

# The Framingham Function Overestimates Stroke Risk for Diabetes and Metabolic Syndrome Among Spanish Population

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**Objective.** To estimate stroke risk for diabetes, isolated or associated to metabolic syndrome (MS) according WHO and National Cholesterol Education Program (NCEP) criteria.

**Design.** Multicentre and prospective cohort study.

**Setting.** Primary health care.

**Participants.** Subjects between 55-85 years-old without any evidence of stroke, included from 1998 in a random population sample for MS follow-up during routine practice in Reus (Tarragona, Spain).

**Main measurements.** Stroke risk was achieved using Framingham function by means of a computerized algorithm using a diagnostic factorial design (diabetes and/or MS). Theoretical stroke risk and cumulated incidence of stroke events (1998-2003) were compared.

**Results.** Among 728 subjects (412 women, mean age=66 years old, body mass index =29 kg/m<sup>2</sup>), 457 (62.8%) did not have diabetes, nor MS, 93 (12.8%) had MS without diabetes, 72 (9.9%) diabetes without MS, and 106 (14.5%) presented both conditions (WHO rules). According NCEP criteria were 60.7%, 14.8%, 7.8% and 16.7%, respectively. Ten-year estimated stroke risk accounted for (WHO/NCEP) 8.4/9.1%, 10.8/10.5%, 18/17.3%, and 18.8/19.1%. Cumulated incidence for stroke events were: 2.8%, 1.4%, 5.4%, and 3.8% (WHO), and 2.5%, 2.8%, 3.5%, and 5.8%, respectively (NCEP).

**Conclusions.** Stroke risk scores were extremely increased among diabetic subjects irrespective to MS diagnose. The Framingham function probably overestimates stroke risk among Spanish individuals.

**Key words:** Diabetes. Metabolic syndrome. X-syndrome. Stroke. Stroke risk.

LA ESCALA DE FRAMINGHAM SOBREALORA EL RIESGO CEREBROVASCULAR DE LA DIABETES Y EL SÍNDROME METABÓLICO EN LA POBLACIÓN ESPAÑOLA

**Objetivo.** Estimar el riesgo de accidente cerebrovascular (ACV) de la diabetes, en el contexto del síndrome metabólico (SM) o fuera de él, según los criterios de la Organización Mundial de la Salud (OMS) y del National Cholesterol Education Program (NCEP).

**Diseño.** Estudio multicéntrico y prospectivo de cohortes.

**Emplazamiento.** Atención primaria de salud.

**Participantes.** Sujetos de 55-85 años libres de ACV incluidos desde 1998 en una muestra poblacional aleatoria y representativa para el seguimiento del SM en Reus (Tarragona).

**Mediciones principales.** El riesgo de ACV se estimó con la escala de Framingham aplicando un algoritmo informático de cálculo automático y un diseño factorial por diagnósticos (diabetes y/o SM). Se comparó el riesgo teórico con la incidencia real de acontecimientos cerebrovasculares (1998-2003).

**Resultados.** Entre 728 sujetos (412 mujeres; edad media de 66 años; índice de masa corporal 29), 457 (62,8%) no tenían diabetes ni SM, 93 (12,8%) con SM no tenían diabetes, 72 (9,9%) con diabetes no tenían SM y 106 (14,5%) presentaban ambas enfermedades (según criterios de la OMS). Según el NCEP, estas proporciones fueron del 60,7; el 14,8; el 7,8 y el 16,7%. El riesgo de ACV medio a 10 años para los 4 grupos (OMS/NCEP) fue: 8,4/9,1; 10,8/10,5; 18/17,3 y 18,8/19,1%, respectivamente. La incidencia acumulada de acontecimientos cerebrovasculares fue del 2,8; 1,4; 5,4 y 3,8% (OMS) y 2,5; 2,8; 3,5 y 5,8% (NCEP).

**Conclusiones.** El riesgo de ACV calculado mediante la fórmula de Framingham es muy elevado en sujetos con diabetes, con independencia de su integración en el SM. Es muy probable que la escala también sobredimensione este riesgo en la población española.

**Palabras clave:** Diabetes. Síndrome metabólico. Síndrome X. Enfermedad cerebrovascular. Riesgo cerebrovascular.

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A commentary follow  
 this article  
 (pág. 000)

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## Introduction

Stroke is one of the main causes of mortality, hospitalization, disability, and excess health costs in most developed countries. In reality, its social impact results from its motor and cognitive sequelae and associated comorbidity. Although valid preventive strategies are available, their use in routine clinical practice is inconsistent.<sup>1,2</sup>

