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Epidemiology of ischemic stroke subtypes: results from the follow-up of a population-based registry

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Summary

BACKGROUND

Stroke is the leading cause of disability and the second most common cause of death worldwide. While the incidence of stroke is decreasing in advanced economies, the trend is increasing in alarming rate in low- and middle- income countries. With the population aging the total stroke incidence and the burden of post-stroke disability might increase over time. Demographic changes and implementation of therapeutic strategies could modify also the distribution of the different etiologies of ischemic strokes over time. Indeed, recent evidence suggests that in the last two decades there has been an increase in ischemic stroke due to cardioembolism (CE) and a reduction of those due to large-artery atherosclerosis (LAA) in Whites and in high-income countries.
Stroke registries are important to assess stroke incidence, prevalence, and mortality, to identify risk factors and prognostic factors, to compare local with regional, national, and international data, to formulate guidelines, to improve health services and medical assistance, and to plan adequate therapeutic trials.

AIMS OF THE STUDY

The purposes of this study were: **1)** to assess the incidence, characteristics, short- and long-term prognosis of first-ever ischemic stroke (FEIS) **(Chapter III)**; **2)** to assess the prevalence, incidence, characteristics, short- and long-term prognosis of ischemic stroke etiologic subtypes **(Chapter IV); 3)** to evaluate the contribution of atrial fibrillation (AF) to the incidence and prognosis of FEIS, and also to compare these recent data on AF with those from the 1994-1998 study in order to evaluate possible epidemiological changes over two decades **(Chapter V)**; **4)** to evaluate the contribution of AF diagnosed after stroke onset (newly diagnosed atrial fibrillation; NDAF) to the incidence, and prognosis of FEIS, and to speculate about the neurogenic or cardiogenic origin of NDAF **(Chapter VI)**.

METHODS

Cases of FEIS were ascertained from January 1, 2011 until December 31, 2013 in a prospective population-based registry of patients residing in the L'Aquila district, central Italy. To be included in the study, patients had to reside in the district at the time of the event and had to present a first-ever stroke (FES). Study design, case-finding procedures, and methodology were the same of the former L'Aquila Stroke Registry that was conducted in 1994-1998. All subjects with neurological symptoms suggestive of a cerebrovascular event occurring during the study period were screened. Events were identified by active monitoring of inpatient and outpatient health services within the district and in nearby areas. In each clinical ward, all patients admitted for a cerebrovascular event were identified and examined within 7 days from stroke onset by a senior physician; thereafter all patients were screened by a consulting neurologist to validate the event. Death certificates were checked monthly and clinical data of all patients deceased with a diagnosis of ischemic stroke and not otherwise included in the registry were reviewed. Hot pursuit (active identification of all events as they occurred) and cold pursuit (retrospective identification of the same events) were combined in the ascertainment of cases to ensure the complete identification of the

events. All cases were followed up to 5 years (August 31, 2018) by quarterly planned in-person visits or by a structured telephone interview, either in person or with a close relative or with the general practitioner. Recorded outcome events were transient ischemic attack, recurrent nonfatal and fatal stroke, nonfatal and fatal myocardial infarction, and death from either vascular or nonvascular causes.

Descriptive statistics are reported as absolute numbers with percentages, mean ± standard deviation (SD), or median with interquartile range (IQR). Groups were compared using the Student's t-test or the Pearson χ^2 test, and with the Mann-Whitney U test for non-normally distributed variables. Two-sided statistical significance was set at a P level <0.05. Crude incidence rates were calculated with data from the 2011 census (ISTAT, 2011). Standardized rates were obtained by the direct method with 10-year age grouping of the Italian (ISTAT, 2011) and European population (EUROSTAT, 2011) as standard. The risk of outcome events at 30 days, 1 year, and 5 years was measured using the Kaplan–Meier method. Comparisons of stroke recurrence and overall survival probability between patients with and without AF and between NDAF and PDAF were performed by the log-rank test. Age, sex, AF type, NDAF, NIHSS score at onset, and the lack of premorbid antithrombotic treatment were used as covariates in the Cox regression analysis in order to identify predictors of mortality.

Chapter III: Incidence, characteristics, short- and long-term prognosis of FEIS in a population-based registry

RESULTS

Among the 1,280 patients with FES included in the registry, 919 (71.8%) had a FEIS (52.8% women; mean age±SD, 76.5±12.0 years); women were 6.8 years older at FEIS onset as compared with men (79.7±10.8 vs 72.9±12.2 years; P<0.0001). The crude incidence rate of FEIS was 102.68 per 100,000 person-years (95% CI, 96.15-109.53), 93.89 (95% CI, 86.23-102.01) per 100,000 person-years when standardized to 2011 Italian population, and 79.09 (95% CI, 71.49-87.27) per 100,000 person-years when standardized to the 2011 European population. Arterial hypertension (76.2%) and AF (32.0%) were the most prevalent vascular risk factors in patients with FEIS. The case-fatality rate (CFR) of FEIS patients was 18.0% at 30 days, 28.2% at 1 year, and 43.4% at 5 years. The 5-year cumulative probability of survival in patients with FEIS was 56.6%. The Cox regression analysis, adjusted by sex, age, and vascular risk factors, showed that AF and diabetes mellitus were independent predictors of mortality at 30 days and at 1 year. Out of 754 (82.0%) patients that survived more than 30 days after the event, 64 (8.4%) patients had a FEIS recurrence, 22 (2.9%) a transient ischemic attack, and 15 (2.0 %) a myocardial infarction. The 5-year cumulative probability of recurrent ischemic strokes in patients with a FEIS was 7.1%.

CONCLUSIONS

We found in our population a fairly low incidence of FEIS, low rates of vascular follow-up events, and similar CFRs compared to concurrent registries. These results are likely due to improved control of vascular risk factors, effective primary preventive measures, and improved ischemic stroke management during the acute phase.

Chapter IV: Epidemiology of ischemic stroke subtypes according to TOAST criteria

RESULTS

Among the 919 patients with a FEIS included in the registry, the distribution of etiologic subtypes according to TOAST criteria was as follows: LAA (118, 12.8%), CE (321, 34.9%), small artery occlusion (SAO) (109, 11.9%), other causes (OC) (43, 4.7%), undetermined causes (UND) (328, 35.7%). Patients with CE were older at FEIS onset (79.28±10.21 years) and those with OC were younger (62.28±16.86 years) with respect to patients with LAA (74.49±11.40 years), SAO (70.75±11.93 years) and UND (76.50±10.54 years) (P<0.001). The proportion of arterial hypertension (P<0.001), AF (P<0.001), hypercholesterolemia (P=0.009), cigarette smoking (P<0.001), and coronary heart disease (P=0.013) varied significantly among the different etiologic subtypes. In particular, arterial hypertension was more frequent in patients with SAO (85.3%), and in those with CE (80.4%), hypercholesterolemia was more frequent in patients with SAO (28.4%) and in those with LAA (28.0%), while it was less frequent in CE (16.5%) and in those with OC (14.0%), cigarette smoking was more frequent in patients with OC (32.6%) and less frequent in those with CE (8.4%), and coronary heart disease was more frequent in patients with CE (19.9%) and in those with SAO (17.4%). The proportion of AF was 78.8% in CE, and 12.5% in UND. The distribution of diabetes mellitus and peripheral artery disease was similar among FEIS etiologic subtypes. Stroke was more severe (median [IQR] NIHSS at onset, 7 [4-15]) and more disabling (median [IQR] mRS score at discharge; 3 [2-5]), in patients with CE with respect to those with other etiologic subtypes (P<0.001 for all comparisons). The highest overall incidence rate was found in the CE subtype (35.86 per 100,000 person-years; 32.47 per 100,000 person-years after standardization by the 2011 Italian population; 29.96 per 100,000 person-years after standardization by the 2011 European population).

Patients with CE strokes had the highest 30-day (26.5%), 1-year (40.8%), and 5-year (56.7%) CFRs with respect to other subtypes (P<0.001). After 5 years, the highest probability of stroke recurrence was found in CE (8.7%), followed by OC (4.7%) and LAA (4.2%), whereas the lowest recurrence rate was in SAO (1.8%) and in UND (1.8%). The highest 5-year survival was found in SAO (80.7%), followed by UND (61%) and LAA (56.8%), while the lowest was in CE (43.3%). The multivariate Cox regression analysis including age, sex, and etiologic subtypes, showed that CE was an independent predictor of morality at 1 year, while SAO was inversely associated with mortality risk at 30 days and 1 year, and was mostly driven by the higher stroke severity in patients with CE strokes.

CONCLUSIONS

This study shows that CE is the most common cause of stroke. Given the higher stroke severity and the poorer outcomes associated with CE, effective preventive measures including prevention, detection and treatment of cardiac risk factors might contribute to a significant reduction of the overall stroke burden. Moreover, since the correct identification of stroke etiology is of utmost importance for effective secondary prevention, further efforts are needed to reduce the proportion of patients with UND.

Chapter V: Contribution of atrial fibrillation to the incidence and prognosis of first-ever ischemic stroke

RESULTS

During the study period we identified 919 FEIS in the resident population. After the exclusion of 9 patients without ECG evaluation, AF was documented in 294 (32.3%) of the remaining 910 patients. One hundred eighty-eight patients (63.9%) were women; mean age±SD at stroke onset was 82.1±8.1 years (83.2±7.6 years in women and 80.1±8.5 years in men; P=0.001). AF was paroxysmal in 64 patients (21.8%) and permanent in 230 (78.2%). The prevalence of AF increased with age in both sexes, from 6.5% in patients younger than 60 years up to 52.9% in those 90 years and older and was higher in women than in men in all age groups.

Stroke at onset (median NIHSS score at onset [IQR]: 9 [4-17] vs 5 [3-10]; P<0.001) and at discharge (median NIHSS score at discharge [IQR]: 5 [2-11] vs 3 [2-4]; P<0.001) was more severe and more disabling (median mRS score at discharge [IQR]: 4 [3-5] vs 3 [2-4]; P<0.001) in patients with AF than in those without the arrhythmia. Two hundred eighty-nine patients (98.3%) with AF and a premorbid CHA2DS2VASc score ≥2 were at high risk of thromboembolic events. At stroke onset 123 patients (41.8%) were on antiplatelets and 73 (24.9%) on a vitamin K antagonist, and only 26.0% had an INR value in the therapeutic range. The 30-day, 1-year and 5-year CFRs were about two-fold higher in patients with AF than in those without the arrhythmia. The probability of fatal and nonfatal recurrent strokes was higher in patients with AF compared to those without the arrhythmia at 1 year (4.4% vs 3.4%; log rank test P<0.001), while it was similar at 5 years (7.5% vs 7.0%; log rank test P=0.921). In patients with AF the probability of survival was significantly lower in AF patients than in those without at 1 (58.2% vs 79.4%; log rank test P<0.001) and 5 year (38.4% vs 66.1%; log rank test P<0.001). The Cox analysis, including age, sex, AF type, premorbid antithrombotic treatment and stroke severity at onset according to the NIHSS score, showed that the absence of premorbid antithrombotic treatment at stroke onset at 30 days, and stroke severity at 30 days and at 1 year were independent predictors of mortality.

When comparing epidemiological data of the recent 2011-2013 registry with those of 1994-1994, we found a 1.2 years increase of the overall mean age at FEIS onset (from 75.3±10.7 to 76.5±12.0), that was mainly due to the increase of the mean age in women (from 77.0±10.1 to 79.7±10.8 years in women; from 73.4±11.0 to 72.9±12.2 years in men), a decrease from 82.6% to 71.8% of the relative proportion of FEIS paralleled by a 75% decrease of FEIS incidence (incidence rate ratio [IRR] 0.43; 95% CI 0.40-0.46; P<0.001), and decrease in 30-day and 1-year mortality (30-day standardized mortality ratio [SMR] 0.74; 95% CI 0.68- 0.80; 1-year SMR 0.75; 95% CI 0.70-0.79). While, from 1994-1998 through 2011-2013 there was an overall 31.3% (from 24.6% to 32.3%; P<0.001) increase of AF prevalence, a 36.4% increase of arterial hypertension (from 61.6% to 84.0%; P<0.001), a 80.4% decrease of cigarette smoking (from 18.9% to 3.7%; P<0.001), a 53.2% decrease of coronary heart disease (from 34.2% to 16.0%; P<0.001), and a 55.4 % decrease peripheral artery disease (from 16.8% to 7.5%; P<0.001).

When comparing the overall crude incidence rate of FEIS among patients with AF in the present study with that reported in the previous one we observed a 44% reduction of the incidence rate ratio (IRR 0.56; 95% CI 0.49–0.64; P<0.0001), and a decrease in 30-day and 1-year mortality in patients with and without AF, with a slightly more evident reduction in

patients without AF (30-day SMR 0.62; 95% CI 0.53- 0.71; 1-year SMR 0.68; 95% CI 0.61-0.75) than in patients with AF (30-day SMR 0.70; 95% CI 0.61-0.78; 1-year SMR 0.73; 95% CI 0.65-0.79), while the cumulative probability of fatal and nonfatal stroke recurrences at 1 year in patients without AF (from 4.7% to 3.4%; P=0.159) and in those with AF (from 6.9% to 4.4%; P=0.127) remained stable.

CONCLUSIONS

In patients with FEIS, the presence of comorbid AF is associated with higher stroke severity and disability, with a higher risk of short-term recurrence and with a lower survival probability.

Better diagnosis and management of atherothrombotic vascular risk factors contributed to the reduction of the FEIS incidence, nevertheless, the burden of AF increased over the last two decades suggesting the need for improved primary preventing measures targeting AF and related embolic complications.

Chapter VI: Contribution of newly diagnosed atrial fibrillation to the short- and long-term prognosis of first-ever ischemic stroke in a prospective population-based registry

RESULTS

Among the 294 patients with FEIS and AF, the arrhythmia was diagnosed after the stroke in 66 (22.4%) patients identified as NDAF and had already been diagnosed before the stroke in 228 (77.6%) patients identified as PDAF. Patients with NDAF represented 7.3% of all FEIS patients. The prevalence of NDAF increased from 6% in patients aged 60-69 years to 11.5% in those aged 90 years and over, while the prevalence of PDAF increased from 11.2% in patients aged 60-69 years to 41.4% in those aged 90 years and over, and was slightly higher in women than in men in both age groups. Mean age and vascular risk factors profile was similar in patients with NDAF and PDAF. Patients with NDAF had more severe strokes at onset (median NIHSS score [IQR]: 12 [5-15] vs 8 [4-16]; P=0.028), a higher proportion (39.4% vs 29.8%; P<0.001) of TACI, and greater residual disability and dependence at discharge (median mRS score [IQR]: 4 [3-6] vs 3 [2-5]; P<0.001) compared to patients with PDAF. Both groups of patients had similar proportions of insular involvement and of left- and right-sided insular infarcts. The 1-year CFR was significantly higher in NDAF than in PDAF patients. At 1 year the cumulative probability of nonfatal and fatal stroke recurrence was higher in PDAF than in NDAF patients (5.3% vs 1.5%; P=0.010, log rank test) as the probability of survival (61.4% vs 47.0% vs; P= 0.033, log rank test). Contrariwise, at 5 years, the cumulative probability of nonfatal and fatal stroke recurrence (7.9% vs 6.1%; P=0.607, log rank test) and the probability of survival (39.9% vs 33.3%; P=0.079, log rank test) did not differ significantly. Causes of death were similar at all time-points in both groups. At the Cox regression analysis the main determinants of FEIS mortality were stroke severity at onset and the lack of premorbid antithrombotic treatment, whereas NDAF *per se* was not an independent predictor of mortality.

CONCLUSIONS

In our population-based study, 22.4% of AF-related FEIS occurred in patients with NDAF. Since in NDAF and PDAF patients we found similar proportions of insular involvement, of vascular risk factors, and of long-term stroke recurrences we believe that our data may support the cardiogenic origin rather than the neurogenic origin of NDAF.

Although in only 7.3% of FEIS the newly diagnosed arrhythmia could have been potentially preventable, community AF screening initiatives in individuals potentially at risk together with the implementation of preventive thromboembolic strategies and the education of patients to maintain treatment adherence might contribute to reduce not only stroke occurrence but also its severity and prognosis.

Abstract

BACKGROUND: Stroke is the leading cause of disability and the second most common cause of death worldwide.Stroke registries are important to formulate guidelines and to improve health services and medical assistance.

AIM: To obtain recent epidemiological data on first-ever ischemic stroke (FEIS) **(Chapter III)** and of ischemic stroke etiologic subtypes**(Chapter IV);** to evaluate the contribution of atrial fibrillation (AF) to the incidence and prognosis of FEIS, and to evaluate possible epidemiological changes over two decades comparing these recent data on AF with those from the 1994-1998 study **(Chapter V)**; to evaluate the contribution of AF diagnosed after stroke onset (newly diagnosed atrial fibrillation; NDAF) to the incidence, and prognosis of FEIS **(Chapter VI)**.

METHODS: All the residents in the district of L'Aquila diagnosed with a FEIS in 2011-2013 were included in a prospective population-based registry and were followed up to 5 years. Case-fatality and vascular events were assessed.

RESULTS: Among the 1,280 patients with first-ever stroke included in the registry, 919 (71.8%) had a FEIS(52.8% women; mean age±SD, 76.5±12.0 years);women were 6.8 years older at FEIS onset as compared with men. The crude incidence rate of FEIS was 102.68 per 100,000 person-years, 93.89 when standardized to 2011 Italian population, and 79.09 when standardized to the 2011 European population. The case-fatality rate (CFR) of FEIS patients was 18.0% at 30 days, 28.2% at 1 year, and 43.4% at 5 years. The 5-year cumulative probability of survival in patients with FEIS was 56.6%.
The distribution of etiologic subtypes according to TOAST criteria was as follows: large-artery atherosclerosis (12.8%), cardioembolism (CE; 34.9%), small artery occlusion (11.9%), other causes (4.7%), undetermined causes (35.7%). CE strokes had the highest incidence rate, were more severe and more disabling, had the highest 30-day, 1-year, and 5-year CFRs, and the lowest 5-year survival with respect to those with other etiologic subtypes. The Cox analysis showed that CE was an independent predictor of morality at 1 year, that was mostly driven by the associated higher stroke severity.
Among 919 FEIS, 9 patients without ECG evaluation were excluded and AF was documented in 32.3%. Stroke severity, post-stroke disability, and 30-day, 1-year and 5-year CFRs were significantly higher in patients with AF than in those without. The arrhythmia was NDAF in 22.4% and PDAF in 77.6%. Mean age and vascular risk factors profile was similar in patients with NDAF and PDAF. Patients with NDAF had more severe strokes, greater residual disability discharge, and higher CFRs.
From 1994-1998 to 2011-2013 there was a decrease from of the relative proportion of FEIS, a 75% decrease of FEIS incidence, and a decrease in 30-day and 1-year mortality. While, there was an overall 31.3% increase of AF prevalence, and a 44% reduction of the incidence rate ratio and a decrease in 30-day and 1-year mortality in patients with and without AF.

CONCLUSIONS: We found in our population a fairly low incidence of FEIS, low rates of vascular follow-up events, and similar CFRs compared to concurrent registries. CE is the current most common stroke etiological subtype and AF is the most prevalent risk factor in this group. These results are likely due to effective primary preventive measures, and improved

ischemic stroke management during the acute phase, nevetheless, a better diagnosis and management of atherothrombotic vascular risk factors contributed to the reduction of the FEIS incidence over two decades, and to the increase of CE- and AF-related strokes.
Given the high burden of stroke due to CE and in particular to AF, primary preventive measures targeting detection and treatment of cardiac risk factors, together with the implementation of preventive thromboembolic strategies and the education of patients to maintain treatment adherence might contribute to reduce not only stroke occurrence but also its severity and prognosis.

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Chapter I

1.1 Introduction and background

Stroke is the leading cause of disability and the second most common cause of death worldwide (Feigin et al., 2015). While the incidence of stroke is decreasing in advanced economies, the trend is increasing in alarming rate in low- and middle- income countries. With the population aging the total stroke incidence and the burden of post-stroke disability might increase over time. One prediction, calculated from the age-specific stroke incidence reported in international studies, suggested that worldwide total stroke burden would increase 5-fold from 13 milion disability- adjusted life in the 1990s to 68 million disability adjusted life years (DALYs) by 2020 (WHO, 2004). Anyhow, age-specific stroke incidence rates may be declining sufficiently to compensate for changing demographics; serial population stroke studies conducted during the past 3 decades have demonstrated decreasing stroke incidence despite increasing population ages.

Demographic changes and implementation of therapeutic strategies could have modified also the distribution of the different etiologies of ischemic strokes over time. Recent evidence suggests that in the last two decades there has been an increase in ischemic stroke due to cardioembolism (CE) and a reduction of those due to large-artery atherosclerosis (LAA) in Whites and in high-income countries (Ornello et al., 2018). These changes derived from the greater diffusion of antihypertensives and statins as preventive treatments (Bogiatzi et al., 2014, Yiin et al., 2014) that may have contributed to reduce ischemic stroke due to LAA, and from the ageing of the population and the still widespread underuse of anticoagulants particularly in the elderly that contributed to increase CE stroke. Indeed, atrial fibrillation (AF), that is the major risk factor for CE strokes, is highly age dependent; with the greater life-expectancy the absolute number of individuals with AF is anticipated to increase substantially in the coming decades. Data indicates that AF incidence is increasing,

leading projections of an increase in AF prevalence by at least 2.5-fold by 2050 in the United States (Go et al., 2001; Ball et al., 2013). The consequences of this increase in AF prevalence on the incidence of AF-related stroke is still not well studied and it will depend on the effectiveness of AF detection, and on the effect of the implementation of prevention treatment with the new oral anticoagulants (NOACs).

1.1.1 Definition

Despite continuous progresses in the understanding of stroke pathophysiology and recognition, only in 1980 a consensus definition was reached defining stroke as "*rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin*" (Aho et al., 1980). Along with steady advances in diagnostic techniques it soon became clear that the current definition and the 24 hours criterion used to discriminate stroke from transient ischemic attack (TIA), was misleading and unreliable. Timely opportunity to assess *in vivo* correlates of irreversible brain injury through widespread use of neuroimaging techniques, such as magnetic resonance imaging (MRI) with diffusion-weighed imaging (DWI), warranted a revision of the aforementioned criteria. The Stroke Council of the American Heart Association/American Stroke Association in 2013 released an update of ischemic stroke definition as "*an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction*" and central nervous system (CNS) infarction as "*brain, spinal cord, or retinal cell death attributable to ischemia, based on: 1. Pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2. Clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded*" (Sacco et al., 2013). The fundamental revision of prior reports is a broader definition of stroke encompassing any evidence of irreversible brain

injury regardless of the presence of clinical symptoms. The key components of the new stroke definition are consistently in line with a 2009 statement from an AHA/ASA committee redefining TIA as "*a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction*" (Easton et al., 2009). Hence, the new tissue-based definition of infarction relies on neuroimaging confirmation or the classic 24 hours threshold, if early imaging is unavailable. The "acute cerebrovascular syndrome" umbrella term includes potential diagnoses of ischemic stroke, TIA and hemorrhage in the first 24 hours or until neuroimaging is performed. The update definition will have major impact on epidemiological surveillance of incident, prevalent and fatal strokes possibly leading to a decline in stroke mortality largely driven by inclusion of less severe strokes in the total count of stroke cases. These changes must be considered in future prediction models of national and international stroke trend statistics to avoid misleading results due to reclassification of stroke and updates in disease coding systems.

1.1.2 Epidemiology

Stroke is a major public health issue in terms of human, social and economic burden worldwide. Demographic, social and epidemiological shifts turned stroke into a global epidemic by no means limited to high-income countries, thus highlighting a worrisome trend. In 2005, 26 million first-ever strokes (FES) occurred with 5.7 million of deaths attributable to stroke (Strong et al., 2007). Only in the US, approximately 795.000 incident strokes take place yearly with a new stroke occurring every 40 seconds and a stroke death every 4 minutes (Mozaffarian et al., 2015). In 1993, the World Bank sponsored the Global Burden of Disease (GBD) study in order to provide consistent estimates of incidence, morbidity and mortality worldwide for over 130 major diseases. The most remarkable introduction was a new measure of disease burden quantified in terms DALYs, namely the number of years of healthy life lost because of a specific medical condition. In the year

2010, stroke ranked as the second leading cause of death and the third most common cause of DALYs worldwide (Lozano et al., 2012; Murray et al., 2012). It is worth noting that in some western countries stroke has dropped to the fifth cause of death possibly highlighting recent advancements in prevention strategies and broad access to healthcare facilities, mostly limited to high- income countries (Kochanek et al., 2014). Accordingly, WHO estimates for 2001 reported that stroke deaths in low and middle-income countries account for 85.5% of stroke deaths worldwide with seven-fold higher DALYs compared to high-income countries (Mathers et al., 2006). A 2009 systematic review by Feigin et al. analyzed 56 population-based studies reporting on incidence and prevalence stroke rates in two income country groups (high income and low to middle income countries according to the World Bank's country classification) over four decades. Age- adjusted stroke incidence rate declined by up to 42% in high income countries (from 163/100.000 person-years in 1970-79 to 94/100.000 person-years in 2000-08) and paralleled a two-fold increase in low to middle income countries (52 per 100.000 person-years in 1970-79 to 117/100.000 person-years in 2000-08); these figures exceeded for the first time the rate reported in high-income countries over the last decade (Feigin et al., 2009). These trends in low to middle income countries were largely driven by the older population group (>75 years) but also the younger group (<75 years) disclosed a similar increase in stroke incidence rates (four-fold increase > 75 years, two-fold increase <75 years). Though several biases can undermine this finding in low-income countries, such as improved health care system and increased referral to health facilities, these are not likely to account for consistent diverging trends compared to high-income countries. Ageing of the population, demographic growth, changes in lifestyle and modifiable risk factors may all underpin the increasing number of incident strokes in low to middle-income countries. Overall in 2010, incident strokes decreased to 16.9 million cases worldwide (from 26 millions in 2005) out of which 69% took place in low to middle-income countries (Feigin et al., 2014). GBD estimates of stroke incidence in 2010 ranged from 60/100.000 person-years in Kuwait to 504/100.000 person-years in Lithuania, further

upholding a statistical significant decrease in high-income countries by 12% and a non-statistical significant 12% increase in low to middle- income countries from 1990 to 2010 (Feigin et al., 2014). Data about incidence rates according to major stroke subtypes are scarce and limited to high-income counties: from 1980-2008 a drop by 11% of ischemic stroke incidence (p=0.53) along with a consistent reduction on primary intracerebral hemorrhage (ICH) was reported (p=0.45) (Feigin et al., 2009). Interestingly, a transient rise in spontaneous intraparenchymal and subarachnoid hemorrhage (SAH) was observed in the early 1990s as a reflection of more complete case ascertainment ensuing widespread introduction of neuroimaging techniques.

Converging evidence points towards a steady decrease in stroke mortality since the early 20^{th} century with a steeper decline from the 1970s in the US (Lackland et al., 2014). Declining stroke mortality rates were further borne out by many other studies exploring secular mortality trends across different countries. WHO mortality data from 1950 to 2005 in 48 countries worldwide showed a reduction by 50% in many countries, up to 85% in Japan (Mirzaei et al., 2011). Different data of trend downturns possibly reflect environmental factors as well as effectiveness of prevention strategies. In Japan, holding the highest recorded mortality rate in 1957 (433 per 10^5 males), robust reduction in dietary salt intake from 360 mmol/day in 1950 to 187 mmol/day in 1988 is possibly responsible for lowering blood pressure levels and stroke deaths in at risk population (Kesteloot et al., 1992). The finding of decline in stroke mortality was reported in both high-income and low to middle- income economies: a 37% reduction in mortality rate was observed in high-income countries and 20% in low-income countries between 1990 and 2010 (Feigin et al., 2014). Nevertheless, substantial geographical variations were noted in the same time period with an unexpected increase of stroke mortality in sub-Saharan Africa, South Asia, central and Latin America standing in stark contrast with mortality trends worldwide (Feigin et al., 2014). The same investigators did not observe a strong correlation between the decline of

stroke incidence and mortality, suggesting a more complex interplay of factors as a key factor for stroke mortality decrease.

Yet, the reduction of stroke mortality seems to be primarily due to both a reduction in stroke incidence and improved case fatality rate. Interestingly, trend analysis of stroke mortality and recurrence rates follows similar timelines prompting a possible contributing role of secondary prevention in stroke mortality decline. A systematic review by Hong et al. assessed fatal and recurrent strokes in control arms of 59 randomized controlled trials (RCT) of secondary stroke prevention therapies from 1960 to 2009 (Hong et al., 2011). Recurrent stroke annual rates fell from 8.71%, in the trials launched 1960, to 4.98% in 2000, with an almost 50% reduction over 5 decades. As with FES, recurrence rate decline is greatly affected by improve risk factors management, underlining the suggestion that a significant proportion of strokes can be prevented. The more robust association found is between better blood pressure control and reduced stroke incidence and mortality rates. In the US a definite steeper decline in stroke deaths dates back in the 1960s when high blood pressure (HBP) recognition and blood pressure (BP) lowering campaigns took place (Moser 1983). Accordingly, the mean systolic blood pressure (SBP) in the US population declined from 131 mmHg, in 1960, to 122 mmHg, in 2008 (Burt et al., 1995; Wright et al., 2011). Increased awareness, effective healthcare planning strategies and prioritization on preventive strategies contributed to this remarkable public health achievement considering an estimated preventable 7.1 million deaths due to hypertension (WHO 2002).

Along with BP control, other modifiable stroke risk factors may possibly have played a key role in lowering stroke incidence and mortality. Research on the benefit of tight glucose control in diabetes mellitus provided conflicting results. A meta-analysis of 5 RCT investigating whether intensive treatment is beneficial on cardiovascular outcomes in diabetes mellitus patients showed a positive impact on coronary heart disease events but no significant effect on stroke (odds ratio: 0.93, 0.81-1.06) and all- cause mortality (Ray et al., 2009). As a consequence of converging evidence pointing towards a role of insulin resistance

to increased stroke risk, the Insulin Resistance Intervention After Stroke Trial (IRIS) addressed this issue (IRIS trial). Non-diabetic patients were given pioglitazone, an insulin resistance lowering medication, as a part of their secondary prevention therapy. The primary outcome was a composite of stroke recurrence and MI. Pioglitazone has been found to be associated with lower risk of stroke recurrence and MI after ischemic stroke or TIA compared with placebo (9.0% vs 11.8% after 4.8 years; OR 0.76; 95% CI, 0.62– 0.93; P=0.007); however, treatment with pioglitazone was not associated with a lower risk of stroke recurrence alone (6.5% vs 8.0%; OR 0.82; 95% CI 0.61–1.10; P=0.19) (Kernan et al., 2016).

AF is a significant risk factor for stroke with highest burden of disease in the elderly. Scarce data exist about secular trends in incidence and prevalence of AF. In the Framingham Study, the prevalence of AF increased steadily in the overall population with age-adjusted prevalence rates of 3.2%, from 1968 to 1970, to 9.1%, from 1987 to 1989 (Wolf et al., 1996). These findings compare closely to those reported from other studies. A community-based study of secular trends of AF among adult residents in Olmsted County, Minnesota, disclosed an age and sex adjusted AF incidence rate increase from 3.04/1000, in 1980, to 3.68/1000 person-years, in 2000 (Miyasaka et al., 2006). Incidence rise was statistically significant (P=0.014) with a 12.6% increase over 21 years. Multifactorial contributions are advocated in this trend, but a possible ascertainment bias cannot be overlooked since telemetry and serial electrocardiograms (ECG) have become more and more common. The apparent increase of prevalent cases of AF stands quite in contrast with the decline in incident strokes but it should be considered in the implementation in primary and secondary prevention therapies. Since 1989 a wealth of data coming from clinical trials unveiled the superiority of oral anticoagulants (OACs) over antiplatelet agents among people with AF. Meta-analytic results indicated that OACs lower the risk of all strokes (odds ratio= 0.68) and ischemic strokes (odds ratio= 0.53) compared to aspirin alone (Aguilar et al., 2007). Mounting evidence supporting clinical benefit of OACs in AF determined a significant

increase in OAC prescription with a rise in warfarin use from 24.5%, in 1992, to 56.3%. in 2002 (Lakshminarayan et al., 2006). Data from the 'Get with the Guidelines-Stroke Program' also showed a rise in the proportion of AF patients treated with OAC at hospital discharge from 2003 to 2009 (28% to 69.1%), most likely as a reflection of increase physician recognition of OAC clinical benefit (Reeves et al., 2011). Nevertheless, the overall effect of OAC on all-cause mortality (odds ratio= 0.99) fatal and disabling stroke (odds ratio= 0.79) was not statistically significant, therefore further studies are warranted to assess AF contribution to decline in stroke deaths (Aguilar et al., 2007).

Several other factors have been claimed to explain the observed trend in stroke mortality. The widespread introduction of advanced neuroimaging techniques and, above all MR imaging, enabled increased recognition of less fatal strokes over time. A better case ascertainment would then result in apparent case-fatality rate (CFR) decline as a reflection of inclusion of less severe strokes.

