RISK FACTORS FOR STROKE IN YOUNG INDONESIAN WOMEN

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We live in a moment of history
where change is so speeded up,
that we begin to see the present only
when it is already disappearing.

R.D. Laing, British Psychiatrist, 1967

To Henny,
Ingi and Ati.

Acknowledgements

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Publications and manuscripts based on studies described in thesis

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Chapter 3   Kisjanto J, Ranakusuma TAS, Kaligis RWM, Tadjudin MK, Valkenburg HA, Grobbee DE. A case-control study of risk factors for stroke in young women in Jakarta, Indonesia: Design and methods. Med J Christ Univ Indonesia 1995;24:30-6.

Chapter 4   Kisjanto J, Prihartono J, Kaligis RWM, Tadjudin MK, Ranakusuma TAS, Valkenburg HA, Grobbee DE. Risk factors for stroke in young women. A case-control study in Indonesia. (Submitted)

Chapter 5   Kisjanto J, Prihartono J, Valkenburg HA, Grobbee DE. Social and economic determinants of stroke risk in young Indonesian women. (Submitted)

Chapter 6   Kisjanto J, Prihartono J, Valkenburg HA, Grobbee DE. Hypertension. Diagnosis and Treatment in Young Indonesian Women. (Submitted)

CHAPTER 1

INTRODUCTION

Stroke is usually considered a disease of the middle-aged and elderly and is believed to be uncommon in young adults. In the seventies in the United States of America and in some European countries the proportion of strokes occurring in this age group was estimated at 3 to 5% (1-3). In the last two decades the interest in stroke in the young has increased, as it appeared that it may not be as uncommon as formerly believed with more recent reports of a proportional occurrence between 8.5% to 13.5% (4-6). Importantly, the relative frequency of stroke in young adults seems to vary between ethnic groups and geographical areas. In countries like India and Libya the proportion of all strokes occurring in relatively young subjects may be 19 to 30% (7,8). Unfortunately, results from studies are not directly comparable because of the wide variation in available technologies for clinical investigation of stroke patients, selection patterns in hospital admission, demographic profiles of populations and because of differences in other characteristics related to stroke such as socioeconomic status, environmental factors and race (9). In spite of the limited data available and the difficulties in comparability of research findings, the conclusion seems justified that the importance of stroke in the young has been underestimated. Furthermore, the problem may be more pronounced in certain regions. In particular in Asia, stroke in young women presents a relatively frequent and dramatic problem. This recognition has inspired the research summarized in this thesis.

The etiologic and prognostic features that characterize stroke in older persons need not apply to young adults. Also, the manifestations and risk factors for stroke may differ between men and women, at different ages, and between racial groups (10). It should be realized that stroke is not an etiologically homogenous disorder but reflects the outcome of such different pathologies as cerebral hemorrhage and infarct. There are reports that certain stroke types are more frequent in young women than in men, with an approximate 50% excess in incidence of the least common type of stroke, the subarachnoid hemorrhage (11).

There are very few publications about stroke in Indonesia, which is one of the developing countries in the world, and as far as we know there is only one report on stroke in young Indonesian adults (13). The present study was conducted to improve our knowledge on frequency and risk factors of stroke in young women in Indonesia. The work was performed from 1989 to 1993 and formed part of the "World Health Organization Multicenter Case-control Study of Disease and Steroid Contraceptive Use". The results of the main study have in part been published (14).

Following the introduction, the second chapter provides a review of the incidence, prevalence and etiology of stroke in the young. In chapter three the design and methods of the research project presented in this thesis are described. The fourth chapter discusses risk factors for stroke in young Indonesian women. In chapter five, the importance of socioeconomic factors in the occurrence of stroke in young women is addressed, while the awareness of hypertension, its treatment, and the quality of blood pressure control is described in chapter six. Finally, the thesis is concluded with a general discussion of the findings and their implications for public health in Indonesia and for further research.

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CHAPTER 2

EPIDEMIOLOGY OF STROKE IN THE YOUNG.
A REVIEW.

Epidemiology of Stroke In The Young. A Review

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Introduction

Stroke constitutes an important cause of morbidity and mortality. Its non-fatal sequelae are often associated with a considerable loss of quality of life (1-4). Stroke is generally regarded as a disease that occurs predominantly at older age with an exponential rise in incidence beyond the age of 65 years. Among the young stroke is considered relatively rare. Yet, several studies, predominantly performed in industrialized countries, have indicated that 5 to 10% of all strokes occur before the age of 45 years. Reports from less developed countries, such as India, Indonesia and Saudi Arabia have shown that up to 15 to 30% of all strokes occur in the young (5-7). In young subjects the distribution of different types of stroke and the underlying causes of stroke may be different from those in older subjects. Despite the importance of these notions for prevention, data on stroke in the young, however, are limited. Furthermore, the burden on society of a stroke in a young subject follows not only from the costs of medical evaluation and treatment, but also from the costs of rehabilitation and lost productivity, in particular when permanent physical impairment remains for the rest of life. We describe the epidemiology of stroke in the young.

Incidence

In earlier years data from only a few studies were available on the incidence of stroke in young subjects, and most give an incidence estimate based on an age range of 15 to 55 years (8-28). Recently, a report of the MONICA project has provided incidence rates for men and women aged 35 to 44 years in different countries around the world (29). Several population-based registry or cohort studies have been performed that also provide information about stroke incidence in the young. Findings are summarized in table 1. The incidence of stroke in the young differs considerably across geographical areas within a country and between countries. In most studies stroke incidence in the young was higher in men than women. Other have reported a female preponderance

Table 1. Stroke incidence (per 100.000 per year) for men and women aged 35-44 years.

Country	Men	Women
Azia		
China-Beijing*	18	19
China-Shanghai	10	12
Africa		
Libya-Benghazi	39	40
Northern Europe		
Denmark-Glostrup*	29	26
Denmark-Copenhagen	14	15
Finland-Kuopio*	90	55
Finland-North Karelia*	97	24
Finland-Turku*	54	31
Sweden-Gothenburg*	28	26
Sweden-North*	39	33
Western Europe		
Germany-Halle*	23	25
Germany-Karl Marx*	27	29
Germany-DDR Monica*	11	22
Germany-Rhein-Neckar*	25	16
Southern Europe		
Italy-Friuli*	26	22
Italy-Belluno	55	37
Eastern Europe		
Lithuania-Kaunas*	56	41
Poland-Warsaw*	35	15
Russia-Moscow*	31	8
Russia-Novosibirsk*	62	36
Yugoslavia-Novi Sad*	39	23

* MONICA centers

(13,15,17,25,30-34). The gender difference may reflect differences in etiology of the disease across different age groups and countries. Direct quantitative comparison of the studies, however, is hampered by differences in methodology, in completeness of case ascertainment, and because studies were conducted during different time periods where stroke incidence may have changed over time.

Subtype of stroke

Stroke is generally classified into three types; subarachnoid hemorrhage, intracerebral hemorrhage, and intracerebral infarction. Data on incidence of type specific stroke in the young is very limited. Most of the studies have reported data on total stroke only. This is due to the fact that information about symptoms and history only are inadequate to make a reliable a distinction between types of stroke and that Computer Tomography (CT) scan was not available in these studies. The available data on different types of strokes in the young mostly comes from either registries or from hospital-based case-control studies. In the latter, one should be aware of several factors that determine whether or not a subject is sent to a hospital and whether these factors are related to the type of stroke; e.g., gender or severity. This may result in biased findings. Furthermore, the distribution of type of stroke is per definition based on non-fatal stroke cases only, which may lead to an underrepresentation of that type of stroke with the highest early case-fatality

Results from the Belluno stroke registry in Italy showed no difference in incidence of cerebral infarction, cerebral hemorrhage or subarachnoid hemorrhage among subjects aged 45 years or less (14/100.000). In the Novosibirsk registry, however, 77% of all strokes that occurred before the age of 45 years was a cerebral infarction (35). In the Framingham Heart study, 77% of all stroke in men aged 30-59 years was a cerebral infarction, whereas 16% was a subarachnoid hemorrhage (36). For women, these percentages were 71% and

22%, respectively. An excess of cerebral infarction in the young conforms with findings from other studies (16,18,21,37,38), whereas some authors have reported a higher frequency of hemorrhagic stroke (28, 39-42). An excess of 50 % in incidence of subarachnoid hemorrhage in young women has been reported (43). However, in the Framingham Heart Study and in a prospective follow-up study among 42.862 men and women in Finland with a particular focus on subarachnoid hemorrhage, no difference between men and women was found (36,44). Direct comparison between studies is difficult due to different study designs. Furthermore, the distribution of type of stroke may be different in different areas across the world, i.e., higher frequency of cerebral infarction in western industrialized countries and an increased frequency of hemorrhagic stroke in Asian countries.

In the Oxfordshire Stroke registry the proportion of subarachnoid hemorrhage to all stroke declined with age from 45% in the ages 35-44 years to 4% in those aged 65-74 years, whereas the proportion of cerebral infarction increased with age (45).

Case-fatality

Case-fatality usually refers to death from stroke within 28 to 30 days after its occurrence. The 28-30 days case-fatality depends on the age structure, the health status and the distribution of types of stroke of the population studied and varies from 17 to 34% (46). Information on case-fatality among the young is limited. In the Novosibirsk stroke registry, the 30 day mortality from all strokes was 26.7% in subjects with a stroke before the age of 45 years (35). In subjects with a cerebral infarction before the age of 45 years, the 30 day case-fatality was 8.7%. The combination of these findings implies a higher case fatality for stroke of the hemorrhagic type. In the Framingham Heart Study among subjects aged 30 to 60 years who suffered from a subarachnoid hemorrhage, the 30 day case fatality was 50% for men and 29% for women, whereas for intracerebral hemorrhage it

was 50% and 67%, respectively. In a study by Bevan et al (28) comprising 113 patients aged 15 to 45 years, the overall case-fatality rate was 20.4%. Compared with the life expectancy of the general population of the same age and sex, stroke patients do significantly worse, irrespective of age or the length of follow-up. Much of the difference is explained by the high early case-fatality.

Risk factors for stroke

For middle-aged and elderly subjects a large number of factors have been identified of which is known that their presence increases the risk of stroke. In the young adult, however, there is a wide variety of causes of sometimes rare but often identifiable and treatable disorders. More than 40 possible etiologies of non-hemorrhagic cerebral infarction in young adults have been described (11,38,39,47). However, in a considerable percentage (7 to 20%) of the young stroke cases an underlying etiology was not found. The most important risk factors for stroke in middle-aged and elderly subjects are summarized in table 2, in which risk factors are categorized into constitutional factors; factors indicating a pathophysiologic mechanism; life style factors; factors that reflect presence of organ damage; and miscellaneous factors.

Information on the association between risk factors and stroke in the young stems mainly from case-control studies in which characteristics of subjects with a stroke were compared to those who remained free from stroke. Most studies are based on hospitalized patients. At least three methodologic issues need to be addressed. First, in some studies risk factors were assessed after stroke occurrence. This implicates that certain risk factors may have changed (reduced or increased) as a consequence of a stroke. Second, data are mostly based on hospital data. This could imply that the prevalence of risk factors which determine referral to a hospital may be increased among the cases and may

Table 2. Most important risk factors for stroke.

	Middle-aged/ elderly	Young
Constitutional factors		
Male gender	↑	=
Blacks	↑	·
Positive family history	↑	↑
Pathophysiologic factors		
Elevated systolic pressure	↑	↑
Elevated diastolic pressure	↑	·
Elevated cholesterol	↑/=	·
Diabetes Mellitus	↑	↑=
Elevated fibrinogen	↑	·
Protein C/protein S abnormalities	·/↑	↑
Elevated homocysteine	↑	·
Life style factors		
Smoking	↑	↑
Increased alcohol consumption	J-shape	↑=
Increased sodium intake	↑	·
Decreased potassium intake	↑	·
Oral contraceptive use	·	↑
Indicator of organ damage		
Previous stroke	↑	·
Previous TIA	↑	·
Previous myocardial infarction	↑	·
Atrial fibrillation	↑	·
Stenosis internal carotid artery	↑	·
Non-atherosclerotic cardiac abnormalities		
Patent foramen ovale	·	↑=
Mitral valve prolapse	·	↑
Arterial dissection	·	↑
Aneurism	·	↑
Miscellaneous		
Migraine	·	↑
Trauma	·	↑
Pregnancy related thrombosis	·	↑
Drug abuse	·	↑

↑ : risk increased
= : risk similar
· : no data available

induce an bias towards a positive association with stroke. Third, results are based on non-fatal cases of stroke. The prevalence of risk factors that are related to an increased case-fatality may be underestimated in the cases and consequently may bias the finding towards an absence of an relationship. However, despite these limitations the findings of the available studies are of great importance.

