

Probability of Stroke: A Risk Profile From the Framingham Study

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A health risk appraisal function has been developed for the prediction of stroke using the Framingham Study cohort. The stroke risk factors included in the profile are age, systolic blood pressure, the 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. Based on 472 stroke events occurring during 10 years' follow-up from biennial examinations 9 and 14, stroke probabilities were computed using the Cox proportional hazards model for each sex based on a point system. On the basis of the risk factors in the profile, which can be readily determined on routine physical examination in a physician's office, stroke risk can be estimated. An individual's risk can be related to the average risk of stroke for persons of the same age and sex. The information that one's risk of stroke is several times higher than average may provide the impetus for risk factor modification. It may also help to identify persons at substantially increased stroke risk resulting from borderline levels of multiple risk factors such as those with mild or borderline hypertension and facilitate multifactorial risk factor modification. (*Stroke* 1991;22:312-318)

Stroke is the third leading cause of death in the United States and is a major source of disability in persons older than age 60 years. In the face of an elderly population of increasing size, stroke is likely to be responsible for even greater disability and death. Epidemiologic study has identified key risk factors for stroke and has provided an estimate of the relative impact of these factors. Using data collected over 36 years of follow-up in the general population sample at Framingham, Mass., a stroke risk profile or health risk appraisal function has been developed. This profile contains a number of ingredients not available at the time of the previous stroke risk handbook, which was based on 16 years of follow-up.¹ The inclusion of previously diagnosed cardiovascular disease (coronary heart disease

[includes history of myocardial infarction, angina pectoris, and coronary insufficiency], cardiac failure, and intermittent claudication), atrial fibrillation, and left ventricular hypertrophy by electrocardiogram as ingredients in the profile has improved the efficiency of the risk prediction and gives a more realistic assessment of the importance of the stroke risk factors.

Key to the usefulness of determining the likelihood of stroke by means of a risk profile is evidence that modification of several potent risk factors will reduce stroke probability. Epidemiologic study and clinical trial results have shown that reduction of elevated blood pressure and cessation of cigarette smoking can reduce stroke incidence. Warfarin (and perhaps aspirin) therapy in persons with atrial fibrillation, reversal of left ventricular hypertrophy by electrocardiogram, and treatment of cardiac failure and coronary heart disease may also effect a reduction in stroke incidence.

Subjects and Methods

Probability of stroke was determined in subjects aged 55-84 years and free of stroke at the time of two examination cycles, examinations 9 and 14, and is based on 10 years of follow-up from each of these examinations. Stroke risk factors included age, systolic blood pressure, use of antihypertensive therapy, and the presence of diabetes mellitus or cigarette

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TABLE 1. Stroke Events During 10 Years of Follow-Up From Examinations 9 and 14, Men and Women Aged 55–84 Years

Stroke subtype	Men		Women	
	No.	%	No.	%
Atherothrombotic brain infarction	97	45.5	113	43.6
Transient ischemic attack only	51	23.9	55	21.2
Cerebral embolus	41	19.3	64	24.7
Intracerebral hemorrhage	11	5.2	10	3.9
Subarachnoid hemorrhage	9	4.2	14	5.4
Other	4	1.9	3	1.2
Total	213	100.0	259	100.0

smoking. The presence of prior cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy by electrocardiogram are the other ingredients in the risk profile. Definitions of these risk factors have been reported.² Definite hypertension was present if the blood pressure was $\geq 160/95$ mm Hg, normal blood pressure was that $<140/90$ mm Hg, and borderline or mild hypertension were represented by blood pressure levels in between. Active surveillance for stroke has been under way for 25 years as part of a comprehensive study of stroke precursors, stroke subtype, and outcome.

The Cox proportional hazards regression model was used as the model for the stroke profile.³ In the past, the logistic regression model was employed.^{1,4} Like the logistic model, the Cox model provides a simple formula for estimating the probabilities of stroke for specified levels of the risk factors. Its added advantage is that it permits the computation of stroke probabilities for variable lengths of follow-up, whereas the logistic model allows estimation for only a prespecified length of follow-up (e.g., 6, 8, or 10 years).

