

Separate prediction of intracerebral hemorrhage and ischemic stroke

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ABSTRACT

Objectives: To develop and validate 10-year cumulative incidence functions of intracerebral hemorrhage (ICH) and ischemic stroke (IS).

Methods: We used data on 27,493 participants from 3 population-based cohort studies: the Atherosclerosis Risk in Communities Study, median age 54 years, 45% male, median follow-up 20.7 years; the Rotterdam Study, median age 68 years, 38% male, median follow-up 14.3 years; and the Cardiovascular Health Study, median age 71 years, 41% male, median follow-up 12.8 years. Among these participants, 325 ICH events, 2,559 IS events, and 9,909 nonstroke deaths occurred. We developed 10-year cumulative incidence functions for ICH and IS using stratified Cox regression and competing risks analysis. Basic models including only established nonlaboratory risk factors were extended with diastolic blood pressure, total cholesterol/high-density lipoprotein cholesterol ratio, body mass index, waist-to-hip ratio, and glomerular filtration rate. The cumulative incidence functions' performances were cross-validated in each cohort separately by Harrell C-statistic and calibration plots.

Results: High total cholesterol/high-density lipoprotein cholesterol ratio decreased the ICH rates but increased IS rates (p for difference across stroke types <0.001). For both the ICH and IS models, C statistics increased more by model extension in the Atherosclerosis Risk in Communities and Cardiovascular Health Study cohorts. Improvements in C statistics were reproduced by cross-validation. Models were well calibrated in all cohorts. Correlations between 10-year ICH and IS risks were moderate in each cohort.

Conclusions: We developed and cross-validated cumulative incidence functions for separate prediction of 10-year ICH and IS risk. These functions can be useful to further specify an individual's stroke risk. *Neurology*® 2014;82:1804-1812

GLOSSARY

ARIC = Atherosclerosis Risk in Communities; **BMI** = body mass index; **CHS** = Cardiovascular Health Study; **CI** = confidence interval; **HDL-C** = high-density lipoprotein cholesterol; **HR** = hazard ratio; **ICH** = intracerebral hemorrhage; **IS** = ischemic stroke.

Stroke is the second leading cause of death and one of the major causes of disability in most Western countries.¹ The incidence of stroke steadily increases from middle age onward. Although most strokes are ischemic strokes (IS), approximately 10% are intracerebral hemorrhages (ICHs), which have a higher case fatality than IS: 41.0% vs 14.3%.²

Multiple risk factors that influence stroke risk are well established and can be used to estimate an individual's stroke risk over a 10-year time period.³⁻⁶ Distinguishing the risk of stroke types, i.e., ICH vs IS, could be valuable for various reasons. First, risk factors may vary or may have different or even opposing effects.⁷ Consequently, the likely effects of modifying these risk factors may vary

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per stroke type. Second, although antithrombotic therapy has a net preventive effect on stroke by decreasing the occurrence of IS, it also increases the risk of ICH.⁸ Therefore, decision-making for antithrombotic therapy could be improved by predicting ICH and IS risk separately. Third, the consequences (e.g., the case fatality) of both types differ and a more refined risk communication can be facilitated.

In addition, established stroke risk scores were developed using standard survival analysis with censoring for competing death events. Standard survival analysis will generally overestimate the cumulative incidence, because it fails to consider those who die of nonstroke causes as ineligible for development of stroke events. Methods to adjust for competing risks are now increasingly being used for cardiovascular risk prediction.⁹ In this study, we aimed to develop and validate separate prediction models for estimation of the 10-year cumulative incidences of ICH and IS.

METHODS Study design and population. We performed a combined analysis of individual data from 3 population-based cohort studies: the Atherosclerosis Risk in Communities (ARIC) Study, the Rotterdam Study, and the Cardiovascular Health Study (CHS).

The ARIC Study¹⁰ comprises 15,792 individuals aged 45 to 64 years at baseline recruited from 4 different regions in the United States from 1987 to 1989. The Rotterdam Study¹¹ consists of 7,983 inhabitants of Ommoord, Rotterdam, the Netherlands, aged 55 years and older. Baseline examinations were conducted from 1990 to 1993. In the CHS,¹² individuals older than 65 years living in 4 US communities were recruited from the Health Care Financing Administration (or Medicare) eligibility lists in 2 phases. First, 5,201 participants were recruited from 1989 to 1990. In a second wave, 687 African Americans were recruited from 1992 to 1993 leading to a cohort of 5,888 participants. For details on baseline measurements of the 3 studies, see appendix e-1 on the *Neurology*[®] Web site at Neurology.org.