Constitutional factors

Results from cohort studies or population-based registries have indicated a male preponderance in young stroke subjects (table 1). However, some population-based case-control studies showed a female preponderance. Whether or not a true difference in gender exists and whether such difference varies across countries may not yet be concluded from these studies.

Young blacks have an increased risk of stroke compared to young white subjects (48). This holds for both cerebral infarction and cerebral hemorrhage. Several reports have indicated that among young stroke subjects a positive family history for stroke is more common than among controls (49). This agrees with findings for middle-aged and elderly subjects, in particular for subarachnoid hemorrhage (50).

Pathophysiologic factors

Elevated blood pressure Numerous observational studies have shown a gradual increase in risk of stroke with increasing diastolic and systolic blood pressure (figure 1). There appears to be no cut-off point above which the risk of stroke increases rapidly (51). The risk for both cerebral infarction and cerebral hemorrhage gradually increases with increasing levels of systolic blood pressure. For example, the incidence of cerebral hemorrhage was, in males, 4 times higher in the 140-179 mmHg group and 8 times higher in the 180 mmHg-

and-over group than in the normotensive (110-139 mmHg) group (40). Similar to systolic blood pressure, the incidence of cerebral hemorrhage increases markedly with elevation of diastolic blood pressure. Compared to the diastolic normotensive (70-89 mmHg) group, the risk is 4 times higher in males and 3.5 times higher in females in the 90-109 mmHg group, and 9 times higher in males and 16 times higher in females in the 100 mmHg-or-over group. Intervention studies on the efficacy of blood pressure lowering drugs have shown a reduction in stroke risk compatible with the attributable risk predicted from the observational studies in both middle-aged and elderly subjects; around 40%.

Figure 1. Association of diastolic blood pressure and risk of fatal stroke (51).
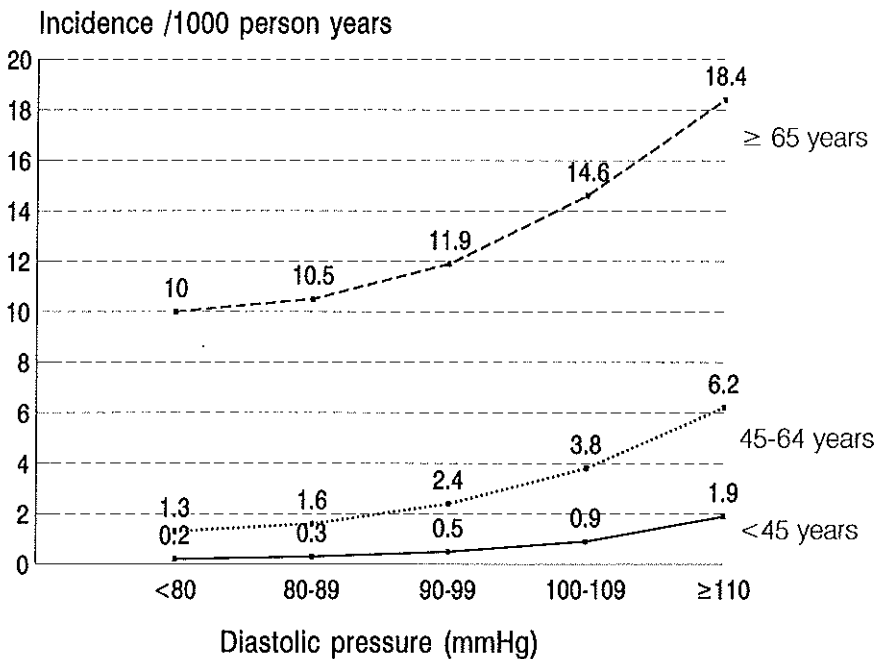

Data from observational studies in which baseline measured blood pressure was related to stroke before the age of 45 years are virtually absent, due to the limited size of the examined cohorts. Evidence on the association between blood pressure and risk of stroke before the age of 45 years comes from case-control

studies. Most of these studies showed a higher systolic blood pressure level in cases compared to controls (52). Also the prevalence of hypertension was higher. Lidegaard et al (31) in their study reported presence of hypertension in about 15%; 16.0% of the men and 13.6% of the women. Eldar et al (53) among young adults in Israel, observed that hypertension was the most common problem, being present in more than a third in both sexes. As discussed by Marshall (33) hypertension may remain unrecognized in the young until a cerebral ischemic event occurs because of inadequate diagnostic surveillance.

Elevated blood lipids Observational studies have provided data on the association between elevated levels of cholesterol and risk of stroke. However, contrasting results have been reported. Some have observed an increased stroke risk with increasing total cholesterol levels (54,55), whereas others found no association (51,56). Findings from the MRFIT study showed a linear positive association with cerebral infarction and an inverse relation with cerebral hemorrhage (57) (figure 2). These differences may point towards different etiologies. Data from observational studies in which baseline measured cholesterol was related to stroke before the age of 45 years are virtually absent. Several case-control studies have demonstrated a higher serum total cholesterol level among the young stroke cases compared to controls. Fogelholm and Aho (14) emphasized the importance of hypertriglyceridemia rather than hypercholesterolemia as a risk factor for stroke in the young. A Finnish study showed that high serum triglyceride levels were positively associated with stroke risk only among subjects aged 30 to 49 years (58). This finding conforms to that of others. An overview describing ten prospective studies in the young, showed that the relative contribution of elevated cholesterol to stroke may be stronger than in the elderly. The Framingham study has suggested a protective effect of high density lipoprotein cholesterol (HDL-C), with low HDL-C predictive of increased risk of stroke (59).

Figure 2. Association of total cholesterol and risk of fatal ischemic and hemorrhagic stroke (57).
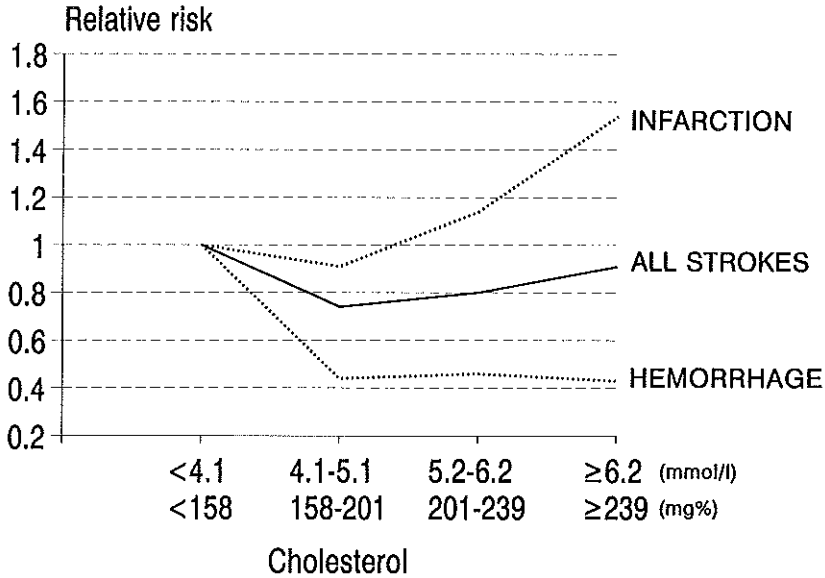
Data from a collaborative case-control study in young adults in Italy (52) have shown that in the univariate analysis, serum total cholesterol, serum HDL-cholesterol and serum triglycerides were all significantly associated with the occurrence of cerebral ischemia. In the multivariate analysis, because of mutual correlations, serum cholesterol lost its statistical significance and serum HDL-cholesterol emerged as a protective factor for vascular disease.

Diabetes mellitus Diabetes mellitus is a profound risk factor for stroke in middle-aged and elderly subjects. Several studies on this issue have consistently shown that diabetes mellitus doubles or triples the risk of stroke. For stroke in the young findings generally suggest only a limited role of diabetes mellitus. Several reports have shown no association with diabetes mellitus (52).

Protein C / protein S abnormalities Although 4 % of cerebral infarction in the young has been estimated to result from hemostatic disturbances that predispose to thrombosis. Recently, the association between cerebral infarction and deficiencies of elements of the natural anticoagulant system (protein C and protein S) has been recognized. In a study by Barinagarrementeria et al (60) of 36 patients, isolated protein S deficiency was detected in 13.8%. In other studies similar results were found. This may indicate that deficiency in one of the natural anticoagulants may precipitate thrombosis in the presence of a minor triggering factor. Factors such as cardiac abnormalities, smoking, use of oral contraception may trigger a stroke to occur in subjects with or diminished capacity for natural physiologic anticoagulation.

Another relevant disorder in the coagulation is the presence of antiphospholipid antibodies, inducing a prothrombotic state and which has been associated with a number of neurological conditions, including cerebral infarction and transient ischemic attacks. In particular in the young, presence of antiphospholipid antibodies has been implicated as a cause of ischemic stroke (61). In a collaborative study in the United Kingdom and Spain a prevalence of antiphospholipid antibodies of 6.8% was found in a large cohort of young patients with stroke (62). Nencini et al (39) in a study of young stroke patients found a prevalence of 18%. A hospital-based series of 68 patients below the age of 50 years presenting with neurological symptoms showed that patients with antiphospholipid antibodies were more likely to have amaurosis fugax, unilateral paresthesias and a family history of migraine (63). Definitive data to substantiate an etiologic role for antiphospholipid antibodies in stroke are, however, still lacking and the issue remains controversial (37).

Considering the importance of a prothrombotic state, especially caused by deficiency of protein S / protein C in the development of cerebral infarction, and its potential for treatment, it should be looked for in every young patient with cerebral infarction, in particular in the presence of a triggering event.

Life style factors

Smoking Smoking is a risk factor for stroke in both young and older subjects. A meta-analysis of 32 prospective risk factor studies (64) found a relative risk for stroke of smoking between 1.5 and 2. The risk is higher for cerebral infarction and subarachnoid hemorrhage compared to cerebral hemorrhage, higher for females compared to men, and increases with the number of cigarettes smoked per day. Results from a study to assess the impact of cigarette smoking on stroke in young adults also showed that a smoker was 1.6 times more likely to have a cerebral infarction than a non-smoker (65). An analysis of the influence of cessation of smoking in the Framingham study indicated that the risk of stroke decreased significantly and quickly. Five years after cessation the risk of stroke was similar to that of non-smokers (66).

Alcohol consumption In a Finnish population, acute alcoholic intoxication within the preceding 24 hours was reported in 40% of stroke patients aged 55 years and younger (20). This, however, is unlikely to reflect the importance of alcohol in other populations, although in some studies alcohol use was associated with an increased risk of stroke (52). Carolei et al (34) reported alcoholic intoxication as a likely cause in only 1.5% of stroke cases aged 15-44 years.

Dietary intake of potassium Clinical, animal, experimental and epidemiologic evidence suggests that a high dietary intake of potassium is associated with lower blood pressure. In hypertensive rats, a high intake of potassium is reported to protect against stroke, even though blood pressure is not affected. According to Khaw et al (67) a 10 mmol increase in daily potassium intake (approximately one serving of fresh fruit or vegetables) is associated with a 40% reduction in the risk of stroke-associated mortality (P<0.001). This effect was independent of other dietary variables, including the intake of calories, fat, protein, fiber, calcium, magnesium and alcohol. The effect was also apparently independent of known cardiovascular risk factors, including age, sex, blood pressure, blood

cholesterol level, obesity, fasting blood glucose level and cigarette smoking. Their findings support the hypothesis that a high intake of potassium from food sources may protect against stroke-associated death. The relative risks for stroke among those with potassium intake in the bottom tertile, as compared to those in the top two combined, were 2.6 in men and 4.8 in women, representing a statistically significant increased risk for women but not for men. Data, however, on the contribution of dietary intake of sodium to stroke are not available.

