ORIGINAL RESEARCH

Field Synopsis of the Role of Sex in Stroke Prediction Models

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***Background*—**Guidelines for stroke prevention recommend development of sex-specific stroke risk scores. Incorporating sex in Clinical Prediction Models (CPMs) may support sex-specific clinical decision making. To better understand their potential to guide sex-specific care, we conducted a field synopsis of the role of sex in stroke-related CPMs.

***Methods and Results*—**We identified stroke-related CPMs in the Tufts Predictive Analytics and Comparative Effectiveness CPM Database, a systematic summary of cardiovascular CPMs published from January 1990 to May 2012. We report the proportion of models including the effect of sex on stroke incidence or prognosis, summarize the directionality of the predictive effects of sex, and explore factors influencing the inclusion of sex. Of 92 stroke-related CPMs, 30 (33%) contained a coefficient for sex or presented sex-stratified models. Only 12/58 (21%) CPMs predicting outcomes in patients included sex, compared to 18/30 (60%) models predicting first stroke ($P<0.0001$). Sex was most commonly included in models predicting stroke among a general population (69%). Female sex was consistently associated with reduced mortality after ischemic stroke (n=4) and higher risk of stroke from arrhythmias or coronary revascularization (n=5). Models predicting first stroke versus outcomes among patients with stroke (odds ratio=5.75, 95% CI 2.18–15.14, $P<0.001$) and those developed from larger versus smaller sample sizes (odds ratio=4.58, 95% CI 1.73–12.13, $P=0.002$) were significantly more likely to include sex.

***Conclusions*—**Sex is included in a minority of published CPMs, but more frequently in models predicting incidence of first stroke. The importance of sex-specific care may be especially well established for primary prevention. **(*J Am Heart Assoc*. 2016;5: e002809 doi: 10.1161/JAHA.115.002809)**

Key Words: prevention • prognosis • risk factor • risk model • sex • stroke

There is growing recognition of the importance of sex differences in stroke. There are sex-based differences in anatomy,[1–3] vascular biology,[4,5] neuroprotective factors,[6,7] functional neuroanatomy,[8] vascular risk factors and comorbidities,[9–12] and lifestyle factors and social roles[13,14] that may be important in stroke incidence and prognosis. The literature has shown sex differences in the risk of incident stroke,[13,15,16] likelihood of favorable outcomes after a stroke,[13] and responses to thrombolysis treatment.[17–19] The importance of sex-specific risk in clinical management of stroke was underscored in the first American Heart Association/American Stroke Association guideline dedicated to stroke prevention in women.[20] In addition to drawing attention to the lack of strong, level A evidence available to support sex-specific recommendations, the guidelines recommended development of female-specific stroke risk scores that consider risk factors that are sex-specific, or stronger or more prevalent in women.

Clinical prediction models (CPMs) are multivariable statistical algorithms that produce patient-specific estimates of clinically important outcome risks based on individual patient characteristics. The number of CPMs for cardiovascular disease (CVD) reported in the literature has steadily increased over the last 2 decades,[21] reflecting their promise as tools to improve decision making, individualize care, and support patient-centered outcomes research. One so far unexplored implication of the dissemination of risk models into clinical practice is their potential to support appropriate

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/5/5/e002809/DC1/embed/inline-supplementary-material-1.pdf

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sex-specific care decisions in sexually dimorphic conditions such as stroke.[22] While several commonly used CPMs for cardiovascular risk present sex-stratified models or include sex in risk scores,[23–25] the frequency and directionality of sex in the stroke-related risk model literature have not been described.

We therefore conducted a field synopsis of the role of sex in stroke-related prediction models using a registry of CPMs that predict clinical outcomes for patients at risk for and with established CVD. We aimed to describe the frequency with which sex is included in stroke CPMs, determinants of inclusion of sex, and the directionality of the predictive effects of sex.

Methods

The Tufts CPM Registry

The Tufts Predictive Analytics and Comparative Effectiveness (PACE) CPM Registry is based on a systematic review of PubMed for English-language articles containing CPMs for CVD published from January 1990 to May 2012. Detailed descriptions of article inclusion and exclusion criteria and construction of the registry are described elsewhere.[21] CVD included coronary heart disease, heart failure, arrhythmias, stroke, venous thromboembolism, and peripheral vascular disease. Articles were included if (1) the primary stated aim was to develop a CPM, (2) they contained a model predicting binary clinical end points (either CVD incidence or prognosis), (3) the model contained at least 2 predictor variables, and (4) the model allowed calculation of outcome risk for an individual patient.

Selection of Stroke Models

The Tufts CPM Database includes 796 total CPMs extracted from 505 articles related to the topic of CVD. From each article, if multiple CPMs were presented for a unique index condition–outcome pair, a single model was selected as a "primary model." Primary models were (1) those designated as primary by the authors of the published article, (2) where no model was so specified, the most clinically oriented model (eg, versus extension models with radiographic information), or (3) by consensus among extractors if none of the above applied. Stroke-related models were those with a stroke-related condition as either the index condition or the predicted outcome, or both. Stroke-related conditions included ischemic stroke, hemorrhagic stroke, cerebrovascular accident when stroke subtypes were not specified or were mixed, transient ischemic attacks, and cerebral venous thrombosis. CPMs predicting the development of CVD in general (nonspecific to stroke) were excluded.

Study- and Model-Level Descriptive Characteristics

The index condition and predicted outcomes were classified for each model. Index condition categories included population sample (populations at risk for incident CVD), ischemic stroke, hemorrhagic stroke, cerebrovascular accident, transient ischemic attacks, cerebral venous thrombosis, arrhythmic conditions, carotid disease, coronary artery disease, and patients undergoing revascularization procedures (ie, coronary artery bypass graft, or percutaneous coronary intervention). Outcomes were categorized as stroke (including transient ischemic attacks), morbidity, mortality, or a composite of morbidity and mortality. Models were classified as either predicting first stroke (among individuals without a prior stroke) or predicting outcomes among patients with stroke or a history of stroke.

From each article, we extracted author names and affiliations, publication year, study design, cohort sample size, cohort/trial enrollment period, the number of women in the cohort, and the cohort age distribution (mean or median). Given observed relationships between the sex composition of research groups and conduct of clinical research,[26–28] articles were classified as to whether any of the first, last, or corresponding authors were women by searching author academic or professional websites (ie, LinkedIn, ResearchGate) for sex-identifying photos or pronouns.