The subjects eligible for the current analysis were those without prior stroke (n = 15,297 in the ARIC cohort, n = 7,546 in the Rotterdam Study, n = 5,639 in the CHS), who did not use anticoagulation (n = 15,222 ARIC Study, n = 7,177 Rotterdam Study, n = 5,572 CHS), and who did not have atrial fibrillation (n = 15,217 ARIC cohort, n = 6,910 Rotterdam Study, n = 5,446 CHS) at baseline. The latter 2 exclusion criteria were used because specific guidelines and prediction models already exist for these patients.¹³ In addition, we excluded participants who were not African American or Caucasian, leaving n = 27,493 subjects (n = 15,170 ARIC Study, n = 6,910 Rotterdam Study, n = 5,413 CHS) for the analysis.

Based on previous literature, we considered age, sex, African American ethnicity, current smoking, systolic blood pressure, antihypertensive medication use, diabetes mellitus, and history of coronary heart disease as candidate predictors in a basic nonlaboratory model for each stroke type.^{3-5,14-16} Subsequently, we evaluated model extension by the following office-based risk

factors: diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol (HDL-C), body mass index (BMI), waist-to-hip ratio, and estimated glomerular filtration rate.^{4,5,7,15}

Standard protocol approvals, registrations, and patient consents. All studies received approval from medical ethical committees, and participants gave written informed consent.

Outcome definitions. Details of outcome ascertainment are described elsewhere¹⁷⁻¹⁹ and in appendix e-1. In brief, ARIC outcomes were ascertained through yearly telephone interviews, follow-up examinations, community hospital surveillance, and reported deaths. In the Rotterdam Study, participants were continuously monitored for events through automated linkage of the study database with files from general practitioners and the municipality. Medical records of nursing homes were also evaluated. CHS outcomes were ascertained through 6 monthly telephone interviews, surveillance of Health Care Financing Administration Medicare Utilization files, and reported deaths.

For ICH, we excluded ascertained subarachnoid and traumatic hemorrhages. IS was defined as a combined endpoint of classified ischemic and unspecified stroke as a proxy for true IS events to avoid underestimation.²⁰ Strokes were classified as ischemic if there was no evidence for other diagnoses based on imaging and evident clinical features, or if there was surgical or autopsy evidence of ischemia (also see table e-1). Any stroke was defined as the sum of ICH and IS. Censoring date was December 31, 2009 for the ARIC Study, January 1, 2009 for the Rotterdam Study, and June 30, 2008 for the CHS dataset.

Statistical analysis. Two separate prediction models for the 10-year cumulative incidence of ICH and IS were developed using Cox regression modeling and considering competing risks (see appendix e-1 for more details). In addition, we developed an “any stroke” model, which can be subdivided into an ICH and IS component. The cause-specific Cox regression models were stratified by study cohort and developed with time since study entry as the time scale. In the basic models, effect modification by sex was evaluated for age, systolic blood pressure, diabetes mellitus, and history of coronary heart disease. An interaction term for systolic blood pressure and antihypertensive medication use was included.^{3,14} In the extended models, we evaluated replacement of total and HDL-C variables by the total cholesterol/HDL-C ratio and systolic by diastolic blood pressure.²¹ Finally, we tested heterogeneity of effects across studies by study-predictor interaction terms, and across stroke types by type-predictor interaction terms in full extended models.

Discriminative ability was assessed using Harrell concordance statistic (C statistic) adjusted for competing risks by setting the follow-up time to the maximum value if competing death occurred.²² Model calibration was assessed by calibration plots and χ^2 statistics, comparing predicted with observed cumulative incidences using the R “CumInc” function of the R “mstate” library. Equal sized groups per study were made according to age tertiles for ICH and quintiles for IS. To understand the impact of using cumulative incidence functions instead of standard survival analysis, we compared the discriminative ability and model calibration of these 2 statistical methods for ICH and IS prediction.