Although stroke incidence and mortality are globally decreasing, stroke burden in terms of prevalent cases and DALYs are expected to increase in both high–income and low to middle-income countries with a predicted 70 million stroke survivors and 200 million DALYs lost by 2030 (Feigin et al., 2014). Stroke prevalence depends on incidence, mortality and mean length of survival after stroke. Despite prevalent cases having a major impact on economic and social burden, data regarding stroke prevalence are scarce and ascertainment is often incomplete. A report from the World Health Organization in 2005 estimated stroke prevalence from mortality statistics (Truelsen et al., 2006). The highest prevalence rates were reported in Czech Republic, Greece, Portugal, and Slovenia and the lowest in Cyprus, Lithuania, Poland, and Slovakia for male population. Among women the highest prevalence rates were estimated for Czech Republic, Greece, Hungary, Portugal and the lowest in Cyprus, France, Lithuania, Poland, and Slovakia. A systematic review analysed data from 9 prevalence studies across different countries worldwide. Age- standardized prevalence rates ranged between 46.1 (Four regions across US) to 73.3/1000 inhabitants (L'Aquila,

Newcastle) with remarkable difference according to gender (58.8 to 92.6/1000 in males, 32.2 to 61.2/1000 in females) (Feigin et al., 2003). GBD estimated prevalence ranged from 82 (Burundi) to 1187 (Canada) per 100.000 people with roughly 33 million prevalent stroke cases in the year 2010 (Feigin et al., 2014). These data are most noticeable in high-income countries where stroke prevalence increased by 27%, most of such a rise being driven by the older segment of the population. Besides, stroke prevalence increased in low to middle-income countries as well (+8.5%), though this change was not statistically significant. Differences in the management of acute stroke, access to health-care services and early case fatality rate are presumably responsible for different prevalence according to income level. Yet, accurate estimates of prevalent cases are still missing and desirable, as they would allow for a careful health-care planning and projections about stroke burden in the future years. The importance of stroke related disability cannot be overemphasized in the truly assessment of disease burden. The offset of mortality reduction is the increasing number of stroke survivors with stroke related disability. In attempt to address this issue, the DALYs provide a powerful tool to fill the gap between simply calculated years of life lost and the weighted factor of disability or poor health into the projected years of life. In 2010, 102.2 million DALYs lost came from stroke worldwide (out of which 78% in low to middle-income countries) (Feigin et al., 2014). Country specific stroke burden showed significant geographical variations with 398 (Canada) to 5227 (Afghanistan) DALYs lost per 100,000 inhabitants (Feigin et al., 2014). More in-depth analysis revealed that age specific stroke burden is out of proportion in low to middle-income countries where DALYs in <75 years population are almost five-fold higher than those in high-income countries (61,013,232 and 12,280,317, respectively) (Feigin et al., 2014). Increasing demand for more specific health-care planning and resource rationalization warrants well-design comparable epidemiological studies to better outline natural trends in stroke statistics, economic and social burden of disease.

1.1.3 Stroke risk factors

1.1.3.1 Non modifiable risk factors

Age is the most important risk factor for stroke with stroke rate almost doubling each 10 years after age 55 (Wolf et al., 1992; Feigin et al., 2003). Exponential increase of stroke occurrence with ageing was noted also in young adults aged 15 to 49 years (Putaala et al., 2009; Truelsen et al., 2006). Age specific incidence of ischemic stroke subtypes shows a wide degree of variability. In a single center consecutive cohort, cardioembolic stroke due to structural abnormalities such as patent foramen ovale (PFO) and mitral valve prolapse was diagnosed in 24% of young stroke patients (age 16-49) (Cerrato et al., 2004). In another single center hospital-based cohort of young adults with ischemic stroke, cardioembolism was found in 34% of cases, while atherothrombosis accounted for 12% of cases and non-atherosclerotic vasculopathy, including dissection, for 14% of cases (Rasura et al., 2006). Also, very old patients are more likely to suffer cardioembolic strokes mainly because of increased prevalence of AF with ageing (Arboix et al., 2006). Atherothrombotic strokes and small vessel disease are more common in middle-aged patients, possibly for the contribution of increase prevalence of hypertension, smoking, obesity and diabetes (Cerrato et al., 2004; Arboix et al., 2006). Sex is another non-modifiable risk factor in outlining overall stroke risk. Stroke incidence is 33% higher in males than in females whilst significant drop in male to female incidence ratio occurs in older age bands, this discrepancy being largely driven by greater life expectancy and increased risks exposure in women (Appelros et al., 2009). There are several epidemiological studies providing insights into stroke risk differences according to race and ethnicity. In the Northern Manhattan Study age- adjusted incidence rate showed large variability according to race/ethnicity (88 in whites, 149 in Hispanics, and 191/100.000 people per year in blacks) (White et al., 2005). Even stroke mortality is five-fold higher in blacks aged 45-55 years compared to whites, though environmental factors and economic income can account for up to 38% of excess stroke mortality among blacks

(Gillum, 1988; Otten et al., 1990). According to some reports, relative rates of various etiological subtypes also seem to be affected by race: whites have a greater proportion of cardioembolic strokes than Hispanics and blacks; conversely, they show a higher proportion of intracranial atherosclerotic strokes and a non-significant trend towards higher small vessel disease strokes (White et al., 2005). Similarly, Asians (Chinese and Japanese above all) have high stroke incidence rates but untangling the puzzle of genetic profile and environmental factors is fraught with difficulties (He et al., 1995). For instance, Japan unexpectedly highest mortality rate worldwide (433 per 10^5 in men in 1957) is deemed to be mainly caused by uncontrolled hypertension rather than genetic susceptibility.

Genetic risk factors

Genetic variability may contribute to stroke risk by means of several mechanisms (Boehme at al., 2017). First, single gene disorders may have stroke as their primary or unique manifestation, as is in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Chabriat et al., 2009). Second, single gene disorders may cause a multisystem disorder, such as sickle cell anemia, of which stroke is one of the manifestations. Third, some common variants of genetic polymorphisms, including 9p21 variants (Matarin et al., 2008), have been associated with a significant, yet modest, stroke risk. Fourth, genetic causes of conventional stroke risk factors, such as atrial fibrillation, diabetes mellitus, or arterial hypertension, are obviously associated with stroke risk (Gretarsdottir et al., 2008). In those cases, genetic studies might help to distinguish stroke subtypes and contribute to patient management (Boehme et al., 2017).

Currently, heredity is generally considered a nonmodifiable risk factor; however, some genetic factors may even be modifiable, if not curable, already; for example, those with sickle cell anemia can be treated with exchange transfusion to reduce stroke risk. Genetic factors may also be modifiable because environmental factors may also interact with genetic

mutations; thus, those with a predisposition to diabetes mellitus or hypertension could engage in dietary and other lifestyle modifications to reduce their risk of disease (Boehme et al., 2017).

1.1.3.2 Modifiable risk factors

Hypertension

Blood pressure is the single most important independent risk factor for stroke. The INTERSTROKE study suggests that hypertension accounts for 34.6% of stroke risk factor burden worldwide (O'Donnell et al., 2010). Evidence underscoring the association between stroke and HBP dates back to the 1960s (Freis, 1960). It has been consistently shown that the relationship between hypertension and stroke is strong, linear, graded and without any evidence of a threshold down, at least up to 115/75 mmHg (Lewington et al., 2002). A meta-analysis by Lewington and co- workers including nearly 1 million adults found that each incremental rise of 20 mmHg in SBP or 10 mmHg in diastolic blood pressure (DBP) is associated with twice as high stroke mortality rate (Lewington et al., 2002). The correlation holds true for all ages but the strength of the association declines in the elderly. This finding is the most noticeable according to estimates reported by the Framingham Study investigators of nearly 90% lifetime hypertension risk for non-hypertensive population at age 55 or 65 (Vasan et al., 2002). The benefit of hypertension treatment is underpinned by several studies including a meta-analysis of 147 trials concluding that a 10 mmHg reduction of SBP yields a 41% reduction in stroke risk (Law et al.,2009). Hypertension exerts a major impact on both small vessel and large vessel stroke subtypes, as shown by many observational studies (Arboix et al., 2004).

Cardiac disease

AF is by far the most common cardiac condition associated with stroke (Pistoia et al., 2016). For each decade of life above 55 years, the risk of developing atrial fibrillation more than doubles (Benjamin et al., 1994). People with atrial fibrillation carry a three to five-fold relative risk of ischemic stroke compared to those without AF (Wolf et al., 1991; Andrew et al., 2013). Moreover, with advancing age the relative contribution of other known cardiovascular risk factors tends to decline except for AF being the solely independent risk factor for stroke in people aged 80- 89 years (Wolf et al., 1991). Results from the Framingham Study showed that attributable stroke risk for AF increases from 1.5%, at age 50-59, to 23.5%, at age 80-89 (Wolf et al., 1991). Additional cardiac conditions yield an increased risk of stroke; right-to-left atrial shunt is a well-recognized cause of paradoxical embolism where emboli originating in the systemic circulation gain access to arterial circulation through cardiac abnormal communications such as PFO. Atrial septum aneurysm (ASA) has also been found to be more prevalent among young patients with cryptogenic stroke (CS) compared to control group (odds ratio=4.3) (Cabanes et al., 1993). Myocardial infarction (MI) has long been recognized as a risk factor for stroke. Acute coronary events account approximately for 1.8% of all FES (Mooe et al., 1999). Conversely, stroke complicates MI outcome in 1.2% of cases (Wienbergen et al., 2001). Other cardiac abnormalities yield increase risk of ischemic stroke such as cardiac valve disease, left ventricular fraction less than 40%, isolated arrhythmias other than AF, prosthetic valves and cardiac tumors but the relative contribution of each condition varies across studies (Pujadas et al., 2004).

Diabetes mellitus

Diabetes is an independent risk factor for stroke. Diabetes is increasing throughout the world with worrisome figures in most Western countries: in 2010, roughly 20.7 million adults were affected by diabetes in the U.S. with an estimated prevalence of about 50% in people aged >

65 years (Mokdad et al., 2001; Centers for Disease Control and Prevention, 2011). Approximately 20% of patients with diabetes will die from stroke. Pooled data from 102 prospective studies outlined a two-fold excess risk for ischemic stroke in diabetes patients (HR= 2.27) (Emerging Risk Factors Collaboration, 2010). Interestingly, diabetes exerts a time-dependent effect on stroke risk with 3% increased risk by each year of disease duration (Banerjee et al., 2012). Diabetes is presumably involved in early stages of vascular disease, as prompted by the association found between impaired fasting glucose, beginning at 110 mg/dL, and increased age-adjusted stroke rate (9.6 vs. 8.2/10.000 person-years in impaired fasting glucose and controls, respectively) (Sui et al., 2011). In the Greater Cincinnati/Northern Kentucky Stroke Study, stroke risk in diabetic patients consistently increased in all ages with a maximum in the 45 to 54 years age group in whites (RR= 5.3) (Kissela et al., 2005). The most common stroke etiological subtype in diabetic patients is small vessel disease followed by atherothrombotic stroke (Zhang et al., 2007; Tuttolomondo et al., 2008). Notably, many processes other than blood glucose level may play a role in atherosclerosis through direct effect on vessel walls, namely insulin resistance and hyperinsulinemia (Shinozaki et al., 1996).

Converging evidence suggests that insulin may act enhancing arterial smooth cell proliferation, cholesterol synthesis and low density lipoprotein (LDL) deposition in atherosclerotic plaques (Pfeifle et al., 1981; Stout et al., 1977; Oppenheimer et al., 1989).

Dyslipidemia

Despite clear positive association between high total cholesterol level and coronary heart disease, the role of dyslipidemia and stroke is still uncertain. The lack of overt association is underpinned by opposite effect on hemorrhagic and ischemic stroke risk. Beneficial effect in preventing ischemic stroke is offset by increased risk of intracranial hemorrhage. In the Multiple Risk Factor Intervention Trial (MRFIT) enrolling approximately 350.977 men aged

35-57, a positive association was found between low total cholesterol levels (<160 mg/dL) and deaths from non-hemorrhagic stroke along with a three-fold increase in hemorrhagic stroke deaths. Similarly, the Asia Pacific Cohort Studies Collaboration (APCSC) outlined a 20% increase in ischemic and 20% decline in hemorrhagic stroke risk by every 1 mmol/L (equal to 38.6 mg/dL) total cholesterol increase (Zhang et al., 2003). In the Women Health Study (WHS) ischemic stroke hazard ratio was 2.27 for high total cholesterol (> 244 mg/dL), 1.74 for high LDL-C (> 151 mg/dL) and 0.78 for high HDL-C patients (> 65 mg/dL) (Kurth et al., 2007). Likewise, the Hisayama Study, prospectively following- up 2351 adults free from cerebrovascular disease at baseline, found a positive association between high LDL cholesterol levels and atherothrombotic stroke subtype whereas the association with small vessel disease failed to reach statistical significance after multivariate adjustment (Imamura et al., 2009). On the other hand, high density lipoprotein (HDL-C) levels seem to play a protective role in patients at risk for ischemic stroke, this benefit being more robust in people aged >75 years (OR= 0.51) and atherothrombotic stroke subtype (OR= 0.20) (Sacco et al., 2001).

Higher mortality from hemorrhagic stroke in patients with low total cholesterol level is supposed to be supported by protective effect on hematoma expansion, increased integrity of vessels and resistance to rupture. Investigators from the Ibaraki Prefectural Health Study reported that patients with LDL cholesterol levels above 160 mg/dL had half the risk of dying from hemorrhagic stroke compared to those with LDL levels below 80 mg/dL (Noda et al., 2009). It is noteworthy that some studies revealed an inverse relationship between serum cholesterol levels and mortality from ischemic stroke (Smith et al., 2010; Olsen et al., 2007). Higher proportion of less severe non-cardioembolic strokes and protective effect of statins have been called into question to explain this relationship.

Cigarette smoking

Converging evidence points toward increase stroke risk in tobacco smokers, with relative risk being more than doubled compared to non-smokers (Kawachi et al., 1993; Wolf et al., 1988). Excess stroke risk in former smokers seems to level off and return to that of non-smokers 2 to 4 years after smoking cessation (Kawachi et al., 1993). Data from the Stroke Prevention in Young Women Study suggested a dose- response relationship between number of cigarettes per day and excess stroke risk (OR= 2.2 for 1-10 cigarettes/day, OR= 9.1 >40 cigarettes/day) (Bhat et al., 2008). A possible synergistic effect between tobacco smoking and other stroke risk factors, such as the use of oral contraceptives (OCs), has been described as well (WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1996). The odds of ischemic stroke are 1.3 for female smokers, 2.1 for females taking OCs and 7.2 for female smokers taking OCs (i.e. much higher than expected solely on the basis of each risk factor contribution alone). Smoking exerts both short term (pro-thrombotic influence on atherosclerotic plaques) and long-term detrimental effects (enhanced atherosclerotic process) on overall stroke risk (Burns et al., 2003). The impact on SAH is even more robust. Smoking yields a 2- to 4-fold increase in SAH risk especially among women, according to different studies (Kurth et al., 2003 a; Kurth et al., 2003 b; Feigin et al., 2005). Overall, pooled data from 32 studies provided a relative stroke risk of 1.5 with notable differences among stroke subtypes: 1.9 for cerebral infarction, 0.7 for hemorrhagic stroke and 2.9 for SAH (Shinton et al., 1989).

Obesity

Various lifestyle risk factors including obesity have been associated with increased stroke risk. Excess body weight is generally measured in terms of body mass index (BMI) as defined by body weight in kilograms divided by the square of height in meters (Kg/m^2): range values for overweight are 25 to 29 Kg/m^2 whereas > 30 Kg/m^2 defines obesity and > 40 Kg/m^2 morbid obesity. A meta-analysis including 900.000 adults from 57 prospective studies found a 40%

increase in stroke mortality rate for each 5 Kg/m^2 increase in BMI in people with a baseline BMI ranging between 25 and 50 whilst no association was found in the 15-24 BMI group (Prospective Studies Collaboration, 2009). Relative risk for ischemic stroke is 1.22 in overweight and 1.64 in obese adults but no excess risk was found for hemorrhagic stroke in a meta-

analysis, after controlling for other risk factors (Strazzullo et al., 2010). These results are not in keeping with a meta-analysis from the Japan Arteriosclerosis Longitudinal Study (JALS) group which found a positive association with hemorrhagic stroke both in men (HR= 2.51) and women (HR= 1.98) (Yatsuya et al., 2010 a). A positive and linear relationship between obesity and stroke was demonstrated for all major ischemic stroke subtypes, namely cardioembolic, lacunar and atherothrombotic (Yatsuya et al., 2010). Whether weight loss can prevent cardiovascular disease, including stroke, is matter of debate. Recently, the Swedish Obese Subjects trial highlighted a beneficial effect of bariatric surgery in declining overall stroke risk (adjusted HR= 0.66) over 10 to 20 years (Sjöström et al., 2013).

1.1.3.3 Nontraditional risk factors

Inflammation and infection

Levels of inflammatory biomarkers, and mostly high sensitivity C reactive protein (hs-CRP), have been associated with an increased risk of stroke as well as other cardiovascular diseases and all-cause mortality (Boehme et al., 2017). A meta- analysis of 54 prospective cohort studies found a 27% increase in the risk of ischemic stroke among subjects with increased levels of hs-CRP compared with those with normal levels (Kaptoge et al., 2010), while another meta-analysis found a 46% higher risk of ischemic stroke and no difference in the risk of hemorrhagic stroke (Zhou et al., 2016). However, a case-control genetic study found that the presence of single-nucleotide polymorphisms associated with elevated levels of hs-CRP did not increase the risk of stroke (Zacho et al., 2008). The association between

inflammation and stroke might result from the inflammatory character of atherosclerosis, thus being a simple epiphenomenon of vascular disease burden because of other conventional risk factors (Boehme et al., 2017); however, there is some evidence that inflammatory markers, such as hs-CRP, may interact with other immune mediators to activate platelets and complement proteins (Eisenhardt et al., 2009).

Inflammation may contribute to stroke risk through infection (Boehme et al., 2017). A prospective cohort study found that a composite measure of chronic infection, assessed by serologies against *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus 1 and 2, and cytomegalovirus, was associated with an increased risk of all strokes (Elkind et al., 2010). Also HIV infection was found to be associated with both ischemic and hemorrhagic stroke (Ovbiagele et al., 2011; Chow et al., 2014) as a possible consequence of direct injure of the arterial walls (Boehme et al., 2017), an increased vascular disease burden among subjects with HIV compared with those without, or an adverse cardiovascular profile of antiretroviral agents (Gutierrez et al., 2013).

Chronic inflammation, such as is seen in rheumatoid arthritis, favors the development and progression of atherosclerosis (Bang et al., 2015). Effective suppression of inflammation by antirheumatic drugs, including methotrexate and tumor necrosis factor-α blocking agents, may reduce the risk of vascular events (Ozbalkan et al., 2010). Several chronic inflammatory diseases, including psoriasis and related disorders, bullous skin disorders, ulcerative colitis, Crohn disease, inflammatory arthritis, systemic autoimmune diseases, and systemic vasculitis, showed an increased risk of CVD with chronic inflammatory disease, calling for the importance of clinical management of such conditions to reduce cardiovascular risk (Dregan et al., 2014).

Chronic kidney disease

A meta-analysis showed that a baseline estimated glomerular filtration rate of <60 mL/min per 1.73 m^2 was independently related to incident stroke across a variety of participants and study designs (Lee et al., 2010). Besides, chronic kidney disease is an independent predictor of mortality and poor outcome in patients with acute stroke (Yahalom et al., 2009). In addition, the prevalence of traditional vascular risk factors is high in patients with chronic kidney disease (Sarnak et al., 2003). Healthcare providers should evaluate the presence of chronic kidney disease in their vascular disease patients as a part of preventive care and treatment strategies (Brosius et al., 2006; Bang et al., 2015).

Diet and nutrition

Both poor nutrition and overnutrition predispose subjects to stroke (Bang et al., 2015). Beneficial effect of food intake on stroke risk is likely to be mediated by the interplay of a wide range of nutrients rather that one single food component, such as long-chain ω-3 fatty acids (Chowdhury et al., 2012). An observational study (REGARDS) (Tsivgoulis et al., 2015) and a meta-analysis (Sofi et al., 2010) showed that high adherence to a Mediterranean diet (high consumption of fruit, vegetables, nuts, whole grains and olive oil; moderate consumption of fish; and low consumption of red meat) was associated with a lower risk of ischemic stroke. However, low intake of fat and animal protein may be associated with increased risk of hemorrhagic stroke (Iso et al., 2001). There is also a growing evidence of the role of potassium intake in pathophysiology of stroke due to blood pressure lowering (D'Elia et al., 2011; Aburto et al., 2013), calling for the need of randomized trials of dietary intake or supplementation for prevention of stroke and its complications.

Psychosocial stress

Higher levels of psychosocial stress, including anxiety, hostility, and job strain, are independently associated with increased risk of stroke (Everson-Rose et al., 2014; Henderson et al., 2013; Fransson et al., 2015), either by way of cumulative effects of repeated emotional experiences of because of an extreme acute emotional episode (Bang et al., 2015).

Depression, anxiety, and fatigue

Two meta-analyses showed that depressive symptoms are associated with risk of stroke (Pan et al., 2011; Dong et al., 2012). Although less convincing than depression, anxiety and phobic attacks (Chen et al., 2010), or extreme fatigue or vital exhaustion (Kornerup et al., 2010) are reported to be related with occurrence of stroke.

Air pollution

There is accumulating evidence of a relationship between air pollution and ischemic stroke risk (Ljungman et al., 2014; Shah et al., 2015). Particulate matter may potentiate the effect of traditional risk factors (von Bornstädt et al., 2014). Several direct and indirect effects of exposure to air pollutants have been claimed to explain its association with ischemic stroke, including effects on the heart rhythm, plasma viscosity, endothelial dysfunction, and inflammation (Bang et al., 2015).

Obstructive sleep apnea (OSA)

Evidence suggests that poor sleep quality and daytime sleepiness may be linked to vascular events (Boden-Albala et al., 2012). Patients with stroke or TIA have a high prevalence (50-70%) of OSA (Hermann et al., 2009), which is associated with endothelial dysfunction and

arterial stiffness (Cereda et al., 2013). Polysomnography is recommended in acute stroke patients with high risk for OSA (Wallace et al., 2012), and continuous positive airway pressure therapy is recommended, in addition to physical exercise, to patients with stroke or TIA with moderate to severe OSA, daytime symptoms, and high cardiovascular risk profile (Hermann et al., 2009).

1.1.4 Pathophysiology of ischemic stroke

Stroke can be classified into either ischemic or hemorrhagic stroke. Ischemic stroke is the most prevalent stroke type, accounting for approximately 80-85% of strokes (Sudlow et al., 1997). Infarction results from a reduction or blockade of blood flow from decreased systemic perfusion, severe stenosis or occlusion of a blood vessel with subsequent focal cell death. Conversely, hemorrhage is a focal collection of blood within the CNS causing neuronal damage by means of focal disruption and compression of surrounding tissue. Focal infarction is supported by three major mechanisms:

1. *Thrombosis*: refers to *in situ* occlusion of a blood vessel developing acutely or gradually. Vessel lumen obstruction can result from a disease of arterial wall (i.e. dissection, atherosclerosis) with or without superimposed thrombosis;

2. *Embolism*: a clot formed elsewhere in the vascular system travels along blood vessels and embeds in an artery causing focal obstruction of a single vessel and its downstream branches. The heart is the most common source of arterial emboli but other arteries and venous vessels are possible sources as well. Fat, septic and air emboli can also occur;

3. *Hypoperfusion*: decrease systemic perfusion may lead to generalized ischemia of the brain which, in turn, becomes more critically in border zone areas (i.e. tissue at the junction of two

main arterial territories) causing so-called "watershed" infarcts. The brain receives up to 20% of cardiac output and accounts for roughly 25% of overall oxygen consumption. Because of the lack of energy storage on its own, the nervous system relies critically on blood supply for oxygen and glucose delivery. In order to avoid reductions in blood supply it is of utmost importance that cerebral blood flow (CBF) is maintained fairly constant through cerebral autoregulation. According to Ohm's law, flow is proportional to the difference in inflow and outflow pressure (ΔP) divided by the resistance to flow (R): flow = ΔP/R. Vessel diameter accounts primarily for resistance whereas ΔP depends on cerebral perfusion pressure (CPP). Autoregulation enables blood flow to remain constant despite minorvariations in perfusion pressure and occurs within mean SBP range of 60 to 150 mmHg in most individuals (Paulson et al., 1990; Phillips et al., 1992). As cerebral autoregulation is impaired in moderate to severe ischemia, CBF varies passively with CPP decline. Homeostatic cell functions failure occurs at different critical flow threshold levels: flow rates below 50mL/100g/min cause inhibition of protein synthesis; at 25mL/100g/min anaerobic glycolysis and subsequent lactic acidosis occurs; between 18 to 16mL/100g/min adenosine triphosphate (ATP) depletion and neuronal dysfunction takes place until complete loss of ion homeostasis occurring below 15mL/100g/min with subsequent brain infarction (Markus et al., 2004). Thus, CBF disruption triggers a cascade finally responsible for cell death where a complex interplay of cellular and metabolic mechanisms plays a key role. Firstly, as a consequence of ischemia, release of glutamate neurotransmitter at neuronal synapses increases (Caplan, 2009). Glutamate binds to postsynaptic N-methyl-D-aspartate (NMDA) and a-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) receptors resulting in calcium and sodium influx into cells, cellular edema and activation of the catabolic processes that destroy cellular integrity, a process referred to as excitotoxicity (Choi et al., 1998). AMPA-mediated glutamate effects also enhance nitric oxide (NO) production leading to further brain injury by direct damage of cellular components and increased levels of peroxynitrite, a byproduct of NO and superoxide reaction (Love et al., 1999). Peroxynitrite

determines single strand breaks in DNA activating DNA repair proteins with consequent NAD+ depletion. Reactive oxygen species (ROS) also permeabilize mitochondrial membrane resulting in apoptosis and DNA damage initiators release, respiratory chain failure and ATP depletion (Mattson et al., 2003). Excitotoxicity and oxidative stress activate microglia and astrocytes which react by secreting cytokines, chemokines and matrix metalloproteinases (MMPs). Cytokines upregulate the expression of cell adhesion molecules with secondary migration of activated leukocytes into the CNS and activation of inflammatory pathway (Lakhan et al., 2009). Degradation of collagens and laminins from the basal lamina by MMP causes a breakdown of vessel integrity, blood-brain barrier disruption and leakage of macromolecules into the cerebral compartment (Simard et al., 2007). Vasogenic edema is the final result of this complex cascade and adds to cytotoxic edema caused by failure of ATP-dependent cell metabolism, sodium influx, accumulation of water and cell swelling (Klatzo et al., 1987; Simard et al., 2007; Yang et al., 2011). Brain edema can also exert detrimental effects *per se* by critical decrease of CPP, increased intracranial pressure and brain herniation which roughly occurs in 10% of anterior circulation infarctions, often referred to as "malignant" for the presence of space-occupying edema (Huttner et al., 2009). Provided blood flow is restored, sometimes paradoxical secondary damage, called ischemia/reperfusion injury, occurs. The increase of ROS triggers the synthesis of transcription factors including NF-B, hypoxia inducible factor 1, interferon regulator factor 1 and STAT3. As cytokine synthesis is upregulated, cell adhesion molecules on endothelial cells like intercellular adhesion molecule 1, P-selectin and E-selectin promote migration of leukocytes to the periphery of the infarct (Yilmaz et al., 2008). Complement cascade and release of activated C3a and C5a anaphylatoxins take place with further enhancement of inflammatory pathway (D'Ambrosio et al., 2001). Noteworthy, inhibition of complement activation was found to be beneficial in animal models of ischemia/reperfusion injury (Arumugam et al., 2009).

1.1.5 Clinical syndromes

Medical history and clinical examination remain the mainstay of stroke diagnosis. The most distinctive and reliable feature of stroke lies in its abrupt onset. The temporal profile of neurological syndrome with symptoms developing over second or minutes marks the event as vascular. Embolic stroke syndrome occurs abruptly with symptoms reaching peak intensity almost all at once, while atherothrombotic stroke develops somewhat more slowly, over several minutes to hours, sometimes in a stepwise fashion, especially in the case of posterior circulation strokes. Besides, temporal evolution of symptoms is also a matter of importance that most strokes, after reaching a plateau phase, show spontaneous improvements, at least to some extent, unless early death occurs. Noteworthy, sometimes improvement can be as abrupt as onset depicting the so-called 'spectacular shrinking deficit' (clinical hallmark of embolic stroke with distal clot migration and clinical resolution) (Minematsu et al., 1992). More often, neurological deficit evolves towards gradual improvement over weeks to months leaving some degree of physical disability, as in atherothrombotic strokes. Neurological signs and symptoms depend on lesion size and location. Apart from some not localizing deficits when occurring in isolation (i.e. hemiparesis), certain constellations of neurological deficits are highly specific for definite anatomical locations depicting well-recognizable neurovascular syndromes.

Clinical determination of the affected vascular territory may aid establishing whether the presenting stroke is hemorrhagic or ischemic and selecting the most appropriate treatment. Nevertheless, not all strokes present with overt clinical syndromes. The shift towards a tissue-based definition of stroke implied a critical reappraisal of so-called 'silent infarctions' (Sacco et al., 2013). Appreciation of small infarcts or microbleeds on MR imaging scans of patients with otherwise unremarkable past medical history has been established in many datasets (Chodosh et al., 1988). It is up to the physician to determine if a silent infarction has a past clinical correlate that passed unnoticed, overlooked or disregarded. In addition,

increasing amount of small ischemic insults may become clinically evident as a combination of cognitive, gait and other functional impairments. Hence, proper recognition of specific neurovascular syndromes is a matter of utmost importance and remains one of the pillars of clinical neurologist skills.

1.1.5.1 Anterior circulation syndromes

The common carotid artery (CCA) arises from the brachio-cephalic trunk to the right and from the aortic arch to the left, travels upwards through the neck and divides into two branches, i.e. the internal and external carotid arteries (ECA) at C4 levels, below the jaw angle. The internal carotid artery (ICA) therefore penetrates the skull base, travels along a bony canal (intrapetrous tract), enters the cavernous sinus outlining an S-shaped double curve (carotid siphon) and continues into the subarachnoid space, finally branching off into four arteries, i.e.: the middle cerebral artery (MCA) and anterior cerebral artery (ACA), the anterior choroidal artery and the posterior communicating artery (PCoA).
Bamford et al., using data from the Oxford Community Stroke Project (OCSP), defined four sub-categories of cerebral infarction on the basis of presenting symptoms and signs (Bamford et al., 1991). The OCSP criteria rely on bedside clinical features labeling definite anatomical sites and thus orienting towards specific neurovascular syndromes. The classification is also feasible, has good inter-observer reliability and provides the physician with a useful tool for both prognostic and etiologic evaluation (Lindley et al., 1993; Bamford et al., 1991). The OCSP classification encompasses four subtypes of cerebral infarction: total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), lacunar infarcts (LACI) and posterior circulation infarcts (POCI) (Supplemental Table 2). TACI can be identified through a combination of higher cerebral dysfunction, homonymous visual defect and ipsilateral motor and/or sensory deficit involving at least two among face, arm and leg. Radiological correlates of TACI rely on ischemic changes over the entire ICA territory or either more than 1/3 of the MCA territory or ipsilateral basal ganglia infarction in

addition of MCA cortical or ACA territory infarction. Higher cortical dysfunction refers to any combination of motor and sensory speech disorders, agnosia, apraxia, acalculia, agraphia, alexia, right-left confusion. Higher cortical dysfunction or any other deficits are inferred whenever formal testing assessment is not feasible. Conversely, when only two out of the three components of TACI syndrome are present, stroke is assigned to PACI category as follows: higher cortical dysfunction alone or motor/sensory deficit more restricted than as defined by LACI (v.i.). Usually, PACI syndrome occurs when ischemic changes are noticed in the ACA or MCA territory with extension not fulfilling radiological criteria for both TACI and LACI subtypes. Two main mechanisms underpin stroke in the anterior (i.e. carotid) circulation: carotid artery (CCA or ICA) occlusion with downstream embolization into the territory of tributary vessels (artery-to-artery embolism) or thrombotic occlusion of either carotid or its distal branches. Differentiation of brain infarction involving complete MCA or ICA territory may be difficult on clinical grounds but transient monocular loss contralateral to neurological deficits provides a useful diagnostic hint towards carotid artery occlusion. *Amaurosis fugax* occurs in no more than 10 to 25% of carotid artery occlusion, presumably because of efficient collateral supply from ICA-ECA anastomosis in the orbit. Clinical syndrome resulting from proximal occlusion of MCA stem presents as contralateral hemiplegia, hemianesthesia and homonymous hemianopia with head and gaze deviation towards the affected hemisphere. Left-sided lesions also present with global aphasia whilst right-sided ones with anosognosia in right-handed patients. Transient disorder of consciousness may occur as a result of ill-defined widespread neurological dysfunction. Superior division MCA branches occlusion mimics proximal MCA stem occlusion except for relative leg sparing (‘facio-brachial’ paralysis) without decreased alertness. Global aphasia soon evolves into a motor disorder of speech (Broca aphasia). On the other hand, Wernicke aphasia along with superior quadrantopia or homonymous hemianopia commonly takes place when ischemic changes affect the inferior division MCA branches. In addition, brain infarction of the solely penetrating MCA branches gives rise to striato-capsular

infarction presenting with limited form of Broca aphasia, incomplete motor impairment and homonymous hemianopia.

Occlusion of A1 segment of ACA rarely results in ischemic stroke clinical syndrome as blood supply is ensured by collateral flow from anterior communicating artery.

Conversely, ACA occlusion beyond the A2 segment underpins a clinical picture dominated by sensory-motor impairment of contralateral foot, leg and proximal arm with relative sparing of hand and face, gaze deviation towards the side of lesion and the so-called 'trans-cortical motor aphasia' (i.e. reduced motor speech, limited ability to name objects despite spared ability to repeat spoken sentences). The most striking feature of ACA infarcts is a behavioral disorder with apathy, abulia, lack of spontaneity in gestures and speech which sometimes evolve into the clinical scenario of akinetic mutism. Ischemia of the head of caudate nucleus supplied by ACA penetrating branches sometimes justifies the occurrence of transient choreo-athetosis and other dyskinetic disorders during acute phase of ACA infarctions.

Anterior choroidal artery infarction yields a clinical syndrome similar to MCA territory ischemia, except for notable sparing of higher cortical functions: contralateral hemiplegia, hemihypesthesia and homonymous hemianopia are caused by involvement of deep structures (namely, posterior limb of internal capsule and adjacent white matter) with almost completely preserved language functions and cognition. Nevertheless, some degree of visuo-spatial neglect and slight impairment of speech may eventually occur in right and left-sided lesion, respectively.

1.1.5.2 Posterior circulation syndromes

The vertebro-basilar system, a.k.a. posterior circulation, is an important vascular network supplying the occipital lobes, part of temporal lobes, the cerebellum and the brainstem accounting for approximately 20% of CBF.

