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 roles13,14 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...
sex-specific care decisions in sexually dimorphic conditions such as stroke. While several commonly used CPMs for cardiovascular risk present sex-stratified models or include sex in risk scores, 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. 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, transient ischemic attacks, cerebral venous thrombosis, arrhythmias, 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, 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).

**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](https://example.com/figure1.png)

*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).
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%).

**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 | With Sex Incorporated | Without Sex | Sex Considered For Inclusion | Consideration Not Reported |
|----------------------------------------------------------|---------------------------|-----------------------|-------------|-----------------------------|---------------------------|
| Ischemic stroke—M&M (n=13)                              |                           | 15                    | 38          | 46                          |                           |
| Population sample—stroke (n=13)¹                         |                           | 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.

¹Includes 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.

**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).
In Table 2, we summarize the characteristics of stroke-related clinical prediction models that have included sex as a covariate. The table details various aspects such as the study population, sex composition, outcomes, covariates, and follow-up durations. Each row represents a different study, with details about the PubMed ID, first author, publication year, inclusion of sex, population characteristics, outcome(s), covariates, cohort sample size, percent female in cohort, number of events, mean age, and follow-up duration.

For instance, the study by Anderson et al. (1991) with PubMed ID 1985385 included members of the FHS and FHS-OS cohorts aged 30 to 74, initially free of CVD and cancer. The outcome(s) were CVD (MI, CHD death, angina pectoris, coronary insufficiency, stroke, TIA, CHF, PVD) with covariates including sex, cholesterol, LVH, DM, DMx Female, DM, Smoking, Age, SBP. The study followed 5,573 participants for 12 years.

Similarly, the study by Wolf et al. (1991) with PubMed ID 2003301 included subjects of FHS, age 55 to 84, free of stroke. The outcome was stroke at 10-year follow-up with covariates including LVH, Age, AF, CVD, Smoking, DM, SBP, Antihypertensive Therapy. The study followed 5,734 participants for 10 years.

The table continues with details from other studies, each providing a unique perspective on the role of sex in stroke-related clinical prediction models.
| 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 |
|-----------|--------------|-----------|------------------|---------------------|------------|------------|------------|-------------------|-----------------|--------------|----------------|------------------|
| 20535515  | Wu\textsuperscript{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\textsuperscript{36} | 2010      | Covariate        | Protective          | 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) |
|           |              |           |                  |                     |             |            |            |                   |                 |              |               |                  |
| 8290048   | Lisk\textsuperscript{37} | 1994      | Covariate        | Harmful            | 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 |

Continued
| PubMed ID | First Author | 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 |
|-----------|--------------|------|------------------|----------------------|------------|------------|------------|-------------------|-----------------|--------------|----------------|-------------------|
| 9645975   | Arboix       | 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     | 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         | 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) | IPA, 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       | 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     | 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 |

Continued
### 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<sup>42</sup> | 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          |
| 1527533   | Hankey<sup>43</sup> | 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<sup>43</sup> | 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<sup>43</sup> | 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  |

TIA—morbidity and mortality
| 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 |
|-----------|--------------|-----------|------------------|----------------------|------------|------------|------------|------------------|------------------|---------------|----------------|--------------------|
| 12902080  | Charlesworth  | 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       | 2009      | Covariate        | Harmful              | OR: 1.778 (1.096–2.884) | Patients who underwent isolated CABG | Postoperative cerebrovascular accident | Cerebrovascular Disease, PVD, LVD, Surgery, Sex, Age | 4567 | 12 | 114 | 60.7 (9.3) | Hospitalization period |
| 10356104  | Hart          | 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          | 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) |
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 |
|-----------|--------------|-----------|------------------|----------------------|------------|------------|------------|-------------------|------------------|--------------|----------------|---------------------|
| 19762550  | Lip⁴⁸        | 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 | | 5333 | 8 | 25 | 66 (14) | 1 year |
| 12473877  | West⁴⁹      | 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 | | 9014 | 17 | 388 | NR | Mean=6 years |
| 16210253  | Clayton⁵⁰   | 2005      | Covariate        | Harmful HR: 1.14 (0.77 - 1.69) | Patients with stable symptomatic angina and preserved LVEF who require treatment for angina | Stroke | | 7311 | 21 | 179 | 63.5 (9.2) | Mean=4.9 years |
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 |
|-----------|--------------|-----------|-----------------|----------------------|------------|------------|------------|---------------------|-------------------|--------------|----------------|-------------------|
| 22064650  | Podolecki51  | 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 |
| 21051669  | Calvillo-King52 | 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           |
| 18823637  | Koopman53    | 2009      | Covariate       | Protective HR: 0.63 (0.19–0.99) | 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  | Ferro54      | 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; CAGB, 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)xfemale, (log(age))^2xfemale, diabetesxfemale, and ECG-LVHxfemale.
†Directionality cannot be determined for this model without considering the following interaction term with sex: treatmentxfmale.
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, and those specific to women. 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. The prevention guidelines also underscored the need to consider risk factors unique to women, especially...
Field Synopsis of the Role of Sex in Stroke CPMs  Paulus et al

likely to be less in contraceptive use) or risk factors more common in women (ie, more, no models included sex-specific factors that vary by 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. 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). 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 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.

