Stroke Risk Profile: Adjustment for Antihypertensive Medication

The Framingham Study

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Background and Purpose We sought to modify existing sex-specific health risk appraisal functions (profile functions) for the prediction of first stroke that better assess the effects of the use of antihypertensive medication.

Methods Health risk appraisal functions were previously developed from the Framingham Study cohort. These functions were Cox proportional hazards regression models relating age, systolic blood pressure, diabetes mellitus, cigarette smoking, prior cardiovascular disease, atrial fibrillation, left ventricular hypertrophy by electrocardiogram, and the use of antihypertensive medication to the occurrence of stroke. Closer examination of the data indicated that antihypertensive therapy effect is present only for systolic blood pressures between 110 and 200 mm Hg. Adjustments to the regressions to better fit the observed data were developed and tested for statistical significance and goodness-of-fit of the model residuals.

Results Modified functions more consistent with the data were developed, and, from these, tables to evaluate 10-year risk of first stroke were computed.

Conclusions The stroke profile can be used for evaluation of the risk of stroke and suggestion of risk factor modification to reduce risk. The effect of antihypertensive therapy in the evaluation of stroke risk can now be better evaluated. (***Stroke.* 1994;25:40-43.**)

Key Words • antihypertensive agents • cerebrovascular disorders • risk factors

Wolf et al[1] presented sex-specific health risk appraisal functions (or profile functions) relating risk factors including systolic blood pressure and the use of antihypertensive medication to the probability of developing a stroke. Those functions were Cox proportional hazards regression models. For men there was an elevation of risk for those on antihypertensive medication. For women there was an elevation of risk and also an interaction of systolic blood pressure level and being on antihypertensive medication. In both sexes these effects were presented as applying to all levels of systolic blood pressures. Closer examination of the data indicated that an added effect is present only for systolic blood pressures between 110 and 200 mm Hg. Modifications to the health risk appraisal functions were developed to take this into account. These modifications are more consistent with the data and supply better statistical fits to the data. In the following the modified functions are presented along with tables that can be used to estimate 10-year probabilities of first stroke.

Received July 28, 1993; final revision received September 29, 1993; accepted September 29, 1993.

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Subjects and Methods

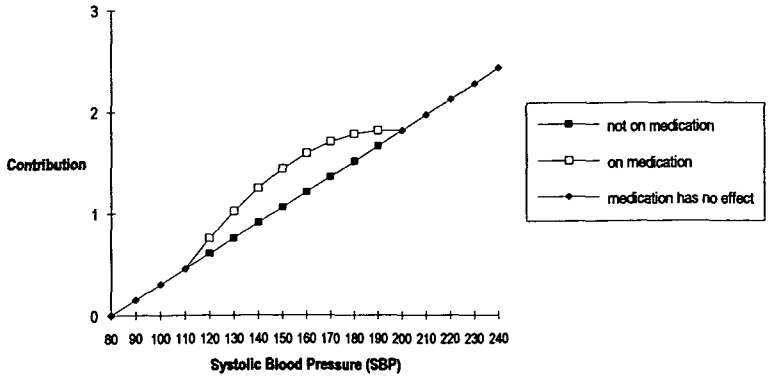
The data used were the same as those used to develop the first functions.[1] Health risk appraisal functions were developed using subjects aged 55 to 84 years, free of stroke at the time of two examination cycles (examinations 9 and 14), and followed for 10 years from each of these examinations. Stroke risk factors included age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior cardiovascular disease (coronary heart disease, cardiac failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophy by electrocardiogram. All these factors are the same as previously used and are defined elsewhere.[1,2]

The Cox proportional hazards regression model was used as the model for the stroke profile.[3] In the analysis of Wolf et al,[1] use of antihypertension medication was entered into the analysis as a dummy variable, and the interaction of it with systolic blood pressure was investigated as the product of the dummy variable for the antihypertensive medication and systolic blood pressure. More consistent with the data is the replacement of the latter two variables with a variable of the form

$$NEWHRXSBP = HRX*(SBP-110)*(200-SBP)$$

for systolic blood pressures between 110 and 200 mm Hg. Here *HRX* is a dummy variable defined as 1 if the individual is on antihypertensive medication and 0 if not, and *SBP* is the individual's systolic blood pressure. The variable *NEWHRXSBP* equals 0 for systolic blood pressures below 110 or greater than 200 mm Hg.

