Wall thickness of the carotid artery as an indicator of generalized atherosclerosis

The Rotterdam Study

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Wall thickness of the carotid artery as an indicator of generalized atherosclerosis
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De wanddikte van de halsslagaders als
indicator voor gegeneraliseerde atherosclerose
Het Erasmus Rotterdam, Gezondheid en Ouderen (ERGO) onderzoek

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Contents

Publications and manuscripts based on studies described in this thesis

Chapter 1 — Bots ML, Grobbee DE. Cardiovascular diseases in The Netherlands over the past 25 years: Prevalence, incidence and trends in morbidity and mortality. Neth J Cardiol 1991;16:4:151-5.

Chapter 3.1 — Bots ML, Meurs JCHM van, Grobbee DE. Assessment of early atherosclerosis: A new perspective. J Drug Res 1991;16:150-4.

Chapter 3.2 — Bots ML, Mulder PGH, Hofman A, Es GA van, Grobbee DE. Reproducibility of carotid vessel wall thickness measurements. The Rotterdam Study. J Clin Epidemiol *(in press)*.

Chapter 4.1 — Bots ML, Witteman JCM, Grobbee DE. Carotid intima-media thickness in elderly women with and without atherosclerosis of the abdominal aorta. Atherosclerosis *(in press)*.

Chapter 4.2 — Bots ML, Hofman A, Grobbee DE. Carotid intima-media thickness and lower extremity arterial atherosclerosis. The Rotterdam Study *(submitted)*.

Chapter 4.3 — Bots ML, Hofman A, Jong PTVM de, Grobbee DE. Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study *(submitted)*.

Chapter 4.4 — Bots ML, Hofman A, Grobbee DE. Common carotid intima-media thickness and cardiovascular disease in the Rotterdam Study. A cross-sectional analysis. In: Hombach V, Koenig W, eds. Current aspects in atherosclerosis. Oxford: Blackwell Scientific Publishers *(in press)*.

Chapter 5.1 — Bots ML, Hofman A, Grobbee DE. Cardiovascular determinants of common carotid intima-media thickness. The Rotterdam Study *(submitted)*.

Chapter 5.2 — Bots ML, Hofman A, Bruyn AM de, Jong PTVM de, Grobbee DE. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Study. Arterioscler Thromb 1993;13:64-9.

Chapter 5.3 — Bots ML, Hofman A, Grobbee DE. A low diastolic blood pressure in the elderly and atherosclerosis. The Rotterdam Study *(submitted)*.

Chapter 6 — Bots ML, Breslau PJ, Briët E, Bruyn AM de, Vliet HDDM van, VandenOuweland FAM, Jong PTVM de, Hofman A, Grobbee DE. Cardiovascular determinants of carotid artery disease. The Rotterdam Study. Hypertension 1992;19:717-20.

Chapter 7 — Bots ML, Swieten JC van, Breteler MMB, Jong PTVM de, Gijn J van, Hofman A, Grobbee DE. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet 1993;341:1232-7.

Chapter 1

Cardiovascular disease in the elderly

1 Changes in morbidity and mortality from cardiovascular disease in the elderly: The example of The Netherlands

Introduction

In most industrialized countries cardiovascular disease, notably coronary heart disease and stroke, is an important cause of morbidity and mortality.[1] In particular among the elderly, cardiovascular disease constitutes the prime cause of death, and even more importantly, is a major determinant of chronic disability and suffering. Demographic studies have indicated that the proportion of elderly subjects will continue to rise well into the twentieth century. Yet, studies on changes in morbidity and mortality over time for this age group are limited.

The present study presents findings on secular trends of incidence of acute myocardial infarction in The Netherlands from 1970 to 1985, with special emphasis on the elderly. Furthermore, changes in cardiovascular hospital admission rates and in cardiovascular mortality will be discussed.

Methods

Sources and definitions

The presented data relate to the Dutch situation only and have been obtained from various sources. Firstly, from studies performed in General Practitioners practises and from population surveys.[2,3,4,5,6,7,8,9] Not surprisingly, these studies differed with respect to design and diagnostic procedures. For example, in studies carried out in general practise, the presence of a disease was assessed by noting the patients complaints, the results of a physical examination and (sometimes) the outcome of clinical tests. In population surveys, a standardized diagnostic instrument, such as a questionnaire, was used. The presence of the disease of interest was assessed on the basis of a pre-set combination of answers. A well-known example is the "Rose-questionnaire", which is used to assess the prevalence of coronary heart disease in unselected populations.[10] Because of these divergences in methodology, inference based on the comparison of the results from both types of studies should be made with care.

Data on changes over time in the incidence of acute myocardial infarction in The Netherlands come from the NIVEL project. In this study, which was performed in a random sample of General Practitioners practises containing a representative sample of the Dutch population in 1978 and again in 1985, the incidence of suspected acute myocardial infarction was investigated.[6] The participating general practitioners should act

in case of a suspected acute myocardial infarction as if it was a definite acute myocardial infarction.

A second source of some of the presented data is the Dutch Information System for Hospital Care and Day-nursing, which is part of the Dutch Center for Health Care Information (SIG).[11] The hospital admission rate reported by the information system, reflects the number of patients that is admitted to Dutch hospitals as the result of a cardiovascular event. The present data were obtained from 1978 to 1990. In this period approximately 95 % or over of all Dutch hospitals participated in the registry. Some aspects of Hospital Care and Day-nursing registry need to be considered. Subjects who are admitted several times to a hospital within one year due to the same complaints or disease appear in the registry more than once (double counts). Similarly, subjects that are transferred from one hospital to another for the same cardiovascular event, will appear twice in the registry. Furthermore, criteria that are used to diagnose coronary heart disease and stroke may differ over time. Finally, in the registry no distinction is made between the first event, the second or subsequent events.

Mortality data used in the present study were based on death certificates collected by the Central Bureau of Statistics.[12] In The Netherlands death certificates are coded centrally. In both national registries coronary heart disease was defined according to the 9th International Classification of Diseases (ICD); ICD 410-414. The most important acute form of coronary heart disease is the acute myocardial infarction (ICD 410). Registration of myocardial infarction using a specific ICD code is done since 1969. Other forms of acute or subacute coronary heart disease were coded ICD 411. Diseases coded ICD 412-414 may in general be regarded as chronic coronary heart disease. ICD code 430 to 438 refer to cerebrovascular disease.

Results are presented as age-adjusted rates, providing time trends from which the effect of demographic changes in the population has been removed. This provides a more direct view on the natural history of the disease and the potential effects of preventive measures and changes in risk profile.

Results

Coronary heart disease

The results from several studies performed in the mid seventies and eighties in The Netherlands on the incidence of acute myocardial infarction are presented in table 1.1. The incidence of acute myocardial infarction increased with age and was higher in men than in women. The results from the NIVEL project showed a fall in incidence of suspected acute myocardial infarction over time for men aged 55 to 64 years and no

change in incidence rates for men aged 65 years or over (table 1.1). With respect to elderly women, a considerable decrease in incidence of suspected acute myocardial infarction was observed from 1978 to 1985.

In 1990, approximately 11 % (70,214 patients) of all hospital admissions of subjects aged 55 years or over was related to coronary heart disease. Twenty three thousand (4 %) were due to an acute myocardial infarction. Corresponding figures for 1978 were 8 % and 5 %, respectively. The age-adjusted hospital admission rates of acute myocardial infarction and coronary heart disease for both men and women aged 55 years or over are presented in figure 1.1. Compared to women, higher rates were observed among men. With respect to acute myocardial infarction, the age-adjusted morbidity rates in men and women showed a slight increase from 1978 to 1985. After 1985 a decline was observed, in particular among men (figure 1.1 left). Morbidity rates for coronary heart disease, however, have increased considerably (figure 1.1 right), mainly reflecting an increase in hospital morbidity rate of chronic coronary heart disease (ICD 412-414). Among men, coronary heart disease hospital morbidity rates have increased from 1,784/100,000 person-years in 1978 to 2,824/100,000 person-years in 1990. For women, morbidity rates rose from 747/100,000 person-years to 1,219/100,000 person-years, respectively.

Table 1.1 Age specific incidence rates of acute myocardial infarction in The Netherlands. For men and women, per 1,000 person-years.

	The Hague[2] 1970-72	Zeist[3] 1971-74	Nijmegen[4] 1971-74	Rotterdam[5] 1972-74	NIVEL[6] 1978*	1985*
Men						
55-64 yr	10.1	10	10.5	8.1	14.6	11.8
65-69 yr	13.4	14	16.8†	10.6	20.2	20.2‡
Women						
55-64 yr	2.4	2	3.2	3.0	4.6	3.0
65-69 yr	5.6	5	8.4†	6.8	12.4	9.6‡

* Suspected acute myocardial infarction.
† Age-group 65-74 years.
‡ Age-group 65 years or over.

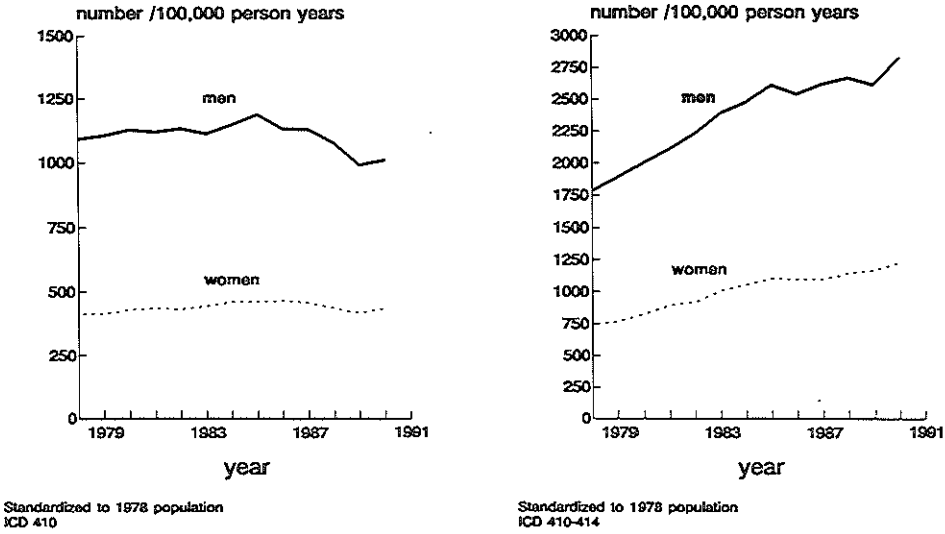


Figure 1.1 *Age-adjusted hospital admission rates over the period 1978-1990 in The Netherlands of acute myocardial infarction (left) and coronary heart disease (right). For men and women.*[11]

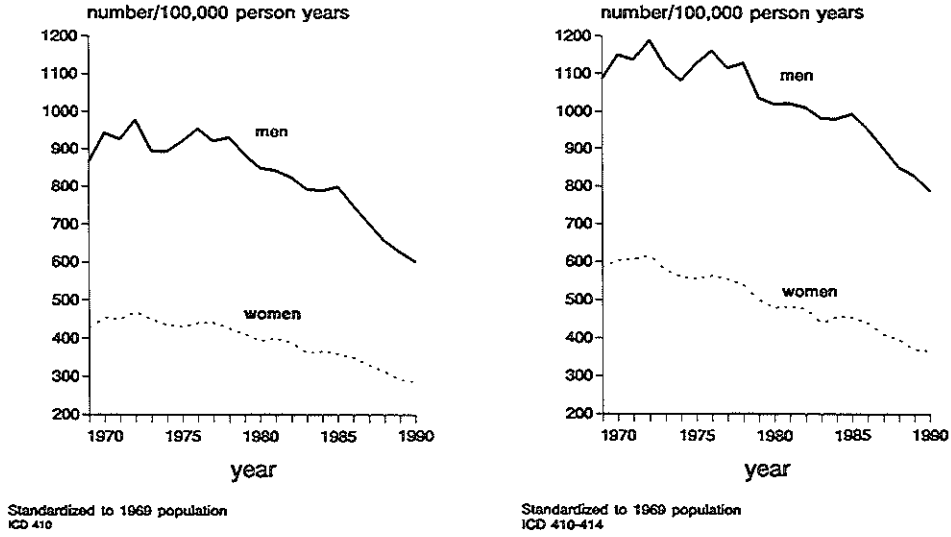


Figure 1.2 *Age-adjusted mortality rates over the period 1969-1990 in The Netherlands from acute myocardial infarction (left) and coronary heart disease (right). For men and women.*[12]

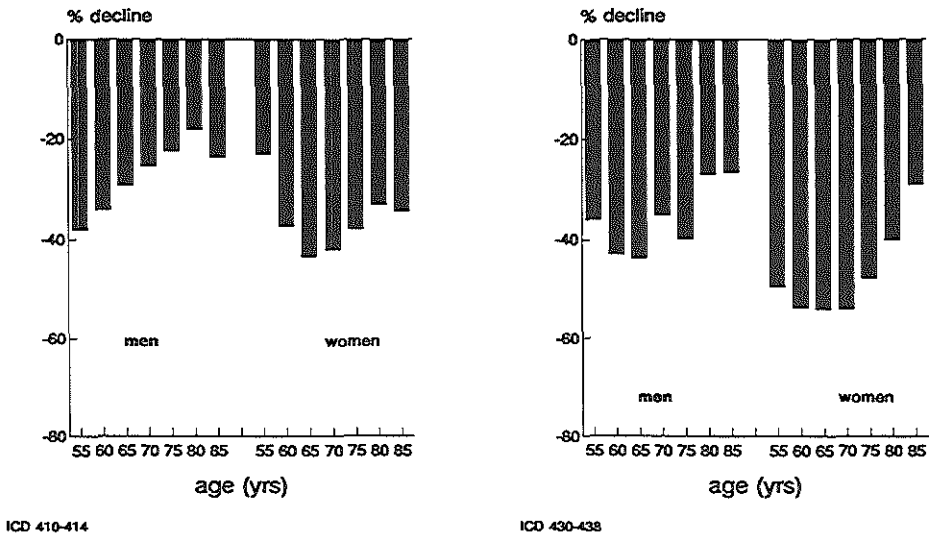


Figure 1.3 *Age-specific percentage decline in mortality from coronary heart disease (left) and cerebrovascular disease (right) for men and women. Percentage decline in mortality in 1988-1990 relative to 1969-1971.*

In The Netherlands about 21,000 subjects aged 55 years or over die annually from coronary heart disease, in particular from acute myocardial infarction. Coronary heart disease mortality represents 20 % of all annual deaths in this age group. The highest level of coronary heart disease mortality was reached in 1972 (figure 1.2). The age-adjusted coronary heart disease mortality rates in this age group have declined since 1972 in both men and women: Among men from 1,189/100,000 person-years in 1972 to 789/100,000 person-years in 1990 and in women from 614/100,000 person-years to 364/100,000 person-years (figure 1.2).

Changes in age specific coronary heart disease mortality rates for men and women are presented in figure 1.3 (left). For men, the strongest decrease in mortality was observed in younger subjects. For women, a comparable trend was found beyond the age of 65 years.

Cerebrovascular disease

The incidence of stroke as observed in several studies performed in The Netherlands is presented in table 1.2. Stroke is a disease particularly attacking subjects aged 55 years or over. A steep increase with age is found. The age-specific incidence rates reveal no differences between men and women.

Approximately 4 % of all hospital admissions in The Netherlands in 1990 were a consequence of cerebrovascular disease. This concerned 22,547 subjects. Figures for 1978 were 4 % and 16,496, respectively. Age-adjusted hospital admission rates for cerebrovascular disease are presented in figure 1.4 (left). Apparently, stroke admission rates for men are higher than those for women. The morbidity rates in men increased until 1986, followed by a decline. Similar trends were found for women. Overall in the period 1978-1990, the age-adjusted hospital morbidity rates of cerebrovascular disease rose slightly from 694/100,000 person-years to 754/100,000 person-years in men and from 521/100,000 person-years to 557/100,000 person-years in women.

Cerebrovascular mortality is shown in figure 1.4 (right). A steady decline in mortality from cerebrovascular disease has been noted in both men and women. With respect to men, rates fell from 457/100,000 person-years in 1969 to 302/100,000 person-years in 1990. In the same period a steeper decline in mortality was observed among women: from 470/100,000 person-years to 260/100,000 person-years. Despite the decline, cerebrovascular mortality with around 12,000 deaths each year, still accounts for 10 % of all annual deaths in The Netherlands in those aged 55 years or over.

Changes in age specific cerebrovascular disease mortality rates for men and women are presented in figure 1.3 (right). No major differences across age groups in percentage decrease in stroke mortality was found for men, although in the older subjects

Table 1.2 Age-specific stroke incidence rates in The Netherlands.* For men and women, per 1,000 person-years.

	Tilburg[8] 1978-82	Nijmegen[7] 1971-83	NIVEL[9] 1986-87
Men			
< 55 yr	0.2	--	0.2
55-64 yr	3.1	2.2†	3.8
65-74 yr	9.9	7.3	6.8
≥ 75 yr	18.7	14.6	18.0
Women			
< 55 yr	0.2	--	0.2
55-64 yr	1.6	1.5†	1.0
65-74 yr	7.4	4.9	4.8
≥ 75 yr	20.6	18.9	17.3

* Total number of strokes, including subjects with more than one stroke during the period of observation.
† Age-group 50-64 years.

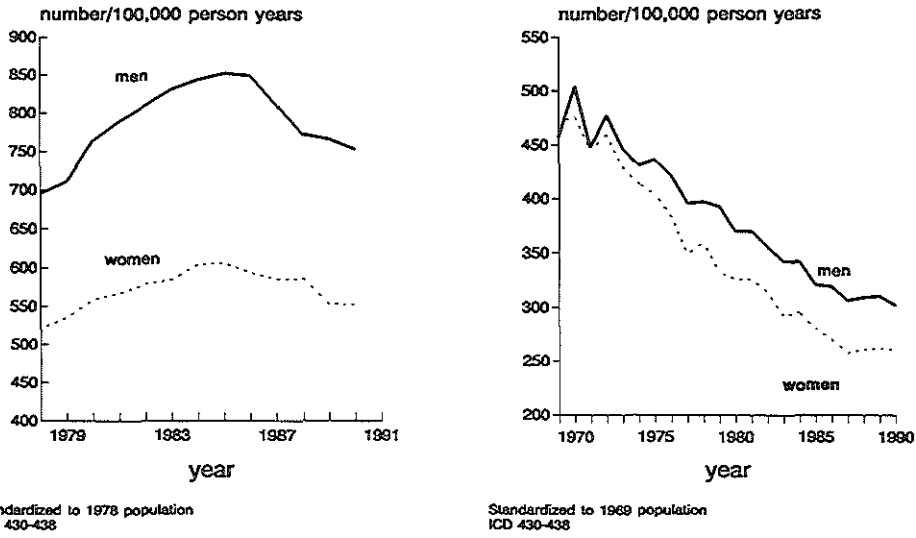


Figure 1.4 Age-adjusted hospital admission rates over the period 1978-1990 in The Netherlands of cerebrovascular disease for men and women (left).[11] *Age-adjusted cerebrovascular mortality rates over the period 1969-1990 in The Netherlands for men and women (right).*[12]

a somewhat lower decline in mortality was observed. A similar trend was seen in women.

Discussion

Since 1969 the pattern of coronary heart disease and cerebrovascular disease morbidity and mortality in the elderly has changed considerably in The Netherlands. A substantial fall in age-adjusted acute coronary heart disease mortality has been observed during this period. In addition, a decline in incidence of acute myocardial infarction in this age-group appears to have taken place. However, the available Dutch data on this issue are limited. A sharp rise in morbidity rates of chronic coronary heart disease was observed. With the data for The Netherlands it is not possible to assess whether a change in stroke incidence over time has occurred. Cerebrovascular mortality has shown a steady and consistent decline over the past 25 years, and hospital admission rates of stroke show a decline since 1986.

Some aspects of the NIVEL study, in which a fall in incidence of suspected acute myocardial infarction over time was observed, should be addressed. In the NIVEL project, in case of a suspected acute myocardial infarction a participating general

practitioner should act as if it was a definite acute myocardial infarction. Thus, provided that from 1978 to 1985 the assessment of an acute myocardial infarction by a general practitioner and the referral pattern of elderly patients to hospitals have not changed, the NIVEL findings suggest a fall in the incidence of acute myocardial infarction from 1978 to 1985.

In The Netherlands, the hospital morbidity rates are susceptible to double counts. Changes over time in mechanisms that lead to double counts may be of importance to explain the trends in hospital morbidity rates. The increased possibilities of diagnostic procedures and treatment of coronary heart disease may have caused a rise in frequency of hospital admissions of subjects with coronary heart disease symptoms. In addition, transferral of subjects with severe coronary pathology to specialized hospitals may occur more often, possibly due to improvement of treatment of severe coronary heart disease. Furthermore, improved medical care may have reduced case fatality and consequently subjects with a previous myocardial infarction who in earlier days would have died still come to medical care on a regular basis or present with a second or third event. These changes may have lead to an increase of double counts over time. Similar mechanisms may be involved in cerebrovascular disease morbidity rates. Consequently, the increasing trends in hospital morbidity rates may, to some extent, be overestimated, whereas rates which show no change over the years, may actualy reflect decreasing hospital morbidity rates. The extent of the contribution of double counts on the trends in hospital morbidity rates in The Netherlands, however, can not be ascertained.

Another note of caution should be put forward. Hospital admission rates are not particularly suitable to monitor change of incidence over time due to problems inherent to this registry, such as no distinction between first, second or subsequent event, and the use of different criteria over time to diagnose disease. Furthermore, those events that do not come to attention to hospital care are not included in the registry.

The role of vital statistics in describing trends in mortality has been disputed because of the limited validity and accuracy of death certificates.[13,14] Some of the factors that may contribute to differences in coding of death certificates are differences in awareness of the disease and its manifestations across physicians, variation in care with which the certificates are being completed, changes in coding classifications and changes in diagnostic possibilities. The issue is, however, whether the contribution of these factors to differences in coding of death certificates has changed over time. For The Netherlands, neither data on the changes in awareness of coronary heart disease and cerebrovascular disease nor data on changes in care of completing death certificates are available. The presented mortality trends in this study were all coded according to the 9th International Classification of Diseases. Improvement over time of diagnostic

procedures in the assessment of coronary heart disease, and probably also in cerebrovascular disease, may have had an effect on the trends in mortality.[14] A greater accuracy in diagnosing coronary heart disease and stroke may lead to a reduction of the number of false positive diagnosed subjects with coronary heart disease or stroke. On the other hand, the clinician may be reluctant to diagnose definite coronary heart disease or cerebrovascular disease in the absence of results from tests which assess 'definite' coronary heart disease or cerebrovascular disease. This may lead to an increase of the proportion of subjects with coronary heart disease and stroke, that are not being coded correctly. The effect of both mechanisms may, in some extent, have contributed to an overestimation of the observed fall in coronary heart and stroke mortality rates.[14] However, results from a study by Hoogendoorn indicated that the fall in acute myocardial infarction (ICD 410) in The Netherlands since 1972 could not be attributed to an increase in mortality rates of other forms of acute or subacute coronary heart disease (ICD 411).[15] Furthermore, the trends in coronary heart disease and cerebrovascular disease coincide with similar trends in total mortality, indicating that decreasing cardiovascular mortality is not due to temporal changes in coding from one ICD category to another.[16] Some degree of misclassification in causes of death will, however, remain, the extent of which can not be ascertained. It is unlikely that the consistent decline in cardiovascular mortality, which has been observed over the years can be attributed to diagnostic errors in certified causes of death only.

The changes in mortality from cardiovascular disease in the elderly in The Netherlands, are similar to most of the trends described for other countries,[1,17,18] although these reports have mainly presented data for the entire population rather than for the elderly specific. Several international studies have attempted to explain the decline in cardiovascular mortality, without, however, being able to completely resolve the questions.[19,20,21,22,23] In particular, the lack of reliable explanatory data was underlying the inability of explaining the decline in mortality of coronary heart disease and stroke. The decline in mortality from coronary heart disease and cerebrovascular disease may be the result of primary preventive efforts; a decrease in the occurrence of disease. A favorable change in the cardiovascular risk profile of the elderly population may be underlying this finding. For the Netherlands, however, data to support this view are limited; a strong reduction in smokers and an increase in subjects treated for high blood pressure from 1978 to 1985 has been observed.[24,27] A diminishing case fatality may have contributed to the decline in mortality from coronary heart disease and stroke. This may be the result of developments in secondary and tertiary preventive strategies. In addition, favorable changes in cardiovascular risk factors in the elderly population may have lead to occurrence of milder, less severe cardiovascular events. Finally, the

improvement over time of diagnostic procedures in the assessment of coronary heart disease and cerebrovascular disease, may have lead to an increase of the proportion of subjects with milder and less severe cardiovascular disease, leading to a decreased case fatality rate. Whether these changes have indeed contributed to the decline in mortality in The Netherlands and if so to what extent, remains to be established. Probably also an autonomous trend over time exists for which the reasons remain unknown.

In absolute figures, coronary heart disease and stroke still remain one of the major health problems in the ageing Dutch population. Due to demographic changes, an increasing number of people in The Netherlands will experience the burden of cardiovascular disease in the near future. The cardiovascular epidemic has not yet been eradicated, but the trends over the past 25 years suggest that much of its magnitude may be prevented. It is generally accepted that cardiovascular disease is caused by an interplay between atherosclerotic vessel wall abnormalities, stenosis and thombogenic factors. Essential to a successful preventive approach is access to knowledge of mechanisms leading to development of cardiovascular disease in the elderly. For the elderly, data on the causes and consequences of several cardiovascular risk indicators with respect to risk of cardiovascular disease are scarce and contrasting results have been reported.[25,26,27] The relative importance of well established risk factors for atherosclerosis, such as elevated blood pressure, serum lipids, and smoking, may change with age and consequently their contribution to changes in morbidity and mortality.[28] In addition, other factors may become more important with advancing age, i.e., factors which trigger cardiovascular events to occur in the presence of atherosclerotic vessel wall disease.[29] Studying the early signs of atherosclerotic vessel wall disease, its 'natural' history and factors which contribute to the development of atherosclerosis may greatly contribute to our knowledge of atherosclerosis in this age group. In addition, approaches of non-invasive assessment of atherosclerosis, measurement of cardiovascular risk indicators and monitoring changes over time in relation to occurrence of new events may cast light on the possibilities of a successful preventive approach for the development of cardiovascular disease and its morbid consequences in the elderly.[30,31,32]

References

1. Thom TJ. International mortality from heart disease: Rates and trends. Int J Epidemiol 1989;18 (suppl 1):S20-8.
2. Haas JH de. Eerste myocardinfarct in Groot-Den Haag: Een retrospectieve epidemiologische survey. Hart Bull 1975;6:36-49.
3. Magnus K, Matroos A, Strackee J. Incidentie en mortaliteit van het acute hartinfarct en de fataal verlopende coronaire hartaanval in de regio Zeist. Hart Bull 1978;9:20-6.

4. Bekker BV. Interim verslag WHO registratie project ischaemische hartziekten, Nijmegen, 1974. Nederlandse Hartstichting, 's Gravenhage.

5. Does E van der, Lubsen J, Pool J, et al. Acute coronary events in general practise. Objectives and design of the IMIR study. Hart Bull 1976;7:91-8.

6. Continue Moribiditeits Registratie Peilstations Nederland 1985. Stichting Nederlands Instituut Voor onderzoek van de EersteLijnsgezondheidszorg (NIVEL). Utrecht, 1985.

7. Nijmeegs Universitair Huisartsen Instituut. Morbidity figures from general practice. Data from four general practices, 1978-1982. Nijmegen, 1985.

8. Herman B, Leyten ACM, Luijk JH van, et al. Epidemiology of stroke in Tilburg, The Netherlands. The population-based stroke incidence register: II. Incidence, initial clinical picture and medical care, and three-week case fatality. Stroke 1982;13:629-34.

9. Continue Moribiditeits Registratie Peilstations Nederland 1987. Stichting Nederlands Instituut Voor onderzoek van de EersteLijnsgezondheidszorg (NIVEL). Utrecht, 1987.

10. Rose GA, Blackburn H, Gillum RF, et al. Cardiovascular survey methods. World Health Organisation, Geneva 1982.

11. Dutch Information System for Hospital Care and Day-nursing (LMR). Hospital admission rates by cause, age and gender, 1978-1990. Dutch Centre for Health Care Information (SIG), Utrecht, 1990.

12. Centraal Bureau of Statistics. Mortality by cause, age and gender, 1969-1990. Serie A1, 1990.

13. Stehbens WE. An appraisal of the epidemic rise of coronary heart disease and its decline. Lancet 1987;i:606-10.

14. Burnand B, Feinstein AR. The role of diagnostic inconsistency in changing rates of occurrence for coronary heart disease. J Clin Epidemiol 1992;45:929-40.

15. Hoogendoorn D. Some notes on the current situation regarding the epidemic of acute myocardial infarction. Ned Tijdschr Geneeskd 1990;132:592-5.

16. Bots ML, Grobbee DE. Cardiovascular diseases in The Netherlands over the past 25 years: Prevalence, incidence, and trends in morbidity and mortality. Neth J Cardiol 1991:4:141-5.

17. Bonita R. Epidemiology of stroke. Lancet 1992;i:342-4.

18. Bonita R, Stewart A, Beaglehole R. International trends in stroke mortality: 1970-1985. Stroke 1990;20:989-92.

19. Rose G. Cause of the trends and variation in CHD mortality in different countries. Int J Epidemiol 1989;18 (suppl 1):S174-9.

20. Higgins MW, Luepeker RV, eds. Trends in coronary heart disease mortality. The influence of medical care. Oxford University Press. Oxford, 1989.

21. Malmgren R, Bamford J, Warlow C, et al. Geographical and secular trends in stroke incidence. Lancet 1987;ii:1196-1200.

22. Kuller L, Reisler DM. An explanation for variations in distribution of stroke and arteriosclerotic heart disease among populations and racial groups. Am J Epidemiol 1971;93:1-9.

23. Reed DM. The paradox of high risk of stroke in populations with low risk of coronary heart disease. Am J Epidemiol 1990;131:579-88.

24. Stichting Volksgezondheid en Roken. Jaarverslag. 's Gravenhage, 1988.

25. Benfante R, Reed D. Is elevated serum cholesterol level a risk factor for coronary heart disease in the elderly. JAMA 1990;263:393-6.

26. Castelli WP, Wilson WF, Levy D, et al. Cardiovascular risk factors in the elderly. Am J Cardiol 1989;63:12H-9H.

27. Bots ML, Grobbee DE, Hofman A. Epidemiology of blood pressure in the elderly. Epidemiol Rev 1991;13:294-314.

28. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. J Chron Dis 1978;31:201-306.

29. Oliver MF. Prevention of coronary heart disease: Propaganda, promises, problems and prospects. Circulation 1986;73:1-9.

30. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

31. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

32. Salonen R, Seppänen K, Rauramaa R, et al. Prevalence of carotid atherosclerosis and serum cholesterol levels in Eastern Finland. Arteriosclerosis 1988;8:788-92.

Chapter 2

The scope of this thesis

2 The scope of this thesis

The past decades have led to a better understanding of the etiology and pathogenesis of atherosclerosis and its clinical sequelae. Several risk factors have been identified that promote atherosclerosis to develop and of which it is currently known that their presence increases the risk of cardiovascular disease. At present, cardiovascular disease is believed to be caused by an interplay of advanced atherosclerotic vessel wall changes, stenosis and thrombosis. However, the question why some people suffer from a cardiovascular event whereas others may be spared from symptomatic cardiovascular disease remains unanswered. This is in particular important for subjects of older age, since in these subjects some extent of atherosclerosis is already present.

Non-invasive techniques to accurately assess atherosclerotic vessel wall abnormalities may be used to study the atherosclerotic process in population-based studies in order to gain further insight in factors that initiate the atherosclerotic process, lead to progression of atherosclerosis, and cause disease to manifest itself in the absence or presence of atherosclerotic vessel wall abnormalities. High resolution B-mode ultrasonography of carotid arteries may provide a tool to study signs of early and advanced atherosclerosis, to monitor the process of development of atherosclerosis and to study factors which promote development and progression of atherosclerotic vessel wall disease and subsequent clinical cardiovascular disease in populations at large.[1,2]

The main objectives of the studies presented in this thesis were to evaluate the feasibility of non-invasive assessment of hemodynamically important stenosis of the carotid artery and common carotid intima-media thickness, in an elderly non-hospitalized population; to study the value of increased intima-media thickness of the distal common carotid artery as an indicator of generalized atherosclerosis; to study determinants of increased common carotid intima-media thickness.

In chapter 3, a general outline is given of the principles of the ultrasound technique and a detailed description of the ultrasound reading protocol as it is used in the Rotterdam Study is provided. Furthermore, the reproducibility of the ultrasonographic measurements of common carotid intima-media thickness is presented in this chapter. The associations between intima-media thickness of the distal common carotid artery and indicators of atherosclerosis in other arteries are described in chapter 4. Results from studies on the association between common carotid intima-media thickness and cardiovascular risk factors are discussed in chapter 5, whereas chapter 6 deals with the prevalence and determinants of carotid atherosclerosis diagnosed as hemodynamically important stenosis. The findings presented in chapter 7 concern the association between cerebral white matter lesions and non-invasively assessed atherosclerosis.

References

1. Wikstrand J, Wiklund O. Frontiers in cardiovascular science. Quantitative measurements of atherosclerotic manifestations in humans. Arterioscler Thromb 1992;12:114-9.

2. Pearson TA, Heiss G. Atherosclerosis. Quantitative imaging, risk factors, prevalence and change. Circulation 1993;87 (suppl II):II-1-82.

Chapter 3

Non-invasive assessment of early atherosclerosis

3.1 Ultrasound principles and reading protocol

3.2 Reproducibility of common carotid intima-media thickness measurements

3.1 Non-invasive assessment of early atherosclerosis. Ultrasound principles and reading protocol. The Rotterdam Study

Introduction

In most industrialized countries cardiovascular diseases, notably coronary heart disease and stroke, are an important cause of morbidity and mortality. This applies particularly to the elderly, in which they represent by far the leading cause of death.[1] These dramatic, disabling or fatal disorders are generally caused by an interplay between atherosclerotic lesions of the arterial wall, arterial stenosis and thrombosis.[2,3] The development of atherosclerotic lesions is a slow process in which gradual thickening of the vessel wall occurs and localized atherosclerotic plaques may arise.[4] The mechanisms which cause atherosclerosis have not been sufficiently elucidated yet. Furthermore, knowledge on factors which may trigger clinical events to occur with advancing age in the presence or absence of atherosclerotic abnormalities is limited.[5]

Several non-invasive techniques exist to assess the presence and extent of atherosclerosis of the carotid artery.[6] Non-invasive duplex ultrasonography, combined with Doppler spectral analysis, may be used to assess hemodynamically significant stenosis of the carotid artery.[7] Presence of stenosis may be regarded as an advanced stage of atherosclerosis. The early stages of atherosclerosis, however, can not be assessed by this method, since they do not lead to detectable changes in the Doppler velocity profile of the blood.[8] Recently, it has been shown that with high resolution B-mode ultrasonography vessel wall characteristics of the carotid arteries can be non-invasively assessed in an effective and accurate way.[9,10,11] This technique facilitates the evaluation of the lumen diameter, the intima-media thickness and the presence and extent of plaques of the carotid arteries.

The ultrasound principle and the ultrasound reading protocol of the Rotterdam Study, that is used for the study of vessel wall characteristics of the carotid arteries, are described.

Ultrasound principles

Ultrasound image

A piezo-electric element within a transducer sends ultrasonic waves into human tissue in a pulsed manner.[12] Part of the waves are absorbed by the various components of the tissue and part of them are reflected. From the characteristics of the reflected waves, a two dimensional (2-D) image of various structures of the tissue underlying the scan head

of the transducer is constructed. The extent and strength of the reflection of ultrasound waves by the tissue depends on differences in acoustic impedance between the various anatomic layers of the human tissue.[13] When ultrasound waves propagate through the layers of the neck, and no difference in acoustic impedance exists between the anatomic structures, no reflection will occur, and on the 2-D image the structures will not be seen separately. When differences in acoustic impedance do exist, the structures may be seen separately on the image, depending on the axial resolution of the image. The acoustic impedance is determined by the density of the tissue and its flexibility. Calcified tissue (high density, low flexibility) will reflect all incoming ultrasonic waves, whereas blood (low density, high flexibility) will reflect hardly any ultrasound wave. On the 2-D image strong reflectors appear as white structures and weak reflectors are black.

When ultrasound waves travel through human tissue, reduction of the intensity of the ultrasound waves occurs, which is partly caused by absorption, scattering, and reflection of the ultrasound waves. The magnitude of the signal therefore depends on the distance between the structure (vessel wall) and the source of the waves (transducer). Consequently, structures similar in density and flexibility but at different distances from the transducer, may generate different echoes on the ultrasound image. This is not a desirable feature. A 'Time Gain Compensator' (TGC) is standardly used, by which the amplitude of the reflected ultrasound signal is increased proportional to the depth of the structure. Besides the time gain compensator, the amplitude of all reflected ultrasound waves may be changed by manually raising the gain settings. The higher the gain, the more increase of the reflected signal occurs. On the 2-D image, the intensity of the reflected signals of both weak and strong reflectors will be increased. At very high gain settings, reflections from both weak and strong reflectors may blur the 2-D image completely and it becomes very difficult to separate various structures on the image. Furthermore, 'noise' (artifact reflection) will be displayed which is generated within the amplifier.[14] In other words, the ratio reflected signal (vessel wall) to reflections due to artifact will seriously decrease when the gain is increased manually. Moreover, the length of the waves of the signal increases with increasing gain, leading to a decrease in resolution.[13]

Ultrasound image and axial resolution

Whether different structures can be identified on the ultrasound image, depends on the resolution of the equipment used. To be able to distinguish between two structures which are both in the same direction as the ultrasound waves, the axial resolution is very important. The axial resolution of the image is the minimal distance between two structures for being able to distinguish them.[14] For the exact theoretical background we

refer to existing literature.[12,13,14] In short, the resolution can be estimated using the formula

$$\text{Resolution} = 0.5 \times \text{Pulse length}$$

Two reflecting structures can be distinguished on the image when the distance between them in the axial direction is at least half of the pulse length. When the structures are closer than half the pulse length, they will not be seen separately on the ultrasound image. An interface may appear if the acoustic impedance between the structures is large enough to create a reflection of ultrasound waves. The location and extent of the interface, however, does not correlate well with the absolute thickness of the structure seen on the image.[9,11]

The length of the pulse is being determined by the number of waves in one pulse (n) and the length of the ultrasound wave (Lambda).

$$\text{Pulse length} = n \times \text{Lambda}$$

Lambda can be calculated as the ratio of the velocity of the ultrasound waves in the tissue to the frequency of the transducer. When the frequency of the transducer increases, the axial resolution will also increase. However, high frequencies of a transducer limit the ability to visualize deeper structures. A transducer of 7.5 Mhz appears to be a good compromise between the resolution and depth of investigation for the assessment of carotid atherosclerosis. The actual obtained axial resolution of the ultrasound images used in the Rotterdam Study is around 0.3 to 0.5 mm, whereas the manufacturer specification provides an estimate of the axial resolution of 0.5 mm.[15]

Ultrasound image and anatomical correlates

The vessel wall of the carotid artery is composed of three layers: adventitia, media and intima. The lumen contains the blood. When ultrasound waves spread through these structures, a typical longitudinal 2-D B-mode image will appear caused by differences in acoustic impedance between these layers. Reflection of ultrasound waves will occur when they go, with respect to the near wall, from adventitia to media, from media to intima, and from intima to blood, and with respect to the far wall from blood (lumen) to intima, from intima to media and from media to adventitia.[16] In figure 3.1.1, a characteristic longitudinal 2-D image of the distal common carotid artery is presented. The anterior wall (AW), the lumen and the posterior wall (PW) are clearly visible. Both near (AW) and far wall (PW) of the distal common carotid artery are displayed as two bright white lines separated by a hypoechogenic space. For the near wall this represents the

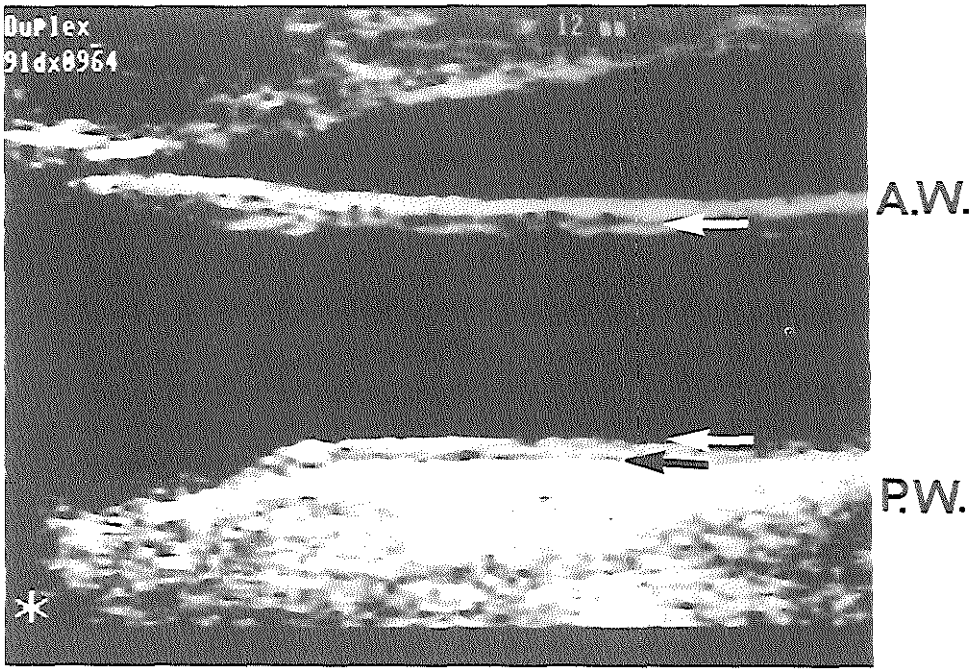


Figure 3.1.1 Characteristic longitudinal ultrasound image of the distal common carotid artery.

adventitia, the media and the intima, respectively. The far wall 2-D image consists of the intima, media and adventitia, respectively. The blood containing lumen appears black on the image.

