Predictors of Stroke Mortality in Elderly People from the General Population: The CArdiovascular STudy in the ELderly

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Predictors of stroke mortality in elderly people from the general population

The CArdiovascular STudy in the ELderly

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Abstract. Stroke occurs particularly frequently in elderly people and, being more often disabling than fatal, entails a high social burden. The predictors of stroke mortality have been identified in 3282 subjects aged ⩾65 years, taking part in the CArdiovascular STudy in the ELderly (CASTEL), a population-based study performed in Northeast Italy. Historical and clinical data, blood tests and 14-year fatal events were recorded. Continuous items were divided into quintiles and, for each quintile, adjusted relative risk (RR) with 95% confidence intervals [CI] was derived from multivariate Cox analysis. Age, historical stroke (RR: 5.2; 95% CI: 3.18–8.6) and coronary artery disease (RR: 1.38; CI: 1.18–2.1), atrial fibrillation (RR: 2.40; CI: 1.42–4.0), arterial hypertension (RR: 1.33; CI: 1.15–1.76), systolic blood pressure ⩾163 mmHg (RR: 1.84; CI: 1.20–2.59), pulse pressure ⩾74 mmHg (RR: 1.50; CI: 1.13–2.40), cigarette smoking (RR: 1.60; CI: 1.03–2.47), electrocardiographic left ventricular hypertrophy (RR: 1.72; CI: 1.10–2.61), impaired glucose tolerance (IGT, RR: 1.83; CI: 1.10–3.0), uric acid (UA) >0.38 mmol/l (RR: 1.61; CI: 1.14–2.10), serum potassium ⩾5 mEq/l (RR: 1.70; CI: 1.24–2.50) and serum sodium ⩽139 mEql/l (RR: 1.34; 1.10–2.10) increased the risk of stroke. In the CASTEL, stroke was the first cardiovascular cause of death. Some independent predictors usually unrelated to stroke mortality (namely pulse pressure, pre-diabetic IGT, UA and blood electrolytes disorders) have been identified.

Key words: Elderly, Epidemiology, Risk factors, Stroke mortality

Abbreviations: BL – borderline; BMI – body mass index; BP – blood pressure; CAD – coronary artery disease; CI – confidence intervals; EKG – electrocardiogram; FEV_1 – maximal expiratory flow in 1 sec; HT – sustained hypertensive; IGT – impaired glucose tolerance; LVH – left ventricular hypertrophy; LVH_{EKG} – electrocardiographic left ventricular hypertrophy; LVMI – left ventricular mass index; NT – normotensive; RR – relative risk; SD – standard deviation; TC – total cholesterol; UA – uric acid

Introduction

Stroke is the primary cause of cardiovascular death in Eastern and the secondary one in Western societies [1]. Due to its high morbidity and mortality, stroke is a worldwide health care problem [2] exacting an enormous financial toll [3], as more than 50% of survivors have severe and permanent disability [4].

Most epidemiological studies identified the key risk factors for stroke, and have provided an estimate of their relative weight in middle-aged subjects [5–7]. Although the incidence of stroke rises sharply with advancing age, studies assessing the risk of stroke in the elderly are sparse, and almost limited to men [8–13]. A part from the recent data derived from the cardiovascular health study [14], the risk pattern of stroke in the elderly from the general population are therefore not well defined.

In this paper, we identified in a cohort of elderly subjects from Northeast Italy the factors able to increase the risk of fatal stroke. This study is part of the CArdiovascular STudy in the ELderly (CASTEL), a population-based prospective study aimed at identifying cardiovascular risk factors and, more in general, the predictors of mortality in the elderly. The 14-year results are described herein.

Materials and methods

General protocol

The CASTEL enrolled 3282 subjects aged 65 years or above, representing 73% of elderly subjects from the Northern Italian towns of Castelfranco and Chioggia. Previous surveys [15, 16] showed for this cohort a cardiovascular risk pattern comparable to that of the Italian general population [17, 18]. The general characteristics of the two cohorts are summarised in Table 1.