Separate models were developed for each sex. In addition to the risk factors listed above, three other variables (total serum cholesterol concentration, hematocrit, and the interaction of systolic blood pressure and antihypertensive therapy) were entered into the Cox model employing the stepwise option of the Statistical Analysis System's Cox proportional hazards model procedure, PROC PHGLM.⁵ Only those variables attaining the 0.05 level of probability were retained in the final models. All of these variables were tested for the proportional hazards assumption.

Results

During 10 years of follow-up, 472 stroke events occurred in the cohort of 2,372 men and 3,362 women (Table 1). Brain infarction and transient ischemic attack accounted for 66.9% of the events, cerebral embolus for 22.2%, and intracranial hemorrhage (combining both subarachnoid and intracerebral hemorrhages) for 9.3%. The mean levels of stroke risk factors, their regression coefficients, and their relative risks based on the Cox model were similar in men and women (Tables 2 and 3). An interaction between antihypertensive therapy and systolic blood pressure is significant in women but not in men. The

average 10-year probability of stroke was higher in men than in women, 9.6% versus 6.5%. Stroke probability increased steadily with age, from 5.9% at 55–59 years to 22.3% at 80–84 years in men and from 3.0% to 23.9% over this age range in women (Table 4).

The probability of stroke in an individual depends on the presence and level of risk factors. For example, a 70-year-old man with a systolic blood pressure of 120 mm Hg is contrasted with one whose pressure is 180 mm Hg (Figure 1). The presence of additional risk factors is associated with an increase in the 10-year probability of stroke. However, at any risk factor level the presence of a systolic blood pressure of 180 mm Hg is associated with approximately twice the stroke probability of a systolic blood pressure of 120 mm Hg.

Based on information collected by a physician during the course of taking a comprehensive medical history and conducting a physical examination, plus a laboratory examination that includes an electrocardiogram, the probability of stroke may be determined using a point system (Tables 5 and 6). For example, a 70-year-old man with a systolic blood pressure of 180 mm Hg despite being on antihypertensive therapy who is diabetic and smokes cigarettes receives a total of 19 points: for age, 5 points; for systolic blood pressure, 7 points; for antihypertensive therapy, 2 points, for diabetes mellitus, 2 points; and for cigarette smoking, 3 points. No additional points are assigned since he is free of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. A score of 19

TABLE 2. Summary Statistics for Significant Risk Factors in Stroke Profiles

Risk factor	Men	Women
Age (mean yr)	65.4	66.1
Systolic blood pressure (mean mm Hg)	139.3	142.8
Antihypertensive therapy (%)	16.1	25.0
Diabetes mellitus (%)	10.6	7.9
Cigarette smoking (%)	33.8	26.4
Cardiovascular disease (%)	22.2	14.2
Atrial fibrillation (%)	2.8	2.2
Left ventricular hypertrophy (%)	3.5	2.9

Cardiovascular disease: history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure. Left ventricular hypertrophy by electrocardiogram.

TABLE 3. Regression Coefficients and Relative Risks for Significant Risk Factors in Cox Proportional Hazards Regressions for Stroke Profiles in Subjects Aged 55–84 Years and Free of Stroke at Examinations 9 and 14

Risk factor	Men		Women	
	Coefficient	Relative risk*	Coefficient	Relative risk*
Age	0.0505	1.66	0.0657	1.93
Systolic blood pressure	0.0140	1.91	0.0197	1.68
Antihypertensive therapy	0.3263	1.39	2.5432	†
Blood pressure×therapy interaction	0.0	...	−0.0134	†
Diabetes mellitus	0.3384	1.40	0.5442	1.72
Cigarette smoking	0.5147	1.67	0.5294	1.70
Cardiovascular disease	0.5195	1.68	0.4326	1.54
Atrial fibrillation	0.6061	1.83	1.1497	3.16
Left ventricular hypertrophy	0.8415	2.32	0.8488	2.34

Each coefficient and relative risk is adjusted for effects of other risk factors.

*Relative risk for age and systolic blood pressure are given for 10-unit changes; all other variables are dichotomous, 1 if yes and 0 if no. All variables are significant at $p < 0.05$.