Use of oral contraceptives Oral contraceptive use has been reported to be very common among young women hospitalized with strokes (34%) (16). Still this frequency appears not significantly different from the estimated rate of use in the population of the same age (32%). Carolei (34), in a prospective study, observed a lower prevalence of oral contraceptive use among stroke cases (12.5%). It is believed that the use of the oral contraceptive pill is related to risk of ischemic and hemorrhagic strokes (68). Several case-control studies and large prospective cohort studies have concluded that oral contraceptive use increases the risk of stroke (69-76). While it is very likely that high-dose estrogen oral contraceptive agents are associated with increased stroke risk, controversy remains whether this may be generalized to all doses, particularly the more recently marketed low-dose preparations (77). Whether newer contraceptive preparations have a similar risk is presently being investigated (78). Stroke in young women should not be attributed to oral contraceptives, until other causes have been eliminated (47). On the other hand immunological studies showed anti-ethynyloestradiol antibodies in the blood of most females with brain infarction after using contraceptive drugs (79-81). Arterial lesions were found by radiological and histological investigations (82,83), suggesting that the use of oral contraceptives may in itself be a cause and not simply a risk factor for cerebral ischemia. No relation was found between the duration of the use of the contraceptives and cerebro-vascular complications.

In a study of 148 stroke patients with early cerebral angiography (47), migraine was found among 41.2% of the females whose cerebral ischemia was attributed to oral contraceptives. As only 17.6% of the cases was smokers, these results suggest that use of oral contraceptive drugs when associated with migraine may be more responsible for brain ischemia than oral contraceptives associated with smoking. In contrast, data of the prospective Royal College of General Practitioners' Oral Contraception study (76) suggest that the risk of stroke associated with use of oral contraceptives appears to be restricted to women who smoke.

Indicators of organ damage and malformation

Atrial fibrillation Atrial fibrillation is associated with an increased risk of ischemic stroke in subjects of older age (84). Associated cardiac disorders were also shown to influence stroke risk. Patients whose only stroke risk factor was congestive heart failure or coronary artery disease had stroke rates approximately three times higher than did patients without any risk factors. Patients with atrial fibrillation and mitral valve disease or prosthetic heart valves are also at high stroke risk (85). Some echocardiographic findings may also help predict increased stroke risk (86,87). Patients with non-rheumatic atrial fibrillation, however, were shown to have a low risk of stroke. The contribution of atrial fibrillation to stroke at a young age has not been firmly established yet.

Non-atherosclerotic cardiac abnormalities In particular in young stroke subjects, cardiac abnormalities of non-atherosclerotic origin, such as mitral valve prolapse and patent foramen ovale, have been suggested to underly in the stroke events. Embolism from the heart has been found to be the cause of stroke in 12% to 29% of adults younger than 45 years (8,11,16,17,23,27,88,89). Two-dimensional (2-D) echocardiography enables accurate assessment of these cardiac abnormalities. Echocardiography is a useful screening procedure in young adults with stroke, and any possible "pathologic" finding should be

carefully evaluated before attributing stroke to cardioembolism. The main screening potential of echocardiography is to detect mitral valve prolapse with redundant valves, a patent foramen ovale when paradoxical embolism is suspected, and atrial myxoma in patients without cardiac symptoms and with unclear findings on auscultation (37).

In Europe and North America, mitral valve prolapse and patent foramen ovale with or without interatrial septum aneurysm have often been considered to be the most common "occult" cardiopathies associated with stroke (32,90-93). Among the potential underlying cardiac causes of stroke in the young adults, mitral valve prolapse also appears to be common, as it has been found in 35% of young patients with ischemic stroke, compared with 7% of matched control subjects without stroke (91,94). Still, a low prevalence of mitral valve prolapse in young adults with stroke has also been reported (11,21,95), but in these studies echocardiography was not performed systematically, and thus the percentages are likely to have been underestimated. To estimate the real prevalence, strict criteria should be used for the diagnosis of a "pathologic" mitral valve prolapse, and it is likely that the morphology of the valves, e.g. redundance of the leaflets is also important (96). However, the data from the Italian collaborative case-control study of focal cerebral ischemia in young adults (52) showed that mitral valve prolapse was not associated with a significant increase in risk of stroke in this age group.

A patent foramen ovale is not uncommon in healthy young adults, and this defect is not "emboligenic" by itself. Yet, a paradoxical embolic phenomenon may be considered when the patient also has documented peripheral venous thrombosis or when stroke was triggered by a Valsalva maneuver (92,93,97,98). In general, the discovery of an isolated patent foramen ovale in a young adult with a recent cerebral infarct may be more an incidental finding than the origin of stroke, and the clinician should be encouraged to look for alternative causes.

Arterial dissection and ruptured arteriovenous malformation In a large series by Gautier et al (6), and in the experience gathered in the Lausanne Stroke Registry (32), dissection of the cervico-cerebral arteries was the first and second cause of stroke (21%) among 323 patients not older than 45 years. These findings suggest that one in every four to five young adults with stroke may have arterial dissection, although other reports gave lower figures (19,26,28). One explanation of varying percentages of arterial dissection is the extent to which angiography has formed part of the diagnostic work up. Lisovoski in a study of 148 patients, where cerebral arteriograms were performed in all cases, found arterial dissection in 10,1% of he subjects (47). Barinagarrementeria et al (99) in their study of 242 patients under 40 years, using CT scan in all cases and angiography in 78%, found evidence for arterial dissection in 16,9% of the subjects. Among the young a ruptured arteriovenous malformation has been implicated as a cause of stroke. In particular, in the presence of elevated blood pressure, this may constitute an important cause of intracerebral hemorrhage.

Miscellaneous factors

Migraine Between 5 and 25% of cerebral infarcts in the young have been attributed to migraine, but the lower limit of this range is probably closest to the truth (19,25,32,89,90,101,115). The diagnosis of migraine stroke is primarily based on exclusion of other conditions, and it is essential to use strict criteria, otherwise a diagnosis of migraine stroke will be made in every migraine patient who develops a stroke. A diagnosis of migraine stroke can be made reliably only in known migraine patients who develop a cerebral infarct during a typical attack of migraine (32,90,101,102). According to the Italian collaborative case-control study (52) only migraine with aura shows a clear association with focal cerebral ischemia.

Trauma A traumatic factor could be related to stroke in 13 (22%) of 60 patients under 45 years old from the Oxford Community study (21). This relatively high

proportion was, however, not confirmed in other studies (28,34), and may reflect a particular characteristic of the population studied.

Pregnancy induced thrombosis During pregnancy changes in the coagulation and fibrinolytic systems occur which may produce a hypercoagulable state along with a decreased ability to lyse fibrin (103). In addition, platelet aggregation is enhanced during pregnancy and the puerperium (104). Further increases in fibrinogen, coagulation factor VIII C and platelets also occur in the puerperium (105). It has been suggested that these changes may predispose pregnant and postpartum women to cerebral thrombotic and embolic events (116).

In absolute terms, the incidence of stroke is relatively low during pregnancy and the puerperium. Yet, it has been estimated that pregnancy is associated with a 13 fold increase in ischemic cerebral infarction compared with non-pregnant women between the ages of 15 and 39 years (106). In contrast, however, a population-based epidemiologic study by Wiebers and Whisnant (107) found an incidence of cerebral infarctions among pregnant women of 5.2 per 100,000 person-years which is only slightly higher than the incidence for cerebral infarction of 3.5 per 100,000 non-pregnant women aged 15-39 years.

Hemorrhagic strokes have been reported to account for 5-10% of all maternal deaths associated with pregnancy (108,109). In India, puerperal stroke is usually due to dural venous sinus occlusion and has been reported to be important (13,110). Srinivasan (110) reviewed the experience in Maduray, India, where puerperal stroke accounted for 15 to 20% of strokes in the young. Reports from other Indian investigators (111-113) also indicate a high frequency of this cause, suggesting that it is 10-12 times more frequent than in western countries. This further illustrates the notion that some causes of stroke in the young seem to be more prevalent in certain geographic areas only.

Drug abuse Use and misuse of a variety of drugs is increasingly recognized as a factor contributing to ischemic and hemorrhagic stroke in young adults, although limited data exist to quantify the risk of stroke associated with drug abuse. Of concern is the apparent increase in reported cases of stroke associated with cocaine use. In one study at an urban university hospital in the USA, the proportion of stroke cases historically associated with drug use/abuse was conservatively estimated to be 10 to 15% (114).

Conclusion

Stroke in young adults is not a negligible problem. The occurrence varies from 5 to 20% of all stroke cases. Most of the strokes in the young appear to be ischemic, but in some areas or studies hemorrhagic stroke is more common. This may point to different etiologies. Among the young subject, a number of risk factors is similar to that of elderly subjects; elevated blood pressure, smoking, heavy alcohol use. Abnormalities in the natural anticoagulant capacity of protein C and protein S may increase the risk of stroke in the young in particular in the presence of minor triggering factors, such as pregnancy, cardiac abnormalities, use of oral contraceptives, elevated blood pressure and smoking. Factors such as mitral value prolapse, arterial dissection and arterial aneurysm appear to be important too.

Most of the data concerning risk factors for stroke in the young have been collected in hospital based case-control studies. There is a need for pooling data from several cohort studies in order to come closer to identification of risk factors of stroke in the young. The EUROSTROKE project is an example of such an approach (117).

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CHAPTER 3

A CASE-CONTROL STUDY OF RISK FACTORS FOR STROKE IN YOUNG WOMEN IN JAKARTA, INDONESIA: DESIGN AND METHODS

Hypertension Diagnosis and Treatment in Young Indonesian Women

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Introduction

Since the introduction approximately 30 years ago, of orally ingested steroid hormones contraceptives (SHC), by 1990 it was estimated that 73 million women were using these drugs on a continuous basis (1). Overviews of the results of relevant studies have strongly suggested that oral contraceptive use was associated with an increased incidence of venous thromboembolic disease, thrombotic stroke and myocardial infarction (2-4). However recently SHC products and prescribing habits have changed. Lower doses of estrogen and progestogen are used, and in some countries progestogen-only contraceptives are widely used (5). Hence the question arises whether the current mode of SHC use has changed these risks. Consequently the World Health Organization (WHO) planned a case-control study of cardiovascular disease and steroid hormone contraceptive use; paying particular attention to satisfactory study size, precise diagnostic criteria, and close supervision and coordination of the study in order to maintain standardisation of data quality (6).

This paper describes the design and methods of the Indonesian component of the "WHO multicenter case-control study of cardiovascular disease and steroid hormone contraceptive use", with emphasis on stroke.

Research on risk factors of stroke in young women is scarce. There is no information about stroke in young women in Indonesia, and as far as we know no similar study has so far been conducted in Indonesia.

Design and Methods

A hospital-based case-control study was carried out in Jakarta, the capital city of Indonesia covering both a rural and urban area with approximately 8 million inhabitants, from January 1 1989 until May 31 1993. Fourteen hospitals (Appendix I) within the city area of Jakarta participated in the study. Cases were

young women aged 20-44 years of age, admitted with first-time stroke. The controls, as many as possible up to a maximum of three per case, were selected for each case from other female patients admitted to the same hospital within a four month period following the date of admission of the case. All controls were age-matched, such that they fell within the same 5 year age group as the case. Controls were selected from other diagnostic categories (Appendix II).

All cases and controls were interviewed in a standard fashion using the same WHO questionnaire (available on request). It was not possible to "blind" interviewers to the objectives of the project, but patients were not informed of the specific aims of the study. The hospitalized women had their precise diagnosis (Appendix III) recorded by the study personnel (physicians) and the stroke cases were confirmed by a neurologist. The completed questionnaire was sent by registered airmail to the WHO coordinating center in London, where the classification was reconfirmed (Appendix IV).

Study Questionnaire

The questionnaire, which was administered by physician interviewers was subdivided into three parts. The first, *Form A*, determined the eligibility of all potential cases and controls. Verbal informed consent from all cases and controls was obtained and recorded in this part of the questionnaire after reading a standard explanatory paragraph to each potential recruit.

Form B was answered by all eligible cases and controls. It included questions on past medical history, frequency of usage of medical services, reproductive history, use of medications, family history of cardiovascular disease, smoking, coffee and alcohol use, level of education attained and social class (assessed on the basis of housing, income, education and/or occupation). Information regarding hypertension was obtained from responses to three questions : whether the respondent had ever (excluding pregnancy) suffered from high blood pressure; whether she had had a blood pressure problem during pregnancy (pregnancy-associated hypertension); whether medication to control blood

pressure had been used in the three months prior to the illness which had caused hospital admission. A current smoker was defined as a woman who had smoked at least 1 cigarette in the 3 months prior to the illness which had caused hospitalisation.

Form C contained information on how a diagnosis (pulmonary embolism, deep vein thrombosis and myocardial infarction, atrial fibrillation or stroke) was reached and what procedures had been undertaken (lumbar puncture, brain ct-scan, angiogram or magnetic resonance imaging). The diagnosis "stroke" was further divided in cerebral infarction due to cardiac emboli and other causes, subarachnoid hemorrhage, intracerebral hemorrhage and non-specific stroke according to the criteria mentioned in appendix III.