Briefly, an initial survey was organised, and mortality was monitored yearly for 14 years. Historical

Table 1. Baseline characteristics of two elderly populations of the CASTEL

Items	Chioggia (N = 1028)	Castelfranco (N = 2254)	*p*-Value between two towns
Age (years)	74.3 ± 5.3	73.5 ± 5.2	<0.002
Males:females	426:602	855:1399	NS
Systolic BP (mmHg)	155.7 ± 23.6	162.2 ± 24.7	<0.0001
Diastolic BP (mmHg)	85.7 ± 10.8	90.3 ± 12.0	<0.0001
Heart rate (bpm)	75.7 ± 11.9	76.1 ± 11.2	NS
BMI (kg/m^2)	27.3 ± 4.7	26.6 ± 4.5	NS
TC (mmol/l)	5.28 ± 1.15	5.85 ± 1.12	<0.0001
Triglycerides (mmol/l)	1.3 ± 0.49	1.43 ± 0.54	<0.0001
Creatinine (μmol/l)	79.6 ± 35.4	79.6 ± 26.5	NS
UA (mmol/l)	0.32 ± 0.09	0.31 ± 0.08	NS
Frank diabetes (%)	27.3	17.3	<0.001
Hystorical CAD (%)	9.6	11.4	NS
Hystorical stroke (%)	4.6	8.6	<0.0001
Smoking habits			
Never smokers (%)	62.7	69.3	
Former smokers (%)	19.1	17.5	<0.002
Current smokers (%)	18.2	13.2	
No of cigarettes (daily)	6.7 ± 0.5	5.7 ± 0.4	NS

data were recorded by means of Rose's questionnaire [19]. During the initial survey, trained doctors measured BP in triplicate with a sphygmomanometer at 15-min intervals, together with pulse rate. This procedure was repeated thrice at 1-month intervals. To minimise the effects of the alarm reaction, only the average of the last two measurements was taken into consideration. Subjects were considered to be sustained hypertensive when having a systolic blood pressure (BP) $\geqslant$ 160 mmHg and/or a diastolic BP $\geqslant$95 mmHg and/or a history of hypertension. Those with systolic BP values ranging between 140 and 159 mmHg and diastolic BP between 90 and 94 mmHg were labelled as borderline (BL). The difference between systolic and diastolic BP was the pulse pressure.

At the beginning of the screening, subjects were categorised into those who had a normal glucose tolerance (blood glucose <6.10 mmol/l without any antidiabetic treatment or any history of diabetes) and those with impaired glucose tolerance (IGT). The latter were considered as diabetic if taking antidiabetic drugs or having a fasting blood glucose level $\geqslant$6.99 mmol/l in at least two separate samples, without therapy [20].

Subjects were classified into never, current ($\geqslant$1 cigarette daily) or former smokers (having given up their smoking habit for at least 1 year prior to the screening). Current smokers were subsequently segregated into quintiles based on number of cigarettes smoked daily.

Body mass index (BMI) was calculated as the ratio between weight and squared height. 'Overweight' was defined as an index >25 kg/m^2 [21]. Body surface area was calculated in m^2 with the formula of Du Bois and Du Bois [22]. All subjects were screened for albuminuria with a dipstick using a random morning urine sample, as 24-hour samples are impractical for population screenings due to inconvenience and frequent collection errors [23]; urine infection was previously excluded.

Subjects having serum uric acid (UA) levels >0.38 mmol/l (last quintile of UA) were labelled as hyperuricemic, those with serum potassium levels >5 mmol/l (last quintile) as hyperkaliemic, and those having serum sodium levels <139 mmol/l (first quintile) as hyponatremic. Maximal expiratory flow in 1 sec (FEV_1) was measured with a dry spirometer, and reference values were individually calculated [24].

In a randomly chosen subset of 504 subjects, left ventricular mass was calculated from the following algorithm [25]: 1.04 [(end-diastolic diameter + end-diastolic posterior wall thickness + end-diastolic septum thickness)^3 − end-diastolic diameter^3] − 13.6. Left ventricular mass index (LVMI, in g/m^2) was calculated by dividing left ventricular mass by body surface area [25]. According to Hammond [26], echocardiographic diagnosis of left ventricular hypertrophy was based on an LVMI >134 g/m^2 in males and >110 g/m^2 in females.

Electrocardiogram (EKG) was analysed on the basis of the Minnesota Code [27] by an expert who did not know the aim of the study. Diagnosis of atrial fibrillation was based on the code 8-3 and that of electrocardiographic left ventricular hypertrophy (LVH_{EKG}) on the code 3-1 or 3-3.

