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ORIGINAL ARTICLE

Population impact of losartan use on stroke in the European Union (EU): Projections from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study

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The Losartan Intervention for Endpoint reduction in hypertension (LIFE) study was designed to compare losartan- *vs* atenolol-based antihypertensive treatment on cardiovascular morbidity and mortality in a population of 9193 hypertensive patients with left ventricular hypertrophy (LVH). In LIFE, the losartan-based treatment further reduced the primary composite end point (cardiovascular death, myocardial infarction, or stroke) by 13% (risk reduction (RR) 0.87, 95% confidence interval (CI) 0.77–0.98, $P = 0.021$). The further reduction in stroke with losartan (RR 0.75, 95% CI 0.63–0.89, $P = 0.001$) was the major contributing factor to the reduction in the primary end point. Our objective was to project the reduction in stroke observed with a losartan- *vs* an atenolol-based antihypertensive treatment regimen in the LIFE study to the European Union (EU) population. The number of stroke events averted was estimated by identifying the number of persons in the EU expected to meet the LIFE inclusion criteria, and multiplying this figure by the cumulative incidence risk difference in stroke from LIFE at 5.5 years. The age- and gender-specific prevalence of hypertension, electrocardiographically (ECG)-diagnosed LVH among those with hypertension (inclusion criteria), and heart failure among those with LVH and hypertension (exclusion criteria) were applied to the EU census estimates. We conservatively projected that an estimated 7.8 million individuals aged 55–80 years in the EU are affected by hypertension and ECG-diagnosed LVH. Use of a losartan-based antihypertensive treatment in this population is projected to prevent approximately 125 000 first strokes over a 5.5-year period. A population-wide prevention strategy of using losartan in patients with LVH and hypertension has the potential to have a major public health impact by reducing the morbidity and mortality of stroke in the EU.

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Introduction

As the second leading cause of death worldwide and a leading cause of long-term disability, stroke imposes a significant burden on society and on healthcare budgets.[1,2] High blood pressure is the most important modifiable risk factor for stroke. Increased age and the presence of left ventricular hypertrophy (LVH) have also been identified as important risk factors for stroke.[3] The annual costs of stroke were an estimated $51.2 billion in the United States in 2003, of which $31.0 billion were direct costs and $20.2 billion were indirect costs.[4] The costs of stroke have been estimated to account for 3–4% of total healthcare costs in Western European countries. Per-patient costs of stroke in the European Union (EU) have recently been estimated using time horizons from 6 months to the patient's lifetime.[5–11] Lifetime direct costs of stroke (1996) estimated from a model with two randomized trials of stroke treatment conducted in

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13 countries were $82 000.[12] The incidence and costs of stroke are expected to increase substantially as the population of industrialized countries ages in the coming decades.[13]

The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study was a randomized, double-masked, active-control clinical endpoint trial that studied a population of 9193 hypertensive patients with electrocardiographic (ECG) LVH in Denmark, Finland, Iceland, Norway, Sweden, the United Kingdom, and the United States. The major hypothesis of LIFE was that, in patients with essential hypertension and LVH, losartan would reduce the incidence of cardiovascular morbidity and mortality to a greater extent than the beta-blocker atenolol, possibly through a greater effect on regression of LVH. Cardiovascular morbidity included nonfatal, clinically evident acute myocardial infarction, and nonfatal stroke; mortality was death due to fatal myocardial infarction, fatal stroke, sudden death, progressive heart failure, or other cardiovascular causes.[14]

In LIFE, randomization of the angiotensin II antagonist losartan further reduced the adjusted combined risk of cardiovascular morbidity and mortality by 13% (risk reduction (RR) 0.87, 95% confidence interval (CI) 0.77–0.98, $P=0.021$) as compared with atenolol. The between-group differences were mainly driven by differences in stroke, the most common component of the composite end point. The risk of stroke was reduced by 25% (RR 0.75, 95% CI 0.63–0.89, $P=0.001$), with the differential in stroke benefit being independent from blood pressure control. There were no significant differences in cardiovascular mortality (RR 0.89, 95% CI 0.73–1.07, $P=0.206$) or MI (RR 1.07, 95% CI 0.88–1.31, $P=0.491$).[15]

That losartan-based therapy reduced the incidence of stroke by 25% against a beta-blocker-based therapy, which has been shown to reduce the incidence of stroke by 25 to 47% against placebo, is of great clinical importance.[16–19] Our objective was to estimate the number of strokes that could potentially be averted with use of losartan-based therapy in comparison to atenolol-based therapy in older patients with hypertension and ECG-confirmed LVH in the EU over a 5.5-year period.