Case Ascertainment

Cases were referred to the collaborating hospitals by one of several possible ways, depending on the severity of the cases and local facilities. The three most common methods were self-referral, referral after consultation with doctors in general practice or hospital outpatient departments and secondary referrals (patients who were transferred to a collaborating hospital from another hospital, most likely because better diagnostic or therapeutic facilities were available). A recruitment unit was set up in each hospital, so that all appropriately-aged women admitted to the hospital with a suspected first time diagnosis of stroke were interviewed by study personnel.

Cases who were too ill, had speech or cognitive impairment or died in hospital before recruitment, and hence could not be interviewed, were included in the study but information from proxy respondents or surrogates was used. For cases who required a surrogate respondent, the closest available and most suitable relative or friend was interviewed and three hospital controls were selected and interviewed in the usual way.

In order to prevent cases being missed in the collaborating hospitals, the optimal source(s) of information recording the admission of patients who had, or were likely to have, suffered a stroke were consulted on a regular basis by the field workers (female physicians). Typical sources were accident and emergency records, centralized admission records and relevant medical ward registers. Because of the potential for inaccurate hospital admission data, female patients in an extended age range (eg 18-47 years) and/or with inadequate or imprecise admission diagnoses were screened to ensure that no cases were missed. The frequency of checking admission records depended on the typical duration of hospitalization for stroke. Hospital discharge data were reviewed regularly to evaluate completeness of recruitment.

Eligibility criteria for cases

All women aged 20-44 with a first time diagnosis of stroke were considered eligible, except those who had a hysterectomy and/or menopause; a pregnancy within 6 weeks of the event precipitating admission; a past medical history of stroke; a history of operation, severe trauma or illness requiring medical attention and prolonged bedrest in the 6 weeks prior to the event precipitating admission to hospital; or died within 24 hours of admission to hospital. A log was kept of all identified eligible cases who either refused to join the study or were not studied for some other reason.

Control Ascertainment

Up to 3 controls in the same 5 year age band (20-24, 25-29 years, etc) were selected for each case from patients admitted to the same hospital with any of the specified diagnoses (Appendix II). Hospitalized women, admitted up to 2 weeks before or within 4 months after the date of admission of the case, were eligible as controls. A log was kept of all identified eligible controls who refused to join the study or who were not studied for any reason.

The procedure for control selection was customized to hospital-specific circumstances. A typical system involved the compiling of a list of all the wards admitting women with any of the specified diagnoses (Appendix II), randomizing the order and visiting them in that same fixed order whenever controls were being sought. When a selected ward had more than the required number of controls, the selection of control(s) within the ward again was carried out in a randomized fashion. When cases were admitted to hospitals where it was not possible to acquire controls because of the restricted types of patients admitted (eg cardiology hospital), controls were recruited from specified alternative hospitals. These were selected on the basis of admitting women from a similar catchment area as the hospital to which the case had been admitted.

Eligible criteria for controls

Patients aged 20-44 years who were admitted to a collaborating hospital with any of the diagnoses specified in Appendix II were considered suitable for inclusion in the study, provided that they satisfied the same eligibility criteria as the cases.

Ethical considerations

Before the study began in any collaborating hospital, written approval was obtained from the responsible body for granting ethical permission to carry out the research. The protocol was approved by the WHO Scientific and Ethical Review Group and the Secretarial Committee for Research in Human Subjects.

Measurements

Clinical findings were obtained from the medical record. Height and weight were measured with participants in light clothing and without shoes. The duplicate measurement of blood pressure was made with a mercury

sphygmomanometer in supine position upon first arrival at the hospital. Concomittantly, the pulse rate was counted. Blood was obtained by venipuncture between 7 and 11 AM after an overnight fasting. The laboratory determinations were done in the laboratory department of each of the 14 participitating hospitals. Routine blood examination, e.g. erythrocyte sedimentation rate, haemoglobin and leucocytes were measured in all patients. Fasting plasma glucose was measured by a hexokinase method. Total plasma cholesterol was measured by a colorimetric method and an urine sample was examined for the presence of protein, glucose and sediment.

Comments

The design and methods of this study were well planned in advance to be applicable for a worldwide multicenter study. The protocol was standardized and contained strict criteria. Although the study took place in one city of Indonesia, not all hospitals applied the same standard procedure. Physical examination including blood pressure measurement was performed in all hospitals in all patients. But height and weight measurement and total serum cholesterol content were not done routinely.

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Appendix I. Number of stroke cases and controls from the 14 hospitals in Jakarta participating in the study.

	Hospital	Stroke cases	Controls
1.	Cipto Mangunkusumo	75	188
2.	Dharma Jaya	6	-
3.	Fatmawati	37	119
4.	Gatot Subroto	14	22
5.	Harapan Kita	-	-
6.	Husada	30	132
7.	Islam	1	11
8.	Jakarta	8	20
9.	Pelni	11	53
10.	Persahabatan	2	2
11.	Pertamina	5	1
12.	St. Carolus	21	90
13.	Sumber Waras	19	40
14.	Tjikini	6	4
	Total	**235**	**682**

Appendix II. Diagnostic categories for control patients.

- Benign neoplasms other than those of the breast, brain, cranial nerves, thyroid and reproductive organs
- Diseases of the eye (excluding retinal vein and retinal artery thrombosis)
- Disease of the ear
- Influenza
- Pneumonia (without pleuritic chest pain)
- Acute bronchitis (excluding acute or chronic obstructive airway disease)
- Other acute respiratory infection
- Other acute infectious diseases
- Disease of the tonsils, sinuses, and salivary glands
- Nasal polyps, deflected septum
- Spontaneous pneumothorax
- Dental disorders
- Appendicitis (pathological confirmation necessary)
- Hernia
- Intestinal obstruction (of neither vascular nor malignant origin)
- Diverticular disease
- Anal fissure and fistula
- Hemorrhoids
- Abscess of anal and rectal regions
- Acute kidney and bladder infections
- Renal stone, renal colic
- Skin diseases including infections
- Disorders of bone and joints (excluding chronic arthritis such as rheumatoid arthritis)
- Trauma (including burns)
- Snake bite
- Plastic surgery resulting from trauma
- Accidental poisoning

Appendix III. Diagnosis of stroke

Definition: rapidly developing clinical signs of focal (and in the circumstance of a subarachnoid hemorrhage, diffuse) disturbance of cerebral function lasting more than 24 hours, with no apparent causes other than of vascular origin. Stroke includes subarachnoid hemorrhage, intra-cerebral hemorrhage, cerebral thrombosis or embolism, but not transient cerebral ischemia.

Suggestive symptoms:

- Sudden weakness or loss of strength in arm and/or leg
- Sudden sensory disturbance in face, arm or leg
- Sudden difficulty with speech
- Sudden partial or total blindness or double vision
- Sudden headache, nausea, vomiting and neck stiffness

When possible the diagnosis of stroke is confirmed by computed tomography or angiography. In those centers where these facilities are not available, clinical data will be collected on all cases of stroke and the Guy's Hospital score (7) will be used to classify the type of stroke. The extra necessary clinical data to use the Guy's Hospital score are diastolic blood pressure, level of consciousness during 24 hours of admission (drowsy/unarousable), presence of bilateral extensor plantars reflexes, apoplectic onset (sudden), aortic or mitral valve disease, cardiac failure, cardiomyopathy, atrial fibrillation and cardiothoracic ratio, in addition to details of past medical history, described under exclusion criteria.

Subclassification of stroke

1. Subarachnoid hemorrhage
This diagnosis will be made in the presence of a diffuse clinical presentation

with typical symptoms of acute headache, nausea, vomiting and meningism, along with CSF changes of blood staining. If a CT scan is available, this should show no changes with the possible exception of blood in the subarachnoid space. Ideally the CSF data should be sufficient to preclude a "traumatic" tap.

2. Cerebral hemorrhage

This diagnosis will be made if within 3 weeks of the clinical event a CT scan, brain scan or cerebral angiogram has been carried out, or in the absence of such procedures CSF is reported as blood stained (ideally with data sufficient to preclude a "traumatic" tap) and the clinical presentation is focal.

3. Cerebral infarction with cardiac source for embolism

This diagnosis will be made if a CT scan, brain scan or cerebral angiogram has been carried out within 3 weeks of the event and in the presence of clinical signs of rheumatic heart disease and / or atrial fibrillation.
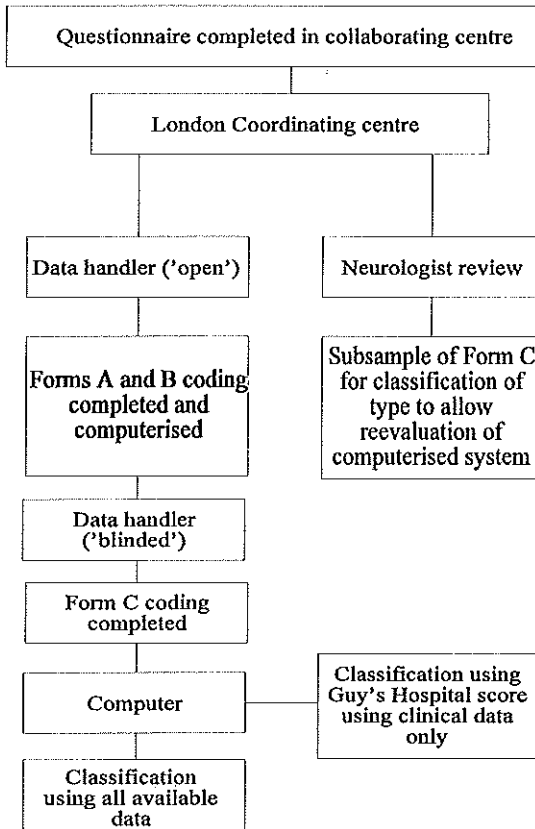
4. Other cerebral infarction

As for (3) above without the abnormal clinical cardiac signs.

5. Unknown type

This is based on the presence of clinical signs and symptoms compatible with stroke in the absence of a brain scan, a CT scan, a cerebral angiogram and a lumbar puncture.

6. Other

As for (5) and when clinical signs are present compatible with another diagnosis, e.g. retinal vein thrombosis, venous thrombosis etc.

Appendix IV. Flow Chart for Stroke diagnosis confirmation

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┌─────────────────────────────────────────────┐
│ Questionnaire completed in collaborating centre │
└─────────────────────────────────────────────┘
              │
      ┌─────────────────────────┐
      │ London Coordinating centre │
      └─────────────────────────┘
         │                    │
┌──────────────────┐   ┌──────────────────┐
│ Data handler ('open') │   │ Neurologist review │
└──────────────────┘   └──────────────────┘
         │                    │
┌──────────────────┐   ┌──────────────────┐
│ Forms A and B coding │   │ Subsample of Form C │
│   completed and   │   │ for classification of │
│   computerised    │   │    type to allow    │
│                   │   │    reevaluation of   │
│                   │   │ computerised system  │
└──────────────────┘   └──────────────────┘
         │
┌──────────────────┐
│   Data handler    │
│    ('blinded')    │
└──────────────────┘
         │
┌──────────────────┐
│  Form C coding    │
│   completed       │
└──────────────────┘
         │
┌──────────────────┐   ┌──────────────────┐
│     Computer      │───│ Classification using │
│                   │   │ Guy's Hospital score │
│                   │   │  using clinical data │
│                   │   │        only          │
└──────────────────┘   └──────────────────┘
         │
┌──────────────────┐
│  Classification   │
│ using all available │
│      data         │
└──────────────────┘
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CHAPTER 4

RISK FACTORS FOR STROKE IN YOUNG WOMEN A CASE-CONTROL STUDY IN INDONESIA

Risk factors for stroke in young women
A case-control study in Indonesia

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Introduction

Stroke is one of the most dramatic expressions of cardiovascular disease. Strokes often occur without a warning, are frequently fatal and if non-fatal lead to major impairment and loss of quality of life. All the more impact has a stroke if it occurs in a young individual who may experience the consequences over a lifetime. In recent decades many factors that increase the risk of stroke have been established. These include increased age, high blood pressure, smoking, obesity, heavy alcohol use, ischemic heart disease, atrial fibrillation, previous transient ischemic attacks, diabetes, and certain dietary factors (1-11). In contrast, research on risk factors of stroke in the young and particularly in women is scarce (12). In Thailand, Indonesia and other Asian countries where the young generation forms a large part of the population the incidence of stroke in women is higher than of myocardial infarction, with many victims occurring at a relatively young age (13). To reduce the incidence of stroke in this part of the world, it is important to know about the way certain risk factors may be particularly important in the young and whether risk factors for stroke differ according to age and gender. We conducted a case-control study of risk factors for stroke in young Indonesian women.