A schematic representation of the interfaces is shown in figure 3.1.2. The upper border of the echo (*a*) is called 'leading edge', whereas the lower border of the echo (*b*) is the 'far edge'. With respect to the far wall, the leading edge of the first bright line reflects the lumen-intima interface, whereas the leading edge of the second bright line indicates the media-adventitia interface. The distance between the lumen-intima interface (3*a*) and the media-adventitia (4*a*) interface represents the intima-media thickness. The distance of the intima-lumen interface on the near wall (2*a*) to the leading edge of the first bright line on the far wall (3*a*) corresponds with the lumen diameter. The location of the leading edge appears to be independent of the gain setting.[9,11] The lower border (*b*) of the interface, however, does not correlate well with the anatomical change from, for example, the intima to the media layer of the far wall. The reflections caused by the

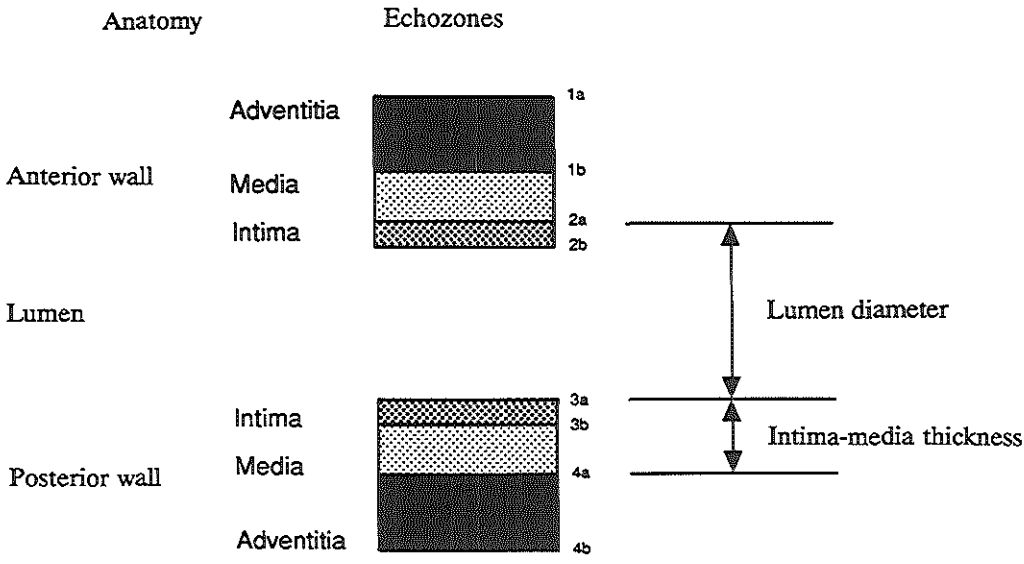


Figure 3.1.2 Schematic presentation of the ultrasound reflections of a characteristic longitudinal image of the distal common carotid artery (Closely adapted from reference 11 with permission).

structures of the intima may go far into the media layer, due to the limited resolution of the ultrasound image.[10,11] Furthermore, the location of the lower border of the interface appears to be dependent of the gain setting, i.e., the higher the gain setting, the thicker the distance between interface *a* and interface *b* on the ultrasound image.[11] Therefore, for the assessment of the lumen diameter and intima-media thickness, the use of the leading edges of the interfaces is strongly recommended.[17]

Ultrasound reading protocol

Ultrasound image and the assessment of vessel wall characteristics

In the Rotterdam Study, ultrasonography of both carotid arteries is performed with a 7.5 MHz linear array transducer using a Duplex scanner (ATL UltraMark IV, Advanced

Technology Laboratories, Bethel, Washington, USA). The subject is in supine position. The head is turned approximately 45 degrees in opposite direction. The ultrasound examination starts at the right carotid artery. An initial ultrasound scan is made showing a longitudinal view of the common carotid artery, the carotid bifurcation and the internal carotid artery. Then, a careful search is performed for the intima-lumen interface of the near wall, the lumen-intima interface and the media-adventitia interface of the far wall of the distal common carotid artery. When an optimal longitudinal image is obtained (figure 3.1.1), it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for three optimal 2-D images of the distal common carotid artery. Subsequently, the carotid artery is on-line evaluated for the presence (yes/no) of atherosclerotic lesions, defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. For the bifurcation and the internal carotid artery one image showing the site with the largest distance between lumen-intima interface and media-adventitia interface, is frozen on the R wave of the electrocardiogram and stored on video tape. The initial ultrasound scan, and the frozen images are recorded on VHS video tape.

The actual measurements of lumen diameter and intima-media thickness are performed off-line using a procedure and additional dedicated software, that has been closely adapted from the Wallenberg Laboratory for Cardiovascular Research (Prof Dr J. Wikstrand), Gothenburg, Sweden.[11] A frozen image which was stored on video tape, is digitized and displayed on the screen of a Laser 286/2 personal computer using a frame grabber (VP 1400-KIT-512-E-AT, Imaging Technology). After calibration, two vertical lines are drawn on the digitized image, using a graphic XY tablet and a mouse (Summagraphics MM II 1201). The distance between the two lines is set on 10 mm. The first vertical line is placed at the beginning of the dilatation of the distal common carotid artery, which serves as a reference point for the start of the measurement. With a cursor, the intima-lumen interface at the near wall and the lumen-intima-interface and the media-adventitia interface at the far wall of the distal common carotid artery are marked over a length of 10 mm. This is presented in figure 3.1.3. Computer software calculates the mean values as well as maximal values for lumen diameter and the intima-media thickness. The average of the lumen diameter and the intima-media thickness of each of the three frozen images are calculated. For each subject a mean lumen diameter and a mean intima-media thickness ((left + right)/2) are taken as a measure for current lumen diameter and wall thickness of the distal common carotid artery, respectively.

A similar procedure is followed for the measurements of the intima-media thickness of the carotid bifurcation and the internal carotid artery. Since clear interfaces

At present, in vivo ultrasound imaging can not discriminate between the intima layer and the media layer of the carotid artery vessel wall. Increased common carotid intima-media thickness may therefore reflect an atherosclerotic or adaptive intima thickening as well as an adaptive thickening of the media. Currently, no histologic studies are available that have addressed the issue whether increased common carotid intima-media thickness reflects presence of fatty streaks or fibrous plaques. Yet, in several studies, ultrasonographically determined increased common carotid intima-media thickness has been associated with elevated levels of cardiovascular risk factors.[27,28,29,30] Moreover, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis.[31] These results support the view that non-invasively assessed intima-media thickness of the common carotid artery may be regarded as a measurement of atherosclerosis.

Ultrasound image and experience in the Rotterdam Study

From March 1990 to July 1991, the first 1,500 participants of the Rotterdam Study had a ultrasound evaluation of the carotid arteries. During that period the ultrasound scanning protocol mainly focused on the assessment of intima-media thickness of the distal common carotid artery and on the determination of presence or absence of plaques in the common carotid artery and in the carotid bifurcation. Furthermore, presence of hemodynamically important stenosis of the right carotid artery was assessed. In July 1991, measurement of intima-media thickness of the carotid bifurcation and the internal carotid artery as well as measurement of intima-media thickness of atherosclerotic lesions in the carotid artery were added to the ultrasound reading protocol of the Rotterdam Study.

This thesis is based on information of carotid vessel wall characteristics of the first 1,000 participants of the Rotterdam Study. In the Rotterdam Study, ultrasonography is performed according to the ultrasound reading protocol by trained sonographers. Sonographers are involved in both the scanning of participants and in performing the measurements of vessel wall characteristics from the stored images on video tape. An ultrasound examination of both carotid arteries takes about 20 minutes for each subject. A complete assessment of vessel wall characteristics of the carotid artery from the video tapes takes an additional 30 minutes for each subject.

Of the first 1,000 participants, carotid ultrasound scans could not be obtained in 12 subjects, because of technical failure of the equipment. Of 31 subjects measurement of intima-media thickness at either the left or the right distal common carotid artery could not be performed from the stored images because of poor visualization. In these subjects, the estimate of intima-media thickness for each subject, was based on the

measurement of the side for which a value was available. The distribution of common carotid intima-media thickness, observed among the first 1,000 participants of the Rotterdam Study is presented in figure 3.1.4. Data on presence or absence of atherosclerotic plaques in the common carotid artery and in the carotid bifurcation were obtained in 99 % and 84 % of the subjects, respectively. The reproducibility of the common carotid intima-media thickness measurements in the Rotterdam Study is reported separately (chapter 3.2).

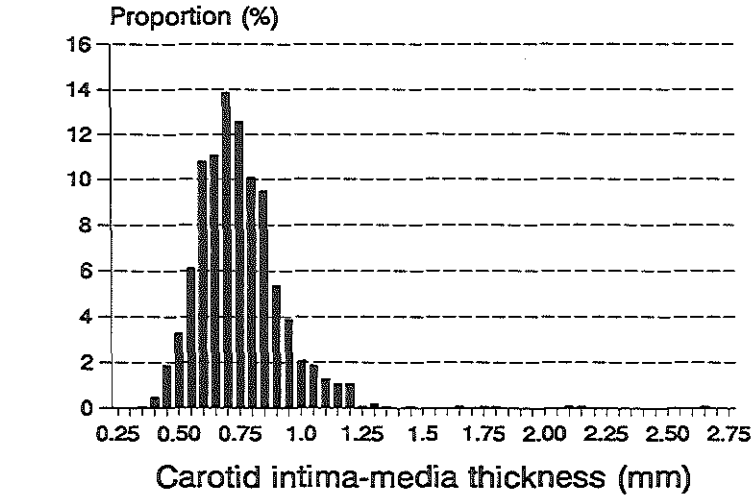


Figure 3.1.4 Distribution of common carotid intima-media thickness obtained from the first 1,000 participants of the Rotterdam Study.

References

1. Thom TJ, Epstein FH, Feldman JJ, et al. Trends in total mortality and mortality from heart disease in 26 countries from 1950 to 1978. Int J Epidemiol 1985;14:510-20.
2. Fuster V, Badimon L, Badimon JJ, et al. The porcine model for understanding of thrombogenesis and atherogenesis. Mayo Clin Proc 1991;66:818-31.
3. Meade TW. Thrombosis and cardiovascular disease. Ann Epidemiol 1992:2:353-64.
4. Malinow MR. Atherosclerosis regression and arterial repair. In: Pathobiology of the human atherosclerotic plaque. Glagov S, Newmann WP, Schaffer SA, eds. New York: Springer Verlag, 1990;433-68.
5. Oliver MF. Prevention of coronary heart disease: Propaganda, promises, problems and prospects. Circulation 1986;73:1-9.

6. Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987;15:635-44.

7. Feussner JR, Matchar DB. When and how to study the carotid arteries. Ann Intern Med 1988;109:805-18.

8. Hennerici M, Reifschneider G, Trockel U, et al. Detection of early atherosclerotic lesions by duplex scanning of the carotid artery. J Clin Ultrasound 1984;12:455-64.

9. Bond MG, Ball M. Assessment of ultrasound B-mode imaging for detection and quantification of atherosclerotic lesions in arteries of animals. Bethesda, Maryland: National Heart, Lung, and Blood Institute (NHLBI No1-HV-12916), 1986.

10. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

11. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery. Fundamental principles and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

12. Kremkau FW. Diagnostic ultrasound. Physical principles and exercise. New York: Grune & Stratton, 1980.

13. Wells PNT. Physics and instrumentation. In: Ultrasonics and clinical diagnosis. Goldberg BB, Wells PNT SA, eds. Edinburgh, United Kingdom. Churchill Livingstone, 1983;1-30.

14. Fish P. Physics and instrumentation of diagnostic medical ultrasound. West Sussex, England. John, Wiley & Sons, 1990.

15. Advanced Technology Laboratories. 7.5 MHz high frequency linear array specification, 1988.

16. Pignoli P. Ultrasound B-mode imaging for arterial wall thickness measurement. Atherosclerosis Rev 1984;12:177-84.

17. Wikstrand J, Wiklund O. Frontiers in cardiovascular science. Quantitative measurements of atherosclerotic manifestations in humans. Arterioscler Thromb 1992;12:114-9.

18. Pignoli P. Ultrasonic evaluation of arterial intima and media thickness: Development and validation of methodology. In: Pathobiology of the human atherosclerotic plaque. Glagov S, Newmann WP, Schaffer SA, eds. New York: Springer Verlag, 1990;705-32.

19. Wong M, Edelstein J, Wollman J, et al. Ultrasonic-pathological comparison of the human arterial wall. Verification of intima-media thickness. Arterioscler Thromb 1993;13:482-6.

20. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

21. McGrath LT, Elliott RJ. Formation of a lipid gradient across the human aortic wall during ageing and development of atherosclerosis. Atherosclerosis 1991:87:211-20.

22. Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. 1989;9 (suppl 1):19-32.

23. Friedman MH. Some atherosclerosis may be a consequence of the normal adaptive vascular response to shear. Atherosclerosis 1990;82:193-6.

24. Glagov S, Zarins C, Giddens DP, et al. Hemodynamics and atherosclerosis. Insights and perspectives gained from studies of human arteries. Arch Pathol Lab Med 1988;112:1018-31.

25. Glagov S, Vito R, Giddens DP, et al. Micro-architecture and composition of artery walls: Relationships to location, diameter and the distribution of mechanical stress. J Hypertension 1992;10 (suppl 6):S101-4.

26. Ross R. The pathogenesis of atherosclerosis. An update. N Engl J Med 1986;314:488-96.

27. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

28. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

29. Salonen R, Salonen JT. Carotid atherosclerosis in relation to systolic and diastolic blood pressure: Kuopio ischaemic heart disease risk factor study. Ann Med 1991;23:23-7.

30. Poli A, Tremoli E, Colombo A, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

31. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990:81:33-40.

3.2 Reproducibility of common carotid intima-media thickness measurements. The Rotterdam Study

Introduction

High resolution B-mode ultrasonography, combined with doppler spectral analysis, may be used to assess hemodynamically significant stenosis of the carotid artery.[1,2] Presence of stenosis may be regarded as an advanced stage of atherosclerosis. The early stages of atherosclerosis, however, can not be assessed by this method since they do not lead to detectable changes on the doppler velocity profile of the blood.[3] Furthermore, the assessment of percentage stenosis is less suitable for research on change in carotid atherosclerosis over time in unselected, asymptomatic subjects. Recently, the interest has been shifted towards non-invasive assessment of carotid intima-media thickness and plaque thickness rather than percentage stenosis in an attempt to come closer to the vessel wall changes potentially associated with atherosclerosis. This approach is currently being used in several ongoing population-based studies, including the Rotterdam Study.[4,5,6,7,8] Carotid intima-media thickness has a dual role in these studies. On the one hand it is used as an outcome variable to study determinants of presence and progression of intima-media thickness. On the other hand, it may serve as an indicator to predict occurrence of atherosclerotic disease in the future. The central role which the assessment of carotid intima-media thickness has in these studies emphasizes the importance of assessing reproducibility of the measurements.

We studied the reproducibility of ultrasonographically assessed common carotid intima-media thickness and determined which part of the variability can be attributed to within and between subjects variation and which part to measurement imprecision. Furthermore, we assessed whether measurement imprecision of common carotid intima-media thickness occurs randomly, and whether it is associated with selected risk factors for carotid atherosclerosis.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study of a cohort of 8,000 elderly subjects, aged 55 years or over, living in the suburb of Ommoord in the city of Rotterdam, The Netherlands. The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants. Rationale and design of the Rotterdam Study have been described

elsewhere.[4] The objective of the Rotterdam Study is to study determinants and prognosis of major disabling diseases in an ageing population. Incidence and risk factors of neurogeriatric disease, locomotor disease, ophthalmologic disease and cardiovascular disease are being investigated. With respect to cardiovascular disease, the Rotterdam Study focuses on the contribution of thrombogenic factors to atherosclerotic disease and on the presence and progression of atherosclerosis of the vessel wall and its determinants. The study comprises an extensive home interview, followed by two visits at the research center for a clinical examination.

From October 1, 1990 to April 1, 1991 we conducted a reproducibility study among 80 participants of the Rotterdam Study, randomly selected from the first 1,000 participants, who completed the baseline study protocol of the Rotterdam Study.

Ultrasonography

Ultrasonography of both left and right carotid artery was performed in all participants, using a 7.5 MHz linear array transducer (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypoechogenic space (figure 3.1.1). The distance of the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.[9] Studies have indicated that the far wall intima-media thickness as seen with ultrasound, truly reflects the anatomical intima-media layer.[9,10]

According to the Rotterdam Study ultrasound protocol, a careful search was performed for the lumen-intima interface and the media-adventitia interface of the far wall of the distal common carotid artery. When an optimal longitudinal image was obtained, it was frozen on the R wave of the electrocardiogram and stored on video tape. This procedure was repeated three times at both sides. Subsequently, the presence of atherosclerotic plaques in the common carotid arteries and carotid bifurcation was on-line (yes/no) evaluated. A plaque was defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. The actual measurements were performed off-line. The frozen images on the video tape were digitized and displayed on a screen using additional dedicated software. This procedure has been described in detail previously.[10,11] In short, with a cursor the interfaces of the distal common carotid artery were marked over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. This method permits the determination of mean values for intima-media thickness. The

average of the intima-media thickness of each of the three frozen images was calculated. For each subject mean intima-media thickness ((left + right)/2) was taken as measure for current wall thickness of the distal common carotid artery.

Eighty, randomly selected, subjects were invited within 3 months after their baseline carotid ultrasonography for a second ultrasound scan. The baseline ultrasound examinations were performed by one of the two sonographers. At the second visit all subjects were seen by both sonographers. Ultrasound scans that were made at the first visit were read by one reader only. The ultrasound images made at the second visit were read by four readers, including the reader of the baseline scans. Two of the four readers read all the ultrasound scans, whereas the other two read only half of them. The replicate measurements involved the mean posterior intima-media thickness.

Cardiovascular risk factors

During two visits at the research center several cardiovascular risk factors were measured. Height and weight were measured and body mass index (kg/m^2) was calculated. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the analysis. Information on smoking behavior was obtained using a computerized questionnaire. Subjects were categorized in groups of current smokers, former smokers and those who never smoked.

A venipuncture was performed, applying minimal stasis, using a 21 gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). All samples were quickly frozen in liquid nitrogen and then stored in -80 ^{0}C before assay. Serum total cholesterol was determined using an automated enzymatic procedure.[12] High density lipoprotein (HDL) cholesterol was measured similarly, after precipitation of the non HDL fraction with phosphotungstate-magnesium. Plasma fibrinogen level was assessed according to the Clauss method (Diamed AG, Switzerland).[13]

Assessment of measurement imprecision

Measurement imprecision is generally taken to be a random phenomenon, in which the measured values are supposed to lie around the true value of the subject. The deviations from the true value are assumed to be independently and identically distributed within and between subjects with zero mean and the same variance σ_e^2. Homogeneity of the variance σ_e^2 can be tested against the alternative hypothesis that it increases with the true value of the subjects. The mathematical background of the method used to assess measurement imprecision in the present study is given in the Appendix.

Data analysis

For the intima-media thickness of the left and right distal common carotid artery the absolute mean differences and standard deviations (SD) of the repeated measurements between sonographers, between readers and between visits are presented. In addition, intraclass correlation coefficients are given. With respect to differences between visits, it should be noted that the measurements of the first visit represent data from two sonographers read by one reader. For the second visit, data from two sonographers and four readers were available of which a random sample of measurements in which the sonographers and the readers were equally represented, was used in the analysis. This situation most directly reflects the current practical situation with respect to measurements of intima-media thickness performed at baseline and at follow-up in the Rotterdam Study.

Analysis of variance was used to determine which part of the variability could be attributed to within and between subjects variation and which part to measurement imprecision. A correlation analysis was used to assess the association between the estimated measurement error and estimated true intima-media thickness. Furthermore, the association between the estimated measurement error and several selected risk factors for carotid atherosclerosis measured at baseline (first visit) was studied. Analyses were performed using BMDP statistical software.

Table 3.2.1 General characteristics of the 80 participants of the reproducibility study and of the first 1,000 participants of the Rotterdam Study.

	Reproducibility study participants	First 1,000 Rotterdam Study participants
Number	80	1,000
Age (yrs)	67.9 (7.7)	68.3 (8.3)
Sex (% female)	56	61
Body mass index (kg/m^2)	26.4 (3.8)	26.6 (3.8)
Current smoking (%)	20	24
Systolic blood pressure (mmHg)	129 (19)	133 (21)
Diastolic blood pressure (mmHg)	68 (12)	70 (11)
Serum total cholesterol (mmol/l)	6.8 (1.3)	6.8 (1.2)
Serum HDL cholesterol (mmol/l)	1.37 (0.41)	1.34 (0.38)
Fibrinogen (g/l)	2.6 (0.6)	2.8 (0.7)

Values are percentages and means with standard deviation in parentheses

Results

In table 3.2.1 general characteristics are presented of the eighty participants of the reproducibility study and of the first 1,000 participants of the Rotterdam Study. No major differences in mean levels and standard deviations across the two groups were present.

Paired measurements of the intima-media thickness could be obtained in 95 % (75/80) of the subjects. Mean values (SD) of the common right carotid intima-media thickness at the first visit was 0.75 mm (0.19). For the left common carotid artery this value was 0.74 mm (0.18). In table 3.2.2 the absolute mean differences of the paired measurements of the common carotid intima-media thickness between sonographers, readers and visits are presented. The mean differences were small. Correlation coefficients ranged from 0.63 to 0.88 between the paired measurements (table 3.2.2). The reproducibility of the common carotid intima-media thickness measurements between visits was somewhat lower than between sonographers or readers. When the examinations were performed by the same sonographer and reader at both occasions the results showed a slight improvement without however, changing the direction or the significance of the findings.

Analysis of variance indicated that 87 % of the variability of the common carotid intima-media thickness measurements was due to differences between subjects. The

Table 3.2.2 Absolute mean differences in mm (SD) in the measurement of intima-media thickness between sonographers, readers and visits.

	Between sonographers*			Between readers†			Between visits‡		
	n§	difference	r|	n	difference	r	n	difference	r
Right side	77	0.061 (0.09)	0.84	77	0.079 (0.05)	0.76	77	0.086 (0.09)	0.71
Left side	79	0.063 (0.07)	0.78	80	0.074 (0.05)	0.88	79	0.096 (0.11)	0.66
Both sides┌	75	0.040 (0.07)	0.63	77	0.069 (0.04)	0.88	76	0.071 (0.09)	0.74

* One occasion, two sonographers, one reader.

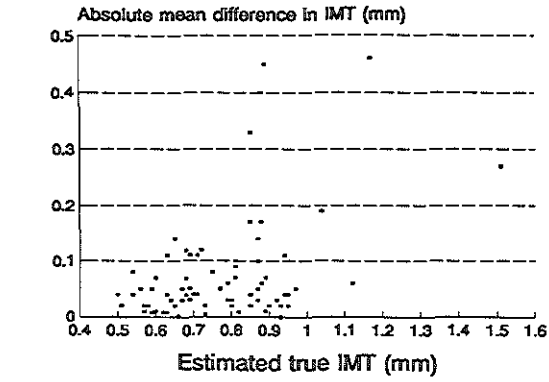
† One occasion, one sonographer, two readers.

‡ Two occasions, different sonographers (n=2), different readers (n=4).

§ n = number of paired measurements.

| r = Intraclass correlation coefficient between measurements of two sonographers, readers or visits, respectively.

┌ Both sides refers to (left + right)/2.



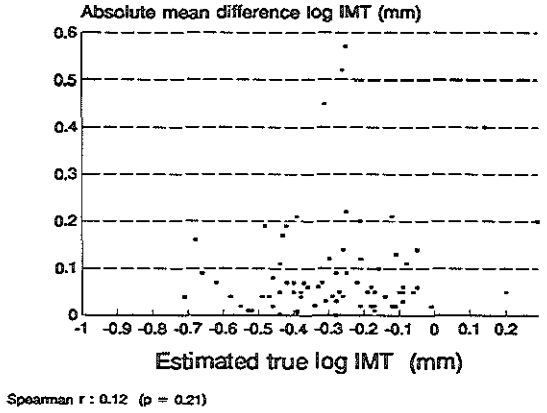


Figure 3.2.1 *Association between the absolute mean difference in common carotid intima-media thickness measurements at two subsequent visits and the estimated true common carotid intima-media thickness (top) and between the logarithmically transformed absolute mean difference in common carotid intima-media thickness measurements at two subsequent visits and the logarithm of the estimated true common carotid intima-media thickness (bottom).*

remaining thirteen percent could be attributed to sonographers and readers, most of which was due to differences between readers.

In figure 3.2.1 (top) the association between estimated standard deviation of the measurement error and the estimated true intima-media thickness, is presented. With increasing intima-media thickness the measurement error significantly increased. After logarithmic transformation of the intima-media thickness values, the estimated measurement error was no longer significantly associated with the level of intima-media

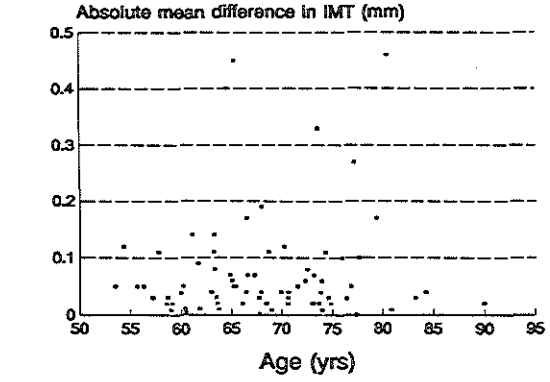
thickness (figure 3.2.1, bottom). Regression of the estimated standard deviation of the measurement error (formula 7, see Appendix) on the estimated true value of intima-media thickness (formula 6, see Appendix) through the origin yielded a proportionality parameter of 0.07. The estimated variance of $\sigma_{ln\varepsilon}^2$ (using formula 3, see Appendix) after logarithmical transformation of x_1 and x_2, resulted in a value of 0.0103, from which the square root term (formula 9, see Appendix) leads to 0.10. This value is similar to the estimated proportionality parameter of 0.07.

Estimates of the association between the observed absolute difference in intima-media thickness measurements at two subsequent visits, and several selected risk factors for carotid atherosclerosis were obtained. The absolute difference in common carotid intima-media thickness measurements between two subsequent visits was not significantly associated with age, body mass index, serum total cholesterol, HDL cholesterol, systolic blood pressure level, diastolic blood pressure level and fibrinogen. Furthermore, the magnitude of the observed difference was not related to sex and current smoking. Data on age, level of systolic blood pressure and HDL cholesterol are presented in figure 3.2.2.

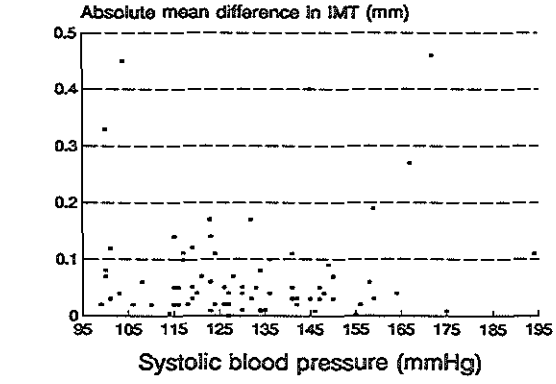
Discussion

Using the ultrasound protocol of the Rotterdam Study, visualisation and subsequent analysis of carotid arteries could be obtained in a large proportion of the eligible participants. The mean differences in repeated measurements between sonographers, between readers and between visits were small. Our findings indicate a good correlation between paired measurements of common carotid intima-media thickness. The variability of the measurements of common carotid intima-media thickness attributable to sonographers and readers was relatively small. Measurement error in the assessment of common carotid intima-media thickness does not appear to occur completely random, but increases with increasing common carotid intima-media thickness. Measurement error, however, is not related to levels of most of the potential risk factors of carotid atherosclerosis.

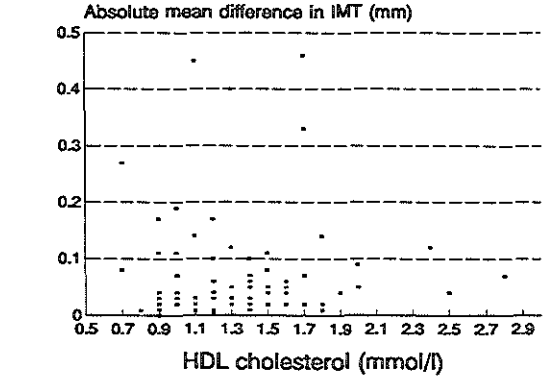
Some aspects of the study need to be considered. The value of this reproducibility study is conditional on the assumption that ultrasonographically measured common carotid intima-media thickness is a valid method to assess arterial wall thickness. Results from several in vitro experiments, in which the validity of the ultrasound measurement was studied, have indicated that the interfaces of the ultrasound image and the anatomical correlates of human arteries, are closely related.[9,10] However, whether intima-media thickness is an indicator of atherosclerosis per se can be disputed, since



Spearman r : 0.04 (p = 0.33)



Spearman r : -0.03 (p = 0.55)



Spearman r : 0.15 (p = 0.85)

Figure 3.2.2 Association between the absolute mean difference in common carotid intima-media thickness measurements at two subsequent visits with age (top), systolic blood pressure (middle), high density lipoprotein cholesterol (bottom).

atherosclerosis is viewed as a disorder which is restricted to the intimal layer of the arterial vessel wall and ultrasound imaging can not discriminate between the intima layer and the media layer of vessel wall. Also, data relating common carotid artery intima-media thickness to clinically relevant cardiovascular events are still largely lacking. Yet, ultrasonographically determined increases in intima-media thickness have been associated with elevated levels of established cardiovascular risk factors[6,7,8,14,15,16,17] and with an increased risk of myocardial infarction.[18] Moreover, increased common carotid intima-media thickness has been related to atherosclerosis in the abdominal aorta and to atherosclerosis in the arteries of the lower extremities (chapter 4).

In several studies the reproducibility of ultrasonographically assessed common carotid intima-media thickness has been determined. Wendelhag and co-workers, using the same ultrasound and reading method to assess carotid intima-media thickness as used in the Rotterdam Study, performed a reproducibility study among 50 subjects.[10] All subjects underwent two ultrasound scans on one occasion performed by two sonographers. Both observers measured the intima-media thickness of both examinations. A mean difference (SD) in intima-media thickness between observers of 0.09 mm (0.11) was found. Similar results were reported by Persson and co-workers.[19] In a Finnish study carotid atherosclerosis was assessed using the average of two wall thickness measurements of the common carotid arteries, performed at the greatest thickness shown on the ultrasound image.[20] In the reproducibility study among 10 randomly selected men, the mean difference in intima-media thickness measurements between observers was 0.087 mm. In the multicenter Cardiovascular Health Study the mean difference (SD) between sonographers in the measurement of intima-media thickness of the carotid artery was 0.18 mm (0.24).[21] One should take into account, however, that the Cardiovascular Health Study is a multicenter study and the difference between observers was based on only one measurement of intima-media thickness. Both aspects may have lead to an increase of the measurement error. The reproducibility findings observed in the Rotterdam Study are similar to those found in these few other studies. Furthermore, our findings indicate that most of the variability of the common carotid intima-media thickness measurements within subjects could be attributed to differences between readers. This suggests that additional training may improve the results.

In prospective follow-up studies, including the Rotterdam Study, carotid intima-media thickness is used as a determinant of an outcome or, alternatively, as an outcome variable to study determinants of presence and progression of vessel wall abnormalities.[4,5,6,7,8] In general, measurement imprecision of the exposure occurring equally in all subjects independent of the outcome (random), will tend to reduce the magnitude of an observed association between a determinant and the outcome, without

actually changing the direction of the observed association. A large amount of measurement error in the assessment of the exposure, relative to the true value of the exposure, may, however, blur a true association completely.[22,23] If the effect of measurement error of the exposure on the association is appreciable, it may be appropriate to consider a statistical adjustment to provide a better estimate of the association under study; i.e., obtaining an estimate that would have been observed if no measurement imprecision had been present. A number of methods has been described to correct epidemiologic measures of association, such as correlation coefficients, regression coefficients, relative risks, for measurement error in the exposure.[24,25] These methods are based on the assumption that measurement error of the exposure occurs randomly. When common carotid intima-media thickness is used in the analysis as a determinant of an outcome, such as atherosclerotic cardiovascular disease, our results indicate that measurement error of intima-media thickness appears not to occur completely randomly across the various levels of wall thickness. In this case, logarithmic transformation of the intima-media thickness may be considered. This appears particularly true if one wishes to correct the observed associations for measurement imprecision using methods described by others.[23,24,25]

When common carotid intima-media thickness serves as an outcome variable to study determinants of progression of atherosclerosis, imprecision of carotid intima-media thickness measurements may lead to misclassification of subjects. When measurement error of the outcome is not associated with the risk factor, it is assumed that misclassification occurs equally among exposed and non-exposed (non-differential misclassification). The findings of the present reproducibility study suggest that the misclassification of common carotid intima-media thickness, is predominantly of a non-differential type. This may attenuate the observed association, whereas the direction will probably not change. In addition, it should be noted that when measurement imprecision only affects the dependent variable (outcome), a linear regression coefficient is not attenuated, but only the precision of the estimate is reduced. Correction for measurement error therefore is not appropriate.[25] Evidently, an increase in the number of subjects may help to increase precision of the estimate.

In conclusion, our findings suggest that intima-media thickness measurements of the common carotid artery are highly reproducible. Measurement error of common carotid intima-media thickness appears not to be associated with most of the potential determinants of intima-media thickness. When correction of epidemiologic measures of association for measurement error in the intima-media thickness is wanted, preferably the logarithmically transformed values should be used .

Appendix

Measurement imprecision is generally taken to be a random phenomenon, which occurs when repeated measurements that are performed on the same subject under stationary conditions, show variation. The measured values are supposed to lie around the true value of the subject. The deviations from the true value are assumed to be independently and identically distributed within and between subjects with zero mean and the same variance σ_e^2. Homogeneity of the variance σ_e^2 can be tested against the alternative hypothesis that it increases with the true value of the subjects. Results from a reproducibility study may be used to address this question. A measured intima-media thickness, x, can be considered the result of the true intima-media thickness, u, and the measurement imprecision, e:

$$x = u + e \tag{1}$$

When measurement error occurs randomly, the parameter e can be characterized as having a normal distribution with zero mean and variance σ_e^2. The variance of e can be estimated, using data from replicate measurements. The difference between paired measurements (x_1, x_2) equals the difference between the measurement errors at both occasions:

$$x_1 = u + e_1 \qquad x_2 = u + e_2 \tag{2}$$

leading to

$$x_1 - x_2 = e_1 - e_2 \tag{3}$$

The variance of this difference between paired measurements is $2\sigma_e^2$. If the variance of the difference is similar for all subjects, then an estimate of σ_e^2 from all subjects is straightforwardly obtained:

$$\hat{\sigma}_e^2 = \frac{1}{2n} \Sigma(x_1 - x_2)^2 \tag{4}$$

where the summation is over all n subjects. When, however, evidence is available that σ_e^2 increases with the true value of u, then σ_e^2 has to be estimated from the two measurements x_1 and x_2 for each subject separately as

$$\hat{\sigma}_e^2 = \frac{[x_1 - \bar{x}]^2 + [x_2 - \bar{x}]^2}{(2-1)} \tag{5}$$

where

$$\bar{x} = \frac{(x_1 + x_2)}{2} \tag{6}$$

The estimated standard deviation of the measurement error for each subject is simply the square root:

$$\hat{\sigma}_e = \frac{1}{2}\sqrt{2}\ |x_1 - x_2| \tag{7}$$

The true value of u for each subject is estimated by the average of both replicate measurements, (see 6). Correlation analysis can be used to assess the association between the estimated measurement imprecision (7) and the estimated true value of intima-media thickness (6). When σ_e appears to be associated with u, the measurement error can not be considered independent of the true value, indicating that the model used, x

$= u + e$, is not appropriate. In case that σ_e is proportional to the true value, then a logarithmic transformation may be useful:

$$\ln x = \ln u + \ln e \tag{8}$$

with the assumption that $\ln e$ is normally distributed with mean zero and variance $\sigma_{\ln e}^2$. If this logarithmic model is the correct model, then the proportionality relation between σ_e and the true value u can be shown to be

$$\sigma_e = u \sqrt{\exp(\sigma_{\ln e}^2)\ [\exp(\sigma_{\ln e}^2)-1]} \tag{9}$$

clearly indicating that the proportionality parameter is completely determined by $\sigma_{\ln e}^2$. In that case the proportionality parameter, which can be estimated by regressing (7) on (6) without intercept, should approximately equal the square root term in (9) with $\sigma_{\ln e}^2$ estimated as in (4) after logarithmic transformation of the measurements x_1 and x_2.

References

1. Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987;15:635-44.

2. Feussner JR, Matchar DB. When and how to study the carotid arteries. Ann Intern Med 1988;109:805-18.

3. Hennerici M, Reifschneider G, Trockel U, et al. Detection of early atherosclerotic lesions by duplex scanning of the carotid artery. J Clin Ultrasound 1984;12:455-64.

4. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

5. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: Design and rationale. Ann Epidemiol 1991;1:263-76.

6. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

7. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

8. Salonen R, Seppänen K, Rauramaa R, et al. Prevalence of carotid atherosclerosis and serum cholesterol levels in Eastern Finland. Arteriosclerosis 1988;8:788-92.

9. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

10. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

11. Bots ML, Meurs JHCM van, Grobbee DE. Assessment of early atherosclerosis: A new perspective. J Drug Res 1991;16:150-4.

12. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

13. Clauss A. Gerinnungsphysiologische schnellmethode zur bestimmung des fibrinogens. Acta Haematol 1957;17:237-46.

14. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.

15. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

16. Poli A, Tremoli E, Colombo A, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

17. Salonen R, Salonen JT. Carotid atherosclerosis in relation to systolic and diastolic blood pressure: Kuopio ischaemic heart disease risk factor study. Ann Med 1991;23:23-7.

