

## ORIGINAL ARTICLE

# Comparing ischaemic stroke in six European countries. The EuroHOPE register study

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**Background and purpose:** The incidence of hospitalizations, treatment and case fatality of ischaemic stroke were assessed utilizing a comprehensive multi-national database to attempt to compare the healthcare systems in six European countries, aiming also to identify the limitations and make suggestions for future improvements in the between-country comparisons.

**Methods:** National registers of hospital discharges for ischaemic stroke identified by International Classification of Diseases codes 433–434 (ICD-9) and code I63 (ICD-10), medication purchases and mortality were linked at the patient level in each of the participating countries and regions: Finland, Hungary, Italy, the Netherlands, Scotland and Sweden. Patients with an index admission in 2007 were followed for 1 year.

**Results:** In all, 64 170 patients with a disease code for ischaemic stroke were identified. The number of patients registered per 100 000 European standard population ranged from 77 in Scotland to 407 in Hungary. Large differences were observed in medication use. The age- and sex-adjusted all-cause case fatality amongst hospitalized patients at 1 year from stroke was highest in Hungary at 31.0% (95% confidence interval 30.5–31.5). Regional differences in age- and sex-adjusted 1-year case fatality within countries were largest in Hungary (range 23.6%–37.6%) and smallest in the Netherlands (20.5%–27.3%).

**Conclusions:** It is feasible to link population-wide register data amongst European countries to describe incidence of hospitalizations, treatment patterns and case fatality of ischaemic stroke on a national level. However, the coverage and validity of administrative register data for ischaemic stroke should be developed further, and population-based and clinical stroke registers should be created to allow better control of case mix.

**Introduction**

Trends in stroke mortality from the late 1960s to the mid 1990s have shown considerable differences

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between countries [1]. Low and declining mortality rates have been observed in Western Europe whilst already high stroke mortality has continued to increase even further in Eastern Europe. Stroke incidence is strongly age-dependent, and Europe has one of the most rapidly ageing populations in the world. Large differences in mortality along with scarcity of data on treatment practices and outcomes of ischaemic

mic stroke in European countries indicate a need for nationwide comparative databases as a first step in identifying explanations for differences.

Case fatality following stroke has been used in hospital benchmarking as a measure of outcome in several countries, including Canada, Finland, Denmark, Hungary, Italy, the Netherlands, Sweden, UK and the USA [2,3]. International comparisons of outcome for hospital benchmarking have been based either on administrative national discharge registers or data collected in a similar way from individual hospitals in different countries [2]. The latter studies are typically based on a limited number of hospitals, and thus their results may not be generalizable to stroke care within or between countries. Studies based on administrative databases include generic problems such as differences in coding practice, lack of internationally standardized codes, and methodology [3]. A major impediment in many countries for performing nationwide benchmarking is the inability to link data within and between different national administrative databases.

In the European Healthcare Outcomes, Performance and Efficiency (EuroHOPE) study national administrative databases were linked at the individual patient level. As there are differences between European countries in healthcare systems, in levels of prosperity and in sociocultural characteristics, also differences in healthcare performance could be assumed. For testing this hypothesis, hospitalizations, prevalence of comorbidities, treatment and case fatality were assessed for ischaemic stroke patients hospitalized in 2007 in six European countries and regions: Finland, Hungary, Italy (Lazio Region and City of Turin), the Netherlands, Scotland and Sweden. The case fatality of ischaemic stroke patients between regions in each country was also compared. Limitations are identified and suggestions are made for future improvements in between-country comparisons.

## Methods

In the EuroHOPE project retrospective observational databases of stroke treatment episodes were created using national administrative registers whilst exploiting experiences from the Finnish Performance, Effectiveness and Costs of Treatment Episodes (PERFECT) project [4–8]. Patients from the hospital discharge registers of the six participating European countries with admissions with a diagnostic code for stroke between 1 January 2007 and 31 December 2007 were included. Patients were followed for 365 days from the index admission.

## Episode definition and register linkage

The treatment episode starts from the initial acute hospital stay (i.e. index admission) with incident stroke diagnosis, includes all continuous hospital treatment and transfers of patients between hospitals, and ends with the patient's death during hospital stay, discharge to home or discharge to a long-term care facility such as a nursing home.

