Etiology and prevention of stroke

The Rotterdam Study

Zoltán Vokó

The Rotterdam Study was supported by the Netherlands Organization for Scientific Research (NWO), the Health and Development Research Council (ZON), the municipality of Rotterdam, and the NESTOR stimulation program for geriatric research in The Netherlands (ministry of Health, Welfare and Sports, and ministry of Education, Science and Culture). The author is grateful to the participants, general practitioners and field workers in the Rotterdam Study.
Generous support was provided by the Ministry of Health of Hungary, and by The Netherlands Institute for Health Sciences, Erasmus University Rotterdam, The Netherlands.
The support of the Foundation "Vereniging Trustfonds Erasmus Universiteit Rotterdam", The Netherlands, is gratefully acknowledged.

ISBN 90-9013768-8

Cover photograph: Overview of lone rower sculling. Corbis©
Layout and cover design: Bon Mot, Rotterdam
Printed by Optima Grafische Communicatie, Rotterdam

Etiology and prevention of stroke

The Rotterdam Study

Etiologie en preventie van herseninfarcten

Het ERGO-onderzoek

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam op gezag van de rector magnificus
Prof. dr. P.W.C. Akkermans M.A.
en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden
op woensdag 21 juni 2000 om 9:45 uur

door

Zoltán Vokó

geboren te Budapest

Promotiecommissie

Promotores	:	Prof.dr. A. Hofman Prof.dr. P.J. Koudstaal
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chapter 1

Introduction

Stroke puts a large burden on western societies. It is the third leading cause of death in these countries, and one of the major causes of disability.[1-3] Stroke mortality has been declining substantially in developed countries for some decades.[1,2,4] Data on stroke incidence are relatively rare, but existing figures suggest that incidence of stroke declined until the 1980s and since then levelled off.[1,4] In ageing populations the number of affected subjects will grow in the coming years.[3]

In the last few decades epidemiologic research identified numerous risk factors for stroke.[3] Yet, there are remaining questions related to the etiology and prevention of stroke and some of these are addressed in this thesis. In chapter 2, we study whether the classical stroke risk factors as identified in the Framingham risk profile still predict accurately the probability of stroke. Chapters 3, 4 and 5 are devoted to the associations between hypertension, serum cholesterol, family history of stroke and the risk of stroke. In chapters 6, 7, and 8, we investigate the role of dietary antioxidants, aspirin and carotid endarterectomy in the prevention of stroke. Prevention measures aim to modify risk factors. It is an interesting question how change in a risk factor is related to stroke. In chapter 9, we show our results on the association between change in systolic blood pressure and the occurrence of stroke. We use this study as an example to call attention to possible bias caused by the prevailing method of analysing the relationship between change in a determinant and the risk of disease.

A major theme in this thesis is the possible prevention of stroke. We should note that stroke is not one entity, but a group of disorders. The two major types of stroke, ischemic stroke and cerebral hemorrhage are caused by very different pathomechanisms. Even though their risk factors overlap they should ideally be studied separately.[3] Understanding the etiology of stroke, and finding clues for its prevention, is crucial in reducing the burden of stroke.

The importance of prevention of stroke is further emphasised by the fact, that besides supportive care and treatment of acute complications, currently there is no treatment for acute ischemic stroke, except for tissue plasminogen activator (tPA) in a minority of cases.[5-7]

One of the most effective strategies on the community level to prevent stroke is to shift the population distribution of major modifiable host and environmental risk factors towards lower risk.[8] Cholesterol lowering might be an option. Clinical trials have shown a large benefit in stroke prevention with the use of statins, the last generation cholesterol lowering drugs.[9-12] On the other hand, observational epi-

demiological studies provided controversial results.[13-19] In chapter 4, we revisit the relation between cholesterol level and the risk of stroke. In chapter 6, we investigate whether dietary antioxidants can prevent stroke.

The mass strategy of prevention involves many low risk subjects. The safety of the interventions is critical for the potential side effects not to exceed the benefits. Hence, the actual intervention is usually limited to modifying health behaviour or environmental factors. Aspirin use and carotid endarterectomy, neither of them free from risk of adverse events, are being used in low risk subjects.[20-23] We evaluate these interventions in chapters 7 and 8.

A complementary approach to a mass prevention strategy is to prevent stroke in subjects at high risk for stroke.[8] The control of hypertension is a simple example of this high-risk approach. A problem related to the control of blood pressure is the optimal target blood pressure in treated hypertensive subjects.[24-27] We address this issue in chapter 3.

In chapter 10, the main findings of the work are summarised along with their limitations and potential implications. Finally, envisaged directions in epidemiological research on the etiology of stroke and in research methods are given.

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chapter 2

How does the Framingham stroke risk profile perform in Rotterdam?

Background and purpose – *Our aim was to evaluate the predictive performance of the Framingham stroke risk profile.*
Methods – *This study was conducted within the Rotterdam Study, a prospective population-based cohort study of subjects aged 55 years or over that started in 1990. This analysis concerns 4930 subjects who were free from stroke at baseline and on whom we had complete information on all the risk factors included in the Framingham risk profile. We assessed whether the profile correctly estimated the number of strokes that occurred within three years of follow-up and whether it could discriminate between high and low risk subjects.*
Results – *During follow-up 141 strokes and transient ischemic attacks (TIA) occurred, where 127 were expected. The estimated three-year risk of stroke and TIA ranged from 1.4‰ to 54.8%. The area under the receiver operator characteristic curve was 0.72 for stroke and TIA, and 0.75 when only stroke was considered as an outcome.*
Conclusions – *The Framingham stroke risk profile predicts the number of strokes reasonably well, and can be a useful tool to discriminate between subjects with different risk for stroke.*

Risk profiles can estimate probability of an event conditionally on specific characteristics of the subject. The most well-known stroke risk profile was published from the Framingham Study a decade ago.[1] The profile included the now "classical" stroke risk factors. The function can predict the number of strokes in a population and can identify persons at increased risk of stroke.

The object of our study was to evaluate the performance of the Framingham stroke risk profile in the Rotterdam Study. We wanted to see whether the function could predict stroke accurately in a different population. Furthermore, we wanted to assess whether after the advances in the control of hypertension, diabetes, and the treatment of cardiovascular diseases in the last decade, the major classical stroke risk factors could still largely predict the risk of stroke.

Subjects and Methods

Study population

We evaluated the performance of the Framingham stroke risk profile in the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in a suburb of Rotterdam, The Netherlands, were invited. The rationale and design of the Rotterdam Study have been described elsewhere.[2]

Baseline data collection was performed between 1990 and 1993. Written informed consent and permission to retrieve information from medical records were obtained from every participant. The study has been approved by the Medical Ethics Committee of Erasmus University/Academic Hospital Rotterdam. In total 7983 subjects participated (response rate 78%). Among them 7603 subjects completed the baseline interview and examination, and reported no previous stroke at baseline. Although on most variables more than 90 % of data was available, we had information on all the risk factors included in the Framingham risk profile only in 4930 subjects. Those who were not included in this analysis were on average slightly older and more often took antihypertensive medication, suffered from diabetes mellitus or had coronary heart disease.

Assessment of strokes and transient ischemic attacks (TIA)

At baseline, information on health status and medical history was obtained using a computerized questionnaire. Previous stroke was assessed by direct questioning: "Did you ever suffer from a stroke diagnosed by a physician?". If the answer was 'yes', medical records were checked for additional information. A previous stroke was coded if it was confirmed by medical records.[3] Once subjects enter the Rotterdam Study they are continuously monitored for major events through automated linkage with the files from the GPs. With respect to the vital status, information is obtained at regular intervals from the municipal authorities in Rotterdam. When an event or death has been reported, additional information is obtained by interviewing the GP and scrutinizing information from hospital discharge records in case of admittance or referral. Information on all possible strokes was reviewed by a neurologist (PJK) who classified the stroke as definite, probable or possible. The stroke was considered definite if the diagnosis was based on both clinical symptoms and neuro-imaging. A probable stroke was considered if no CT or MRI was made but if symptoms were highly suggestive for stroke according to the GP or treating neurologist. In case of fatal stroke a cardiac cause of death should have been excluded to reach a diagnosis of probable stroke. The stroke was considered possible if the treating neurologist diagnosed a 'possible stroke' without neuro-imaging, or if a GP recorded a fatal stroke and could not exclude a cardiac cause of death.

If CT or MRI was performed which showed a haemorrhage or infarct the type of

stroke was coded accordingly. In case of no abnormality on CT or MRI the stroke was classified as ischemic. When no CT or MRI was performed, a stroke could be coded possible hemorrhagic or ischemic in case of typical complaints or case history. A case history of sudden hemiplegia or other focal signs with permanent unconsciousness or death within hours without neuro-imaging was coded as possible hemorrhagic stroke. If there was limited impairment, i.e. isolated afasia, isolated weakness of one limb, isolated facial weakness or isolated hemianopia the stroke was considered possible ischemic. Furthermore, in case of complete improvement within 72 hours or documented atrial fibrillation at time of the diagnosis the stroke also was considered possible ischemic.

Reported TIAs were classified based on all available information as definite, probable or possible by study physicians. Only definite and probable TIAs were included in the analysis.

This analysis concerns strokes and TIAs that occurred within three years after entry in the study cohort.

Definition of risk factors included in the risk profile

Risk factors included in the function were defined similarly in the Rotterdam Study and in the Framingham Study.[4] With respect to smoking subjects were categorized as current smokers and non-smokers, including former smokers. Diabetes mellitus was defined as random or post-load serum glucose level higher than 11.1mmol/l or use of antidiabetic medication.[5] Sitting blood pressure was measured at baseline at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained on one occasion, separated by a count of the pulse rate, was used in this analysis.[6] Use of antihypertensive medication was ascertained as part of the baseline interview in the subjects' home when participants were asked to report and show all vials of medications (either prescription or OTC) that were used during the preceding week. Names or brands of drugs were recorded and classified according to their corresponding Anatomical-Therapeutical-Chemical-code (ATC-code). Atrial fibrillation and left ventricular hypertrophy were assessed by electrocardiogram. Definition of cardiovascular disease included history of intermittent claudication, angina pectoris, coronary revascularisation procedure, myocardial infarction, and cardiac failure. Prevalence of angina pectoris and intermittent claudication was assessed by means of a Dutch version of the cardiovascular questionnaire of Rose et al.[7] Heart failure was defined in a two step approach. First, the presence of shortness of breath at rest or exertion, ankle edema and crepitations was determined. If at least two of these were present in combination with evidence of cardiac disease, while shortness of breath could not be attributed to chronic obstructive pulmonary disease, heart failure was considered present. Secondly, the examining physician used standardized questions to verify the indication of cardiovascular medication with the participant. In case diuretics, glycosides or angiotensine con-

verting enzyme inhibitors were used, the indication of heart failure was verified and classified as no, possible or definite. Only participants with a definite indication for heart failure, in whom objective evidence of cardiac disease was found, were included.[8] History of myocardial infarction was assessed primarily by direct questioning. Self-reported events were confirmed by additional information from the general practitioner or cardiologist.[9]

Statistical analysis

We estimated the risk of stroke and TIA for each subject by imputing the subject specific values of the risk factors in the Framingham stroke risk profile. A risk profile that is applicable in practice should estimate the probability of events that are comparable in severity and future prognosis. Although the original risk function was developed to estimate the risk of stroke or TIA, we therefore performed additional analyses in which we only included stroke as event of interest.

We first assessed how well the function estimates the number of events that occurred within three-years of follow-up. For that we used two methods. First, we compared the predicted three-year probability of events with the actual three-year cumulative incidence of event in deciles of predicted probability.[10] Second, we applied a smoother to obtain a non-parametric estimate of the "actual probability" of stroke in each subject. The "actual probability" was calculated by robust locally weighted regression. We used a tricube weight function, and a bandwidth of 0.8.[11] The relationship between the predicted probability and the "actual probability" is presented on a scatterplot.

Next, to see how the risk profile could separate subjects who did or did not have an event during the follow-up we calculated the area under the receiver operating characteristic (ROC) curve.[12] A discriminating function yields a wide range of predicted risks and assigns higher predicted risks to subjects who will have an event than to subjects who will not have an event. The better the discrimination the larger the area under the ROC curve is.

Results

Baseline characteristics of the study population are presented in Table 1. They were quite comparable to those from the Framingham Study.[1] Within three years after entry 94 strokes and 49 TIAs occurred, resulting in 141 subjects with incident stroke or TIA (two subjects had both a TIA and stroke during the follow-up).

Table 2 shows the three-year cumulative incidence of events in deciles of the estimated probability and the numbers of observed and expected cases. The total number of expected cases was 127, the estimated three-year risk ranged from 1.4‰ to 54.8%. Ninety percent of subjects had an estimated three-year risk of stroke or TIA smaller than 5.3%. From the table it can be seen that the function estimates

Table 1
Baseline characteristics of the study population

Risk factor	Men	Women
Age (year)	67.0 (7.1)	67.9 (7.7)
Systolic blood pressure (mmHg)	138.4 (21.7)	138.8 (22.5)
Antihypertensive therapy	29.7	34.1
Diabetes mellitus	10.8	10.4
Smoking	28.5	19.3
Cardiovascular disease*	24.7	16.0
Atrial fibrillation	2.4	1.6
Left ventricular hypertrophy	4.9	4.0

Values are means (SD) or percentages.
* Cardiovascular disease: history of intermittent claudication, angina pectoris, coronary revascularisation procedure, myocardial infraction, or cardiac failure.

Table 2
Expected number of events (stroke and TIA), observed number of events, and observed three-year cumulative incidence in deciles of the estimated three-year risk

Decile of estimated three-year risk (%)	Expected number of events	Observed number of events		Three-year cumulative incidence (%)	
		Stroke and definite/ prob. TIAs	Stroke	Stroke and definite/ prob. TIAs	Stroke
0.0 – 0.52	2	6	2	1.22	0.41
0.53 – 0.76	3	4	2	0.81	0.41
0.77 – 1.00	4	6	3	1.22	0.61
1.01 – 1.28	6	7	3	1.42	0.61
1.29 – 1.60	7	4	3	0.81	0.61
1.61 – 2.01	9	7	3	1.42	0.61
2.02 – 2.57	11	13	11	2.64	2.23
2.58 – 3.45	15	22	17	4.46	3.45
3.46 – 5.27	21	33	24	6.69	4.87
5.28 –	49	39	26	7.91	5.27

prob.: probable; TIA: transient ischemic attack.

the risk of stroke in most categories reasonably well. Figure 1 shows the scatter plot of the predicted three-year probability of stroke and TIA and the "actual probability" of events. It shows that in the range of probability of 0.01-0.05, where the vast majority of subjects belong, the function somewhat underestimates the actual

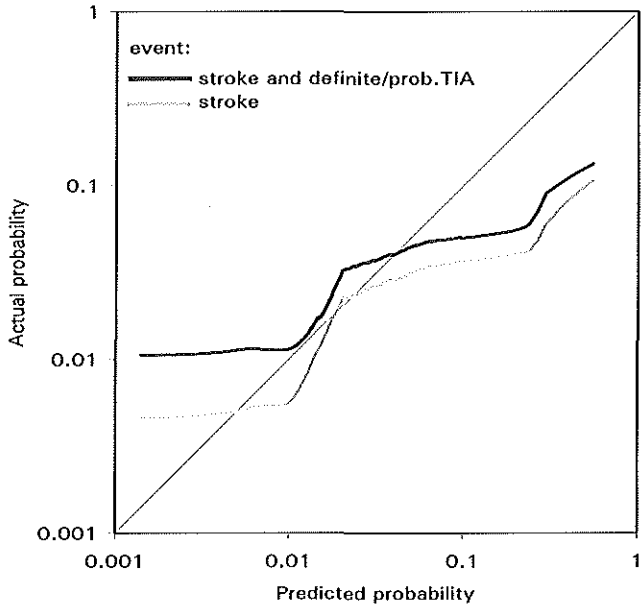

Figure 1
Scatterplot of the predicted three-year probability of event and of the actual probability of event (logarithmic scales).

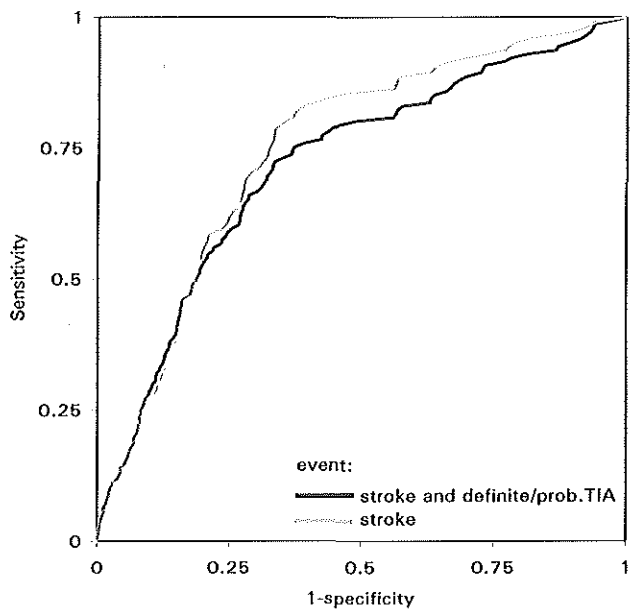

Figure 2
ROC curve of the Framingham stroke risk profile.

probability of stroke and TIA. On the other hand, as expected, the function slightly overestimates the probability of event if only stroke is considered.

Figure 2 presents the ROC curve of the function. The area under the curve was 0.72 (95% confidence interval 0.68-0.76) and 0.75 (95% confidence interval 0.71-0.79) for stroke or TIA, and for stroke only, respectively. This shows that the function discriminates equally regardless whether only stroke or stroke and TIA are

Table 3
Sensitivity and specificity* of the Framingham stroke risk profile corresponding to different cut-off points of the estimated probability

Cut-off point	Sensitivity	Specificity
0.026	70	71
0.024	75	68
0.022	80	65
0.017	85	54
0.012	90	37
0.008	95	22

* Only stroke was considered as an event of interest.

considered as outcome. We additionally tabulated the sensitivity and specificity of the function corresponding to different cut-off points of the estimated three-year risk (Table 3). Only stroke was considered here as event of interest. The table shows that, for example, choosing an estimated risk of 2.4% or higher for identifying high risk subjects would mean that 75% of the future cases would be correctly identified whereas 32% of subjects who would not have a stroke within three years would be labeled as high risk.

Discussion

We evaluated the performance of the Framingham stroke risk profile. We found that the function estimates the three-year risk of stroke reasonably well. The total number of expected events is close to the observed number, and the prevalence of the event is fairly well predicted in most categories of the estimated risk. Our results show that major classical stroke risk factors still largely predict the risk of stroke. The estimated probability had a wide range, and the function could discriminate between subjects with different risk for stroke.

We evaluated the first version of the Framingham stroke risk profile.[1] A slightly modified version of the original function was published later, but without all the necessary deatil to enable validation in another dataset.[13]

Out study has some limitations. The follow-up was only three years. Also, there was a relatively large proportion of subjects that we could not include in the analysis because of missing data for one or more of the covariates in the model. Nevertheless, in practice the function can be used only in subjects with information on all their risk factors.

Since the main use of a risk profile is to classify subjects into groups with different prognosis the most important feature of a risk profile from the practical point

chapter 3

J-shaped relation between blood pressure and stroke in treated hypertensives

The objective of this study was to investigate the relationship between hypertension and risk of stroke in the elderly. The study was carried out within the framework of the Rotterdam Study, a prospective population-based cohort study. The risk of first-ever stroke was associated with hypertension (relative risk 1.6, 95% confidence interval 1.2-2.0), and with isolated systolic hypertension (relative risk 1.7, 95% confidence interval 1.1-2.6). We found a continuous increase in stroke incidence with increasing blood pressure in non-treated subjects. In treated subjects we found a J-shaped relation between blood pressure and the risk of stroke. In the lowest category of diastolic blood pressure the increase of stroke risk was statistically significant compared to the reference category. Hypertension and isolated systolic hypertension are strong risk factors for stroke in the elderly. The increased stroke risk in the lowest strata of blood pressure in treated hypertensive patients may indicate that the therapeutic goal "the lower the better" is not the optimal strategy in the elderly.

Hypertension is a well-established risk factor for stroke in elderly people.[1-6] There is increasing evidence showing the importance of isolated systolic hypertension in the etiology of stroke,[1,7-13] and now it is recognized as an independent risk factor for cardiovascular morbidity and mortality.[14-16] The results of clinical trials indicated that treatment of hypertension could reduce the risk of stroke considerably, also in the elderly.[17-21] Although two clinical trials have investigated the optimal target blood pressure level in treated hypertensive patients, it is still a question whether the risk of stroke continues to decrease the further the blood pressure is reduced in hypertensive patients.[22-24]

We carried out a prospective cohort study in an elderly Dutch population to investigate the relationship between hypertension and stroke in the elderly. Furthermore, we studied the relationship between blood pressure level and the risk of stroke separately in subjects using and not using antihypertensive medication.