18. Bots ML, Hofman A, Bruyn AM de, et al. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Elderly Study. Arterioscler Thromb 1993;13:64-9.

19. Persson J, Stavenow, Wikstrand J, et al. Noninvasive quantification of atherosclerotic lesions. Reproducibility of ultrasonographic measurement of arterial wall thickness and plaque size. Arterioscler Thromb 1992;12:261-6.

20. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high resolution B-mode ultrasonography: Inter- and intra-observer variability. Ultrasound Med Biol 191;17:225-30.

21. O'Leary DH, Polak JF, Wolfson SK, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. Stroke 1991;22:1155-63.

22. Rothman KJ. Modern epidemiology. Boston: Little, Brown & Co., 1986.

23. Beaton GH, Milner J, Corey P, et al. Sources of variance in 24 hour dietary recall data: Implications for nutrition study design and interpretation. Am J Clin Nutr 1979;32:2546-59

24. Willet W. Correction for effects for measurement error. In: Willet W, ed. Nutritional Epidemiology. Oxford University Press, New York, 1990.

25. Philips AN, Smith GD. How independent are 'independent' effects? Relative risk estimation when correlated exposures are measured imprecisely. J Clin Epidemiol 1991;44:1223-31.

Chapter 4

Common carotid intima-media thickness: A measure of generalized atherosclerosis

4.1 Atherosclerosis of the abdominal aorta

4.2 Atherosclerosis of the arteries of the lower extremities

4.3 Atherosclerosis of the carotid arteries

4.4 Prevalent cardiovascular disease

4.1 Carotid intima-media thickness in elderly women with and without atherosclerosis of the abdominal aorta

Introduction

Recently, it has been shown that with high resolution B-mode ultrasonography vessel wall characteristics of the carotid arteries can be non-invasively assessed in an effective and accurate way in populations at large.[1,2,3,4,5] This technique provides for the evaluation of the lumen diameter, the intima-media thickness and the presence and extent of plaques of the carotid artery. In several currently ongoing follow-up studies, high resolution B-mode ultrasonography of the carotid arteries is used to investigate the signs of early atherosclerotic vessel wall disease, its 'natural' history and factors which contribute to the development of atherosclerosis.[1,3,4,5] It is of importance to assess whether findings observed for carotid atherosclerosis may be extrapolated to other arterial vessels, such as the coronary arteries, the abdominal aorta and arteries of the lower extremities.[6]

The present study was conducted to assess the association between rontgenographically assessed atherosclerosis of the abdominal aorta and ultrasonographically determined intima-media thickness of the distal common carotid arteries in elderly women.

Methods

Population

In 1985, 855 women, aged 55 to 75 years, participated in a population-based study on determinants of osteoporosis.[7] All subjects were examined radiographically for calcified deposits in the abdominal aorta. These calcified deposits have been shown to represent intimal atherosclerosis,[8] and have been associated with cardiovascular disease at several sites[9] and with cardiovascular mortality.[10,11] In 1990, sixty four women were randomly selected from those with and those without aortic calcifications. Forty four subjects (69 %) consented to participate, 17 with and 27 without calcifications of the abdominal aorta. The non-responding women were on average slightly older (1.5 years), and had lower systolic (difference 7 mmHg) and diastolic blood pressure (difference 5 mmHg) levels compared to the participants. These differences were not statistically significant. No differences were found in body mass index, smoking behavior, and serum cholesterol levels between the two groups.

Measurements

Abdominal aorta

Atherosclerosis of the abdominal aorta was assessed using a lateral X-ray of the lumbar spine (T12-S1), on which the presence of calcified deposits was determined. Calcifications were considered present when linear densities were clearly visible in an area parallel and anterior to the lumbar spine (L1-L4).[12] In 1985, all films were examined by two independent observers without knowledge of the risk factor status of the subjects. The severity of the atherosclerosis was graded from 0 (no calcifications) to 4 (aorta outlined with calcifications). For the present study subjects were selected on the basis of presence of advanced atherosclerosis of the abdominal aorta (grade 3 or grade 4) or absence of atherosclerosis (grade 0).

Carotid arteries

Ultrasonography of both left and right carotid artery was performed in 1990 in all participants, using a 7.5 MHz linear array transducer (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (figure 3.1.1). The distance of the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.[13] Studies have indicated that the far wall intima-media thickness as seen with ultrasound, truly reflects the anatomical intima-media layer.[13,14]

According to the ultrasound protocol, a careful search is performed for the lumen-intima interface and the media-adventitia interface of the far wall of the distal common carotid artery. When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times at both sides. Subsequently, the presence of atherosclerotic plaques in the common carotid arteries and carotid bifurcation is on-line (yes/no) evaluated. A plaque is defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. The actual measurements of intima-media thickness are performed off-line. The frozen images on the video tape are digitized and displayed on a screen of a personal computer using additional dedicated software. This procedure has been described in detail previously.[15] In short, with a cursor the interfaces of the distal common carotid artery are marked over a length of 10 mm. The beginning of the

Table 4.1.1 General characteristics of women with and without signs of aortic atherosclerosis.

	Aortic atherosclerosis			
	Absent		Present	
Number	27		17	
Age (yrs)	64.4	(4.1)	68.1	(5.3)*
Body mass index (kg/m^2)	26.3	(3.4)	25.5	(3.5)
Serum total serum cholesterol (mg/dl)	257.8	(45.0)	288.5	(54.3)
Systolic blood pressure (mmHg)	151.3	(20.9)	150.9	(22.6)
Diastolic blood pressure (mmHg)	83.0	(8.6)	83.5	(14.3)
Hypertension (%)†	48		59	
Current smoking (%)	7		29	

Values are percentages or means with standard deviations in parentheses

* Statistically significant difference across groups ($p < 0.05$)

† Systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 95 mmHg or currently using antihypertensive drugs

dilatation of the distal common carotid artery serves as a reference point for the start of the measurement. This method permits the determination of mean and maximum values for the common carotid intima-media thickness. The average of the intima-media thickness of each of the three frozen images is calculated. For each subject mean intima-media thickness ((left + right)/2) is taken as measure for current wall thickness of the distal common carotid artery.

Cardiovascular risk factors

In 1985 additional information was obtained on smoking habits (current, former, never), and use of antihypertensive drugs (yes/no) by a self-administered questionnaire, which was checked during an interview by a physician. Height and weight were measured without shoes and with indoor clothing. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the analysis. Hypertension was defined as a systolic blood pressure level of 160 mmHg or over and/or a diastolic blood pressure level of 95 mmHg or over and/or current use of antihypertensive drugs. Serum total cholesterol was determined using an automated enzymatic procedure.[16]

Data analysis

Of three subjects (one with and two without aortic calcifications) measurement of

common carotid intima-media thickness could not be performed from the stored images because of poor visualization. Complete data on the carotid arteries were obtained of 41 women.

Mean levels of intima-media thickness of the distal common carotid arteries and mean proportions of atherosclerotic plaques in the carotid bifurcation were compared between subjects with and without atherosclerosis of the abdominal aorta using a linear regression analysis. Multiple linear regression was used for analysis of differences across groups, adjusted for age and several cardiovascular risk factors. The differences are presented with a 95 % confidence interval (CI).

Results

In table 4.1.1 general characteristics of women with and without signs of atherosclerosis of the abdominal aorta are given. The age-adjusted mean intima-media thickness of the right common carotid artery was significantly increased among subjects with atherosclerosis of the abdominal aorta compared to those without atherosclerosis with a mean difference of 0.15 mm [95 % CI 0.03,0.26]. This difference constitutes an average increase of approximately 18 %. For the left common carotid artery a similar difference was observed, which, however, did not reach statistical significance. Analysis of both left and right side combined, revealed a statistically significant difference in common carotid intima-media thickness of 0.11 mm [95 % CI 0.01,021] across subjects with and without atherosclerosis of the abdominal aorta. Additional adjustment for differences across groups in body mass index, serum cholesterol, hypertension and smoking did not materially change the magnitude of the observed association (adjusted difference of 0.12 mm [95 % CI -0.01,0.25]).

The age adjusted prevalence of atherosclerotic plaques in the left and right carotid bifurcation was slightly, and not significantly, higher among subjects with aortic atherosclerosis (table 4.1.2).

Discussion

The present study among 41 elderly women shows a significant positive association between atherosclerosis of the abdominal aorta and non-invasively assessed increased intima-media thickness of the distal common carotid arteries.

Before interpretation of the results some aspects of this study need to be considered. First, the validity of rontgenographic assessment of aortic calcification in the diagnosis of atherosclerosis has been studied by comparison with assessments made on

Table 4.1.2 Intima-media thickness (mm) and presence of atherosclerotic plaques of the carotid artery for women with and without signs of atherosclerosis of the abdominal aorta.

	Aortic atherosclerosis		Mean	Age-adjusted mean
	Absent	Present	difference [95 % CI]*	difference [95 % CI]
Intima-media thickness				
Right side	0.83 (0.12)	1.01 (0.23)	0.18 [0.07,0.29]	0.15 [0.03,0.26]
Left side	0.84 (0.16)	0.94 (0.16)	0.10 [-0.01,0.20]	0.06 [-0.04,0.17]
Both sides†	0.83 (0.13)	0.98 (0.17)	0.16 [0.06,0.26]	0.11 [0.01,0.21]
Atherosclerotic plaques				
Right bifurcation (%)	26	30	4 [-24,32]	12 [-18,42]
Left bifurcation (%)	22	18	-4 [-30,22]	0 [-28,28]
Either right or left (%)	37	29	-8 [-38,22]	2 [-30,34]
Both sides (%)‡	11	18	7 [-12,29]	10 [-14,34]

Values are proportions or means with standard deviations in parentheses

* 95 % confidence interval.

† Both sides refers to (left + right)/2.

‡ Refers to atherosclerotic plaques present at both left and right carotid bifurcation.

necropsy material.[8] The method was shown to be highly specific. In all cases (n=20), visible calcifications represented advanced atherosclerosis. The sensitivity of the method was somewhat lower: In 5 of 31 subjects in which no calcification was radiographically diagnosed, atherosclerotic plaques of varying degrees were found in the aorta at necropsy.[8] Rontgenographic assessed aortic calcifications have been shown to be associated with cardiovascular risk factors[12,17,18] and their presence has been found to be a predictor of coronary heart disease[19] and of cardiovascular mortality.[10,11] Moreover, presence of calcification in the abdominal aorta has been associated with atherosclerotic abnormalities in other arterial vessels.[9]

Secondly, the question as to what extent a 5 year interval between the assessment of atherosclerosis of the abdominal aorta and the measurement of the common carotid intima-media thickness may have affected our results must be considered. Based on earlier findings it is not likely that the calcifications of the abdominal aorta present at baseline would disappear over a five year period.[20] However, some women with initially no atherosclerosis of the abdominal aorta may have developed aortic atherosclerosis during these 5 years. Provided that a true association exists between common carotid intima-media thickness and aortic atherosclerosis, this misclassification will have biased the observed association towards zero. Thus, the true association may actually be

stronger than observed. Alternatively, women with atherosclerosis in the aorta may be more rapid 'progressors' with respect to systemic atherosclerosis. Furthermore, development of atherosclerosis in the carotid artery occurs in general later in life than in the abdominal aorta.[21,22] As a consequence, a 5-year time difference between the assessment of aortic atherosclerosis and of atherosclerotic vessel wall characteristics of the carotid arteries may have increased the likelihood of finding an association. Both mechanisms, however, do not invalidate the inference of our findings.

Direct comparison of our findings with those from other studies is difficult because we are not aware of any study relating common carotid intima-media thickness to atherosclerosis of the abdominal aorta. In one study, no association was observed between ultrasonographically determined presence of atherosclerotic carotid plaques and atherosclerotic plaques in the abdominal aorta.[23] Differences in selection of study population (hypercholesterolemic middle-aged men) and in definition of atherosclerosis of the abdominal aorta may explain this contrasting finding.

It is still a matter of debate whether increased common carotid intima-media thickness indicates atherosclerosis and is a precursor of atherosclerosis or that it merely reflects an adaptive response of the vessel wall to changes in shear stress and tensile stress.[24] Ultrasonographically determined increased intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors[4,5,25,26,27,28] and with an increased risk of myocardial infarction.[29] Furthermore, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis.[30] Our finding among non-hospitalized elderly subjects that an increased common carotid intima-media thickness is associated with aortic atherosclerosis, adds to the existing evidence that intima-media thickness of the distal common carotid artery may be regarded as a measure of atherosclerosis.

Results from several studies suggest that smoking, high blood pressure and high serum total cholesterol level are in the causal pathway of leading to atherosclerosis of both the carotid artery and the abdominal aorta.[4,5,23,25,26,27] As a consequence, they should not be considered as confounding variables of the observed association between common carotid intima-media thickness and aortic atherosclerosis and should, in principle, not be controlled for in the analyses. When, on the other hand, the interest is whether the observed association is independent from cardiovascular risk factors, one may want to additionally adjust for these factors. Our finding that adjustment for differences in serum cholesterol, (systolic) hypertension and smoking does not attenuate the association between atherosclerosis of the abdominal aorta and common carotid intima-media thickness, suggests that other factors may play a role in the development of atherosclerosis of both the carotid arteries and the abdominal aorta or that the effect of

these known risk factors may be different across different arterial sites.

In conclusion, the findings of the present study provide evidence that among subjects with atherosclerotic plaques in the abdominal aorta, the intima-media thickness of the distal common carotid arteries is increased. Since the sample size of the present study is relatively small, further studies are needed to confirm this finding.

References

1. Hofman A, Grobbee DE, Jong PTVM de, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.
2. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in The Cardiovascular Health Study. Stroke 1992;23:1752-60.
3. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.
4. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.
5. Salonen R, Seppänen K, Rauramaa R, et al. Prevalence of carotid atherosclerosis and serum cholesterol levels in Eastern Finland. Arteriosclerosis 1988;8:788-92.
6. Gordon T, Kannel WB. Predisposition to atherosclerosis in the head, heart and legs. The Framingham Heart Study. JAMA 1972;221:661-9.
7. Hemert van AM, Vandenbrouke JP, Birkenhäger JC, et al. Prediction of osteoporotic fractures in the general population by a fracture risk score. A 9-year follow-up among middle-aged women. Am J Epidemiol 1990;132:123-35.
8. Hyman JB, Epstein FH. A study of the correlation between roentgenographic and post-mortem calcification of the aorta. Am Heart J 1954;47:540-3.
9. Sternby NH. Atherosclerosis in a defined population. An autopsy survey in Malmö, Sweden. Acta Pathol Microbiol Scand 1968;194 (suppl):1-216.
10. Witteman JCM, Kok FJ, Saase van JLCM, et al. Aortic calcification as a predictor of cardiovascular mortality. Lancet 1986;ii:1120-2.
11. Eggen DA. Relationship of calcified lesions to clinically significant atherosclerotic lesions. Ann NY Acad Sci 1968;149:752-67.
12. Witteman JCM, Grobbee DE, Kok FJ, et al. Increased risk of atherosclerosis in women after the menopause. Br Med J 1989;298:642-4.
13. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.
14. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.
15. Bots ML, Meurs JCHM van, Grobbee DE. Assessment of early atherosclerosis: A new perspective. J Drug Res 1991;16:150-4.

16. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

17. Niskanen LK, Suhonen M, Siitonen O, et al. Aortic and lower limb artery calcification in type 2 (non-insulin-dependent) diabetic patients and non-diabetic control subjects. Atherosclerosis 1990;84:61-71.

18. Witteman JCM, Kannel WB, Wolf PA, et al. Aortic calcified plaques and cardiovascular disease. The Framingham Heart Study. Am J Cardiol 1990;66:1060-4.

19. Siitonen O, Uusitupa M, Pyörälä K, et al. Aortic calcification and their relationship to coronary heart disease and cardiovascular risk factors in patients with newly diagnosed non-insulin dependent diabetes and in non-diabetic subjects. Cardiology 1987;74:335-9.

20. Witteman JCM, Grobbee DE, Valkenburg HA, et al. Cigarette smoking and progression of atherosclerosis in women. A 9-year population-based follow-up study. Circulation (in press).

21. Weber G, Bianciardi G, Bussani R, et al. Atherosclerosis and ageing. A morphometric study on arterial lesion of elderly and very elderly necropsy subjects. Arch Pathol Lab Med 1988;112:1066-70.

22. Schwartz CJ, Mitchell JRA. Observations on localization of arterial plaques. Circulation 1962;11:63-73.

23. Giral P, Pithois-Merli I, Filitti V, et al. Risk factors and early extracoronary atherosclerotic plaques detected by three-site ultrasound imaging in hypercholesterolemic men. Arch Intern Med 1991;151:950-6.

24. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

25. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

26. Poli A, Tremoli E, Colombo A, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

27. Bots ML, Hofman A, Bruyn AM de, et al. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Elderly Study. Arterioscler Thromb 1993;13:64-9.

28. Bonithon-Kopp C, Scarabin P, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb 1991;11:966-72.

29. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.

30. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990;81:33-40.

4.2 Carotid intima-media thickness and lower extremity arterial atherosclerosis. The Rotterdam Study

Introduction

To further understand the early phase of atherosclerosis, its 'natural' history and factors that contribute to its development, possibilities need to be explored to more directly obtain information on the arterial system in non-hospitalized subjects. Recently, it has been shown that with high resolution B-mode ultrasonography vessel wall characteristics of the carotid arteries can be non-invasively assessed in an effective and accurate way in populations at large.[1,2] This technique facilitates the evaluation of the lumen diameter, the intima-media thickness and the presence and extent of plaques of the carotid artery and has now been applied in a number of studies.[3,4,5,6,7] The applicability of the findings of these studies with respect to the atherosclerotic process are conditional on the extent to which non-invasively assessed carotid intima-media thickness reflects atherosclerotic vessel wall disease in other arteries that are at high risk of atherosclerosis, such as the coronary arteries, the abdominal aorta and arteries of the lower extremities.[8] In other words, may increased common carotid intima-media thickness of the common carotid artery be regarded as an indicator of generalized atherosclerosis.

In this paper we report on the association of non-invasively assessed common carotid intima-media thickness and atherosclerosis of the lower extremities among the first 1,000 participants of the Rotterdam Study.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study of a cohort of subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, The Netherlands. Eventually the cohort will comprise over 8,000 subjects. The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere.[9] In brief, the objective of the Rotterdam Study is to clarify determinants of chronic disabling diseases in an ageing population. Incidence and risk factors of cardiovascular diseases, locomotor diseases, neurogeriatric diseases, and ophthalmologic diseases are being studied. The study comprises an extensive home interview, followed by two visits at the Rotterdam Study research center for clinical examinations.

Ultrasonography of the carotid arteries

Ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer using a Duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (figure 3.1.1).[10] The distance of the leading edge of the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.[11] Studies have indicated that the posterior (far) wall intima-media thickness as seen with ultrasound, truly reflects the anatomical intima-media layer.[10,12]

According to the Rotterdam Study ultrasound protocol, a careful search is performed for the lumen-intima interface and the media-adventitia interface of the far wall of the distal common carotid artery.[13] When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for both sides. Subsequently, the common carotid artery and the carotid bifurcation is on-line evaluated for the presence (yes/no) of atherosclerotic lesions, defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. The actual measurements of intima-media thickness are performed off-line. From the video tape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software. This procedure has been described in detail previously.[12,13] In short, with a cursor the interfaces of the distal common carotid artery are marked over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery serves as a reference point for the start of the measurement. This method permits the determination of mean values as well as maximal values for intima-media thickness. The average of the intima-media thickness of each of the three frozen images is calculated. For each subject a mean intima-media thickness ((left + right)/2) is taken as a measure for current wall thickness of the distal common carotid artery, respectively. With respect to focal lesions the presence or absence of calcifications and acoustic shadowing is noted. For all measurements, alternative choices are present as 'can not tell' and 'not recorded'.

Arteries of the lower extremities

The presence of atherosclerosis in the arteries of the lower extremities was evaluated by measuring the systolic blood pressure level of the posterior tibial artery at both left and right side using an 8 MHz continuous wave doppler probe (Huntleigh 500 D, Huntleigh

Technology, Bedfordshire, UK) and a random-zero sphygmomanometer.[14] For each side a single blood pressure reading was taken with the subject in supine position. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg. The lowest ankle-arm index in either leg was used in the analysis.[15] In addition, separate analyses were performed in which for each subject an estimate of the ankle-arm index was obtained by averaging the ankle-arm index of both legs. In agreement with the approach followed by Fowkes[15] and by Schroll and Munck[16], lower extremity arterial disease was considered present when the ankle-arm index was lower than 0.90 at at least one side.

Cardiovascular risk factors

In the Rotterdam Study, information on current health status, medical history, drug use, and smoking behavior was obtained using a computerized questionnaire, which included a Dutch version of the Rose questionnaire for assessment of prevalent coronary heart disease.[17] A history of stroke and myocardial infarction was obtained through direct questioning and considered positive when confirmed by a physician. With respect to smoking behavior, subjects were categorized in groups of current smokers, former smokers and those who never smoked. During two visits at the research center several cardiovascular risk indicators were measured. Height and weight were measured and body mass index (kg/m^2) was calculated. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the present analysis. Hypertension was defined as a systolic blood pressure of 160 mmHg or over or a diastolic blood pressure of 90 mmHg or over or currently using antihypertensive drugs.[18]

A venipuncture was performed, applying minimal stasis, using a 21 gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Serum total cholesterol was determined using an automated enzymatic procedure.[19] High density lipoprotein (HDL) cholesterol was measured similarly, after precipitation of the non HDL fraction with phosphotungstate-magnesium.

Data analysis

The present analysis is based on findings in the first 1,000 participants of the Rotterdam study. Carotid ultrasound scans could not be obtained in 12 subjects, because of technical failure of the equipment. Doppler readings from both posterior tibial arteries were not available in 18 subjects. Of 31 subjects measurement of intima-media thickness at either the left or the right carotid artery could not be performed from the stored images

because of poor visualization. With respect to the measurement of the ankle-arm index, data on the left or the right side were not available for 16 subjects. In both situations, the estimate of intima-media thickness and of ankle-arm index for each subject, was based on the measurement of the side for which a value was available.

The association between common carotid intima-media thickness and ankle-arm index was evaluated using linear regression analysis. Multiple linear regression was used for analyses, adjusted for age, gender and several cardiovascular risk factors, such as hypertension, smoking, body mass index, serum total cholesterol, and serum HDL cholesterol. Logistic regression analysis was used to assess the risk of presence of lower extremity arterial disease, associated with a common carotid intima-media thickness above 0.89 mm (highest quintile). The associations are presented with a 95 % confidence interval (CI). Analysis of trends across groups of increasing levels of common carotid intima-media thickness was performed with linear regression analysis.

Table 4.2.1 General characteristics of the study population.

		Women	Men
Number		592	378
Age (yrs)		68.7 (7.9)	68.4 (7.6)
Body mass index (kg/m^2)		27.1 (4.2)	25.9 (3.1)
Smoking (%)	Current	20	29
	Former	30	64
Systolic blood pressure (mmHg)		134 (22)	134 (19)
Diastolic blood pressure (mmHg)		70 (11)	72 (10)
Hypertension (%)*		33	23
Serum total cholesterol (mmol/l)		7.0 (1.2)	6.4 (1.2)
Serum HDL cholesterol (mmol/l)		1.4 (0.3)	1.2 (0.4)
Prevalent cardiovascular disease (%)		15	21
Angina pectoris		8	7
Myocardial infarction		5	15
Stroke		2	3
Carotid intima-media thickness (mm)		0.76 (0.19)	0.81 (0.19)
Ankle-arm index	Left side	1.17 (0.22)	1.19 (0.21)
	Right side	1.17 (0.24)	1.20 (0.23)
Lower extremity arterial disease (%)		13	10

Values are percentages and means with standard deviation in parentheses.

* Hypertension defined as a systolic pressure ≥ 160 mmHg or a diastolic pressure ≥ 90 mmHg or currently using antihypertensive drugs

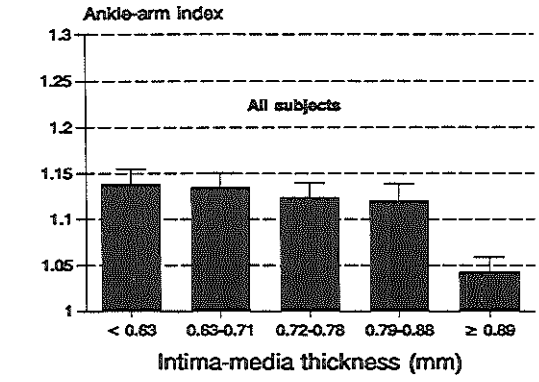
The distributions of the measurements of common carotid intima-media thickness and ankle-arm index were skewed. Analyses in which the values were logarithmically transformed yielded results similar to those with untransformed data. Because interpretation of results from logarithmically transformed data is rather difficult, the non-transformed results are presented.

A positive history of a major cardiovascular event, i.e., a positive history of stroke, angina pectoris or myocardial infarction, was significantly associated with an increased common carotid intima-media thickness and a reduced ankle-arm index. Since this may bias the association between intima-media thickness and the ankle-arm index towards a positive finding, separate analyses were performed among subjects free from symptomatic cardiovascular disease.

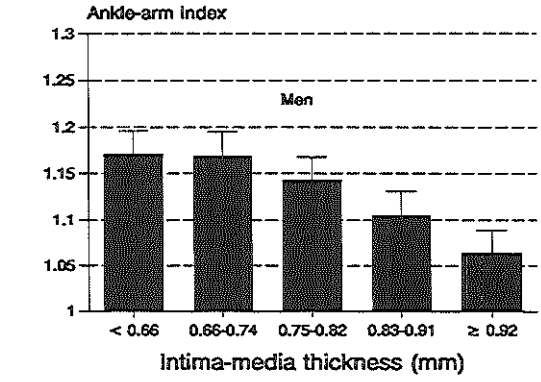
Results

Data on carotid arteries and arteries of the lower extremity were available for 970 (97%) of the subjects. Baseline characteristics of this group are presented in table 4.2.1.

Linear regression analysis showed a significant inverse association between common carotid intima-media thickness and the ankle-arm index (figure 4.2.1, top). The age- and gender adjusted results indicated that an increase of 0.1 mm in common carotid intima-media thickness was associated with a mean reduction of the ankle-arm index of 0.021 [95 % CI 0.014,0.028]. For men, a gradual decrease of the ankle-arm index was observed with increasing levels of common carotid intima-media thickness, whereas for women the ankle-arm index decreased beyond a common carotid intima-media thickness of 0.86 mm (figure 4.2.1, middle and bottom, respectively). A difference in the magnitude of the association between men and women was observed in the linear regression analysis: for men 0.025 [95 % CI 0.014,0.036] and for women 0.017 [95 % CI 0.007,0.027]. Exclusion of subjects with prevalent cardiovascular disease ($n=147$), did not materially alter the magnitude and significance of the age- and gender adjusted findings (mean reduction of 0.020 [95 % CI 0.011,0.029]). Adjustments for differences in serum lipids, hypertension, body mass index and current smoking attenuated the association between common carotid intima-media thickness and ankle-arm index: analysis among all subjects gave a mean reduction of the ankle-arm index of 0.016 [95 % CI 0.008,0.024] with an increase of 0.1 mm in common carotid intima-media thickness, whereas analysis among asymptomatic subjects yielded a mean reduction of 0.015 [95 % CI 0.006,0.024]. When the average of the ankle-arm index of both legs was used in the analysis instead of the lowest value at either leg, similar associations between common carotid intima-media thickness and ankle-arm index were obtained (table 4.2.2).



Adjusted for age and gender



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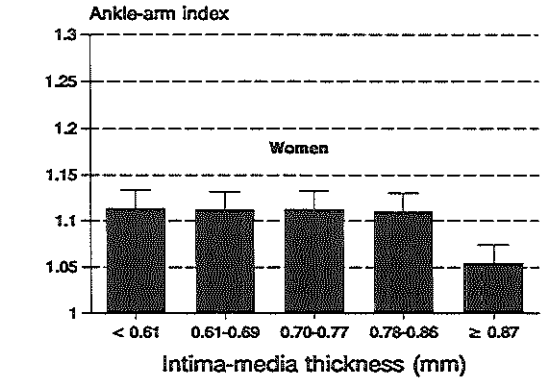


Adjusted for age

Figure 4.2.1 Mean ankle-arm index across groups with increasing common carotid intima-media thickness presented for all subjects, men and women.

Table 4.2.2 Age adjusted findings on the association between intima-media thickness and ankle-arm index when defined as the average of the ankle-arm index of both legs.

	All subjects	Asymptomatic subjects*
Women	-0.013 [-0.003,-0.023]	-0.014 [-0.002,-0.026]
Men	-0.027 [-0.017,-0.037]	-0.026 [-0.014,-0.038]
Both men and women‡	-0.021 [-0.013,-0.029]	-0.020 [-0.012,-0.032]
Both, men and women, adjusted§	-0.016 [-0.006,-0.026]	-0.014 [-0.006,-0.022]

Results are expressed as a mean change in the ankle-arm index [95 % CI] with an increase of 0.1 mm in intima-media thickness.

* Subjects without a positive history of stroke, angina pectoris, myocardial infarction.

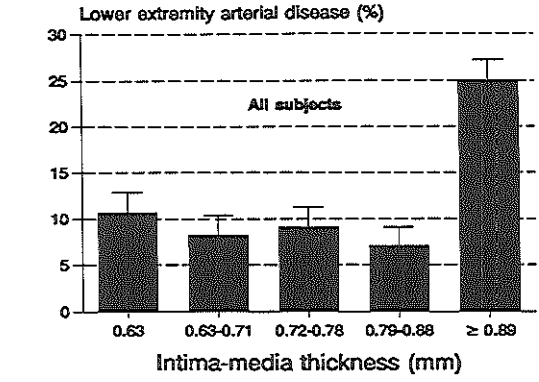
‡ Adjusted for age and gender

§ Adjusted for age, gender, hypertension, smoking, HDL cholesterol, and body mass index

The results for lower extremity arterial disease, defined as an ankle-arm index below 0.90 in at least one side,[15,16] are presented in figure 4.2.2. For all subjects, a gradual linear increase of the prevalence of lower extremity arterial disease with increasing levels of common carotid intima-media thickness could not be demonstrated (figure 4.2.2, top). Similar findings were observed for men and women (figure 4.2.2, middle and bottom, respectively). The common carotid intima-media thickness in subjects with lower extremity arterial disease was increased as compared to that of subjects without disease with an age- and sex adjusted difference of 0.100 mm [95 % CI 0.064,0.136].

In table 4.2.3, the prevalence of lower extremity arterial disease, defined according to different arbitrarily chosen cutoff levels of the ankle-arm index, is presented in quintiles of common carotid intima-media thickness. Irrespective of the definition of lower extremity arterial disease, an increase of the presence of lower extremity arterial disease with common carotid intima-media thickness was found, in particular, beyond a common carotid intima-media thickness of 0.89 mm.

The age- and gender adjusted odds ratio of lower extremity arterial disease for those with an common carotid intima-media thickness above 0.89 mm to that of subjects with an intima-media thickness below 0.89 mm was 3.4 [95 % CI 2.2,5.2]. Attentuation of the odds ratio was found when additional adjustments were made for differences in serum lipids, hypertension, body mass index, and smoking: odds ratio 2.2 [95 % CI 1.4,3.5]. Analyses among men and women separately, revealed odds ratio's of 3.3 [95 % CI 1.6,6.8] and 2.3 [95 CI % 1.3,3.9], respectively. Analysis among subjects free from prevalent cardiovascular disease yielded an age- and gender adjusted odds ratio of 3.1 [95 % CI 1.8,5.2]. Further adjustment for cardiovascular risk factors did not substantially alter the magnitude and the significance of the findings.



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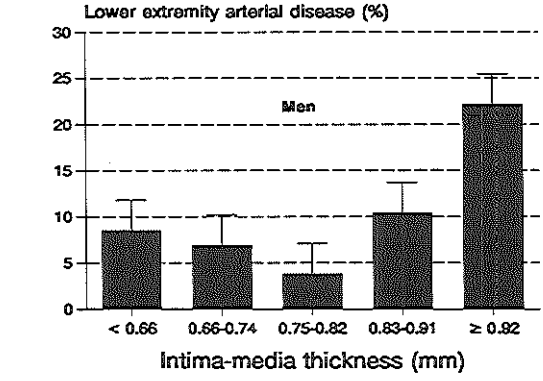

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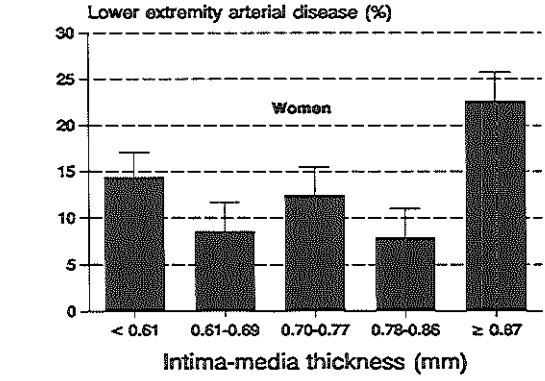


Adjusted for age

Figure 4.2.2 Lower extremity arterial disease across groups with increasing common carotid intima-media thickness presented for all subjects, men and women.

Table 4.2.3 Prevalence (%) of lower extremity arterial disease (LEAD) across strata of common carotid intima-media thickness.

Definition LEAD	Quintiles of intima-media thickness (mm)				
	< 0.63	0.63-0.71	0.72-0.78	0.79-0.88	≥ 0.89
Index < 0.75	3.0	3.8	5.2	3.5	9.5
Index < 0.80	5.9	4.5	5.6	4.4	14.4
Index < 0.85	7.7	5.9	7.9	5.6	20.9
Index < 0.90	10.6	8.2	9.1	7.1	24.9
Index < 0.95	12.6	12.0	13.6	13.7	31.2
Index < 1.00	15.3	15.8	18.6	20.0	40.5

Results are adjusted for differences in age and gender

Discussion

Our findings in a population-based sample of elderly subjects, indicate that a gradual increase in ultrasonographically assessed common carotid intima-media thickness is associated with a steady reduction of the ankle-arm index, in particular among men. Furthermore, men and women with a common carotid intima-media thickness in the upper quintile (above 0.89 mm) are considerably more likely to have lower extremity arterial disease compared to those whose intima-media thickness is below 0.89 mm. This association was not dependent on the used cutoff level of the ankle-arm index for the definition of lower extremity arterial disease. These findings were similar for subjects free from symptomatic cardiovascular disease.

Some aspects of this study should be considered. First, the ankle-arm index was based on a single blood pressure reading performed at one occasion. As a consequence, some misclassification will have occurred, which may have reduced the observed associations, provided that a true association exists and misclassification occurred to the same extent among subjects with and without an increased intima-media thickness of the distal common carotid artery.

Second, whether the average of the ankle-arm index of both legs or the lowest value measured at one of the legs provides the best information about the presence or absence of atherosclerotic vessel wall disease in the arteries of the lower extremities, can not be answered satisfactory at present.[14,15,20] Furthermore, the definition of presence

or absence of lower extremity arterial disease among non-hospitalized elderly subjects is based on an arbitrarily chosen cut-off point of the level of the ankle-arm index measured in subjects at rest and at present no agreement exists on the level of the cut-off point.[14,15] Our findings with respect to the association with common carotid intima-media thickness indicate no superiority for either definition of ankle-arm index nor for the level of the cutoff point used to define lower extremity arterial disease.

Finally, it is conceivable that an increased common carotid intima-media thickness does not reflect atherosclerosis and that it is not a precursor of atherosclerosis. It may merely be an adaptive response of the vessel wall to changes in shear stress and tensile stress.[21] Furthermore, atherosclerosis is viewed as a disorder which is restricted to the intimal layer of the arterial vessel wall[22], and ultrasound imaging can not discriminate between the intima layer and the media layer of vessel wall. In several studies, ultrasonographically determined increased intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors.[4,5,6,23,24,25] In addition, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis.[26] These results support the view that non-invasively assessed intima-media thickness of the common carotid artery may be regarded as a measure of atherosclerosis.

Our finding among non-hospitalized elderly subjects that an increased common carotid intima-media thickness is associated with a lower ankle-arm index, as an indicator of the presence of atherosclerotic vessel wall abnormalities of the arteries of the lower extremities, demonstrates that intima-media thickness of the common carotid artery may reflect generalized atherosclerosis. This notion is supported by results from a study among 208 hypercholesterolemic men, aged 25 to 64 years, in which a strong association was found between ultrasonographically determined presence of atherosclerotic carotid plaques and atherosclerotic plaques in the femoral artery.[27] Furthermore, findings from a population-based study in which ultrasonographically determined increase in intima-media thickness was associated with an increased risk of myocardial infarction[28] and from other studies that were performed among hospital-based populations or among otherwise selected populations, in which a positive association was observed between non-invasively assessed carotid atherosclerotic vessel wall abnormalities and coronary atherosclerosis[28,29,30,31] and atherosclerosis of the arteries of the lower extremities[32], may strengthen this view.

The results from the present study suggest that a common carotid intima-media thickness above 0.89 mm may be a better predictor of the presence of lower extremity arterial disease than values below 0.89 mm. One explanation for finding no uniform association for a value lower than 0.89 mm, may be that a common carotid intima-media

thickness at that level may be associated with minor atherosclerotic vessel wall abnormalities which do not give rise to a sufficient reduction of systolic blood pressure in the arteries of the lower extremities.

In several studies smoking, high blood pressure, elevated levels of serum total cholesterol and low levels of HDL cholesterol have been associated with carotid atherosclerosis, indicated as increased intima-media thickening,[4,5,6,23,24,25] and with lower extremity arterial atherosclerotic disease.[14,16] These results may suggest that these cardiovascular risk factors are in the causal pathway of atherosclerosis of both the common carotid artery and the arteries of the lower extremity. Consequently, these risk factors should not be considered as confounding variables of the observed association between carotid intima-media thickness and lower extremity arterial atherosclerosis and should in principle not be controlled for in the analyses. When, on the other hand, the main interest is to assess whether the observed association between carotid intima-media thickness is independent from cardiovascular risk factors, one may want to additionally adjust for these factors. In the present study among elderly subjects, adjustment for differences in smoking, hypertension and elevated levels of serum lipids did not severely attenuate the observed association between common carotid intima-media thickness and ankle-arm index. This indicates that either, besides these factors, others factors, yet unknown, may play a role in the development of atherosclerosis of both the common carotid arteries and the arteries of the lower extremity or, alternatively, that the effect of these risk factors on atherosclerosis may be different across different arterial sites.

In conclusion, this study provides evidence that increased common carotid intima-media thickness reflects generalized atherosclerosis, as indicated by its association with atherosclerosis of the arteries of the lower extremity.

References

1. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high resolution B-mode ultrasonography: Inter- and intra-observer variability. Ultrasound Med Biol 1991;17:225-30.

2. O'Leary DH, Polak JF, Wolfson SK, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. Stroke 1991;22:1155-63.

3. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

4. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

5. Salonen R, Seppänen K, Rauramaa R, et al. Prevalence of carotid atherosclerosis and serum cholesterol levels in Eastern Finland. Arteriosclerosis 1988;8:788-92.

6. Bots ML, Hofman A, Bruyn AM de, et al. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Elderly Study. Arterioscler Thromb 1993;13:64-9.

7. Psaty BM, Furberg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly. Initial findings from the Cardiovascular Health Study. JAMA 1992;268:1287-91.

8. Gordon T, Kannel WB. Predisposition to atherosclerosis in the head, heart and legs. The Framingham Heart Study. JAMA 1972;221:661-9.

9. Hofman A, Grobbee DE, Jong PTVM de, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

10. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

11. Wikstrand J, Wiklund O. Frontiers in cardiovascular science. Quantitative measurements of atherosclerotic manifestations in humans. Arterioscler Thromb 1992;12:114-9.

12. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

13. Bots ML, Meurs JCHM van, Grobbee DE. Assessment of early atherosclerosis: A new perspective. J Drug Res 1991;16;150-4.

14. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the ageing process: A review. J Clin Epidemiol 1992;45:529-42.

15. Fowkes FGR, Houseley E, Cawood EHH, et al. Edinburgh artery study: Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384-92.