Stroke comprises three subtypes: ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage, with ischaemic stroke being the most common, at around 70%–80% of all strokes [9].

In EuroHOPE International Classification of Diseases version 9 (ICD-9) discharge codes 433–434 and ICD-10 code I63 were classified as ischaemic stroke, 431/I61 as intracerebral haemorrhage, 430/I60 as subarachnoid haemorrhage and 436/I64 as undefined stroke. This study included only patients with ischaemic stroke; patients having also subsequent haemorrhagic stroke during the same hospital episode were excluded. Additional exclusion criteria were prior admission due to stroke in the hospital discharge register (HDR) during the previous 365 days of index admission; tourists, visitors or other residents with incomplete national personal identification numbers; unknown place of residence and patients under 18 years of age.

Data on comorbidities were gathered for the purpose of case mix adjustment from the primary and secondary diagnoses of the country-specific HDR and from medication purchases recorded in the prescribed drug register for a period of 1 year before the index admission. Data on medication purchases were also gathered for the first year after the index admission. All-cause case fatality and date of death within 1 year were recorded from the register of causes of death in each participating country. Data on date of death and medication purchase were linked with the HDR using personal identification numbers in all countries except the Netherlands where deductive algorithms were used [8].

## The incidence of hospital admission, treatment and outcome of ischaemic stroke

Crude incidence of hospital admission and incidence of hospital admission adjusted by age and sex to the European standard population [10] are reported per 100 000 population. Medication use was estimated (using respective ATC codes) by the proportions of patients purchasing, at least once during the year before and year after the ischaemic stroke, the following preventive medications: dipyridamol, clopidogrel,

warfarin, antihypertensives (diuretics, angiotensin-converting enzyme inhibitors, beta blockers), insulin or other hypoglycaemic drugs, and statins. Data on use of aspirin were not available as it is an over-the-counter drug. Hospital-specific information on the level of service provided (comprehensive stroke centre, primary stroke centre or general ward) according to the international classification [11,12] was dependent on whether our clinical experts in each country had access to this information. Data on thrombolysis were gathered from the procedure codes in the HDR according to classifications used in each country. Outcome was measured as all-cause case fatality within 30, 90 and 365 days of index hospitalization.

### Statistical methods

Adjustment was made for age and sex when comparing countries and regions. Based on the experiences in the PERFECT project [4] the observed/expected approach described by Ash *et al.* [13] was used. Specifically, the method uses logistic regression modelling for risk adjustment. Indicators were produced at national and at regional levels within the countries. Regional information is based on patients' place of residence registered in the HDR. The regions within each country have been defined according to the national legislation. All data were analysed using Stata version 12 from StataCorp (College Station, TX, USA).

A detailed description of the methods of the EuroHOPE stroke project is available online ([www.eurohope.info](http://www.eurohope.info)).

## Results

There were 64 170 admissions with a diagnostic code for ischaemic stroke in the registers of the six countries during the year 2007. The incidence and baseline characteristics of the patients in the participating countries are shown in Table 1.

The most common comorbid diseases during the previous year were hypertension, coronary artery disease, atrial fibrillation, cancer and diabetes (Table 1). Antithrombotic treatment (excluding aspirin) prior to the ischaemic stroke was most common in Finland.

The proportion of patients treated at comprehensive stroke centres, primary stroke centres and general hospitals showed considerable variation amongst countries (Table 2). The proportion of patients who had a record of being treated with thrombolysis was 3.5% in Finland; there was lack of data on this treatment in the other countries.

The age- and sex-adjusted case fatality rates at 30-day, 90-day and 1-year follow-up are shown in Table 2. Regional variation existed in the age- and sex-adjusted 1-year case fatality (Fig. 1). The difference between regions having lowest and highest case fatality was 10.1 percentage points in Finland (from 15.9% to 26.0%), 14.0 (from 23.6% to 37.6%) in Hungary, 10.2 (from 10.9% to 21.1%) in Italy, 6.8 (from 20.5% to 27.3%) in the Netherlands, 8.8 (from 24.6% to 33.4%) in Scotland and 9.0 (from 16.3% to 25.3%) in Sweden.