Each vertebral artery (VA) arises from the subclavian artery, ascends through the neck, posterior to the ICA, in the foramina of cervical vertebrae from C6 to C1, pierces the dura mater and becomes intracranial, combining with the contralateral VA to form the basilar artery (BA) at the base of the pons. Prior to union, the VA branches off into the postero-inferior cerebellar artery (PICA) supplying the posterior and inferior surface of cerebellar hemispheres. VA lumen size varies considerably and in up to 10% of cases one vessel is so small that the entire blood supply from the vertebra-basilar system basically comes from one VA. The BA ascends in a shallow groove on the anterior surface of the pons providing many vessels to the brainstem: the paramedian, short circumferential and long circumferential arteries, the anterior- inferior cerebellar arteries (AICAs), the superior cerebellar arteries (SCAs) and the paramedian interpeduncular arteries. Finally, the BA divides into two PCAs at the level of proximal midbrain just past the emergency of oculomotor nerves. Anatomic variants of this structural arrangement are found in up to 30% of general population: in some cases one (20-25%) or both (5-10%) PCAs arise directly from the ICA (so- called persistent fetal circulation). Occlusion of the VA involving the PICA branch results in lateral medullary syndrome also known as Wallemberg syndrome. Despite relatively small infarct core, dense arrangement of nuclei and long tracts in the lateral medulla accounts for a wide range of clinical findings: vertigo, nausea, nystagmus (vestibular nuclei), contralateral pain and thermal hypesthesia (spino-thalamic tract), ipsilateral Horner syndrome (descending sympathetic tract), hoarseness, dysphagia and dysphonia (IX e X nerve nuclei), ipsilateral lateropulsion and limb ataxia (inferior cerebellum and inferior cerebellar peduncle) and pain, burning and impaired sensation over the ipsilateral half of the face (spinal trigeminal nucleus) are the cardinal clinical features. Conversely, medial medullary syndrome is characterized by ipsilateral atrophy and deviation of tongue when protruded (ipsilateral XII nerve involvement) and contralateral hemiparesis sparing the face.

Patients with BA occlusion present with dramatic neurological impairment, the extent of which depends on the site of occlusion. Complete BA occlusion yields bilateral long tract

and cerebellar signs along with variable impairment of cranial nerves. Typically, decreased arousal to coma is present following disruption of the reticular activating system (RAS). Whenever pons infarction affects long tracts with RAS sparing, patients become quadriplegic, but consciousness is preserved (so-called 'locked-in' syndrome). Infarction of rostral brainstem, deep and cortical regions fed by distal BA and its branches causes the 'top of the basilar syndrome' that includes decreased arousal, memory defects, akinetic mutism, visual hallucinations and defects, ptosis and ocular movement disorders (convergence spasm, paralysis of vertical gaze, retraction nystagmus, pseudoabducens palsy, retraction of upper eyelids, skew deviation of the eyes) in various combinations.

SCA occlusion causes ipsilateral limb ataxia and Horner syndrome, contralateral impairment of pain and thermal sensation and palatal myoclonus in some cases. On the other hand, the main findings in AICA infarctions are vestibular and cochlear signs and symptoms with frequent occurrence of vertigo, vomiting, nystagmus, tinnitus and sometimes unilateral deafness. Facial weakness, contralateral loss of pain and temperature sense, ipsilateral limb ataxia and Horner syndrome may also occur.

Occlusion of the PCAs yields a great variety of clinical syndromes as a consequence of high degree of anatomical variability and large blood supply territory involving the brainstem, deep gray nuclei and cortical regions. Accordingly, the site of occlusion and the extent of collateral blood supply determine the site and extent of brain infarction. Paramedian arteries arise from the P1 segment of each PCA but often a common trunk (i.e. Percheron artery) branches off the same posterior cerebral stem and provides blood supply to both paramedian nuclei of the thalamus.

Decreased arousal that may eventually progress to stupor or coma followed by impaired learning and memory, confabulation, aphasia and disorders of personality are common clinical findings in thalamic paramedian nuclei ischemia (Schmahmann et al., 2003). Infero-lateral branches originate from the P2 segment and supply the ventro-posterior complex of the thalamus: corresponding neurovascular syndrome is known as Déjerine-Roussy

syndrome, its clinical hallmarks being contralateral dense sensory loss gradually evolving into pain, paresthesia and hyperpathia in the affected body parts. Mood disorders and athetotic posturing of the hand may eventually develop.

Occlusion of cortical branches to the temporal and occipital lobes most commonly causes homonymous hemianopia following infarction of the calcarine cortex.

Macular vision sparing is not uncommon due to collateral blood supply from the MCA to the occipital pole. Left posterior cortical infarcts also cause a number of visual agnosias, i.e. impaired ability to name objects or items after visual inputs: alexia, amnestic aphasia and color anomia to name but a few. Concomitant bilateral PCA infarctions give rise to unique clinical syndromes according to the infarct location: Balint syndrome (bilateral occipito-parietal border-zone infarcts), amnestic Korsakoff syndrome (bilalteral hippocampal and parahyppocampal infarcts), cortical blindess with or without anosognosia, i.e. Anton syndrome (bilateral occipital cortex infarcts) and prosopagnosia (bilateral mesio-temporal-occipital infarcts). In addition, interpeduncular branches stem from the PCA at P1 segment and central midbrain syndromes may arise from their occlusion: oculomotor nerve palsy combined with contralateral motor deficit (Weber syndrome), contralateral ataxic tremor (Benedikt syndrome) or ataxic hemiparesis (Claude syndrome).

Accordingly, the OCSP classification defines posterior circulation infarcts as a combination of ipsilateral cranial nerve palsy and contralateral motor and/or sensory deficit or bilateral motor and/or sensory deficit or disorder of conjugate eye movement or cerebellar dysfunction without ipsilateral long tract deficit or isolated homonymous visual field defect. Radiological POCI entails any lesion in the posterior circulation territory not meeting radiological criteria for LACI.

1.1.5.2 Lacunar syndromes

The first description of lacunar cavities in the brain by Durant-Fardel dates back in 1843 and was further substantiated by Pierre Marie in the early 20th century but Fisher was the first to correlate small LACI with definite and well-recognizable clinical syndromes.
More than 20 lacunar syndromes have been reported but just five have been found predictive for definite LACI: pure motor hemiparesis, pure sensory stroke, ataxic hemiparesis, sensorimotor stroke and dysarthria-clumsy hand syndrome. As a group, these have a positive predictive value of 87% for radiological confirmation of LACI (Gan et al., 1997). Pure motor hemiparesis is the most common among lacunar syndromes and presents with motor weakness of face, arm and leg on one side of the body without any cortical or sensory sign associated. The motor impairment can develop abruptly or, less frequently, be announced by several motor TIAs as in the 'capsular warning syndrome'.
Lacunae responsible for pure motor hemiparesis usually lie in the internal capsule or close by in the corona radiata (lenticulo-striate territory) or at the base of the pons (paramedian penetrating branches off the BA).
Pure sensory stroke is another common lacunar syndrome underlied by a small vessel occlusion in the thalamus or, less often, in the parietal white matter. Sensory complaints affect contralateral arm, face and leg without any associated motor or cortical sign.
In ataxic hemiparesis syndrome patients develop hemiparesis and ipsilateral ataxia out of proportion to the motor deficit. Lesion sites specific for this syndrome are the pons, midbrain, internal capsule or parietal white matter. Sensorimotor syndrome is characterized by a combination of motor impairment and numbness in half of the body contralateral to the lesion, which is usually located in the postero-lateral thalamic nuclei or posterior limb of the internal capsule. Finally, dysarthria and clumsiness of one hand can occur in lacunar strokes located in the contralateral paramedian midpons. This latter syndrome is often accompanied by facial weakness, dysphagia and slight motor impairment of the affected hand.

The OCSP classification of LACI underscores the importance of motor deficit somewhat more widespread than those occurring in PACI, i.e. involving at least two of face, arm and leg in the absence of any of the following signs: dysphasia, visuo- spatial disturbance, predominant proprioceptive sensory loss, features which clearly localize the lesion in the vertebro-basilar distribution (for instance gaze palsies or crossed deficits) and impaired level of consciousness. Neuroimaging correlates for LACI are small round lesions in deep white matter, basal ganglia or brainstem with lesion diameter up to 1.5 cm.

1.1.6 Ischemic stroke etiologic subtypes

Ischemic stroke is a somewhat heterogeneous disease with a number of etiologies described. Classification systems distinguishing among possible causes serve different purposes, i.e. grouping patients in clinical trials, describing patient characteristics in risk factors association studies and, above all, identifying the most likely etiology for therapeutic decision-making in everyday clinical practice. To this end, an ideal classification system should ensure accuracy, reliability and feasibility for treatment and prognostication of ischemic stroke. Several classification criteria have been proposed over the last decades (Chen et al., 2012). Derived from the Harvard Stroke Registry Classification, the National Institute of Neurological

Disorders and Stroke (NINDS) Data Bank criteria date back in the late 1980s (Foulkes et al., 1988). Weaknesses of this classification system were underestimation of atherothrombotic group based on very restrictive criteria (>90% stenosis on extra- cranial vessels) with subsequent overestimation of undetermined etiology group.

Since the release of the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria in 1993, most physicians relied on this classification for clinical and research purposes (Adams et al., 1993) (Supplemental Table 4). Originally designed to characterize stroke patients in a trial investigating any potential efficacy of danaparoid in different subtypes of ischemic

stroke, these criteria have become the most widely used in literature and allow for consistent comparison between studies. The TOAST classification is composed of 5 major subtypes, namely large-artery atherosclerosis (LAA), small-artery occlusion (SAO), l (CE), stroke of other determined cause (OC) and stroke of undetermined etiology (UND). Despite its widespread use, the TOAST classification has several shortcomings: 1) lacunar infarcts are defined by size criterion, thus infarctions in small penetrating branches due to M1 middle cerebral artery (MCA) stenosis would be missed if appropriate vascular imaging is withheld; 2) cardiac sources are classified as high or medium risk, therefore late or incomplete diagnostic work-up would assign other etiology strokes (i.e. arterial dissection) to cardioembolic category if appropriate vascular imaging is missing; 3) stroke of undetermined etiology category encompasses a number of heterogeneous stroke syndromes including CSs despite extensive diagnostic work-up, strokes due to multiple overlapping causes and missed diagnoses by late or incomplete diagnostic evaluation. To overcome these limitations another evidence-based algorithm has been developed from the original TOAST classification by adding three subcategories to each causative subtype. The SSS- TOAST identifies the level of confidence in assigning a mechanism so that each stroke subtype etiology is further defined as 'evident', 'probable' and 'possible' according to coexistence of multiple mechanisms and overall stroke risk threshold related to each of them (Ay et al., 2005). In a further refinement, an automated version of the SSS-TOAST called the Causative Classification System (CCS) was devised enabling stroke classification through a questionnaire-style classification scheme (Arsava et al., 2010). The current CCS version relies on five data sources: clinical data, complete vascular imaging, cardiac evaluation, brain imaging and work-up for uncommon stroke causes. Some differences from the original TOAST criteria must be highlighted: 1) up to 20 mm infarction diameter is allowed for SAO category; 2) undetermined stroke is broken into many subcategories (i.e. unknown, incomplete work-up, unclassified stroke–multiple mechanisms-, cryptogenic embolism - angiographic evidence of an abrupt cutoff in an otherwise normal artery or subsequent

complete recanalization of a previously occluded artery). Inter-rater reliability for CCS has been proven to be high (Arsava et al., 2010).

Nevertheless, the CCS has several shortcomings: evidence-based data come from different and heterogeneous studies; complete vascular and brain imaging is required and aortic plaques belong to cardioembolic category, unlike other classifications. As a consequence, agreement between these two classifications (TOAST and SSS- TOAST) is only moderate (agreement rate 70%) and caution is warranted when comparing data from these algorhythms (Mc Ardle et al., 2014).

The ASCO (Atherosclerosis, Small-vessel disease, Cardiac source, Other cause) classification encompasses the same major categories as the TOAST system assigning to each a level of likelihood by means of a score from 1 to 3 (Amarenco et al., 2009). Each patient receives a phenotypic score (e.g. A1-S3-C2-02) on the basis of causality of each causative category.

Despite specific strengths of each systems and the desirable goal of a single, accurate and feasible classification scheme, the TOAST classification system is still the most widely used in either research and real-world practice.

Large-artery atherosclerosis

A confident diagnosis of stroke due to LAA can be made whether relevant (>50%) stenosis or occlusion of a major cerebral vessel or its branch cortical arteries occurs (Adams et al., 1993). Diagnostic work-up should include vascular imaging of both intracranial and extracranial vessels through duplex imaging, arteriography or other available imaging techniques, e.g. Magnetic Resonance Angiography (MRA or computer tomography angiography (CTA). Potential cardiac sources of embolism should be ruled out. Supportive clinical and brain imaging findings are reported as follows: 1) cortical, brainstem or cerebellar syndromes (aphasia, neglect, restricted motor involvement, ataxia); 2) brain

imaging evidence of infarcts with at least 1.5 cm diameter in either cortical, cerebellar, brainstem location; 3) past history of recurrent TIAs in the same vascular territory; 4) carotid bruit or decreased pulses.

Atherosclerosis underpins ischemic stroke either by causing critical blood flow reduction beyond stenotic lesions or by serving as a source of focal thrombosis that eventually breaks off into arterial emboli to distal branches. Sometimes a combination of both mechanisms takes place. Extra-cranial vessels most commonly involved are CCA branching and origin of ICA. Intracranial arteries more prone to atherosclerotic process are the carotid siphon, proximal MCA, intracranial VAs and BA origin (Sacco et al., 1995; Wityk et al., 1996). Carotid extracranial disease is more common in white and male gender whereas intracranial atherosclerosis is more prevalent in black, Hispanic and Asian ethnicity, type 1 diabetes and female gender (Sacco et al., 1995; Wityk et al., 1996). Carotid plaques typically evolve over long periods of time but may acutely become unstable and develop local fissure, endothelial erosions or intraplaque hemorrhages that eventually prompt local platelet aggregation and thrombus formation. Histological assessment of 565 symptomatic carotid plaques found high prevalence of cap rupture (61.4%), large lipid core (61.5%) and dense macrophage infiltrate (66.9%) in unstable plaques (Redgrave et al., 2006). Ischemic stroke risk in patients with ≥50% symptomatic carotid stenosis is up to 32% within 12 weeks and falls rapidly thereafter, as does benefit from endoarterectomy (Fairhead et al., 2005; Rothwell et al., 2004). These findings underscore the existence of a timely window of opportunity in treatment of unstable atherosclerotic plaques.

Cardioembolism

The underlying mechanism of CE stroke is occlusion of cerebral vessels with debris from a cardiac source. CE is responsible for approximately 25-35% of all ischemic strokes, with

the even higher frequency described in developing countries (Bogousslavsky et al., 1988; Timsit et al., 1993; Arboix et al., 1997). The proportion of CE stroke increases steadily with ageing accounting for about 14.6% in people aged < 65 years and 36% in the elderly (> 85 years) (Arboix et al., 2010). CE stroke is associated with the higher in-hospital mortality (27.3%) compared to lacunar (0.8%) and atherothrombotic strokes (21.7%) (Arboix et al., 2010). Disease burden of CE is also sustained by early and late embolic recurrences (Hornig et al., 1994; Arboix et al. a, 1998; Hart et al., 1983). Recurrent embolization within 14 days of ischemic stroke occurs in approximately 20.3%, with higher mortality rates (19.6%) compared to patients without recurrence (8.8%), but these figures vary slightly according to different studies (Yasaka et al., 1993; Cerebral Embolism Task Force et al., 1986; Arboix et al., 1998 b). Accordingly, early recurrence is the major predictive factor for in-hospital mortality in patients with CE (Arboix et al., 1998 a). A cardiac embolus may consist of platelet aggregates, thrombus, platelet-thrombi, cholesterol, calcium, and bacteria. No single mechanism is responsible for the development of cardiac emboli, and the pathophysiology of the emboli formation depends on the specific underlying cardiac disease.

Several cardiac disorders are thought to be source of embolus, but not all sources pose equal stroke risks; the TOAST criteria divide cardiac sources into high risk and medium risk categories, according to the relative propensities for embolism. At least one cardiac source of embolism should be documented to make a confident diagnosis of cardioembolic stroke. High risk sources carry a relatively high risk of initial and recurrent stroke convincingly linked to a cardioembolic mechanism, and include: mechanical prosthetic valve, mitral stenosis with AF, AF (other than lone AF), left atrial or atrial appendage thrombus, sick sinus syndrome, MI within 4 weeks, left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, and infective endocarditis.

Medium-risk sources are frequent in the general population, and the associated risk of initial and recurrent stroke with any of these conditions is either low or uncertain. A stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is

classified as a possible cardioembolic stroke. Medium risk sources are: mitral valve prolapse, mitral annulus calcification, mitral stenosis without AF, left atrial turbulence (smoke), ASA, PFO, atrial flutter, lone AF, bioprosthetic cardiac valve, non bacterial thrombotic endocarditis, congestive heart failure (HF), hypokinetic left ventricular segment and MI between 4 weeks and 6 months prior to ischemic stroke.

It is a widely held notion that AF is the most common cardiac source of systemic emboli, accounting for 79.1% of cardioembolic strokes, followed by hypertensive left ventricular hypertrophy in 29.8% of patients, left ventricular dysfunction in 22.6%, rheumatic mitral valve disease in 12.4%, and mitral annular calcification in 9.9%, in one hospital based cohort study (Arboix et al., 2010). Stroke related to AF is associated with significantly higher in-hospital mortality rates than other non-AF cardioembolic cause (32.6% vs. 14.8%), underscoring early recurrence as a possible contribution to higher mortality in cardioembolic strokes (Arboix et al., 2000 a).

Small vessel disease

According to the TOAST criteria, small vessel occlusion relates to one of the classical lacunar syndromes with no evidence of brain infarction on MR/CT or relevant brainstem or subcortical lesions with diameter less than 1.5 cm. Past medical history of diabetes and hypertension makes small vessel disease diagnosis more likely. Potential cardiac source of embolism and relevant (>50%) large artery stenosis should be ruled out.

Small vessel disease typically affects small penetrating branches arising from distal VA, BA, posterior cerebral artery (PCA), ACAs and M1 segment of MCA. Small vessel occlusion is underpinned by either lipohyalinosis (i.e. a lipid hyaline build-up secondary to hypertension) or fibrinoid degeneration of penetrating arteries or atheroma formation at the branching site of parental artery. Some reports of small lacunae in patients with high-risk cardiac embolic sources or following aortic arch angiography have also suggested a possible embolic origin,

but these cases were not pathologically proven (Cacciatore et al., 1991). Most symptomatic lacunae are associated with occlusion of perforating branches ≈200 to 800 μm in diameter by atheromatous plaques, whilst most asymptomatic LACIs relate to occlusion of ≈40 to 200 μm arterioles by lipohyalinosis, according to post-mortem histopathology studies (Lammie et al., 2002). Hypertension has been consistently been associated with small vessel disease. Noteworthy, a population-based study conducted in Japan found a steady decline of lacunar stroke incidence rate since 1960s paralleling improved control of HBP and decrease prevalence of tobacco smoking (Kubo et al., 2006). Diabetes, age, LDL cholesterol level, tobacco smoking and possibly homocysteine are other likely risk factors for SAO (Bezerra et al., 2012; Sacco et al., 2006). Of interest, a systematic review of studies comparing risk factors among lacunar vs. non-lacunar strokes found an only marginal excess risk for hypertensive patients (RR= 1.11) and no differences for diabetes (RR= 0.95) in a subgroup analysis confined to studies using a risk–factor free definition for lacunar stroke (Jackson et al., 2005). Several studies depict LACI frequency among population of African and Hispanic descent compared to non-Hispanic whites. Small vessel stroke proportion in Whites accounts approximately for 11-15% while higher proportion has been reported in South Americans (14-43%), African Americans (18-31%) and Caribbean blacks (23-51%) (Sacco et al., 2006; Rost et al., 2010; Sacco et al, 1995; Saposnik et al., 2003; Koch et al., 2005; Smadja et al., 2001). Along with variability in vascular risk factors prevalence, genetic susceptibility has been also called into question to explain racial-ethnic disparities in stroke subtypes distribution. The APOE e4 allele concomitant to high amyloid beta peptide levels has been positively associated with lacunar stroke risk (OR=1.72 and 1.93 per standard deviation increase in Aβ 1-40 and Aβ 1-42 levels, respectively) (Van Dijk et al., 2004). Apart from hereditary cerebral small vessel angiopathies (e.g. CADASIL, CARASIL, HERNS), many other susceptibility genes have been found to confer higher risk for LACI (TPA -7351C/T polymorphism, ACE DD genotype) (Hassan et al., 2002; Jannes et al., 2004).

Stroke of other determined etiology

Rare causes of ischemic stroke include non-atherosclerotic vasculopathies, hematological disorders and hypercoagulability disorders. A definite diagnosis of 'other determined etiology' according to TOAST criteria entails clinical and brain imaging evidence of ischemic stroke and diagnostic test unveiling at least one possible uncommon stroke cause. Diagnostic work-up should rule out large artery atherothrombosis and cardioembolism. This category accounts for 9 to 4% of all ischemic strokes but is by far more prevalent in young adults (Bogiatzi et al., 2014; Smajlović et al., 2015). In this age group, strokes related to uncommon etiology constitute 19 to 22% of all ischemic strokes but proportion as high as 44% has been reported as the spectrum of etiologies may differ by geographical regions (Chatzikonstantinou et al., 2012; Yesilot Barlas et al., 2013; Nakagawa et al., 2013). Other uncommon stroke causes include non-atherosclerotic non-inflammatory arteriopathies, non-atherosclerotic inflammatory arteriopathies, genetic or acquired coagulopathies, hematological disorders and coagulopaties related to systemic conditions and miscellaneous rare causes. (Yesilot Barlas et al., 2013). In a large cohort of 3,331 patients with a FES aged 15 to 50 at 15 European stroke centers, cervical artery dissection (CAD) was the most common among stroke of other determined etiology (13% of all ischemic strokes), followed by genetic thrombophilia and systemic vasculitis (Yesilot Barlas et al., 2013). Arterial dissections occur whenever intimal tear allows blood to collect between arterial wall layers with subsequent formation of intramural hematoma. A population-based study from Minnesota estimated an average annual incidence rate for CAD of 2.6 per 100,000 person-years but most cases are likely to be missed for late or incomplete work-up (Lee et al., 2006). Brain infarction takes place in approximately 56% of CAD (Lee et al., 2006). Converging evidence suggests that mild trauma is a common precipitating factor for CAD (up to 40% of cases) and is more frequent in VA dissection but a number of connective tissue and vascular disorders may be involved in etiology and pathophysiology of CAD as a part of multifactorial

susceptibility (Engelter et al., 2013; Debette et al., 2011). Arterial dissection has been described in association with fibromuscular dysplasia, Ehlers-Danlos syndrome type IV, Marfan syndrome, osteogenesis imperfecta, homocystinuria, autosomal dominant polycystic kidney disease and alpha-1 antitrypsin deficiency, to name but a few (Brandt et al., 2005). As stroke related to uncommon causes is by far more frequent in the young, etiological diagnosis warrants a different and more complex diagnostic work-up in this age group.

Stroke of undetermined etiology

Stroke of undetermined etiology is the most heterogeneous group in the TOAST classification system: patients with potential multiple etiologies (i.e. satisfying criteria for at least two of the aforementioned categories) are grouped together with those disclosing entirely negative work-up. Accordingly, stroke of undetermined etiology category is further broken into three subgroups: 1) two or more causes identified; 2) negative evaluation; 3) incomplete evaluation. Whenever stroke cause remains unexplained despite extensive evaluation, stroke is referred to as cardioembolic. In about 20 to 40% of strokes etiology cannot be determined (Sacco et al., 1989; Schneider et al., 2004). Nevertheless, according to the TOAST criteria, no identifiable cause based on late or incomplete evaluation also allows for the diagnosis of stroke of undetermined etiology. Moreover, the TOAST classification does not indicate specific diagnostic work-up necessary to ensure complete evaluation. According to ASA/AHA guidelines (Powers et al., 2018) a minimum emergency work-up should include at least: non contrast CT or brain MR imaging, blood glucose, oxygen saturation, serum electrolytes and renal function tests, complete blood count, markers of cardiac ischemia, prothrombin time/international normalized ratio, activated partial thromboplastin time and ECG. Patients with cryptogenic stroke should also be offered complete brain and neck vascular imaging by MRA/CTA or ultrasonography, as well as

transthoracic echocardiography (TTE), followed by transesophageal echocardiography (TEE) if etiology is still unclear (Easton et al., 2009; Furie et al., 2011). Ancillary investigations such as long-term monitoring of cardiac rhythm, tests for hypercoagulability states, search for genetic and metabolic causes of stroke or pelvic and lower extremity duplex for suspected paradoxical embolism should be considered on a case-by-case basis. Interestingly, Nam et al. found a significant higher proportion of patients with poor functional outcome at 3 months in the UND group due to incomplete evaluation when compared to all other strokes (49.6% vs. 24.5%) (Nam et al., 2012). Actually, recognition of missed etiologies by extensive work-up may point out conditions with high risk of early recurrence and allow for appropriate treatment.

1.1.7. Embolic Stroke of Undetermined Source

Strokes that do not clearly meet the criteria for an established subtype are classified as CSs or strokes of undetermined source (Ay et al., 2007). About one-third of ischemic strokes remain cryptogenic after the standard evaluations (Marnane et al., 2010) The clinical and neuroimaging characteristics of CSs often suggest a distant embolic source rather than in situ cerebral small-vessel occlusion, which has led to the recent formulation of an entity called embolic stroke of undetermined source (ESUS) (Hart et al., 2014).

A designation of ESUS requires a TTE, 24 hours of continuous heart rhythm monitoring, vascular imaging of the cervical and intracranial arteries supplying the brain, and exclusion of other well-defined but rare causes, such as vasculitis or arterial dissection (Hart et al., 2014). Comparisons between ESUS and CS are hindered by varying definitions of CS. The ASCOD classification does not recognize CS because all patients are assigned a combination of scores representing the underlying severity of LAA, small-vessel disease, and cardiac disease (Amarenco et al., 2013); a typical ESUS patient would have a low ASCOD score for small-vessel disease and medium scores for atherosclerosis or cardiac

pathology. In the TOAST classification, a patient lacking a basic evaluation (eg, because of early death after stroke) is diagnosed as a stroke due to undetermined cause; it is likely that many of these cases would not have qualified as ESUS because even a basic evaluation would have identified an obvious source, such as carotid stenosis or AF. The proposed definition of ESUS most closely aligns with the CCS classification's definition of CS (Ay et al., 2007), which requires unrevealing cardiac evaluation and imaging of the entire cerebral circulation. Several potential causes of embolism may underlie ESUS. Some cases may represent artery-to-artery embolism from LAA plaques in the cerebral circulation that go unrecognized because they do not cause significant stenosis of the arterial lumen. Current stroke classification systems mostly require ≥50% luminal stenosis to invoke large artery disease (Amarenco et al., 2013; Adams et al., 1983). However, recent evidence suggests that vulnerable atherosclerotic plaque can rupture and cause downstream artery-to-artery embolism without necessarily causing luminal stenosis (Freilinger et al., 2012; Gupta et al., 2016), and these currently unrecognized plaques may explain some ESUS cases. The other likely underlying source of ESUS is the heart. Indirect evidence at the time of stroke suggests that many CSs arise from cardiac embolism (Sacco et al., 1989), and long-term follow-up of CS patients with continuous heart rhythm monitoring often reveals paroxysmal AF that was not apparent at the time of stroke (Gladstone et al., 2014; Sanna et al., 2014).

Together, these considerations suggest an imperfect but substantial overlap among CS, ESUS, and cardioembolic stroke. CS can be used to refer to a stroke with incomplete evaluation. However, if CS is stringently defined, it essentially equals ESUS. CS and cardioembolic stroke are not synonymous because some cases of CS likely reflect nonstenosing LAA, but the overlap between cryptogenic and cardioembolic stroke is substantial because many cases of CS likely reflect undiagnosed paroxysmal AF (Gladstone et al., 2014; Sanna et al., 2014). In addition, emerging evidence suggests that some seemingly CSs originate in the left atrium even though AF is not present (Kamel et al., 2016).

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Chapter II

AIMS, MATERIALS AND METHODS

2.1 AIMS OF THE STUDY

Stroke registries are important to assess stroke incidence, prevalence, and mortality, to identify risk factors, associated medical diseases, and prognostic factors, to compare local with regional, national, and international data, to formulate guidelines, improve health services and medical assistance, and to plan adequate therapeutic trials.

L'Aquila stroke registry is a prospective ongoing population-based study set up in 1994 to obtain epidemiological and clinical data on stroke cases occurring in the L'Aquila district, in central Italy (Carolei et al., 1997; Marini et al., 2001; Sacco et al., 2006). The purposes of this study were:

- To assess the incidence, characteristics, short- and long-term prognosis of first-ever ischemic stroke (FEIS) **(Chapter III)**.

- To assess the prevalence, incidence, characteristics, short- and long-term prognosis of ischemic stroke etiologic subtypes **(Chapter IV)**.

- To evaluate the contribution of atrial fibrillation (AF) to the incidence and prognosis of FEIS. It was also aimed to compare these recent data on AF with those from the 1994-1998 study (Marini et al., 2005 Carolei et al., 1997; Sacco et al., 2006) in order to evaluate possible epidemiological changes over two decades **(Chapter V)**.

- To evaluate the contribution of AF diagnosed after stroke onset (newly diagnosed atrial fibrillation; NDAF) to the incidence, and prognosis of FEIS, and to speculate about the neurogenic or cardiogenic origin of NDAF **(Chapter VI)**.

2.2 MATERIALS AND METHODS

Study design

Cases of FEIS were ascertained from January 1, 2011 until December 31, 2013 in a prospective population-based registry of patients residing in the L'Aquila district, central Italy. To be included in the study, patients had to reside in the district at the time of the event and had to present a first-ever stroke (FES). Study design, case-finding procedures, and methodology followed the standards of data reporting for population-based studies (Feigin et al., 2004). Besides, the study was conducted according to the principles of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (von Elm et al., 2007). Study design, case-finding procedures, and methodology were the same of the former L'Aquila Stroke Registry (LASR) that was conducted in 1994-1998 and described elsewhere (Carolei et al., 1997; Sacco et al., 2006).

Study population

The district of L'Aquila (Figure 1) is a mountainous area of 5034.46 km^2 of the Abruzzo region, central Italy, with 108 towns and a continental weather pattern (Carolei et al., 1996). The population is served by 4 public hospitals, 5 private hospitals, 266 general practitioners, 78 on-call physicians, and the service known as the 118-emergency medical service (EMS). The total resident population at the 2011 census (ISTAT 2011), 52% rural, was 298,343, including 21,861 (7%) non-Italian residents, of whom about 22% were non-Caucasian (Supplemental Table 1). The 1991, 2001, and 2011 censuses showed that the total resident population remained stable over the last three decades (Table 1), despite a 26% reduction of subjects aged 0-24 years, a 4.5% increase of those aged 25-64 years, and a 15.2% increase of subjects aged 65 years and over; this trend was observed in both men and women

(Supplemental Figure 1). Medical care is free of charge for hospitalized patients, allowing easy access to medical services, whereas the payment of a fee is required for outpatient visits and ancillary investigations.

Definitions

Stroke was defined as rapidly developing signs of focal or global disturbance of cerebral function, lasting longer than 24 hours, or leading to death, with no apparent cause other than that of vascular origin (Aho et al., 1980) (codes 430 to 434 and 436 to 437, International Classification of Diseases, 9th Revision [ICD-9] (WHO, 1977).

Cerebral infarction was defined as a neurological deficit of sudden onset, documented by a brain computed tomography (CT) or magnetic resonance imaging (MRI) indicating the presence of infarction or the absence of hemorrhage in a defined vascular distribution. A *probable cerebral infarction* was diagnosed in the absence of brain neuroimaging or necropsy examinations and of clinical symptoms reflecting increased intracranial pressure such as headache and vomiting, decreased alertness or coma, and gradual progression to death within 24 hours of onset. Ischemic stroke syndromes were classified according to the Oxfordshire Community Stroke Project (OCSP) classification (Bamford et al., 1991) (Supplemental Table 2).

Intracerebral haemorrhage (ICH) was defined as a neurological deficit, documented by a brain CT or MRI indicating the presence of an intracerebral hemorrhage. In the absence of brain neuroimaging or necropsy examinations and of occlusive peripheral vascular disease, a diagnosis of probable intracerebral hemorrhage was made in the presence of clinical symptoms reflecting increased intracranial pressure such as headache and vomiting, decreased alertness or coma, and gradual progression to death within 24 hours of onset.

Subarachnoid hemorrhage was diagnosed in a patient who presented with a typical clinical syndrome of neurological deficit that may progress to coma, usually with headache, nuchal

rigidity, and evidence of hemorrhage in the subarachnoid space by lumbar puncture, brain CT, MRI, or necropsy.-*Ill-defined* or *unclassified cerebrovascular events* were considered all strokes that could not be categorized as ischemic, hemorrhagic, or due to subarachnoid hemorrhage because of the absence of adequate clinical signs or symptoms and confirmatory investigations.

Case-finding procedures

All subjects with neurological symptoms suggestive of a cerebrovascular event occurring during the study period were screened. Events were identified by active monitoring of inpatient and outpatient health services within the district and in nearby areas. In each clinical ward, all patients admitted for a cerebrovascular event were identified and examined within 7 days from stroke onset by a senior physician; thereafter all patients were screened by a consulting neurologist to validate the event. To verify all admissions, two consultant neurologists screened the admission and discharge lists on a daily basis. The EMS, emergency rooms, neuroradiology, neurophysiology, and neurosonology services were systematically checked. Regular contacts were also maintained with rehabilitation and long-term care services. Nearby hospitals were regularly monitored to identify those residents who had cross-boundary medical care. The study purpose was explained in advance to general practitioners, who were asked to refer all stroke cases or give information about patients evaluated at home. Death certificates were checked monthly and clinical data of all patients deceased with a diagnosis of ischemic stroke and not otherwise included in the registry were reviewed. Hot pursuit (active identification of all events as they occurred) and cold pursuit (retrospective identification of the same events) were combined in the ascertainment of cases to ensure the complete identification of the events (Feigin et al., 2004).

