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Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study

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Aims Antihypertensive drug therapy is a major strategy of stroke prevention among hypertensive patients. The aim of this study was to estimate the excess risk of stroke associated with non-adherence to antihypertensive drug therapy among hypertensive patients.

Methods and results We conducted a population-based study using records from Finnish national registers for 1 January 1995 to 31 December 2007. Of the 73 527 hypertensive patients aged 30 years or older and without pre-existing stroke or cardiovascular disease, 2144 died from stroke and 24 560 were hospitalized due to stroke during the follow-up. At the 2- and 10-year follow-up after the start of continuous antihypertensive medication, non-adherent patients had 3.81 [95% confidence interval (CI) 2.85–5.10] and 3.01 (95% CI: 2.37–3.83) times higher odds of stroke death when compared with the adherent patients. The corresponding odds ratio (OR) for stroke hospitalization was 2.74 (95% CI: 2.35–3.20) at Year 2 and 1.71 (95% CI: 1.49–1.96) at Year 10. In the stroke-event year, the ORs were higher, 5.68 (95% CI: 5.05–6.39) for stroke death and 1.87 (95% CI: 1.72–2.03) for hospitalization. Among those using agents acting on the renin–angiotensin system combined with diuretics or β-blockers, these ORs were 7.49 (95% CI: 5.62–9.98) and 3.91 (95% CI: 3.23–4.75), respectively. The associations between non-adherence and stroke followed a dose–response pattern—the poorer the adherence, the greater the risk of death and hospitalization due to stroke.

Conclusion These data suggest that poor adherence to antihypertensive therapy substantially increases near- and long-term risk of stroke among hypertensive patients.

Keywords Adherence • Antihypertensive therapy • Stroke • Hypertension • Mortality

Introduction

Stroke causes 11% of all deaths worldwide and is the second commonest cause of death after ischaemic heart disease.[1] In 2010, stroke-related disability was the third commonest cause of reduced, disability-adjusted life-years.[2] This public health problem not only affects Western countries as the continuing industrialization of Asia and Africa is introducing unhealthy lifestyles that are accompanied by an increased risk of stroke and other cardiovascular diseases.[3,4]

High blood pressure is the leading risk factor for the global disease burden, increasing, in particular, the risk of stroke and heart disease.[5] Antihypertensive therapy is the most effective primary prevention strategy used against stroke.[6–10] At least two previous studies have highlighted the importance of patients' adherence to antihypertensive therapy in terms of successful primary prevention of stroke and other cardiovascular events.[11,12] However, these studies measured adherence only at one point in time and thus, by design, were unable to investigate changes in adherence over time prior to a stroke event or determine the short- and long-term risk associated with poor adherence.

We used nationwide prescription, hospitalization, and death registers to determine the excess risk of stroke associated with

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non-adherence to antihypertensive therapy among hypertensive patients without pre-existing stroke or cardiovascular events. To describe the evolution of stroke risk associated with poor adherence over time, we estimated the year-by-year trajectories between adherence and stroke risk prior to the first presentation of non-fatal and fatal incident stroke.

Methods

Study design

We conducted a record-linkage study that was based on the *Statistics Finland Labour Market* data file that covers all Finns with a linkage to death records during the period 1 January 1995 to 31 December 2007. These data are collected on an annual basis from different administrative sources to provide labour-force statistics. We used the individually unique personal identification codes of Finns to link these data to medication records from the *National Drug Reimbursement Register* and the *Drug Prescription Register* kept by the Social Insurance Institution of Finland, along with information on principal causes of hospitalizations between 1 January 1987 and 31 December 2007, provided by the National Institute for Health and Welfare (linkage permission TK 53–1519–09).