16. Schroll M, Munck O. Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population of 60 year old men and women. J Chronic Dis 1981;34:261-9.

17. Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. World Health Organisation, Geneva 1982.

18. Joint National Committee on High Blood Pressure. 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1988;148:1023-38.

19. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

20. Crique MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.

21. Glagov S, Vito R, Giddens DP, et al. Micro-architecture and composition of artery walls: Relationships to location, diameter and the distribution of mechanical stress. J Hypertension 1992;10 (suppl 6):S101-4.

22. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

23. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

24. Poli A, Tremoli E, Colombo A, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

25. Bonithon-Kopp C, Scarabin P, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb 1991;11:966-72.

26. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990;81:33-40.

27. Giral P, Pithois-Merli I, Filitti V, et al. Risk factors and early extracoronary atherosclerotic plaques detected by three-site ultrasound imaging in hypercholesterolemic men. Arch Intern Med 1991;151:950-6.

28. Craven TE, Ryu JE, Espeland MA, et al. Evaluation of the associations between carotid atherosclerosis and coronary artery stenosis. A case-control study. Circulation 1990;82:1230-42.

29. Wofford JL, Kahl FR, Howard GR, et al. Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. Arterioscler Thromb 1991;11:1786-94.

30. Tanaka H, Nishino M, Ishida M, et al. Progression of carotid atherosclerosis in Japanese patients with coronary artery disease. Stroke 1992;23:946-51.

31. Megnien JL, Sene V, Jeannin S, et al. Coronary calcification and its relation to extracoronary atherosclerosis in asymptomatic hypercholesterolemic men. Circulation 1992;85:1799-1807.

32. Sutton KC, Wolfson SK, Kuller LH. Carotid and lower extremity arterial disease in elderly adults with isolated systolic hypertension. Stroke 1987;18:817-22.

4.3 Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study

Introduction

High resolution B-mode ultrasonography enables us to accurately assess vessel wall characteristics of the carotid arteries in populations at large.[1,2] This technique facilitates the evaluation of the lumen diameter, the intima-media thickness and the presence and extent of plaques of the carotid artery.[3,4,5,6,7] Furthermore, B-mode combined with doppler spectral analysis (duplex) may be used to assess hemodynamically significant stenosis of the carotid artery.[8] Since the common carotid artery is relatively spared from development of severe atherosclerosis, the applicability of measurement of common carotid intima-media thickness with respect to the atherosclerotic process is conditional on the extent to which increased common carotid intima-media thickness reflects atherosclerotic vessel wall disease in other arteries that are at high risk of atherosclerosis, such as the carotid bifurcation, the internal carotid artery, the coronary arteries, the abdominal aorta, and the arteries of the lower extremities. It is important to answer the question to what extent increased intima-media thickness of the common carotid artery may be regarded as an indicator of generalized atherosclerosis.

In this paper we report on the association of non-invasively assessed common carotid intima-media thickness and atherosclerotic abnormalities in the carotid bifurcation and internal carotid artery among the first 1,000 participants of the Rotterdam Study.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study of people aged 55 years or over, to investigate the incidence of, and risk factors for chronic disabling diseases.[9] The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants. All inhabitants aged 55 years or more, living at one point in time in the Rotterdam suburb of Ommoord were invited to participate. The study comprises an extensive home interview, followed by two visits at the Rotterdam Study research center for clinical examinations.

Ultrasonography of the carotid arteries

To measure carotid intima-media thickness, ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (figure 3.1.1).[10] The distance of the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.[10,11] Studies have shown that the posterior (far) wall intima-media thickness as seen with ultrasound, truly reflects the anatomical intima-media layer.[10,11] According to the Rotterdam Study ultrasound protocol, a careful search is performed for the lumen-intima interface and the media-adventitia interface of the far wall of the distal common carotid artery.[6] When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for both sides. The actual measurements of intima-media thickness are performed off-line. From the video tape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software. This procedure has been described in detail previously.[6,11] In short, with a cursor the interfaces of the distal common carotid artery are marked over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery serves as a reference point for the start of the measurement. This method permits the determination of mean values as well as maximal values for intima-media thickness. The average of the intima-media thickness of each of the three frozen images is calculated. For each subject a mean intima-media thickness ((left + right)/2) is taken as a measure for current wall thickness of the distal common carotid artery, respectively.

The common carotid artery and the carotid bifurcation were both on-line and off line (from tapes) evaluated for the presence (yes/no) of atherosclerotic lesions. Plaques were defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. No attempt was made to quantify the size or extent of the lesions.

Hemodynamically significant stenosis of the carotid artery was ultrasonographically assessed using a 7.5 MHz sector transducer in combination with a 5 MHz pulsed Doppler.[12] For reasons of feasibility, only the right carotid artery was evaluated for stenosis. Interpretation of velocity profiles was done on-line according to standard criteria.[13] The right internal carotid artery was categorized as normal (0 % reduction of lumen diameter), minimal lesions (1-15 % reduction), moderate stenosis (16-49 % reduction) or severe stenosis (≥ 50 % reduction).

Cardiovascular risk factors

Information on current health status, medical history, drug use, and smoking behavior was obtained using a computerized questionnaire. Subjects were categorized in groups of current smokers, former smokers and those who had never smoked. During two visits at the research center several cardiovascular risk indicators were measured. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the analysis. Hypertension was defined as a systolic blood pressure level of 160 mmHg or over and/or a diastolic blood pressure level of 90 mmHg or over and/or current use of antihypertensive drugs. A venipuncture was performed, applying minimal stasis, using a 21 gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Serum total cholesterol and high density lipoprotein (HDL) cholesterol was determined by means of an automated enzymatic procedure.[14]

Data analysis

The present analysis is based on findings in the first 1,000 participants of the Rotterdam Study. In 12 persons ultrasonography of the carotid arteries could not be performed due to technical or logistic reasons. In 19 subjects, extreme tortuosity of the internal carotid artery prevented reliable measurements. Data on atherosclerotic lesions in the carotid bifurcation was not available for 140 subjects. Of 31 subjects measurement of common carotid intima-media thickness at either the left or the right carotid artery could not be performed from the stored images because of poor visualization. The estimate of common carotid intima-media thickness was based on the measurement of the side for which a value was available.

Mean common carotid intima-media thickness was compared between subjects with and without atherosclerotic abnormalities in the carotid bifurcation and in the right internal carotid artery using a linear regression analysis. Multiple linear regression was used for analyses adjusted for age, gender and several cardiovascular risk factors, such as hypertension, smoking, serum total cholesterol, and HDL cholesterol. The associations are presented with a 95 % confidence interval (CI).

Results

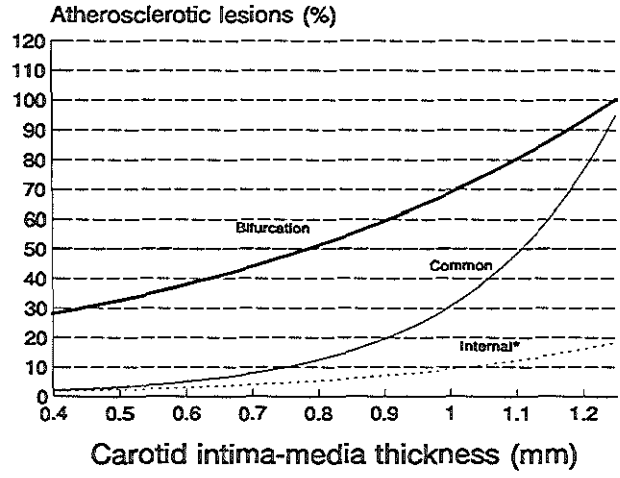
General characteristics of the study group are presented in table 4.3.1. Figure 4.3.1 shows that the presence of atherosclerotic lesions in the common carotid artery and in the carotid bifurcation, as well as the prevalence of a minimal, moderate or severe stenosis of the right internal carotid artery gradually increases with increasing common carotid

Table 4.3.1 General characteristics of the study population.

		Women	Men
Number		600	388
Age (yrs)		68.9 (8.0)	68.6 (7.7)
Body mass index (kg/m^2)		27.1 (4.2)	25.9 (3.1)
Smoking (%)	Current	20	29
	Former	30	64
Systolic blood pressure (mmHg)		134 (21)	134 (19)
Diastolic blood pressure (mmHg)		70 (11)	72 (11)
Hypertension (%)		33	23
Cholesterol	Total (mmol/l)	7.0 (1.2)	6.4 (1.2)
	HDL (mmol/l)	1.4 (0.3)	1.2 (0.4)
Carotid intima-media thickness (mm)		0.76 (0.19)	0.81 (0.19)

Values are percentages and means with standard deviation in parentheses.

intima-media thickness. Among subjects with a common carotid intima-media thickness of 1.0 mm or over, the prevalence of atherosclerosic lesions in the common carotid artery or in the carotid bifurcation was more than 30 % and 70 %, respectively.



Adjusted for age and gender

Figure 4.3.1 *Association between increasing common carotid intima-media thickness and prevalence of atherosclerotic lesions in the common carotid artery, and in the carotid bifurcation, and prevalence of hemodynamically important stenosis of the internal carotid artery.* * *Stenosis includes a minimal, moderate or severe stenosis.*

Table 4.3.2 Common carotid intima-media thickness (IMT) in subjects with and without atherosclerotic lesions of the carotid arteries (in mm).*

	n†	IMT (SD) in subjects without lesions	IMT (SD) in subjects with lesions	Difference‡	Difference§
Common carotid artery	137	0.75 (0.14)	0.98 (0.31)	0.21 [0.18,0.24]	0.21 [0.18,0.24]
Carotid bifurcation	434	0.72 (0.14)	0.84 (0.22)	0.08 [0.06,0.11]	0.07 [0.05,0.10]
Right internal carotid artery|	43	0.77 (0.19)	0.90 (0.30)	0.12 [0.02,0.22]	0.10 [0.01,0.19]

Values are means with (standard deviation) or with [95 % confidence interval].
* Lesions present in at least the left or the right carotid artery.
† Number of subjects with the abnormality present.
‡ Difference adjusted for age and gender.
§ Adjusted for differences in hypertension, smoking, body mass index and serum lipids.
| Presence of moderate or severe stenosis (≥ 16 % lumen reduction).

Among subjects with lesions in the carotid bifurcation, mean common intima-media thickness was significantly increased compared to that of subjects without lesions with a difference adjusted for age and gender of 0.08 mm [95 % CI 0.06,0.11]. Similar results were found for subjects with a moderate to severe hemodynamically important stenosis of the internal carotid artery with an age- and gender adjusted difference of 0.12 mm [95 % CI 0.0.02,0.22]. Additional adjustment for differences in HDL cholesterol, hypertension, current smoking and body mass index did not substantially alter the findings (table 4.3.2). Analyses for men and women separately revealed similar results.

Discussion

The findings in this population-based study of elderly subjects indicate that an increased common carotid intima-media thickness is significantly associated with atherosclerotic lesions in other sites of the carotid artery, such as the carotid bifurcation and the right internal carotid artery.

Some aspects of the present study need to discussed. The strong rise in prevalence of atherosclerotic lesions in the common carotid artery with increased common carotid intima-media thickness, is at least partly due to the inclusion of these lesions in the measurement of intima-media thickness of the distal common carotid artery. Thus, a considerable proportion of those subjects with a common carotid intima-media thickness

of 1.0 mm or above, very likely have an atherosclerotic lesion in the distal part of the common carotid artery.

It is conceivable that an increased common carotid intima-media thickness does not reflect atherosclerosis as such and that it is not a precursor of atherosclerosis. It may merely be an adaptive response of the vessel wall to changes in shear stress and tensile stress.[15] Furthermore, atherosclerosis is viewed as a disorder which is restricted to the intimal layer of the arterial vessel wall,[16] and ultrasound imaging can not discriminate between the intima layer and the media layer of the vessel wall. However, in several studies, ultrasonographically determined increased intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors.[4,5,6,17,18,19] In addition, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis.[20] Furthermore, we have shown earlier that an increased common carotid intima-media thickness is associated with atherosclerosis in the abdominal aorta[21] and in the arteries of the lower extremities.[22] Prospective findings from the Kuopio Ischemic Heart Disease study indicated that an increase in common carotid intima-media thickness is associated with an increased risk of myocardial infarction.[23] These results support the view that non-invasively assessed intima-media thickness of the distal common carotid artery may be regarded as an indicator of generalized atherosclerosis.

References

1. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high resolution B-mode ultrasonography: Inter- and intra-observer variability. Ultrasound Med Biol 1991;17:225-30.

2. O'Leary DH, Polak JF, Wolfson SK, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. Stroke 1991;22:1155-63.

3. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

4. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

5. Salonen R, Seppänen K, Rauramaa R, et al. Prevalence of carotid atherosclerosis and serum cholesterol levels in Eastern Finland. Arteriosclerosis 1988;8:788-92.

6. Bots ML, Hofman A, Bruyn AM de, et al. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Elderly Study. Arterioscler Thromb 1993;13:64-9.

7. Psaty BM, Furberg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly. Initial findings from the Cardiovascular Health Study. JAMA 1992;268:1287-91.

8. Feussner JR, Matchar DB. When and how to study the carotid arteries. Ann Intern Med 1988;109:805-18.

9. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

10. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

11. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

12. Bots ML, Breslau PJ, Briët E, et al. Cardiovascular determinants of carotid artery disease: The Rotterdam Elderly Study. Hypertension 1992;19:717-20.

13. Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987;15:635-44.

14. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

15. Glagov S, Vito R, Giddens DP, et al. Micro-architecture and composition of artery walls: Relationships to location, diameter and the distribution of mechanical stress. J Hypertension 1992;10 (suppl 6):S101-104.

16. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-134.

17. Haapanen A, Koskenvuo M, Kaprio J, et al. K. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-16.

18. Poli A, Tremoli E, Colombo A, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-261.

19. Bonithon-Kopp C, Scarabin P, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb 1991;11:966-972.

20. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990;81:33-40.

21. Bots ML, Witteman JCM, Grobbee DE. Carotid intima-media wall thickness in elderly women with and without atherosclerosis of the abdominal aorta. Atherosclerosis *(in press)*

22. Bots ML, Hofman A, Grobbee DE. Carotid intima-media wall thickness and lower extremity arterial atherosclerosis. the Rotterdam Study (submitted).

23. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.

4.4 Common carotid intima-media thickness and cardiovascular disease. The Rotterdam Study

Introduction

High-resolution B-mode ultrasonography enables accurate assessment of signs of early and advanced atherosclerotic vessel wall abnormalities, in particular of the carotid artery.[1,2,3] This technique provides for the evaluation of the lumen diameter, the intima-media thickness and the presence and extent of plaques of the carotid artery.[4] Whether increased common carotid intima-media thickness may be used as an indicator of presence of atherosclerotic vessel wall disease in other arterial beds is still a matter of debate. To approach this issue, we studied the association of non-invasively assessed common carotid intima-media thickness and prevalent cardiovascular disease among the first 1,000 participants of the Rotterdam Study.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study of a cohort of approximately 8,000 subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, The Netherlands. The incidence and risk factors of neurogeriatric diseases, locomotor diseases, ophthalmologic diseases and cardiovascular diseases are being studied.[5]. The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants.

Ultrasonography of the carotid arteries

Ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer using a Duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). The Rotterdam Study ultrasound protocol requires a careful search for the lumen-intima interface and the media-adventitia interface on the far wall of the distal common carotid artery (figure 3.1.1).[6,7] When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for both the left and right side. The actual measurements of intima-media thickness are performed off-line. From the video tape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software.[8] With a cursor the interfaces of the distal common carotid artery are marked over a length of

10 mm. The beginning of the dilatation of the distal common carotid artery serves as a reference point for the start of the measurement. For each side, three measurements are averaged, and the mean value ((left + right)/2) is taken as a measure for current wall thickness of the distal common carotid artery, respectively.

Cardiovascular disease and risk factors

Information on current health status, medical history, drug use, and smoking behavior was obtained using a computerized questionnaire, which included a Dutch version of the Rose questionnaire for assessment of prevalent angina pectoris and intermittent claudication.[9] A history of stroke and myocardial infarction was obtained through direct questioning and considered positive when confirmed by a physician. At the research center height and weight were measured and body mass index (kg/m^2) was calculated. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The average of two measurements obtained at one occasion was used in the present analysis. Hypertension was defined as a systolic blood pressure of 160 mmHg or over or a diastolic blood pressure of 90 mmHg or over, or current use of antihypertensive drugs. Total and high density lipoprotein (HDL) cholesterol was determined using an automated enzymatic procedure.[10]

Data analysis

Of the first 1,000 participants, carotid ultrasound scans could not be obtained in 12 subjects, because of technical failure of the equipment. Of 31 subjects measurement of intima-media thickness at either the left or the right common carotid artery could not be performed from the stored images because of poor visualization. For these subjects, the estimate of intima-media thickness for each of these subjects was based on the measurement of the side for which a value was available.

Mean levels of common carotid intima-media thickness were compared between subjects with and without prevalent cardiovascular disease using linear regression analysis. In addition, the associations between cardiovascular disease and common carotid intima-media thickness were assessed using logistic regression analyses, with presence of cardiovascular disease as the dependent variable. The lowest quintile of the common carotid intima-media distribution (< 0.63 mm) served as reference category. The odds ratios are presented with a 95 % confidence interval (CI). Multiple linear regression and multiple logistic regression were used for analyses adjusted for possible confounders such as age, gender and cardiovascular risk factors.

Table 4.4.1 General characteristics of the study population.

		Women	Men
Number		600	388
Age (yrs)		68.8 (8.0)	68.5 (7.6)
Body mass index (kg/m^2)		27.1 (4.2)	25.9 (3.1)
Smoking (%)	Current	20	29
	Former	30	64
Systolic blood pressure (mmHg)		134 (22)	134 (19)
Diastolic blood pressure (mmHg)		70 (11)	72 (10)
Hypertension (%)		33	23
Cholesterol	Total (mmol/l)	7.0 (1.2)	6.4 (1.2)
	HDL (mmol/l)	1.4 (0.3)	1.2 (0.4)
Carotid intima-media thickness (mm)		0.76 (0.19)	0.81 (0.19)

Values are percentages and means with standard deviation in parentheses.

Results

In table 4.4.1 general characteristics of the study population are presented. Mean common carotid intima-media thickness was increased among subjects with cardiovascular disease, i.e., a positive history of either stroke, angina pectoris, myocardial infarction or intermittent claudication, compared to those without cardiovascular disease with a mean difference of 0.07 mm [95 % CI 0.04,0.10] (table 4.4.2). This difference constitutes an increase of nearly 10 %. Similar findings were observed for coronary heart disease. Mean differences in common carotid intima-media thickness across groups with and without stroke, angina pectoris and intermittent claudication were more pronounced in men compared to women (table 4.4.2). Additional adjustment for differences in HDL cholesterol, body mass index, hypertension and smoking, did not substantially alter the magnitude of the findings.

The odds ratio of cardiovascular disease with an 0.1 mm increase in common carotid intima-media thickness was 1.24 [95 % CI 1.08,1.43] for women and 1.19 [95 % CI 1.04,1.36] for men. Additional adjustment for differences in cardiovascular risk factors revealed an adjusted odds ratio of cardiovascular disease for women of 1.22 [95 % CI 1.06,1.41] and for men 1.20 [95 % CI 1.05,1.39]. Among subjects with a common carotid intima-media thickness in the upper quintile (0.89 mm or over), cardiovascular disease was on average 4.65 times more likely than in subjects with an intima-media thickness lower than 0.63 mm (figure 4.4.1).

Table 4.4.2 Intima-media thickness (IMT) of the common carotid artery in mm for subjects with and without prevalent cardiovascular disease.

	Stroke	Angina pectoris	Myocardial infarction	Intermittent claudication	Coronary heart disease*	Cardio-vascular disease†
Women						
Number‡	13	49	30	6	71	85
IMT disease absent	0.76 (0.19)	0.75 (0.19)	0.74 (0.15)	0.76 (0.19)	0.74 (0.15)	0.74 (0.15)
IMT disease present	0.84 (0.13)	0.78 (0.16)	0.91 (0.38)	0.83 (0.12)	0.84 (0.29)	0.84 (0.27)
Age adjusted difference	0.02 [-0.08,0.12]	0.01 [-0.04,0.06]	0.11 [0.04,0.17]	0.03 [-0.11,0.17]	0.07 [0.03,0.11]	0.07 [0.03,0.10]
Men						
Number	12	26	57	6	69	77
IMT disease absent	0.81 (0.19)	0.80 (0.19)	0.80 (0.18)	0.81 (0.19)	0.80 (0.19)	0.79 (0.18)
IMT disease present	0.88 (0.12)	0.88 (0.23)	0.87 (0.22)	0.93 (0.20)	0.87 (0.22)	0.88 (0.22)
Age adjusted difference	0.07 [-0.03,0.17]	0.07 [0.0,0.14]	0.06 [0.01,0.11]	0.11 [-0.06,0.26]	0.06 [0.01,0.11]	0.08 [0.03,0.13]
All						
Number	25	75	87	12	140	162
IMT disease absent	0.78 (0.19)	0.77 (0.19)	0.76 (0.16)	0.78 (0.19)	0.76 (0.16)	0.76 (0.16)
IMT disease present	0.85 (0.13)	0.82 (0.19)	0.88 (0.29)	0.88 (0.16)	0.85 (0.26)	0.86 (0.24)
Adjusted difference§	0.05 [-0.02,0.12]	0.03 [-0.01,0.07]	0.08 [0.04,0.12]	0.07 [-0.04,0.18]	0.07 [0.04,0.11]	0.07 [0.04,0.10]

Values are means with (SD) or with [95 % confidence interval].

* Coronary heart disease defined as angina pectoris according to the Rose questionnaire or a positive history of a myocardial infarction, confirmed by a physician.

† Coronary heart disease, stroke and intermittent claudication combined into one group.

‡ Number of diseased subjects.

§ Adjusted for differences in age and gender.

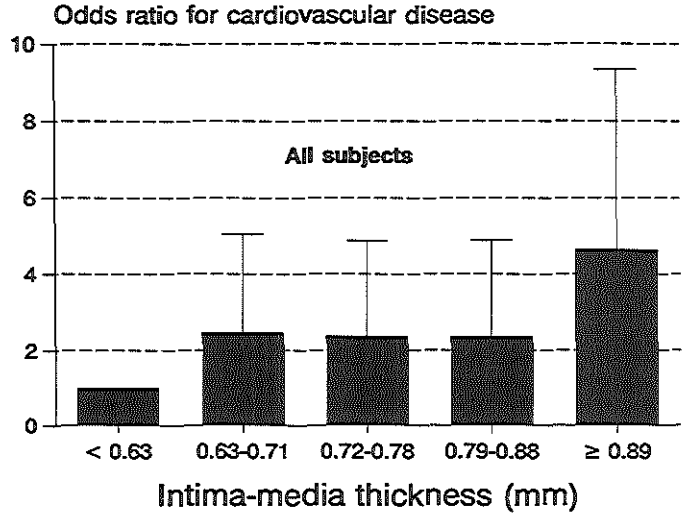


Figure 4.4.1 Odds ratio and 95 % CI of cardiovascular disease with increasing common carotid intima-media thickness (quintiles). Subjects with a common carotid intima-media thickness less than 0.63 mm were used as reference group.

Discussion

In the present study, we provide evidence that among non-hospitalized elderly men and women, increased common carotid intima-media thickness is significantly and positively associated with prevalent cardiovascular disease.

Some aspects of the present study need to be considered. Firstly, the associations between common carotid intima-media thickness and stroke or intermittent claudication were based on a relatively small number of diseased subjects. Consequently, the precision of the estimates is limited. Secondly, findings from some studies have suggested that symptoms, as assessed by the Rose questionnaire, are less likely to be associated with presence of atherosclerotic vessel wall disease among older women compared to symptoms reported by men.[11,12] Provided a true association is present between common carotid intima-media thickness and coronary heart disease and intermittent claudication, this may partly explain the differences in magnitude of the association between men and women. Finally, it is conceivable that increased common carotid intima-media thickness does not represent atherosclerosis, but merely reflects an adaptive response of the vessel wall to changes in shear stress, tensile stress and blood flow.[13] Also, atherosclerosis is viewed as a disorder which is restricted to the intima layer of the

arterial vessel wall,[14] and ultrasound imaging can not discriminate between the intima layer and the media layer of vessel wall. The present population-based study among elderly subjects shows a significant association between increased common carotid intima-media thickness and prevalent cardiovascular disease. This finding is consistent with results from other studies[4,6,8,15,16,17,18,19,20] and may indicate that increased intima-media thickness of the distal common carotid artery reflects atherosclerotic vessel wall abnormalities in other arteries. Whether increased common carotid intima-media thickness predicts the occurrence of cardiovascular disease can not be answered with these cross-sectionally obtained data. As for now, data on this issue are limited. Salonen and co-workers have demonstrated the value of increased common carotid intima-media thickness in predicting myocardial infarction.[21] Results from several ongoing population-based studies, for which at present the follow-up time has been too short to be able to assess the value of increased common carotid intima-media thickness as a predictor of cardiovascular disease, are urgently awaited.

Most studies on carotid ultrasound were either performed among men only or have presented results that were adjusted for gender. Data on the association between common carotid intima-media thickness and cardiovascular disease for women are very limited, if any are present. An important finding from our study is that among women aged 55 years or over, the direction of the association between common carotid intima-media thickness and stroke, angina pectoris, myocardial infarction and intermittent claudication, is similar to that found in men.

In conclusion, this population-based study among elderly subjects provides evidence that an ultrasonographically assessed increase in intima-media thickness of the common carotid artery is associated with prevalent symptomatic cardiovascular disease. An increased common carotid intima-media thickness may reflect atherosclerotic vessel wall disease in other arteries.

References

1. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high resolution B-mode ultrasonography: Inter- and intra-observer variability. Ultrasound Med Biol 1991;17:225-30.

2. O'Leary DH, Polak JF, Wolfson SK, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. Stroke 1991;22:1155-63.

3. Riley WA, Barnes RW, Applegate WB, et al. Reproducibility of noninvasive ultrasonic measurement of carotid atherosclerosis. The Asymptomatic Carotid Artery Plaque Study. Stroke 1992;23:1062-8.

4. Wikstrand J, Wiklund O. Frontiers in cardiovascular science. Quantitative measurement of atherosclerotic manifestations in humans. Arterioscler Thromb 1992;12:114-9.

5. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

6. Bots ML, Hofman A, Bruyn AM de, et al. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Elderly Study. Arterioscler Thromb 1993;13:64-9.

7. Bots ML, Meurs JCHM van, Grobbee DE. Assessment of early atherosclerosis: A new perspective. J Drug Res 1991;16;150-4.

8. Bots ML, VanSwieten JC, Breteler MBB, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. Lancet 1993;341:1232-7.

9. Rose GA, Blackburn H, Gillum RF, et al. Cardiovascular survey methods. World Health Organisation, Geneva 1982.

10. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

11. LaCroix AZ, Guralnik JM, Curb J, et al. Chest pain and coronary heart disease mortality among older men and women in three communities. Circulation 1990;81:437-46.

12. Harris RB, Weissfeld LA. Gender differences in the reliability of reporting symptoms of angina pectoris. J Clin Epidemiol 1991;44:1071-8.

13. Glagov S, Vito R, Giddens DP, et al. Micro-architecture and composition of artery walls: Relationships to location, diameter and the distribution of mechanical stress. J Hypertension 1992;10 (suppl 6):S101-4.

14. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

15. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

16. Poli A, Tremoli E, Colombo A, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

17. Bonithon-Kopp C, Scarabin P, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb 1991;11:966-72.

18. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990;81:33-40.

19. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: A population-based ultrasonography study in eastern Finnish men. J Intern Med 1991;229:225-31.

20. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. Stroke 1992;23:1752-60.

21. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.

Chapter 5

Determinants of common carotid intima-media thickness

5.1 Established cardiovascular risk factors

5.2 Isolated systolic hypertension

5.3 Low diastolic blood pressure

5.1 Cardiovascular determinants of common carotid intima-media thickness. The Rotterdam Study

Introduction

The occurrence of a cardiovascular event is considered to be the consequence of an interplay between thrombogenic factors and progressive atherosclerotic vessel wall abnormalities. Recently, it has been shown that with high-resolution B-mode ultrasonography signs of early atherosclerotic vessel wall changes can be assessed non-invasively in an effective and accurate way. In particular, the carotid artery has been studied extensively.[1,2,3] This technique provides for the evaluation of the lumen diameter, the intima-media thickness and the presence and extent of plaques of the carotid artery. Thus, high resolution B-mode ultrasonography of the carotid arteries may be used to gain further insight into the process of atherosclerosis, its 'natural' history and factors that contribute to its development.[4]

Most of the studies on ultrasonographically assessed carotid atherosclerosis have been performed either among hospital-based populations[5,6,7,8,9,10,11,12,13] or among groups of subjects, who were selected based on presence or absence of a prevalent condition.[14,15,16,17,18,19,20,21,22,23,24,25,26] There is, however, a growing number of studies that has been performed in populations at large.[27,28,29,30,31,32,33,34] Yet, little data is available on the association between cardiovascular risk indicators and common carotid intima-media thickness in non-hospitalized elderly men and women.[35]

We report on the association of selected cardiovascular risk indicators and non-invasively assessed common carotid intima-media thickness among the first 1,000 participants of the Rotterdam Study.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study of a cohort of subjects, aged 55 years or over, living in the suburb of Ommoord in Rotterdam, The Netherlands. The cohort will eventually comprise over 8,000 subjects. The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere.[36] In brief, the objective of the Rotterdam Study is to clarify determinants of chronic disabling diseases in an ageing population. Incidence and risk factors of neurogeriatric diseases, locomotor diseases,

ophthalmologic diseases and cardiovascular diseases are being studied. The study comprises an extensive home interview, followed by two visits at the Rotterdam Study research center for clinical examinations. The present findings come from a cross-sectional analysis of data obtained from the first 1,000 participants of the Rotterdam Study. The participation rate at the time of the present analysis was 72 %.

Ultrasonography of the carotid arteries

Ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer using a Duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (figure 3.1.1).[37] The distance of the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.[4] Studies have indicated that the far wall intima-media thickness as seen with ultrasound, reflects the true anatomical intima-media layer.[37,38]

According to the Rotterdam Study ultrasound protocol, a careful search is performed for the lumen-intima interface and the media-adventitia interface of the far wall of the distal common carotid artery.[39] When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for both sides. Subsequently, the common carotid artery is on-line evaluated for the presence (yes/no) of atherosclerotic lesions, defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. The initial ultrasound scan and all the frozen images are recorded on video tape. The actual measurement of intima-media thickness are performed off-line. From the video tape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software. This procedure has been described in detail previously.[23,38] In short, the interfaces of the distal common carotid artery are marked over a length of 10 mm with a cursor. The beginning of the dilatation of the distal common carotid artery serves as a reference point for the start of the measurement. This method permits the determination of mean values as well as maximal values for intima-media thickness. The average of the intima-media thickness of each of the three frozen images was calculated. For each subject a mean intima-media thickness [(left + right)/2] was taken as a measure for current wall thickness of the distal common carotid artery, respectively. With respect to focal lesions the presence or absence of calcifications and acoustic shadowing was noted.

Cardiovascular risk indicators

In the Rotterdam Study, information on current health status, medical history, current drug use, and smoking behavior was obtained using a computerized questionnaire, which includes a Dutch version of the Rose questionnaire for assessment of prevalent angina pectoris and intermittent claudication.[40] A history of stroke and myocardial infarction was obtained through direct questioning and considered positive when confirmed by a treating physician.

With respect to smoking behavior, subjects were categorized in groups of current smokers, former smokers and those who never smoked. Additionally, currently smoking subjects were divided in subgroups according to their daily cigarette use of 1-4 cigarettes, 5-9 cigarettes, 10-14 cigarettes, 15-19 cigarettes, and 20 cigarettes or over. Finally, cigarette smoking was expressed in pack-years, calculated as the average daily number of cigarettes smoked divided by 20, times the reported number of years of smoking.

During two visits at the research center several cardiovascular risk indicators were measured. Height and weight were measured and body mass index (kg/m^2) was calculated. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the present analysis. Hypertension was defined as a systolic blood pressure of 160 mmHg or over or a diastolic blood pressure of 90 mmHg or over or currently using antihypertensive drugs for the indication hypertension.[41]

A venipuncture was performed, applying minimal stasis, using a 21 gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Serum total cholesterol was determined using an automated enzymatic procedure.[42] High density lipoprotein (HDL) cholesterol was measured similarly, after precipitation of the non-HDL fraction with phosphotungstate-magnesium.

Data analysis

The present analysis is based on findings in the first 1,000 participants of the Rotterdam Study. Carotid ultrasound scans could not be obtained in 12 subjects, because of technical failure of the equipment. Of 31 subjects measurement of intima-media thickness at either the left or the right common carotid artery could not be performed from the stored images because of poor visualization. The estimate of intima-media thickness for each of these subjects was based on the measurement of the side for which a value was available.

The association between common carotid intima-media thickness and several continuously distributed cardiovascular risk factors was evaluated using linear regression

The association between common carotid intima-media thickness and several continuously distributed cardiovascular risk factors was evaluated using linear regression analysis. Analyses of trends for categorical vairables were performed with linear regression analysis. Multiple linear regression was used for analyses adjusted for age. The associations are presented with a 95 % confidence interval (CI).

Results are presented for men and women separately. In addition, results are given for subjects with and without a positive history of a major cardiovascular disorder, i.e., a positive history of stroke, angina pectoris, myocardial infarction or intermittent claudication.

Results

Baseline characteristics of the first 1,000 participants of the Rotterdam Study are presented in table 5.1.1. Mean levels of body mass index, total cholesterol, and HDL cholesterol, as well as the prevalence of hypertension, were higher among women as compared to men. Symptomatic cardiovascular disease, and current and former smokers were more common among men as compared to women.

Table 5.1.1 General characteristics of the study population.

		Women	Men
Number		600	388
Age (yrs)		68.8 (8.0)	68.5 (7.6)
Body mass index (kg/m^2)		27.1 (4.2)	25.9 (3.1)
Current smoking	Current (%)	20	29
	Former (%)	30	64
Systolic blood pressure (mmHg)		134 (22)	134 (19)
Diastolic blood pressure (mmHg)		70 (11)	72 (10)
Hypertension (%)		33	23
Serum total cholesterol (mmol/l)		7.0 (1.2)	6.4 (1.2)
Serum HDL cholesterol (mmol/l)		1.4 (0.3)	1.2 (0.4)
Prevalent cardiovascular disease (%)		15	21
Angina pectoris		8	7
Myocardial infarction		5	15
Stroke		2	3
Intermittent claudication		1	2
Carotid intima-media thickness (mm)		0.76 (0.19)	0.81 (0.19)

Age and gender

Age was significantly and positively associated with common carotid intima-media thickness. For women intima-media thickness increased with 0.010 mm per year [95 % CI 0.008,0.011], whereas for men this was 0.008 mm per year [95 % CI 0.005,0.011]. Mean common carotid intima-media thickness was increased in men as compared to women, with an age adjusted difference of 0.05 mm [95 % CI 0.03,0.08].

Body mass index

Only for men, body mass index was associated with common carotid intima-media thickness: an increase of 1 kg/m^2 in body mass index was associated with an age-adjusted increase in common carotid intima-media thickness of 0.007 mm [95 % CI 0.001,0.013]. No clear association was observed for women: -0.001 mm [95 % CI -0.004,0.002] (figure 5.1.1, top). Similar findings were observed in subjects with and without prevalent cardiovascular disease (table 5.1.2).

Serum cholesterol

No association was observed between serum total cholesterol level and common carotid intima-media thickness (figure 5.1.1, middle). An increase of 1 mmol/l in serum total cholesterol level was associated with a non-significant age-adjusted change in common carotid intima-media thickness of -0.004 mm [95 % CI -0.016, 0.008] and 0.005 mm [95 % CI -0.011,0.021] for women and men, respectively.

HDL cholesterol was inversely related to common carotid intima-media thickness (figure 5.1.1, bottom). For women, a decrease of 1 mmol/l in serum HDL cholesterol level was associated with am increase in common carotid intima-media thickness of 0.033 mm [95 % CI -0.008,0.075], whereas for men, an increase in intima-media thickness of 0.048 mm [95 % CI 0.002,0.094] was found.

Analyses among subjects free of cardiovascular disease showed similar results with respect to direction and magnitude of the associations. The magnitude of the inverse association between HDL cholesterol and common carotid intima-media thickness was slightly stronger among subjects with prevalent cardiovascular disease as compared to subjects without cardiovascular disease (table 5.1.2). Due to the small number of subjects with prevalent cardiovascular disease, however, the precision of the estimate obtained for these subjects is limited.

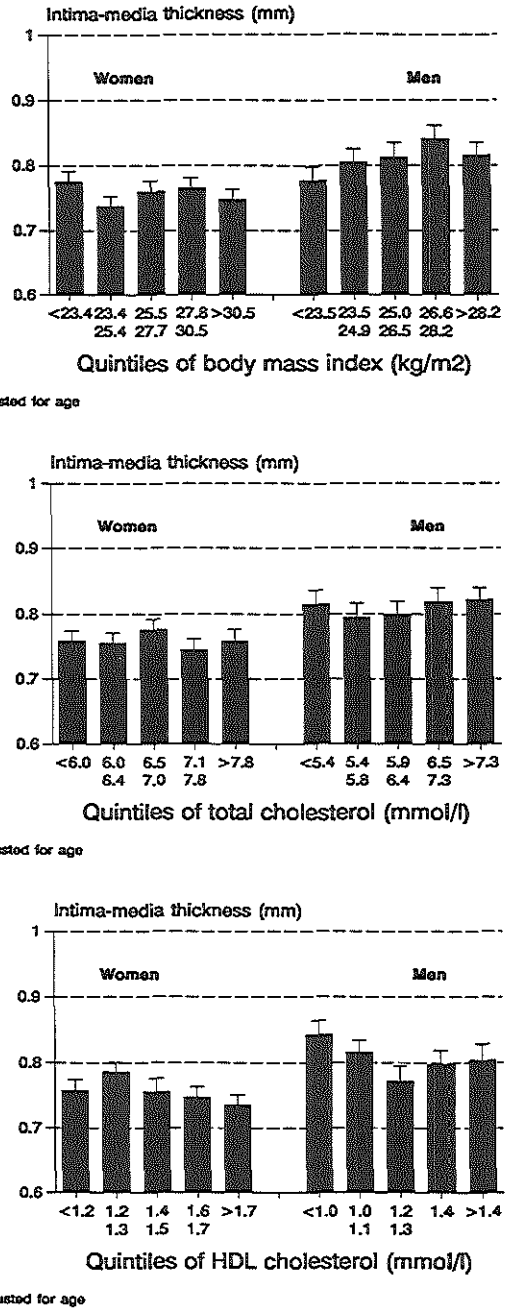


Figure 5.1.1 Mean common carotid intima-media thickness (SE) across groups with increasing levels of body mass index (top), total cholesterol (middle) and HDL cholesterol (bottom), for women and men separately.

Table 5.1.2 The association between common carotid intima-media thickness and cardiovascular risk factors. Results are presented as age-adjusted coefficients of linear regression.

	Subjects free of cardiovascular disease*	Subjects with cardiovascular disease*
Women		
Number	515	85
Age (years)	0.008 [0.007,0.009]	0.012 [0.005,0.019]
Serum total cholesterol (mmol/l)	0.004 [-0.006,0.014]	-0.024 [-0.062,0.014]
Serum HDL cholesterol (mmol/l)	-0.028 [-0.063,0.007]	-0.073 [-0.273,0.130]
Body mass index (kg/m^2)	0.001 [-0.003,0.003]	-0.006 [-0.017,0.005]
Systolic blood pressure (per 10 mmHg)†	0.016 [0.009,0.0023]	0.018 [-0.010,0.038]
Diastolic blood pressure (per 10 mmHg)†	0.012 [-0.002,0.026]	-0.010 [-0.056,0.035]
Men		
Number	311	77
Age (years)	0.007 [0.005,0.010]	0.008 [0.001,0.014]
Serum total cholesterol (mmol/l)	0.007 [-0.011,0.025]	-0.004 [-0.045,0.037]
Serum HDL cholesterol (mmol/l)	-0.033 [-0.081,0.015]	-0.167 [-0.367,0.043]
Body mass index (kg/m^2)	0.007 [0.001,0.013]	0.019 [0.004,0.034]
Systolic blood pressure (per 10 mmHg)†	0.022 [0.011,0.033]	0.044 [0.008,0.080]
Diastolic blood pressure (per 10 mmHg)†	0.019 [-0.002,0.040]	0.100 [0.036,0.164]

Results are expressed as a change in common carotid intima-media thickness in mm [95 % confidence interval] with an increase of one unit of the level of the cardiovascular risk factor.