For each model, the model sample size, number of outcome events, covariates, parameter estimates, intercept or baseline hazard, and the model's discriminative ability were collected. Data were extracted in duplicate in electronic forms to ensure consistency; discrepancies were resolved by consensus involving a third investigator.

Classification of Sex in Stroke-Related CPMs

Each CPM was classified according to how sex was included in the model: (1) as a covariate, (2) as a stratification variable where male- and female-specific models were presented separately (with intercepts, covariates, and parameter estimates allowed to vary by sex), (3) whether the model was built from a sex-restricted cohort of only men or only women, or (4) none of the above (sex not included).

For models where sex was not included, the articles were reviewed with respect to whether sex was reported to be considered as a candidate for inclusion based on statistical or clinical criteria. Statistical criteria were considered to be either (1) exploration of the univariable relation between sex and the outcome, and/or (2) consideration of sex as a candidate in the final multivariable model. A description of the distribution (eg, proportion) of males or females in the cohort was not considered to be evidence of statistical

consideration. Clinical rationale consisted of a statement describing a lack of clinical or biological plausibility of a relationship between sex and outcome risk, typically referencing either expert opinion or citing published literature. Sex-specific information was extracted by the following coauthors: J.K.P., L.Y.H.L., G.R., J.S.L.

Statistical Analysis

Counts and proportions were used to describe how sex was included in stroke-related prediction models, for the total sample of models, and stratified by stroke as an outcome versus index condition. A pair of sex-stratified models (1 male and 1 female) was counted as 1 model in the denominator. For all subsequent analyses, models developed from sex-restricted cohorts were excluded as sex effects would be impossible to evaluate or include. Among all models with coefficients for sex, the directionality (harmful versus protective) of the predictive effect of female sex was summarized by index condition–outcome pair.

In order to identify study- and model-related factors associated with the inclusion of sex in prediction models for stroke (sex covariate or sex-stratified versus sex not included), odds ratios, 95% CI, and *P* values were calculated using logistic regression. Regression analyses used the SAS statistical package, version 9.3 (SAS Institute, Cary, NC).

This study was not human subjects research, as it involved only the secondary analysis of de-identified, aggregated data from published literature. Approval from the institutional review committee was therefore not needed, and informed consent not applicable, as there is no way to identify individual patients, nor was individual patient data used for this study.

Results

Among the 796 Tufts PACE CPM Registry models extracted from 505 articles, 591 were identified as primary models for cardiovascular disease and 92 (16%) of these included cerebrovascular disease as an index condition or outcome (all models listed in Table S1). Roughly one third (33%) of the stroke-related models included sex as either a covariate or presented separate models stratified by sex (Figure 1A). A minority (4%) of the models were developed from a sex-restricted cohort. Two models (2%) included an interaction term between sex and another covariate. Among models developed from cohorts including both men and women, sex was significantly more likely to be included as a covariate or stratification variable in models where first stroke was the predicted outcome (60%, 18/30), versus models predicting outcomes among patients with stroke or history of stroke (21%, 12/58) ($P<0.0001$) (Figure 1B and 1C). Among the 58

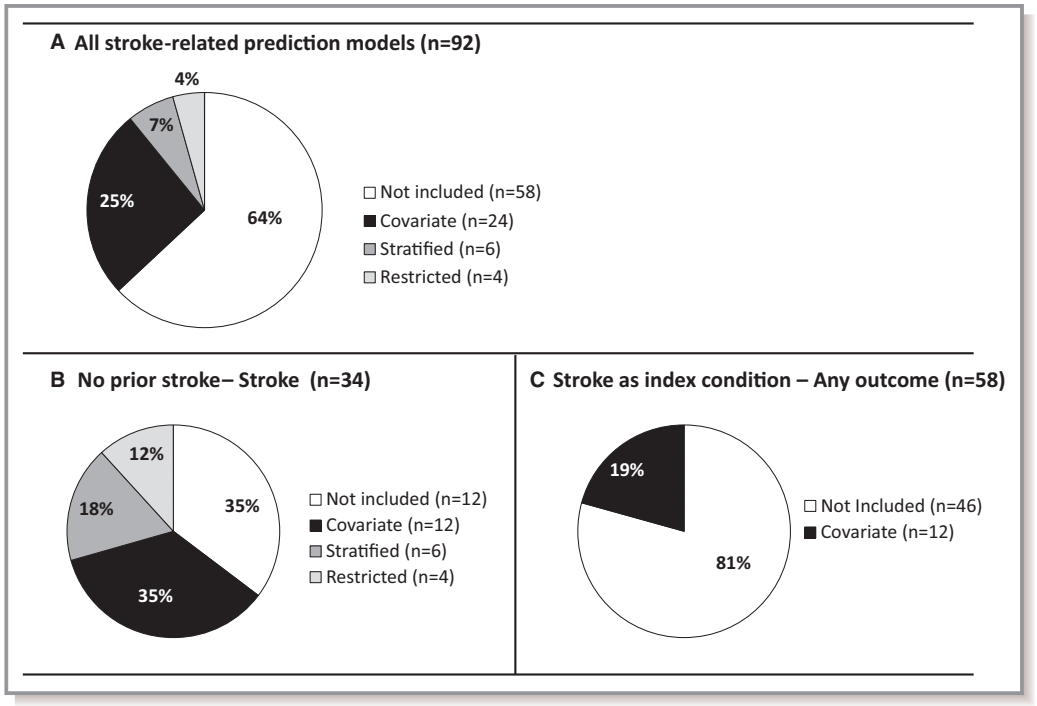

Figure 1. The inclusion of sex in stroke-related clinical prediction models (n=92). The frequency with which sex is included as either a covariate, model stratification variable, or as a cohort inclusion criterion ("restriction") is presented for stroke-related prediction models overall (A), in models predicting risk of first stroke (B), and in models predicting outcomes among patients who have experienced stroke (C).