Subjects and Methods

A case-control study was conducted among 917 Indonesian women aged 20 to 44 years of age. The study formed part of a WHO multicenter case-control study of cardiovascular disease and steroid hormone contraceptive use (14). The present analysis concerns only the Indonesian component of the WHO study. Details of the design and conduct of the study have been published separately (15). Fourteen hospitals in Jakarta, Indonesia participated in the study from January 1, 1989 until May 31, 1993. Cases were young women aged 20 to 44 years admitted with first time stroke. Controls, up to a maximum of three were selected for each case from other female patients admitted to the same hospital.

For the present study, subjects were selected from women hospitalized for various conditions such as involving the eye, ear-nose-throat, lungs, kidney and bowel, but excluding diseases of the arterial and venous system. All controls were matched within the same 5 year age band (20-24, 25-29 years etc.) as the cases. Controls were selected from patients admitted to hospital up to 2 weeks before or within 4 months after the date of admission of the case. Wards chosen to recruit control patients were randomized, and per ward eligible control patients were randomly selected. All cases and controls were interviewed in a standard fashion using a dedicated questionnaire. In case a stroke patient was unable to answer the questions a proxy or surrogate respondent was used, being a close relative or a friend. Whenever possible, in a later stage attempts were made to confirm the data obtained from the proxy respondent by renewed interviewing of the case. Information was available from proxy respondents in 90 (38%) of the cases. A preliminary diagnosis of stroke was confirmed by a neurologist and later certified by the WHO coordinating center in London according to predefined criteria.

Blood pressure was measured in supine position as the average of duplicate readings using a calibrated mercury sphygmomanometer. Hypertension was defined as a systolic blood pressure $\geq$ 160 mmHg or a diastolic blood pressure $\geq$ 95 mmHg, or use of anti- hypertensive medication. Fasting venous blood samples were collected for total cholesterol determination (CHOD-PAP method - Boehringer Mannheim). As not all hospitals had sufficient laboratory facilities or capacity and because of budgetary restrictions, serum cholesterol levels could only be determined in a subsample of the group (173 cases and 226 controls). An elevated cholesterol was defined as a value $\geq$250 mg/dl (16). A diagnosis of diabetes mellitus was based on medical history and on urine glucose content. Cigarette smoking and alcohol use were recorded by interview. For the analyses these variables were dichotomised into yes/no.

The diagnosis of stroke was based on rapidly developing clinical signs of focal (and for subarachnoid hemorrhage, diffuse) disturbance of cerebral function lasting more than 24 hours, with no apparent cause other than vascular. The diagnostic classification of stroke subtypes followed the guidelines proposed by the WHO Collaborative Study of Cardiovascular Disease and the Use of Steroid Hormone Contraception (14), with strokes classified as intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke and stroke of unknown type whenever insufficient clinical information was available to categorize a stroke according to the protocol. Data from definitive investigations such as CT scanning and cerebral angiograms were only available in 4 % of the patients and not considered a prerequisite for the diagnosis.

Informed consent was obtained from all patients and the study was approved by the local responsible body for granting ethical permission. None of the cases, and only one of the controls eligible for the study refused participation. The protocol was also approved by the WHO Scientific and Ethical Review Group and the Secretarial Committee for Research in Human Subjects.

Data analysis

The data-analytic approach was two-fold. First, means and standard errors were calculated for the continuously distributed variables and comparisons between cases and controls were made using t-tests or Chi-square tests when appropriate. Second, using conditional logistic regression analyses, odds ratios with corresponding 95% confidence intervals were calculated as an approximation of relative risk. Factors that showed significant elevated risks in the univariate analyses were subsequently entered into a multivariate model to assess their importance adjusted for the other risk factors as potential confounders. Statistical packages used were SPSS and STATA (StataCorp, USA).

Results

General characteristics and risk factor levels for cases and controls are presented in table 1. Overall, nearly 50% were ischemic strokes, about 25% intracerebral hemorrhages, 5% subarachnoid hemorrhages and about 20% of unknown type. There were no significant differences in mean age between these different stroke types. The age-specific distribution of stroke types among the 235 stroke patients is given in figure 1. The subgroup of cases and controls in whom serum cholesterol was measured was closely similar to the overall study population in most relevant characteristics (table 2).

Figure 1. Age specific distribution of stroke type among 235 young female patients.
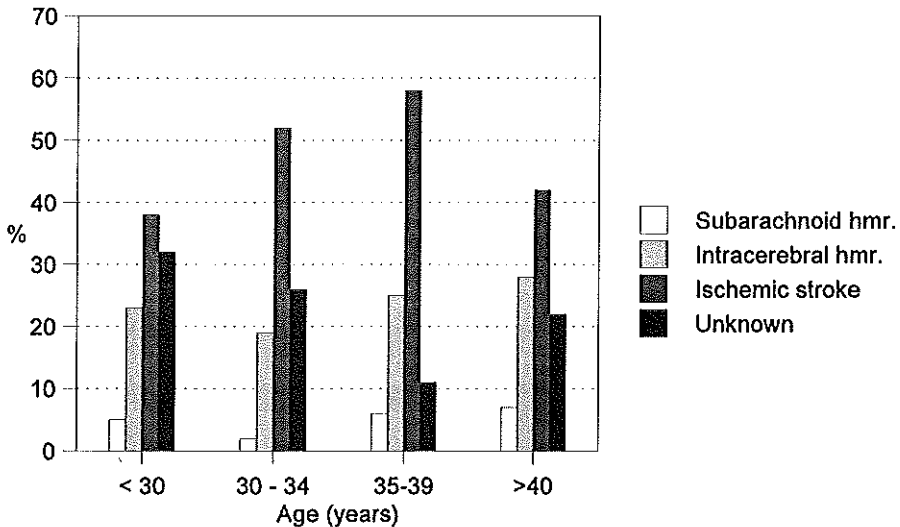
Table 1. General characteristics of stroke cases and controls.

	cases n=235	controls n=682	p value
Age (yrs)	36.7 (0.4)	36.1 (0.4)	*
Height (cm)[1]	154.9 (0.7)	155.0 (0.3)	0.87
Weight (kg)[1]	55.4 (1.2)	52.3 (0.6)	0.02
BMI[2] (Weight/Height[2])	23.1 (0.5)	21.7 (0.2)	0.005
Systolic BP[3] (mmHg)	153.7 (2.7)	118.6 (0.6)	<0.001
Diastolic BP[3] (mmHg)	98.1 (1.5)	76.9 (0.4)	<0.001
Cholesterol[4] (mg%)	207.0 (4.3)	180.9 (3.1)	<0.001
Hypertension[5] (%)	56.2	6.5	<0.001
Hypercholesterolemia[4,6] (%)	19.7	6.2	<0.001
Smoking (%)	6.8	5.6	0.49
Alcohol use (%)	3.8	1.8	0.07
Diabetes (%)	11.5	3.1	<0.001

Values are means with standard errors in parentheses or percentages

*	Matching factor
1	Comparison based on 173 cases and 263 controls
2	BMI: Body Mass Index
3	BP: Blood Pressure
4	Comparison based on 173 cases and 226 controls
5	Hypertension defined as a blood pressure at or above 160/95 mmHg and/or antihypertensive medication
6	Hypercholesterolemia defined as a cholesterol level at or above 250 mg/dl

Table 2. Characteristics of stroke cases and controls in whom cholesterol was measured.

	cases n=173	controls n=226	p value
Age (yrs)	37.1 (0.5)	36.9 (0.4)	*
Height (cm)[1]	155.1 (0.8)	155.0 (0.6)	0.92
Weight (kg)[1]	56.1 (1.4)	52.2 (1.0)	0.02
BMI[2] (Weight/Height[2])	23.3 (0.5)	21.7 (0.4)	0.009
Systolic BP[3] (mmHg)	153.6 (3.1)	119.7 (1.2)	<0.001
Diastolic BP[3] (mmHg)	97.5 (1.7)	77.7 (0.8)	<0.001
Cholesterol (mg%)	207.0 (4.3)	180.9 (3.1)	<0.001
Hypertension[4] (%)	59.0	8.9	<0.001
Hypercholesterolemia[5] (%)	19.7	6.2	<0.001
Smoking (%)	6.4	5.8	0.66
Alcohol use (%)	4.1	3.1	0.61
Diabetes (%)	5.8	0.9	0.005

Values are means with standard errors in parentheses or percentages

*	Matching factor
1	Comparison based on 173 cases and 263 controls
2	BMI: Body Mass Index
3	BP: Blood Pressure
4	Hypertension defined as a blood pressure at or above 160/95 mmHg and/or antihypertensive medication
5	Hypercholesterolemia defined as a cholesterol level at or above 250 mg/dl

There were no significant differences in smoking habits and alcohol consumption between stroke cases and their controls, but in both groups few women were smokers or alcohol users. Cases were significantly heavier than controls and more frequently had diabetes. Mean systolic and diastolic blood pressure and total serum cholesterol were higher in cases than controls and so was the frequency of hypertension and hypercholesterolemia.

Among the cases, those with subarachnoid hemorrhage or intracerebral hemorrhage had significantly higher blood pressure levels than patients with ischemic stroke (difference 24.5 mmHg (SE 6.2, p = <0.01) in systolic blood pressure and 11.8 mmHg (3.4, p = 0.001) in diastolic blood pressure respectively). Nonetheless, patients with ischemia still had significantly higher blood pressure than their corresponding controls (difference 30.3 mmHg (2.8, p < 0.001) in systolic blood pressure and 19.2 mmHg (1.7, p < 0.001) in diastolic blood pressure respectively). Total serum cholesterol was significantly higher in both patients with ischemia or intracerebral hemorrhage compared to their controls (difference 25.1 mg% (8.0, p = 0.002), and 41.8 mg% (10.3 p < 0.001 respectively), while in patients with subarachnoid hemorrhage cholesterol levels were not different from those in controls (table 3).

Table 3. Blood pressure and cholesterol levels in cases according to stroke type.

	Subarachnoid Hemorrhage n=13	Intracerebral Hemorrhage n=59	Ischemic Stroke n=111
Systolic BP[1](mmHg)	186.9 (14.5)	170.2 (5.1)	148.7 (3.9)
Diastolic BP[1](mmHg)	111.5 (6.8)	106.9 (2.9)	96.0 (2.1)
Cholesterol[2] (mg%)	176.6 (8.4)	219.8 (9.0)	209.4 (6.0)

Values are means with standard errors in parentheses

1   BP: Blood Pressure

2   Comparison based on 134 cases; 5 subarachnoid hemorrhages; 41 intracerebral hemorrhages; 88 ischemic strokes

Hypertension, an elevated serum cholesterol and diabetes were significantly associated with total stroke in this study, but cigarette smoking and alcohol use were not (table 4). Interestingly, an increase in body mass index by one unit (kg/m^2) was associated with an 8% increase in total stroke risk (p = 0.06). This risk was reduced to 6% and not statistically significant when adjusted for presence of hypertension.

Table 4. Unadjusted relative risks for total stroke in young Indonesian women.

	Odds Ratio	95% C.I.	p value
Hypertension[1]	20.6	14.6, 29.1	<0.001
Total cholesterol[2]	5.0	2.1, 11.8	<0.001
Diabetes Mellitus	4.3	2.3, 7.9	<0.001
Cigarette smoking	1.2	0.7, 2.3	0.49
Alcohol use	2.2	0.9, 5.7	0.07

1   Hypertension defined as a blood pressure at or above 160/95 mmHg and/or antihypertensive medication
2   Analysis based on 173 cases and 226 controls

In the multivariate analysis, with all risk factors combined in the model, hypertension and diabetes remained strong independent risk factors for stroke, but the association with cholesterol was attenuated and not statistically significant (table 5). Finally, when risks according to stroke sub-types were considered, again a strong association of hypertension and diabetes with ischemic stroke was observed, but not with cholesterol (table 6). For the other types of stroke too few cases and/or measurements were available to perform meaningful separate analyses.

Table 5. Mutually adjusted relative risks for total stroke in young Indonesian women.

	Odds Ratio	95% C.I.	p value
Hypertension[1]	34.8	10.2, 118.6	<0.001
Total cholesterol[2]	2.8	0.8, 9.8	0.11
Diabetes Mellitus	12.9	1.9, 86.3	0.008
Cigarette smoking	2.1	0.4, 10.8	0.36
Alcohol use	1.6	0.7, 131.2	0.80

1 Hypertension defined as a blood pressure at or above 160/95 mmHg and/or antihypertensive medication
2 Analysis based on 173 cases and 226 controls

Table 6. Mutually adjusted risks for ischemic stroke in young Indonesian women.