For cross-validation, models were fit in 2 cohorts and evaluated in the other. Reclassification by extending basic models was assessed by the continuous net reclassification improvement.²³ Ninety-five percent confidence intervals (CIs) were estimated by bootstrapping datasets with recalculation of the observed cumulative incidences within each bootstrap sample. Scatter plots showing the relationship between the ICH and IS

components within any stroke risk were made for each dataset using extended models. Finally, we constructed an Excel risk calculator for the risk assessment of 10-year ICH, IS, and any stroke (as a sum of ICH and IS) risks (appendix e-2). Total cholesterol/HDL-C ratios are automatically calculated from total cholesterol and HDL-C. To individualize absolute risk differences and numbers needed to treat for each stroke type and any stroke events, estimated treatment effects expressed as hazard ratios (HRs) can be added.⁹

Missing covariable values were imputed for each study separately using single imputation with the R “aregImpute” function of the R “Hmisc” library. Imputation models included all potential predictors and the log cumulative hazard for each outcome. Hypothesis tests were 2-sided and decisions on selection of predictor main effects were made based on an improvement of the Akaike Information Criterion after exclusion from a full model. Interactions and nonlinear effects were included using a *p* value <0.05. The effect of excluding predictors with highly significant heterogeneous HRs (*p* < 0.01 for ICH, *p* < 0.001 for IS and competing death) on cross-validated model performance was

evaluated in sensitivity analyses (see tables e-2 to e-6). We used R version 2.14.2 for all statistical analyses.

RESULTS Study population. The baseline characteristics of included ARIC (median age 54, 45% male), Rotterdam Study (median age 68, 38% male), and CHS (median age 71, 41% male) participants are given in table 1. In total, 325 participants experienced an ICH, 2,559 experienced an IS event, and 9,909 died from a competing death cause. The total number of individuals with ICH was low, especially in the ARIC Study, in which only 103 experienced an ICH. The 10-year cumulative incidence for ICH was approximately one-ninth of the 10-year cumulative incidence of IS in all studies (table 2).

Hazard ratios. Sex, diabetes, prior coronary heart disease, waist-to-hip ratio, and estimated glomerular

Table 1 Baseline characteristics

	ARIC Study (n = 15,170)	Rotterdam Study (n = 6,910)	CHS (n = 5,413)
Age, y, median (IQR)	54 (49, 59)	68 (62, 76)	71 (68, 76)
Sex, male, n (%)	6,828 (45)	2,633 (38)	2,240 (41)
African American ethnicity, n (%)	4,072 (27)	0	838 (15)
Systolic BP, mm Hg, median (IQR)	119 (108, 131)	137 (123, 153)	134 (121, 149)
Missing data, n (%)	14 (0)	728 (11)	9 (0)
Diastolic BP, mm Hg, median (IQR)	70 (66, 80)	73 (66, 81)	70 (63, 78)
Missing data, n (%)	16 (0)	729 (11)	16 (0)
Antihypertensive medication use, n (%)	3,787 (25)	2,085 (30)	2,487 (46)
Missing data, n (%)	85 (1)	6 (0)	7 (0)
Current smoking, n (%)	3,981 (26)	1,520 (23)	654 (12)
Missing data, n (%)	15 (0)	205 (3)	6 (0)
Diabetes mellitus, n (%)	1,780 (12)	637 (11)	843 (16)
Missing data, n (%)	141 (1)	975 (14)	55 (1)
Prior coronary heart disease, n (%)	1,707 (12)	949 (16)	1,071 (20)
Missing data, n (%)	330 (2)	1,074 (15)	47 (1)
Total cholesterol, mmol/L, median (IQR)	5.5 (4.8, 6.2)	6.6 (5.8, 7.4)	5.5 (4.8, 6.1)
Missing data, n (%)	239 (2)	700 (10)	46 (1)
HDL-C, mmol/L, median (IQR)	1.3 (1.0, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)
Missing data, n (%)	237 (2)	726 (11)	54 (1)
BMI, kg/m ² , median (IQR)	26.9 (24.0, 30.4)	26.0 (23.8, 28.4)	26.1 (23.5, 29.2)
Missing values, n (%)	25 (0)	772 (11)	17 (0)
Waist-to-hip ratio, median (IQR)	0.94 (0.88, 0.98)	0.90 (0.84, 0.97)	0.94 (0.87, 0.98)
Missing values, n (%)	28 (0)	1,081 (16)	34 (1)
eGFR, mL/min/1.73 m ² , median (IQR)	89.0 (79.7, 102.3)	77.3 (67.3, 87.7)	76.7 (64.2, 89.9)
Missing values, n (%)	146 (1)	2,254 (33)	59 (1)
Statin therapy use, n (%)	85 (1)	141 (2)	121 (2)
Missing values, n (%)	115 (1)	6 (0)	7 (0)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; BP = blood pressure; CHS = Cardiovascular Health Study; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range.