Table 1. Inclusion of Sex in Stroke Prediction Models, by Index Condition–Outcome Pair (n=84)*

Index Condition—Outcome Pair (n=Total Number of Models)	Proportion (%) of Models		
		Without Sex	
	With Sex Incorporated	Sex Considered For Inclusion	Consideration Not Reported
Ischemic stroke—M&M (n=13)	15	38	46
Population sample—stroke (n=13)†	69	23	8
Ischemic stroke—mortality (n=10)	40	30	30
Hemorrhagic stroke—mortality (n=9)	0	67	33
Revascularization—stroke (n=6)	33	67	17
Hemorrhagic stroke—M&M (n=4)	25	50	25
TIA—morbidity (n=4)	25	75	0
Arrhythmia—stroke (n=4)	75	25	0
CVA—mortality (n=3)	0	100	0
Hemorrhagic stroke—morbidity (n=3)	0	67	33
CVA—morbidity (n=3)	0	67	33
CVT—M&M (n=3)	67	0	33
TIA—M&M (n=3)	67	33	0
Ischemic stroke—morbidity (n=2)	0	0	100
CAD—stroke (n=2)	100	0	0
Carotid disease—M&M (n=2)	50	0	50

CAD indicates coronary artery disease; CVA, cerebrovascular accident; CVT, cerebral venous thrombosis; M&M, morbidity and mortality; TIA, transient ischemic attack.
*Sex-restricted models excluded.
†Includes 6 sex-stratified models and 3 models with sex as a covariate. For all other index condition–outcome pairs, sex was included as a covariate.

stroke models that did not include sex as a covariate or stratification variable, approximately two thirds (64%) reported that sex had been considered as a candidate for inclusion based on clinical or statistical criteria. None of the stroke models included a covariate for sex-specific risk factors, such as pregnancy or oral contraceptive use, nor did they include risk factors more common in women, such as migraine. Agreement between raters (J.K.P., L.Y.H.L., G.R., J.S.L.) classifying information on sex was high (average Cohen's kappa by rater pair=92.5%).

Sex in Stroke Models by Index Condition–Outcome Pair

The most frequently occurring stroke model predicted incident stroke among a general population sample (n=17 models) (Table 1). Among the 13 population sample-stroke models built from cohorts not restricted to either men or women, the majority (69%) were either stratified by sex (6/13) or included sex as a covariate (3/13). In contrast, among models developed from cohorts of patients with ischemic stroke or a history of ischemic stroke, sex was included as a covariate in only 15% (2/13) of models predicting a composite of morbidity and mortality, and 40% (4/10) of models predicting mortality alone. Sex was not included in any of the 9 models predicting mortality among patients with hemorrhagic stroke, though 6 reported considering sex for inclusion. Sex was included in only 6% (1/16) of models predicting any outcome among patients with hemorrhagic stroke, as compared to 24% (6/25) of such models among ischemic stroke patients. Study- and model-level characteristics of the 30 stroke-related CPMs that included sex are presented in Table 2.[25,29–54]

Directionality of the Predictive Effect of Female Sex on Stroke Risk and Prognosis

Although inconsistently included, the predictive effect of female sex on risk when included was in a consistent direction in 6 of 7 index condition–outcome pairs with at least 2 models (Figure 2). Being a woman was protective for the development of incident stroke in a population sample (n=2) and for mortality after ischemic stroke (n=4). In contrast, female sex was associated with increased risk of stroke in patients with arrhythmia (n=3) and those undergoing revascularization procedures (n=2).

Table 2. Study- and Model-Level Characteristics of Stroke-Related Clinical Prediction Models Including Sex (n=30)

PubMed ID	First Author	Pub. Year	Inclusion of Sex	Effect of Female Sex	Population	Outcome(s)	Covariates	Cohort Sample Size	% Female in Cohort	No. of Events	Mean Age (SD)	Follow-Up Duration
Population sample—stroke												
1985385	Anderson[29]	1991	Covariate	NA*	Members of FHS and FHS-OS cohorts, age 30 to 74, initially free of CVD and cancer	CVD (MI, CHD death, angina pectoris, coronary insufficiency, stroke, TIA, CHF, PVD)	Sex, Cholesterol, LVH, DM×Female, DM, Smoking, Age, SBP	5573	NR	NR	NR	12 years
2003301	Wolf[30]	1991	Stratified	NA	Subjects of FHS, age 55 to 84, free of stroke	Stroke at 10 year follow-up	LVH, Age, AF, CVD, Smoking, DM, SBP, Antihypertensive Therapy	5734	59	M: 213 F: 259	65.8 (NR)	10 years
8266381	D'Agostino[25]	1994	Stratified	NA	Subjects of FHS, age 55 to 84, free of stroke	Stroke at 10 year follow-up	Antihypertensive Therapy, LVH, AF, CVD, Smoking, Age, DM, SBP	5734	59	NR	NR	10 years
11809350	Lumley[31]	2002	Stratified	NA	Population-based cohort study of men and women age 65 and older	5 year risk of stroke	SBP, 15-ft Walk Time, LVH, Creatinine, DM, Impaired Fasting Glucose, Age, AF, History of CVD	5711	59	NR	73 (NR)	5 years (median=6.3)
17088464	Wu[32]	2006	Stratified	NA	Men and women, age 35 to 59, in Beijing and Guangzhou (from USA-PRC study cohort)	Ischemic stroke	DM, BMI, Cholesterol, Smoking, SBP, Age	9903	51	M: 158 F: 108	46 (6)	11 years (mean=15.1)
17586511	Jee[33]	2008	Stratified	NA	Koreans age 30 to 84 insured by the National Health Insurance Corporation	Stroke	DM, Smoking, Cholesterol, Alcohol Use, Age, Physical Activity, BMI, SBP	1 223 740	36	M: 29 216 F: 18 017	M: 46.6 (11) F: 49.4 (12.1)	10 years (mean=13)
18036028	Assmann[34]	2007	Covariate	Protective HR: 0.54 (0.31–0.93)	Adult employees in PROCAM study (excluded subjects with history of angina pectoris, MI, or stroke)	Cerebral ischemic events (ischemic stroke or TIA)	Smoking, DM, Age, SBP, Sex	26 975	32	85	45.7 (6.8)	10 years (mean=12)

