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TENDÊNCIAS NA INCIDÊNCIA E PROGNÓSTICO DO ACIDENTE VASCULAR CEREBRAL

Tese de Candidatura ao grau de Doutor em Ciências Biomédicas submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

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Agradecimentos

à Professora Doutora Maria Carolina Costa e Silva pela sua imensa paciência e disponibilidade na orientação científica deste trabalho, bem como à amizade demonstrada ao longo de todo estes anos;

ao Professor Doutor Manuel Jorge Maia Pereira Correia, meu co-Orientador e mentor do projecto inicial, pelo seu apoio e incentivo durante a elaboração deste trabalho, bem como à amizade que fomos construindo ao longo da última década;

ao Professor Trevor Bailey pelo muito que me ensinou sobre análise espacial e pela sua importante contribuição na elaboração de um dos artigos que integram esta dissertação;

ao Professor Peter Sandercock e ao Professor William Whiteley pela contribuição que deram na leitura e revisão de alguns dos trabalhos presentes nesta dissertação;

ao Dr. Rui Felgueiras e ao Dr. Pedro Abreu, neurologistas, pela sua colaboração nas diferentes fases do projecto ACINrpc e na elaboração de parte dos artigos que compõem esta dissertação;

à Dra. Emília Moreira e à Dra. Carla Branco, psicólogas, pelo enorme contributo que deram ao projecto, realizando as avaliações neuropsicológicas dos doentes;

à Engª Cláudia Quintas, bolseira da Fundação para a Ciência e Tecnologia, pela persistência e dedicação com que executou muitas das tarefas associadas à realização do último projecto;

aos internos de neurologia e a todos os profissionais de saúde, que durante os últimos catorze anos colaboraram, directa ou indirectamente, nos diferentes projectos;

à Fundação para a Ciência e Tecnologia, entidade que financiou os dois últimos projectos ("Long-term prognosis of stroke and transient focal symptoms", POCTI/SAU-ESP/59885/2004; "Tendências na incidência e prognóstico dos Acidentes Neurológicos: o segundo estudo de base populacional no norte de Portugal", PIC/IC/82858/2007);

aos meus colegas do ICBAS por todo apoio demonstrado ao longo do tempo que levou a concluir este trabalho;

à minha família e amigos, pelas palavras de apoio e incentivo que me foram transmitidas bem como pela compreensão pelos momentos que não pudemos partilhar;

o meu profundo agradecimento

Resumo

Os principais objectivos desta dissertação foram: (1) estudar o prognóstico a curto e longo prazo dos doentes com um acidente vascular cerebral (AVC); (2) modelar a incidência diária de AVC em função de diferentes alterações nos parâmetros meteorológicos; (3) descrever os aspectos metodológicos utilizados no projecto ACINrpc e, (4) determinar a variação na incidência de AVC no Norte de Portugal.

As bases de dados utilizadas neste trabalho pertencem aos dois projectos ACINrpc (1998-00 e 2009-11). Nestes estudos prospectivos de base populacional realizados no Norte de Portugal, todos os doentes com um primeiro AVC na vida ou com um sintoma neurológico focal transitório foram identificados usando métodos de detecção abrangentes, incluindo a referenciação directa pelos médicos das instituições envolvidas no estudo e a revisão dos registos do serviço de urgência e das altas hospitalares. Os profissionais de saúde foram encorajados a referenciar/notificar qualquer doente com um possível episódio deste tipo. Os doentes foram examinados no início do estudo e aos três meses. Os doentes da primeira coorte (1998-2000) também foram examinados aos 12 meses e aos sete anos.

Utilizando a mesma metodologia, foi recolhida informação sobre o perfil sócio-demográfico, factores de risco vascular prévios ao evento, diagnóstico e meios de diagnóstico/tratamentos efectuados. A escala de Rankin modificada (mRS) foi utilizada para avaliar a capacidade funcional. Para avaliar a gravidade do AVC foi utilizada, no primeiro estudo a *Unified for Neurological Stroke Scale* e, no segundo estudo a *National Institute of Health Stroke Scale*. Para além destes dados, o Instituto de Meteorologia de Portugal forneceu, para o período compreendido entre Setembro de 1998 e Outubro de 2000, informação diária sobre os parâmetros meteorológicos (temperatura, humidade e pressão atmosférica). Utilizou-se a definição de AVC da Organização Mundial de Saúde. Classificou-se o AVC segundo os tipos patológicos definidos Sudlow e Warlow. Para definir os subtipos de AVC Isquémico utilizou-se a classificação clínica OCSP (Oxfordshire Community Stroke Project) e a classificação etiológica TOAST (Trial of Org 10172 in Acute Stroke Treatment)

A distribuição de Poisson foi usada para modelar o número de eventos incidentes. No caso do número de eventos que se seguem a uma “quantidade” variável de exposição, como no caso dos valores dos parâmetros meteorológicos, utilizando diferentes períodos de risco, for usada uma regressão de Poisson. No caso de uma “exposição” constante (não relevante para o modelo) e das variáveis explanatórias serem categóricas, como na

modelação da incidência por grupo etário, sexo e período do estudo, os dados podem ser sumariados numa tabela de contingência com restrições nas frequências em cada cela, usando-se um modelo linear generalizado com uma função de ligação, um modelo log-linear. Esta distribuição foi também assumida para calcular os intervalos de confiança a 95% para as taxas de incidência brutas e padronizadas para a população portuguesa e europeia. Foi ainda usado um modelo binomial para contrastar o efeito dos parâmetros meteorológicos em subgrupos de doentes.

Em relação ao prognóstico, o tempo de sobrevivência foi estimado utilizando o método de Kaplan-Meier, enquanto que o modelo de riscos proporcionais de Cox foi utilizado para identificar os preditores independentes de sobreviver livre de AVC ou de eventos vasculares. Com base no grau de incapacidade aos três meses medido numa escala ordinal variando entre zero e seis foi estimada a possibilidade de um pior prognóstico aos sete anos recorrendo a uma análise Ridit.

A diferença na incidência de AVC entre o meio urbano e rural resulta do maior risco de AVC isquémico na população jovem do meio urbano e na população idosa do meio rural. Embora no meio rural os doentes sejam mais idosos, a menor prevalência de factores de risco vascular associada a uma igual gestão do doente com AVC, pode justificar o facto de não existirem diferenças no prognóstico a longo prazo no meio urbano e rural. Por outro lado, uma simplificação na avaliação do grau de incapacidade aos três meses permite avaliar o perfil de risco dos doentes com AVC Isquémico. Este estudo permitiu confirmar que uma ligeira diferença no estado funcional aos 3 meses está associada a um diferença significativa na sobrevivência e estado funcional aos 7 anos, o que tem implicações no planeamento e avaliação económica dos tratamentos para o AVC agudo.

Esta investigação permitiu encontrar uma associação entre os parâmetros meteorológicos e a ocorrência de AVC e também com a sua gravidade. A variação do efeito da temperatura ambiental de acordo com o “timing” da exposição, a ausência de associação ao enfarte lacunar e a associação ao enfarte cardioembólico, reflectem a plausibilidade desta associação e podem explicar divergências nos resultados encontrados noutros estudos de base populacional ou hospitalar.

Este trabalho destaca também a importância da avaliar os doentes com sintomas focais transitórios para identificar os que têm AVC, sendo um critério metodológico a considerar em estudos futuros. Para o declínio da taxa de mortalidade por AVC em Portugal, contribuiu uma diminuição na incidência de AVC entre 1998 e 2011. Observou-se um efeito de ‘*género*’ no sentido em que a diminuição do risco de AVC, em particular do AVC hemorrágico ou incapacitante, foi muito superior nas mulheres.

Abstract

The main objectives of the present work were: (1) to study short- and long-term prognosis of stroke patients; (2) to model the daily stroke incidence according to short- or long-term weather changes; (3) to describe the methodological aspects of stroke incidence studies used in the ACINrpc project and, (4) to determine changes in stroke incidence in Northern Portugal.

The data used is part of the two ACINrpc projects (1998-2000 and 2009-2011). In these two prospective community-based studies implemented in Northern Portugal, all patients with a first-ever-in-lifetime stroke or focal neurologic transient symptoms were ascertained using comprehensive methods, including referrals from physicians working in the study area and data retrieved from emergency/discharge records. Physicians were encouraged to report/notify any patient who might have experienced such a kind of event. Patients were examined at baseline and followed-up at three months. For the first cohort (1998-2000) patients were also followed at one and seven years.

Information about socio-demographic characteristics, prior-to-stroke vascular risk factors, diagnostic and clinical evaluation/treatment and destination after discharge was collected using the same methodology throughout the two study periods. Functional status was assessed with the modified Rankin Scale (mRS) and stroke severity was measured using the Unified for Neurological Stroke Scale (first study) and the National Institute of Health Stroke Scale (second study). For the first study period, an additional dataset with information on daily temperature, humidity and air pressure, between September 1998 and October 2000, was obtained from the National Meteorological Office. Stroke was defined according to the World Health Organization and classified into pathological types according to Sudlow and Warlow standard definitions. The Oxfordshire Community Stroke Project classification and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used to define ischemic stroke subtypes.

The Poisson distribution was used for modeling the number of incident events. When the events related to varying amounts of “exposure”, as for values of meteorological parameters using different hazard periods, the Poisson regression was used. When “exposure” is constant (not relevant in the model) and explanatory variables are categorical, as in the model of incidence according to age-group, sex and study period, the data may be summarized in a contingency table with restrictions on cell frequencies. In this case a generalized linear model with a link function was used, a log-linear model. This distribution was also assumed for calculating the 95% confidence intervals for crude

and standardized incidence rates for the Portuguese and European population. The binomial model was used to contrast effects of meteorological parameters across subgroups of patients.

As far as prognosis is concerned, the Kaplan-Meier estimates for overall survival were calculated and predictors of survival free from stroke or vascular events were determined using Cox proportional hazards models. Ridit analysis was used to estimate the odds of a more serious 7-year outcome according to adjacent values of the 3-month modified Rankin Score (mRS).

The age pattern of ischemic stroke incidence marks the difference between rural and urban populations; the youngest urban and the oldest rural residents were at a higher risk. Although patients from rural areas were older, the relatively lower prevalence of simultaneously occurring risk and prognostic factors among them as well as the similar management of rural and urban patients may justify why rurality is not associated with long-term survival. It was also described that a three grade simplified mRS summarises the risk profile and stroke characteristics in 3-month survivors with ischaemic stroke. Moreover we found that modest differences in functional status at 3 months are associated with significant differences in survival and functional status over 7 years, results that have relevant implications for health care planning and economic assessment of treatments for acute stroke.

We found that outdoor temperature and related meteorological parameters are associated with stroke occurrence and stroke severity. The different hazard periods for temperature effects, the absence of association with lacunar infarcts and the association with cardioembolic infarcts may explain the heterogeneous effects of weather on stroke occurrence found in community-based and hospital admission studies.

This work also highlights the importance of screening all transient focal episodes for identifying patients with stroke and this may be a methodological criterion to be included in future stroke incidence studies. The decline in stroke incidence between 1998 and 2011 contributed for the decline in stroke mortality rates in Portugal. We may add that there was a “gender decline” in the sense that an overall stroke incidence, hemorrhagic stroke incidence and disabling stroke incidence was evidenced in women and not in men. Advances in the quality of inpatient care and primary/secondary prevention in the elderly contributed decisively for the better stroke outcome across the last decade.

Publicações e apresentações públicas

As publicações e apresentações públicas que foram editadas ou realizadas no contexto e no decorrer desta dissertação são aqui enumeradas por ordem cronológica.

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[T] Trabalhos incluídos nesta dissertação

Índice Geral

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INTRODUÇÃO

Embora as taxas de mortalidade por acidente vascular cerebral (AVC) tenham vindo a diminuir nas últimas décadas, o AVC continua a figurar como uma das principais causas de morte a nível mundial.[1] O AVC é também responsável por um elevado número de hospitalizações, e as suas sequelas pós-AVC têm como consequência uma diminuição da qualidade de vida dos sobreviventes, incapacidade para o trabalho e/ou actividades diárias, e um alto consumo de recursos de saúde.[2]

Em Portugal, até finais do século XX, a informação disponível sobre o AVC baseava-se nas taxas de mortalidade publicadas pelo Instituto Nacional de Estatística. Com base nessa informação, Portugal apresentava, no período compreendido entre 1985 e 1994, uma das mais altas taxas de mortalidade por AVC da Europa Ocidental.[3] Para além desta elevada mortalidade, num estudo realizado em 1992, a prevalência estimada do AVC era de 8% com cerca de 20% dos sobreviventes a apresentarem uma incapacidade grave.[4] No que diz respeito à incidência de AVC e factores de risco associados, os primeiros estudos entretanto realizados apresentavam algumas limitações metodológicas, nomeadamente em termos de representatividade do AVC na comunidade e critérios de diagnóstico diferentes.[5-6] No entanto, os estudos prospectivos na comunidade são os únicos que permitem determinar de forma real a taxa de

incidência de AVC e co-morbilidades associadas. Permitem ainda conhecer melhor a sua etiologia e deste modo desenvolver estratégias mais eficazes para a sua prevenção e tratamento.[7] Tendo como objectivo investigar a elevada taxa de mortalidade por AVC no Norte de Portugal, foi realizado entre Outubro de 1998 e Setembro de 2000, um estudo de incidência de acidentes neurológicos (ACINrpc: Acidentes Neurológicos - registo prospectivo na comunidade), no qual tive a oportunidade de estar envolvido desde a fase inicial.[8] A metodologia adoptada obedeceu aos critérios internacionais estipulados para a realização de um estudo de incidência "ideal".[9] Este estudo permitiu obter dados fiáveis sobre a taxa de incidência do primeiro acidente neurológico na vida, incluindo o AVC,[10] o Acidente Isquémico Transitório (AIT)[11] e o Acidente Neurológico Transitório não AIT (ANT).[12] Permitiu ainda obter informação sobre a prevalência dos factores de risco vascular (FRV) mais relevantes e determinar o prognóstico a curto prazo, em populações urbanas e rurais (Tabela 1). A partir dos resultados obtidos, na Região Norte de Portugal, foi possível estimar que por ano 28.000 pessoas sofriam um primeiro AVC na vida, sendo este número ainda superior nas regiões rurais.

Tabela 1. Taxa de **i**ncidência anual e indicadores de prognóstico no estudo decorrido entre 1998 e 2000, em populações urbanas e rurais

		Urbana		Rural		Global	
Evento	Indicador	taxa	IC 95%	taxa	IC 95%	taxa	IC 95%
AVC	Incidência (/100 000)	269	244-293	305	265-344	279	259-300
	Padronizada*	173	153-192	202	169-234	181	164-198
	28 dias						
	Letalidade (%)	14.6	10.2-19.3	16.9	13.7-20.6	16.1	13.6-19.1
	12 Meses						
	Recorrência (%)	7,6	5,5-10,4	11,5	8,0-16,3	8,9	7,0-11,2
	Mortalidade (%)	30,1	26,1-34,4	28,8	23,3-35,0	29,7	26,4-33,2
	Dependência** (%)	42,7	37,4-48,2	36,0	29,0-43,7	40,4	36,1-44,8
AIT	Incidência (/100 000	61	49-73	96	67-133	67	56-78
	Padronizada	40	23-69	67	45-104	44	26-73
	12 Meses						
	Recorrência (%)	21,9	15,1-30,7	27,8	15,9-44,0	23,4	17,2-31,0
	Mortalidade (%)	9,5	5,3-16,6	19,4	9,8-35,0	12,1	7,7-18,5

*População Europeia, **Valor na escala de Rankin modificada >2

Em comparação com outras regiões da Europa Ocidental,[13] a incidência de AVC em Portugal era tendencialmente mais elevada quer em zonas rurais (305/100.000) quer em zonas urbanas (269/100.000). Estes valores de incidência apenas eram superados por países do Leste da Europa.[13-14] No entanto a alta incidência nos mais velhos verificava-se em estudos realizados em ambientes rurais ou mistos (rural/urbano) contrastando

com estudos realizados em ambiente urbano e, por outro lado, a incidência nos mais novos era superior na cidade do Porto quando comparada com a de outros estudos em meio citadino.[15] Estes resultados foram o ponto de partida para tentar compreender e melhorar a prevenção/tratamento precoce do AVC. Surgiram assim várias questões de investigação que constituíram o tema central desta tese. As primeiras questões que importava responder relacionam-se com a prevalência dos FRV e a incidência e prognóstico do AVC:

Será que a população rural em comparação com a urbana tinha uma maior prevalência dos tradicionais factores de risco vascular? Será que por esse facto a incidência dos diferentes tipos de AVC era diferente nas duas populações? Será o seu prognóstico a longo prazo será diferente?

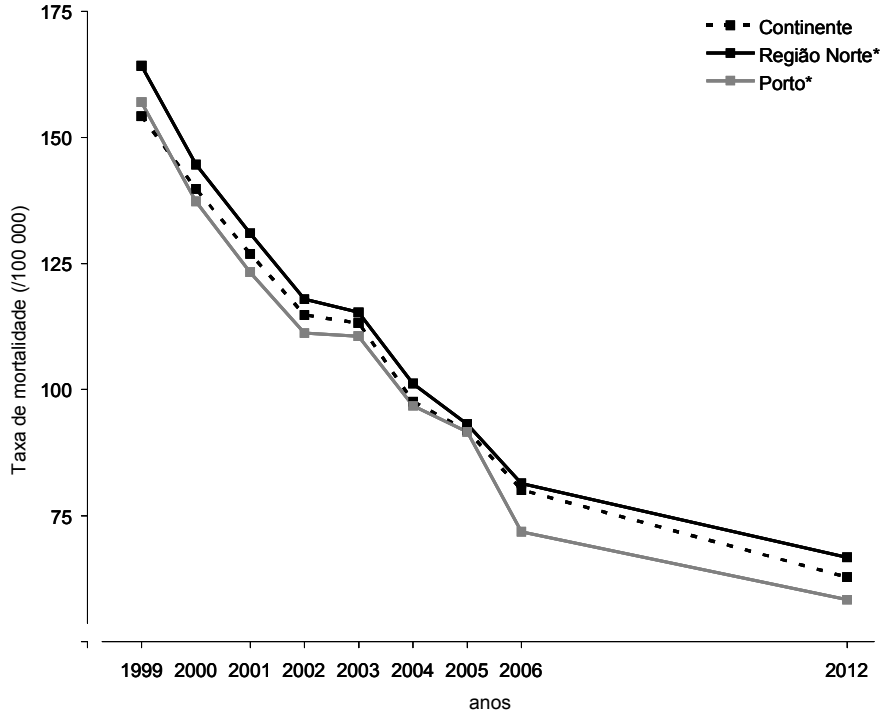
Os primeiros resultados do estudo ACINrpc mostraram também que a elevada incidência era acompanhada por uma baixa taxa de letalidade aos 28 dias (14,6% no meio rural e 16,9% no meio urbano), contrariamente ao que se poderia supor a partir das estatísticas oficiais de mortalidade que apontavam para uma taxa de mortalidade padronizada de 154/100.000 habitantes.[16] De notar que os valores encontrados para a taxa de letalidade no estudo eram similares aos de outros estudos de base populacional.[15,17-18] Este facto poderá ser explicado quer pelas altas taxas de incidência nos mais jovens quer pela diferente distribuição de subtipos de enfarte cerebral.[8,10] Surgiu, pois, daqui uma outra questão de investigação abordada no âmbito desta dissertação:

Será que a elevada incidência de AVC era acompanhada por uma menor gravidade (incapacidade), especialmente no caso do enfarte cerebral?

Tendo como ponto de partida a sazonalidade na ocorrência de AVC encontrada em diferentes estudos,[19-22] encontrou-se, no norte de Portugal, uma diferença ambiental marcada entre o meio urbano (Porto) e o meio rural (Vila Pouca de Aguiar) relacionada com os parâmetros meteorológicos, particularmente com as temperaturas mínimas e máximas em Vila Pouca de Aguiar.[23] No Inverno, registou-se um pico na ocorrência de AVC em Vila Pouca de Aguiar, enquanto no Verão se verificou um menor número de AVCs no Porto. Vários estudos tinham já apontado para a associação entre a temperatura e mortalidade por AVC[22,24-25] mas poucos tinham estudado a associação entre os parâmetros meteorológicos, em particular a temperatura, como despoletadores do AVC. Neste contexto surgiu uma outra questão de investigação:

Será que a exposição transitória com efeito transitório a valores extremos dos parâmetros meteorológicos, nomeadamente a temperatura ambiental, responsável pelo desencadear do AVC, isto é, por variações na incidência, em particular na população idosa?

Embora reconhecendo que as estatísticas oficiais de mortalidade por AVC não são isentas de viés, é possível observar um declínio destas taxas entre os anos de 1999 e 2012, tanto em Portugal Continental (de 154,2 para 62,8/100.000), como na Região Norte (de 164,2 para 66,7/100.000) (Figura 1).[16,26-33] Variações na taxa de mortalidade podem resultar de variações na incidência e/ou prognóstico, quer actuando ao nível da prevenção dos FRV quer por ganhos significativos no tratamento precoce da patologia.



*1999-2005: Região Norte (5 distritos) e distrito do Porto; 2006 e 2012: Região Norte (NUTs III) e Grande Porto

Figura 1. Evolução das taxas de mortalidade por doença cerebrovascular

Desde a realização do primeiro estudo (1998-2000) verificaram-se avanços consideráveis ao nível da intervenção no AVC com o objectivo de alterar o seu "peso" na comunidade, destacando-se melhorias na prevenção dos principais FRV[36] e a implementação de intervenções terapêuticas, nomeadamente a organização de Unidades de AVC e a utilização do tratamento trombolítico na fase aguda.[34-35] Em resultado dessas estratégias o cidadão comum está mais informado quanto à conveniência de exercer uma vigilância regular dos FRV, em particular da tensão

arterial,[37] mas é ainda insuficiente a divulgação e o alerta na população para a emergência do AVC. Após a organização das Unidades de AVC, foi criado um programa - "Via Verde do AVC" - cujo objectivo é minimizar o tempo decorrido entre o aparecimento dos sintomas e o início do tratamento do AVC, esperando-se que tenha reflexos nos indicadores de mortalidade e morbilidade. Este programa requer tanto a organização da emergência pré-hospitalar e hospitalar como o alerta da população, de modo a que a procura de ajuda médica seja a imediata ao início dos sintomas.[38-40]

Para monitorizar a eficácia das estratégias de prevenção primária/secundária, é crucial ter informação sobre a evolução do padrão da doença e suas causas. Os dados epidemiológicos sobre tendências temporais na incidência, etiologia e prognóstico dos acidentes neurológicos, fornecem indicadores sobre a eficácia da actuação dos sistemas de saúde na prevenção dos factores de risco modificáveis, partilhados com outras doenças relacionadas com o envelhecimento, e no tratamento dos doentes em ambiente de consulta ou internamento. Assim, uma década após a realização do estudo ACINrpc foi possível desenhar e concretizar, na região norte de Portugal, o projecto ACIN2: "*Tendência da incidência e prognóstico dos acidentes neurológicos: o segundo estudo de base populacional no norte de Portugal*" (PIC/IC/82858/2007). A implementação do estudo requereu um planeamento cuidadoso e eficaz, adequado à obtenção de dados actuais de forma comparável com o estudo anterior. No decurso deste estudo levantaram-se várias questões, nomeadamente no que diz respeito à comparação dos resultados dos dois estudos:

> *Como planear o estudo de modo semelhante ao primeiro, de forma a obter resultados comparáveis, contemplando: (a) a reorganização do Serviço Nacional de Saúde entretanto ocorrida; (b) a utilização de meios informáticos no tratamento das diferentes fontes de informação, que apresentam diferentes níveis de informatização e, (c) a inclusão de critérios metodológicos adicionais entretanto publicados? Qual a variação na incidência e prognóstico a curto prazo do AVC que ocorreu no espaço de uma década no Norte de Portugal?*

Estrutura da Tese

Para responder às primeiras questões apresenta-se no Capítulo 2 um artigo onde se estudou a incidência e prognóstico a curto e longo prazo (sete anos) do primeiro AVC na vida. Para o efeito, recorreu-se à modelação do tempo de sobrevivência e co-variáveis descritivas dos eventos ocorridos durante o *follow-up*, nomeadamente utilizando um

moedelo de riscos proporcionais de Cox (*Cox Proportional Hazards Model*). Nesta análise utilizou-se a informação recolhida durante a realização do primeiro estudo ACINrpc, referente a doentes com um primeiro AVC na vida, e a informação obtida no *follow-up* realizado aos sete anos.

No Capítulo 3 apresenta-se um artigo cujo objectivo foi estudar a importância do grau de incapacidade aos três meses no prognóstico a longo prazo (sete anos) dos doentes com enfarte cerebral (EC). O grau de incapacidade foi aferido utilizando a escala de Rankin modificada. De acordo com os valores na escala de Rankin aos sete anos e utilizando uma análise Ridit, foi possível reduzir a escala para três níveis (sem incapacidade, incapacidade moderada e incapacidade severa). Para medir o efeito da incapacidade aos três meses no prognóstico a longo prazo foi utilizado um modelo de riscos proporcionais de Cox, ajustado para possíveis variáveis confundidoras.

Para responder à questão seguinte apresenta-se no Capítulo 4 um artigo no qual se investigou a associação entre a incidência de AVC e determinados parâmetros meteorológicos na cidade do Porto. Para o efeito utilizaram-se modelos lineares generalizados adequados ao estudo de acontecimentos raros (distribuição de Poisson). A informação sobre os parâmetros meteorológicos pertence à série secular do Observatório da Serra do Pilar (Porto), incluindo os registos diários da temperatura máxima e mínima, pressão atmosférica, humidade relativa e precipitação, durante o período de 15 de Setembro de 1998 a 15 de Outubro de 2000. Relativamente a este tema, foi apresentado um trabalho numa reunião científica cujo objectivo foi estudar especificamente a relação entre temperatura ambiente e precipitação e o risco de ter uma hemorragia intracerebral primária (HICP), utilizando um estudo caso-cruzado ('*case-crossover*', anexo II).

Para reforçar a importância metodológica de avaliar os episódios neurológicos focais transitórios (ANT) na detecção de AVC/AIT, e realizar o seu seguimento no curto prazo, apresenta-se no Capítulo 5 um artigo sobre a incidência de AVC/AIT nos doentes com sintomas vestibulares.

Para responder às últimas questões desta dissertação, apresenta-se no Capítulo 6 um artigo em que se comparam os aspectos metodológicos utilizados nos dois estudos ACIN, com o objectivo de estimar variações na incidência e prognóstico a curto prazo do AVC na população da cidade do Porto. Para estudar o padrão evolutivo da incidência por sexo e idade foram utilizados modelos lineares generalizados (distribuição de Poisson). No âmbito deste tema, foram ainda apresentados três trabalhos em reuniões científicas nos quais se descreve a evolução das taxas de incidência e letalidade do AVC, da HICP

e da hemorragia subaracnoideia, comparando o meio urbano com o rural (anexo II). Apresenta-se ainda, em anexo, um artigo com uma análise preliminar sobre a caracterização dos utentes da Via Verde do AVC, no qual se focam alguns aspectos metodológicos adoptados no segundo estudo.

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CAPÍTULO 2

STROKE TYPES IN RURAL AND URBAN NORTHERN PORTUGAL: INCIDENCE AND 7-YEAR SURVIVAL IN A COMMUNITY-BASED STUDY

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Cerebrovascular Diseases Extra, 2013;3:137-149

EXTRA
Cerebrovascular Diseases

Cerebrovasc Dis Extra 2013;3:137–149
DOI: 10.1159/000354851
Published online: October 18, 2013

1664–5456/13/0031–0137$38.00/0
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Original Paper

Stroke Types in Rural and Urban Northern Portugal: Incidence and 7-Year Survival in a Community-Based Study

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Key Words
Stroke · Incidence · Survival · Prognosis · Rural/urban Portugal

Abstract
Background/Aim: Differences in stroke incidence and mortality between regions could stem from differences in the incidence of particular stroke types and long-term prognosis. The aim of this study was to investigate whether different risk profiles and stroke types underlie the difference in stroke incidence and patient long-term survival in rural and urban populations. ***Methods:*** All suspected first-ever-in-a-lifetime strokes occurring between October 1998 and September 2000 in 37,290 residents of rural municipalities and in 86,023 individuals living in the city of Porto were entered into a population-based registry. Standard definitions of stroke types and overlapping comprehensive sources of information were used for patient identification. Patients were examined by neurologists at 3 months, 1 year and 7 years after the index event. ***Results:*** From a total of 688 patients included (226 in rural and 462 in urban areas), 76.2% had an ischaemic stroke (IS; 75.3 vs. 77.9%), 16.1% a primary intracerebral haemorrhage (PICH; 16.3 vs. 14.6%) and 3.3% a subarachnoid haemorrhage (SAH; 2.7 vs. 3.7%); in 4.4% (4.9 vs. 4.1%), the stroke type could not be determined. The annual incidence rate per 1,000 was 2.13 (95% CI, 1.95–2.31), 0.45 (95% CI, 0.37–0.53), 0.09 (95% CI, 0.06–0.14) and 0.12 (95% CI, 0.08–0.17), respectively. The age-specific rural/urban incidence rate ratios for IS in the youngest group (<55 years) was 0.27 (95% CI, 0.11–0.69), increasing to 1.47 (95% CI, 1.07–2.01) for those aged 65–74 years and to 1.87 (95% CI, 1.39–2.52) for those between 75 and 84 years. Rural compared to urban patients with an IS were predominantly men, had a prevalence ratio (PR) of 1.28 (95% CI, 1.05–1.56), were 65 years or older (PR = 1.18; 95% CI, 1.08–1.30) and had

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Cerebrovasc Dis Extra 2013;3:137–149
DOI: 10.1159/000354851

in general a lower prevalence of risk factors. There was no evidence of rural/urban differences in 28-day case fatality for the stroke types, although IS tended to be less fatal among urban patients (10.3 vs. 13.1%), whereas PICH (33.3 vs. 24.2%) and SAH (35.3 vs. 16.7%) were less fatal among rural patients. Independently of rural/urban residence, predictors of poor survival after the acute phase (28 days) were age >65 years (HR = 3.57; 95% CI, 2.6–4.9), diabetes (HR = 1.5; 95% CI, 1.2–1.9), ischaemic heart disease (HR = 1.8; 95% CI, 1.3–2.6), atrial fibrillation (HR = 1.5; 95% CI, 1.1–2.0) and smoking habits (HR = 1.6; 95% CI, 1.1–2.3). ***Conclusions:*** The age pattern of IS incidence marks the difference between rural and urban populations; the youngest urban and the oldest rural residents were at a higher risk. Although patients from rural areas were older, the relatively lower prevalence of simultaneously occurring risk and prognostic factors among them as well as the similar management of rural and urban patients may justify why rurality is not associated with long-term survival.

Introduction

Despite the continuous decrease in mortality rates from stroke in Portugal in the last two decades [1], disparities still remain in standardized rates among rural (77.1/100,000) and urban (71.8/100,000) areas in northern Portugal [2]. We have shown that this excess mortality in rural areas could be partially explained by a higher incidence of stroke and not by short-term case fatality, i.e., 30.1% in rural areas compared to 27.9% in the city of Porto in the first year following the first-ever-in-a-lifetime stroke (FELS) [3]. Rather than being a single pathological entity, stroke is a disease that includes distinct types having different incidence rates, risk profiles, management guidelines and outcomes that may lead to different disease burdens in different regions. Comparing the incidence of different stroke types as well as the risk profiles and long-term survival of patients with these stroke types in rural and urban populations may add important knowledge about their aetiology, prevention and prognosis. In order to accurately assess the incidence of different stroke types, studies investigating stroke incidences must meet ideal criteria [4, 5], such as the use of diagnostic brain imaging for the majority (ideally for all) of the patients [6]. In accordance to these criteria, a community-based prospective stroke registry was set up in northern Portugal [3]. The aim of this article is to present data on stroke types regarding incidence, risk profile and long-term survival for understanding the patterns of stroke in rural and urban populations.

Population and Methods

The ACINrpc was a community-based study of the incidence and outcome of FELS and transient neurological focal symptoms and signs. The overall design of the project has been described in detail elsewhere [3]. In brief, the study population comprised 123,112 individuals registered and identified by a unique health service at five health centres on September 30, 1999 (mid-study period): 37,089 in rural areas and 80,023 in the city of Porto. This population was not significantly different from the corresponding geographic population [3]. Case ascertainment lasted from October 1, 1998, to September 30, 2000, and included both 'hot- and cold-pursuit data collection' using a variety of overlapping sources of information.

A study neurologist examined all suspected cases as soon as possible, and a CT was performed after the event. Medical records from hospitals and/or general practitioners (GP) were checked for details of any previous event and vascular risk factors (VRF). The principal investigator reviewed the information of each patient and classified the type of stroke;

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DOI: 10.1159/000354851

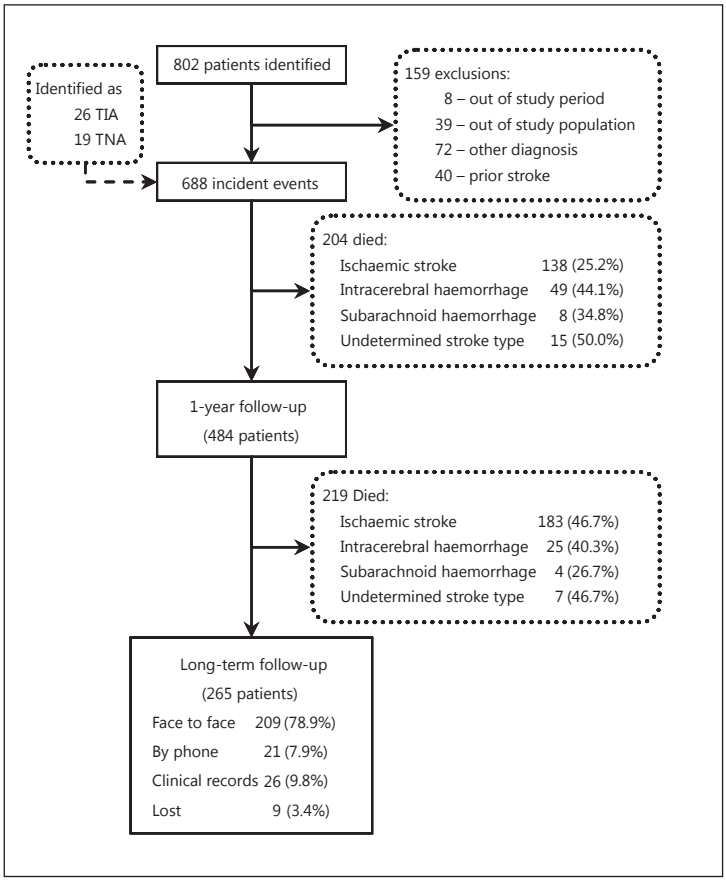

Fig. 1. Ascertainment and inclusion of FELS in northern Portugal and details of the 7-year follow-up.

whenever appropriate, the classification was established after consensus between the neurologist who first examined the patient and the principal investigator.

All patients were followed up by neurologists at 3 months, 1 year and 7 years after the index event. The long-term follow-up began in September 2005, and every attempt was made to include all patients alive at the 1-year follow-up (fig. 1). The process began by updating the telephone contacts of the patients using health centre/hospital administrative files and all available information on patient medical records. This was followed by a first contact by phone made 15 days before the end of the 7-year period, and, when this failed, two letters were sent explaining the study purpose and suggesting a date for a consultation. Patients who collaborated but were not willing to complete the consultation were contacted by phone, and for those unable to come to the hospital, home visits were scheduled. For patients known to be deceased based on previous information, a family member/caregiver had to give information about the date and circumstances of death; otherwise, a search was done in the computer files held at the Northern Regional Health Administration. In case of death, information about date and circumstances of death was confirmed by manual inspection of written monthly reports at each health centre since current legislation forbids the use of death certificates for research purposes. This information was linked to existing clinical records for assigning the underlying cause of death, determined by a study neurologist. If no contact or information could be obtained, the patient was considered lost to follow-up.

Stroke was defined according to the World Health Organization [7], and stroke types were classified according to Sudlow and Warlow [5] as ischaemic stroke (IS), primary intra-

cerebral haemorrhage (PICH) and subarachnoid haemorrhage (SAH). If no brain CT scan was performed within 30 days and no autopsy, lumbar puncture or angiography (in case of suspected SAH) results were available, stroke was classified as undetermined. For VRF, the following definitions were used: for hypertension, a history of high blood pressure (BP) or an anti-hypertensive treatment or systolic BP >160 mm Hg and/or diastolic BP >95 mm Hg on at least two different measures; for diabetes, a previous diagnosis/treatment of diabetes mellitus with oral anti-diabetic/insulin or fasting glycaemia >126 mg/dl, postprandial glycaemia ≥200 mg/dl and/or a glucose tolerance test with values of glycaemia ≥200 mg/dl at the second hour; for hypercholesterolaemia, a previous diagnosis/treatment of hypercholesterolaemia or a serum total cholesterol level after 12 h of fasting ≥240 mg/dl; and for cardiac disease, a previous diagnosis of angina, myocardial infarction (MI) or atrial fibrillation by EKG confirmation, a previous diagnosis of a transient ischaemic attack (TIA), and smoking, categorized as never smoked, smoked regularly but not in the preceding 12 months (ex-smoker) and current smoker.

The Ethics Committee of the Hospital de Santo António, where the study coordination centre was located, approved the study. Informed consent was obtained from each participant, or from the next of kin when appropriate, before any clinical assessment. Since medical records are part of the National Health Service institutions, for follow-up purposes clinical files were used whenever the patient could not be contacted.