Owing to data-protection regulations concerning living persons, Statistics Finland provided only an 11% sample of the whole data set. To maintain power in the mortality analyses, we further obtained an oversample of those who died in the period between 1 January 1995 and 31 December 2007 (for whom the data-protection regulations are less strict) and thus covered altogether 80% of all deaths in that period. We used sampling weights, constructed from the sampling probabilities, in order to take account of the sampling design. Thus the results derived from the analyses of this study were nationally representative. We restricted the sample in this study to hypertensive persons over 30 years of age, as stroke events are rare at younger ages (*Figure 1*).

Hypertension

Persons diagnosed with hypertension and requiring continuous antihypertensive medication were identified from the *Drug Reimbursement Register* from 1 January 1970 to 31 December 2007. This register contains information on those granted special reimbursement for antihypertensive medication and the date the medication was granted. To examine adherence to antihypertensive therapy in primary prevention (with the date of initiation of drug treatment), patients eligible for antihypertensive medication from as early as 1 January 1970 to 31 December 2007 were identified from the register. We excluded those using antihypertensive drugs for any indications other than hypertension. The Finnish national sickness insurance scheme covers all permanent residents in Finland (5.2 million in 2003) and provides special reimbursement for many chronic diseases, including hypertension.

Adherence to antihypertensive therapy

Since 1994, all prescriptions reimbursed by the sickness insurance scheme have been recorded in the *Drug Prescription Register*. From this register, we obtained data for antihypertensive drugs, coded as C02 (antihypertensives), C03 (diuretics), C07 (beta-blocking agents), C08 (calcium channel blockers), or C09 (agents acting on the renin–angiotensin system) according to the WHO Anatomical Therapeutic Chemical Classification[13] from 1 January 1995 through 31 December 2007. The Social Insurance Institution obtains these data from all pharmacies in Finland as part of the national drug reimbursement scheme. These records cover the entire study population but exclude hospitalized patients.

In this study, year-by-year adherence was determined as the days covered by filled prescriptions (i.e. purchases) for antihypertensive medication during the period from 1 January 1995 to 31 December 2007. The rates of filled prescriptions are considered to be accurate measures of medical adherence in a closed pharmacy system, such as in Finland, especially when the refills are measured at several points in time.[14] In Finland, all prescriptions are written by a physician, and each prescription can cover a maximum use of 3 months.

For the analysis, annual adherence and non-adherence were defined on the grounds of days covered by the purchases of antihypertensive drugs. A period of 365 days was defined as adherent for a patient if he or she had three or more purchases of antihypertensive drugs within that period, and the distance between the first and the last purchase was 180 days or more. The period of 365 days was defined as non-adherent if these requirements were not met. This approach corresponds to an adherence level of $<80\%$, a generally used definition of poor medication adherence.[14,15] To ensure that our findings were not sensitive to this 80% cut-off definition of non-adherence, we ran sensitivity analyses using alternative cut-offs, such as $<30\%$ (poor adherence), 30–80% (intermediate adherence), and $>80\%$ (high adherence), defined by yearly antihypertensive purchases of zero to one, two, and three or more, respectively.

Stroke

The primary outcomes of the study were non-fatal stroke (hospitalizations) and fatal stroke (deaths) between 1995 and 2007. The hospitalizations or deaths due to stroke during the follow-up were indicated by an underlying cause of hospitalization or death from a cerebrovascular disease (ICD-10 code I60–I69). So that reverse causation bias would be minimized, patients who had a history of a non-fatal cardiovascular event leading to hospital care prior to the non-fatal or fatal stroke (in the period between 1987 and 1994) were excluded from the analyses (ICD-10 codes I00-I99 except I10). Non-cases consisted of hypertensive patients who had no cardiovascular or stroke events during or prior to the follow-up period according to mortality and hospitalization registers.

Despite the high coverage of the hospitalization register, some stroke patient may have been misclassified as non-cases in the analysis of non-fatal stroke. However, a validation study showed a 90% agreement between the hospitalization records and a gold-standard clinical examination for stroke diagnosis.[16] At the time of this study, $>97\%$ of the stroke diagnoses in Finland were verified by either X-ray computed tomography, magnetic resonance imaging, or necropsy.[17] Any outcome misclassification was therefore likely to be small and not related to the adherence measurement.