METHODS

Study population

This study was conducted in the framework of the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in the suburb of Rotterdam, The Netherlands, were invited. The rationale and design of the Rotterdam Study have been described elsewhere.[25]

Baseline data collection was performed between 1990 and 1993. Written informed consent and permission to retrieve information from medical records were obtained from every participant. The study has been approved by the Medical Ethics Committee of the University Hospital of Rotterdam. In total 7983 subjects participated (response rate 78%). Among them 7725 subjects reported no previous stroke at baseline, of them 6927 visited the research center where their blood pressure was measured. Among them the distribution of age and gender, and the frequency of diabetes, angina, and of previous myocardial infarction was similar to the rest of the cohort.

Outcome

Once subjects enter the study they are continuously monitored and followed through linkage with automated medical records of the general practitioners working in the study area. Furthermore, bimonthly updates from the municipality records are obtained. When an event or death is reported, additional information is obtained by interviewing the general practitioner and scrutinizing the medical files or hospital discharge records in case of admittance or referral. This analysis concerns events that occurred till December 31, 1996. Complete follow-up was available for 6287 subjects (91%).

All suspected stroke cases reported were reviewed by a neurologist (P.J.K.), who classified them as definite, probable or possible strokes or as non-stroke events,[26] and determined stroke subtypes.

Determinant

Sitting blood pressure was measured at baseline at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained on one occasion, separated by a count of the pulse rate, was used in this analysis.[27] Use of medication was ascertained as part of the baseline interview in subjects' home. Hypertension was defined as systolic blood pressure equal to or higher than 160 mmHg, or diastolic blood pressure equal to or higher than 95 mmHg, or use of antihypertensive medication.[27] Isolated systolic hypertension was defined as systolic blood pressure equal to or higher than 160 mmHg, diastolic blood pressure lower than 90 mmHg and not being treated for hypertension.

Potential confounders

With respect to smoking behavior subjects were categorized as current or former smokers, and those who never smoked. Diabetes mellitus was defined as random or post-load serum glucose level higher than 11.1mmol/l or use of antidiabetic medication.[28] Prevalence of angina pectoris and claudication was assessed by means of a Dutch version of the cardiovascular questionnaire of Rose et al.[29] Ankle-to-arm systolic blood pressure index was defined as the ratio of the systolic blood pressure measured at the arm and at the ankle at the same side.[30] A history of transient ischemic attack (TIA) was assessed on the basis of answers to the questions about experiencing a short period with disturbances of sensibility, strength, speech, or vision. If a positive answer was given, more detailed information was obtained, and the event was categorized as typical TIA, atypical TIA or no TIA, by a neurologist (PJK).[31] History of stroke or myocardial infarction was assessed primarily by direct questioning. Self-reported events were confirmed by additional information from the general practitioner, cardiologist or neurologist.[32,33]

Statistical analysis

All first-ever strokes were included in the analysis. Relative risks and 95% confidence intervals were estimated through Cox-regression.

We compared the risk of stroke between hypertensive and normotensive subjects and between subjects with isolated systolic hypertension and non-treated subjects having systolic blood pressure lower than 160 mmHg and diastolic blood pressure lower than 90 mmHg. The risk estimates were adjusted for age, gender, smoking habits and diabetes mellitus. We refrained from adjustment for cardiovascular diseases because they were considered to be intermediate steps in the disease process or indicators of severe hypertension.

We also investigated the effect of blood pressure level on stroke risk among treated and non-treated subjects. To reduce confounding caused by severe atherosclerosis associated with high systolic and low diastolic blood pressure these analyses were adjusted for age, gender, smoking habits, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularisation procedure), myocardial infarction, atrial fibrillation, typical and atypical TIA.

Missing data of potential confounders were handled by the indicator method.[34] On all confounders more than 90% of data was available.

Results

Table 1 shows the baseline characteristics of the study population. The study cohort was followed for an average of 4.7 years. Among them 277 first-ever strokes

Table 1
Baseline Characteristics of the Study Population

Characteristic	Hypertensive subjects (n = 2351)	Normotensive subjects (n = 3936)
Age (year)	71.5 (8.9)	68.4 (8.9)
Systolic blood pressure (mmHg)	156.7 (22.4)	130.5 (16.1)
Diastolic blood pressure (mmHg)	79.9 (12.4)	70.4 (9.8)
Serum cholesterol (mmol/l)	6.7(1.2)	6.6(1.2)
Men	34.3	42.4
Current smoker	18.4	25.2
Former smoker	40.4	41.9
Diabetes mellitus	16.4	7.7
Atrial fibrillation	3.2	2.4
Intermittent claudication	2.3	1.2
Angina pectoris	9.7	5.3
Coronary revascularization	3.8	2.6
History of myocardial infarction	16.1	10.8
History of typical TIA	1.9	1.3
History of atypical TIA	2.5	1.4

Values are means (SD) or percentages.

Table 2
Association Between Hypertension, Isolated Systolic Hypertension, and Risk of First-ever Stroke

Determinant	Persons at risk	Number of strokes	Strokes/ 1000 person-years	Relative risk (95% CI)	
				Adjusted for age and gender	Additional adjustment*
Hypertension					
no	3936	130	7.0	1.00 (reference)	1.00 (reference)
yes	2351	147	13.8	1.59 (1.25-2.02)	1.58 (1.24-2.01)
Isolated systolic hypertension					
no	3241	92	5.9	1.00 (reference)	1.00 (reference)
yes	345	25	15.8	1.80 (1.15-2.81)	1.69 (1.08-2.64)

CI: confidence interval.
*: adjusted for smoking habit and diabetes mellitus.

occurred. Of these strokes 7.2% were hemorrhagic, 73.7% ischemic, and 19.1% could not be specified.

A statistically significant association between hypertension, isolated systolic hypertension and the risk of first-ever stroke was observed (Table 2).

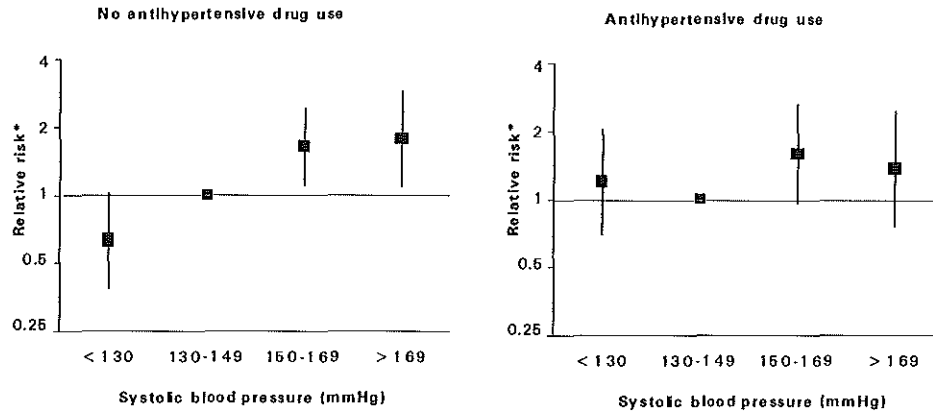

Figure 1
Association between systolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of systolic blood pressure. Values are plotted on logarithmic scale.
* Adjusted for age, gender, smoking habit, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularisation procedure), myocardial infarction, atrial fibrillation, typical and atypical TIA.

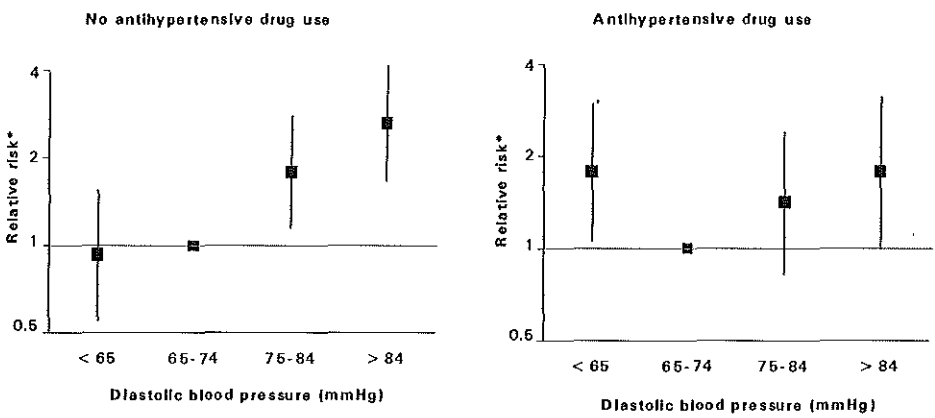

Figure 2
Association between diastolic blood pressure and risk of first-ever stroke, according to antihypertensive treatment. Reference category is the second lowest category of diastolic blood pressure. Values are plotted on logarithmic scale.
* Adjusted for age, gender, smoking habit, diabetes mellitus, ankle-to-arm index, minor vascular events (intermittent claudication, angina pectoris, history of coronary revascularisation procedure), myocardial infarction, atrial fibrillation, typical and atypical TIA.

In subjects who did not use antihypertensive medication a continuous increase in risk was observed with increasing level of both systolic (Figure 1) and diastolic blood pressure (Figure 2). In patients who used antihypertensive drugs a J-shaped relation was found between both systolic and diastolic blood pressure and the incidence of stroke. For diastolic blood pressure the increase of the risk in the lowest category as compared to the reference was statistically significant.

To examine the possibility that the J-curve that we found was due to the excess amount of subjects with isolated systolic hypertension among those with the lowest diastolic blood pressure, we excluded subjects with isolated systolic hypertension. This did not materially change our results. We carried out analysis with adjustment for systolic blood pressure, and also with exclusion of subjects with history of myocardial infarction or coronary revascularisation procedure. This did not change the shape of the relationship between diastolic blood pressure and stroke.

Discussion

We found associations of hypertension, and isolated systolic hypertension with the occurrence of stroke. This is the first study clearly showing a J-shaped relation between diastolic blood pressure and the incidence of stroke in treated hypertensive subjects.

Regarding the relation between hypertension, isolated systolic hypertension and risk of stroke in the elderly, our results are in accordance with the results of other epidemiological studies.[1-13]

However, we may have slightly underestimated the risk of stroke in hypertensive subjects, since some subjects could have started taking antihypertensive medication after baseline and this could have decreased their risk. Nevertheless, we think that this has not greatly influenced our major findings.

Most of the studies published on the association of blood pressure and the risk of stroke indicate a continuous increase in risk over the whole range of blood pressure,[35] although few could evaluate the relationship between blood pressure and stroke risk in elderly subjects with very low blood pressure.[36] Nonetheless, in a case-control study an increased risk of stroke was reported in treated hypertensive patients with low diastolic or systolic blood pressure.[37] In the Cardiovascular Health Study, a cohort study similar to the Rotterdam Study, the risk of stroke tended to increase in treated hypertensive patients whose systolic blood pressure was lower than 128 mmHg.[6] In a cohort of Norwegian elderly subjects an upturn of stroke mortality was seen at low diastolic blood pressure.[38] Although none of these results were statistically significant they are in accord with our finding, and they suggest that the optimal target level of blood pressure in elderly hypertensive patients might be higher than the conventional "normal" level. Similar results have been repeatedly reported on the relation between blood pressure and myocardial infarction.[39,40]

In this case, however, the relationship does not seem to be restricted to treated subjects.[41-44]

Two intervention trials have addressed the question of the optimal blood pressure reduction. In the Behandla Blodtryck Battre trial there was no difference in cardiovascular mortality and morbidity between subjects with essential hypertension who had their diastolic blood pressure lowered below 80 mmHg or between 90-100 mmHg. However, only few cases of strokes and myocardial infarctions occurred during the follow-up, thus the power of this study is limited.[22] The Hypertension Optimal Treatment trial investigated the relation between three levels of target diastolic blood pressure (≤90, ≤85 or =80 mmHg) and the incidence of cardiovascular morbidity and mortality in hypertensive patients. For stroke the lowest risk was in the group with diastolic blood pressure below 80 mmHg and an average systolic blood pressure at 142.2 mmHg. However, the study did not have enough power to study the relationship under 130 mmHg systolic blood pressure and 75 mmHg diastolic blood pressure thus it neither confirmed nor excluded the possibility of a J-shaped relation.[24]

One explanation for the J curve could be that the progression of atherosclerosis causes a wide pulse pressure through vessel wall stiffening accompanied by low diastolic pressure, and that is why low diastolic blood pressure is associated with excess cardiovascular morbidity.[45-47] Our data suggest that advanced atherosclerosis can not, or only partly explain the phenomenon, since we found the J-shaped relationship after adjustment for major cardiovascular risk factors and cardiovascular diseases, and after exclusion of subjects with myocardial infarction and coronary revascularisation procedure.

Excess amount of subjects having isolated systolic hypertension among those with the lowest diastolic blood pressure could be another plausible explanation for the J-curve we found. However, this was not the case in our study. The relationship between diastolic blood pressure and stroke remained essentially the same after adjustment for systolic blood pressure or exclusion of subjects with isolated systolic hypertension.

It is likely that another mechanism can play a role in the increased stroke risk among treated hypertensive subjects with very low blood pressure also. Chronic hypertension shifts the lower and upper blood pressure limits of cerebral blood flow autoregulation towards higher pressure.[48] This adaptive change protects the brain against high intravascular pressure on the one hand, but at the same time makes the brain more susceptible to ischemia at low blood pressure. In elderly subjects this change may be irreversible.[49]

Within the group of treated subjects we could not investigate to what extent low blood pressure was due to the antihypertensive treatment itself. Nevertheless, low blood pressure did not increase the risk of stroke in non-treated subjects.

The risk of stroke in elderly hypertensives seems lowest at blood pressure levels

around 140/80 mmHg. In the face of current evidence cautious reduction of blood pressure in elderly individuals is recommended.

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chapter 4

Cholesterol and risk of stroke. There is no paradox

Background – *Whether high serum cholesterol is associated with stroke is still controversial. The objective of this study was to investigate the relationship between serum cholesterol and occurrence of ischemic stroke.*

Methods and Results – *This study was conducted within the Rotterdam Study, an ongoing prospective population-based cohort study of persons aged 55 years or over, living in a suburb of Rotterdam, The Netherlands. Baseline data collection was performed between 1990 and 1993. All subjects were continuously monitored and followed through linkage with automated medical records of the general practitioners working in the study area. This analysis concerns 6659 subjects who were free from stroke at baseline, had their baseline serum cholesterol level assessed, and did not use lipid lowering drugs at baseline. The mean follow-up time was 4.5 years and 273 first ischemic strokes occurred during the follow-up. High serum cholesterol level significantly increased the risk of ischemic stroke in subjects who were free from cardiovascular diseases and diabetes mellitus (highest quartile versus lowest quartile, relative risk 2.3; 95% confidence interval 1.2-4.4). Serum total cholesterol/high density lipoprotein cholesterol ratio was associated with the risk of stroke neither in the total study population nor in subjects free from cardiovascular diseases and diabetes mellitus.*

Conclusions – *We found evidence that high serum cholesterol level considerably increases the risk of ischemic stroke.*

Clinical trials with HMG-CoA reductase inhibitors have shown a 30 percent reduction in the risk of stroke by these drugs.[1-4] However, observational studies have provided controversial results about the relationship between serum cholesterol and the risk of stroke. Some confirm that cholesterol increases the risk of stroke,[5-8] the bulk of the evidence points to no relation.[9-11] Although statins may have other beneficial effects than cholesterol lowering which may partly explain their effect,[12] this apparent paradox needs further explanation.

In this paper we present results on the relationship between serum total cholesterol, serum total cholesterol/high density lipoprotein cholesterol ratio and the risk of ischemic stroke from a prospective population based cohort study and reconsider previous results.

METHODS

Study population

This study was conducted within the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in a suburb of Rotterdam, The Netherlands, were invited. The rationale and design of the Rotterdam Study have been described elsewhere.[13]

Baseline data collection was performed between 1990 and 1993. Written informed consent and permission to retrieve information from medical records were obtained from every participant. The study has been approved by the Medical Ethics Committee of the University Hospital of Rotterdam. In total 7983 subjects participated (response rate 78%). Among them 7603 subjects completed the baseline interview and examination, and reported no previous stroke at baseline. We excluded 164 subjects who used lipid lowering drugs at baseline. From the remaining cohort serum cholesterol was measured in 6659 subjects and these were included in this study.

Outcome

Once subjects enter the study they are continuously monitored and followed through linkage with automated medical records of the general practitioners working in the study area. Furthermore, bimonthly updates from the municipality records are obtained. When an event or death is reported, additional information is obtained by interviewing the general practitioner and scrutinizing the medical files or hospital discharge records in case of admittance or referral. This analysis concerns events that occurred till December 31, 1996.

All suspected stroke cases reported were reviewed by a neurologist (PJK), who classified them as definite, probable or possible strokes or as non-stroke events, and determined stroke subtypes.[14] Hemorrhagic strokes were excluded from the analysis. Unspecified strokes were included in the analysis, because, since their vast majority is ischemic, including them causes less misclassification than excluding them. Nevertheless, to estimate the amount of possible bias, separate analyses were carried out with exclusion of unspecified strokes.

Determinant

A vein puncture was performed using a 21 gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium) and non-fasting blood was taken. A detailed description of the blood sampling has been given elsewhere.[15] Briefly, samples were taken with minimal stasis, put on ice immediately after sampling, processed within 30 minutes and snap frozen and stored in liquid nitrogen (-80° Celsius), and later stored at -20° Celsius for prolonged storage. Serum total cholesterol was determined using an automated enzymatic procedure.[16] Similarly, high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with

phosphotungstate-magnesium.

Potential confounders

With respect to smoking subjects were categorized as current or former smokers, and those who never smoked. Diabetes mellitus was defined as random or post-load serum glucose level higher than 11.1 mmol/l or use of antidiabetic medication.[17] Hypertension was defined as systolic blood pressure equal to or higher than 160 mmHg, or diastolic blood pressure equal to or higher than 95 mmHg, or use of antihypertensive medication.18 Prevalence of angina pectoris was assessed by means of a Dutch version of the cardiovascular questionnaire of Rose et al.[19] History of stroke or myocardial infarction was assessed primarily by direct questioning. Self-reported events were confirmed by additional information from the general practitioner, cardiologist or neurologist.[20,21] A history of transient ischemic attack (TIA) was assessed on the basis of answers to the questions about experiencing a short period with disturbances of sensibility, strength, speech, or vision. If a positive answer was given, more detailed information was obtained, and the event was categorized as typical TIA, atypical TIA or no TIA, by a neurologist (PJK).[22]

Statistical analysis

All first-ever non-hemorrhagic strokes were included in the analysis. Serum cholesterol level was categorized into quartiles. Relative risks and 95% confidence intervals were estimated through Cox-regression.

Subjects with high cholesterol are likely to start using lipid lowering drugs and consequently reduce their serum cholesterol level. To verify this assumption we checked the proportion of subjects who started using lipid lowering drugs after the baseline examination in the different categories of serum cholesterol. Furthermore, we studied whether the proportion of drug users was different in subjects who suffered from cardiovascular diseases. We could carry out these analysis because since January 1, 1991 the database of the Rotterdam Study was linked to an automated pharmacy database which registers all prescription forms filled in at the pharmacies of the study area by subjects belonging to the Rotterdam Study cohort.

We performed additional analyses after exclusion of subjects with history of coronary revascularisation procedure, myocardial infarction or transient ischemic attack or with presence of diabetes mellitus, angina pectoris or atrial fibrillation on ECG.

To see whether the effect of cholesterol was modified by age, the association was analyzed separately in strata up to and above age 70 years.

Missing data of potential confounders were handled by the indicator method.[23] On confounders more than 90% of data was available except diabetes mellitus (84%).

Results

Table 1 shows the baseline characteristics of the study population. The study cohort was followed for an average of 4.5 years. Among them 293 first-ever strokes occurred. Of these strokes 6.8% were hemorrhagic (90% confirmed by brain scan), 72% ischemic (61% were confirmed by brain scan), and 21.2% could not be specified. Hemorrhagic strokes were excluded from the analysis.

Serum total cholesterol was not associated with the risk of first-ever stroke in the total study population (Table 2). On the other hand, in subjects free from diabetes mellitus and cardiovascular diseases high cholesterol level statistically significantly

Table 1
Baseline characteristics of the study population

Characteristic	Subjects without ischemic stroke (n = 6386)	Subjects with ischemic stroke (n = 273)
Age (year)	69.1 (9.0)	77.6 (9.4)
Serum cholesterol (mmol/l)	6.6 (1.2)	6.4 (1.2)
Men	40.0	35.2
Current smoker	22.8	25.5
Former smoker	41.9	32.5
Hypertension	33.2	52.3
Diabetes mellitus	11.1	22.8
Angina pectoris	6.4	9.9
History of myocardial infarction	11.4	22.5

Values are means (SD) or percentages.

Table 2
Relationship between serum total cholesterol and occurrence of ischemic stroke

Serum cholesterol (mmol/l)	Subjects at risk	Number of strokes	Relative risk*	
			In the total study population	In subjects free from diabetes mellitus and cardiovascular diseases
<5.9	1569	80	1.0 (reference)	1.0 (reference)
5.9–6.6	1992	87	1.0 (0.7, 1.4)	1.7 (0.9, 3.3)
6.7–7.4	1370	42	0.8 (0.5, 1.2)	1.5 (0.7, 3.1)
>7.4	1708	64	1.0 (0.7, 1.5)	2.3 (1.2, 4.4)

* Adjusted for age, gender, smoking habit, hypertension, diabetes mellitus, angina pectoris, coronary revascularisation procedure, previous myocardial infarction, atrial fibrillation, previous TIA.

