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Summary/Samenvatting

7.1 | Summary

This thesis describes the relation between atherosclerosis, hormones and genetic factors in relation to the risk of stroke. The results are based on the Rotterdam Study, a large population based cohort study among 7,983 persons aged 55 years or older. A total of 7,721 persons were free from previous stroke. The cohort was followed for morbidity, including stroke. Until January 1, 1999, 432 persons suffered from a first stroke.

Chapter 2 describes the incidence and survival of stroke. The incidence rate increased with age and was higher in men than in women over the entire age range. The incidence rate varied from 1.7 per 1000 personyears in men aged 55 to 59 to 69.8 per 1000 personyears in men aged 90 years or over. Corresponding rates for women were 1.2 and 33.1 per 1000 personyears, respectively. Although incidence rates were higher in men than in women, lifetime risks were similar (21% for persons aged 55 years). The explanation is that the longer life expectancy in women counterbalances the higher incidence rates of stroke in men. Because of this, women have their stroke on average at a higher age than men. We observed no differences in survival between men and women.

Chapter 3 shows the relation between several measures of atherosclerosis and risk of stroke. **Chapter 3.1** reviews the knowledge regarding subclinical markers of atherosclerosis and risk of stroke. In **chapter 3.2** the relation between an increased wall thickness in the carotid artery and subtypes of stroke is described. We found that an increased wall thickness did not only increase the risk of stroke, but also the risk of intracerebral hemorrhage and lacunar infarction, irrespective of cardiovascular risk factors. The relevance of carotid plaques in persons without a previous stroke or TIA was not yet clear. **Chapter 3.3** describes the prospective study on the relation between plaques, measured at six locations in the carotid artery, and stroke and subtypes of cerebral infarction. We found that plaques increased the risk of stroke, irrespective of location in the carotid artery. Further, plaques were related to infarctions in the anterior, but not the posterior circulation. There was a strong relation between carotid plaques and risk of lacunar infarction. We concluded that carotid plaques are sources of emboli as well as markers of generalized atherosclerosis. Presence of calcifications in coronary arteries as assessed by electron beam tomography is another measure of atherosclerosis that we investigated in **chapter 3.4**. The amount of calcification was related to a history of stroke. Other cardiovascular risk factors did not explain this relation. **Chapter 3.5** shows the results of our study on the relation between arterial stiffness, a functional measure of

atherosclerosis, and risk of stroke. Stiffness in the aorta was not clearly related to a history of stroke, whereas persons with severe carotid stiffness were 12 times more likely to to have had a stroke. Finally we compared different measures of atherosclerosis in relation to stroke, namely carotid plaques and intima-media thickness, ankle-arm index and calcifications in the aorta (**chapter 3.6**). We found that carotid intima-media thickness and aortic calcifications were strongest related to the risk of stroke. Cardiovascular risk factors largely explained the relation that we found between ankle-arm index and stroke. The relations with other measures of atherosclerosis remained after adjustment for cardiovascular risk factors. Aortic calcifications and intima-media thickness were independently of each other related to the risk of stroke. They may be used to identify persons at high risk of stroke who may benefit from intervention.

Chapter 4 deals with the relation between endogenous sex hormones (testosterone and estrogen) and risk of stroke in men and postmenopausal women. Estradiol was not related to the risk of stroke, neither in men nor in women. The effect of estrogen replacement in postmenopausal women on cardiovascular disease is a hot topic. Our results are in line with recent clinical trials that failed to report a beneficial effect from estrogen replacement therapy on the risk of stroke. A decreased testosterone level was related to an increased risk of stroke in men, in particular in those who did not smoke. The relation remained after adjustment for comorbidity. It is still too early to conclude that men with decreased testosterone levels may benefit from testosterone replacement therapy. The precise underlying mechanism needs to be explained.

In **chapter 5**, the relation between two candidate genes and stroke is described. In **chapter 5.1** we report that there is no clear relation between the D-allele in the angiotensin converting enzyme (ACE) gene polymorphism and risk of stroke. **Chapter 5.2** describes the relation between mutations in the hemochromatosis gene and stroke. Two mutations (C282 and H63D) were related to the risk of stroke and increased carotid intima-media thickness in persons who smoked or had hypertension.

Finally, in **chapter 6** we discuss our findings in the light of other studies. We comment on methodological issues regarding atherosclerosis and stroke subtypes. We further discuss the results and comment on mechanisms underlying the relation between atherosclerosis and stroke. Also, we discuss the results regarding sex hormones and genetic factors in relation to stroke. Subsequently we comment on the clinical relevance of our findings. We state

that in ageing societies, prevention of stroke is of great importance in men as well as in women. Further, the combination of information on wall thickness and arterial calcifications could be used to identify persons at high risk of stroke. From our results on sex hormones we cannot conclude that estrogen replacement therapy in women has no effect in on the risk of stroke. The mechanism underlying the relation between testosterone and stroke in men needs clarification before we can conclude that testosterone replacement therapy in men can have beneficial effects on the risk of stroke. The results on genetic factors suggest that information on genetic factors may be used to intensify preventive therapy in persons with a specific genetic make-up.

Finally we do recommendations for future research on the role of atherosclerosis, hormones and genetic factors in relation to stroke. A few measures of atherosclerosis need prospective evaluation in relation to stroke. Further, we do suggestions for research that may help the identification of persons at risk for stroke and who may benefit most from preventive therapy. We further discuss how the assessment of stroke subtypes can be improved in population-based studies. Further epidemiological research can help the prevention of stroke.