Data collection and follow-up

Clinical and laboratory data were recorded on standardized and anonymized forms and stored in a computerized database. Basic information included medical history, cardiovascular and neurological evaluations, and routine laboratory blood tests, including the last available International Normalized Ratio (INR) value. Where available, we recorded the results of ancillary investigations such as 12-lead electrocardiography (ECG), transthoracic echocardiography, transesophageal echocardiography, Doppler ultrasonography of neck vessels, transcranial Doppler, brain CT and MRI studies with diffusion-weighted imaging (DWI) sequences, CT angiography and MR angiography. Risk factors such as arterial hypertension, diabetes mellitus, AF, hypercholesterolemia, cigarette smoking, coronary heart disease, peripheral artery disease, and previous transient ischemic attack (TIA) were also recorded. Definitions of risk factors are reported in the Supplemental Methods.

The presence of AF at stroke onset and its occurrence during the acute phase of the event had to be confirmed by a standard 12-lead ECG or cardiac monitoring. The 2010 European Heart Rhythm Association definition of AF was applied (European Heart Rhythm Association, 2010). First detected episodes of AF were classified as NDAF and considered as paroxysmal AF, in the presence of spontaneous conversion to sinus rhythm, or as permanent AF if sustained. Already known AF was classified as previously diagnosed (PDAF) and considered as paroxysmal or permanent based on medical history and availability of previous ECG recordings. For the study purpose, episodes of persistent AF were included in the permanent group.

In hospitalized patients, we also recorded the following variables: level of consciousness on admission according to the Glasgow Coma Scale (GCS) score; neurological impairment on admission and at discharge based on the National Institutes of Health Stroke Scale (NIHSS) score; disability or dependence in the daily activities at discharge assessed by means of the modified Rankin Scale (mRS) score (Rankin et al., 1957; van Swieten et al., 1988);

premorbid CHA_2DS_2VASc score (Lip et al., 2010) (Supplemental Table 3); and premorbid and post-stroke antithrombotic treatments, classified according to the Anatomical Therapeutic Chemical (ATC) Classification System (WHO).

All cases were reviewed and Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were applied in order to define etiologic subtype of ischemic stroke as large artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), other cause (OC), and undetermined cause (UND) (Supplemental Table 4).

All cases were followed-up by quarterly planned in-person visits or by a structured telephone interview, either in person or with a close relative or with the general practitioner, up to August 31, 2018. Recorded outcome events were TIA, recurrent nonfatal and fatal stroke, nonfatal and fatal myocardial infarction, and death from either vascular or nonvascular causes. Definitions of outcome events are reported in the Supplemental Methods.

Statistical analysis

Descriptive statistics are reported as absolute numbers with percentages, mean ± standard deviation (SD), or median with interquartile range (IQR). Groups were compared using the Student's t-test or the Pearson χ^2 test, and with the Mann-Whitney U test for non-normally distributed variables. Two-sided statistical significance was set at a P level <0.05. Crude incidence rates were calculated with data from the 2011 census (ISTAT, 2011). Standardized rates were obtained by the direct method with 10-year age grouping of the Italian (ISTAT, 2011) and European population (EUROSTAT, 2011) as standard (Table 2, Supplemental Figure 2).

Confidence intervals (CIs) for incidence rates were calculated assuming a Poisson distribution for the number of cases. Missing values were not entered when assessing baseline variables; we entered missing values using the median of the variables when

performing regression analyses, where applicable. The risk of outcome events at 30 days, 1 year, and 5 years was measured using the Kaplan–Meier method.

Comparisons of stroke recurrence and overall survival probability between patients with and without AF and between NDAF and PDAF were performed by the log-rank test. Age, sex, AF type, NDAF, NIHSS score at onset, and the lack of premorbid antithrombotic treatment were used as covariates in the Cox regression analysis in order to identify predictors of mortality in FEIS patients with AF. Comparisons between survival curves for patients with different stroke types were performed by the log-rank test. Statistical analyses were performed with SPSS Statistics version 20.0 and R statistical software.

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Chapter III

INCIDENCE, CHARACTERISTICS, SHORT- AND LONG-TERM PROGNOSIS OF FIRST-EVER ISCHEMIC STROKE

3.1 AIM OF THE STUDY

Updated epidemiological data are important to develop guidelines, to plan therapeutic trials, and to improve dedicated health services and medical assistance. Based on these premises, this study was aimed at providing recent data on FEIS incidence, characteristics, short- and long-term prognosis.

3.2 MATERIAL AND METHODS

Study design, study population, definitions, case-finding procedures, data collection, follow-up, and statistical analysis are reported in Chapter II.

3.3 RESULTS

From January 1, 2011, to December 31, 2013, 2,116 patients with clinical signs attributable to stroke were identified. After comprehensive evaluations, 836 patients (39.5%) were excluded because of nonfatal (n=173) or fatal (n=70) recurrent stroke, residence out of the district (n=213), stroke due to head trauma (n=90), perinatal intraventricular hemorrhage (n=1), focal neurologic symptoms not attributable to stroke (n=241), and symptoms attributable to a previous stroke (n=48) (Table 3). After those exclusions, 1,280 patients with a FES were included (Table 4). Fifty-five subarachnoid hemorrhages (4.3%, 95% CI 3.2-5.4), 268 intracerebral hemorrhages (20.9%, 95% CI 18.7-23.2), 919 ischemic strokes (71.8%, 95% CI 69.3-74.3), and 38 ill-defined acute cerebrovascular events (3.0%, 95% CI

2.0-3.9) were included in the registry (Figure 2).

Out of 919 patients with the diagnosis of FEIS, 485 (52.8%) were women and 434 men, with an age between 7 and 99 years (mean age±SD 76.5±12.0 years)(Table 5); women were 6.8 years older at FEIS onset as compared with men (79.7±10.8 vs 72.9±12.2 years; P<0.0001). Among the included patients, 12 (1.3%) were aged less than 45 years, 45 (4.9%) between 45 and 54 years, 75 (8.2%) between 55 and 64 years, 195 (21.2%) between 65 and 74 years, 340 (37.0%) between 75-84 years, and 252 (27.4%) 85 years or greater. Figure 3 shows the distribution by age and sex of the FEIS patients included in the registry.

Nine hundred and nine patients (98.9%) were hospitalized, including 899 within the district and 10 out of the district; one patient (0.1%) was included in the study after a report by a general practitioner, and 9 (1.0%) by death certificates (Table 6).

Among hospitalized patients, the mean length of hospital stay was 10.2±6.7 days.

The clinical diagnosis was supported by brain neuroimaging in 918 (99.9%) patients, of whom 607 underwent brain CT, 13 brain MRI, and 298 both; one patient was diagnosed as a probable ischemic stroke based upon clinical criteria. Pathologic examination was not performed in any patient.

The crude incidence rate of FEIS was 102.68 per 100,000 person-years (95% CI, 96.15-109.53) (Table 7 and Figure 4). After standardization by the 2011 Italian population, the incidence rate was 93.89 (95% CI, 86.23-102.01) per 100,000 person-years. After standardization by the 2011 European population the incidence rate was 79.09 (95% CI, 71.49-87.27) per 100,000 person-years. The rate (Table 7) was higher in women compared with men (105.66 vs 99.54 per 100,000 person-years) and was highest among subjects aged more than 85 years (791.62 per 100,000 person-years).

The prevalence of the main vascular risk factors among patients with FEIS is reported in Table 8. Arterial hypertension (76.2%) and AF (32.0%) were the most prevalent vascular risk factors in patients with FEIS. The median±IQR NIHSS score was 5 [3-10] at stroke onset, and 4 [2-8] at discharge. The median±IQR mRS score at discharge was 3 [2-4].

One hundred and sixty-three patients died within 30 days from FEIS, with a case- fatality rate of 18.0% (95% CI, 16.6-20.6) (Table 9). One hundred and eleven patients (67.3%) died from cerebral causes, 42 (25.5%) from cardiac causes, and 11 (6.7%) from nonvascular causes; the cause of death could not be determined in 1 (0.6%) patient (Table 10).

Two hundred and fifty-nine patients died within 1 year from FEIS, with a case- fatality rate of 28.2% (95% CI, 25.4-31.2) (Table 7). One hundred and thirty-four patients (51.7%) died from cerebral causes, 72 (27.8%) from cardiac causes, and 51 (19.7%) from nonvascular causes; the cause of death could not be determined in 2 (0.8%) patients (Table 10).

At the 5-year follow-up, 399 (43.4%) died, of whom 154 (38.6%) from cerebral causes, 137 (34.3%) from cardiac causes, and 104 (26.1%) from nonvascular causes; the cause of death remained unknown in 4 (1.0%) patients (Table 8). Kaplan-Meier curve (Figure 5) showed that the 5-year cumulative probability of survival in patients with FEIS was 56.6%. The Cox regression analysis (Table 11), adjusted by sex, age, and vascular risk factors, showed that AF and diabetes mellitus were independent predictors of mortality at 30 days and at 1 year, while hypercholesterolemia was inversely associated with the mortality risk.

Out of 754 (82.0%) patients that survived more than 30 days after the event, 64 (8.4%) patients had a FEIS recurrence, 22 (2.9%) a transient ischemic attack, and 15 (2.0 %) a myocardial infarction. The rate of nonfatal stroke recurrence (59; 7.8%) was sevenfold higher than of that of fatal stroke (8; 1.1%). Kaplan-Meier curve (Figure 6) showed that the 5-year cumulative probability of recurrent ischemic strokes in patients with a FEIS was 7.1%.

3.4 DISCUSSION

This study was aimed to report an update on ischemic stroke epidemiology in Italy. Epidemiological data about stroke characteristics in the district of L'Aquila are relevant at national level, since the population of the district remained stable from 1991 to 2011 (Table 1) and its age structure is comparable to that of the whole Italian population (Supplemental Figure

2). In the present study, FEIS accounted for less than three quarters of all FES. The 71.8% of FEIS cases found in the present study was lower than the 82% pooled proportional frequency found between 2000 and 2008 in other high-income countries (Feigin et al., 2009), and is lower than the 81% found in New Zealand between 2011-2012 (Krishnamurthi et al., 2018), than the 80.9% found in France between 2007-2012 (Guéniat et al., 2018), than the 80.8% in Greece between 2010-2012 (Tsivgoulis et al., 2018), than the 77.7% found in Greece between 2010-2011 (Stranjalis et al., 2014), and only slightly lower than the 75.1% reported in Argentina between 2013-2015 (Bahit et al., 2016), but it is higher than the 64.2% reported in Japan in 2011 (Takashima et al., 2017). The lower proportion of FEIS cases in the present study as compared with other comparable studies is possibly attributable to differences in populations' structures and risk factors profiles and may be the result of higher effectiveness of primary prevention strategies.

In the present study, arterial hypertension was found in more than 76% of FEIS patients, being by far the most prevalent stroke risk factors. This result is in line with those of the previous Italian ones (Sacco et al., 2011; Janes et al., 2013), in which the prevalence of arterial hypertension ranged from 54 to 77%, with the study performed in New Zealand (65%) (Krishnamurthi et al., 2018), in France (62.8%) (Guéniat et al., 2018), and in Germany (86.9%) (Palm et al.,2011). After arterial hypertension, the most prevalent risk factor was atrial fibrillation (32.0%), in line with the most recent Italian population-based study (Janes et al., 2013) and with the French study performed between 2007-2012 (Guéniat et al., 2018).

The FEIS annual crude incidence rate of 102.68 per 100,000 person-years was the lowest ever recorded in Italy (Sacco et al., 2011; Janes et al., 2013; Corso et al., 2013) and, respectively, lower than those reported in Greece (477.1 per 100,000 person-years)(Tsivgoulis et al., 2018), in Germany (186 per 100,000 person-years) (Palm et al.,2011), and in Australia (134 per 100,000 person-years) (Leyden et al., 2013), and higher than those reported in New Zealand (97 per 100,000 person-years) (Krishnamurthi et al., 2018), in Argentina (78.9 per 100,000 person-

years) (Bahit et al., 2016), in Japan (99.8 per 100,000 person-years) (Takashima et al., 2017), and in Nigeria (30.54 per 100,000 person-years) (Okon et al., 2015).

After standardization to the European population, our rate (79.9 per 100,000 person-years) was lower than that reported in Greece (425.9 per 100,000 person-years) (Tsivgoulis et al., 2018), in Argentina (139.9 per 100,000 person-years) (Bahit et al., 2016), and in Japan (91.3 per 100,000 person-years) (Takashima et al., 2017).

We also found a higher incidence of FEIS in women than in men that was in line with the results of an Argentinian (Bahit et al., 2016), German (Palm et al.,2011), and a previous Italian studies (Corso et al., 2013), and at variance with other studies reporting a higher incidence in men than in women (Okon et al., 2015; Krishnamurthi et al., 2018; Guéniat et al., 2018; Tsivgoulis et al, 2018; Takashima et al., 2017).

The mean age at stroke onset found in the present study was 76.5±12.0 years and was higher than that reported by the European Community Stroke Project (Di Carlo et al., 2006), and by the Ludwigshafen Stroke Study (Palm et al.,2011).

The mean age at FEIS stroke onset that we found in the present study (76.5±12.0 years) was 1.2 years higher than that reported in the 1994-1998 L'Aquila Stroke Registry (75.3 years) (Sacco et al., 2006), that was mainly due to the increase of the mean age in women (from 77.0±10.1 to 79.7±10.8 years in women; from 73.4±11.0 to 72.9±12.2 years in men), while the crude annual incidence rate was lower (102.68 per 100,000 person-years) compared to this previous study (241.44 per 100,000 person-years). Over that time, effective primary preventive measures, including smoking cessation and blood pressure control, may have contributed to decrease FEIS incidence and to postpone its onset. Nevertheless, it is not possible to exclude the role of competing fatal diseases in the reduction of the incidence of FEIS.

In the present study, the CFR was 18.0% at 30 days, 28.2% at 1 year, and 43.4% at 5 years. Our 30-day CFR (18.0%) was similar to the 15.6% reported in the Argentinian study (Bahit et al., 2016), to the 16.2% CFR at 28-day reported by the Greek study (Tsivgoulis et al., 2018), to the 16% CFR at 28-days reported by the Australian study (Leyden et al., 2013), and to the 16.8%

CFR at 28-day reported by the recent Italian registry (Janes et al., 2013), while it was higher than the 6.9% CFR at 28-day at reported by the Japanese study (Takashima et al., 2017) and than the 10.8% CFR at 28-days reported by a previous Italian study (Corso et al., 2013), Our 1-year CFR (28.2%) was similar to that reported in France between 2007-2012 (26.3%) (Guéniat et al., 2018), and to that reported by a previous study in Italy (25.3%) (Corso et al., 2013). During the short-term period after a FEIS, cerebral deaths are the most common causes of death, possibly depending on stroke severity. Nevertheless, from FEIS onset up to 5 years there is a progressive decrease of cerebral deaths and an increase of cardiac deaths, suggesting that FEIS-related mortality during the short-term period after stroke mostly depends on stroke severity and related complications, and improved management of the acute phase represents the main goal during the acute phase of a FEIS for improving survival. Moreover, considering the relative low frequency of stroke recurrences (7.1% at 5 years), secondary prevention of stroke is perhaps not the only consideration amongst strategies for the long-term reduction of FEIS-mortality, and optimization of prevention strategies for heart diseases should be considered.

3.5 CONCLUSIONS

We found in our population a fairly low incidence of FEIS, low rates of vascular follow-up events, and similar CFRs compared to concurrent registries. These results are likely due to improved control of vascular risk factors, effective primary preventive measures, and improved ischemic stroke management during the acute phase.

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Chapter IV

EPIDEMIOLOGY OF ISCHEMIC STROKE SUBTYPES ACCORDING TO TOAST CRITERIA

4.1 AIM OF THE STUDY

The aim of this study was to determine the incidence, recurrence, and long-term survival rates of ischemic stroke subtypes by a mechanism-based classification scheme (Trial of ORG 10172 in Acute Stroke Treatment, or TOAST). Providing recent epidemiological data about the underlying etiology of FEIS is paramount to plan targeted treatment for ischemic stroke prevention.

4.2 MATERIAL AND METHODS

Study design, study population, definitions, case-finding procedures, data collection, follow-up, and statistical analysis are reported in Chapter II.

4.3 RESULTS

Among the 919 patients with a FEIS included in the registry, the distribution of etiologic subtypes was as follows: large-artery atherosclerosis (LAA) (118, 12.8%), cardioembolism (CE) (321, 34.9%), small artery occlusion (SAO) (109, 11.9%), other causes (OC) (43, 4.7%), undetermined causes (UND) (328, 35.7%) (Figure 7).

OC strokes were due to acquired hypercoagulability state (45.2%), congenital thrombophilia (31.0%), arterial dissection (16.6%), venous thrombosis (2.4%), embolism post-thromboendoarterectomy (2.4%), and hypoperfusion due to cardiac arrest (2.4%).

Strokes were UND because of incomplete evaluation in 84.1%, because no likely etiology determined despite an extensive evaluation was found in 7.9%, and because of the presence two or more potential causes in 7.9%.

Patients with CE were older at FEIS onset (79.28±10.21 years) and those with OC were younger (62.28±16.86 years) with respect to patients with LAA (74.49±11.40 years), SAO (70.75±11.93 years) and UND (76.50±10.54 years) (P<0.001).

The proportion of risk factors for each etiologic subtype is presented in Table 12. The proportion of arterial hypertension (P<0.001), AF (P<0.001), hypercholesterolemia (P=0.009), cigarette smoking (P<0.001), and coronary heart disease (P=0.013) varied significantly among the different etiologic subtypes.

In particular, arterial hypertension was more frequent in patients with SAO (85.3%), and in those with CE (80.4%), hypercholesterolemia was more frequent in patients with SAO (28.4%) and in those with LAA (28.0%), while it was less frequent in CE (16.5%) and in those with OC (14.0%), cigarette smoking was more frequent in patients with OC (32.6%) and less frequent in those with CE (8.4%), and coronary heart disease was more frequent in patients with CE (19.9%) and in those with SAO (17.4%). The proportion of AF was 78.8% in CE, and 12.5% in UND. The distribution of diabetes mellitus and peripheral artery disease was similar among FEIS etiologic subtypes (Table 12).

Stroke was more severe (median [IQR] NIHSS at onset, 7 [4-15]; median [IQR] NIHSS at discharge, 5 [2-11]) in patients with CE with respect to those with other etiologic subtypes (P<0.001 for both comparisons) (Table 12). Stroke was more disabling in patients with CE (median [IQR] mRS score at discharge; 3 [2-5]), LAA (median [IQR] mRS score at discharge; 3 [2-4]), and UND (median [IQR] mRS score at discharge; 3 [2-4]), with respect to those with SAO (median [IQR] mRS score at discharge; 2 [1-3]), and OC (median [IQR] mRS score at discharge; 2 [1-3.8]) (P<0.001)) (Table 12).

Age- and sex-specific annual incidence rates by ischemic stroke etiologic subtype are presented in Table 13. The highest overall incidence rate was found in the CE subtype

(35.86 per 100,000 person-years; 32.47 per 100,000 person-years after standardization by the 2011 Italian population; 29.96 per 100,000 person-years after standardization by the 2011 European population), whereas the lowest was found in the OC subtype (4.80 per 100,000 person-years; 4.88 per 100,000 person-years after standardization by the 2011 Italian population; 4.59 per 100,000 person-years after standardization by the 2011 European population). Among all etiologic subtypes, the highest incidence rates were found in patients aged 75 years and older Table 13.

Figure 8 presents Kaplan-Meier estimates of the cumulative probability of recurrence for the different subtypes. After 5 years, the highest probability of stroke recurrence was found in CE (8.7%), followed by OC (4.7%) and LAA (4.2%), whereas the lowest recurrence rate was in SAO (1.8%) and in UND (1.8%).

In Table 14 are reported the 30-day, 1-year, and 5-year CFRs according to etiologic subtypes. Patients with CE strokes had the highest 30-day (26.5%), 1-year (40.8%), and 5-year (56.7%) CFRs with respect to the other subtypes ($P<0.001$), while patients with SAO had the lowest 30-day (1.8%), 1-year (5.5%), and 5-year (19.3%) CFRs.

Figure 9 presents Kaplan-Meier survival probability according to the different etiologic subtypes up to 5 years. The highest 5-year survival was found in SAO (80.7%), followed by UND (61%) and LAA (56.8%), while the lowest was in CE (43.3%).

The multivariate Cox regression analysis (Table 15) including age, sex, and etiologic subtypes, showed that CE was an independent predictor of morality at 1 year, while SAO was inversely associated with mortality risk at 30 days and 1 year (Model 1). When including stroke severity at onset according to the NIHSS score as variable (Model 2) in the Cox regression analysis (Table 15), it did not confirm that CE and SAO were independently associated with mortality, while stroke severity according to the NIHSS score at onset was an independent predictor of 30-day and 1-year mortality. Those results possible suggest that stroke severity has a crucial role in the risk of death and that the higher case-fatality in CE is

probably mostly determined by the worse stroke severity in this subtype, than from stroke etiology itself.

4.4 DISCUSSION

The present study provides for recent epidemiological data on ischemic stroke etiology according to the TOAST criteria in a European population. Good quality stroke incidence study evaluating the distribution of etiologic subtypes and outcomes contributes to evidence-based projections of future stroke burden, allow proper evaluation of the effectiveness of prevention strategies and planning future pattern of intervention.

Complete case ascertainment is hampered by admission practice variability worldwide, deaths before referral, admission refusal, or non-referral because of cases managed in the familiar setting. For all these reasons, population-based studies represent the most reliable source of stroke epidemiology when compared with hospital-based ones. Nevertheless, even with extensive case finding procedures, it is not possible to exclude that a number of patients with minor stroke may disregard their symptoms and not seek medical attention. Considering that the TOAST mechanism-based classification scheme is based on the results of brain neuroimaging and the findings of ancillary diagnostic investigations, it follows that population-based studies with a high rate of hospitalization, better estimate the distribution of ischemic stroke etiologic subtypes. Although medical care is provided free of charge, and even though it is our country policy that all patients presenting with a possible acute cerebrovascular event should be offered hospital admission for further investigations and treatment, regardless of stroke severity, it is not possible to exclude that some people did not consult their physician. In our study the hospitalization rate of FEIS was 98.9%, that is higher than those reported from other countries worldwide (41% in Japan) and across Europe (about 95%) (Asplund et al., 1995; Kolominsky-Rabas et al., 1998).

In this study, the distribution of vascular risk factors highlights the high prevalence of hypertension across all TOAST subtypes; the higher prevalence was found in SAO (85.3%), possibly confirming the role of hypertension in small artery disease. The prevalence of hypertension reported by our FEIS patients is significantly higher than that found by previous reports among all etiologic subtypes (Kolominsky-Rabas et al., 2001). AF was reported in 12.5% of patients with UND within the group of those having two or more potential stroke causes. The highest prevalence of hypercholesterolemia was found in SAO (28.4%) and in LAA (28.0%), possibly confirming the role of high cholesterol levels in the pathogenesis of atherosclerosis.

Patients with UND had a vascular risk factor profile that was intermediate between that of LAA and CE; it is important to point out that the group of UND is heterogeneous as it includes cases due to unknown causes because of incomplete or negative findings even after an extensive investigation, but also cases with two or more known overlapping etiologic causes. Considering that overall CE and LAA are the most prevalent etiologic subtypes with respect to the others, it is reasonable that a high proportion of patients in UND might have an occult arterial or cardiac source of embolism, thus influencing the vascular risk factor profile of UND.

When age-adjusted for the European population, the highest incidence rates in the present study were found for CE (29.96 per 100,000 person-years) and UND (28.76 per 100,000 person-years) and the lowest for OC subtype (4.59 per 100,000 person-years). Our incidence rate standardized for the 2011 European population, with respect to that reported by the ESPro register performed in 1994-1998 (Kolominsky-Rabas et al., 2001), was lower for SAO (10.19 vs 25.8 per 100,000 person-years) and UND (28.76 vs 39.3 per 100,000 person-years), similar for LAA (10.59 vs 15.3 per 100,000 person-years) and for CE (26.96 vs 30.2 person-years), while was higher for OC (4.59 vs 2.1 per 100,000 person-years). Incidence rates increased with age across all etiologic subtypes, with a more robust rise in CE and UND groups; those findings are in line with the results of the ESPro register (Kolominsky-Rabas et al., 2001).

In our study the 34.9% of FEIS patients had a CE stroke (34.9%), and they were mostly female (60.4%) and older (79.28 years) at FEIS onset with respect to other etiologic subtypes; a finding largely consistent with the higher survival probability of women and with the higher prevalence of atrial fibrillation in the older age groups in the general population.

With respect to other recent population-based registries on FEIS patients, our relative proportion of CE was similar to the 33% reported in Whites in United Kingdom in 2007 (Markus et al. 2007), to the 34% in Ireland in 2010 (Marnane et al., 2010), and to the 33% in Croatia in 2012 (Pikija et al., 2012), while it was higher than the 24% in France in 2005-2006 (Béjot et al., 2008), to the 25% in Italy in 2004-2008 (Corso et al., 2013), to the 28% in United Kingdom in 1999-2005 (Hajat et al., 2010), to the 27% reported in Chile in 2000-2002 (Lavados et al., 2007), and than the 15% in Brazil in 2005-2006 (Lange et al 2015). Differences in the proportion of elderly persons in the referral general population, and in the rate and duration of cardiac rhythm monitoring, are the most likely determinants of differences in CE prevalence across different studies. However, these studies underlie that in the current century, about one third of FEIS patients suffers from a CE strokes. Then, it is important to point out that the impact of this etiologic subtype is not only attributable to its high prevalence, but also to the highest burden in terms of neurological impairment, residual disability, mortality and recurrence rate of CE strokes with respect to other etiologic subtypes.

Indeed, this study found that CE strokes were more severe at stroke onset according to the NIHSS score, and together with UND was associated with a worse post stroke disability according to the mRS score. Moreover, in the present study, the highest 30-day, 1- and 5-year CFRs were found in CE and the lowest in SAO, and accordingly have respectively the lowest and the higher 5-year survival probability. The highest recurrence rate at the 5-year follow up was found in CE (8.7%) and the lowest in SAO (1.8%) and UND (1.8%) subtypes. Our analyses, support the hypothesis that CE strokes are independently associated with the risk of death during the short- and long-term period after FEIS, nevertheless this association seems to

be mostly determined by the higher stroke severity attributable to CE, than due to this etiologic subtype itself.

In this study a significant proportion of patients were diagnosed as having UND strokes (35.7%), mostly (84.1%) because of incomplete evaluation. The proportion of strokes of UND etiology is extremely variable across studies and may depends mostly on the rate of patients admitted to peripheral hospitals that have more limited access to diagnostic investigations. This subgroup includes cases where more than one cause was found, a category which is expected to increase as more advanced investigations are performed to identify the cause of ischemic stroke. Ischemic stroke due to UND also includes cases with incomplete examination as thorough diagnostic work-up is unfortunately still not routinely performed in every patient with ischemic stroke. Some cases remain incompletely investigated because of very early death after FEIS, but increased use of available diagnostic tests would be appropriate for surviving patients to reduce the proportion of stroke due to UND. Moreover, ischemic stroke due to UND can be due to negative examination (i.e. cryptogenic stroke). There is an increasing interest in trying to understand the causes of cryptogenic stroke. Cryptogenic events might often be caused by occult arterial sources of thromboembolism, paroxysmal atrial fibrillation, patent foramen ovale, or minor-risk cardiac structural abnormalities (Hart et al., 2014). However, even with detailed investigation, only a third of patients with cryptogenic stroke have possible sources of embolism, some of which are probably coincidental (Hart et al., 2014; Li et al., 2015). Similarly, although long-term monitoring of heart rhythm identifies paroxysmal atrial fibrillation in up to a third of patients with cryptogenic events (Gladstone et al., 2014; Sanna et al., 2014), the clinical relevance of short episodes of atrial fibrillation is uncertain and a recent study questioned the role of paroxysmal atrial fibrillation as the major cause of cryptogenic stroke (Li et al., 2015).

A recent systematic review and meta-analysis (Ornello et al., 2018) analyzing the worldwide distribution of ischemic stroke subtypes according to the TOAST criteria found that overall, ischemic strokes were attributable to CE in 22%, LAA in 23%, SAO in 22%, OC in 3%, and UND 26%, although differences in the distribution of stroke etiologic subtypes according to ethnicity was found, since CE was the leading ischemic stroke etiology in Whites, while LAA in Asians. Interestingly, it has been reported an increasing temporal trend, from 1993 to 2015, for CE in Whites and LAA in Asians. Although it is not possible to exclude that the observed geographic and temporal variations might have depended on changes of the demographic structure of the resident populations, certainly it cannot be ignored the role of genetic and environmental factors and the differences in the local implementation of primary preventive measures. These results further support the increasing burden of CE in stroke epidemiology and the need for the development of targeted preventive measures.

4.5 CONCLUSIONS

Our study, together with other recent evidence about demographic and secular trends of stroke etiologic subtypes, shows that CE is the most common cause of stroke. Given the higher stroke severity and the poorer outcomes associated with CE, effective preventive measures including prevention, detection and treatment of cardiac risk factors might contribute to a significant reduction of the overall stroke burden. Moreover, since the correct identification of stroke etiology is of utmost importance for effective secondary prevention, further efforts are needed to reduce the proportion of patients with UND.

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Chapter V

THE CONTRIBUTION OF ATRIAL FIBRILLATION TO THE INCIDENCE AND PROGNOSIS OF FIRST-EVER ISCHEMIC STROKE

5.1 AIM OF THE STUDY

The purpose of this study was to investigate the incidence, prevalence, and characteristics of patients with a first-ever in a lifetime ischemic stroke and AF, and to evaluate the influence of this arrhythmia on the their short- and long-term prognosis. Moreover, it also aimed to evaluate the presence of epidemiological changes of FEIS associated with AF over two decades (from 1994-1998 to 2011-2013).

5.2 MATERIAL AND METHODS

Study design, study population, definitions, case-finding procedures, data collection, follow-up, and statistical analysis are reported in Chapter II.

5.3 RESULTS

During the study period we identified 919 FEIS in the resident population. After the exclusion of 9 patients without ECG evaluation, AF was documented in 294 (32.3%) of the remaining 910 patients. All patients but one were hospitalized; mean duration (days±SD) of hospital stay was 10.7±7.1 days. Two hundred ninety-three (99.7%) patients received brain neuroimaging evaluations: 239 (81.3%) brain CT, 54 (18.4%) brain CT and MRI; one patient was diagnosed as a probable ischemic stroke based upon clinical criteria.

One hundred eighty-eight patients (63.9%) were women and 106 (36.1%) were men; mean age±SD at stroke onset was 82.1±8.1 years (83.2±7.6 years in women and 80.1±8.5 years in men; P=0.001).

AF was paroxysmal in 64 patients (21.8%) and permanent in 230 (78.2%). Permanent AF was nonvalvular in 213 patients (92.6%) and valvular in 17 (7.4%).

The prevalence of AF (Table 16) increased with age in both sexes, from 6.5% in patients younger than 60 years up to 52.9% in those 90 years and older and was higher in women than in men in all age groups (Figure 10). By assuming the reported relative risk of 5 for AF, the estimated etiologic fraction was 25.9% for the whole cohort (Wolf et al., 1991).

In Table 17 are reported the baseline characteristics of patients with and without AF. Patients with the arrhythmia with respect to patients without were mostly women, aged ≥80 years, with arterial hypertension and less frequently hypercholesterolemic and cigarette smokers.

Stroke at onset (median NIHSS score at onset [IQR]: 9 [4-17] vs 5 [3-10]; P<0.001) and at discharge (median NIHSS score at discharge [IQR]: 5 [2-11] vs 3 [2-4]; P<0.001) was more severe and more disabling (median mRS score at discharge [IQR]: 4 [3-5] vs 3 [2-4]; P<0.001) in patients with AF than in those without the arrhythmia (Table 17).

When analyzing the distribution of the clinical stroke subtypes, patients with AF with respect to those without the arrhythmia, had more total anterior circulation infarcts (TACI), similar proportions of partial anterior circulation infarcts (PACI), and less lacunar (LACI) and posterior circulation infarcts (POCI) (Table 17). The proportion of insular involvement in brain lesions was significantly higher in patients with AF (40.8%) than in those without the arrhythmia (19.3%) (P<0.001), while no difference in lesion side distribution was found (Table 17).

Two hundred eighty-nine patients (98.3%) with AF and a premorbid CHA_2DS_2VASc score ≥2 were considered at high risk of thromboembolic events (Lip et al., 2010). At stroke onset 123 patients (41.8%) were on antiplatelets and 73 (24.9%) on a vitamin K antagonist

(VKA); only 19 patients (26.0%) had an INR value in the therapeutic range. At discharge, 40.3% of the surviving patients were prescribed antiplatelets and 29.9% a VKA.

The overall crude annual incidence rate of FEIS in patients with AF (Table 18) was 32.85 (95% CI 29.30-36.82) per 100,000 person-years, 28.77 (95% CI 24.62-33.42) per 100,000 person-years when standardized to the 2011 Italian population, and 23.77 (95% CI 19.69-28.44) per 100,000 person-years when standardized to the 2011 European population; all rates were higher in women than in men. As reported in Table 18, age- and sex-specific incidence rates increased with age in both sexes with a steep increase from the age of 65 years onward.

As showed in Table 19, 30-day, 1-year and 5-year CFRs were about two-fold higher in patients with AF than in those without the arrhythmia. The computation of the attributable death risk at 1 year, using the CFR obtained in patients with and without the arrhythmia (41.8% vs 20.6%) and the prevalence rate of AF that we found (32.3%), indicated that ≈25% of the stroke patients died because of the presence of AF.