Statistical Analysis

The distribution of patient characteristics at baseline according to stroke type is described. The crude incidence rates age-standardized to the Portuguese [8] and European populations [9] are reported, and the 95% confidence intervals (CI) were calculated by the Poisson distribution. The rural/urban ratios of VRF prevalence, stroke incidence and case fatality were calculated based on cross-tabulation and were used to compare rural and urban patients. The Kaplan-Meier estimates for the cumulative risk of death for stroke types over a period of 7 years after the index event were calculated in rural and urban patients. After checking the assumption of proportional hazards with the Schoenfeld's test, the rural/urban hazard ratios (HR) were calculated using a Cox model including the baseline risk profiles. Since this assumption failed when considering the time from the index event until death over the 7-year follow-up, this model was restricted to patients surviving the acute phase (28 days).

Results

Of the 688 FELS (226 in rural and 462 in urban areas), 76.2% were IS (75.3 in rural vs. 77.9% in urban), 16.1% were PICH (16.3 vs. 14.6%), 3.3% SAH (2.7 vs. 3.7%) and 4.4% of undetermined stroke type (4.9 vs. 4.1%). More cases in rural compared to urban areas were ascertained by 'hot-pursuit' and sooner after the event. Nearly 56% of the patients were admitted to the hospital, with a similar proportion for IS in both rural and urban areas but a lower proportion of PICH in the rural area (69.7 vs. 96.2%). Overall, a CT scan was performed in 96.9% of the patients (not done in 12 urban and 9 rural patients) and in 70.3% within 24 h following the event.

Vascular Risk Profiles and Incidence

Although patients were mostly women (58.7%), men predominated in rural areas (48.2 vs. 37.9%) either with an IS or PICH; patients from rural areas were older than patients from urban areas, especially those with an IS (table 1). Hypertension was the most prevalent VRF (60.9%), whereas a previous TIA was seldom registered (8.6%). In general, the prevalence of

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DOI: 10.1159/000354851

Table 1. Ascertainment and patient characteristics (in %) by stroke type in urban and rural areas

	Urban				Rural				Ratio rural:urban			
	IS (n = 348)	PICH (n = 78)	SAH (n = 17)	All (n = 462)	IS (n = 176)	PICH (n = 33)	SAH (n = 6)	All (n = 226)	IS		PICH	
									ratio	95% CI	ratio	95% CI
First source of information												
'Hot pursuit'	76.4	56.4	23.5	69.5	97.2	97.0	83.3	94.7	1.27	1.19–1.35	1.72	1.40–2.11
Health centre	5.5	–	–	5.6	47.2	60.6	16.7	48.7				
Hospital	71.0	56.4	23.5	63.9	50.0	36.4	66.7	46.0				
Patient assessment												
Emergency services	93.7	97.4	100.0	92.0	93.8	97.0	100.0	91.2	1.00	0.95–1.05	1.00	0.93–1.07
<3 h	36.8	50.0	52.9	39.5	48.8	71.9	66.7	52.9	1.33	1.08–1.63	1.45	1.07–1.97
In-patient admission	50.3	96.2	100.0	57.8	50.6	69.7	100.0	52.2	1.01	0.84–1.20	0.72	0.58–0.91
Time between onset and CT scan <24 h	67.2	83.3	70.6	69.1	67.0	66.7	50.0	65.9	1.00	0.88–1.13	0.80	0.62–1.04
Patient characteristics												
Male gender	38.2	37.5	29.4	37.9	48.9	51.5	–	48.2	1.28	1.05–1.56	1.39	0.89–2.15
Mean age ± SD, years	71.0±13.1	67.2±14.6	59.9±19.0	70.3±13.9	73.6±9.4	67.5±12.3	58.8±19.7	72.5±10.9				
>65 years	71.0	55.1	52.9	68.2	84.1	60.6	50.0	80.1	1.18	1.08–1.30	1.10	0.78–1.54
Hypertension	62.9	69.2	52.9	62.3	58.0	69.7	–	58.0	0.92	0.79–1.07	1.01	0.77–1.32
Hypercholesterolaemia	41.4	28.2	17.6	37.9	28.4	9.1	16.7	24.8	0.69	0.53–0.90	0.32	0.10–1.00
Diabetes	29.6	24.4	11.8	27.1	21.6	9.1	–	18.6	0.73	0.53–1.01	0.37	0.12–1.18
Atrial fibrillation	17.2	3.8	–	13.9	17.0	–	–	13.3	0.99	0.66–1.47	–	
MI/angina	11.5	10.3	5.9	10.6	5.7	3.0	–	5.3	0.49	0.25–0.96	0.30	0.04–2.27
TIA	12.4	2.6	–	9.7	7.4	–	–	6.2	0.60	0.33–1.08	–	
Smoking habits												
Current smoker	17.2	12.8	23.5	16.9	8.0	6.1	–	8.0	0.46	0.27–0.80	0.47	0.11–2.04
Ex-smoker	9.2	5.1	–	7.8	5.7	12.1	–	6.2	0.60	0.30–1.19	2.36	0.63–8.89

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Table 2. Age-specific annual incidence per 1,000 for stroke types in urban and rural northern Portugal (1998–2000)

Age group (in years)	Person-years	IS			PICH			SAH			Undetermined		
		n	rate	95% CI	n	rate	95% CI	n	rate	95% CI	n	rate	95% CI
Urban													
00–34	68,706	2	0.03	0.00–0.11	2	0.03	0.00–0.11	1	0.01	0.00–0.08	0	0.00	0.00–0.05
35–44	24,806	15	0.60	0.34–1.00	4	0.16	0.04–0.41	3	0.12	0.02–0.35	0	0.00	0.00–0.15
45–54	23,500	24	1.02	0.65–1.52	9	0.38	0.18–0.73	3	0.13	0.03–0.37	2	0.09	0.01–0.31
55–64	19,584	48	2.45	1.81–3.25	17	0.87	0.51–1.39	1	0.05	0.00–0.28	0	0.00	0.00–0.19
65–74	19,544	102	5.22	4.21–6.23	20	1.02	0.63–1.58	6	0.31	0.11–0.67	5	0.26	0.08–0.60
75–84	11,812	108	9.14	7.42–10.9	14	1.19	0.65–1.99	1	0.08	0.00–0.47	6	0.51	0.19–1.11
≥85	4,094	49	11.97	8.85–15.8	12	2.93	1.51–5.12	2	0.49	0.06–1.76	6	1.47	0.54–3.19
All	172,046	348	2.02	1.81–2.24	78	0.45	0.36–0.57	17	0.10	0.06–0.16	19	0.11	0.07–0.17
ASRP			1.63	1.44–1.82		0.38	0.29–0.48		0.09	0.05–0.14		0.08	0.04–0.14
ASRE			1.26	1.10–1.44		0.32	0.24–0.42		0.08	0.04–0.13		0.06	0.03–0.11
Rural													
00–34	33,690	1	0.03	0.00–0.17	0	0.00	0.00–0.11	1	0.03	0.00–0.17	0	0.00	0.00–0.11
35–44	9,972	2	0.20	0.02–0.72	0	0.00	0.00–0.37	1	0.10	0.00–0.56	1	0.10	0.00–0.56
45–54	8,360	2	0.24	0.03–0.86	7	0.84	0.34–1.72	0	0.00	0.00–0.44	0	0.00	0.00–0.44
55–64	8,386	19	2.27	1.36–3.54	6	0.72	0.26–1.56	1	0.12	0.00–0.66	0	0.00	0.00–0.44
65–74	8,350	64	7.66	5.90–9.79	10	1.20	0.57–2.20	2	0.24	0.03–0.86	3	0.36	0.07–1.05
75–84	4,152	71	17.10	13.4–21.6	8	1.93	0.83–3.80	1	0.24	0.01–1.34	4	0.96	0.26–2.47
≥85	1,268	17	13.41	7.81–21.5	2	1.58	0.19–5.69	0	0.00	0.00–2.91	3	2.37	0.49–6.92
All	74,178	176	2.37	2.02–2.72	33	0.44	0.31–0.62	6	0.08	0.03–0.18	11	0.15	0.07–0.27
ASRP			2.12	1.79–2.45		0.42	0.28–0.59		0.08	0.03–0.18		0.13	0.06–0.25
ASRE			1.51	1.23–1.79		0.35	0.23–0.51		0.07	0.02–0.16		0.09	0.04–0.19
All													
00–34	102,396	3	0.03	0.01–0.09	2	0.02	0.00–0.07	2	0.02	0.00–0.07	0	0.00	0.00–0.04
35–44	34,778	17	0.49	0.28–0.78	4	0.12	0.03–0.29	4	0.12	0.03–0.29	1	0.03	0.00–0.16
45–54	31,860	26	0.82	0.53–1.20	16	0.50	0.29–0.82	3	0.09	0.02–0.28	2	0.06	0.01–0.23
55–64	27,970	67	2.40	1.86–3.04	23	0.82	0.52–1.23	2	0.07	0.01–0.26	0	0.00	0.00–0.13
65–74	27,894	166	5.95	5.05–6.86	30	1.08	0.73–1.54	8	0.29	0.12–0.56	8	0.29	0.12–0.56
75–84	15,964	179	11.21	9.57–12.9	22	1.38	0.86–2.09	2	0.13	0.02–0.45	10	0.63	0.30–1.15
≥85	5,362	66	12.31	9.52–15.7	14	2.61	1.43–4.38	2	0.37	0.04–1.35	9	1.68	0.77–3.19
All	246,224	524	2.13	1.95–2.31	111	0.45	0.37–0.53	23	0.09	0.06–0.14	30	0.12	0.08–0.17
ASRP			1.76	1.60–1.93		0.39	0.32–0.48		0.08	0.05–0.13		0.10	0.06–0.15
ASRE			1.33	1.19–1.48		0.33	0.26–0.41		0.07	0.04–0.12		0.07	0.04–0.11
Incidence rate ratios rural/urban													
00–54			0.27	0.11–0.69		1.05	0.43–2.57		0.64	0.13–3.09		1.12	0.10–12.4
55–64			0.92	0.54–1.57		0.82	0.33–2.09		2.34	0.15–37.3		–	
65–74			1.47	1.08–2.01		1.17	0.55–2.50		0.78	0.16–3.86		1.40	0.34–5.88
75–84			1.87	1.39–2.52		1.63	0.68–3.87		2.84	0.18–45.5		1.90	0.54–6.72
≥85			1.12	0.65–1.94		0.54	0.12–2.40		–			1.61	0.40–6.45
All			1.19	0.95–1.50		1.10	0.69–1.75		0.89	0.32–2.50		1.62	0.62–4.27

ASRP = Age-standardized rate for the Portuguese population, 1999; ASRE = age-standardized rate for the European population.

VRF was lower in rural compared to urban patients, namely cardiac disease (IS and ICH), hypercholesterolaemia and smoking habits (IS).

The crude overall annual incidence rate per 1,000 population was 2.13 (95% CI, 1.95–2.31) for IS, 0.45 (95% CI, 0.37–0.53) for PICH, 0.09 (95% CI, 0.06–0.14) for SAH and 0.12 (95% CI, 0.08–0.17) for strokes of undetermined type; adjusted for the European population, these rates were 1.33 (95% CI, 1.19–1.48), 0.33 (95% CI, 0.25–0.41), 0.07 (95% CI, 0.04–0.12) and 0.07 (95% CI, 0.04–0.11), respectively (table 2). The ratio of rates indicates that the incidence of IS in the youngest group (<55 years) was lower in rural compared to urban populations, particularly in men (0.12; 95% CI, 0.02–0.91). The opposite trend was found among those aged 65–84 years (2.19; 95% CI, 1.37–3.49 in men and 1.65; 95% CI, 1.12–2.45 in women; results not shown). For the remaining stroke types, there was no evidence of differences in the age pattern of incidence rates between the rural and urban environment.

Short- and Long-Term Survival

Of the 688 FELS patients, 204 (29.7%) died during the first year; the 7-year follow-up details for the 484 survivors are described in figure 1. Nine patients were lost after the 1-year follow-up (1.1–2.4 years), mostly because they had changed residence or went abroad (7 IS, 1 PICH and 1 SAH). Among the 209 (78.9%) patients examined by the neurologist, 21 (10%) were visited at their homes. The follow-up time ranged from 7 to 8.6 years.

By day 28, 59 (11.3%), 34 (30.6%), 7 (30.4%) and 11 (36.7%) patients had died after the first IS, PICH, SAH and undetermined stroke, respectively. There was no evidence of rural/urban differences in 28-day case fatality for the different stroke types, although IS tended to be less fatal among urban patients (10.3 vs. 13.1%), whereas PICH (33.3 vs. 24.2%) and SAH (35.3 vs. 16.7%) were less fatal among rural patients, corresponding to rural/urban ratios of 1.26 (95% CI, 0.77–2.06), 0.73 (95% CI, 0.37–1.44) and 0.47 (95% CI, 0.07–3.16), respectively. The cumulative risk of death at 7 years followed the same pattern: IS was less fatal in urban patients (57.4 vs. 61.5%), and PICH (67.4 vs. 64.6%) or SAH (61.2 vs. 33.3%) were less fatal in rural patients. The proportional mortality from stroke (first or recurrent stroke) was 74.8% (83/111) at 28 days, 48.0% (98/204) during the first year and 30.3% (128/423) at the end of follow-up after 7 years. Figure 2 shows the risk of death at 28 days and by year for ischaemic and haemorrhage stroke (PICH and SAH), indicating a relatively constant yearly risk after 3 years in patients with an IS. Table 3 shows the independent baseline predictors of long-term survival after the acute phase. Besides age, diabetes (HR = 1.48; 95% CI, 1.15–1.92), MI/angina (HR = 1.80; 95% CI, 1.25–2.58), atrial fibrillation (HR = 1.47; 95% CI, 1.07–2.00) and being a current smoker (HR = 1.60; 95% CI, 1.13–2.28) increased the risk of death, whereas hypercholesterolaemia was a protective factor (HR = 0.45; 95% CI, 0.34–0.59). Stroke type and rural/urban residence were not associated with survival after the acute phase.

Discussion

This is the first study to present a comprehensive picture of the burden of stroke among rural and urban populations, looking at the incidence of stroke types as well as at vascular risk profiles and long-term survival of patients. A high proportion of patients were ascertained by 'hot-pursuit'; almost all underwent a CT soon after the initial symptoms, thus improving the reliability of the results for the incidence of stroke types [5]. Differences in procedural aspects mostly stem from the organization of the National Health Service; health centre services are more readily available than hospital services for rural populations, and in the city this is mainly a question of choice since there are no barriers of distance. Almost all

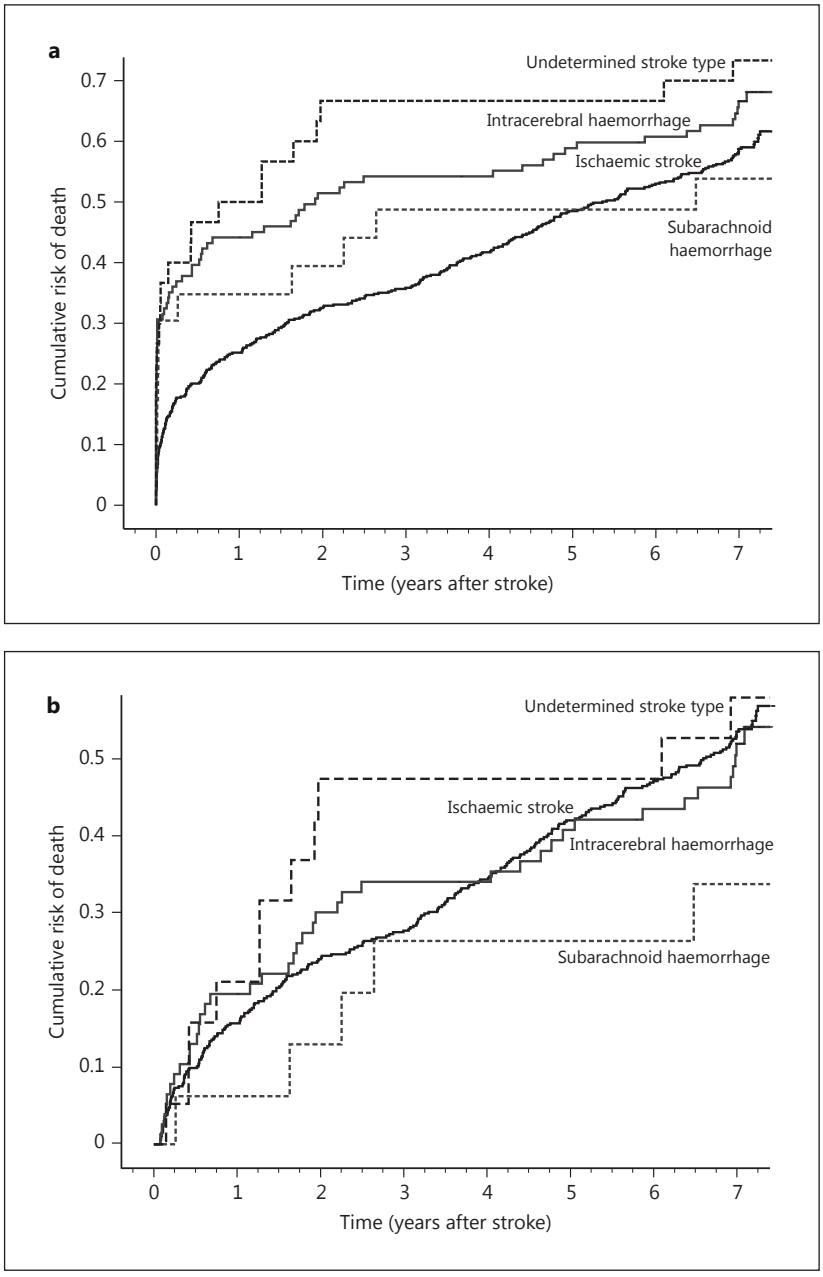

Fig. 2. Kaplan-Meier estimates of the cumulative death risk for all patients (**a**) and the cumulative death risk in 28-day stroke survivors by stroke type (**b**). N = Cumulative number of patients.

Stroke type	0–28 days	29 days to 1 year	1–2 years	2–3 years	3–4 years	4–5 years	5–6 years	6–7 years
Ischemic								
At risk, n	524	465	392	351	331	301	266	242
Death, n (N)	59 (59)	73 (132)	38 (170)	17 (187)	30 (217)	35 (252)	23 (275)	28 (303)
Risk, %	11.3	15.7	9.8	4.9	9.1	11.6	8.7	11.6
95% CI	8.8–14.3	12.7–19.3	7.2–13.1	3.1–7.7	6.4–12.6	8.5–15.7	5.9–12.7	8.1–16.2
Hemorrhagic								
At risk, n	134	93	77	66	61	61	56	54
Death, n (N)	41 (41)	16 (57)	9 (66)	5 (71)	0 (71)	5 (76)	2 (78)	7 (85)
Risk, %	30.6	17.2	12.0	7.6	0.0	8.2	3.6	13.0
95% CI	23.4–38.9	10.9–26.1	6.4–21.3	3.3–16.5	0.0–5.9	3.6–17.8	1.0–12.1	6.4–24.4

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DOI: 10.1159/000354851

Table 3. HR for the association between factors at presentation and death among 28-day survivors

	Univariate		Multivariate	
	HR	95% CI	HR	95% CI
Sociodemographics				
Rural versus urban	1.18	0.93–1.49	1.00	0.79–1.29
Men versus women	1.00	0.80–1.26	0.94	0.71–1.24
Age >65 versus ≤65 years	3.58	2.62–4.90***	3.57	2.58–4.95***
Risk factors (yes vs. no)				
Hypertension	0.81	0.64–1.02	0.86	0.68–1.09
Diabetes	1.21	0.94–1.56	1.48	1.15–1.92**
Atrial fibrillation	2.01	1.49–2.72***	1.47	1.07–2.00*
MI/angina	1.58	1.11–2.23**	1.80	1.25–2.58**
TIA	0.92	0.61–1.37	0.99	0.66–1.47
Hypercholesterolaemia	0.46	0.36–0.60***	0.45	0.34–0.59***
Smoking habits				
Ex-smoker	0.65	0.42–1.02	0.80	0.49–1.31
Current smoker	1.07	0.80–1.43	1.60	1.13–2.28**
Diagnosis (vs. IS)				
PICH	0.96	0.69–1.34	1.12	0.79–1.58
SAH	0.52	0.21–1.25	0.63	0.26–1.75
Undetermined stroke type	1.15	0.63–2.10	1.28	0.69–2.36

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

patients (91–92%) were seen at an 'emergency service'; however, in rural areas it was mostly at the health centre (open 24 h) and this is why these patients are more often observed within 3 h after the stroke. Nevertheless, in case of a PICH, there were fewer hospital admissions of rural compared with urban patients, though they remained in-patients in the health centre. Overall, the health services provided were similar for rural and urban patients, and based on previous studies we know that individuals living in rural areas are more prone to attend the family doctor at the health centre in case of most stroke warning signs than individuals living in urban areas [10].

There was a higher incidence of both IS and PICH in rural than urban areas. Nevertheless, the comparison of standardized rates obscured the differences in the incidence age pattern in the two populations, particularly in IS. On average, the first IS happened almost 3 years earlier in life among the urban population, leading to a higher IS incidence in the youngest group (<55 years), especially in men, whereas for those aged 75–84 years living in rural areas, the average risk is almost twice as high than in the city. Although patients living in rural areas were older, they had, in general, less traditional VRF than patients living in urban areas, in particular cardiac disease and hypercholesterolaemia in patients with IS. The reduced information and awareness of VRF [10] in rural areas and the consequent lack of monitoring probably led to an under-reporting and/or under-diagnosis, mainly by GPs, since by description of ascertainment, health centre services are 'more accessible' in rural areas. On the other hand, our results go in the same direction than those from a Dutch study [11], in which self-reported health problems pointed to a better health in rural areas, although this could not be confirmed by the information available on GP records.

Figure 3 shows the joint distribution of IS and PICH incidence across community-based studies with standardized rates (European population) or if data were available for calculation [12–34]. The IS incidence ranged from 57/100,000 in Menorca [29] to 255/100,000 in

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DOI: 10.1159/000354851

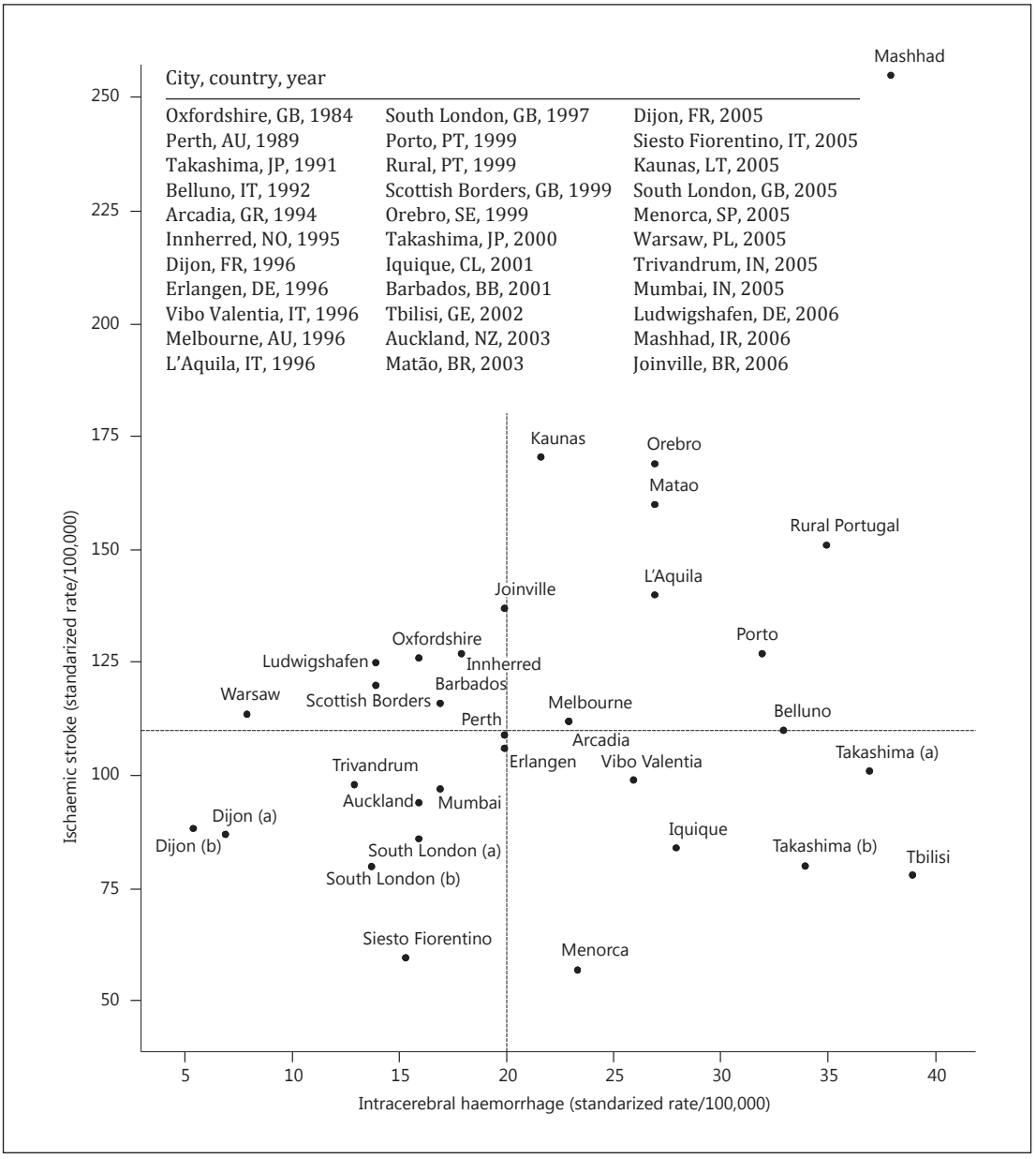

Fig. 3. Joint distribution of standardized IS and intracerebral haemorrhage incidence in community-based studies. The lines represent the median values.

Mashhad [33], and the incidence of PICH ranged from 6/100,000 in Dijon [29] to 39/100,000 in Tbilisi [26]. Both Portuguese urban and rural populations are in the upper-right quadrant, indicating a relatively high incidence of both IS and PICH, with the first being only higher in Mashhad, Kaunas, Orebro and Matão [23, 28, 29, 33] and the latter in Mashhad, Tbilisi and Takashima [14, 26, 33]. Apart from Japan, studies in Greece [16], Italy [15, 19, 21] and Georgia [26] also reported a relatively high incidence of PICH, probably linked to the high prevalence of hypertension and excess of salt in the Mediterranean diet, similar to the Japanese diet with a high consumption of salted fish [35]. The standardized incidence of SAH in this group of studies ranged from 1 to 16/100,000 (median = 6/100,000), and the values in Portugal are

close to the median. The comparison of the incidence of stroke types may be biased since the incidence of undetermined strokes could be as high as 59/100,000 (Trivandrum [30]), resulting from the low proportions of patients investigated with brain CT/MR scan and/or with a postmortem examination. Though we verified that there was no linear correlation between the year of the study and the standardized incidence of the different stroke types, the same could not be said in relation to the prevalence of VRF as a trend towards a lower incidence of PICH was found in repeated studies in Takashima [14], South London and Dijon [18, 29] (fig. 2). Nevertheless, in comparison with other studies, the prevalence of hypertension in patients from an urban area, representing a population-attributable risk for IS of 45.2% and for PICH of 73.6% [36], is among the highest (only exceeded in Oxfordshire [12] and Iquique [24]) for IS, and is the highest among Portuguese patients with PICH [15, 27, 37]; the same was found for diabetes mellitus, though the proportion of active smokers was relatively low compared to other studies [12, 15]. Besides traditional risk factors, environmental factors such as cold weather [38] and dietary habits may explain the relatively high variation shown in incidence rates.

There was no evidence of rural/urban differences in short- and long-term case fatality for the stroke types, though IS tended to be less fatal in patients from urban areas, whereas PICH and SAH were less fatal in patients from rural areas. The overall early case fatality after an IS (11.3%) found in this study is among the lowest values reported in all studies (range 10–26%) [12, 13, 15–26, 28, 32, 34]; the values for PICH (30.6%) and SAH (30.4%) are also among the lowest within the respective ranges (20–61% for PICH [23, 25] and 8–50% for SAH [15, 18, 20]). The cumulative risk of death at 7 years follows an identical pattern as the 28-day case fatality in rural/urban populations, and the values are close to those reported in Perth after a FELS and higher than in Oxfordshire after an IS and lower for haemorrhagic stroke for a 5-year follow-up [39, 40]. As in these studies, the proportional mortality from stroke in this study abruptly decreased after the acute phase. Neither stroke type nor residence was a predictor of long-term survival after the acute phase, but most risk factors were at the same time prognostic factors. Besides age <65 years, diabetes, atrial fibrillation, heart disease and smoking habits were predictors of poor survival, while hypercholesterolaemia was not. These results confirm recent findings [41, 42] and may justify why long-term survival is not associated with urban/rural environment. Since the stroke care chain is similar for patients from rural and urban areas, the older rural patients may have indeed a better survival than expected because risk/prognostic factors are less prevalent among them.

We have shown that the high incidence of stroke in rural compared to urban populations from northern Portugal is largely accounted for by the high incidence of cerebral infarcts, particularly in the rural elderly. The relatively better prognosis of IS and PICH in northern Portugal compared to other regions may result from the relatively high incidence of IS among the youngest age group living in the city as well as the relatively low prevalence of VRF in the eldest rural patients, pointing to different public health strategies. For better understanding the rural/urban differences in IS incidence, future analysis should be focused on the incidence of clinical subtypes of IS, aetiology and associated VRF.

Acknowledgement

This work was supported by a grant from the Merk, Sharp & Dhome Foundation, Portugal and the Fundação para a Ciência e Tecnologia grant FCT/FEDER project POCI/SAU-ESP/59885/2004. The Northern Region Health Authorities agreed and funded the investigator meetings.

Cerebrovasc Dis Extra 2013;3:137–149
DOI: 10.1159/000354851

Disclosure Statement

The authors have no conflicts of interest with respect to this work.

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CAPÍTULO 3

FUNCTIONAL STATUS THREE MONTHS AFTER THE FIRST ISCHAEMIC STROKE IS ASSOCIATED WITH LONG-TERM OUTCOME: DATA FROM A COMMUNITY-BASED COHORT

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Cerebrovascular Diseases, 2014;38:46-54

Abstract

Background: The impact of public health interventions to reduce disability after stroke may be underestimated if only the modest effects on short-term disability are measured. We estimated the impact of differences in short-term functional outcome on long-term functional outcome.

Methods: In a prospective community-based study from October 1998 to September 2000, the first-ever ischemic strokes were registered in a population of 95,816 in Northern Portugal. Patients were examined at baseline and followed-up at three months, one and seven years. The Oxfordshire classification and the Unified Neurological Stroke Scale were used to define the stroke type and the severity of neurological impairments. The functional status was assessed with the modified Rankin Scale (mRS). Ridit analysis was used to estimate the odds of a more serious 7-year outcome based on the adjacent values of the 3-month mRS. Cox proportional hazards models were used for estimating the effect of 3-month mRS on survival, adjusting for patients' characteristics, stroke type and severity.

Results: The odds of a more serious 7-year outcome was different among patients with mRS=1 and 2 and also with mRs=3 and 4, defining the no significant (mRS=0-1), moderate (mRS=2-3) and severe disability (mRS=4-5). Of the 380 first-ever strokes, at 3 months, 126 (33.2%) had mRS<2, 114 (30.0%) mRS=2-3, 73 (19.2%) mRS=4-5, and 67 (17.6%) had died. We found linear relations between the 3-month mRS and the patient's baseline profile, stroke type and severity. The Kaplan-Meier 7-year survival estimates for 3-month survivors with mRS 0-1, 2-3 and 4-5 were 67, 50 and 23%, respectively. For mRS at 3 months of 2-3 versus 0-1 the hazard ratio (HR) for death was 1.61, (95% CI: 1.10-2.38) and for mRS=4-5 versus 2-3 the HR was 2.20 (95% CI: 1.52-3.20); after adjustment the HRs were 1.19 (95% CI: 0.77-1.84) and HR=1.87 (95% CI: 1.18-2.95), respectively. A change in the 3-month mRS from 4-5 to 2-3 would have a "number needed to change" of 9 (95% CI: 6-18) patients to avoid one death in the long run; identical outcome is obtained by shifting the mRS from 2-3 to 0-1 in 27 (95% CI: 15-141) patients.

Conclusions: In patients with ischemic stroke who survive to 3 months, a three grade simplified mRS summarizes the patient risk profile and stroke characteristics. These data confirm that modest differences in functional status at 3 months are associated with significant differences in survival and functional status over 7 years follow-up and have implications for health care planning and the health economic assessment of treatments for acute stroke.

Introduction

By the year 2015, it is estimated that there will be 67 million stroke survivors worldwide [1], a majority of them with some disability. Treatments for acute ischemic stroke make only modest gains in short-term disability. However, small changes in short-term disability might translate into longer-term improvements in survival and functional status. If differences in functional outcome at three months are associated with differences in long-term survival, or prolonged differences in levels of independence, then such data could materially influence estimates of the cost-effectiveness of many interventions. The modified Rankin Scale (mRS) has been widely used to measure functional outcome of stroke patients as an endpoint either in randomized clinical trials [2] or in the early months after stroke [3]. Further studies have shown its prognostic value for long-term survival in short-term survivors, that is, between 3 and 6 months and seven or more years [4-6]. Yet mortality from stroke has constantly declined in the last two decades as well as the mortality-to-incidence ratio, indicating the success of stroke management in the acute phase and the consequent increase in the number of stroke survivors [7]. Therefore, it is important to discriminate short-term levels of disability (cut-points) that evolve to a worse long-tem mRS score. We aim to optimize mRS cut-points for estimating the impact of functional status three months after a stroke on long-term functional outcome and survival in a prospective, population-based cohort of patients with ischemic stroke.Patients and Methods

In a prospective population-based study, all patients with a first-ever-in-lifetime ischemic stroke were registered in four primary healthcare centers (HC) in Northern Portugal (two urban and two rural centers with 58,727 and 37,089 users, respectively) between 1st October 1998 and 30th September 2000. The study was designed to meet the criteria of an “ideal” population-based study [8]. We aimed to comprehensively ascertain stroke cases by monitoring the (i) referrals from general practitioners (GP) and other hospital physicians working at the healthcare centers and hospitals; (ii) data retrieved from admission/discharge records; (iii) hospital outpatient records; (iv) nursing homes, private hospitals/practices and seniors residences; and (v) death certificates/autopsy. The study is described in more detailed elsewhere [9]. All patients gave written informed consent. The Ethics Committee of Hospital Santo António, where the study Coordination Centre was located, approved the study. Before any clinical assessment, informed consent was obtained from each participant, or from the next of kin when appropriate.

Baseline Assessment

All patients were assessed by a study neurologist immediately after the index event [9]. Definite ischemic stroke was defined as a focal neurological deficit lasting for more than 24 h with no evidence of hemorrhage on brain imaging [10]. We registered demographic details, vascular risk factors (VRF), radiological and laboratory investigations, treatment patterns and destination details after discharge. CT brain lesions were read by a neuro-radiologist blind to clinical symptoms/signs; based on the description of the CT, the neurologist assigned any acute lesion compatible with neurological symptoms and signs. To quantify neurological impairments at baseline, we used the Unified for Neurological Stroke Scale (UNSS), which is a continuous scale of stroke impairment that had good inter-rater agreement [11] and validity [12]. As our investigative resources were limited, and most classification systems available at the time of the inception of the study failed to classify patients into causal groups, we classified the subtype of stroke according to the Oxfordshire Community Stroke Project Classification [13] as: Total Anterior Circulation Infarct (TACI), Partial Anterior Circulation Infarct (PACI), LaCunar Infarct (LACI) or Posterior Circulation Infarct (POCI). The criteria used to define VRF were for hypertension, a history of high blood pressure (BP) or anti-hypertensive treatment or systolic BP >160 mm Hg and/or diastolic BP >95 mm Hg in at least two different measures; for diabetes, a previous diagnosis/treatment of diabetes mellitus with oral anti-diabetic/insulin or fasting glycaemia >126 mg/dl, postprandial glycaemia ≥200 mg/dl and/or glucose tolerance test with values of glycaemia ≥200 mg/dl at the 2nd hour; for hypercholesterolemia, a previous diagnosis/treatment of hypercholesterolemia or serum total cholesterol level after 12 h fasting ≥240 mg/dl; for atrial fibrillation, evidence from the electrocardiogram (ECG) or registration in patient's record of atrial fibrillation; patients were classified as current smokers if they smoked at the event date or at any time during the preceding 12 months [14].

Long-term Follow-up

All patients were followed-up prospectively at three months, one and seven years. The long-term follow-up began by updating telephone contacts using HC/hospital administrative records; first a phone contact was made and when it failed, patients were contacted by mail (at least two consecutive attempts) [14]. For patients known to have died, we asked a family member or caregiver to inform us of the date and circumstances of death; otherwise, we searched the computerized files held at the Northern Regional Health Administration. This information was linked to existing clinical records, and the underlying cause of death was assigned by a study neurologist. A vascular cause of

death was defined as (a) death due to first or recurrent stroke, (b) death due to acute myocardial infarction (MI) whenever the event was confirmed by ECG, myocardial necrosis markers or necropsy and (c) death due to other vascular causes: suspected but not confirmed MI, heart failure, thoracic/abdominal aortic aneurysm rupture or sudden death of presumed vascular origin.

Patients were examined at the neurological outpatient clinic and those who were unable to visit the clinic were examined at home. If no contact could be established, information was obtained from the health center or hospital records. Whenever these initiatives failed, the patient was considered lost to follow-up. Functional status at discharge and at 3 months, 1 and 7 years was assessed with the modified Rankin Scale (mRS).