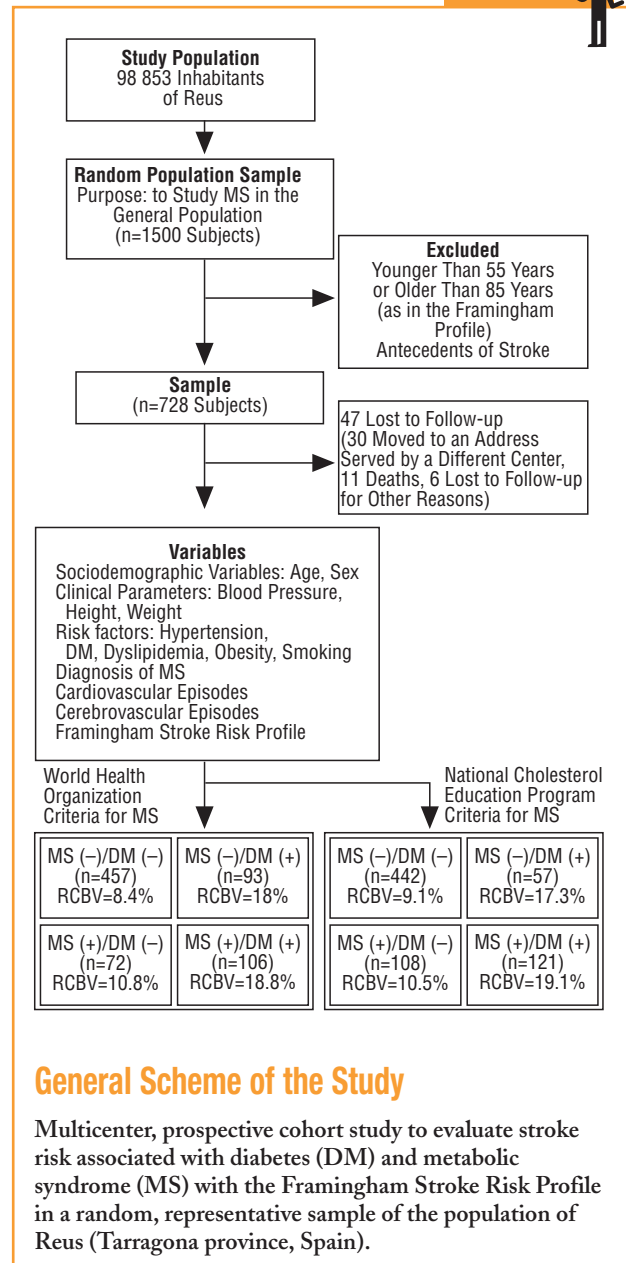
It has now been shown beyond question that type 2 diabetes and metabolic syndrome (MS) increase cardiovascular risk; however, a parallel increase in the risk of stroke is less evident.<sup>3</sup> In Spain, this risk has yet to be evaluated in detail on the basis of a careful comparison of different sources of information specifically for diabetes either with or without SM. Aside from the problems with long-term follow-up of a cohort and the establishment of minimum diagnostic criteria for stroke, three main obstacles may also account for the absence of information. First, there is no standard profile for measuring the risk of stroke. Although mathematical models are available, the risk contributed by diabetes varies between different modes of stroke injury (lacunar infarct, atherothrombosis, cardioembolism, hemorrhage), making it difficult to estimate risk under different circumstances.<sup>4</sup> In addition, formulas obtained for other populations are not often used because they do not reflect the Mediterranean lifestyle, although they might be used in the absence of other more appropriate sources of information. Second, conjectures regarding classification have led to the appearance of at least 4 definitions of MS in recent years.<sup>5-10</sup> Third, confirmation of an episode of stroke, especially if transitory or asymptomatic, is complex in older persons, especially within the setting of primary care.

Diabetes is usually assumed to be a risk factor for stroke, but it is not known whether considering diabetes as part of MS increases the risk or whether the influence of diabetes is independent of MS. In view of these limitations, the aim of this study was to provide a preliminary estimate of overall stroke risk, calculated with the Framingham Stroke Risk Profile, associated with type 2 diabetes in the presence or absence of MS. A further aim was to compare theoretical risk estimates with the actual incidence of stroke in a cohort followed at primary care centers for 5 years, from 1998 to 2003.

## Patients and Methods

In 1998 a prospective multicenter cohort study was begun in an urban area with a population of close to 100 000, with an age structure similar to that of the population of the region of Catalonia (northeastern Spain) as a whole. A random sample representative of the population over 14 years of age was studied. The aims were to estimate the prevalence of MS, the associated risk

## Material and methods



of vascular events, and the incidence of vascular events, and to identify the factors with the greatest influence on risk that were amenable to preventive measures. The population sample needed for a theoretical prevalence of MS of 17% with  $\pm 2\%$  precision and an alpha risk of .05 was estimated as 1500, assuming a 20% drop-out rate.

The study was approved by our institution's ethics committee, and participants gave their informed consent to take part in the study. All participants were advised that a database would be created and that information from their primary care medical record would be entered about their age, sex and address, basic health status (familial and personal antecedents, toxic habits, height, and weight), and results of laboratory tests in blood (biochemical profile, hemogram, lipid profile, oral glucose tolerance

test if one or more risk factors for diabetes were present, hemoglobin A<sub>1c</sub>, and fasting insulin level) and urine (microalbuminuria and 24-hour urinalysis as needed). The database also recorded cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity), relevant electrocardiographic findings (atrial fibrillation, left ventricular hypertrophy, and ischemic heart disease), and an associated record of vascular events and treatments.

Diabetes was diagnosed on the basis of the recommendations of the World Health Organization (WHO) as fasting venous blood glucose 7 mmol/L (126 mg/dL) or higher, glucose 2 hours after oral glucose overload (75 g) of 11.1 mmol/L (200 mg/dL) or higher, with appropriate measures to confirm the diagnosis in patients who were asymptomatic.<sup>11</sup> The criteria used in this study to diagnose MS (Table 1) were based on recommendations of WHO<sup>5</sup> and the National Cholesterol Education Program (NCEP).<sup>6</sup>

Heart disease was assumed to be present when there was a clinical history of ischemic heart disease or heart failure, and when the available results of complementary tests (electrocardiogram, exercise test, and scintigraphy) were suggestive. Cerebrovascular disease was assumed if there was a clinical history suggestive of transitory ischemic accident, transitory cerebrovascular accident, or positive imaging tests. All subjects with no record of cerebrovascular complications underwent basic neurological examination intended to rule out silent processes. If there was a reasonable suspicion, the participant was asked to complete a questionnaire (Mini Mental Status Exam) and to undergo an imaging test (computed tomography). Peripheral vasculopathy was diagnosed if there was no peripheral pulse or if vasculopathy was demonstrated with Doppler echography. Left ventricular hypertrophy was diagnosed on the basis of conventional electrocardiographic criteria (Sokolow-Lyon and Cornell), and echocardiographic findings, when available.