Other clinical characteristics

Socio-demographic factors extracted from the Statistics Finland Labour Market data file included sex, age, education, and household income. The four educational categories were based on the highest level of education achieved, obtained from the National Register of Completed Education and Degrees: basic education, secondary education, lower tertiary education, and higher tertiary education. Income was measured as household disposable income per consumption unit. It comprised all taxable income received by family members after taxes had been subtracted, including wages, capital income, and taxable income transfers. Different weights were used for adults and children in the calculation of the household consumption units: for the first adult, 1.0; for other adults, 0.7; and for children, 0.5.

Any history of such chronic diseases as diabetes mellitus (ICD-10 code E10-E14) and cancer (ICD-10 code C0-C97) between 1 January 1987 and 31 December 1994 (i.e. prior to the study period for adherence) were

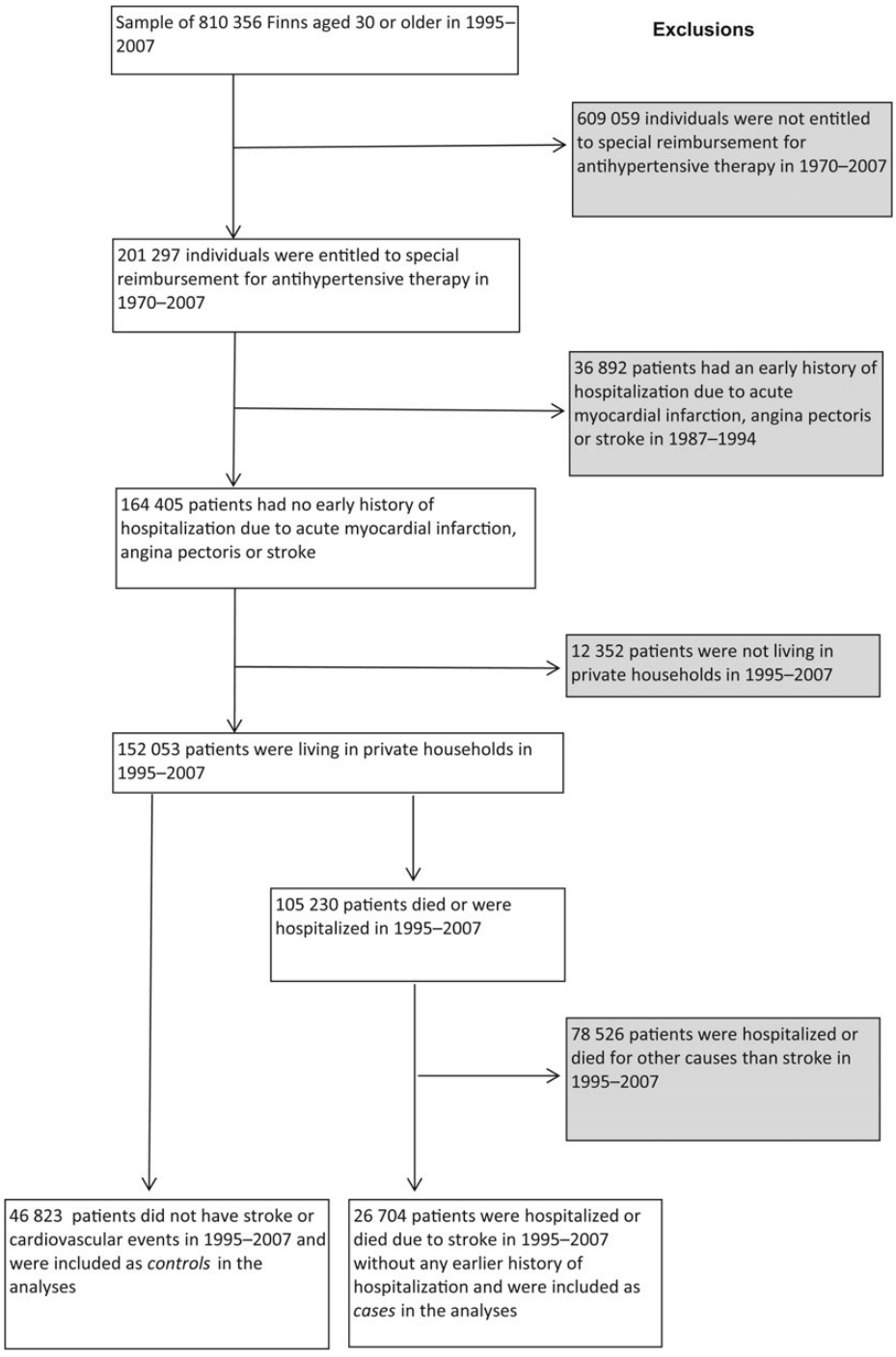

Figure 1 Flowchart.

included as covariates in the analyses. The use of drugs against thrombus, diabetes mellitus, and dyslipidaemia was identified from the *Drug Reimbursement Register* during the follow-up from 1 January 1995 through 31 December 2007.

Statistical analysis

We used binary and multinomial logistic regression to assess the year-by-year association between adherence to antihypertensive therapy and non-fatal or fatal stroke. These models were adjusted for age, sex, length of antihypertensive therapy (i.e. the number of years from the start of the diagnosed continuous need for antihypertensive medication to the time term entered in the model), education, household income, diabetes mellitus, and history of cancer. In addition to modelling all of the antihypertensive drugs combined, we performed analyses for specific classes of antihypertensives: (i) diuretics and/or β-blockers only, (ii) agents acting on the renin–angiotensin system only, and these

drugs combined with calcium channel blockers, (iii) agents acting on the renin–angiotensin system combined with diuretics and/or β-blockers, and (iv) calcium channel blockers only, and these drugs combined with diuretics and/or β-blockers.