* Refers to subjects without and with a positive history of stroke, angina pectoris, myocardial infarction or intermittent claudication.

† Women and men with and without cardiovascular disease and not using cardiovascular drugs (women n=318/27) and men n=224/16).

Blood pressure

Systolic and diastolic blood pressure levels were positively associated with common carotid intima-media thickness in both men and women. An increase of 10 mmHg in systolic blood pressure was significantly associated with a mean increase in intima-media thickness of 0.014 mm [95 % CI 0.007,0.021] in women and with an increase of 0.022 mm [95 % CI 0.013,0.032] in men. An increase of 10 mmHg of diastolic blood pressure, was associated with a non-significant increase of 0.004 [95 % CI -0.009,0.017] among women, whereas for men a significant increase of 0.020 [95 % CI 0.002,0.038] was observed. When subjects currently using blood pressure lowering drugs were excluded from the

analysis, the magnitude of the associations between systolic blood pressure and common carotid intima-media thickness did not change substantially. With respect to diastolic blood pressure, the magnitude of associations became stronger after exclusion of these subjects: for women 0.010 [95 % CI -0.003, 0.023], and for men 0.025 mm [95 % CI 0.005,0.045].

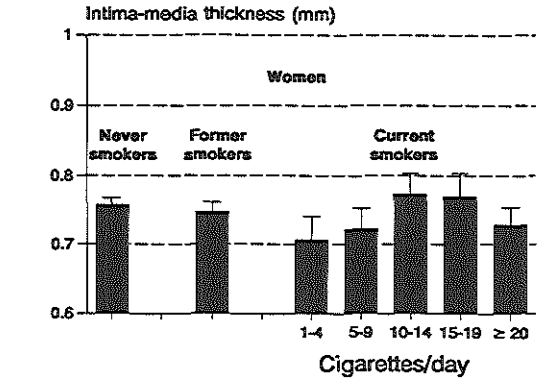
The magnitude of the association between systolic blood pressure and common carotid intima-media thickness was stronger among subjects with prevalent cardiovascular disease, in particular among men. For diastolic blood pressure contrasting results across groups of prevalent cardiovascular disease were found (table 5.1.2).

The mean common carotid intima-media thickness of subjects with hypertension was increased compared to that of subjects without hypertension with mean differences of 0.051 mm [95 % CI 0.020,0.082] and 0.072 mm [95 % CI 0.028,0.116] for women and men, respectively. A more detailed analysis of the associations between intima-media thickness and high systolic or low diastolic blood pressure may be found in chapter 5.2 and 5.3, respectively

Smoking

In women, mean common carotid intima-media thickness did not differ significantly across groups of current smokers and never smokers with a difference of 0.019 mm [95 % CI -0.017,0.055]. Similar findings were found for former smokers compared to never smokers. Among men, however, current and former smoking was significantly related to common carotid intima-media thickness. Compared to the mean common carotid intima-media thickness of subjects who had never smoked, mean intima-media thickness of former smokers, and of current smokers was significantly increased, with a difference of 0.097 mm [95 % CI 0.029,0.165] and 0.098 mm [95 % CI 0.032,0.166], respectively. Analyses in tertiles of serum total cholesterol, revealed no signifcant interaction between smoking and total cholesterol.

In figure 5.1.2, top and middle, results on the association between common carotid intima-media thickness and various categories of cigarette smoking are presented for women and men, respectively. No dose-response relationship was observed among current smokers in either sex. When smoking was classified on the basis of pack-years of cigarette smoking, however, a significant gradual increase in common carotid intima-media thickness with increasing levels of pack-years was observed in men, but not in women (figure 5.1.2, bottom).



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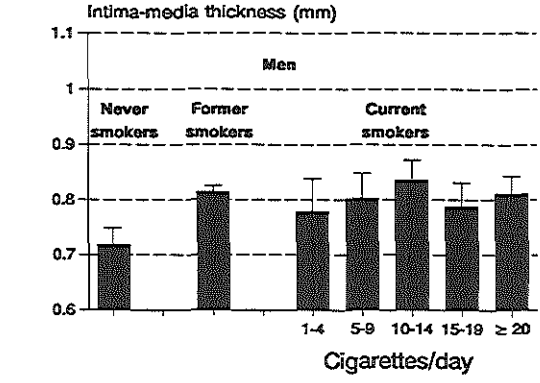

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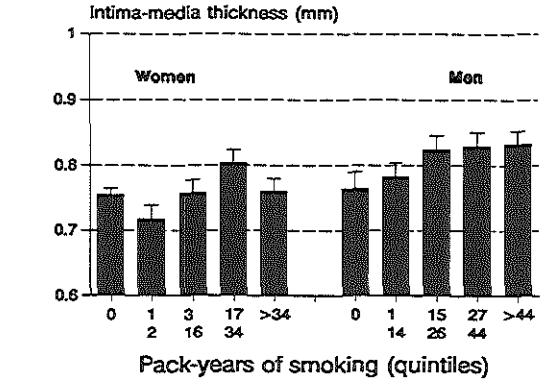


Adjusted for age

Figure 5.1.2 *Mean common carotid intima-media thickness (SE) across groups of cigarette smoking for women (top) and men (middle) and with increasing levels of pack-years of cigarette smoking (bottom).*

Discussion

We provide evidence that among non-hospitalized older men and women, common carotid intima-media thickness is significantly and positively associated with age, systolic blood pressure, and hypertension. An increase in body mass index and in pack-years of cigarette smoking, as well as a decrease of HDL cholesterol are significantly associated with an increase in common carotid intima-media thickness in older men. The direction of the associations is similar in both women and men. The associations between cardiovascular risk factors and common carotid intima-media thickness were slightly stronger among subjects with prevalent cardiovascular disease compared to subjects free of cardiovascular disease. With respect to the level of serum total cholesterol no association with common carotid intima-media thickness was observed for either men or women.

Before these results can be accepted, some aspects of this study need to be considered. Comparison of our findings with those from other studies on ultrasonographically assessed (common) carotid intima-media thickness and cardiovascular risk factors should be done with care, since considerable differences exist across studies that may be of influence on the reported associations. Firstly, most previous ultrasound studies have been performed in hospitalized populations,[5,6,7,8,9,10,11,12,13,14,15] or in selected groups of subjects.[16,17,18,19,20,23,24] Our findings and those from others,[10,11] indicate that among subjects with prevalent cardiovascular disease, associations between carotid intima-media thickness and cardiovascular risk factors are generally stronger compared to those observed among subjects free of cardiovascular disease. Secondly, differences in age-range of populations across studies may contribute to the varying results. Due to the cross-sectional design of studies, in particular among elderly subjects, selective survival may have influenced the associations, i.e., the majority of subjects with elevated levels of certain risk factors and those whose arteries are susceptible to these factors in the development of atherosclerosis may have died already as a consequence of atherosclerosis. Consequently, subjects whose arteries are less susceptible to elevated levels of these risk factors may be overrepresented in the studied population. Finally, differences in the assessment and definition of carotid atherosclerosis may contribute to differences in results across studies, because the association between some risk factors and carotid atherosclerosis may be different for several sites of the carotid artery.[13,33]

Increased common carotid intima-media thickness may not necessarily represent atherosclerosis in itself. It may merely reflect an adaptive response of the vessel wall to changes in shear stress, tensile stress and blood flow.[43] Furthermore, atherosclerosis is viewed as a disorder which is restricted to the intima layer of the arterial vessel wall[44], and ultrasound imaging can not discriminate between the intima layer and the media

layer of vessel wall. The present population-based study among subjects aged 55 years or over, indicates a clear association between common carotid intima-media thickness and cardiovascular risk factors, in particular in men. Similarly, in other studies, either population-based or performed among a selected group of subjects, ultrasonographically determined increased intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors.[16,17,23,24,32,33,33] In addition, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis.[31] These results, including our findings, support the view that non-invasively assessed intima-media thickness of the common carotid artery may be regarded as an indicator of atherosclerosis.

Results from the majority of studies on ultrasonographically assessed carotid atherosclerosis have shown positive associations for age, systolic blood pressure, hypertension, serum total cholesterol, and pack-years of cigarette smoking and an inverse relation for HDL cholesterol (table 5.1.3). Apart from age, systolic blood pressure appears to be a strong determinant of common carotid intima-media thickness. Our findings among men are in accordance with those from other investigations, despite the considerable differences across studies. In the present study, however, no association was observed between common carotid intima-media thickness and total cholesterol. This finding is consistent with an earlier report of the Rotterdam Study, in which no association was found between serum total cholesterol and the presence of a hemodynamically significant stenosis in the right carotid artery.[45] Selective mortality and a decrease in relative importance of serum cholesterol with age[46] may in part explain this finding. However, findings from the Cardiovascular Health Study among subjects aged 65 years or over, did show a positive association between common carotid intima-media thickness and total cholesterol levels. Thus the contrasting observation remains unexplained.

Most studies on the association between cardiovascular risk factors and (common) carotid intima-media thickness were either performed among men only or have presented results that were adjusted for gender. Data on the association between common carotid intima-media thickness and cardiovascular risk factors for women are very limited. Psaty and co-workers reported positive associations between common carotid intima-media thickness and systolic blood pressure, that were similar for men and women.[24] Bonithon-Kopp and co-workers, in a study among 517 French women, aged 45 to 54 years, reported positive associations for systolic (or diastolic) blood pressure, smoking, LDL cholesterol and an inverse relation with HDL cholesterol. In their study, carotid atherosclerosis was categorized according to intima-media thickness measurement and presence of plaques (tables 5.1.3 and 5.1.4).[33] The present study demonstrates that the direction

Table 5.1.3 Characteristics and results from studies on the association of cardiovascular risk factors and carotid atherosclerosis, based on ultrasonographically assessed carotid intima-media thickness (IMT).

First author	Type	Prevalent condition	Number (M/F)	Age	D †	Association present‡	Association absent§
Carotid atherosclerosis: IMT as a continuous variable from measurements at the common carotid only							
Bots[23]	S	Asymptomatic, ISH	33/66¶	≥ 55	a	ISH	
Haapanen[32]	P	None	88/10*	31-77	b	Current smoking	
Markussis[26]	S	Hypopitiuitarism	31/42¶	26-75	c	Age, SBP, smoking (pack-years), hypopitiuitarism	LDL, HDL, glucose, insulin, fibrinogen
O'Leary[33]	P	None	2255/2946	≥ 65	d	Age, male, SBP, HT, LDL, HDL, TG, smoking (current, former), CHD, stroke, LVH, diabetes, glucose, insulin, left ventricular mass	DBP, Obesity
Poli[17]	S	Hypercholesterolemia	38/29¶	NR	e	Age, total cholesterol	
Psaty[24]	S	Asymptomatic, ISH	867/1322¶	≥ 65	d	ISH, SBP, DBP (inverse)	
Salonen[30]	P	None	1224 men	42-60	f	Age, PP, SBP, LDL, CHD, diabetes, pack-years	DBP, HDL, BMI, fibrinogen
Tell[13]	H	Cerebrovascular symptoms	775/806	≥ 20	g	Age, HT, smoking (former, current)	Male, diabetes, race
Wendelhag[16]	S	Hypercholesterolemia	60/42¶	20-72	h	Age, total cholesterol, LDL, apoB, smoking (pack-years)	Pack-years among controls
Carotid atherosclerosis: IMT as an average or summary score from measurements obtained at several sites of the carotid artery							
Crouse[11]	H	Coronary stenosis (y/n)	182/194	NR	i	Age, HT, HDL, uric acid, smoking (pack-years), LVH	Total cholesterol, BMI
Dempsey[9]	H	Referred for any reason	790 NR	17-94	j	Age, HT, smoking (pack-years)	Diabetes

Handa[8]	H	Cerebrovascular disease	164/68	24-74	i	Age, male, total cholesterol, diabetes, stroke	Ht, smoking, obesity
Kawamori[25]	S	Diabetes (y/n)	170/125	20-89	k	Age, LDL, smoking (pack-years), diabetes	HDL, HT, SBP, DBP, HT, BMI
Rubens[10]	H	Coronary stenosis (y/n)	183/199	NR	i	CHD, age, HT, HDL, LVH, smoking, uric acid, diabetes, race, HT	Gender, LDL, obesity, LVH
Ruy[22]	S	Hypercholesterolemia	47 men	..	l	TG response, smoking	LDL, HDL, BMI
Carotid atherosclerosis: based on cutoff points from IMT measurements at several sites of the carotid artery							
Bonithon[33]	P	Asymptomatic	517 women	45-54	m	Age, SBP, DBP, total cholesterol, LDL, HDL, current smoking, TG, apolipoprotein B	TG, BMI, fibrinogen, apo A-I
Heiss[27], Wu[28]	P	Asymptomatic	772‖	45-64	n	Age, SBP, DBP, HT, LDL, HDL, TG, BMI, smoking (current, former pack-years), fibrinogen	Factor VII activity, factor VIII activity, antithrombin III
Prati[34]	P	None	630/718	18-99	o	Age, male, SBP, HDL, smoking (pack-years), alcohol use	DBP, LDL, fibrinogen, diabetes, cholesterol, Lp(a)

Abbreviations: BMI = body mass index; CHD = coronary heart disease; DBP = diastolic blood pressure; HDL = High density lipoprotein cholesterol; ISH = isolated systolic hypertension; HT = hypertension; LDL = Low density lipoprotein cholesterol; LVH = left ventricular hypertrophy; M/F = male/female; NR = not reported; PP; pulse pressure; SBP = systolic blood pressure; TG = triglyceride

* H = Hospital-based study; P = Population-based study; S = Otherwise selected populations.
† Definition described in table 5.1.4.
‡ Refers to significant positive associations or, with respect to HDL cholesterol, a significant inverse association in a multivariate analysis.
§ Refers to no significant associations in a multivariate analysis.
‖ Case-control study among subjects with and without carotid atherosclerosis.
¶ Case-control study among subjects with and without prevalent condition.
# Case-control study among twins discordant for smoking.

Table 5.1.4. Definitions used in studies presented in table 5.1.3. to characterize carotid atherosclerosis

a.	Mean of left and right carotid artery. For each side, an average of three measurements of intima-media thickness of the 10 mm of the far wall of the distal common carotid artery.
b.	Measurement of the intima-media thickness at the thickest site at the far wall of both common carotid arteries.
c.	Mean of left and right carotid artery. For each side, an average of three (point) measurements of intima-media thickness of the 10 mm of the mid part of the far wall of the common carotid artery.
d.	Mean of left and right carotid artery. For each side, an average of three measurements of intima-media thickness of the 10 mm of the near and far wall of the common carotid artery. Maximum wall thickness was considered only.
e.	Mean of left and right carotid artery. For each side, an average of intima-media thickness of the 10 mm of the far wall of the distal common carotid artery.
f.	Average of six measurements: three measurements at the site showing the greatest intima-media thickness at the far wall of both the left and right common carotid artery.
g.	A mean plaque score based on measurements of maximum plaque thickness performed at near or far wall of the distal common carotid arteries.
h	Only the right carotid artery. An average of three measurements of intima-media thickness of the 10 mm of the far wall of the distal common carotid artery.
i.	Average of measurements of both common and internal carotid arteries. For each site, summation of maximal intima-media thickness, at near and far wall, at four well defined sites.
j.	The average of measurements of maximum plaque thickness of internal and common carotid arteries of both sides.
k.	Mean of left and right carotid artery. Greatest value of the average of measurements at the thickest site in the common carotid artery, and two other sites (1.0 cm distal and proximal of the site showing the maximum intima-media thickness), obtained from the far wall of both carotid arteries.
l.	Average of measurements of both carotid arteries. For each site, summation of maximal intima-media thickness, at near and far wall, at three well-defined sites.
m.	Classification in three categories; normal (maximum far wall common carotid intima-media thickness < 0.75 mm, and no plaques), thickening (maximum far wall common carotid intima-media thickness > 0.75 mm, and no plaques), and plaque (echostructure encroaching into the common carotid lumen, or bifurcation intima-media thickness ≥ 1.75 mm).
n.	At both near and far wall of 1.0 cm, measurements of maximum intima-media thickness of the internal and common carotid artery and the carotid bifurcation. For cases the values were above the 90th centile of the distribution, for control subjects below the 75th centile.
o.	Classification in four categories; normal, thickening (far wall carotid intima-media thickness > 1.0 mm), no stenotic plaques, stenotic plaque (> 40 % stenosis). Subjects classified to the most severe lesions.

of the associations between most of the cardiovascular risk factors and common carotid intima-media thickness among subjects aged 55 years or over, is similar to that of elderly men. However, the magnitude of the observed associations differs across men and women. The difference between men and women in the associations between common carotid intima-media thickness and various risk factors is intriguing. Overall, the extent of carotid atherosclerosis as indicated by intima-media thickness appears to be less pronounced in women than in men; women have thinner arterial walls.[10,11,13,24] It may be hypothesized that a certain degree of common carotid intima-media thickness may indicate the process of atherosclerosis, whereas a lower level of common carotid intima-media thickness may reflect a vessel wall thickness that is predominantly determined by non-atherosclerotic processes. Alternatively, it may be more difficult to assess the

contribution of several risk factors on the thickness of the arterial wall in subjects with thinner walls. Further studies, however, are needed to confirm these notions.

In conclusion, this population-based study among elderly subjects provides evidence that an ultrasonographically assessed increase in intima-media thickness of the common carotid artery is associated with elevated levels of most of the established cardiovascular risk factors. These associations are most pronounced in men.

References

1. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high resolution B-mode ultrasonography: Inter- and intra-observer variability. Ultrasound Med Biol 1991;17:225-30.
2. O'Leary DH, Polak JF, Wolfson SK, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. Stroke 1991;22:1155-63.
3. Riley WA, Barnes RW, Applegate WB, et al. Reproducibility of noninvasive ultrasonic measurement of carotid atherosclerosis. The Asymptomatic Carotid Artery Plaque Study. Stroke 1992;23:1062-8.
4. Wikstrand J, Wiklund O. Frontiers in cardiovascular science. Quantitative measurement of atherosclerotic manifestations in humans. Arterioscler Thromb 1992;12:114-9.
5. Craven TE, Ryu JE, Espeland MA, et al. Evaluation of the associations between carotid atherosclerosis and coronary artery stenosis. A case-control study. Circulation 1990;82:1230-42.
6. Tanaka H, Nishino M, Ishida M, et al. Progression of carotid atherosclerosis in Japanese patients with coronary artery disease. Stroke, 1992;23:946-51.
7. Wofford JL, Kahl FR, Howard GR, et al. Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. Arterioscler Thromb 1991;11:1786-94.
8. Handa N, Matsumoto M, Meada H, et al. Ultrasonic evaluation of early carotid atherosclerosis. Stroke 1990:21:1567-72.
9. Dempsey RJ, Moore RW. Amount of smoking independently predicts carotid artery atherosclerosis severity. Stroke 1992;23:693-6.
10. Rubens J, Espeland MA, Ryu J, et al. Individual variation in susceptibility to extracranial carotid atherosclerosis. Arteriosclerosis 1988;8:389-97.
11. Crouse JR, Toole JF, McKinney WM, et al. Risk factors for extracranial carotid artery atherosclerosis. Stroke 19878;18:990-6.
12. Tell GS, Howard GH, McKinney WM. Cigarette smoking cessation and extracranial carotid atherosclerosis. JAMA 1989;261:1178-80.
13. Tell GS, Howard GH, McKinney WM. Risk factors for site specific extracranial carotid artery plaque distribution as measured by B-mode ultrasound. J Clin Epidemiol 1989;42:551-9.
14. Sutton KC, Wolfson SK, Kuller LH. Carotid and lower extremity arterial disease in elderly adults with isolated systolic hypertension. Stroke 1987;18:817-22.
15. Megnien JL, Sene V, Jeannin S, et al. Coronary calcification and its relation to extracoronary atherosclerosis in asymptomatic hypercholesterolemic men. Circulation, 1992;85:1799-1807.

16. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

17. Poli A, Tremoli E, Colombo A, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

18. Persson J, Stavenow, Wikstrand J, et al. Noninvasive quantification of atherosclerotic lesions. Reproducibility of ultrasonographic measurement of arterial wall thickness and plaque size. Arterioscler Thromb 1992;12:261-6.

19. Giral P, Pithois-Merli I, Filitti V, et al. Risk factors and early extracoronary atherosclerotic plaques detected by three-site ultrasound imaging in hypercholesterolemic men. Arch Intern Med 1991;151:950-6.

20. Giral P, Filitti V, Levenson J, et al. Relation of risk factors for cardiovascular disease to early atherosclerosis detected by ultrasonography in middle-aged normotensive hypercholesterolemic men. Atherosclerosis 1990;85:151-9.

21. Insull W, Bond MG, Wilmoth S, et al. Ultrasound lesions of the carotid artery and risk factors in men. In: Pathobiology of the human atherosclerotic plaque. Glagov S, Newman WP, Schaffer, eds. New York, Springerverlag, 1990:663-70.

22. Ryu J, Howard G, Craven TE, et al. Postprandial triglyceridemia and carotid atherosclerosis in middle-aged subjects. Stroke 1992;23:823-8.

23. Bots ML, Hofman A, Bruyn AM de, et al. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Elderly Study. Arterioscler Thromb 1993;13:64-9.

24. Psaty BM, Furberg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly. Initial findings from the Cardiovascular Health Study. JAMA 1992;268:1287-91.

25. Kawamori R, Yamasaki Y, Matsushima H, et al. Prevalence of carotid atherosclerosis in diabetic patients. Diabetes Care 1992;15:1290-4.

26. Markussis V, Beshyah SA, Fisher C, et al. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. Lancet 1992;ii:1188-92.

27. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

28. Wu KK, Folsom AR, Heiss G, et al. Association of coagulation factors and inhibitors with carotid artery atherosclerosis. Early results of the Atherosclerosis Risk in Communities (ARIC) study. Ann Epidemiol 1992;2:471-80.

29. Salonen R, Seppänen K, Rauramaa R, et al. Prevalence of carotid atherosclerosis and serum cholesterol levels in Eastern Finland. Arteriosclerosis 1988;8:788-92.

30. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: A population-based ultrasonography study in eastern Finnish men. J Intern Med 1991;229:225-31.

31. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990:81:33-40.

32. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

33. Bonithon-Kopp C, Scarabin P, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb 1991;11:966-72.

34. Prati P, Vanuzzo D, Casaroli M, et al. Prevalence and determinants of carotid atherosclerosis in a general population. Stroke 1992;23:1705-11.

35. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. Stroke 1992;23:1752-60.

36. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

37. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

38. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

39. Bots ML, Meurs JCHM van, Grobbee DE. Assessment of early atherosclerosis: A new perspective. J Drug Res 1991;16;150-4.

40. Rose GA, Blackburn H, Gillum RF, et al. Cardiovascular survey methods. World Health Organisation, Geneva 1982.

41. Joint National Committee on High Blood Pressure. 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1988;148:1023-38.

42. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

43. Glagov S, Vito R, Giddens DP, et al. Micro-architecture and composition of artery walls: Relationships to location, diameter and the distribution of mechanical stress. J Hypertension 1992;10 (suppl 6):S101-4.

44. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

45. Bots ML, Breslau PJ, Briët E, et al. Cardiovascular determinants of carotid artery disease: The Rotterdam Elderly Study. Hypertension 1992;19:717-20.

46. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. J Chron Dis 1978;31:201-306.

5.2 Isolated systolic hypertension and vessel wall thickness of the carotid artery. The Rotterdam Study

Introduction

Several studies have indicated that isolated systolic hypertension is a strong predictor of the future occurrence of atherosclerotic cardiovascular disease and total mortality in the elderly.[1,2,3] Moreover, results from a double-blind, randomized, placebo-controlled trial of systolic hypertension in the elderly showed that antihypertensive treatment of isolated systolic hypertension, defined as a systolic blood pressure of 160 mmHg or over and a diastolic blood pressure of less than 90 mmHg, leads to a considerable reduction of cardiovascular morbidity and mortality in this age group.[4]

Isolated systolic hypertension is generally regarded as a consequence of a reduced compliance of the aorta and the large arteries.[5,6] Stiffening of the arteries contributes to a disproportionate rise in systolic blood pressure.[7] Age-related structural changes in the vessel wall, such as an increase in the ratio of collagen to elastin, have been recognized as major determinants of reduced arterial compliance.[8] Similar changes of the vessel wall are found in atherosclerosis. Furthermore, the presence of atherosclerosis has been associated with reduced arterial compliance.[9] The relative contribution of atherosclerosis to the pathogenesis of reduced arterial compliance and subsequent development of isolated systolic hypertension, however, is still debated.[5,7] Recently, it has been shown that with high-resolution B-mode ultrasonography, the presence and extent of atherosclerosis of the carotid arteries can be non-invasively assessed in an effective and accurate way in populations at large.[10,11,12]

We present the findings among the first 1,000 participants of the Rotterdam Study on the association of isolated systolic hypertension in asymptomatic elderly subjects and vessel wall thickness of the distal common carotid artery.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study of a cohort of around 8,000 elderly persons, aged 55 years or over. All residents of the suburb of Ommoord in Rotterdam, The Netherlands are invited to participate in the study, which has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere.[13] In short, the objective of the

Rotterdam Study is to clarify the determinants of chronic disabling diseases in an aging population. Incidence and risk factors of neurogeriatric diseases, locomotor diseases, ophthalmologic diseases, and cardiovascular diseases are being studied. With respect to cardiovascular disease, the Rotterdam Study focuses on the contribution of thrombogenic factors to atherosclerotic disease and on the presence and progression of atherosclerosis of the vessel wall and its determinants. The study includes an extensive home interview followed by two visits at the research center for a clinical examination. The participation rate of the cohort at the time of the present analysis was 72 %.

Ultrasonography of the carotid arteries

Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear- array transducer and a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). According to the Rotterdam Study ultrasound protocol, a careful search was performed for the lumen-intima interface and media-adventitia interface of the far wall of the distal common carotid artery.[14,15] The distances between the interfaces represent the intima-media thickness.[16,17] When an optimal longitudinal image was obtained, it was 'frozen' on the R wave of the electrocardiogram and stored on videotape. This procedure was repeated three times for both sides. Subsequently, the common carotid artery was evaluated for the presence of atherosclerotic lesions, defined as a focal widening relative to adjacent segments, with protrusion into the lumen. The entire ultrasound procedure was recorded on videotape. The actual measurements were performed off-line. From the videotape, the frozen images were digitized and displayed on the screen of a personal computer by use of additional dedicated software. This procedure has been described in detail previously.[17] In short, with a cursor the interfaces of the distal common carotid artery were marked over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery served as a reference point for the start of the measurement. This method permits the determination of mean values as well as maximal values for intima-media thickness. The average of the intima-media thickness of each of the three frozen images was taken as the measure for current wall thickness of the distal common carotid artery. In addition, for each subject a total intima-media thickness was calculated ([left + right]/2). With respect to focal lesions, the presence or absence of calcifications and acoustic shadowing was noted. For all criteria, alternative choices were present as 'can not tell' and 'not recorded'.

Cardiovascular risk factors

Information on current health status, medical and family history of chronic disease, drug

use, and smoking behavior was obtained by use of a computerized questionnaire, which included a Dutch version of the Rose questionnaire for assessment of prevalent coronary heart disease.[18] A history of stroke and myocardial infarction was obtained through direct questioning. With respect to smoking behavior, subjects were categorized in groups of current smokers, former smokers, and those who have never smoked. During two visits at the research center, several cardiovascular risk indicators were measured. Height and weight were measured and body mass index (kg/m^2) was calculated. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the analysis. Isolated systolic hypertension was defined as a systolic blood pressure of 160 mmHg or over and a diastolic blood pressure below 90 mmHg.[19] Subjects with a systolic blood pressure below 160 mmHg and a diastolic blood pressure below 90 mmHg were considered normotensive.

A venipuncture was performed, applying minimal stasis, with a 21 gauge butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Blood samples were collected into siliconized Vacutainer tubes (Becton & Dickinson, Paris, France) containing clotting activator and separator for serum or 0.129 M sodium citrate for plasma. Serum was separated by centrifugation at room temperature for 10 minutes at 1,600*g*. Plasma was separated by a two-stage centrifugation, first for 10 minutes at 1,600*g* at 4 ^{0}C and subsequently for 10 minutes at 4 ^{0}C and 10,000*g*, which yielded platelet-poor plasma. All samples were quickly frozen in liquid nitrogen and then stored at -80 ^{0}C before assay. Serum total cholesterol was determined by an automated enzymatic procedure.[20] High density lipoprotein (HDL) cholesterol was measured similarly after precipitation of the non HDL fraction with phosphotungstate-magnesium. Plasma fibrinogen level was assessed according to the Clauss method (Diamed AG, Switzerland).[21]

Data analysis

Among the first 1,000 participants of the Rotterdam Study, subjects receiving antihypertensive drugs, those who reported a hospitalization because of a stroke or a myocardial infarction, and those who had a positive Rose questionnaire for angina pectoris or intermittent claudication were excluded from the analysis. Of the remaining subjects (n=583) who were not on antihypertensive treatment and free of cardiovascular disease, 33 had isolated systolic hypertension. From the remaining eligible population, 66 age- and sex-matched normotensive control subjects were randomly selected.

Mean levels and proportions of several cardiovascular risk indicators and mean vessel wall thickness and lumen diameter of subjects with and without isolated systolic

Table 5.2.1 Baseline characteristics of subjects with and without isolated systolic hypertension.

	No ISH	ISH	p value
Number	66	33	
Age (years)	71.7 (7.8)	72.0 (8.3)	*
Sex (% male)	39	39	*
Body mass index (kg/m^2)	25.9 (3.3)	26.0 (4.3)	0.98
Systolic pressure (mmHg)	129.6 (15.5)	169.1 (8.0)	†
Diastolic pressure (mmHg)	66.8 (10.1)	76.2 (10.1)	< 0.01
Current smoking (%)	23	33	0.26
Total cholesterol (mmol/l)	6.44 (1.27)	6.81 (1.12)	0.16
HDL cholesterol (mmol/l)	1.33 (0.37)	1.41 (0.36)	0.34
Fibrinogen (g/l)	2.93 (0.84)	2.91 (0.76)	0.88

Values are percentages and means with standard deviation in parentheses

* Matching variables

† Difference results from selection of study group

hypertension were compared. The differences are presented with a 95 % confidence interval (CI). Multiple linear regression analysis was used for analysis of differences across groups, adjusted for several confounding variables, notably body mass index, serum lipids, smoking and fibrinogen. Analysis of covariance was used to estimate adjusted mean values of vessel wall thickness for tertiles of systolic and diastolic blood pressure. A linear regression model was used to test for trends.[22]

Results

In all subjects (n=99), the intima-media thickness of the far wall of the left common carotid artery could be assessed from the images stored on video tape. The intima-media thickness of the right common carotid artery could be measured in 98 subjects. The lumen diameter could be measured in 93 and 95 subjects, respectively.

Baseline characteristics of both groups are presented in table 5.2.1. Mean systolic blood pressure was different across groups as expected from the selection criteria. Diastolic blood pressure levels also were significantly different across the two groups. Compared with control subjects, subjects with isolated systolic hypertension had higher mean serum total cholesterol and higher mean HDL cholesterol levels, and there were more current smokers among them. The differences, however, did not reach statistical significance.

Mean intima-media thickness of the right common carotid artery was higher in those with isolated systolic hypertension than in normotensive subjects (table 5.2.2). The mean difference was 0.07 mm [95 % CI 0.01,0.14]. Results for the left common carotid artery were similar, with a mean difference of 0.06 mm [95 % CI -0.01,0.13]. No difference between the left and right carotid arteries was observed. Measurements at both sides were combined as total intima-media thickness ([left + right]/2). After adjustment for differences in serum lipids, body mass index, smoking, and fibrinogen, total intima-media thickness remained significant across groups, with a mean difference of 0.08 mm [95 % CI 0.02,0.14]. Additional adjustment for differences in diastolic blood pressure between groups did not alter the results.

In subjects with isolated systolic hypertension, the end-diastolic lumen diameter was significantly wider than in control subjects for both right and left sides: mean difference 0.70 mm [95 % CI 0.38,1.01] and 0.49 mm [95 % CI 0.17,0.80], respectively. Adjustments for differences in body mass index, serum lipids, smoking, fibrinogen, and

Table 5.2.2 Dimensions of the distal common carotid artery in subjects with and without isolated systolic hypertension.

	No ISH	ISH	Mean difference	Adjusted mean difference*
Intima-media thickness (mm)				
Left side	0.81 (0.03)	0.87 (0.03)	0.06 [-0.01,0.13]	0.08 [0.02, 0.15]
Right side	0.79 (0.02)	0.86 (0.03)	0.07 [0.01, 0.14]	0.08 [0.01, 0.14]
Both sides‡	0.80 (0.02)	0.86 (0.03)	0.06 [0.01, 0.12]	0.08 [0.02, 0.14]
Lumen diameter (mm)†				
Left side	6.09 (0.10)	6.58 (0.11)	0.49 [0.17, 0.80]	0.60 [0.34, 0.86]
Right side	6.24 (0.09)	6.94 (0.14)	0.70 [0.38, 1.01]	0.74 [0.43, 1.03]
Both sides‡	6.18 (0.09)	6.77 (0.12)	0.59 [0.29, 0.89]	0.64 [0.38, 0.89]
Plaques (%)				
Left side	3	13	10	9 [-1, 20]
Right side	5	9	4	6 [-5, 15]
Both sides§	5	15	10	12 [-1, 25]

Values are percentages and means with standard errors or 95 % confidence intervals in parentheses

* Adjusted for differences in body mass index, serum lipids, smoking, and fibrinogen

† End-diastolic lumen diameter

‡ Both sides refers to [left + right]/2

§ Both sides refers to plaques present in either the left or the right common carotid artery or both

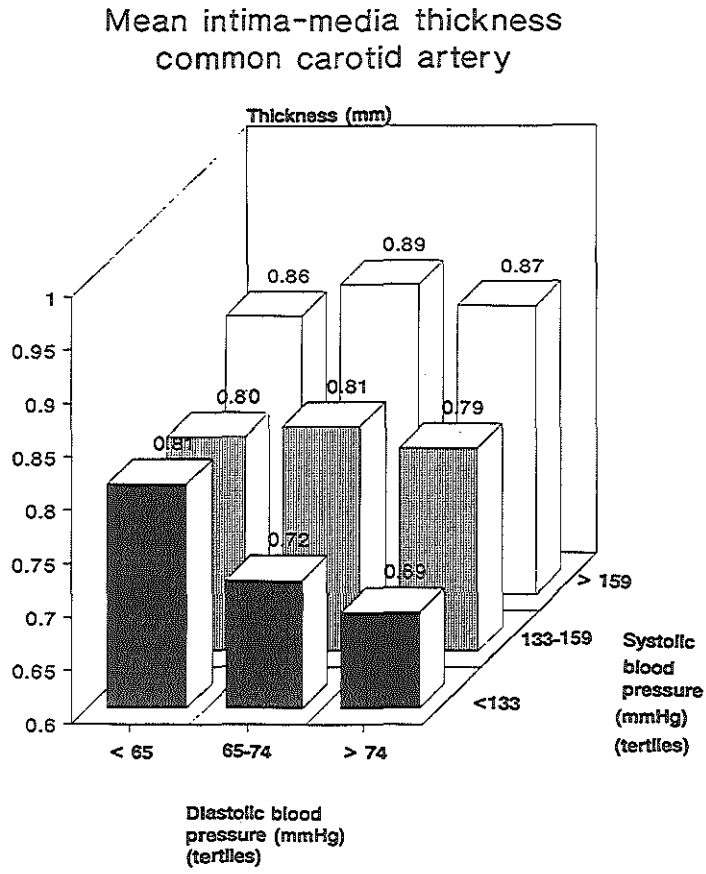


Figure 5.2.1 Mean common carotid intima-media thickness (mm) by levels of systolic and diastolic blood pressure. Adjusted for differences in age, sex, body mass index, serum lipids, smoking and fibrinogen.

diastolic blood pressure did not substantially alter the results (table 5.2.2). Atherosclerotic lesions were more frequently observed in those with isolated systolic hypertension (adjusted difference, 12 %). This finding, however, was of borderline statistical significance [95 % CI -1,25].

Subjects were categorized in tertiles according to their level of diastolic blood pressure and in tertiles based on their systolic blood pressure. We compared mean total intima-media thickness within strata of diastolic and systolic blood pressure (figure 5.2.1).

Mean intima-media thickness gradually increased with rising levels of systolic blood pressure within all strata of diastolic blood pressure (test for trend, $p < 0.05$, except for the lowest tertile: $p = 0.09$). In addition, subjects in the lowest tertile of diastolic and systolic blood pressures appeared to have a higher mean intima-media thickness than those with relatively higher diastolic blood pressure levels and similar systolic blood pressure levels. This finding, however, did not reach the level of significance. With respect to subjects in the other tertiles of systolic blood pressure, no such trend could be demonstrated.

Discussion

Our data indicate that the intima-media thickness of the common carotid artery, assessed with high-resolution B-mode ultrasonography, is significantly higher in asymptomatic elderly subjects with isolated hypertension than in those without elevated blood pressure. Moreover, the end-diastolic lumen diameter is significantly larger in those with isolated systolic hypertension. These findings are independent of differences in age, sex, body mass index, serum lipids, fibrinogen and smoking. In addition, atherosclerotic thickening of the intima-media increased gradually with rising levels of systolic blood pressure. Furthermore, atherosclerotic plaques appeared to be more common in those with elevated systolic blood pressure without, however, reaching statistical significance.

Before the findings can be accepted some aspects of the study need to be considered. First, subjects were classified on the basis of a blood pressure reading performed on one occasion. In particular, some misclassification of subjects with isolated systolic hypertension may have occurred. This may have reduced the observed difference between the groups, provided that a true association exists between isolated systolic hypertension and common carotid intima-media thickness.

Second, to eliminate selection bias, subjects on antihypertensive treatment and those with symptomatic cerebrovascular, cardiovascular, or peripheral arterial disease were excluded. Subjects using antihypertensive drugs may have artificially lowered blood pressure levels. Furthermore, in these subjects, a clustering of cardiovascular risk factors may be present, which is positively related to carotid atherosclerosis.[10,11,12] In addition, subjects with prevalent coronary heart disease may have a relatively low blood pressure as a consequence of their disease or may receive additional drugs that may have an anti-hypertensive effect. If not excluded, these subjects are more likely to be part of the control group and this may artificially reduce the magnitude of the difference between the groups.

Finally, it may be argued that the method used to assess carotid atherosclerosis

may not truly reflect the atherosclerotic process. Atherosclerosis is viewed as a disorder that is restricted to the intima layer of the arterial vessel wall.[23] Ultrasound technique cannot discriminate between the intima layer and the media layer of vessel wall. However, an ultrasonographically determined increase in common carotid intima-media thickness may be regarded as an indicator of generalized atherosclerosis since it has been associated with elevated levels of cardiovascular risk factors and with an increased risk of myocardial infarction.[10,11,12,24,25] Moreover, atherosclerotic carotid artery disease has been related to atherosclerosis in coronary arteries and peripheral arteries.[26,27,28]

A decrease of the compliance of the aorta and the large arteries has been suggested to be the principal hallmark of isolated systolic hypertension.[5] The finding of an increased intima-media thickness and a larger lumen diameter among elderly subjects with isolated systolic hypertension is compatible with a diminished arterial compliance. Our observations of an increased intima-media thickness and a higher prevalence of atherosclerotic plaques in the carotid arteries, however, indicate that atherosclerosis may be associated with isolated systolic hypertension. These findings are compatible with results from studies that have shown a reduced arterial compliance in subjects with atherosclerosis[9,29], with studies that have reported a positive association between isolated systolic hypertension and atherosclerosis[30,31] and with a study in which ultrasonographically assessed carotid intima-media thickness was associated with systolic blood pressure elevation.[32,33] The time-dependent relation between atherosclerosis, reduced arterial compliance, and isolated systolic hypertension cannot be determined with our data because of the cross-sectional design of this study.