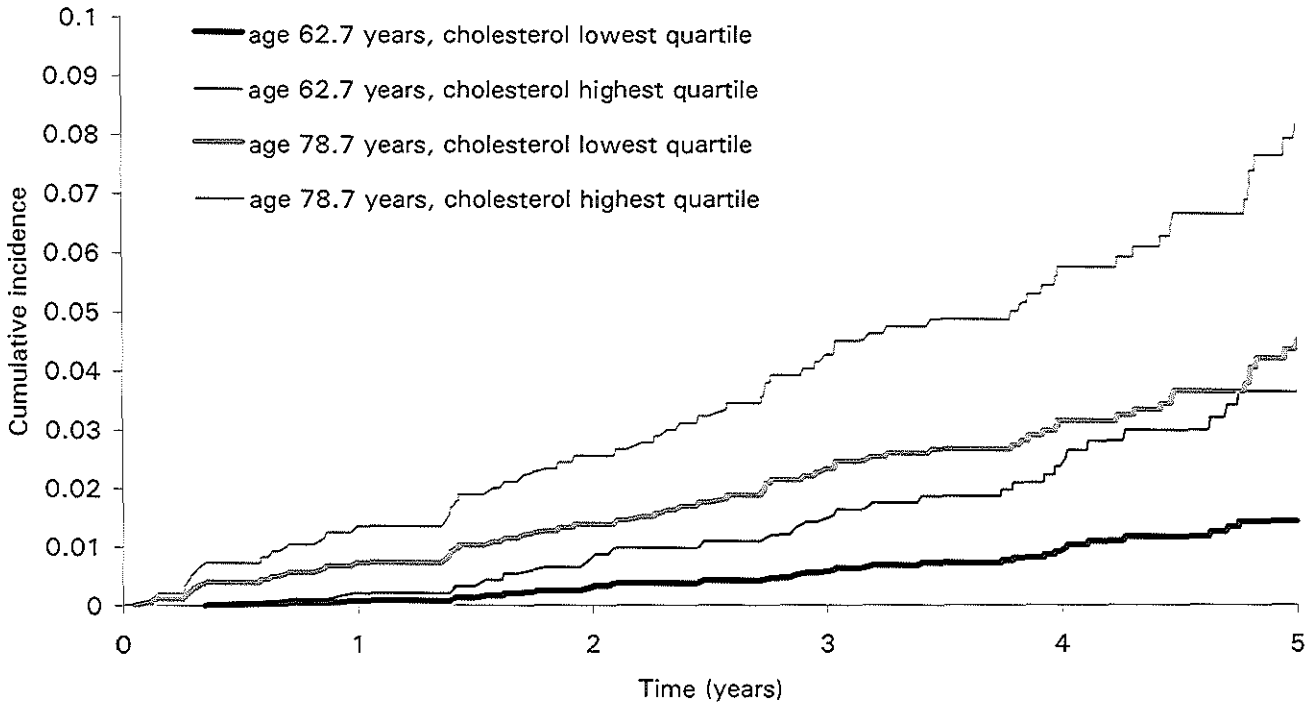

Figure 1
Cumulative incidence of ischemic stroke in men free from diabetes mellitus and cardiovascular diseases with low and high serum cholesterol levels according to two age strata.

increased the risk of stroke (Table 2). Exclusion of unspecified strokes did not materially change the result.

Serum total cholesterol/ high density lipoprotein cholesterol ratio was associated with the risk of stroke neither in the total study population nor in subjects free from cardiovascular diseases and diabetes mellitus.

Those who suffered from cardiovascular diseases, including angina pectoris, atrial fibrillation, coronary revascularisation procedure, myocardial infarction and transient ischemic attack were more likely to start using lipid lowering drugs after baseline examination than those who were free from these diseases (15 versus 10 percent). Similarly, of those who had high cholesterol level at baseline (upper quartile) 25% started lipid lowering drugs thereafter as opposed to only 2% of subjects in the lower quartile. Nevertheless, exclusion of subjects who started using lipid lowering drugs after baseline examination did not materially change our results.

The relative risk of stroke was somewhat higher in younger subjects than in the elderly, relative risk in the highest quartiles 2.5 (95% confidence interval 0.8, 7.9) and 2.0 (95% confidence interval 0.9, 4.5) This was due to the higher background risk in older subjects. As an illustration for the phenomenon we plotted the absolute risk of stroke for men according to two age strata. It is apparent that high cholesterol increases the risk of stroke considerably also in the older age group (Figure 1).

Discussion

We found that high serum cholesterol level increased the risk of ischemic stroke in subjects free from diabetes mellitus and cardiovascular diseases at baseline.

In our study, like in almost all others, serum cholesterol level was determined only once. Due to regression dilution bias this may dilute the association between typical cholesterol level and the risk of stroke.[24,25] Furthermore, subjects with high cholesterol were more likely to start using lipid lowering drugs and probably to change their diet after baseline examination, and this could also result in an underestimation of their risk of stroke. Nevertheless, exclusion of subjects who started using lipid lowering drugs after baseline did not materially change our results.

Current evidence about the relationship between cholesterol and the risk of stroke is inconsistent. Several methodological difficulties should be addressed regarding available results.

Since stroke may alter serum lipid levels,[26,27] case-control studies may lead to biased results if lipid levels are measured immediately after stroke. In a case-control study in which serum cholesterol levels were determined three months after stroke, a statistically significant relationship was found between serum cholesterol level and having experienced an ischemic stroke.[28] However, this still does not tell whether increased levels indeed increase the risk. The cohort studies in which cholesterol level was assessed before stroke yielded controversial results.[5-11] In a meta-analysis

of 45 cohorts, no relationship was found between serum cholesterol and the risk of stroke.[9] On the other hand, high serum cholesterol increased the risk of death from non-hemorrhagic stroke among subjects screened for the Multiple Risk Factor Intervention Trial.[5] A recent meta-analysis of Asian cohorts also showed a positive association between cholesterol and ischemic stroke,[10] and in a Danish study the risk of stroke was statistically significantly higher in subjects with cholesterol level above 8 mmol/l than in subjects with cholesterol level under 5 mmol/l.[6]

Several factors may explain the controversy. In many studies – also among those involved in the meta-analysis of the Prospective Studies Collaboration[9] – stroke subtypes were not analyzed separately. Since low cholesterol level is associated with hemorrhagic stroke,[29,30] studies in which any stroke is the outcome are unlikely to demonstrate increased stroke risk with high cholesterol level, and this is even more unlikely when fatal stroke is considered as outcome, since the case-fatality rate of hemorrhagic strokes is higher,[31-36] thus their proportion is higher among fatal strokes than among any strokes.

In the meta-analysis of the Prospective Studies Collaboration all cholesterol values above 6.38 mmol/l were lumped, and this may partly explain why no association was found, since this could obscure the possible effect of very high cholesterol levels.[9,37]

Our study points to yet another explanation, related to possible confounding effects of other cardiovascular pathology. In our study serum total cholesterol did not increase the risk of stroke in the total study population, but only in subjects free from diabetes mellitus and cardiovascular diseases at baseline. Since the association between high serum cholesterol level and coronary heart disease is already known for almost four decades,[38] patients suffering from coronary heart disease are likely to change their diet or use lipid-lowering drugs, and consequently reduce their serum cholesterol level. This probably holds for subjects suffering from diabetes or having a transient ischemic attack, as well. Indeed, in our study those subjects who suffered from cardiovascular diseases were more likely to start using lipid lowering drugs. It is plausible that similar differences exist regarding life style changes. Since diabetes mellitus and presence of cardiovascular diseases increase the risk of stroke,[39-42] this may result in an underestimation of the true risk associated with elevated cholesterol, as is illustrated with our findings.

In our analysis exclusion of subjects with cardiovascular diseases carried the additional advantage that proportionally more strokes were caused by atherothrombosis, which is more likely to be associated with high cholesterol,[43-45] since the excluded subjects had a higher probability to have a cardioembolic stroke than the remaining subjects.[46]

Coronary heart disease causes another difficulty in studying the relationship between cholesterol and stroke due to a strong competing risk effect.[7] The pattern of atherosclerosis follows a sequence of progression. First plaques becomes established

in the aorta, then in the coronary arteries, and finally in the cerebral arteries.[47-48] Subjects with high cholesterol levels may die of myocardial infarction before occurrence of stroke, which results in an underestimation of the strength of association between cholesterol and stroke.

In summary, our study supports the view that high serum cholesterol is a risk factor for ischemic stroke.

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chapter 5

Family history of cardiovascular diseases and risk of stroke

The Rotterdam Study

Background and Purpose – *Family history of stroke increases the risk of stroke, but it remains unclear whether this risk depends on the age of the proband, the kind or number of family member(s) affected, or the age at stroke in the relative. Furthermore, it is unclear whether the risk of stroke is also increased for persons with a positive family history of cardiovascular disease. We studied these questions in a prospective population based cohort.*

Methods – *This study was conducted within the Rotterdam Study, a prospective population-based cohort study of subjects aged 55 years or over that started in 1990. This analysis concerns 7259 subjects who were free from stroke at baseline, and whose family history of cardiovascular disease could be assessed.*

Results – *The mean follow-up time was 4.4 years and 310 first-ever strokes occurred during the follow-up. History of stroke in any first degree relative significantly increased the risk of stroke (relative risk 1.3; 95% confidence interval 1.0, 1.6). The risk was even higher for persons who had more than one relative with history of stroke or a first degree relative who suffered from a stroke before the age of 65. Family history of early myocardial infarction also increased the risk of stroke, albeit not statistically significantly.*

Conclusions – *Our findings suggest that genetic susceptibility does play a role in the etiology of stroke, although overall familial aggregation seems to be modest. However, genetic factors appear to be important in early onset forms of the disease.*

Although initial case-control or cross-sectional studies showed conflicting results,[1-7] in recent years several reports from methodologically more robust prospective cohort studies have appeared that almost all point to an increased risk of stroke for persons with a positive family history of stroke.[8-14] Nevertheless, several questions have remained. It is unclear whether the risk of stroke varies with the kind of relative (father, mother, sibling, offspring),[14] and whether the risk depends on the age at stroke of the relative or on the number of relatives affected. Furthermore, data on the relationship between family history of myocar-

dial infarction and risk of stroke is scarce.[12,13,15] Our objective was to collect further evidence on the relationship between family history of cardiovascular diseases and the occurrence of stroke.

Subjects and Methods

Study population

This study was conducted in the framework of the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in a suburb of Rotterdam, The Netherlands, were invited. The rationale and design of the Rotterdam Study have been described elsewhere.[16]

Baseline data collection was performed between 1990 and 1993. Written informed consent and permission to retrieve information from medical records were obtained from every participant. The study has been approved by the Medical Ethics Committee of the University Hospital of Rotterdam. In total 7983 subjects participated (response rate 78%). Among them 7603 subjects completed the baseline interview and examination, and reported no previous stroke at baseline. Of them 7259 gave information on family history of stroke and myocardial infarction.

Outcome

Once subjects enter the study they are continuously monitored and followed through linkage with automated medical records of the general practitioners working in the study area. Furthermore, bimonthly updates from the municipality records are obtained. When an event or death is reported, additional information is obtained by interviewing the general practitioner and scrutinizing the medical files or hospital discharge records in case of admittance or referral. This analysis concerns events that occurred till December 31, 1996.

All suspected strokes were reviewed by a neurologist (PJK), who classified them as definite, probable or possible strokes or as non-stroke events, and determined stroke subtypes.[17]

Determinant

Patients were requested to describe their pedigree structure at home, guided by a structured questionnaire. Family history of stroke and myocardial infarction was assessed by direct questioning for each relative listed in the pedigree. For this analysis family history of stroke and myocardial infarction was defined as history of stroke or myocardial infarction of any parents, siblings or offspring. Events before or at the age of 65 were considered early events.

Potential confounders

With respect to smoking behavior subjects were categorized as current or former smokers, and those who never smoked. Diabetes mellitus was defined as random or post-load serum glucose level higher than 11.1 mmol/l or use of antidiabetic medication.[18] Serum total cholesterol was determined by an automated enzymatic procedure.[19] Hypertension was defined as systolic blood pressure equal to or higher than 160 mmHg, or diastolic blood pressure equal to or higher than 95 mmHg, or use of antihypertensive medication.[20] Prevalence of angina pectoris was assessed by means of a Dutch version of the cardiovascular questionnaire of Rose et al.[21] History of stroke or myocardial infarction was assessed primarily by direct questioning. Self-reported events were confirmed by additional information from the general practitioner, cardiologist or neurologist.[22,23]

Statistical analysis

All first-ever strokes were included in the analysis. Relative risks and 95% confidence intervals were estimated through Cox-regression. To study the overall effect of family history of stroke we first adjusted only for age and gender. Next, to control for the effect of shared lifestyle factors and of possibly genetically determined specific cardiovascular risk factors, we further adjusted for smoking habit, serum total cholesterol level, hypertension, diabetes mellitus, angina pectoris, coronary revascularisation procedure and myocardial infarction. Similar analyses were carried out with family history of myocardial infarction and in this case additional analyses were done with adjustment for family history of stroke and early stroke.

Separate analyses were carried out for family history of stroke and myocardial infarction in different first degree relatives (father, mother, sibling and offspring). Furthermore, we analysed the relationship according to the age at stroke or myocardial infarction in first degree relatives.

To study whether genetic hereditability of hypertension or diabetes mellitus could play a role in the association between family history of stroke or myocardial infarction and occurrence of stroke, we compared the prevalence of hypertension and diabetes mellitus at baseline in subjects with and without family history of stroke or myocardial infarction.

Missing data of potential confounders were handled by the indicator method.[24] On confounders more than 90% of data was available except previous myocardial infarction (89%) and diabetes mellitus (80%).

Results

Table 1 shows the baseline characteristics of the study population. The study cohort was followed for an average of 4.4 years. Among them 310 first-ever strokes

Table 1
Baseline characteristics of the study population

Characteristic	Subjects without family history of stroke (n = 5102)	Subjects with family history of stroke (n = 2157)
Age (year)	69.9 (9.6)	69.3 (8.7)
Serum cholesterol (mmol/l)	6.6 (1.2)	6.7 (1.2)
Men	40.5	36.4
Current smoker	23.7	20.2
Former smoker	40.7	41.6
Hypertension	34.4	39.8
Diabetes mellitus	12.9	10.6
Angina pectoris	6.4	7.7
History of myocardial infarction	12.6	12.9

Values are means (SD) or percentages.

occurred. Of these strokes 7.1% were hemorrhagic (77% confirmed by brain scan), 74.8% ischemic (61% confirmed by brain scan), and 18.1% could not be specified.

A statistically significant association between family history of stroke and the risk of first-ever stroke was observed (Table 2). Furthermore, those with more than one first degree relative with a previous stroke had a higher risk than those with only one relative with stroke.

When different first degree relatives were considered separately, modestly increased risks were found for siblings and parents. The strongest relationship was found for history of stroke in offspring.

Relative risks were higher when family history of early stroke was studied. Here, the strongest risk increase was again with history of stroke in offspring. The risk for maternal history was somewhat higher then for paternal history of stroke (Table 3), but the difference was not statistically significant.

We found no evidence for a relationship between family history of any myocardial infarction and the occurrence of stroke. However, family history of early myocardial infarction slightly increased the risk of stroke, although this did not reach statistical significance (relative risk 1.2; 95% confidence interval 0.9, 1.7). Family history of myocardial infarction in more than one first degree relative increased the risk further (relative risk 1.6; 95% confidence interval 0.8, 3.0). Adjustment for family history of stroke or early stroke did not materially change these results.

Finally, hypertension at baseline was more frequent in persons with family history of stroke or myocardial infarction or both than in persons without family history of stroke and myocardial infarction (Table 4). This was not the case for diabetes

Table 2
Relationship between family history of stroke and occurrence of stroke

Determinant	Subjects at risk	Number of strokes	Relative risk	
			Crude*	Adjusted†
No family history of stroke	5102	209	1.0 (reference)	1.0 (reference)
History of stroke				
in any first degree relative	2157	101	1.3 (1.0, 1.6)	1.3 (1.0, 1.6)
in one first degree relative	1864	81	1.2 (0.9, 1.5)	1.2 (0.9, 1.6)
in more than one first degree relative	293	20	1.5 (1.0, 2.4)	1.5 (0.9, 2.4)
in mother	983	40	1.2 (0.8, 1.6)	1.2 (0.8, 1.6)
in father	714	29	1.3 (0.9, 1.9)	1.3 (0.9, 1.9)
in any parent	1610	64	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)
in sibling	674	43	1.3 (0.9, 1.8)	1.3 (0.9, 1.8)
in offspring	45	5	3.2 (1.3, 7.8)	2.9 (1.2, 7.1)

* Adjusted for age and gender.
† Adjusted for age, gender, smoking habit, total cholesterol, hypertension, diabetes mellitus, coronary heart disease.

Table 3
Relationship between family history of early stroke and occurrence of stroke

Determinant	Subjects at risk	Number of strokes	Relative risk	
			Crude*	Adjusted†
No family history of stroke	5102	209	1.0 (reference)	1.0 (reference)
History of early stroke				
in any first degree relative	631	36	1.6 (1.1, 2.3)	1.6 (1.1, 2.3)
in one first degree relative	600	33	1.6 (1.1, 2.3)	1.6 (1.1, 2.3)
in more than one first degree relative	31	3	2.0 (0.6, 6.1)	1.9 (0.6, 6.1)
in mother	181	12	1.8 (1.0, 3.3)	1.8 (1.0, 3.3)
in father	174	7	1.2 (0.6, 2.6)	1.3 (0.6, 2.8)
in any parent	350	18	1.5 (0.9, 2.5)	1.6 (1.0, 2.6)
in sibling	278	16	1.5 (0.9, 2.5)	1.5 (0.9, 2.5)
in offspring	26	4	3.5 (1.3, 9.6)	3.1 (1.1, 8.4)

* Adjusted for age and gender.
† Adjusted for age, gender, smoking habit, total cholesterol, hypertension, diabetes mellitus, coronary heart disease.

Table 4
Prevalence of hypertension and diabetes mellitus at baseline in subjects according to family history

Family history	Prevalence of hypertension at baseline (%)	Prevalence of DM† at baseline (%)
No family history of stroke or MI*	33.3	13.7
History of stroke in any 1st degree relative	39.2	10.4
History of MI in any 1st degree relative	36.3	11.0
History of both stroke and MI in 1st degree relative	40.7	12.2

* MI, myocardial infarction.
† DM, diabetes mellitus.

mellitus. However, adjustment for these and other major stroke risk factors did not change the results suggesting that this could not explain the relation between positive family history of stroke and occurrence of stroke (Table 2 and Table 3).

Exclusion of hemorrhagic strokes did not materially change any of our results.

Discussion

We found a relationship between family history of cardiovascular diseases and occurrence of first-ever stroke. History of stroke in any first degree relative increased the risk of stroke by 30 percent, and the risk was higher if the stroke occurred before age 65 years in the relative. Similarly, although to a lesser extent, family history of early myocardial infarction increased the risk of stroke. To our knowledge this is the first study which showed an increasing risk of stroke with increasing number of first degree relatives who had had a stroke.

We should note that our study has some limitations. First of all, stroke is a heterogeneous group of disorders. Unfortunately, we did not have enough information to use detailed categorisation of cases according to the assumed pathophysiology. Nevertheless, we could at least classify major subtypes of strokes. Since only 7 percent of all cases were hemorrhagic strokes they could not be analysed separately. Although our primary analysis included all first-ever strokes, exclusion of hemorrhagic strokes did not materially change the results.

Family history of stroke was assessed as part of the baseline interview. Since this information was not verified some misclassification could occur. Family history of myocardial infarction is more frequently under- than overreported,[25-28] and it is likely that the same holds for family history of stroke. Consequently, our results somewhat underestimate the true risk of stroke associated with positive family history of cardiovascular diseases.

Our estimated relative risk of stroke in subjects with family history of stroke is somewhat lower than the result (relative risk 1.6; 95% confidence interval 1.0, 2.4) from the Family Heart Study, which is a multicenter study involving subjects from four different cohorts.[14] This study has also reported the risk separately for subjects with positive family history of stroke in different first degree relatives. Contrary to our results the Family Heart Study found no evidence that history of stroke in siblings or in offspring increases the risk of stroke.[14] However, the risk estimates in the Family Heart Study have wide confidence intervals overlapping the estimates from our study.

Regarding the higher risk in subjects with family history of early stroke, our findings are in line with the results of Jousilahti et al.[13] They found in a prospective follow-up study of 14371 middle aged subjects that history of stroke in parents before age 60 increased the risk of any stroke in men and women by 90 and 73 percent, respectively, and of ischemic stroke by 53 and 71 per cent. In addition to that we found and increased risk in subjects with a child or sibling who had had a stroke before age 65. Unfortunately, the Finnish study did not present data on family history of stroke above age 60, thus the relative impact of age at stroke can not be directly judged from their report.