For this study we selected adults aged between 55 and 85 years (the range used for risk calculation in the Framingham profile) without antecedents of stroke. To calculate risk we used the scale developed by D'Agostino and colleagues based on data from the Framingham study, and the recent revision by Straus et al.<sup>12-14</sup> This system places particular importance on age, sex and mean systolic blood pressure (taking into consideration the use of antihypertensive medication). The initial score was recalibrated on the basis of the presence of any of the following risk factors for stroke: smoking, diabetes, established cardiovascular disease (congestive heart failure, myocardial infarction or other forms of coronary ischemia, intermittent claudication, or peripheral artery ischemia), atrial fibrillation, and left ventricular hypertrophy. The scores for 10-year stroke risk ranged from 1% to 80%. All data for stroke risk were processed with specially-designed software developed for this study.

The statistical analysis was done with conventional software (SPSS version 11.0) running on a personal computer. Descriptive statistics were obtained first; then factorial analysis of the data for each diagnosis (MS/diabetes × Yes/no) was done for 4 groups (neither, either diagnosis separately, or both). Qualitative data are reported here as frequencies followed by percentages in parentheses. Quantitative data are expressed as the arithmetic mean followed by the standard deviation in parentheses. The  $\chi^2$  test was used for inferential bivariate qualitative statistics. Quantitative analyses were done with Student's *t* test or analysis of variance after normal distribution was verified with the Kolmogorov-Smirnov test. The stroke risk profile was calculated for each group as mean probability with a 95% confidence interval (95% CI).

**TABLE 1** Parameters Used to Diagnose Metabolic Syndrome

**World Health Organization (WHO) criteria**

Altered glucose metabolism/diabetes mellitus
and/or
Insulin resistance as documented with laboratory tests
<i>and 2 or more of the following conditions:</i>
Blood pressure 140/90 mm Hg or higher
Elevated triglycerides (1.7 mmol·l <sup>-1</sup> or 150 mg·dl <sup>-1</sup> or higher) and/or decreased HDL-cholesterol (<0.9 mmol·l <sup>-1</sup> or 35 mg·dl <sup>-1</sup> in men; <1.0 mmol·l <sup>-1</sup> or 39 mg·dl <sup>-1</sup> in women)
Central obesity (men: waist-hip ratio >0.90; women: waist-hip ratio >0.85) and/or BMI>30 kg·m <sup>-2</sup>
Microalbuminuria (urinary excretion of albumin 20 µg·min <sup>-1</sup> or higher, or albumin/creatinine ratio 20 mg·g <sup>-1</sup> or higher)
At least one invariable component and 2 or more variable components required <sup>5</sup>

**National Cholesterol Education Program (NCEP) criteria**

<i>3 or more of the following conditions</i>
Waist circumference more than 102 cm in men or more than 88 cm in women
Elevated triglycerides (1.7 mmol·l <sup>-1</sup> or 150 mg·dl <sup>-1</sup> )
HDL-cholesterol fraction less than 1.03 mmol·l <sup>-1</sup> or 40 mg·dl <sup>-1</sup> in men, or less than 1.29 mmol·l <sup>-1</sup> or 50 mg·dl <sup>-1</sup> in women
Blood pressure 130/85 mm Hg or higher
Fasting glucose 6.1 mmol·l <sup>-1</sup> or 110 mg·dl <sup>-1</sup> or higher

**Results**

The sample consisted of 728 subjects (412 women, 56.6%). Mean age was 66.4 (7.3) years, mean body mass index (BMI) was 29.3 (4.9) kg/m<sup>2</sup>, and mean systolic blood pressure was 14.01 (18.5) mm Hg. Treatment with antihypertensive medication was recorded for 335 persons (46%). According to WHO parameters, 199 individuals (27.3%) fulfilled the criteria for MS, and 178 (24.4%) fulfilled the criteria for type 2 diabetes. The diagnosis of diabetes was based on fasting blood glucose levels in 103 persons (57.9%) and on glucose 2 hours after oral glucose overload in 75 (42.1%) persons.

More than half of the sample (457 persons, 62.8%) had neither diabetes nor MS, 93 (12.8%) has MS but not diabetes, 72 (9.9%) had diabetes but not MS, and 106 (14.5%) had both (WHO criteria). According to NCEP criteria, the corresponding figures were 60.7%, 14.8%, 7.8%, and 16.7%. Table 2 shows how the sample was distributed according to WHO criteria for diabetes and MS, as a function of the parameters used to calculate stroke risk. We found no statistically significant differences between the 4 groups in sex, age, or smoking habit, although differences appeared for the rest of the variables. Indivi-

**TABLE 2** Distribution of Subjects According to Parameters in the Framingham Profile for Calculating Stroke Risk\*

	WHO Diagnostic Group				P
	MS (-) DM (-) (n=457)	MS (+) DM (-) (n=93)	MS (-) DM (+) (n=72)	MS (+) DM (+) (n=106)	
<i>Qualitative parameter</i>					
Sex, women	256 (56.0)	55 (59.1)	38 (52.8)	63 (59.4)	.781
Pharmacological antihypertensive treatment	184 (40.3)	49 (52.7)	29 (40.3)	73 (68.9)	<.001
Smoking habit	57 (12.5)	13 (14.0)	10 (13.9)	15 (14.2)	.948
Coronary artery disease	36 (7.9)	12 (12.9)	17 (23.6)	26 (24.5)	<.001
LVH	7 (1.5)	0 (0)	8 (11.1)	5 (4.7)	<.001
Atrial fibrillation	15 (3.3)	1 (1.1)	8 (11.1)	6 (5.7)	.006
<i>Quantitative parameter</i>					
Age, years	66 (7.5)	66.7 (7.2)	67.6 (8)	67.1 (6.6)	.21
BMI, kg.m <sup>-2</sup>	28.4 (4.6)	31.7 (4.4)	27.8 (4)	32.3 (5)	<.001
Systolic blood pressure, mm Hg	137.1 (17.8)	150.1 (19.6)	137.6 (18.4)	146.4 (16.3)	<.001

\*WHO indicates World Health Organization; MS, metabolic syndrome; DM, diabetes mellitus; LVH, left ventricular hypertrophy; BMI, body mass index; SS, statistical significance. Qualitative parameters are expressed as the number of cases with percentages in parentheses. Quantitative parameters are expressed as the mean with standard deviation in parentheses.