†Because blood pressure×therapy interaction is significant, relative risks here depend on levels of blood pressure and are not summarized as single value.

points yields a 10-year stroke probability of 32.9%. Relating this 32.9% probability to the average probability for a man of this age provides perspective; the average 10-year probability of stroke for a man aged 70 years is 13.7% (Table 4). Thus, this hypothetical 70-year-old man has a stroke risk that is 2.4 times average. His physician can urge that he comply with the antihypertensive regimen and thereby reduce his systolic blood pressure to 120 mm Hg and help him to give up the cigarette habit. If he accomplishes these measures, his stroke risk will be substantially reduced. As a 70-year-old

nonsmoker with a treated systolic blood pressure of 120 mm Hg who is still diabetic, he now receives a score of 11 points, corresponding to a 10-year stroke probability of 11.2%. This probability is lower than the average stroke risk for men aged 70 years (13.7%) and represents a 66% reduction in stroke risk. Since control of hypertension and cessation of cigarette smoking reduces stroke risk in a relatively short time (i.e., within 6–24 months^{6,7}), the probability of stroke would be reduced from nearly three times average to a level that is average for age. Control of hypertension would also help reduce this man's chances of developing coronary heart disease, cardiac failure, and left ventricular hypertrophy. Of course, cessation of cigarette smoking would reduce his risk of developing intermittent claudication, a number of cancers, and chronic pulmonary disease and perhaps reduce the possibility of diabetic complications.

Discussion

Hypertension is the major risk factor for stroke,^{8,9} and stroke incidence is proportional to the level of the blood pressure.¹⁰ Through most of adult life the

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

Age group (yr)	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 %.

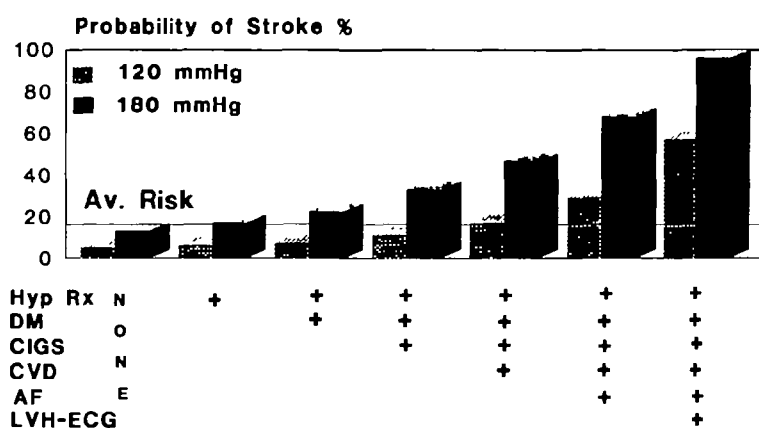


FIGURE 1. Bar graph of probability of stroke during 10 years in men aged 70 years at two systolic blood pressure levels: Impact of other risk factors. Hyp Rx, antihypertensive therapy; DM, diabetes mellitus; CIGS, cigarette smoking; CVD, previously diagnosed coronary heart disease, cardiac failure, or intermittent claudication; AF, atrial fibrillation; LVH-ECG, left ventricular hypertrophy by electrocardiogram.

TABLE 5. Probability of Stroke Within 10 Years for Men Aged 55–84 Years and Free of Previous Stroke: Framingham Study

Risk factor	Points										
	0	1	2	3	4	5	6	7	8	9	10
Age (yr)	54–56	57–59	60–62	63–65	66–68	69–71	72–74	75–77	78–80	81–83	84–86
SBP (mm Hg)	95–105	106–116	117–126	127–137	138–148	149–159	160–170	171–181	182–191	192–202	203–213
Hyp Rx	No		Yes								
DM	No		Yes								
Cigs	No			Yes							
CVD	No			Yes							
AF	No				Yes						
LVH	No						Yes				

Points	10-yr probability	Points	10-yr probability	Points	10-yr probability
1	2.6%	11	11.2%	21	41.7%
2	3.0%	12	12.9%	22	46.6%
3	3.5%	13	14.8%	23	51.8%
4	4.0%	14	17.0%	24	57.3%
5	4.7%	15	19.5%	25	62.8%
6	5.4%	16	22.4%	26	68.4%
7	6.3%	17	25.5%	27	73.8%
8	7.3%	18	29.0%	28	79.0%
9	8.4%	19	32.9%	29	83.7%
10	9.7%	20	37.1%	30	87.9%