Methods

This analysis projected the population impact on stroke incidence of using losartan-based as opposed to atenolol-based treatment in the 15 EU member states. The EU presently includes Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Spain, Sweden, the Netherlands, and the United Kingdom. Gender- and age-specific population estimates for each EU member were based on the year 2000 US Census Bureau International Database (IDB).[13]

LIFE inclusion/exclusion criteria

The LIFE study design, inclusion/exclusion criteria, organization, and end point definitions have been described previously.[14] In LIFE, eligible participants were men or women 55–80 years of age with previously treated or untreated hypertension and ECG-determined LVH. LVH was diagnosed by ECG based on the gender-specific Cornell voltage–duration product criteria or the Sokolow–Lyon voltage criteria. Patients with LVH diagnosed by ECG were randomized provided that off antihypertensive therapy mean trough sitting diastolic blood pressure was 95–115 mmHg or sitting mean systolic blood pressure reading was 160–200 mmHg (inclusive). Exclusion criteria included recent myocardial infarction, stroke, heart failure, or known left ventricular ejection fraction $\leqslant 40\%$.

Population inclusion/exclusion criteria

We identified the number of persons in the EU, based on age and hypertension with ECG-diagnosed LVH, expected to meet criteria of the LIFE trial. We excluded patients with heart failure. Age- and gender-specific population-based prevalences were used for each of the three main criteria, and were applied to recent population census estimates at the country level.[13]

Hypertension

Hypertension prevalence estimates in the EU were identified from the published literature. To be included, a study must provide a hypertension prevalence estimate representative of a particular country or region within the country, (b) based on the $\geqslant$160/95-mmHg threshold, and (c) based on at least two blood pressure readings per individual to reduce measurement error. In addition, the study must contain a sample that broadly covered the LIFE population. Namely, the sample must contain both male and female patients and cover at least a portion of the LIFE age range.

Published studies were available for England,[20] Finland,[21] France,[22] Germany,[23] Italy,[24] Spain,[25] Sweden,[26] and the Netherlands.[27] Each study used sampling of a population registry to ensure the study population was representative of the particular country or region. Six of these studies (from England, Finland, Germany, Italy, Spain, and Sweden) formed the basis of a recent analysis by Wolfe-Maier *et al*.[28] Six studies that formed the basis of the Wolfe-Maier *et al* paper reported hypertension prevalence based on the 140/90-mmHg threshold. The prevalence of hypertension using the 160/95-mmHg threshold for these six studies was obtained directly from the authors of the Wolfe-Maier paper.[28]

We were unable to identify hypertension prevalence sources that met the criteria above for seven

EU countries (Austria, Belgium, Denmark, Greece, Ireland, Luxembourg, and Portugal). For these countries, prevalence data were matched based on geographic proximity. The German prevalence was used for Austria, the Netherlands for Belgium and Luxembourg, Sweden for Denmark, Italy for Greece, the United Kingdom for Ireland, and Spain for Portugal.

The portion of the LIFE age range (55–80 years) covered by the eight hypertension studies varied across studies. Three of the studies (Finland,[21] France,[22] and Spain[25]) covered only the 55–64-years age range. Four of the studies (England,[20] Germany,[23] Italy,[24] and Sweden[26]) covered only the 55–74-years age range. The Dutch study was the only one to cover the entire age range.[27] To provide a hypertension prevalence estimate for the 65–74-years age group for countries without data in the 65–74-years age group, the mean prevalence in countries with data for the 65–74-years age group were used. Prevalence in the 75–80-years age group was assumed to be the same as the prevalence in the 70–74-years age group in countries where data were unavailable.