	Odds Ratio	95% C.I.	p value
Hypertension[1]	15.6	4.7, 52.5	<0.001
Total cholesterol[2]	2.1	0.6, 7.9	0.28
Diabetes Mellitus	7.8	1.1, 58.1	0.04
Cigarette smoking	2.0	0.3, 14.9	0.52
Alcohol use	1.4	0.1, 137.1	0.92

1   Hypertension defined as a blood pressure at or above 160/95 mmHg and/or antihypertensive medication
2   Analysis based on 173 cases and 226 controls

Discussion

The results of this case-control study, using data obtained in 235 young Indonesian women admitted to hospital with non-fatal stroke, indicate that hypertension and diabetes mellitus are dominant risk factors in this group. The importance of an elevated serum total cholesterol as a risk factor for stroke in this study appears to be less marked, although present. Among the cases, a diagnosis of hemorrhagic stroke was relatively frequent, and higher than commonly observed in older populations (17).

To accept these findings certain aspects of the study need to be addressed. In this study only strokes were included that were not immediately fatal, survived at least 24 hours and were admitted to hospital. However, symptomatic non-fatal stroke in young women almost always results in hospital admission. As virtually all cases and controls eligible for this study participated, this will further improve generalizability. The blood pressure was measured after the stroke which may have affected the result of the measurement. However, patients were in general measured untreated and after the acute phase. Although inferior to blood pressure measurements recorded before the event, the measurements suffice as a proxy for previous blood pressure levels and provide a clear indication of risk. The diagnosis of diabetes mellitus in this study was not based on the blood sugar level, but on a positive history and urine sugar levels. While this will have led to some misclassification, the prevalence of 3.1% observed in the controls precludes a marked underestimation of the expected numbers.

The findings in this study show the primary risk factors for stroke in young women to be largely similar as those established in older, male populations. However, due to the relatively low frequency of stroke and the absence of advanced atherosclerotic arterial disease in this age group, the relative risks for stroke observed for elevated blood pressure and diabetes mellitus are substantially higher than generally reported for older subjects. Based on the frequency of hypertension in the controls and the relative risk estimated from the case-control analyses, the population attributable risk of stroke associated with

hypertension in young Indonesian women is 36 %.

There are only few other studies addressing stroke and its risk factors in young women (18-20). In this hospital-based study of 235 young women with stroke, the prevalence of subtypes of strokes was in accordance with other studies (21-23) indicating that ischemic stroke in young adults is more common than hemorrhagic stroke. The relatively large proportion of "other" or "unknown" forms of stroke was due to the fact that not in all cases sufficient diagnostic data were available to allow meaningful classification of the stroke.

By nature of the design of the study little differences in mean age between cases and controls were present. Although height was similar in the two groups, stroke cases were heavier and consequently body mass index was higher. A larger body mass index tended to be associated with increased risk of stroke which, however, could largely be explained by an increased frequency of hypertension among obese women.

Smoking was, as expected, uncommon in this group of young women, and although the risks was elevated (RR = 2.1; 95% CI 0.4, 10.8) this did not reach significance. The low prevalence of smokers among the women included in this study, agrees with findings in another study recently conducted in a rural area of West Java, Indonesia (24), where only 5% of women were cigarette smokers, in contrast to 83.7% of the men. In a meta-analysis of 32 prospective risk factor studies (25) the relative risk for stroke related to smoking varied between 1.5 and 2.0 and was higher for females compared to males. In another study in young adults (26), it was shown that a smoker was 1.6 times more likely to develop a cerebral infarction than a non-smoker. In our analyses, although confidence limits are wide, the point estimate of the relative risk of 2.1 associated with smoking emphasizes its importance as a risk factor in Indonesia would smoking rates in women increase as they have done in westernized societies. No increase in risk of stroke associated with alcohol remained after adjustment for confounders, but again the numbers of users were small in this

group of predominantly Muslim Indonesian women and the precision of the risk estimate is low.

In the total group of strokes, systolic blood pressure was about 35 mmHg higher than in the controls and the diastolic blood pressure about 21 mmHg. This difference was most outspoken for subarachnoid and intracerebral hemorrhage, where the differences varied between 51 and 68 mmHg for systolic blood pressure and between 30 and 35 mmHg for diastolic blood pressure. Hypertension, defined using the WHO criteria as blood pressure levels above 160/95 mmHg and or current use of antihypertensive medication, was present in 56 % of the cases and 6 % of the controls and contributed strongly to the occurrence of stroke. This is in accordance with other studies (21,22), where hypertension proved to be a major risk factor for stroke in young adults, although the relative risk in the study presented here is much higher.

Total serum cholesterol levels in the cases were on the average 26 mg% higher than in the control group, a highly significant difference in the univariate comparison. In patients with subarachnoid hemorrhage it was not elevated. In the multivariate analysis the relative risk of cholesterol for stroke was 2.8 and not reaching statistical significance, presumably because of confounding by hypertension. This is in agreement with the data of a case-control study in young adults in Italy (23), where in the univariate analysis, serum total cholesterol, HDL-cholesterol and triglyceride were all significantly associated with the occurrence of cerebral ischemia. In the multivariate analysis however, because of mutual correlations, serum cholesterol lost its statistical significance and serum HDL-cholesterol emerged as a protective factor for vascular disease. A limitation of our study is that cholesterol was only measured in a subgroup of cases and controls, which limits the power of the study and hence has led to wide confidence limits. The reasons, however, were entirely logistic and financial and are unlikely to have induced a biased estimate of the risk.

Diabetes mellitus was present in almost 12% of the cases, while in the control group only 3% had diabetes. An elevated risk of diabetes mellitus for stroke is in

accordance with other studies in older populations (27-29). The point estimate of the relative risk for stroke of 12.9 in these young women, however, is considerably higher than the relative risk of 2 reported previously (30). This could be due to the small numbers, and hence wide confidence intervals, although the lower limit of the 95% confidence interval is 1.9.

Certain differences in risk profile were present according to stroke type. In subarachnoid hemorrhage the blood pressure was higher than in intracerebral hemorrhage or ischemia, but total cholesterol serum level lower than in the other stroke types. The limited numbers of subjects with subarachnoid hemorrhage and intracerebral hemorrhage prevented, however, further detailed analyses.

In conclusion, the findings in our study suggest that hypertension and diabetes mellitus are the most important risk factors for stroke in young Asian women. As strokes in Asian women are more frequent than commonly acknowledged, increased attention to diagnosis and management of these disorders is warranted. Other potential risk factors such as smoking and alcohol consumption are as yet rare in this population, but may gain in importance as women become more emancipated and lifestyle changes towards that characteristic of more westernized societies.

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CHAPTER 5

SOCIAL AND ECONOMIC DETERMINANTS OF STROKE RISK IN YOUNG INDONESIAN WOMEN

Social and economic determinants of stroke risk in young Indonesian women

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Introduction

Stroke is an important cause of mortality and disability. In industrialized societies, stroke trends have generally decreased in recent decades. However, from a limited number of reports, it appears that stroke is becoming more common in the so-called "developing world", notably in Asia (1). Also, there are data to suggest that stroke rates are relatively high in Asian women (2). A low socio-economic status may particularly be associated with stroke risk (3-7). Findings in a recent study in Hong Kong suggest that while a higher socio-economic status is associated with higher risk of death from ischemic heart disease, this may not apply for cerebrovascular disease (8). The International Clinical Epidemiology Network has provided information on the prevalence of some known risk factors for stroke in the developing world, including age, hypertension, body mass index, cholesterol and smoking (9). However, this report does not give information on the extent to which stroke risk may vary according to socio-economic status.

We examined the association between stroke risk and several social and economic indicators among young Indonesian women.

Subjects and Methods

A case-control study was conducted among 917 Indonesian women aged 20 to 44 years (235 stroke cases and 682 control patients). The study formed part of a WHO multicenter case-control study of cardiovascular disease and steroid hormone contraceptive use (10). The present analysis concerns only the Indonesian component. Fourteen hospitals in Jakarta, the capital of Indonesia, participated in the study from January 1, 1989 until May 31, 1993. Cases were young women aged 20 to 44 years admitted with first time stroke. Controls, up to a maximum of three per case, were selected from other female patients admitted to the same hospital. All controls were matched by age, such that they fell within the same 5 year group as the case. All cases and controls were interviewed in a standard fashion using a dedicated questionnaire. Details of the

design and methods of the main study and its Indonesian component have been published separately (10,11).

The diagnostic classification of stroke subtypes followed the guidelines proposed by the WHO Collaborative Study of Cardiovascular Disease and the Use of Steroid Hormone Contraception (10), with strokes classified as intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke and stroke of unknown type whenever insufficient clinical information was available to categorize a stroke according to the protocol.

Social and economic status was evaluated using a score based on information of income, type of housing and luxury household items. Subjects were classified according to four groups: low, middle low, middle high and high. The low class had an income lower than US$ 50 a month, no stone house and no luxury household items. The low middle class had an income between US$ 51 to 250 a month, semi-stone house or small apartment, television and/or motor-bike. The high middle class had an income between US$ 251 to 500 a month, stone house or apartment, television, motor-bike or non-luxury car. The highest class reflected any level above the high middle class. For statistical analyses, as only 7 % of the cases and 6 % of the controls were in the highest class, middle high and highest were combined into one "high" group which resulted in approximately equal numbers of subjects in the three socio-economic groups.

Level of education was also classified into three groups: illiterate or elementary education only, secondary education and tertiary education, comprising both university or vocational education irrespective of completion. Marital status was classified as single, married, and divorced, the latter group comprising both divorced and widowed women.

For all variables, proportions or means and standard deviations were calculated. Next, as an approximation of relative risk, age-adjusted odd ratios for stroke according to indicators of social and economic status were estimated using multivariate conditional logistic regression analyses with inclusion of

confounding variables in the model when appropriate.

Results

Mean age among the 235 cases was 36.1 (SD 6.3) years, and among the 682 controls 36.7 (6.4) years. After combining the "middle-high"and "high"classes into one "high"class, the distribution of indicators of low, middle and high social and economic status over the groups of cases and controls differed, reaching borderline overall significance (p = 0.08, Table 1). Furthermore, cases in the higher socioeconomic strata were significantly older than controls. Among both cases and controls, those in the highest social and economic class were significantly older than those in the lower classes.

Table 1 Indicators of social and economic status in cases and controls.

	cases (n = 235)	controls (n = 682)
Social and economic status		
High	17 (7)	39 (6)
Middle-high	55 (24)	226 (33)
Middle-low	104 (44)	266 (39)
Low	59 (25)	151 (22)
*Classification in three groups**		
High	72 (31)	265 (39)
Middle	104 (44)	266 (39)
Low	59 (25)	151 (22)
Marital status		
Single	25 (11)	89 (13)
Divorced	17 (7)	62 (9)
Married	193 (82)	531 (78)
Education		
Illiterate/Elementary	103 (44)	248 (36)
Secondary	101 (43)	327 (48)
University/Vocational	31 (13)	107 (16)

Values are numbers with percentages in parentheses

*   Statistical analyses are based on this classification

The low socioeconomic group formed a higher percentage among cases (25%) than among the controls (22%). The distribution of the marital status was not much different between the cases and controls.

The proportion of subjects with only primary education or no education at all appeared to be somewhat larger among cases compared to controls: 44% for the cases and 36% for the controls (p = 0.04).

In table 2, the risk of stroke according to socio-economic variables is shown. The middle and low socio-economic groups had a relative risk for total stroke of 1.46 (95% confidence interval 1.02, 2.10) and 1.54 (0.97, 2.43) respectively. The increased risk appeared largely restricted to ischemic stroke (table 3). Adjustment for hypertension did not change the results.

Table 2. Age-adjusted odd ratios for first ever stroke according to various socio-economic indicators in young Indonesian women.