The Stata statistical software package, version MP 11.2, was used for all of the analyses. We considered a two-sided *P*-value of <0.05 as significant.

Results

Characteristics of the patients

The characteristics of the 73 527 hypertensive patients at the time of the first presentation of stroke or at the end of the follow-up by disease status are reported in *Table 1*. Those who were hospitalized or died due to stroke (cases) were older, less educated and had lower household income than those who did not experience a fatal or non-fatal incident during the follow-up (non-cases). Moreover, the cases were more often diagnosed with diabetes or cancer.

Trajectories of non-adherence and stroke

Table 2 shows the results for the association between adherence to antihypertensive therapy and fatal and non-fatal incident stroke as assessed prospectively from the hypertension diagnosis onwards. At 2, 5, and 10 years of follow-up, the odds ratios (ORs) for stroke death adjusted for age, sex, length of antihypertensive therapy, education, household income, diabetes mellitus, and history of cancer were 3.81 [95% confidence interval (CI) 2.85–5.10], 3.68 (95% CI: 2.92–4.65), and 3.01 (95% CI: 2.37–3.83) times higher among the non-adherent when compared with the adherent patients, respectively. The corresponding ORs for stroke hospitalization were 2.74 (95% CI: 2.35–3.20), 2.28 (95% CI: 2.00–2.60), and 1.71 (95% CI: 1.49–1.96).

Table 3 shows the results of the retrospective analysis of stroke risk from the event backwards. Higher ORs for non-adherence occurred nearer the stroke event. Thus the adjusted ORs for stroke death among the non-adherents compared with the adherent patients were: 5.68 (95% CI: 5.05–6.39), 3.99 (95% CI: 3.51–4.54), 3.41 (95% CI: 2.93–3.96), and 2.24 (95% CI: 1.79–2.81) at 0, 2, 5, and 9 years prior to death from stroke or the end of the follow-up (*Table 3*). The corresponding ORs for hospitalization due to stroke were 1.87 (95% CI: 1.72–2.03), 2.19 (95% CI: 2.03–2.36), 2.17 (95% CI: 1.99–2.38), and 1.77 (95% CI: 1.55–2.02), respectively. Repeating these analyses without adjustments had little effect on these associations (Supplementary material online, *Table S1*).