At 30 days, cerebral (66.6% and 69.7%; P=0.680) and cardiac death (27.2% and 23.7%; P=0.617) were the most common causes in patients with and without AF; from day 31 onward and up to 5 years we observed in both groups a progressive reduction of the proportion of cerebral deaths and an increase of cardiac deaths (Table 20, Figure 11).

At the 5-year follow-up, AF patients had 24 (8.2%) recurrent stroke, including 3 fatal events, while patients without the arrhythmia had 45 (7.3%) recurrent stroke, including 7 fatal events. The probability of fatal and nonfatal recurrent strokes was higher in patients with AF compared to those without the arrhythmia at 1 year (4.4% vs 3.4%; log rank test P<0.001), while it was similar at 5 years (7.5% vs 7.0%; log rank test P=0.921) (Figure 12).

In patients with AF the probability of survival was significantly lower in AF patients than in those without at 1- (58.2% vs 79.4%; log rank test P<0.001) and 5-year (38.4% vs 66.1%; log rank test P<0.001) (Figure 13).

The Cox analysis, including age, sex, AF type, premorbid antithrombotic treatment and stroke severity at onset according to the NIHSS score, showed that the absence of premorbid antithrombotic treatment at stroke onset at 30 days, and stroke severity at 30 days and at 1 year were independent predictors of mortality (Table 21).

AF-RELATED FIRST-EVER ISCHEMIC STROKE PREVALENCE, INCIDENCE AND PROGNOSIS FROM 1994-1998 TO 2011-2013

Over the two study periods (1994-1998 vs 2011-2013) we found a 1.2 years increase of the overall mean age at FEIS onset (from 75.3±10.7 to 76.5±12.0), that was mainly due to the increase of the mean age in women (from 77.0±10.1 to 79.7±10.8 years in women; from 73.4±11.0 to 72.9±12.2 years in men) (Sacco et al., 2006). From 1994-1998 to 2011-2013, the relative proportion of FEIS decreased from 82.6% to 71.8% and was paralleled by a 75% decrease of FEIS incidence (incidence rate ratio [IRR] 0.43; 95% CI 0.40-0.46; P<0.001) (Table 22, Figure 14). When comparing the 1994-1998 CFRs of FEIS patients with those of 2011-2013 we found a decrease in 30-day and 1-year mortality (30-day standardized mortality ratio [SMR] 0.74; 95% CI 0.68- 0.80; 1-year SMR 0.75; 95% CI 0.70-0.79). While, from 1994-1998 through 2011-2013 there was an increased AF prevalence from the 60-69 years age group onward; the overall increase was 31.3% (from 24.6% to 32.3%; P<0.001), 37.5% in women (from 28.5% to 39.2%; P<0.001) and 21.2% in men (from 20.3% to 24.6%; P=0.051) (Marini et al., 2005). This trend was mainly driven by the overall 46.8% increase of AF prevalence in the age group 80-89 years (from 29.5% to 43.3%; P<0.001) from 1994-1998 through 2011-2013, that was 43.9% in women (from 31.4% to 45.2%; P<0.001) and 47.4% in men (from 26.8% to 39.5%; P=0.007) (Table 23, Figure 15). Comparing risk factors distribution in patients with AF, from 1994-1998 through 2011-2013 there was an increase in the proportion of patients aged 80 years and older and in the

proportion of patients with arterial hypertension, while we observed a reduction of the proportion of cigarette smokers, coronary heart disease and peripheral artery disease (Table 24). The variations corresponded to a 46.3% increase of the proportion of patients aged ≥80 years (from 45.8% to 67.0%; P<0.001), a 36.4% increase of hypertensive patients (from 61.6% to 84.0%; P<0.001), a 80.4% decrease of cigarette smokers (from 18.9% to 3.7%; P<0.001), a 53.2% decrease of patients with coronary heart disease (from 34.2% to 16.0%; P<0.001), and a 55.4 % decrease of patients with peripheral artery disease (from 16.8% to 7.5%; P<0.001) (Table 24).

When comparing the stroke type distribution according to the OCSP classification in the 1994-1998 and in the 2011-2013 registry we observed a significant reduction of the proportion of LACI (9.6% to 5.1%; P=0.018) and a significant increase of the proportion of POCI (from 7.8% to 14.6%; P=0.001), while the proportion of TACI and PACI was stable (Figure 16).

When comparing the overall crude incidence rate of FEIS among patients with AF in the present study with that reported in the previous one we observed a 44% reduction of the incidence rate ratio (IRR 0.56; 95% CI 0.49–0.64; P<0.0001) (Table 25, Figure 17). The overall IRR reduction occurred in both sexes and was 48% in men (IRR 0.52; 95% CI 0.41-0.64; P<0.0001) and 41% in women (IRR 0.59; 95% CI 0.50-0.70; P<0.0001). The trend of the IRR reduction was present in men aged 65 years and over, and in women aged 55 years and over (Table 25, Figure 17).

From 1994-1998 through 2011-2013, the cumulative probability of fatal and nonfatal stroke recurrences at 1 year in patients without AF (from 4.7% to 3.4%; P=0.159) and in those with AF (from 6.9% to 4.4%; P=0.127) was stable.

When comparing the 1994-1998 CFRs with those reported in 2011-2013 (Table 26), we found a decrease in 30-day and 1-year mortality in patients with and without AF, with a slightly more evident reduction in patients without AF (30-day SMR 0.62; 95% CI 0.53-

0.71; 1-year SMR 0.68; 95% CI 0.61-0.75) than in patients with AF (30-day SMR 0.70; 95% CI 0.61-0.78; 1-year SMR 0.73; 95% CI 0.65-0.79) (Table 26).

5.4 DISCUSSION

This study was conducted over 3 years and investigated the burden of AF in a large prospective population-based study including patients with a FEIS.

The overall prevalence of AF among our FEIS patients was 32.3%, a proportion higher than those reported in other comparable population- (from 16.8% to 31.3%) (Pikija et al., 2012; Kelly et al., 2012; Palm et al., 2012; Béjot et al, 2009) and hospital-based studies (from 15.2% to 31.7%) performed between 2000 and 2013 (Andersen et al., 2011; Medic et al., 2013; Bembenek et al., 2015).

Our AF patients were older at stroke onset (82.1±8.1 years) with respect to that of the patients included in other population-based studies (from 72.8±11.0 to 79.9±14.1 years) and was paralleled by a higher proportion of women (63.9%) with respect to the proportions reported in the same quoted studies (from 48.8% to 53.8%) (Pikija et al., 2012; Kelly et al., 2012; Palm et al., 2012). Nevertheless, it is not possible to exclude that differences in AF prevalence may depend on discrepancies on the proportion of the segment of elderly women in the various general populations (Arboix et al., 2001; Rosamond et al., 2008).

Comparison of the proportion of AF in stroke patients with other studies is made difficult by variations in case ascertainment procedures and in patients' selection. Indeed, the 32.3% AF prevalence that we found in our study was lower with respect to the 22% reported by a registry performed in Northern Italy in 2004-2008 (Corso et al., 2013) and to the 19% reported by another registry performed in France in the period 1985-2006 (Béjot et al., 2009). However, those discrepancies mostly depended on the presence of patients with premorbid AF only in the Italian study (Corso et al., 2013), and on the inclusion restricted to patients with cardioembolic stroke only, thus excluding AF patients with undetermined strokes attributable to two or more causes in the French study (Béjot et al., 2009).

In our study, the prevalence of AF increased with age from 6.5% in patients younger than 60 years up to 52.9% in those 90 years and older, and was similar to that reported in a Swedish study (from 8.6% in patients younger than 60 years, up to more than 50% in those 90 years and older) (Friberg et al., 2014).

In our study the association of AF with age ≥80 years and with arterial hypertension was strong. The same associations were reported in the population-based cohort of the Framingham Heart Study (Benjamin et al., 1994) and in the Swedish stroke register Risks-Stroke (Friberg et al., 2014).

Besides, our patients with AF, with respect to those without the arrhythmia had higher proportions of TACI (32.0% vs 12.5%) and corresponding higher median NIHSS scores on admission (9 vs 5) and mRS scores at discharge (4 vs 3). Similar findings were reported by the North Dublin Population Stroke study (Hannon et al., 2010) and by the Framingham Study documenting a greater stroke severity at onset and a poorer functional status measured by the Barthel Index score in AF than in non-AF patients, both acutely and at the 3-month follow-up (Lin et al., 1996).

Treatment of AF patients with antithrombotic drugs lowers the risk of cardioembolic stroke and of systemic embolism (Ezekowits et al., 1992; Connolly et al., 2009; Granger et al., 2011), nevertheless, only 24.9% of our AF patients with a premorbid CHA2DS2VASc score ≥2 were on a VKA at stroke onset.

Similar low proportions of patients treated with oral anticoagulants were reported in population-based studies performed in West Germany (24.1%) (Palm et al., 2012), in France (21.6%) (Béjot et al., 2009), and in the United Kingdom (16.8%) (Yiin et al., 2017).

In our study, after the index stroke, 40.3% of the surviving patients were prescribed antiplatelets and 29.9% a VKA; the corresponding proportion of patients receiving a VKA at hospital discharge was 36.4% in the Swedish stroke register Risks-Stroke (Friberg et al., 2014). These low proportions of oral anticoagulants prescribed soon after the stroke may have

depended on the current practice during the study period to maximize safety, mostly in patients with large infarcts, at greater risk of hemorrhagic transformation (Cucchiara et al., 2016).

In our patients the crude annual incidence rate of AF-related FEIS was 32.85 per 100,000 person-years, with a lower rate in men (24.31 per 100,000 person-years) than in women (40.96 per 100,000 person-years). Our reported crude rate was lower than the 41 per 100,000 person-years that was found in the OXVASC study performed in 2002-2012, also reporting a lower incidence rate in men than in women (Yiin et al., 2014) and lower than the 42 per 100,000 person-years reported in the North Dublin Population Stroke Study performed in 2005-2006 (Hannon et al., 2010).

In our study the presence of AF was associated with a higher short- and long-term mortality, indeed in-hospital, 30-day, 1-year, and 5-year CFRs were two-fold higher in patients with AF than in patients without the arrhythmia; similarly higher 30-day and 1-year CFRs were reported by a Danish hospital-based study (Andersen et al. 2011) and by the Program of Research Informing Stroke Management (PRISM) study (Gattellari et al., 2011). The 30-day, 1-year, and 5-year cumulative survival probability was lower in patients with AF than in those without the arrhythmia. Moreover, patients with AF had a higher risk of recurrent stroke at 1 year with respect to those without, while it was similar at 5 years.

Analyzing death causes, we found that at 30 days cerebral death was the most common causes in patients with and without AF; from day 31 onward and up to 5 years we observed in both groups a progressive reduction of the proportion of cerebral deaths and an increase of cardiac deaths. This study also showed that the absence of premorbid antithrombotic treatment and stroke severity at onset mostly influence post-stroke mortality in patients with AF.

Despite the decrease of FEIS incidence in the L'Aquila district in the last two decades, the relative proportion in FEIS associated with a 31.3% AF increased over time. This phenomenon may be the consequence of a better control of atherothrombotic risk factors, of a more extended search for the arrhythmia associated to a progressive ageing of the general population. Indeed, those findings may be partly explained by the parallel 29.8% increase of patients aged 80 years

and over in the general population over the two study periods, and corroborated by the observed 46.3% increased proportion of patients aged 80 years and over and by the significant reduction of atherothrombotic risk factors as hypertension, cigarette smoking, coronary heart disease, and peripheral artery disease within the group of patients with AF. Those findings are only partially overlapping to the findings of a recent study, which confirmed the reduction of the proportion of cigarette smoking from 1981-1986 to 2002-1012 (Yiin et al., 2017).

The higher burden of AF is also highlighted by the higher rate of recurrences and case-fatality compared to those without the arrhythmia, and although the rate of both recurrences and case-fatality declined over two decades, they remain significantly high, especially if compared with those of patients without the arrhythmia.

Overall the results of this study underlie the positive effects on stroke epidemiology of primary preventive strategies including lifestyle change, increased use of preventive disease-modifying treatments with antihypertensives, antiplatelets, and statins that definitely affected the natural history of atherothrombosis (Yiin et al., 2014; Bogiatzi et al., 2014), but highlight that more attention should be paid on the development of preventive strategies affecting the natural history of AF.

5.5 CONCLUSIONS

In patients with FEIS, the presence of comorbid AF is associated with higher stroke severity and disability, with a higher risk of short-term recurrence and with a lower survival probability. Better diagnosis and management of vascular risk factors contributed to the reduction of the FEIS incidence, nevertheless, the burden of AF increased over the last two decades suggesting the need for improved primary preventing measures targeting AF and related embolic complications.

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Chapter VI

THE CONTRIBUTION OF NEWLY DIAGNOSED ATRIAL FIBRILLATION TO THE SHORT- AND LONG-TERM PROGNOSIS OF FIRST-EVER ISCHEMIC STROKE IN A PROSPECTIVE POPULATION-BASED REGISTRY

6.1 AIM OF THE STUDY

This study aimed to assess the clinical characteristics of NDAF and PDAF and their burden on the short- and long-term prognosis of patients with a FEIS.

6.2 MATERIAL AND METHODS

Study design, study population, definitions, case-finding procedures, data collection, follow-up, and statistical analysis are reported in Chapter II.

6.3 RESULTS

During the study period we identified 919 patients with a FEIS. After the exclusion of 9 patients without ECG evaluation, AF was documented in 294 (32.3%) of the remaining 910 patients. All patients but one were hospitalized. Two hundred ninety-three (99.7%) patients received brain neuroimaging evaluations: 239 (81.3%) brain CT, 54 (18.4%) brain CT and MRI; one patient was diagnosed as a probable ischemic stroke based upon clinical criteria.

The arrhythmia was diagnosed after the stroke in 66 (22.4%) patients identified as NDAF and had already been diagnosed before the stroke in 228 (77.6%) patients identified as PDAF. Patients with NDAF represented 7.3% of all FEIS patients.

The prevalence of NDAF increased from 6% in patients aged 60-69 years to 11.5% in those aged 90 years and over, while the prevalence of PDAF increased from 11.2% in patients aged 60-69 years to 41.4% in those aged 90 years and over (Figure 18), and was slightly higher in women than in men in both age groups (Figure 19 and Table 27).

The baseline characteristics of NDAF and PDAF patients are reported in Table 28. The proportion of patients with paroxysmal AF was higher in NDAF than in PDAF, while the proportion of patients on premorbid antithrombotic treatment was lower in NDAF than in PDAF.

Patients with NDAF had more severe strokes at onset (median NIHSS score [IQR]: 12 [5-15] vs 8 [4-16]; P=0.028), a higher proportion (39.4% vs 29.8%; P<0.001) of TACI, and greater residual disability and dependence at discharge (median mRS score [IQR]: 4 [3-6] vs 3 [2-5]; P<0.001) compared to patients with PDAF (Table 28). Both groups of patients had similar proportions of insular involvement and of left- and right-sided insular infarcts (Table 28). At stroke onset, the INR value was in the therapeutic range in 19 (26.0%) of 73 PDAF patients (32.0%) on a vitamin K antagonist (VKA); none of the NDAF patients were treated with a VKA. The median follow-up duration was 6.2 years [IQR 7.5-5.0]. Follow-up was by in-person visit in 49.7% of patients and by a structured telephone interview in 50.3%. No patient was lost to follow-up.

The 1-year CFR was significantly higher in NDAF than in PDAF patients (Table 29).

At 1 year the cumulative probability of nonfatal and fatal stroke recurrence was higher in PDAF than in NDAF patients (5.3% vs 1.5%; P=0.010, log rank test) (Figure 20) as the probability of survival (61.4% vs 47.0% vs; P= 0.033, log rank test) (Figure 21).

Contrariwise, at 5 years, the cumulative probability of nonfatal and fatal stroke recurrence (7.9% vs 6.1%; P=0.607, log rank test) (Figure 20) and the probability of survival (39.9% vs

33.3%; P=0.079, log rank test) (Figure 21) did not differ significantly. Causes of death were similar at all time-points in both groups (Table 30).

At the Cox regression analysis (Table 31) the main determinants of FEIS mortality were stroke severity at onset and the lack of premorbid antithrombotic treatment, whereas NDAF *per se* was not an independent predictor of mortality.

6.4 DISCUSSION

In our population-based study we found that FEIS patients with NDAF and PDAF had similar vascular risk factors profiles. Nevertheless, NDAF patients had significantly greater stroke severity, post-stroke disability and dependence, and mortality than PDAF patients.

Interest in AF detected after an ischemic stroke began in the mid-1990s (Vingerhoets et al. 1993, Lin et al., 1995) in the hypothesis that NDAF could imply different pathogenic mechanisms other than PDAF. The complexity and the partial consistency of the current evidence on the pathophysiology of NDAF have so far contributed to the heterogeneity of the terms used for its definition. For the purpose of our study we classified as NDAF all cases of AF that were detected for the first time after the stroke, including in this group both patients with premorbid but undiagnosed AF and patients with a first episode of AF almost or shortly after the index stroke. NDAF was otherwise defined as *post-stroke AF,* implying that the arrhythmia was triggered by the stroke (Sposato et al., 2015), as *occult AF* including any undiagnosed arrhythmia in any patient regardless of stroke history (Andrade et al., 2015), and as *AF diagnosed after the stroke* where the arrhythmia was detected during the follow up period (Sposato et al., 2018).

The overall prevalence of AF among our FEIS patients was 32.3%, a proportion higher than those reported in some comparable population- (16.8%) (Pikija et al., 2012) and hospital-based studies (15.2%) (Andersen et al., 2011), and similar to those reported in other

population- (from 29.9% to 31.3%) (Kelly et al., 2012; Palm et al., 2012) and hospital-based studies (from 27.3% to 31.7%) (Medic et al., 2013; Bembenek et al., 2015).

Our 22.4% of NDAF was similar to the 24% reported in the Swedish stroke register Risks-Stroke (Friberg et al., 2014) , higher than the 18.2% found in the Massachusetts hospital-based study (Borowsky et al., 2017), and respectively lower than the 28.5% reported in the OXVASC study (Yiin et al., 2014), the 29% reported in the Japanese hospital-based Fukuoka Stroke Registry (Nakamura et al., 2016), and the 58.6% reported in a Taiwanese hospital-based study (Hsieh et al., 2018). The observed inter-studies variability of NDAF prevalence is possibly related to differences in the demographic and socioeconomic characteristics of the reference populations and to the different methods of screening for AF.

We found similar premorbid thromboembolic risk and vascular risk factors in NDAF and PDAF patients. In the Massachusetts hospital-based study patients with NDAF when compared to those with PDAF were younger, had similar proportions of arterial hypertension and diabetes mellitus, and a lower premorbid thromboembolic risk (Borowsky et al., 2017). At variance with our findings, no differences in stroke severity between NDAF and PDAF patients were reported in the Massachusetts hospital-based study (Borowsky et al., 2017) and in the Taiwanese hospital-based study (Hsieh et al., 2018), although both studies reported higher proportions of vascular risk factors in PDAF than in NDAF patients.

We found significantly higher 1-year CFRs in patients with NDAF than in PDAF and no differences at 5 years. In our study AF *per se*, whether already known before or diagnosed after the stroke, did not independently predict mortality. Since we also found that stroke severity at onset and the lack of premorbid antithrombotic treatment were independent predictors of mortality, it is possible to infer that the worst outcome of NDAF compared to PDAF patients should be attributed to the greater severity of the stroke (median NIHSS score at onset [IQR]: 12 [5-15] vs 8 [4-16]) and to the lower proportion of premorbid antithrombotic treatments (40.9% versus 74.1%). Our data agrees with the results of the PROSPER study (Xian et al., 2017), which suggests that the ongoing premorbid

antithrombotic treatment in patients with AF is associated with less FEIS severity and disability at discharge and better long-term survival.

The Massachusetts study (Borowsky et al., 2017) reported in-hospital CFRs similar to ours in both NDAF and PDAF patients, while the Taiwanese study (Hsieh et al., 2018) reported a higher 1-year mortality in patients with *known AF* than in those with *AF diagnosed after the stroke*. In both studies the higher load of vascular risk factors in PDAF patients might have contributed to the worse outcome. Nevertheless, in line with our data, the Taiwanese study reported that severity of stroke symptoms at onset and the lack of a prior treatment with antithrombotics are the major independent predictors of stroke outcome.

Several studies have investigated the pathogenesis of NDAF (Rizos et al., 2016; Rizos et al., 2017; Gonzalez Toledo et al., 2013; Frontzek et al., 2014; Sposato et al., 2018; Scheitz et al., 2015) According to some of them (Rizos et al., 2016; Rizos et al., 2017), NDAF may follow a previously undetected cardiac arrhythmia, identified only after the stroke through cardiac monitoring, while according to other studies (Gonzalez Toledo et al., 2013; Frontzek et al., 2014) it could be the consequence of a dysfunction of the autonomic regulation of cardiac rhythm induced by the cerebral infarction itself. The neurogenic hypothesis of NDAF is corroborated by the role of the insular cortex on the central autonomic control, on brain-heart interactions, and on the observation that insular involvement in cerebral infarction is more frequent in NDAF than in PDAF or in sinus rhythm patients (Gonzalez Toledo et al., 2013; Frontzek et al., 2014). Contrariwise, other studies reported in NDAF patients a lower proportion of vascular risk factors and of stroke recurrences together with a higher proportion of insular involvement, compared to patients with previously known AF, supporting the neurogenic origin of AF detected after the stroke (Gonzalez Toledo et al., 2013; Frontzek et al., 2014; Sposato et al., 2018). Since in NDAF and PDAF patients we found similar proportions of insular involvement, of vascular risk factors, and of long-term stroke recurrences we believe that our data may support the cardiogenic origin of NDAF.

The higher proportion of paroxysmal AF that we found in NDAF compared to PDAF

patients does not exclude the possibility that brief episodes of AF had already occurred, albeit not diagnosed until the FEIS occurrence.

The results of the present study emphasize the effects deriving from the *post-hoc* identification of NDAF. The supposed cardiogenic origin of NDAF gives rise to the consideration that, even if the proportion of all FEIS associated with NDAF is small (7.3% in our study), it anyhow represents a subset of individuals with a potentially preventable stroke. For this reason, a thorough screening for AF at the population level in individuals with known risk factors for AF should be encouraged.

6.5 CONCLUSIONS

In our population-based study, 22.4% of AF-related FEIS occurred in patients with NDAF. Although in only 7.3% of FEIS the newly diagnosed arrhythmia could have been potentially preventable, community AF screening initiatives in individuals potentially at risk together with the implementation of preventive thromboembolic strategies and the education of patients to maintain treatment adherence might contribute to reduce not only stroke occurrence but also its severity and prognosis.

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STRENGTHS AND LIMITATIONS

Our population-based study had a prospective design, included consecutive patients with a FEIS from a well-defined geographic area, recruited over three years and followed-up to 5 years, with no age limits for recruitment. We adopted a protocol with strict criteria for the identification of FEIS patients and for the diagnosis of AF.

A considerable strength of our study is the large number of patients included in the registry and the availability of all clinically relevant information including stroke risk, clinical, and functional status assessment scales.

Using multiple overlapping methods of case ascertainment, it is likely that high completeness had been achieved and that selection bias had been ruled out. We used standard definitions, which made our data comparable with those of other studies. The high rate of hospitalization and of available brain neuroimaging add to the quality of the data set. We classified patients having NDAF or PDAF based upon medical history and ECG evaluation. The long-term follow-up allowed thorough analysis of recurrences and cumulative survival probability. As the registry is still ongoing, it might therefore be able to possibly detect the effects of more recent interventions such as the implementation of thrombolysis and endovascular treatment for ischemic stroke and the use of NOAC for secondary prevention of ischemic stroke.

However, our study suffers from limitations shared with other epidemiological studies. The ascertainment of all incident ischemic stroke cases could be challenging because in patients with mild neurological deficit the spontaneous improvement of symptoms within a short time can lead patients not to seek medical care. Although all patients included in the analysis had at least one standard ECG evaluation, we cannot exclude the possibility that in some patients the arrhythmia remained undetected, leading to an underestimation of the prevalence of AF-related strokes.

Comparability between data from the 1994–1998 and the 2011–2013 registry was ensured by the identical study protocol and by continuity of the team work assuring the correctness of the methodological approach. However, some differences between the two studies exist; firstly, non-Italian residents increased from less than 0.5% at the 1991 census, to 2% at the 2001 census, up to 7% at the 2011 census, secondly, the possibility of having missed asymptomatic cases not seeking medical attention cannot be excluded, thirdly in the 1994–1998 registry the NIHSS score was not measured and so stroke severity between the two study periods could not be compared, lastly the duration of the study period is ongoing in order to match the 5- year duration of the 1994-1998 registry.

TABLES AND FIGURES

Table 1. Resident Population in the L'Aquila District at the 1991, 2001, and 2011 Censuses.

Age group (yrs)	1991			2001			2011		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
0-14	24755	23636	48391	20160	19331	39491	18750	17628	36378
15-24	21156	20670	41826	17884	17051	34935	15376	14584	29960
25-34	21997	21872	43869	21556	21125	42681	19251	18380	37631
35-44	20769	20020	40789	22401	22051	44452	21899	21794	43693
45-54	15894	16037	31931	20639	20069	40708	22438	22869	45307
55-64	16658	19298	35956	15521	16158	31679	20067	20294	40361
65-74	13626	17742	31368	14581	18237	32818	14094	15435	29529
75-84	7906	11315	19221	8873	13930	22803	10142	14774	24916
85+	1542	2945	4487	2640	5217	7857	3323	7245	10568
Total	144303	153535	297838	144255	153169	297424	145340	153003	298343

Table 2. Italian (ISTAT, 2011) and European (EUROSTAT, 2011) Populations by Age and Gender Groups.

	Italy			Europe		
Age group (yrs)	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
0-14	4,285,033	4,041,015	8,326,048	40,192,263	38,180,657	78,372,920
15-24	3,036,127	2,885,687	5,921,814	30,272,098	29,068,875	59,340,973
25-34	3,524,422	3,532,488	7,056,910	33,845,878	33,315,282	67,161,160
35-44	4,649,839	4,709,928	9,359,767	36,897,666	36,492,341	73,390,007
45-54	4,381,588	4,536,985	8,918,573	35,837,152	36,210,748	72,047,900
55-64	3,613,816	3,851,853	7,465,669	30,272,051	32,132,704	62,404,755
65-74	2,909,563	3,322,989	6,232,552	21,163,651	24,766,494	45,930,145
75-84	1,831,636	2,629,630	4,461,266	12,551,513	18,597,031	31,148,544
85+	513,483	1,177,662	1,691,145	3,270,305	7,634,044	10,904,349
Total	28,745,507	30,688,237	59,433,744	244,302,577	256,398,176	500,700,753

Table 3. Characteristics of the 836 Patients Excluded from the Study.

Excluded patients	n	%
Non stroke patients	241	28.8
Sequelae of previous stroke	48	5.7
Stroke in non residents	213	25.5
Recurrent stroke	243	29.1
Post-traumatic intracerebral hemorrhages	90	10.8
Perinatal cerebrovascular disease	1	0.1

FES indicates first-ever stroke

Table 4. Demographic Characteristics of Patients with a First-Ever Stroke.

Sex	n	%	Age (years) mean±SD	min	max
Men	607	47.7	72.7±12.7	7	96
Women	673	52.6	79.211.6	25	103
Both	1280	100	76.1±12.6	7	103

SD indicates standard deviation

Table 5. Demographic Characteristics of Patients with a First-Ever Ischemic Stroke.

Sex	n	%	Age (years) mean±SD	min	max
Men	434	47.2	72.9±12.2	7	96
Women	485	52.8	79.7±10.8	31	99
Both	919	100	76.5±12.0	7	99

SD indicates standard deviation

Table 6. Recruitment Sources of Patients with a First-Ever Ischemic Stroke.

Included patients	n	%
Hospitalized	909	98.9
Within the district	899	97.8
Out of the district	10	1.1
Referred by GP only	1	0.1
Death certificates	9	1.0

GP indicates general practitioner

Table 7. Incidence Rate (per 100,000 person-years) of First-Ever Ischemic Stroke by Age and Sex.

	Men				Women				Both			
Age group, y	N	At risk	Rate	95% CI	N	At risk	Rate	95% CI	N	At risk	Rate	95% CI
0-44	7	225828	3.10	1.25-6.39	5	217155	2.30	0.75-5.37	12	442983	2.71	1.40-4.73
45-54	28	67314	41.60	27.64-60.11	17	68604	24.78	14.44-39.67	45	135918	33.11	24.15-44.30
55-64	58	60201	96.34	73.17-124.53	18	60885	29.56	17.52-46.72	76	121086	62.77	49.46-78.55
65-74	120	42282	283.80	235.36-339.27	75	46305	161.97	127.42-202.99	195	88587	220.12	190.34-253.24
75-84	153	30426	502.86	426.49-588.90	187	44322	421.91	363.71-486.75	340	74748	454.86	407.89-505.74
85+	68	9969	682.11	530.07-863.95	183	21738	841.84	724.70-972.40	251	31707	791.62	697.03-895.39
All (crude)	434	436020	99.54	82.41-105.08	485	459009	105.66	96.47-115.49	919	895029	102.68	96.15-109.53
Standardized (Italy)*			93.23	82.41-105.08			94.50	83.94-106.02			93.89	86.26-102.01
Standardized (Europe)±			79.00	68.25-90.96			79.17	68.66-90.84			79.09	71.49-87.27

CI indicates confidence interval

Table 8. Baseline Characteristics of Patients with a First-Ever Ischemic Stroke.

Characteristics	(N=919)
Age, mean±SD years	75.78±11.68
Female, n (%)	464 (50.5)
Atrial fibrillation, n (%)	294 (32.0)
Hypertension, n (%)	700 (76.2)
Diabetes mellitus, n (%)	225 (24.5)
Hypercholesterolemia, n (%)	193 (21.0)
Cigarette smoking, n (%)	121 (13.2)
Coronary heart disease, n (%)	138 (15.0)
Peripheral artery disease, n (%)	53 (5.8)
NIHSS score at stroke onset, median [IQR]	5 [3-10]
NIHSS score at discharge, median [IQR]	4 [2-8]
mRS score at discharge, median [IQR]	3 [2-4]

IQR indicates Interquartile Range; mRS score, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

Table 9. 30-day, 1-year and 5-year Case-Fatality Rates in Patients with a First-Ever Ischemic Stroke.

	FEIS (N=919)		
	n	%	95% CI
30-day	165	18.0	15.6-20.6
1-year	259	28.2	25.4-31.2
5-year	399	43.4	67.4-87.4

CI indicates confidence interval

Table 10. 30-day, 1-year and 5-year Death Causes in Patients with a First-Ever Ischemic Stroke.

	30-day		1-year		5-year	
Death cause	n	%	n	%	n	%
Vascular						
Cerebral	111	67.3	134	51.7	154	38.6
Cardiac	42	25.5	72	27.8	137	34.3
Non-vascular	11	6.7	51	19.7	104	26.1
Unknown	1	0.3	2	0.8	4	1.0
Total	165	100	259	100	399	100

Table 11. Predictors of 30-day and 1-year Mortality in Patients with a First-Ever Ischemic Stroke.

	30-day		1-year	
	HR (95% CI)	P value	HR (95% CI)	P value
Atrial fibrillation	1.46 (1.04-2.05)	0.031	1.36 (1.04-1.78)	0.025
Female	0.96 (0.67-1.37)	0.812	1.00 (0.76-1.33)	0.988
Age*	1.00 (0.98-1.02)	0.987	1.01 (0.99-1.03)	0.271
Hypertension	0.78 (0.53-1.15)	0.208	0.80 (0.58-1.01)	0.152
Diabetes mellitus	1.69 (1.20-2.39)	0.003	1.58 (1.19-2.09)	0.002
Hypercholesterolemia	0.48 (0.27-0.87)	0.015	0.55 (0.34-0.83)	0.005
Cigarette smoking	0.68 (0.32-1.44)	0.311	0.75 (0.43-1.32)	0.324
Coronary heart disease	1.37 (0.88-2.12)	0.160	1.45 (1.02-2.06)	0.037
Peripheral artery disease	0.87 (0.47-1.60)	0.658	0.91 (0.56-1.48)	0.706

HR indicates hazard ratio; CI, confidence interval
*For each 1 year increase

Table 12. Baseline Characteristics of Patients with First-Ever Ischemic Stroke According to Etiologic Subtypes.

Characteristics	Large Artery Atherosclerosis (N=118)	Cardioembolism (N=321)	Small-Artery Occlusion (N=109)	Other Cause (N=43)	Undetermined Cause (N=328)	P value
Age, mean±SD years	74.49±11.40	79.28±10.21	70.75±11.93	62.28±16.86	76.50±10.54	<0.001
Female, n (%)	46 (39.0)	194 (60.4)	40 (36.7)	20 (46.5)	164 (50.0)	<0.001
Atrial fibrillation, n (%)	0 (-)	253 (78.8)	0 (-)	0 (-)	41 (12.5)	<0.001
Hypertension, n (%)	86 (72.9)	258 (80.4)	93 (85.3)	24 (55.8)	239 (72.9)	<0.001
Diabetes mellitus, n (%)	25 (21.2)	80 (24.9)	26 (23.9)	7 (16.3)	87 (26.5)	0.594
Hypercholesterolemia, n (%)	33 (28.0)	53 (16.5)	31 (28.4)	6 (14.0)	70 (21.3)	0.009
Cigarette smoking, n (%)	25 (21.2)	27 (8.4)	19 (17.4)	14 (32.6)	36 (11.0)	<0.001
Coronary heart disease, n (%)	16 (13.6)	64 (19.9)	19 (17.4)	5 (11.6)	34 (10.4)	0.013
Peripheral artery disease, n (%)	9 (7.6)	19 (5.9)	6 (5.5)	2 (4.7)	17 (5.2)	0.897
NIHSS score at onset, median [IQR]	5 [3-11]	7 [4-15]	4 [3-6]	4 [2.3-8.8]	5 [3-10]	<0.001
NIHSS score at discharge, median [IQR]	4 [2-8.75]	5 [2-11]	3 [2-4]	4 [1.5-5.5]	4 [2-8]	<0.001
mRS score at discharge, median [IQR]	3 [2-4]	3 [2-5]	2 [1-3]	2 [1-3.8]	3 [2-4]	<0.001

mRS score, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; SD indicates standard deviation

Table 13. Age-Specific Annual Incidence Rates (per 100,000 person-years) by Ischemic Stroke Subtype.