	Odds Ratio (95% CI*)
Social and economic status	
High	1[1]
Middle	1.46 (1.02 , 2.10)
Low	1.54 (0.97 , 2.43)
Marital status	
Single	1[1]
Divorced	1.03 (0.50, 2.14)
Married	1.39 (0.81, 2.40)
Education	
Illiterate/Elementary	1[1]
Secondary	0.73 (0.52, 1.03)
Universitary/vocational	0.68 (0.42, 1.09)

*   CI: confidence interval
[1]   Reference category

Better education tended to be associated with lower stroke risks (test for inverse trend in risk across the three groups p = 0.06). When the group with more than primary education was compared to the rest, the risk of stroke was 0.72 (0.52, 0.99). This reduced risk could, however, largely be explained by a lower

frequency of hypertension among the better educated groups (relative risk after adjustment for hypertension 0.84 (0.55, 1.28)). Moreover, the risk particularly arose from an association of low education with risk of subarachnoid hemorrhage (table 3). Marital status was not associated with total stroke risk. Cigarette smoking and alcohol use were uncommon in this predominantly Muslim group of women and were not significantly related to stroke risk.

Table 3. Age-adjusted odd ratios for different stroke types according to various socio-economic indicators in young Indonesian women. Groups have been collapsed to mantain adequate numbers.

	Ischemic stroke (n = 111) OR (p-value)	Intracerebral Hemorrhage (n = 59) OR (p-value)	Subarachnoid Hemorrhage (n = 13) OR (p-value)
Social and economic status			
High	1^1	1^1	1^1
Middle/low	1.8 (0.02)	1.3 (0.39)	0.9 (0.85)
Marital status			
Single	1^1	1^1	1^1
Married/divorced	1.8 (0.18)	1.3 (0.70)	1.5 (0.67)
Education			
Illiterate/Elementary	1^1	1^1	1^1
Secondary/Tertiary	0.6 (0.06)	0.96 (0.90)	0.3 (0.06)

[1]   Reference category

Discussion

Our findings, in a hospital based case-control study involving 235 stroke cases and 682 controls, show that social and economic status is related to stroke risk in young Indonesian women. Stroke risks are higher when social and economic position is lower, as judged by income, housing and possession of luxury items. Also, education appears to be inversely related to risk of stroke, probably through an inverse association of education with hypertension. The latter may reflect a stronger health consciousness among better educated women. Marital

status appears not to be associated with risk of stroke.

A number of limitations of our study needs to mentioned. The analyses are based on cases and controls that were admitted to a hospital. As a consequence, the selection may have been biased to on average higher social and economic levels. The distribution across different social and economic groups in the study is comparable to data from the Indonesian Central Bureau of Statistics. According to a recent publication from the Ministry of Health, 16.7 % of the population is in the lowest socio-economic groups (12). Whether or not selection has occurred, the risk estimates within this study remain valid. The scoring system to classify social and economic status was specifically developed for use in the present study and has not been validated for its present application. The classification system, however, resembles the approach taken by the Indonesian Central Bureau of Statistics. While crude, we feel that a system for classifying social and economic status should closely reflect the local situation, even in spite of loss of some generalizability. Still, it seems likely that the risks we observed with low social and economic status and education are relatively insensitive to differences across populations even though the distribution of poverty within countries may vary.

There is very little published data on stroke risk in relation to social and economic status in westernized societies, and even less for Indonesia, but findings in those studies available are consistent with our results (3-7). In contrast, there is ample data to show that age-standardized total mortality rates, mortality from heart disease and mortality from cancer all are higher among the social and economically deprived. Similarly, an unfavorable trend in cardiovascular risk profile has been demonstrated with a lower social and economic status.

The finding of low education as a specific risk factor for subarachnoid stroke was unexpected. As this result is based on a rather small number (n = 13) of cases of subarachnoid stroke the finding should be interpreted with caution. Larger studies are needed to address this association with more confidence.

There are several ways by which an increased risk of stroke among women from lower social and economic groups can be explained. In chapter 4 we report our findings on the risk of stroke associated with hypertension among these young women. However, in our study the differences between socio-economic groups in stroke frequency cannot be explained by differences in blood pressure, and adjustment for this risk factor did not change the results. Alternative explanations include social class related differences in smoking, alcohol use, diet, physical activity and (job related) stress (13-17). Also, differences in levels of plasma fibrinogen and other clotting factors have been implicated (17). In our study, no data on these factors are available, with the exception of alcohol use and smoking both of which were extremely uncommon among this predominantly Muslim group of women and are unlikely to account for the differences in risk observed.

In conclusion our findings indicate that risk of stroke is higher among Indonesian women from lower social and economic classes. This notion, together with the observation that Asian women appear to be particularly at risk for stroke, emphasizes the importance of social and economic determinants of risk. Further research to explain the increased risk is clearly indicated. Moreover, strategies for prevention of stroke and of cardiovascular disease in general should take the importance to reach women of lower social and economic class into account.

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CHAPTER 6

HYPERTENSION DIAGNOSIS AND TREATMENT IN YOUNG INDONESIAN WOMEN

.

A case-control study of risk factors for stroke in young women in Jakarta, Indonesia: Design and methods

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Introduction

Stroke is an important cause of chronic disability and mortality. While stroke rates have generally decreased in westernized societies, this is not quite as clear for several developing countries and stroke trends even appear to increase in Asia. Data from several studies suggest that in Asia, women are particularly at risk of stroke. High blood pressure is well established as a major determinant of hemorrhagic and ischemic stroke in older subjects. Recently, it was shown that among young Indonesian women, elevated blood pressure is similarly associated with risk of stroke and indeed one of the most important risk factors for this condition (1). At present very little is known about the distribution of blood pressure among Indonesian women, and the quality of diagnosis and treatment of hypertension is unclear.

The present study describes the prevalence, diagnosis and treatment of hypertension in 682 young Indonesian women.

Subjects and methods

In the course of a case-control study on stroke, conducted during 1989-1993, 682 women aged 20-44 years were selected at random from subjects hospitalized for non-cardiovascular disease in 14 hospitals in Jakarta, Indonesia. Details on the case-control study have been published separately (2, 3). For the present study, subjects were selected from women hospitalized for various conditions such as involving the eye, ear-nose-throat, lungs, kidney and bowel, but excluding diseases of the arterial and venous system.

Trained research physicians administered to each women a standard questionnaire, which included questions on medical history, socio-economic status and smoking habits (published as appendix to reference 3). All subjects were asked whether they had ever been told by a physician that they had high blood pressure. Duplicate blood pressure measurements were made in all 682 women using a mercury sphygmomanometer with the subject in supine position.

The mean of the blood pressure readings was used in the analysis. Systolic blood pressure was recorded at the Korotkoff first sound (phase I) and the diastolic blood pressure was recorded at the disappearance of sounds (phase V). Data on height and weight were available in 263 women, and serum cholesterol level in 226 women.

Indices of smoking, marital status, educational level and socio-economic status were registered. Social and economic status was evaluated using a score based on information of income, type of housing and luxury household items. Subjects were classified according to four groups: low, middle-low, middle-high and high. The low class had an income lower than US$ 50 a month, no stone house and no luxury household items. The low middle class had an income between US$ 51 to 250 a month, semi-stone house or small apartment, television and/or motor-bike. The high middle class had an income between US$ 251 to 500 a month, stone house or apartment, television, motor-bike or non-luxury car. The highest class reflected any level above the high middle class. For statistical analyses, as only 7 % of the cases and 6 % of the controls were in the highest class, middle high and highest were combined into one "high" group which resulted in approximately equal numbers of subjects in the three socio-economic groups. Level of education was classified into three groups: illiterate or elementary education only, secondary education and tertiary education, including universitary and vocational education irrespective of eventual completion.

The data were analysed in a number of ways. First, proportions, means and standard deviations were obtained. To assess associations between variables multivariate linear regression analysis was used.

Results

In total 682 young women were included in the study. The general characteristics of the study population are given in table 1. Mean systolic blood pressure was 118.6 mmHg (SD 16.5) and mean diastolic blood pressure was

76.9 mmHg (SD 11.1). Only 38 women (5.6%) were current smoker and 17 women (2.5%) reported to have smoked in the past. The mean serum cholesterol level was 180.9 mg% (SD 47.0) in those in whom measurements had been performed.

In figure 1, mean blood pressure levels according to age groups are given in those women not on drug treatment for hypertension. The mean increase in systolic blood pressure per year increase in age was 0.6 mmHg (SE 0.1, p < 0.001) and in diastolic blood pressure 0.3 mmHg (SE 0.1, p < 0.001), among those not treated for hypertension. Also, body mass index was strongly related with both systolic and diastolic blood pressure; 1.3 mmHg/(Kg/m^2) (SE 0.3, p < 0.001) and 0.9 mmHg/(Kg/m^2) (0.2, p < 0.001) respectively.

Figure 1. Mean untreated blood pressure levels and frequency of hypertension in Indonesian women according to different age groups

| 0,9 | 4,4 | 6,6 | 9,1 | % hypertension |
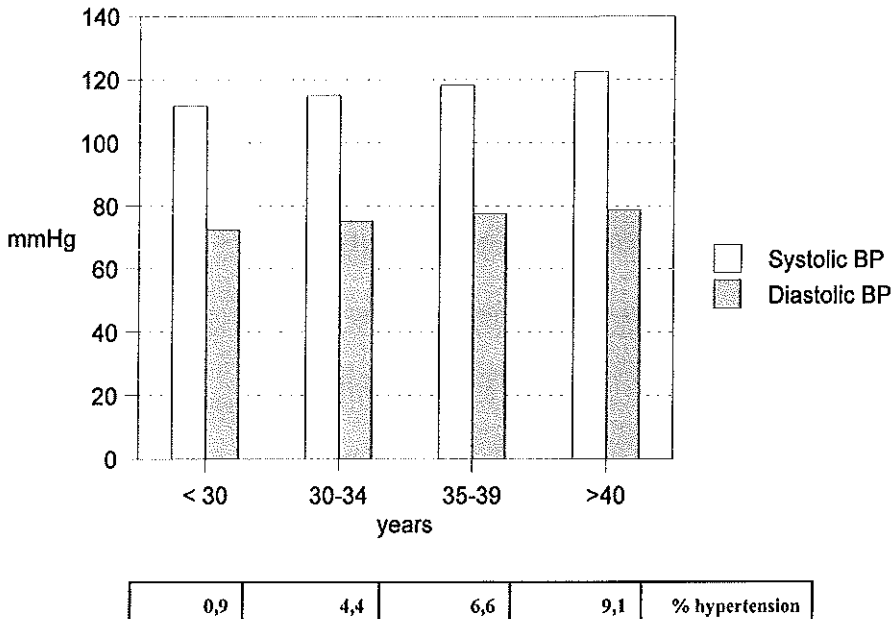
Table 1 General characteristics of the study population (n=682)

	mean	SD	range
Age (yrs)	36.1	6.3	20 - 44
Systolic BP (mmHg)	118.6	16.5	60 - 210
Diastolic BP (mmHg)	76.9	11.1	30 - 120
Height (cm)[1]	155.0	5.5	140 - 172
Weight (kg)[1]	52.3	9.6	34 - 190
Body mass index (kg/cm^2)[1]	21.7	2.6	15 - 34
Cholesterol (mg%)[2]	180.9	47.0	95 - 483

	percentage
Smokers	5.6
Ex-smokers	2.5
Education	
Illiterate/elementary	36.3
Secondary	48.0
University/vocational	15.7
Socio Economic Status	
High	5.7
High-middle	33.2
Low-middle	39.0
Low	22.1

[1]   data available in 263 women
[2]   data available in 226 women

The frequency of hypertension and the degree of detection and treatment in the study population are shown in table 2 and figure 2.

Table 2. Frequency of hypertension according to various criteria .

	n (%)
Systolic and/or diastolic blood pressure	
>= 160/95 mmHg (WHO)	40 (5.9)
>= 140/90 mmHg (JNC-V)	165 (24.2)
Systolic and/or diastolic blood pressure	
>= 160/95 mmHg (WHO) or treatment	44 (6.5)
>= 140/90 mmHg (JNC-V) or treatment	166 (24.3)
Previous physician diagnosis	33 (4.8)
Current treatment	14 (2.1)

Using the World Health Organization (WHO) cut-off point of 160/95 and/or treatment with antihypertensive drugs, there were 44 (6.5 %) hypertensive women.(4, 5) According to the criteria of the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V) cut-off point of 140/90 and/or treatment with antihypertensive drugs, there were 166 (24.3 %) hypertensive women (6). Thirty-three women (4.8 %) had a previous physician diagnosis of hypertension and of these 14 (42.4 %) were taking antihypertensive medicine. Of those with a previous diagnosis but currently untreated, 9 had blood pressure levels in the hypertensive range.