Analyses for specific classes of antihypertensives

Table 3 also shows these analyses by class of prescribed antihypertensive drugs. For agents acting on the renin–angiotensin system combined with diuretics and/or β-blockers, the adjusted ORs for stroke death were 7.49 (95% CI: 5.62–9.98), 4.51 (95% CI: 3.29–6.19), 2.37 (95% CI: 1.63–3.43), and 1.85 (95% CI: 1.13–3.03) at 0, 2, 5, and 9 years prior to death from stroke or the end of the follow-up. The corresponding ORs for hospitalization due to stroke were 3.91 (95% CI: 3.23–4.75), 3.45 (95% CI: 2.93–4.07), 2.87 (95% CI: 2.42–3.40), and 2.12 (95% CI: 1.67–2.70), respectively. Analyses for other classes of antihypertensive drugs showed weaker associations with adherence and are shown in Supplementary material online, *Table S2A–C*.

Table 1 Characteristics of hypertensive patients at the time of the first presentation of stroke (non-fatal and fatal) or the end of follow-up

	Cases Non-fatal stroke ($n = 24\,560$)	Controls ($n = 46\,823$)	*P*-value
Age, years	73.0 (10.7)	65.1 (12.1)	<0.001
Male	43%	44%	<0.001
Education (%)			<0.001
Upper tertiary	2	4	
Lower tertiary	8	15	
Secondary	15	30	
Basic	75	51	
Household income[a]	24.1 (18.5)	38.9 (27.0)	<0.001
Diabetes (%)	10	2	<0.001
History of cancer (%)	4	2	<0.001
Follow-up, years	7.0 (3.8)	12.7 (1.8)	<0.001
Medication[b] (%)			
Thrombus	47	11	<0.001
Diabetes mellitus	29	20	<0.001
Dyslipidaemia	34	38	<0.001
	Fatal stroke ($n = 2144$)	**($n = 46\,823$)**	
Age, years	76.2 (11.1)	65.1 (12.1)	<0.001
Male	40%	44%	<0.001
Education (%)			<0.001
Upper tertiary	2	4	
Lower tertiary	8	15	
Secondary	14	30	
Basic	76	51	
Household income[a]	21.2 (17.5)	38.9 (27.0)	<0.001
Diabetes (%)	10	2	<0.001
History of cancer (%)	6	2	<0.001
Follow-up, years	7.1 (3.4)	12.7 (1.8)	<0.001
Medication[b] (%)			
Thrombus	22	11	<0.001
Diabetes mellitus	23	20	<0.001
Dyslipidaemia	11	38	<0.001

Data are means (SD) or percentages. Comparisons were done with two-sample t-tests or χ^2 tests, as appropriate.
[a]Household income in thousands of Euros.
[b]Use of drugs against selected diseases during the follow-up.

Analysis of dose–response association

Table 4 shows the trajectories of stroke risk using the three-level adherence definition of high, intermediate, and poor adherence. In each year prior to the event, the greatest risk of stroke death was observed for the participants with poor adherence. In the year of the event, for example, their odds of stroke death was 7.99 (95%

Table 2 Annual odds ratios for non-fatal and fatal stroke according to non-adherence vs. adherence after the requirement of continuous antihypertensive medication