SBP, systolic blood pressure; Hyp Rx, under antihypertensive therapy; DM, history of diabetes mellitus; Cigs, smokes cigarettes; CHD, history of myocardial infarction, angina pectoris, or coronary insufficiency; CVD, history of intermittent claudication or congestive heart failure; AF, history of atrial fibrillation; LVH, left ventricular hypertrophy on electrocardiogram.

systolic and diastolic pressures are highly correlated, and the systolic blood pressure is at least as powerful a predictor of stroke as the diastolic pressure.^{10,11} At older ages, diastolic pressure tends to decline as systolic pressure levels off. However, even in the presence of isolated systolic hypertension (systolic pressure ≥ 160 mm Hg and diastolic pressure < 90 mm Hg) stroke risk is more than doubled, and risk is directly related to the systolic blood pressure. A full-scale trial of treatment of isolated systolic hypertension in the elderly is under way; a pilot study showed a 50% reduction in hypertensive end points, principally stroke, but there was insufficient power to achieve statistical significance.¹²

Although diastolic blood pressure has been used as the basis for enrollment in clinical trials of antihypertensive therapy, treatment has resulted in a reduction in systolic blood pressure commensurate with the reduction in diastolic pressure.⁸ Among those with elevated blood pressure, even borderline hypertensives (accounting for 70% of hypertensives) have a substantially increased stroke risk.^{13,14} In the Medical Research Council trial of treatment of mild hypertension,¹⁴ treatment with antihypertensive drugs is not advocated. The authors state, "The trial has shown that if 850 mildly hypertensive patients are given active antihypertensive drugs for one year about one stroke will be prevented. This is an important but infrequent benefit."¹⁴ To conclude that no

borderline hypertensive person should receive active pharmacological therapy would be incorrect. While acknowledging that the "shotgun" approach of prescribing drug therapy for all borderline hypertensives to prevent stroke might be unwarranted, it is likely that some such persons are clearly at significantly increased stroke risk and will require pharmacological intervention. Unlike the Medical Research Council trial, in which the discussion focused on prevention of stroke during 1 year in a group of men whose mean age was 51 years, stroke prevention must be a long-term effort, particularly in persons older than age 60 years, when stroke incidence reaches important levels. Mild hypertension need not be treated solely with drugs; hygienic measures such as modification of the diet with salt restriction and weight reduction are often effective in controlling blood pressure.¹⁵ In addition, at borderline or moderate levels of risk factor abnormalities such a unifactorial approach is inappropriate; prevention of atherosclerotic cardiovascular disease including stroke requires a multifactorial approach. The stroke risk profile provides the framework for identification of those individuals at sufficiently increased risk of stroke to warrant vigorous risk factor management. For example, the probability of stroke in 70-year-old men and women with borderline hypertension (a systolic blood pressure of 160 mm Hg) varies dramatically according to the presence of other risk factors (Figure 2).

TABLE 6. Probability of Stroke Within 10 Years for Women Aged 55–84 Years and Free of Previous Stroke: Framingham Heart Study

Risk factor	Points										
	0	1	2	3	4	5	6	7	8	9	10
Age (yr)	54–56	57–59	60–62	63–65	66–68	69–71	72–74	75–77	78–80	81–83	84–86
SBP (mm Hg)	95–104	105–114	115–124	125–134	135–144	145–154	155–164	165–174	175–184	185–194	195–204
Hyp Rx	No; if yes, see below										
DM	No			Yes							
Cigs	No			Yes							
CVD	No		Yes								
AF	No						Yes				
LVH	No				Yes						

If currently under antihypertensive therapy, add points depending on SBP:

Points	SBP (mm Hg)										
	95–104	105–114	115–124	125–134	135–144	145–154	155–164	165–174	175–184	185–194	195–204
Points	6	5	5	4	3	3	2	1	1	0	0

Points	10-yr probability	Points	10-yr probability	Points	10-yr probability
1	1.1%	10	6.3%	19	31.9%
2	1.3%	11	7.6%	20	37.3%
3	1.6%	12	9.2%	21	43.4%
4	2.0%	13	11.1%	22	50.0%
5	2.4%	14	13.3%	23	57.0%
6	2.9%	15	16.0%	24	64.2%
7	3.5%	16	19.1%	25	71.4%
8	4.3%	17	22.8%	26	78.2%
9	5.2%	18	27.0%	27	84.4%

SBP, systolic blood pressure; Hyp Rx, under antihypertensive therapy; DM, history of diabetes mellitus; Cigs, smokes cigarettes; CHD, history of myocardial infarction, angina pectoris, coronary insufficiency; CVD, history of intermittent claudication, or congestive heart failure; AF, history of atrial fibrillation; LVH, left ventricular hypertrophy on electrocardiogram.