Data Analysis

Ridit analysis [15] was used to estimate the odds of a more serious outcome (distribution of mRS scores 7 years post-stroke) according to adjacent values of mRS at 3 months, that is, by comparing the outcome between patients with mRS=i and mRS=i-1, for i=1 to 5. On the basis of this analysis, groups of patients with an equally likely long-term outcome were created (a simplified version of the mRS at 3 months). The distribution of patients' characteristics, VRF and clinical evaluation at baseline across these groups was tested for linear trend. The Kaplan-Meier estimates for overall survival were calculated according to the original and grouped mRS scores in 3-month survivors. Cox proportional hazards models were used for estimating the effect of mRS scores on survival, adjusting for possible confounding variables (gender, age, VRF, pre-stroke mRS, UNSS score and OCSP subtype), after checking the assumption of proportionality with the Schoenfeld's test. Patients where censored at the time of the last contact with the HC/Hospital if no information on vital status was available at the 7-year follow-up. Using death rates/person-years at 7 years, we estimated the number of patients who would need to have a lower mRS score at 3 months to avoid one death at 7 years. The number needed to change (NNC) to avoid one death at 7 years is given by 1/(mortality rate in the mRS=i group – mortality rate in mRS=i-1 group).

Results

From the 623 patients suspected of stroke registered at the 4 HC, 124 were excluded and among the 499 included, 380 had an ischemic stroke (figure 1). At 3 months 126 (33.2%) had a mRS score <2, 114 (30.0%) a 2-3 mRS score, 73 (19.2%) a 4-5 mRS score, and 67 (17.6%) died (table 1). A worse functional status at 3 months was associated with age, increasing from a median of 70 to 79 years, prevalence of atrial fibrillation, increasing from 9.5% to 34.3% and pre-stroke mRS ≥2, increasing from 1.6% to 43.8%. A more favourable functional status at 3 months was associated with male gender, the proportion decreasing from 59.5% to 37.3% and the prevalence of hypercholesterolemia, decreasing from 49.2% to 16.4%. All patients had a CT scan; 245 (64.5%) in the first 24 h and 62 (16.3%) between 24 and 48 h after stroke onset; the proportion of patients with a symptomatic lesion on CT ranged from 34.1% in patients with mRS=0-1 to 54.8% when mRS=4-5. Stroke type and severity were also associated with a poor 3-month outcome, the proportion of TACI increasing from 2.4% to 52.2% contrasting with LACI, decreasing from 61.1 to 11.9%.

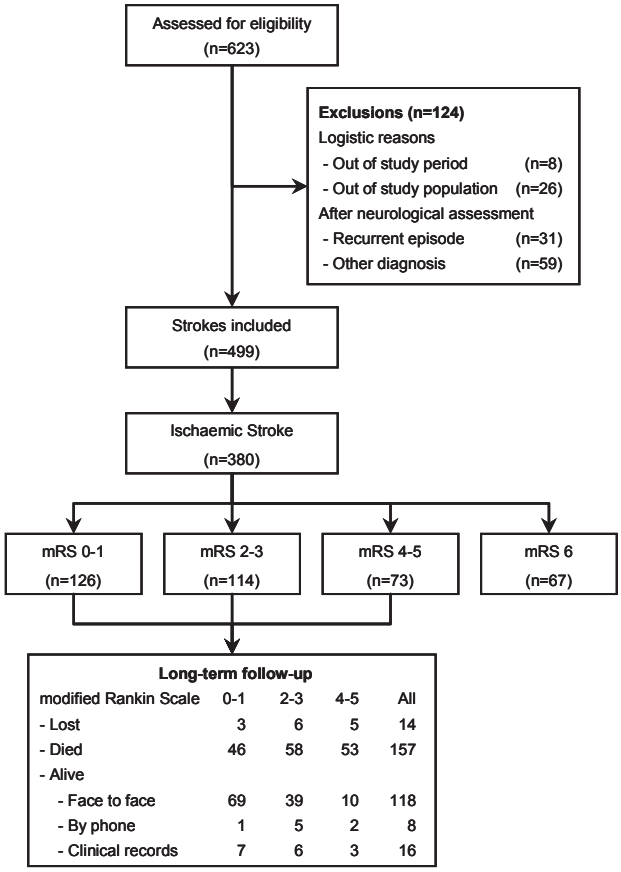


Figure 1. Flowchart of inclusion of patients and details of 7-year follow-up

Of the 313 three-month survivors, 157 (50.2%) died before 7-year follow-up and 14 (4.5%) were lost either because they could not be traced after the first year (9) or had unknown mRS (5). Of the 142 patients alive 7 years post-stroke, 118 (83.1%) were examined by a neurologist of the research team (6 of them at home and the remainder at the hospital), 8 (5.6%) were contacted by phone and for the remaining 16 information was sought at hospital/HC records (figure 1). For the 299 patients with known 7-year status, Ridit analysis indicated that the odds of a worst functional status at 7 years was 1.71 (z=3.1, p<0.001) when comparing a patient with mRS=2 to mRS=1, and 1.55 (z=2.3, p<0.02) for mRS=4 versus mRS=3; this analysis was repeated for the 142 that survived 7 years and the corresponding odds were 1.93 (z=2.7, p<0.007) and 4.06 (z=3.4, p<0.001), respectively.

Table 1. Distribution of patients' characteristics at baseline and according to status at three months

			Status at three months										
			Alive										
	All (n=380)		All (n=313)		mRS 0-1 (n=126)		mRS 2-3 (n=114)		mRS 4-5 (n=73)		mRS 6 (n=67)		P value linear trend
Characteristics	N	%	N	%	N	%	N	%	N	%	N	%	
Men	170	44.7	145	46.3	75	59.5	46	40.4	24	32.9	25	37.3	<0.001
Median age (IQD)	73.0	(7.5)	72.0	(7.3)	70.0	(7.3)	73.0	(8.1)	77.0	(7.8)	79.0	(6.5)	<0.001
Hypertension	229	60.3	36	53.7	76	60.3	71	62.3	46	63.0	36	53.7	0.6
Hypercholesterolemia	136	35.8	11	16.4	54	49.2	50	43.9	21	28.8	11	16.4	<0.001
Diabetes	100	26.3	23	34.3	29	23.0	26	22.8	22	30.1	23	34.3	0.07
Atrial fibrillation	60	15.8	23	34.3	12	9.5	12	10.5	13	17.5	23	34.3	<0.001
Previous TIA	38	10.0	6	9.0	15	11.9	11	9.6	6	8.2	6	9.0	0.4
Current smoker	50	13.2	3	4.5	19	15.1	22	19.3	6	8.2	3	4.5	0.02
Pre-stroke mRS*													<0.001
0-1	296	78.5	260	83.1	124	98.4	88	77.2	48	65.8	36	56.3	
2-3	71	18.8	46	14.7	2	1.6	25	21.9	19	26.0	25	39.1	
4-5	10	2.7	7	2.2	-	-	1	0.9	6	8.2	3	4.7	
Symptomatic lesion on CT	170	44.7	137	43.8	43	34.1	54	47.4	40	54.8	33	49.3	0.006
Mean UNSS (sd)	23.3	(9.0)	29.2	(3.7)	29.2	(3.7)	26.2	(5.8)	17.3	(8.7)	14.0	(9.5)	<0.001
OCSP Classification													<0.001
TACI	87	22.9	35	52.2	3	2.4	17	14.9	32	43.8	35	52.2	
PACI	70	18.4	12	17.9	20	15.9	23	20.2	15	20,5	12	17.9	
LACI	154	40.5	8	11.9	77	61.1	53	46.5	16	21.9	8	11.9	
POCI	69	18.2	12	17.9	26	20.6	21	18.4	10	13.7	12	17.9	

*Three missings in the mRS=6 group; IQD=Interquartile deviation

Figure 2 shows the distribution of functional status at 7 years according to the 3-month mRS scores compared in the Ridit analysis; the shading in the left side draws attention to the similar 7-year functional outcome of survivors for patients with mRS=0-1, 2-3 and 4-5 at 3 months, while the right side shows the proportion of patients deceased at 7 years according to mRS at 3 months. The proportions of patients with severe disability (mRS=4-5) were 8.1, 9.3 and 17.6% according to mRS at 3 months 0-1, 2-3 and 4-5 contrasting with no significant disability (mRS=0-1), 36.6, 13.9 and 0% (table 2).

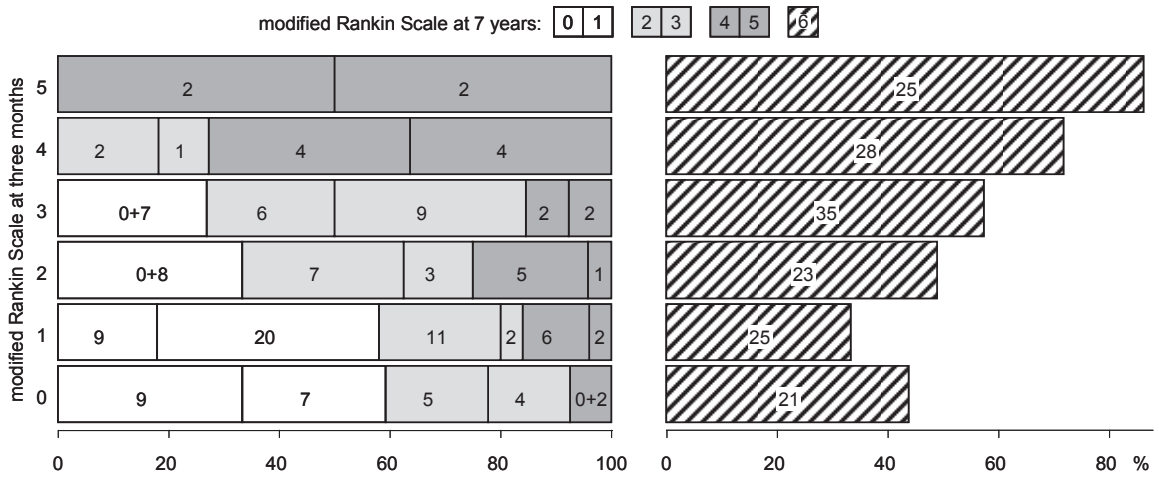


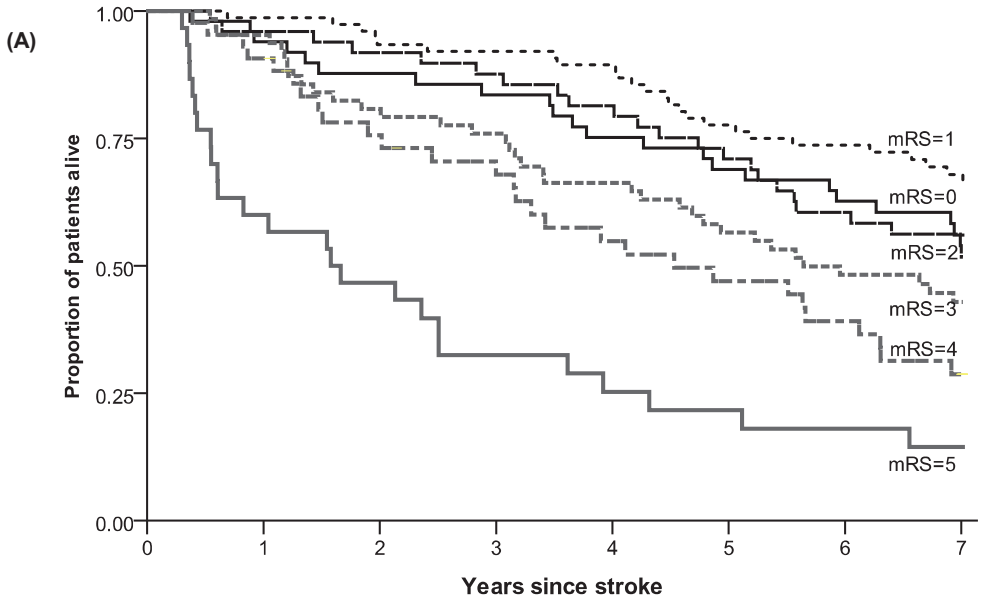
Figure 2. Distribution of mRS at 7 years according to mRS at 3 months; left side shows the mRS for survivors at 7-years by an increasing order of mRS score and the right side shows proportion of deceased. Number of patients in squares

Table 2. Distribution of status at 7 years for 3-month survivors and number needed to change to avoid one death at 7 years (NNC)

Status at 3 months	Status at seven years								Person-years	Mortality rate/1000	NNC mRS	
	mRS 0-1		mRS 2-3		mRS 4-5		mRS 6					
	N	%	N	%	N	%	N	%			N	95%CI
mRS 0-1	45	36.6	22	17.9	10	8.1	46	37.4	725.4	63.4		
mRS 2-3	15	13.9	25	23.1	10	9.3	58	53.7	575.1	10.1	27	15-141
mRS 4-5	0	0.0	3	4.4	12	17.6	53	77.9	248.8	21.3	9	6-18

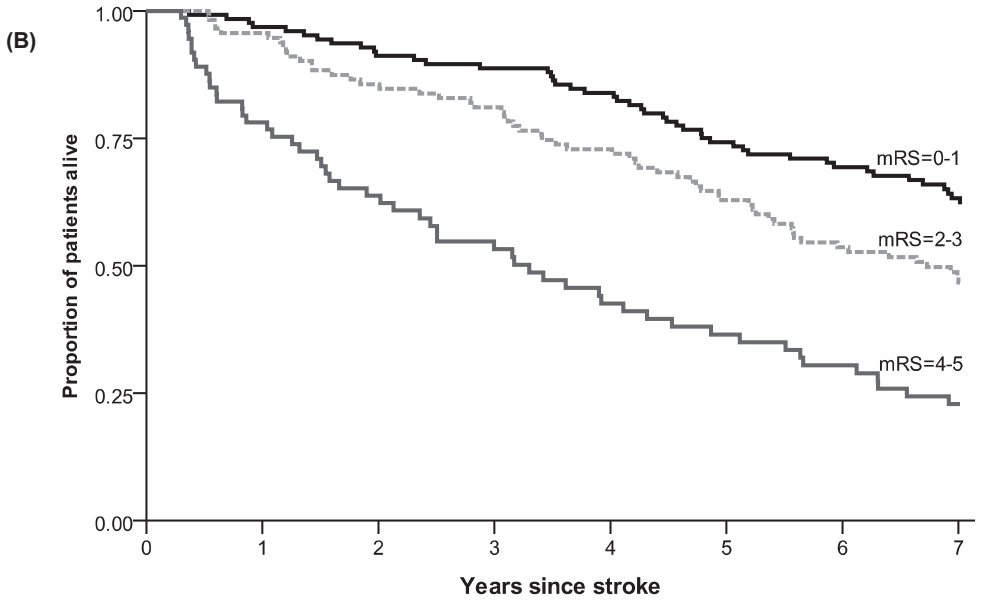
Test for linear trend = 50.1, df=1, p<0.001

For the 3-month survivors, the median survival time was 6.9 years. The proportional 7-year survival for patients with 3-month mRS of 0, 1, 2, 3, 4, 5 was 56, 67, 52, 43, 29 and 14%, respectively; for the simplified mRS (0-1, 2-3, 4-5) the values were 77, 50 and 23% (figure 3). The main causes of death were vascular (43.3%); they were a recurrent stroke (20.4%), an acute MI (14.6%), a sudden death (5.1%) or other vascular causes (3.2%).



No at risk (% surviving)

mRS	3 months	1st year	2nd year	3rd year	4th year	5th year	6th year	7th year
0	50 (100)	47 (94)	42 (88)	40 (84)	36 (75)	33 (69)	30 (63)	27 (61)
1	76 (100)	75 (99)	71 (93)	70 (92)	68 (90)	59 (78)	53 (74)	50 (72)
2	50 (100)	48 (96)	44 (92)	42 (88)	39 (81)	34 (71)	28 (61)	24 (52)
3	64 (100)	61 (95)	50 (81)	47 (76)	41 (66)	34 (57)	29 (48)	26 (43)
4	43 (100)	39 (91)	30 (76)	26 (68)	21 (55)	18 (47)	15 (39)	11 (29)
5	30 (100)	18 (60)	14 (47)	9 (33)	7 (25)	6 (22)	5 (18)	4 (14)



No at risk (% surviving)

mRS	3 months	1st year	2nd year	3rd year	4th year	5th year	6th year	7th year
0-1	126 (100)	122 (97)	113 (91)	110 (89)	104 (84)	92 (74)	83 (69)	77 (67)
2-3	114 (100)	109 (96)	94 (86)	89 (81)	80 (73)	68 (63)	57 (54)	50 (50)
4-5	73 (100)	57 (78)	44 (64)	35 (53)	28 (43)	24 (37)	20 (30)	15 (23)

Figure 3. Long-term survival from assessment at three-month after an ischemic stroke according to (A) functional status at three months (mRS: modified Rankin Scale), (B) simplified mRS (0-1, 2-3, 4-5)

Patients with mRS=2-3 compared to mRS=0-1 at 3 months had a higher death hazard (HR=1.61, 95% CI: 1.10-2.38) as well as those with mRS=4-5 compared to mRS=2-3 (HR=2.20, 95% CI: 1.52-3.20) (table 3). After controlling for pre-stroke mRS, patient's profile at baseline, presence/absence of symptomatic lesion, UNSS score and OCSP classification, the death hazard for a patient with mRS=4-5 at 3 months compared to mRS=2-3 was 1.87 (95% CI: 1.18-2.95). Age, male gender, diabetes, current smoking, pre-stroke mRS ≥2 and stroke type (TACI or PACI vs. LACI) are associated with shorter survival times, hypercholesterolemia with longer survivorship and stroke severity (UNSS) is not associated with long-term survival.

Table 3. Cox's regression models estimates of the hazard ratios for death at seven years according to baseline characteristics for patients alive at three months after a first-ever-in-a-lifetime ischemic stroke

	Univariate			Multivariate		
Characteristics	HR	95%CI	P value	HR	95%CI	P value
Men vs. Women	1.29	0.94-1.76	0.1	1.87	1.27-2.74	0.001
Age (10 years)	2.14	1.78-2.58	<0.001	2.18	1.78-2.67	<0.001
Risk factors (yes vs. no)						
Hypertension	0.79	0.57-1.08	0.1	1.05	0.75-1.47	0.8
Diabetes	1.29	0.91-1.84	0.2	1.90	1.29-2.81	0.001
Hypercholesterolemia	0.52	0.37-0.73	<0.001	0.56	0.38.0.82	0.003
Atrial fibrillation	1.86	1.22-2.84	0.004	0.88	0.54-1.41	0.6
Previous TIA	0.68	0.37-1.26	0.2	1.09	0.56-2.10	0.8
Current smoker	1.59	1.07-2.36	0.021	2.47	1.53-4.00	<0.001
Pré-stroke mRS: 2-5 vs. 0-1	2.87	2.00-4.10	<0.001	2.01	1.31-3.08	0.001
Symptomatic lesion on CT	1.27	0.93-1.74	0.1	1.18	0.84-1.66	0.4
UNSS (for 1 point less)	1.04	1.02-1.06	<0.001	0.98	0.95-1.02	0.4
OCSP Subtype (vs. LACI)			(<0.001)			(0.011)
TACI	2.51	1.66-3.81	<0.001	2.16	1.14-4.11	0.019
PACI	2.22	1.47-3.34	<0.001	1.88	1.21-2.92	0.005
POCI	1.05	0.65-1.69	0.8	0.95	0.57-1.16	0.9
3-month mRS			(<0.001)			(0.008)
2-3 vs. 0-1	1.61	1.10-2.38	0.015	1.19	0.77-1.84	0.4
4-5 vs. 2-3	2.20	1.52-3.20	<0.001	1.87	1.18-2.95	0.008

For one extra 7-year survivor, a change in the 3-month mRS from 5 to 4 would be needed in 6 (95% CI: 3-19) patients; using the simplified mRS scores the NNC=9 (95% CI: 6-18) in the 3-month mRS from 4-5 to 2-3 or NNC=27 (95% CI: 15-141) in mRS from 2-3 to 0-1

(table 2). In the same way, we may calculate NNC to avoid disability/death (mRS 4-6) and the respective NNC are 7 (95% CI 5-12) and 24 (95% CI 14-121).

Discussion

We have found that differences in functional status at 3 months after stroke, from no significant (mRS: 0-1) to moderate disability (mRS: 2-3) or from moderate-to-severe disability (mRS: 4-5), are associated with important differences both in long-term survival and functional ability. After accounting for confounding by patient's characteristics at baseline, stroke severity and stroke type, functional status at 3 months was an important predictor of long-term outcome following ischemic stroke. A simplified version of the mRS at 3 months (no significant, moderate and severe disability), captures the patient's baseline profile and stroke presentation and is a long-term predictor of functional outcome. Because the patient's vascular risk profile, namely, age, gender, diabetes, hypercholesterolemia, smoking habits, pre-stroke dependence and stroke type, is a predictor of long-term survival, it seems that a 3-month mRS is a mediator variable between stroke and long-term outcome. Indeed the mRS has been considered not just a pure handicap measure, but rather a global health index with strong accent on physical disability that may be used as a time-efficient functional outcome measure [16]. A small difference in 3-month disability leads to important differences in long-term survival. We have tried to show it with the "number needed to change"; for example, our data suggest that a treatment in the acute phase that results in a difference in mRS at 3 months from severe (4-5) to moderate disability (2-3) would have a 'number needed to change" of 9 patients to avoid one death in the long run.

Another important issue is the long-term disability in survivors. Our data confirms that the mRS at 3 months is also strongly associated with the mRS at 7 years post-stroke, since the odds are approximately 2 to 1 that a patient with moderate disability will have a more serious disability than a patient with no significant disability and 4 to 1 that a patient with severe disability has a poor outcome in comparison with one with moderate disability. By 7 years, 22.5% (32/142) of patients were severely disabled and 37.5% of them were already dependent at three months; this proportion is similar to the one found in the only study reporting 5-year long-term disability in stroke survivors [17]. Again, we may use the concept of "improving" survival/disability by shifting the mRS score at 3 months to lower categories, and by doing a shift from severe (4-5) to moderate (2-3) disability, we may avoid disability/death in one patient. At present this gain is obtained by the existing acute treatments (first hours pos-stroke) [18] and inpatient admission to stroke units [19],

procedures that were adopted in Portugal in the last decade. Public campaigns on surveillance of vascular risk factors, stroke awareness and stroke code activation implemented in Portugal [20-21] and in most European countries since the beginning of this century, may contribute as well for an expected gain. So, if the relationship between the short and long-term mRS holds, we may expect a decreasing trend in the disability-adjusted life-years, as remarked in the recent results for the 1990-2010 period [7].

The results of this population-based study are in agreement with others showing that patients surviving the acute phase but with higher grades of disability have shorter survivals than those with no significant disability [4-6]. Besides the mRS at 3 months, the other factors associated with long-term survival are also identical to those we have found, namely age, male gender, vascular risk factors and pre-stroke dependence [4-6, 22-25]. Stroke subtype has also been consistently associated with long-term survival; usually patients with TACI and/or PACI have shorter survivals [4, 22, 26]. The long-term prognostic value of stroke severity seems to depend upon the scale used. While the Scandinavian stroke scale score was not associated with long-term survival [5], the National Institutes of Health Stroke Scale (NIHSS) was strongly associated with 3-year mortality [22]. In this study, stroke severity was associated with long-term survival but was not an independent predictor of survival after adjusting for short-term functional status. Since stroke severity was strongly associated with mRS at 3 months, we may conclude that the long-term effect of functional status at 3 months includes and adds predictive value to stroke severity. In comparison with the NIHSS, the UNSS has some limitations, since it is not restricted to measure the extension of the cerebral lesion, including activities like walking that measure functionality. However, we used UNSS to measure stroke severity because it was the only one adequately tested for validity and reliability [11-12] at the time of the incidence study (1998). On the other hand and independently of the scale used, the evaluation was not done at the same time point after symptoms onset in every patient. It should be taken into consideration that this is a population-based study, with a consequent difficulty to observe the patients shortly after symptoms onset; however 67% of them were observed in the first 24 h [9]. However, because this was a population-based study, some bias of hospital-based studies, namely reference bias, was avoided.

The results of our study are important when estimating the cost-effectiveness of interventions in the acute phase, since modest short-term improvements may translate into substantial long-term gains [27-28]. Given the close relationship between functional status measured on the mRS and health related quality of life [29], these data have implications for both clinical care and for health economics.

In conclusion, our data confirm that the level of disability at three months is a strong independent predictor not only of survival but also of long-term functional outcome. We think that early (3-month) functional status is an important predictor (perhaps the most important) of long-term functional outcome, but further studies with enlarged sample size are needed to corroborate these results. Our results can keep stroke survivors and their relatives updated about stroke long-term prognosis and have implications on the study of cost-effectiveness of acute stroke treatments, health care planning policies and research.

Acknowledgments

This work was supported by a grant from the Merck, Sharp & Dhome Foundation and by the FCT/FEDER project POCI/SAU-ESP/59885/2004. The authors thank the Northern Region Health Authorities for the collaboration and funding of the investigators meetings. Thanks are also due to their fellow participants working in the Department of Neurology of the Hospital Santo Antonio (Porto) and Hospital de S. Pedro (Vila Real), and all the GPs and nurses working in the healthcare centers involved in this study. A special thanks to the patients and their families whose cooperation and help made this study possible.

Disclosure statement

The authors have no conflicts of interests with respect to this work.

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CAPÍTULO 4

ARE STROKE OCCURRENCE AND OUTCOME RELATED TO WEATHER PARAMETERS? RESULTS FROM A POPULATION-BASED STUDY IN NORTHERN PORTUGAL

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Cerebrovascular Diseases, 2011;32:542-551

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2011;32:542–551
DOI: 10.1159/000331473

Received: March 29, 2011
Accepted: August 3, 2011
Published online: November 18, 2011

Are Stroke Occurrence and Outcome Related to Weather Parameters? Results from a Population-Based Study in Northern Portugal

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Key Words
Epidemiology of stroke · Seasonal variation · Poisson model · Stroke incidence · Weather

Abstract
Background: Changes in meteorological parameters have been associated with cardiovascular mortality and stroke. The high incidence of stroke in Portugal may be modelled by short- or long-term weather changes whose effect may be different across stroke types and severity. ***Methods:*** Data include all patients with a first-ever-in-a-lifetime stroke registered in a population of 86,023 residents in the city of Porto from October 1998 to September 2000. Specific stroke types were considered and ischaemic stroke (IS) subtype was defined according to the Oxfordshire Community Stroke Projet classification and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Information on daily temperature, humidity and air pressure was obtained from the National Meteorological Office. The Poisson distribution was used to model the daily number of events as a function of each weather parameter measured over different hazard periods, and the binomial model to contrast effects across subgroups. Differential effects of meteorological parameters and hazard periods upon stroke occurrence and outcome were analysed in a stepwise model. ***Results:*** Among the 462 patients registered, 19.6% had a primary intracerebral haemorrhage (PICH) and 75.3% an IS. Among patients with IS, 21.6% were total anterior circulation infarcts (TACIs), 19.8% partial anterior circulation infarcts (PACIs), 19.5% posterior circulation infarcts (POCIs) and 39.1% were lacunar infarcts (LACIs). The aetiology of IS was large artery atherosclerosis in 6.9%, cardioembolism in 23.3% and small artery occlusion in 35.6%. The incidence of PICH increased by 11.8% (95% CI: 3.8–20.4%) for each degree drop in the diurnal temperature range in the preceding day. The incidence of IS increased by 3.9% (95% CI: 1.6–6.3%) and cardioembolic IS by 5.0% (95% CI: 0.2–10.1%) for a 1°C drop in minimum temperature in the same hazard period. The incidence of TACIs followed the IS pattern while for PACIs and POCIs there were stronger effects of longer hazard periods and no association was found for LACIs. The relative risk of a fatal versus a non-fatal stroke increased by 15.5% (95% CI: 6.1–25.4%) for a 1°C drop in maximum temperature over the previous day. ***Conclusions:*** Outdoor temperature and related meteorological parameters are associated with stroke occurrence and severity. The different hazard periods for temperature effects and the absence of association with LACIs may explain the heterogeneous effects of weather on stroke occurrence found in community-based and hospital admission studies. Emergency services should be aware that specific weather conditions are more likely to prompt calls for more severe strokes.

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Introduction

The association between temperature and mortality from all causes was described in a cross-country European study, showing that Portugal has the highest coefficient of seasonal variation in mortality among 14 countries despite having the highest mean winter temperature (–3.5 to 13.5°C) [1]. Deaths from acute myocardial and cerebral infarction contribute to the excess winter mortality [2–4], but routine mortality statistics may over-report the number of stroke deaths [5, 6] confounded by post-stroke complications. On the other hand, the incidence of stroke in most countries has a seasonal pattern, peaking during winter [7–9], with a lesser frequency in spring [10, 11], autumn [12] or summer months [13]. These seasonal/monthly effects are important to adopt preventive measures and to estimate the overall hospital and/or stroke units' workload, but fell short of demonstrating meteorological factors underlying and triggering stroke occurrence, in particular a first-in-a-lifetime stroke.

Irrespective of a seasonal effect, an association between weather parameters and hospital admissions for stroke was found in several studies [14–18], pointing out the short-term effects of temperature, atmospheric pressure as well as their short-term variations (24–48 h). In prospective community-based incidence studies, heterogeneous results concerning the effect of outdoor temperature on the incidence of stroke have been reported [12, 19, 20]. The high incidence of stroke in Portugal [5] may in part be explained by exposure to aggressive meteorological conditions. Moreover, it has been suggested that mortality increases to a greater extent during falls in temperature in regions with warm winters and in populations with cooler homes [21]. Portugal, and in particular the city of Porto, with its maritime climate and traditionally unheated homes, represents a 'natural experimental environment' to test whether outdoor temperature or other meteorological parameters are associated with the occurrence of stroke. Since different aetiological mechanisms/risk profiles are present in specific stroke types, we may hypothesize that these effects will be different according to stroke type and severity. Moreover, the effects of each parameter may be different according to the hazard period.

Materials and Methods

Identification and Classification of Stroke Patients

All first-ever-in-a-lifetime strokes registered in a population of 86,023 residents in the city of Porto between October 1998 and September 2000 were included. Case ascertainment methods included direct referrals by general practitioners and hospital admissions as well as routine checking contacts with nursing homes, private hospitals/practices and review of death certificates/autopsy findings. Details on methods for identification of patients have been provided elsewhere [5]. All patients were examined by neurologists, and CT scans were performed; for those who died soon after the event or were identified by death certificates, information was given by relatives or an eye witness. Stroke was defined according to the WHO as 'rapidly developing clinical symptoms and/or signs of focal, and at times global loss of cerebral function (patients in deep coma or cerebral haemorrhage), with symptoms lasting more than 24 h or leading to death, with no apparent cause other than of vascular origin' [22]. Pathological types of stroke were defined according to Sudlow and Warlow [23] and the ischaemic stroke (IS) subtype by the Oxfordshire Community Stroke Project (OCSP) classification [24] and the aetiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [25]. For patients identified away from the event onset, classification relied primarily on medical record documentation. A stroke was considered to be fatal if death occurred within 28 days.

Meteorological Characteristics and Data

The city of Porto is situated on the right bank and very close to the mouth of the river Douro, in northern Portugal, and had a population of about 250,000 in the 2001 Census, comprising 15 administrative divisions. The study evolved in 10 of these divisions, the catchment area of the Hospital de Santo António. Porto has a Mediterranean climate, with warm dry summers and mild rainy winters, but unlike the coastal south of Europe, it is often windy and usually cooler in winter with rainy weather for long periods. Daily maximum (T_{max}) and minimum temperature (T_{min}) (°C), relative humidity (%), atmospheric pressure at sea level (hPa), and total precipitation (mm/m^2) at the Observatório da Serra do Pilar were obtained from the National Meteorological Office. This weather station provides data representative of the southeast Porto catchment area. Besides the crude values of meteorological data available we have also considered temperature variations within 1 day, i.e. diurnal temperature range (DTR), since it has been described to be associated with acute stroke death [26].

Statistical Analysis

The description of stroke types and IS subtypes includes the daily mean of events and the respective 95% confidence interval (95% CI), stratified by season. Case fatality by season is also described. The Poisson distribution was used to model the daily number of events as a function of each weather parameter using a log-link function [27]. Generalized additive Poisson models were used alternatively, to check whether explanatory variables should enter the model as linear terms or smoothed functions with varying degrees of freedom (d.f.), enabling some flexibility in the shape of the function describing the relation. For ascertaining the effect of meteorological variables on daily stroke occurrence, a series of models were considered for exposure at different hazard periods before the event – the previous 24-hour value and the averaged values for the previous 7- and 14-day periods. Using a stepwise procedure, the final model for the specific event was built, considering as predictors the values for the three periods, besides the seasonal effect. Finally, the binomial distribution (logistic model) was used to estimate the relative risk of a fatal stroke

Table 1. Distribution of patient characteristics and vascular risk factors by types and subtypes of IS

Diagnosis/prognosis	All		Age ≥65 years		Women	
	n	%	n	%	n	%
All strokes	462		331	71.6	287	62.1
Fatal stroke[1]	78	16.9	65	83.3	54	69.2
Pathological types						
PICH	78	16.9	46	59.0	48	61.5
IS	348	75.3	259	74.4	215	61.8
OCSP classification						
TACI	75	21.6	66	88.0	59	78.7
PACI	69	19.8	60	87.0	47	68.1
LACI	136	39.1	86	63.2	74	54.4
POCI	68	19.5	47	69.1	35	51.5
TOAST criteria						
Large artery atherosclerosis	24	6.9	18	75.0	14	58.3
Cardioembolism	81	23.3	76	93.8	56	69.1
Small artery occlusion	124	35.6	78	62.9	69	55.6
Other determined/undetermined	119	34.2	87	73.1	76	63.9

[1] Death within 28 days from onset.

under different weather conditions. The effects (General Linear Model coefficients) are presented as the rate ratio for a unit drop in the temperature parameters (T_{max}, T_{min}, DTR) and unit increase in the other parameters for Poisson models and as the odds ratio for binomial models, with the respective 95% CI. The likelihood ratio χ^2 was used for comparing the fitted models against the intercept-only model. All analyses were done with the PASW Statistics 17.0 and by R statistical software Version 2.8.1. For statistical tests, a value <0.05 was used to indicate a significant association. For all analyses, we assumed a stable population at risk throughout the study period and so no adjustment for deaths and births were made.

Results

Patients' Characteristics

Based on a detailed clinical examination, including CT scans (97.4% of the patients and 83.5% within the first 48 h) and/or autopsy or lumbar puncture findings, a total of 462 patients were diagnosed with a first stroke. The stroke was fatal in 78 patients (16.9%) and 83.3% of them were ≥65 years old. The distribution according to pathological types and subtypes is described in table 1. Patients with primary intracerebral haemorrhage (PICH) were younger than those with IS ($\chi^2 = 7.5$, d.f. = 1, $p = 0.006$) and those with a lacunar (LACI) or posterior circulation infarct (POCI) were younger than those with total circulation (TACI) or partial circulation infarct (PACI) ($\chi^2 = 22.9$, d.f. = 3, $p < 0.001$). TACIs were more frequent in women compared with the remainder ($\chi^2 = 16.4$, d.f. = 3, $p < 0.001$) and cardioembolism was more frequent in the oldest ($\chi^2 = 24.8$, d.f. = 3, $p < 0.001$).

Seasonal Patterns in Weather Parameters and the Incidence of Stroke

Weather parameters varied across seasons as expected, low values of T_{max}, T_{min} and relative humidity and high values of atmospheric pressure in winter contrasting with high temperatures in summer, high relative humidity in summer and autumn and low atmospheric pressure in summer and spring (table 2). Precipitation attains the highest values in spring and autumn. There was no seasonality in the overall number of strokes, PICH or IS in spite of the increasing trend from summer to spring in the number of POCI ($\chi^2 = 8.8$, d.f. = 3, $p < 0.04$). There was seasonality in case fatality from PICH, higher in summer (62.5%) compared to the remaining seasons ($\chi^2 = 8.0$, d.f. = 3, $p < 0.05$). The overall trend in PICH, IS and the incidence of fatal stroke throughout the study period are shown in figure 1 together with the values of the meteorological parameters. T_{max} and T_{min} (not shown) were highly correlated (r = 0.78) as well as relative humidity and DTR (r = –0.63); DTR increased with T_{max} (r = 0.38) and decreased with precipitation (r = –0.45), while relative humidity increased with precipitation (r = 0.31). The

Table 2. Description of weather parameters, incident events and case fatality by season

Weather and population characteristics	All (n = 731)		Summer (n = 188)		Autumn (n = 178)		Winter (n = 181)		Spring (n = 184)	
	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI	mean	95% CI
Weather parameters										
Temperature, °C										
Maximum	19.0	18.6–19.3	23.7	23.2–24.1	17.7	17.2–18.2	15.5	14.9–16.0	18.9	18.3–19.5
Minimum	10.3	10.0–10.6	14.7	14.4–15.0	9.1	8.5–9.7	6.2	5.7–6.7	10.9	10.4–11.4
Diurnal range	8.7	8.5–8.9	8.9	8.5–9.4	8.6	8.2–9.0	9.3	8.8–9.7	8.0	7.5–8.4
Relative humidity, %	77.0	76.2–77.9	78.1	76.6–79.5	78.8	77.3–80.3	74.2	72.2–76.2	77.1	75.6–78.6
Precipitation, mm/m^2	3.1	2.6–3.7	2.0	1.1–2.9	3.6	2.4–4.8	2.1	1.4–2.9	4.6	3.4–6.1
Rainy days, %	43.6	40.0–47.2	20.7	14.9–26.6	55.6	48.8–63.5	43.6	36.4–50.9	54.9	47.6–62.2
Atmospheric pressure (above 1,000 hPa)	19.4	18.9–19.9	16.3	15.8–16.9	21.5	20.5–22.5	23.8	22.8–24.9	16.2	15.3–17.1
Daily incident events[1]										
All strokes	7.3	6.6–8.0	5.9	4.8–7.2	7.4	6.0–8.8	7.9	6.5–9.3	8.1	6.7–9.5
PICH	1.3	0.9–1.5	1.1	7.6–1.6	1.3	0.8–2.0	1.2	0.7–1.9	1.5	0.9–2.2
IS	5.6	5.0–6.2	4.3	3.4–5.5	5.8	4.7–7.2	5.9	4.8–7.3	6.0	4.9–7.4
LACI	2.2	1.7–2.6	2.1	1.4–2.9	2.0	1.4–2.9	2.2	1.5–3.0	2.4	1.7–3.3
TACI	1.2	0.9–1.5	0.8	0.7–1.9	1.7	1.2–2.6	0.9	0.6–1.6	1.2	0.7–1.9
PACI	1.1	0.8–1.4	0.8	0.5–1.4	1.2	0.7–1.7	1.5	0.9–2.2	0.9	0.6–1.5
POCI	1.1	0.8–1.4	0.6	0.2–1.1	0.9	0.5–1.5	1.4	0.8–2.1	1.5	0.9–2.2
Case-fatality, %										
All strokes	16.9	13.5–20.3	21.9	13.6–30.1	14.0	7.7–20.4	14.6	8.4–20.9	17.8	11.2–24.4
PICH	33.3	22.9–43.8	62.5	38.8–86.2	30.0	9.9–50.1	22.2	3.0–41.4	25.0	7.7–42.3
IS	10.9	7.6–14.2	8.6	2.0–15.1	9.0	3.0–14.9	9.7	3.7–15.7	15.6	8.4–22.9

[1] Incidence per 1,000,000 population.

relative peaks in PICH (fig. 1) and fatal strokes closely followed the constant drop and relative trough in T_{max} and DTR.