Coronary artery disease (CAD) at entry was defined as a history of myocardial infarction and/or angina and/or electrocardiographic signs of ischaemia (Minnesota code 4-1, 4-3, 5-1 or 5-3, if codes 6-4, 7-1 and 7-2 were absent) and/or echocardiographic hypokinesia.

Annual mortality obtained from the registrar's office was double-checked for causes of death by re-

ferring to hospitals, retirement homes or physicians' files. Causes of death were codified according to the International Classification of Disease. In 85% of the cases, autopsy or computerised tomography was performed in order to distinguish haemorrhagic from ischaemic events. Annual cumulative survival curves were generated with the life-table method and compared with the Mantel–Haenszel approach. Continuous variables were expressed as mean ± standard deviation (SD) and divided into quintiles. For each quintile the RR (95% CI) adjusted for confounders was calculated from logistic models [28, 29].

Results

Univariate analysis

The mean age at entry was 73.8 ± 5.3 years (range: 65–91). In the five quintiles of age (656 subjects each) the mean age was 67.5 ± 1.2, 70.4 ± 0.8, 73 ± 1.1, 76 ± 1.4 and 83 ± 3.2 years, respectively (all quintiles $p < 0.0001$ vs. each others). The last quintile, ranging from 80 to 95 years of age, corresponded to the current definition of very old. At the 14th year, 1616 subjects were dead and 1666 were alive (mortality rate: 49.2%).

Historical stroke was reported in 126 cases (3.8%), 68 women and 58 men, respectively (insignificant difference between genders). During the follow-up period, there were 170 new cases of fatal stroke (stroke mortality rate: 5.2%, insignificant difference between genders). Cumulative curves of survival showed that stroke was the first cause of cardiovascular mortality (Figure 1).

Multivariate prediction of stroke mortality

In the whole population, 13 items (age, historical stroke and CAD, BL IGT, arterial hypertension, systolic BP, pulse pressure, atrial fibrillation, LVH_{EKG}, UA, status of current smoker and serum potassium and sodium) turned out to be independent predictors of stroke mortality in multivariate Cox analysis (Table 2). Systolic and pulse pressure as continuous variables had the same predictive value as the label of hypertension.

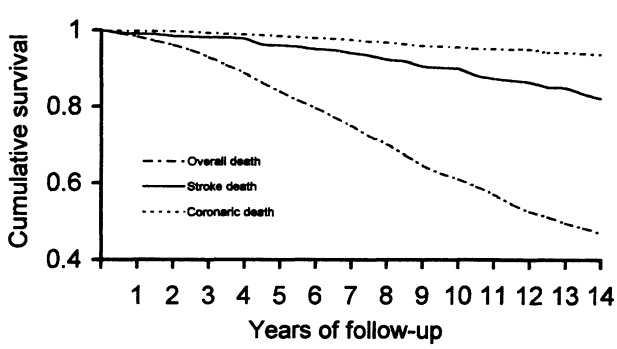

Figure 1. 14-years cumulative survival for overall (- - - -), coronaric (– – –) and stroke (——) mortality in 3282 elderly subjects from the CASTEL.

Role of clinical history

Historical stroke (RR: 5.2, [CI: 3.18–8.6]) and historical CAD (RR: 1.38, [CI: 1.18–2.1]) were the most important risk factors of stroke mortality.

Role of hypertension

Arterial hypertension was found to be an independent predictor of fatal stroke, mainly among sustained hypertensive (HT) (RR: 1.33, [CI: 1.15–1.76]) and BL hypertensive subjects (RR: 1.18, [CI: 1.02–1.63]). Besides, stroke mortality progressively increased from first to last quintile of systolic BP (3.7, 4.4, 4.6, 6.6, 6.7%, respectively; each quintile $p < 0.005$ vs. the previous one). It also increased sharply when pulse BP was > 74 mmHg (Table 2). Based on multivariate analysis, pulse pressure appeared to be a better predictor of fatal stroke than systolic BP (Table 3).

Role of atrial fibrillation

Atrial fibrillation was diagnosed in 145 subjects, without any difference between males and females (4.1 vs. 4.6%). Stroke mortality was higher in subjects with (11.7%) than without atrial fibrillation (4.9%; $p < 0.0005$); among the former, it was significantly higher in females than males (16.1 vs. 3.8%; $p < 0.02$) and increased with increasing age until 79 years (RR: 2.3, 6.4 and 7.8 in the age classes <73, 74–76 and 77–79 years, respectively; all differences $p < 0.001$). In multivariate analysis also, atrial fibrillation strongly predicted stroke mortality ($\chi^2 = 9.9$, $p < 0.002$, Cox coefficient: 0.93 ± 0.27) until 79 years of age.