The resulting estimated prevalence of hypertension varied across the eight EU countries. The prevalence of hypertension (standardized to the EU age and gender distribution among those 55–80 years of age) used in this projection was as follows: Finland 45.4%, France 50.7%, Germany 60.0%, Italy 46.5%, Spain 45.4%, Sweden 46.1%, the Netherlands 34.2%, and the United Kingdom 48.2%.

LVH hypertrophy

Estimates of the prevalence of LVH in patients with essential hypertension depend largely on the measurement technique and scoring algorithm used, and the patient population studied.[29,30] As these factors can significantly affect LVH prevalence, we sought to identify an estimate of LVH prevalence based on the same measurement technique and scoring algorithm used in LIFE. A pilot study designed to determine the prevalence of ECG-diagnosed LVH among mainly treated hypertensive patients who otherwise met LIFE criteria provided such an estimate. The pilot study was conducted in Scandinavia and studied 1500 mainly treated hypertensive patients who otherwise met entry criteria for LIFE.[14] In this study, the prevalence of LVH was 22%.[14]

Heart failure

We excluded patients with heart failure. We were unable to identify a European data source for the prevalence of heart failure among those aged 55–80 years with hypertension and LVH. Therefore, we used the US National Health and Nutrition Examination (NHANES-III) survey (non-Hispanic Caucasian population).[31,32] NHANES III was conducted from October 1988 through October 1994 and comprised a national probability sample of the United States. In NHANES-III, heart failure was identified from patient self-reporting of physician-diagnosed heart failure. Sampling weights were used to take into account the complex survey design.

Patients were classified as having hypertension if SBP $\geqslant$160 mmHg or DBP $\geqslant$95 mmHg, or if patients self-reported current use of antihypertensive medication. Patients were classified as having LVH on the basis of a standard 12-lead resting ECG using the LIFE criteria. The prevalence of heart failure among hypertensive patients with LVH was 21.0% among males 55–80 years of age, and 23.1% among female patients 55–80 years of age. Thus, the heart failure exclusion reduced the LIFE target population by slightly over one-fifth.

Cumulative incidence of stroke

We estimated the incidence of first stroke from the LIFE database using the cumulative incidence competing risks method to account for the possibility that a patient may die without having had a stroke.[33] To adjust for incomplete patient follow-up and possible imbalances between treatment groups in baseline risk characteristics, we based these estimates on Cox models adjusting for degree of LVH and Framingham risk score.

Sensitivity analysis

We evaluated the sensitivity of the projection using one-way sensitivity analysis. The variables used in the sensitivity analysis included (a) hypertension prevalence, (b) LVH prevalence, (c) heart failure prevalence, and (d) stroke cumulative incidence difference between losartan- and atenolol-treated patients in LIFE.

The hypertension prevalence was varied using the lowest hypertension prevalence used in the projection (Netherlands, age and gender standardized prevalence of 34.2%) and the highest hypertension prevalence (Germany, 60.0%). The prevalence of LVH was varied from a low of 9% (from a Spanish study of mild hypertensive patients, average age of 49 years, treated in primary care)[29] to a high of 40% (based on the average value of studies reporting echocardiogram-diagnosed LVH).[30,34–40] Heart failure prevalence was evaluated by increasing and decreasing the baseline heart failure prevalence (21.0 and 23.1% for male patients and female patients) by 50%. The stroke cumulative incidence difference was based on the upper and lower boundary of the 95% confidence interval for the parameter (0.6 and 2.6%).

Results

Projected number meeting LIFE entry criteria

There were an estimated 377.4 million residents in the EU in the year 2000 (Table 1) of which 90.3 million (24.0% of total) were aged 55–80 years. The number of individuals 55–80 years of age with hypertension was 45.7 million (12.1% of total). An estimated 10.1 million of these patients (2.7% of total) met the LVH criteria. After excluding those with heart failure, an estimated 7.8 million (2.1% of total) met the main LIFE inclusion criteria.

Cumulative incidence of stroke

Table 2 shows the cumulative incidence of first stroke using the cumulative incidence method from 0–5.5 years. Losartan-treated patients had a statistically significant lower incidence of first stroke ($P<0.003$) at each 6-month interval. Furthermore, the difference in incidence of first stroke between the atenolol and losartan arms (ie, the risk difference) increased over time—from 0.2% at 6 months to 1.6% at 5.5 years. This represented a 25% reduction in the risk of stroke for the losartan-based compared with the atenolol-based treatment regimens.