## Discussion

EuroHOPE utilized a multinational patient level comprehensive database with nationwide coverage to evaluate how hospitalized ischaemic stroke patients are treated within the healthcare system [14]. It is based on administrative registers and is not population-based, such as the WHO MONICA project [15]. Validation of the EuroHOPE data against medical record review in each participating country and region would have been optimal, but as resources were not available to do this the validity of our approach was estimated using previous methodological and epidemiological data.

### Validity of stroke diagnoses in the HDR and Causes of Death Register

A Finnish validation study found a HDR diagnostic sensitivity of 80% and positive predictive value of 82% for ischaemic stroke with comprehensive coverage in the Causes of Death Register [16]. In Sweden, the positive predictive value for first-ever strokes of two administrative registers combined was 94% and the sensitivity 92%, but data specific for ischaemic stroke were not reported [17]. Completeness of hospital discharge records for stroke assessed against stroke audit databases at national level for 2006–2009 data for Scotland showed that only around 50% of incident ischaemic strokes were identified using the I63 code as a large proportion receive the I64 code of ill-defined stroke (Sarah Wild, personal communication). To our knowledge, accuracy data of ischaemic stroke diagnoses in the HDR are not available for the other participating countries.

The sensitivity of the HDR depends on the hospitalization rate of stroke, for which estimates vary amongst the participating countries (Table 3). Population-based studies suggest that almost all stroke patients are hospitalized in Finland, Hungary, Italy and Sweden, but around 30% are treated in the community in the Netherlands and Scotland (Table 3)

**Table 1** Incidence and baseline characteristics of ischaemic stroke patients in six European countries: Finland, Hungary, Italy (Lazio Region and City of Turin), the Netherlands, Scotland and Sweden during the year 2007

	Finland	Hungary	Italy	The Netherlands	Scotland	Sweden
Adult population	4 204 459	8 163 506	5 346 579	12 793 540	4 096 793	7 251 275
Ischaemic stroke hospitalizations	8735	34 148	9024	12 263	3591	19 065
<i>N</i> per 100 000	265	480	169	96	88	344
<i>N</i> per 100 000 European standard population	190	407	145	97	77	218
Ischaemic stroke admissions of all stroke codes registered (%)	78	87	66	59	46	76
Mean age, years	72.6	69.5	73.8	71.6	72.9	76.2
Female gender (%)	49.1	52.4	45.1	48.2	52.7	49.4
Hospital days within previous year	4.6	4.9	2.4	3.0	6.4	4.6
Patients with comorbid conditions (%)						
Hypertension	70.9	76.5	65.4	77.2	NA	70.3
Coronary heart disease	9.9	13.3	6.9	3.6	NA	8.0
Atrial fibrillation	9.1	4.5	3.7	2.7	NA	9.0
Cardiac failure	5.1	4.6	2.8	1.7	NA	5.6
Diabetes mellitus	20.0	21.7	23.2	19.6	NA	16.8
Peripheral artery disease	2.6	8.7	2.1	0.5	NA	0.9
Cancer	6.4	2.9	2.7	3.7	NA	3.2
COPD and asthma	13.0	14.9	17.6	19.3	NA	11.0
Dementia	5.0	2.8	1.3	1.3	NA	3.1
Depression	14.4	15.3	11.3	15.4	NA	17.9
Mental disorders	4.2	5.7	1.9	5.6	NA	3.2
Alcoholism	1.2	1.0	0.0	0.3	NA	0.8
Patients with medication purchases during 365 days prior to stroke (%)						
Clopidogrel	3.4	8.5	4.1	NA	NA	4.1
Dipyridamole	10.3	1.9	0.0	NA	NA	4.9
Warfarin	15.1	0.6	2.8	NA	NA	8.0
Diuretic	39.8	1.9	41.7	NA	NA	45.3
Beta blocker	52.7	45.4	20.0	NA	NA	46.8
ACE inhibitor	26.4	59.6	35.6	NA	NA	24.0
Angiotensin receptor blocker	17.7	5.5	24.7	NA	NA	13.4
Statin	33.6	30.8	28.4	NA	NA	24.0
Insulin	7.7	5.5	5.9	NA	NA	8.3
Other hypoglycaemic drugs	16.0	18.8	19.3	NA	NA	11.7

NA, not available; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme. Data are mean or %.