	Non-fatal stroke		Fatal stroke	
	No. of patients	Non-adherence vs. adherence[a] odds ratio (95% CI)	No. of patients	Non-adherence vs. adherence[a] odds ratio (95% CI)
Years[b]				
2	26 293	2.74 (2.35–3.20)	23 360	3.81 (2.85–5.10)
3	26 655	2.74 (2.37–3.16)	23 462	3.95 (3.01–5.18)
4	26 717	2.79 (2.45–3.19)	23 199	4.10 (3.21–5.24)
5	27 238	2.28 (2.00–2.60)	23 484	3.68 (2.92–4.65)
6	27 221	2.13 (1.87–2.43)	23 355	2.85 (2.24–3.62)
7	26 474	2.22 (1.95–2.52)	22 613	3.09 (2.46–3.89)
8	25 486	2.03 (1.78–2.32)	21 612	2.72 (2.13–3.47)
9	24 242	1.78 (1.49–1.96)	20 407	2.82 (2.22–3.58)
10	23 480	1.71 (1.49–1.96)	19 656	3.01 (2.37–3.83)

[a]Adjusted for age, sex, length of antihypertensive therapy, education, household income, diabetes mellitus, and history of cancer.
[b]Years after the requirement of continuous antihypertensive medication.

CI: 6.28–10.18) times higher than that for those with high adherence. The corresponding OR for the participants with intermediate adherence was 3.60 (95% CI: 2.95–4.39). Similar results were found for hospitalizations due to stroke. The OR for hospitalization 9 years prior to the event was 3.32 (95% CI: 2.59–4.25) for the participants with poor adherence and 1.98 (95% CI: 1.64–2.39) for those with intermediate adherence when they were compared with the highly adherent patients. These findings support a dose–response association between poorer adherence to antihypertensive medication and a greater risk of death or hospitalization due to stroke.

Discussion

In this large-scale, population-based linkage study, hypertensive patients who subsequently died or were hospitalized due to stroke had a lower adherence to antihypertensive medication already 2 years after receiving special reimbursement for continuous antihypertensive therapy than did the patients who did not experience stroke during the follow-up. Non-adherence to antihypertensive medication was associated with a 5.7-fold increased odds of fatal stroke during the year of death and a two-fold increased risk of non-fatal stroke. For those using agents acting on the renin–angiotensin system combined with diuretics and/or β-blockers, the corresponding OR was 7.5 for stroke death and 3.9 for hospitalization. Our dose–response analyses based on categories of high, intermediate, and low adherence to antihypertensive medication confirmed that the near- and long-term risk of fatal and non-fatal stroke increased at each step down the level of adherence.

To our knowledge, this is the first study to estimate trajectories of adherence to antihypertensive therapy prior to fatal or non-fatal incident stroke among hypertensive patients. Our findings are in agreement with previous investigations that have suggested a high adherence to antihypertensive therapy is associated with a lower risk of stroke or other cardiovascular events.[12,18] An Italian study also found that, compared with patients with poor adherence, those with good (hazard ratio 0.69, $P < 0.001$) or excellent adherence (hazard ratio 0.53, $P < 0.001$) had a significantly lower risk for the combined outcome of all-cause death, fatal or non-fatal stroke, and fatal or non-fatal acute myocardial infarction even though separate analyses for the stroke outcomes showed no statistically significant differences between the adherence groups.[12] An ecologic time-series study based on yearly official reports of stroke and coronary disease mortality and the use of antihypertensive medication in three Hungarian counties found a correlation between the use of high-ceiling diuretics or calcium channel blockers and decreased stroke mortality.[18] Our analysis was unique, as none of these studies assessed adherence repeatedly over time at the individual level.

A major strength of our study was the large-scale population-based sample of Finns with an 80% oversample of deaths and linkage to comprehensive drug and hospitalization registration that allowed us to conduct a year-by-year analysis of adherence trajectories in relation to stroke events. The nationwide closed record system for both prescriptions and deaths meant that there was virtually no drop out or sample attrition during the follow-up. Information on hospitalization was essential to ensure that the patients were free of stroke and cardiovascular disease at baseline and thus were targets for primary rather than secondary prevention. We assessed stroke risk on the basis of records of non-fatal and fatal stroke, of which the latter, in particular, is a valid stroke outcome. For example, in a study of in-hospital deaths coded for participants in the Minnesota Heart Study,[19] death certificates missed a proportion of stroke deaths, but deaths that were identified as stroke deaths were virtually all correct on the death certificates. The Finnish death register, which we used, has been ranked high with respect to reliability and accuracy in international comparisons.[20] Therefore, bias due to coding error is an unlikely explanation for our results.