Seventy-year-olds with borderline hypertension and no associated risk factor abnormalities have a probability of stroke that is not above average. However, in the presence of diabetes mellitus, cigarette smoking, antecedent cardiovascular disease, atrial fibrillation, and electrocardiographic abnormalities, the 10-year stroke risk is increased from an average of ≤9% in women and 12.3% in men to >80% (Figure 2).

While it would probably not be prudent to treat all 70-year-olds with a systolic blood pressure of 160 mm Hg with drugs, restricting pharmacological therapy to those with multiple risk factor abnormalities would be far more suitable. By focusing on those borderline hypertensives with two or more risk factor abnormalities, an extraordinary improvement in therapeutic efficiency is achieved (Table 7). Of the 442

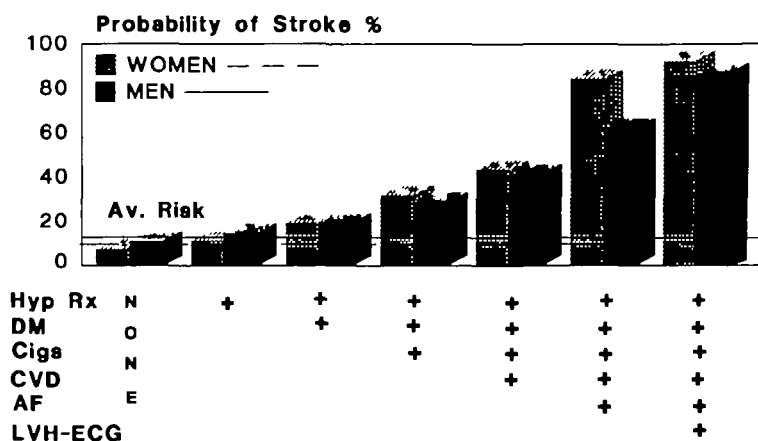


FIGURE 2. Bar graph of probability of stroke during 10 years in 70-year-old men and women at systolic blood pressure of 160 mm Hg: Impact of other risk factors. Hyp Rx, antihypertensive therapy; DM, diabetes mellitus; Cigs, cigarette smoking; CVD, previously diagnosed coronary heart disease, cardiac failure, or intermittent claudication; AF, atrial fibrillation; LVH-ECG, left ventricular hypertrophy by electrocardiogram.

TABLE 7. Efficiency of Stroke Prevention in High-Risk Men and Women With Systolic Blood Pressure of 160 mm Hg

	Men			Women		
	No.	No.	%	No.	No.	%
Total	442	97	21.9	817	111	13.6
Stroke cases						
Predicted	91.3	35.5	...	143.1	45.5	...
Treated	48.5	17.6	...	103.7	31.5	...
"Prevented"	42.8	17.9	41.8	39.4	14.0	35.5

men and 817 women with a systolic blood pressure of 160 mm Hg, 97 (21.9%) of the men and 111 (13.6%) of the women had two or more risk factor abnormalities. Applying the risk function to this group, there will be 35.5 strokes in men and 45.5 in women over 10 years. If, in addition to convincing the cigarette smokers to quit, the systolic blood pressure in these high-risk individuals is reduced to 120 mm Hg, there would be only 17.6 stroke events in men and 31.5 in women. Using the stroke risk profile, it is possible to identify a group of approximately 22% of the men and 14% of the women in whom treatment might be expected to prevent 41.8% of the strokes in men and 35.5% of the strokes in women during 10 years. (In addition, antiplatelet therapy for the prevention of myocardial infarction, the most frequent cause of death in stroke victims and candidates, might also be prescribed in these high-risk persons.) The stroke risk profile provides quantitative guidelines the physician can use to educate and counsel his or her patients to modify their risk factors for stroke.