Meteorological Parameters and the Incidence and Outcome of Stroke

The incidence of PICH was associated with DTR and precipitation; for 1°C drop in DTR over the preceding 24 h, the incidence increased by 11.8%, and for each millimetre of precipitation it increased by 3.1%, reaching 5.7% (95% CI: 0.7–11.1%) when considering the average 14-day period (table 3). The incidence of IS, on the other hand, was associated with both Tmax and T_{min} for the three hazard periods considered; for a 1°C drop in temperature, the incidence increased between 3.3 and 4.3%. There were nevertheless different hazard periods for the effects of T_{max} and T_{min} according to IS subtype; the incidence of TACI increased by 5.9% for a 1°C drop in T_{max} over the preceding 24 h, the incidence of PACI increased by 6.6% after a 1°C drop in T_{min} over the previous 24 h or 7-day period and that of POCI increased between 5.8 and 7.4% when T_{max}/T_{min} drops over different hazard periods. The incidence of LACI was not associated with any meteorological parameter. According to aetiology, only the incidence of cardioembolic IS increased by 5.0% (95% CI: 0.2–10.1%) for a 1°C drop in T_{min}. In the stepwise models, the most important predictors of PICH and IS were DTR and T_{min} in the previous 24 h, respectively (table 4). A 24-hour short-term effect of T_{min} and relative humidity was only associated with the incidence of TACI, while for PACI and POCI only the average 7/14 days effect of DTR, relative humidity and T_{max} were included in the model. Despite the effects of relative humidity in the incidence of LACI, the fit was no better than for the intercept-only model. Using the binomial model, the odds of a fatal versus non-fatal stroke increased by 15.5% (6.1–25.4%) after a 24-hour drop in T_{max}, and no significant differences were found across age and gender for IS. The contrasting short-term effects of DTR and T_{min} on the incidence of PICH and IS are displayed in figure 2a, b, and the effects of T_{max} on fatal and non-fatal strokes are displayed in figure 2c.

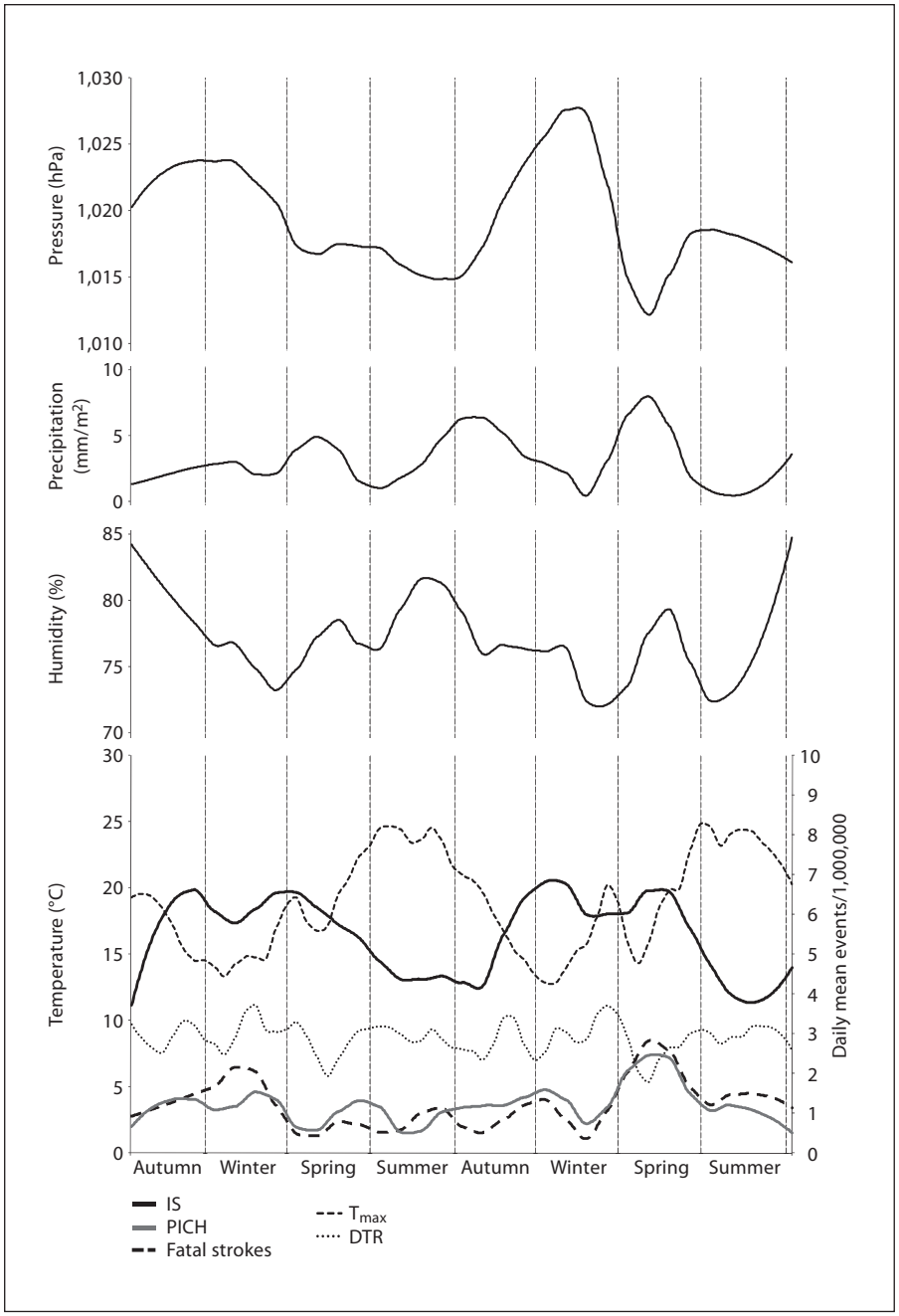

Fig. 1. LOWESS smoothed values of daily incidence of events (per million per day) and meteorological parameters (T_{max}, DTR, relative humidity, atmospheric pressure and precipitation) at Porto during the study period.

Discussion

This study shows that the high incidence of a first-ever-in-a-lifetime stroke in Portugal may be related to adverse effects of meteorological conditions. Moreover, irrespective of seasonal variations, these effects varied according to pathological type. The incidence of PICH was associated with precipitation and DTR while the incidence of IS was associated with temperature (T_{max}/T_{min}) and relative humidity. Moreover, the relative importance of the hazard period was associated with stroke severity and the OCSP classification. The predominant effects after a 24-hour hazard period were observed in the incidence of PICH, TACI, cardioembolic IS and fatal strokes. The effect of DTR and relative humidity was more important after a 7-day hazard period for PACI and after a 14-

Table 3. Association between incident stroke events and meteorological parameters according to exposure period

Weather parameter/ hazard period	PICH		IS									
			all		TACI		PACI		LACI		POCI	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Season												
Autumn	1.32	0.68–2.55	1.34*	0.98–1.84	2.04†	1.07–3.88	1.28	0.63–2.60	0.99	0.61–1.62	1.64	0.71–3.80
Winter	1.17	0.60–2.29	1.38†	1.01–1.88	1.11	0.54–2.31	1.71	0.88–3.32	1.07	0.66–1.73	2.42†	1.11–5.29
Spring	1.53	0.81–2.89	1.40†	1.03–1.91	1.39	0.70–2.77	1.10	0.53–2.27	1.18	0.74–1.88	2.73†	1.27–5.86
Temperature, ↓ 1°C												
Maximum												
Previous 24 h	1.05*	1.00–1.10	1.03‡	1.01–1.06	1.06†	1.01–1.12	1.03	0.98–1.08	1.02	0.98–1.06	1.04	0.98–1.09
Mean 7 days	1.04	0.98–1.10	1.04‡	1.01–1.07	1.04	0.98–1.10	1.04	0.98–1.11	1.02	0.98–1.07	1.07†	1.01–1.14
Mean 14 days	1.04	0.99–1.11	1.04‡	1.01–1.07	1.03	0.97–1.10	1.06*	1.00–1.13	1.02	0.98–1.07	1.07†	1.00–1.14
Minimum												
Previous 24 h	1.00	0.95–1.05	1.04§	1.02–1.06	1.04	0.99–1.09	1.07†	1.01–1.12	1.02	0.98–1.05	1.06†	1.01–1.11
Mean 7 days	1.02	0.96–1.08	1.04‡	1.01–1.07	1.02	0.97–1.08	1.07†	1.01–1.13	1.02	0.98–1.06	1.07†	1.01–1.14
Mean 14 days	1.03	0.98–1.09	1.04‡	1.02–1.07	1.03	0.97–1.09	1.06*	1.00–1.13	1.03	0.99–1.07	1.07†	1.00–1.13
Diurnal range												
Previous 24 h	1.12‡	1.04–1.20	0.99	0.95–1.02	1.04	0.96–1.12	0.92†	0.85–1.00	1.01	0.96–1.07	0.96	0.88–1.03
Mean 7 days	1.10	0.98–1.23	1.00	0.94–1.05	1.06	0.94–1.20	0.89*	0.78–1.01	1.02	0.94–1.12	0.98	0.86–1.11
Mean 14 days	1.07	0.92–1.24	0.98	0.91–1.05	1.02	0.88–1.19	0.97	0.83–1.14	0.95	0.84–1.06	0.99	0.84–1.16
Relative humidity, %												
Previous 24 h	1.02	0.99–1.04	1.00	0.99–1.01	1.03†	1.00–1.05	1.00	0.98–1.02	1.00	0.98–1.01	1.00	0.98–1.02
Mean 7 days	1.01	0.98–1.04	1.01	1.00–1.02	1.01	0.98–1.04	1.01	0.98–1.04	1.01	0.98–1.03	1.01	0.98–1.05
Mean 14 days	1.00	0.96–1.04	1.00	0.99–1.02	1.01	0.97–1.05	1.02	0.98–1.06	0.99	0.96–1.01	1.02	0.98–1.06
Precipitation, mm/m^2												
Previous 24 h	1.03‡	1.01–1.05	1.00	0.99–1.02	0.99	0.96–1.03	1.00	0.97–1.03	1.00	0.98–1.02	1.02	1.00–1.05
Mean 7 days	1.04*	1.00–1.08	1.00	0.98–1.03	1.01	0.97–1.06	0.97	0.91–1.03	1.01	0.97–1.04	1.02	0.97–1.07
Mean 14 days	1.06†	1.01–1.11	1.00	0.97–1.03	1.02	0.96–1.08	0.97	0.91–1.04	0.98	0.93–1.03	1.03	0.97–1.09
Atmospheric pressure, hPa												
Previous 24 h	1.00	0.97–1.03	1.01	0.99–1.02	1.02	0.98–1.05	1.02	0.98–1.05	1.00	0.98–1.02	1.01	0.97–1.04
Mean 7 days	1.00	0.97–1.04	1.01	0.99–1.03	1.01	0.98–1.05	1.03	0.99–1.08	1.00	0.98–1.02	1.02	0.98–1.06
Mean 14 days	0.99	0.97–1.01	1.01	0.99–1.02	1.00	0.98–1.02	1.04*	0.99–1.08	1.00	0.98–1.02	1.03	0.99–1.07

* $p < 0.1$, † $p < 0.05$, ‡ $p < 0.01$, § $p < 0.001$, otherwise $p > 0.1$; ↓ = decrease; RR = rate ratio

day period for POCI. No association was found for LACI, irrespective of the hazard period.

Despite an overall increase from summer to spring in the incidence of stroke, there was no evidence for a seasonal effect in our region, either for PICH or for IS. This pattern of variation has been previously described in other population-based studies undertaken in England, Italy, France and Russia [12, 19, 20, 28], while most studies based on registers of hospital admissions found evidence of seasonality [10, 11, 14]. This may reflect the fact of being 'community-based' thus including events, some of them reported by general practitioners, that otherwise would be excluded. Moreover, they report only associations for a first-ever-in-a-lifetime event, usually with low proportions of severe cases compared to hospital admission studies or emergency transport events, the latter also being more subject to misclassification bias [29–31]. The lack of seasonality in community-based studies may also result from the different seasonal effects on PICH and OCSP subtypes and their case mix in different populations. The incidence of PICH and TACI, peaking in spring and autumn compared to summer, points to the apparently steepest variation in T_{max}/T_{min} in these seasons whilst the incidence of PACI peaks in autumn and winter, pointing to possibly less acute effects of temperature. In addition, there appears to be a seasonal pattern in POCI and complete absence of seasonality in LACI, which represents as much as 39% of IS in this study.

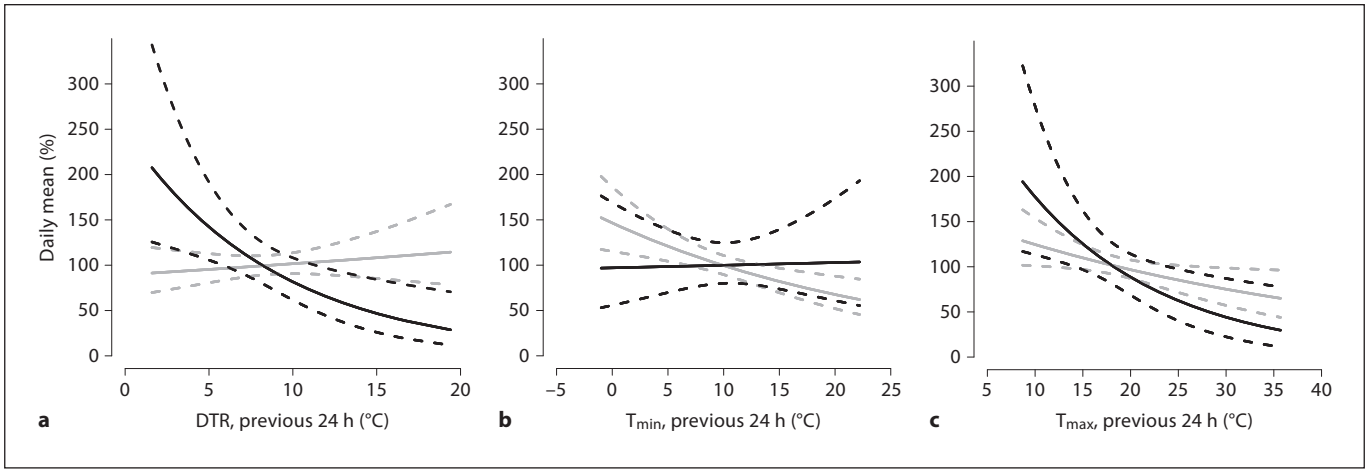

Fig. 2. Fitted number of PICH (black) and IS (grey) (scaled to be a percentage of mean daily strokes) plotted against DTR (**a**) and T_{min} (**b**); fitted number of fatal (black) and non-fatal (grey) strokes plotted against T_{max} (**c**). (Poisson models for the specific events). Dashed lines represent 95% CI.

Table 4. Association between incident stroke events and meteorological parameters according to exposure period (multiple-regression models)

Stroke type/weather parameter	RR	95% CI	p
PICH			(0.003)[1]
DTR – previous 24 h	1.12	1.04–1.20	0.003
IS			(0.001)
T_{min} – previous 24 h	1.04	1.02–1.06	0.001
IS subtype			
TACI			(0.011)
T_{min} – previous 24 h	1.05	1.00–1.11	0.045
RH – previous 24 h	1.03	1.01–1.06	0.018
PACI			(0.006)
DTR – mean 7 days	0.78	0.66–0.92	0.003
RH – mean 7 days	1.05	1.00–1.10	0.034
Tmax – mean 14 days	1.07	1.00–1.14	0.037
LACI			(0.061)
RH – mean 7 days	1.04	1.00–1.08	0.029
RH – mean 14 days	0.95	0.91–0.99	0.018
POCI[2]			(0.016)
DTR – mean 14 days	0.80	0.64–1.00	0.045
RH – mean 14 days	1.06	1.00–1.12	0.037
Fatal stroke[2]			(0.001)
T_{max} – previous 24 h	1.17	1.08–1.26	0.0001
Nonfatal stroke[2]			(0.004)
RH – mean 7 days	1.02	1.01–1.04	0.010
DTR – mean 14 days	0.88	0.81–0.96	0.005

For temperature (T_{max}, T_{min}, DTR), the coefficients are for a 1°C drop. RH = Relative humidity; RR = rate ratio.

[1] (value of p for the overall model).

[2] Coefficients adjusted for seasonal effect.

It was hypothesized that the effect of meteorological parameters would be evidenced in specific stroke types since the prevalence of different risk factors varies according to aetiology and clinical type [32, 33]. Despite the reduced number of events, PICH and TACI are more closely related to temperature in shorter hazard periods. Since their prognosis is worst, it is not surprising that a cold diurnal temperature (T_{max}) is associated with the likelihood of a fatal stroke. The fact that T_{min} (nocturnal) rather than T_{max} is a better predictor of overall and in particular cardioembolic IS, the incidence of IS may be related to the already reported circadian rhythm of IS, peaking in the morning and closely following the morning surge in blood pressure [34, 35]. Other factors that can trigger a stroke after cold exposure, such as activation of coagulation-related factors [36], haemoconcentration and increased blood viscosity [37] may have a greater impact in cardioembolic IS, the more frequent aetiological mechanism of TACI and PACI. On the other hand, the incidence of PICH is consistently associated with precipitation, increasing with the hazard period (24 h, 7 and 14 days). This is the empirical evidence of a fact already mentioned by neurologists at emergency departments all over the country – why do we see more strokes on rainy days? Our data confirm this hypothesis, but when considering the effect of all-weather parameters, DTR in the previous day seems to explain this effect. This triggering effect of drops in DTR, characteristic of spring months might be explained by the concurrence of other atmo-

spheric parameters since they coincide with rises in precipitation, relative humidity and steepest drops in T_{max} (inversely correlated with DTR) and atmospheric pressure (fig. 1). An inverse relationship with atmospheric pressure was found in Siberia [19] as well as an increase in the incidence associated with a mild ambient temperature. In our study, this effect was found when T_{max} approached T_{min}, characterizing spring time with cold days but not so cold nights. These extreme climate features were apparent in the second spring of the study period and not so marked in the first year, a pattern also found in the incidence of PICH. When dealing with weather effects on health events, it is important to look for unusual combinations of meteorological parameters and sometimes characterize the days based on these combinations, as in the study undertaken in Israel [29]. These triggering exposures were rare and usually concentrated, and their effects might be detected by an adequate data smoothing of events as shown in figure 1. They may be overlooked when dealing with extended time series data. Indeed, this fact might explain why contradictory findings on the effects of meteorological parameters have been reported in several studies, most of them finding an inverse relation between incidence and temperature, others a direct relation [15, 31] and both direct and indirect relations across different regions within the country [30]. The right answer is probably given by an Australian study [28] reporting an increase in incidence for extreme temperature values.

Until now, few community-based studies have examined the relation between first-ever-in-a-lifetime stroke and weather parameters. In England [20] and Italy [28], only the incidence of specific events increased with falls in temperature, PICH and fatal stroke, respectively, while in Russia [19] the relation was present for both PICH and IS. From previous reports, we know that the incidence of first-ever stroke is higher in Russia and Portugal compared to England. Population characteristics, mainly the endemic level of vascular risk factors already related to weather changes [38, 39], as well as housing and environmental features, may explain these contradictory findings. Hypertension has a high prevalence in Portugal linked to the excess salt intake, i.e. almost twice as high as that recommended by the WHO [40] as well as a high prevalence of vascular risk factors in general [41]. Therefore, extreme values in environmental temperature, either during daytime or night-time would more likely trigger cardiovascular events. On the other hand, the surrounding conditions for the effect of temperature to be felt cannot be disregarded. The Eurowinter Group, with data from Finland, Germany, the Netherlands, the UK, Italy and Greece [21], has shown that high indices of cold-related mortality were associated with high mean winter temperatures, low living-room temperatures, limited bedroom heating, a low proportion of people wearing protective clothes and inactivity. In the region of the city under study, i.e. the old part of the city near the river bank, most of these conditions prevail and thus we may conclude that in Porto we had conditions for an almost 'experimental' environmental study, excluding in general possible effect modifiers such as eating/conditioning systems.

The major limitation of this study is the reduced number of events, especially when the analysis involves stratification by IS subtypes or overall case fatality. However, the reduced study power for comparing incident strokes according to the OCSP or TOAST classification using the binomial model (that excludes days with no events), had no influence on our conclusion that the effects of cold days on outcome (fatal and non-fatal events) are different. The conclusions of most studies rely on subgroup analysis and although they concluded that there was an effect, some of them did not attempt to verify whether subgroups behave differently [33]. Another important analysis would be to investigate subgroups according to circumstances associated with the onset and time to maximum deficit, as has already been done for myocardial infarction [42]. We have also assumed that meteorological conditions are homogeneous in the study area and the risk to be similar across different environments and circumstances, which might not be true. The data specification included the day when stroke occurred without specifying the hour of the day, and so the 24-hour exposure to meteorological parameters also refers to the preceding calendar day. This means that the value of T_{min} (usually during night-time) might by more distant from the event onset than T_{max} (usually during daytime). It would be rather difficult to know the 'exact' event time since patients might not remember the exact time and more importantly this is impossible when symptoms are felt when awakening.

Our results point out two major conclusions: stroke type and IS subtypes must be considered when studying the effects of weather on incidence, confirming and corroborating the different aetiological mechanisms of stroke. Moreover, it is not only exposure (intensity) that matters, but also the hazard period involved. Since the trigger effect is associated with severity/outcome, emergency services (either dial emergency number or hospital emergency departments) should be aware that specific

weather conditions are more likely to prompt calls for more severe strokes. Further studies with larger data sets involving time trends may be useful to show whether the effects remain after all recent developments in stroke prevention and treatment.

Acknowledgments

This work was supported by grants from FEDER/FCT POCTI/SAU-ESP/54885/2004 and PIC/IC/82858/2007, and the Northern Region Health Authorities.

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CAPÍTULO 5

LONG-TERM PROGNOSIS OF PATIENTS PRESENTING FIRST-EVER VESTIBULAR SYMPTOMS IN A COMMUNITY-BASED STUDY

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International Journal of Stroke and Cerebrovascular Diseases, 2014;23:2190-2198

Abstract

Background: Vestibular symptoms (VSs) are frequent complaints in patients attending ambulatory care and the emergency room. They may represent a peripheral vestibular disorder or a stroke/transient ischemic attack (TIA), yet many patients have VSs that cannot be clearly classified at presentation. This study aims to characterize and determine the long-term prognosis of these patients.

Methods: In a prospective community-based study involving 104,700 individuals registered at 4 health centers of Northern Portugal, patients with a first-ever-in-lifetime focal neurologic symptom (FNS) were ascertained using comprehensive methods, including referrals from physicians working in the study area and data retrieved from emergency/discharge records. Physicians were encouraged to report/notify any patient who might have experienced an FNS, including those with vertigo or vertigo-like symptoms, imbalance, presyncope, or nonspecific dizziness. After neurologic assessment patients were classified as having a peripheral vestibular symptom (pVS), a stroke/TIA, or an unclassified vestibular symptom (uVS). They were followed up 7 years after the index event at the outpatient clinic; predictors of survival free from stroke or vascular events were determined using Cox proportional hazards models.

Results: Of the 1163 patients with an FNS, 360 (31.0%) were included, 16.7% had a stroke/ TIA, 57.8% had pVS, and 25.6% had uVS. Most patients presented only isolated VSs (62.8%); 63% were women and mean age was 60.1 years (standard deviation=16); hypertension (47.8%), hypercholesterolemia (41.9%), and diabetes (19.2%) were the most prevalent vascular risk factors (VRFs). Cranial computed tomography (CT) scan was performed in 63.3%. Adjusting for age, sex, VRFs, and diagnosis (TIA, pVS and uVS), the long-term risk of stroke was higher when CT showed silent infarctions (hazard rate [HR]=3.96; 95% confidence interval [CI], 1.63-9.60) and the risk of vascular events (stroke, myocardial infarction, or vascular death) was higher in patients with 2 or more VRFs (HR=2.70; 95% CI, 1.25-5.86). Identical results were obtained when restricting the model to patients with pVS or uVS.

Conclusions: First-ever-in-lifetime VSs are common in patients with FNS and may represent a good opportunity for preventing a serious vascular event, particularly in patients with vascular comorbidity (silent infarctions and VRFs).

Key Words: Vestibular symptoms—long-term prognosis—brain imaging—vascular risk factors—community-based study.

Background

Vestibular symptoms (VSs), including dizziness, vertigo, or imbalance, are common in health care settings and could be the main complaint of patients with a stroke/TIA, predominantly in the vertebrobasilar artery territory.[1-3]

In clinical practice, the approach to the ‘‘dizzy patient’’ is based on the quality of the symptom, distinguishing those with vertigo (spinning or motion, concerning a vestibular disorder), presyncope (impending faint, concerning a cardiac disorder), imbalance (unsteadiness, concerning a central nervous system disorder), and nonspecific dizziness (any other dizziness).[4] In most of the world medical centers, brain computed tomography (CT) scan is still the most available imaging tool used to investigate patients with acute VSs when a central nervous system disorder is thought. Despite the availability, brain CT scan has low accuracy in the identification of acute stroke in the posterior fossa.[5] Even diffusion weighted imaging - magnetic resonance has a high false-negative rate in acute vertebrobasilar stroke (around 20%), more often when lesions are located in the brain stem.[6-7] Therefore, diagnosis is manly based on clinical grounds and many recent publications have concerned an effort to improve bedside diagnosis.[8-11] Even so, the distinction between possible etiologies for VS is often difficult, especially when more complex presentations involve other comorbidities that may impair a definitive diagnosis. Prospective community registries are adequate to describe the prognosis of these patients, avoiding the selection bias present in hospital cohorts. This study addresses 2 relevant issues. First, to estimate how many ischemic events are expected in patients with first-ever-in-life VS and their relative importance in stroke/TIA incidence; second, to understand the seriousness of unclassified vestibular symptoms (uVSs) by looking at the 7-year outcomes of these patients, compared with those presenting with ischemic or peripheral etiology.

Methods

The ACINrpc (prospective community register of neurologic attacks) included all first-ever-in-life stroke or transient focal neurologic symptoms (FNSs) which could be attributed to a dysfunction of the central nervous system, in individuals registered at 4 health centers (HCs) of Northern Portugal, 86,023 residents in the city of Porto and 18,677 in a rural municipality, between the October 1, 1998, and the September 30, 2000. For case ascertainment, ‘‘hot and cold pursuit’’ methods were used.[12] These

included referrals from general practitioners and other physicians working at HC/hospitals within the study area, mainly at the emergency room, as well as data retrieved from admission/discharge or outpatient clinical records. Contacts were also established with nursing homes and senior residences; death certificates respecting these populations were consulted. More detailed aspects are described elsewhere.[13-14] General practitioners were encouraged to report/notify any patient presumed to have experienced an FNS, including those with vertigo or vertigo-like symptoms, imbalance, presyncope, or nonspecific dizziness. For reporting patients to the study center, a predefined form was used including demographic/social information, details of symptoms onset, and up to 4 major complaining symptoms. After neurologic assessment we excluded those who presented symptoms after head trauma, who contemporaneously to the FNS had ear or central nervous system infection, and those who presented with a presyncope associated with a medical disorder such as hypoglycemia, severe anemia, hypotension, drug intoxication, or acute/decompensated cardiac disorder. Patients with previous similar FNS or stroke were also excluded.

Patients were observed by a research team neurologist as soon as possible after the acute event and followed up at 3 months, 1 year, and 7 years. The investigation and treatment of each patient was under the responsibility of the assistant physician (HC/hospital). In case of a central nervous system disease, patients were regularly followed as outpatient by a research team neurologist. The 7-year follow-up was done preferentially at the neurology outpatient clinic; when that was not possible, a telephone contact and/or revision of hospitals'/HC' clinical records were conducted. If no information was available, the patient was considered lost to follow-up. Informed consent was obtained from each participant or from the next of kin, when appropriate, before any clinical assessment. Patients who expressed their unwillingness to participate were excluded (refusals).

Definitions

For all patients included whose 4 major complaints included VS, the presenting symptoms were grouped as follows: (1) isolated VS (with or without nausea/vomiting); (2) VS plus other FNSs; (3) VS plus tinnitus/hypoacusis; (4) VS plus generalized non-FNSs (generalized weakness, faintness or confusion); and (5) VS plus cephalalgia. According to diagnosis/etiology based on clinical criteria, patients were classified with: (1) Stroke/TIA; (2) Peripheral vestibular symptom (pVS), including benign paroxysmal positional vertigo or labyrinthitis; and, (3) unclassified vestibular symptom (uVS) when none of the previous or any other determined diagnosis was established. Stroke was

defined according to the World Health Organization criteria.[15] In this cohort, stroke was diagnosed in patients presenting an acute vestibular syndrome associated with ‘‘other’’ central nervous signs, with or without acute symptomatic lesion on CT or magnetic resonance imaging (MRI), and ischemic stroke subtype was defined according to the Oxfordshire Community Stroke Project classification.[16] TIA was defined according to standard criteria,[14] and in this cohort, it was diagnosed in patients with monophasic episodes of VSs associated with central signs, lasting less than 24 hours. In our cohort, patients diagnosed with a peripheral vestibular disorder presented paroxystic vertigo induced by head movement, with typical nystagmus, associated with other otologic manifestations (hypoacusis or tinnitus), in the absence of central nervous signs. Besides isolated VSs other nonfocal symptoms/signs such as blurred vision, bilateral weakness, imbalance without objective ataxia, or decreased consciousness might be present.

Laboratory data included a cranial CT scan and triplex scan of carotid and vertebral arteries at entry (either requested by the assistant physician or if considered necessary by the study neurologist); CT brain lesions were read by a neuroradiologist blind to clinical symptoms/signs. Based on the description of the CT, the neurologist assigned any acute lesion compatible with neurologic symptoms and signs as symptomatic; other ischemic lesions (infarctions or lacunas) were considered nonsymptomatic. Triplex scan was considered abnormal in the presence of greater than or equal to 50% stenosis or occlusion of an artery.

For the presence of previous vascular risk factors (VRFs), the following definitions were considered: hypertension, previous diagnosis and/or treatment of high blood pressure (BP), systolic BP .160 mm Hg and/or diastolic BP .95 mm Hg in at least 2 different measures; diabetes mellitus, previous diagnosis and/or under treatment with oral antidiabetic/insulin, fasten glycemia.126 mg/dL, postprandial glycemia $200 mg/dL, and/or glucose tolerance test with values of glycemia $200 mg/dL at second hour; hypercholesterolemia, previous diagnosis and/or treatment, serum total cholesterol level after 12 hours of fasting $240 mg/dL; current smoker, smoker at event date or in the last 12 months; atrial fibrillation, evidence from the electrocardiogram (EKG) or registration in patient’s record; acute myocardial infarction (MI), confirmed by an increase in serum cardiac enzymes, EKG abnormalities or diagnosis confirmed by doctor at any time and angor, history of chest pain with or without superior limb pain related to physical exercise or emotion and release by rest.

Throughout the follow-up period, the following major vascular events were recorded: stroke, MI (confirmed by EKG, tissular necrosis markers, or necropsy), and death of vascular etiology other than MI or stroke (suspected but not confirmed MI or heart failure,

thoracic or abdominal aortic aneurysm rupture, or sudden death of presumed vascular origin).

Data Analysis

The description of patients included according to etiology (ischemic, peripheral, or unclassified) is presented and a logistic regression model was used to estimate the independent predictors of a stroke/TIA at onset of symptoms, considering the sociodemographic profile and relevant VRF in the univariate analysis ($P < .3$). After checking the assumption of proportional hazards with the Schoenfeld test, Cox models were used to estimate survival free from stroke or a vascular event (stroke, MI, or vascular death) in patients with transient symptoms (excluding those with stroke) according to etiology (ischemic, peripheral, and unclassified), VRF, and laboratory findings, adjusted for age and gender. This analysis was repeated excluding patients with TIA. Patients were censored if death or death from a nonvascular cause occurred before the respective end point.

Results

During the registration period, 1922 patients were reported as having FNSs. In a first step 759 were excluded, either by logistic reasons (n = 122) or after neurologic assessment, because their symptoms were nonfocal (n = 274), recurrent episodes (n = 198), including 60 who had a previous stroke, or the symptoms were because of infectious/toxic diseases, non-neurologic, or neurologic noncentral diseases (Fig 1). Among the 1163 included, 363 (31.2%) presented a VS—29 (8.0%) had a stroke (a primary intracerebral hemorrhage, 2 partial anterior circulation infarcts, 3 lacunar infarcts, and 23 posterior circulation infarcts), 31 (8.5%) had a TIA, 3 (.8%) other diagnosis (drop attack, functional disorder, and hydrocephalus), 208 (57.3%) had a pVS, and 92 (25.3%) had an uVS. Considering all first-ever incident cerebrovascular events in this population (579 strokes and 141 TIA), 5% of all patients with stroke and 22% of all patients with TIA presented/complained of VS, either isolated or concomitantly with other symptoms.

Most patients were referred directly to the study center (60.0%), a higher proportion among those with stroke/TIA (75.0% vs. 57.0%; Table 1). Hospital emergency department (ED) and 24 hours HC service were the most sought (94.7%) and 60.6% of patients were observed in the first 24 hours. The mean age at event onset was 60.1 years (range, 11-93), with a higher proportion of patients with stroke/TIA 65 years of age or older (60.0% vs. 41.0%); 62.8% were women. Hypertension was the most prevalent

VRF (47.8%) followed by hypercholesterolemia (41.9%), diabetes (19.2%), angina/MI (7.8%), and atrial fibrillation (4.2%); 14.7% were current smokers. The logistic regression model indicated that age greater than 65 years (odds ratio [OR] 5 1.91; 95% CI, 1.04-3.54), male sex (OR 5 2.36; 95% CI, 1.28-4.35), diabetes (OR 5 2.70; 95% CI, 1.40-5.19), and atrial fibrillation (OR 5 6.30; 95% CI, 1.99-19.9) increased the likelihood of VS of ischemic etiology. This etiology was more frequent in patients that had VS plus FNS (80.9%) or VS plus with other nonfocal neurologic symptoms (22.2% and 22.9%), and more rare in patients with isolated VS (3.5%) or VS plus tinnitus/hypoacusis (2.9%).

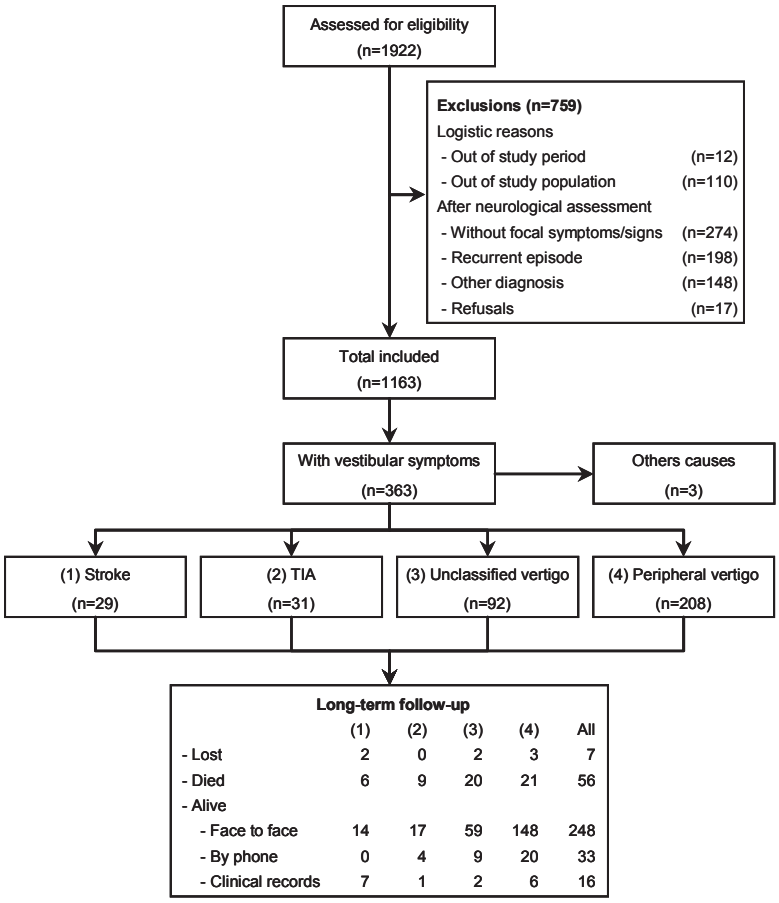

Figure 1. Flowchart of inclusion of patients and details of 7-year follow-up.