Role of IGT

Stroke mortality rate was 6.6% in diabetic patients and 7.4% in those with pre-diabetic IGT; both rates were significantly higher ($p < 0.03$) than that of normoglycemic subjects (4.6%). In multivariate analysis, pre-diabetic IGT predicted fatal stroke ($\chi^2 = 4.29$, [CI: 1.10–3], Cox coefficient 0.57 ± 0.26) while frank diabetes was always rejected from the Cox model. When compared to frankly diabetic subjects, those with pre-diabetic IGT had significantly higher levels of diastolic BP (90.2 ± 11.7 vs. 88.5 ± 11.5 mmHg; $p < 0.05$), UA (0.35 ± 0.08 vs. 0.31 ± 0.08; $p < 0.01$) and total cholesterol (5.76 ± 1.09 vs. 5.53 ± 1.16; $p < 0.01$).

Role of LVH_{EKG}

Women with LVH_{EKG} had higher stroke mortality than those without this item (8.1 vs. 5%, RR: 1.72, [CI:

Table 2. Stroke mortality rate, adjusted RR and 95% CI in 3282 elderly subjects of the CASTEL

Items	Mortality (%)	Relative risk	CI (95%)
Cardiovascular risk factors			
Hystorical stroke	12.4	5.2*	(3.18–8.6)
Hystorical CAD	13.4	1.38*	(1.18–2.1)
Pre-diabetic IGT	7.4	1.83**	(1.10–3.0)
Sustained hypertension	5.9	1.33**	(1.19–1.83)
Borderline hypertension	4.6	1.18**	(1.02–1.63)
Systolic BP (mmHg)	4.4	1.20	(0.62–1.88)
2nd quintile (141–150)	4.6	1.23	(0.68–2.0)
3rd quintile (151–162)	6.6	1.84**	(1.20–2.59)
4th quintile (163–180)	6.7	1.88*	(1.27–2.75)
5th quintile ($\geqslant$181)			
Pulse pressure (mmHg)			
2nd quintile (55–64)	5.1	1.26	(1.01–2.08)
3rd quintile (65–73)	4.8	1.37	(1.09 –2.12)
4th quintile (74–87)	6.3	1.50**	(1.13–2.40)
5th quintile ($\geqslant$88)	7.0	1.94*	(1.24–2.80)
Atrial fibrillation	11.7	2.40**	(1.42–4.0)
Left ventricular hypertrophy	8.1	1.72**	(1.10–2.61)
Serum uric acid (mmol/l)			
1st quintile ($\leqslant$0.23)	4.8	1.22	(1.02–1.65)
2nd quintile (0.24–0.28)	4.7	1.03	(0.67–1.70)
4th quintile (0.33–0.37)	5.1	1.09	(0.78–1.75)
5th quintile ($\geqslant$0.38)	7	1.61	(1.14–2.10)**
Smoking habits			
Former	3.2	1.22	(0.67–1.75)
Current	6.4	1.60*	(1.03–2.47)
Blood electrolytes disorders			
Potassium (mEql/L)			
1st quintile ($\leqslant$3.5)	4.1	0.57	(0.34–0.96)
2nd quintile (3.6–4.1)	4.9	0.72	(0.44–1.17)
4th quintile (4.5–4.9)	5.5	1.01	(0.69–1.21)
5th quintile ($\geqslant$5)	6.7	1.70**	(1.24–2.50)
Sodium (mEq/L)			
1st quintile ($\leqslant$139)	6.5	1.34**	(1.10–2.10)
2nd quintile (140–142)	5.4	1.02	(0.73–1.31)
4th quintile (143–144)	4.2	0.76	(0.52–1.01)
5th quintile ($\geqslant$145)	3.9	0.98	(0.61–1.13)

For categorical variables, the opposite or missing category served as reference groups with RR = 1 (e.g., no historical stroke, never smoked, 1st quintile).
*$p < 0.001$; **$p < 0.01$.

1.74–3.37; ($p < 0.004$), while no difference was found in men. No relation was found between echocardiographic left ventricular hypertrophy and stroke mortality in both genders.