Appendix. Probability of Stroke: Risk Profile From Framingham Study

In this appendix we present the mathematical and computational details for using the stroke risk profile. The profile is a Cox proportional hazards regression model. The presentation will allow one to estimate the probability of stroke for any period from 1 to 10 years for men or women 55–84 years of age. The Cox model provides a simple formula for estimating the probabilities of stroke for specified levels of the risk factors. We will first illustrate the computations using the stroke profile model given in Table 3 for men.

In Table 3 all the risk factors are defined and their coefficients are given. From these, a linear function is computed. For men its general form is $L=0.0505 \times \text{Age} + 0.0140 \times \text{SBP} + 0.3263 \times \text{Hyp Rx} + 0.3384 \times \text{DM} + 0.5147 \times \text{Cigs} + 0.5195 \times \text{CVD} + 0.6061 \times \text{AF} + 0.8415 \times \text{LVH}$, where SBP is systolic blood pressure, Hyp Rx is use of antihypertensive therapy, DM is presence of diabetes mellitus, Cigs is cigarette smoking, CVD is previously diagnosed coronary heart disease, cardiac failure, or intermittent claudication, AF is presence of atrial fibrillation, and LVH is left ventricular hypertrophy by electrocardiogram. This function is next

evaluated at the values of the means for each variable. We call this value M. For men its value is $M=0.0505 \times 65.4 + 0.0140 \times 139.3 + 0.3263 \times 0.161 + 0.3384 \times 0.106 + 0.5147 \times 0.338 + 0.5195 \times 0.222 + 0.6061 \times 0.028 + 0.8415 \times 0.035 = 5.6770$, where the mean values are given in Table 2. This value of M is next subtracted from the general function L to produce a function we will call A. For men this function is $A=L-M=L-5.6770$. The function A is then exponentiated, and we call this function B. That is, $B=e^A$.

Now we choose the number of years for which we desire predictions. For our particular stroke function this can be any year from 1 to 10. For each selection there is a value that is the estimated probability of surviving without a stroke for individuals whose risk factor values are equal to the mean values of those observed in the data (i.e., as given in Table 2). We will call these values S(t), where the S is to indicate survival without a stroke and t is to index the number of years. For men the values of S(t) for $t=1, \dots, 10$ are

t	S(t)
1	0.9948
2	0.9889
3	0.9826
4	0.9740
5	0.9642
6	0.9551
7	0.9422
8	0.9270
9	0.9144
10	0.9044

The value of t employed in Table 6 was 10. The user can develop other tables using values other than 10.

We are now ready to obtain the predicted probability that a man with a selected set of risk factors will develop a stroke within t years. This is obtained by computing the value of B defined above for the selected set of risk factors and then computing the desired probability as $p=1-(S(t))^B$. As an example, consider a man 70 years of age with a systolic blood pressure of 140 mm Hg who smokes, does not take antihypertensive medication, is free of diabetes, does not have a previous cerebrovascular disease, and does not have a history of atrial fibrillation or left ventricular hypertrophy. The value of L for this individual is $L=0.0505 \times 70 + 0.0140 \times 140 + 0.3263 \times 0 + 0.3384 \times 0 + 0.5147 \times 1 + 0.5195 \times 0 + 0.6061 \times 0 + 0.8415 \times 0 = 6.0097$. The values of A and B are $A=L-5.6770=6.0097-5.6770=0.3327$ and $B=e^A=e^{0.3327}=1.3947$. Finally, the predicted probability that this individual will develop a stroke within 10 years is $p=1-(S(10))^B=1-0.9044^{1.3947}=1-0.8692=0.1308$ or 13.08%. The predicted probability that the individual will develop a stroke within 5 years is $p=1-(S(5))^B=1-0.9642^{1.3947}=1-0.9504=0.0496$ or 4.96%.

For women the same mechanics as displayed above are employed. The coefficients for the function L are obtained from Table 3. The reader should note that

there is one added variable in the function for women, and it is the variable $SBP \times Hyp Rx$, which is the interaction of the systolic blood pressure and the antihypertensive medication status. The value of M for women is 7.5766, and the values of $S(t)$ for $t=1, \dots, 10$ are

t	$S(t)$
1	0.9977
2	0.9920
3	0.9864
4	0.9802
5	0.9741
6	0.9665
7	0.9584
8	0.9509
9	0.9448
10	0.9353

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