Table 2 Incident event data

	ARIC Study (n = 15,217)	Rotterdam Study (n = 6,910)	CHS (n = 5,446)
Overall incident events, n			
Intracerebral hemorrhage	103	99	123
Ischemic stroke	920	820	819
Competing nonstroke death	3,727	3,035	3,147
10-y incident events, n (cumulative incidence, %)			
Intracerebral hemorrhage	42 (0.3)	57 (0.8)	62 (1.1)
Ischemic stroke	360 (2.4)	523 (7.6)	530 (9.8)
Competing nonstroke death	1,179 (7.8)	1,814 (26.3)	1,433 (26.5)
Median follow-up duration, y (IQR)	20.7 (17.5, 21.7)	14.3 (7.2, 16.2)	12.8 (7.4, 18.3)
Person-years of follow-up	279,741.9	81,997.6	66,325.4

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Health Study; IQR = interquartile range.

filtration rate were not found to be statistically significant and were excluded from ICH models, whereas these were included in IS models. Table 3 shows the multivariable-adjusted HRs and 95% CIs for incident ICH and IS events (see table e-7 for competing death). For both ICH and IS, replacement of total and HDL-C by total cholesterol/HDL-C ratio and the simultaneous inclusion of systolic

and diastolic blood pressure (despite correlations of 0.69, 0.59, and 0.51 in ARIC, Rotterdam, and CHS cohorts) improved the Akaike Information Criterion (figures e-1 through e-4 show the multivariable adjusted relations with ICH and IS event rates). The extended ICH model is reported without BMI, although BMI statistically significantly decreased the ICH hazard: 0.97 (95% CI 0.94–0.99) per unit

Table 3 Included predictors and hazard ratios (95% confidence intervals)

Predictor	Basic ICH	Extended ICH	Basic IS	Extended IS
Age per 10-y increase	1.85 (1.55-2.21)	1.95 (1.63-2.35)	—	—
In men	—	—	1.89 (1.75-2.05)	1.87 (1.72-2.04)
In women	—	—	2.13 (1.99-2.28)	2.09 (1.94-2.25)
Sex, male	—	—	2.62 (1.55-4.42)	2.21 (1.31-3.74)
African American	1.78 (1.33-2.39)	1.54 (1.14-2.09)	1.34 (1.20-1.50)	1.35 (1.20-1.51)
Current smoking	1.53 (1.17-2.00)	1.51 (1.15-1.98)	1.63 (1.49-1.80)	1.62 (1.47-1.78)
Diabetes	—	—	1.77 (1.60-1.95)	1.67 (1.52-1.85)
Antihypertensive medication use	5.53 (1.26-24.32)	5.59 (1.32-23.67)	3.83 (2.33-6.30)	3.31 (2.02-5.45)
Systolic BP per 10 mm Hg increase				
If medication use	1.10 (1.01-1.20)	1.04 (0.95-1.15)	1.11 (1.08-1.14)	1.09 (1.06-1.13)
If no medication use	1.26 (1.19-1.34)	1.19 (1.11-1.29)	1.20 (1.17-1.23)	1.17 (1.14-1.21)
Prior coronary heart disease				
In men	—	—	1.64 (1.42-1.89)	1.60 (1.39-1.85)
In women	—	—	1.22 (1.07-1.40)	1.19 (1.04-1.37)
Diastolic BP per 10 mm Hg increase	—	0.25 (0.11-0.55)	—	0.71 (0.52-0.98)
Diastolic BP per 10 mm Hg increase squared	—	1.10 (1.05-1.16)	—	1.03 (1.00-1.05)
Total cholesterol/HDL-C ratio	—	0.55 (0.39-0.78)	—	1.05 (1.03-1.08)
Total cholesterol/HDL-C ratio squared	—	1.05 (1.01-1.08)	—	—
GFR per 10 mL/min/1.73 m ² increase	—	—	—	0.77 (0.70-0.86)
GFR squared	—	—	—	1.01 (1.01-1.02)
Waist-to-hip ratio per 0.1 increase	—	—	—	1.11 (1.05-1.18)