Evidence from other studies may be used to address this issue. Early in life, interindividual differences exist in arterial stiffness.[34] Apart from structural changes in the vessel wall, these differences may be attributed to differences in neural, humoral, and physical stimuli.[6] A reduced arterial compliance has been associated with elevated blood pressure in young adults.[35] Data from the Framingham Heart Study have indicated that in middle-aged subjects, elevated systolic blood pressure and pulse pressure are major determinants of isolated systolic hypertension in the future.[36] Witteman and co-workers, in a 9 year follow-up study among 614 women aged 45-64 years, observed a gradual progression of radiographically diagnosed atherosclerosis of the abdominal aorta with increasing levels of systolic blood pressure,[37] suggesting that systolic blood pressure is causally related to the atherosclerotic process. Our observation indicating a gradual increase in common carotid intima-media thickness with rising levels of systolic blood pressure is in accordance with those findings. These data may indicate that a reduced arterial compliance may lead to a mild elevation of systolic blood pressure (or pulse pressure). Blood pressure elevation sets a pathophysiological process in progress, possibly

atherosclerosis, that may lead to a further reduction of the compliance of the large arteries and a subsequent rise in systolic blood pressure. This process may enhance arterial stiffness and atherosclerosis, leading to a further increase in systolic blood pressure and to development of isolated systolic hypertension. Additionally, isolated systolic hypertension in itself, may further enhance the development of atherosclerosis.

Some early reports have suggested that in the elderly, in addition to a rise in systolic blood pressure, diastolic blood pressure may actually fall as a result of reduced arterial compliance of the aorta and large arteries.[31,38] With age, the lowering effect of arterial stiffening on the diastolic blood pressure may outweigh the elevating effect of increased peripheral resistance on diastolic pressure.[38] This hypothesis implies that in the elderly, a low diastolic blood pressure might be regarded as an indicator of prevalent vascular damage (atherosclerosis). Data to support this may be found in results from recent studies in the very old, suggesting a lower mortality rate in those with diastolic blood pressure levels ranging from 85 to 95 mmHg than in those with low diastolic blood pressure levels.[39,40] Furthermore, a low diastolic blood pressure (<75 mmHg) has been associated with an increased risk of progression of atherosclerosis of the abdominal aorta compared with diastolic blood pressure values ranging from 75 to 84 mmHg.[37] Our data, however, did not demonstrate an increased vessel wall thickening for all levels of systolic blood pressure in subjects with low diastolic blood pressures compared with subjects with relatively higher diastolic blood pressures. These relations need further attention.

In conclusion, our observations among asymptomatic elderly subjects with isolated systolic hypertension indicate that atherosclerosis, as assessed by ultrasonographically determined intima-media thickness and plaques, is probably involved in isolated systolic hypertension. Whether increased vessel wall thickness is the result of isolated systolic hypertension or whether it may also contribute to blood pressure elevation remains to be established.

References

1. Kannel WB, Wolf PA, McGee DL, et al. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham Study. JAMA 1981;245:1225-9.
2. Shekelle RB, Ostfeld AM, Klawans HL. Hypertension and the risk of stroke in an elderly population. Stroke 1974;5:71-5.
3. VandenBan GJC, Kampman E, Schouten EG, et al. Isolated systolic hypertension in Dutch middle-aged and all-cause mortality: A 25-year prospective study. Int J Epidemiol 1989;18:95-9.
4. SHEP cooperative research group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991;265:3255-64.
5. Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. J Hypertension 1990;8:393-405.

6. Dustan HP. Atherosclerosis complicating chronic hypertension. Circulation 1971;50:871-9.

7. O'Rourke M. Arterial stiffness, systolic blood pressure and logical treatment of arterial hypertension. Hypertension 1990;15:339-47.

8. Dobrin PB. Mechanical properties of arteries. Physiol Rev 1978;58:397-449.

9. Hirai T, Sasayama S, Kawasaki T, et al. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation 1989;80:78-86.

10. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

11. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

12. Salonen R, Seppänen K, Rauramaa R, et al. Prevalence of carotid atherosclerosis and serum cholesterol levels in eastern Finland. Arteriosclerosis 1988;8:788-92

13. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

14. Bots ML, Meurs JCHM van, Grobbee DE. Assessment of early atherosclerosis: A new perspective. J Drug Res 1991;16;150-4.

15. Wikstrand J, Wiklund O. Frontiers in cardiovascular science. Quantitative measurements of atherosclerotic manifestations in humans. Arterioscler Thromb 1992;12:114-9.

16. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

17. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

18. Rose GA, Blackburn H, Gillum RF, et al. Cardiovascular survey methods. Geneva, World Health Organisation, 1982.

19. Joint National Committee on High Blood Pressure. 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1988;148:1023-38.

20. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

21. Clauss A. Gerinnungsphysiologische schnellmethode zur bestimmung des fibrinogens. Acta Haematol 1957;17:237-46.

22. Rothman KJ. Modern epidemiology. Boston, Little, Brown & Co, 1986.

23. Stary HC, Blankenhorn DH, Chandler AB, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

24. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.

25. Bonithon-Kopp C, Scarabin P, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb 1991;11:966-72.

26. Craven TE, Ryu JE, Espeland MA, et al. Evaluation of the associations between carotid atherosclerosis and coronary artery stenosis. A case-control study. Circulation 1990;82:1230-42.

27. Wofford JL, Kahl FR, Howard GR, et al. Relation of extent of extracranial carotid artery atherosclerosis as measured by B-mode ultrasound to the extent of coronary atherosclerosis. Arterioscler Thromb 1991;11:1786-94.

28. Sutton KC, Wolfson SK, Kuller LH. Carotid and lower extremity arterial disease in elderly adults with isolated systolic hypertension. Stroke 1987;18:817-22.

29. Stefanafis C, Wooley CF, Bush CA, et al. Aortic distensibility abnormalities in coronary artery disease. Am J Cardiol 1987;59:1300-4.

30. Coleandrea MA, Friedman GD, Nichaman MZ, et al. Systolic hypertension in the elderly. An epidemiologic assessment. Circulation 1970;41:239-45.

31. Fineberg MH. Systolic hypertension. Its relationship to atherosclerosis of the aorta and larger arteries. Am J Med 1927;127:835-42.

32. Salonen R, Salonen JT. Carotid atherosclerosis in relation to systolic and diastolic blood pressure: Kuopio ischaemic heart disease risk factor study. Ann Med 1991;23:23-7.

33. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: a population-based ultrasonography study in eastern Finnish men. J Intern Med 1991;229:225-31.

34. Riley WA, Freedman DS, Higgs NA, et al. Decreased arterial elasticity associated with cardiovascular risk factors in the young. The Bogalusa Heart Study. Arteriosclerosis 1986;6:378-86.

35. Merode T van, Hick PJJ, Hoeks APG, et al. Carotid artery wall properties in normotensive and borderline hypertensive subjects of various age. Ultrasound in Med & Biol 1988;14:563-9.

36. Wilking SVB, Belanger A, Kannel WB, et al. Determinants of isolated systolic hypertension. JAMA 1988;260:3451-5.

37. Witteman JCM. Systolic and diastolic blood pressure and progression of atherosclerosis in women. In: Witteman JCM. Cardiovascular disease in women. An epidemiological study of atherogenic factors (Thesis). Den Haag, Ando bv;1991:25-39.

38. Wiggers CJ. Physical and physiological aspects of arteriosclerosis and hypertension. Ann Intern Med 1932;6:12-30.

39. Langer RD, Ganiats TG, Barrett-Connor E. Paradoxical survival of elderly men with high blood pressure. Br Med J 1989;298:1356-7.

40. Mattila K, Haavisto M, Rajaja S, et al. Blood pressure and five year survival in the very old. Br Med J 1988;296:887-9.

5.3. Low diastolic blood pressure in the elderly and atherosclerosis. The Rotterdam Study

Introduction

In the elderly, the compliance of the large arteries is a major determinant of the level of systolic blood pressure. Increased systolic blood pressure may promote progression of atherosclerosis[1,2] and consequently, a stiffening of the large arteries. This process may subsequently lead to a further increase in systolic blood pressure. Additional to a rise in systolic blood pressure, diastolic blood pressure may actually fall as a result of reduced arterial compliance of the aorta and large arteries.[3,4] As a consequence, a considerable proportion of older subjects with a relatively low diastolic blood pressure, may have prevalent vascular damage (i.e., atherosclerosis); in particular, those with a relatively high pulse pressure. This sequence of events in which low diastolic pressure in certain elderly individuals becomes a marker of atherosclerosis, may well explain findings on the so called J-shaped curve relating diastolic blood pressure to subsequent cardiovascular events.[5,6,7]

To investigate this hypothesis we studied the association of common carotid intima-media thickness, as an indicator of generalized atherosclerosis, to diastolic blood pressure in the first 1,000 participants of the Rotterdam Study.

Methods

Population

The Rotterdam Study is a prospective follow-up study among 8,000 people aged 55 years or over, to investigate the incidence of, and risk factors for chronic disabling diseases.[8] The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants. All inhabitants aged 55 years or more in the Rotterdam suburb of Ommoord were invited to participate.

Ultrasonography of the carotid arteries

To assess carotid intima-media thickness, ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (figure 3.1.1).[9] The distance of the leading edge of the leading edge of the first bright line of the far

wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicates the intima-media thickness.[9,10] Studies have indicated that the posterior (far) wall intima-media thickness as seen with ultrasound, truly reflects the anatomical intima-media layer.[9,10]

The Rotterdam Study ultrasound protocol demands a careful examination of the lumen-intima interface and the media-adventitia interface on the far wall of the distal common carotid artery. When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for each left and right side. Subsequently, the common carotid artery is on-line evaluated for the presence (yes/no) of atherosclerotic lesions, defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. The actual measurements of intima-media thickness are performed off-line. From the videotape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software.[10] From the average of the three frozen images per carotid artery, a mean common carotid intima-media thickness ((left+right)/2) is taken a measure for current wall thickness of the distal common carotid artery.

Cardiovascular risk factors

Information on current health status, medical history, drug use, and smoking behavior was obtained using a computerized questionnaire. Subjects were categorized into groups of current smokers, former smokers and those who had never smoked. During two visits at the research center several cardiovascular risk indicators were measured. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained at one occasion was used in the analysis.

Data analysis

The present analysis is based on findings in the first 1,000 participants of the Rotterdam Study. Carotid ultrasound scans could not be obtained in 12 subjects, because of technical failure of the equipment. Of 31 subjects measurement of intima-media thickness at either the left or the right carotid artery could not be performed from the stored images because of poor visualization. For these subjects, the estimate of intima-media thickness for each of these subjects was based on the measurement of the side for which a value was available. Of 35 subjects information on either blood pressure or prevalent cardiovascular disease was not available.

Inspection of the data by categories of blood pressure revealed a J-shaped curve

between diastolic blood pressure and common carotid intima-media thickness. The presence and goodness of fit of the curve was further examined with polynomial regression analysis using the BMDP statistical package.[11] Diastolic blood pressure levels were categorized by intervals of 10 mmHg. The diastolic blood pressure category showing the lowest intima-media thickness was used as reference category. Dummy variables were used to assess the significance of the differences in common carotid intima-media thickness between the reference category and the other categories of diastolic blood pressure using linear regression. All results were adjusted for differences in age and gender.

Separate analyses were performed for all subjects (n=988), for those with symptomatic cardiovascular disease, i.e., angina pectoris, myocardial infarction, stroke or intermittent claudication, and currently using any blood pressure lowering drug (n=411), and for those who were free from symptomatic cardiovascular disease and currently not using blood pressure lowering drugs (n=542).

Table 5.3.1 General characteristics of the study population.

	Women	Men
Number	600	388
Age (yrs)	68.8 (8.0)	68.7 (7.6)
Body mass index (kg/m^2)	27.1 (4.2)	25.9 (3.1)
Current smoking (%)		
Current	20	29
Former	30	64
Systolic blood pressure (mmHg)	134 (22)	134 (19)
Diastolic blood pressure (mmHg)	70 (11)	72 (10)
Hypertension (%)	32	24
Serum total cholesterol (mmol/l)	6.96 (1.21)	6.43 (1.16)
Serum HDL cholesterol (mmol/l)	1.43 (0.33)	1.20 (0.40)
Prevalent cardiovascular disease (%)	15	21
Angina pectoris	8	7
Myocardial infarction	5	15
Stroke	2	3
Intermittent claudication	1	2

Values are percentages and means with standard deviation in parentheses.

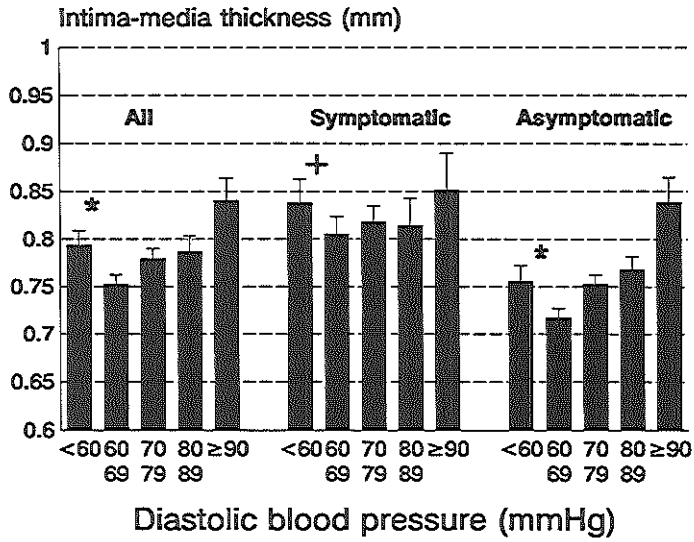


Figure 5.3.1. Association between diastolic blood pressure and common carotid intima-media thickness for all subjects (all), for those with symptomatic cardiovascular disease and currently using blood pressure lowering drugs (symptomatic), and for those free from cardiovascular disease, and currently not using blood pressure lowering drugs (asymptomatic).

** $p < 0.05$ compared to subjects with a diastolic blood pressure of 60-69 mmHg.*

+ $p = 0.32$

Results

In table 5.3.1 general characteristics of the studied subjects are presented. Figure 5.3.1 presents the association of common carotid intima-media thickness with increasing levels of diastolic blood pressure. Polynomial regression analysis indicated a significant J-shaped curve with diastolic blood pressure as both single and squared fitted into the model. Mean common carotid intima-media thickness was significantly increased in subjects with a diastolic blood pressure below 60 mmHg compared to that of subjects with a diastolic blood pressure between 60 to 69 mmHg with a mean difference of 0.039 mm [95 % CI 0.003,0.078] for all subjects, and of 0.038 mm [95 % CI 0.0,0.076] for subjects free from symptomatic cardiovascular disease and not using blood pressure lowering drugs. For subjects with symptomatic cardiovascular disease and currently using blood pressure lowering drugs, a J-shaped association was less prominent (difference 0.033 mm [95 % CI -0.031, 0,099]) (figure 5.3.1). Beyond a diastolic pressure of 70 mmHg or over, a significant gradual increase in common carotid intima-media thickness was observed in the analyses for all subjects and for asymptomatic subjects.

Table 5.3.2. Common carotid intima-media thickness (in mm) and diastolic blood pressure. Results from subjects free from symptomatic cardiovascular disease and not currently using blood pressure lowering drugs.†

	Diastolic blood pressure (mmHg)				
	< 60	60-69‡	70-79	80-89	≥ 90
Age (years)					
55-74	0.73 (0.019)	0.69 (0.012)	0.73 (0.011)*	0.75 (0.016)*	0.82 (0.033)*
≥ 75	0.86 (0.033)	0.81 (0.022)	0.84 (0.028)	0.88 (0.037)	0.93 (0.077)
Pulse pressure (mmHg)					
< 60	0.70 (0.025)	0.68 (0.013)	0.71 (0.014)	0.72 (0.022)	0.74 (0.056)
≥ 60	0.80 (0.022)	0.76 (0.015)	0.79 (0.014)	0.81 (0.020)	0.87 (0.036)*

Values are means with standard errors in parentheses.

* Significant difference ($p < 0.05$) with the reference category, i.e. diastolic pressure 60-69 mmHg.

† Results are adjusted for age and gender.

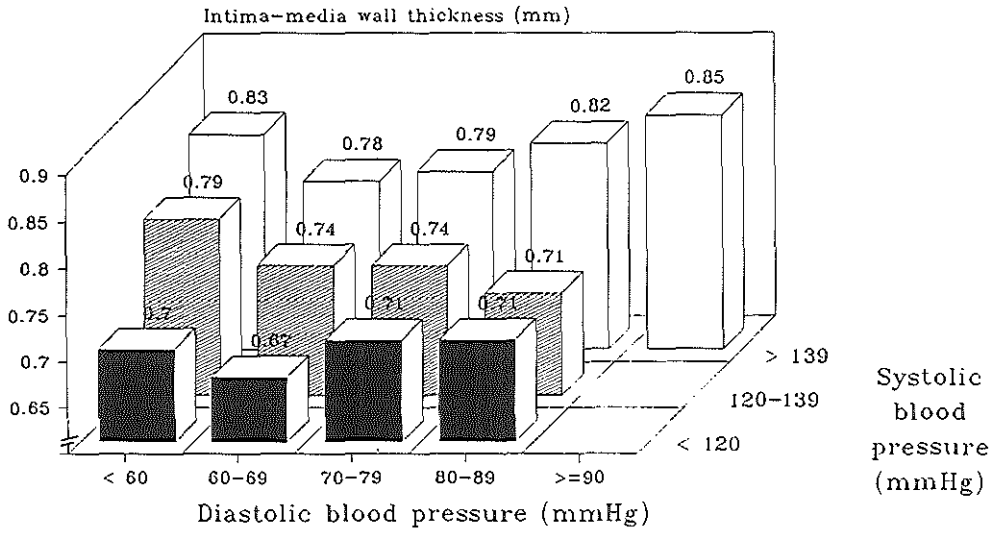
‡ Reference category

Analyses across age-strata showed that the J-shaped curve in subjects aged 55 to 75 years did not materially differ from that observed among those aged 75 years or over (table 5.3.2). The J-shaped curve was slightly more prominent in subjects with relatively high pulse pressures, i.e., higher than the median value (60 mmHg) than in those with pulse pressures below 60 mmHg (table 5.3.2).

Subjects were categorized in three strata of systolic blood pressure level. We compared mean common carotid intima-media thickness within strata of diastolic and systolic blood pressure (figure 5.3.2). Mean intima-media thickness gradually increased with rising levels of systolic blood pressure within all strata of diastolic blood pressure (test for trend $p < 0.05$). In addition, subjects with diastolic blood pressure levels lower than 60 mmHg had higher mean common carotid intima-media thickness as compared to those with diastolic blood pressure levels between 60 to 69 mmHg. This was found across all strata of systolic blood pressure.

Discussion

The present study shows a J-shaped relationship between diastolic blood pressure and common carotid intima-media thickness; among older subjects a low diastolic blood pressure is associated with an increased common carotid intima-media thickness. This finding was in particular present in subjects free from cardiovascular disease and currently not using blood pressure lowering drugs, and less pronounced in subjects with



Adjusted for age and gender

Figure 5.3.2. Association between diastolic blood pressure and common carotid intima-media thickness in strata of systolic blood pressure. Results for subjects free from symptomatic cardiovascular disease and currently not on blood pressure lowering drugs.

symptomatic cardiovascular disease and currently using blood pressure lowering drugs. The J-shaped curve was slightly more prominent in subjects with high pulse pressures (≥ 60 mmHg), and present across all strata of systolic blood pressure.

Some aspects of the present study should be addressed. The inclusion of subjects with prevalent symptomatic cardiovascular disease could artificially induce a J-shaped curve, since atherosclerotic cardiovascular disease is associated with increased common

carotid intima-media thickness and may be related to a low diastolic blood pressure; for example through a reduced left ventricular function. Inclusion of subjects currently using blood pressure lowering drugs may have biased the results in the same direction.

Increased common carotid intima-media thickness may not necessarily be atherosclerosis and is not in itself a precursor of atherosclerosis. It may merely reflect an adaptive response of the vessel wall to changes in shear stress and tensile stress.[12] Furthermore, atherosclerosis is viewed as a disorder which is restricted to the intima layer of the arterial vessel wall, and ultrasound imaging can not discriminate between the intima layer and the media layer of vessel wall. In several studies, ultrasonographically determined increased common carotid intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors[13,14,15,16] and with atherosclerosis of the abdominal aorta.[17] In addition, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis.[18] These results support the view that non-invasively assessed intima-media thickness of the common carotid artery may be regarded as an indicator of atherosclerosis.

At present, the available data on the association between ultrasonographically assessed carotid intima-media thickness and diastolic blood pressure are not consistent across studies and contrasting results have been reported. Some have found no association between intima-media thickness and diastolic blood pressure,[19,20] whereas others reported a positive association.[21] Part of this controversy may be related to the presence and extent of a J-shaped relationship. Results from the Cardiovascular Health Study, comprising 2,189 subjects aged 65 years and over, who were not on antihypertensive treatment and free of cardiovascular disease, have, however, shown a steady inverse association between diastolic blood pressure and common carotid intima-media thickness across all levels of systolic blood pressure with no evidence of a J-shaped relationship.[22] Sutton-Tyrell and co-workers in a study among older subjects with and without isolated systolic hypertension found that a diastolic blood pressure below 75 mmHg is a strong marker for carotid atherosclerosis as defined as an atherosclerotic index based on presence of atherosclerotic abnormalities at several sites of the carotid artery.[23] This association, however, was confined to subjects with isolated systolic hypertension, only. Results of the present study indicating a J-shaped curve between common carotid intima-media thickness and diastolic blood pressure comply with the hypothesis that in the elderly a low diastolic blood pressure may reflect prevalent atherosclerosis. The finding that this phenomenon is slightly more pronounced in subjects with higher systolic blood pressures is in accordance with the hypothesis. Whether a low diastolic blood pressure is a consequence rather than a cause of atherosclerosis, however,

can not be addressed with these cross-sectionally obtained data.

In a number of prospective population-based follow-up studies among elderly subjects, a relatively low diastolic blood pressure at baseline has been associated with an increased risk of coronary heart disease and of mortality. This unexpected finding has been attributed to deteriorating health.[24] Others have suggested that the presence of severe coronary atherosclerosis is an important factor in the J-shaped relation between diastolic blood pressure and myocardial infarction.[25,26] Particularly patients with critic coronary stenosis appear to be at risk of myocardial ischaemia, when blood pressure perfusion falls below the threshold of autoregulation.[27] The role of use of blood pressure lowering drugs in the explanation of the J-shaped curve has been put forward.[28] Results from trials on the efficacy of antihypertensive drugs performed among elderly subjects could not confirm a causative role for use of blood pressure lowering drugs on the origin of the J-shaped curve, since the J-shaped curve was found in both treated and untreated groups.[29] An alternative hypothesis may be that a low diastolic blood pressure in the elderly reflects the presence of atherosclerosis, which itself is associated with an increased risk of cardiovascular disease. The J-shaped curve observed in our study, and findings from other studies,[22,23] favor this view. At present, the factors that have been proposed to explain the J-shaped curve are inconclusive.[30]

Prospective studies on the relation between progression of atherosclerosis and change in diastolic blood pressure are needed to confirm the hypothesis that in the elderly a low diastolic blood pressure is a consequence rather than a cause of atherosclerosis.

References

1. SHEP cooperative research group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991;265:3255-64.
2. Witteman JCM, Grobbee DE. Systolic and diastolic blood pressure and progression of atherosclerosis in women. In: Witteman JCM. Cardiovascular disease in women. An epidemiological study of atherogenic factors (Thesis). Den Haag, Ando bv, 1991:25-39.
3. Wiggers CJ. Physical and physiological aspects of arteriosclerosis and hypertension. Ann Intern Med 1932;6:12-30.
4. Fineberg MH. Systolic hypertension. Its relationship to atherosclerosis of the aorta and larger arteries. Am J Med 1927;127:835-42.
5. Langer RD, Ganiats TG, Barrett-Connor E. Paradoxical survival of elderly men with high blood pressure. Br Med J 1989;298:1356-7.
6. Mattila K, Haavisto M, Rajaja S, Heikinheimo R. Blood pressure and five year survival in the very old. Br Med J 1988;296:887-9.
7. Taylor JO, Cornoni-Huntley J, Curb JD, et al. Blood pressure and mortality risk in the elderly. Am J Epidemiol 1991;134:489-504.

8. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

9. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

10. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

11. Dixon WJ, ed. BMDP Statistical Package Manual. Berkeley CA: University of California Press, 1990.

12. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

13. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

14. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

15. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

16. Poli A, Tremoli E, Colombo A, Sirtori M, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

17. Bots ML, Witteman JCM, Grobbee DE. Carotid intima-media wall thickness in women with and without atherosclerosis of the abdominal aorta. Atherosclerosis *(in press)*

18. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990;81:33-40.

19. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: a population-based ultrasonography study in Eastern Finnish men. J Intern Med 1991;229:225-31.

20. O'Leary DH, Polak JF, Wolfson SK, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The cardiovascular Health Study. Stroke 1991;22:1155-63.

21. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

22. Psaty BM, Furberg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly. Initial findings from the Cardiovascular Health Study. JAMA 1992;268:1287-91.

23. Sutton-Tyrell K, Alcorn HG, Wolfson SK, et al. Predictors of carotid stenosis in older adults with and without isolated systolic hypertension. Stroke 1993;24:355-61.

24. Staessen J, Bulpitt C, Clement D, et al. Relation between mortality and treated blood pressure in elderly patients with hypertension: Report of the European Working Party on High Blood Pressure in the Elderly. Br Med J 1989;298:1552-6.

25. Cruickshank JM. Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction. Br Med J 1988;297:1227-30.

26. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. Lancet 1987;i:581-4.

27. Floras JS. Antihypertensive treatment, myocardial infarction, and nocturnal myocardial ischaemia. Lancet 1988;ii:994-6.

28. Alderman MH, Ooi LVL, Madhavan S, et al. Treatment-induced blood pressure reduction and the risk of myocardial infarction. JAMA 1989;262:920-4.

29. Coope J, Warrender TS, McPherson K. The prognostic significance of blood pressure in the elderly. J Human Hypertension 1988;2:79-88.

30. Bots ML, Grobbee DE, Hofman A. High blood pressure in the elderly. Epidemiol Rev 1991;13:294-314.

Chapter 6

Determinants of carotid artery stenosis

6 Cardiovascular determinants of carotid artery disease. The Rotterdam Study

Introduction

Symptoms of cerebral ischemia have been related to atherosclerotic lesions of the carotid artery.[1,2] Furthermore, the presence of severe atherosclerotic carotid artery disease has been associated with an increased risk of cerebral ischemia and infarction.[3,4] Data on the prevalence of hemodynamically significant stenosis of the carotid artery and its determinants in a nonhospitalized elderly population are limited. Noninvasive duplex ultrasonography, combined with Doppler spectral analysis, may be used to assess hemodynamically significant stenosis of the carotid artery in an effective and accurate way.[5]

We report on the prevalence of hemodynamically significant stenosis of the right carotid artery among the first 1,000 participants in the Rotterdam Study. In addition, we assessed associations between carotid artery disease and several cardiovascular risk indicators, including hemostatic factors.

Methods

Population

The Rotterdam Study is a single center prospective follow-up study of a cohort of approximately 8,000 subjects, aged 55 years or over, living in a suburb of Rotterdam, The Netherlands. The study has been approved by the Medical Ethics Committee of the Erasmus University and written informed consent is obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere.[6] In short, the objective of the study is to clarify the determinants of occurrence of chronic, disabling cardiovascular, neurogeriatric, locomotor and ophthalmologic diseases. With respect to cardiovascular disease, the Rotterdam Study focuses on the contribution of thrombogenic factors to atherosclerotic disease and on the presence and progression of atherosclerosis of the vessel wall. The study comprises an extensive home interview, followed by two visits at the research center for a clinical examination.

Ultrasonography of the carotid arteries

Ultrasonography of the carotid arteries was performed using a Duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA). Hemodynamically significant stenosis of the carotid artery was assessed using a 7.5 MHz sector transducer in combination with a 5 MHz pulsed Doppler. For reasons of

feasibility, only the right carotid artery was measured. Interpretation of velocity profiles was done on-line according to standard criteria.[7] The right internal carotid artery was categorized as normal (0 % reduction of lumen diameter), minimal lesions (1-15 % reduction), moderate stenosis (16-49 % reduction) or severe stenosis (≥50 % reduction).[7] People whose velocity profiles indicated a reduction of the lumen diameter of 16 % or over returned to the research center within two weeks for a second scanning procedure of both carotid arteries.

Cardiovascular risk factors

Information on current health status, medical and family histories, drug use, and smoking behavior was obtained using a computerized questionnaire. With respect to smoking behavior, subjects were categorized in groups of current smokers, former-smokers and those who have never smoked. During two visits at the research center several cardiovascular risk indicators were measured. Height and weight were measured according to the guidelines of the World Health Organisation.[8] Body mass index (kg/m^2), was used as an indicator of obesity. Sitting blood pressure was measured at the right upper arm using a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analysis.[9] Hypertension was defined as a systolic blood pressure of 160 mmHg or over and/or a diastolic blood pressure of 95 mmHg or over and/or use of antihypertensive drugs.[9]

A venipuncture was performed, applying minimal stasis, using a 21 gauge Butterfly needle. Samples were collected into siliconized Vacutainer tubes containing 3.8 % trisodium citrate and centrifuged for 10 min at 1,600 g at 4 ^{0}C. Plasma was separated, subsequently centrifuged for 10 min at 10,000 g at 4 ^{0}C and stored at -80^{0}C before assay. Serum total cholesterol was determined using an automated enzymatic procedure.[10] High density lipoprotein (HDL) level was measured similarly, after precipitation. Plasma fibrinogen level was assessed according to the Clauss method (Diamed AG, Switzerland).[11] Factor VIIc and factor VIIIc activity were assayed by means of Automatic Coagulation Laboratory (ACL) (Instrumentation Laboratory, IJsselstein, The Netherlands), using factor VII and factor VIII deficient plasma (Ortho Diagnostic System, Beerse, Belgium) with Thromborel S (Behringwerke, Germany) and Thrombosil I (Ortho Diagnostic Systems, Beerse, Belgium), as reagents, respectively. Plasma obtained from 40 healthy men was pooled and used to serve as reference for the measurements of factor VIIc and factor VIIIc activity. Factor VIIc and factor VIIIc levels of the donors were all within normal range and no differences between reference pools could be detected.

Table 6.1 General characteristics of 954 participants of the Rotterdam Study, in categories of percentage of stenosis.

		Carotid artery stenosis			
		0 %	1-15 %	16-49 %	≥ 50 %
Number	aged 55-74 yrs	575	137	18	10
	aged ≥ 75 yrs	142	58	11	3
Age (years)		68.1 (7.6)	70.0 (8.4)	72.9 (9.0)	69.4 (7.1)
Male (%)		39	38	38	69
Body mass index (kg/m^2)		26.6 (3.7)	26.9 (4.4)	27.4 (5.3)	27.1 (3.9)

Values are percentages or means with standard deviations in parentheses

Data analysis

The mean levels and proportions of several risk indicators of subjects with minimal lesions, and moderate-to-severe stenosis were compared with those of subjects without stenosis. The latter group was considered as a reference group. Multiple linear regression analysis was used for analysis of differences across groups adjusted for several confounding variables. Differences are presented with a 95 % confidence interval (CI) and a two-sided p value. For results on factor VIIc activity, subjects currently using anti-coagulant drugs have been excluded (n=47). Analyses for trends across groups were similarly performed using multiple regression analysis.

Results

Of the first 1,000 participants of Rotterdam Study, 769 persons were aged 55 to 75 years and 231 aged 75 years or over. In 27 persons, ultrasonography could not be performed due to technical or logistic reasons. In 19 subjects, it was not possible to obtain reliable measurements of the internal carotid artery, mainly because of extreme tortuosity of the artery. Complete Duplex data of the right carotid artery were available of 954 subjects. Baseline characteristics are presented in table 6.1.

A moderate stenosis, 16-49 % reduction of the lumen diameter, of the right internal carotid artery was found in 29 subjects (11 men) 3.0 % [95 % CI 2.0,4.1]. A stenosis of more than 50 % was observed in 13 persons (9 men) (1.4 %). The prevalence of right-sided severe carotid artery stenosis among men and women aged 55-75 years was 2.4 % [95 % CI, 0.6,4.1] and 0.7 % (95 % CI, 0.0,1.4), respectively.

Because of the small number of subjects with severe carotid artery disease,

subjects with moderate or severe stenosis were considered as one group in the analysis. Table 6.2 presents mean values for blood pressure, smoking, serum lipids, and hemostatic factors for those with no stenosis, minimal lesions and moderate-to-severe stenosis of the right carotid artery. The observed differences in serum lipids and hemostatic factors between subjects with minimal lesions and those without stenosis did not reach the level of statistical significance. The presence of hypertension, however, significantly differed across groups. This finding remained significant after adjustment for differences in age, sex, and body mass index.

Subjects with moderate-to-severe carotid artery stenosis had, compared to subjects without stenosis, significantly lower mean levels of HDL-cholesterol (table 6.2). Current smoking and hypertension were more common among subjects with moderate-to-severe carotid artery disease. These findings were independent from age, sex, and body mass index. Current smoking was strongly associated with elevated levels of fibrinogen ($p < 0.01$) and mean fibrinogen levels across groups were compared adjusted for smoking. Elevated plasma fibrinogen was independently of age, sex, body mass index, and smoking, related to atherosclerotic carotid artery disease. Mean levels of factor VIIc and factor VIIIc activity were higher in the stenotic group compared to the reference group, without, however, reaching statistical significance. Across groups with increasing severity of carotid atherosclerosis, significant trends were found for hypertension ($p < 0.01$), smoking ($p = 0.01$), HDL cholesterol ($p = 0.03$), and fibrinogen ($p = 0.03$).

Discussion

Our data indicate that the prevalence of right-sided severe carotid artery stenosis among persons aged 55 to 75 years is 1.4 %: 2.4 % in men and 0.7 % in women. For subjects aged 75 years or over, prevalence was 1.4 %. Hypertension is significantly more common in subjects with minimal and moderate-to-severe carotid artery disease. Furthermore, subjects with moderate-to-severe stenosis have a higher mean fibrinogen level and a lower mean HDL cholesterol level compared to subjects without stenosis. Among them were significantly more current smokers. In addition, participants with moderate-to-severe stenosis have higher mean levels of factor VIIc and factor VIIIc activity. Although the differences in hemostatic factors did not reach statistical significance, they may suggest an increased activation of coagulation system in moderate-to-severe atherosclerotic carotid artery disease. Trend analysis suggested that a gradual increase in severity of carotid atherosclerosis may be associated with an unfavorable change in mean levels of cardiovascular risk factors.

Table 6.2 Comparisons of cardiovascular characteristics at baseline of subjects with minimal and moderate to severe stenosis of the carotid artery relative to the reference group (0 % stenosis).

Cardiovascular determinants	Baseline values Carotid artery stenosis 0 %	 1-15 %	 ≥ 16 %	Adjusted values* Carotid artery stenosis 0 %	 1-15 %	 ≥ 16 %	Adjusted difference between moderate-to-severe stenosis and reference group	[95 % CI]	*p* value
Systolic pressure (mmHg)	133.4 (0.7)	139.7 (1.5)	138.2 (3.3)	133.8 (0.71)	138.6 (1.36)	135.4 (3.0)§	1.6	[-4.2,7.7]	0.57
Diastolic pressure (mmHg)	70.3 (0.4)	72.0 (0.8)	67.7 (1.8)	70.3 (0.39)	72.1 (0.74)	67.8 (1.6)	-2.5	[-5.6,0.7]	0.13
Hypertension (%)	34	47	53	33 (2)	44 (3)	49 (7)§	16	[1,30]	0.03
Current smoking (%)	23	26	32	22 (2)	28 (3)	35 (6)§	13	[0,25]	0.05
Cholesterol (mmol/l)	6.74 (0.04)	6.76 (0.08)	6.60 (0.23)	6.74 (0.04)	6.77 (0.08)	6.67 (0.18)	-0.07	[-0.6,0.4]	0.73
HDL cholesterol (mmol/l)	1.35 (0.01)	1.32 (0.02)	1.21 (0.04)	1.35 (0.01)	1.32 (0.02)	1.25 (0.05)§	-0.10	[-0.20,0.0]	0.05
Fibrinogen (g/l)	2.72 (0.02)	2.81 (0.05)	3.02 (0.13)	2.73 (0.02)	2.77 (0.05)	2.97 (0.10)§	0.24	[0.04,0.45]	0.02
Factor VIIc (IU/ml)†	1.08 (0.01)	1.09 (0.02)	1.11 (0.04)	1.08 (0.01)	1.09 (0.02)	1.14 (0.03)	0.06	[-0.01,0.12]	0.08
Factor VIIIc (IU/ml)	2.06 (0.03)	2.10 (0.06)	2.28 (0.14)	2.06 (0.03)	2.07 (0.06)	2.27 (0.13)	0.21	[-0.05,0.47]	0.12

Values are percentages or means with standard errors in parentheses

* Values are adjusted for differences in age, sex, body mass index and when appropriate for cholesterol and smoking.

† Those currently using anticoagulant drugs (n=47) have been excluded

§ Test for trend $p < 0.05$

In our present study, only the right carotid artery was evaluated. Because carotid artery disease appears to be randomly distributed across both left and right sides[12], a number of subjects in our reference group may have had left-sided carotid artery stenosis. This may reduce the magnitude of observed differences between groups, provided a true association exists between the observed cardiovascular riskfactors and stenosis of the carotid artery. Consequently, the observed associations in our study might actually have been stronger if a classification based on two carotid arteries could have been used.

Selective survival and selective non-response may have led to underestimation of the prevalence of one-sided carotid artery disease, the extent of which, however, can not be ascertained. Estimates of prevalence of moderate and severe carotid artery stenosis vary across studies. In a survey among 316 asymptomatic subjects, aged 55 to 74 years, Josse and co-workers observed a prevalence of 1.6 %.[13] Colgan and associates reported a prevalence of 3.2 % severe carotid artery stenosis among 348 unselected asymptomatic subjects.[14] Others found a prevalence of 5-6 %.[12,15,16] The differences across studies may in part be due to differences in methods of assessing stenosis (duplex vs continuous wave), in definitions of the cutoff point of carotid artery stenosis, in age groups and in non-response. Yet, our estimate is quite similar to those observed by others, when one takes into account that carotid artery disease appears to be randomly distributed across both left and right sides.[12]

In previous studies the presence of hypertension and current smoking were associated with moderate and severe carotid artery disease.[12,15,16] The lack of association with total cholesterol in our study may in part be explained by selective survival. In addition, a decrease in relative importance of this factor with age, may also have contributed to this finding.[17]

Results from several studies have suggested an important role for coagulation and hemostasis in initiation and progression of cardiovascular disease.[18,19] An elevated fibrinogen level is a major cardiovascular risk factor.[18] Increased levels of factor VIIc and factor VIIIc activity have been associated with increased risk of coronary heart disease.[20] In elderly subjects with atherosclerotic disease, raised levels of factor VIIc and factor VIIIc activity were recently observed.[21,22] Our results support these findings and suggest that these mechanisms are indeed operative in carotid artery disease. Confirmation, however, is needed. The baseline findings of the Rotterdam Study reflect cross-sectional measurements, so it therefore cannot be ascertained whether the differences between stenotic and nonstenotic groups indicate mechanisms that cause atherosclerotic lesions or are a consequence of atherosclerosis. In view of this, it is important to confirm these associations in prospective follow-up studies.