**TABLE 3** 10-Year Stroke Risk in Each Group\*

Metabolic Syndrome	Diabetes Mellitus			
	n (%)	DM (-) 95% CI	n (%)	DM (+) 95% CI
MS (-) (WHO)	457 (8.4)	7.7-9	93 (18)	14.6-21.5
MS (-) (NCEP)	442 (9.1)	7.9-13.2	57 (17.3)	15.5-19.7
MS (+) (WHO)	72 (10.8)	9-12.7	106 (18.8)	16.3-21.4
MS (+) (NCEP)	108 (10.5)	9-13.5	121 (19.1)	14.6-23.4

\*WHO indicates World Health Organization; NCEP, National Cholesterol Education Program; MS, metabolic syndrome; DM, diabetes mellitus. Mean percentage probability of having a stroke episode is shown with 95% confidence interval and number of cases in each category.

duals with MS but not diabetes were similar to persons with diabetes but not MS in age, sex, smoking habit, use of antihypertensive medication, and number of previous cardiovascular events. The proportion of persons with electrocardiographic evidence of atrial fibrillation (11% vs 1%) and left ventricular hypertrophy (8% vs 0%) was larger in the group with diabetes only (without MS). In the group of persons with MS but not diabetes, the proportion of persons with obesity (72% vs 26% with BMI>30), dyslipidemia (55% vs 17%), and hypertension (82% vs 57%) was larger, and mean systolic blood pressure was significantly higher.

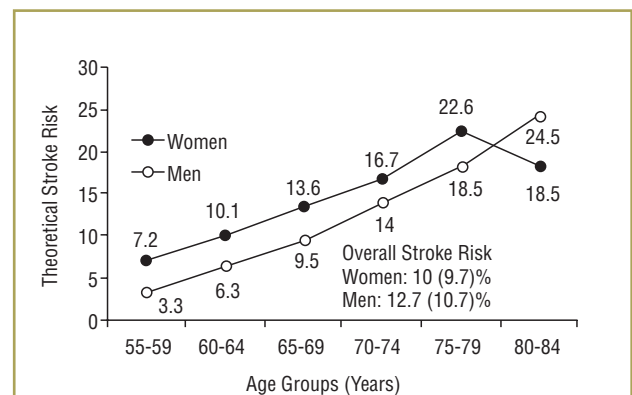
Stroke risk at 10 years for the whole sample was 11.2% (10.2%) (95% CI, 10.4%-11.9%). In patients diagnosed according to NCEP criteria, 10-year stroke risk was 10.2% (9.7%) (95% CI, 9.8%-11.3%). The distribution of risk by group according to each set of criteria is shown in Table 3.

Using as the reference value the 8.4% stroke risk in persons with neither diabetes nor MS, a diagnosis of MS was associated with a 28.6% increase in stroke risk. However, a diagnosis of diabetes was associated with a 114.3% increase, and when both diagnoses appeared together, this was associated with a 123.8% increase in mean estimated stroke risk. When risks were estimated for diagnoses based on the NCEP criteria, the figures were very similar.

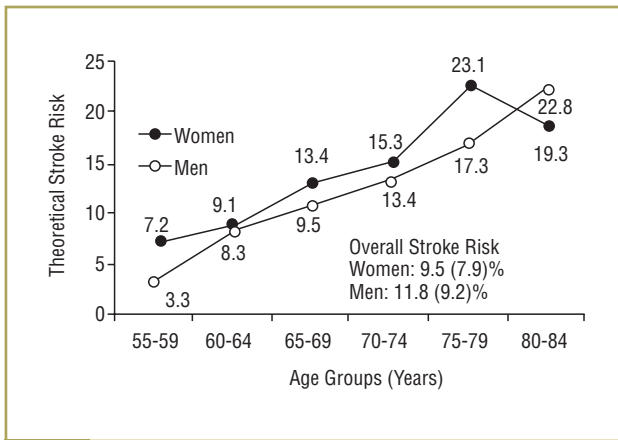
Figure 1 shows the differences in stroke risk for men and women in each age group according to diagnoses based on the WHO criteria. Figure 2 illustrates the risks in both sexes as calculated according to the NCEP criteria for diabetes and MS. The highest probability of stroke in men was found for the 75 to 79-year-old group. In women, the highest risk was found for the 80 to 84 year-old-group; this

was the only age group in which the estimated risk for women was higher than the risk for men. The two sets of plots overlapped to a considerable degree.

During the study period 47 patients (6.4%) were lost to follow-up because they moved to a new address served by a different health center (30), for reasons that were not stated (6), or because of death. Of the 11 subjects who died, 6 of the deaths were attributed to a cardiovascular problem. Table 4 summarizes the distribution of cerebrovascular episodes recorded in each of the 4 groups (diagnosis based on WHO or NCEP criteria) during the first 5



**FIGURE 1** Mean theoretical 10-year stroke risk estimated with the Framingham functions according to age and sex of the sample (World Health Organization criteria).



**FIGURE 2** Mean theoretical 10-year stroke risk estimated with the Framingham functions according to age and sex of the sample (National Cholesterol Education Program criteria).