Abbreviations: BP = blood pressure; GFR = glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; ICH = intracerebral hemorrhage; IS = ischemic stroke.

increase. However, the BMI association varied significantly across the 3 studies (see table e-2) and exclusion improved the cross-validated model performance (see table e-5). BMI was removed from the extended IS model because it was not statistically significant ($p = 0.27$).

Midrange total cholesterol/HDL-C ratio values as compared with low and high values decreased ICH risk, whereas high total cholesterol/HDL-C ratio monotonically increased IS risk (see figures e-2 and e-4). The association of the total cholesterol/HDL-C ratio statistically differed across stroke types ($p < 0.001$). The HRs for ICH additionally censored for IS and vice versa are given in tables e-8 and e-9; these did not largely differ from those shown in table 3.

Model performance. For ICH prediction, C statistics of cumulative incidence functions were higher than C statistics of standard survival models (see tables 4 and e-10). For IS prediction, C statistics of both statistical methods were comparable. Extending the basic cumulative incidence functions generally led to small improvements in C statistics, ranging from 0.001 to 0.020 for ICH, and 0.001 to 0.009 for IS.

The continuous total net reclassification improvements were positive, with more pronounced changes in the ARIC cohort. Improvements in C statistics were reproduced by cross-validation except for IS predictions in Rotterdam Study data (table 4). C statistics for any stroke predictions were similar to IS predictions, and did not improve with model extension (table e-11).

As compared with standard survival models, calibration generally improved using cumulative incidence functions, especially within the elderly, except for ICH prediction below the second age tertile in the CHS cohort (see table e-10 and figures e-5 to e-8). Overall, model calibration did not differ to a relevant extent between basic and extended models for both ICH and IS prediction (figures e-5 to e-8). Results on calibration by the any-stroke cumulative incidence functions were similar to those for IS prediction (table e-11).

Predicted ICH risk tended to increase with IS risk for each study, but the correlation between both predicted risks was moderate in ARIC, Rotterdam, and CHS cohorts ($r = 0.57, 0.59, 0.37$, respectively; figure 1). The Excel risk calculator