We conclude that in a considerable proportion of the elderly population moderate

or severe carotid artery stenosis is present. Hypertension, smoking and low HDL cholesterol levels are significantly associated with atherosclerosis of the carotid artery. Furthermore, elevated fibrinogen levels show an independent relationship with carotid artery disease. These findings suggest that an unfavorable cardiovascular risk profile, including changes in hemostatic factors, may be related to carotid artery disease.

References

1. Jungquist G, Nilsson B, Ostberg H, et al. Carotid artery blood flow velocity related to transient ischemic attack and stroke in a population study of 69-year-old men. Stroke 1989;20:1327-30.
2. Admani AK, Mangion DM, Naik DR. Extracranial carotid artery stenosis: Prevalence and associated risk factors in elderly stroke patients. Atherosclerosis 1991;86:31-7.
3. Autret A, Pourcelot L, Saudeau D, et al. Stroke risk in patients with carotid stenosis. Lancet 1987;i:888-90.
4. Meissner I, Wiebers DO, Whisant JP, et al. The natural history of asymptomatic carotid artery occlusive lesions. JAMA 1987;258:2704-7.
5. Feussner JR, Matchar DB. When and how to study the carotid arteries. Ann Intern Med 1988;109:805-18.
6. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.
7. Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987;15:635-44.
8. World Health Organisation. Measuring obesity. Classification and description of anthropomometric data. Report on a WHO consultation on the epidemiology of obesity. Geneva: WHO, 1987.
9. Joint National Committee on High Blood Pressure. 1988 report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1988;148:1023-38.
10. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.
11. Clauss A. Gerinnungsphysiologische schnellmethode zur bestimmung des fibrinogens. Acta Haematol 1957;17:237-46.
12. Jungquist G, Hanson BS, Isacsson SO, et al. Risk factors for carotid artery stenosis: An epidemiological study of men aged 69 years J Clin Epidemiol 1991;44:347-53.
13. Josse MO, Touboul PJ, Mas JL, et al. Prevalence of asymptomatic internal carotid artery stenosis. Neuroepidemiol 1987;6:150-2.
14. Colgan MP, Strode GR, Sommer JD, et al. Prevalence of asymptomatic carotid disease: Results from duplex scanning in 348 unselected volunteers. J Vasc Surg 1988;8:674-8.
15. Fowl RJ, Marsch JG, Love M, et al. Prevalence of hemodynamically significant stenosis of the carotid artery in an asymptomatic population. Surg Gyn Obst 1991;172:13-6.
16. Ramsey DE, Miles RD, Lambeth A, Summer DS. Prevalence of extracranial carotid artery disease: A survey of an asymptomatic population with noninvasive techniques. J Vasc Surg 1987;5:584-8.

17. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. J Chron Dis 1978;31:201-306.

18. Meade TW. Hypercoagulability and ischaemic heart disease. Blood Reviews 1987;1:2-8.

19. Fitzgerald DJ, Roy L, Catella F, et al. Platelet activation in unstable angina pectoris. N Engl J Med 1986;315:983-9.

20. Meade TW, North WRS, Chakrabarti R, et al. Haemostatic function and ischaemic heart disease: Early results of the Northwhick Park Heart Study. Lancet 1980;i:1050-4.

21. Kario K, Matsuo T, Nakao K. Factor VII hyperactivity in the elderly. Thromb Haemost 1991;65:25-7.

22. Tracy RP, Bovill EG, Fried LP, et al. Coagulation factors in men and women over 65 years: Cardiovascular Health Study. (abstract) 31st Annual Conference on Cardiovascular Disease Epidemiology. Florida, USA, 1991.

Chapter 7

Cerebral white matter and atherosclerosis

7 Cerebral white matter lesions and atherosclerosis in the Rotterdam Study

Introduction

Cerebral white matter lesions frequently seen on magnetic resonance images of brains of elderly subjects[1,2,3] are associated with a positive history of stroke and coronary heart disease and with elevated levels of established cardiovascular risk factors.[4,5,6,7] Recently, we have found a positive association between cerebral white matter lesions and hemostatic factors in an elderly population.[6] These findings may indicate that some of these lesions in the elderly may be due to atherosclerosis, possibly mediated by cardiovascular risk factors.

Non-invasive techniques for assessing the presence and extent of atherosclerotic vessel wall abnormalities at different arterial sites allow the association between cerebral white matter lesions and atherosclerosis to be studied more directly. Duplex ultrasonography, combined with Doppler spectral analysis, can assess hemodynamically significant stenosis of the carotid artery[8] and high resolution B-mode ultrasonography allows accurate detection of early atherosclerosis of the carotid artery wall.[9,10,11,12,13] The ratio of systolic blood pressure in the ankle to the systolic blood pressure in the arm (ankle-arm index) reflects the presence of atherosclerotic vessel wall abnormalities of the arteries of the lower extremities,[14,15] whereas myocardial infarction, confirmed by electrocardiography, indicates coronary atherosclerosis.[16]

In this paper we present findings on the association of cerebral white matter lesions and non-invasively assessed atherosclerosis among 111 participants of the Rotterdam Study.

Methods

Population

The Rotterdam Study is prospective follow-up study of people aged 55 years or over, to investigate the incidence of, and risk factors for chronic disabling diseases.[17] The study has been approved by the Medical Ethics Committee of Erasmus University and written informed consent is obtained from all participants. All inhabitants aged 55 years or more, living at one point in time in the Rotterdam suburb of Ommoord were invited to participate. The participation rate of the cohort at the time of this analysis was 80 %.

Participants aged 65 to 85 years, were invited to participate in an additional study of the presence and determinants of cerebral white matter lesions on magnetic resonance

images directly after they had finished the baseline study protocol of the Rotterdam Study.[6] They were randomly selected, stratified by 5 years age-groups and gender. Of the 134 subjects initially selected, six were excluded: three because of a pacemaker or metal prostheses or surgical clips, one because of a major psychiatric illness and two because they were wheelchair-bound and unable to walk. Of the 128 subjects that were eligible for magnetic resonance imaging, 111 (87 %) consented to participate.

Carotid arteries

Hemodynamically significant stenosis of the carotid artery was ultrasonographically assessed using a 7.5 MHz sector transducer in combination with a 5 MHz pulsed Doppler (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA).[18] Interpretation of velocity profiles was done on-line.[19] The right internal carotid artery was categorized as normal (0 % reduction of lumen diameter), minimal lesions (1-15 % reduction), moderate stenosis (16-49 % reduction) or severe stenosis (≥ 50 % reduction).

To assess carotid intima-media thickness, ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer. On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (figure 3.1.1).[20] The distance of the leading edge of the first bright line on the far wall (lumen-intima interface) and the leading edge second bright line (media-adventitia interface) indicates the intima-media thickness.[20,21] Studies have indicated that the posterior (far) wall intima-media thickness as seen with ultrasound, truly reflects the anatomical intima-media layer.[20,21]

The Rotterdam Study ultrasound protocol demands a careful examination of the lumen-intima interface and the media-adventitia interface on the far wall of the distal common carotid artery.[13] When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for each left and right side. Subsequently, the common carotid artery is on-line evaluated for the presence (yes/no) of atherosclerotic lesions, defined as a focal widening relative to adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. The actual measurement of intima-media thickness is performed off-line. From the videotape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software.[13,21] From the average of the three frozen images per carotid artery, a mean common carotid intima-media thickness ((left+right)/2) is taken a measure for current wall thickness of the distal common carotid artery.

In a separate reproducibility study, 80 participants of the Rotterdam Study had a second ultrasound scan of both carotid arteries within 3 months of the first scan to measure posterior common carotid intima-media thickness. Mean differences (SD) in common carotid intima-media thickness between repeated measurements of two sonographers and of two off-line ultrasound readers were 0.040 (0.07) and 0.069 (0.04), respectively. Mean difference (SD) in common carotid intima-media thickness between measurements at the first and the second visit was 0.071 (0.09).

Coronary arteries

Resting standard 12-lead electrocardiogram was obtained with an ACTA Gnosis IV (EsaoteBiomedica, Firenze, Italy), and were read and coded.[22] The assessment of a possible or definite myocardial infarction was based on the presence of major, moderate and minor Q/QS abnormalities and a clinical evaluation of the electrocardiogram by a cardiologist (Dr H.A.C.M Kruijssen). The presence of a possible or definite myocardial infarction on the electrocardiogram was used as an indicator of prevalent atherosclerotic coronary artery disease.[16]

Arteries of the lower extremities

The presence of atherosclerosis in the arteries of the lower extremities was evaluated by measuring the systolic blood pressure level of both left and right posterior tibial arteries with a 8 MHz continuous wave doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK), and a random-zero sphygmomanometer.[14,15] For each side a single blood pressure reading was taken with the subject in supine position. The lowest ankle-arm index in either leg was used in the analysis,[14] an ankle-arm index less than 0.90 at at least one side was used to select a group with a high probability of having peripheral arterial disease.[15,23]

Cardiovascular risk factors

Information on current health status, medical history, drug use, and smoking behaviour was obtained using a computerized questionnaire. Subjects were categorized into groups of current smokers, former smokers and those who had never smoked. During two visits at the research centre several cardiovascular risk indicators were measured. Sitting blood pressure was measured in the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used. Hypertension was defined as a systolic blood pressure level of 160 mmHg or over and/or a diastolic blood pressure level of 95 mmHg or over and/or current use of antihypertensive drugs. A venipuncture was performed, applying minimal

stasis, using a 21 gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Serum total cholesterol and high density lipoprotein (HDL) cholesterol were determined with an automated enzymatic procedure.[24]

Cerebral white matter lesions

With magnetic resonance imaging (1.5 T Philips Gyroscan), multiple slice spin-echo sequences were performed with a repetition time of 2000 msec and an echotime of 50 and 100 msec, producing a T2-weighted image. Images were obtained in the axial plane with a slice thickness of 7 mm and a slice increment of 1.4 mm. The magnetic resonance imaging scans were assessed blind to any clinical information, or other measurements. We distinguished between cerebral white matter lesions adjacent to the ventricles (periventricular), and punctate or confluent lesions at some distance from the ventricles (focal). Small caps on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal.[1,5,25] Infarcts on magnetic resonance imaging were recorded, but not included in the rating of the cerebral white matter lesions. The severity of cerebral white matter lesions was graded as grade 0 (no or slight periventricular hyperintensity, less than 5 punctate lesions and no confluent lesions); grade 1 (moderate periventricular hyperintensity or more than 5 punctate lesions, or both, but no confluent lesions); or grade 2 (severe periventricular hyperintensity or confluent lesions, regardless of the presence of punctate lesions). In addition, for some analyses subjects with grade 1 or 2 were classified as those with cerebral white matter lesions and subjects with grade 0 were classified as without cerebral white matter lesions.[6]

Data analysis

In three subjects, extreme tortuosity of the artery prevented reliable measurements. For five subjects, technical failure prevented common carotid intima-media thickness measurements. For four subjects, measurement of vessel wall thickness was not possible from the stored images because of poor visualization. For 102 subjects (92 %) measurements of posterior intima-media thickness were available, and data on presence of plaques in the common carotid artery and the bifurcation were obtained in 94 % and 78 % of the subjects, respectively. Ankle-arm index were obtained from all subjects. Of 6 subjects no electrocardiogram data were available.

Mean common carotid intima-media thickness and ankle-arm index were compared between subjects with and without cerebral white matter lesions. For continuously distributed, multiple linear regression analysis was used to assess differences across groups, adjusted for age and gender. The differences are presented with a 95 % confidence interval (CI). Analyses for trends between groups with increasing severity of

cerebral white matter lesions were done with a multiple regression analysis. The risk of cerebral white matter lesions associated with binary variables such as presence of plaques in the carotid artery, definite or possible myocardial infarction, and presence of peripheral arterial disease was assessed with logistic regression, with presence of cerebral white matter lesions as the depended variable. Measures of the strength of the association are presented with odds ratio's with 95 % CI. Since the prevalence of cerebral white matter lesions strongly increases with age and tends to be different across gender,[6] all associations between other variables and cerebral white matter lesions were adjusted for differences in age and gender.

In a separate analysis, a multiple linear regression model was used to assess whether the observed associations between cerebral white matter lesions and intima-media thickness, myocardial infarction and ankle-arm index, remained after adjustments for cardiovascular risk factors, including hypertension, total serum cholesterol, HDL cholesterol and smoking.

Results

In table 7.1 general characteristics of subjects with and without cerebral white matter lesions on the magnetic resonance imaging scan are presented. Compared to subjects without cerebral white matter lesions, those with cerebral white matter lesions were older and among them were more women.[6] In an earlier paper, we have reported on the association between cerebral white matter lesions and cardiovascular risk factors.[6]

Indicators of atherosclerosis in those with and without cerebral white matter lesions is shown in table 7.1. Intima-media thickness of the common carotid artery was significantly higher in subjects with cerebral white matter lesions compared to those without lesions, with a adjusted mean difference of 0.13 mm [95 % CI 0.04,0.21]. The results for the logistic regression analysis indicated that an increase of 0.1 mm in common carotid intima-media thickness was associated with 50 % increase in the probability of cerebral white matter lesions (table 7.2). The prevalence of a minimal, moderate to severe hemodynamically significant stenosis of the right internal carotid artery did not differ between the two groups.

The ankle-arm index was significantly reduced in subjects with cerebral white matter lesions with a difference adjusted for age and gender of -0.11, 95 % CI -0.21,-0.01. A decrease of 0.1 in ankle-arm index was associated with 20 % increase in the probability of cerebral white matter lesions (table 7.2). Similar results were observed

Table 7.1 Characteristics of subjects with and without cerebral white matter lesions.

		White matter lesions		
		Absent n = 81	Present n = 30	p value|
Cardiovascular risk factors				
Age (yrs)		72.4 (5.8)*	77.7 (5.4)*	< 0.01
Sex (% female)		49	67	0.11
Body mass index (kg/m^2)		26.4 (3.6)*	26.5 (3.0)*	0.88
Smoking	Current (%)	30	10	0.04
	Former (%)	47	52	0.18
	Never (%)	23	38	0.14
Systolic pressure (mmHg)†		132 (18)*	141 (19)*	0.08
Diastolic pressure (mmHg)†		69 (10)*	70 (9)*	0.63
Hypertension (%)‡		28.3	41.4	0.20
Cholesterol				
	Total (mmol/l)	6.56 (1.34)*	6.83 (1.25)*	0.25
	HDL (mmol/l)	1.29 (0.32)*	1.24 (0.30)*	0.40
Carotid arteries				
Stenosis (%)				
	0 %	74	75	0.97
	1-16 %	22	21	0.80
	≥ 16 %	4	4	0.84
Intima-media thickness (mm)		0.81 (0.16)*	0.96 (0.24)*	< 0.01
Plaques§				
	Common carotid artery (%)	14	11	0.74
	Carotid bifurcation (%)	57	83	0.02
Coronary arteries				
Definite myocardial infarction (%)		7	19	0.24
Possible myocardial infarction (%)		3	8	0.26
Combined (%)		10	27	0.03
Peripheral arteries				
Ankle-arm index		1.13 (0.21)*	1.03 (0.25)*	0.03
Lower extremity arterial disease (%)		14	30	0.05

* Means [SD]

† Subjects on antihypertensive drugs excluded

‡ Systolic pressure ≥ 160 mmHg and/or diastolic pressure ≥ 95 mmHg and/or on antihypertensive drugs

§ Plaques located in anterior or posterior wall of the common carotid artery and bifurcation, in at least one carotid artery.

| Unadjusted P-value for differences across groups

Table 7.2 Associations between atherosclerosis and cerebral white matter lesions.

		Odds ratio* of having cerebral white matter lesions		Odds ratio adjusted for age and gender of having cerebral white matter lesions	
Carotid arteries					
Stenosis	0 %	1.0*		1.0*	
	1-16 %	0.9	[0.3,2.7]	0.7	[0.2,2.3]
	≥ 16 %	2.1	[0.2,10.4]	5.3	[0.7,46.3]
Intima-media thickness		1.5	[1.2,1.9]‡	1.5	[1.1,2.1]‡
Plaques†					
	Common carotid artery	0.8	[0.2,3.2]	0.9	[0.2,4.1]
	Carotid bifurcation	3.8	[1.1,12.5]	3.9	[1.0,14.5]
Coronary arteries					
Definite myocardial infarction		3.3	[0.9,12.8]	2.1	[0.5,9.2]
Possible myocardial infarction		3.0	[0.4,23.4]	6.9	[0.7,70.0]
Combined		3.6	[1.1,11.6]	3.1	[0.8,11.4]
Peripheral arteries					
Ankle-arm index		1.2	[1.0,1.5]§	1.2	[1.0, 1.5]§
Peripheral arterial disease		2.7	[1.0,7.6]	2.4	[0.8,7.6]

* Used as reference category

† Plaques located in anterior or posterior wall of the common carotid artery and bifurcation, in at least one carotid artery.

‡ Per 0.1 mm increase

§ Per 0.1 decrease

when the left or right common carotid artery and the left or right ankle-arm index were used in the analysis. Peripheral arterial disease was found in 30 % of subjects with cerebral white matter lesions compared with 16 % of subjects without lesions.

The prevalence of definite and possible myocardial infarction, based on the electrocardiogram, was 27 % in subjects with cerebral white matter lesions compared to 10 % in those without lesions. The observed associations for peripheral arterial disease and prevalence of myocardial infarction did not, however, reach significance.

Significant trends were found for carotid intima-media thickness (figure 7.1, top) and ankle-arm index (figure 7.1, middle) between with increasing severity of cerebral white matter lesions. Although myocardial infarction was more common among subjects

with grade 1 or grade 2 cerebral white matter lesions, a significant gradual increase in the prevalence of myocardial infarction with increasing severity of cerebral white matter lesions was not demonstrated (figure 7.1, bottom). For subjects aged 65 to 74 years the association between cerebral white matter lesions and common carotid intima-media thickness was stronger than in subjects aged 75 to 84 years. Mean differences across groups were 0.16 mm [95 % CI 0.03,0.27] and 0.09 mm [95 % CI -0.04,0.22], respectively. Similar results were obtained for ankle-arm index. The strength of the association between myocardial infarction and cerebral white matter lesions, however, increased with age. For those aged 75 to 84 years a difference of 24 % [95 % CI -2,50] was observed compared to 4 % [95 % CI -8,16] for subjects aged 65 to 74 years. The magnitude of the association between cerebral white matter lesions and common carotid intima-media thickness did not differ between elderly men and women. With respect to the ankle-arm index, a mean difference in ankle-arm index of -0.14 [95 % CI -0.03,-0.025] was observed between women with and without cerebral white matter lesions, whereas for men the difference was -0.04 [95 % CI -0.24,0.20]. For myocardial infarction, an opposite association was found with a stronger association in men as compared to women.

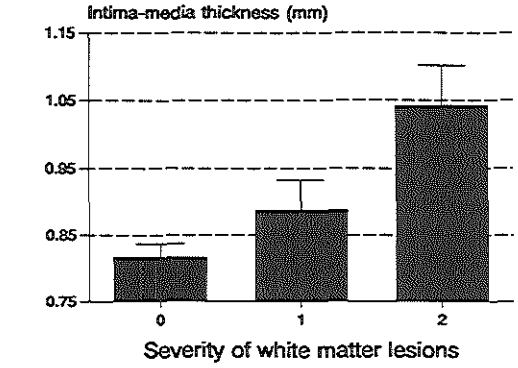
Table 7.3 Odds ratio [95 % CI] of an increased common carotid intima-media thickness, myocardial infarctions and ankle-reduced arm index for cerebral white matter lesions, with and without adjustment for several cardiovascular risk factors.

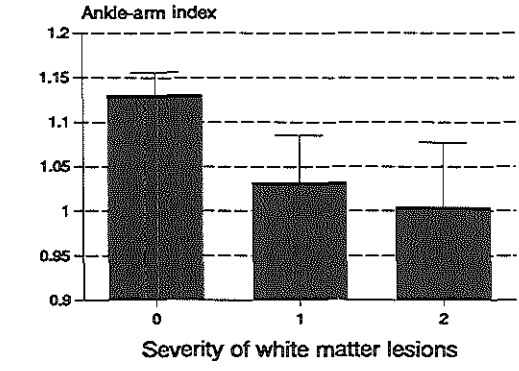
	Odds ratio per 0.1 mm increase in intima-media thickness		Odds ratio of myocardial infarction*		Odds ratio per 0.1 decrease in ankle-arm index	
No adjustment	1.5	[1.2,1.9]	3.6	[1.1,11.6]	0.8	[0.7,1.0]
Age and gender	1.5	[1.1,2.1]	3.1	[0.8,11.4]	0.8	[0.6,1.0]
Hypertension†	1.4	[1.1,2.1]	2.9	[0.8,10.9]	0.8	[0.7,1.1]
Total cholesterol†	1.5	[1.1,2.2]	3.0	[0.8,11.3]	0.8	[0.7,1.0]
HDL cholesterol†	1.5	[1.1,2.1]	2.8	[0.7,10.6]	0.8	[0.7.1.0]
Current smoking†	1.5	[1.1,2.2]	3.3	[0.9,12.5]	0.8	[0.6,1.0]
All‖	1.4	[1.0,2.1]	2.9	[0.7,11.6]	0.8	[0.6,1.1]

* Combined definite and possible myocardial infarction diagnosed on electrocardiogram.

† Results obtained by multivariate logistic regression. Each risk factor is entered separately in a model in which age and gender are included.

‖ All risk factors are used in the logistic regression model.





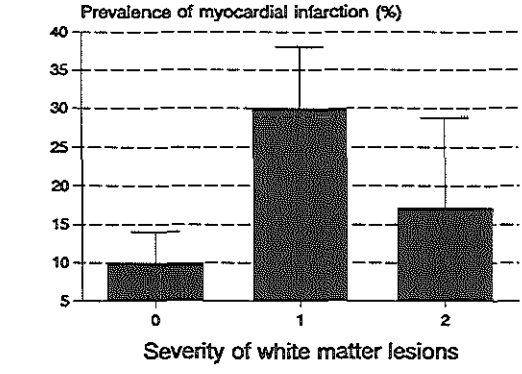


Figure 7.1 *Atherosclerosis across groups with increasing severity of white matter lesions. (top) Intima-media thickness (SE). Linear trend test: $p < 0.01$; (middle) Ankle-arm index (SE) of the tibial posterior arteries. Linear trend test: $p = 0.05$; (bottom) Prevalence of definite and possible myocardial infarction (SE). Linear trend test: $p = 0.19$.*

The results of additional multivariate adjustment of cardiovascular risk factors on the size of the odds ratios for intima-media thickness, ankle-arm index and prevalence of possible or definite myocardial infarction in subjects with cerebral white matter lesions are presented in table 7.3. Adjustment for differences in risk factors slightly reduced the magnitude of the association with common carotid intima-media thickness without changing the direction of the association between carotid atherosclerosis and cerebral white matter lesions. Similar results were found for myocardial infarction. No change was observed in the magnitude of the association between cerebral white matter lesions and ankle-arm index after additional adjustment of cardiovascular risk factors.

Discussion

Our findings, in a population-based study of magnetic resonance images of brains of elderly people, provide evidence that cerebral white matter lesions are associated with atherosclerosis as non-invasively demonstrated by increasing common carotid intima-media thickness and a reduced ankle-arm index. Atherosclerotic plaques in the carotid bifurcation, evidence of myocardial infarction on the electrocardiogram and peripheral arterial disease are more common in subjects with cerebral white matter lesions. Trend analyses suggest that a gradual increase in severity of cerebral white matter lesions is associated with an increase of intima-media thickness and a decrease of the ankle-arm index. Hemodynamically significant stenosis of the right internal carotid artery was, however, not associated with cerebral white matter lesions.

Before these findings can be accepted some aspects of the study need to be considered. Firstly, increased carotid intima-media thickness may not necessarily be atherosclerosis and is not in itself a precursor of atherosclerosis. It may merely reflect an adaptive response of the vessel wall to changes in shear stress and tensile stress.[26] Furthermore, atherosclerosis is viewed as a disorder which is restricted to the intima layer of the arterial vessel wall, and ultrasound imaging can not discriminate between the intima layer and the media layer of vessel wall. In several studies, ultrasonographically determined increased common carotid intima-media thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors.[10,13,27,28] In addition, progression of common carotid intima-media thickness over time has been associated with risk factors for atherosclerosis.[11] These results support the view that non-invasively assessed intima-media thickness of the common carotid artery may be regarded as a measurement of atherosclerosis.

Secondly, the ankle-arm index was based on a single blood pressure reading performed on one occasion. Some misclassification may have occurred, which may have

reduced the observed difference between the groups, provided a true association exists and misclassification occurred to the same extent among subjects with and without cerebral white matter lesions.

In several studies cerebral white matter lesions have been found to be related to elevated levels of established cardiovascular risk factors.[1,4,5,6] In addition, elevated levels of hemostatic and rheological factors have been associated with cerebral white matter lesions.[6,7] Post-mortem neuropathological studies have indicated that cerebral white matter lesions seen on magnetic resonance imaging are associated with degenerative changes in arterioles which are related to the process of atherosclerosis.[29,30,31] Our observation of an association of cerebral white matter lesions and carotid-, coronary- and peripheral atherosclerosis in free living subjects supports these findings.

In the present study, the frequency of haemodynamic important stenosis of the right internal carotid artery among subjects with cerebral white matter lesions did not differ from those without lesions. This finding can probably not be explained by the fact that only the right carotid artery was evaluated for stenosis, since stenosis of the internal carotid artery appears to be randomly distributed across both left and right sides.[32] Our finding contrasts with the occurrence of uni- or bilateral stenosis in 8 of 53 volunteers with cerebral white matter lesions observed in a study of Fazekas.[33] Post-mortem neuropathological studies, however, have indicated that cerebral white matter lesions are predominantly associated with arteriolosclerosis, a type of small-artery disease. Furthermore, the findings of the present study with respect to stenosis are in accordance with findings from others, in which a relatively low prevalence of carotid artery stenosis was observed in subjects with lacunar infarcts, another type of small-artery disease.[34,35] These results may indicate that the haemodynamic consequences of stenosis of the carotid artery may not be responsible for the development of cerebral white matter lesions, and rather support the view that cerebral white matter lesions represent generalized vascular disease.

In our study among elderly subjects, adjustment for differences in smoking, hypertension and elevated levels of serum lipids, only partly attenuated the observed associations between cerebral white matter lesions and carotid atherosclerosis and myocardial infarction, whereas the association between cerebral white matter lesions and peripheral arterial atherosclerosis remained unchanged. These findings suggest that the association between cerebral white matter lesions and large vessel atherosclerosis can not be entirely attributed to confounding by common cardiovascular risk factors, but rather favours the hypothesis that cerebral white matter lesions are partly a direct consequence of atherosclerotic vessel wall disease, which in it self is related to elevated levels of cardiovascular risk factors. An alternative explanation is that, besides these factors,

others factors, yet unknown, play a role in the development of atherosclerosis of the carotid arteries, coronary arteries and peripheral arteries and cerebral white matter lesions or that the effect of these risk factors on both atherosclerosis and cerebral white matter lesions may be different across different arterial sites. A time dependent relationship between cerebral white matter lesions and atherosclerosis can not be determined on the basis of these cross-sectional data.

Whether cerebral white matter lesions give rise to dementia is still debated. Conflicting results about the association between cognitive impairment and evidence of cerebral white matter lesions have been reported. In some studies cerebral white matter lesions were associated with impaired cognitive functioning[4,36,37], whereas in others no such association could be observed.[2,3,25] The type of cerebral white matter lesions on magnetic resonance images may also be of importance. Periventricular hyperintensities were found more often in demented patients than in age-matched controls in most studies.[25,38] The extent and the location of cerebral white matter lesions may also partly explain some of the negative results.[39] In addition, differences between studies with regard to the association with dementia may have to be attributed to differences in selection of subjects, in sample sizes, in classification of presence or absence of cerebral white matter lesions and in the assessment of cognitive functioning. Finally, as our findings and those of others, suggest that cerebral white matter lesions are clearly associated with atherosclerosis, differences in etiology of cerebral white matter lesions may also have contributed to the contrasting results.

In conclusion, we found that cerebral white matter lesions, as seen on magnetic resonance images of a population sample of elderly subjects showed a clear association with atherosclerotic abnormalities in the carotid artery, the coronary arteries and in the peripheral vessels.

References

1. Kertesz A, Black SE, Tokar G, et al. Periventricular and subcortical hyperintensities on magnetic resonance imaging. 'Rims, caps and unidentified bright objects.' Arch Neurol 1988;45:404-8.
2. Hendrie HC, Farlow MR, Austrom MG, et al. Foci of increased T2 signal intensity on brain MR scans of healthy elderly subjects. AJNR 1989;10:703-7.
3. Hunt AL, Orrison WW, Yeo RA, et al. Clinical significance of MRI white matter lesions in the elderly. Neurology 1989;39:1470-4.
4. Van Swieten JC, Geyskes GG, Derix MMA, et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. Ann Neurol 1991;30;825-30.
5. Lechner H, Schmidt R, Bertha G, et al. Nuclear magnetic resonance image white matter lesions and risk factors for stroke in normal individuals. Stroke 1988;19;263-5.

6. Breteler MMB, Van Swieten JC, Bots ML, et al. Cerebral white matter lesions, vascular risk factors and cognitive function in a population-based study: The Rotterdam Elderly Study. (submitted).

7. Schneider R, Ringelstein EB, Zeumer H, et al. The role of plasma hyperviscosity in subcortical arteriosclerotic encephalopathy (Binswanger's disease). J Neurol 1987;243:67-73.

8. Feussner JR, Matchar DB. When and how to study the carotid arteries. Ann Intern Med 1988;109:805-18.

9. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

10. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.

11. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990;81:33-40.

12. Psaty BM, Furberg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly. Initial findings from the Cardiovascular Health Study. JAMA 1992;268:1287-91.

13. Bots ML, Hofman A, Bruyn AM de, et al. Isolated systolic hypertension and vessel wall thickness of the carotid artery: The Rotterdam Study. Arterioscler Thromb 1993;13:64-9.

14. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the ageing process: A review. J Clin Epidemiol 1992;45:529-42.

15. Fowkes FGR, Houseley E, Cawood EHH, et al. Edinburgh artery study: Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20:384-92.

16. Savage RM, Wagner G, Ideker E, et al. Correlation of postmortem anatomic findings with electrographic changes in patients with myocardial infarcts. Retrospective study in patients with typical anterior and posterior infarcts. Circulation 1977;55:279-85.

17. Hofman A, Grobbee DE, DeJong PTVM, et al. Determinants of disease and disability in the elderly. The Rotterdam Elderly Study. Eur J Epidemiol 1991;7:403-22.

18. Bots ML, Breslau PJ, Briët E, et al. Cardiovascular determinants of carotid artery disease: The Rotterdam Elderly Study. Hypertension 1992;19:717-20.

19. Taylor DC, Strandness DE. Carotid artery duplex scanning. J Clin Ultrasound 1987;15:635-44.

20. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

21. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

22. Rose G, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. World Health Organization. Geneva, 1982.

23. Schroll M, Munck O. Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population of 60 year old men and women. J Chronic Dis 1981;34:261-9.

24. Vangent CM, Vandervoort HA, De Bruyn AM, et al. Cholesterol determinations. A comparative study of methods with special reference to enzymatic procedures. Clin Chem Acta 1977;75:243-51.

25. Mirsen TR, Lee DH, Wong CJ, et al. Clinical correlates of white-matter changes on magnetic resonance imaging scans of the brain. Arch Neurol 1991;48:1015-21.

26. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

27. Haapanen A, Koskenvuo M, Kaprio J, et al. Carotid arteriosclerosis in identical twins discordant for cigarette smoking. Circulation 1989;80:10-6.

28. Poli A, Tremoli E, Colombo A, Sirtori M, et al. Ultrasonographic measurement of the common carotid artery wall thickness in hypercholesterolemic patients. Atherosclerosis 1988;70:253-61.

29. Van Swieten JC, van den Hout JHW, Van Ketel BA, et al. Periventricular lesions in the white matter on magnetic resonance imaging in the elderly. A morphometric correlation with arteriolosclerosis and dilated perivascular spaces. Brain 1991;114:761-74.

30. Awad IA, Johnson PC, Spetzler RF, et al. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. II. Postmortem pathological correlations. Stroke 1986;17:1090-7.

31. Braffman BH, Zimmerman RA, Trojanowski JQ, et al. Brain MR: Pathologic correlation with gross and histopathology. 2. Hyperintense white-matter foci in the elderly. AJR 1988;151:559-66.

32. Jungquist G, Hanson BS, Isacsson SO, et al. Risk factors for carotid artery stenosis: An epidemiological study of men aged 69 years. J Clin Epidemiol 1991;44:347-53.

33. Fazekas F, Niederhorn K, Schmidt R, et al. White matter signal abnormalities in normal individuals: Correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. Stroke 1988;1285-8.

34. Kappelle LJ, Koudstaal PJ, Gijn J van, et al. Carotid angiography in patients with lacunar infarction - a prospective study. Stroke 1988;19:1093-6.

35. Norrving B, Cronqvist S. Clinical and radiological features of lacunar versus nonlacunar minor stroke. Stroke 1989;20:59-64.

36. Junqué C, Pujol J, Vendrell P, et al. Leuko-araiosis on magnetic resonance imaging and speed of mental processing. Arch Neurol 1990;47:151-6.

37. Boone KB, Miller BL, Lesser IM, et al. Neuropsychological correlates of white matter lesions in healthy elderly subjects. A threshold effect. Arch Neurol 1992;49:549-54.

38. Bowen BC, Barker WW, Loewenstein DA, et al. MR signal abnormalities in memory disorder and dementia. AJNR 1990;11:283-90.

39. Gorelick PB, Chatterjee A, Patel D, et al. Cranial computed tomographic observations in multi-infarct dementia. A controlled study. Stroke 1992;23:804-11.

Chapter 8

Measurements of carotid artery wall thickness: Practice and prospects

8 Measurement of carotid artery wall thickness: Practice and prospects

The studies described in this thesis have predominantly focused on the feasibility and the value of non-invasive assessment of intima-media thickness of the distal common carotid artery as a non-invasive measure of generalized atherosclerosis in a non-hospitalized population. In this chapter the main findings from our studies are put in perspective to the results from other studies. In addition, some issues concerning non-invasive quantitative measurement of atherosclerosis are discussed.

Practise

Performance

The experience in the Rotterdam Study has shown that in approximately 99 % of the subjects reliable data on intima-media thickness of the distal common carotid artery can be obtained. Similar results have been reported by others.[1,2,3] Results from measurements of intima-media thickness at the carotid bifurcation and the internal carotid artery are slightly more difficult to acquire. The percentage of subjects from which measurements are successfully obtained varies across studies from approximately 75 % to around 99 %.[4] The complete procedure from actually doing the ultrasound to performing the measurements of lumen diameter and intima-media thickness from the videotaped images is time-consuming. Equipment that makes the performance of the measurement more user friendly or even semi- or fully-automatic, without compromising the validity and reproducibility of the measurement is most welcome. The first results using such an approach appear to be very promising.[5]

Precision

In the Rotterdam Study, lumen diameter and common carotid intima-media thickness have been evaluated using longitudinal 2-D ultrasound images. These 2-D images provide the most optimal view on the lumen diameter and the common carotid intima-media thickness. Furthermore, when a lesion was spotted, an additional image was taken, to assess the maximum intima-media thickness of the lesion as precise as possible.

Because there is no way of knowing whether or not the incident ultrasound beam is in the middle of the artery, some have argued that this approach results in a considerable measurement error of lumen diameter and intima-media thickness, which may lead to either under- or overestimation of the true value (figure 8.1). When, however, clear interfaces (chapter 3.1) are obtained from both the anterior wall and the posterior wall on the same image the likelihood of large errors in the measurement of

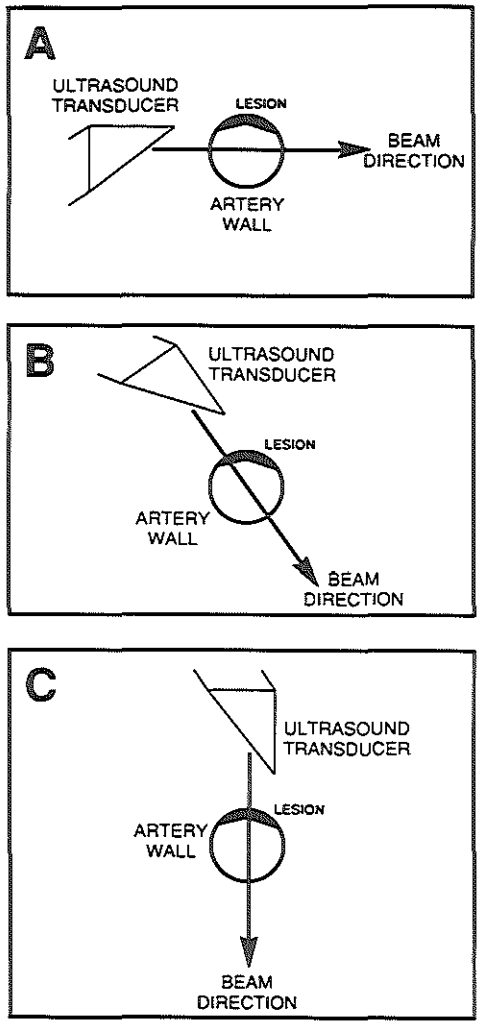


Figure 8.1 *Schematic presentation of possible approaches leading to under- or overestimation of the lumen diameter and the intima-media thickness of the common carotid artery (with permission reproduced from reference 4).*

lumen diameter and far wall intima-media thickness is limited. In particular because the presence of clear interfaces of both the anterior wall and the posterior wall indicates that the transducer ultrasound beam finds itself well into the longitudinal axis of the vessel. In general, for the distal common carotid artery lumen diameter and intima-media thickness measurements, such images were obtained. This approach was combined with having the sonographer select the most optimal image, a procedure which may further limit large errors in the measurement. Moreover, results from our reproducibility study

suggest that the error in the measurement due to this theoretical disadvantage appears to be rather small. Findings from our reproducibility study are similar to those reported by others, although some differences in methodology are present across studies.[6,7,8,9]

Validity

Non-invasive ultrasonography is presently used in a number of studies to assess presence and extent of atherosclerosis. In these studies carotid artery intima-media thickness is measured and used as an indicator of atherosclerosis in the carotid artery and elsewhere. However, measurements of intima-media thickness are currently not performed in a uniform way. In some studies intima-media thickness measurements are performed on the near and far wall of the carotid artery, whereas others measure only the far wall intima-media thickness, according to the 'leading edge principle' (chapter 3.1).[10] Validation studies have compared the precise location of the interfaces as seen with high resolution B-mode ultrasonography with the histologic layers of the arterial wall. Results from these studies have indicated that the intima-lumen interface of the near wall and the lumen-intima interface and the media-adventitia interface at the far wall as seen with ultrasound truly reflects lumen diameter and intima-media thickness.[11,12] Furthermore, the thickness of the intima-media measured with ultrasound has been compared to histologically assessed intima-media thickness. These findings are presented in table 8.1, and strongly suggest that high resolution B-mode ultrasonography is capable of accurately measuring far wall intima-media thickness, whereas the thickness of the near wall intima-media may substantially be underestimated with ultrasound. The intima-media thickness measurement of the near wall of the carotid artery is at best an approximation of the true near wall intima-media thickness. Moreover, the precision of the estimate of the near wall intima-media thickness depends on the axial resolution of the equipment used and on the gain setting; the higher the axial resolution, the more precise the measurement, and the higher the gain, the lower the axial resolution.[11,12,12] For comparison of

Table 8.1 Comparison of histologic and sonographic measurements of the common carotid intima-media thickness.

		Number of arteries	Intima-media thickness	
			Histologic	Sonographic
Far wall	Pignoli[11]	44	0.48 (0.06)	0.52 (0.08)
	Wong[13]	36	0.86 (0.20)	0.88 (0.11)
Near wall	Wong[13]	36	1.04 (0.31)	0.83 (0.12)

Values are means with standard deviations in parentheses.

of results on carotid intima-media thickness across studies, findings should preferably be presented for near and far wall intima-media thickness separately rather than as a mean result only.