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. Similarly, all 3 models for stroke incidence among patients with arrhythmias indicated that women were at higher risk, concordant with the literature. Conversely, our finding that all 4 models estimate lower risk of death after

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

| Sample size | Odds Ratio (95% CI) | P Value |
|-------------|---------------------|---------|
| 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/cohoot sample size), n=80 |                     |         |
| ≥10%/45 models | 0.34 (0.13–0.89) | 0.03    |
| Percent women in the cohort |                     |         |
| >50% females, n=75 | 0.84 (0.30–2.34) | 0.74    |
| >50%/24 models |                     |         |
| 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.

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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). 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\(_2\)DS\(_2\)-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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None.

References
1. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TSM. Left atrial size. Physiologic determinants and clinical applications. J Am Coll Cardiol. 2006;47:2357–2363.
2. Crouse JR, Goldbourt U, Evans G, Pinsky J, Sharrett AR, Sorlie P, Riley W, Heiss G. Arterial enlargement in the atherosclerosis risk in communities (ARIC) cohort. In vivo quantification of carotid arterial enlargement. The ARIC Investigators. Stroke. 1994;25:1354–1359.
3. Schulz UG, Rothwell PM. Sex differences in carotid bifurcation anatomy and the distribution of atherosclerotic plaque. Stroke. 2001;32:1525–1531.
4. Matteis M, Troisi E, Monaldo BC, Caltagirone C, Silvestrini M. Age and sex differences in cerebral hemodynamics: a transcranial Doppler study. Stroke. 1998;29:963–967.
Field Synopsis of the Role of Sex in Stroke CPMs

Paulus et al

18. Shobha N, Sylaja PN, Kapral MK, Fang J, Hill MD. Differences in stroke outcome based on sex. J Cereb Blood Flow Metab. 2005;25:809–814.

21. Wessler B, Lai L, Kramer W, Cangelosi M, Raman G, Lutz J, Kent D. Clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. Stroke. 2003;34:1114–1119.

23. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Murphy LR, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Wasserfallen J, Whisnant JP, Wyse RG, Xie MX, Yang MS, Yi D. Risk factors for ischemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a prospective community-based study. Lancet. 2010;376:1121–1130.

25. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke. 1994;25:40–43.

26. Janssens AM, Komarova M, Jovin R, Sheets N, Ubel P. Association between researcher gender and sex of participants in clinical cancer research. In: ASCO Annual Meeting Proceedings. 2008:6607.

27. Campbell LG, Mehtani S, Dozier ME, Rinehart J. Gender-heterogeneous working groups produce higher quality science. PLoS One. 2013;8:e79147.

28. Pollit DP, Beck CT. International gender bias in nursing research, 2005–2006: a gender-disaggregated content analysis. Int J Nurs Stud. 2009;46:1110–1112.

29. Anderson KM, Odel PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1999;121:293–298.

30. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. Stroke. 1991;22:312–318.

31. Lumley T, Kronmal RA, Cushman M, Manolio TA, Goldstein S. A stroke prediction score in the elderly: validation and web-based application. J Clin Epidemiol. 2002;55:129–136.

32. Wu Y, Li X, Li X, Li Y, Zhao L, Chen Z, Li Y, Rao X, Zhou B, Detrano R, Liu K. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. Circulation. 2006;114:2217–2225.

33. Jee SH, Park JW, Lee S-Y, Nam B-H, Ryu HG, Kim SY, Kim YN, Lee JK, Choi SM, Yun JE. Stroke risk prediction model: a risk profile from the Korean study. Atherosclerosis. 2006;197:318–325.

34. Assmann G, Schulte H, Cullen P, Seedorf U. Assessing risk of myocardial infarction and stroke: new insights from the Prospective Cardiovascular Munster (PROCAM) study. Eur J Clin Invest. 2007;37:925–932.

35. Wu Y, Zhang L, Yuan X, Wu Y, Yi D. Quantifying links between stroke and risk factors: a study on individual health risk appraisal of stroke in a community of Chongqing. Neurol Sci. 2011;32:211–219.

36. Chien KL, Su T-C, Hsu HC, Chang WT, Chen PC, Sung FC, Chen M-F, Lee Y-T. Constructing the prediction model for the risk of stroke in a Chinese population: report from a cohort study in Taiwan. Stroke. 2010;41:1856–1864.

37. Lisk DR, Pauwels W, Rhoades H, Putnam RD, Grotta JC. Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. Neurology. 1994;44:133–139.

38. Arboix A, Garcia-Eroles L, Massons J, Oliveres M. Predictive clinical factors of in-hospital mortality in 231 consecutive patients with cardioembolic cerebral infarction. Cerebrovasc Dis. 1998;8:8–13.

39. Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists’ Collaborative Group. Lancet (London, England). 1999;353:2105–2110.

40. Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacket W. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke. 2006;37:2947–2952.

41. Roquer J, Ois A, Rodriguez Campello A, Gomis M, Munteles E, Jimenez Conde J, Martinez-Rodriguez JE. Clustering of vascular risk factors and in-hospital death after acute ischemic stroke. J Neurol. 2007;254:1636–1641.

42. Saposnik G, Kapral MK, Liu Y, Hall R, O’Donnell M, Raptis S, Tu JV, Mamdani M, Austin PC. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. Circulation. 2011;123:739–749.

43. Hankey GJ, Slattery JM, Warlow CP. Transient ischemic attacks: which patients are at high (and low) risk of serious vascular events? J Neurol Neurosurg Psychiatry. 1992;55:640–652.

44. Charlesworth DC, Likosky DS, Marrin CAS, Maloney CT, Quinton HB, Morton JR, Leavitt BJ, Clough RA, O’Connor GT. Development and validation of a prediction model for strokes after coronary artery bypass grafting. Ann Thorac Surg. 2003;76:436–443.

46. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF-HF clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Stroke. 1999;30:1223–1229.

47. Wang Y, Lim LL-Y, Heller RF, Fisher J, Levi CR. A prediction model of 1-year mortality for acute ischemic stroke patients. Arch Phys Med Rehabil. 2003;84:1006–1011.

48. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijs HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest. 2010;137:263–272.

49. West MJ, White HD, Simes RJ, Kirby A, Watson JD, Anderson NE, Hankey GJ, Wonders S, Hunt D, Tonkin AM. Risk factors for non-haemorrhagic stroke in...
patients with coronary heart disease and the effect of lipid-modifying therapy with pravastatin. J Hypertens. 2002;20:25 V–2517.

50. Clayton TC, Lubsen J, Pocock J, Voko Z, Kirwan BA, Fox KAA, Poole-Wilson PA. Risk score for predicting death, myocardial infarction, and stroke in patients with stable angina, based on a large randomised trial cohort of patients. BMJ. 2005;331:869.

51. Podoleczyk TS, Lenarczyk RK, Kowalczyk JP, Mazurek MH, Siatkowski AM, Chodor PK, Pruszkowska-Skrzep PI, Sedlickova AA, Polonski L, Kalarus ZF. The risk of stroke in patients with acute myocardial infarction treated invasively. Coron Artery Dis. 2012;23:9–15.

52. Calvillo-King L, Luan X, Zhang S, Tahir M, Halm EA. Predicting risk of perioperative death and stroke after carotid endarterectomy in asymptomatic patients: derivation and validation of a clinical risk score. Stroke. 2010;41:2786–2794.

53. Koopman K, Uyttenboogaard M, Vroomen PC, van der Meer J, De Keyser J, Luijckx GJ. Development and validation of a predictive outcome score of cerebral venous thrombosis. J Neurol Sci. 2009;276:66–68.

54. Ferro JM, Bacelar-Nicolau H, Rodrigues T, Bacelar-Nicolau L, Canhao P, Grassard I, Bousser M-G, Dutta AP, Massaro A, Mackowiak-Cordiali M-A, Leys D, Fonts E, Staj J, Binaragarrementeria F. Risk score to predict the outcome of patients with cerebral vein and dural sinus thrombosis. Cerebrovasc Dis. 2009;28:39–44.

55. Meschia JF, Bushnell C, Boden-Alba B, Braun LT, Bravata DM, Chatrud SW, Creager MA, Eckel RH, Elkind MSV, Fornage M, Goldstein LB, Greenberg SM, Horvath SE, Iadecola C, Jauch EC, Moore WS, Wilson JA. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:3755–3832.

56. Bineau S, Dufouil C, Helmer C, Ritchie K, Emparna JP, Ducimetière P, Alpérovitch A, Bousser MG, Zouros C. Framingham stroke risk function in a large population-based cohort of elderly people: the 3C study. Stroke. 2009;40:1564–1570.

57. Delfippis AP, Young R, Carrubba CJ, McEvoy JW, Buddoff MJ, Blumenthal RS, Kronmal RA, Clelland RL, Nasir K, Blaha MJ. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162:266–275.

58. Kerman WN, Ovbiagele B, Black HR, Bravata DM, Chimonowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a primary guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160–2236.

59. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. JAMA. 2011;305:822–823.

60. Levine DA, Walter JM, Karve SJ, Skolarus LE, Levine SR, Mulhern KA. Smoking and mortality in stroke survivors: can we eliminate the paradox? J Stroke Cerebrovasc Dis. 2014;23:1282–1290.

61. Flanders WD, Eldridge RC, McClellan W. A nearly unavoidable mechanism for collider bias with index-event studies. Epidemiology. 2014;25:762–764.

62. Boden-Alba B, Litwak E, Elkind MSV, Rundek T, Sacco RL. Social isolation and outcomes post stroke. Neurology. 2005;64:1888–1892.

63. Lisabeth LD, Reeves MJ, Baek J, Skolarus LE, Brown DL, Zahurancic DB, Smith MA, Morgenstern LB. Factors influencing sex differences in poststroke functional outcome. Stroke. 2015;46:860–863.

64. Wierberdin RG, Ikrar MA, Hofman A, Koudstaal PJ, Breteler MMP. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. Eur J Epidemiol. 2012;27:287–295.

65. Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA. 2012;307:1952–1958.

66. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33:1500–1510.

67. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D’Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA. 2003;290:1049–1056.

68. Hill MD, Kent DM, Hinchee J, Rowley H, Buchan AM, Wechsler LR, Higashida RT, Fischbein NJ, Dillon WP, Gent M, Firtz CS, Schulz GA, Furlan AJ. Sex-based differences in the effect of intra-arterial treatment of stroke: analysis of the PROACT-2 study. Stroke. 2006;37:2322–2325.

69. Niewada M, Kobayashi A, Sandercock PAG, Kamiński B, Czlonkowska A. Influence of gender on baseline features and clinical outcomes among 17,370 patients with confirmed ischaemic stroke in the international stroke trial. Neuroepidemiology. 2005;24:123–128.

70. Eriksson M, Glader EL, Norving B, Terén A, Stenqvist B. Sex differences in stroke care and outcome in the Swedish national quality register for stroke care. Stroke. 2009;40:909–914.

71. Peters SAE, Huxley RR, Sattar N, Woodward M. Sex differences in the excess risk of cardiovascular diseases associated with type 2 diabetes: potential explanations and clinical implications. Curr Cardiovasc Risk Rep. 2015;9:36.

72. Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793–795.

73. Kent DM, Rothwell PM, Ioinindis JPA, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials. 2010;11:85.

74. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. JAMA. 2007;298:1209–1212.

75. Towfighi A, Markovic D, Ovbiagele B. Sex differences in revascularization interventions after acute ischemic stroke. J Stroke Cerebrovasc Dis. 2013;22; e347–e353.

76. Pisters R, Lane DA, Newmait R, De Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093–1100.
| PMID      | Index Condition - Primary | Index Condition - Secondary | Outcome - Primary | Outcome - Secondary | Sex in the model               |
|-----------|----------------------------|-----------------------------|-------------------|---------------------|--------------------------------|
| 10809270  | Stroke                     | Hemorrhage                  | Morbidity         | NOS                 | No - Considered                |
| 11147987  | Stroke                     | TIA                         | Morbidity         | Stroke              | No - Considered                |
| 11283388  | Stroke                     | Hemorrhage                  | Mortality         | NOS                 | No - Considered                |
| 11401607  | Arrhythmia                 | NOS                         | Morbidity         | Stroke              | No - Considered                |
| 11445104  | Stroke                     | Ischemic                    | Morbidity and Mortality | NOS  | No - Considered                |
| 11470384  | Stroke                     | Ischemic                    | Mortality         | NOS                 | No - Considered                |
| 11809350  | Population Sample          | NOS                         | Morbidity         | Stroke              | Stratified                     |
| 11935058  | Stroke                     | CVA                         | Mortality         | NOS                 | No - Considered                |
| 11935058  | Stroke                     | CVA                         | Mortality         | NOS                 | No - Considered                |
| 12473877  | CAD                        | Stable                      | Morbidity         | Stroke              | Yes                            |
| 12529793  | Stroke                     | Hemorrhage                  | Morbidity and Mortality | NOS  | No - Considered                |
| 12690211  | CAD                        | Revascularization           | Morbidity         | Stroke              | No - Considered                |
| 12881825  | Stroke                     | Ischemic                    | Mortality         | NOS                 | No - Not considered            |
| 12902078  | CAD                        | Revascularization           | Morbidity         | Stroke              | No - Not considered            |
| 12902080  | CAD                        | Revascularization           | Morbidity         | Stroke              | Yes                            |
| 12941677  | Arrhythmia                 | NOS                         | Morbidity         | Stroke              | Yes                            |
| 12941677  | Arrhythmia                 | NOS                         | Morbidity and Mortality | Stroke and Death | No - Considered                |
| 14526040  | Carotid Disease            | NOS                         | Morbidity         | Stroke              | No - Considered                |
| 14684776  | Stroke                     | Ischemic                    | Morbidity and Mortality | NOS  | No - Considered                |
| 14684776  | Stroke                     | Ischemic                    | Mortality         | NOS                 | No - Considered                |
| 15993230  | Stroke                     | TIA                         | Morbidity         | Stroke              | No - Considered                |
| 16085199  | Population Sample          | NOS                         | Morbidity         | Stroke              | Restricted                     |
| 16085199  | Population Sample          | NOS                         | Morbidity         | Stroke              | Restricted                     |
| 16210253  | CAD                        | Stable                      | Morbidity         | Stroke              | Yes                            |
| 16354736  | Stroke                     | Hemorrhage                  | Mortality         | NOS                 | No - Not considered            |
| Code         | Study Type            | Outcome                        | Condition       |
|--------------|-----------------------|--------------------------------|-----------------|
| 1648236722   | Stroke                | Morbidity                      | Stroke          |
| 1695503423   | Stroke                | Mortality                      | Stroke          |
| 1706830524   | Stroke                | Morbidity and Mortality        | Stroke          |
| 1706830524   | Stroke                | NOS                            | No - Considered |
| 1708846425   | Population Sample     | NOS                            | No - Considered |
| 1719233526   | Population Sample     | Morbidity                      | Stroke          |
| 1737982027   | Stroke                | Mortality                      | Stroke          |
| 1756987728   | Stroke                | NOS                            | No - Considered |
| 1758651129   | Population Sample     | Morbidity and Mortality        | Stroke          |
| 1771824930   | Stroke                | Mortality                      | Stroke          |
| 1800464531   | Stroke                | Mortality                      | Stroke          |
| 1802836833   | Stroke                | Mortality                      | Stroke          |
| 1803524134   | Population Sample     | Morbidity                      | Stroke          |
| 1803602835   | Population Sample     | Morbidity                      | Stroke          |
| 1840373836   | Stroke                | Mortality                      | Stroke          |
| 1840373836   | Stroke                | NOS                            | No - Considered |
| 1859143237   | Population Sample     | Morbidity and Mortality        | Stroke          |
| 1862363738   | Stroke                | Mortality                      | Stroke          |
| 1895568439   | Stroke                | Morbidity                      | Hemorrhage      |
| 1923813240   | Stroke                | NOS                            | No - Considered |
| 1924397041   | CAD                   | Morbidity                      | Stroke          |
| 1935965242   | Stroke                | Mortality                      | Stroke          |