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Table 2. Continued

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20535515	Wu[35]	2011	Stratified	NA	Patients admitted for stroke at community hospitals in Chongqing, China	Stroke	M: Age, HTN, CAD, Family History, Hyperlipidemia, DBP, Education, Physical Exercise, Salt Consumption, DM F: Age, HTN, Family History, DM, DBP, Hyperlipidemia, BMI, Education, Alcohol Use, Salt Consumption	1034	NR	NR	NR	NA (Case–Control)
20671251	Chien[36]	2010	Covariate	Protective RR: 0.65 (0.50–0.85)	Participants without stroke at baseline	Stroke at 10-year follow-up	AF, Family History of Stroke, DM, Age, DBP, SBP, Sex	3513	40	240	54.6 (NR)	10 years (mean=15.9)
Hemorrhagic stroke—morbidity												
8290048	Lisk[37]	1994	Covariate	Harmful OR: 4.11	Hemispheric ICH ER presentation, all patients surgical	Poor outcome (Rankin 5–6 vs Rankin 0–4 at discharge)	Age, Sex, DBP, SBP, Surgery, Pupil Abnormality, Hyperventilation, GCS, Hemorrhage Size, Subarachnoid Blood, Early Admission Interval, Hemorrhage Location, Mass Effect, Mental Status, Ventricular Extension	75	59	35	58.6 (16.4)	Mean=18 days

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Table 2. Continued

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Ischemic stroke—morbidity and/or mortality												
9645975	Arboix[38]	1998	Covariate	Protective OR: 0.44 (0.21–0.93)	Patients with cardioembolic stroke admitted to Barcelona Hospital	Dead (all-cause) or alive at discharge (within 7 days)	Age, Sex, CHF, Mental Status, Limb Weakness	231	63	63	NR	Hospitalization period
10382694	Rothwell[39]	1999	Covariate	Harmful HR: 2.05 (1.29–3.24)	Patients with a carotid distribution TIA, minor ischemic stroke, non-disabling major ischemic stroke, or retinal infarction in the previous 6 months, with ipsilateral carotid stenosis on angiography	Any major stroke (fatal or lasting longer than 7 days) or death from any other cause within 30 days of surgery	PVD, SBP, Sex	3007	NR	117	NR	30 days
17068305	Kent[40]	2006	Covariate	NA[†]	Patients with acute stroke being evaluated for thrombolysis, treated within 0 to 6 hours	Good outcome (Modified Ranking Scale 0 or 1)	tPA, Sex, Prior Stroke, Age, Time to Treatment, Age×NIHSS, tPA×Time to Treatment, SBP, NIHSS, tPA×SBP, tPA×Sex, DM, tPA×Prior Stroke	2131	45	773	65.9 (11.4)	Hospitalization period
18004645	Roquer[41]	2007	Covariate	Protective HR: 0.64 (0.46–0.88)	Patients admitted to hospital with first ever acute ischemic event	Early death or in-hospital mortality	Age, Sex, NIHSS, Glycemia	1527	50	197	73 (12)	Hospitalization period
21300951	Saposnik[42]	2011	Covariate	Protective OR: 0.82 (0.70–0.96)	Community-based patients presenting with an acute ischemic stroke at hospitals in Ontario, Canada	Mortality at 30 days following acute ischemic stroke	AF, Cancer, CHF, Sex, Age, Glucose, Renal Dialysis, Preadmission Disability, Stroke Severity, Stroke Subtype	12 262	47	1004	72.04 (13.86)	30 days

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Table 2. Continued

PubMed ID	First Author	Pub. Year	Inclusion of Sex	Effect of Female Sex	Population	Outcome(s)	Covariates	Cohort Sample Size	% Female in Cohort	No. of Events	Mean Age (SD)	Follow-Up Duration
21300951	Saposnik[42]	2011	Covariate	Protective OR: 0.85 (0.75–0.96)	Community-based patients presenting with an acute ischemic stroke at hospitals in Ontario, Canada	Mortality at 1 year following acute ischemic stroke	AF, Cancer, CHF, Sex, Age, Previous MI, Smoking, Glucose, Renal Dialysis, Preadmission Disability, Stroke Severity, Stroke Subtype	12 262	47	1853	72.04 (13.86)	1 year
TIA—morbidity and mortality												
1527533	Hankey[43]	1992	Covariate	Protective HR: 0.51 (0.33–0.79)	Patients with TIA and no prior stroke referred to a university hospital	Survival free of stroke, MI, or vascular death at 1 year and 5 years	Sex, PVD, TIA, Carotid and Vertebral-Basilar TIAs, Number of TIAs in last 3 months, LVH, Age, Residual Neurological Signs	469	32	118	62.1 (12)	Mean=4.1 years
1527533	Hankey[43]	1992	Covariate	Protective HR: 0.70 (0.39–1.23)	Patients with TIA and no prior stroke referred to a university hospital	Survival free of stroke at 1 and 5 years	Sex, PVD, TIA, Carotid and Vertebral-Basilar TIAs, Number of TIAs in last 3 months, LVH, Age, CAD, Residual Neurological Signs	469	32	63	62.1 (12)	Mean=4.1 years
1527533	Hankey[43]	1992	Covariate	Protective HR: 0.36 (0.18–0.71)	Patients with TIA and no prior stroke referred to a university hospital	Survival free of coronary event at 1 year and 5 years	Sex, PVD, TIA, Carotid and Vertebral-Basilar TIAs, Number of TIAs in last 3 months, LVH, Age, CAD, Residual Neurological Signs	469	32	58	62.1 (12)	Mean=4.1 years

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Table 2. Continued

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Revascularization—stroke												
12902080	Charlesworth[44]	2003	Covariate	Harmful OR: 1.04 (0.86–1.22)	Patients undergoing isolated CABG surgery in northern New England between 1992 and 2001	Perioperative stroke (new focal neurologic deficit that appears and is still evident >24 hours after onset, during or after CABG and established before discharge)	Sex, DM, PVD, EF <40%, Age, Renal Failure, Priority Level	33 062	28	532	NR	Hospitalization period
19243970	Antunes[45]	2009	Covariate	Harmful OR: 1.778 (1.096–2.884)	Patients who underwent isolate CABG	Postoperative cerebrovascular accident	Cerebrovascular Disease, PVD, LVD, Surgery, Sex, Age	4567	12	114	60.7 (9.3)	Hospitalization period
Arrhythmia—stroke												
10356104	Hart[46]	1999	Covariate	Harmful RR: 1.6 (1.24–1.96)	Patients with sustained or recurrent AF without mitral stenosis or prosthetic cardiac valves who were recruited from inpatient and outpatient facilities, assigned to aspirin or aspirin plus warfarin (with or without previous stroke or TIA)	Incident ischemic stroke (annualized risk)	Sex, Age, Prior Stroke/TIA, SBP, Hypertension, Alcohol Use	2012	28	101	69 (10)	Mean=2.0 years
12941677	Wang[47]	2003	Covariate	Harmful HR: 1.73 (1.16–2.59)	Participants with new-onset AF, 705 of whom were not treated with warfarin at baseline	Stroke	DM, Sex, Prior Stroke/TIA, Age, SBP	868	47	111	75 (9)	5 years (mean=4.3)