**TABLE 4** Year Cumulative Incidence of Cerebrovascular Episodes\*

Metabolic Syndrome	Diabetes mellitus	
	DM (-)	DM (+)
MS (-) (WHO)	13 (2.8%) (n=457)	5 (5.4%) (n=93)
MS (-) (NCEP)	11 (2.5%) (n=442)	2 (3.5%) (n=57)
MS (+) (WHO)	1 (1.4%) (n=72)	4 (3.8%) (n=106)
MS (+) (NCEP)	3 (2.8%) (n=108)	7 (5.8%) (n=121)

\*WHO indicates World Health Organization; NCEP, National Cholesterol Education Program; MS, metabolic syndrome; DM, diabetes mellitus. The number of stroke episodes diagnosed in the preceding 5 years is shown, followed by the percent figure in parentheses and the number of cases in each category.

years of the study. A total of 23 episodes were recorded (3.2%); none was fatal and only 2 produced substantial motor or cognitive sequelae. The distribution of cerebrovascular episodes in each of the four groups as defined by WHO (2.8%, 1.4%, 5.4%, and 3.8%) and the NCEP (2.5%, 2.8%, 3.5% and 5.8%) showed that cumulative incidence was significantly lower than the expected incidence predicted from stroke risk calculated with the Framingham functions, especially in the groups of patients who did not have a diagnosis of diabetes.

## Discussion

Type 2 diabetes, hypertension (especially high systolic blood pressure), obesity, dyslipidemia, and microalbuminuria are frequently associated with, and can lead to, increased stroke risk, particularly for ischemic stroke.<sup>15,16</sup> These mutual influences of different risk factors make it difficult to dis-

cern the risk due to diabetes alone against the overall risk associated with MS. Because the available epidemiological data are scarce, the present study aims to provide a preliminary estimate for the Spanish population.

Notwithstanding the modest size of our sample, the results indicate that the overall estimated stroke risk was higher among individuals with diabetes or MS than in the population with neither of these entities. The profile used here was derived from the Framingham study on the basis of results for the population in the USA and has not yet been validated in Spain or other countries in this area. Although the stroke risk estimates obtained for our population may thus be inaccurate, it is also likely that influential environmental and genetic factors were distributed randomly across the 4 groups compared here. Thus the trends seen in the between-group comparisons are likely to reflect relative differences between groups.

Our research group is specialized in diabetes and MS prevention, so the routine use of the oral glucose tolerance test provided information on the diagnosis of our patients' glucemia status. A recent, thorough review of the available scientific evidence examined the main stroke risk factors in detail, and noted the relevant role of hypertension in raising the relative risk of stroke 3-fold to 5-fold.<sup>14</sup> In contrast, the same review suggested that the risk associated with diabetes was lower, but left the issue unresolved as the level of scientific evidence was considered to be lower. In fact, the role of hyperglycemia as a modifiable stroke risk factor has always been controversial: some studies openly support this source of risk, whereas others dismiss the relevance of this factor.<sup>17,18</sup>

Conflicting results have also been reported in the Spanish literature. For example, a study in the Manresa area (eastern Spain) found an association between stroke and hyperglycemia after 28 years of follow-up.<sup>19</sup> Along similar lines, another prospective study in the city of Barcelona found an association between diabetes and a worse prognosis for intracerebral hemorrhage.<sup>20,21</sup> In contrast, other research found age- and sex-related differences in the incidence that were independent of glucemia values.<sup>22</sup> The results reported here cannot resolve all these contradictions, nor are they intended to defend a glucocentric position. They simply insinuate that the risk of stroke posed by diabetes might be independent of the influence diabetes exerts when considered part of MS, at least when the latter is defined according to WHO or NCEP criteria and risk is evaluated with the Framingham Stroke Risk Profile. In fact, diabetes alone leads to a notable increase in basal stroke risk, whereas the presence of MS together with diabetes leads only to a small additional increase. To explain these values, it should be considered that according to the definition used to develop the Framingham Stroke Risk Profile, diabetes receives a high direct score and raises the level of stroke risk in all patients with this diagnosis. Moreover, the higher incidence of electrocardiographic

Discussion  
Key points**What Is Known About the Subject**

- Diabetes is a well-known cerebrovascular risk factor.
- Cerebrovascular disease involves evident excess health costs resulting from its associated mortality and morbidity.
- A method to calculate stroke risk, based on the Framingham functions derived for the US population, is available but is rarely used in Spain.

**What This Study Contributes**

- Stroke risk calculated with the Framingham functions is high.
- The actual incidence of cerebrovascular events observed in the present study was clearly lower than the risk calculated with the Framingham functions, suggesting that they overestimate risk.
- Considering diabetes as part of metabolic syndrome according to WHO or NCEP criteria clearly amplifies stroke risk.
- Stroke risk scales adapted to the Spanish population are needed.

findings in these patients, although it may be coincidental, also raises the score.

In contrast, the increased stroke risk cannot be attributed to the prolonged duration of diabetes because nearly half of our subjects were diagnosed with the oral glucose tolerance test, i.e., in the initial stages of the disease. Naturally, the prevalence of diabetes we assumed for our study population was similar to that reported in other epidemiological studies that used the oral glucose tolerance test.<sup>23</sup> However, although the percentage of individuals with obesity, dyslipidemia and systolic hypertension was lower in this group, mean stroke risk was still higher than in persons with MS in the absence of diabetes. This supports the idea that diabetes is given too much weight in the Framingham Stroke Risk Profile, at least when the profile is used for the Mediterranean population studied here.