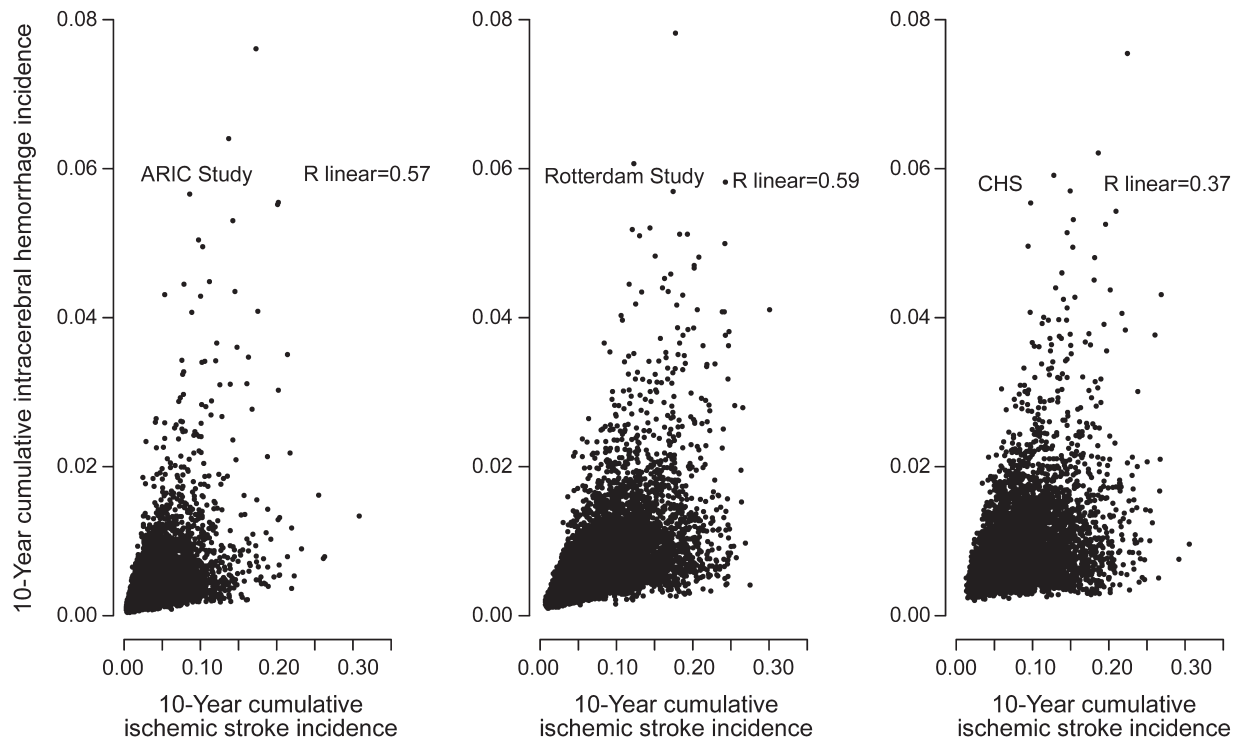
Table 4 Prognostic performance

Model development in ARIC, Rotterdam, and CHS	Basic ICH model	Extended ICH model	Basic IS model	Extended IS model
Evaluated in ARIC Study				
C statistic (95% CI)	0.805 (0.739, 0.871)	0.811 (0.743, 0.879)	0.789 (0.768, 0.811)	0.798 (0.777, 0.819)
Total NRI (95% CI)	—	0.28 (−0.06, 0.62)	—	0.29 (0.18, 0.39)
Event NRI (95% CI)	—	0.10 (−0.17, 0.47)	—	0.28 (0.17, 0.38)
Nonevent NRI (95% CI)	—	0.18 (0.17, 0.20)	—	0.01 (0.00, 0.03)
Evaluated in Rotterdam Study				
C statistic (95% CI)	0.625 (0.555, 0.695)	0.626 (0.556, 0.696)	0.696 (0.677, 0.716)	0.697 (0.677, 0.717)
Total NRI (95% CI)	—	0.19 (−0.03, 0.45)	—	0.15 (0.06, 0.23)
Event NRI (95% CI)	—	−0.16 (−0.37, 0.18)	—	0.11 (0.02, 0.21)
Nonevent NRI (95% CI)	—	0.35 (0.31, 0.37)	—	0.03 (0.01, 0.07)
Evaluated in CHS				
C statistic (95% CI)	0.676 (0.603, 0.750)	0.696 (0.624, 0.767)	0.658 (0.637, 0.679)	0.663 (0.642, 0.684)
Total NRI (95% CI)	—	0.04 (−0.26, 0.31)	—	0.05 (−0.026, 0.13)
Event NRI (95% CI)	—	0.03 (−0.23, 0.30)	—	−0.20 (−0.31, −0.12)
Nonevent NRI (95% CI)	—	0.00 (−0.02, 0.03)	—	0.25 (0.23, 0.28)
Cross-validation				
C statistic (95% CI) in ARIC Study	0.729 (0.652, 0.806)	0.734 (0.653, 0.814)	0.760 (0.737, 0.783)	0.768 (0.745, 0.790)
C statistic (95% CI) in Rotterdam Study	0.622 (0.552, 0.693)	0.626 (0.556, 0.696)	0.694 (0.674, 0.713)	0.692 (0.672, 0.712)
C statistic (95% CI) in CHS	0.667 (0.595, 0.740)	0.684 (0.614, 0.753)	0.651 (0.630, 0.672)	0.654 (0.633, 0.676)

Abbreviations: ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Health Study; CI = confidence interval; ICH = intracerebral hemorrhage; IS = ischemic stroke; NRI = net reclassification improvement.

Event NRI is calculated as the difference in the probability being reclassified upward and the probability being reclassified downward conditional on experiencing the event within 10 years: $p(\text{up}|\text{event}) - p(\text{down}|\text{event})$. Nonevent NRI is calculated as the difference in the probability being reclassified downward and the probability being reclassified upward conditional on not experiencing the event within 10 years: $p(\text{down}|\text{event}) - p(\text{up}|\text{event})$. Total NRI is calculated as the sum of event NRI and nonevent NRI.