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Table 2. Continued

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19762550	Lip[48]	2010	Covariate	Harmful OR: 2.53 (1.08–5.92)	Ambulant and hospitalized patients with AF without mitral stenosis or previous heart valve surgery and who did not use either VKA or heparin at discharge	Risk factor of stroke or thromboembolism in patients with atrial fibrillation	DM, Sex, HTN, PVD, Age, Stroke/TIA, CHF/LVD	5333	8	25	66 (14)	1 year
CAD—stroke												
12473877	West[49]	2002	Covariate	Protective RR: 0.70 (0.52–0.94)	Patients with MI or hospital discharge diagnosis of unstable angina 3 to 36 months before randomization and plasma total cholesterol of 4 to 7 mmol/L, randomly assigned to pravastatin or placebo	Nonhemorrhagic stroke in patients with coronary artery disease	Sex, AF, Stroke at Baseline, DM, BMI, HTN, Creatinine Clearance, HDL Cholesterol, Triglycerides, Total Cholesterol, UA, Statin Use, Age, Smoking, SBP, MI	9014	17	388	NR	Mean=6 years
16210253	Clayton[50]	2005	Covariate	Harmful HR: 1.14 (0.77–1.69)	Patients with stable symptomatic angina and preserved LVEF who require treatment for angina	Stroke	Previous Stroke, Smoking, DM, Age, SBP, QT Interval, EF <60%, Angina Medication, Angina, Previous Angiography, Lipid-Lowering Therapy, Glucose, Creatinine, Previous MI, WBC, Sex	7311	21	179	63.5 (9.2)	Mean=4.9 years

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Table 2. Continued

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22064650	Podolecki[51]	2012	Covariate	Harmful HR: 2.61 (2.04–3.18)	Patients with acute myocardial infarction who were screened with coronary angiography and underwent PCI	Stroke (ischemic or hemorrhagic)	Previous Stroke/TIA, Sex, GFR, Nephropathy, Prior AMI, Smoking	2520	30	52	62 (NR)	Median=25.5 months
Carotid disease—morbidity and mortality												
21051669	Calvillo-King[52]	2010	Covariate	Harmful HR: 1.47 (1.11–1.94)	Medicare beneficiaries who underwent carotid endarterectomy and were otherwise asymptomatic	Perioperative death or stroke	Severe Disability, Race, Stenosis >50%, CHF, CAD, VHD, Distant Stroke or TIA, Sex	6553	45	197	74.5 (6.6)	30 days
CVT—morbidity and mortality												
18823637	Koopman[53]	2009	Covariate	Protective HR: 0.63	Cerebral venous thrombosis patients aged >15 years who were evaluated in the hospital	Predictive score for poor outcome (MRS >2) or death	CNS Infection, VTE, Malignancy, GCS, Age, Mental Status, Intracranial Hemorrhage, Sex	90	78	16	36.2 (NR)	Mean=1.58 years
19420921	Ferro[54]	2009	Covariate	Protective HR: 0.63 (0.19–0.99)	Patients of Internal Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT)	CVT risk score	Malignancy, Coma, VTE, Mental Status, Sex, Intracranial Hemorrhage	624	75	19	NR	Median=1.3 years

AF indicates atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CNS, central nervous system; CVD, cardiovascular disease; CVT, cerebral venous thrombosis; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiography; EF, ejection fraction; ER, emergency room; FHS, Framingham Heart Study; GCS, Glasgow Coma Scale; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; HTN, hypertension; ICH, Intracerebral Hemorrhage; ISCVT, Internal Study on Cerebral Vein and Dural Sinus Thrombosis; LVD, left ventricular dysfunction; LVH, left ventricular hypertrophy; MI, myocardial infarction; MRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; OR, odds ratio; OS, offspring; PROCAM, Prospective Cardiovascular Munster study; PVD, peripheral vascular disease; RR, risk ratio; SBP, systolic blood pressure; TIA, transient ischemic attack; tPA, tissue plasminogen activator; UA, unstable angina; VHD, valvular heart disease ; VKA, Vitamin K antagonists; VTE, venous thromboembolism; WBC, white blood cells.

*Directionality of the predictive effect of female sex cannot be determined without considering the following interaction terms with sex: log(age)×female, $(\log(age))^2$×female, diabetes×female, and ECG-LVH×male.

†Directionality cannot be determined for this model without considering the following interaction term with sex: treatment×male.

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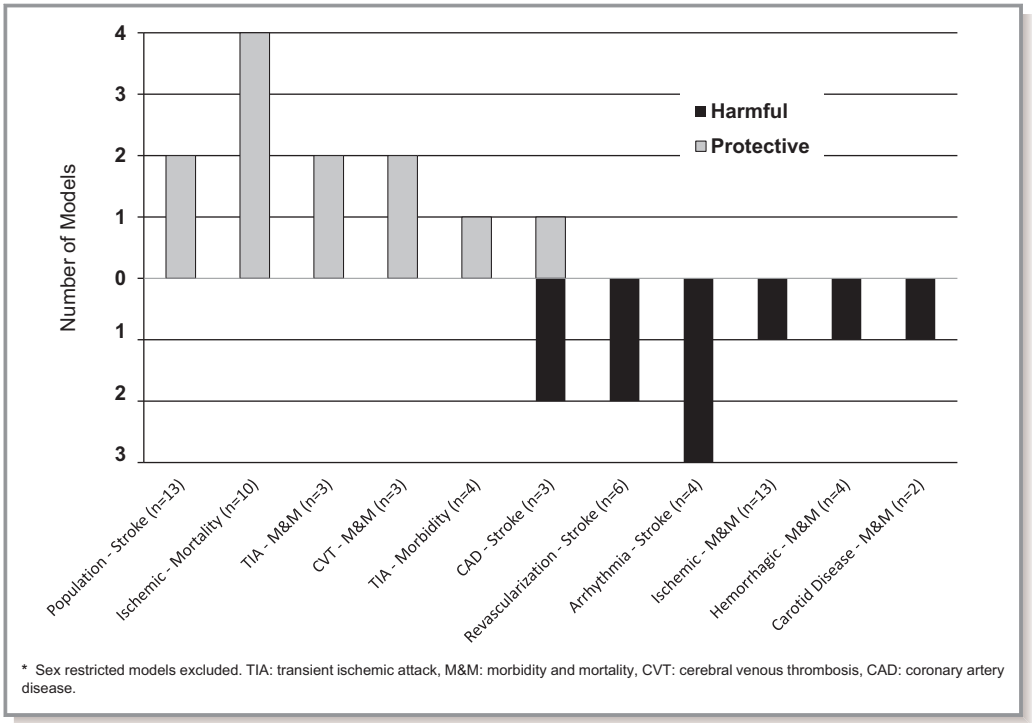