The results reported here, taken together, suggest three interpretations: *a)* the data confirm, once again, the risk of stroke posed by diabetes; *b)* the data reflect the fact that the Framingham profile overestimates the risk from diabetes; or *c)* both 1 and 2 together. Our analysis of cerebrovascular accidents during the preceding 5 years of follow-up points toward the second possibility. The cumulative

incidence for this period was 3.2%, as compared to the theoretical 10-year incidence of 8.4% estimated with the Framingham functions. Use of the NCEP criteria (based on easily observable clinical features) to diagnose MS rather than the WHO criteria yielded estimates for incidence that were more plausible if diabetes and MS are considered together as a single predictive factor of stroke risk (5.8% for both factors combined). A similar finding was reported in the long-term Manresa study of Pirelli factory employees (7.14% vs 1.2%), although that study included only men.<sup>19</sup> These authors recorded 72 episodes during 28 years, whereas in our sample of residents in the Reus area we documented 23 episodes in 5 years. Despite the obvious differences between these 2 populations, both sets of findings support the notion that the Framingham Stroke Risk Profile overestimates risk.

The differences in the incidence of stroke episodes between the 4 diagnostic groups seem negligible considering their low impact, and attempts to explain them would be little more than conjecture. However, they suggest that the NCEP definition of MS provides estimates of risks that come closer to the actual incidence, which is apparently lower than the impact that can be inferred from the Framingham stroke risk scale.

It has often been noted that published studies on the Spanish population are scarce, and this limitation is especially evident for the population of older persons.<sup>24</sup> Although it would appear to make little sense to study older patients in terms of prevention, many such patients are not hospitalized or do not undergo CT scans even though the prognosis for life expectancy and cerebrovascular function are known to be worse in this age group.<sup>25</sup> Moreover, differences in health care have been found in relation to gender,<sup>26,27</sup> ethnic group and other factors.<sup>22</sup> It is revealing that the incidence of thromboembolic stroke in men who participated in the Framingham study was 40% higher than in men in Honolulu, whereas episodes of hemorrhagic stroke were almost identical. These epidemiological data emphasize the fact that the Framingham Stroke Risk Profile offers multiple possibilities for overestimating risk depending on the variable in question.

The most controversial issue for primary care is whether diabetes (or MS) should be considered a risk equivalent or simply a risk factor.<sup>28</sup> This can only be clarified with prospective studies with a longer follow-up period that appropriately record cerebrovascular episodes in persons with well-documented MS. Multiple preventive strategies are available for stroke (e.g., intensive therapy for hypertension or diabetes, lipid-lowering medication, antiplatelet aggregants, anticoagulants, surgery). In general these measures are effective, but involve considerable costs and should be adapted to individual cases.<sup>29</sup> This task could be facilitated by a scale to measure stroke risk adapted to the characteristics of the Mediterranean population, similar to the scale developed recently to estimate cardiovascular

risk.<sup>30</sup> For now the Framingham functions can be used with due caution, although the data from the present study suggest that they should not be recommended for systematic use in population screening.

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## References

- Gresham GE, Kelly-Hayes M, Wolf PA, Beiser AS, Kase CS, D'Agostino RB. Survival and functional status 20 or more years after first stroke: the Framingham study. *Stroke*. 1998;29:793-7.
- Gil AC. Nuevos enfoques terapéuticos en la prevención del ictus. *Rev Neurol*. 2002;35:801-04.
- Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*. 2001;24:683-9.
- Megherbi SE, Milan C, Minier D, Couvreur G, Osseby GV, Tilling K, et al. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. *Stroke*. 2003;34:688-94.
- World Health Organization. Report of a WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization. Department of Noncommunicable Disease Surveillance; 1999.
- Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-97.
- Balkau B, Charles MA, Drivsholm T, Borch-Johnsen K, Wareham-Yudkin JS, Morris R, et al. The European Group for the Study of Insulin Resistance (EGIR). Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes Metab*. 2002;28:364-76.
- Bloomgarden ZT. American Association of Clinical Endocrinologists (AACE) consensus conference on the insulin resistance syndrome: 25-26 August 2002, Washington DC. *Diabetes Care*. 2003;26:1297-303.
- Grupo de Trabajo Resistencia a la Insulina de la Sociedad Española de Diabetes. Resistencia a la insulina y su implicación en múltiples factores de riesgo asociados a la diabetes tipo 2. *Med Clin (Barc)*. 2002;119:458-63.
- Costa B, Cabré JJ, Martín F. Síndrome metabólico, resistencia a la insulina y diabetes. ¿Qué se oculta bajo la punta del iceberg? *Aten Primaria*. 2003;31:436-45.
- Alberti KG, Zimmet PZ, for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15:539-53.
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1992;22:312-8.
- D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. *The Framingham Study*. *Stroke*. 1994;25:40-3.
- Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: scientific review. *JAMA*. 2002;288:1388-95.
- Álvarez Sabin J. Etiología y factores de riesgo del infarto cerebral. *Rev Clin Esp*. 1996;196(Supl. 3):3-5.
- Gil de Castro R, Gil Nunez AC. Factores de riesgo del ictus isquémico (I). Factores de riesgo convencionales. *Rev Neurol*. 2000;31:314-23.
- Baird TA, Parsons MW, Alan Barber P, Butcher KS, Desmond PM, Tress BM, et al. The influence of diabetes mellitus and hyperglycaemia on stroke incidence and outcome. *J Clin Neurosci*. 2002;9:618-26.
- Saitoh T, Daimon M, Eguchi H, Hosoya T, Kawanami T, Kurita K, et al. Type 2 diabetes is not a risk factor for asymptomatic ischemic brain lesion-the Funagata study. *Intern Med*. 2002;41:351-6.
- Tomás L, Puig T, Balaguer I. Accidente vascular cerebral: incidencia, mortalidad y factores de riesgo en 28 años de seguimiento. Estudio de Manresa. *Rev Esp Cardiol*. 2000;53:15-20.
- Arboix A, Massons J, García-Eroles L, Oliveres M, Targa C. Diabetes is an independent risk factor for in-hospital mortality from acute spontaneous intracerebral hemorrhage. *Diabetes Care*. 2000;23:1527-32.
- Arboix A, Morcillo C, García-Eroles L, Oliveres M, Massons J, Targa C. Different vascular risk factor profiles in ischemic stroke subtypes: a study from the "Sagrat Cor Hospital of Barcelona Stroke Registry". *Acta Neurol Scand*. 2000;102:264-70.
- Rodríguez BL, D'Agostino R, Abbott RD, Kagan A, Burchfiel CM, Ross GW, et al. Risk of hospitalized stroke in men enrolled in the Honolulu Heart Program and the Framingham Study: a comparison of incidence and risk factor effects. *Stroke*. 2002;33:230-6.
- The DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. *Diabetes Care*. 2003;26:61-9.
- Matias-Guiu J. La epidemiología cerebrovascular. *Rev Esp Cardiol*. 2000;53:13-4.
- Olindo S, Cabré P, Deschamps R, Chatot-Henry C, René-Corail P, Fournière P. Acute stroke in the very elderly. Epidemiological features, stroke subtypes, management, and outcome in Martinique, French West Indies. *Stroke*. 2003;34:1593-97.
- Conthe P, Lobos JM, González Juanatey JR, Gil A, Pajuelo FJ, Novials A, et al. (Estudio ESPERANZA). Diferencias en la atención de las mujeres con alto riesgo cardiovascular respecto a los varones: estudio multidisciplinario. *Med Clin (Barc)*. 2003;120:451-5.
- Morin M, González R, Gil AC, Vivancos J. El ictus en la mujer. Epidemiología hospitalaria en España. *Rev Neurol*. 2003;37:701-5.
- Maiques Galán A. ¿Qué riesgo coronario presentan nuestros pacientes diabéticos? *Aten Primaria*. 2002;29:205-12.
- Straus SE, Majumdar SR, McAlister FA. New evidence for stroke prevention: clinical applications. *JAMA*. 2002;288:1396-8.
- Marrugat J, Solanas P, D'Agostino R, Sullivan L, Ordovas J, Córdón F, et al. Estimación del riesgo coronario en España utilizando la ecuación de Framingham calibrada. *Rev Esp Cardiol*. 2003;56:253-61.