Cranial CT/MRI was performed in 228 patients (63.3%) of whom 82 (36.0%) in the first 24 hours; ischemic lesions were detected in 28.9%of all CTs. Only 12 of the 29 patients with stroke showed newrelevant lesions; among the 31 patients with TIA, 28 had cranial CT and in 8 (28.6%) it showed ischemic nonsymptomatic lesions, proportion not significantly different from 21.6 (37 of 171) in patients with other VS. The triplex scan showed signs of stenosis in 61 patients (46.2%) of the 132 (36.7%) investigated.

Table 1. Ascertainment of patients, characteristics, and diagnostic procedures

Characteristics	Stroke/TIA (n=60)	Other vestibular symptom: Unclassified (n=92)	Other vestibular symptom: Peripheral (n=208)	Other vestibular symptom: All (n=300)	All (n=360)	Stroke/TIA vs. others P value
Identification, n (%)						
1st source: Direct	45 (75.0)	56 (60.9)	115 (55.3)	171 (57.0)	216 (60.0)	.009
Hospital	26 (43.3)	39 (42.4)	83 (39.9)	122 (40.7)	148 (41.1)	.08
Health Centre	19 (31.7)	17 (18.5)	32 (15.4)	49 (16.3)	68 (18.9)	
Assessment						
Emergency room	59 (98.3)	84 (91.3)	198 (95.2)	282 (94.0)	341 (94.7)	.2
Delay from onset <24h	36 (60.0)	50 (54.3)	132 (63.5)	182 (60.7)	218 (60.6)	.9
Patients characteristics, n (%)						
Age, mean (SD)	67.9 (11.9)	61.8 (17.9)	57.1 (15.9)	58.5 (16.7)	60.1 (16.4)	
Range	38-92	15-93	11-84	11-93	11-93	
>65 years	36 (60.0)	45 (48.9)	78 (37.5)	123 (41.0)	159 (44.2)	.007
Women	31 (51.7)	59 (64.1)	136 (65.4)	195 (65.0)	226 (62.8)	.051
Hypertension	34 (56.7)	45 (48.9)	93 (44.7)	138 (46.0)	172 (47.8)	.1
Hypercholesterolemia	27 (45.0)	33 (35.9)	91 (43.8)	124 (41.3)	151 (41.9)	.6
Diabetes	21 (35.0)	17 (18.5)	31 (14.9)	48 (16.0)	69 (19.2)	<.001
Myocardial infarction/Angina	7 (11.7)	10 (10.9)	11 (5.3)	21 (7.0)	28 (7.8)	.2
Atrial fibrillation	8 (13.3)	3 (3.3)	4 (1.9)	7 (2.3)	15 (4.2)	<.001
Current smoker	11 (18.3)	16 (17.4)	26 (12.5)	42 (14.0)	53 (14.7)	.4
Number of risk factors*, n (%)						.001
0	13 (21.7)	41 (44.6)	101 (48.6)	142 (47.3)	155 (43.1)	
1	29 (48.3)	32 (34.8)	79 (38.0)	111 (37.0)	140 (38.9)	
2	13 (21.7)	15 (16.3)	24 (11.5)	39 (13.0)	52 (14.4)	
3+	5 (8.3)	4 (4.3)	4 (1.9)	8 (2.7)	13 (3.6)	
Presenting symptoms, n (%)						<.001
Vestibular symptom alone	8 (13.3)	59 (64.1)	159 (76.4)	218 (72.7)	226 (62.8)	
+ Focal	38 (63.3)	6 (6.5)	3 (1.4)	9 (3.0)	47 (13.1)	
+ Tinnitus/ Hypoacusis	1 (1.7)	8 (8.7)	25 (12.0)	33 (11.0)	34 (9.4)	
+ Faintness/ Confusion	6 (10.0)	13 (14.1)	8 (3.8)	21 (7.0)	27 (7.5)	
+ Cephalalgias	7 (11.7)	6 (6.5)	13 (6.3)	19 (6.3)	26 (7.2)	
CT-scan/MRI,† n (%)	57 (95.0)	52 (56.5)	119 (57.2)	171 (57.0)	228 (63.3)	<.001
Before 24h	36 (63.2)	15 (28.8)	31 (26.1)	46 (26.9)	82 (36.0)	
With ischemic lesions	20 (55.6)	7 (46.7)	9 (29.0)	16 (36.8)	36 (43.9)	.06
After 24h	21 (36.8)	37 (71.1)	88 (73.9)	125 (73.1)	146 (64.0)	
With ischemic lesions	9 (42.9)	10 (27.0)	11 (12.5)	21 (16.8)	30 (20.5)	.006
Triplex scan, n (%)	24 (40.0)	29 (31.5)	79 (38.0)	108 (36.0)	132 (36.7)	.6
Abnormal (with stenosis)	13 (54.2)	14 (48.3)	34 (43.0)	48 (44.4)	61 (46.2)	.4
Medication (during 1st year follow-up), n (%)						
Antiplatelet therapy	36 (60.0)	33 (35.9)	43 (20.7)	76 (25.3)	112 (31.1)	<.001
Antihypertensive therapy‡	33 (97.1)	39 (86.7)	85 (91.4)	124 (89.9)	157 (91.3)	.2
Lypid-lowering therapy‡	11 (40.7)	8 (24.3)	24 (26.4)	32 (25.4)	43 (28.5)	.1
Hypoglycaemic therapy‡	18 (85.7)	14 (82.4)	24 (77.2)	38 (79.2)	56 (81.2)	.5
Multitherapy in patients with >1RF	15 (83.3)	13 (68.4)	20 (71.4)	33 (70.2)	48 (73.8)	.3

Abbreviations: MRI, magnetic resonance imaging; SD, standard deviation; TIA, transient ischemic attack; VS, vestibular symptom; RF, risk factor.

*includes hypertension, diabetes, angina/myocardial infarction and atrial fibrillation.

†only 7 patients with MRI (2 with unclassified VS and 5 with peripheral VS).

‡calculated in patients with hypertension, hypercholesterolemia and diabetes, respectively.

During the first year follow-up 195 patients (95.1%) with VRF were under preventive vascular therapy and 41 (26.5%) of those with no previous VRF began therapy after the episode. Antiplatelet therapy was more prescribed in patients with stroke/TIA and other therapeutic agents equally likely prescribed in all patients with the specific VRF; lipid-lowering therapy was seldom prescribed (Table 1).

At the 7-year follow-up, 56 patients (15.6%) had died and 7 (1.9%) were lost to follow-up (Fig 1). Most patients alive at the end of follow-up were examined at the outpatient clinic by a research team neurologist (83.5%) and 33 (11.1%) were contacted by phone to inform about details of vascular events that had happened meanwhile. For all patients, clinical records were checked for relevant information. Patients with stroke/TIA had 18 (30%) vascular events: 8 recurrent strokes, 7 first-ever strokes (after a TIA), and 3 other vascular events (2 MI and 1 vascular death). Patients with uVS had 17 (18.5%) vascular events, 7 strokes, 6 MI, and 4 vascular deaths. In the pVS group, there were 23 (11.1%) vascular events, 15 strokes, 3 MI, and 5 vascular deaths. In the univariate analyses, the number of VRF, the presence of silent infarctions, and VS due to TIA shortened survival free from stroke or a vascular event (Table 2 and Fig 2). In the multivariate model including these variables, only in the presence of ischemic lesions on CT scan there was an almost 4-fold risk of stroke in the long-term follow-up (hazard rate [HR] 5 3.96; 95% CI, 1.63-9.60), whereas the longterm risk of a vascular event increased in patients with 2 or more VRFs (HR 5 2.70; 95% CI, 1.25-5.86). After excluding patients with TIA, the multivariate models yielded identical results (Table 3); patients with at least 2 VRFs were at a higher risk of stroke (HR 5 5.75; 95% CI, 1.71-19.4) or of a vascular event (HR 5 5.15; 95% CI, 2.26- 11.7), whereas the presence of any ischemic lesion on CT scan increased the risk of stroke (HR 5 5.75; 95% CI, 1.71-19.4).

Discussion

This is the first prospective community-based study to analyze the diagnosis of patients presenting with firstever-in-lifetime VS, and according to this presenting symptom, trying to understand their seriousness in a prolonged long-term follow-up. In most patients, the symptoms at presentation had peripheral etiology (57.3%), but still in 16.5% of them it was the complaining symptom of a first-ever-in-the-lifetime stroke/TIA, indicative in this population of 5% of first-ever strokes and 22% of first-ever TIA. Despite being observed and followed up by neurologists close to onset and at 3 months, in 25.3% of patients the VS remained unclassified. For this relatively high proportion of patients, some discharged with a ‘‘symptomatic diagnosis’’ and others with alternative possible diagnosis (as

migraine or functional disorder) we may conclude that the presence of silent infarctions on CT and VRFs are the more important predictors of a serious vascular event, such as stroke, MI, or vascular death.

Table 2. Cox proportional hazard rates (HR) for stroke and vascular events in the seven-year follow-up in patients with transient VS (n=331)

Patients characteristics and diagnostic procedures	Stroke					Vascular events				
	No. events‡	Univariate		Multivariate		No. events‡	Univariate		Multivariate	
		HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Socio-demographic										
Men vs. Women	12/18	1.20	0.58-2.49	1.17	0.55-2.50	22/29	1.36	0.78-2.36	1.55	0.87-2.77
Age (years)*	17/13	1.05	1.02-1.08	1.03	0.99-1.07	35/16	1.06	1.04-1.09	1.06	1.03-1.08
Risk factors (Yes vs. No)										
Hypertension	20/10	2.39	1.12-5.10			33/18	2.24	1.26-3.97		
Hypercholesterolemia	12/18	0.92	0.44-1.91			24/27	1.25	0.72-2.16		
Diabetes	9/21	2.09	0.96-4.57			15/36	2.10	1.15-3.83		
Angina/Myocardial infarction	6/24	3.36	1.37-8.22			10/41	4.05	1.60-10.2		
Atrial fibrillation	4/26	5.19	1.81-14.9			5/46	3.35	1.68-6.69		
Current smoker	3/27	0.73	0.22-2.40			6/45	0.86	0.37-2.02		
No. risk factors (vs. 0)†										
1	14/6	2.94	1.13-7.64	1.89	0.71-5.05	20/12	2.12	1.03-4.33	1.42	0.69-2.93
2+	10/6	4.85	1.76-13.4	2.43	0.80-7.35	19/12	4.91	2.38-10.1	2.70	1.25-5.86
CT-scan (vs. without ischemic lesions)										
Not done	8/9	1.07	0.41-2.77	1.08	0.40-2.90	16/19	1.03	0.53-2.00	0.96	0.48-1.91
With ischemic lesions	13/9	5.74	2.45-13.4	3.96	1.63-9.60	16/19	3.40	1.75-6.61	1.95	0.98-3.88
Triplex scan (vs. without stenosis)										
Not done	19/4	1.64	0.56-4.83			32/8	1.39	0.64-3.02		
With stenosis	7/4	2.35	0.69-8.04			11/8	1.85	0.74-4.59		
Diagnosis (vs. peripheral VS)										
Transient ischemic attack	7/15	3.74	1.52-9.17	1.79	0.64-5.06	10/23	3.60	1.71-7.57	1.49	0.65-3.43
Unclassified VS	8/15	1.31	0.56-3.10	0.87	0.36-2.11	18/23	1.99	1.07-3.68	1.36	0.72-2.57

Abbreviations: CI, confidence interval; CT, computed tomography; HR, hazard rates; VS, vestibular symptom.

*Number of events according to age in 2 groups: ≥ 65, <65 years.

†According to univariate analysis includes hypertension, diabetes, angina/myocardial infarction, and atrial fibrillation.

‡Number of events of each category against reference category.

The relatively high proportion of unclassified patients in this study reflects the known difficulty of managing VS patients, especially when they present a first-ever episode. Even so, we have achieved a similar proportion of definitive diagnosis as reported in other studies retrospectively based on ED visits.[17] The high incidence of stroke/TIA among patients with VS maybe justified by the fact that our study is community-based and mainly because we excluded many patients with only non- FNSs such as presyncope

or other toxic/infectious etiologies. Moreover, by including only the first-ever-in-life episode, many patients with usually benign and highly prevalent chronic or recurrent etiologies, such as paroxysmal positional vertigo or Meniere disease, were excluded. This was a more restrictive approach because we were mainly interested in symptoms that could be attributed to a vascular cause. More and less restrictive approaches may justify the wide range of central causes of vertigo/dizziness found in other studies, such as .5% using a National Health Insurance database,[18] and proportions between 3.2% and 9.2%[3,17,19-21] based on patients seen at EDs or 42% in patients seen at na emergency neurologic consultation.[22]

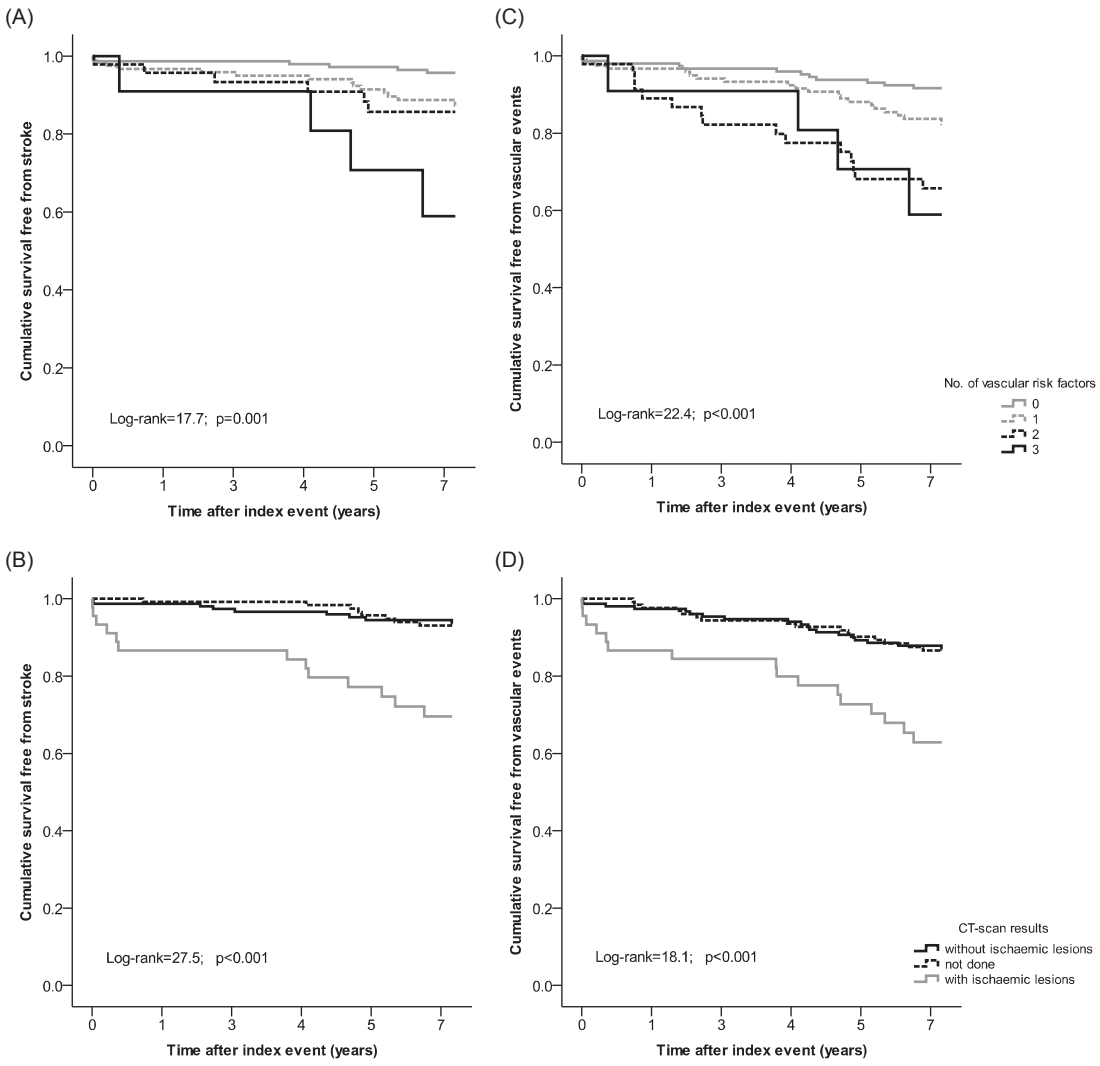

Figure 2. Kaplan–Meier survival free from stroke and free from a vascular event according to the number of vascular risk factors (A) and (C) and computed tomography scan results (B) and (D).

Table 3. Cox proportional hazard rates (HR) for stroke and vascular events in the seven-year follow-up for patients with peripheral and unclassified VS (n=300)

Patients characteristics and diagnostic procedures	No. events‡	Stroke		No. events‡	Vascular events	
		HR	95% CI		HR	95% CI
Socio-demographic						
Men vs. Women	9/14	1.21	0.50-2.92	18/23	1.68	0.88-3.20
Age (years)*	13/10	1.03	0.99-1.07	28/13	1.06	1.03-1.09
No. risk factors (vs. 0)†						
1	10/4	2.10	0.64-6.89	15/9	1.49	0.64-3.45
2+	9/4	5.75	1.71-19.4	17/9	5.15	2.26-11.7
CT-scan (vs. without ischemic lesions)						
Not done	8/5	1.35	0.43-4.15	14/14	0.82	0.39-1.73
With ischemic lesions	10/5	5.75	1.86-17.7	13/14	2.20	1.00-4.83
Diagnosis						
Unclassified vs. peripheral VS	8/15	0.76	0.31-1.87	18/23	1.32	0.70-2.50

Abbreviations: CI, confidence interval; CT, computed tomography; HR, hazard rates; VS, vestibular symptom.

*Number of events according to age in 2 groups: ≥ 65, <65 years.

†According to univariate analysis includes hypertension, diabetes, angina/myocardial infarction and atrial fibrillation.

‡Number of events of each category against reference category.

Considering that most patients were notified by physicians at ED, the proportion found is relatively high, reaching 3.7% (8 of 228) in patients whose complaint was isolated vertigo, again much higher than reported in patients admitted to hospital ED (.7%).[3] As it would be expected the diagnosis of stroke/TIA was more frequent among patients complaining or presenting any focal abnormality on examination (80.9%), but other presentations in which vertigo was accompanied by headache, faintness/confusion were also common in patients with stroke/TIA. Moreover, the likelihood of vertigo with central cause was higher in men and increased with age and the number of risk factors, namely atrial fibrillation and diabetes. These results corroborated previous findings in ED patients with a triage complaint of vertigo[20] and in studies comparing patients with and without vertigo.[3,18]

As it might be expected, patients with TIA had a higher long-term risk of stroke or other vascular events than patients with a peripheral etiology, although after adjusting for age, gender, VRFs, and the presence of nonsymptomatic (silent) ischemic lesions on CT, the diagnosis/etiology lost importance. For patients without definite diagnosis, the long-term risk of vascular events is somewhere between those with known etiologies. Probably the recognition and description of symptoms by these patients was not so accurate to allow a better interpretation by the physician. After excluding patients with a TIA from the analysis

of long-term prognosis, the high risk of upcoming vascular events in patients with 2 or more VRFs compared with those with no risk factors suffers a remarkable increase from 2.7 to 5.2, indicating that in this reduced group VRFs are even more important. It is possible that a referral bias exists because patients with VRFs maybe more prone to attend medical care and thus to be notified by their physicians. Identical findings were reported in patients hospitalized with a principal diagnosis of vertigo (excluding central vertigo).[23] Another interesting finding is the fact that age (.65 years) is not a prognostic factor when the outcome is stroke, contrary to a vascular event. This maybe explained by the fact that patients presenting VS from central cause are a younger group compared with what is found in the general population,[13-14] and their risk profile, excluding diabetes and atrial fibrillation, is similar to that of patients with pVS or uVS. This may also explain the diagnosis difficulties and the ‘‘useless’’ of the CT scan for diagnostic purposes in patients with vertigo as remarked in other studies.[21] This inadequacy of CT scan might be even more pronounced because in some patients (36%) it was performed in the first 24 hours after the first-ever episode of VS, and it was not repeated few days later, making it difficult to identify eventual symptomatic lesions and a consequent change in diagnosis.[24] On the other hand and independently from diagnosis, CT scan results, namely, the presence of nonsymptomatic ischemic lesions of any type/location (mostly lacunas) increases significantly the long-term risk of stroke, both including (HR 5 3.96) or excluding patients with TIA (HR 5 5.75). Again, we cannot rule out a possible bias because CT/MRI might had been more likely performed in patients for whom an ischemic etiology was admitted. Nevertheless the risk of stroke/vascular event in patients without CT/MRI was similar to that of patients showing no ischemic lesions.

In spite of the low short-term risk of stroke of patients with an acute VS when compared with other transient focal symptoms/signs,[25] VRF and the presence of silent ischemic lesions deserve better secondary prevention for avoiding vascular events in the long run. Our results illustrate more closely the spectrum of a first-ever VS at community level and their prognosis than other retrospective studies based only on ED visits, relying mostly on International Classification of Diseases codes and so disregarding subtle neurologic findings that might indicate a central nervous system dysfunction.[20,23,26] Even so, we may have missed episodes that do not come to medical attention, although less likely first episodes, because in the public perception whenever these symptoms are present the person seeks medical care[27] providing a good opportunity for risk factors surveillance. We recognize 2 major limitations in this study. The first is the lack of useful imaging data, namely, MRI in the acute setting or a later repeated CT scan that could have helped in the identification of TIA/stroke and eventually diminish the number of patients with

undetermined etiology. The second is the lack of systematic data about medication used before and after the acute event. Even so, during the first year follow-up, a considerable number of patients were not under an adequate therapy according to the risk factors presented, particularly antiplatelet and lipid-lowering therapy. Moreover, these secondary preventive measures were more likely undertaken in patients with a TIA rather than in those with uVS, which might partially explain why the diagnosis was not an important prognostic factor.

Conclusions

More than 8% of patients with a first-ever stroke/TIA present to the assistant physician with a first-ever complaint of VS. About a quarter of all patients presenting with VS remain with no definitive diagnosis. However, independently of diagnosis, the prognosis is mostly dependent on the number of VRF and on the presence of old, nonsymptomatic ischemic lesions on the acute CT scan. To prevent future vascular events, we purpose that those patients with VRF and/or old asymptomatic ischemic lesions should have a vascular workup similar to those diagnosed with stroke/TIA and a strict control of their VRF.

Acknowledgment: Author contributions: R.F. drafted the article and was responsible for data validation; R.M. was responsible for data management and statistical analysis; M.C. conceived and designed the community-based study and was responsible for neurologic evaluation; M.C.S. contributed to analysis and interpretation of data and critical revision of the article. All authors read and approved the final article.

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CAPÍTULO 6

DECLINE OF STROKE INCIDENCE AND POSTSTROKE DISABILITY IN PORTO, PORTUGAL BETWEEN 1998 AND 2011

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(submetido)

Abstract

Background

The recognition of the burden of stroke in Portugal led to the implementation of preventive and therapeutic measures and, despite of the population aging, mortality rates have been declining. Monitoring changes in incidence/outcome highlights the efficacy of these measures.

Objective

Two prospective community registries of focal neurological attacks were used to estimate changes in stroke incidence and to determine factors associated with changes in stroke outcome.

Methods

Identical definitions and sources of information were used to ascertain all first-ever-in-a-lifetime strokes occurring in the metropolitan area of Porto in the periods 1998-2000 and 2009-11. In the second study a record-linkage methodology based on the National Health Number was implemented.

Results

Eleven years apart stroke incidence decreased 25% (incidence rate ratio=0.75, 95% CI 0.67-0.84), with a 27% reduction in disabling strokes and 21% in non-disabling strokes. A concomitant 40% (95% CI 23-53%) reduction in case-fatality was observed after adjustment. These reductions were more marked in women than in men, in particular an incidence reduction in primary intracerebral hemorrhage of 62% compared with 21% in men. After adjustment for patient and stroke characteristics, the improvement in 28-day severity in the second study resulted from differences in the oldest patients and inpatient care.

Conclusions

There was a “gender decline” in the incidence of stroke, hemorrhagic stroke and disabling stroke in the sense that it was evidenced in women rather than men. The implementation of stroke units and changes in secondary prevention in the elderly underlie the better stroke outcome in the second period.

One decade ago Portugal had one of the highest stroke incidence rates among Western European countries, 305 per 100,000 in rural and 269 per 100,000 in urban populations, and a low case-fatality at 28 days, 14.6% in rural and 16.9% in urban areas.[1] This high incidence could explain why stroke was the leading cause of death in Portugal. However, mortality from stroke declined from 154.2 to 91.6 per 100,000 between 1999 and 2005 and from 164.2 to 93.1 in the Northern Region of Portugal,[2-3]and these changes may be associated with a decline in incidence and/or changes in survivorship. Conclusions from the WHO MONICA project on populations aged 35 to 64 years indicated that changes in stroke mortality were mainly attributable to changes in case fatality rather than in event rates,[4] but the study fell short from demonstrating that they resulted from disease severity and management. Nevertheless disability-adjusted life-years lost from stroke in Portugal had a 39.4% reduction in the 1990-2005 period,[5] indicating that changes in stroke severity might be implied.

Soon after the first study was carried out, several health measures were advanced by the National Health Authorities, resulting from recognizing that stroke was the leading cause of death and hospital inpatient care calling to integrated primary, secondary and tertiary prevention actions.[6] Among others, it was purposed to intensify population-based campaigns about the disease and risk factors[7] and to identify VRF carriers using a periodical medical examination; the organization of stroke units and implementation of Stroke Code pathways[8] were the measures directed to patients.

Using the updated methodology for 'ideal' population-based studies,[9] a second incidence study was undertaken in the northern region of Portugal. In this article we focused in urban populations living in the region of Porto, and we are mainly interested in knowing whether the reduction in mortality stems from a decrease in incidence rates, particularly a decrease in short-term stroke severity and measures implemented meanwhile.

Subjects and Methods

The ACIN2 (prospective community registry of Neurological Attacks) is the second population-based study in the North of Portugal for studying the incidence and outcome of stroke and transient focal neurologic attacks (TNA) which could be attributed to a dysfunction of the central nervous system. We used the criteria for epidemiological population-based stroke research proposed by Sudlow and Warlow[10] and updated by Feigin and Carter[9] for achieving complete case ascertainment.

Study Population

Following the reorganization of the Portuguese National Health Service (NHS) in 2008, the metropolitan area of Porto (Figure 1) was divided in 9 major health divisions, two of them, the Western and Eastern Porto ACES (association of health centers) for persons living in the city of Porto. The study population comprised all individuals registered in the Western Porto ACES (WPACES), involving approximately 57% of the city population residing in 12 administrative regions. This health unit aggregates five health centers (HC) and 105 family doctors, including the three HC involved in the study undertaken in 1998-2000, and the Centro Hospitalar do Porto, which includes the Hospital Santo António (HSA) that receives all patients from the WPACES who are referred for emergency/specialized care. The national health number (NHN) database from the WPACES was used to define the study population and served as reference to collect medical information. The NHN provides a unique patient identifier for every resident in Portugal after registration at a particular health unit/family doctor, for accessing the NHS network.

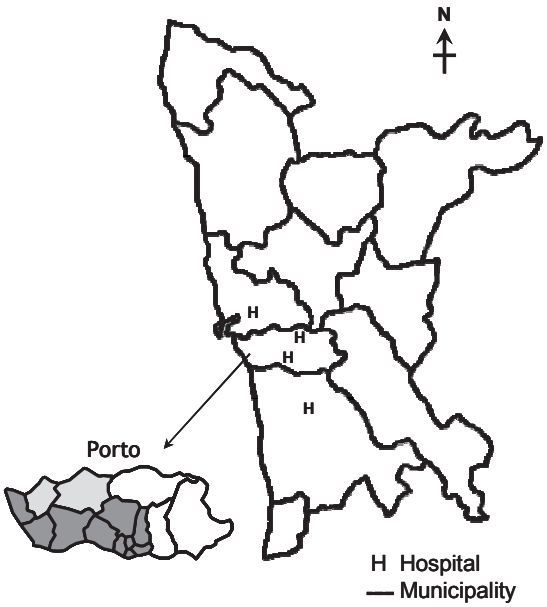

Figure 1. Map of the metropolitan area of Porto, showing areas included in both studies (dark shaded) and added in the second study (light shaded), and main hospitals involved

Case ascertainment and follow-up

To make studies comparable we used identical sources of information. (1) All family doctors were informed about the project and were asked to report, as soon as possible

after the event, any patient suspected of a stroke or TNA either by using the project website (www.acin2.com) or by other means (mail, fax, phone, electronic hospital outpatient clinic booking). This dedicated website was created on purpose for the ACIN2 and was used by all physicians at the HSA for reporting patients admitted at Emergency Department (ED), hospital ward or examined at the ultrasound/radiology laboratories. This topic was addressed every day by the neurology team at the emergency room and at weekly meetings of the neurology department. This webpage, identified by the patient NHN, contained the essential information for each event/patient: details of place, time and clinical characteristics, diagnostic procedures, and proposed diagnosis. (2) While in the first study hospital discharge registers, ED records and a sample of imaging department records were reviewed, in the present study a record-linkage methodology based on the NHN was implemented. For this purpose, several computer-generated lists were provided by the entities involved in the study: ED admissions, inpatient discharges and brain/cervical arteries imaging procedures. (3) In the first study death certificates could be scrutinized, but the new legislation issued in Portugal forbids access to this "individual" information for research purposes; to overcome this issue we screened the HSA and the National Network for integrated long-term care death lists. Autopsies performed at HSA pathology department or at the Medical Forensic Institute in Porto (covering the Northern Region) whose death cause was stroke were reviewed in both studies. (4) Regular contacts with private hospitals and nursing homes were made in both studies to capture patients not attending the NHS.

In the present study we used two additional case-ascertainment methods recently implemented in the NHS. The pre-hospital stroke code activation lists and the computer-generated list of all primary care patients (HCs) with a diagnostic code of stroke/TIA. The reorganization of the NHS in the city of Porto centralized the emergency care out-of-hospital in a single dedicated unit (Service for Urgent Situations), open daily from 8h-24h. This unit receives approximately 4,300 patients per month and the clinical information is hand-written. To scrutinize all records would be an exceedingly time-consuming task and so we selected a two month sample to estimate an eventual loss of cases. Prospective methods included direct "individual" referrals and daily check of ED admissions at HSA; at other hospitals in the region of Porto (Figure 1) this was done on a monthly basis. Retrospective methods included a monthly, quarterly or yearly based review of hospital diagnostic coding data (International Classification of Disease, Ninth revision codes 430 to 438, 342 and 781) and the overall Northern Region pre-hospital stroke code activation records, for identifying cross-boundary flow of patients. At the end of the study period the

computerized register of ED visits of the remaining 21 hospitals in the Northern Region were checked.

Between October 1, 2009 and September 30, 2011, all possible strokes occurred in patients registered at Western Porto unit were recorded. Surveillance of all sources of information continued for a further three months to ensure full registration. Patients were examined by a neurologist as soon as possible after the event at ED, during their hospital stay or at a special study outpatient clinic and, followed up at three months. As in the first study, the principal investigator (M.C.) reviewed the medical history of each patient to ascertain the first-ever-in-a-lifetime stroke (FELS) and its pathological type. If a patient died soon after the event, we attempted to obtain additional information from an eyewitness and clinical records. For patients unable to communicate we interviewed close relatives or other suitable informants.

The objectives and field work planning were presented to the Northern Region Health Authorities for granting permission to perform the study. The study was approved by the Porto Hospital Center Ethics Committee. Informed consent was obtained from the prospectively included patients or from next of kin, when appropriate, before any clinical assessment. The Portuguese Data Protection Authority approved all procedures implemented.

Definitions

As in the first study,[1] stroke was defined according to the World Health Organization as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer or leading to death, with no apparent cause other than of vascular origin'.[11] Pathological types were classified according to Sudlow and Warlow as ischemic stroke, primary intracerebral hemorrhage (PICH) and subarachnoid hemorrhage (SAH).[12] Patients without brain CT scan performed within 30 days, no brain MRI, no post-mortem confirmation, and no lumbar puncture or angiography in case of suspected SAH, were classified as stroke of undetermined type.

Information on vascular risk factors (VRF) was collected using the same methodology throughout the two study periods. The criteria used for hypertension was a history of known hypertension or antihypertensive treatment; for diabetes, a previous diagnosis/treatment of diabetes mellitus with oral anti-diabetic/insulin or fasting glycaemia>126mg/dl, postprandial glycaemia≥200mg/dl and/or glucose tolerance test with values of glycaemia≥200mg/dl at the 2nd hour; for hypercholesterolemia, a previous diagnosis/treatment of hypercholesterolemia; for atrial fibrillation, evidence from the

electrocardiogram or documented in patient's record; patients were classified as current smoker if they smoked at the event date or at any time during the preceding 12 months.

The pre-stroke and post-stroke (approximately 1 month after the event) modified Rankin Scale (mRS) scores were recorded for every patient and were used for classifying disability resulting from stroke as follows: a minor (non-disabling) stroke if the post-stroke score was less than 2 or the mRS score did not change after the event; otherwise they were considered non-minor (disabling).

Statistical methods

Following identical criteria of the first study, incidence rates were calculated using the population registered in the WPACES at the middle of the study period (September 30, 2010) and the confidence intervals (CI) were calculated based on the Poisson distribution. These rates were standardized to the European population.[13] Specific incidence rates and ratios (IRR) and the respective 95%CI were calculated for pathological stroke type and severity using as standard the Portuguese population of the 2011 Census.

Poisson regression models were used to analyze the relationship between study period, gender, age group (<55, 55-64, 65-74, 75-84 and ≥85 years), and stroke risk. The outcome was the number of strokes within each age/gender/period strata, with the population counts from the 2011 Portuguese Census for each strata serving as the offset. We examined all models with the various combinations of effects: main effects for age, gender and, period and effect modification terms: age-gender, age-period, and gender-period using the deviance that follows approximately a chi-squared distribution with degrees of freedom equal to the number of cells minus the number of parameters. The preferred model was that with fewer parameters that fitted the data ($p>0.05$), unless a model with an extra effect provided a significantly improved fit ($p<0.05$) over the simplest model evaluated by the difference in chi-square values for the two models with the difference in degrees of freedom. Models were tested for all strokes combined and a sensitivity analysis was performed for minor and non-minor stroke separately. Proportions and median values of baseline characteristics were compared in the two periods using the chi-square test and the median test following also a chi-square distribution. Setwise regression models were used to ascertain a period effect in short-term disability (28-day mRS score). The first model included the set of baseline and stroke characteristics and the effect of period, followed by all two-way interaction effects with period entered in the equation using a stepwise procedure; in the following model the set of management variables was added and again in a stepwise manner their interaction effects with period

(final model). A robust Poisson model[14] was used to estimate the prevalence ratio of pre-stroke risk factors and the ratio of case-fatality rates by stroke type adjusted for age and sex, using the values of the first period as reference.

Results

The population of the second study comprised 189968 individuals registered at WPACES on September 2010, from whom 1020 were notified as stroke patients. Diagnosis was confirmed in 942 (92.4%) and 78 were excluded (31 with incorrect diagnosis, 36 out of study population and 11 for other reasons). A FELS occurred in 721 patients, 674 from the above and 47 (6.5%) first notified as TNA (compared to 3.2% in the first study). From prospective methods we identified 643 (89.2%) patients, from discharge lists 41 (5.7%), from HCs list and imaging department records more 28 (3.9%) cases and the remaining 9 (1.2%) by checking ED lists of hospitals outside metropolitan area; in the first study 69.5% patients were found by prospective methods and 19.3% by manual searching of ED lists at HSA and emergency transportation calls (equivalent in the present study to patients identified by prospective methods), 4.8% in discharge lists, 0.6% from imaging records and 5.6% by death certificates.

Incidence

Eleven years apart the incidence of FELS decreased from 269 to 190 per 100,000 and from 173 to 125 after standardized to the European population (Table 1). The overall reduction was 25%, 16% in men and 33% in women (Table 2). PICH incidence rate reduced 44% and that of ischemic stroke 16%; this reduction was higher for women compared to men. The incidence rate of fatal stroke declined 54%, 28% in men and 66% in women. The incidence in strokes that resulted in none or slight disability (mRS 0-1) declined 29%. Figures 2(A) to (D) display the age-sex specific incidence for all strokes and the age-specific incidence for minor and non-minor stroke in the two study periods. The Poisson models that fitted data for all strokes and both minor and non-minor strokes includes the interaction between gender and age (Supplemental table), indicating a higher incidence in men compared to women in the youngest and no difference in the oldest. While in minor strokes there is a constant effect of period for all age-gender strata, IRR=0.79 (95%CI, 0.65-0.96), for all strokes and non-minor strokes the effect of period depends on gender; the overall decrease in all strokes for the 2nd period, IRR=0.75 (95%CI, 0.67-0.84), was significant in women, IRR=0.67 (95%CI, 0.57-0.79) and not in men, IRR=0.85 (95%CI, 0.72-1.02) (Table 3); for non-minor strokes the overall IRR=0.73

(95%CI, 0.63-0.84), IRR=0.62 (95%CI, 0.51-0.75) for women and, IRR=0.89 (95%CI, 0.71-1.12) for men.