* Sex restricted models excluded. TIA: transient ischemic attack, M&M: morbidity and mortality, CVT: cerebral venous thrombosis, CAD: coronary artery disease.

Figure 2. The directionality of the predictive effect of female sex in stroke prediction models, by index condition–outcome pair.* Among models that included a covariate for sex, the directionality (harmful vs protective) of the predictive effect of being a female on outcome risk is summarized by unique index condition–outcome pairs. For example, among 13 models predicting risk of stroke in a population sample, 2 models included sex as a covariate. In both of these models, the predictive effect of being a woman was protective, or associated with reduced risk of a first stroke.

Determinants of Including Sex in Stroke CPMs

Models developed from larger cohort sample sizes (>1000 people: odds ratio=4.58, 95% CI 1.73–12.13, P=0.002) and those models predicting first stroke as an outcome (versus predicting outcomes among patients with stroke or history of stroke) (odds ratio=5.75, 95% CI 2.18–15.14, P<0.001) were more likely to include sex as either a covariate or stratification variable (Table 3). Having a woman as first, last, or corresponding author was associated with lower odds of including sex, although these studies were significantly less likely to be based on large cohorts (mean sample size of 9094 versus 54 733, P=0.03). A higher proportion of events in a cohort was inversely associated with including sex (P=0.03), though models with lower proportions of events (<10%) were 17 times more likely to be those predicting first stroke as an outcome versus outcomes among patients with stroke.

Discussion

Despite appreciation of differences between men and women in stroke risk and outcomes, we found that sex was included in only about 1 of 3 stroke-related CPMs. While sex was a covariate in the majority of models predicting first stroke in general, and even more often in models predicting stroke in general population samples, models of outcomes among patients with stroke or a history of stroke usually did not include sex as a risk factor. The predictive effect of female sex —when included in stroke-related CPMs—was notably consistent between models developed on the same index condition–outcome pair, although being female was associated with higher risk for some outcomes and lower risk for others.

The importance of sex-specific risk assessment in primary stroke prevention is emphasized in both the 2014 American Heart Association/American Stroke Association primary prevention guidelines,[55] and those specific to women.[20] The relevance of sex-specific risk in primary prevention is supported by our observation that sex was included in 69% of the population sample–stroke models. The stroke prevention guidelines for women called for development of woman-specific stroke risk scores that may improve upon currently available tools. In fact, the performance of some of these commonly used models—in terms of measures of calibration and discrimination—has been shown to vary by sex.[31,56,57] The prevention guidelines also underscored the need to consider risk factors unique to women, especially

Table 3. Univariable Cohort and Study-Level Characteristics and Odds of Including Sex as a Covariate or Stratification Variable*

	Odds Ratio (95% CI)	*P* Value
Sample size		
Cohort >1000 people (median), n=86		
>1000=43 models	4.58 (1.73–12.13)	0.002
Number of events ≥114 (median), n=82		
≥114 events=42 models	1.47 (0.57–3.74)	0.43
Proportion of events (events/cohort sample size), n=80		
≥10%=45 models	0.34 (0.13–0.89)	0.03
Percent women in the cohort		
>50% females, n=75		
>50%=24 models	0.84 (0.30–2.34)	0.74
Age		
Mean/median age (continuous), n=71	0.95 (0.90–1.01)	0.08
Mean/median age >67 (median), n=71		
Age >67 years, n=36	0.24 (0.08–0.71)	0.01
Time		
Cohort year, n=70	0.95 (0.91–1.01)	0.06
Publication year, n=83	0.97 (0.90–1.04)	0.37
Other		
First stroke as outcome vs prediction of outcomes in stroke patients, n=87		
Models predicting first stroke: n=30	5.75 (2.18–15.14)	0.0004
AUC (Lower [0.6–0.8] vs higher [>0.8]), n=47		
Lower, n=27	3.71 (0.98–14.05)	0.053
Is 1st/last/corresponding author a female?, n=80		
Yes=25 models	0.32 (0.11–0.99)	0.047

AUC indicates area under the curve.
*Models from sex-restricted cohorts excluded.

those that affect younger women of reproductive age. Our review did not identify any prediction models specific to younger women (or pregnant women), reinforcing this critical gap in the literature highlighted by the guidelines. Furthermore, no models included sex-specific risk factors (ie, oral contraceptive use) or risk factors more common in women (ie, migraine). As the median age of patients in model development cohorts was 67 years, the impact of these risk factors is likely to be less influential. Additionally, because age was included in the majority of stroke models, this covariate may act as a proxy for menopausal status or other reproductive factors that vary by age.