[18]. Unlike the other countries with comprehensive coverage and linkage of the HDR, in the Netherlands a considerable proportion of hospitals do not participate in the Dutch HDR. The proportion of undefined stroke (ICD-10 I64) in the HDR was small in Finland and Hungary but high in Italy (17.8%) and the Netherlands (21.5%), and very high in Scotland (37.7%). As a consequence, the incidence of ischaemic stroke in these countries is underestimated and estimates of case fatality may be biased. A potential source of bias is misclassification or miscoding of stroke subtypes. Transient ischaemic attacks (TIAs) or ill-defined strokes were not included as coding practices with regard to TIA and ill-defined stroke might vary between countries, and there is evidence that TIA diagnoses and codifying TIAs with ischaemic stroke are not accurate in administrative registries [19,20]. Ischaemic stroke patients having a previous stroke more than 1 year before the hospital admission were

not excluded. This may have led to inclusion of more than 10% of patients who have had an earlier stroke [21,22].

The low incidence of hospitalizations in the Netherlands and Scotland, and the large proportion of undefined strokes in the Netherlands, Scotland and Italy, raise questions regarding comparability of patients at baseline. In the Netherlands and Scotland some of the patients with milder symptoms may have been treated at home, and also elderly patients with poor prognosis may have been treated conservatively in nursing homes [18].

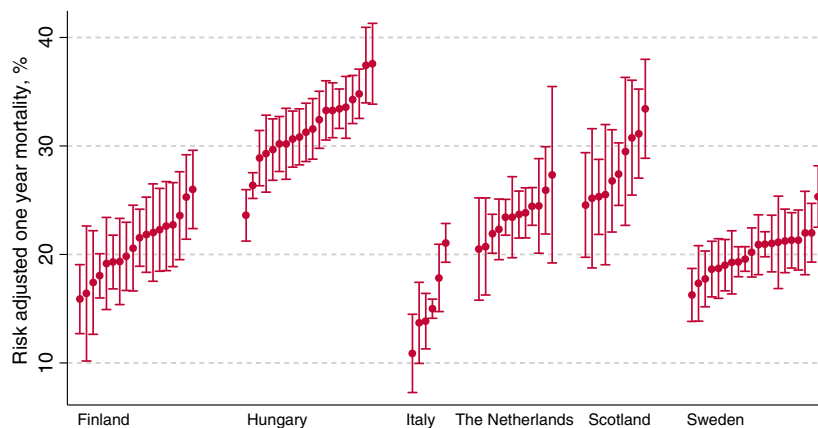
#### Validity of other variables

Scientific evidence on the accuracy of the HDR data on comorbidities, medication use, stroke centre treatment or thrombolysis are lacking in all the countries. However, baseline data on comorbid conditions were

**Table 2** Stroke centre classification, medication and case fatality of patients admitted to a hospital due to ischaemic stroke in six European countries and regions in 2007 (Italy: Lazio Region and City of Turin)

	Finland	Hungary	Italy	The Netherlands	Scotland	Sweden
Stroke centre classification of the first hospital episode (%)						
Comprehensive stroke centre	38.9	46.5	0.0	NA	87.5	NA
Primary stroke centre	32.2	40.7	35.8	NA	3.8	NA
General hospital	28.9	12.8	64.2	NA	7.8	NA
Patients with medication purchases in 365 days after the stroke (%)						
Clopidogrel	8.0	13.0	13.7	NA	NA	6.3
Dipyridamole	35.3	2.7	0.1	NA	NA	21.3
Warfarin	27.2	0.9 <sup>a</sup>	7.3	NA	NA	13.9
Diuretic	37.3	43.4	45.5	NA	NA	47.7
Beta blocker	45.2	37.3	22.8	NA	NA	46.6
ACE inhibitor	31.2	50.4	42.7	NA	NA	34.6
Angiotensin receptor blocker	21.5	7.0	26.1	NA	NA	14.9
Statin	55.4	32.7	43.0	NA	NA	48.1
Insulin	7.2	5.1	8.2	NA	NA	8.9
Other hypoglycaemic drugs	14.0	15.7	19.0	NA	NA	11.0
All-cause case fatality, age and sex adjusted (95% CI)						
30 day	10.2 (9.6–10.8)	16.3 (15.8–16.7)	7.5 (6.9–8.0)	12.4 (11.8–13.0)	13.2 (12.1–14.3)	9.3 (8.9–9.7)
90 day	14.5 (13.8–15.2)	22.6 (22.1–23.1)	10.7 (10.1–11.3)	16.7 (16.1–17.4)	19.0 (17.8–20.2)	13.3 (12.9–13.7)
365 day	20.7 (19.9–21.5)	31.0 (30.5–31.5)	16.0 (15.3–16.7)	23.4 (22.6–24.1)	28.2 (26.8–29.6)	20.1 (19.6–20.6)