In our study the estimated risk of stroke did not differ much in subjects with maternal or paternal history of stroke, but maternal history of early stroke increased the risk of stroke more than paternal history. Available data regarding this issue is controversial. Results from the Framingham Study, the Family Heart Study and from the study of Jousilahti et al. showed 19 to 96% higher risks with paternal history than with maternal history.[11,13,14] On the other hand, Welin et al. reported maternal but not paternal history of death of stroke as an independent risk factor for stroke,[9] although this finding was not confirmed by the study of Wannamethee et al.[12]

Previous results about the relationship between family history of myocardial infarction and risk of stroke were controversial. In an Italian case-control study no association was found,[15] in a British cohort parental death from heart trouble increased the risk of stroke, and this risk was virtually not modified by parental age at death,[12] and in a Finnish cohort parental history of coronary heart disease before age 60 increased the risk of both any stroke and ischemic stroke.[13] Our findings confirm the Finnish results.

In our study hypertension was more frequent at baseline in subjects with family history of stroke or myocardial infarction than in subjects with no family history of these disorders. This may indicate a partly common genetical pathway of the diseases. Nevertheless, our analysis showed that adjustment for major stroke risk factors, including hypertension, did not change the results. Therefore, shared life-style factors and inheritance of conventional vascular risk factors cannot fully explain our findings. Although shared environment may contribute to the familial aggregation of stroke, we think that our study strongly supports that genetic susceptibility plays

an important role in the etiology of stroke.

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chapter 6

Dietary antioxidants prevent stroke in smokers

The Rotterdam Study

High intake of fruits, vitamin C, β-carotene, or selenium prevented stroke in a cohort of Dutch elderly people. The protective effect was confined to smokers.

Oxidative stress reportedly plays a role in the etiology of stroke. Therefore dietary intake of antioxidants might lower the risk of stroke. High intake of fruits has been reported to protect against stroke.[1] The joint investigation of the Nurses' Health Study and of the Health Professionals' Follow-up Study also found a protective effect of fruits and vegetables and the effect was slightly stronger in smokers than in non-smokers.[2] It has been suggested that dietary antioxidants may account for the beneficial effects of fruits and vegetables.[3] Our aim was to investigate the relationship between specific dietary antioxidants, including flavonoids, antioxidant vitamins, and selenium and the risk of stroke, and to assess whether the putative protective effect of these antioxidants differs between smokers and non-smokers.

This study was conducted within the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in a suburb of Rotterdam, The Netherlands, were invited.[4] Baseline data collection was performed between 1990 and 1993, and the total cohort consists of 7983 subjects (response rate 78%).

At baseline, a modified 170-item semiquantitative food frequency questionnaire was applied in two steps for dietary assessment. During a home interview subjects filled in a simple questionnaire, and then during a subsequent visit to the research center a trained dietician interviewed them.[5] 7006 subjects completed the baseline interview and examination. The food frequency questionnaire was not administered to subjects participating in the pilot study (n=277), living in nursing homes (n=479), subjects with known reduced cognitive function (n=122) and an additional 482 subjects due to logistic reasons (no dietician available). From the 5646 with food frequency data 5234 subjects reported no previous stroke at baseline and had a complete follow-up, and these were included in this analysis.

History of stroke was assessed primarily by direct questioning. Self-reported events were confirmed by additional information from the general practitioner or neurologist. During follow-up subjects are continuously monitored through linkage with automated medical records of the general practitioners working in the study area. Furthermore, bimonthly updates from the municipality records are obtained. When an event or death is reported, additional information is obtained by interviewing the general practitioner and scrutinising the medical files or hospital discharge records in case of admittance or referral. All suspected stroke cases that were reported were reviewed by a neurologist (PJK), who classified the stroke as definite, probable or possible and defined subtypes. This analysis concerns strokes that occurred till December 31, 1996.

Relative risks (and 95% confidence intervals) of stroke for specific antioxidant intakes were estimated through Cox-regression, adjusted for age and gender. Dietary intake items – vitamin C, vitamin E, β-carotene, flavonoids, selenium, total food energy – were categorised in tertiles (low medium and high intake). Those who were taking vitamin supplements were included in the highest tertile for the concerning analysis. All analyses were adjusted for total energy intake. For the analysis of vitamin E intake we additionally adjusted for polyunsaturated fatty acid intake. Since diet is likely associated with health behaviour and the health status of an individual we also adjusted for smoking, hypertension, diabetes mellitus, history of coronary heart disease and transient neurological attacks. To assess possible effect modification by smoking status, we performed analyses separately for current-smokers and non-smokers (including former smokers). Furthermore, to assess the independent effect of the different dietary components, we fitted models with inclusion of all antioxidants under study.

The study cohort was followed for an average of 4.7 years. Among them 173 first-ever strokes occurred. Of these strokes 8.7% were hemorrhagic, 79.2% ischemic, and 12.1% could not be specified.

Higher intake of vitamin C, β-carotene, and selenium was associated with a lower risk of stroke in the total study population (Table 1). Stratification for smoking behaviour showed that this protective effect was confined to smokers. This may be because smokers have higher free radical activity, as reflected by the higher level of free radical activity mediated lipid peroxidation products in their blood. Consumption of fruits and flavonoids also considerably decreased the risk of stroke in smokers, although the latter did not reach statistical significance (Table 1). Inclusion of all antioxidants under study in the statistical model did not materially change the results for the individual risk factors. Intake of vegetables and vitamin E was not associated with the risk of stroke.

Our results show that high intake of vitamin C and β-carotene may protect against stroke in smokers. High intake of selenium, which plays a very important role in oxidant defence, seems also beneficial in preventing stroke.

Table 1
Fruits, vegetables, dietary antioxidants and the risk of first-ever stroke

Determinant	Relative risk*		
	Total population	Non-smokers	Smokers
Fruits			
2nd tertile	1.2 (0.8, 1.7)	1.5 (0.9, 2.5)	0.7 (0.4, 1.5)
3rd tertile	1.0 (0.7, 1.5)	1.4 (0.8, 2.2)	0.3 (0.1, 0.8)
Vegetables			
2nd tertile	0.9 (0.6, 1.4)	1.0 (0.7, 1.6)	0.7 (0.3, 1.6)
3rd tertile	1.0 (0.7, 1.5)	0.9 (0.6, 1.5)	1.2 (0.6, 2.5)
Vitamin C			
2nd tertile	0.7 (0.5, 1.0)	0.9 (0.6, 1.4)	0.3 (0.2, 0.8)
3rd tertile	0.7 (0.5, 1.0)	1.0 (0.6, 1.5)	0.2 (0.1, 0.5)
Vitamin E			
2nd tertile	1.3 (0.8, 2.0)	1.3 (0.8, 2.1)	1.3 (0.5, 2.9)
3rd tertile	1.2 (0.7, 2.3)	1.3 (0.6, 2.7)	0.9 (0.3, 3.2)
ß-carotene			
2nd tertile	0.7 (0.5, 1.0)	0.8 (0.5, 1.3)	0.4 (0.2, 0.9)
3rd tertile	0.7 (0.5, 1.1)	0.8 (0.5, 1.3)	0.5 (0.2, 1.1)
Flavonoids			
2nd tertile	1.1 (0.8, 1.6)	1.2 (0.8, 1.9)	1.0 (0.5, 1.9)
3rd tertile	0.8 (0.5, 1.2)	0.9 (0.6, 1.5)	0.4 (0.2, 1.2)
Selenium			
2nd tertile	0.6 (0.4, 0.9)	0.8 (0.5, 1.2)	0.3 (0.1, 0.7)
3rd tertile	0.6 (0.4, 1.0)	0.9 (0.5, 1.5)	0.2 (0.1, 0.6)

* First (lowest) tertile is the reference.

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chapter 7

Aspirin use and risk of stroke in the elderly

The Rotterdam Study

The objective of the study was to assess the association between aspirin use and the risk of stroke in a population-based study in the elderly. The study was carried out within the framework of the Rotterdam Study, a prospective population-based cohort study. In the total study population there was a weak, non-significant association between aspirin use and the risk of stroke (adjusted relative risk 1.29, 95% CI 0.91-1.83). Stratification by history of vascular diseases revealed that aspirin considerably increased the risk of first ever stroke in subjects free from vascular disease, (adjusted relative risk 1.80; 95% CI 1.03-3.13). In persons with vascular disease no association was observed between aspirin use and risk of stroke, (adjusted relative risk 0.99, 95% CI 0.56-1.73). Our finding suggest that aspirin use may increase the risk of stroke in elderly subjects free from vascular disease.

Randomised clinical trials have shown that aspirin can prevent stroke in patients after a transient ischemic attack or minor stroke.[1] On the other hand, the role of aspirin in primary stroke prevention is not clear. Two large clinical trials and a meta-analysis have even suggested that aspirin may increase the risk of stroke, in particular hemorrhagic stroke, in low risk subjects, but this finding was not statistically significant.[1-3] Recently, it was reported from the Cardiovascular Health Study that aspirin use increased the risk of stroke in aspirin using elderly women free from cardiovascular diseases.[4]

We further investigated the association between aspirin use and occurrence of stroke in a population-based cohort study in Dutch elderly.

Methods

Study population

This study was conducted within the framework of the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, of a suburb of Rotterdam, The Netherlands, were invited. Institution-

alised persons are included. The rationale and design of the Rotterdam Study have been described elsewhere.[5] In summary, the objective of the study is to investigate determinants of neurogeriatric, cardiovascular, locomotor and ophtalmologic diseases in the elderly.

In total 7983 subjects participated in the baseline examination (response rate 78%). Because our aim was to study the effect of aspirin use in primary prevention of stroke we excluded participants who had a history of stroke at baseline, leaving 7725 subjects. Among them there were 7431 subjects whose drug use was ascertained. The 294 excluded subjects were older than the rest of the cohort, their mean (SD) age was 74.7 (12.0) years; 99 (34%) of them were men. After exclusion of subjects who used oral anticoagulation or antiplatelet therapy other than aspirin, the cohort comprised 7153 subjects. The incidence rate of stroke among these excluded subjects was higher than in the rest of the cohort: 14.9 versus 10.6/1000 person-years. Baseline data collection was performed between 1990 and 1993, when all study subjects were interviewed at their homes and subsequently examined at a research center. Informed consent and permission to retrieve information from medical records were obtained from every participant.

Assessment of strokes

At baseline, information on health status and medical history was obtained using a computerised questionnaire. Previous stroke was assessed by direct questioning: "Did you ever suffer from a stroke diagnosed by a physician?". If the answer was 'yes', medical records were checked for additional information. A previous stroke was coded if it was confirmed by medical records.[6]

Once subjects enter the Rotterdam Study they are continuously monitored for major events through automated linkage with the files from the GPs. General practitioners who send information on all possible events and deaths on a regular basis cover together 85% of the cohort. The general practitioners of the remainder of the cohort are contacted once a year to obtain follow-up information. With respect to the vital status, information is obtained at regular intervals from the municipal authorities in Rotterdam. When an event or death has been reported, additional information is obtained by interviewing the GP and scrutinising information from hospital discharge records in case of admittance or referral. Information on all possible strokes was reviewed by a neurologist (PJK) who classified the stroke as definite, probable or possible. The stroke was considered definite if the diagnosis was based on both clinical symptoms and neuro-imaging. A probable stroke was considered if no CT or MRI was made but if symptoms were highly suggestive for stroke according to the GP or treating neurologist. In case of fatal stroke a cardiac cause of death should have been excluded to reach a diagnosis of probable stroke. The stroke was considered possible if a neurologist diagnosed a 'possible stroke' without neuro-imaging, or if a GP recorded a fatal stroke and could not exclude a cardiac

cause of death.

If CT or MRI was performed which showed a haemorrhage or infarct the type of stroke was coded accordingly. In case of no abnormality on CT or MRI the stroke was classified as ischemic. When no CT or MRI was performed, a stroke could be coded possible hemorrhagic or ischemic in case of typical complaints or case history. A case history of sudden hemiplegia or other focal signs with permanent unconsciousness or death within hours without neuro-imaging was coded as possible hemorrhagic stroke. If there was limited impairment, i.e. isolated afasia, isolated weakness of one limb, isolated facial weakness or isolated hemianopia the stroke was considered possible ischemic. Furthermore, in case of complete improvement within 72 hours or documented atrial fibrillation at time of the diagnosis the stroke also was considered possible ischemic.

This analysis concerns events that occurred until March 1, 1996. Complete follow-up was available for 6385 subjects (86%).

Determinant

Drug use was ascertained as part of the baseline interview when participants were asked to show all drugs they were using regularly at that time. Medication was classified by ATC codes.[7] Aspirin users were defined as persons who were regularly taking acetylsalicylic acid or its calcium salt (calcium carbasalate) at the time of the baseline interview.

Potential confounders

Cerebrovascular risk indicators and history of stroke were assessed at baseline examination. With respect to smoking behaviour subjects were categorised as current or former smokers, and those who never smoked. Diabetes mellitus was defined as random or post-load serum glucose level higher than 11.1 mmol/l or use of antidiabetic medication.[8] Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer.[9] The average of two measurements obtained on one occasion, separated by a count of the pulse rate, was used in this analysis. Prevalence of angina pectoris and claudication was assessed by means of a Dutch version of the cardiovascular questionnaire of Rose et al.[10] Chest pain and pain in the legs but not fulfilling Rose criteria were assessed by the questions "Have you ever had any pain or discomfort in your chest?" and "Do you get pain or a feeling of severe tiredness in either leg on walking?", respectively. These symptoms were considered potential confounders because they might have served as an indication for aspirin use and were associated with stroke in our data, thus controlling for them reduces the potential bias of confounding by indication. A history of transient ischemic attack (TIA) was assessed on the basis of answers to the question "Did you experience a short period with disturbances of sensibility in your face, arms, or legs, which had lasted less than 24 hours over the last 3 years?". Similar questions

were asked for disturbances in strength, speech, and vision. If a positive answer was given, more detailed information was obtained, and the event was categorised as typical transient ischemic attack (TIA), atypical TIA or no TIA, by a neurologist (PJK).[11] History of myocardial infarction (MI) was assessed primarily by direct questioning. Myocardial infarction was considered to have happened if it was self-reported and ECG characteristics matched, e.g. pathological Q-waves or significant loss of R-wave potential in the precordial leads of a single ECG was seen, or it was confirmed by additional information from the general practitioner or cardiologist based on elevated cardiac enzymes or prior ECG abnormalities. In addition MI was also considered if ECG findings was typical for MI, regardless of the absence of symptoms.[12]

Statistical analysis

We compared the risk of first-ever stroke in aspirin users vs. non-users by estimating relative risk (RR) and 95 % confidence intervals (CI) through Cox's proportional hazards regression. All first-ever strokes were included in the analysis. Additional analyses were carried out on ischemic strokes and with the exclusion of possible strokes.

Analyses were adjusted for age and gender. In order to control for confounding by indication as much as possible, additional adjustment was done for the following cerebrovascular risk indicators: smoking habit, diabetes mellitus, systolic blood pressure, antihypertensive medication, presence of atrial fibrillation on ECG, angina pectoris, intermittent claudication, chest pain, pain in the leg, history of coronary revascularisation procedure (including percutaneous transarterial coronary angioplasty, and coronary bypass surgery), myocardial infarction, typical and atypical TIA.

To study whether the effect of aspirin was different for subjects at high or low risk of stroke stratified analyses were performed for subjects with or without vascular disease. Vascular disease was defined as history of typical or atypical TIA, intermittent claudication, angina pectoris, coronary revascularisation procedure or myocardial infarction, or presence of atrial fibrillation on ECG at entry. There were 5508 subjects whose history of vascular disease could be ascertained. Subjects with vascular disease was older than subjects without vascular disease, mean age(SD) 72.5 (8.9) versus 67.9 (8.5) years, and there were relatively more men among them, 47.3 versus 37.0%.

Missing data on potential confounders were handled by the indicator method.13 Use of imputation or total dataset methods produced essentially the same results. For all variables less than 10 percent of data was missing.

Table 1
Baseline characteristics of the study population

Characteristic	Aspirin users (n = 662)	Aspirin non-users (n = 5723)
Age (year)	73.0 (9.5)	69.6 (9.2)
Systolic blood pressure (mmHg)	140.8 (23.0)	139.7 (22.3)
Diastolic blood pressure (mmHg)	72.7 (11.6)	74.0 (11.8)
Serum cholesterol (mmol/l)	6.5 (1.2)	6.6 (1.2)
Men	48.9	36.9
Current smoker	20.9	22.5
Former smoker	46.5	40.0
Diabetes mellitus	15.2	10.7
Atrial fibrillation	4.8	2.0
Intermittent claudication	2.6	1.3
Angina pectoris	15.0	5.6
Coronary revascularisation	13.6	1.3
History of myocardial infarction	29.8	9.9
History of typical TIA	9.1	0.5
History of atypical TIA	6.7	1.2

Values are means (SD) or percentages.

Results

Table 1 shows the baseline characteristics of the study population. Ten percent of subjects used acetylsalicylic acid or its calcium salt in this cohort. Of these subjects 47% used acetylsalicylic acid, 52% calcium carbasalate and 1% both. 66% of drug users were taking their drug daily, and 95% of the users took a tablet at least once every three days, and the remaining 5% of subjects were taking acetylsalicylic acid weekly. Of the 44 subjects who suffered a stroke and were taking medication 17 used aspirin and 27 used calcium carbasalate. The mean defined daily dose of the drug was 249mg, 90% of the users took no more than 500mg per day. There was no difference in dosage between subjects with or without history of vascular diseases. Those who suffered a stroke during the follow-up took neither more nor less drug than those who had no stroke.

The study cohort was followed for an average of 3.9 years. In total, 265 strokes occurred until the end of follow-up, 220 of which were definite or probable. Of all strokes, 8.3% were hemorrhagic, 73.6% ischemic, and 18.1% non-specified. From the 44 stroke cases that occurred among aspirin users 29 were ischemic, three were hemorrhagic, one was subarachnoid haemorrhage and eleven were unspecified.

Table 2
Association Between aspirin use and occurrence of first-ever stroke

Determinant	Persons at risk	Number of strokes	Strokes/1000 person-years	Relative risk (95% CI) Adjusted for age and gender	Relative risk (95% CI) Additional adjustment*
Total study population					
non-users	5723	221	9.8	1.0 (reference)	1.0 (reference)
users	662	44	18.3	1.42 (1.03-1.98)	1.29 (0.91-1.83)
Without vascular disease					
non-users	3946	106	6.9	1.0 (reference)	1.0 (reference)
users	227	15	18.1	1.76 (1.02-3.05)	1.80 (1.03-3.13)
With vascular disease					
non-users	984	65	17.1	1.0 (reference)	1.0 (reference)
users	351	19	15.1	0.90 (0.54-1.50)	0.99 (0.56-1.73)

CI: confidence interval.
* Adjusted additionally for smoking habit, diabetes mellitus, systolic blood pressure, antihypertensive drug use, atrial fibrillation, intermittent claudication, angina pectoris, chest pain, pain in the legs, coronary revascularisation procedure, history of myocardial infarction, history of typical and atypical TIA.

In the total cohort, there was a weak, non-significant association between aspirin use and the risk of any stroke (Table 2). In the stratum of subjects without vascular diseases aspirin use almost doubled the risk of stroke, (RR 1.80; 95% CI 1.03-3.13). Separate analyses for men and women produced essentially the same results with wider confidence intervals. Among subjects with vascular disease there was no association between aspirin use and the risk of stroke, (RR 0.99; 95% CI: 0.56-1.73). Exclusion of possible cases only marginally changed these results RR 1.91 (1.05-3.48) and RR 0.94 (0.52-1.70) for subjects without and with vascular diseases, respectively.

Our analysis included all types of stroke. Of the 15 cases that occurred in subjects free from vascular disease and using aspirin one stroke was subarachnoid haemorrhage, and two were intracerebral haemorrhage. When only ischemic stroke was considered the estimated relative risk was 1.09 (0.71-1.67) in the total study population, RR 1.46 (0.73-2.96) and RR 0.87 (0.45-1.69) in the strata of subjects without and with vascular disease, respectively.

Discussion

In this population-based study we found that aspirin use is associated with an increased risk of any stroke, but only in subjects without vascular disease. The risk of ischemic stroke increased as well, albeit less than the risk of all strokes, and not statistically significantly.

The result is consistent with previous studies. Aspirin was shown to be effective in prevention of myocardial infarction, stroke, and vascular death in subjects with prior myocardial infarction, stroke, transient ischemic attacks, unstable angina, revascularisation surgery, angioplasty, atrial fibrillation, valvular disease, and peripheral vascular disease.[1] However, the role of aspirin in primary prevention is not yet established. Results from trials of primary prevention among men showed a non-significant increased risk of stroke among aspirin users,[1-3] and an increased risk of ischemic stroke has been reported recently, as well from the Cardiovascular Health Study among elderly women free from vascular diseases who used aspirin.[4,14]

What might explain the increased risk of stroke associated with aspirin use in low risk subjects? The possibility of an increase in the incidence of hemorrhagic stroke in aspirin users is not unexpected. But in addition, aspirin may have a paradoxical thrombogenic effect, probably by inhibition of PGI2 production in endothelial cells.[15] Recent reports have shown that aspirin antagonizes tissue plasminogen activator mediated thrombolysis, probably by inhibiting the expression of the inducible nitric oxide synthase.[16-19] These mechanisms may explain the potential adverse effect of aspirin on the incidence of ischemic stroke. If aspirin has a paradoxical thrombotic side effect, it is expected to be detected in subjects who have very little to gain from its beneficial effect, i.e. in subjects without vascular disease.