| 1942092143   | Stroke                | Mortality                      | Stroke          |
| 1968702344   | Stroke                | Morbidity                      | Hemorrhage      |
| 1976255045   | Arrhythmia            | NOS                            | Stroke          |
| 1982855046   | Stroke                | Mortality                      | Stroke          |
| 1993873147   | Stroke                | Morbidity and Mortality        | Stroke          |
| 2000165548   | Population Sample     | Hypertension                   | Stroke          |
| 2001860849   | Stroke                | Morbidity                      | Stroke          |
| Study ID          | Category                  | Condition Type | Morbidity/Mortality Type                  | NOS Type | Consideration          |
|-------------------|---------------------------|----------------|------------------------------------------|----------|------------------------|
| 20155439          | Stroke                    | Hemorrhage     | Mortality and Mortality                  | NOS      | No - Considered        |
| 20223889          | Stroke                    | Ischemic       | Morbidity and Mortality                  | NOS      | No - Not considered    |
| 20233732          | Stroke                    | CVA            | Morbidity                                | NOS      | No - Considered        |
| 20431079          | Carotid Disease           | NOS            | Morbidity and Mortality                  | Stroke and Death | No - Not considered    |
| 20535515          | Population Sample         | NOS            | Morbidity                                | Stroke   | Stratified             |
| 20671251          | Population Sample         | NOS            | Morbidity                                | Stroke   | Yes                    |
| 20876438          | Stroke                    | Ischemic       | Morbidity                                | NOS      | No - Not considered    |
| 21037471          | Stroke                    | Hemorrhage     | Morbidity                                | NOS      | No - Considered        |
| 21114132          | Stroke                    | Ischemic       | Morbidity and Mortality                  | NOS      | No - Not considered    |
| 21300951          | Stroke                    | Ischemic       | Morbidity                                | NOS      | Yes                    |
| 21300951          | Stroke                    | Ischemic       | Mortality                                | NOS      | Yes                    |
| 21489563          | Population Sample         | Hospital       | Morbidity                                | Stroke   | No - Not considered    |
| 22064650          | CAD                       | ACS            | Morbidity                                | Stroke   | Yes                    |
| 1527533           | Stroke                    | TIA            | Morbidity and Mortality                  | NOS      | Yes                    |
| 1527533           | Stroke                    | TIA            | Morbidity                                | Stroke   | Yes                    |
| 1885480           | Stroke                    | NOS            | Mortality                                | NOS      | No - Considered        |
| 1985385           | Population Sample         | NOS            | Morbidity                                | Stroke   | Yes                    |
| 2001088           | Stroke                    | TIA/Minor Stroke| Morbidity and Mortality                  | NOS      | No - Considered        |
| 2003301           | Population Sample         | NOS            | Morbidity                                | Stroke   | Stratified             |
| 7612319           | Population Sample         | NOS            | Morbidity and Mortality                  | Stroke and Death | Restricted            |
| 7625160           | Stroke                    | Hemorrhage     | Mortality                                | NOS      | No - Considered        |
| 8213274           | Stroke                    | Hemorrhage     | Morbidity and Mortality                  | NOS      | No - Not considered    |
| 8266381           | Population Sample         | NOS            | Morbidity                                | Stroke   | Stratified             |
| 8290048           | Stroke                    | Hemorrhage     | Morbidity                                | NOS      | No - Not considered    |
| 8290048           | Stroke                    | Hemorrhage     | Morbidity and Mortality                  | NOS      | Yes                    |
| 8901723           | CAD                       | Revascularization| Morbidity                                | Stroke   | No - Considered        |
| 9227690           | Stroke                    | Hemorrhage     | Mortality                                | NOS      | No - Not considered    |
| 9645975           | Stroke                    | Ischemic       | Mortality                                | NOS      | Yes                    |
| 9660379           | Stroke                    | Ischemic       | Mortality                                | NOS      | No - Considered        |
| Reference | Title and Authors |
|-----------|-------------------|
| 1. | Qureshi AI, Sung GY, Razumovsky AY, Lane K, Straw RN, Ulatowski JA. Early identification of patients at risk for symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. *Crit Care Med*. 2000;28:984–990. |
| 2. | Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284:2901–2906. |
| 3. | Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891–897. |
| 4. | Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870. |
| 5. | Baird AE, Dambrosia J, Janket S, Eichbaum Q, Chaves C, Silver B, Barber PA, Parsons M, Darby D, Davis S, Caplan LR, Edelman RE, Warach S. A three-item scale for the early prediction of stroke recovery. *Lancet (London, England)*. 2001;357:2095–2099. |
| 6. | Wang Y, Lim LL, Levi C, Heller RF, Fischer J. A prognostic index for 30-day mortality after stroke. *J Clin Epidemiol*. 2001;54:766–773. |
| 7. | Lumley T, Kronmal RA, Cushman M, Manolio TA, Goldstein S. A stroke prediction score in the elderly: Validation and Web-based application. *J Clin Epidemiol*. 2002;55:129–136. |
| 8. | Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. *Stroke*. 2002;33:1041–1047. |
| 9. | West MJ, White HD, Simes RJ, Kirby A, Watson JD, Anderson NE, Hankey GJ, Wonders S, Hunt D, Tonkin AM. Risk factors... |
for non-haemorrhagic stroke in patients with coronary heart disease and the effect of lipid-modifying therapy with pravastatin. *J Hypertens.* 2002;20:2513–2517.