Role of UA

A U-shaped trend of stroke mortality rate was found in relation to UA (in the five quintiles: 4.8, 4.7, 4, 5.1, and 7%).[1] In the Cox analysis, hyperuricemia predicted fatal strokes with an RR of 1.61, [CI: 1.04–2.61].

Role of cigarette smoking

Current smokers had a higher risk of fatal stroke (RR: 1.60, [CI: 1.03–2.60]) than non-smokers, whereas no difference was found between former- and never-smokers (Table 2). Excess mortality was particularly high in subjects who had smoked $\geqslant$40 years (7.2 vs. 1.8%, $p < 0.01$). No significant relationship was shown between fatal stroke and number of cigarettes smoked daily.

Role of blood electrolytes

The risk of fatal stroke was significantly higher when potassium levels were $\geqslant$5 mEq/l (RR: 1.70,

[1] $p < 0.04$ last vs. first and second, $p < 0.001$ last vs. third.

Table 3. Results of the multivariate Cox analysis of fatal stroke in 3282 elderly subjects from the CASTEL

	Improvement χ^2	*p*-Value	Cox-coefficient ± SE
Age	4.10	<0.04	0.08 ± 0.03
History of stroke	23.29	<0.0001	1.64 ± 0.31
Hystory of CAD	13.86	<0.04	1.19 ± 0.24
Arterial hypertension	12.22	<0.05	0.39 ± 0.11
Atrial fibrillation	11.01	<0.0001	1.26 ± 0.31
Systolic BP	10.15	<0.001	0.01 ± 0.003
Pulse pressure	9.97	<0.002	0.01 ± 0.004
Pre-diabetic IGT	3.17	<0.05	0.62 ± 0.31
LVH_{EKG}	3.10	<0.05	0.56 ± 0.31
Current smokers	6.34	<0.01	0.05 ± 0.01
Serum UA	0.43	<0.007	0.19 ± 0.07
Serum potassium	3.29	<0.05	0.43 ± 0.23
Serum sodium	3.00	<0.05	−0.04 ± 0.02

Only the items that were accepted by the equation are summarised.

[CI: 1.24–2.50]) and when serum sodium levels were ⩽139 mEq/l (RR: 1.34, [CI: 1.10–2.10]). When both the above-mentioned disorders were simultaneously present, RR was 3.03, [CI: 1.67–5.46].

Very old subjects

In very old subjects, only three items (age, historical stroke and LVH_{EKG}) predicted stroke mortality, and increased pulse pressure (>74 mmHg) had the same meaning as hypertension.

Discussion

In this study, historical stroke was the best predictor of stroke mortality. Many evidences show that survivors from an acute stroke are pre-disposed to other life-threatening diseases [30–32]. For example, in the Dubbo Study [33], patients with a history of stroke had a 27% risk excess of a new stroke compared to those free from prior cerebrovascular events.

Atrial fibrillation, pulse pressure, history of CAD, LVH_{EKG}, IGT, smoking, UA and electrolytes were other predictors. Atrial fibrillation, a common clinical problem in the elderly [34, 35], notoriously predisposes stroke [34, 36, 37]. Approximately 17% of all autopsied elderly subjects have atrial fibrillation [37], and emboli from the heart are responsible for up to 20% of cases of stroke [38]. In the CASTEL, however, differently from Framingham [39], atrial fibrillation had no prognostic value after the age of 80 years. This could be of interest when evaluating the opportunity of treating very old subjects with warfarin.

Hypertension is known to be a predictor of stroke [40], and practically all the studies have demonstrated a relationship between BP levels and stroke [41–43]. This was confirmed in the present study, where RR of stroke mortality was 1.18, [CI: 1.02–1.63] in BL and 1.33, [CI: 1.15–1.76] in HT, as compared to normotensive (NT) subjects. The pulse component of BP was of the greatest importance even after the age of 80 years, with a progressive increase of RR with increasing pulse pressure and a sharp rise above the value of 74 mmHg. It is difficult to discuss this point, as only systolic and diastolic BP have been systematically taken into consideration in the literature [44, 45], whereas pulse BP has been neglected in this respect, particularly in the elderly. High pulse pressure is known to be associated with an increase of the carotid intima-media thickness [46]; nevertheless, in the CASTEL, stroke mortality was not higher in subjects with carotid murmurs in the neck, the only index of carotid damage available on a large scale in 1983–1985.