A potential weakness of our study originates from the difficulties in exposure status assessment. It was suggested that aspirin taken occasionally as an antiinflammatory medication or pain killer during the follow-up could bias the result of the studies on aspirin use in which aspirin use is assessed at entry.[20] Indeed, it is possible that stroke is associated with this type of drug use as well. However, since it is very likely that occasional use of aspirin as antiinflammatory drug is at least as frequent among subjects who are not using aspirin regularly as among regular aspirin users, this can not explain our result. Furthermore, it is entirely possible that some subjects started using aspirin regularly after baseline examination. Nevertheless, this would result in an underestimation of the effect of aspirin, therefore our estimate can be considered as a conservative one.

One might argue that the association found between aspirin use and risk of stroke is not causal but due to confounding by indication. We reduced this possibility by including all known major risk factors for vascular disease in the analysis and we carried out separate analyses in subjects with and without vascular disease, as well. Since we can not think of an indication for aspirin other than those considered in this study, which itself increased the risk of stroke, it is very unlikely that confound-

ing by indication explains our result.

Another alternative explanation to causal relation between aspirin use and risk of stroke could be that the group of aspirin users include subjects who stopped aspirin use before the occurrence of stroke,[20] and the rebound effect was responsible for stroke.[21,22] However, if aspirin were beneficial in prevention of stroke in low risk subjects then it would have to be entirely overwhelmed by the adverse rebound effect in our study, which could occur if many subjects stopped taking the drug, or if stopping the treatment enormously increased the risk of stroke, even in subjects with an otherwise very low risk. In our view a more plausible explanation is that aspirin can not prevent stroke in low risk subjects, and that aspirin has an adverse effect, maybe partly due to stopping medication.

In conclusion, our results indicate that aspirin use may be associated with an increased risk of stroke in elderly people without a history of vascular diseases and atrial fibrillation. This finding needs further study, which should address the effects of aspirin on all major vascular events - stroke, myocardial infarction, and death - to study the net effect of aspirin use in primary prevention in elderly people. Even if the net effect is beneficial considering all benefits and harms of aspirin use, it may be possible to identify subgroups of subjects who gain and who lose with the use of aspirin in prevention of cardiovascular diseases. Evidence on safety of a drug used for primary prevention should be stringent, since its beneficial effect is usually minimal in individuals, who are at low risk anyway, and can be offset by side effects.[23]

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chapter 8

Prevention of stroke by carotid endarterectomy. A Bayesian random effect meta-analysis

The study assessed the effect of carotid endarterectomy on all-cause mortality and stroke-free survival based on the combined data from randomized trials. We searched for all published randomized clinical trials in which carotid endarterectomy was compared to medical treatment. Nine trials that met pre-specified criteria were located. For each trial identical measures of disease frequency were calculated from published data, and were analyzed by regression analysis following a Bayesian approach. Carotid endarterectomy does not increase life expectancy but prolongs stroke-free survival. This beneficial effect after three years of operation is present only when the estimated incidence rate of stroke or death in patient receiving only medical treatment is above about 8.3 per 100 patient-years. With increasing risk of stroke or death surgery becomes more effective. Carotid endarterectomy prolongs stroke-free survival but its application should be limited to patients at high risk of stroke.

In developed countries stroke is the third leading cause of death. Its annual incidence is about 0.15 percent.[1] The first year survival probability is less than 75 percent and one year after the event more than 25 percent of the survivors are unable to function independently.[2]

It is estimated that 20-30 percent of stroke cases is related to carotid artery stenosis. The underlying mechanism is usually thromboembolism, originating from an atherosclerotic plaque of the internal carotid artery.[3] Carotid endarterectomy aims to remove the plaque and restore the lumen of the vessel. This is a frequently performed vascular surgical procedure.[4,5] Although the first published operation was carried out decades ago,[6] and more than 1 million people have been operated since 1980 in the United States only,[5] there are still unanswered questions regarding the efficacy of carotid endarterectomy in the prevention of cerebral infarction and death.[7-17] Many observational studies and several clinical trials comparing carotid endarterectomy plus best medical care with medical treatment alone have been done or are under way.

This paper is a quantitative analysis of the randomized clinical trials addressing this question published thus far. Our aim was to assess the safety of carotid endarterectomy by comparing the one-month incidence of death, and the combined event of stroke or death between the surgical and the medical arms of the trials reported. Furthermore, we wanted to assess whether carotid endarterectomy improves long-term survival and stroke-free survival. Other parameters of interest were therefore the incidence rate ratios of death, and of the combined event stroke or death (incidence rates expressed as number of events per person-years of follow-up 'at risk') from the first month onwards. In the statistical analysis a regression method was applied using a Bayesian approach with non-informative priors.[18,19] Our method can be considered as a generalization of the method described by Thompson et al.,[20] taking into consideration the comments of van Houwelingen and Senn.[21]

Materials and methods

Selection of trials

We searched the Medline database for all published randomized clinical trials in which one of the treatment arms was carotid endarterectomy. We completed the search by checking the references of the articles found. Eleven trials that met this criterion were located.[22-33] Those trials were included in the analysis that fulfilled the following pre-defined criteria:

1. The indication of carotid endarterectomy was stroke prevention rather than treatment of acute stroke.
2. The methodology of the trial as described was judged appropriate (no excessive loss to follow-up, symmetrical outcome assessment, analyzed by treatment assignment from the moment of randomization onwards).
3. The parameters of interest in this analysis could be calculated from published data, or from additional data obtained by writing to the author of the original report.

From the Joint study of extracranial arterial occlusion only a separately published subgroup fulfilled the above criteria.[22] The subgroups based on the degree of carotid artery stenosis of the European Carotid Surgery Trial and of the North American Symptomatic Carotid Endarterectomy Trial were analyzed separately in this overview.[25,32,33]

The following trials were excluded. About one trial in 230 patients only a short summary was published and it was not possible to obtain the information required.[30] The trial carried out at the Mayo Clinics (71 patients) was excluded because the parameters of interest could not be calculated from the available data.[28] From one trial report only stroke-free survival could be estimated.[26] In one trial report data on any strokes were not available and our analysis concerns major strokes - producing

symptoms for more than seven days.[32]

Table 1 shows some characteristics of the trials included in the analysis. It is noted that in the trials involving subjects with high grade stenosis the comparison was between immediate surgery combined with medical therapy and medical therapy alone. In several trials involving subjects with moderate, slight or asymptomatic stenosis the effect of immediate surgery and waiting policy, i.e. avoiding the operation as long as possible was compared.

In total, our analysis concerns 8991 patients, 4780 allocated to surgery and 4211 to medical treatment.

Data extraction from individual trials

The follow-up period was split up into two parts: the first month post-operative period and the period after the first month until three years. To calculate the first month cumulative incidence of stroke or death in the surgical group the number of events were divided by the number of patients 'at risk', which was taken as the number of subjects enrolled in a group, and it was assumed that no patient was lost to follow-up in the first month.

When stroke-free survival curves were given,[25,29,31] the combined incidence rates of stroke and death from the first month onwards for the surgical and from the randomization onwards for the medically treated cohorts respectively were estimated as follows. For the medical cohorts the stroke-free survival probability closest to three years was read off from the curve and converted to an incidence rate with the use of the following equations, assuming exponential stroke-free survival with a constant incidence rate from the moment of randomization onwards:

$$CI_M(t) = 1 - e^{-IR_M \cdot t} \qquad \text{equation 1}$$

From this we have

$$IR_M = \frac{\ln(1 - CI_M(t))}{-t} \qquad \text{equation 2}$$

where $CI_M(t)$ and IR_M denote the t-year cumulative incidence and incidence rate, respectively, in the medical group.

For the surgical cohorts the stroke-free survival probability at the same time point was determined as the product of the one-month stroke-free survival probability and the stroke-free survival probability from the first month onwards. Hence, the stroke-free survival probability at three years was divided by the one-month stroke-free survival probability (as estimated the way stated previously) to obtain the stroke-free survival probability from the first month onwards. The latter was again converted to an incidence rate, assuming exponential stroke-free survival with a constant incidence rate from the first month onwards. Thus the following equa-

Table 1
Some characteristics of the trials included in the analysis

Study	Symptoms before entry	Angiologic requirements of eligibility	Treatment comparison
Joint study[20]	TIA* no neurological deficit	ICA† stenosis > 30% on angiogram occlusions excluded	CEA‡ + medical treatment vs. medical treatment (unspecified)
Shaw et al.[21]	symptoms of carotid artery disease	operable ICA lesion on angiogram	CEA vs. medical treatment (unspecified)
Veteran 309[24]	TIA, TMB§ or small completed stroke within 120 days	ICA stenosis $\geq$ 50% on angiogram occlusions excluded no more severe intracranial lesion	CEA + best medical care vs. best medical care (incl. 325 mg aspirin/day)
ECST[30]	TIA, TMB or nondisabling stroke within 6 months	ICA lesion on angiogram no clear treatment preference of the treating physician no more severe intracranial lesion	CEA + best medical care vs. best medical care (usually included aspirin) 12% operated in the medical group
NASCET[23, 31]	TIA, TMB or nondisabling stroke within 120 days	ICA stenosis $\geq$ 30% on angiogram occlusions excluded no more severe intracranial lesion	CEA + best medical care vs. best medical care (incl. 1300 mg aspirin/day) 18% with stenosis less than 70% and 6% with stenosis of 70-99% operated in the medical group
Clagett et al.[22]	no history of TIA, TMB, or stroke absence of nonfocal cerebro-vascular symptoms	abnormal OPPG¶	immediate surgery vs. waiting policy (incl. 1300mg aspirin/day) 29% operated in the waiting policy group
CASANOVA[25]	no neurological symptoms no subclavian steal	ICA stenosis 51-89% on angiogram no intracranial, CCA#, or bilateral vertebral artery stenosis > 50%	immediate surgery vs. waiting policy (incl. 1300mg aspirin and 75mg dipyridamole) 57% operated in the waiting policy group

Veteran 167[27]	no symptoms at the side of the lesion	ICA stenosis $\geq$ 50%	CEA + 1300 mg aspirin vs. 1300 mg aspirin
ACAS[29]	no symptoms at the side of the lesion, in the vertebro-basilar system, or from the contralateral carotid territory within 45 days	ICA stenosis $\geq$ 60% on angiography or Doppler ultrasound with 95% PPV** or 90% PPV + positive OPPG	immediate surgery vs. no surgery 325 mg aspirin + risk factor reduction in both groups 5% operated on in the medical group

* TIA, transient ischaemic attack
‡ CEA, carotid endarterectomy
¶ OPPG, ocular pneumoplethysmography
** PPV, positive predictive value
† ICA, internal carotid artery
§ TMB, transient monocular blindness
# CCA, common carotid artery

tions were used:

$$CI_S(t) = 1 - (1 - CI_S(1\text{month})) \cdot e^{-IR_S \cdot (t - \frac{1}{12})} \qquad \text{equation 3}$$

From this we have:

$$IR_S = -(\ln \frac{1 - CI_S(t)}{1 - CI_S(1\text{month})}) \Big/ (t - \frac{1}{12}) \qquad \text{equation 4}$$

where $CI_S(t)$, $CI_S(1\,month)$ and IR_S denote the t-year and one month cumulative incidence and the incidence rate from one month onwards, respectively, in the surgical group.

For one trial the actual curves were not given, but the estimates needed could be extracted by a standard actuarial method.[22]

If time to event curves were not provided, incidence rates were calculated as the number of strokes or deaths divided by the total person-years of follow-up 'at risk'. The mean follow-up time was usually not published separately for the study groups. To divide approximately the total amount of follow-up time over the two groups, we took the ratio of the number of patients at risk at the end of the first month as the ratio of the amounts of follow-up time after the first month in the two groups. If it was not stated otherwise, we assumed that the follow-up time given in each report corresponded to the time either until death or until censoring and in each trial patients who sustained a non-fatal stroke have been followed until death or until censoring. Therefore the total person-years of follow-up reported minus half the mean follow-up for each patient who had non-fatal stroke was taken as the denominator for the incidence rate extraction for the combined outcome of stroke or death.

Since no survival curves were reported for death from all causes for any trials, this latter method was used to estimate incidence rates of death, as well.

The observed 3-year cumulative incidences of stroke or death were read off from stroke-free survival curves if the curves were published. When the curves were not given, trial-specific three-year cumulative incidences of stroke or death were estimated from the incidence rates by exponential conversion (see "equation 1 and 3").

Statistical methods for pooling

To assess the relationship between the incidence rates of the events of interest from the first month onwards in the surgical and medical groups respectively, a linear regression model was used. We assumed that the measures of the disease frequencies "observed" in the trials are measured with some error due to sampling variability, and there are "true" underlying surgical risk and long term incidence rates of events both in the medical and surgical groups in each trial.

The following relationship between the "true" event rate tIR_{Mi} under the medical treatment in the i^{th} trial and the "true" event rate tIR_{Si} in the surgical group of the i^{th} trial is assumed:

$$\ln(tIR_{Si}) = a + b \cdot \ln(tIR_{Mi}) + e_i \qquad \text{equation 5}$$

where a and b are regression coefficients to be estimated and the error term e_i is assumed to be normally distributed with zero mean and unknown standard deviation. Note that this is a direct generalization of the standard random-effect approach in meta-analysis. If $b = 1$, then our model reduces to the well-known model of DerSimonian and Laird.[34] In fact the model assumes a bivariate normal distribution for the "true" event rates in the two treatment groups, and is therefore identical to the bivariate random effects meta-analysis model described by van Houwelingen et al.[35] The observed number of events in a treatment group of a trial is assumed to be Poisson distributed with mean equal the follow-up in person-years in that group multiplied by the "true" event rate in that group. Furthermore, in analogy with standard random effects models used for meta-analysis it was assumed that the logarithms of the "true" incidence rates of the medically treated groups were normally distributed with mean and variance to be estimated from the data. The model was fitted by a Bayesian analysis method analogous to the methods described by Thompson et al. using Gibbs sampling by the program BUGS,[18-20] but taking into consideration the comments of van Houwelingen and Senn.[21] Throughout uninformative prior distributions were used.

When the analysis showed that b was likely to be close to one (i.e. no evidence of "linear" heterogeneity of incidence rate ratios), this parameter was set to one in the model and a was recalculated. In this case the pooled estimate of tIR_S/tIR_M was taken as $\exp(a)$. When the analysis showed that b is likely to differ from one, both a and b were estimated and were considered as the result of the pooled analysis. In this case the implication of the analysis is that for any given value of tIR_M the value of tIR_S can be estimated as $\exp(a + b \times \ln(tIR_M))$.

For estimating the "true" three years cumulative incidence ratio for stroke or death as a function of the "true" incidence rate of stroke or death in the medical group (tIR_M), we extended the above-described bivariate model. In the extended model we assumed a trivariate normal distribution of the "true" log odds of stroke or death in the surgical group in the first month, of the "true" log incidence rate of stroke or death in the medical and in the surgical group. After fitting the model for calculating the three-year cumulative incidence ratios "equation 1 and 3" were applied. The model was fitted using the program BUGS employing a non-informative prior distribution on the unknown model parameters. The BUGS syntax for this problem can be obtained from the authors.

Results

Table 2 shows the observed surgical risks and incidence rates in the trials. The pooled estimate of the one-month cumulative incidence of stroke or death in the surgical group obtained from the trivariate model was 6 percent (95 percent confidence interval 4.8-7.5).

The regression analysis of death rates yielded b = 1.21 (95 percent confidence interval 0.96-1.53). As this indicated that there was no evidence for *b* being different from 1, the model was refitted as described above (see statistical methods for pooling). This yielded a ln(incidence rate ratio) of a = -0.025 (95 percent confidence interval -0.13, 0.088). After exponentiating, the pooled incidence rate ratio for death becomes 0.98 (95 percent confidence interval 0.88-1.09).

Pooled regression analysis of incidence rates of stroke or death yielded the following relationship between the incidence rates of stroke or death from the first month onwards:

$$E(\ln IR_{Si}) = 1.07 + 0.32 \cdot \ln(IR_{Mi}),$$

where IR_{Si} and IR_{Mi} stand for the trial-specific underlying "true" incidence rates in the surgical and medical arms, respectively. The 95 percent confidence interval of the intercept (*a* in "equation 5") in the model was 0.18, 1.93 and of the slope (*b* in "equation 5") it was -0.11-0.76. The latter indicates that there is evidence that the second parameter differs from one, so there is heterogeneity in incidence rate ratios between trials, and the parameter can therefore not be set to one in the model. The relationship between IR_S and IR_M suggested by the model is plotted in figure 1 together with the 95 percent confidence interval. Observed values for each trial are also indicated. The figure shows that the effect of surgery on the incidence rate of stroke or death from the first month onwards increases with the incidence rate of death or stroke in a comparable patient treated medically. The figure also shows that the model fits the available data reasonably well, with two outliers, which originate from the very small trials of Shaw et al. and of Clagett et al.[22,24] Omission of these trials does not influence the result.

The relationship between the incidence rate of stroke or death in medically treated patients and the three-year cumulative incidence ratio of stroke or death comparing patients assigned to surgery with patients assigned to medical treatment is plotted in figure 2. Observed values are also plotted for each individual trial or trial subgroup. It can be seen that the actual observations are well fitted by the functional relationship. The figure shows that the break-even point, the value of the base-line incidence rate above which surgery is beneficial in regard the three-year risk of stroke or death is 7.7 strokes or deaths / 100 person-years (95% confidence interval 7.1, 8.3) if we apply the pooled estimate of the surgical risk. So above a baseline risk of 8.3 stroke or deaths / 100 person-years immediate surgery is significantly better.

Table 2
Number of subjects involved trial specific one-month cumulative incidences of death and of stroke or death in the surgical group, and incidence rates form randomisation onwards in the medical and after one month in the surgical group

Study	N_{surg}*	N_{med}†	Outcome: death			Outcome: stroke or death		
			CI_{surg}‡	IR_{med}§	IR_{surg}¶	CI_{surg}	IR_{med}	IR_{surg}
Joint study	169	147	3.6	5.4	4.0	11.2	7.5	4.6
Shaw et al.	20	21	15.0	5.1	12.3	35.0	13.8	17.5
Veteran 309	91	98	3.3			5.5	9.3	6.3
ECST 0-19% stenosis	78	62	1.3	3.2	4.4	6.4	4.4	5.1
ECST 20-29% stenosis	162	117	0.6	4.2	4.8	1.9	5.7	6.2
ECST 30-39% stenosis	200	139	1.0	4.7	4.6	7.0	5.5	5.6
ECST 40-49% stenosis	190	122	1.1	3.2	4.0	9.5	4.4	4.3
ECST 50-59% stenosis	350	240	1.1	4.5	4.4	6.3	6.1	5.2
ECST 60-69% stenosis	232	137	2.2	3.8	3.9	9.5	6.1	4.5
ECST 70-79% stenosis	231	170	1.7	4.9	4.4	9.1	7.0	5.2
ECST 80-89% stenosis	251	159	0.4	4.9	5.1	4.8	7.9	5.9
ECST 90- % stenosis	113	65	1.8	4.8	5.5	4.4	10.0	5.8
NASCET <50% stenosis	678	690	1.2#	2.0	1.8	6.6#	6.7	5.3
NASCET 50-69% stenosis	430	428	1.2#	2.4	1.9	6.6#	8.3	4.7
NASCET 70- % stenosis	328	331	0.6	4.0	2.8	5.8	16.3	5.3
Clagett et al.	15	14	0	2.2	7.3	0	2.2	7.3
CASANOVA	206	204	1.5	6.8	6.4	3.4	10.8	9.3
Veteran 167	211	233	1.9	7.8	7.9	4.3	9.9	8.0
ACAS	825	834	0.5	3.9	3.7	2.7	7.0	5.3

* N_{surg}, number of subjects in the surgical groups
† N_{med}, number of subjects in the medical group
‡ CI_{surg}, cumulative incidence in the surgical group (%)
§ IR_{med}, "observed" incidence rate (number of events / 100 person-years) in the medical group from randomization onwards
¶ IR_{surg}, "observed" incidence rate (number of events / 100 person-years) in the surgical group from the first month onwards
# estimates could be calculated only for the two subgroups combined

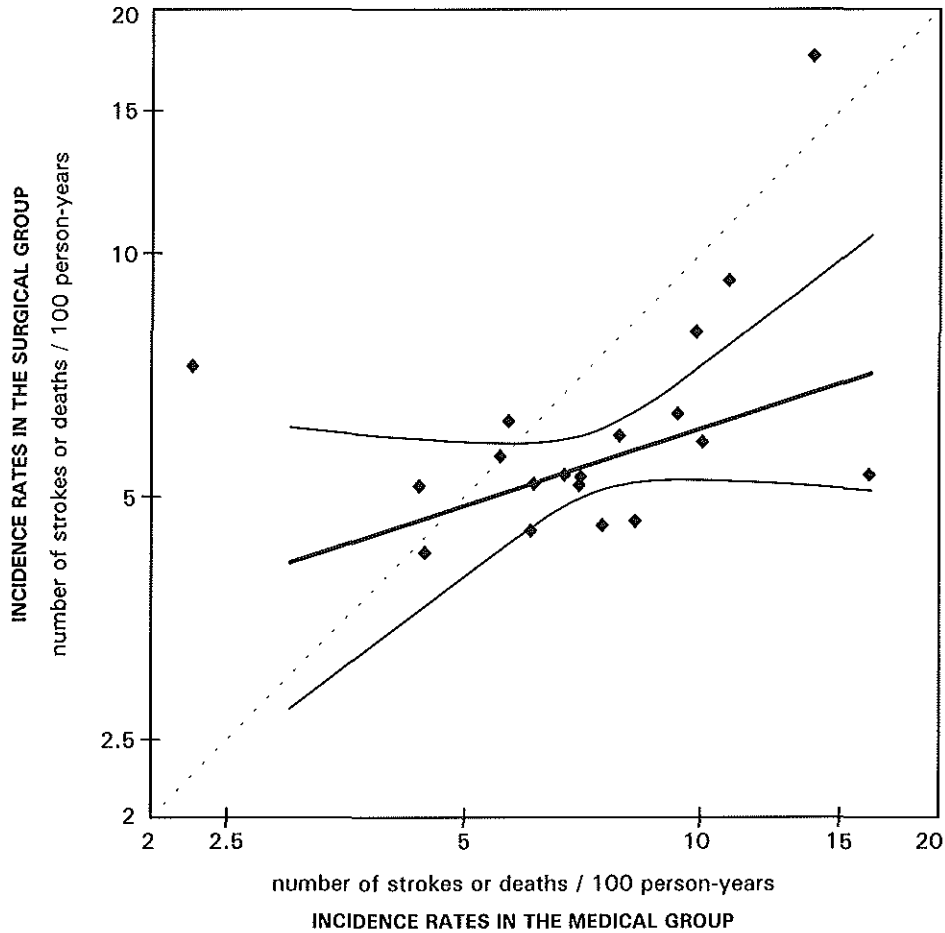

Figure 1
Relationship between incidence rates of stroke or death in the medical and in the surgical group, estimated regression line with its 95% confidence interval. Dotted line is the line of equality. Observed data from the trials are indicated with ♦. Values are plotted on logarithmic scales.