Table 3 Annual odds ratios for non-fatal and fatal stroke according to non-adherence vs. adherence prior to the first presentation of stroke or the end of follow-up, all antihypertensive drugs and agents acting on renin–angiotensin system and diuretics or β-blockers

	Non-fatal stroke		Fatal stroke	
	No. of patients	Non-adherence vs. adherence[a] odds ratio (95% CI)	No. of patients	Non-adherence vs. adherence[a] odds ratio (95% CI)
All antihypertensive drugs				
Years[b]				
−9	29 884	1.77 (1.55–2.02)	26 925	2.24 (1.79–2.81)
−8	32 868	1.78 (1.58–2.00)	28 694	1.85 (1.50–2.30)
−7	36 458	2.14 (1.94–2.36)	30 697	2.54 (2.12–3.03)
−6	40 525	2.30 (2.10–2.53)	33 126	2.50 (2.10–2.97)
−5	44 753	2.17 (1.99–2.38)	35 568	3.41 (2.93–3.96)
−4	49 226	2.21 (2.03–2.41)	38 047	3.61 (3.13–4.16)
−3	53 621	2.25 (2.08–2.44)	40 248	3.40 (2.95–3.91)
−2	58 250	2.19 (2.03–2.36)	42 544	3.99 (3.51–4.54)
−1	63 293	2.31 (2.15–2.49)	44 868	4.34 (3.85–4.90)
0	65 676	1.87 (1.72–2.03)	46 634	5.68 (5.05–6.39)
Agents acting on renin–angiotensin system and diuretics or β-blockers				
Years[b]				
−9	9631	2.12 (1.67–2.70)	8655	1.85 (1.13–3.03)
−8	10 551	2.29 (1.85–2.83)	9191	1.64 (1.03–2.60)
−7	11 589	2.57 (2.14–3.10)	9748	2.26 (1.54–3.33)
−6	12 726	3.06 (2.57–3.66)	10 418	2.11 (1.42–3.14)
−5	13 887	2.87 (2.42–3.40)	11 103	2.37 (1.63–3.43)
−4	15 134	2.82 (2.38–3.34)	11 803	3.20 (2.27–4.50)
−3	16 362	3.09 (2.61–3.65)	12 463	3.44 (2.46–4.83)
−2	17 586	3.45 (2.93–4.07)	13 089	4.51 (3.29–6.19)
−1	18 922	3.16 (2.69–3.71)	13 736	3.90 (2.87–5.32)
0	19 625	3.91 (3.23–4.75)	14 251	7.49 (5.62–9.98)

[a]Adjusted for age, sex, length of antihypertensive therapy, education, household income, diabetes mellitus, and history of cancer.
[b]Years prior to the first presentation of stroke or the end of follow-up.

Our results have some limitations. First, although pharmacy refill records are objective measures and are collected routinely, they do not necessarily indicate whether the participants actually took the medications. It is possible that some of the participants characterized as adherents did not actually take their medication despite filling their prescriptions. Such misclassifications would lead to an overestimation of adherence but would bias the adherence–stroke relation only if they affect differently those who develop stroke vs. do not. Secondly, as the diagnosis of hypertension was based on health care records (more precisely eligibility to special reimbursement due to chronic hypertension) rather than a clinical examination at baseline, some imprecision in the inclusion of the participants is possible. While the participants were likely to be true hypertension cases, they did not include undiagnosed hypertensive individuals with a need for antihypertensive medication. However, this limitation is an unlikely source for major confounding in the association between adherence and stroke risk. Thirdly, data on such covariates as body mass index, smoking, alcohol consumption, and resting blood pressure were not available from the registers, and therefore analyses to identify subgroups particularly vulnerable to the harmful effects of non-adherence or patients with poorly controlled blood pressure despite adherence to drug therapy were precluded. Fourthly, the healthy user bias (i.e. the correlation between adherence and other behaviour-related risk factors) may artificially inflate associations between non-adherence and disease outcomes in observational studies on preventive medications, such as ours.[21] However, this was an unlikely explanation for the accelerated decline in adherence that we observed 4 years before stroke death. Fifthly, the stringent exclusion criteria of our study population may have affected the assessment of the prevalence of adherence to medication. Further research to determine the generalizability of our findings is needed.