Figure 1 Contribution of intracerebral hemorrhage and ischemic stroke to 10-year any stroke incidence



ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Health Study.

for predicting the 10-year cumulative incidence of any stroke subdivided into ICH and IS components can be accessed online (appendix e-2). HRs used in the calculator are provided in tables e-7 to e-9.

DISCUSSION In this study, we developed and cross-validated 10-year ICH and IS risk models within middle-aged and elderly individuals. As compared with standard survival analysis, the cumulative incidence functions showed improved discriminative ability for ICH prediction and better model calibration, especially in the elderly. Extending basic nonlaboratory models led to limited improvement of discriminative ability. By using our cumulative incidence functions, individuals can be identified with low 10-year IS risk but high ICH risk, and vice versa.

Studies on hemorrhagic stroke prediction are scarce. By performing a systematic literature search (see appendix e-1), we found only 2 studies, both conducted in Chinese populations. One study²⁴ was performed in a cohort of 4,400 steelworkers free of stroke at baseline with an average age of 45 years. The number of hemorrhagic strokes was low: 33 in the development set and 15 in the validation set. Multivariable-adjusted HRs of age (1.89 per 10 years) and systolic blood pressure (1.22 per 10 mm Hg) were similar to ours. For diastolic blood pressure

(1.49 per 10 mm Hg) and total cholesterol (1.00 per mmol/L), nonlinearity was not explored, and therefore associations are not comparable with ours. In addition, the model was not validated in the general population and the elderly. In the other study,²⁵ major bleeding risk scoring schemes designed for patients with atrial fibrillation were validated in 3,602 individuals without atrial fibrillation. C statistics of the various risk scores ranged from 0.59 to 0.72. Individuals with previous stroke were, however, not excluded, and ICH event ascertainment was registry-based. Other prognostic studies focused on either assessment of any stroke risk^{3,4,14,16,26-32} or IS risk^{5,6,20,33,34} usually within a time horizon of 5 to 10 years.

In contrast, we developed models for the separate 10-year risk assessment of ICH and IS while considering competing risks. By combining data from 3 large population-based cohorts, we acquired a sufficient number of ICH events for multivariable prediction modeling. The number of ICH events was low in the ARIC Study, probably explained by the younger age of this cohort. Furthermore, we included elderly individuals older than 75 years. Especially in the elderly, competing risks become relevant, because the competing death rate rapidly increases. We demonstrated that also in the elderly, predictions were well calibrated as opposed to predictions using standard survival analysis.

Our results must be interpreted in the light of some limitations. First, we did not consider biomarkers, genetic risk factors, and imaging tests. For example, studies have demonstrated an independent association of C-reactive protein with IS but not ICH risk,³⁵ and carotid intima-media thickness measurement and *APOE* genotype with both ICH and IS risk.^{36,37} However, carotid intima-media thickness and *APOE* genotype are generally difficult to assess during an office-based risk assessment, which would limit the translation to clinical practice, and C-reactive protein was not available as a baseline variable in the ARIC Study. Second, neuroimaging was not performed in all participants with stroke symptoms. Consequently, a proportion of strokes were not further specified. We included these as IS, which could have led to a small overestimation of the IS risk and underestimation of ICH risk. Third, the quality of the individual studies may have influenced the overall validity of the results. For example, the Rotterdam Study had more missing values for the included predictors than the other 2 cohorts. Because of the computational demand of constructing the cumulative incidence function, it was infeasible to perform multiple imputation. Therefore, the precision of our models is subject to a small overestimation. In addition, validity of our results is hampered if the missingness was actually nonrandom. Fourth, the baseline age ranges of the ARIC, Rotterdam, and CHS cohorts did not entirely overlap. As a consequence, the age association was not fully determined by the 3 datasets combined. Finally, we excluded individuals with stroke, atrial fibrillation, or anticoagulation use at baseline, and individuals who were not Caucasian and not African American, such as Asian and Hispanic participants. Also, we did not consider use of antiplatelet and statin therapy in the analysis. The effect of these preventive drugs should have been captured in the baseline survival function or within the associations of included predictors. The validity of our predictions can thus be affected if the use of these drugs differs by population or varies over time because of changing medical practice. Consequently, our predictions should be validated in other and more recent populations. For patients with atrial fibrillation, clinicians should use the specific stroke and bleeding risk models validated for this population.