Based on the results of many previous studies [41, 47], a history of myocardial infarction or angina pectoris is also considered to be strongly associated with an increased risk of stroke. This was also true in the CASTEL, where subjects with a history of CAD were at an increased risk of stroke. It is therefore a good practice to make all efforts to identify and to treat subjects with CAD, with the dual aim to prevent both coronary and cerebrovascular events.

Although not as sensitive as the echocardiogram, EKG remains an acceptable index of LVH, having a specificity around 12% [48]. In population studies, and in the CASTEL study too, LVH_{EKG} was a predictor of stroke [49–51]. The simplistic conclusion that this is due to coexistent arterial hypertension must be rejected, as LVH_{EKG} independently contributed to cerebrovascular risk.

Diabetes mellitus, a strong risk factor for atherosclerosis [52, 53], seems to have a less consistent role in the pathogenesis of cerebrovascular disease. In fact, some studies have indicated that subjects with IGT have an increased risk of stroke [52, 54, 55], whereas other investigations [33, 54] have denied this possibility. In the CASTEL, subjects with pre-diabetic IGT had an increased risk of stroke, independently from other cardiovascular risk factors. On the contrary, frank diabetes had no prognostic role, being probably overwhelmed, in the multivariate analysis, by other variables such as hypertension [52] and history of CAD [40]. IGT is one of the aspects of the 'X syndrome' [56], whose role in generating stroke has been clearly demonstrated [57].

Smoking acts as a risk factor for stroke in a dose-dependent manner and may also interact with hypertension, making the identification of its specific role difficult. Tobacco has short- as well as long-term effects on vessels [58] and contributes to the development of atherosclerosis and its complications [59]. In the CASTEL, only current smokers experienced an increased stroke mortality. This is in agreement with the belief that a reduction of risk of stroke follows

smoking cessation [60] and confirms the opportunity to promote community-based educational programs against tobacco not only among young and middle-aged subjects, but also among elderly people.

A possible prognostic role of UA has been emphasised in recent years [61, 62], but its meaning as an independent risk factor for cardiovascular disease and in particular for stroke remains uncertain. In the ARIC study [63], UA did not result to be *per se* a risk factor for atherosclerosis, since, when the known risk factors for cardiovascular diseases were included in multivariate analysis, UA lost any prognostic role. Nevertheless, in a recent study on middle-aged diabetic patients [64], hyperuricemia was a strong predictor of stroke events, independently of other cardiovascular risk factors such as hypertension [65, 66], nephropathy [61], overweight [62] and diuretic therapy [66] (all conditions accompanied by higher UA levels). In the CASTEL, hyperuricemia (last quintile of UA) was found to be a strong and independent predictor of stroke mortality. The mechanism of this association remains unexplained, but it has been recently shown that human atherosclerotic plaque contains a considerable amount of UA [67], and hyperuricemia – via purine metabolism – may promote thrombus formation [68]. Finally, the reason why the curve of stroke mortality was patently J-shaped remains unknown, although it can be postulated that subjects with the lowest UA levels have a muscular mass below the standard and are consequently disadvantaged in survival.

A positive relationship between dietary sodium/potassium intake and stroke has been reported [69]. Electrolyte disorders are common in the elderly, particularly in diabetic [70] and nephropathic [71] subjects, probably due to both hypervolaemia and renal decay. In the CASTEL, hyperkalaemia and hyponatremia were independent predictors of stroke, and the RR was particularly high (3.03, [CI: 1.67–5.46]) when the above-mentioned disorders were simultaneously present. Animal studies have shown that local cerebral ischaemia produces electrolyte disturbances via lactic acidosis [72], and a recent report in humans has also shown a significant association between cerebral injuries and hyponatremia [73].

Conclusions

The CASTEL has confirmed the important role of age, hypertension, atrial fibrillation, cigarette smoking, LVH and history of stroke and CAD as risk factors for stroke, while it has failed to confirm that of gender, diabetes, serum lipids, alcohol intake, BMI and carotid murmurs. Instead, the CASTEL has identified additional risk factors such as pulse BP, IGT, UA and the blood electrolyte disorders. Finally, in our study, the risk pattern appears to be quite different in subjects who are just elderly and in those who are very old. Further data are needed to generate strategies for treatment and programs of public health policy related to prevention of stroke in elderly people.

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