Given that randomization to different adherence groups is unethical, it is unlikely that trial evidence will be available on the effect of adherence to antihypertensive medication on fatal or non-fatal stroke events. Our findings from observational data show a lower adherence to antihypertensive medication already 9 years before a fatal or non-fatal stroke event among hypertensive patients; in the year of the stroke event, the association with non-adherence was the

Table 4 Annual relative risk ratios for non-fatal and fatal stroke according to the three-level definition of adherence prior to the first presentation of stroke or the end of follow-up[a]

Years[b]	Adherence[c]	Non-fatal stroke Relative risk ratio (95% CI)	Fatal stroke Relative risk ratio (95% CI)
−9	High	1.00	1.00
	Intermediate	1.98 (1.64–2.39)	2.78 (2.04–3.79)
	Poor	3.32 (2.59–4.25)	3.97 (2.60–6.05)
−8	High	1.00	1.00
	Intermediate	1.96 (1.64–2.34)	2.02 (1.47–2.79)
	Poor	3.07 (2.46–3.83)	2.94 (1.94–4.48)
−7	High	1.00	1.00
	Intermediate	1.96 (1.66–2.31)	2.68 (2.05–3.51)
	Poor	3.90 (3.19–4.76)	2.45 (1.55–3.87)
−6	High	1.00	1.00
	Intermediate	2.23 (1.92–2.59)	2.11 (1.58–2.82)
	Poor	4.14 (3.40–5.04)	4.13 (2.92–5.84)
−5	High	1.00	1.00
	Intermediate	2.21 (1.92–2.55)	3.75 (2.98–4.71)
	Poor	3.03 (2.49–3.69)	5.87 (4.34–7.96)
−4	High	1.00	1.00
	Intermediate	2.15 (1.88–2.47)	3.10 (2.46–4.91)
	Poor	3.57 (2.97–4.30)	6.21 (4.64–8.30)
−3	High	1.00	1.00
	Intermediate	2.21 (1.95–2.51)	2.75 (2.19–3.46)
	Poor	3.93 (3.29–4.68)	4.60 (3.32–6.37)
−2	High	1.00	1.00
	Intermediate	2.03 (1.80–2.30)	3.25 (2.63–4.02)
	Poor	3.89 (3.31–4.56)	7.53 (5.82–9.74)
−1	High	1.00	1.00
	Intermediate	2.55 (2.27–2.85)	3.39 (2.78–4.14)
	Poor	3.30 (2.81–3.88)	5.82 (4.56–7.45)
0	High	1.00	1.00
	Intermediate	1.72 (1.52–1.95)	3.60 (2.95–4.39)
	Poor	2.64 (2.21–3.15)	7.99 (6.28–10.18)

[a]Adjusted for age, sex, length of antihypertensive therapy, education, household income, diabetes mellitus, and history of cancer.
[b]Years prior to the first presentation of stroke or the end of follow-up.
[c]High adherence >80%, intermediate adherence 30–80%, poor adherence <30%.

strongest. A dose–response relationship (the more non-adherent the greater the risk) was evident across the entire follow-up. These results emphasize the importance of hypertensive patients remaining adherent to antihypertensive therapy in order to minimize such serious complications as fatal and non-fatal stroke events.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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