10. Hallevy C, Ifergane G, Kordysh E, Herishanu Y. Spontaneous supratentorial intracerebral hemorrhage. Criteria for short-term functional outcome prediction. *J Neurol.* 2002;249:1704–1709.

11. Ricotta JJ, Char DJ, Cuadra SA, Bilfinger T V, Wall LP, Giron F, Krukenkamp IB, Seifert FC, McLarty AJ, Saltman AE, Komaroff E. Modeling stroke risk after coronary artery bypass and combined coronary artery bypass and carotid endarterectomy. *Stroke.* 2003;34:1212–1217.

12. Wang Y, Lim LL-Y, Heller RF, Fisher J, Levi CR. A prediction model of 1-year mortality for acute ischemic stroke patients. *Arch Phys Med Rehabil.* 2003;84:1006–1011.

13. Likosky DS, Leavitt BJ, Marrin CAS, Malenka DJ, Reeves AG, Weintraub RM, Caplan LR, Baribeau YR, Charlesworth DC, Ross CS, Braxton JH, Hernandez FJ, O’Connor GT. Intra- and postoperative predictors of stroke after coronary artery bypass grafting. *Ann Thorac Surg.* 2003;76:428–34; discussion 435.

14. Charlesworth DC, Likosky DS, Marrin CAS, Maloney CT, Quinton HB, Morton JR, Leavitt BJ, Clough RA, O’Connor GT. Development and validation of a prediction model for strokes after coronary artery bypass grafting. *Ann Thorac Surg.* 2003;76:436–443.

15. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D’Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA.* 2003;290:1049–1056.

16. Tu J V, Wang H, Bowyer B, Green L, Fang J, Kucey D. Risk factors for death or stroke after carotid endarterectomy: observations from the Ontario Carotid Endarterectomy Registry. *Stroke.* 2003;34:2568–2573.

17. Weimar C, Konig IR, Kraywinkel K, Ziegler A, Diener HC. Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models. *Stroke.* 2004;35:158–162.

18. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JNE, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet (London, England).* 2005;366:29–36.

19. Zhang X-F, Attia J, D’Este C, Yu X-H, Wu X-G. A risk score predicted coronary heart disease and stroke in a Chinese cohort. *J Clin Epidemiol.* 2005;58:951–958.

20. Clayton TC, Lubsen J, Pocock SJ, Voko Z, Kirwan B-A, Fox KAA, Poole-Wilson PA. Risk score for predicting death,
myocardial infarction, and stroke in patients with stable angina, based on a large randomised trial cohort of patients. BMJ. 2005;331:869.

21. Weimar C, Benemann J, Diener H-C. Development and validation of the Essen Intracerebral Haemorrhage Score. J Neurol Neurosurg Psychiatry. 2006;77:601–605.

22. Kass-Hout TA, Moye LA, Smith MA, Morgenstern LB. A scoring system for ascertainment of incident stroke; the Risk Index Score (RISc). Methods Inf Med. 2006;45:27–36.

23. Mocco J, Ransom ER, Komotar RJ, Schmidt JM, Sciacca RR, Mayer SA, Connolly ESJ. Preoperative prediction of long-term outcome in poor-grade aneurysmal subarachnoid hemorrhage. Neurosurgery. 2006;59:529–538.

24. Kent DM, Selker HP, Ruthazer R, Bluhmki E, Hacke W. The stroke-thrombolytic predictive instrument: a predictive instrument for intravenous thrombolysis in acute ischemic stroke. Stroke. 2006;37:2957–2962.

25. Wu Y, Liu X, Li X, Li Y, Zhao L, Chen Z, Li Y, Rao X, Zhou B, Detrano R, Liu K. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. Circulation. 2006;114:2217–2225.

26. Yang X, So W-Y, Kong APS, Padilla-Martinez JJ, Gonzalez-Cornejo S. Development and validation of stroke risk equation for Hong Kong Chinese patients with type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care. 2007;30:65–70.

27. Ruiz-Sandoval JL, Chiquete E, Romero-Vargas S, Padilla-Martinez JJ, Gonzalez-Cornejo S. Grading scale for prediction of outcome in primary intracerebral hemorrhages. Stroke. 2007;38:1641–1644.

28. Prosser J, MacGregor L, Lees KR, Diener H-C, Hacke W, Davis S. Predictors of early cardiac morbidity and mortality after ischemic stroke. Stroke. 2007;38:2295–2302.

29. Jee SH, Park JW, Lee S-Y, Nam B-H, Ryu HG, Kim SY, Kim YN, Lee JK, Choi SM, Yun JE. Stroke risk prediction model: a risk profile from the Korean study. Atherosclerosis. 2008;197:318–325.

30. Poungvarin N, Suwanwela NC, Venketasubramanian N, Wong LKS, Navarro JC, Bitanga E, Yoon BW, Chang HM, Alam SM. Grave prognosis on spontaneous intracerebral haemorrhage: GP on STAGE score. J Med Assoc Thai. 2006;89 Suppl 5:S84–93.

31. Solberg OG, Dahl M, Mowinckel P, Stavem K. Derivation and validation of a simple risk score for predicting 1-year mortality in stroke. J Neurol. 2007;254:1376–1383.

32. Roquer J, Ois A, Rodriguez Campello A, Gomis M, Munteis E, Jimenez Conde J, Martinez-Rodriguez JE. Clustering of
vascular risk factors and in-hospital death after acute ischemic stroke. *J Neurol*. 2007;254:1636–1641.

33. Huang B-R, Liao C-C, Huang W-H, Hsu Y-H, Hsu J-C, Yen H-C, Lin C-L. Prognostic factors of spontaneous intracerebral haemorrhage in haemodialysis patients and predictors of 30-day mortality. *Intern Med J*. 2008;38:568–574.

34. Okamoto K, Horisawa R. Prediction of subarachnoid hemorrhage from a ruptured cerebral aneurysm by discriminant analysis in women. *J Stroke Cerebrovasc Dis*. 2007;16:245–250.