NA, not available; ACE, angiotensin-converting enzyme. <sup>a</sup>Data on dicoumarol, the prevalent oral anticoagulant in Hungary, are not available.

**Figure 1** Age- and sex-standardized case fatality during the first year after incident ischaemic stroke in 2007 at different regions of six countries: Finland, Hungary, Italy (Lazio Region and City of Turin), the Netherlands, Scotland and Sweden.

collected by combining the HDR data with data on purchase of medicines. The former seem to capture the more severe conditions such as cancer or myocardial infarctions, whilst the latter capture conditions such as hypertension or diabetes which less often lead to hospitalization and are poorly recorded in hospital data. Nevertheless, only limited access to medication purchase data from the Netherlands and from the City of Turin in Italy was available, and no medication purchase data at all from Scotland. Despite these shortcomings, prevalence rates of cardiovascular diseases, atrial fibrillation and diabetes at baseline as estimated by our method are similar to those reported

for ischaemic stroke patients in population-based studies [1,23].

### Selection of patients

In order to assess the possible differences in selection of patients to our database, our incidence data were compared with those of population-based incidence studies. Population-based stroke incidence studies have reported age- and sex-specific ischaemic stroke incidence rates for many of the participating countries [9,18,24–29]. In addition, the World Health Organization (WHO) has produced its own estimates for total

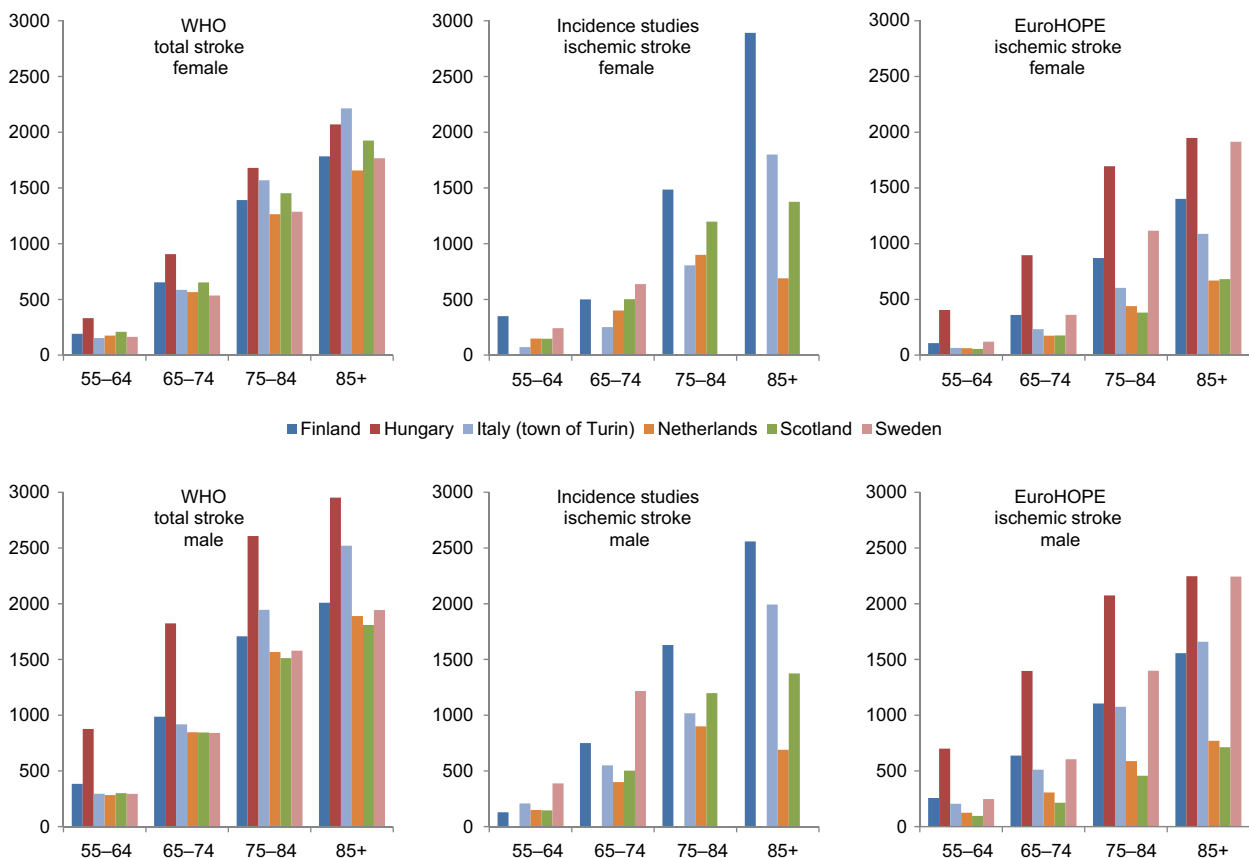
**Table 3** Selection of patients to the EuroHOPE database – factors which may decrease the coverage of ischaemic stroke cases in the registers of the EuroHOPE countries (percentages of cases)

