table A.3
Procedures

Procedure	ICD-9
Ablation	373.4
CABG	361.0; 361.1; 361.2; 361.3; 361.4; 361.5; 361.6; 361.7; 361.9; 362; 363.1; 363.2; 363.3; 363.4; 363.9
PCI	006.6; 360.3; 360.4; 360.6; 360.7; 360.9

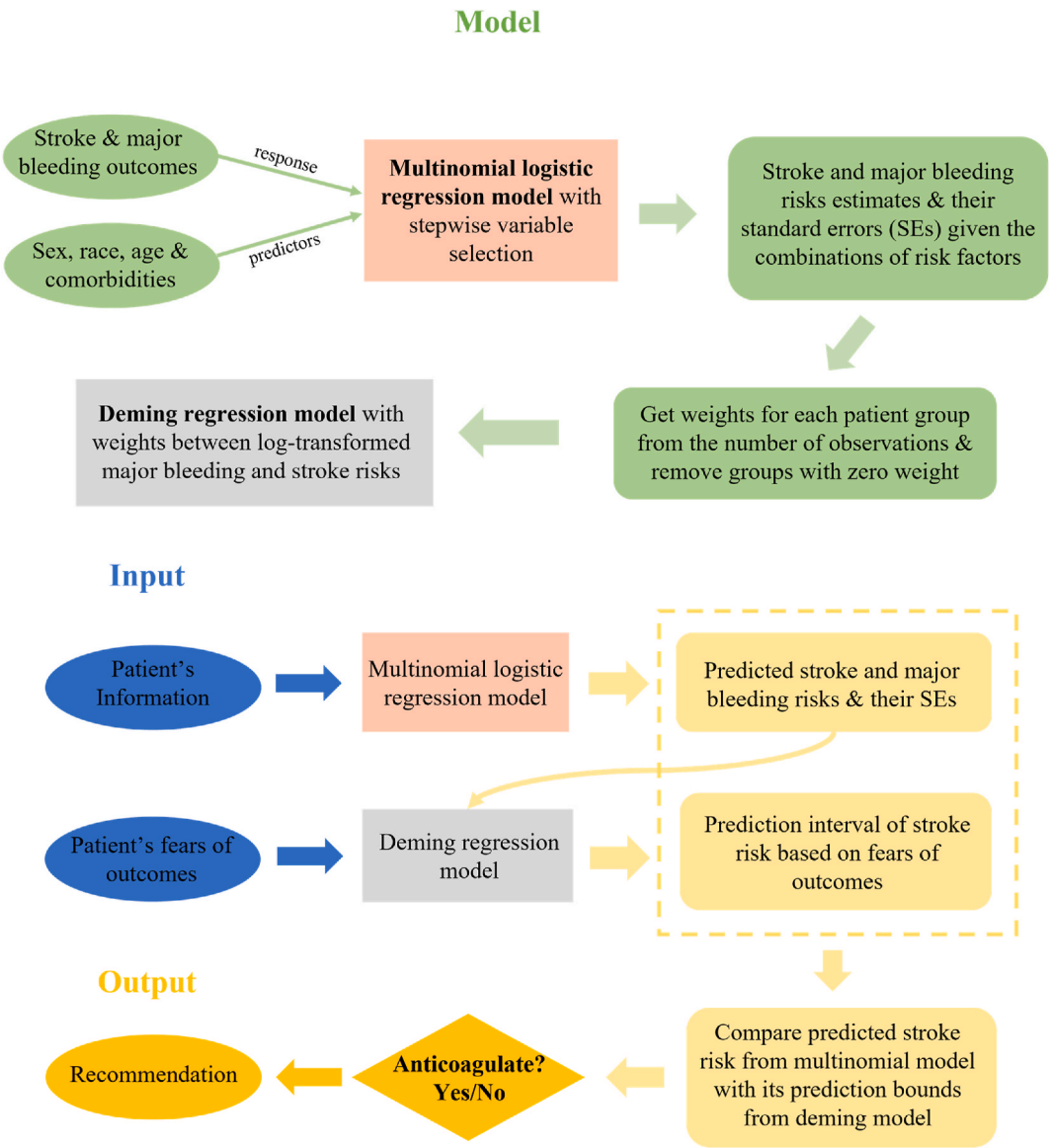

Fig. A.1. Schematic of the method.

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