The effect of this variable on the stroke profile is illustrated in the Figure. For women the regression coefficient for *SBP* in the new stroke profile is 0.0161, and for *NEWHRXSBP* it is 0.00026. For systolic blood pressures below 110 mm Hg or above 200 mm Hg, the stroke profile function gives the same weight to individuals whether they are on or off antihypertensive medication, and it is 0.0161**SBP*. For those with systolic blood pres-



Graph shows contribution of systolic blood pressure (SBP) on female stroke profile function. The contribution is 0.0161*SBP for women with SBP below 110 mm Hg or above 200 mm Hg regardless of their antihypertensive medication use and for those with SBP between 110 and 200 mm Hg if they are not on antihypertensive medication. The contribution is 0.0161*SBP+0.00026*(SBP−110)*(200−SBP) for those with SBP between 110 and 200 mm Hg and also on antihypertensive medication.

sures between 110 mm Hg and 200 mm Hg and not on medication, the contribution of the blood pressure to the stroke profile is $0.0161*SBP$, while for those with systolic blood pressures between 110 mm Hg and 200 mm Hg and on medication the contribution is $0.0161*SBP+0.00026*(SBP-110)*(200-SBP)$. The Figure depicts the contribution to the stroke profile for systolic blood pressures between 80 mm Hg and 240 mm Hg.

The values 110 mm Hg and 200 mm Hg were selected for use in the *NEWHRXSBP* variable because most systolic blood pressures of those on antihypertensive medication fell in that interval (96%) and because they represented discontinuities in the frequency distributions. The selection of other values did not improve the fit to the data.

The Statistical Analysis System's Cox proportional hazards model procedure, PROC PHREG,[4] was used for analysis. Models using the antihypertensive therapy variable and the interaction of it with systolic blood pressure levels were contrasted with models using the *NEWHRXSBP* variable, for both statistical significance and goodness-of-fit as judged by analyses of the models' residuals.[4]

Results

During 10 years of follow-up from examinations 9 and 14, 472 stroke events occurred in 2372 men and 3362 women. Descriptive statistics of these are given in the previous article.[1] The new variable *NEWHRXSBP* was statistically significant for both sexes in Cox regression models that included all the risk factors listed above except for antihypertensive medication ($P=.0006$ for women and $P=.05$ for men).

For both the female and male models the addition of the dummy variables for antihypertensive medication and the interaction of this with systolic blood pressure did not add significantly to the regressions that already included *NEWHRXSBP*. This latter variable was sufficient to replace them. Further, analysis of the residuals indicated that the use of *NEWHRXSBP* provided the best model fit to the data. Finally, selection of values other than 110 and 200 mm Hg for *NEWHRXSBP* did not improve statistical significance and model fit. Table 1 presents the Cox regression coefficients and their standard errors, relative risks, and 95% confidence intervals for the risk factors of the new health risk appraisal functions. Tables 2 and 3 give the probabilities of stroke within 10 years for men and women aged 55 to 84 years and free of previous stroke, respectively, computed from these functions. Table 4 gives the average 10-year probabilities of first stroke by age groups for each sex. Table 4 can be used for comparison with probabilities computed from Tables 2 and 3. These tables replace tables of the previous article[1] as follows: the new Table 1 here replaces the previous Table 3, Table 2 replaces the previous Table 5, Table 3 replaces the previous Table 6, and the present Table 4 replaces the previous Table 4.