Although this summary is not intended to be inclusive of all studies examining the role of sex and gender in stroke, it is striking that sex was incorporated in fewer than 20% of models predicting outcomes among patients with an existing stroke-related condition. The relative scarcity of sex in these models is congruent with current secondary prevention guidelines, which are largely the same for men and women.[58] Sex was more likely to be included in outcome models in patients with ischemic stroke than in models of hemorrhagic stroke patients, which may result from the greater stroke severity observed in hemorrhagic stroke patients. However, this result should be interpreted cautiously, given many other differences across these model groups, such as cohort sample size. The paucity of sex in models predicting outcomes and prognosis among patients with acute stroke is likely to be the result of weaker predictive effects of sex in these circumstances. For example, prognosis among acute stroke patients is largely determined by age and stroke severity, captured in scales such as GCS and National Institutes of Health Stroke Scale, and sex is likely to play a much less influential role. Similarly, the relative infrequency of sex's inclusion in models of outcome events after stroke (including stroke recurrence) may also be understood in light of the potential for index event bias, which can generate paradoxical findings when the index and recurrent events have common risk factors, and studies select patients who have experienced the index event (ie, incident stroke).[59–61] The selection of patients with a first stroke influences the association between (both measured and unmeasured) stroke risk factors and sex in patients who are included in the study in ways that could obscure the predictive effects of sex on the incidence of subsequent strokes or other outcomes. It is also possible that sex is considered more often in primary versus secondary prevention model development because well-known primary prevention heart disease models are sex stratified or include sex as a covariate. However, we do not think this is likely, because we found that the majority of models reported considering sex as a candidate (and we suspect an even greater number tested the predictive effect of sex but did not report this step) and this did not vary between primary and secondary prevention models. Finally, it is noteworthy that none of the models included sex-related factors that have been associated with poorer outcomes following stroke, such as marital status and social isolation.[62,63]

While our descriptive analysis of the directionality of the predictive effect of female sex should be cautiously interpreted given the relatively small number of models for each index condition–outcome pairing, several of these findings align with prior literature. In both models predicting stroke in a general population that included a coefficient for sex, being a woman was associated with reduced risk, consistent with prior studies.[13,64] Similarly, all 3 models for stroke incidence among patients with arrhythmias indicated that women were at higher risk, concordant with the literature.[65–67] Conversely, our finding that all 4 models estimate lower risk of death after

ischemic stroke for women than otherwise similar men was surprising given the inconsistency of the literature, which has frequently reported worse prognoses in women (particularly in populations untreated with thrombolysis).[17,68–70] Finally, it is notable that about half of the models predicting stroke in a population sample were sex stratified (thereby allowing the effects of risk factors to vary among men and women), in keeping with evidence that sex modifies the effect of some risk factors on stroke risk.[20,71]

Our field synopsis of the role of sex in stroke-related CPMs has several limitations. With a sample of 92 stroke-related CPMs, our attempts to identify cohort and study-related factors associated with the inclusion of sex are likely to be statistically underpowered, and should be considered hypothesis generating in nature. Similarly, efforts to summarize the directionality of the predictive effect of sex on risk of incident stroke and outcomes after stroke were based on 3 or fewer models for a given index condition–outcome pair. Formal quantitative synthesis of coefficients for sex was therefore not feasible. Moreover, as this was a review of CPMs, and not of all studies examining the role of sex and gender in stroke (such as those endeavoring to estimate *causal* relationships, while adjusting for possible confounders), causal effects of sex on stroke outcomes may be obscured in the present studies by various biases or model-building procedures. Finally, it is likely that the number of models has continued to proliferate in the published literature since the creation of the Tufts CPM Registry in 2012.

While the call for sex-specific risk assessment in stroke appears well motivated by the literature, such calls should be viewed as part of a larger initiative to make recommendations more "patient-specific," as there are numerous factors (including sex) that can influence a patient's prognosis and potential for treatment benefit and harm.[72–74] CPMs have the potential to enable appropriate tailoring of prevention and treatment strategies for stroke in men and women, and to improve estimation of sex-based treatment disparities, which have been documented among stroke patients.[13,75] Sex differences in outcome risk—estimable from CPMs—represent an appropriate determinant of clinical decision making, in addition to differences in treatment indications/contraindications and patient preferences. Thus, studies that endeavor to quantify disparities in care for sexually dimorphic conditions, such as stroke, should account for sex differences in outcome risk, in addition to baseline patient factors and preferences.[22] For example, given the incorporation of women's higher stroke risk in the CHA_2DS_2-VASc score[48] and the lack of sex-specific harm in the HAS-BLED score,[76] we would expect to see higher rates of anticoagulation therapy in women than otherwise similar men with atrial fibrillation. However, lower rates of prophylactic anticoagulation therapy have been observed in women, suggesting inappropriate "reverse targeting."[13,77] Whether use of CPMs can help reduce sex disparities by providing accurate sex-specific prognostic information at the point of care is an important question deserving more research.

In summary, our field synopsis shows that sex is most consistently included in CPMs predicting first stroke, suggesting that the importance of sex-specific care may be especially well established for primary prevention. We also noted that incorporation of sex in CPMs was more likely with larger sample sizes, which suggests that model development from cohorts of adequate sample size may uncover additional and more consistent predictive effects of sex, including stroke prognosis. We did not identify any CPMs specific to stroke risk in younger women, which is consistent with recent guidelines that highlighted a critical need to better understand risk in younger women and women of reproductive age. Efforts to establish the effects of sex on stroke incidence and prognosis, and differential effects of other risk factors in men and women, are important for individualizing stroke prevention and treatment. Implementation of sex-specific CPM as decision support in clinical care as a means of reducing sex disparities merits further research.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1: List of stroke-related clinical prediction models identified in the Tufts CPM Database from 1990-2012					
PMID	**Index Condition - Primary**	**Index Condition - Secondary**	**Outcome - Primary**	**Outcome - Secondary**	**Sex in the model**
10809270[1]	Stroke	Hemorrhage	Morbidity	NOS	No - Considered
11147987[2]	Stroke	TIA	Morbidity	Stroke	No - Considered
11283388[3]	Stroke	Hemorrhage	Mortality	NOS	No - Considered
11401607[4]	Arrhythmia	NOS	Morbidity	Stroke	No - Considered
11445104[5]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Considered
11470384[6]	Stroke	Ischemic	Mortality	NOS	No - Considered
11809350[7]	Population Sample	NOS	Morbidity	Stroke	Stratified
11935058[8]	Stroke	CVA	Mortality	NOS	No - Considered
11935058[8]	Stroke	CVA	Mortality	NOS	No - Considered
12473877[9]	CAD	Stable	Morbidity	Stroke	Yes
12529793[10]	Stroke	Hemorrhage	Morbidity and Mortality	NOS	No - Considered
12690211[11]	CAD	Revascularization	Morbidity	Stroke	No - Considered
12881825[12]	Stroke	Ischemic	Mortality	NOS	No - Not considered
12902078[13]	CAD	Revascularization	Morbidity	Stroke	No - Not considered
12902080[14]	CAD	Revascularization	Morbidity	Stroke	Yes
12941677[15]	Arrhythmia	NOS	Morbidity	Stroke	Yes
12941677[15]	Arrhythmia	NOS	Morbidity and Mortality	Stroke and Death	No - Considered
14526040[16]	Carotid Disease	NOS	Morbidity	Stroke	No - Considered
14684776[17]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Considered
14684776[17]	Stroke	Ischemic	Mortality	NOS	No - Considered
15993230[18]	Stroke	TIA	Morbidity	Stroke	No - Considered
16085199[19]	Population Sample	NOS	Morbidity	Stroke	Restricted
16085199[19]	Population Sample	NOS	Morbidity	Stroke	Restricted
16210253[20]	CAD	Stable	Morbidity	Stroke	Yes
16354736[21]	Stroke	Hemorrhage	Mortality	NOS	No - Not considered