Projected number of strokes averted

Table 3 demonstrates the number of patients with first stroke events per EU member state at 5.5 years that could potentially be averted with losartan. Overall, we project that in the target population, 125 269 first strokes could be averted with losartan. The potential number of cases averted was largest in Germany (35 438), followed by Italy (19 171), France (18 430), the United Kingdom (17 472), and Spain (12 877). Figure 1 charts the potential number of first stroke events averted by country over 5.5 years, in order of potential impact. Figure 2 shows the cumulative number of first strokes that could potentially be averted in the EU. This figure reveals both, continued risk of stroke and continued effect of losartan over atenolol over time.

Sensitivity analysis

The projection was most sensitive to the prevalence of LVH, based on the range of values used in the one-way sensitivity analysis (Figure 3). The number of

Table 2 Cumulative incidence of first stroke in LIFE (percent of patients with event)

Follow-up (years)	*Atenolol*	*Losartan*	*Difference*	*95% CI*
0.5	0.9	0.7	0.2	0.1, 0.4
1.0	1.5	1.2	0.4	0.1, 0.6
1.5	2.1	1.6	0.5	0.2, 0.9
2.0	2.8	2.1	0.7	0.2, 1.1
2.5	3.3	2.5	0.8	0.3, 1.3
3.0	3.7	2.8	0.9	0.3, 1.5
3.5	4.3	3.3	1.1	0.4, 1.8
4.0	4.9	3.7	1.2	0.4, 2.0
4.5	5.3	4.0	1.3	0.5, 2.2
5.0	6.0	4.5	1.5	0.5, 2.4
5.5	6.5	4.9	1.6	0.6, 2.6

Note: Adjusted for LVH and baseline Framingham risk score.
CI = confidence interval.

Table 1 Estimated number of persons (in thousands) and percent of persons in EU meeting LIFE inclusion/exclusion criteria

	Total population	*55–80 population*	*55–80, with hypertension population*	*55–80, with hypertension, LVH population*	*55–80, with hypertension, LVH, w/o heart failure population (LIFE criteria)*	*Percent meeting LIFE criteria (among total population)*	*Percent meeting LIFE criteria (among 55–80 population)*
	N	*N*	*N*	*N*	*N*	*(%)*	*(%)*
Austria	8113	1910	1138	250.4	194.8	2.4	10.2
Belgium	10 264	2439	845	185.8	144.5	1.4	5.9
Denmark	5337	1213	546	120.2	93.6	1.8	7.7
Finland	5169	1171	575	126.6	98.5	1.9	8.4
France	59 382	12 952	6728	1480.1	1151.9	1.9	8.9
Germany	82 188	21 708	12 937	2846.1	2214.9	2.7	10.2
Greece	10 559	2697	1259	276.9	215.5	2.0	8.0
Ireland	3792	671	317	69.8	54.4	1.4	8.1
Italy	57 719	14 980	7002	1540.4	1198.2	2.1	8.0
Luxembourg	439	95	32	7.1	5.5	1.3	5.8
Portugal	10 048	2360	1167	256.8	199.7	2.0	8.5
Spain	40 016	9466	4702	1034.4	804.8	2.0	8.5
Sweden	8924	2185	994	218.7	170.3	1.9	7.8
The Netherlands	15 908	3312	1114	245.0	190.6	1.2	5.8
United Kingdom	59 522	13 253	6374	1402.3	1092.0	1.8	8.2
EU total	377 380	90 412	45 730	10 060.8	7829.3	2.1	8.7

55–80 = 55–80 years of age.