	Finland, %	Hungary, %	Italy, %	The Netherlands, %	Scotland, %	Sweden, %
Stroke hospitalization rate for non-fatal cases	95 [22]	90 <sup>a</sup>	87 [27]	60	62	84 [29]
Proportion of hospitalized patients registered and linkable in the HDR	100	100	100	63	100	100
Sensitivity of ischaemic stroke coding in the HDR for population-based ischaemic stroke	80 [16]	NA	NA	NA	68 (LOT)	NA
Positive predictive value of ischaemic stroke coding in the HDR	82 [16]	NA	NA	NA	95	NA
Proportion of undefined stroke coding out of all stroke diagnoses in the EuroHOPE database	0.4	3	18	22	38	8

HDR, hospital discharge register; NA, not available; LOT, based on comparison of data from hospital records and stroke register for the Lothian region, 2010–2011. <sup>a</sup>Expert opinion of the EuroHOPE research group.

stroke incidence per age group [30]. As expected, ischaemic stroke incidence estimates were lower with the EuroHOPE methodology than in the population-based studies (Fig. 2). On the other hand the population-based studies were conducted 20 years prior to the present study, and ischaemic stroke incidence has

mostly declined since [9], e.g. in Finland at a rate of 2% per annum [31], although in the Netherlands the incidence seems to have been rather stable over time [32]. The ranking of the countries seems to be similar in the previous studies, and the incidence rates in Scotland and in the Netherlands are low in the Euro-

**Figure 2** Incidence of ischaemic stroke in subgroups of age and gender in Finland, Hungary, Italy (Lazio Region and City of Turin), the Netherlands, Scotland and Sweden according to the WHO survey [30], population-based epidemiological studies [18,24–26,29] and the EuroHOPE data.



HOPE data as patients treated out of hospital were not included in the present study. Based on this comparison, our method is expected to be reasonably accurate and generalizable for national monitoring of stroke (comparisons of regions within countries), and applicable for international comparisons in all the participating countries and regions except for Italy, Scotland and the Netherlands.

### Baseline characteristics and treatments

Deficient reporting of comorbidity was found in Italy (particularly in the City of Turin), the Netherlands and Scotland due to incomplete reporting of secondary diagnoses in the hospital discharge data and lack of comparable out-of-hospital medication data. Nevertheless, our data suggest that there were marked differences in prescription patterns between the countries (Table 2): warfarin, dipyridamole and statins were recorded as being used in Finland and antihypertensives and antidepressants in Sweden more often than in other countries both before and after stroke, and the use of preventive medications in general was lowest in Hungary. However, data on warfarin use in Hungary were not obtained.