		Large-Artery Atherosclerosis			Cardioembolism			Small-Artery Occlusion		
Age group, y	At Risk	No.	Rate	95% CI	No.	Rate	95% CI	No.	Rate	95% CI
0-44	442983	1	0.23	0.04-1.28	3	0.68	0.23-1.99	0	-	-
45-54	135918	5	3.68	1.57-8.61	8	5.89	2.98-11.62	13	9.56	5.59-16.36
55-64	121086	12	9.91	5.67-17.32	15	12.39	7.51-20.44	16	13.21	8.13-21.47
65-74	88587	31	34.99	24.66-49.67	47	53.06	39.90-70.54	30	33.87	23.72-48.34
75-84	74748	45	60.20	45.00-80.53	127	169.90	142.83-202.10	35	46.82	33.67-65.11
85+	31707	24	75.69	50.87-112.61	121	381.62	319.50-455.76	15	47.31	28.67-78.05
All (crude)	895029	118	13.18	11.01-15.79	321	35.86	28.05-37.39	109	12.18	10.10-14.69
Standardized (Italy)*			11.95	9.33-15.07		32.47	28.05-37.39		11.27	8.74-14.32
Standardized (Europe)±			10.59	7.92-13.84		26.96	22.61-31.91		10.19	7.58-13.39

CI indicates confidence interval

* Standardized according to the Italian population (ISTAT 2011)

± Standardized according to the European population (EUROSTAT 2011)

(Continued)

Table 13. Age-Specific Annual Incidence Rates (per 100,000 person-years) by Ischemic Stroke Subtype. *(continued)*

		Other Cause			Undetermined Cause		
Age group, y	At Risk	No.	Rate	95% CI	No.	Rate	95% CI
0-44	442983	7	1.58	0.77-3.26	1	0.23	0.04-1.28
45-54	135918	7	5.15	2.49-10.63	12	8.83	5.05-15.43
55-64	121086	6	4.96	2.27-10.81	26	21.47	14.65-31.46
65-74	88587	8	9.03	4.58-17.82	79	89.18	71.57-111.12
75-84	74748	9	12.04	6.33-22.88	124	165.89	139.17-197.74
85+	31707	6	18.92	8.67-41.28	86	271.23	219.70-334.82
All (crude)	895029	43	4.80	3.57-6.47	328	36.65	32.89-40.83
Standardized (Italy)*			4.88	3.27-7.00		33.65	29.15-38.65
Standardized (Europe)±			4.59	2.91-6.89		28.76	24.25-33.86

CI indicates confidence interval

* Standardized according to the Italian population (ISTAT 2011)

± Standardized according to the European population (EUROSTAT 2011)

Table 14. 30-day, 1-year, and 5-year Case Fatality Rates in Patients with First-Ever Ischemic Stroke According to Etiologic Subtypes.

	Large Artery Atherosclerosis (N=118)			Cardioembolism (N=321)			Small-Artery Occlusion (N=109)			Other Cause (N=43)			Undetermined Cause (N=328)			P value
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	
30-day	17	14.4	9.2-21.9	85	26.5	22.0-31.6	2	1.8	0.5-6.4	8	18.6	9.7-32.6	53	16.2	12.6-20.5	<0.001
1-year	27	22.9	16.2-31.2	131	40.8	35.6-46.3	6	5.5	2.5-11.5	12	27.9	16.7-42.7	83	25.3	20.9-30.3	<0.001
5-year	51	43.2	34.6-52.2	182	56.7	51.2-62.0	21	19.3	13.0-27.7	17	39.5	26.4-54.4	128	39.0	33.9-44.4	<0.001

CI indicates confidence interval

Table 15. Predictors of 30-day and 1-year Mortality in Patients with a First-Ever Ischemic Stroke.

Model 1.

	30-day		1-year	
	HR (95% CI)	P value	HR (95% CI)	P value
Age*	1.01 (0.99-1.03)	0.565	1.01 (1.00-1.03)	0.133
Female	0.95 (0.68-1.32)	0.761	1.01 (0.77-1.31)	0.970
TOAST criteria				
Large-Artery Atherosclerosis	1.32 (0.77-2.28)	0.317	1.31 (0.85-2.02)	0.227
Cardioembolism	1.57 (0.93-2.65)	0.094	1.61 (1.06-2.44)	0.026
Small-Artery Occlusion	0.20 (0.05-0.88)	0.033	0.33 (0.14-0.81)	0.015
Other Cause	1.58 (0.67-3.71)	0.293	1.66 (0.83-3.30)	0.150
Undetermined Cause	1.00		1.00	

HR indicates hazard ratio; CI, confidence interval
*For each 1 year increase

Model 2.

	30-day		1-year	
	HR (95% CI)	P value	HR (95% CI)	P value
Age*	1.01 (0.99-1.03)	0.172	1.02 (1.00-1.04)	0.015
Female	0.70 (0.48-1.00)	0.050	0.76 (0.58-1.02)	0.063
NIHSS score at onset±	1.09 (1.07-1.11)	<0.001	1.09 (1.07-1.11)	<0.001
TOAST criteria				
Large-Artery Atherosclerosis	0.92 (0.50-1.68)	0.782	1.03 (0.65-1.64)	0.886
Cardioembolism	1.17 (0.67-2.07)	0.579	1.29 (0.83-2.00)	0.258
Small-Artery Occlusion	0.18 (0.73-4.51)	0.098	0.43 (0.17-1.14)	0.090
Other Cause	1.81 (0.73-4.51)	0.202	1.65 (0.78-3.48)	0.190
Undetermined Cause	1.00		1.00	

HR indicates hazard ratio; CI, confidence interval
*For each 1 year increase
±For 1 point increase

Table 16. Prevalence of Atrial Fibrillation in Patients with a First-Ever Ischemic Stroke According to Age and Sex.

	All FEIS	AF+	
Age group	n	n	%
Men			
0-39	4	0	-
40-49	14	0	-
50-59	43	1	2.3
60-69	84	14	16.7
70-79	143	32	22.4
80-89	119	47	39.5
90+	24	12	50.0
All	431	106	24.6
Women			
0-39	1	0	-
40-49	12	0	-
50-59	19	3	15.8
60-69	32	6	18.8
70-79	122	41	33.6
80-89	230	104	45.2
90+	63	34	54.0
All	479	188	39.2
Total			
0-39	5	0	-
40-49	26	0	-
50-59	62	4	6.5
60-69	116	20	17.2
70-79	265	73	27.5
80-89	349	151	43.3
90+	87	46	52.9
All	910	294	32.3

FEIS indicates first-ever ischemic stroke; AF, atrial fibrillation

Table 17. Baseline Characteristics of First-Ever Ischemic Stroke Patients with and without Atrial Fibrillation.

Characteristics	AF- (N=616)	AF+ (N=294)	OR (95% CI)	P value
Female	291 (47.2)	188 (63.9)	1.98 (1.49-2.64)	<0.001
Age, mean±SD years	73.8±12.6	82.1±8.1		<0.001
Age ≥80 years	239 (38.8)	197 (67.0)	3.20 (2.39-4.29)	<0.001
Hypertension	453 (73.5)	247 (84.0)	1.89 (1.32-2.71)	<0.001
Diabetes mellitus	150 (24.4)	75 (25.5)	1.06 (0.77-1.47)	0.705
Hypercholesterolemia	146 (23.7)	47 (16.0)	0.61 (0.43-0.88)	0.008
Cigarette smoking	110 (17.9)	11 (3.7)	0.18 (0.09-0.34)	<0.001
Coronary heart disease	91 (14.8)	47 (16.0)	1.10 (0.75-1.61)	0.633
Peripheral artery disease	31 (5.0)	22 (7.5)	1.53 (0.87-2.69)	0.140
Hospitalized patients, n (%)	-	1 (0.3)		-
NIHSS score at onset, median [IQR]	5 [3-10]	9 [4-17]		<0.001
NIHSS score at discharge, median [IQR]	3 [2-4]	5 [2-11]		<0.001
mRS score at discharge, median [IQR]	3 [2-4]	4 [3-5]		<0.001
OCSP classification				
TACI, n (%)	77 (12.5)	94 (32.0)		
PACI, n (%)	314 (50.9)	142 (48.3)		<0.001
LACI, n (%)	99 (5.3)	15 (5.1)		
POCI, n (%)	126 (20.5)	43 (14.6)		
Insular involvement, n (%)	119 (19.3)	120 (40.8)		<0.001
Right, n (%)	54 (45.4)	62 (51.7)		0.331
Left, n (%)	65 (54.6)	56 (46.7)		0.219
Bilateral, n (%)	-	2 (1.6)		-

AF indicates atrial fibrillation; CI, confidence interval; IQR, interquartile range; LACI, lacunar infarcts; NIHSS, National Institutes of Health Stroke Scale; OR odds ratio; OCSP, Oxfordshire Community Stroke Project Classification; PACI, partial anterior circulation infarcts; POCI, posterior circulation infarcts; SD, standard deviation; TACI, total anterior circulation infarcts.

Table 18. First-Ever Ischemic Stroke Incidence (per 100,000 person-years) in Patients with Atrial Fibrillation.

	Men				Women				All			
Age group, y	No.	At risk	Rate	95% CI	No.	At risk	Rate	95% CI	No.	At risk	Rate	95% CI
0-44	0	225828	-	-	0	217155	-	-	0	442983	-	-
45-54	0	67314	-	-	2	68604	2.92	0.80-10.63	2	135918	1.47	0.40-5.37
55-64	6	60201	9.97	4.57-21.74	2	60882	3.29	0.90-11.98	8	121086	6.61	3.35-13.04
65-74	21	42282	49.67	32.49-75.92	17	46305	36.71	22.92-58.79	38	88587	42.90	31.26-58.87
75-84	43	30426	141.33	104.95-190.30	74	44322	166.96	133.03-209.53	117	74748	156.53	130.63-187.54
85+	36	9969	361.12	260.97-499.51	93	21738	427.82	345.25-518.72	129	31707	406.85	342.54-483.18
All (crude)	106	436020	24.31	20.10-29.40	188	459009	40.96	35.31-47.25	294	895029	32.85	29.30-36.82
Standardized (Italy)*			21.92	16.84-28.04			35.19	28.87-42.49			28.77	24.62-33.42
Standardized (Europe)†			18.01	13.09-24.18			29.25	23.01-36.67			23.77	19.69-28.44

CI indicates confidence interval

Table 19. 30-day, 1-year, and 5-year Case-Fatality Rates in Patients with and without Atrial Fibrillation

	AF – (N=616)			AF + (N=294)			
	N	CFR	95% CI	N	CFR	95% CI	P value
30-day	76	12.3	10.0-15.2	81	27.5	22.8-32.9	<0.001
1-year	127	20.6	17.6-24.0	123	41.8	36.3-47.6	<0.001
5-year	209	33.9	30.3-43.5	181	61.6	55.9-66.9	<0.001

AF indicates atrial fibrillation; CI, confidence interval; CFR, case-fatality rate.

Table 20. In-hospital, 30-Day, 1-Year and 3-Year Death Causes in First-Ever Ischemic Stroke Patients with and without AF.

Death cause	AF – (N=616) N (%)	AF + (N=294) N (%)	P value
30-day			
Vascular			
Cerebral	53 (69.7)	54 (66.6)	0.680
Cardiac	18 (23.7)	22 (27.2)	0.617
Non-vascular	5 (6.6)	5 (6.2)	0.917
Unknown	-	-	-
Total	76 (100)	81 (100)	
1-year			
Vascular			
Cerebral	66 (52.0)	64 (52.0)	0.992
Cardiac	34 (26.8)	36 (29.3)	0.660
Non-vascular	27 (21.2)	22 (17.9)	0.502
Unknown	-	1 (0.8)	0.309
Total	127 (100)	123 (100)	
5-year			
Vascular			
Cerebral	77 (36.8)	73 (40.3)	0.480
Cardiac	73 (34.9)	62 (34.3)	0.889
Non-vascular	57 (27.3)	45 (24.9)	0.589
Unknown	2 (1.0)	1 (0.6)	0.648
Total	209 (100)	181 (100)	

AF indicates atrial fibrillation

Table 21. Predictors of 30-Day and 1-Year Mortality in Patients with First-Ever Ischemic Stroke and Atrial Fibrillation.

	30 days		1 year	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Female	0.79 (0.47-1.34)	0.386	0.88 (0.57-1.35)	0.555
Age*	1.00 (0.96-1.04)	0.855	1.02 (0.99-1.06)	0.186
Permanent AF	1.19 (0.67-2.13)	0.553	0.90 (0.58-1.40)	0.639
NIHSS score at onset	1.08 (1.05-1.11)	<0.001	1.09 (1.06-1.12)	<0.001
No premorbid antithrombotic treatment	2.15 (1.24-3.73)	0.007	1.41 (0.89-2.23)	0.147

AF indicates atrial fibrillation; CI confidence interval; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale.
* per each 10 years

Table 22. Incidence Rates (per 100,000 person-years) of First-Ever Stroke in the 1994-1998 and 2011-2013 Registries.

	1994-1998				2011-2013					
Age group, y	N	At risk	Rate	95% CI	N	At risk	Rate	95% CI	IRR (95% CI)	P
Men										
0-44	29	426696	6.80	4.55-9.76	7	225828	3.10	1.25-6.39	0.46 (0.17-1.06)	0.078
45-54	69	91333	75.55	58.78-95.60	28	67314	41.60	27.64-60.11	0.55 (0.34-0.87)	0.007
55-64	226	80448	280.93	245.53-319.98	58	60201	96.34	73.17-124.53	0.34 (0.25-0.46)	<0.001
65-74	567	70518	804.05	739.46-872.74	120	42282	283.81	235.36-339.27	0.35 (0.29-0.43)	<0.001
75-84	580	41948	1382.66	1273.10-1499.03	153	30426	502.86	426.49-588.90	0.36 (0.30-0.44)	<0.001
85+	229	10455	2190.34	1918.37-2489.37	68	9969	682.11	530.07-863.95	0.31 (0.23-0.41)	<0.001
All (crude)	1700	721398	235.65	224.60-247.11	434	436020	99.54	90.40-109.35	0.42 (0.38-0.47)	<0.001
Standardized (Italy)*			259.52	241.52-278.80			93.23	82.41-105.08	0.36 (0.31-0.41)	<0.001
Standardized (Europe)§			220.22	202.02-239.61			79.00	68.25-90.96	0.36 (0.30-0.42)	<0.001
Women										
0-44	21	414392	5.07	3.14-7.75	5	217155	2.30	0.75-5.37	0.45 (0.13-1.24)	0.147
45-54	39	90265	43.21	30.72-59.06	17	68604	24.78	14.44-39.67	0.57 (0.30-1.04)	0.059
55-64	122	88640	137.64	114.31-164.31	18	60885	29.56	17.52-46.72	0.21 (0.12-0.35)	<0.001
65-74	525	89948	583.67	534.93-635.64	75	46305	161.97	127.42-202.99	0.28 (0.21-0.35)	<0.001
75-84	773	63113	1224.79	1140.43-1313.67	187	44322	421.91	363.71-486.75	0.34 (0.29-0.40)	<0.001
85+	413	20405	2024.01	1835.21-2226.66	183	21738	841.84	724.70-972.40	0.42 (0.35-0.50)	<0.001
All (crude)	1893	766763	246.88	235.90-258.25	485	459009	105.66	96.47-115.49	0.43 (0.39-0.47)	<0.001
Standardized (Italy)*			272.42	254.28-291.50			94.50	83.94-106.02	0.35 (0.30-0.40)	<0.001
Standardized (Europe)§			232.06	213.81-251.46			79.17	68.66-90.84	0.34 (0.29-0.40)	<0.001
Total										
0-44	50	841088	5.94	4.41-7.84	12	442983	2.71	1.40-4.73	0.46 (0.22-0.87)	0.011
45-54	108	181598	59.47	48.79-71.80	45	135918	33.11	24.15-44.30	0.56 (0.38-0.80)	0.001
55-64	348	169088	205.81	184.77-228.58	76	121086	62.77	49.46-78.55	0.30 (0.23-0.39)	<0.001
65-74	1092	160466	680.52	640.87-721.96	195	88587	220.12	190.34-253.24	0.32 (0.28-0.38)	<0.001
75-84	1353	105061	1287.82	1220.52-1357.84	340	74748	454.86	407.89-505.74	0.35 (0.31-0.40)	<0.001
85+	642	30860	2080.36	1924.03-2245.81	251	31707	791.62	697.03-895.39	0.38 (0.33-0.44)	<0.001
All (crude)	3593	1488161	241.44	233.62-249.46	919	895029	102.68	96.15-109.53	0.43 (0.40-0.46)	<0.001
Standardized (Italy)*			266.18	253.24-279.61			93.89	86.26-102.01	0.35 (0.32-0.39)	<0.001
Standardized (Europe)§			226.28	213.31-239.84			79.09	71.49-87.27	0.35 (0.31-0.39)	<0.001

IRR indicated incidence rate ratio.

*The data were standardized according to the Italian population (ISTAT 2011)

*The data were standardized according to the European population (EUROSTAT 2011)

Table 23. Comparison of the Prevalence of Atrial Fibrillation According to Age and Sex Between the 1994-1998 and the 2011-2013 Registries.

Age group	1994-1998			2011-2013			
	All FEIS	AF		All FEIS	AF		
	N	N	%	N	N	%	P value
Men							
0-39	15	0	-	4	0	-	-
40-49	41	3	7.3	14	0	-	-
50-59	122	14	11.5	43	1	2.3	0.073
60-69	385	53	13.8	84	14	16.7	0.491
70-79	615	130	21.1	143	32	22.4	0.754
80-89	448	120	26.8	119	47	39.5	0.007
90+	50	20	40.0	24	12	50.0	0.416
All	1676	340	20.3	431	106	24.6	0.051
Women							
0-39	13	0	-	1	0	-	-
40-49	23	1	4.3	12	0	-	-
50-59	68	5	7.4	19	3	15.8	0.261
60-69	260	52	20.0	32	6	18.8	0.867
70-79	712	210	29.5	122	41	33.6	0.360
80-89	669	210	31.4	230	104	45.2	<0.001
90+	109	51	46.8	63	34	54.0	0.364
All	1854	529	28.5	479	188	39.2	<0.001
Total							
0-39	28	0	-	5	0	-	-
40-49	64	4	6.3	26	0	-	-
50-59	190	19	10.0	62	4	6.5	0.400
60-69	645	105	16.3	116	20	17.2	0.797
70-79	1327	340	25.6	265	73	27.5	0.514
80-89	1117	330	29.5	349	151	43.3	<0.001
90+	159	71	44.7	87	46	52.9	<0.001
All	3530	869	24.6	910	294	32.3	<0.001

AF indicates atrial fibrillation; FEIS, first-ever ischemic stroke

Table 24. Comparison of Risk Factors Distribution in Patients with Atrial Fibrillation Included in the 1994–1998 and in the 2011–2013 Registries.

	1994-1998 (n=869)		2011-2013 (n=294)		
Characteristics	**n**	**%**	**n**	**%**	**P value**
Women	529	60.9	188	63.9	0.349
Age ≥80	398	45.8	197	67.0	<0.001
Hypertension	535	61.6	247	84.0	<0.001
Diabetes mellitus	210	24.2	75	25.5	0.643
Coronary heart disease	297	34.2	47	16.0	<0.001
Hypercholesterolemia	167	19.2	47	16.0	0.216
Cigarette smoking	164	18.9	11	3.7	<0.001
Peripheral artery disease	146	16.8	22	7.5	<0.001

OR indicates odds ratio; CI, confidence interval

Table 25. First-Ever Ischemic Stroke Incidence in Patients with Atrial Fibrillation in 1994-1998 and 2011-2013 Registries.

	1994-1998				2011-2013					
Age group, y	N	At risk	Rate	95% CI	N	At risk	Rate	95% CI	Relative incidence (95%CI)	P value
Men										
0-44	1	427715	0.23	0.01-1.30	0	225828	-	-	-	-
45-54	7	90605	7.73	3.11-15.92	0	67314	-	-	-	-
55-64	17	80620	21.09	12.28-33.76	6	60201	9.97	4.57-21.74	0.47 (0.19-1.20)	0.1084
65-74	106	70375	150.62	123.33-182.22	21	42282	49.67	32.49-75.92	0.33 (0.20-0.53)	<0.001
75-84	145	41800	346.89	292.80-408.04	43	30426	141.33	104.95-190.30	0.55 (0.38-0.80)	0.010
85+	64	10285	622.27	479.54-793.93	36	9969	361.12	260.97-499.51	0.58 (0.39-0.87)	0.0082
All (crude)	340	721400	47.13	42.25-52.42	106	436020	24.31	20.10-29.40	0.52 (0.41-0.64)	<0.001
Standardized (Italy)*			51.83	43.85-60.85			21.92	16.84-28.04	0.42 (0.29-0.57)	<0.001
Standardized (Europe)±			42.57	34.38-51.58			18.01	13.09-24.18	0.42 (0.27-0.58)	<0.001
Women										
0-44	0	415405	-	-	0	217155	-	-	-	-
45-54	2	89650	2.23	0.61-8.06	2	68604	2.92	0.80-10.63	1.31 (0.10-18.02)	0.7870
55-64	17	89120	19.08	11.91-30.55	2	60882	3.29	0.40-11.98	0.17 (0.02-0.73)	0.0076
65-74	135	89875	150.21	126.93-177.75	17	46305	36.71	22.92-58.79	0.24 (0.15-0.40)	<0.0001
75-84	242	62715	385.87	340.30-437.53	74	44322	166.96	133.03-209.53	0.43 (0.33-0.56)	<0.001
85+	132	20060	658.03	550.20-779.75	93	21738	427.82	345.25-518.72	0.65 (0.49-0.85)	0.0006
All (crude)	529	766825	68.99	63.35-75.12	188	459009	40.96	35.31-47.25	0.59 (0.50-0.70)	<0.001
Standardized (Italy)*			76.58	67.10-87.01			35.19	28.87-42.49	0.46 (0.34-0.58)	<0.001
Standardized (Europe)±			63.96	54.55-74.53			29.25	23.01-36.67	0.46 (0.33-0.59)	<0.001
Total										
0-44	1	843120	0.12	0.02-0.67	0	442983	-	-	-	-
45-54	9	180255	4.99	2.28-9.48	2	135918	1.47	0.40-5.37	0.29 (0.06.1.36)	0.0975
55-64	34	169740	20.03	13.87-27.99	8	121086	6.61	3.35-13.04	0.33 (0.15-0.71)	0.0031
65-74	242	160250	151.01	133.16-171.26	38	88587	42.90	31.26-58.87	0.28 (0.19-0.39)	<0.001
75-84	387	104515	370.28	334.36-409.0	117	74748	156.53	130.63-187.54	0.28 (0.19-0.39)	<0.001
85+	196	30345	645.91	558.88-742.58	129	31707	406.85	342.54-483.18	0.62 (0.49-0.77)	<0.001
All (crude)	869	1488225	58.39	54.64-62.40	294	895029	32.85	29.30-36.82	0.56 (0.49-0.64)	<0.001
Standardized (Italy)*			64.61	58.31-71.40			28.77	24.62-33.42	0.45 (0.32-0.57)	<0.001
Standardized (Europe)±			53.52	47.31-60.33			23.77	19.69-28.44	0.44 (0.33-0.59)	<0.001

±The 1994-1998 data were standardized according to European population (EUROSTAT 1991); the 2011-2013 data were standardized according to European population (EUROSTAT 2011)

*The 1994-1998 data were standardized according to the Italian population (ISTAT 1991); the 2011-2013 data were standardized according to the Italian population (ISTAT 2011)

Table 26. Standardized Mortality Ratios of First-Ever Ischemic Stroke in Patients with and Without Atrial Fibrillation Comparing Case Fatality Rates of the 2011-2013 Registry With those of the 1994-1998 Registry.

	30-day		1-year	
	SMR	**95% CI**	**SMR**	**95% CI**
All without	0.62	0.53-0.71	0.68	0.61-0.75
All with	0.70	0.61-0.78	0.73	0.65-0.79

CI indicates confidence interval; SMR, standardized mortality ratio.

Table 27. Prevalence of Newly and Previously Diagnosed Atrial Fibrillation in Patients with a First-Ever Ischemic Stroke According to Age and Sex.

	FEIS	NDAF		PDAF	
Age groups	n	n	%	n	%
Men					
0-39	4	-	-	-	-
40-49	14	-	-	-	-
50-59	43	-	-	1	2.3
60-69	84	4	4.8	10	11.9
70-79	143	5	3.5	27	18.9
80-89	119	8	6.7	39	32.8
90+	24	2	8.3	10	41.7
All	431	19	4.4	87	20.2
Women					
0-39	1	-		-	-
40-49	12	-		-	-
50-59	19	-	-	3	15.8
60-69	32	3	9.4	3	9.4
70-79	122	11	9.0	30	24.6
80-89	230	25	10.9	79	34.3
90+	63	8	12.7	26	41.3
All	479	47	9.8	141	29.4
Total					
0-39	5	-	-	-	
40-49	26	-	-	-	
50-59	62	-	-	4	6.5
60-69	116	7	6.0	13	11.2
70-79	265	16	6.0	57	21.5
80-89	349	33	9.5	118	33.8
90+	87	10	11.5	36	41.4
All	910	66	7.3	228	25.1

AF indicates atrial fibrillation; FEIS, first-ever ischemic stroke; NDAF, newly diagnosed AF; PDAF, previously diagnosed AF.

Table 28. Baseline Characteristics of First-Ever Ischemic Stroke Patients with Newly and Previously Diagnosed Atrial Fibrillation.

Characteristics	NDAF (N=66)	PDAF (N=228)	P value
Age, mean±SD years	82.36±7.60	81.98±8.22	0.733
Female, n (%)	47 (71.2)	141 (61.8)	0.163
AF type			
Paroxysmal, n (%)	22 (33.3)	42 (18.4)	0.010
Permanent, n (%)	44 (66.7)	186 (81.6)	
Hypertension, n (%)	52 (78.8)	195 (85.5)	0.188
Diabetes mellitus, n (%)	18 (27.3)	57 (25.0)	0.709
Hypercholesterolemia, n (%)	7 (10.6)	40 (17.5)	0.176
Cigarette smoking, n (%)	3 (4.5)	8 (3.5)	0.696
Coronary heart disease, n (%)	7 (10.6)	40 (17.5)	0.176
Peripheral artery disease, n (%)	3 (4.5)	19 (8.3)	0.303
Previous TIA, n (%)	4 (6.1)	10 (4.4)	0.574
Premorbid CHA_2DS_2VASc score, median [IQR]	4 [3-5]	4 [3-5]	0.729
Premorbid antithrombotic treatment, n (%)	27 (40.9)	169 (74.1)	<0.001
Antiplatelet, n (%)	27 (40.9)	96 (42.1)	0.862
VK antagonist, n (%)	-	73 (32.0)	-
INR in therapeutic range, n (%)	-	19 (26.0)	-
NIHSS score at stroke onset, median [IQR]	12 [5-19]	8 [4-16]	0.028
mRS score at discharge, median [IQR]	4 [3-6]	3 [2-5]	<0.001
OCSP classification, n (%)			
TACI, n (%)	26 (39.4)	68 (29.8)	<0.001
PACI, n (%)	30 (45.5)	112 (49.1)	
LACI, n (%)	3 (4.5)	12 (5.3)	
POCI, n (%)	7 (10.6)	36 (15.8)	
Insular involvement, n (%)	24 (36.4)	104 (45.6)	0.182
Right, n (%)	11 (45.8)	56 (53.9)	0.178
Left, n (%)	12 (50.0)	47 (45.1)	0.664
Bilateral, n (%)	1 (4.2)	1 (1.0)	0.349

AF indicates atrial fibrillation; CI, confidence interval; IQR, interquartile range; mRS, modified Rankin scale; NDAF, newly diagnosed AF; NIHSS, national institute of health stroke scale; OCSP, Oxfordshire Community Stroke Project Classification; TACI, total anterior circulation infarcts; PACI, partial anterior circulation infarcts; LACI, lacunar infarcts; POCI, posterior circulation infarcts; OR, odds ratio; PDAF, previously diagnosed AF; SD, standard deviation; TIA, transient ischemic attack; VK antagonist, vitamin K antagonist.

Table 29. 30-Day and 1-Year Case-Fatality Rates in Newly and Previously Diagnosed Atrial Fibrillation in Patients with a First-Ever Ischemic Stroke.

	NDAF (n=66)			**PDAF** (n=228)			**P value**
	No.	CFR (%)	95% CI	No.	CFR (%)	95% CI	
30-day	21	31.8	21.9-43.8	60	26.3	21.0-32.4	0.378
1-year	35	53.0	41.2-64.6	88	38.6	32.5-45.1	0.036
5-year	44	66.7	54.7-76.8	137	60.1	53.6-66.2	0.333

AF indicates atrial fibrillation; CFR case-fatality rate; CI, confidence interval; NDAF, newly diagnosed AF; PDAF, previously diagnosed AF

Table 30. Causes of Death at Different Time Points in Newly and Previously Diagnosed Atrial Fibrillation in Patients with a First-Ever Ischemic Stroke.

Death cause	NDAF (n=66) n (%)	PDAF (n=228) n (%)	P value
30 days			
Cerebral*	17 (81.0)	37 (61.7)	0.107
Cardiovascular	3 (14.3)	19 (31.7)	0.123
Nonvascular	1 (4.8)	4 (6.7)	0.755
Unknown	-	-	-
Total	21 (100)	60 (100)	
1 year			
Cerebral*	22 (62.9)	42 (47.8)	0.130
Cardiovascular	8 (22.8)	28 (31.8)	0.324
Nonvascular	5 (14.3)	17 (19.3)	0.511
Unknown	-	1 (1.1)	-
Total	35 (100)	88 (100)	
5 years			
Cerebral*	24 (54.5)	49 (35.8)	0.050
Cardiovascular	10 (22.7)	52 (38.0)	0.064
Nonvascular	10 (22.7)	35 (25.5)	0.707
Unknown	-	1 (0.7)	-
Total	44 (100)	137 (100)	

*including new fatal stroke

Table 31. Predictors of 30-Day and 1-Year Mortality in 294 Patients with a First-Ever Ischemic Stroke and Atrial Fibrillation at The Multivariate Cox Regression Analysis.

	30-day		1-year	
Covariates	HR (95% CI)	P value	HR (95% CI)	P value
Age*	1.00 (0.96-1.04)	0.979	1.02 (0.99-1.06)	0.175
Female	1.24 (0.74-2.08)	0.410	1.08 (0.71-1.66)	0.716
Permanent AF	0.69 (0.30-1.44)	0.325	0.92 (0.55-1.54)	0.759
NDAF	0.90 (0.51-1.60)	0.705	1.06 (0.68-1.64)	0.817
NIHSS score at onset±	1.08 (1.05-1.11)	<0.001	1.09 (1.06-1.12)	<0.001
No premorbid antithrombotic treatment	1.56 (1.04-2.33)	0.030	1.35 (1.03-2.26)	0.048

AF indicates atrial fibrillation; HR, hazard ratio; NDAF, newly diagnosed atrial fibrillation; NIHSS, national institute of health stroke scale

Figure 1. Geographical Location of L'Aquila District.

Population	298,343 (52% rural)
Surface area	5034.46 km^2
Elevation	mountainous
Latitude	41°41' – 42°31' N
Location	central Italy
Towns	108

Figure 2. Distribution of Cerebrovascular Events.

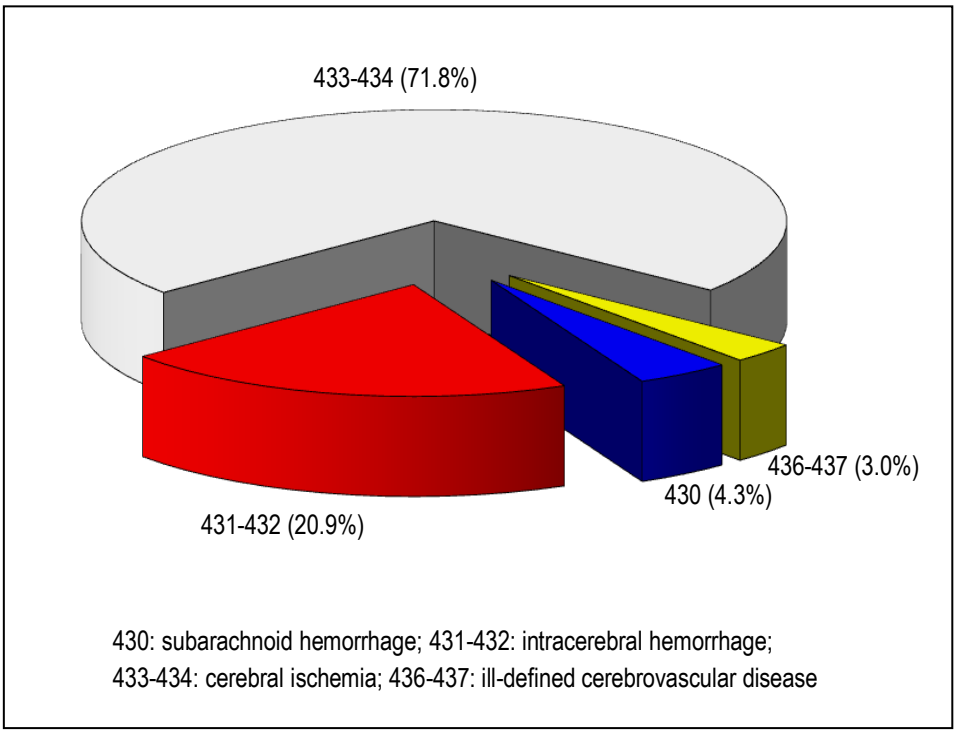


Figure 3. Distribution by Age and Sex of Patients with a First-Ever Ischemic Stroke.