Table 3 Projected number of first-stroke events with atenolol and losartan in the EU after 5.5 years of treatment

	Projected number of strokes		
	Atenolol	*Losartan*	*Strokes averted*
Austria	12 664	9547	3117
Belgium	9394	7082	2312
Denmark	6085	4587	1498
Finland	6403	4827	1576
France	74 872	56 442	18 430
Germany	143 968	108 530	35 438
Greece	14 006	10 558	3448
Ireland	3536	2666	870
Italy	77 880	58 710	19 170
Luxembourg	357	269	88
Portugal	12 983	9787	3196
Spain	52 313	39 436	12 877
Sweden	11 071	8346	2725
The Netherlands	12 390	9340	3050
United Kingdom	70 981	53 509	17 472
EU total	508 903	383 636	125 267

Note: Among 7.8 million who would qualify for the LIFE trial.

strokes averted was 51 246 based on the low-LVH estimate, and increased to 227 761 for the high-LVH estimate (a range of 176 515 first stroke events from low to high). The cumulative incidence difference for stroke was the next most sensitive variable, ranging from 46 976 to 203 562 strokes averted (a range of 156 586 strokes). This was followed by hypertension prevalence, which ranged from 84 728 to 148 663 strokes averted (a difference of 63 935), and heart failure prevalence (range from 143 121 to 107 417; range of 35 704).

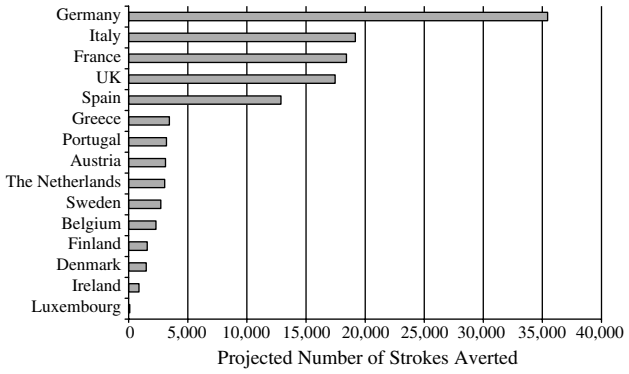

Figure 1 Projected number of first stroke events averted with atenolol and losartan in the EU after 5.5 years of treatment by country.

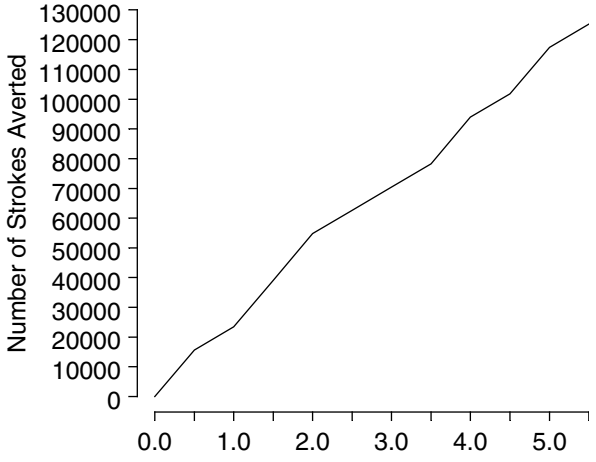

Figure 2 Projected cumulative number of first stroke events averted with the use of a losartan- *vs* an atenolol-based antihypertensive regimen in the EU over a 5.5-year period.

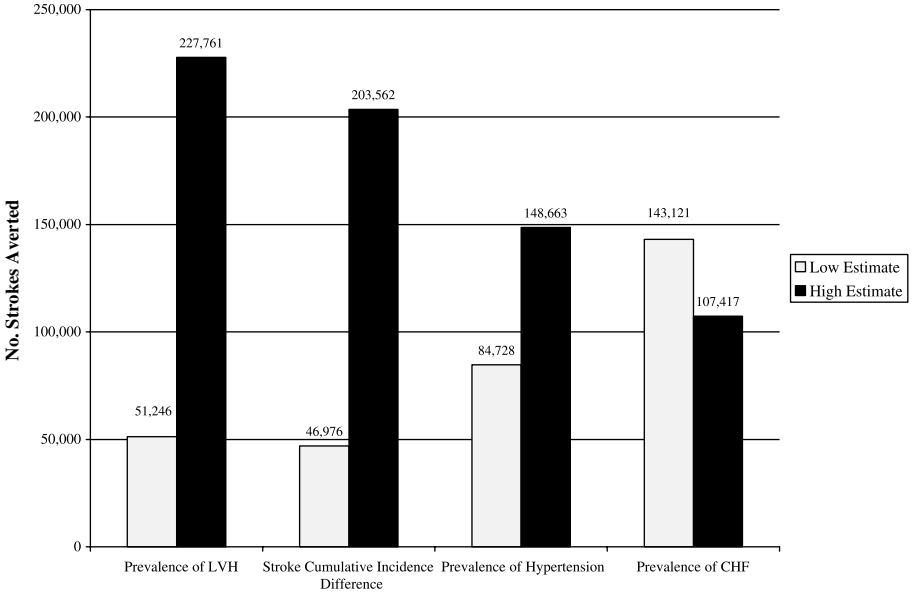

Figure 3 One-way sensitivity analysis of key variables on the projected number of strokes averted. Baseline estimate of strokes averted is 125 267 over a 5.5-year period.