Table 1. Annual incidence rates of first-ever stroke per 100,000 in Porto, Portugal over eleven years, by gender and age

	Men				Women				Total			
Age, years	at Risk	n	rate	95% CI	at Risk	n	rate	95% CI	at Risk	n	rate	95% CI
1998-2000												
<35	16178	2	6	1-22	18175	3	8	2-24	34353	5	7	2-17
35-44	5276	10	95	45-174	7127	12	84	43-147	12403	22	89	56-134
45-54	5168	17	164	96-263	6582	21	160	99-244	11750	38	162	114-222
55-64	4202	34	405	280-565	5590	32	286	196-404	9792	66	337	261-429
65-74	3916	57	728	551-943	5856	76	649	511-812	9772	133	681	565-796
75-84	1991	42	1055	760-1426	3915	87	1111	890-1370	5906	129	1092	904-1281
≥85	519	13	1252	667-2142	1528	56	1832	1384-2380	2047	69	1685	1311-2133
Total	37250	175	235	200-270	48773	287	294	260-328	86023	462	269	244-293
ASRE			179	148-209			167	141-193			173	153-192
2009-2011												
<35	37690	8	11	5-21	37774	2	3	0-10	75464	10	7	3-12
35-44	14530	18	62	37-98	15702	12	38	20-067	30232	30	50	33-71
45-54	12690	42	165	119-224	14624	21	72	44-110	27314	63	115	89-148
55-64	10482	70	334	260-422	12976	45	173	126-232	23458	115	245	200-290
65-74	7052	73	518	406-651	9506	70	368	287-465	16558	143	432	361-503
75-84	4264	80	938	744-1168	7790	136	873	726-1020	12054	216	896	776-1015
≥85	1296	36	1389	973-1923	3592	108	1503	1220-1787	4888	144	1473	1232-1714
Total	88004	327	186	166-206	101964	394	193	174-212	189968	721	190	176-204
ASRE			151	133-169			102	89-116			125	113-136

ASRE indicates age-standardized rate for the European population

Patient characteristics and assessment

In both cohorts, the included patients were more often women, with a lower proportion in the second cohort (p<0.02). Median age in the second cohort was 2 years higher than in the first cohort (p<0.04), and 4 years higher in women (p<0.005) (Table 4). The proportion of patients independent before stroke decreased in the second study but the PR=1.02 (95%CI, 0.95-1.09) after adjustment. In general, the prevalence of VRF increased in the 2009-2011 period; after adjustment the prevalence ratio for hypertension was 1.20 (95%CI, 1.08-1.33), 1.45 (95%CI, 1.09-1.93) for atrial fibrillation, 1.29 (95%CI, 1.06-1.56) for hypercholesterolemia, and 2.12 (95%CI, 1.80-2.49) for former smokers; the prevalence of diabetes and myocardial infarction/angina remained stable. The pattern of

stroke has changed with a reduction in the proportion of hemorrhagic stroke from 20.6% to 15.3%.

Table 2. Annual incidence rates of first-ever stroke per 100,000 in Porto, in the two study periods stratified by pathological type and disability in men and women

	1998-2000		2009-2011			
	rate	95% CI	rate	95% CI	IRR*	95% CI
All first stroke	260	236-285	195	181-209	0.75	0.67-0.84
Men	239	204-274	202	181-223	0.84	0.71-1.01
Women	281	248-314	188	169-207	0.67	0.57-0.83
Pathological type						
Ischemic stroke	196	176-217	164	151-177	0.84	0.73-0.95
Men	181	151-212	164	145-183	0.91	0.74-1.11
Women	211	182-240	165	147-182	0.78	0.66-0.93
Primary intracerebral haemorrhage	44	35-55	25	20-30	0.56	0.41-0.76
Men	41	28-59	31	24-41	0.79	0.51-1.23
Women	47	35-63	18	13-25	0.38	0.25-0.59
Subarachnoid haemorrhage	9	5-15	6	3-8	0.59	0.31-1.14
Men	7	2-16	6	3-10	0.85	0.29-2.48
Women	12	6-20	5	3-10	0.48	0.21-1.10
Rankin score at 28 days						
mRS 0-1	72	59-85	51	44-58	0.71	0.57-0.89
Men	86	66-110	59	47-70	0.69	0.50-0.94
Women	59	45-77	44	35-54	0.74	0.53-1.02
mRS 2-3	66	54-78	77	68-86	1.16	0.94-1.44
Men	58	42-78	84	70-97	1.40	1.00-1.97
Women	73	57-92	71	60-83	0.99	0.75-1.31
mRS 4-5	80	67-94	47	40-53	0.58	0.46-0.73
Men	61	44-81	37	28-46	0.60	0.41-0.88
Women	97	79-119	55	45-66	0.57	0.43-0.75
mRS 6	44	34-55	20	16-25	0.46	0.34-0.64
Men	33	22-50	23	17-32	0.72	0.44-1.20
Women	53	39-69	18	12-24	0.34	0.22-1.52
Minor stroke (non-disabling)†	92	78-106	72	64-81	0.79	0.65-0.96
Men	98	77-123	77	64-90	0.78	0.59-1.04
Women	86	69-107	68	57-79	0.80	0.61-1.04
Non-minor stroke (disabling)	169	149-188	122	111-134	0.73	0.63-0.84
Men	140	113-166	125	109-142	0.89	0.71-1.13
Women	195	167-222	120	106-136	0.62	0.51-0.75

*IRR indicates incidence rate ratio (2009-2011 versus 1998-2000), standardized to the 2011 Census population of Portugal; †excluding 2 patients in 1998-2000

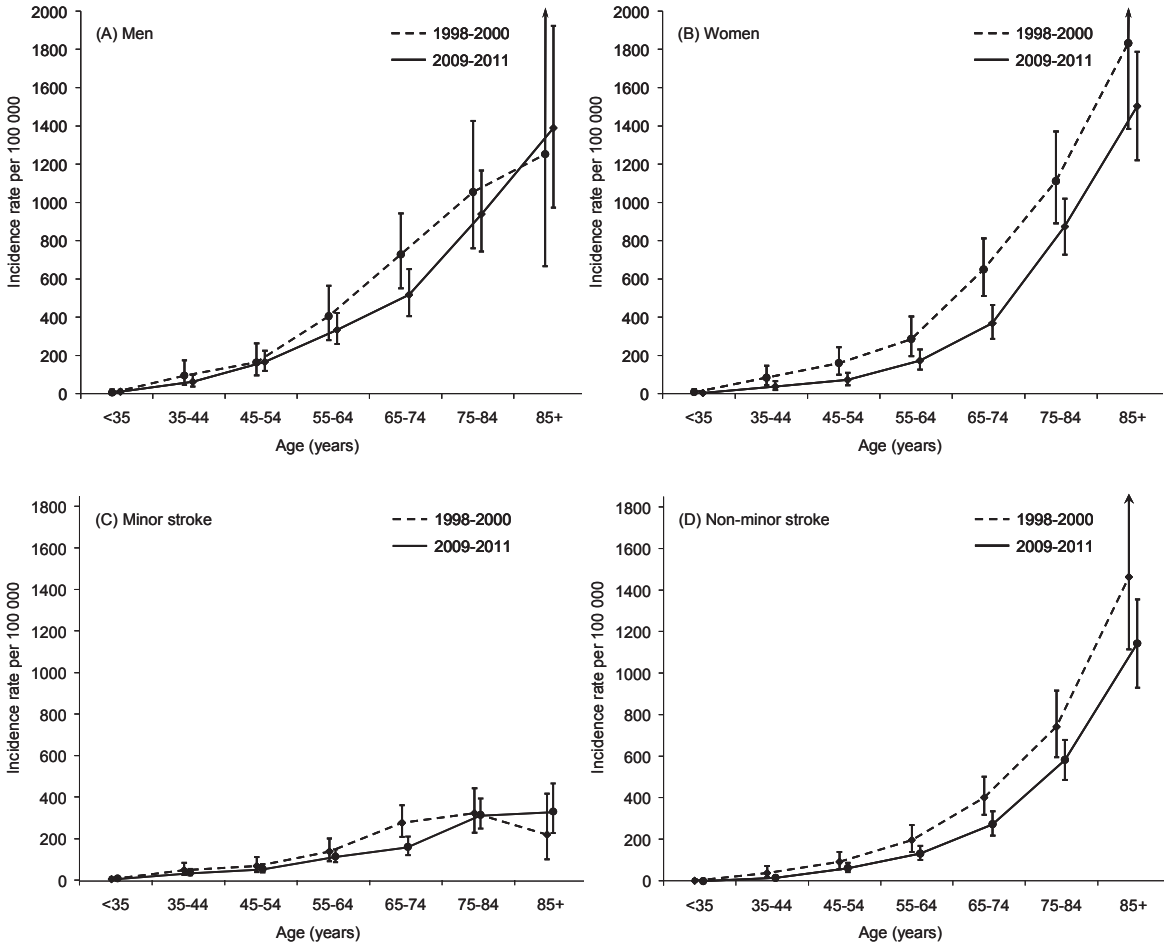

Figure 2. Age specific annual incidence rates of first-ever stroke in (A) men, (B) women, (C) minor stroke and (D) non-minor stroke in the two study periods. Errors bars are 95% confidence intervals

Overall, 19 patients in the first period and 8 in the second did not attend ED services; the proportion of patients assessed in the first 24h after stroke onset was similar in both cohorts, while brain imaging (CT/MRI) performed in the first 24h hours in these patients increased from 84.5% to 91.9% ($p<0.001$). In-patient admissions increased from 57.8% to 64.2% ($p<0.03$), including 18 patients in the first study and 42 in the second study who had a stroke while in hospital for another reason.

The degree of handicap has decreased in the second period, mainly shifting from severe (mRS>4) to moderate disability (1<mRS<5) (Figure 3(A)). Stroke case-fatality in the first 28 days decreased 37.9%, from 16.9% to 10.5%, and after adjustment 40% (95%CI, 23-53%). Overall there was a significant mRS decrease in the second period after adjusting for patient and stroke characteristics, that lost importance when the interaction of period with age was included in the model, indicating that the better outcome was achieved in

patients over 74 years compared to others (Table 5); moreover the overall higher level of disability of inpatients decreased in the second period. Figure 3(B) and (C) resumes these effects. Given there was non random missing data in pre-stroke disability in the first period (38 patients excluded from the previous analyses), we repeated the models using several inputting methods and the relative importance of these factors was not altered.

Table 3. Incidence rate ratios (2nd vs. 1st period) by gender and incidence rate ratios (men vs. women) by age in the two study periods for all stroke and non-minor stroke; period incidence rate ratio (2nd vs. 1st) and incidence rate ratios (men vs. women) by age for minor stroke

		All strokes (PG + GA)			Non minor stroke (PG + GA)			Minor stroke (P + GA)		
Gender		IRR 2^{nd} vs. 1^{st}	95% CI	P	IRR 2^{nd} vs. 1^{st}	95% CI	P	IRR 2^{nd} vs. 1^{st}	95% CI	P
Men		0.85	0.72-1.02	0.076	0.89	0.71-1.12	0.327			
Women		0.67	0.57-0.79	<0.001	0.62	0.51-0.75	<0.001			
All								0.79	0.65-0.96	0.017
Study period	Age-group	IRR* M vs. W	95% CI	P	IRR* M vs. W	95% CI	P	IRR M vs. W	95% CI	P
1st period	< 55	1.32	0.94-1.86	0.112	1.74	1.06-2.88	0.030			
	55-64	1.48	1.07-2.05	0.018	1.27	0.83-1.94	0.279			
	65-74	1.10	0.83-1.44	0.520	0.76	0.54-1.09	0.134			
	75-84	0.88	0.68-1.14	0.328	0.86	0.63-1.18	0.363			
	85+	0.72	0.51-1.02	0.068	0.69	0.46-1.02	0.065			
2nd period	< 55	1.69	1.22-2.32	0.001	2.53	1.57-4.08	<0.001			
	55-64	1.89	1.39-2.56	<0.001	1.84	1.23-2.74	0.003			
	65-74	1.40	1.09-1.80	0.009	1.11	0.80-1.53	0.536			
	75-84	1.12	0.90-1.41	0.314	1.25	0.95-1.66	0.111			
	85+	0.92	0.66-1.28	0.623	1.00	0.69-1.44	0.993			
All	< 55							1.09	0.72-1.68	0.676
	55-64							1.87	1.20-2.92	0.006
	65-74							2.04	1.39-3.01	<0.001
	75-84							0.92	0.64-1.33	0.656
	85+							0.62	0.28-1.37	0.242

Incidence rate ratio standardized to the 2011 Census population of Portugal

*The IRR for the second period are obtained from the values of the first multiplied by the ratio of the period IRR in men and women (0.85/0.67 for all stroke and 0.89/0.62 for non-minor stroke)

Table 4. Patient's characteristics, assessment and management in the two study periods

	1998-2001 (n=462)		2009- 2011 (n=721)		
	n	%	n	%	P value
Baseline					
Women	287	62.1	394	54.6	0.011
Median age (IQR), y	72 (63-81)		74 (61-83)		0.037
Men	69 (60-76)		69 (58-78)		0.742
Women	74 (65-83)		78 (68-85)		0.005
Prestroke disability (mRS >1)*	115	27.1	238	33.0	0.037
Hypertension	288	62.3	531	73.6	<0.001
Diabetes	125	27.1	192	26.6	0.872
Atrial fibrillation	64	13.9	154	21.4	0.001
Myocardial infarction/Angina	49	10.6	96	13.3	0.166
Hypercholesterolemia	175	37.9	336	46.6	0.003
Smoking habits					<0.001
Current smoker	78	16.9	117	16.2	
Former smoker	36	7.8	134	18.6	
No vascular risk factors†					<0.001
0	117	25.3	129	17.9	
1	200	43.3	276	38.3	
2	114	24.7	238	33.0	
3 or more	31	6.7	77	10.8	
Stroke characteristics					
Signs					
Coma	32	6.9	30	4.2	0.037
Motor deficit	324	70.1	528	73.2	0.246
Verbal deficit	116	25.1	171	23.7	0.586
Pathological type‡					<0.001
Ischemic stroke	348	75.3	610	84.6	
Primary intracerebral haemorrhage	78	16.9	88	12.2	
Subarachnoid haemorrhage	17	3.7	22	3.1	
Disabling stroke§	301	65.4	454	63.0	0.389
Assessment and management					
Delay onset to 1st assessment					0.511
< 3h	186	40.3	305	42.3	
3-24h	182	39.4	260	36.1	
> 24h	94	20.3	156	21.6	
Delay onset to CT/MRI<24h	311	67.3	519	72.0	0.087
Inpatient admission	267	57.8	463	64.2	0.027

mRS: modified Rankin Scale; *38 missings in the first study (6 in men and 32 in women); †No of vascular risk factors includes hypertension, diabetes, atrial fibrillation and myocardial infarction/angina; ‡The p value for comparing Ischemic stroke versus others; §28-day mRS > prestroke mRS and 28-day mRS >1

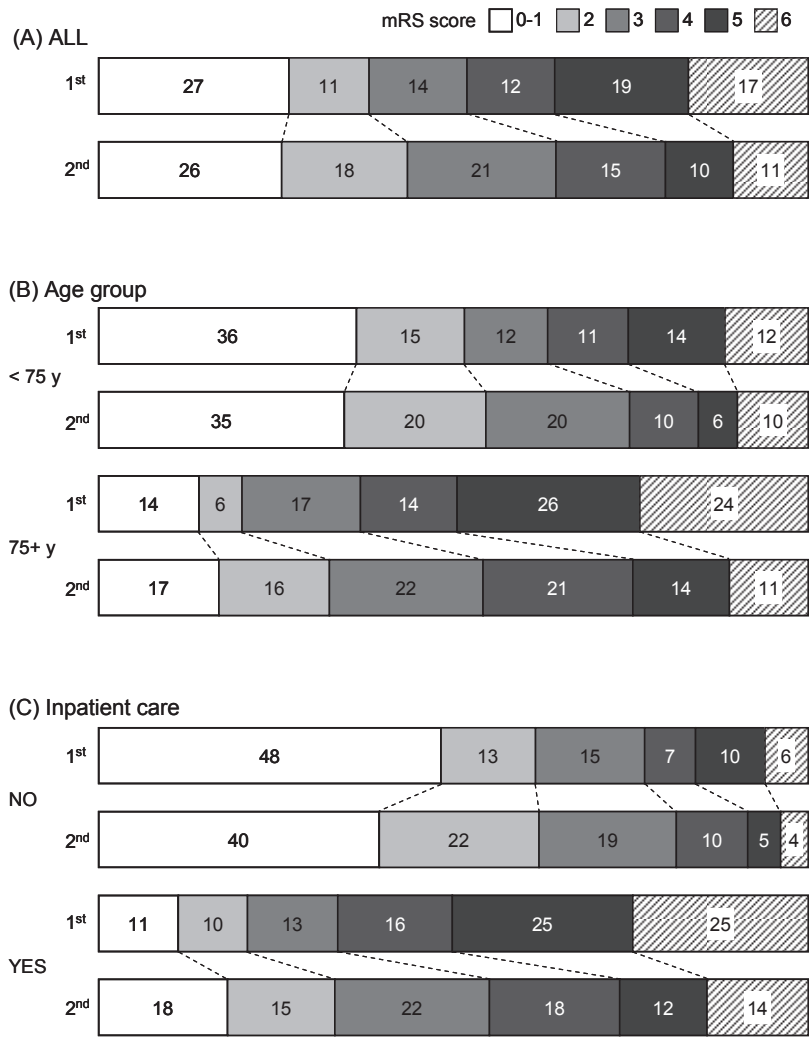

Figure 3. Distribution of modified Rankin Scale scores at 28-days, stratified by study period in (A) all patients, and according to (B) age and (C) inpatient care

Discussion

We have shown that from 1998 to 2011 the incidence of stroke in the metropolitan area of Porto decreased, with a higher decline in disabling strokes than in non-disabling strokes, particularly in strokes that resulted in a 28-day severe disability or death (mRS>3). Women compared to men contributed more for the decline in the incidence rates; in particular an incidence reduction of 62% compared with 21% in men in PICH that might be linked to a 66% reduction in fatal stroke compared to 28% in men. After adjustment for patient and stroke characteristics, the improvement in 28-day severity from 1998 to 2011 resulted from differences across study periods in the oldest patients and inpatient care, suggesting that these were the most important factors accounting for the better stroke outcome. The higher decrease in the incidence of disabling stroke in the second study resulted in a 40% reduction in case-fatality, results that might explain in part the 18.8%

reduction in mortality rate from 71.8 to 58.3 per 100,000 between 2006 and 2012 in Porto.[15-16]

Table 5. Coefficients of the linear regression models of the modified Rankin Scale scores on patients and stroke characteristics and management

	Model 1		Model 2		Model 3		Model 4	
	b	P	b	P	b	P	b	P
Baseline								
Age <65 y vs. others	- 0.23	0.061	- 0.24	0.048	- 0.29	0.015	- 0.28	0.016
Age >74 y vs. others	0.30	0.010	0.57	<0.001	0.56	<0.001	0.55	<0.001
Men vs. Women	- 0.05	0.606	- 0.06	0.518	- 0.07	0.431	- 0.04	0.607
Disable (mRS>1) vs. others	1.26	<0.001	1.25	<0.001	1.17	<0.001	1.19	<0.001
No vascular risk factors	0.24	<0.001	0.25	<0.001	0.19	<0.001	0.19	<0.001
Stroke signs (yes vs. no)								
Coma	2.66	<0.001	2.65	<0.001	2.44	<0.001	2.43	<0.001
Motor deficit	0.55	<0.001	0.55	<0.001	0.53	<0.001	0.55	<0.001
Verbal deficit	0.75	<0.001	0.74	<0.001	0.54	<0.001	0.53	<0.001
Stroke type								
Not ischemic vs. ischemic	0.90	<0.001	0.91	<0.001	0.63	<0.001	0.61	<0.001
Period (2nd vs. 1st)	- 0.30	<0.001	- 0.10	0.402	- 0.21	0.076	0.15	0.349
Period * Age >74 y			- 0.44	0.016	- 0.37	0.037	- 0.36	0.039
Management								
CT/MRI <24 h vs. others					- 0.06	0.501	- 0.05	0.569
Inpatient vs. others					0.99	<0.001	1.36	<0.001
Period * Inpatient							- 0.60	0.001

We do not think that the risk of FELS decreased because of under ascertainment of cases in the second period. We included in both studies all sources of information available at the respective time period and so we can rule out the possibility of a differential ascertainment bias. Indeed the proportion of patients ascertained by prospective methods (direct referrals and ED admissions) was similar, 83.8% in the first and 89.2% in the second period, as well as from discharge lists (4.8% and 5.7%, respectively). Other sources of information were different; the inspection of death certificates performed in the first study is now forbidden by law and we used the hospitals list of deceased patients to overcome this problem. Nevertheless from the 5.6% (26 patients) known by this mean in the first study, 16 would be identified at present in the computer-generated lists. As in the first study, few patients were referred from private hospitals, but that was to be expected because in Portugal the neurologists working (part-

time) in private hospitals work also in public hospitals and so it is not a matter of private/public care but of the physician involved. Moreover, even if the patient is examined at a private hospital, especially in case of severe stroke, he would be sent to a public hospital for further investigation and inpatient care. On the other hand the population in the second study had a unique identifier in a computer generated data-list, while in the first we had counts of the population registered with no possibility of record-linkage and so, if the residence and/or NHN identification was wrong/missing the linkage to the study population was not guaranteed; however in the first study there was an almost perfect geographic correspondence between the population registered and resident in the area. At present, in case of stroke, the emergency transport takes the patient to nearest hospital with a stroke unit while in the first study this was always the reference hospital. The computer-generated list of the population registered and the record linkage process implemented in the second study by means of the NHN is the ideal procedure to avoid wrong denominators, providing more accurate information on patient's clinical history, access to more comprehensive data sources and, a more reliable differential diagnosis. In this respect the first study was more prone to information bias, since previous medical history relied on patient's information and not always on clinical records. Nevertheless the possibility of bias may be diminished because the research team (R.M., M.C., M.C.S.) was the same and the same neurologist reviewed the information available for every patient; this was especially important since in the second study a considerable number of patients (152) were ascertained outside the reference hospital.

The age-gender interaction in incidence rates described in both periods, either for minor or non-minor strokes, with a higher risk of stroke in men than women in the youngest that disappears in the eldest, was reported in other studies with slight variations on the age at the turning point[17-18] The Framingham Heart study[19] was the only one reporting that after 85 years of age the pattern reversed, perhaps due to a high power for detecting the difference in the oldest. Several explanations were advanced for the attenuation of gender differences. Changes in the vascular risk profile in the decade after menopause, increasing the risk of stroke afterwards and/or a selective survival in men, since survivors to older ages may have different susceptibility to stroke than men who had a stroke when young.[18]

For non-disabling stroke this pattern holds irrespective of study period, and the IRR peaks in the 65-74 age-group, with men having a risk of stroke twice as high as women (Table 3). In this period of the life-span, retirement may have more adverse affects in men than women, and men may be more prone and alert to health problems than

women, since the homemaker role of women usually does not involve major differences in their life-style after retirement. On the other hand the gender-period interaction described for disabling strokes indicates that the risk of stroke in men compared to women has changed across the study periods, in men remained stable while in women decreased significantly.

In general the results in the two periods are in accordance to other studies concluding that the FELS occurs in women later in life compared to men.[20] The average age difference of 4-5 years reported was found in the first period, increasing to approximately 9 years in the second (78 vs. 69 years). Despite the increase of the age gap between women and men in the second period, the reduction of stroke risk was more striking in women, meaning that they have postponed the first-ever stroke and they managed to reduce the risk of disabling stroke, in particular the risk of PICH and disability/death as consequence of stroke (mRS>3) compared to men. This could be due to the progressive disappearance of the gender-gap in educational level,[21] and eventually to other social factors, including health awareness.[7]

Using standardized rates for the Segi world population[22] in other studies that compared stroke incidence across different time periods,[23-31] a decrease in incidence between 10% in Aucland[23] and 25% in Joinville[24] was estimated for a 10-year period; in Lund-Orup,[25-26] Tartu[23, 29] and Valley d'Aosta[30-31] the decrease was more marked in women (26.1%, 20% and 22%, respectively) and in Oxfordshire[23, 27] and Takashima[28] in men (16.4% and 22%, respectively). Case-fatality changes were more heterogeneous, ranging from a relative change of 2% in Oxfordshire to 78% in Dijon.[23] The decrease in stroke incidence was higher in Porto (27%), and the reduction of case-fatality (34%) followed that observed in Dijon, however in this study the methodology differed across study periods.[32] The period 1998 to 2011 in Portugal captures higher changes that would not be present if other periods were compared, and these changes may be linked to the implementation of population-based campaigns about stroke and vascular risk factors[7] and identification/treatment of VRF carriers. Indeed the increase in the prevalence of VRF in the second period reinforces this idea, namely the evolution of the recommended cut-off points in several measures (blood pressure and total cholesterol) for initiating therapy. A recent study comparing the prevalence of hypertension in 2003 and 2012 in Portugal concluded that it remained stable, but there was a relevant increase in the proportion taking antihypertensive medication (39% to 75%),[33] justifying the decreasing incidence of hemorrhagic stroke. Nevertheless, we cannot rule out the possibility of an artefact due to the more reliable methods for identifying VRF in the more recent registry. For other VRF, studies in our country showed that in the last years their prevalence remained stable or

increased,[34-35] while the proportion of former smokers more than doubled and it was higher than reported in 2007 for the Portuguese population.[36] Studies in other countries showed that looking at the 1980-2004 period[27] there was a substantial reduction in the prevalence of VRF and in a more recent period (1990-2008) there was an increasing trend in blood pressure levels followed by an increased use of medication for treatment of VRF.[37]

The better outcome in terms of disability/case-fatality across periods is a consequence of improvements towards oldest patients and inpatient care, after adjusting for patients profile and stroke signs and type. This evidences the impact of recent health measures directed to patients, as the organization of stroke units and Stroke Code pathways.[8] Moreover, optimal secondary prevention interventions restricted to younger patients in the first period are at present adopted in the elderly, showing that they even benefit more than the youngest patients.[38] Other studies reporting case-fatality changes, from the 80s/90s until the first years of the 21st century,[23-31] lower than in Porto, probably did not include recent advances in stroke prevention/care in that particular country.

In conclusion we may add that the “gender decline” in the risk of a first-ever stroke, particularly of hemorrhagic and disabling stroke, may be linked to social-cultural changes in the Portuguese population whose age-gender distribution is mirrored by that of Porto. Advances in the quality of inpatient care and primary/secondary prevention in the elderly contributed decisively for the better short-term outcome across the last decade.

Conflicts of interest statement

The authors have no conflicts of interests with respect to this work.

Acknowledgments

This work was supported by the Foundation for Science and Technology (grant number PIC/IC/82858/2007). The authors thanks to the director of the Northern Region Health Planning Department, and their fellow participants working in the Department of Neurology of Hospital de Santo António, the liaison neurologists in the others hospitals and, all general practitioners working in the health centers involved in this study. The authors also thank the Forensic Medical National Institute, National Institute of Medical Emergency, and the National Network for integrated long-term care for the information supplied. A special thank from the authors to the patients and their families.

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Supplemental data

Supplemental table. Deviances and goodness of fit test for Poisson Log-linear Models fitted to the expected number of incident strokes according to the Census 2011 population

Model	Degrees of freedom	All strokes			Non minor stroke			Minor stroke		
		Deviance	Goodness of fit P		Deviance	Goodness of fit P		Deviance	Goodness of fit P	
Null	19	1928.2	<0.001		1472.7	<0.001		533.8	<0.001	
One-factor Models										
Period	18	1905.7	<0.001		1454.9	<0.001		528.3	<0.001	
Gender	18	1928.1	<0.001		1470.8	<0.001		532.5	<0.001	
Age	15	62.6	<0.001		47.5	<0.001		43.0	<0.001	
Two-factor Models										
Period + Gender	17	1905.6	<0.001		1453.0	<0.001		526.9	<0.001	
PG	16	1901.5	<0.001		1447.0	<0.001		526.9	<0.001	
Period + Age	14	40.1	<0.001		29.7	0.008		37.5	0.001	
PA	10	35.6	<0.001		28.0	0.002		29.4	0.001	
Gender + Age	14	51.8	<0.001		43.7	<0.001		35.5	0.001	
GA	10	35.7	<0.001		28.8	0.001		19.6	0.033	
Three-factor Models										
P + G + A	13	29.3	0.006		25.9	0.018		29.9	0.005	
PG + A	12	25.2	0.014		19.8	0.071	(1)	29.9	0.003	
PA + G	9	24.8	0.003					22.4	0.008	
GA + P	9	13.2	0.154	(1)				14.1	0.120	(1)
PG + PA	8				17.3	0.027				
PG + GA	8	9.1	0.337	(2)	4.9	0.767	(2)	14.1	0.080	
PA + GA	5	8.7	0.123					6.5	0.261	(2)
PG + PA + GA	4	2.6	0.633	(3)	1.3	0.856	(3)	6.1	0.191	(3)

All strokes: (1) The simplest model that provided an adequate fit to the data is (GA + P); (2) this hierarchic model (PG + GA) improved significantly the fit of the previous model (chi-square=4.1, df=1, p<0.05) and the model (3) (PG + PA + GA) did not improve the fit (chi-square=10.6, df=5, p>0.05) - Final model PG + GA.

Non minor stroke: (1) The simplest model that provided an adequate fit to the data is (PG + A); (2) this hierarchic model (PG + GA) improved significantly the fit (chi-square=14.9, df=4, p<0.005) and the more complex model (3) (PG + PA + GA) also improved significantly the fit (chi-square=18.5, df=8, p<0.02) - Final model PG + GA (the simplest that improved the fit).

Conclusions: Both models are of partial independence, i.e., the interaction between Gender and Age (higher incidence rates for youngest men compared to women and no differences in the oldest age-groups) is similar in both study periods and the decline in incidence from 1998 to 2011 was higher in women compared to men, irrespective of age-group (Table 3).

Minor stroke: (1) The simplest model that provided an adequate fit to the data is (GA + P); (2) this hierarchic model (PA + GA) did not improve significantly the fit of the previous model (chi-square=7.6, df=4, p>0.1) as well as model (3) (PG + PA + GA), (chi-square=8.0, df=5, p>0.1) - Final model GA + P.

Conclusions: The interaction between Gender and Age (higher incidence rates for men compared to women for those aged 55 to 74 years and no differences in the other age-groups) is similar in both study periods and there was an overall decline in incidence from 1998 to 2011 (Table 3).

CONCLUSÕES

Nos capítulos anteriores (2-6) são apresentados cinco artigos que, naturalmente, apresentam uma discussão própria, onde se comparam os resultados encontrados com os descritos na literatura, discutem-se os pontos fortes e as limitações da investigação bem como as possíveis implicações em termos de saúde pública. Neste capítulo serão abordadas as principais conclusões resultantes desses artigos.

A comparação das taxas de incidência de AVC em diferentes regiões e países permite aumentar o conhecimento dos vários mecanismos etiológicos e dos meios de prevenção. Para possibilitar a comparação é necessário que os diferentes estudos utilizem as mesmas definições, a mesma metodologia e que apresentem essa informação de forma semelhante. Com o segundo projecto ACINrpc pretendeu-se registar todos os primeiros acidentes neurológicos na vida ocorridos no período compreendido entre 1 Outubro de 2009 e 30 de Setembro de 2011. Tal como no primeiro projecto, a metodologia adoptada seguiu de perto os critérios ideais definidos para a realização de estudos de incidência. Para além disso a metodologia foi adaptada à evolução na quantidade e armazenamento de informação clínica em bases de dados informatizadas.

No segundo projecto, a utilização de meios informáticos para efectuar a revisão das diferentes fontes de informação, garantiu uma maior fiabilidade na identificação dos

eventos ocorridos na população, ao contrário do primeiro, onde a revisão das fontes de informação decorreu manualmente, quase que exclusivamente, com recurso a fontes de informação em suporte físico (processos clínicos de doentes, boletins do serviço de urgência escritos, etc). Para além disso, a qualidade da informação clínica informatizada permitiu aferir, com maior clareza, se os eventos identificados correspondiam ao primeiro evento na vida, bem como confirmar muitos dos aspectos relacionados com os antecedentes clínicos do doente, principalmente a presença de factores de risco vascular. Por outro lado, ambos os projectos ACINrpc permitiram demonstrar a importância da inclusão e seguimento dos episódios neurológicos transitórios nos estudos de incidência de AVC.

O primeiro estudo permitiu concluir que o padrão etário na incidência de AVC marca a diferença entre populações rurais e urbanas, com um maior risco para os mais novos no meio urbano e para os mais velhos no meio rural. No entanto, a ruralidade não está associada com o prognóstico a longo prazo, o que pode ser explicado pela menor prevalência dos factores risco associados ao AVC no meio rural e pelo facto de não haver diferenças no tratamento e gestão dos doentes. Com o seguimento a longo prazo, foi também possível concluir que o nível de incapacidade aos três meses é um bom indicador do prognóstico a longo prazo dos doentes com AVC Isquémico, quer em termos de sobrevivência quer em termos de incapacidade. Este conhecimento, para além de permitir informar melhor os doentes com AVC e os seus familiares, tem implicações no planeamento dos serviços de saúde, nomeadamente na avaliação custo/beneficio dos tratamentos na fase aguda e na organização de unidades de reabilitação dirigidas para o doente com AVC.

O conhecimento dos factores que aumentam o risco de sofrer um AVC é amplo, ao contrário dos factores que o podem desencadear (despoletar). Com o estudo realizado no Porto, foi possível concluir que existe uma associação entre a temperatura ambiental e a ocorrência de AVC e sua gravidade. Ressalta também da análise a importância do tipo patológico de AVC, bem como o subtipo de AVC Isquémico, na interpretação destas associações, pois os mecanismos etiológicos subjacentes são diferentes. Para além disso, não é só a intensidade da exposição que interessa mas também a duração da mesma. Os serviços de emergência devem ter presente que determinadas condições meteorológicas podem contribuir quer para um aumento do número de episódios quer para uma maior gravidade dos mesmos.

Com o estudo realizado na cidade do Porto, podemos concluir que o declínio da mortalidade por AVC pode ser explicado, em parte, pela diminuição na incidência e pela melhoria na incapacidade pós-AVC decorrente das gestão dos doentes mais velhos e

tratamento durante o internamento. Para esta diminuição da incidência contribuiu predominantemente a diminuição do risco nas mulheres, em particular, do risco do AVC incapacitante e de AVC hemorrágico. Como referido noutros estudos, parece estar subjacente a este facto as mudanças socioculturais ocorridas entretanto na população portuguesa. Os avanços na qualidade dos cuidados no internamento (unidades de AVC) e a prevenção primária/secundária nos mais velhos contribuíram para uma melhoria no prognóstico destes doentes nos últimos anos.

Perspectivas de investigação futura

Os registos organizados no âmbito dos projectos ACINrpc constituem uma valiosa base de informação quer para a investigação actual quer para investigações futuras no âmbito do AVC ou dos acidentes neurológicos. Num futuro próximo, com o objectivo de comparar a evolução das taxas de incidência entre o meio urbano e o rural, será estudada a evolução das taxas de incidência no meio rural, recorrendo a uma metodologia de análise análoga à utilizada para medir o declínio da incidência no meio urbano. De igual modo, e dada a importância do AIT, será estudada a evolução da incidência destes eventos, comparando o meio urbano com o meio rural.

Com o propósito de verificar se as associações com os parâmetros meteorológicos se mantém, após todos os desenvolvimentos recentes na prevenção e tratamento do AVC, será possível replicar o estudo realizado, utilizando para o efeito a informação recolhida durante os dois períodos (1998-2000 e 2009-2011). Em função da maior dimensão amostral, o estudo poderá ser alargado no sentido de compreender como é que estas associações variam com as diferentes etiologias do AVC isquémico.

Antes da utilização da trombólise no tratamento do AVC na fase aguda, colocava-se pouco ênfase na rapidez e precisão de um diagnóstico de AVC. Mas para a trombólise ser eficaz é necessário que o doente procure e chegue atempadamente à instituição de saúde após o início dos sintomas. Com a informação do segundo estudo ACINrpc será possível estudar o prognóstico dos doentes com AVC em função do percurso que este realiza nas instituições de saúde. Em particular, será possível estender a caracterização dos doentes que utilizaram a Via Verde do AVC aos dois anos do estudo.

A médio prazo, com o seguimento dos doentes do segundo estudo, será possível comparar o prognóstico a longo prazo dos dois coortes de doentes, para analisar até que ponto as melhorias observadas no curto prazo se repercutem no longo prazo.

ANEXO I

AVALIAÇÃO DA VIA VERDE DO ACIDENTE VASCULAR CEREBRAL NO NORTE DE PORTUGAL: CARACTERIZAÇÃO E PROGNÓSTICO DOS UTILIZADORES

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Acta Medica Portuguesa, 2013;26:113-122

Avaliação da Via Verde do Acidente Vascular Cerebral no Norte de Portugal: Caracterização e Prognóstico dos Utilizadores

A Community-Based Study of Stroke Code Users in Northern Portugal

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Acta Med Port 2013 Mar-Apr;26(2):113-122

RESUMO

Introdução: Em 2002 Portugal detinha uma das mais altas taxas de mortalidade por doenças cerebrovasculares entre os países europeus. Várias estratégias foram adoptadas para melhorar a prevenção da doença e o seu tratamento na fase aguda, entre as quais a criação da Via Verde do Acidente Vascular Cerebral. O objectivo deste trabalho é descrever a utilização e resultados desta estratégia no contexto de um registo prospectivo comunitário na Região Norte de Portugal.

Material e Métodos: Foram registados todos os AVCs ocorridos entre 1 de Outubro de 2009 e 30 de Setembro de 2010 nos utentes inscritos no agrupamento de centros de saúde do Porto Ocidental e nos de Mirandela e Vila Pouca de Aguiar. Para a detecção de casos utilizaram-se múltiplas fontes de informação: notificação via WEB, *e-mail*, Alerta P1 e pesquisas sistemáticas em registos disponibilizados pelas entidades envolvidas - urgências hospitalares, listas de altas, procedimentos de diagnóstico, óbitos, Via Verde do Acidente Vascular Cerebral e serviço de atendimento de situações urgentes.