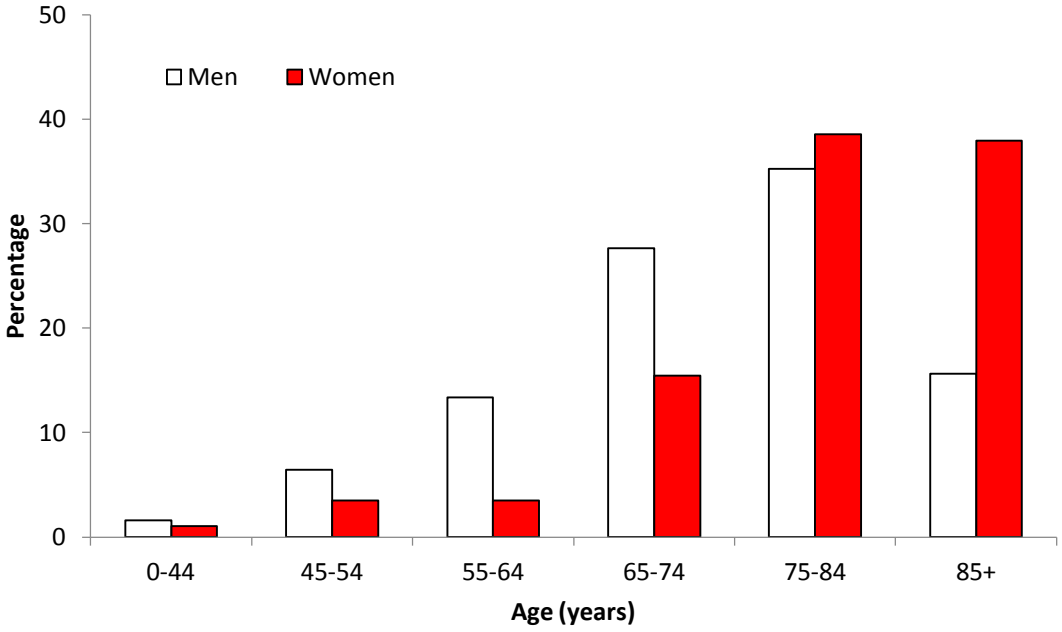


Figure 4. Crude Incidence Rate (per 100,000 person-years) of First-Ever Ischemic Stroke.

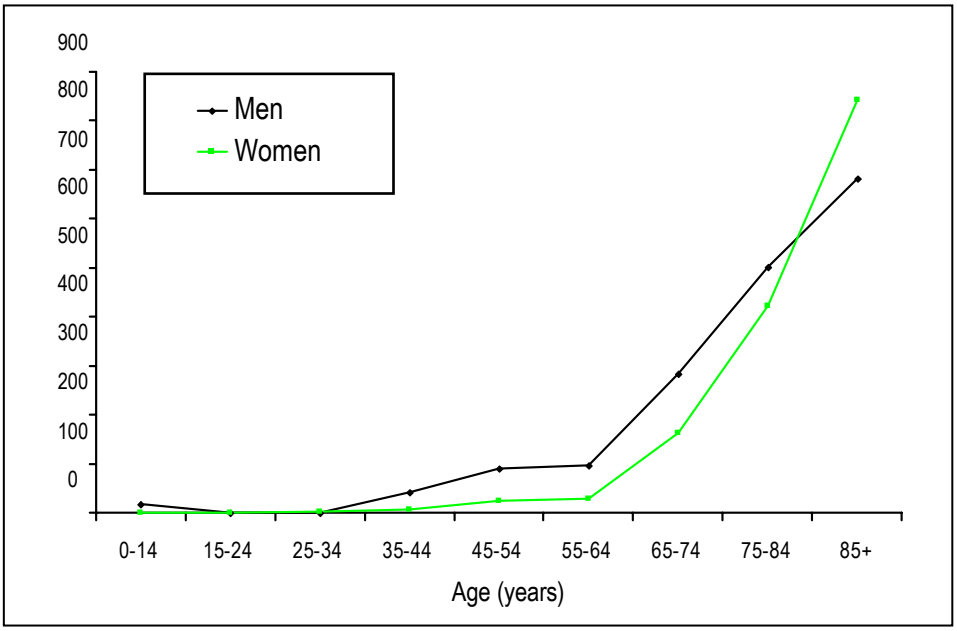
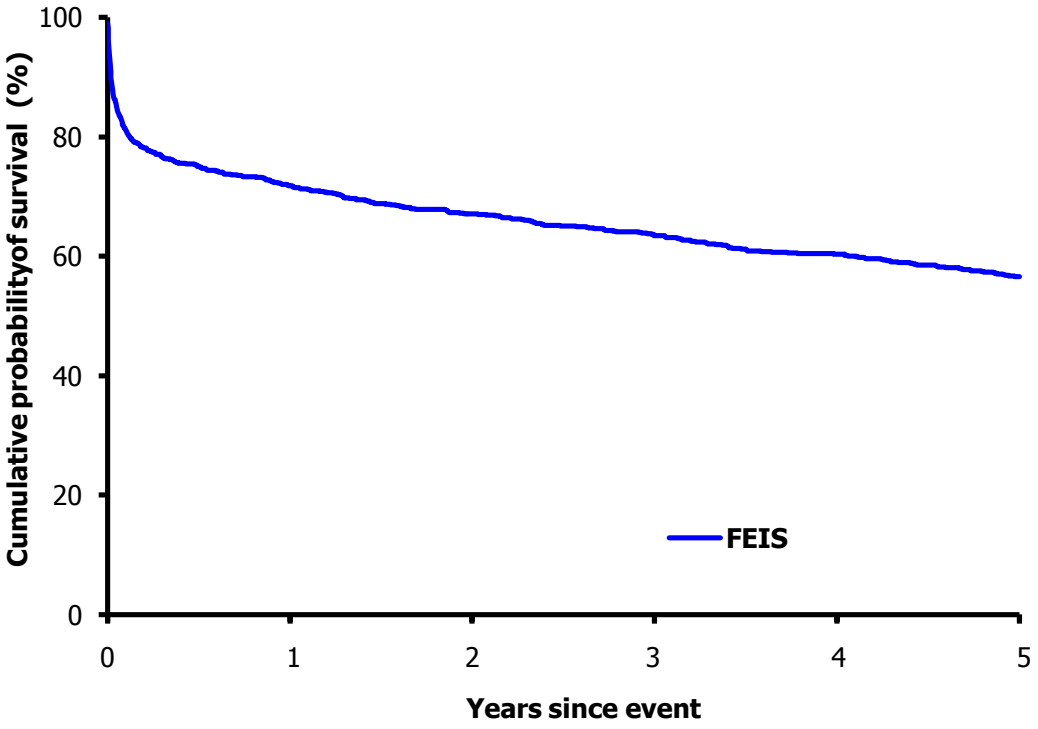
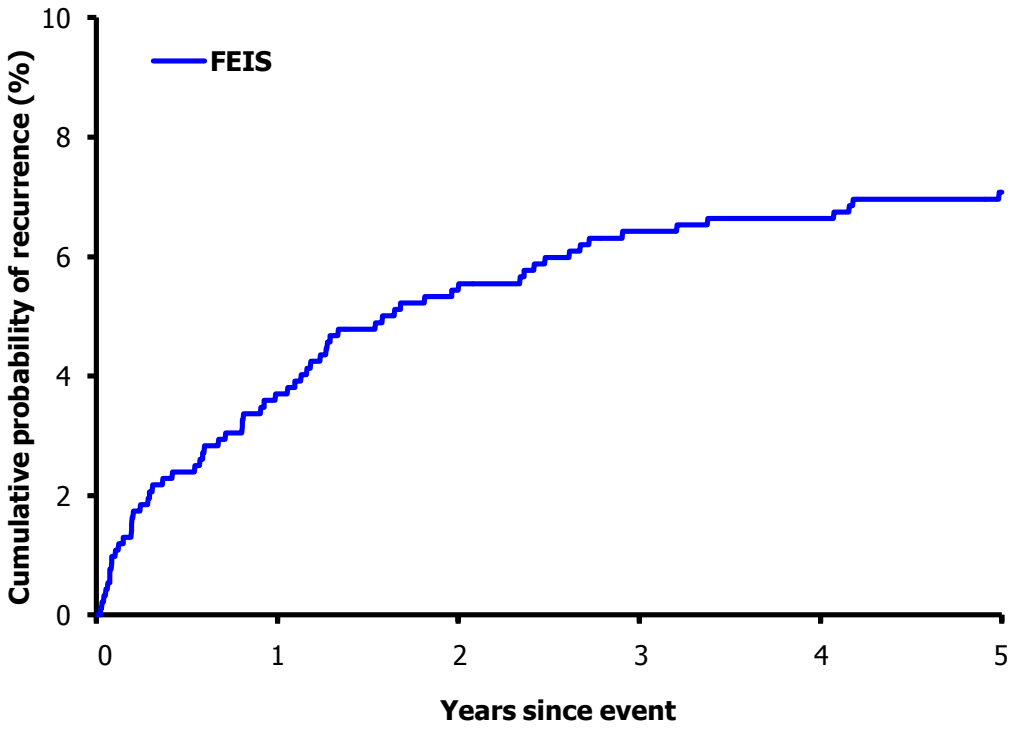


Figure 5. Kaplan–Meier Estimates of Survival Probability in Patients with a First-Ever Ischemic Stroke.



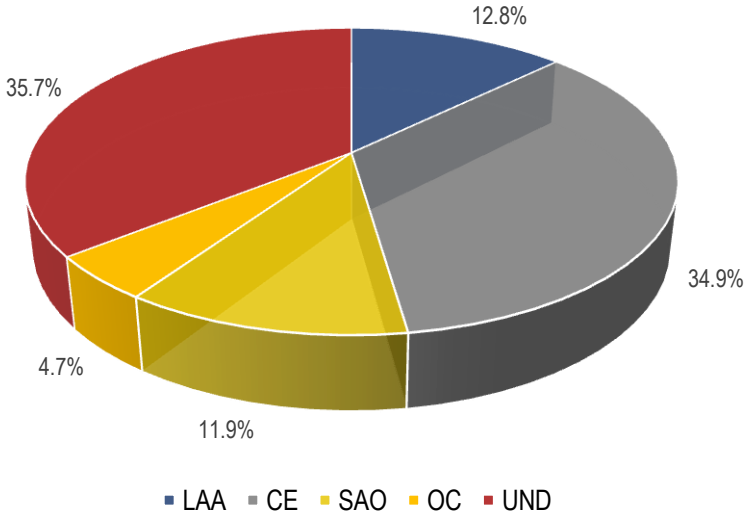
FEIS indicates First-Ever Ischemic Stroke.

Figure 6. Kaplan–Meier Estimates of the Likelihood of Recurrent Stroke in Patients with a First-Ever Ischemic Stroke.



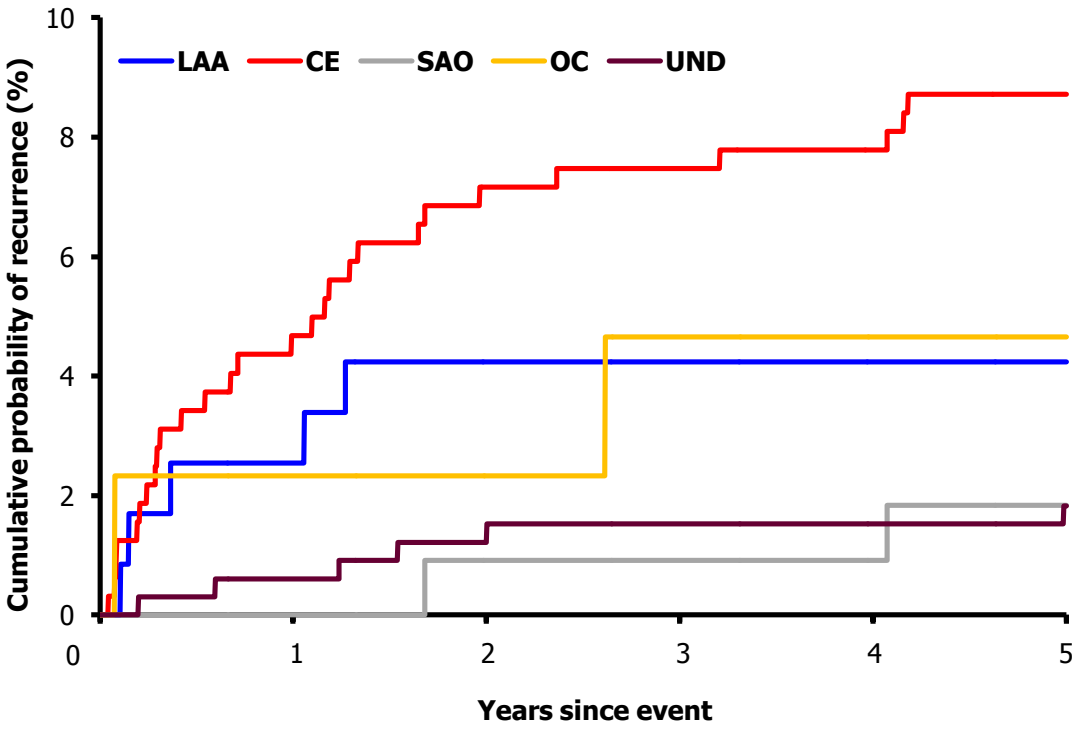
FEIS indicates First-Ever Ischemic Stroke.

Figure 7. Proportions of Etiologic Subtypes.



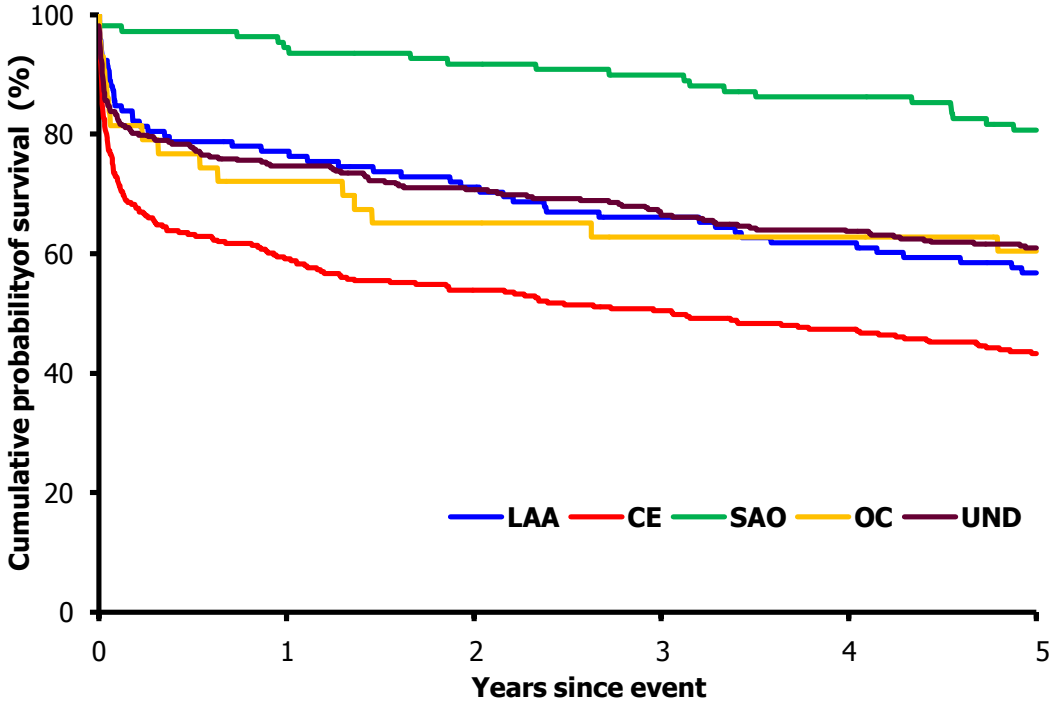
CE indicates Cardioembolism; LAA, Large-Artery Atherosclerosis; OC, Other Cause; SAO, Small-Artery Occlusion; UND, Undetermined Cause

Figure 8. Cumulative Probability of Stroke Recurrences in First Ever Ischemic Stroke Patients According to Etiologic Subtypes.



CE indicates Cardioembolism; LAA, Large-Artery Atherosclerosis; OC, Other Cause; SAO, Small-Artery Occlusion; UND, Undetermined Cause

Figure 9. Cumulative Probability of Survival in Patients with First-Ever Ischemic According to Etiologic Subtypes.



CE indicates Cardioembolism; LAA, Large-Artery Atherosclerosis; OC, Other Cause; SAO, Small-Artery Occlusion; UND, Undetermined Cause

Figure 10. Prevalence of Atrial Fibrillation in Patients with a First-Ever Ischemic Stroke According to Age and Sex.

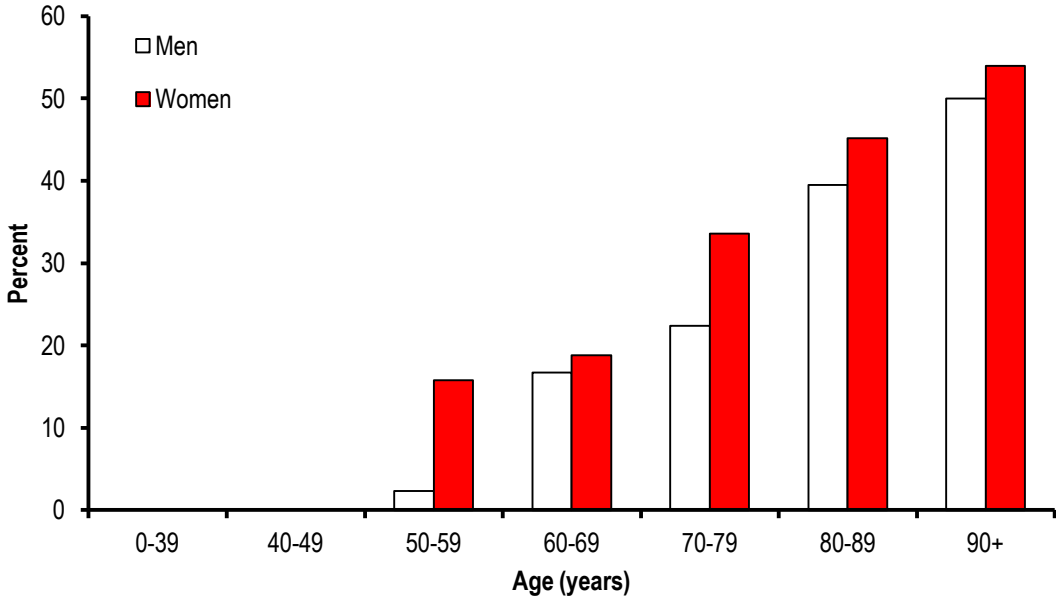


Figure 11a. Death Rate and Death Causes in Patients with Atrial Fibrillation.

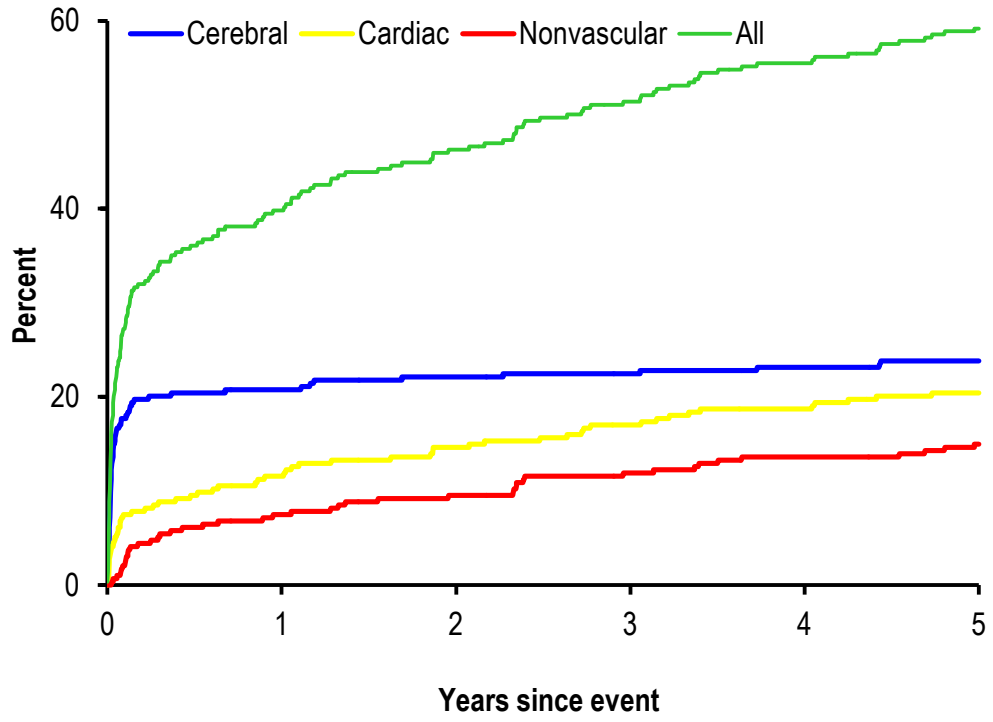


Figure 11b. Death Rate and Death Causes in Patients Without Atrial Fibrillation.

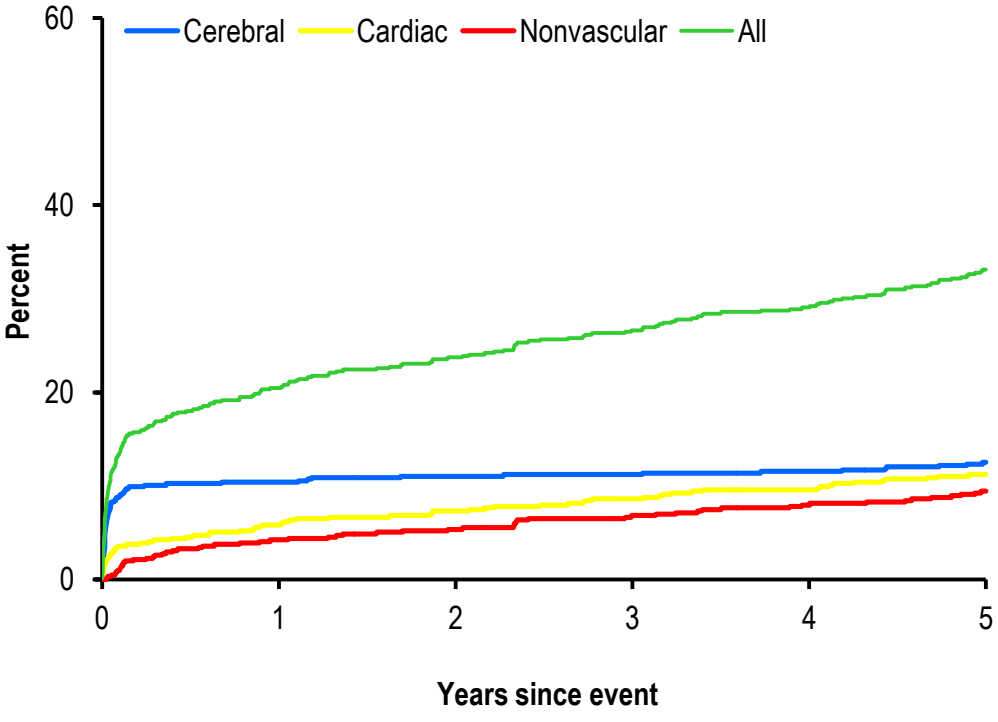
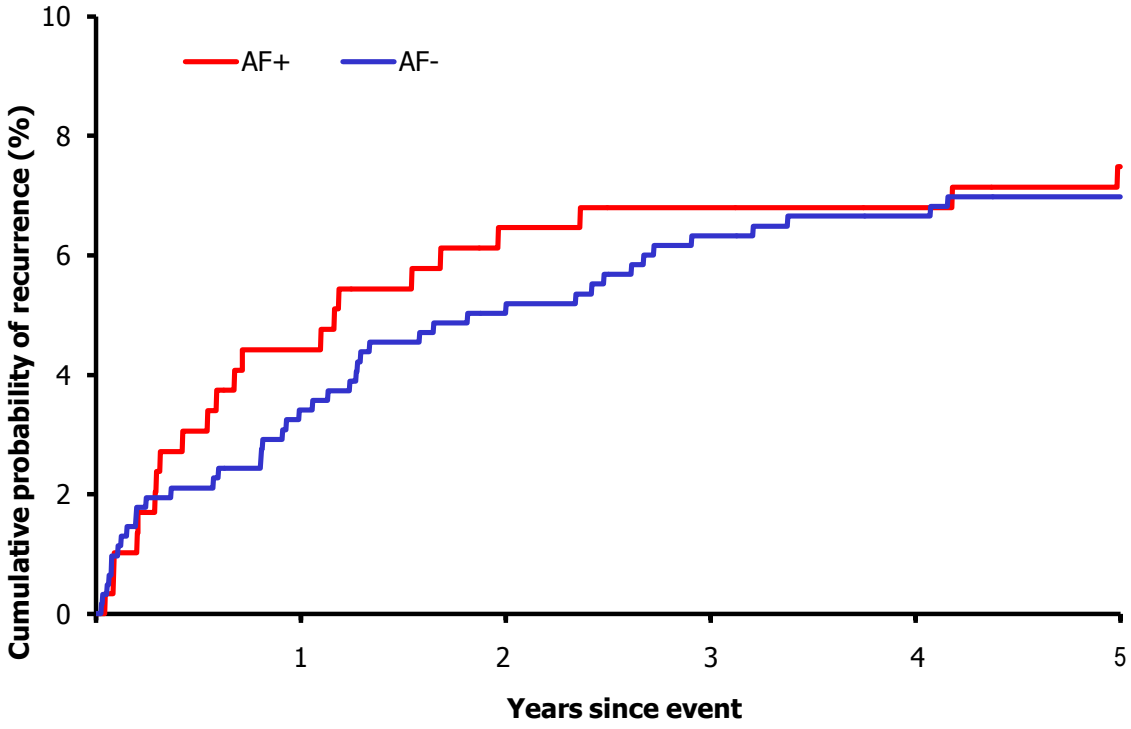
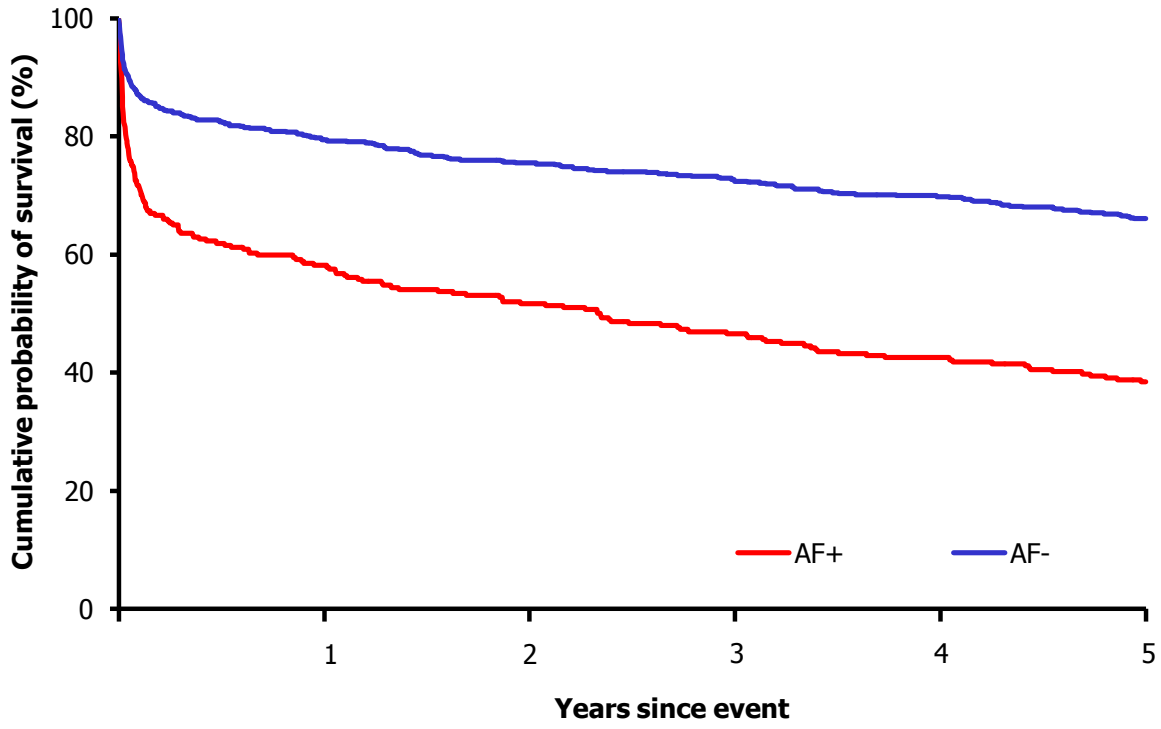


Figure 12. Kaplan–Meier Estimates of the Likelihood of Recurrent Stroke in Patients with and without Atrial Fibrillation.



NDAF indicates newly diagnosed atrial fibrillation; PDAF, previously diagnosed atrial fibrillation.

Figure 13. Kaplan–Meier Estimates of Survival Probability in Patients with and without Atrial Fibrillation.



NDAF indicates newly diagnosed atrial fibrillation; PDAF, previously diagnosed atrial fibrillation.

Figure 14. Comparison of the Incidence of First-Ever Ischemic Stroke by Age and Sex in the 1994-1998 and in 2011-2013 registries.

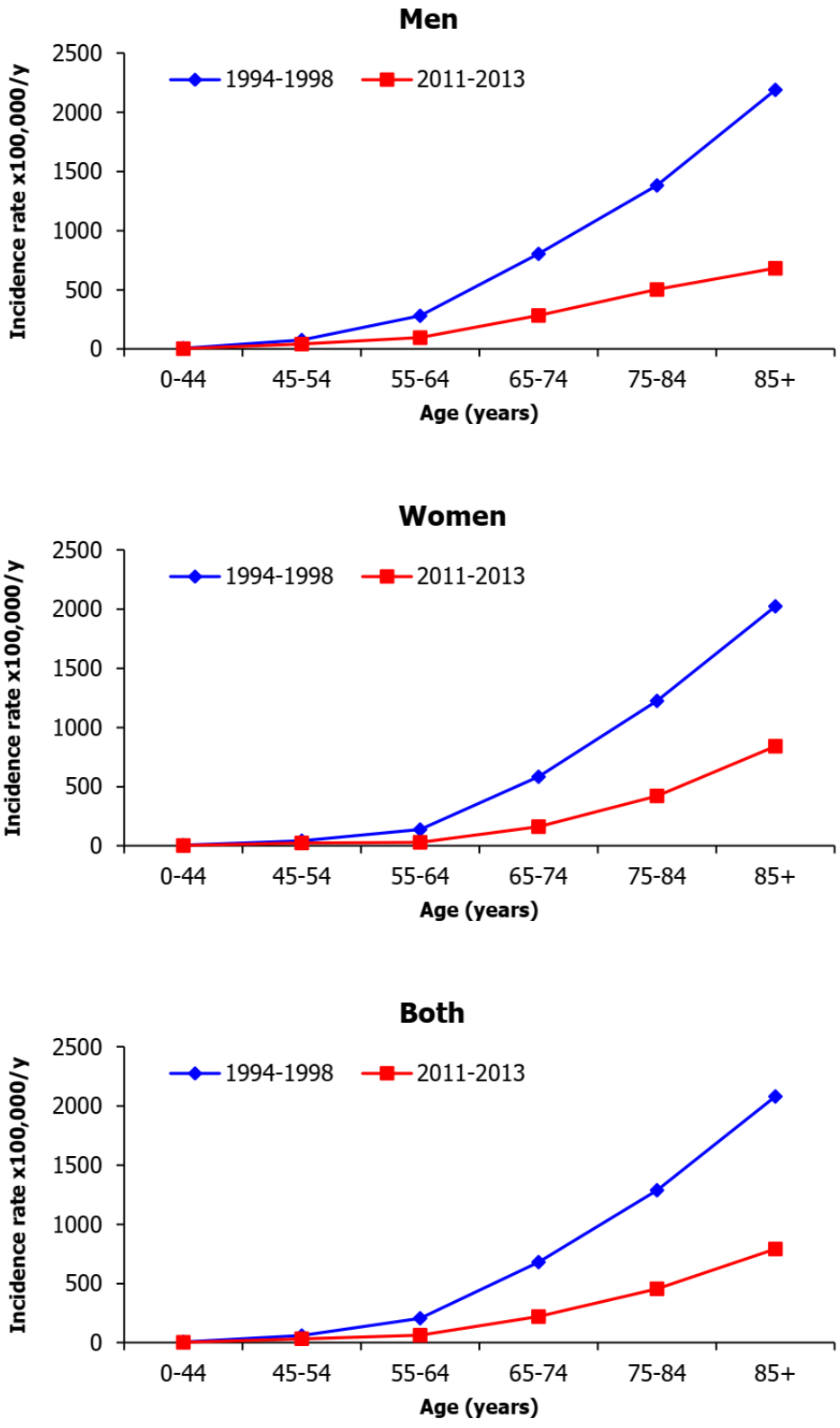


Figure 15. Comparison of the Prevalence of Atrial Fibrillation According to Age and Sex Between the 1994-1998 and the 2011-2013 Registries.