Discussion

The aim of this meta-analysis was to assess the safety and long-term efficacy of the surgical treatment of carotid artery stenosis in comparison to medical treatment alone. Our pre-specified choice of parameters followed directly from this aim. When the individual patient data from the trials are not available, one is entirely dependent on the way data is reported. As there is no uniform approach to the latter, the parameters chosen to be of interest in a meta-analysis are often not reported as such but have to be estimated based on the original reports. In this regard the current meta-analysis is no exception. The individual data were not available and the parameters of interest chosen had to be estimated from published data. In doing so,

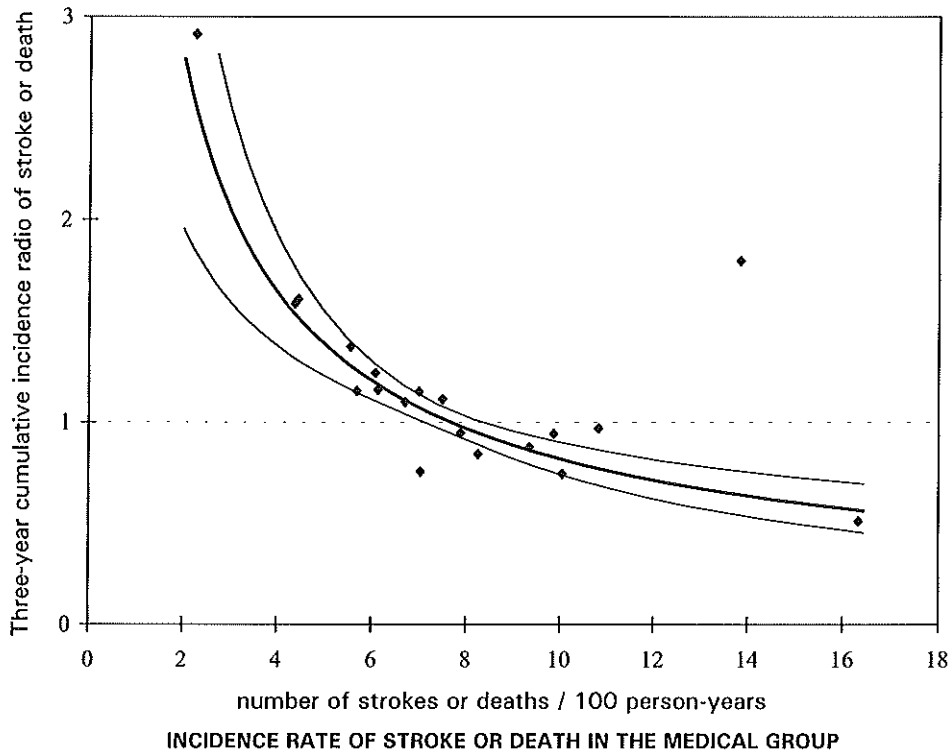

Figure 2
Relationship between the incidence rate of stroke or death in the medical group and the three-year cumulative incidence ratio of stroke or death surgical versus medical group. Observed data from the trials are indicated with ♦. Continuous lines indicate the pooled estimate of the cumulative incidence ratio with its 95% confidence interval as a function of the incidence rate in the medical group.

several assumptions had to be made.

First of all, we assumed that the incidence rates of death, and of stroke or death are constant in the medical group from the moment of randomization onwards and in the surgical group after the first month. This assumption is reasonable because carotid artery stenosis with or without symptoms is a chronic condition. Generally, the degree of stenosis will progress with time and in the long run therefore the incidence rates will increase. However, over a three-year period the increase should be small indeed, if detectable at all in data of the type considered. In many trials or trial subgroups considered the mean follow-up was shorter than four years. We focused on the three-year outcome because over this relatively short period of time the incidence rates should be approximately constant and because we wanted to avoid extrapolation beyond the follow-up period of the majority of patients.

Secondly, we assumed that the person-years of follow-up after the first month in the surgical and medical groups respectively can be approximated as described from the total follow-up for both groups combined and from the number of subjects

at risk after the first month in each group. In most cases this assumption is necessary because the amount of follow-up is not reported by treatment group. For low incidence rates that do not differ too much, this seems to be a reasonable assumption. In this context, we also assumed that the amount of follow-up until stroke or death can be approximated from the amount of follow-up until death as described.

Although participation in some trials was restricted to surgical teams who could show that their complication rate was acceptable,[26,36-38] our estimate of surgical risk is consistent with the reported results from other studies.[39-44] In clinical practice the risk of angiography must be considered also.[45,46] Nevertheless, one can easily plot the curve on figure 2 for different values of the surgical risk applying "equation 1, 3 and 5".

Regarding the long-term effect, it is entirely possible that surgery offers a greater advantage in patients who are at a higher absolute risk of stroke when treated medically. As a consequence, measures of effect may differ from trial to trial depending on the underlying risk of the patients actually randomised.[47] In a meta-analysis a measure of effect (such as the 'odds ratio') is usually pre-specified and the question whether heterogeneity exists for the chosen effect measure is addressed by the so-called heterogeneity test.[48] This approach has at least two disadvantages. First of all, the power of the heterogeneity test is low.[48] Second, the method does not specify how to continue the analysis when the heterogeneity test is 'significant'. Hence, a preferable statistical method allows for the possibility that effects are heterogeneous. Based on published data, such a method should provide an estimate of the treatment effect conditional on some trial characteristics, such as aggregate information of subjects included or risk in the reference category. One method that accomplishes this has been used previously to describe the expected mortality rate of patients treated for hypertension given the rate in the absence of treatment.[49] That method was based on a weighted linear regression of the observed event rates in the treatment group against the observed event rates in the control group. It may produce biased estimates due to imprecision of the observed incidence rates used as independent variable in fitting the model.[50] The method used in this analysis avoids this problem, because the estimated "true" incidence rates in the control groups is used as independent variable.

With respect to long-term efficacy, our analysis suggests that surgery does not increase life expectancy. The reason for this is the initial risk of complications. Even if the operation was completely safe, the reduction in mortality would be modest as the incidence rate ratio of death after the first month comparing surgery to medical treatment is 0.98. A possible explanation is that carotid artery stenosis may just be one manifestation of generalized atherosclerosis which also affects other parts of the vascular system. A reflection of this is that only a minor proportion of deaths attributable to cardiovascular disease is due to stroke. Furthermore, only a fraction of strokes are related to carotid artery stenosis. Hence, the potential impact

of carotid endarterectomy on all cause mortality must be limited.

Nonetheless, our analysis shows that surgery can be expected to prolong stroke-free survival provided that the procedure is limited to patients who have a relatively high risk of stroke due to carotid stenosis. Figure 1 compares observed incidence rates in the medically treated patients with the incidence rate in those surgically treated patients who survive the first month after surgery without a stroke. It shows that patients at low risk of stroke or death when treated medically are unlikely to benefit from surgery. With increasing risk, surgery becomes more effective relative to medical treatment. Since we neglected the first month after surgery in figure 1, to compare the treatments fairly we estimated the 3-year cumulative incidence of stroke or death, taking into account the surgical risk, and then comparing both treatment options. As is shown in figure 2, surgery is beneficial only when the estimated incidence rate of stroke or death for medical treatment is above about 8.3 strokes or deaths / 100 person-years. With increasing risk of stroke or death for medical treatment, surgery becomes more effective. A possible explanation is that at lower risks there are simply too few events that can be prevented by surgery. Hence, its risks predominate. The break-even point above which surgery becomes effective could be a useful guideline in clinical practice if it were possible to estimate the incidence rate of stroke or death in an individual patient before taking the decision to operate. A multivariate risk function for identifying patients within the group of subjects with 70-99 percent carotid artery stenosis who are at high risk of stroke on medical treatment and are at low risk of operative stroke or death has recently been published from the ECST study.[51] Preoperative risk factors of carotid endarterectomy have also been reported. Some patient characteristics play a role, but one of the most important factor seems to be the surgeon.[40,41,52]

Naturally, one of the most powerful predictors of stroke is the degree of carotid stenosis. Several studies and the trials analyzed in this report have shown that the higher the degree of the stenosis, the higher the risk of stroke. In addition, given a certain anatomical degree of stenosis, symptomatic patients have worse prognosis than those without symptoms.[25,32,33,54-58] In patients on medical treatment with severe symptomatic anatomic stenosis, i.e. more than 70% according to the NASCET criteria the average incidence rate of stroke or death is higher than the 8.3 per 100 patient-years.[25,32,53,59] Hence, in these patients surgery is indicated based on the results of this analysis. In patients with a moderate symptomatic or severe asymptomatic stenosis the incidence rate is around the range (7.1, 8.3) where it is not clear which treatment is better.[27,29,31-33,53-57] Hence, these patients may benefit from surgery if they are operated with very low complication rate. Several features have been reported that might help identifying high risk subjects in this category of stenosis, like contralateral disease, impaired cerebral vasomotor reactivity, asymptomatic embolization, and echostructure appearance of the carotid plaque.[58-62] For lower risk patients, i.e. under 7.1 stroke or death per 100 patient-years, surgery should even be consid-

ered as harmful. Based on the results available today and this meta-analysis, a waiting policy in these patients is indicated. This policy should include clinical follow-up and non-invasive assessment of the lesion to determine whether the patient remains at low risk. If this does not seem to be the case, surgery can then be offered.

We conclude that carotid endarterectomy is a relatively safe procedure which prolongs stroke-free survival in patients with a high risk of stroke or death. For moderate or low risk patients, there is at present no evidence that supports that such patients should be operated also.

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chapter 9

Change in a risk factor as a determinant of disease. The pitfall of adjustment for baseline

In studies of the relationship between change in a risk factor and the occurrence of a disease, the baseline value of the risk factor is usually considered as a potential confounder. Therefore it is often adjusted for in the analyses. However, because of the phenomenon of regression towards the mean adjustment for baseline level may cause severe bias. On the other hand, refraining from adjustment in many instances produces unbiased or only slightly biased results. With an estimate of the within subjects variability an unbiased estimate of the effect of change can be obtained using hierarchical modelling. It is expected that methods based on hierarchical models that can deal straightforwardly with measurement error problems like this will be available for routine use soon. If an unbiased estimate of the change can not be obtained, it is better not to adjust for baseline value of the risk factor.

In an increasing number of studies risk factors are measured at several points in time. A question that is often addressed in these studies is whether change in a risk factor over time is associated with disease outcome. In a clinical setting, for example, one could investigate the association between change in a monitored physiological parameter and a certain outcome. In cohort studies where repeated exposure assessment is carried out, one might want to study the relation between change in exposure status and occurrence of disease.

In most of these studies the baseline level of the risk factor is considered a confounder of the relation between change in the risk factor and the risk of the disease. Therefore it is usually adjusted for or stratified on in the analyses, and most of the authors do not present the results without adjustment for baseline.[1-8] Although this practice seems to be appropriate at first sight, it is incorrect. In this paper we show why this method produces biased results, illustrated with an example taken from the Rotterdam Study, and discuss potential solutions.

Table 1
The relationship between change in systolic blood pressure and risk of stroke, estimated odds ratios according to the applied method

method	odds ratio* (95% CI)
adjustment for baseline	1.10 (1.00; 1.22)
no adjustment for baseline	1.00 (0.91; 1.10)

* Corresponding to 10 mmHg increase in blood pressure. Adjusted for age and gender.
CI: confidence interval.

WHY DOES CURRENT PRACTICE PRODUCE BIASED RESULTS?

We wanted to study the relationship between change in systolic blood pressure and the risk of stroke in the Rotterdam Study, which is a prospective population based cohort study among 7983 subjects, aged 55 years or over, living in a suburb of Rotterdam, The Netherlands. The rationale and design of the Rotterdam Study have been described elsewhere.[9] Baseline examinations took place in 1990-1993 and follow-up examinations in 1993-1994, and 1997-1999. In addition, the cohort is continuously being monitored for major disease outcomes, including stroke. Subjects were included in the analysis if they had blood pressure measurements at both the baseline and first follow-up examination, and were free from stroke at the time of first follow-up. The risk of stroke associated with change in blood pressure was estimated by calculating odds ratios through logistic regression with adjustment for age and gender.

High systolic blood pressure itself is a known risk factor for stroke. If change in systolic blood pressure depends on the baseline value, baseline systolic blood pressure would be a potential confounder, i.e. any observed association between change in systolic blood pressure and risk of stroke might result in whole or in part from the relation between the baseline systolic blood pressure and stroke. Following standard methods to deal with confounders, we adjusted for baseline systolic blood pressure in the analysis. The result is presented in Table 1. Based on this we would conclude that there is evidence that an increase in systolic blood pressure increases the risk of stroke.

What if we consider that baseline value of systolic blood pressure is not related to change? In that case, baseline systolic blood pressure would not be a confounder and there would be no need to adjust for it in the analysis. Table 1 presents the result without adjustment for baseline systolic blood pressure, too. This does not provide evidence for an association between change in systolic blood pressure and risk of stroke.

Which analysis is correct?

At first sight it seems that the analysis with adjustment for the baseline value of systolic blood pressure must be the correct one. The population distribution of systolic blood pressure consists of individual distributions, with their mean representing the individuals typical or "true" value.[10] A single measurement may be higher or lower than the individual's actual typical value. This is due to either biological within subject variability, or to measurement error, or usually to both.[11,12] If we take a second measurement in a subject it is more likely that it will be closer to the individual's typical value.[10] As a consequence, if we select a group with extreme observed baseline blood pressure, their group mean of the second measurement will be closer to the population mean.[13,14] The phenomenon is called *regression towards the mean.*[13]

How is this phenomenon related to adjustment for baseline?

Figure 1 illustrates the situation when the typical value (hereafter "true" value) of systolic blood pressure remains unchanged in every subject, meaning "true" change is zero. Nevertheless, even in this situation the observed value will change in most of the individuals. Let us examine in this situation what happens if we adjust for baseline.

When we adjust for the baseline level, we compare the risk of those subjects who had the same observed baseline blood pressure. Figure 1 shows the individual distributions of two subjects with observed baseline systolic blood pressure of 110 mmHg. It can be seen that in the subject whose "true" blood pressure was higher than 110 mmHg blood pressure will *increase* towards the own "true" value, and in the other subject whose "true" blood pressure was lower than 110 mmHg it will *decrease* towards the own "true" value. As a consequence, if we compare the risk of stroke in subjects whose observed blood pressure increased and those whose decreased, then we compare the risk of subjects whose "true" baseline blood pressure was high to those whose "true" baseline blood pressure was low. Those who had a higher "true" blood pressure at baseline are of course at a higher risk for stroke and we would conclude that an increase in systolic blood pressure increases the risk for stroke. It should be emphasised that the observed association between change in blood pressure and risk of stroke in this case is not reflecting a true association, but a statistical phenomenon.

Since all standard methods for controlling confounding – stratification, standardisation or regression analysis – are based on the idea of comparing the risk of subjects conditionally on the value of the potential confounder, they lead to the same bias. The bias will arise regardless whether we categorise change or use it as a continuous variable in the statistical model.

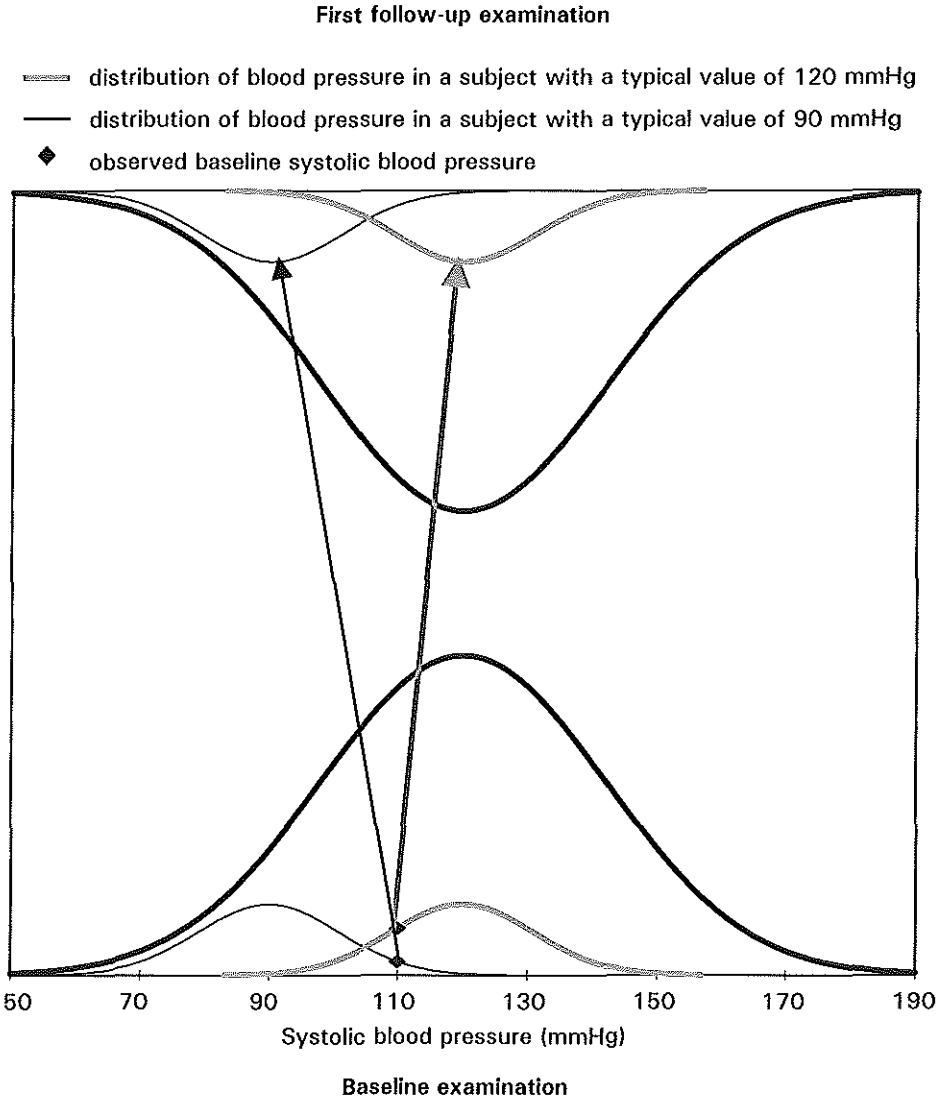

Figure 1
Illustration of the effect of adjustment for baseline systolic blood pressure. The direction of change is illustrated by the arrows.

In many instances "true" change is not zero and is associated with baseline. In this case adjustment for baseline introduces bias as well, for the same reason that was discussed above. No adjustment also fails, since the estimated risk is not adjusted for confounding, caused by the relationship between baseline value and "true" change.

What is the solution?

First, as discussed above we should realise that adjustment for baseline value almost always results in severely biased estimates, since it is based on the assumption that observed change is equal to the change of the individual's "true" value. And this assumption is almost always false, because of the regression towards the mean phenomenon.

Not adjusting for baseline can also cause bias if baseline value is associated with "true" change. Nevertheless, in many instances the variance of the change due to regression towards the mean is large compared to the variance of the "true" change, e.g. when a physiological parameter has large biological within-subject variability, or in case of imprecise measurements. Furthermore, "true" change is often only weakly associated with baseline value. In these cases adjustment causes severe bias, while no adjustment for baseline leads to only slightly biased effect estimate. Therefore, when the choice is between adjusting or not-adjusting for baseline, not adjusting is the recommended approach.