Prospects

Intima-media thickness: Nature

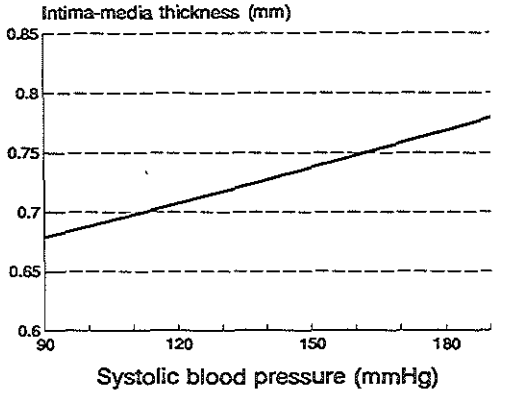
One of the major issues of debate regarding common carotid intima-media thickness measurements is the nature of the measurement, i.e., whether increased common carotid intima-media thickness itself reflects atherosclerosis. Atherosclerosis is viewed as a disorder which is restricted to the intimal layer of the arterial vessel wall,[14] and ultrasound imaging can not discriminate between the intima layer and the media layer of the vessel wall. Thus, an increased common carotid intima-media thickness may reflect either increased intimal thickening, or increased thickening of the medial layer or a combination of both.

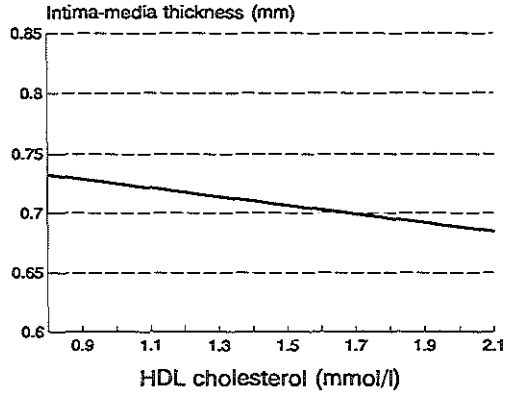
Some studies have reported an association between left ventricular mass and increased common carotid intima-media thickness.[15,16] These results may suggest that the process underlying an increased common carotid intima-media thickness may be hypertrophy of the media layer. Evidence to support the view that increased common carotid intima-media thickness could be regarded as an indicator of atherosclerosis derives from results from several studies, including the Rotterdam Study (table 8.2). Elevated levels of established cardiovascular risk factors, such as age, systolic blood pressure, total cholesterol, body mass index and smoking, are associated with increased intima-media thickness of the common carotid artery, whereas high density lipoprotein cholesterol is inversely related to intima-media thickness.[1,3,17,18] Moreover, recent findings, some of which are preliminary, from population based studies have indicated that increased levels of hemostatic factors (fibrinogen,[19,20] beta thromboglobulin[21]), fibrinolytic factors (tissue plasminogen antigen, plasminogen activator inhibitor I),[22] antioxidants (beta-carotene, vitamin A) and dietary components of supposed atherogenecity[23,24] are associated with increased common carotid intima-media thickness. In addition, results from studies described in the present thesis have shown that increased common carotid intima-media thickness is related to presence of atherosclerosis in the abdominal aorta, in the internal carotid arteries, in the arteries of the lower extremities and in the coronary arteries. In one study, risk factors for atherosclerosis have been related to progression of common carotid intima-media thickness over time[25] and an increased common carotid intima-media thickness has been found to be a predictor of the occurrence of myocardial infarction in the future.[26]

Table 8.2. Associations of increased common carotid intima-media thickness with cardiovascular risk factors, atherosclerosis, and prevalent cardiovascular disease.

Risk factors	→	Atherosclerosis	→	Cardiovascular disease
		Carotid arteries ↑		
		Coronary arteries ?		
Age ↑		Abdominal aorta ↑		
male ↑		Lower extremities ↑		
Diabetes ↑				
Systolic pressure ↑		↑		
Hypertension ↑				Stroke ↑
ISH ↑		**Increased**		Angina pectoris ↑
Total cholesterol ↑	→	**common carotid**	→	Myocardial infarction ↑
HDL cholesterol ↓		**intima-media thickness**		Aortic aneurism ↑
Smoking ↑				Lower extremity arterial disease ↑
Body mass index ↑				
Fibrinogen ↑				
B-thromboglobulin ↑				
tpa-antigen ↑				
PAI-I ↑				
Beta-carotene ↑				
Vitamin A ↑				

The available evidence favors the view that increased common carotid intima-media thickness is an indicator of atherosclerosis. As is shown in chapter 4.3, a common carotid intima-media thickness of 0.90 mm or above, is most likely to reflect the presence of an atherosclerotic lesion at the site of the measurement. At lower values of intima-media thickness of the common carotid artery, medial hypertrophy may also be important. However, it might well be that determinants of common carotid medial hypertrophy are partly similar to those for atherosclerotic intima thickening of the common carotid artery. Studies such as the Rotterdam Study will not resolve this issue completely. Additional histologic studies are needed to determine the processes that are underlying an increased common carotid intima-media thickness.





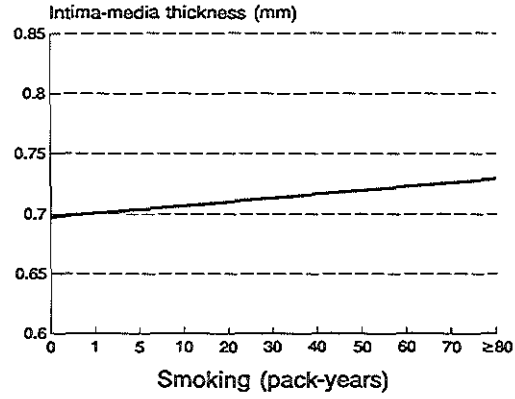


Figure 8.2 *Association of common carotid intima-media thickness with systolic blood pressure, HDL cholesterol, pack-years of smoking.*

Linear regression trends, adjusted for age and gender. Only subjects with an intima-media thickness below 0.90 mm were included. All trends $p < 0.05$.

The question is whether it matters very much should common carotid intima-media thickness not represent local atherosclerosis in itself. Compared to other arteries, such as the coronary arteries or the arteries of the lower extremities, development ofathero-sclerotic lesions in the common carotid artery occurs relatively late in life. Therefore, lesser degrees of common carotid intima-media thickening may indicate presence of atherosclerosis in arteries in which atherosclerosis develops earlier in life. In support of this view, common carotid intima-media thickness ranging from 0.60 mm to 0.90 mm, shows graded associations with some of the cardiovascular risk factors (figure 8.2), with the ankle-arm index and with prevalent coronary heart disease (figure 8.3). Thus, in case that intima-media thickness of the common carotid artery does not represent local atherosclerosis, measurement of common carotid intima-media thickness is still of use as a 'marker', an indicator of atherosclerosis elsewhere in the arterial system and of increased cardiovascular risk.

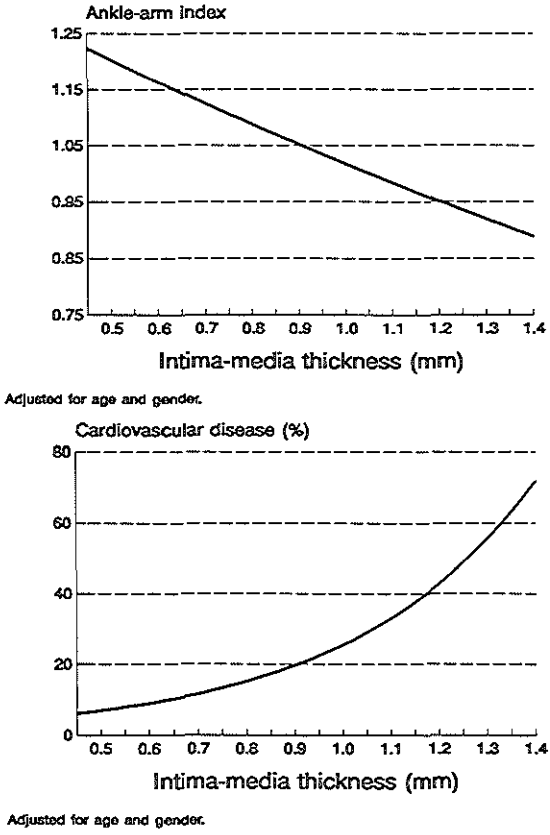


Figure 8.3 *Association of common carotid intima-media thickness with ankle-arm index and with prevalent cardiovascular disease (CVD).*

Intima-media thickness: Occurrence of cardiovascular events

The non-invasive assessment of carotid atherosclerosis is a relatively new possibility which is currently being applied in a number of large prospective follow-up studies. Based on findings from cross-sectionally obtained data, non-invasive assessment of common carotid intima-media thickness appears to provide a promising method to study atherosclerosis directly, at the level of the vessel, in populations at large. However, the usefulness of this approach in terms of predicting cardiovascular disease, assessment of changes over time in atherosclerosis and reflection of change of atherosclerosis elsewhere remains to be proven. With one exception,[26] the follow-up time has at present been too limited to enable the assessment of increased common carotid intima-media thickness as a predictor of fatal and non-fatal cardiovascular disease and total mortality. As a first example, Salonen and co-workers have reported on the value of increased common carotid intima-media thickness in predicting myocardial infarction.[26] In their study an increase of 0.1 mm in maximum common carotid intima-media thickness was associated with an increase in the risk of myocardial infarction of 11 % [95 % CI 6,16]. There is a clear need for confirmation of these data which will become available not very long from now.

Intima-media thickness: Change over time

As for the association between dregrees of wall thickening and incidence of cardiovascular events, there is a need for data on changes over time in common carotid intima-media thickness. Salonen and co-workers have recently reported on determinants of progression of common intima-media thickness, indicating that elevated levels of serum LDL cholesterol, serum selenium and copper, current smoking, and increased platelet aggregatebility were significantly associated with accelerated progression of intima-media thickness.[27] In their study among men aged 42 to 60 years, a relatively large mean (SD) increase of maximal common carotid intima-media thickness was observed; 0.12 mm (0.20) in a two-year period. Recently, Blankenhorn and co-workers, presented findings from an randomized double-blind intervention study among 78 subjects with angiographically proven coronary heart disease on the effect of colestipol-niacin therapy on common carotid intima-media thickness.[28] In their study the increase (SD) in common carotid intima-media thickness over a period of 24 months was 0.04 mm (0.06) in the placebo group. Other studies have estimated an annual average increase in mean common carotid intima-media thickness of approximately 0.01 mm/per year. However, the latter estimate was based on cross-sectionally obtained data. To substantiate the available findings, prospective results from other studies that aim to investigate which factors may be involved in progression of atherosclerosis and

subsequent cardiovascular disease are needed, including the follow-up results from the Rotterdam Study.

Intima-media thickness: Ultrasound protocol

Non-invasive assessment of carotid intima-media thickness may serve several purposes in research, and potentially in clinical medicine. Firstly, an increased intima-media thickness of carotid artery may indicate the presence of local atherosclerosis and may be of use in the prediction of disease related to the flow distribution of that artery (e.g., cerebral ischemia). For example, increased common carotid intima-media thickness may prove to be of value, additional to the currently available methods used to assess carotid abnormalities that are associated with an increased risk of stroke, such as hemodynamically important stenosis. Secondly, common carotid intima-media thickness may be used as an indicator of the total burden of atherosclerosis present in an individual. As such, it may be used as an indicator for presence of atherosclerosis in other arteries such as the coronary arteries, the abdominal aorta or the arteries of the lower extremities. Finally, common carotid intima-media thickness may be used in clinical trials to study the efficacy of non-pharmacological and pharmacological treatment on progression of regression of the atherosclerotic process.[29]

Currently, several non-invasive ultrasound protocols are being used to quantify the presence and extent of carotid atherosclerosis (chapter 5.1). In general, these approaches differ in three aspects, i.e., the site of the measurement (left and right carotid artery; common carotid artery, carotid bifurcation and internal carotid artery; anterior and posterior wall), the length of the segment of the measurement (maximum or mean intima-media thickness), and the outcome variable (presence or absence; summary score; average). In some studies, an atherosclerosis score is used, e.g., an average or a summation of all measurements performed at near and far wall of both left or right carotid artery. Others have focused on the presence or absence of atherosclerotic plaques, whereas the Rotterdam Study, among others, relied mainly on measurements of the far wall intima-media thickness of the common carotid artery. Few have used percentiles of the site specific intima-media thickness measurements to characterize subjects with and without carotid atherosclerosis. These methods have all been successful in relating intima-media thickness measurements to cardiovascular risk factors and presence of cardiovascular disease in cross-sectional analyses. In the Rotterdam Study, we have shown that with respect to associations with cardiovascular risk factors no difference in strength of the associations was found when using measurements obtained from the right or from the left carotid artery (chapter 5.2).

The available evidence is too limited to determine which approach is 'best' to

predict occurrence of cardiovascular disease, to assess change in atherosclerosis over time, and to reflect presence and extent of atherosclerosis in other arteries.

Conclusion

Ultrasonographic assessment of common carotid intima-media thickness provides a promising approach to study atherosclerosis, its natural history and the determinants of presence and progression of atherosclerosis in population-based studies. The notion that measurement of carotid intima-media thickness may be used as an indicator of atherosclerosis also in vessels other than the carotid artery, is supported by findings from the Rotterdam Study and form other studies, and provide an exciting potential. Future findings from ongoing large population-based prospective follow-up studies, including the Rotterdam Study, on determinants of progression of atherosclerosis may identify modifiable risk factors and provide us with new insights for preventive strategies. Finally, when increased common carotid intima-media thickness has proven to be a good predictor of fatal and non-fatal stroke, coronary heart disease and other cardiovascular diseases, non-invasive measurement of common carotid intima-media thickness may be used in clinical trials to study the efficacy of non-pharmacological and pharmacological treatment in the regression of atherosclerosis and prevention of cardiovascular events[30,31,32], and finds its way into clinical practice. The first data have shown encouraging results of lipid lowering therapy in reducing progression of common carotid intima-media thickness and the risk of cardiovascular events.[28,33]

References

1. Wendelhag I, Olov G, Wikstrand J. Arterial wall thickness in familial hypercholesterolemia. Ultrasound measurements of intima-media thickness in the common carotid artery. Arterioscler Thromb 1992;12:70-7.
2. Salonen R, Salonen JT. Carotid atherosclerosis in relation to systolic and diastolic blood pressure: Kuopio ischaemic heart disease risk factor study. Ann Med 1991;23:23-7.
3. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study. Stroke 1992;23:1752-60.
4. Probstfield JL, Byington RP, Egan DA, et al. Methodological issues facing studies of atherosclerotic change. Circulation 1993 ;87 (suppl II):74-81.
5. Touboul PJ, Prati P, Scarabin PY, et al. Use of monitoring software to improve the measurement of carotid wall thickness by B-mode imaging. J Hypertension 1992;10 (suppl 5):S37-41.
6. Salonen R, Haapanen A, Salonen JT. Measurement of intima-media thickness of common carotid arteries with high resolution B-mode ultrasonography: Inter- and intra-observer variability. Ultrasound Med Biol 1991;17:225-30.

7. O'Leary DH, Polak JF, Wolfson SK, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly. The Cardiovascular Health Study. Stroke 1991;22:1155-63.

8. Riley WA, Barnes RW, Applegate WB, et al. Reproducibility of noninvasive ultrasonic measurement of carotid atherosclerosis. The Asymptomatic Carotid Artery Plaque Study. Stroke 1992;23:1062-8.

9. Persson J, Stavenow, Wikstrand J, et al. Noninvasive quantification of atherosclerotic lesions. Reproducibility of ultrasonographic measurement of arterial wall thickness and plaque size. Arterioscler Thromb 1992;12:261-6.

10. Wikstrand J, Wiklund O. Frontiers in cardiovascular science. Quantitative measurements of atherosclerotic manifestations in humans. Arterioscler Thromb 1992;12:114-9.

11. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: A direct measurement with ultrasound imaging. Circulation 1986;74:1399-1406.

12. Wendelhag I, Gustavsson T, Suurküla M, et al. Ultrasound measurement of wall thickness in the carotid artery: Fundamental principles, and description of a computerized analyzing system. Clin Physiol 1991;11:565-77.

13. Wong M, Edelstein J, Wollman J, et al. Ultrasonic-pathological comparison of the human arterial wall. Verification of intima-media thickness. Arterioscl Thromb 1993;13:482-6.

14. Stary HC, Blankenhorn DH, Chandler B, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. Arterioscler Thromb 1992;12:120-34.

15. Psaty BM, Furberg CD, Kuller LH, et al. Isolated systolic hypertension and subclinical cardiovascular disease in the elderly. Initial findings from the Cardiovascular Health Study. JAMA 1992;268:1287-91.

16. Manon MJ, Saba PS, Pini R, et al. Parallel cardiac and vascular adaptation in hypertension. Circulation 1992;86:1909-18.

17. Salonen R, Salonen JT. Determinants of carotid intima-media thickness: A population-based ultrasonography study in eastern Finnish men. J Intern Med 1991;229:225-31.

18. Heiss G, Sharett AR, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: Associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

19. Wu KK, Folsom AR, Heiss G, et al. Association of coagulation factors and inhibitors with carotid artery atherosclerosis. Early results of the Atherosclerosis Risk in Communitties (ARIC) study. Ann Epidemiol 1992;2:471-80.

20. Tracy RP, Bovill EG, Fried LP, et al. Coagulation factors in men and women over 65 years: Cardiovascular Health Study. (abstract) 31st Annual Conference on Cardiovascular Disease Epidemiology. Florida, USA, 1991.

21. Cortes J, Salomaa VV, Heiss G, et al. In-vivo platelet activation and asymptomatic atherosclerosis. The Atherosclerosis Risk In Communitties (ARIC) study, 1986-1989. (abstract). Circulation 1993;87:698.

22. Salomaa VV, Wu KK, Stinson VL, et al. The association of fibrinolytic activity with asymptomatic carotid atherosclerosis: The ARIC study. (abstract) Circulation 1993;87:699.

23. Salonen JT, Salonen R, Seppänen K, et al. Interactions of serum copper, selenium, and low-density lipoprotein cholesterol in atherogenesis. Br Med J 1991;302:756-60.

24. Kritechevsky SB, Shimakawa T, Dennis B, et al. Dietary antioxidants and carotid intima-media wall thickness: The ARIC study (abstract). Circulation 1993;87:679.

25. Salonen R, Salonen JT. Progression of carotid atherosclerosis and its determinants: A population-based ultrasonography study. Atherosclerosis 1990:81:33-40.

26. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb 1991;11:1245-9.

27. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. Circulation 1993;87 (suppl II):56-65.

28. Blankenhorn D, Selzer RH, Crawford DW, et al. Beneficial effects of colestipol-niacin therapy on the common carotid artery. Two- and four year reduction of intima-media thickness measured by ultrasound. Circulation 1993;88:20-8.

29. Margitic SE, Bond MD, Crouse JR, et al. Progression and regression of carotid atherosclerosis in clinical trials. Arterioscler Thromb 1991;11:443-51.

30. Bond MG, Strickland HL, Wilmoth KS, et al. Interventional clinical trials using noninvasive ultrasound endpoints: The Multicenter Isradipine/Diuretic Atherosclerosis Study. J Cardiovasc Pharmacol 1990;15 (suppl 1):S30-3.

31. Bond MG, Wilmoth SK, Enevold GL, et al. Detection and monitoring of asymptomatic atherosclerosis in clinical trials, Am J Med 1989;86 (suppl 4A):33-6.

32. ASCAPS Group. Rationale and design for the Asymptomatic Carotid Plaque Study (ASCAPS). Control Clin Trials 1992;13:293-314.

33. Crouse JR, Furberg CD, Byington RP, et al. The PLAC-2 trial: Effects of pravastatin on atherosclerosis prograssion and clinical events (abstract). Circulation 1993;87:702.

Chapter 9

Summary

9.1 Summary

In The Netherlands, as in most other industrialized countries, coronary heart disease and stroke are important causes of morbidity and mortality. In particular among the elderly, cardiovascular disease is the prime cause of death, and even more important, a major determinant of chronic disability and suffering. Mortality from acute myocardial infarction has been steadily decreasing since 1972 (*chapter 1*). The incidence of acute fatal myocardial infarction in the elderly shows a similar decline. Hospital admission rates of acute myocardial infarction have not changed considerably during this period, whereas a sharp rise in morbidity rates for chronic coronary heart disease was observed. Cerebrovascular mortality has shown a steady and consistent decline since 1969, while hospital admission rates increased until 1986, after which a decline was observed. The decline in cardiovascular mortality and increase in morbidity rates from chronic coronary heart disease may, at least in part, be attributed to changes over time in the presence of major cardiovascular risk factors and to developments in medical care. The precise contribution of each of these factors to the decrease in mortality, however, can not be assessed with the data currently available. In absolute figures, coronary heart disease and stroke still remain major health problems in the ageing Dutch population.

At present, cardiovascular disease is believed to be caused by an interplay of advanced atherosclerotic vessel wall changes, stenosis and thrombosis. However, the question why some people suffer from a cardiovascular event whereas others may be spared from symptomatic cardiovascular disease, even in the presence of significant atherosclerosis, remains unanswered. This is especially important for subjects of older age, since in the elderly some extent of atherosclerosis is frequently present. Non-invasive techniques to accurately assess atherosclerotic vessel wall abnormalities may be used to study the atherosclerotic process in populations at large in order to gain further insight in factors that initiate the atherosclerotic process, lead to progression of atherosclerosis, and cause disease to manifest itself in the absence or presence of atherosclerotic vessel wall abnormalities. High resolution B-mode ultrasonography of carotid arteries may provide a tool to study signs of early and advanced atherosclerosis, to monitor the process of development of atherosclerosis and to study factors which promote development and progression of atherosclerotic vessel wall disease and subsequent clinical cardiovascular disease in populations at large.

The objective of the work presented in this thesis was to evaluate the feasibility of non-invasive assessment of hemodynamically important stenosis of the carotid artery and common carotid intima-media thickness, in an elderly non-hospitalized population, to study the value of intima-media thickness of the distal common carotid artery as an

indicator of generalized atherosclerosis and to study determinants of increased common carotid intima-media thickness (*chapter 2*).

The ultrasound principle and the ultrasound reading protocol of the Rotterdam Study, which is used for the study of vessel wall characteristics of the carotid arteries, are described in detail in *chapter 3*. Results from a reproducibility study of measurement of ultrasonographically assessed common carotid intima-media thickness among 80 participants of the Rotterdam Study who underwent a second ultrasound scan of both carotid arteries within 3 months of the first scan, are presented in the second part of *chapter 3*. The replicate measurements involved the posterior intima-media thickness of the distal common carotid artery. Mean absolute differences (SD) in intima-media thickness of the right common carotid artery between paired measurements of sonographers, readers and visits was 0.061 mm (0.09), 0.079 mm (0.05), and 0.086 mm (0.09), respectively. Similar results were obtained for the left common carotid artery. Measurement error of intima-media thickness, i.e., the absolute difference in measurements between two subsequent visits, increased significantly with increasing common carotid intima-media thickness. This association disappeared after logarithmical transformation of the intima-media thickness data. Cardiovascular risk factors such as age, sex, smoking, body mass index, serum lipids, fibrinogen, and systolic and diastolic blood pressure were not significantly associated with the measurement error of intima-media thickness. These findings indicate that measurements of common carotid intima-media thickness are highly reproducible. Measurement error of intima-media thickness is small and appears to be proportional with the level of intima-media thickness and is not significantly associated with most risk factors for atherosclerotic vessel wall disease.

In *chapter 4*, the associations are evaluated between ultrasonographically measured intima-media thickness of the common carotid arteries and non-invasively assessed atherosclerosis of the abdominal aorta, of the arteries of the lower extremities and of the carotid arteries. Furthermore, common carotid intima-media thickness is related to prevalent cardiovascular disease.

Subjects with atherosclerosis in the abdominal aorta had a significantly increased common carotid intima-media thickness compared to those without aortic atherosclerosis with a mean difference of 0.11 mm [95 % CI 0.01,021]. With respect to atherosclerotis of the arteries of the lower extremities, our results indicate that an increase of 0.1 mm in common carotid artery intima-media thickness is associated with an age- and gender adjusted reduction of the ankle-arm index of 0.021 [95 % CI 0.014,0.028]. The age- and gender adjusted odds ratio of lower extremity arterial disease for subjects with an intima-media thickness above 0.89 mm (upper quintile) to that of subjects with an intima-media thickness below 0.89 mm is 3.4 [95 % CI 2.2,5.2].

The presence of atherosclerotic lesions in the carotid bifurcation increased with increasing common carotid intima-media thickness. Among subjects with lesions in the carotid bifurcation, mean common intima-media thickness was significantly increased compared to that of subjects without lesions with a difference adjusted for age and gender of 0.08 mm [95 % CI 0.06,0.11]. Similar results were found for subjects with a moderate to severe hemodynamically important stenosis of the internal carotid artery (difference 0.10 mm [95 % CI 0.01,0.19]).

Common carotid intima-media thickness was generally increased in subjects with a positive history of either stroke, angina pectoris, myocardial infarction or intermittent claudication. Age and gender adjusted mean common carotid intima-media thickness was significantly increased among subjects with cardiovascular disease compared to those without cardiovascular disease with a difference of 0.07 mm [95 % CI 0.04,0.10]. This difference constitutes an increase of nearly 10 %. The odds ratio of cardiovascular disease with an 0.1 mm increase in common carotid intima-media thickness was 1.24 [95 % CI 1.08,1.43] for women and 1.19 [95 % CI 1.04,1.36] for men. Among subjects with a common carotid intima-media thickness of 0.89 mm or above (upper quintile), cardiovascular disease was on average 4.6 times more likely than in subjects with an intima-media thickness lower than 0.63 mm (lowest quintile).

The findings of the study presented in *chapter 4* provide evidence that an ultrasonographically assessed increase in intima-media thickness of the distal common carotid artery is associated with aortic atherosclerosis, with atherosclerosis of the arteries of the lower extremities, with atherosclerotic abnormalities at other sites of the carotid artery and with prevalent symptomatic cardiovascular disease. An increased common carotid intima-media thickness may reflect atherosclerotic vessel wall disease in other arteries.

The associations between cardiovascular risk indicators and common carotid intima-media thickness are presented in *chapter 5*. Common carotid intima-media thickness increased with age: for women with 0.010 mm per year [95 % CI 0.008,0.011], and for men with 0.008 mm per year [95 % CI 0.005,0.011]]. Intima-media thickness was significantly higher among men as compared to women with an age adjusted difference of 0.05 mm [95 % CI 0.03,0.08]. A decrease of 1 mmol/l in HDL cholesterol was associated with an increase in common carotid intima-media thickness of 0.033 mm [95 % CI -0.008,0.075] in women, and of 0.048 mm [95 % CI 0.002,0.094] in men. A 10 mmHg increase in systolic blood pressure was associated with an increase in intima-media thickness of 0.014 mm [95 % CI 0.007,0.021] in women, and of 0.022 mm [95 % CI 0.013,0.032] in men. Only among men, significant positive linear trends were found for pack-years of cigarette smoking and for body mass index. Serum total cholesterol was not associated with carotid intima-media thickness in either men or women.

In subjects with isolated systolic hypertension, common carotid intima-media thickness of the right common carotid artery was significantly higher compared to those without isolated systolic hypertension with a difference of 0.07 mm [95 % CI 0.01,0.14]. Results for the left carotid artery were similar (difference 0.06 mm [95 % CI -0.01,0.13]). These studies show that common carotid intima-media thickness is associated with most of the established cardiovascular risk factors, in particular in men.

In an elderly population, a considerable proportion of subjects with a relatively low diastolic blood pressure, may have vascular damage (atherosclerosis), in particular those with a relatively high pulse pressure. We observed a J-shaped relation between common carotid intima-media thickness and diastolic blood pressure. This complies with the hypothesis that in the elderly a low diastolic blood pressure may be a consequence rather than a cause of atherosclerosis. This phenomenon was present across all strata of systolic blood pressure. Results from prospective studies on the association of progression of atherosclerosis and change in diastolic blood pressure are needed.

The prevalence of moderate and severe stenosis of the right internal carotid artery in the elderly and its associations with smoking, blood pressure, serum lipids and hemostatic factors are delineated in *chapter 6*. A reduction of the lumen diameter of 16-49 % was found in 29 persons (3.0 %). Severe stenosis (50 % or over) was observed in 13 persons (1.4 %). Taking differences in age, gender, body mass index into account, subjects with moderate to severe carotid artery disease had, compared to participants without stenosis, lower HDL-cholesterol levels (difference 0.10 mmol/l [95 % CI 0.00,0.20]) and higher fibrinogen levels (difference 0.24 g/l [95 % CI 0.04,0.45]). Among them were more persons with hypertension (difference 16 %) and more current smokers (difference 13 %). Factor VIIc and factor VIIIc activity were higher in subjects with carotid artery disease, without, however, reaching statistical significance (difference 0.06 IU/ml [95 % CI -0.01,0.12], and 0.21 IU/ml, [95 % CI -0.05,0.47], respectively). These findings suggest that hypertension, smoking and reduced serum HDL cholesterol, combined with unfavorable increases in hemostatic factors may be related to carotid artery disease in the elderly.

Cerebral white matter lesions frequently seen on magnetic resonance images of brains of elderly subjects, are associated with a positive history of stroke and coronary heart disease and with elevated levels of established cardiovascular risk factors, including hemostatic factors. These findings may indicate that some of these lesions in the elderly are due to atherosclerosis, possibly mediated by cardiovascular risk factors. The association between cerebral white matter lesions and non-invasively assessed atherosclerosis as observed among 111 participants of the Rotterdam Study, aged 65 to 85 years, is described in *chapter 7*. Carotid atherosclerosis was significantly more

pronounced in subjects with cerebral with matter lesions than in subjects without lesions. The difference in common carotid intima-media thickness was 0.13 mm [95 % CI 0.04,0.21], whereas the odds ratio of cerebral white matter lesions associated with the presence of plaques in the carotid bifurcation was 3.9 [95 % CI 1.0,14.5]. The degree of internal carotid artery stenosis, however, was not associated with white matter lesions. The mean ankle-arm index was significantly lower in subjects with cerebral white matter lesions than in subjects without lesions with a difference of -0.11 [95 % CI -0.21,-0.01]. The odds ratio of cerebral white matter lesions associated with the presence of peripheral arterial disease and a possible or definite myocardial infarction was 2.4 [95 % CI 0.8,7.6] and 3.1 [95 % CI 0.8,11.4], respectively. These findings demonstrate that atherosclerosis, indicated by increased common carotid intima-media thickness, presence of carotid plaques and a lower ankle-arm index is related to the presence of cerebral white matter lesions.

Finally, the main findings from the presented studies are put in perspective to results from other studies and some issues concerning non-invasive quantitative measurement of atherosclerosis are discussed in *chapter 8*.

9.2 Samenvatting

In de meeste westerse landen vormen hart- en vaatziekten een belangrijke oorzaak van ziekte en overlijden. Onder personen van hogere leeftijd is het optreden van ziekten van het hart (ischemische hartziekten) en de hersenen (cerebrovasculaire aandoeningen) de belangrijkste oorzaak van overlijden. De afgelopen jaren is de sterfte aan ischemische hartziekten en cerebrovasculaire aandoeningen sterk afgenomen. Deze daling heeft vooral plaats gevonden onder personen van middelbare leeftijd, terwijl de afname in sterfte onder personen van hogere leeftijd minder uitgesproken is. Beschikbare gegevens suggereren dat de daling in sterfte onder personen van middelbare leeftijd het gevolg is van primaire preventie (stoppen met roken, behandeling van verhoogde bloeddruk, verandering van levenswijze), terwijl de daling in sterfte onder de ouderen voornamelijk het gevolg is van secundaire preventie (verbeterde behandeling). Op dit moment zijn we echter nog niet goed in staat aan te geven welke factoren een belangrijke bijdrage hebben geleverd aan de daling van sterfte aan ischemische hartziekten en cerebrovasculaire aandoeningen in Nederland in de afgelopen 25 jaar *(hoofdstuk 1)*.

Hart- en vaatziekten worden in het algemeen veroorzaakt door een combinatie van slagaderverkalking, vernauwing van het bloedvat en een trombose. Bij personen van hogere leeftijd is er altijd een zekere mate van slagaderverkalking (atherosclerose) aanwezig. De vraag waarom de ene persoon met slagaderverkalking getroffen wordt door bijvoorbeeld een hartaanval terwijl een ander met precies dezelfde afwijkingen gevrijwaard blijft van een hartaanval, is vooralsnog onduidelijk. Onderzoek naar factoren die het optreden van hart- en vaatziekten luxeren bij aanwezigheid van slagaderverkalking is derhalve gewenst. Het Erasmus Rotterdam, Gezondheid en Ouderen (ERGO) onderzoek biedt hiervoor een unieke gelegenheid. In het ERGO onderzoek worden namelijk factoren gemeten die het risico op hart- en vaatziekten doen toenemen, en wordt aanwezigheid van slagaderverkalking uitgebreid vastgelegd.

De techniek die in het ERGO onderzoek gebruikt wordt om een indruk te krijgen over de aanwezigheid en mate van slagaderverkalking is de echografie. De halsslagaders zijn voor echografisch onderzoek uitermate geschikt door hun relatief oppervlakkige ligging onder de huid en de gemakkelijke bereikbaarheid. Met behulp van echografisch onderzoek kunnen een aantal karakteristieken van de halsslagader worden vastgelegd. Dit betreft de dikte van de wand van de halsslagaders, de diameter van het bloedvat en de aanwezigheid en mate van verkalkingen (zie figuur 3.1.1).

Dit proefschrift richt zich op de toepasbaarheid en de waarde van het meten van de wanddikte van de halsslagaders met behulp van echografie voor onderzoek naar het verband tussen aanwezigheid en toename van slagaderverkalking en het risico op hart-

en vaatziekten en voor onderzoek naar factoren worden die van invloed zijn op toename van slagader verkalking. De volgende aspecten waren hierbij van belang; Is de meting van de dikte van wand van de halsslagader nauwkeurig en precies uit te voeren; houdt een toegenomen wanddikte van de halsslagader verband met slagaderverkalking elders in het lichaam; gaat een toename in risico factor voor hart- en vaatziekten gepaard met een toename van de wanddikte.

In *hoofdstuk 3* wordt de techniek van de echografie uitvoerig beschreven. Tevens wordt in dit hoofdstuk aangegeven dat met behulp van deze methode, de meting van de dikte van de wand van de halsslagader nauwkeurig en precies is uit te voeren. *Hoofdstuk 4* laat zien dat bij personen met slagaderverkalking elders in het lichaam de wand van de halsslagader dikker is dan bij personen zonder slagaderverkalking. Dit geldt voor personen bij wie er sprake is van slagaderverkalking in de buikslagader, in de slagaders van de benen, en slagaderverkalking op andere plaatsen in de halsslagader. Daarnaast blijkt dat bij personen die klachten hebben (gehad) van pijn op de borst bij inspanning (angina pectoris) of pijn in de benen bij lopen (etalage benen; claudicatio intermittens) of bij personen die ooit een beroerte of hartaanval hebben doorgemaakt, de wand van de halsslagader toegenomen is ten opzichte van personen zonder deze klachten. Deze resultaten geven aan de wanddikte van de halsslagader slagaderverkalking elders in het lichaam weerspiegelt. Daarnaast gaven de resultaten aan dat de verbanden voor mannen sterker waren dan voor vrouwen.

Bevindingen beschreven in *hoofdstuk 5* laten zien dat vrouwen gemiddeld een dunnere wand van de halsslagader hebben dan mannen van gelijke leeftijd. Daarnaast bleek met het stijgen van de leeftijd de wanddikte toeneemt. Een zelfde verband werd gezien met een toename van de systolische bloeddruk (bovendruk). Hoe hoger de bloeddruk, hoe dikker de wand. Voor mannen kwam naar voren dat naarmate er meer sprake was van overgewicht, de wanddikte van de halsslagader toenam, terwijl een toename van het HDL cholesterol gepaard ging met een afname van de wanddikte. Het wel of niet gerookt hebben bleek bij vrouwen geen verband te hebben met de wanddikte van de slagader, terwijl dit voor mannen wel het geval was. Er zijn aanwijzingen dat bij personen van hogere leeftijd, een lage diastolische bloeddruk (onderdruk) het gevolg kan zijn van een voortschrijdende slagaderverkalking. Onze bevindingen voor wat betreft de diastolische bloeddruk wijzen in die richting. Uit het onderzoek kwam naar voren dat een lagere diastolische bloeddruk gepaard ging met een toegenomen wanddikte.

In *hoofdstuk 8* worden de bevindingen beschreven in dit proefschrift in een breder perspectief geplaatst. Op dit moment is er nog veel discussie over het feit of de echografisch gemeten wanddikte van de halsslagader op zich slagaderverkalking is. De dikte van de wand van de halsslagader bestaat uit een binnenbekleding met daarom heen

een spierlaag. In de regel is slagaderverkalking een aandoening van de binnenbekleding van de slagader. Met de echografie worden echter beide lagen gemeten. Dus kan een toegenomen wanddikte tevens een weerspiegeling zijn van een toegenomen spierlaag. De discussie of echografisch vastgestelde wanddikte zelf nu wel of geen slagaderverkalking is wellicht van betrekkelijk belang. Vooral wanneer de wanddikte meting van de halsslagaders gezien wordt als een indicator voor slagaderverkalking elders in het lichaam. De beschikbare gegevens over het verband tussen wanddikte van de halsslagaders, risico factoren voor hart en vaatziekten, en slagaderverkalking wijzen in deze richting.

De echografisch vastgestelde wanddikte van de halsslagaders zal zich nog moeten bewijzen als voorspeller van hart- en vaatziekten. Tevens zijn nog slechts beperkt gegevens beschikbaar over verandering in wanddikte met de tijd en veranderingen van het risico op hart- en vaatziekten enerzijds en de rol van risico factoren hierop. Ook dient de klinische revelantie van het meten van de wanddikte van de halsslagader nog te worden onderzocht. Binnen afzienbare tijd zullen dergelijke gegevens uit het ERGO onderzoek beschikbaar komen.

De onderzoeken beschreven in dit proefschrift tonen aan dat in bevolkings-onderzoek het vastleggen en meten van de dikte van de wand van de halsslagader goed mogelijk is. Daarnaast geeft het ons een 'marker' in handen voor aanwezigheid van gegeneraliseerde slagaderverkalking en maakt het mogelijk vaatwandveranderingen in een vroeg stadium te bestuderen waardoor inzicht verkregen kan worden in het 'natuurlijk' beloop van slagaderverkalking en in factoren die daarop van invloed zijn. Wellicht is de methode tevens geschikt om de middellange termijn effecten van preventie of behandeling in interventie onderzoek te beoordelen.

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Michiel

Curriculum vitae

Michiel Bots was born on October 24th, 1960 in Geertruidenberg, The Netherlands. He attended secondary school (atheneum ß) at the Mgr Frencken College in Oosterhout (NB) and graduated in 1979. He started his medical training in 1979 at the Erasmus University in Rotterdam. He spent 5 months at the Medical Reseach Council Laboratories in The Gambia, West Africa (head: dr. B.M. Greenwood), during which he was involved in a project among children under five years of age, on the assessment of chloroquine resistance using an ELISA test for detecting chloroquine in urine. After receiving his medical degree in 1986, he worked as a resident in Gynaecology and Obstetrics, at the Hospital Zonnegloren in Soest and from april 1987 as a resident in Surgery at the Juliana Hospital in Apeldoorn. In december 1988 he started his training at the Department of Epidemiology & Biostatistics, Erasmus University Medical School, Rotterdam, The Netherlands (chair: Prof. Dr A. Hofman). At that time the work described in this thesis was initiated. At present, he is daily coordinator of the Rotterdam Study. He is a member of the steering committee of a Dutch study on the role of vascular factors in dementia (principal investigators: Prof. Dr D.E. Grobbee, Prof. Dr P.J. Koudstaal and Dr C.Kluft), and he is daily coordinator of a concerted action on incidence and risk factors of ischaemic and haemorrhagic stroke in nine European countries: EUROSTROKE (principal investigators: Prof. Dr D.E. Grobbee, Prof. Dr P.J. Koudstaal).