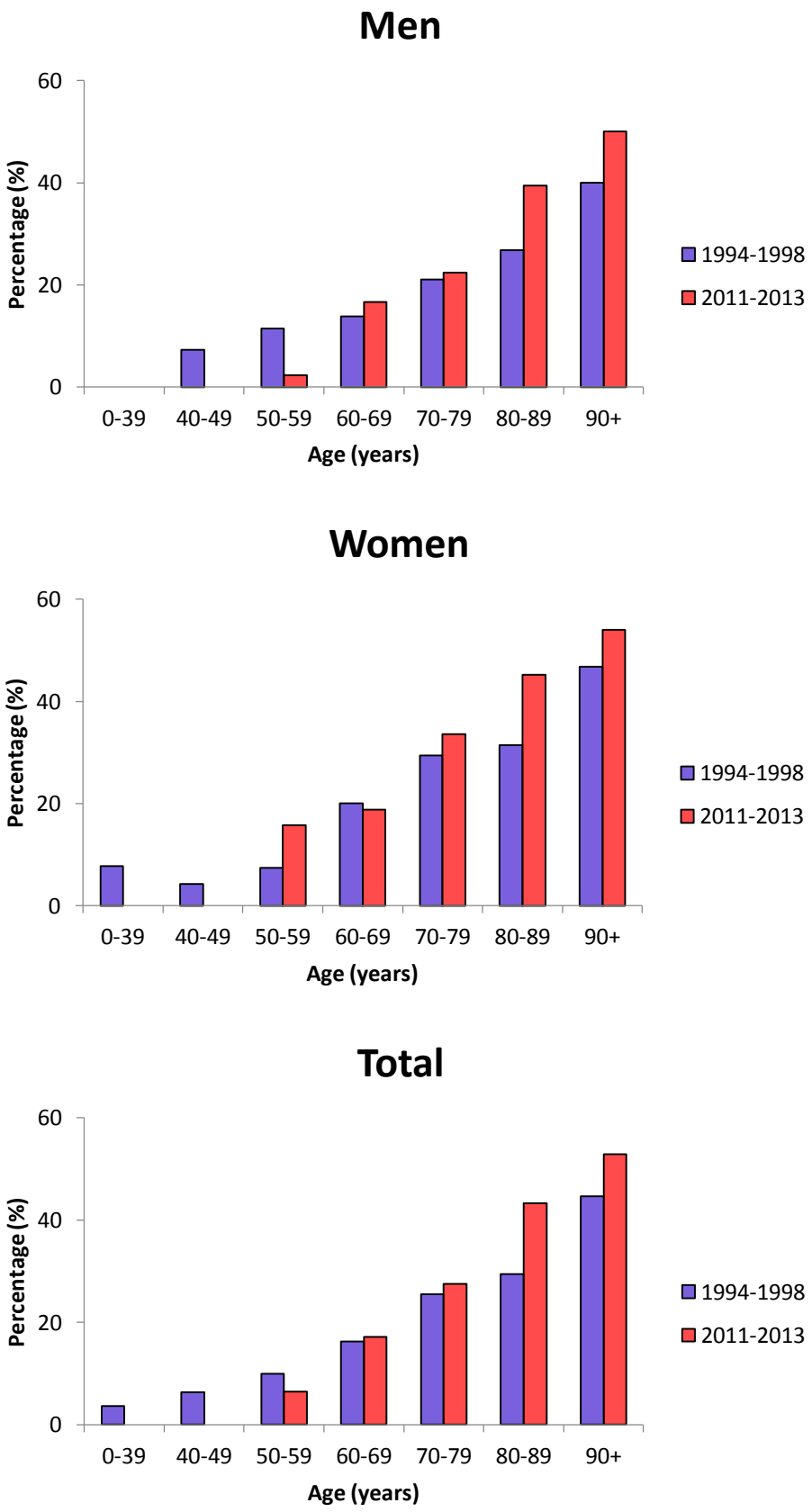
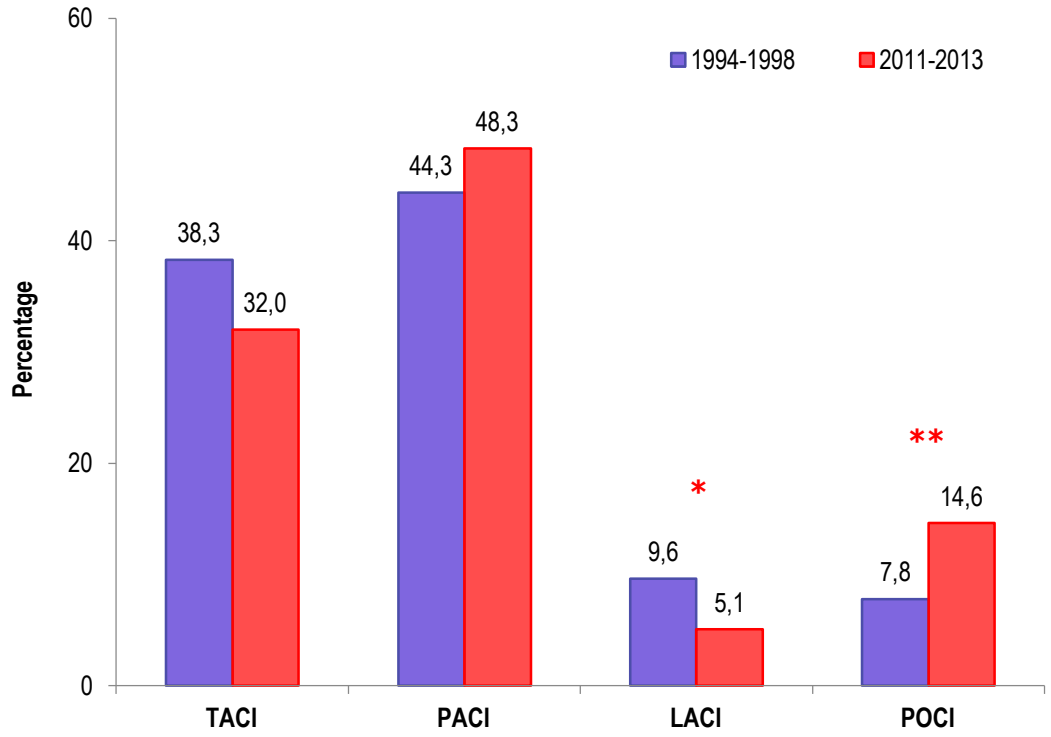


Figure 16. Comparison of Stroke Type Distribution According to the Oxfordshire Community Stroke Project Classification in First Ever Ischemic Stroke Patients with Atrial Fibrillation in the 1994-1998 and 2011-2013 Registries.



OCSP indicates Oxfordshire Community Stroke Project Classification; TACI, total anterior circulation infarcts; PACI, partial anterior circulation infarcts; LACI, lacunar infarcts; POCI posterior circulation infarcts.

* P=0.018; ** P=0.001

Figure 17. Comparison of Incidence Rates (per 100,000 person-years) of First-Ever Ischemic Stroke by Age and Sex in Patients with Atrial Fibrillation in the 1994-1998 and in 2011-2013 Registries.

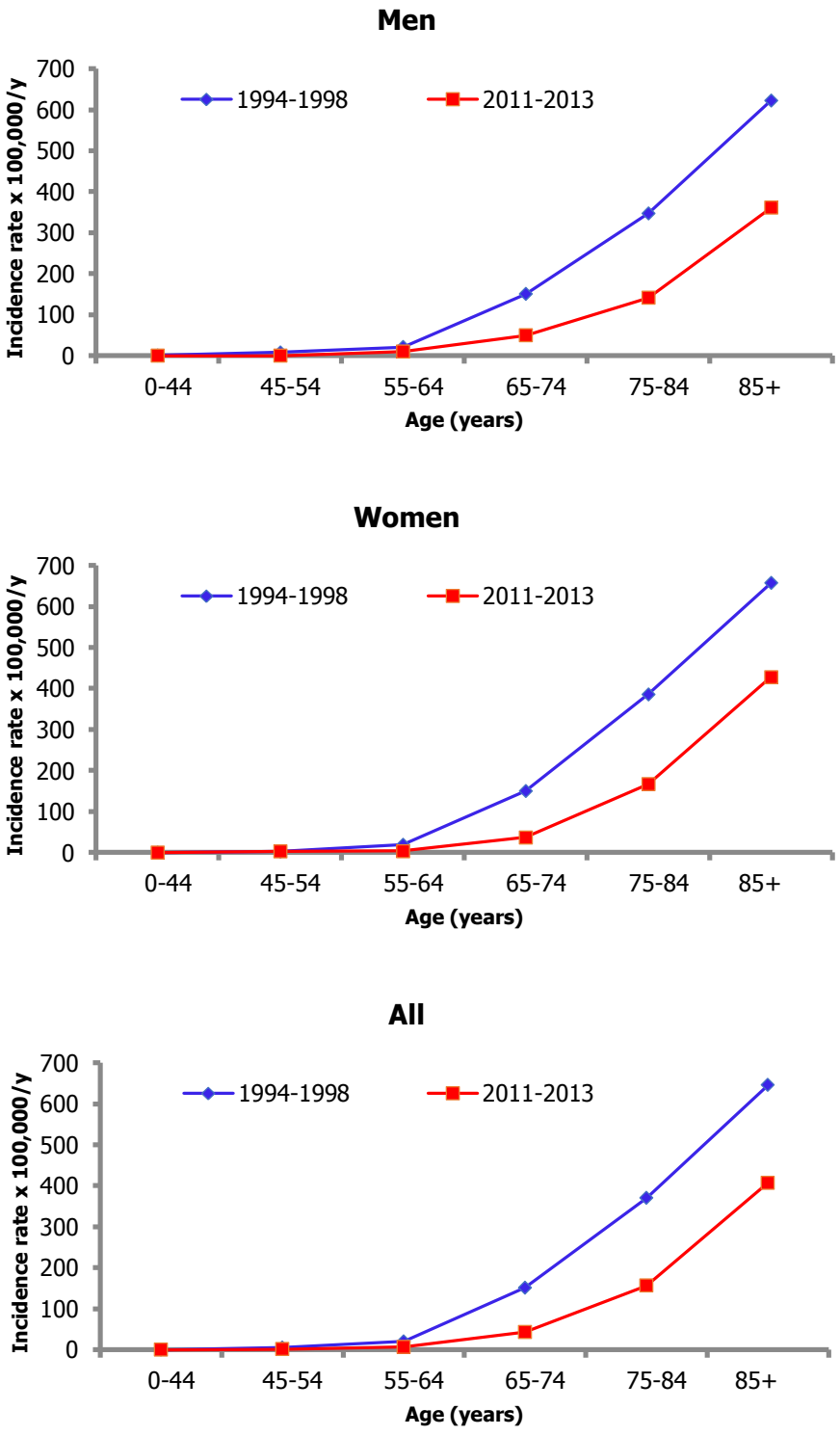
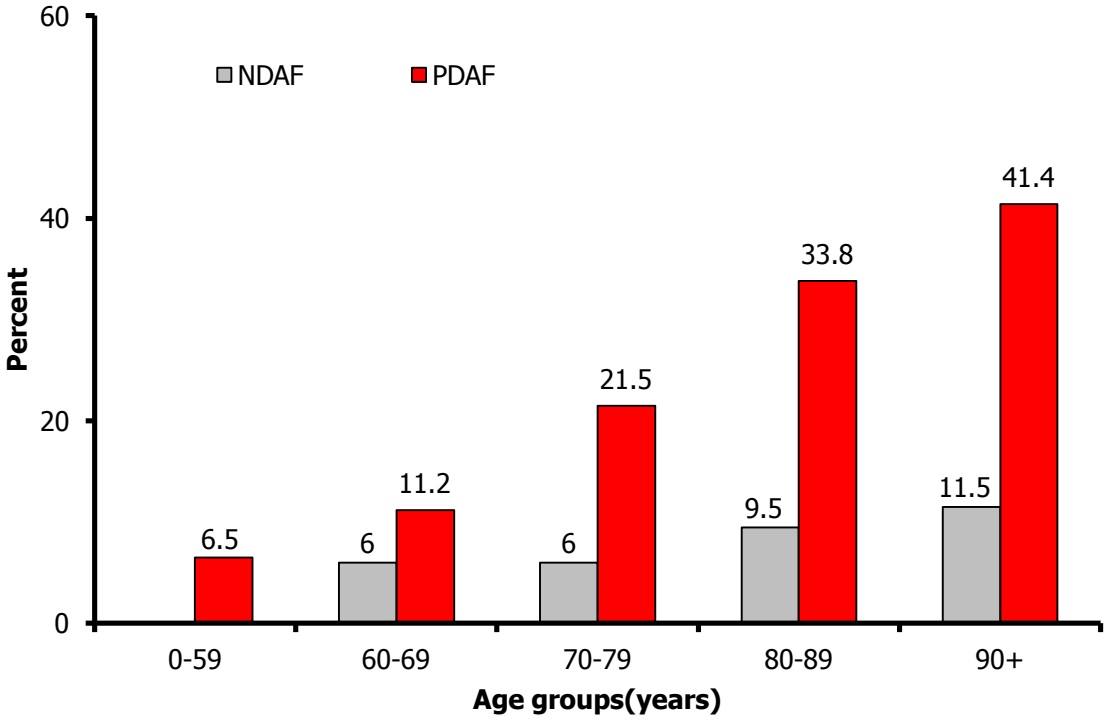
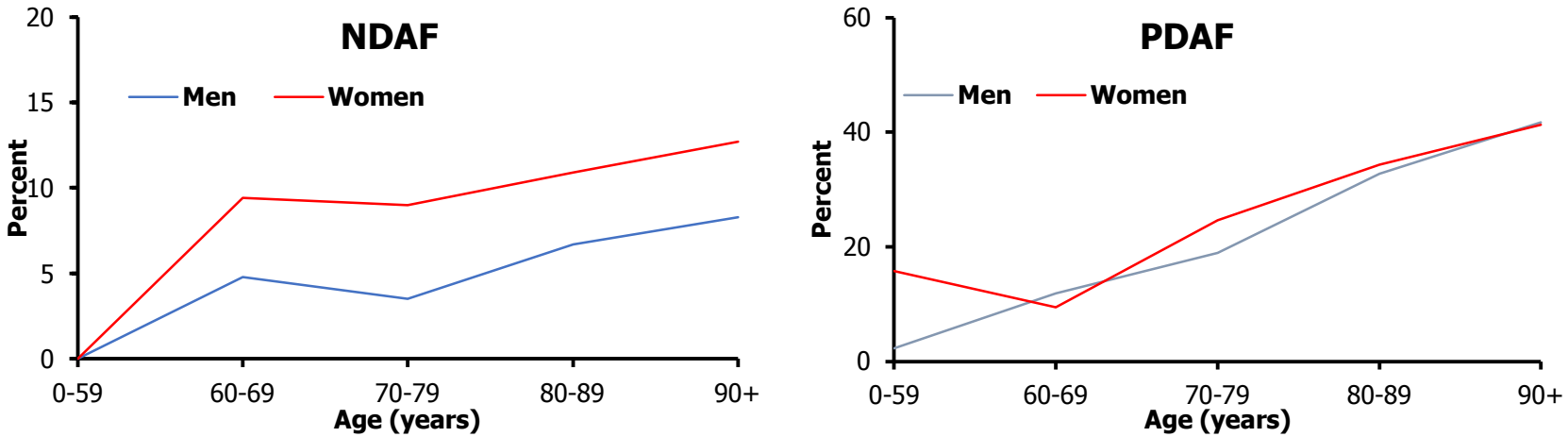


Figure 18. Prevalence of Newly Diagnosed and Previously Diagnosed Atrial Fibrillation in Patients with a First-Ever Ischemic Stroke According to Age Groups.



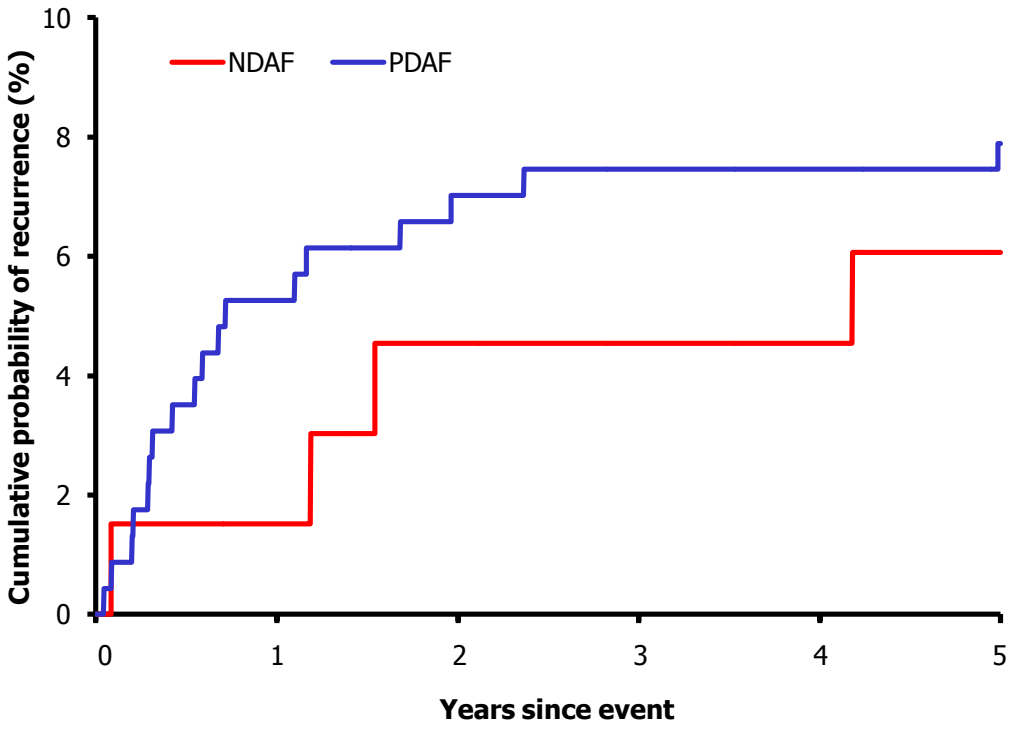
NDAF indicates newly diagnosed atrial fibrillation; PDAF, previously diagnosed atrial fibrillation.

Figure 19. Prevalence of Newly and Previously Diagnosed Atrial Fibrillation in Patients with a First-Ever Ischemic Stroke According to Age and Sex.



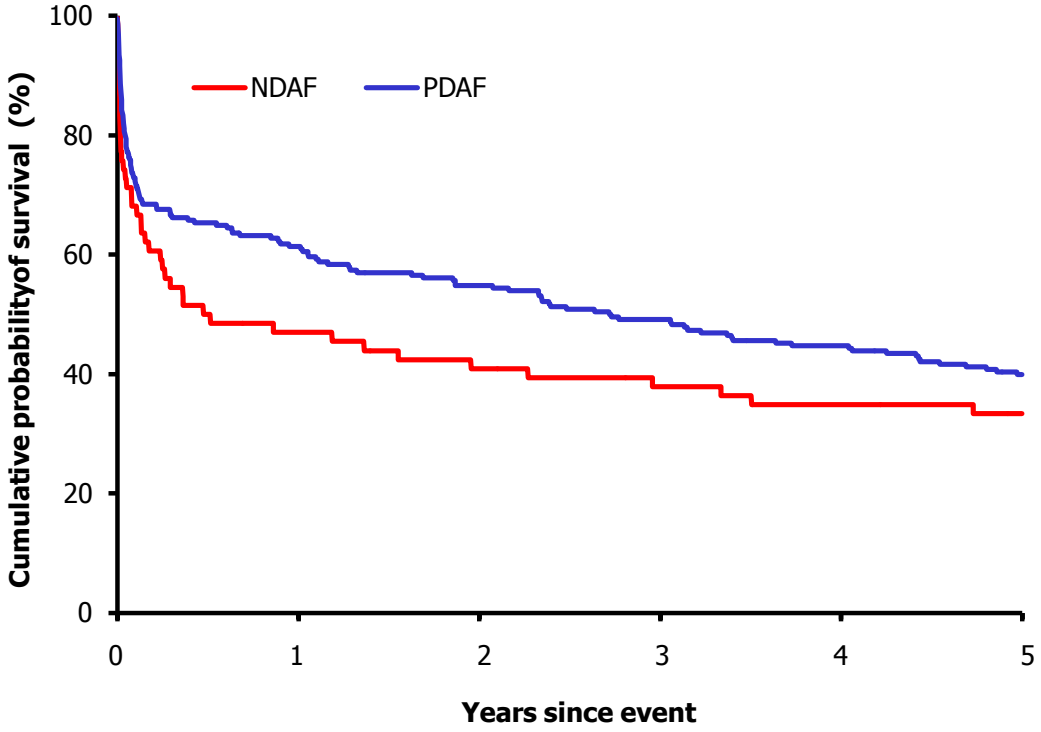
NDAF indicates newly diagnosed atrial fibrillation; PDAF, previously diagnosed atrial fibrillation.

Figure 20. Cumulative Probability of Stroke Recurrences in First Ever Ischemic Stroke Patients with Newly and Previously Diagnosed Atrial Fibrillation.



NDAF indicates newly diagnosed atrial fibrillation; PDAF, previously diagnosed atrial fibrillation.

Figure 21. Cumulative Probability of Survival in First Ever Ischemic Stroke Patients with Newly and Previously Diagnosed Atrial Fibrillation.



NDAF indicates newly diagnosed atrial fibrillation; PDAF, previously diagnosed atrial fibrillation.

SUPPLEMENTAL MATERIAL

Supplemental Methods

Participating centers

Together with the general practitioners, the following centers were involved in the study:

Public hospitals: *Ospedale San Salvatore*, L'Aquila; *Ospedale Civile Santi Filippo e Nicola*, Avezzano (Coordinating center); *Ospedale Santissima Annunziata*, Sulmona; *Ospedale Civile*, Castel di Sangro.

Private hospitals: *Casa di Cura Istituto Neurotraumatologico Italiano (I.N.I.)*, Canistro; *Casa di Cura L'Immacolata*, Celano; *Casa di Cura San Raffaele*, Sulmona; *Casa di Cura di Riabilitazione Nova Salus*, Trasacco; *Casa di Cura Di Lorenzo*, Avezzano.

Nearby hospitals: *Ospedale Santo Spirito*, Pescara; *Ospedale Santissima Trinità*, Popoli; *Ospedale Civile Giuseppe Mazzini*, Teramo; *Ospedale Civile Maria Santissima dello Splendore*, Giulianova.

Risk factors

Atrial fibrillation was defined as a cardiac arrhythmia with the following characteristics: the surface ECG shows 'absolutely' irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern; there are no distinct P waves on the surface ECG; some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1; the atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (>300 bpm) (European Heart Rhythm Association, 2010).

Hypercholesterolemia was defined as fasting total cholesterol serum level ≥200 mg/dL and/or fasting low density lipoprotein (LDL) cholesterol serum level >129 mg/dL at recruitment, or history of hypercholesterolemia that was confirmed in medical records and/or use of lipid-lowering medications (National Cholesterol Education Program Expert Panel on Detection and Treatment of High Blood Cholesterol, 2002).

Diabetes mellitus was defined as fasting blood glucose >6.0 mmol/L, and/or use of insulin/oral hypoglycemic agents and/or history of diabetes that was confirmed in medical records (Genuth et al., 2003).

Arterial hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg (systolic blood pressure >130 mmHg and/or diastolic blood pressure >80 mmHg in diabetic patients) on at least two different

occasions, or history of hypertension confirmed in medical records (Chobanian et al., 2003).

Cigarette smoking was defined as never, current smoker and former smoker of any kind of tobacco.

Patients were defined as smokers if they were current smokers or they had stopped smoking at least 6 months before the index first-ever ischemic stroke and as former smokers when smoking was stopped earlier.

Coronary heart disease was defined as a history of acute myocardial infarction or angina pectoris.

Peripheral artery disease was diagnosed in the presence of a history of intermittent claudication or previous arterial intervention or Doppler ultrasonography documentation.

Clinical definitions

Impaired level of consciousness was defined as any person's arousability and responsiveness to stimuli from the environment other than normal (Kandel et al., 2000). Patients were defined as having impaired level of consciousness if they had a Glasgow Coma Scale <15 at stroke onset.

Outcome events

- *Transient ischemic attack (TIA)* was defined as a focal neurological dysfunction of brief duration, presumed to be of vascular origin and confined to an area of the brain or eye perfused by a specific cerebral artery and of a duration <24 hours, according to the time-based definition (Fisher et al.,1958; Millikan et al., 1965).
- *Recurrent stroke* was defined as any new stroke subsequent to the initial one, with an increased disability at the time of the event, persisting beyond 24 hours.
- *Myocardial infarction* was diagnosed in the presence of rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on the ECG; c) ECG changes indicative of ischemia (ST segment elevation or depression); or d) coronary artery intervention (e.g., coronary angioplasty) (Thygesen et al., 2007).
- *Cerebral death* was defined as death occurring within or after 30 days of the onset of signs or symptoms of the qualifying stroke or of a new stroke, with clinically proven rostrocaudal deterioration, in the absence of other intervening causes.
- *Vascular death* included sudden death (in which the death was seen by an eye witness, with a reliable observation of the time between the onset of symptoms and

death, or the patient was found dead) or death from myocardial infarction (Thygesen et al., 2007), congestive heart failure (Dickstein et al., 2008), systemic embolism, or other cardiovascular causes (including pulmonary embolism and peripheral artery disease).

- *Nonvascular deaths* included cancer, pneumonia, sepsis, neoplasia, and deep vein thrombosis.
- *Unknown death* was diagnosed in the presence of underlying pathology not otherwise specified.
- *All-cause mortality* included death from any cause.

Supplemental References

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Supplemental Table 1. Foreign Resident Population in the L'Aquila District at the 2001 and 2011 Censuses.

Age (years)	2001 n	2001 %*	2011 n	2011 %*	% change (2011 vs 2001)
0-14	1195	3.0	4103	11.3	+276.7
15-24	832	2.4	3295	11.0	+358.3
25-34	2282	5.3	5148	13.7	+158.5
35-44	1638	3.7	5028	11.5	+210.8
45-54	574	1.4	2803	6.2	+342.9
55-64	207	0.7	1025	2.5	+257.1
65-74	111	0.3	299	1.0	+233.3
75+	80	0.3	160	0.5	+66.7
Total	6919	2.3	21861	7.3	+217.4

*of the total population of each age group

Supplemental Table 2. Definition of Clinically Identifiable Subtypes of Cerebral Infarction According to the Oxfordshire Community Stroke Project Classification.

	Clinical OCSP classification	Radiological OCSP classification
Total Anterior Circulation Infarct (TACI)	Combination of: higher cerebral dysfunction, homonymous visual field defect, and ipsilateral motor and/or sensory deficit involving at least two of face, arm and leg. If level of consciousness was impaired and formal testing of higher cerebral function and/or visual fields was not possible, a deficit was assumed to be present.	Lesions with any of the following characteristics: Complete ICA territory infarct, infarct greater than 1/3 of the MCA territory or cortical infarct in the MCA or ACA territories in addition to ipsilateral basal ganglia infarct in the MCA territory.
Partial Anterior Circulation Infarct (PACI)	Two of three components of the TACI syndrome, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those whose syndrome is classified as a LACI.	Cortical or subcortical infarcts in either MCA or ACA territories not meeting TACI or LACI criteria.
Lacunar Infarct (LACI)	Hemi-sensory or motor deficit (proportionally involving at least two of face, arm, and leg) with/without ipsilateral cerebellar signs and absence of any of the following signs: new dysphasia, (b) new visuospatial disturbance, (c) predominant proprioceptive sensory loss, (d) features which clearly localize the lesion in the vertebrobasilar distribution, for example gaze palsies or crossed deficits, (e) impaired level of consciousness.	Spheroidal infarct in deep white matter, basal ganglia or brainstem with a maximum diameter of 1.5 cm.
Posterior Circulation Infarct (POCI)	Ipsilateral cranial nerve palsy and contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; disorder of conjugate eye movement; cerebellar dysfunction without ipsilateral long tract deficit; isolated homonymous visual field defect	Lesions in the posterior circulation not meeting LACI criteria.

ICA indicates internal carotid artery; OCSP, Oxfordshire Community Stroke Project Classification; MCA, middle cerebral artery; ACA, anterior cerebral artery.

Supplemental Table 3. Thromboembolic Risk Assessment in Patients with Atrial Fibrillation According to the CHA_2DS_2VASc Scores.

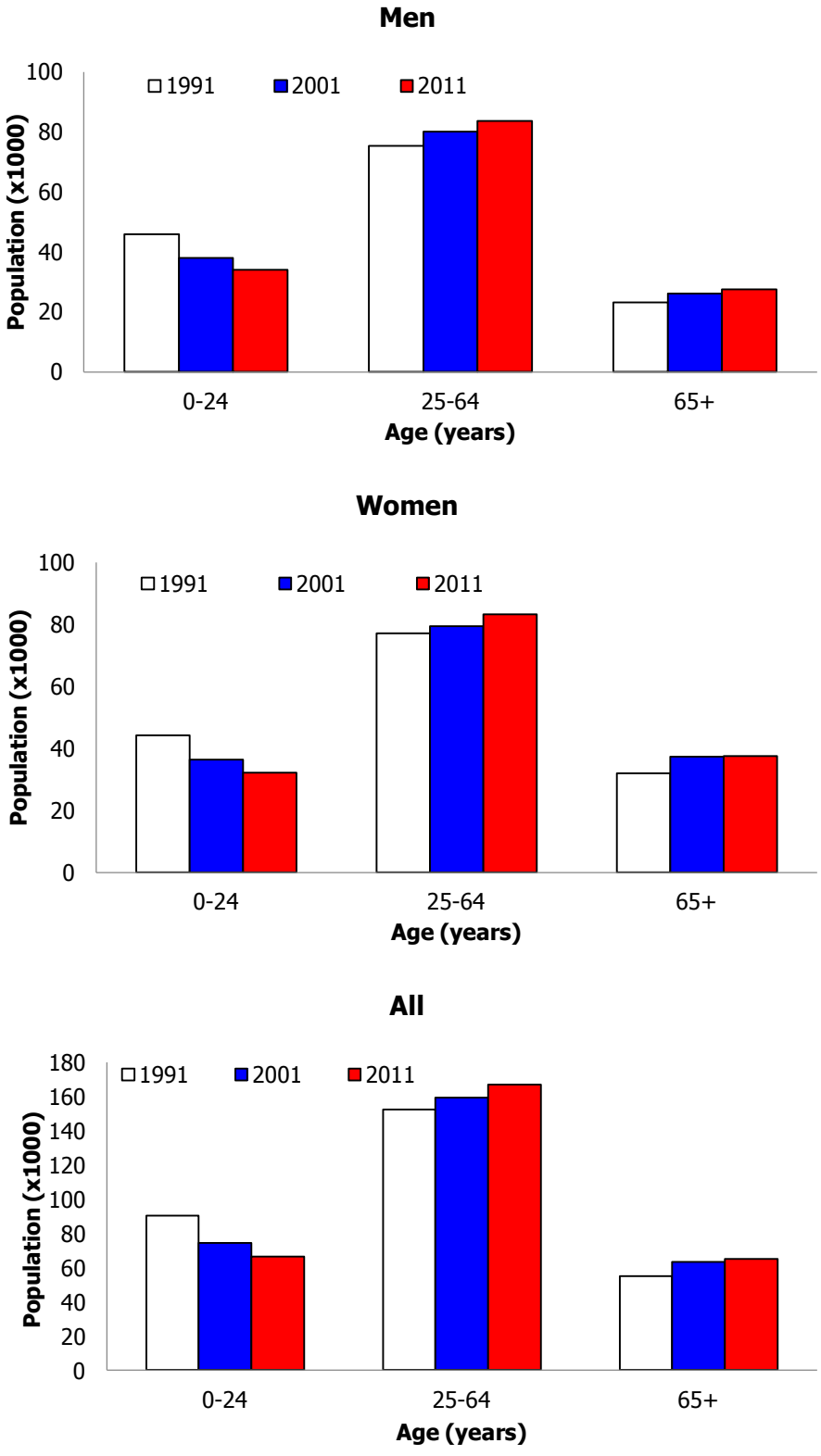
CHA_2DS_2VASc		Score
C	Congestive Heart Failure	1 point
H	Hypertension	1 point
A_2	Age ≥ 75 years	2 points
D	Diabetes	1 point
S_2	Stroke, TIA, Thromboembolism	2 points
V	Vascular Disease	1 point
A	Age 65-74 years	1 point
Sc	Sex category, female	1 point

TIA indicates transient ischemic attack.

Supplemental Table 4. TOAST criteria (Adams et al., 1933, as reported in Ornello et al., 2018)

Large-artery atherosclerosis	These patients will have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis. Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. A history of intermittent claudication, transient ischemic attacks (TIAs) in the same vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriography of a stenosis of greater than 50% of an appropriate intracranial or extracranial artery is needed. Diagnostic studies should exclude potential sources of cardiogenic embolism.
Cardioembolism	At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described for large-artery atherosclerosis. Evidence of a previous TIA or stroke in more than one vascular territory or systemic embolism supports a clinical diagnosis of cardiogenic stroke. Potential large-artery atherosclerotic sources of thrombosis or embolism should be eliminated. A stroke in a patient with a medium-risk cardiac source of embolism and no other cause of stroke is classified as a possible cardioembolic stroke.
Small-artery occlusion	The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction. A history of diabetes mellitus or hypertension supports the clinical diagnosis. The patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated. Potential cardiac sources for embolism should be absent, and evaluation of the large extracranial arteries should not demonstrate a stenosis of greater than 50% in an ipsilateral artery.
Acute stroke of other determined etiology	Patients in this group should have clinical and CT or MRI findings of an acute ischemic stroke, regardless of the size or location. Diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke. Cardiac sources of embolism and large-artery atherosclerosis should be excluded by other studies.
Stroke of undetermined etiology	In several instances, the cause of a stroke cannot be determined with any degree of confidence. Some patients will have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the evaluation was cursory. This category also includes patients with two or more potential causes of stroke so that the physician is unable to make a final diagnosis. For example, a patient with a medium-risk cardiac source of embolism who also has another possible cause of stroke identified would be classified as having a stroke of undetermined etiology. Other examples would be a patient who has atrial fibrillation and an ipsilateral stenosis of 50%, or the patient with a traditional lacunar syndrome and an ipsilateral carotid stenosis of 50%.

Supplemental Figure 1. Age- and Sex-structure Changes of the Resident Population in the L'Aquila District According to 1991, 2001, and 2011 ISTAT Census Data.



Supplemental Figure 2. Comparison of the Age Structure of the Study Population With that of Italy (ISTAT, 2011) and Europe (EUROSTAT, 2011).