16482367[22]	Stroke	CVA	Morbidity	Stroke	No - Considered
16955034[23]	Stroke	Hemorrhage	Mortality	NOS	No - Considered
17068305[24]	Stroke	Ischemic	Morbidity and Mortality	NOS	Yes
17068305[24]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Considered
17088464[25]	Population Sample	NOS	Morbidity	Stroke	Stratified
17192335[26]	Population Sample	DM	Morbidity	Stroke	No - Considered
17379820[27]	Stroke	Hemorrhage	Mortality	NOS	No - Not considered
17569877[28]	Stroke	Ischemic	Morbidity and Mortality	Cardiac and Death	No - Considered
17586511[29]	Population Sample	NOS	Morbidity	Stroke	Stratified
17718249[30]	Stroke	Hemorrhage	Morbidity and Mortality	NOS	No - Considered
17934885[31]	Stroke	CVA	Mortality	NOS	No - Considered
18004645[32]	Stroke	Ischemic	Mortality	NOS	Yes
18028368[33]	Stroke	Hemorrhage	Mortality	NOS	No - Considered
18035241[34]	Population Sample	NOS	Morbidity	Stroke	Restricted
18036028[35]	Population Sample	NOS	Morbidity	Stroke	Yes
18403738[36]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Not considered
18403738[36]	Stroke	Ischemic	Mortality	NOS	No - Not considered
18591432[37]	Population Sample	NOS	Morbidity and Mortality	Stroke and Death	No - Considered
18823637[38]	Stroke	CVT	Morbidity and Mortality	NOS	Yes
18955684[39]	Stroke	Ischemic	Morbidity	Hemorrhage	No - Not considered
19238132[40]	Stroke	CVA	Morbidity	NOS	No - Not considered
19243970[41]	CAD	Revascularization	Morbidity	Stroke	Yes
19359652[42]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Not considered
19420921[43]	Stroke	CVT	Morbidity and Mortality	NOS	Yes
19687023[44]	Stroke	TIA/Minor Stroke	Morbidity	Hemorrhage	No - Considered
19762550[45]	Arrhythmia	NOS	Morbidity	Stroke	Yes
19828550[46]	Stroke	Hemorrhage	Mortality	NOS	No - Considered
19938731[47]	Stroke	CVT	Morbidity and Mortality	NOS	No - Not considered
20001655[48]	Population Sample	Hypertension	Morbidity	Stroke	No - Considered
20018608[49]	Stroke	Ischemic	Morbidity	Stroke	No - Not considered

20155439[50]	Stroke	Hemorrhage	Mortality	NOS	No - Considered
20223889[51]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Not considered
20233732[52]	Stroke	CVA	Morbidity	NOS	No - Considered
20431079[53]	Carotid Disease	NOS	Morbidity and Mortality	Stroke and Death	No - Not considered
20535515[54]	Population Sample	NOS	Morbidity	Stroke	Stratified
20671251[55]	Population Sample	NOS	Morbidity	Stroke	Yes
20876438[56]	Stroke	Ischemic	Mortality	NOS	No - Not considered
21037471[57]	Stroke	Hemorrhage	Morbidity	NOS	No - Considered
21114132[58]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Not considered
21300951[59]	Stroke	Ischemic	Mortality	NOS	Yes
21300951[59]	Stroke	Ischemic	Mortality	NOS	Yes
21489563[60]	Population Sample	Hospital	Morbidity	Stroke	No - Not considered
22064650[61]	CAD	ACS	Morbidity	Stroke	Yes
1527533[62]	Stroke	TIA	Morbidity and Mortality	NOS	Yes
1527533[62]	Stroke	TIA	Morbidity	Stroke	Yes
1527533[62]	Stroke	TIA	Morbidity and Mortality	Cardiac and Death	Yes
1885480[63]	Stroke	NOS	Mortality	NOS	No - Considered
1985385[64]	Population Sample	NOS	Morbidity	Stroke	Yes
2001088[65]	Stroke	TIA/Minor Stroke	Morbidity and Mortality	NOS	No - Considered
2003301[66]	Population Sample	NOS	Morbidity	Stroke	Stratified
7612319[67]	Population Sample	NOS	Morbidity and Mortality	Stroke and Death	Restricted
7625160[68]	Stroke	Hemorrhage	Mortality	NOS	No - Considered
8213274[69]	Stroke	Hemorrhage	Morbidity and Mortality	NOS	No - Not considered
8266381[70]	Population Sample	NOS	Morbidity	Stroke	Stratified
8290048[71]	Stroke	Hemorrhage	Morbidity	NOS	No - Not considered
8290048[71]	Stroke	Hemorrhage	Morbidity and Mortality	NOS	Yes
8901723[72]	CAD	Revascularization	Morbidity	Stroke	No - Considered
9227690[73]	Stroke	Hemorrhage	Mortality	NOS	No - Not considered
9645975[74]	Stroke	Ischemic	Mortality	NOS	Yes
9660379[75]	Stroke	Ischemic	Mortality	NOS	No - Considered

10356104[76]	Arrhythmia	NOS	Morbidity	Stroke	Yes
10382694[77]	Stroke	Ischemic	Morbidity and Mortality	Stroke and Death	No - Considered
10382694[77]	Stroke	Ischemic	Morbidity and Mortality	Stroke and Death	Yes
10654481[78]	CAD	Revascularization	Morbidity	Stroke	No - Considered
10657421[79]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Not considered
10657421[79]	Stroke	Ischemic	Morbidity and Mortality	NOS	No - Not considered
21051669[80]	Carotid Disease	NOS	Morbidity and Mortality	Stroke and Death	Yes

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