Resultados: Ocorreram 600 AVCs em 241 000 habitantes (taxa de incidência de 250 / 100 000), dos quais 434 foram primeiros na vida (180 / 100 000). Foram registados 72 acessos à Via Verde do Acidente Vascular Cerebral, dos quais 66,7% foram diagnosticados como AVC. Considerando os quatro critérios de activação (idade ≤ 80 anos, independência funcional, sinais/sintomas do AVC e tempo após episódio ≤ 3 horas), só 15,9% dos doentes a poderiam utilizar e, dos utilizadores, apenas 56,3% satisfaziam esses critérios. Dos doentes com critérios de activação, foram internados 96,3% pela VV pré-hospitalar, 83,3% pela VV intra/inter-hospitalar e 64,0% dos restantes; a fibrinólise foi realizada em 77,3%, 36,4% e 17,4% dos doentes com enfarte cerebral, respectivamente. O Rankin pós-AVC é mais grave nos utilizadores da VV pré-hospitalar (70,3% vs. 35,3%), mas estes apresentam mais assiduamente os três sinais/sintomas de AVC (44,4% vs. 16,2%). Ajustando para a idade, sexo e número de sinais, o risco de incapacidade grave pós-AVC não é significativamente diferente no acesso pela VV pré-hospitalar (RP = 2,9; IC 95%: 0,8 - 10,2), bem como a taxa de letalidade.

Conclusões: Os critérios para activação da Via Verde do Acidente Vascular Cerebral são muito restritivos. Embora esta seja mais vezes accionada em situações clínicas graves, a proporção de doentes que realizou fibrinólise é relativamente alta em comparação com outros estudos.

Palavras-chave: Acidente Vascular Cerebral; Portugal.

ABSTRACT

Introduction: By 2002 Portugal had one of the highest mortality rates due to cerebrovascular diseases among the European Countries. Meanwhile, several strategies have been adopted to improve prevention and treatment in the acute phase, amongst which the Stroke Code. The purpose of this study is to describe how this measure has been used and its outcome as part of a prospective community based study of stroke/TIA incidence in Northern Portugal.

Materials and Methods: Between 1st October 2009 and 30th September 2010 all strokes occurred in patients registered at Western Porto, Mirandela and Vila Pouca de Aguiar health centres have been recorded. For cases ascertainment multiple sources of information were used, including the WEB, letter, e-mail and Alert P1, as well as systematic searches on databases provided by the entities involved in this study: hospital emergency, discharge records, diagnosis procedures, death certificates, Stroke Code admissions and health centre emergency records.

Results: Six hundred strokes were recorded in a population of 241 000 (incidence rate of 250 / 100 000 person-years) and 434 were first-ever-in-the-lifetime (180 / 100 000). There were 72 Stroke Code calls and in 66.7% of them a stroke was confirmed. Considering the criteria for Stroke Code call (age ≤ 80 years, functional independency, the stroke signs/symptoms, and time after episode ≤ 3 hours), only 15.9% patients "could" have access to it. Of those who used the Stroke Code, only 56.3% fulfilled the criteria. Considering all patients fulfilling Stroke Code criteria, 96.3% that used prehospital Stroke Code were inpatients, as well as 83.3% that used intra/interhospital Stroke Code and 64.0% of the remainder; this trend is also present in patients with ischaemic stroke submitted to fibrinolysis, 77.3%, 36.4% and 17.4%, respectively. A high post-stroke Rankin was more frequent among Stroke Code users (70.3% vs. 35.3%), but they exhibit more often the three stroke signs/symptoms (44.0% vs. 16.2%). After adjusting for age, sex and number of signs, the risk of a more severe post-stroke Rankin is not significantly different among patients using the prehospital Stroke Code (OR = 2.9, 95% CI: 0.8 - 10.2).

Conclusions: The criteria for accessing the Stroke Code are currently restrictive. Though the Stroke Code is accessed in case of more severe patient's conditions, the proportion of patients treated with fibrinolysis is relatively high in comparison with other studies.

Keywords: Stroke; Portugal; Emergency Medical Services.

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Recebido: 24 de Julho de 2012 - Aceite: 05 de Fevereiro de 2013

INTRODUÇÃO

O primeiro registo prospectivo de acidentes neurológicos na comunidade (ACINrpc) realizado uma década atrás[1] obedeceu aos critérios metodológicos ideais para o cálculo da incidência do primeiro Acidente Vascular Cerebral na vida e respectiva taxa de letalidade,[2] permitindo concluir que em Portugal, particularmente na Região Norte, a taxa de incidência era uma das mais altas dos países europeus, 305 e 269 por 100 000 pessoas-ano (202 e 173 padronizadas para a população europeia), respectivamente em áreas rurais e urbanas. A taxa de letalidade aos 28 dias (16,1%) foi semelhante à dos outros países, embora nas estatísticas oficiais da Direcção Geral de Saúde a taxa de mortalidade padronizada fosse de 154 / 100 000, uma das mais altas dos países da Europa Ocidental.[3]

Utilizando dados da Organização Mundial de Saúde (OMS) referentes a 2002, Portugal detinha ainda uma das taxas de mortalidade mais altas entre os países pertencentes ao grupo A (taxas de mortalidade infantil e em adultos muito baixas) estimando-se que a taxa anual de variação para o período de 1990 - 2006 seria das mais baixas.[4] No mesmo período Portugal tem um valor alto extremo na taxa de mortalidade e o mais alto nos anos de vida ajustados à incapacidade (DALYs) por doença cerebrovascular entre os países de mais alto rendimento.[5] Desde então foram implementados avanços consideráveis ao nível da intervenção no AVC com o objectivo de alterar o seu *peso* na comunidade, reflectido não só na incidência, mas também em indicadores de mortalidade e anos de vida com incapacidade.

A tendência decrescente nas taxas de mortalidade em Portugal continental e Região Norte[6] em particular, que em 2006 eram respectivamente 80,7 e 81,4 por 100 000, pode resultar da diminuição da incidência e/ou da intervenção terapêutica com repercussões na taxa de letalidade. A eficácia desta intervenção depende da organização e acessibilidade dos serviços de saúde, mas também do alerta da população para os sinais/sintomas do Acidente Vascular Cerebral (AVC), para que seja cumprida a janela terapêutica das três horas.[7] Uma das estratégias adoptadas nas fases pré, intra e inter-hospitalar foi o programa Via Verde do AVC (VVAVC).[7] O objectivo principal foi o diagnóstico preciso e atempado para um tratamento adequado e teve por base a organização da emergência pré e intra-hospitalar e o alerta da população para os principais sinais/sintomas do AVC. Neste sentido, foi iniciada em 2008 em Portugal, a campanha *Seja mais rápido que o* AVC, dando ênfase ao aparecimento súbito de três sinais/sintomas (*falta de força num braço*, *boca ao lado* e *dificuldade em falar*) e procedimento correcto caso aconteçam - contacto imediato com Instituto Nacional de Emergência Médica (INEM/112), com a consequente activação da Via Verde externa ou pré-hospitalar (VVE).[8]

Uma década após o primeiro estudo ACINrpc está a

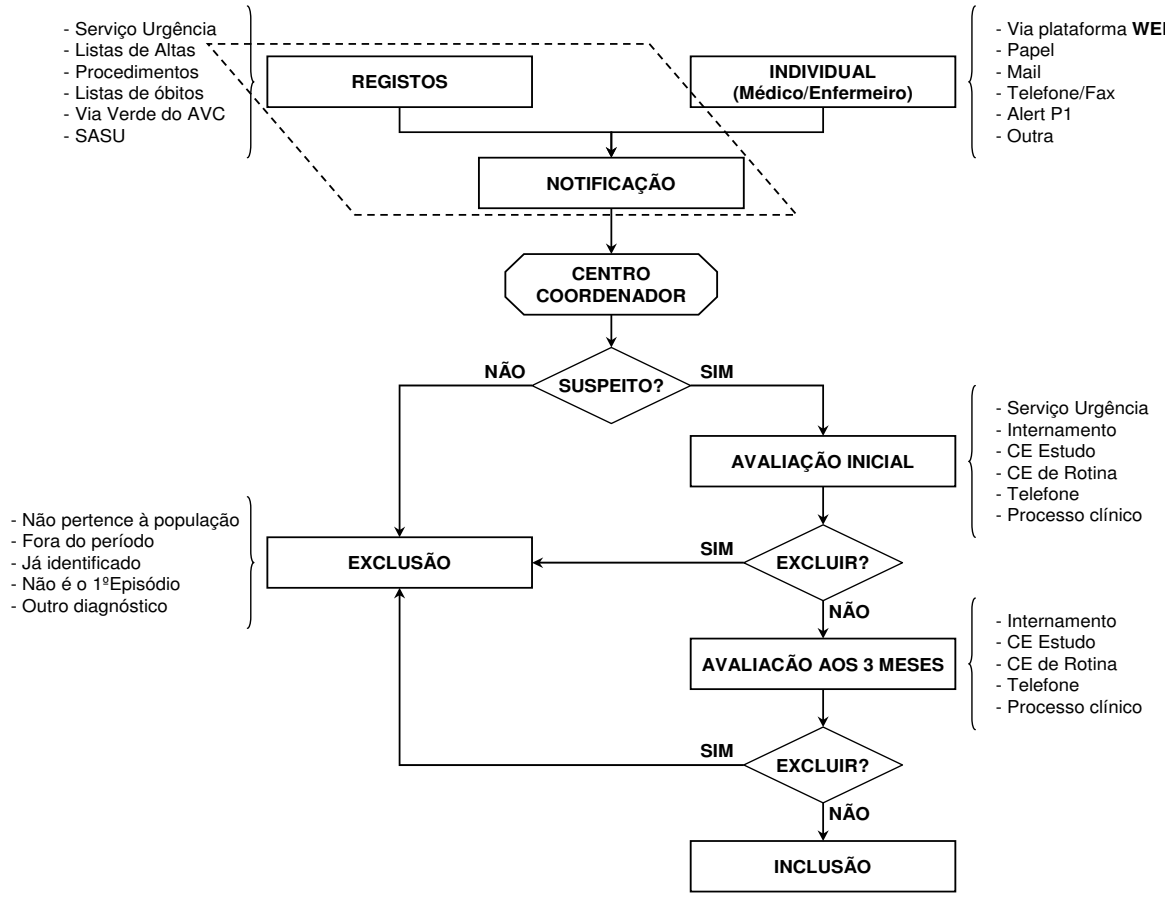


Figura 1 - Metodologia de detecção e inclusão dos casos.

decorrer, na Região Norte, o projecto ACIN2 – Tendência da incidência e prognóstico dos acidentes neurológicos (PIC/IC/82858/2007), no qual são registados os acidentes neurológicos no período compreendido entre 1 Outubro de 2009 e 30 de Setembro de 2011 (http://www.acin2.com). Utilizando os dados do primeiro ano deste estudo, o objectivo deste trabalho é caracterizar os utilizadores e circunstâncias de utilização da VVAVC no Norte de Portugal. Em particular, determinar o perfil sócio-demográfico e clínico associado a esta utilização e o prognóstico dos utilizadores.

MATERIAL E MÉTODOS

Neste estudo comparam-se as características na *baseline*, nomeadamente o acesso a cuidados médicos, dos doentes incluídos num estudo de incidência de AVC obedecendo aos critérios metodológicos ideias definidos por Sudlow and Warlow[2] e actualizados mais tarde por Feigin and Carter,[9] nomeadamente um plano prospectivo com uma procura extensiva dos casos usando fontes de informação múltiplas em populações enumeráveis e estáveis com dimensão adequada, que são seguidos por um período de um mês para aferir o estado vital.

A base comunitária do estudo é a população inscrita em Setembro de 2009 no Agrupamento de Centros de Saúde (ACES) do Porto Ocidental e nos Centros de Saúde de Vila Pouca de Aguiar e Mirandela. Foi pedida autorização e colaboração à Administração Regional de Saúde do Norte, de modo a ter acesso ao registo informatizado de base populacional. Seguidamente, o estudo foi apresentado a todos os directores dos centros de saúde envolvidos, tendo sido referida e explicada a utilização do endereço http://www.acin2.com, onde todos os médicos e enfermeiros poderiam preencher um formulário simples para notificar de forma anónima os doentes *suspeitos*, após obtenção do seu consentimento. O estudo foi divulgado junto dos médicos bem como da população abrangida, utilizando os media e reuniões cientificas.

Detecção dos casos de acidentes neurológicos

A plataforma WEB é a principal fonte de informação e a mais expedita para que o doente seja rapidamente observado pela equipa de neurologia adstrita ao projecto nos vários hospitais envolvidos. No entanto a notificação pode ainda ser feita por carta, telefone/fax, *e-mail* ou pelo Alert P1 (Fig. 1).

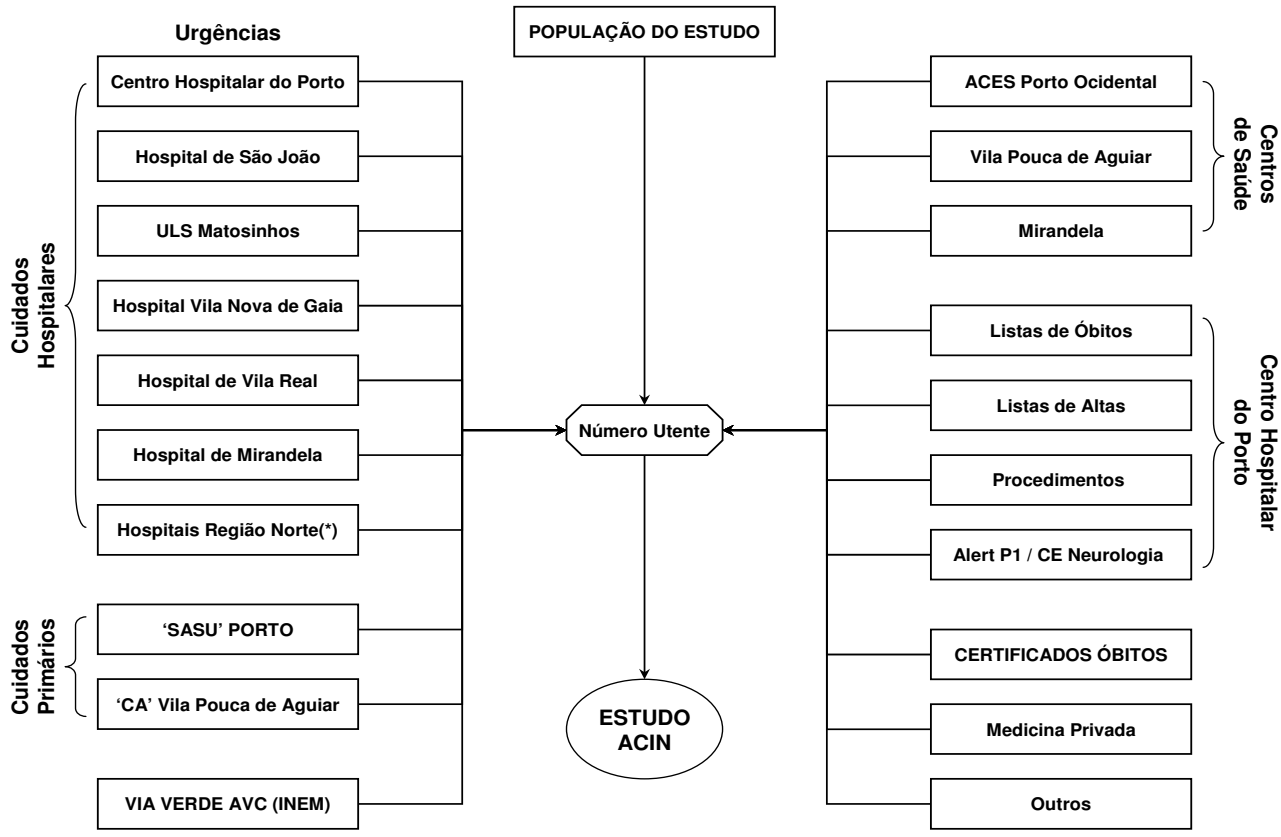
Para a identificação dos casos suspeitos recorreu-se também a pesquisas sistemáticas nos diferentes tipos de registos disponibilizados pelas entidades envolvidas - urgências hospitalares, listas de altas (códigos 430 - 438, 342 e 781), listas de óbitos, VVAVC, serviço de atendimento de situações urgentes (SASU) e listas de procedimentos de diagnóstico. O recurso a estes registos é efectuado no sentido de minimizar a possibilidade de se perderem casos que não tenham sido notificados por outra via (Fig. 2).

A informação referente aos episódios em que a VVE foi activada consta de uma listagem fornecida mensalmente pelo INEM. A VVE consiste num trajecto optimizado em termos de acessibilidade e rapidez de tratamento, que tem por base a chamada telefónica pelo cidadão para o número de emergência médica (112). Para que seja activada é necessário que o doente preencha cumulativamente os seguintes critérios: (a) idade inferior a 80 anos, (b) instalação súbita de pelo menos um dos sintomas *boca ao lado*, *falta de força num dos membros, principalmente num braço* e *dificuldade em falar*, (c) sinais ou sintomas com menos de três horas de evolução e (d) não ter dependência prévia.[7] Verificados estes critérios, é accionado o protocolo designado por VVE que transmite instruções para o transporte via INEM, envolvendo-o directamente no diagnóstico, eventual tratamento pré-hospitalar e adequado encaminhamento para o hospital com as melhores condições de confirmação do diagnóstico, tratamento subsequente e disponibilidade logística para a recepção do doente. Foi feita a ligação dos episódios/utentes da VVE à população do estudo. Quando o doente procura directamente o hospital, pode activar-se a VV intra/inter-hospitalar (VVI), um sistema de assistência intra-hospitalar que facilita de igual modo a terapêutica fibrinolítica, com a minimização do *tempo porta-agulha*.[7] Considerou-se que a VVI foi activada quando esta informação constava dos registos dos episódios de urgência.

Critérios de inclusão no estudo

Foram incluídos todos os AVCs registados entre 1 de Outubro de 2009 e 30 de Setembro de 2010, tendo sido adoptada a definição de AVC da Organização Mundial de Saúde (OMS).[10] Os episódios transitórios (défices permanecendo menos de 24 horas) e as lesões assintomáticas ou *enfartes silenciosos* detectados imagiologicamente foram excluídos. O AVC é classificado como: enfarte cerebral (EC) quando a tomografia computarizada (TC) e/ou ressonância magnética (RM) realizada nos 30 dias após o episódio evidencia um enfarte ou nenhuma lesão relevante e/ou autópsia com evidência de lesão; hemorragia intracerebral primária (HICP) quando a TC e/ou RM realizada nos 30 dias após o AVC evidencia a hemorragia e/ou autópsia com evidência de lesão; hemorragia subaracnoideia (HSA) na existência de história clínica apropriada e/ou TC ou RM cerebral evidencia sangue subaracnoideo e/ou a punção lombar mostra sangue subaracnoideo e/ou angiografia cerebral mostra fonte de hemorragia subaracnoidea e/ou autopsia mostrando hemorragia subaracnoidea com ou sem fonte de HSA.[11] Considerou-se AVC recorrente um novo episódio ocorrendo 28 dias após o inicial ou, se antes deste período envolve um território vascular ou anatómico diferente, conforme se trate de um EC ou HICP, respectivamente.

Todos os casos suspeitos foram observados pela equipa de neurologistas o mais depressa possível após o episódio, e para os doentes incluídos foi preenchido um protocolo com informação sócio-demográfica, acesso (VVE, VVI ou outra), modo de acesso (transporte), circunstâncias e modo de início e informação clínica referente ao episódio, procedimentos de diagnóstico, diagnóstico e tratamentos



(*) Nomeadamente os hospitais que também pertencem aos centros hospitalares em que se encontram inseridos os hospitais de Vila Real e Mirandela

Figura 2 - Fontes de informação com registos de casos suspeitos.

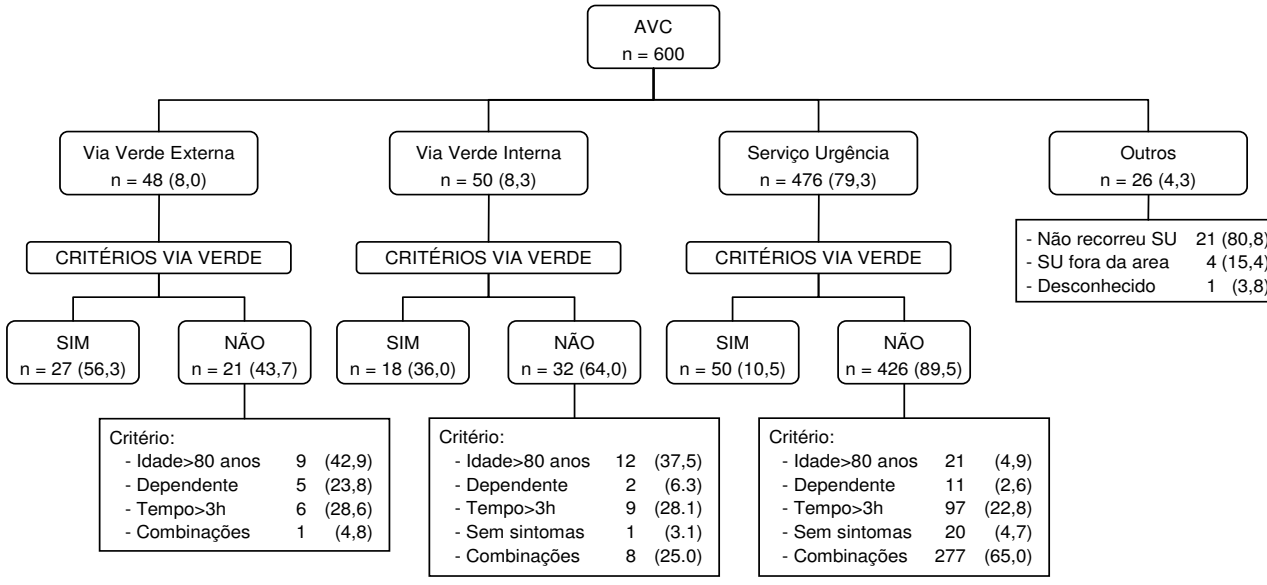


Figura 3 - Utilização da Via Verde do AVC segundo os critérios de activação (%).

subsequentes. Foi registado a pontuação na escala Rankin modificada, pré e pós-AVC,[12,13] bem como a data/hora de todos os procedimentos realizados. A informação foi fornecida pelo doente e/ou consta do respectivo processo clínico. O estudo foi aprovado pela comissão de ética das instituições de saúde onde o estudo decorreu, assinando todos os participantes o *consentimento informado* e, em caso de incapacidade, este foi dado por um parente presente na altura do episódio.

Tabela 1 - Características dos 72 utilizadores da Via Verde externa

Idade média (dp), anos	65,2	(16,2)
Tempo médio (dp) de acesso SU, minutos†	82,3	(44,5)
	n	**%**
Homens	38	52,8
Hospitais da Região Norte		
Centro Hospitalar do Porto	43	59,7
Hospital de São João	11	15,3
Hospital Pedro Hispano	3	4,2
Centro Hospitalar de Vila Nova de Gaia/Espinho	3	4,2
Centro Hospitalar do Nordeste	5	6,9
Centro Hospitalar de Trás-os-Montes e Alto Douro	7	9,7
Sinais		
"Falta de força num dos membros"	50	69,4
"Boca ao lado"	30	41,7
"Dificuldade em falar"	36	50,0
Sem critérios	26	36,1
Dependência prévia	1	3,8
Tempo > 3h	2	7,7
Idade > 80 anos	8	30,8
Nenhum dos sinais	13	50,0
Dois ou mais	2	7,7
Diagnóstico de admissão		
AVC/AIT	49	68,0
Alterações estado de consciência	5	6,9
Crises epilépticas/convulsões	4	5,6
Enxaqueca com aura	1	1,4
Outros	13	18,1

†Média e desvio padrão; ‡Registado pelo CODU (Centro de Orientação de Doentes Urgentes); § Dois dos utilizadores não cumpriam dois dos critérios.

Métodos estatísticos

Procedeu-se à comparação dos episódios de AVC ocorridos em utilizadores e não utilizadores da VVAVC, utilizando o teste do qui-quadrado ou teste exacto de Fisher (variáveis categóricas) e o teste t-student (variáveis contínuas), determinando-se em seguida as características subjacentes à utilização da VVAVC descritas pela razão de possibilidades (RP) e respectivo intervalo de confiança a 95% (IC 95%). Descrevem-se os critérios subjacentes à activação da VVAVC, comparando-se, em seguida, as características e prognóstico dos utilizadores da VVE, VVI e restantes doentes com critérios de activação, eliminando por restrição o efeito de variáveis confundidoras. Foi utilizada a regressão logística para avaliar o prognóstico em função do Rankin pós-AVC agrupado em incapacidade moderada (1 - 3) e incapacidade grave (4 - 5) para utilizadores e não utilizadores da VVE, ajustando para a idade, sexo e diagnóstico. Adoptou-se um valor de $p < 0,05$ como limite do erro tipo I.

RESULTADOS

A população do estudo é constituída por 241 000 utentes registados em Setembro de 2009 no ACES do Porto Ocidental (n = 194 200) e centros de saúde de Vila Pouca de Aguiar (n = 16 200) e Mirandela (n = 30 600). No período de estudo foram incluídos 600 episódios de AVC, dos quais 434 (72,3%) foram primeiros na vida, correspondendo a uma taxa de incidência de 250 por 100 000 pessoas-ano. Considerando o primeiro AVC na vida esta taxa é de 180 / 100 000, 175 na área urbana e 203 na área rural. Durante o mesmo período foram registados 1 380 episódios atendidos no âmbito da VVE na Região Norte, dos quais 72 da população do estudo, o que corresponde a uma taxa de activação de 30 / 100 000 habitantes. A idade média dos utilizadores foi de 65,2 anos e 52,8% eram homens; 59,7% foram encaminhados para o Hospital de Santo António, 16,6% para os hospitais que servem a população rural (Centro Hospitalar do Nordeste e Centro Hospital de Trás-os-Montes e Alto Douro) e os restantes para outros hospitais na região norte (Tabela 1). O sintoma mais frequente foi a *falta de força* (69,4%), seguido da *dificuldade em falar* e *boca ao lado* (41,7%); o tempo decorrido entre o aparecimento destes e a chegada ao SU foi, em média, de 82 minutos. Não teriam critérios de activação da VVE 36,1% dos doentes e no SU foram diagnosticados 68% como AVC/AIT (Acidente Isquémico Transitório).

No registo ACIN, foram incluídos 48 destes doentes com diagnóstico definitivo de AVC, e na Tabela 2 comparam-se as suas características com as dos restantes doentes. A idade média dos doentes registados foi de 72,8 anos, 47,3% são homens e 78% residem em meio urbano, características não significativamente diferentes nos utilizadores

Tabela 2 - Caracterização dos doentes com AVC, utilizadores e não utilizadores da Via Verde externa

	Via Verde externa (*n* = 48)		Outros (*n* = 552)		Total (*n* = 600)		*P*
Idade média (dp), anos	68,2	(11,8)	73,2	(13,8)	**72,8**	**(13,7)**	0,014
	n	%	n	%	**n**	**%**	
Homens	27	56,3	257	46,6	**284**	**47,3**	0,2
Meio urbano	41	85,4	427	77,4	**468**	**78,0**	0,2
Rankin prévio							0,005
Assintomático	34	70,8	227	43,0	**261**	**45,3**	
Sintomas não incapacitantes	7	14,6	80	15,2	**87**	**15,1**	
Incapacidade ligeira	4	8,3	83	15,7	**87**	**15,1**	
Incapacidade moderada	1	2,1	93	17,6	**94**	**16,3**	
Incapacidade moderadamente grave	1	2,1	32	6,1	**33**	**5,7**	
Incapacidade grave	1	2,1	13	2,5	**14**	**2,4**	
Desconhecido			24				
Transporte em ambulância	48	100,0	252	45,7	**300**	**50,0**	
Tempo entre episódio e SU < 3h	41	85,4	192	34,8	**233**	**38,9**	0,001
Sinais							
"falta de força num dos membros"	46	95,8	323	58,5	**369**	**61,5**	0,001
"boca ao lado"	47	97,9	312	56,5	**359**	**59,9**	0,001
"dificuldade em falar"	24	50,0	116	21,0	**140**	**23,3**	0,001
Com os três sinais	23	47,9	75	13,6	**98**	**16,3**	0,001
1º AVC na vida	40	83,3	394	71,4	**434**	**72,3**	0,08†
Isquémico	29	72,5	333	84,5	**362**	**83,4**	0,08‡
Hemorrágico	11	27,5	58	14,7	**69**	**15,9**	
Desconhecido	-		3	0,8	**3**	**0,7**	
AVC recorrente	8	16,7	158	28,6	**166**	**27,7**	
Isquémico	5	62,5	130	82,3	**135**	**81,3**	0,2‡
Hemorrágico	2	25,0	24	15,2	**26**	**15,7**	
Desconhecido	1	12,5	4	2,5	**5**	**3,0**	
Internamentos	45	93,8	316	57,2	**361**	**60,2**	0,001
AVC isquémico§	32	94,1	246	53,1	**278**	**55,9**	0,001
AVC hemorrágico§	12	92,3	66	80,5	**78**	**82,1**	0,3

†Média e desvio padrão; ‡comparação do 1º AVC na vida com AVC recorrente; §comparação do diagnóstico; ¶percentagem sobre o total de AVC desse tipo.

da VVE. A maioria dos doentes que acederam à VVE estavam assintomáticos ou com sintomas não incapacitantes antes do episódio, em contraste com os restantes (85,4% *vs*. 58,2%). Globalmente, o transporte por ambulância foi usado por 50% dos doentes; 85,4% dos utilizadores da VVE chegaram dentro da janela terapêutica, descendo esta proporção para 34,8% nos restantes.

A discriminação entre utilizadores da VVE e restantes é manifesta na proporção que apresenta cumulativamente os três sinais de AVC, 47,9% *vs*. 13,6%, e mais de 95% apresentam os sinais mais característicos - *falta de força* e/ou *boca ao lado*. Globalmente, 72,3% dos doentes tiveram o primeiro AVC na vida, sendo a proporção de AVCs isquémicos ligeiramente superior nestes (83,4% *vs*. 81,3%), independentemente do acesso ser a VVE. A proporção de utentes da VVE internados é muito superior (93,8%) à dos restantes (57,2%), particularmente quando o AVC é isquémico (94,1% *vs*. 53,1%). De notar que 26,3% dos doentes internados utilizaram o acesso pela Via Verde (45 pela VVE e 50 pela VVI). Os determinantes de utilização da VVE entre as características sócio-demográficas e sintomatologia, foram a idade e o número de sintomas, diminuindo 4% por um aumento unitário na idade (RP = 0,96; IC 95%: 0,94 - 0,98) e quintuplicando por cada sintoma adicional (RP = 5,0; IC 95%: 3,0 - 8,4). (Tabela 2).

Na Fig. 3 está descrito o acesso aos cuidados de saúde após um AVC, nomeadamente a activação da VVE ou VVI, serviço de urgência sem VVAVC ou outro. Considerando cumulativamente os quatro critérios de utilização da VVAVC, só 95 (15,9%) doentes a poderiam utilizar e, dos que utilizaram a VVE (8%), apenas 56,3% satisfaziam esses critérios. Globalmente a janela terapêutica (112 / 574 =

19,5%) e a idade superior a 80 anos (42 / 574 = 7,3%) são os critérios que isoladamente impediriam mais frequentemente a utilização da VVAVC.

Dos não utilizadores da VVAVC, 426 (89,5%) não reuniam critérios de activação e destes 97 (22,8%) não seriam eventuais candidatos apenas porque não chegariam dentro da janela terapêutica e 21 (4,9%) apenas pelo critério da idade.

Restringindo a comparação aos doentes com critérios de activação da VVAVC, pode observar-se na Tabela 3 que as características sócio-demográficas, período de atendimento e tempo médio de acesso não são significativamente diferentes nos utilizadores da VVE, VVI ou não utilizadores. A *falta de força* é o sintoma mais frequente (87,4%), seguido da *boca ao lado* (83,2%) e *dificuldade em falar* (31,6%). Nenhum doente na VVI apresenta cumulativamente os três sintomas, em comparação com 22,0% dos não utilizadores e 44,4% dos utilizadores da VVE. Cerca de 76,8% dos doentes são internados, proporção muito superior (96,3%) na VVE, decrescendo na VVI (83,3%) e não utilizadores (64,0%). Esta tendência é também manifesta nos doentes com AVC isquémico que fazem fibrinólise (77,3%, 36,4%

Tabela 3 - Caracterização e prognóstico dos doentes com critérios de activação da Via Verde do AVC

	Via Verde Externa		**Via Verde Interna**		**Não Via Verde**		**Total**		
	(*n* = 27)		**(*n* = 18)**		**(*n* = 50)**		**(*n* = 95)**		***P***
Caracterização									
Idade média (dp), anos	64,2	(9,6)	61,9	(11,6)	64,4	(9,9)	**63,9**	**(10,1)**	0,7
Tempo médio (dp) de acesso SU, minutos	82	(44)	93	(43)	91	(47)	**89**	**(45)**	0,7
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Homens	16	59,3	12	66,7	29	58,0	**57**	**60,0**	0,8
Área urbano	23	85,2	16	88,9	38	76,0	**77**	**81,1**	0,4
Transporte em ambulância	27	100,0	13	72,2	28	56,0	**68**	**71,6**	
Período									0,4
00 - 08h	3	11,1	1	5,6	7	14,0	**11**	**11,6**	
08 - 16h	15	55,6	7	38,9	28	56,0	**50**	**52,6**	
16 - 24h	9	33,3	10	55,6	15	30,0	**3**	**35,8**	
Sintomas									
"falta de força num dos membros"	26	96,3	15	83,3	42	84,0	**83**	**87,4**	0,3
"boca ao lado"	26	96,3	14	77,8	39	78,0	**79**	**83,2**	0,1
"dificuldade em falar"	12	44,4	3	16,7	15	30,0	**30**	**31,6**	0,1
Número de sintomas									0,004
1	2	7,4	4	22,2	15	30,0	**21**	**22,1**	
2	13	48,1	14	77,8	24	48,0	**51**	**53,7**	
3	12	44,4	-		11	22,0	**23**	**2,2**	
1º AVC na vida	21	77,8	14	77,8	38	76,0	**73**	**76,8**	1,0
Tipo de AVC: Isquémico	20	71,4	14	77,8	41	82,0	**75**	**78,9**	0,7
Tratamento e prognóstico									
Internados	26	96,3	15	83,3	32	64,0	**73**	**76,8**	0,005
Isquémicos	19	73,1	11	73,3	23	71,9	**53**	**72,6**	1,0
Fibrinólise	14	77,3	4	36,4	4	17,4	**22**	**41,5**	0,001
Rankin pós episódio									0,027†
Sintomas não incapacitantes	-		2	11,1	1	2,0	**3**	**3,2**	
Incapacidade ligeira	3	11,1	1	5,6	10	20,0	**14**	**14,7**	
Incapacidade moderada	5	18,5	8	44,4	22	44,0	**35**	**36,8**	
Incapacidade moderadamente grave	8	29,6	5	27,8	10	20,0	**23**	**2,2**	
Incapacidade grave	11	40,7	2	11,1	7	14,0	**20**	**21,1**	
Taxa de letalidade aos 28 dias	3	11,1	2	11,1	3	6,0	**8**	**8,4**	0,7

†Média e desvio padrão; ‡Teste exacto de Fisher

e 17,4%, respectivamente). No total de utilizadores da VVE, pode calcular-se uma (sub)estimativa da proporção de doentes com AVC isquémico submetidos a fibrinólise de 41,2% (14 em 34). O Rankin pós-AVC é mais grave nos utilizadores da VVE, 70,3% com dependência grave ou moderadamente grave, em comparação com 38,9% na VVI e 34,0% nos não utilizadores. Ajustando para a idade, sexo e número de sintomas, o risco de incapacidade grave pós-AVC não está significativamente aumentado (RP = 2,9; IC 95%: 0,8 - 10,2) no acesso pela VVE, aumenta no entanto nos homens (RP = 4,2; IC 95%: 1,1 - 15,6) e com o número de sintomas (RP = 24,4; IC 95%: 5,2 - 114).

DISCUSSÃO

Tendo por base um registo prospectivo comunitário decorrido no Norte de Portugal entre Outubro de 2009 e Setembro de 2011, este é o primeiro estudo de base populacional a abordar a utilização da VVAVC, permitindo deste modo conhecer as condicionantes e efeito na população em geral de um programa destinado a minimizar as consequências do AVC. Neste registo foram usadas fontes de informação compreensivas de acordo com os critérios estabelecidos internacionalmente,[14] salientando-se a informação recebida do INEM referente à utilização da VVE. De um modo geral pode concluir-se que a incidência de AVC está a diminuir, de 245 / 100 000 em 1999[1] para 180 / 100 000 após dez anos. A taxa de activação da VVE foi de 30 / 100 000 habitantes, correspondendo a 8% do total de AVC's ocorridos na população, embora apenas 56,3% destes cumprissem os critérios de activação. A restrição imposta pelos actuais critérios faria com que apenas 95 (15,8%) dos casos de AVC pudessem ter um acesso *regulamentar* à VVAVC. Mesmo atendendo a este facto, apenas 27 (28,4% dos que cumpriam critérios) foram conduzidos ao hospital pela VVE.