## COMMENTARY

# Framingham Is in Massachusetts

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The last 10 years have been witness to an important change in the orientation of cardiovascular risk prevention activities, which have moved away from one-off interventions aimed at modifiable risk factors toward a model of more integrated intervention strategies based on prior quantification and risk stratification for disease. Atherosclerosis, the main physiological substrate of cardiovascular disease (CVD), is a chronic process of multifactorial origin in which different risk factors (RF) interact synergically. Assuming that the main objective of CVD prevention is to reduce the probability of becoming ill, it would not make much sense to “standardize” the value of different RF; rather, it makes more sense to act on them in a coordinated manner, using more stringent measures according to the risk of disease.

One of the circumstances that has made this approach possible is the increasing availability of tools able to quantify, or at least stratify, the risk of a CVD episode from certain individual characteristics that are easy to determine, i.e., from RF. Currently about 20 different risk scales are available in a large variety of versions and formats, from tables and scoring systems to sophisticated computer-based programs that calculate risk rapidly. These scales are based on probabilistic mathematical models obtained by applying multivariate analysis techniques to data from long-term follow-up studies of cohorts of individuals. The paradigm for such studies is the Framingham study, in which the incidence of CVD has been related to a number of identified RF. Use of resulting model for other persons has made it possible to estimate cardiovascular risk, i.e., the probability of having a CVD episode during a given period (usually 10 years).

Although mathematical functions have been developed to calculate coronary disease risk, stroke risk, or both simultaneously, the former are much more widespread and more popular than the latter. This seems surprising given that the burden of stroke is similar to that associated with coronary disease in terms of morbidity, mortality, complications, and sequelae.

The study by Costa et al published in this issue of *ATENCIÓN PRIMARIA*<sup>1</sup> estimates the risk of stroke with the Framingham scale in a population sample from the city of

## Key Points

- Estimation and stratification of cardiovascular risk are fundamental steps before cardiovascular risk prevention activities can be carried out effectively.
- Scales derived from the Framingham study used to calculate stroke risk are little used and have not been validated for use in Spain.
- While we await long-term prospective studies that are sufficiently powered to validate the Framingham risk functions and the SCORE project functions for the Spanish population, it seems reasonable to use the latter based on the most recent consensus recommendations.
- Regardless of the risk scale used, accurate ways to estimate risk need to be made available and improved upon for use in daily primary care practice.

Reus (Tarragona, Spain), with the aim of determining the risk associated with type 2 diabetes with and without associated metabolic syndrome (MS). The estimated risk of stroke was higher in persons with MS or diabetes than in other persons, but the association of MS with diabetes did not significantly increase the risk in comparison to diabetes alone. The findings were foreseeable in light of the higher relative score for diabetes compared to the scores for components of MS according to the Framingham scale. Unfortunately, the low number of cerebrovascular episodes during the period of follow-up was insufficient to validate the estimates. However, the results are consistent with those of a recent prospective study of persons in Aragon with type 2 diabetes<sup>2</sup> seen in endocrinology out-patient clinics. This study found that when all four components of MS were present (according to the WHO criteria), there was no increase in stroke risk, although the risk for coronary disease did increase.