35. Assmann G, Schulte H, Cullen P, Seedorf U. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Munster (PROCAM) study. *Eur J Clin Invest*. 2007;37:925–932.

36. Konig IR, Ziegler A, Bluhmki E, Hacke W, Bath PMW, Sacco RL, Diener HC, Weimar C. Predicting long-term outcome after acute ischemic stroke: a simple index works in patients from controlled clinical trials. *Stroke*. 2008;39:1821–1826.

37. Wilson PWF, Bozeman SR, Burton TM, Hoaglin DC, Ben-Joseph R, Pashos CL. Prediction of first events of coronary heart disease and stroke with consideration of adiposity. *Circulation*. 2008;118:124–130.

38. Koopman K, Uyttenboogaart M, Vroomen PC, van der Meer J, De Keyser J, Luijckx GJ. Development and validation of a predictive outcome score of cerebral venous thrombosis. *J Neurol Sci*. 2009;276:66–68.

39. Lou M, Safdar A, Mehdiratta M, Kumar S, Schlaug G, Caplan L, Sears D, Selim M. The HAT Score: a simple grading scale for predicting hemorrhage after thrombolysis. *Neurology*. 2008;71:1417–1423.

40. Oto T, Kandori Y, Ohta T, Domen K, Koyama T. Predicting the chance of weaning dysphagic stroke patients from enteral nutrition: a multivariate logistic modelling study. *Eur J Phys Rehabil Med*. 2009;45:355–362.

41. Antunes PE, de Oliveira JF, Antunes MJ. Risk-prediction for postoperative major morbidity in coronary surgery. *Eur J Cardiothorac Surg*. 2009;35:760–767.

42. Hallevi H, Barreto AD, Liebeskind DS, Morales MM, Martin-Schild SB, Abraham AT, Gadia J, Saver JL, Grotta JC, Savitz SI. Identifying patients at high risk for poor outcome after intra-arterial therapy for acute ischemic stroke. *Stroke*. 2009;40:1780–1785.

43. Ferro JM, Bacelar-Nicolau H, Rodrigues T, Bacelar-Nicolau L, Canhao P, Crassard I, Bousser M-G, Dutra AP, Massaro A, Mackowiack-Cordolani M-A, Leys D, Fontes J, Stam J, Barinagarrementeria F. Risk score to predict the outcome of patients with cerebral vein and dural sinus thrombosis. *Cerebrovasc Dis*. 2009;28:39–44.

44. Lovelock CE, Redgrave JN, Briley D, Rothwell PM. The SCAN rule: a clinical rule to reduce CT misdiagnosis of intracerebral haemorrhage in minor stroke. *J Neurol Neurosurg Psychiatry*. 2010;81:271–275.
45. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137:263–272.

46. Chuang Y-C, Chen Y-M, Peng S-K, Peng S-Y. Risk stratification for predicting 30-day mortality of intracerebral hemorrhage. *Int J Qual Health Care*. 2009;21:441–447.

47. Poungvarin N, Prayoonwiwat N, Ratanakorn D, Towanabut S, Tantirittisak T, Suwanwela N, Phanthumchinda K, Tiamkoa S, Chankrachang S, Nidhinandana S, Laptikultham S, Limsoontarakul S, Udomphanthuruk S. Thai venous stroke prognostic score: TV-SPSS. *J Med Assoc Thai*. 2009;92:1413–1422.

48. Kjeldsen SE, Devereux RB, Hille DA, Lyle PA, Dahlof B, Julius S, Edelman JM, Snapinn SM, de Faire U, Fyhrquist F, Ibsen H, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H. Predictors of cardiovascular events in patients with hypertension and left ventricular hypertrophy: the Losartan Intervention for Endpoint reduction in hypertension study. *Blood Press*. 2009;18:348–361.

49. Ay H, Gungor L, Arsava EM, Rosand J, Vangel M, Benner T, Schwamm LH, Furie KL, Koroshetz WJ, Sorensen AG. A score to predict early risk of recurrence after ischemic stroke. *Neurology*. 2010;74:128–135.

50. Risselada R, Lingsma HF, Bauer-Mehren A, Friedrich CM, Molyneux AJ, Kerr RSC, Yarnold J, Sneade M, Steyerberg EW, Sturkenboom MCJM. Prediction of 60 day case-fatality after aneurysmal subarachnoid haemorrhage: results from the International Subarachnoid Aneurysm Trial (ISAT). *Eur J Epidemiol*. 2010;25:261–266.

51. Flint AC, Cullen SP, Faigeles BS, Rao VA. Predicting long-term outcome after endovascular stroke treatment: the totaled health risks in vascular events score. *AJNR Am J Neuroradiol*. 2010;31:1192–1196.

52. Reid JM, Gubitz GJ, Dai D, Kydd D, Eskes G, Reidy Y, Christian C, Counsell CE, Dennis M, Phillips SJ. Predicting functional outcome after stroke by modelling baseline clinical and CT variables. *Age Ageing*. 2010;39:360–366.

53. Setacci C, Chisci E, Setacci F, Iacononi F, de Donato G, Rossi A. Siena carotid artery stenting score: a risk modelling study for individual patients. *Stroke*. 2010;41:1259–1265.

54. Wu Y, Zhang L, Yuan X, Wu Y, Yi D. Quantifying links between stroke and risk factors: a study on individual health risk appraisal of stroke in a community of Chongqing. *Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol*. 2011;32:211–219.