We evaluated extension of a basic nonlaboratory model using C statistic as a criterion. The C statistic would improve if a predictor is added that increases risk in early cases and/or decreases risk in late cases and controls. The impact on the C statistic depends both on the HR of the added predictor and its distribution in the context of included predictors.³⁸ Because we evaluated the heterogeneity of associations within sensitivity analyses, the varying distribution of

predictor values across the 3 cohorts must have led to the differences in (changes of) the C statistic. However, because discriminative ability generally improved for all 3 cohorts, and the added predictors are expected to incur limited extra costs and potential harms, we recommend the use of the extended models as the preferred choice.

Specifying whether a first stroke is ICH or IS is clinically valuable. More refined estimates of the expected benefits and harms can be made about preventive interventions with different effects on ICH and IS risk. For example, aspirin use is recommended when the potential benefit of reduction in IS outweighs the bleeding risks.³⁹ This trade-off is especially relevant in the elderly,⁴⁰ making well-calibrated predictions at older ages more important. Our cumulative incidence functions may therefore be useful to refine communication of the expected benefit (by number of IS events avoided) and harm (by number of induced ICH events in addition to gastrointestinal bleedings) to support shared decision-making. However, differences in case-fatality rate of ICH and IS should be considered as well. In this context, we anticipate that our prediction models for 10-year ICH and IS risk are useful to further specify an individual's stroke risk.

AUTHOR CONTRIBUTIONS

Dr. Ferket: drafting the manuscript for content, study concept and design, analysis and interpretation of data. Dr. van Kempen: revising the manuscript for content, interpretation of data. Dr. Wieberdink: revising the manuscript for content. Dr. Steyerberg: study concept and design, revising the manuscript for content, interpretation of data. Dr. Koudstaal, Dr. Hofman, Dr. Shahar, Dr. Gottesman, Dr. Rosamond, Dr. Kizer, Dr. Kronmal, and Dr. Psaty: revising the manuscript for content. Dr. Longstreth, Jr.: study concept and design, revising the manuscript for content. Dr. Mosley: revising the manuscript for content. Dr. Folsom, Dr. Hunink, and Dr. Ikram: study concept and design, revising the manuscript for content.

ACKNOWLEDGMENT

The authors thank David van Klaveren and Yvonne Vergouwe (Department of Public Health, Erasmus MC) for their valuable methodologic advice, and Irene Doherty (ARIC Study) and Tony Wilsdon (CHS) for preparing the ARIC and CHS datasets. The contributions of inhabitants, general practitioners, and pharmacists of the Ommoord district to the Rotterdam Study are gratefully acknowledged.

STUDY FUNDING

The Atherosclerosis Risk in Communities Study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute (contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). The authors thank the staff and participants of the ARIC Study for their important contributions. The Rotterdam Study is supported by the Erasmus Medical Center Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Scientific Research (NWO), The Netherlands Organization for Health Research and Development (ZonMW), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. B.S.F. was funded through the Netherlands Organization for Scientific Research

(NWO) training grant 022.002.023. The Cardiovascular Health Study was supported by contracts HHSN268201200036C, HHSN268200800007C, N01 HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided by AG023629 from the National Institute on Aging. A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/PI.htm>.

DISCLOSURE

B. Ferket, B. van Kempen, R. Wieberdink, E. Steyerberg, P. Koudstaal, A. Hofman, E. Shahar, R. Gottesman, and W. Rosamond report no disclosures relevant to the manuscript. J. Kizer has provided expert witness consultation to Pfizer relating to Prempro and stroke. R. Kronmal reports no disclosures relevant to the manuscript. B. Psaty serves on the DSMB of a clinical trial of a device funded by the manufacturer (Zoll LifeCor) and on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. W. Longstreth, Jr., T. Mosley, A. Folsom, M. Hunink, and M. Ikram report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

DISCLAIMER

The funding sources had no role in the design, conduct, or analysis of this study or in the decision to submit the article for publication.

Received August 5, 2013. Accepted in final form February 19, 2014.

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