As an illustration, say a 70-year-old woman presents herself to a physician with the following profile: systolic blood pressure of 135 mm Hg, on antihypertensive therapy, nondiabetic, cigarette smoker, previous history

TABLE 1. Regression Coefficients, Relative Risks, and Confidence Intervals for Risk Factors in Cox Proportional Hazards Regressions for Stroke Profile in Subjects Aged 55-84 Years and Free of Stroke at Examinations 9 and 14

Variable	β	SE	RR	95% CI
Men				
Age, y*	0.0488	0.0103	1.63	1.33-1.99
SBP, mm Hg*	0.0152	0.0031	1.16	1.10-1.24
NEWHRXSBP	0.00019	0.00010	N/A	
CVD	0.5460	0.0151	1.73	1.68-1.78
LVH	0.7864	0.2846	2.20	1.26-3.84
Cigs	0.5224	0.1429	1.69	1.27-2.23
AF	0.5998	0.3011	1.82	1.01-3.29
Diabetes	0.3429	0.1894	1.41	0.97-2.04
Women				
Age, y*	0.0699	0.0089	2.01	1.69-2.40
SBP, mm Hg*	0.0161	0.0024	1.17	1.12-1.23
NEWHRXSBP	0.00026	0.00007	N/A	
CVD	0.4404	0.1462	1.55	1.17-2.07
LVH	0.8055	0.2429	2.24	1.39-3.60
Cigs	0.5419	0.1453	1.72	1.29-2.29
AF	1.1173	0.2302	3.06	1.95-4.80
Diabetes	0.5604	0.1706	1.75	1.25-2.45

RR indicates relative risk; CI, confidence interval; and N/A, not applicable. Variables were defined as follows: SBP, systolic blood pressure; NEWHRXSBP =0 if SBP <110 or SBP >200, else, =HRX*(SBP−110)*(200−SBP) where HRX=1 if on medication, 0 if not; CVD (cardiovascular disease), history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure (yes=1, no=0); LVH, left ventricular hypertrophy on electrocardiogram (yes=1, no=0); Cigs, smokes cigarettes (yes=1, no=0); AF, history of atrial fibrillation (yes=1, no=0); Diabetes, history of diabetes (yes=1, no=0).

*For age and SBP, the RR is computed for an increase of 10 units. All other variables compare presence vs absence.

TABLE 2. Probability of Stroke Within 10 Years for Men Aged 55-85 Years and Free of Previous Stroke in the Framingham Heart Study

	Points										
	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
Age, y	54-56	57-59	60-62	63-65	66-68	69-72	73-75	76-78	79-81	82-84	85
Untreated SBP, mm Hg	97-105	106-115	116-125	126-135	136-145	146-155	156-165	166-175	176-185	186-195	196-205
Treated SBP, mm Hg	97-105	106-112	113-117	118-123	124-129	130-135	136-142	143-150	151-161	162-176	177-205
Diabetes	No		Yes								
Cigs	No			Yes							
CVD	No				Yes						
AF	No				Yes						
LVH	No					Yes					

Points	10-Year Probability, %	Points	10-Year Probability, %	Points	10-Year Probability, %
1	3	11	11	21	42
2	3	12	13	22	47
3	4	13	15	23	52
4	4	14	17	24	57
5	5	15	20	25	63
6	5	16	22	26	68
7	6	17	26	27	74
8	7	18	29	28	79
9	8	19	33	29	84
10	10	20	37	30	88

Variables were defined as follows: SBP, systolic blood pressure; Diabetes, history of diabetes; Cigs, smokes cigarettes; CVD (cardiovascular disease), history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure; AF, history of atrial fibrillation; LVH, left ventricular hypertrophy on electrocardiogram.

of cardiovascular disease, no atrial fibrillation present, and no left ventricular hypertrophy. Using Table 3, this woman receives 5 points for being aged 70, 6 points for having a systolic blood pressure of 135 mm Hg while on antihypertensive therapy, no points for diabetes, 3 points for smoking, 2 points for history of cardiovascular disease, no points for the presence of atrial fibrillation, and no points for left ventricular hypertrophy. This person therefore receives a total of 16 points. A score of 16 points yields a 10-year stroke probability of 19%. Relating this 19% to the average probability for a women this age provides perspective; the average 10-year probability of stroke for a 70-year-old women is 10.9% (Table 4). Thus, this hypothetical woman has a stroke risk that is 1.7 times the average. Her physician can urge her to stop smoking, which would result in a total of 13 points and a probability of 11% for a stroke risk of 1.0 relative to the average risk.