The most appropriate analysis is based on the separation of the variance of change into the variance of "true" change and of the change due to regression towards the mean. The latter can be estimated by measuring the risk factor repeatedly and shortly apart.[15]

Once one has an estimate of this variance, it becomes possible to estimate the effect of "true" change. With the use of an estimate of this variance of the "error", a solution for estimating the effect of the "true" change was proposed by Cain et al. for linear and logistic regression analysis.[16]

Another solution would be directly estimating the effect of "true" change. Methods based on hierarchical models and simulation techniques can deal straightforwardly with problems like this. Since these have become available recently, it is expected that unbiased methods to estimate the effect of change on outcome parameters will be available for routine use in the near future.[17]

In our example blood pressure was measured again in 100 patients at a second visit two weeks later. From these measurements we estimated the within-subject variability to be 116.6 $mmHg^2$. With the application of the method suggested by Cain et al. we found no evidence that change in systolic blood pressure was associated with the risk of stroke ($p = 0.3$). This is in contrast to the analysis with simple adjustment for baseline.

Conclusion

The current approach – adjustment for baseline value of the risk factor – in studies of the association between change in a risk factor and disease produces strongly biased results because of the phenomenon of regression towards the mean. We

illustrated the problem with an example from a cohort study.

The larger the effect of the regression towards the mean and the weaker the association between baseline and "true" change, the less we gain from adjustment for baseline and the more harm we do. Therefore in many instances no adjustment for baseline is the recommended simple approach of the analysis, which leads to only slightly biased effect estimate.

With the use of an estimate of the within-subject variability of the risk factor one can correct for the effect of regression towards the mean in the analysis. It is expected that unbiased methods based on hierarchical models that can deal straightforwardly with measurement error problems like this will be available for routine use soon to estimate the effect of change.[17]

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chapter 10

General discussion

This thesis describes investigations related to the etiology and prevention of stroke. We attempted to answer the following questions:

- Can we predict the probability of stroke based on the presence of major stroke risk factors?
- How is blood pressure related to stroke?
- What may explain the controversial results about the relationship between serum cholesterol and the risk of stroke?
- Is there familial aggregation of stroke?
- Can dietary antioxidants prevent stroke?
- Is the use of aspirin for primary prevention of stroke justifiable?
- How effective and safe is carotid endarterectomy in prevention of stroke?

In the previous chapters studies aiming to answer these questions were presented in details. In this chapter, I first summarise the main findings and their interpretation and potential implications. A separate section is devoted to new analytical methods we used in our studies. Next, I discuss major issues on the validity of the studies. I conclude with a brief outline summary of possible future directions for epidemiological research on etiology of stroke and envisaged short-term developments in research methods.

Main findings

All our studies, except the meta-analysis on the efficacy of carotid endarterectomy in the prevention of stroke, were based on the Rotterdam Study, an ongoing prospective population-based cohort study for which all inhabitants aged 55 years or over, living in a suburb of Rotterdam, The Netherlands, were invited. Baseline data collection was performed between 1990 and 1993. In total 7983 subjects participated (response rate 78%). Of these, 7603 subjects participated at the baseline interview and examination, and reported no previous stroke at baseline. Till the end of 1996 346 strokes occurred among them, the mean follow-up time was 4.46 years.

Risk and prevention of stroke

Can we predict the probability of stroke based on the presence of major stroke risk factors?

We validated the Framingham stroke risk profile within the Rotterdam Study. Risk factors included in the profile were age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy by electrocardiogram. Separate functions were used for men and women.

We estimated the three-year probability of stroke in 4930 subjects. We assessed how the profile estimated the number of strokes and TIAs that occurred within three years of follow-up and how the function could discriminate between high and low risk subjects. The estimated probability had a wide range; and the prevalence of the event was fairly well predicted in most categories of the estimated risk.

The function discriminated equally regardless whether stroke or stroke and TIA were considered as event. For stroke the area under the ROC curve was 0.75. Whether this performance is considered bad or good depends on the actual context in which the function is used. Since usually risk functions are used to identify high risk subjects, reasonably high sensitivity is required. When the function is used as a screening instrument and additional diagnostic investigations are necessary to indicate an intervention, very high specificity is not an indispensable requirement.

How is blood pressure related to stroke?

The risk of first-ever stroke was associated with hypertension (relative risk 1.6, 95% CI 1.2-2.0), and with isolated systolic hypertension (relative risk 1.7, 95% CI 1.1-2.6). We found a continuous increase in stroke incidence with increasing blood pressure in non-treated subjects. In treated subjects we found a J-shaped relation between blood pressure and the risk of stroke. The increased stroke risk in the lowest strata of blood pressure in treated hypertensive patients may indicate that the therapeutic goal "the lower the better" is not the optimal strategy in the elderly.

Advanced atherosclerosis, or an excess of subjects with isolated hypertension among subjects with very low diastolic blood pressure could not explain our finding. We assume that since chronic hypertension shifts the lower and upper blood pressure limits of cerebral blood flow autoregulation towards higher pressure, it makes the brain more susceptible to ischemia at low blood pressure.

We should emphasise that treatment of elderly hypertensive subjects has been proven to safe lives, to prevent myocardial infarctions and strokes, and our findings do not contradict these findings. Our results showed that in treated hypertensive elderly subjects only very low diastolic blood pressures increased the risk of stroke.

One might consider that a blood pressure below 65 mmHg is rarely a target blood pressure in everyday practice and that an increased risk associated with very low blood pressure is merely a theoretical problem. However, 20 percent of the

antihypertensive drug users in this elderly population fell into that category.

What may explain the controversial results about the relationship between serum cholesterol and the risk of stroke?

Clinical trials with HMG-CoA reductase inhibitors have shown a 30 percent reduction in the risk of stroke by these drugs. On the other hand, observational studies have provided controversial results about the relationship between serum cholesterol and the risk of stroke. Some confirm that cholesterol increases the risk of stroke, but the bulk of the evidence points to no relation. Although statins may have other beneficial effects than cholesterol lowering which may partly explain their effect, we thought that this apparent paradox needed further explanation.

In the total study population we found no relationship. However, high serum cholesterol level significantly increased the risk of ischemic stroke in subjects who were free from cardiovascular diseases and diabetes mellitus (highest quartile versus lowest quartile, relative risk 2.3; 95% CI 1.2-4.4). The ratio of serum total cholesterol and high density lipoprotein cholesterol was associated with the risk of stroke neither in the total study population nor in subjects free from cardiovascular diseases and diabetes mellitus.

Several methodological difficulties have to be addressed when weighing and considering available results about the relationship between serum cholesterol level and the occurrence of stroke. Some of the most important ones are the following:

Since low cholesterol level is associated with hemorrhagic stroke, studies in which any stroke is the outcome are unlikely to demonstrate increased stroke risk with high cholesterol level. This is even less likely when fatal stroke is considered as the outcome, since the case-fatality rate of hemorrhagic strokes is higher, thus their proportion is higher among fatal strokes than among any strokes.

Stroke may alter serum lipid levels, therefore case-control studies may lead to biased results if lipid levels measured immediately after stroke are used in the analysis.

Most studies did not control for coronary heart disease. Since the association between high serum cholesterol level and coronary heart disease is already known for almost four decades, patients suffering from coronary heart disease are likely to change their diet or use lipid-lowering drugs, and consequently reduce their serum cholesterol level. Indeed, in our study those subjects who suffered from cardiovascular diseases were more likely to start using lipid lowering drugs. Presence of cardiovascular diseases increases the risk of stroke, and this may result in an underestimation of the true risk associated with elevated cholesterol, as illustrated with our findings.

Our study supports the view that high serum cholesterol is a risk factor for ischemic stroke.

Is there familial aggregation of stroke?

Available evidence suggests that family history of stroke increased the risk of stroke, but it is unclear whether this risk depends on the age of the proband, the kind or number of family member(s) affected, or the age at stroke in the relative. Furthermore, it is unclear whether the risk of stroke is also increased for persons with a positive family history of myocardial infarction.

We found that a history of stroke in any first degree relative significantly increased the risk of stroke (relative risk 1.3; 95% CI 1.0-1.6). The risk was even higher for persons who had more than one relative with history of stroke or a first degree relative who suffered from a stroke before the age of 65. Family history of early myocardial infarction also increased the risk of stroke, albeit not statistically significantly.

Our findings suggest that genetic susceptibility does play a role in the etiology of stroke, although overall familial aggregation seems to be modest. Genetic factors appear more important in early onset forms of the disease.

Can dietary antioxidants prevent stroke?

Oxidative stress reportedly plays a role in the etiology of stroke. Therefore dietary intake of antioxidants might lower the risk of stroke. High intake of fruits has been reported to protect against stroke. Free radical activity is higher in smokers, and it is reflected in the higher level of free radical activity mediated lipid peroxidation products in their blood. Our aim was to study in the Rotterdam Study the relationship between dietary flavonoids, antioxidant vitamins, selenium and the risk of stroke and to investigate whether the effect of these antioxidants is different in smokers and non-smokers.

Higher intake of vitamin C, β-carotene and selenium was associated with a lower risk of stroke in the total study population. After stratification for smoking behaviour it became apparent that this protective effect was only present in smokers. Consumption of fruits and flavonoids also considerably decreased the risk of stroke in smokers, although the latter did not reach statistical significance. Intake of vegetables and vitamin E was not associated with the risk of stroke.

Our findings indicate that high intake of vitamin C, β-carotene and selenium can be a useful method in stroke prevention, especially effective in smokers.

Is the role of aspirin in primary prevention of stroke justifiable?

The role of aspirin in primary stroke prevention is not clear. Two large clinical trials and a meta-analysis have suggested that aspirin may increase the risk of stroke, in particular hemorrhagic stroke, in low risk subjects, but this finding was not statistically significant. Recently it was reported from the Cardiovascular Health Study that aspirin use increased the risk of stroke in elderly women free from cardiovascular diseases.

In the total cohort of the Rotterdam Study there was a weak, non-significant

association between aspirin use and the risk of any stroke. In subjects without vascular diseases aspirin use was associated with the risk of stroke (RR 1.80; 95% CI 1.03-3.13). In these subjects the risk of ischemic stroke increased as well, albeit less than the risk of all strokes, and not statistically significantly. Among subjects with vascular disease there was no association between aspirin use and the risk of stroke (RR 0.99; 95% CI 0.56-1.73).

The possibility of an increase in the incidence of hemorrhagic stroke in aspirin users is not unexpected. But in addition, aspirin may have a paradoxical thrombogenic effect, probably by inhibition of PGI2 production in endothelial cells and by inhibiting the expression of the inducible nitric oxide synthase. If aspirin has a thrombotic side effect, it is expected to be detected in subjects who have very little to gain from its beneficial effect, i.e. in subjects without vascular disease.

It seems necessary to further study the role of aspirin in primary prevention. These studies should address the effect of aspirin on all major vascular events – stroke, myocardial infarction, and death – to study the net effect of aspirin use in primary prevention. Even if the net effect were beneficial considering all benefits and harms of aspirin use, it might be possible to identify subgroups of subjects who gain and who lose with the use of aspirin in prevention of cardiovascular diseases.

How effective and safe is carotid endarterectomy in prevention of stroke?

It is estimated that 20-30 percent of stroke cases is related to carotid artery stenosis. Carotid endarterectomy aims to remove the plaque and restore the lumen of the vessel. Although the first published operation was carried out decades ago and more than 1 million people have been operated since 1980 in the United States only, there are still unanswered questions regarding the efficacy of carotid endarterectomy in the prevention of cerebral infarction and death. We performed a meta-analysis to assess the effect of carotid endarterectomy on all-cause mortality and stroke-free survival based on the combined data from randomized trials.

With respect to long-term efficacy, our analysis suggests that surgery does not increase life expectancy. The reason for this is the initial risk of complications. Even if the operation were completely safe, the reduction in mortality would be modest as the incidence rate ratio of death after the first month comparing surgery to medical treatment is 0.98 (95% CI 0.88-1.09). On the other hand, carotid endarterectomy can prolong stroke-free survival. This beneficial effect after three years of operation is present only when the estimated incidence rate of stroke or death in patient receiving only medical treatment is above about 8.3 per 100 patient-years. With increasing risk of stroke or death surgery becomes more effective.

Based on our analysis carotid endarterectomy should only be considered for patients at high risk of stroke. The break-even point above which surgery becomes effective could be a useful guideline in clinical practice if it were possible to estimate the incidence rate of stroke or death in an individual patient before taking the decision to operate.

One of the most powerful predictors of stroke is the degree of carotid stenosis. In patients on medical treatment with severe symptomatic anatomic stenosis the average incidence rate of stroke or death is higher than the break-even point. In these patients surgery is indicated based on the results of this analysis. In patients with a moderate symptomatic or severe asymptomatic stenosis the incidence rate is around the range where it is not clear which treatment is better. These patients may benefit from surgery if they are operated with a very low complication rate or are at higher risk for stroke than the average of this group. Several features have been reported that might help identifying high risk subjects in this category of stenosis, including contralateral disease, impaired cerebral vasomotor reactivity, asymptomatic embolisation, and echostructure appearance of the carotid plaque. In subjects with less than moderate symptomatic stenosis surgery should even be considered harmful. Based on our meta-analysis, in these patients a waiting policy is indicated. This policy should include clinical follow-up and non-invasive assessment of the lesion to determine whether the patient remains at low risk. When the estimated risk of stroke increases, surgery can be offered.

New methods

A Bayesian random effect meta-analysis

In a meta-analysis a measure of effect (such as the risk or rate ratio) is usually prespecified and the question whether heterogeneity exists for the chosen effect measure is addressed by the so-called heterogeneity test. This approach has at least two disadvantages. First, the power of the heterogeneity test is low. Second, the method does not specify what to do when the heterogeneity test is 'significant'. A statistical method that allows for heterogeneity of effects is preferable. Such a method should provide an estimate of the treatment effect conditional on certain trial characteristics, such as aggregate information of subjects included or risk in the reference category.

Regarding the long-term effect of carotid endarterectomy, it is entirely possible that surgery offers a greater advantage in patients who are at a higher absolute risk of stroke when treated medically. As a consequence, measures of effect may differ from trial to trial depending on the underlying risk of the patients actually randomised. We wanted to estimate the effect of carotid endarterectomy conditional on the risk of subjects treated medically. Conventional methods used for the analysis of this type of data may produce biased estimates due to imprecision of the observed incidence rates used as independent variable in fitting the model. The method we developed avoids this problem, because the estimated "true" incidence rates in the control groups is used as independent variable. In our final model, where we estimated the three-year cumulative incidence ratio of stroke or death, we assumed a trivariate normal distribution of the "true" log odds of stroke or death in the surgical group in the first month, of the "true" log incidence rate of stroke or death in

the medical and in the surgical group. The model was fitted using Gibbs sampling by the program BUGS.

Studying change in a risk factor as a determinant of disease

In an increasing number of studies risk factors are measured at several points in time. A question that is often addressed in these studies is whether change in a risk factor over time is associated with disease.

In most of these studies the baseline level of the risk factor is considered a confounder of the relationship between change in the risk factor and the risk of the disease, therefore it is adjusted for or stratified on in the analyses. We showed that this practice may produce severely biased results, because of the regression towards the mean phenomenon.

We argue that refraining from adjustment in many instances produces unbiased or only slightly biased results. With an estimate of the within subjects variability unbiased estimate of the effect of change can be obtained using hierarchical modelling. It is expected that methods based on hierarchical models that can deal straightforwardly with the problem will be available for routine use soon.

Validity

An etiologic investigation can be conceptualised as a measurement device that aims to estimate an association measure, usually a relative risk. Just like in any other measurement exercise it is important to avoid systematic bias and random errors. The former issue is discussed under validity, the latter one under precision.

Precision of the effect estimate in epidemiologic research is directly related to the size of the study. The precision of the effect estimates is quantified by their confidence intervals.

There are three major threats for validity in etiologic research: selection bias, information bias, and confounding.

Selection bias

Selection bias occurs when selection of subjects is not independent from the occurrence relation under study. This means that the association observed in the study is different from that would have been observed in the source population. One potential reason in our studies for this kind of bias was non-response, since not all eligible subjects participated. Although those who did not participate were likely to be different from study participants with respect to their health status, it is not very likely that the selection was differential in the different exposure categories. Furthermore, the response rate was relatively high (78%).

Another cause of selection bias could be originated from the competing risk of coronary heart disease. The pattern of atherosclerosis follows a sequence of pro-

gression. Plaques start to develop in the aorta, later in the coronary arteries, and finally in the cerebral arteries. Subjects with high cholesterol levels or high blood pressure may die of myocardial infarction before occurrence of stroke, which results in an underestimation of the strength of association between cholesterol or blood pressure and stroke.

Information bias

Information bias can result from the misclassification of the disease status, of the determinant, and of the confounding variables.

In our studies, like in almost all others, the level of the determinants was determined only once at baseline. Due to regression dilution bias this may dilute the association between typical level of the determinant and the risk of stroke.

In our studies based on the Rotterdam Study, misclassification of the determinants and confounders were probably not related to the future occurrence of stroke, and the errors were probably small since these factors were measured at baseline using standardised procedure. Hence the misclassification could only result in a small underestimation of the relative risks and could hamper a bit the adequate control of confounders.

Regarding the assessment of stroke we used state-of-the-art procedures of case ascertainment and standardised criteria for defining certainty of diagnosis and subtypes of strokes. Our data showed that in most cases using all strokes or only probable and definite strokes made a difference only in the precision of the association measures, therefore we usually used all cases. One of the major limitations of our studies is the relatively large proportion of cases with non-specified subtypes due to the lack of neuro-imaging. However, the proportion of hemorrhagic stroke was quite comparable to the findings of other studies indicating that the vast majority of non-specified stroke cases should have been ischemic. Therefore excluding only hemorrhagic strokes when the relationship between a determinant and ischemic stroke was studied is justifiable. Furthermore, exclusion of subjects with unspecified stroke could introduce more misclassification since we would have almost certainly excluded many ischemic stroke cases, as well. Since the reason why no neuro-imaging was performed were linked to some patient characteristics (e.g. age) this would have resulted in selection of cases depending on the risk profile of subjects.

Confounding

A confounder is an alternative to causal explanation between the determinant and the disease. In all of our studies where we intended to quantify the relationship between a certain determinant and the risk of stroke we adjusted for potential confounders.

In some of our studies confounding by indication could play a role. In the study of the relationship between aspirin use and the risk of stroke we used stratification

for vascular disease to overcome this problem. In the study of the relationship of blood pressure and the risk of stroke we stratified for antihypertensive treatment to prevent confounding by indication.

Future research

Etiology of stroke

Although our knowledge of risk factors for stroke has advanced substantially during the past several decades, this field will certainly develop. The list of less well-documented risk factors is quite long,[1] and there is no reason to assume that no new determinants of stroke will be identified. The field of hypercoaguability and inflammation is especially promising in the near future.[2-4]

Stroke is not one entity, but a group of disorders, caused by different mechanisms, and it is necessary to study the different subtypes separately. Advances in neuroimaging will help classifying stroke subtypes. Understanding the differences in the etiology of different subtypes can help us optimising future treatment.

Genetics of stroke is another field where progress in the future can be envisaged.[5] Twin studies and epidemiological studies indicated that there is a genetic component underlying the occurrence of stroke.[6,7] Although research into genetics of strokes presents considerable challenges, advanced genetic epidemiological methods could provide an opportunity to identify "stroke genes". Candidate gene analysis can be an option, but new methods of genetic linkage studies could probably mean a more efficient approach.[8] For classical genetic linkage studies it is necessary to use large, well-defined pedigrees with a specific stroke type. Unfortunately, since the vast majority of strokes occur in the elderly, it is not likely that many large pedigrees will be available for studies. Newer methods of linkage analysis, like affected relative pairs technique, seem more useful.[9] For that large numbers of affected families are needed. This underlines the necessity of international collaboration and collaboration between neurologists and genetic epidemiologists. Understanding the identified major genes could provide new opportunities to prevent and to treat stroke.

Research methods

Epidemiology involves both the theory and the practice of research on occurrence of health related phenomena. Here, I would like to pay attention to some methodological issues that are currently largely overlooked and can be foreseen as a field of improvement in the near future.