Subsequent comparisons of the theoretical risk and the cerebrovascular episodes observed during the 5-year follow-up period in the cohort studied by Costa et al<sup>1</sup> showed this approach to be a useful way to study the validity and applicability of the Framingham functions for the Spanish population—features that had not been studied previously. Both for the whole cohort and for subgroups with diabetes, MS, or both, the actual incidence of stroke was lower than the risk estimated with the Framingham functions. Similar results were obtained when the coronary disease risk function was applied for populations in the Mediterranean area and even populations in northern Europe,<sup>3</sup> and these findings have been interpreted as a logical consequence of the differences in basal characteristics and risks between the populations being compared. It was therefore proposed that correction factors be used<sup>3,4</sup> to minimize the problem.

Although the findings reported by Costa et al<sup>1</sup> suggest that the Framingham model also overestimates the risk of stroke for the Spanish population, this conclusion should be qualified. First, it is likely that the theoretical risk was overestimated because of the high prevalence of diabetes in the Reus cohort (24.5%, as compared to 6% in the Framingham cohort). This marked difference in prevalence can be explained in part by differences in the diagnostic criteria, particularly as more than 40% of the persons with diabetes in the Reus cohort were diagnosed with an oral glucose tolerance test. Second, the large proportion of diagnoses with the oral glucose tolerance test implies a shorter duration of the disease, and thus a lower baseline risk of CVD. Finally, the total number of cerebrovascular episodes recorded during the study period for the Reus cohort was small and clearly insufficient, as the authors note,<sup>1</sup> to hazard an interpretation of the differences between the four subgroups. Additional prospective studies with larger numbers of participants and a longer follow-up period will be needed before the Framingham model for stroke risk can be completely banished from use for the Spanish population.

However, other options are available meanwhile. Risk functions from the SCORE project<sup>5</sup> recently became available. These functions were developed from data for more than 200 000 participants in several European countries, including Spain. This model provides estimates separately or jointly for the risk of death from stroke and coronary disease, and different versions have been devised for areas with a high and a low incidence of CVD.

For diabetes specifically—and leaving aside for now the issue of whether it should be considered a risk equivalent for CVD—use of the Framingham functions has been questioned because of the low number of patients with diabetes who were followed in the original cohort (237 of a total of 5573). Regrettably, the SCORE project did not include diabetes among the RF in the model, although it did recommend using a constant to dou-

ble the estimated risk in men and quadruple the estimated risk in women for any combination of RF5. As an alternative, specific equations for coronary disease and stroke risk<sup>6</sup> have been developed for the population with type 2 diabetes, based on the cohort of the UK Prospective Diabetes Study (UKPDS). In addition to overcoming the limitations of the Framingham and SCORE risk functions, the diabetes-specific equations included RF characteristic of diabetes (years or duration of the disease) or known to be related with stroke risk (atrial fibrillation); however, they also await validation for the Spanish population.

In daily practice, primary care physicians are often overwhelmed by the profusion of risk scales and the multitude of guidelines for prevention, which change, are inconsistent, or have been developed in other regional, national, European or international settings. This panorama is, to a large extent, a reflection of the lack of a genuinely Spanish model for predicting cardiovascular risk, or prospective studies that are able to ensure the validity and applicability of other models that are being imported for use with the Spanish population. National- and regional-level projects are now underway<sup>7</sup> and should, in the near future, provide the hoped-for results. Meanwhile, interdisciplinary initiatives based on consensus are to be welcomed. One such initiative is the recent publication and widespread dissemination of the Spanish version of the European Guidelines on Cardiovascular Disease Prevention (Comité Español Interdisciplinario para la Prevención Cardiovascular),<sup>8</sup> under the auspices of the relevant national health authorities and 11 participating scientific societies.

We should note that CVD prevention does not begin or end with risk calculation. Risk models, while important, can only be considered aids to decision-making with regard to the choice of appropriate preventive interventions aimed at enhancing cardiovascular health in the population. Integration (eventually) of these tools into computer-based medical records, as a clear example of the potential of technology at the service of health professionals, is one possible strategy that might facilitate and improve the identification of risk and recording of RF. In addition, risk stratification and setting intervention and follow-up targets for preventive activities are further strategies for improving cardiovascular health. Framingham, after all, is too remote, and the risk profile functions developed from that study should probably be eschewed. But first we need to close the huge gap that separates the guidelines from the reality of daily practice.

## References

1. Costa B, Cabré JJ, Martín F, Piñol JL, Basora J, Bladé J, and the Grupo de Investigación ITG. La escala de Framingham sobre-

- valora el riesgo cerebrovascular de la diabetes y el síndrome metabólico en población española (in press).
2. Gimeno Orna JA, Lou Arnal LM, Molinero Herguedas E, Boned Julián B, Portilla Córdoba DP. Influencia del síndrome metabólico en el riesgo cardiovascular de pacientes con diabetes tipo 2. *Rev Esp Cardiol*. 2004;57:507-13.
  3. Brindle P, Emberson J, Lampe F, Walker M, Whincup P, Fahey T, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ*. 2003;327:67-1272.
  4. Proceso Asistencial Integrado Riesgo Vascular. Consejería de Salud. Junta de Andalucía, 2003. Available from: <http://www.csalud.junta-andalucia.es>
  5. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, de Backer G, et al, on behalf of the SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987-1003.
  6. Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, et al. Risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study Risk Engine (UKPDS 60). *Stroke*. 2002;33:1776-81.
  7. Estudio DRECA-2: evolución del riesgo cardiovascular en una cohorte de población andaluza en los últimos 12 años (1992-2004). Available from: <http://www.sas.junta-andalucia.es>
  8. Brotons C, Royo-Bordonada MA, Álvarez-Sala L, Armario P, Artigao R, Conthe P, et al. Comité Español Interdisciplinario para la Prevención Cardiovascular (CEIPC). Adaptación española de la guía europea de prevención cardiovascular. *Aten Primaria*. 2004;34(8):427-32.