Computation of the risk for the aforementioned 70-year-old woman by the previous function[1] produced a probability of 23%, which is a difference of 4% from the new estimate. Part of this difference is due to rounding in generating Table 3 but also reflects a slight overestimate by the previous function for women on antihypertensive medication. The exact estimates produced directly by the Cox regressions are 20.2% for the new function and 23.2% for the old function, accounting for 3% of the 4% difference. Rounding produced by generating the tables accounts for 1% of the difference.

Discussion

In a previous article[1] we discussed in detail the importance of control and intervention of the risk factors of stroke and described in detail how to use the stroke profiles or health risk appraisal functions. The focus of this article has been the adjustment for antihypertensive medication. It involved determining the region of blood pressures attained by those on antihypertensive medication and then approximating the risk profiles for these subjects. While the adjustments made for antihypertensive medication in this article do not differ appreciably from those generated by the previous function, they are more consistent with the data and reflect a substantive advancement in the generation of health risk appraisal functions. These functions have traditionally ignored the effects of treatments, assuming that, for example, blood pressures attained on medication are equivalent to uncontrolled blood pressures. This is not the case with our data. Further health risk appraisal functions will have to explore and investigate treatments not only for blood pressure but for other important risk factors such as cholesterol and glucose.

TABLE 3. Probability of Stroke Within 10 Years for Women Aged 55-84 Years and Free of Previous Stroke in the Framingham Heart Study

	Points										
	0	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
Age, y	54-56	57-59	60-62	63-64	65-67	68-70	71-73	74-76	77-78	79-81	82-84
Untreated SBP, mm Hg		95-106	107-118	119-130	131-143	144-155	156-167	168-180	181-192	193-204	205-216
Treated SBP, mm Hg		95-106	107-113	114-119	120-125	126-131	132-139	140-148	149-160	161-204	205-216
Diabetes	No			Yes							
Cigs	No			Yes							
CVD	No		Yes								
AF	No						Yes				
LVH	No				Yes						

Points	10-Year Probability, %	Points	10-Year Probability, %	Points	10-Year Probability, %
1	1	11	8	21	43
2	1	12	9	22	50
3	2	13	11	23	57
4	2	14	13	24	64
5	2	15	16	25	71
6	3	16	19	26	78
7	4	17	23	27	84
8	4	18	27		
9	5	19	32		
10	6	20	37		

Variables were defined as follows: SBP, systolic blood pressure; Diabetes, history of diabetes; Cigs, Smokes cigarettes; CVD (cardiovascular disease), history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure; AF, history of atrial fibrillation; LVH, left ventricular hypertrophy on electrocardiogram.

Finally, in our previous article we discussed in detail how to use the health risk appraisal functions for estimates different than 10 years. The instructions given there are appropriate here except that the antihypertension variable and the interaction of this with systolic blood pressure level are replaced by the new variable *NEWHRXSBP* described above.

TABLE 4. Average 10-Year Probability of Stroke According to Age in Men and Women

Age Group, y	Men	Women
55-59	5.9	3.0
60-64	7.8	4.7
65-69	11.0	7.2
70-74	13.7	10.9
75-79	18.0	15.5
80-84	22.3	23.9
Age-adjusted	9.6	6.5

Values are percentages.

Acknowledgments

This study was supported in part by National Institute of Neurological Disorders and Stroke grant 2-RO1-NS-17950-09 (Dr Wolf), National Heart, Lung, and Blood Institute grant RO1-H140423-04 (Dr D'Agostino), and National Heart, Lung, and Blood Institute contract NIH-NO1-HC-38038 (Dr Wolf).

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