55. Chien K-L, Su T-C, Hsu H-C, Chang W-T, Chen P-C, Sung F-C, Chen M-F, Lee Y-T. Constructing the prediction model for the risk of stroke in a Chinese population: report from a cohort study in Taiwan. *Stroke*. 2010;41:1858–1864.
56. Smith EE, Shobha N, Dai D, Olson DM, Reeves MJ, Saver JL, Hernandez AF, Peterson ED, Fonarow GC, Schwamm LH. Risk score for in-hospital ischemic stroke mortality derived and validated within the get with the guidelines-stroke program. *Circulation*. 2010;122:1496–1504.

57. Creutzfeldt CJ, Becker KJ, Weinstein JR, Khot SP, McPharlin TO, Ton TG, Longstreth WTJ, Tirschwell DL. Do-not-attempt-resuscitation orders and prognostic models for intraparenchymal hemorrhage. *Crit Care Med*. 2011;39:158–162.

58. Kasim KA, Brizzi M, Petersson J, Buchwald F, Sundgren PC. Combined clinical and radiological prognostic model in acute ischemic stroke. *Acta Neurol Belg*. 2010;110:239–245.

59. Saposnik G, Kapral MK, Liu Y, Hall R, O'Donnell M, Raptis S, Tu J V, Mamdani M, Austin PC. IScore: a risk score to predict death early after hospitalization for an acute ischemic stroke. *Circulation*. 2011;123:739–749.

60. Gan X, Xu Y, Liu L, Huang S, Xie D, Wang X, Liu J, Nie S. Predicting the incidence risk of ischemic stroke in a hospital population of southern China: a classification tree analysis. *J Neurol Sci*. 2011;306:108–114.

61. Podolecki TS, Lenarczyk RK, Kowalczyk JP, Mazurek MH, Swiatkowski AM, Chodor PK, Pruszkowska-Skrzep PI, Sedkowska AA, Polonski L, Kalarus ZF. The risk of stroke in patients with acute myocardial infarction treated invasively. *Coron Artery Dis*. 2012;23:9–15.

62. Hankey GJ, Slattery JM, Warlow CP. Transient ischaemic attacks: which patients are at high (and low) risk of serious vascular events? *J Neurol Neurosurg Psychiatry*. 1992;55:640–652.

63. Rodrigues CJ, Joshi VR. Predicting the immediate outcome of patients with cerebrovascular accident: a prognostic score. *J Assoc Physicians India*. 1991;39:175–180.

64. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121:293–8.

65. Kernan WN, Horwitz RI, Brass LM, Viscoli CM, Taylor KJ. A prognostic system for transient ischemia or minor stroke. *Ann Intern Med*. 1991;114:552–557.

66. Wolf PA, D’Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22:312–8.

67. Coppola WG, Whincup PH, Papacosta O, Walker M, Ebrahim S. Scoring system to identify men at high risk of stroke: a strategy for general practice. *Br J Gen Pract*. 1995;45:185–189.

68. Mase G, Zorzon M, Biasutti E, Tasca G, Vitrani B, Cazzato G. Immediate prognosis of primary intracerebral hemorrhage using an easy model for the prediction of survival. *Acta Neurol Scand*. 1995;91:306–309.
69. Niskanen MM, Hernesniemi JA, Vapalahti MP, Kari A. One-year outcome in early aneurysm surgery: prediction of outcome. *Acta Neurochir (Wien).* 1993;123:25–32.

70. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke.* 1994;25:40–43.

71. Lisk DR, Pasteur W, Rhoades H, Putnam RD, Grotta JC. Early presentation of hemispheric intracerebral hemorrhage: prediction of outcome and guidelines for treatment allocation. *Neurology.* 1994;44:133–139.

72. Newman MF, Wolman R, Kanchuger M, Marschall K, Mora-Mangano C, Roach G, Smith LR, Aggarwal A, Nussmeier N, Herskowitz A, Mangano DT. Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. *Circulation.* 1996;94:II74–80.

73. Fogelholm R, Avikainen S, Murros K. Prognostic value and determinants of first-day mean arterial pressure in spontaneous supratentorial intracerebral hemorrhage. *Stroke.* 1997;28:1396–1400.

74. Arboix A, Garcia-Eroles L, Massons J, Oliveres M. Predictive clinical factors of in-hospital mortality in 231 consecutive patients with cardioembolic cerebral infarction. *Cerebrovasc Dis.* 1998;8:8–13.

75. Wardlaw JM, Lewis SC, Dennis MS, Counsell C, McDowall M. Is visible infarction on computed tomography associated with an adverse prognosis in acute ischemic stroke? *Stroke.* 1998;29:1315–1319.

76. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke.* 1999;30:1223–1229.

77. Rothwell PM, Warlow CP. Prediction of benefit from carotid endarterectomy in individual patients: a risk-modelling study. European Carotid Surgery Trialists’ Collaborative Group. *Lancet (London, England).* 1999;353:2105–2110.

78. John R, Choudhri AF, Weinberg AD, Ting W, Rose EA, Smith CR, Oz MC. Multicenter review of preoperative risk factors for stroke after coronary artery bypass grafting. *Ann Thorac Surg.* 2000;69:30–36.

79. Johnston KC, Connors AFJ, Wagner DP, Knaus WA, Wang X, Haley ECJ. A predictive risk model for outcomes of ischemic stroke. *Stroke.* 2000;31:448–455.

80. Calvillo-King L, Xuan L, Zhang S, Tuhrim S, Halm EA. Predicting risk of perioperative death and stroke after carotid endarterectomy in asymptomatic patients: derivation and validation of a clinical risk score. *Stroke.* 2010;41:2786–2794.