Tem sido descrito como factor importante associado à VVE a chegada breve ao serviço de urgência (SU) e subsequente tratamento, sendo este um dos seus objectivos principais.[7] Neste estudo, o tempo decorrido entre o aparecimento dos sintomas e a chegada ao SU foi, em média, 82 minutos, menos nove do que verificou Quain et al[15] num estudo na Austrália, mas ainda elevado. Podem apontar-se alguns factores responsáveis por esta demora, como a falta de conhecimento dos sintomas mais comuns do AVC e dos procedimentos para solicitar uma ajuda mais imediata (112). Estes foram já descritos em vários estudos internacionais,[16-18] referindo o papel preponderante desempenhado pelas campanhas de alerta da população e também de uma adequada interacção/comunicação entre o Centro de Orientação de Doentes Urgentes (CODU) e o INEM. No SU, 68% dos episódios foram classificados como AVC/AIT, valor semelhante aos 70% de uma triagem correcta objectivados para a VVE,[7] assim como noutros estudos internacionais.[19] Por outro lado, a proporção de falsos positivos neste estudo é quase seis vezes superior à encontrada por Robert et al[20] num estudo semelhante realizado em Barcelona. Provavelmente, este facto deve-se ao receio de atrasar o acesso em caso de possível AVC e, mais uma vez, a dificuldades na realização da triagem pré-hospitalar. A sintomatologia mais frequente na activação da VVE foi a *falta de força num dos membros*, seguida da *dificuldade em falar* e *boca ao lado*, idêntico ao relatado noutros estudos.[21,22] Uma explicação é ser uma alteração mais perceptível para quem vê primeiro o doente e contacta o CODU. No entanto, quando nos restringimos aos episódios de AVC, a *dificuldade em falar* é mais frequente nos utilizadores da VVE[23] comparados com os restantes, talvez por ser um sintoma mais reconhecido pelos pacientes, uma vez que é característico da afectação do lobo esquerdo, permitindo, teoricamente, ao doente reconhecer melhor os seu défices (em comparação com o lobo direito) e, desta forma, pedir mais rapidamente ajuda. Por outro lado a *falta de força num dos membros* parece ser desta forma um sintoma mais comum no diagnóstico diferencial de AVC.

A VVE teve uma taxa de activação de 8%, inferior aos 17,9% de Robert et al[20] Este valor mais elevado foi, no entanto, encontrado numa situação mais restritiva, nomeadamente após exclusão dos doentes em que o episódio ocorreu no próprio hospital e dos transferidos de outros hospitais. Por outro lado, no relatório da VVAVC[24] é mencionado um valor de 26% a nível nacional em 2010 para a percentagem de doentes internados em Unidades de AVC em que a VV (externa ou interna) foi activada e, neste estudo, o valor foi semelhante (26,3%). Como seria de esperar, o Rankin prévio foi mais baixo quando foi utilizada a VVE, o que pode ser explicado pelo critério de activação da *independência prévia*. A maioria dos utilizadores da VVE chegaram dentro da janela terapêutica, contrastando com pouco mais de um terço dos não utilizadores, padrão também verificado noutros estudos,[23,25,26] sendo esta percentagem superior à verificada por Derex et al, em França,[27] assim como por Kleindorfer et al, nos EUA.[22] A discriminação entre utilizadores da VVE e restantes foi manifesta na proporção que apresenta cumulativamente os três sinais de AVC, o que poderá estar relacionado com a maior exuberância do quadro clínico traduzida, na subsequente chamada do 112. O facto de a idade média dos utilizadores da VVE ser inferior aos restantes pode novamente estar relacionado com o critério do limite da idade, mas também com o facto dos doentes mais velhos terem tendencialmente mais comorbilidade e, por isso, um crescente grau de dependência, o que restringe novamente a activação da VVAVC. Resultados semelhantes foram encontrados no estudo de Robert et al.[20] Embora se esperasse que doentes com um AVC recorrente reconhecessem melhor os sintomas e por isso ligassem mais frequentemente para o 112, a VVE foi mais utilizada por doentes com o primeiro AVC na vida. Esta tendência foi também relatada por outros autores[21] e pode ser devida ao facto de subsistirem alterações cognitivas sequelares ao primeiro AVC ou a uma dependência para as actividades de vida diária que não permita aos doentes com AVC recorrente preencher os critérios de activação da VVE.

Nem um quinto de todos os AVC's satisfizeram os critérios da VVE e, mesmo nos utilizadores da VVE, pouco mais

de metade satisfaziam os critérios diminuindo este valor para aproximadamente um terço na VVI. O actual protocolo da VVAVC abrange assim uma percentagem reduzida de todos os episódios de AVC registados na população em geral, não atingindo o valor mencionado nos relatórios da VVAVC[7] pois neste o denominador só inclui os doentes internados. A *janela terapêutica* e a idade superior a 80 anos foram os critérios que isoladamente impediriam com mais frequência a utilização da VVAVC. Pode aqui referir-se que a campanha de alerta da população *Seja mais rápido que o* AVC não está ainda a resultar num efeito desejado, ou porque a população não reconhece ainda os principais sinais/sintomas de AVC ou porque, embora reconhecendo, não adopta uma acção rápida e adequada. Este ponto é também focado num estudo realizado no distrito de Viana do Castelo, chamando a atenção para o facto da idade avançada e/ou escolaridade baixa serem barreiras para que este alerta funcione adequadamente.[28] Mesmo nos doentes que preenchiam os critérios da VVAVC a taxa de activação (externa) foi de apenas 28,4%. Em pouco mais de metade destes doentes não foi activada nem a VVE nem a intra-hospitalar, com a agravante de 56,0% destes terem usado o transporte em ambulância para se deslocarem ao SU. Carecemos de uma informação importante referente aos doentes com AVC que recorreram ao CODU para os quais não foi activada a VVE, que poderá eventualmente vir a ser alvo de futura análise com inquérito aos próprios utentes. Mas, por outro lado, há ainda a questão de não ter sido activada a VVI, possivelmente devido ao facto do doente não preencher os critérios clínicos mais restritivos para a realização da fibrinólise, à falta de segurança/experiência de alguns profissionais para a realização deste tratamento ou ainda à falta de formação da equipa de realização da triagem hospitalar. Nos doentes com critérios de acesso à VVAVC, o tempo médio entre o início dos sintomas e entrada no SU não foi significativamente diferente nos utilizadores da VVE, VVI ou não utilizadores, resultados semelhantes aos encontrados por Robert et al.[20] A proporção de doentes internados e de doentes com AVC isquémico que fazem fibrinólise vindos pela VV justifica amplamente a operacionalização da VVAVC, pois é muito superior nestes doentes. Resultados semelhantes foram encontrados noutros estudos, mas esta proporção é superior à encontrada em alguns deles, sobretudo nos realizados em Espanha.[15,20,22,25,29,30] Em termos de prognóstico a curto prazo, o Rankin pós-AVC foi mais grave nos utilizadores da VVE, a exemplo de outros estudos.[20,31] Note-se, no entanto, que, após ajustamento para as características sócio-demográficas e sinais/sintomas, este facto é explicado não pelo acesso ter sido pela VVE mas por estes doentes terem um maior número de sintomas e serem do sexo masculino.

Como limitação deste estudo podemos apontar o facto de não terem sido analisados em detalhe outros critérios constantes das recomendações da VVE,[7] entre outros, o tempo entre o acesso ao SU e a avaliação por um neurologista, realização de TAC, assim como de fibrinólise. Dado não haver diferenças no tempo decorrido entre os sintomas e a entrada no SU nos utilizadores (com critérios) da VVE em comparação com os restantes tal como em outros estudos,[20] a exemplo destes, esta análise mais detalhada poderia ser indicativa de intervalos de tempo intrahospitalares mais baixos e adequados quando a VVAVC é utilizada. Um possivel viés de informação pode surgir do facto de nem sempre ter sido registava no episódio de urgência a utilização da VVI. No entanto, é pouco provável que isso tenha acontecido porque o número de activações da VVI é superior ao da VVE e além disso foi até mesmo mencionada em mais doentes que não obedeciam aos critérios de activação (64,0% na VVI *vs* 43,7%). Será necessário realizar mais estudos de base populacional para definir os riscos reais do uso de fibrinólise em doentes com mais de 80 anos de idade, bem como sobre a eventual extensão da *janela terapêutica*.[32] Outro aspecto importante é o facto de a VVE estar a ser mais frequentemente utilizada nos AVC's mais graves, impedindo um eventual tratamento fibrinolítico por contra-indicações clínicas. Atendendo a que existe uma alta taxa de ocorrência de AVC após um AIT,[1] também o critério referente ao tipo de sintomas poderia ser mais abrangente, seguindo, por exemplo, a campanha americana *Suddens*,[33] acrescentando nomeadamente a perda súbita de visão, tal como acontece no *Código Ictus* em Espanha.[34] Deste modo, poderá ser possível aumentar ou mesmo eliminar o *cut-off* da idade, como sugerido noutros estudos,[32,34] ou aumentar a *janela terapêutica* pelo menos para quatro horas e meia, considerando os resultados de estudos mais recentes.[32,35-37]

Poderá também sugerir-se a intensificação das campanhas populacionais, uma vez que a sua eficácia foi já positivamente avaliada por vários estudos.[16,18,38,39] Devem ser dirigidas a públicos diversos utilizando meios e argumentos compreensivos, pelo menos focando os sintomas e activação da VVAVC. Uma abordagem educacional alternativa, já verificada em alguns estudos,[40-42] seria a dos profissionais de saúde responsáveis pela triagem quer em relação ao quadro clínico objectivado pela VVAVC quer em relação à adequada comunicação entre os responsáveis.

CONCLUSÃO

Embora durante uma década a incidência de AVC tenha diminuído, este estudo mostra que os efeitos de alguns programas nacionais para diminuir as repercussões do AVC a nível comunitário, nomeadamente a VVAVC, poderiam ser mais abrangentes quanto aos critérios de acessibilidade, cobrindo actualmente apenas uma proporção estimada em 16% de todos os casos. Considerando os doentes que cumprem estes critérios, pode concluir-se que os utilizadores da VV têm um espectro sintomatológico/clínico mais grave e são também mais frequentemente internados e tratados por fibrinólise em comparação com os restantes. Mesmo assim, após ajustamento para estas características, a incapacidade pós-AVC não difere significativamente nos utilizadores e não utilizadores da VV.

CONFLITO DE INTERESSES

Os autores declaram não existir qualquer conflito de interesses relativamente ao presente artigo.

FONTES DE FINANCIAMENTO

A informação usada neste artigo é parte integrante do Projecto PIC/IC/82858/2007 financiado pela Fundação para a Ciência e a Tecnologia.

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ANEXO II

COMUNICAÇÕES

Effects of outdoor temperature and rain on the risk of hemorrhagic stroke

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XX IEA World Congress of Epidemiology (2011) [Poster]

Introduction: Changes in meteorological parameters have been associated with stroke occurrence. The incidence of primary intracerebral haemorrhages (PICH) seems to increase in days with cold/mild outdoor temperature. In Portugal, neurologists forward the hypothesis that the incidence of PICH increases in rainy days and not particularly low temperatures. This study aims to study the association between occurrence of PICH and weather parameters.

Methods: Data from ACINrpc-project, involving 78 patients suffering a first-ever-in-the-lifetime PICH over a 2-year period in the city of Porto was used. Information on daily weather parameters was obtained from the National Meteorological Office. A Poisson model was used to estimate the association between weather parameters and PICH incidence. Using a conditional logistic regression model, a case-crossover design was then used to estimate the risk of PICH following specific exposures associated with PICH incidence: low diurnal temperature range (DTR) and rainy days. For each subject, the case period was matched with 4 control periods, the same weekday in the previous four weeks.

Results: PICH incidence increases by 11.8% (95%CI: 3.8-20.4%) for 1ºC drop in DTR and 3.1% (95%CI: 1.1-5.1%) for a 1mm/m² in precipitation. Following a day with a DTR<4ºC the odds ratio is 2.9 (95%CI: 1.4-5.8), increasing to 8.8 (95%CI: 1.7-44.8) after a 48h exposure. Following days with low DTR and rain, the odds ratio is 3.2 (95%CI: 1.3-8.1) and 9.5 (95%CI: 1.1-88.9) for a precipitation>10mm/m² and 40mm/m², respectively.

Conclusion: Precipitation by itself is not associated with PICH incidence, nevertheless has a synergistic effect in low DTR days.

Table A1. Distribution of vascular risk factors in 78 patients with PICH

Vascular risk factor	N	%
Age ≥ 65y	46	59.0
Women	48	61.5
High blood pressure (HBP)	54	69.2
Cardiac disease (CARD)	23	29.5
Diabetes	19	24.4
Smoking habits	14	17.9

Table A2. Estimated percentage of daily variation in Intracerebral haemorrhage by unit variation in the preceding 24 hours of weather parameters

Season/Weather parameter	%	95%CI
Season vs. Summer		
Autumn	32.0	-31.6 to 54.8
Winter	16.9	-40.4 to 29.1
Spring	53.3	-18.6 to 88.5
Temperature (decrease 1ºC)		
Maximum	4.7 *	-0.4 to 10.1
Minimum	-0.3	-5.1 to 4.7
Diurnal range	**11.8** ‡	**3.8 to 20.4**
Relative humidity (%)	1.6	-0.6 to 3.8
Precipitation (mm/m^2)	**3.1** ‡	**1.1** to **5.1**
Atmospheric pressure (hPa)	0.1	-3.0 to 3.4

*p<0.05; ‡p<0.01

Table A3. Assessment of interaction between DTR and precipitation on overall PICH incidence and in the presence of vascular risk factors

DTR (ºC)	Precipitation (mm^2)	Cases	Controls	OR	95%CI
<u>All patients</u>					
≥ 4	< 10	56	259	1.0	
≥ 4	≥ 10	6	27	1.0	0.4-2.5
< 4	< 10	7	13	2.6	0.9-7.1
< 4	≥ 10	9	13	3.2	1.3-8.1
Expected OR:	Additive model: 2.6 + 1.0 – 1.0 = 2.6	Multiplicative model: 1.0 x 2.6 = 2.6			
<u>Oldest (≥ 65 years)</u>					
< 4	≥ 10	7	6	5.0	1.6-16
Expected OR:	Additive model: 0.3 + 1.1 – 1.0 = 0.4	Multiplicative model: 0.3 x 1.1 = 0.3			
<u>with high blood pressure</u>					
< 4	≥ 10	6	7	4.1	1.3-13
Expected OR:	Additive model: 1.3 + 3.2 – 1.0 = 3.5	Multiplicative model: 1.3 x 3.2 = 4.2			
<u>All patients</u>					
≥ 4	< 40	61	282	1.0	
≥ 4	≥ 40	1	4	1.3	0.1-2.2
< 4	< 40	12	22	2.5	1.1-5.3
< 4	≥ 40	4	4	9.5	1.1-89
Expected OR:	Additive model: 2.8	Multiplicative model: 3.2			

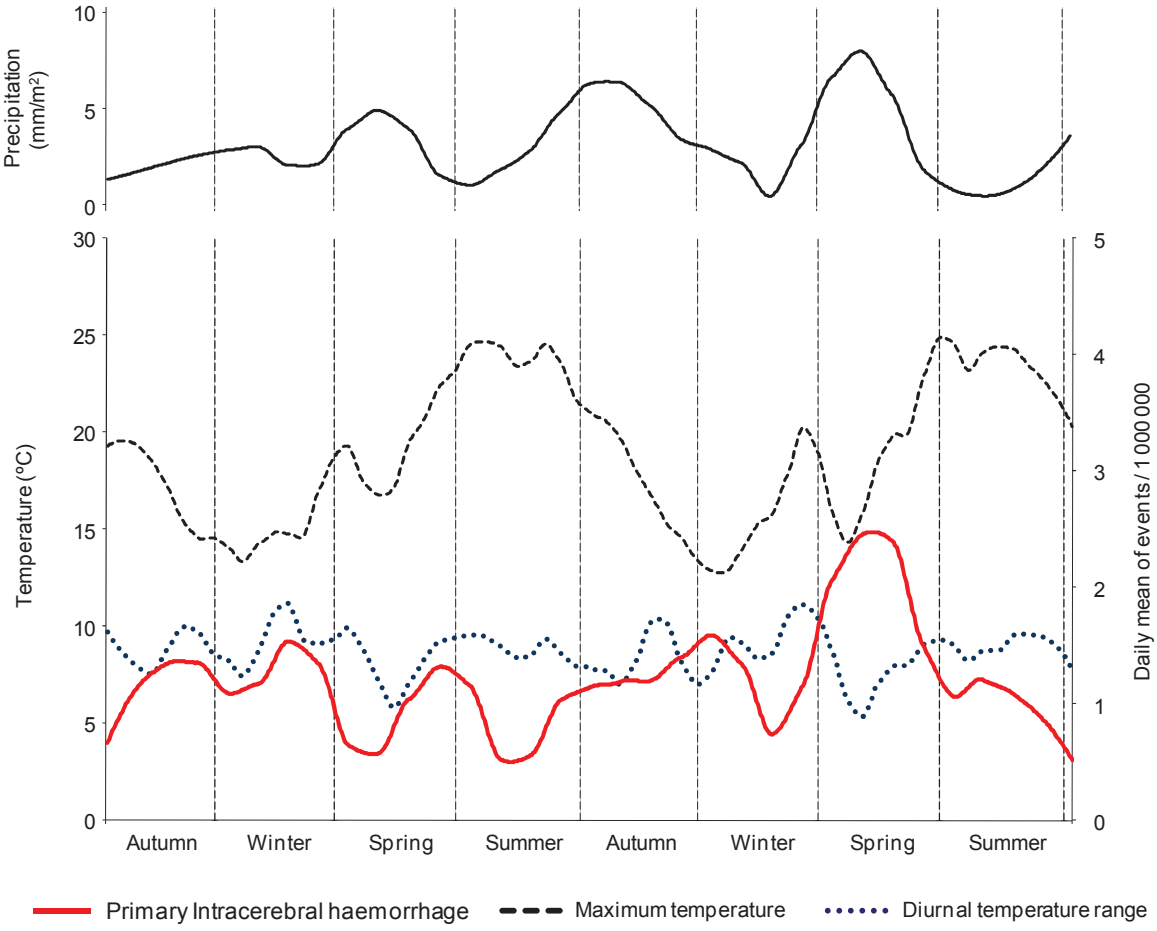

Figure A1. Lowess smoothed values of daily incidence and meteorological parameters at Porto during the study period.

Stroke incidence and case-fatality ten years apart in Northern Portugal - 1999 to 2010: data from a community-based study

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Cerebrovascular Diseases, 33(suppl 2): 556-557. 2012.
21st European Stroke Conference (2012) [Poster]

Background: One decade ago Portugal had one of the highest stroke incidences among the Western European countries. Based on the population ageing stroke incidence is predicted to rise, but on the other hand much has changed since 2000. Population awareness measures were implemented, hopefully reflected in a widen use of preventive strategies, and acute treatment approaches are being constantly tested and innovated. The objective of this study is the comparison of stroke incidence and case-fatality ten years apart, 2000-2010.

Methods: All suspected first-ever-in-a-lifetime strokes occurring between October 2009 and September 2011 in 46775 residents in rural areas and 193349 urban residents were entered into a stroke registry. Based on standard definitions, both hot and cold pursuit sources of information were used for case ascertainment. Patients were observed at onset and at three months. All data is currently being validated and by March 2012 the definitive results will be available. Meanwhile the results presented refer to the preliminary results of the first year (September 2009-10).

Results: Based on the first year results, it is expected a decrease in the annual incidence of stroke, 2.8/1000 (95%CI, 2.6-3.0) to 1.8/1000 (95%CI, 1.6-2.0), though still higher in rural compared to urban populations. Mean age at onset increased from 71 to 73 years, the proportion of women is lower (54.5 vs. 58.7%) and among patients with a definite diagnosis the proportion of ischaemic events increased slightly from 80% to 84% contrasting with primary intracerebral haemorrhages (17 to 13%). The overall 28 days case-fatality decreased from 16.1% (95%CI, 13.6-19.1) to 10.6% (95%CI, 8.0-13.8).

Discussion: Both, incidence of stroke and case-fatality are decreasing ten years apart. The population ageing is also shown in the ageing of patients, but the efficacy of treatment in the acute phase may underlie the decline of case-fatality.

Table A4. Characteristics of patients included

Patients characteristics	Period	Rural	Urban
Median age, years (IR)	1st	74 (67-80)	72 (63-81)
	2nd	76 (66-83)	75(62-83)
Women, %	1st	51.8	62.1
	2nd	51.1	55.7
Stroke type			
Cerebral infarction	1st	77.9	75.3
	2nd	84.8	83.9
Intracerebral Haemorrhage	1st	14.6	16.3
	2nd	11.8	13.1

Table A5. Evolution of overall stroke incidence (/1,000)

	1998-2000			2009-2011		
Characteristics	n	rate	95% CI	n	rate	95% CI
Residence						
Rural	226	3.1	2.7-3.4	237	2.5	2.2-2.9
Urban	462	2.7	2.4-2.9	697	1.8	1.7-1.9
Gender						
Male	284	2.6	2.3-2.9	425	1.9	1.7-2.1
Female	404	3.0	2.7-3.3	509	2.0	1.8-2.2
All	688	2.8	2.6-3.0	934	1.9	1.8-2.1
ASR Portugal		2.3	2.1-2.5		1.6	1.5-1.7
ASR Europe		1.8	1.6-2.0		1.2	1.1-1.3

ASR – Indicates age-standardized rate

Table A6. 28-day case-fatality in rural and urban patients

	1998-2000		2009-2011	
Residence	%	95% CI	%	95% CI
Rural	14.6	10.2-19.3	16.0	11.9-21.4
Urban	16.9	13.7-20.6	10.2	8.2-12.7
All	16.1	13.6-19.1	11.7	9.8-13.9

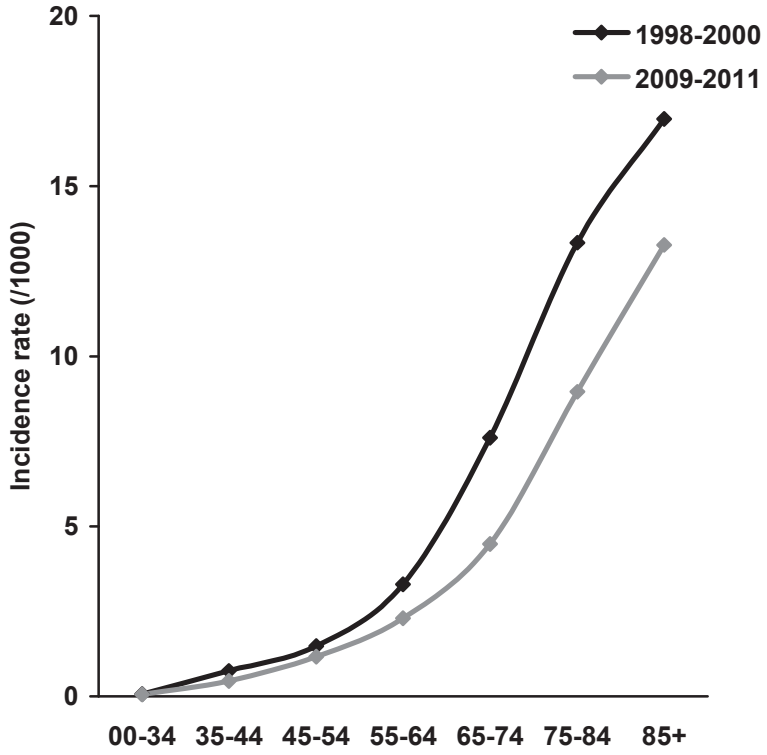

Figure A2. Overall stroke incidence by age-group

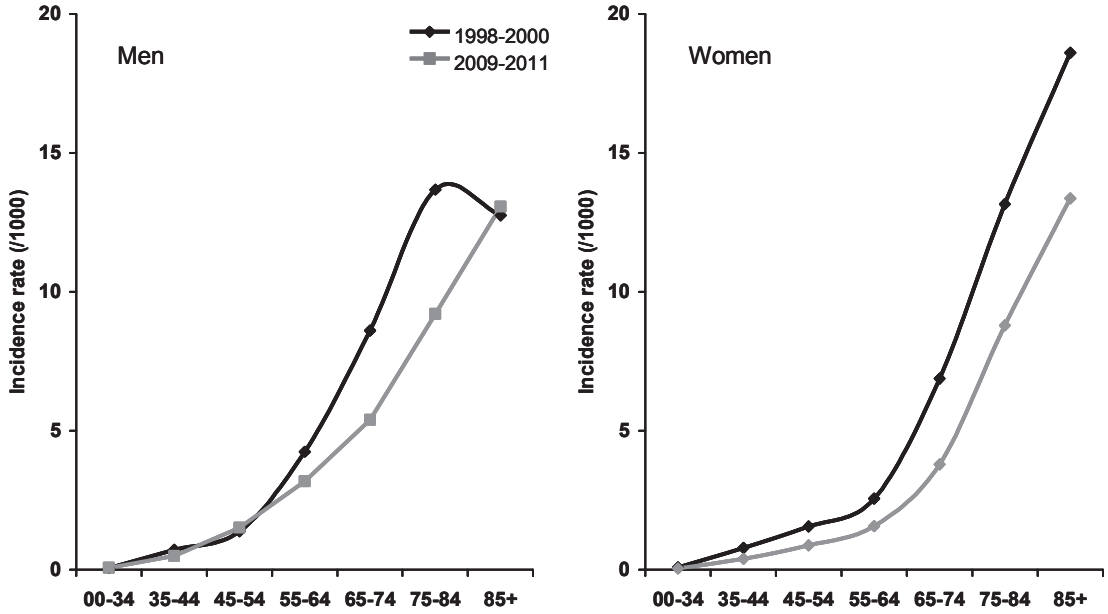

Figure A3. Stroke incidence by age-group and gender

Change in incidence of intracerebral haemorrhage in urban and rural northern Portugal, from 1999 to 2011: a population-based study

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Cerebrovascular Diseases, 35(suppl 3): 623. 2013.
22nd European Stroke Conference (2013) [Poster]

Background: One decade ago stroke incidence in Portugal was higher than in most Western European countries. The objective of this study is to know how much it has been achieved in the incidence and short term prognosis of primary intracerebral haemorrhages (PICH) from 1999 to 2011 in urban and rural areas.

Methods: All suspect first-ever-in-a-lifetime stroke occurring between October 2009 and September 2011 in 46775 residents in rural areas and 193349 residing in the city of Porto were registered and are compared to those ascertained in the 1998-2000 study. Based on standard definitions, both hot and cold pursuit sources of information were used for case ascertainment. Patients were observed at onset and at three months.

Results: During a 24-month period, 115 patients with a first-ever PICH, 27 in rural and 88 in urban areas were registered. The first PICH happens on average 4 years after (67 and 71 years) in the city and 6 years in rural areas (67 and 74 years). There was a decrease in the annual incidence rate of PICH per 100000, from 45 (95% CI, 37-53) to 24 (95% CI, 20-28), and from 33 to 16 after standardization to the European population. In the rural population the incidence dropped from 44/100000 (95% CI, 31-62) to 29 (95% CI, 19-42) and in the urban population from 45/100000 (95% CI, 36-57) to 23 (95% CI, 18-28). Age-specific incidence decreased following similar patterns in rural and urban populations, reaching a relative reduction of 75.7% in urban populations aged 55-64 years. Case-fatality at 28 days decreased from 30.6% (95% CI, 22.8-39.7) to 28.7% (95% CI, 21.2-37.6) and from 33.3 to 22.7% in urban patients; in rural patients increased from 24.2 to 48.1%.

Conclusion: The incidence and case-fatality of PICH decreased ten years apart, in particular in urban populations. The ageing of patients in rural areas could be responsible for their high case-fatality.

Table A7. Patient's characteristics and case-fatality

	1998-2000		2009-2011	
Patients		95% CI		95% CI
Mean age	67.3	64.7-69.9	71.3	68.8-73.8
Rural	67.5	63.1-71.8	73.6	70.0-77.2
Urban	67.2	63.9-70.5	70.6	67.5-73.7
Gender: % Male	42.3	33.5-51.6	59.1	49.9-67.7
Rural	51.5	35.2-67.5	66.7	47.8-81.4
Urban	38.5	28.5-49.6	56.8	46.4-66.7
Case-fatality, %	30.6	22.8-39.7	28.7	21.2-37.6
Rural	24.2	12.8-41.0	48.1	30.7-66.0
Urban	33.3	23.9-44.4	22.7	15.2-32.5

Table A8. Evolution of PICH incidence (/100,000)

	1998-2000			2009-2011		
	n	rate	95% CI	n	Rate	95% CI
Residence area						
Rural	33	44.5	30.6-62.5	27	28.9	19.0-42.0
Urban	78	45.3	35.8-56.6	88	22.8	18.3-28.1
Gender						
Male	47	42.6	31.3-56.7	68	30.4	23.6-38.5
Female	64	47.1	36.3-60.1	47	18.4	13.5-24.4
All	111	45.1	36.7-53.5	115	24.0	19.6-28.3
ASR Europe		32.8	26.1-40.9		15.8	12.5-19.8

ASR – Indicates age-standardized rate

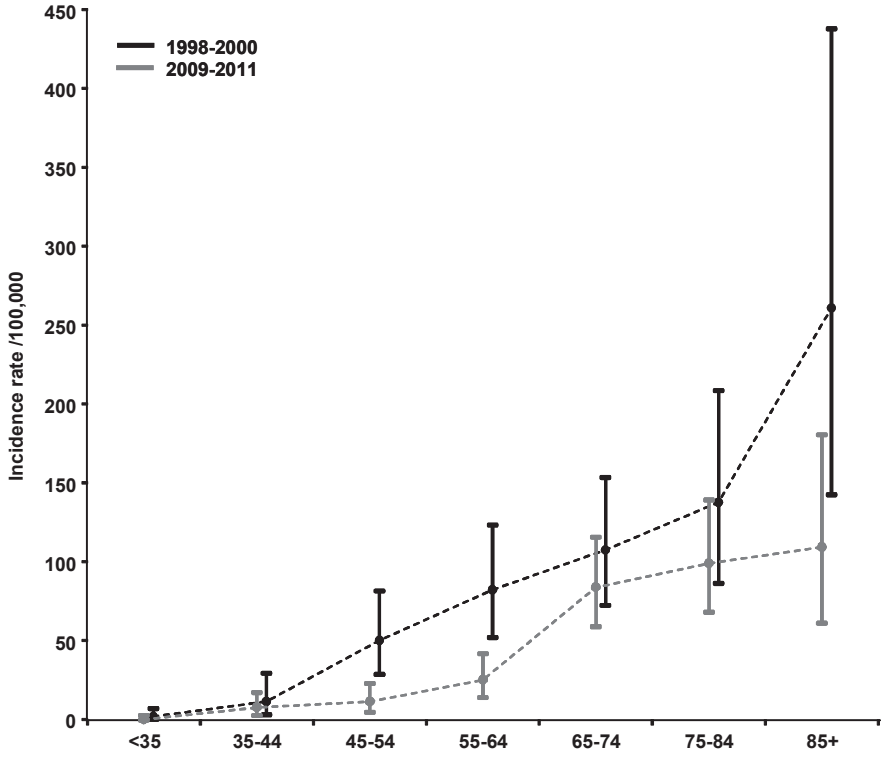

Figure A4. Evolution of PICH incidence by age-group

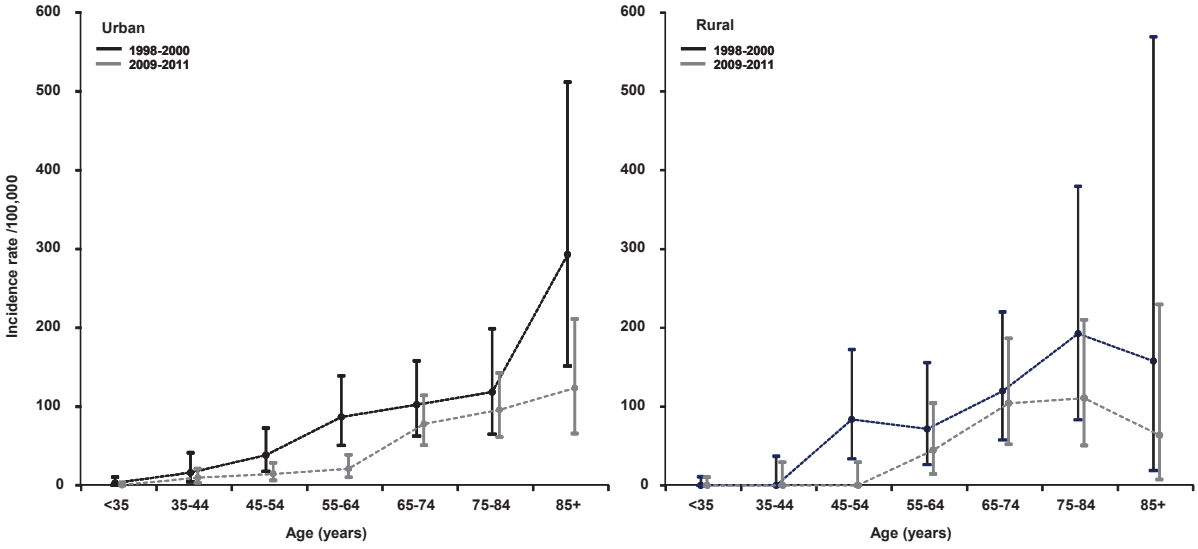

Figure A5. Evolution of PICH incidence by age-group, according to residence area

Change in incidence of subaracnoid haemorrhage from 1999 to 2011 in the northern region of Portugal

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Cerebrovascular Diseases, 35(suppl 3): 620. 2013.
22nd European Stroke Conference (2013) [Poster]

Background: One decade after the first community-based prospective incidence study, we intend to describe current trends in the incidence and short-term prognosis of subarachnoid haemorrhage (SAH) in northern Portugal.

Methods: Data from the second prospective community-based study are presented and compared to the first one. All suspect first-ever-in-a-lifetime stroke occurring between October 2009 and September 2011 in about 240,000 residents were entered into a stroke registry. Based on standard definitions, both hot and cold pursuit sources of information were used for case ascertainment. Patients were observed at onset and at three months.

Results: A total of 30 patients were included, half of them were man compared with 78.3% in the first study ($p<0.04$) and the average age increased from 60 to 63 years ($p>0.5$). The overall crude annual incidence rate decreased from 9.3/100000 (95% CI, 5.9-14.0) to 6.3/100000 (95% CI, 4.2-8.9), and after standardization to the European population from 7.3 (95% CI, 4.3-11.6) to 4.5 (95% CI, 2.9-6.9). The age-specific incidence rates were stable or lower than in the first study, with the previous peak at 65-74 years (29/100000) shifting for the 74-85 years (21/100000). The highest values for those 85 years or older were stable (37.3 and 36.6/100000), but there was an increase in the oldest women, from 26 to 41/100000. Case-fatality at 28 days decreased from 30.4% (95% CI, 15.6-50.9) to 23.3% (95% CI, 11.8-40.9).

Conclusion: Compared to other studies in European countries the incidence of SAH in Portugal is one of the lowest after the decrease in the last decade. The age-sex incidence pattern is changing, mainly by the increase in incidence in the oldest women. Despite being now more common among the oldest, the short-term prognosis remained stable in the last decade.

Table A9. Patient's characteristics and case-fatality

	1998-2000		2009-2011	
Patients		95% CI		95% CI
Mean age	59.7	51.5-67.8	62.8	55.4-70.1
Rural	58.8	38.1-79.5	63.3	49.0-77.5
Urban	59.9	50.2-69.7	62.6	53.3-71.9
Gender: % Male	21.7	9.7-41.9	50.0	33.2-66.8
Rural	0.0	0.0-39.0	50.0	21.5-78.5
Urban	29.4	13.3-53.1	50.0	30.7-69.3
Case-fatality, %	30.4	15.6-50.9	23.3	11.8-40.9
Rural	16.7	3.0-56.4	25.0	7.2-59.1
Urban	35.3	17.3-61.4	22.7	10.1-43.4

Table A10. Evolution of SAH incidence (/100,000)

	1998-2000			2009-2011		
	n	rate	95% CI	n	rate	95% CI
Residence area						
Rural	6	8.1	3.0-17.6	8	8.6	3.7-16.9
Urban	17	9.9	5.8-15.8	22	5.7	3.6-8.6
Gender						
Male	5	4.5	1.5-10.6	15	6.7	3.8-11.1
Female	18	13.2	7.9-20.9	15	5.9	3.3-9.7
All	23	9.3	5.9-14.0	30	6.3	4.2-8.9
ASR Europe		7.3	4.3-11.6		4.5	2.9-6.9

ASR – Indicates age-standardized rate

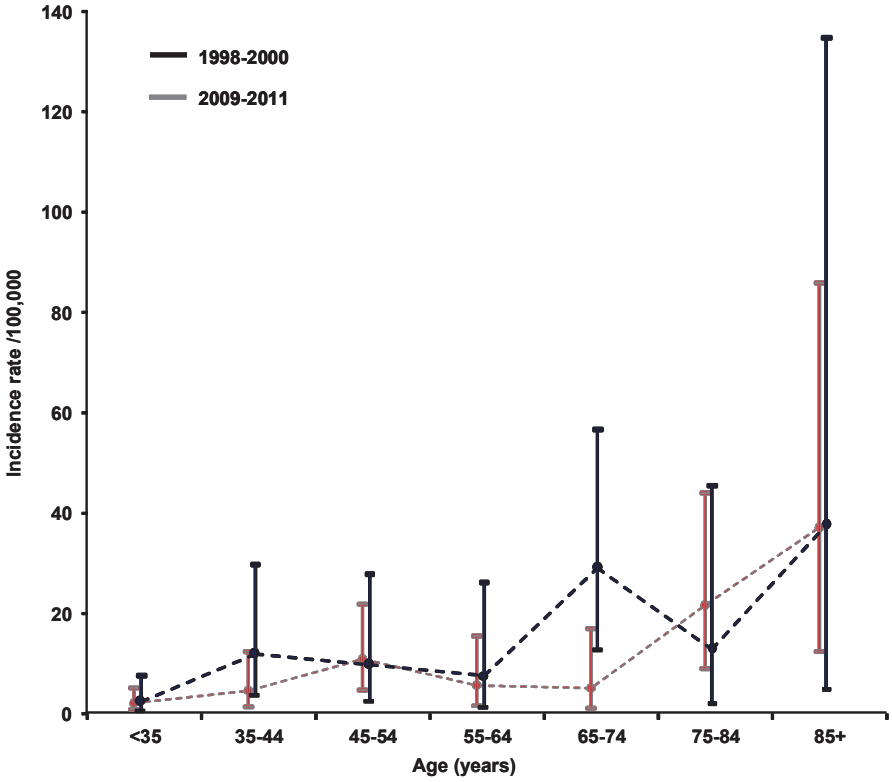

Figure A6. Evolution of SAH incidence by age-group