Discussion

In order to understand the potential population impact of the LIFE trial results, we projected the stroke incidence observed in the LIFE trial to the 15 EU member states. When the main LIFE entry criteria (age 55–80 years, hypertension, LVH, without heart failure) were applied to the EU member states, 7.8 million residents met the criteria. These 7.8 million individuals represent 2.1% of the total EU population. Based on the stroke cumulative risk difference observed in LIFE, we projected that use of a losartan-based treatment regimen would reduce the number of first stroke events by 125 267 over a 5.5-year period in the EU. The results were most sensitive to variation in the prevalence of LVH and cumulative incidence risk difference between losartan- and atenolol-based regimens. The significant reductions in stroke with a losartan-based *vs* atenolol-based regimen should be viewed as representing an incremental improvement relative to the benefits of conventional antihypertensive therapies, beta-blockers and diuretics, which have been shown to reduce the incidence of stroke in placebo-controlled trials by 25 to 47%.[16–19] Thus, identifying the nearly 8 million hypertensive patients in the EU with LVH and treating them with losartan has the potential to substantially reduce morbidity and mortality due to stroke in the region.

The implications of the LIFE trial are particularly important in the EU setting. Western Europe has recently been described as a high-hypertension-prevalence, high-stroke region.[28] The prevalence of hypertension was recently estimated to be approximately 60% higher in six EU countries compared with the United States and Canada. Furthermore, there was a strong, statistically significant ecological association between the prevalence of hypertension and the stroke mortality rate in these countries.[28] Another trend in the EU, like in most industrialized regions, is the ageing population. It is projected that the percentage of persons aged 55 years or older will increase from 27.3 to 37.6% from 2000 to 2025 in the EU.[13] As blood pressure and age are among the most important risk factors for stroke, there is an urgent need to identify effective strategies to prevent new stroke cases in the EU.

The reduction in incidence of strokes projected here would have a significant impact on reducing stroke-related healthcare utilization and costs. Using an estimate of the 1996 lifetime costs of managing stroke from Caro *et al* ($82 000), losartan has the potential to reduce stroke-related direct medical costs by $10.3 billion over 5.5 years.[12] Clearly, a full economic evaluation of LIFE, which incorporates all relevant medical costs, is required to determine the full economic impact of losartan *vs* atenolol in hypertensive patients with LVH. Furthermore, there are consequences of stroke that cannot be evaluated in monetary terms, such as suffering, life satisfaction, and effects on caregivers, that should also be considered.

Our projection from LIFE to the EU population may be a conservative one, by strictly limiting the population for projection to those in the EU who met LIFE entry criteria. For instance, if the benefits seen with losartan in LIFE were also present in hypertensives without ECG-LVH, the reduction in the number of strokes in Europe would be larger than our estimate of 125 267. Also, our projection is conservative because the comparison group for this projection were patients treated with beta-blockers, which have been shown to reduce the incidence of stroke in randomized trials in which blood pressure was substantially reduced.[16–19] Treatment with a beta-blocker, as used in LIFE, is likely to be more effective than average hypertensive treatment provided in the EU community setting in general. It is estimated that only 25–32% of patients with hypertension in the EU are taking any antihypertensive medications, and even fewer patients with hypertension have their condition controlled.[28]

Results from LIFE demonstrated the stroke-reducing benefit of a losartan-based *vs* atenolol-based regimen among patients with hypertension and LVH. When projected to the EU member states, a population-wide prevention strategy of using losartan in patients with LVH and hypertension has the potential to have a major public health impact in reducing the morbidity, mortality, and costs of stroke in the EU.

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