An important issue is the definition of the determinant in etiological research. In many studies only the intensity of the exposure at one point in time is used for classification, such as the baseline value of a determinant in a cohort study. However, the time aspect of the exposure is clearly important. With parsimony in mind a solu-

tion could be to use composite measure of exposure based on the time course and intensity of the exposure. It depends on the particular question under study whether this is appropriate or not. Using a composite measure of exposure in a situation when there is reciprocal causation between factors, e.g. when the confounder has an effect on the future value of the determinants, is especially problematic. This leads us to the more general problem of complex causal network of covariates. In cohort studies, where usually repeated observations are available of determinants, confounders and effect, an estimation of the direct effect of a determinant is usually not straightforward. Methods to handle such causal networks in epidemiological research are becoming available, and will hopefully be used more extensively in the near future.[10]

Another issue is related to measurement error. Our analyses are based on the assumption that the covariates used in the analysis are measured without error. However, it is widely recognised that covariates are often measured with error, which can seriously affect the assessment of the relation between risk factors and occurrence of disease.[11,12] The availability of statistical techniques to fit complex hierarchical models to deal with the problem calls for reconsidering some aspects of study design.[13] In particular, we should collect information on the error in our measurements. In most cases it would simply imply repeated measurements of the covariates in a small subset of study subjects. This latter issue belongs to the more general recognition that in some cases quantitative assessment of the effect of biases, and external adjustment for them could be possible.[14]

Finally, a controversial field in epidemiology is the concept of interaction. In prevailing practice interaction is most widely used as a synonym for rate/odds-ratio modification. This is simply because epidemiologic data analysis is mostly based on multiplicative models but has nothing to do with biologic interaction.[15] However, the applicability of models for biological interaction is still controversial.[16,17] It is important to consider effect modification in causal research, since the effect of a determinant can depend on the presence of another factor if they are complement causes or antagonists.[16] Our study of the effect of dietary antioxidants is an example of this. Restricting the analysis to certain subgroups can prevent confounding and reduce bias, as illustrated in our analyses on the association between aspirin use and the risk of stroke, and between blood pressure and the risk of stroke.

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Summary

Stroke is a common, devastating disorder. It is one of the leading causes of death and disability in developed countries.
It is estimated that the preventable fraction of stroke can be as high as 80%, thus prevention should have a crucial role in reducing the burden stroke puts on societies.

The objective of this thesis was to study some unresolved issues related to risk factors and prevention of stroke. Most investigations were performed within the Rotterdam Study, an ongoing population based cohort study of elderly subjects. The study has been approved by the Medical Ethics Committee of Erasmus University/ Academic Hospital of Rotterdam and all participants gave their informed consent.

In **chapter 2**, we evaluated the performance of the Framingham stroke risk profile. This profile estimates the risk of stroke and transient ischemic attack (TIA) conditionally on the presence of risk factors. We found that the profile estimated the number of strokes and TIAs reasonably well in the different categories of the estimated three-year risk. The profile seemed to be a valuable tool to distinguish between high and low risk subjects.

In **chapter 3**, we studied the relationship between blood pressure and stroke. We confirmed that hypertension and isolated hypertension are strong risk factors for stroke. We found a continuous increase in stroke incidence with increasing blood pressure in non-treated subjects. In treated subjects we found a J-shaped relation between blood pressure and the risk of stroke. Although this increased risk was present only under diastolic blood pressure of 65 mmHg, it may indicate that the therapeutic goal "the lower the better" is not the optimal strategy in the elderly.

In **chapter 4**, we revisited the cholesterol paradox. This paradox refers to the contradiction between the large beneficial effects of the latest generation cholesterol lowering drugs, statins, in the prevention of stroke and the inconsistent findings of observational studies about the relationship between serum cholesterol and the risk of stroke. Our results showed that high serum cholesterol level significantly increased the risk of ischemic stroke in subjects who were free from cardiovascular diseases and diabetes mellitus. We discussed possible explanations for the controversy between studies. In particular, as suggested by our data, inclusion of subjects with changed cholesterol level secondary to cardiovascular disease could conceal the effect of high cholesterol on stroke.

In **chapter 5**, we reported our findings about familial aggregation of stroke. History of stroke in any first degree relative increased the risk of stroke, in particular

for persons who had more than one relative with history of stroke or had a first degree relative who suffered from a stroke before the age of 65. Family history of early myocardial infarction also increased the risk of stroke, albeit not statistically significantly. Shared life-style factors and inheritance of conventional vascular risk factors could not explain the relation between family history of stroke and risk of stroke. Our findings support that genetic susceptibility plays a role in the etiology of stroke.

In **chapter 6**, we assessed the potential role of dietary antioxidants in prevention of stroke. Higher intake of vitamin C, β-carotene, or selenium was associated with a lower risk of stroke in the total study population. After stratification for smoking behaviour it became apparent that this protective effect was only present in smokers. Consumption of fruits and flavonoids also considerably decreased the risk of stroke in smokers.

Chapter 7 describes our results about the association between aspirin use and the risk of stroke. Current evidence shows that aspirin can prevent stroke in patients after a transient ischemic attack or minor stroke. On the other hand, the role of aspirin in primary stroke prevention is not clear. We found that aspirin use was associated with an increased risk of stroke in subjects free from vascular disease. The risk of ischemic stroke increased as well, albeit less than the risk of any stroke, and not statistically significantly. Our finding suggest that aspirin use may increase the risk of stroke in elderly subjects without vascular disease.

Chapter 8 is devoted to the efficacy and safety of carotid endarterectomy. We performed a meta-analysis of randomised controlled trials investigating this question. We developed a new method to handle the possibility that the effect of the surgical procedure was different in the different clinical trials. We found that carotid endarterectomy did not increase life expectancy but prolonged stroke-free survival, although only in high risk subjects. Our analysis supports that carotid endarterectomy is useful in prevention of stroke but its application should be limited to patients at high risk of stroke.

In **chapter 9**, we showed that the current practice of the analysis of the relationship between change in a determinant and the risk of disease may produce results. We illustrated the problem with an example from the Rotterdam Study and proposed solutions.

Although it is likely that new efficient stroke therapies will be developed in the coming years, the most substantial benefit in reducing the burden of stroke will probably come from stroke prevention. Cessation of cigarette smoking, reduction in heavy alcohol consumption, promotion of a "healthy" diet and physical activity are promising tools for mass prevention. Control of hypertension and diabetes, application of antiplatelet therapy, anticoagulation, and carotid endarterectomy in appropriately chosen subjects currently constitute the most valuable interventions for the high-risk approach of prevention of stroke.

Application of available means of prevention and the research focussing on finding new potentially modifiable risk factors for stroke should improve our prospects for substantial reduction of the burden of stroke.

Samenvatting

Beroerte is een veel voorkomende, invaliderende aandoening. Het is een van de meest belangrijke oorzaken van sterfte en blijvende invaliditeit in de Westerse landen. Naar schatting is het aandeel van beroerten dat voorkómen kan worden maar liefst 80%. Preventie zou een cruciale rol moeten spelen in de reductie van de maatschappelijke gevolgen van beroerte.

Dit proefschrift beschrijft onderzoek naar risicofactoren en preventie van beroerte. De meeste onderzoeken werden uitgevoerd in het ERGO-onderzoek (Erasmus Rotterdam Gezondheid en Ouderen), een op de algemene bevolking gebaseerd cohortonderzoek onder personen van 55 jaar en ouder. Het ERGO-onderzoek werd goedgekeurd door de Medisch Ethische Commissie van de Erasmus Universiteit en het Academisch Ziekenhuis Rotterdam en alle deelnemers gaven toestemming voor deelname.

In **hoofdstuk 2** evalueerden we de bruikbaarheid van het risicoprofiel van de Framingham Studie. Dit risicoprofiel schat het risico op beroerte van personen, conditioneel op de aanwezigheid van risicofactoren. We vonden dat het aantal beroerten en TIA's redelijk goed werd geschat in de verschillende categorieën van de geschatte 3-jaars risico's. Het profiel bleek een waardevol instrument om te onderscheiden tussen personen met laag en hoog risico.

In **hoofdstuk 3** bestudeerden we de relatie tussen bloeddruk en beroerte. Wij bevestigden dat hypertensie en geïsoleerde hypertensie sterke risicofactoren voor beroerte zijn. Er werd een continue verhoging van het aantal incidente beroerten met stijging van de bloeddruk gevonden in personen die niet behandeld werden voor hypertensie. In personen die wel behandeld werden vonden we een J-vormige relatie tussen bloeddruk en het risico op beroerte. Alhoewel deze verhoging van het risico alleen aanwezig was bij een diastolische bloeddruk onder 65 mm Hg, suggereert deze uitkomst dat het therapeutische doel "hoe lager hoe beter" niet de optimale strategie is bij ouderen.

In **hoofdstuk 4** onderzochten we de cholesterol-paradox nader. Deze paradox verwijst naar de tegenstelling tussen enerzijds een sterk positief effect van de laatste generatie cholesterolverlagende medicijnen, statines, in de preventie van beroerte en anderzijds inconsistente maar overwegend negatieve bevindingen van observationele studies naar de relatie tussen serum-cholesterol en het risico op beroerte. Onze resultaten lieten zien dat een hoog serum-cholesterol gehalte het risico op een herseninfarct significant verhoogt in personen zonder cardiovasculaire ziekten en diabetes mellitus, maar dit effect was afwezig in personen met preëxistente hart- en

vaatziekten. Een mogelijke verklaring voor genoemde controverse tussen verschillende studies is dan ook dat inclusie van personen met hart- en vaatziekten het effect van hoog cholesterol op het risico op beroerte maskeert.

In **hoofdstuk 5** rapporteerden we onze resultaten over familie-aggregatie van beroerte. Een voorgeschiedenis van beroerte in enig eerstegraads familielid verhoogde het risico op beroerte; in het bijzonder voor personen met meer dan één familielid met beroerte of een eerstegraads familielid met een beroerte voor het 65e levensjaar. Een positieve familie-anamnese voor myocardinfarct voor het 65e levensjaar verhoogde ook het risico op beroerte, maar niet statistisch significant. De relatie tussen familie-anamnese van beroerte en het risico op beroerte kon niet worden verklaard door gemeenschappelijke leefstijlfactoren of erfelijkheid van conventionele risicofactoren. Onze bevindingen ondersteunen de gedachte dat genetische gevoeligheid een rol speelt in de etiologie van beroerte.

In **hoofdstuk 6** evalueerden we de rol van met de voeding ingenomen antioxidanten in de preventie van beroerte. Hogere inname van vitamine C, β-caroteen of selenium was geassocieerd met een lager risico op beroerte in de totale studie-populatie. Na stratificatie voor roken werd het duidelijk dat dit beschermende effect alleen aanwezig was bij rokers. Daarnaast zorgden consumptie van fruit en flavonoïden voor een aanzienlijke daling van het risico op beroerte in rokers.

Hoofdstuk 7 beschrijft onze resultaten over de associatie tussen aspirinegebruik en het risico op een beroerte. Aangenomen wordt dat aspirine beroerte kan voorkómen na een TIA of 'minor stroke'. De rol van aspirine in de primaire preventie van beroerte is echter niet duidelijk. We vonden dat aspirine geassocieerd was met het risico op beroerte in personen zonder vasculaire ziekten. Het risico op herseninfarcten was ook verhoogd, maar minder dan het risico op alle beroerten, en niet statistisch significant. Onze resultaten suggereren dat er geen rol is voor aspirine in de primaire preventie van beroerte in personen zonder vasculaire ziekten.

Hoofdstuk 8 is gewijd aan de effectiviteit en veiligheid van carotis endarteriëctomie. We voerden een meta-analyse uit van gerandomiseerde klinische trials die deze vraag onderzochten. We ontwikkelden een nieuwe methode om rekening te houden met de mogelijkheid dat het effect van de chirurgische procedure verschillend was in de verschillende trials. We vonden dat carotis endarteriëctomie nuttig is in de preventie van beroerte, maar dat de toepassing zou moeten worden beperkt tot patiënten met een hoog risico op beroerte.

In **hoofdstuk 9** toonden we aan dat de huidige praktijk van analyse van de relatie tussen verandering in een determinant en het risico van ziekte ernstig vertekende resultaten kan opleveren. We illustreerden het probleem met een voorbeeld uit het ERGO-onderzoek en stelden oplossingen voor.

Alhoewel het aannemelijk is dat er in de komende jaren nieuwe therapieën voor beroerte zullen worden ontwikkeld, is de meest substantiële winst in de reductie van

de maatschappelijke gevolgen van beroerte te behalen door preventie. Stoppen met roken, reductie van zwaar alcoholgebruik, bevordering van een gezond dieet en lichamelijke activiteit zijn de veelbelovende instrumenten voor massa-preventie. Controle van hypertensie en diabetes, toepassing van plaatjesaggregatie-remmers, antistolling en carotis endarteriëctomie in de juiste personen vormen de meest waardevolle interventies voor de hoog risico-benadering van de preventie van beroerte.

Toepassing van beschikbare methoden van preventie en onderzoek naar nieuwe preventiemogelijkheden zullen onze uitzichten op een substantiële reductie van de maatschappelijke gevolgen van beroerte verbeteren.

Összefoglalás

A stroke (szélütés, agyi érkatasztrófa) gyakori, igen súlyos betegség. A fejlett társadalmakban az egyik vezeto halálok, és a rokkantságnak is az egyik leggyakoribb oka.

Becslések szerint a stroke-ok akár 80%-a is megelőzhető lenne, így a megelőzésnek rendkívül nagy szerepe van abban, hogy az agyérbetegségek miatt a társadalomra nehezedő terhek csökkenthetők legyenek.

Ennek a tézisnek a célja az volt, hogy a stroke kockázati tényezőivel és megelőzésével kapcsolatos megoldatlan kérdéseket kutassa. A legtöbb vizsgálatra a Rotterdam Vizsgálat -folyamatban lévő, idősek körében zajló populációs kohorsz vizsgálat - keretében került sor. A vizsgálatot az Erasmus Egyetem és a Rotterdami Egyetemi Kórház Etikai Bizottsága engedélyezte.

A **2. fejezetben** értékeltük a framinghami stroke kockázati függvényt. A függvény a kockázati tényezők megléte alapján becsli a stroke kockázatát. A függvény elfogadhatóan becsülte a stroke-ok és az átmeneti agyi ischaemiás történések (TIA) számát a becsült hároméves kockázat különböző kategóriáiban. A függvény hasznos eszköznek bizonyult a különböző kockázattal bíró személyek megkülönböztetésében.

A **3. fejezetben** a vérnyomás és a stroke közötti kapcsolatot vizsgáltuk. Vizsgálatunk megerősítette, hogy a magas vérnyomás és az izolált szisztolés magas vérnyomás a stroke jelentős kockázati tényezője. Azt találtuk, hogy vérnyomás csökkentő kezelésben nem részesülő személyekben a stroke kockázata folyamatosan emelkedik a vérnyomás emelkedésével. Kezelt személyekben J-alakú kapcsolatot találtunk a vérnyomás és a stroke kockázata között. Bár emelkedett kockázat csak 65 Hgmm-es diasztolés vérnyomás alatt volt megfigyelhető, ez jelezheti, hogy a „minél alacsonyabb, annál jobb" stratégia nem feltétlenül optimális idősekben.

A **4. fejezetben** újra megvizsgáltuk a koleszterin paradoxont. A paradoxon a legújabb koleszterincsökkentő gyógyszereknek, a statinoknak, a stroke megelőzésben kimutatott igen kedvező hatása és a megfigyeléses vizsgálatok inkonzisztens eredményei közötti ellentmondásra utal. Az eredményeink azt mutatták, hogy a keringési betegségektől és a cukorbetegségtől mentes személyekben a magas koleszterin szint szignifikánsan növelte az agyi ischaemiás infarktus kockázatát. Ismertettük a korábbi vizsgálatok eredményeivel kapcsolatos legfontosabb megfontolásokat. A mi vizsgálatunk azt mutatta, hogy a keringési betegségek megléte elfedheti a magas koleszterin szintnek a stroke kialakulásában betöltött szerepét.

Az **5. fejezetben** közöltük a stroke családi halmozódásával kapcsolatos

eredményeinket. Emelkedett a stroke kockázata azon személyeknél, akik elsőfokú rokonai körében előfordult stroke. Különösen emelkedett a stroke kockázata, ha valakinek több ilyen rokona volt, vagy a rokon 65 éves kora előtt szenvedett stroke-ot. Korai szívinfarktus a családi anamnézisben szintén megnövelte a stroke kockázatát, bár statisztikailag nem szignifikánsan. A közös életmódbeli tényezők és a stroke hagyományos kockázati tényezőinek öröklése nem magyarázták a kapcsolatot a pozitív családi anamnézis és a stroke között. Az eredményeink arra utalnak, hogy a genetikai fogékonyság szerepet játszik a stroke etiológiájában.

A **6. fejezetben** az étrendi antioxidánsok és a stroke kapcsolatát vizsgáltuk. Nagy mennyiségű C-vitamin, β-carotin vagy szelénium bevitele csökkentette a stroke kockázatát. A rétegzett elemzés azt mutatta, hogy a kedvező hatás csak dohányosokban van jelen. A gyümölcs és flavonoid fogyasztás szintén jelentősen csökkentette a stroke kockázatát a dohányosokban.

A **7. fejezet** az aszpirin fogyasztás és a stroke összefüggésével kapcsolatos eredményeinket írja le. A rendelkezésre álló bizonyítékok azt mutatják, hogy átmeneti agyi ischaemiás történést, vagy enyhe stroke-ot szenvedett betegek körében az aszpirin kedvező hatású a stroke megelőzésében. Ugyanakkor nem világos az aszpirin szerepe a stroke primer prevenciójában. Azt találtuk, hogy érbetegségtől mentes személyek körében az aszpirin fogyasztás emelkedett stroke kockázattal jár. Az ischaemiás agyi infarktus kockázata szintén emelkedett, bár kisebb és statisztikailag nem szignifikáns mértékben. Eredményeink arra utalnak, hogy az aszpirin emelheti a stroke kockázatát érbetegségtől mentes idősek körében.

A **8. fejezetet** a carotis endarterectomia hatékonyságának és biztonságának szenteltük. A kérdést vizsgáló randomizált klinikai vizsgálatok meta-analízisét végeztük el. Egy új módszert fejlesztettünk ki, amely képes figyelembe venni, hogy a beavatkozás hatékonysága a különböző vizsgálatokban különbözo volt. Azt találtuk, hogy a carotis endarterectomia nem növeli a várható élettartamot, de magas kockázatú egyénekben megnöveli a stroke nélkül várható élettartamot. Az eredményeink azt mutatatják, hogy a carotis endarterectomia hasznos eszköz a stroke megelőzésében, de az alkalmazását a magas kockázatú egyének körére kell korlátozni.

A **9. fejezetben** megmutattuk, hogy a jelenleg elterjedt módszer, amellyel egy kockázati tényező változása és egy betegség kockázata közti összefüggést vizsgálni szokták nagymértékben torzított eredményhez vezethet. A problémát illusztráltuk, egy, a Rotterdam vizsgálatból vett példával, és javasoltunk megoldásokat.

Ugyan valószínű, hogy a stroke-nak új, hatékony terápiáit fogják kifejleszteni az elkövetkező években, a legnagyobb csökkenés a stroke jelentette terhekben mégis vélhetően a megelőzésből fog származni. A dohányzás elhagyása, a nagymértékű alkoholfogyasztás csökkentése, az „egészséges" étkezési szokások és a testmozgás terjedése ígéretes eszközök az egész populációt megcélzó megelőzésben. A magas vérnyomás és a cukorbetegség kezelése, az antiaggregációs és antikoaguláns kezelés

és a carotis endarterectomia a legértékesebb eszközök a megfelelően kiválasztott magas kockázatú személyek körében a stroke megelőzésére.

A megelőzés rendelkezésre álló eszközeinek alkalmazása és az újak utáni kutatás remélhetőleg jelentos mértékben csökkenteni fogják a stroke jelentette társadalmi terheket.

Epilogue

I am much indebted to many persons who have contributed to this thesis.

I would like to thank to Prof. Dr. Ida Gerendai, Prof. Zoltán Nagy and Prof. Dr. Jacobus Lubsen for introducing me to research. I am especially grateful to Prof. Lubsen for his hospitality, and his continuous support.

Special gratitude is due to Prof. Dr. Albert Hofman, Dr. Monique M.B. Breteler and Prof. Dr. Róza Ádány who gave me the opportunity to perform this research. Dr. Breteler provided excellent guidance and support through all these years. I wish to thank to Prof. Dr. Peter J. Koudstaal for his valuable comments and for keeping my research relevant for clinical practice.

Dr. Sandra Kalmijn helped me most to find my way in the department at the beginning of my research. Lidia Arends and Prof. Dr. Theo Stijnen deserve special gratitude for helping me whenever my knowledge was poor to solve an emerging statistical problem. I am grateful to Dr. Jacqueline C.M. Witteman for her inspiring thoughts and helpful advice.

The excellent secretarial help of Mrs. Marga van den Bergh is gratefully acknowledged.

I wish to thank to Dr. Henning Tiemeier and Dr. Monika Hollander for acting as the two "paranimfs" and organising everything about my promotion.

Finally, I would like to thank to my wife, children and parents for their patience, support and inspiration that encouraged and helped me overcoming the difficulties.

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About the author

Zoltán Vokó was born on 14 November 1968 in Budapest, where he grew up and lives now.

He graduated as a physician in 1994 at the Semmelweis University Medical School in Budapest. During his studies as a member of students research society at the 2nd Department of Anatomy of the university he performed research in neuroendocrinology and taught gross anatomy, histology and embryology. In 1993 as a research fellow of the French Government he spent nine months in Paris at the INSERM at the Unité de Dynamique Systèmes Neroedcriniens. His research was devoted to the physiology of melanin concentrating hormone.

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Since 1996 he has been a lecturer in epidemiology and biostatistics at the School of Public Health in Debrecen, Hungary. At the end of 1997 he started to work for the National Institute for Health Care Research and Information as an epidemiologist. Since December 1998 he has been working as the director of the National Public Health Monitoring Program at the Ministry of Health, Hungary.

He is married to Krisztina Nyomárkay and has two children, Lili and Boldizsár.