There is evidence indicating that treatment in comprehensive stroke centres decreases case fatality amongst ischaemic stroke patients [12]. A recent paper describing data from six centres in France, Lithuania, UK, Spain, Poland and Italy between 2004 and 2006 with follow-up for 1 year showed that better organization of care was associated with improved survival [33]. Unfortunately our data obviously underestimate the proportion of patients obtaining stroke centre treatment, which has also been considered an important quality criterion [34]. Our experts from the participating countries often did not have access to hospital level information about treatment in stroke centres. In addition, the coding of thrombolytic therapy in our data was incomplete and severely underestimates the use of this treatment as has been found also in earlier studies [6]. Other missing quality indicators in all the countries include in-hospital care components, such as use of imaging modalities and rehabilitation. Recently, the European Stroke Organization issued recommendations for establishing stroke care units and stroke centres [34]. It is recommended to carry out a new survey to assess the current situation in Europe.

### Case fatality

The large proportion of patients with diagnostic code 'undefined stroke' makes the comparison for

case fatality rate between Italy, the Netherlands and Scotland and the other countries subject to bias. Also, inability to fully adjust for case mix is a major limitation of our study. It was not possible to adjust for stroke baseline severity, which is known to be a major predictor of outcome [35,36]. Significant national differences in baseline stroke severity might exist, depending on primary and secondary prevention intensity. For optimal case mix adjustment clinical registries are needed [37]. One reason for variability in outcome may also be related to the differences in the gross domestic products, which has to be further explored within the EuroHOPE study [38].

The OECD performance data on age- and gender-standardized 30-day case fatality for ischaemic stroke in the year 2007 were in Finland, Hungary, Netherlands and Sweden 11.0%, 16.1%, 11.8% and 10.6%, respectively (<http://stats.oecd.org/>). These mortality rates are very similar to those found in the present EuroHOPE study, where individual level analyses and long-term follow-up was possible.

Standardized methods were employed to undertake a detailed assessment of regional variation within countries in case fatality after ischaemic stroke amongst hospitalized patients. Wide variation was found between regions in all the participating countries with the highest variation in Hungary. The smallest variation observed in the Netherlands may be partly due to the relatively large size of the regions.

### Health policy and scientific implications

In order to make pertinent choices on how to improve effectiveness of treatment, data are needed on how patients are treated and what their outcomes are in real world settings [7,39]. The EuroHOPE database was modelled in line with the PERFECT database, which is used in Finland to evaluate performance at regional and hospital level in treatment of major diseases, including stroke [4–6,12,40]. The main benefits of these register studies reflect their ability to utilize existing databases to capture the patient population beyond the acute phase, in this case for a year or until death.

Despite uncertainties in the EuroHOPE analysis, three major conclusions can be drawn. First, the incidence and 1-year case fatality of patients admitted with ischaemic stroke seems to be higher in Hungary than in the other countries. However, the impact of the healthcare for this higher case fatality cannot be ascertained as the register data do not allow adjustment for baseline severity. Whilst Hungarian patients have higher incidence, they probably also have

more severe stroke when arriving at hospitals, and the findings of EuroHOPE suggest national measures directed both on primary and secondary prevention and to the development of clinical pathways for stroke care. Secondly, there are large differences in the 1-year case fatality after admissions to hospital with an ischaemic stroke code between regions within all the EuroHOPE countries. Thirdly, detailed data on case mix and treatment practices is currently not comprehensively available in administrative registries on ischaemic stroke. Therefore, additional studies are required to investigate further the apparent differences in outcome. Case fatality in patients with ischaemic stroke was <20% in three regions in Finland and two regions in Sweden. This may reflect differences in case definition and ascertainment, and in patient characteristics, but substantive variation in the extent to which evidence-based practice has been implemented cannot be excluded. A wider adoption of clinician-led analysis of the nature and quality of care delivered to the population of stroke patients is urged. The Scottish Stroke Care Audit is an example of how this can be achieved (<http://www.strokeaudit.scot.nhs.uk/index.html>).

The validity of administrative register data for ischaemic stroke should be developed further to facilitate international comparisons. It would be appropriate to create population-based stroke registers linked to mortality and other data in order to provide more detailed information about case mix. The long-term goal of the EuroHOPE project is to provide regularly updated comparative data on clinical processes and outcomes of patients, including reasons for differences between countries and regions, and ultimately linking quality of treatment and costs. Besides continuing the international collaboration, national efforts to identify best practices and to assess the reasons behind regional differences in outcomes are recommended.

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## Disclosure of conflicts of interest

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare no conflict of interest related to the present paper.



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