Figure 2. Degree of detection and treatment of elevated blood pressure in Indonesian women according to WHO criteria and in Scottish women participating in the Scottish Heart Health Study.
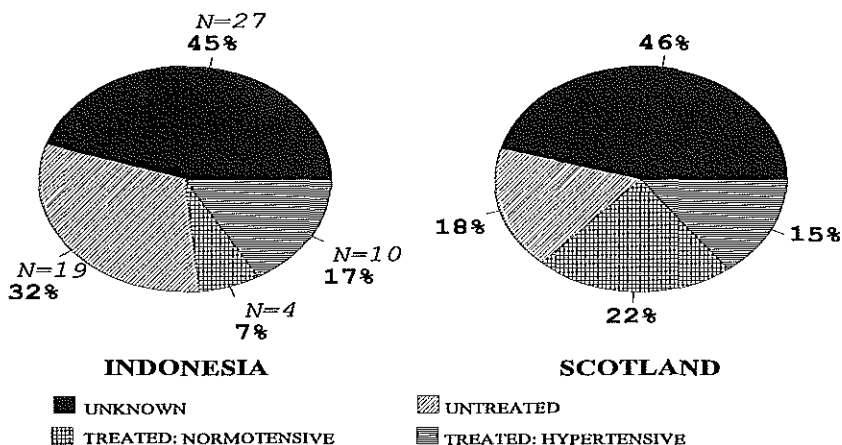
Among treated hypertensive women the mean systolic blood pressure was 142.9 mmHg (SD 14.9), and the mean diastolic pressure 96.4 mmHg (SD 9.3). Of these fourteen treated women four were normotensive according to JNC-V criteria. Three women were treated with calcium antagonists, two with alpha blockers and three were each taking a beta blocker, a diuretic, an ACE- inhibitor, and reserpine respectively. Five women did not know the type of medicine they were using.

Differences in blood pressure and frequency of hypertension across socio-economic and educational groups were generally small and not statistically significant. Also, no significant trend of blood pressure levels with increasing social and economic class nor with education could be demonstrated (data not shown). However, age adjusted serum total cholesterol levels were 30.7 mg% (SE 10.6, p < 0.004) higher in hypertensive women compared to normotensive women.

Discussion

The findings in the present study, among 682 young Indonesian women, indicate

that the frequency of hypertension is high and increasing with age. Moreover, a large proportion of women with elevated blood pressure was unaware of their blood pressure status and among those with a previous diagnosis of hypertension less than half were on treatment and a minority was adequately treated.

To appreciate these findings some aspects of the study need to be addressed. The study is of limited size and the study population was not randomly selected from the population. Rather, subjects were recruited from hospital admissions for various non-cardiovascular conditions in a number of hospitals in Jakarta. As a consequence of the selection process in the present study, the frequency of hypertension observed may differ from what may be found in the general population. While selection of subjects from a more diseased population may potentially increase the frequency of hypertension, the exclusion of patients with cardiovascular disease conversely may result in an underestimate of the real prevalence. More importantly, the population in the study is more likely to be diagnosed and treated as they are from an urbanized area and were referred to a hospital and therefore have had physician contacts. In view of this, the degree of under-treatment as found in the present study is probably even larger in the general population. Moreover, the observed associations with age and body mass are unlikely to be biased by the selection. Still, confirmation and expansion of these findings by studies in non-hospitalized subjects is needed.

A second limitation of this study is that only one duplicate blood pressure recording was obtained. It seems likely that some women will be normotensive on remeasurement. As a first approach to assess the magnitude of the problem, the use of a single blood pressure confirms with many previous epidemiologic studies in westernized countries, including the Scottish Heart Health Study (7), and makes comparisons therefore possible. However, to determine the frequency of hypertension according to current clinical criteria, remeasurement is required and this will change the estimates of the prevalence downward. The finding of an apparent lack of treatment in a large group of women who had a previous diagnosis of hypertension is unaffected by the use of single measurements. Moreover, if anything, the observed associations of blood pressure levels with

age and body mass index are underestimated.

Our findings show that high blood pressure in women is frequent, and that current levels of diagnosis and treatment in Indonesia are inadequate. For example, using data obtained in the Scottish Heart Health Study (7), 50 % more women in Scotland with a previous diagnosis of hypertension were treated and among those treated the degree of blood pressure control in Scotland was much higher. As only 14 women in our study received any blood pressure medication, it is difficult to comment on the current prescribing patterns by Indonesian physicians. However, the majority of the drugs used are generally considered step 2 medication and only one women used a betablokker and one a diuretic. More insight in adherence of standards of drug prescription and determinants of use of newer and more expensive drugs by physicians in Indonesia and other developing Asian countries is definitely needed.

Similar findings from Indonesia and other Asian countries are scarce. From the MONICA-Jakarta survey II in 1993 the prevalence of hypertension in the 25 to 64 years age group rose from 14 % (1987) to 17 % in men, and from 16% to 17% in women (8). In the Hypertension Survey carried out among adults in Singapore in 1974, Malays tended to have slightly higher mean blood pressures as well as prevalence rates of hypertension than Chinese subjects, 14.8 % and 10.8% respectively (9). Other data from Singapore indicate that among Malay and Chinese women death rates for stroke were higher than for coronary heart disease in the period from 1980 to 1984 (10).

In Asian women cerebrovascular stroke rates are remarkably high, and elevated blood pressure has been shown to be the dominant risk factor for this condition. The importance of coronary heart disease in these countries is still not quite as large as in westernized societies but rates are on the increase as life style changes. While smoking is still rare in women, the effects of emancipation may have dramatic effects. There are clear reasons to raise concern about the cardiovascular risk profile in Asian men and women and the levels of blood pressure in women in particular.

Several explanations may be given for the relative lack of hypertension diagnosis and control in these young women. First, blood pressure may not be considered an important health issue by the women themselves or by their physicians. Second, accessibility to health care, use of medication and treatment compliance may be restricted due to social and economic constraints. Most women in our study had no health insurance, and in current medical practice in Indonesia blood pressure measurements are not part of routine examination procedures.

In conclusion, our findings indicate that hypertension in Indonesian women is a neglected problem and that the degree of treatment of high blood pressure is insufficient. In view of the well established risk of stroke and other forms of cardiovascular disease, increased attention for blood pressure detection and control seems warranted. To achieve this, increased awareness of blood pressure status is needed by patients as well as by their treating physicians. The appreciation of social and economic barriers to determine cardiovascular risk factors, including blood pressure, is needed to enable prevention and intervention and revoke an impeding epidemic of heart disease and stroke.

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CHAPTER 7

GENERAL DISCUSSION

Introduction

In this thesis some general issues of stroke in young Indonesian women have been addressed, with special emphasis on hypertension and socioeconomic status as stroke risk factors.

Stroke is an important cause of chronic disability and mortality. It is the third leading cause of death in the western world following coronary heart disease and cancer. In certain areas, however, as well documented for Japan, the morbidity and mortality due to stroke is higher than from coronary heart disease. Although good data are limited this seems also the case in Indonesia. Moreover, in Indonesia and other Asian countries, women are particularly afflicted and present a problem that seems largely neglected in research so far.

Stroke is usually considered as a disease of the middle aged and the elderly, but in the last two decades interest in stroke in young adults has increased. It seems that stroke in the young is not so uncommon. Its relative frequency varies in the western world between 8.5% and 13.5%. In other areas, the relative occurrence may even be higher, ranging from 19% to 30%. In Bandung, Indonesia, in a population-based study 14.3% of the strokes occurred before the age of 45 years (1). Similarly, hospital-based data from Jakarta have shown 11.2 % of strokes occurring at a young age (unpublished results). The high frequency of stroke in young adults in Indonesia agrees with the suggestion raised in the literature that strokes in the young are more frequent in developing countries (2). It is highly relevant, therefore, to address the question why strokes occur more frequent at a young age in these countries and to gain knowledge about risk factors for stroke in young women.

Risk factors for stroke in young Indonesian women

The results of our study point at high blood pressure as a dominant cause of stroke in young Indonesian women. The importance of hypertension as a risk factor for stroke in the middle aged and the elderly is well established. However,

the high frequency of hypertension in young stroke cases in our study may still be surprising, 56 % using the WHO cut-off point (3). Other potential factors such as arhythmias and cardiac abnormalities appeared to be of little relevance. Also, the role of certain life style factors such as smoking or heavy alcohol use is still remote in this population. The use of oral contraceptives as a risk factor or co-determinant of risk in the presence of hypertension merits attention and is the focus of the WHO Collaborative Study from which the present project stemms, but seems at present of little importance in Indonesian women as only 5.4 % of all cases and controls in our study were using those drugs.

Although the rate of hypertension (6.5 % WHO (3), and 24.3 % JNC-V (4)) among our control women was high, the awareness of hypertension is low, as nearly half of the hypertensive women were not detected. One important reason is that currently, in Indonesia, when patients visit a primary health center because of illness, blood pressure is not routinely measured and recorded. Blood pressure is not considered an important health issue by the women themselves and apparently also not by their physicians. Second, accessibility to health care, use of medication and treatment compliance may be restricted due to social and economic constraints, as most people in Indonesia had no health insurance. Another limitation in cardiovascular and cerebrovascular prevention is the shortage of physicians in Indonesia, who must treat an average of 100 patients a day in the primary health centers. Thus, only in patients who complain of headache and have a strong family history of hypertension blood pressure may be measured and not even systematically. In our study, comparing data obtained in the Scottish Heart Health Study (5), among those treated the degree of blood pressure control in Scotland was much higher. Besides that, the current prescribing patterns by Indonesian physicians do not follow treatment guidelines issued by international authorities. Instead, there is a trend of using the newer classes of drugs, which are very expensive but heavily promoted. For example, the safe and effective diuretics are little used, in spite of these drugs being affordable to the people who are mostly not insured. The lower socioeconomic groups, who are at risk for stroke over and beyond the risk associated with hypertension, should clearly be given more attention in strategies to prevent

stroke. There is very little published data on stroke risk in relation to social and economic status in westernized societies, and even less for Indonesia. But findings in those studies available are consistent with our results. For example, Acheson et al. reported a relative risk of 1.6 for stroke associated with low social class (6). This notion, together with the observation that Asian women appear to be particularly at risk for stroke (2), emphasizes the importance of social and economic determinants of risk.

Our finding of an elevated risk of diabetes mellitus for stroke is in accordance with other studies in older populations (7-9). The point estimate of the relative risk for stroke of 12.9 in these young women, however, is considerably higher than the relative risk of 2 reported previously (10).

Unfortunately, in our study, serum cholesterol was only measured in a sample of cases and controls. However, the serum cholesterol level in the cases group was 207 mg %, which is significantly higher than in the control group (181 mg %). In patients with subarachnoid hemorrhage it was not elevated. In the multivariate analysis the relative risk of cholesterol for stroke was 2.8 and just failing significance, presumably because of confounding by hypertension. This is in agreement with the data of the collaborative case-control study in young adults in Italy (11) and with Qizilbash et al (12). The low prevalence of smokers, alcohol use and obesity among the women included in this study makes it difficult to draw relevant conclusions.

Strategies for prevention of stroke in Indonesia

At present we do not know exactly the frequency of occurrence of stroke in Indonesia. There are only few sporadic publications about prevalence of stroke in some hospitals. Useful data on cardiovascular risk factors have emerged from the so called MONICA-Jakarta Survey-I in 1987. The results of the National Household Survey-IV in 1992 and MONICA-Jakarta Survey II in 1993 have inspired the Ministry of Health to pay more attention to the apparent increasing trend of cardiovascular risk and disease in Indonesia, and a team to launch a

cardiovascular prevention pilot project was initiated.

For Indonesia, two prevention strategies, the macro (national) and the micro (patient oriented) strategy, may be distinguished.

In the macro strategy, the Ministry of Health should work together with other ministries and prominent people in the community to arrive at a national strategy. Involvement is particularly necessary for the ministries of education, social affairs, information, finance/tax and agriculture. Information distributed through audio-visual media which can reach the whole population, is likely to be the most effective to educate especially the low socioeconomic class about stroke and its sequelae and how to prevent it. The tax for cigarette and alcohol should be increased to deter the low socioeconomic class to consume it, and advertising on television and elsewhere should be banned. The growth of tobacco should not increase further, and possibly be reduced by substitution with other economically profitable and useful plants.

The micro strategy is patient oriented and aims to improve the awareness, detection and treatment of hypertension through the Indonesian primary health centers. In this strategy, emphasis is on case-finding among persons who visit primary health centers seeking treatment for any illness. In all patients blood pressure readings according to current guidelines should be routinely obtained. As physicians in Indonesian primary health centers are generally overworked, the possibility to have blood pressure measured by trained nurses or even non-medical personnel should be entertained. It is recommended to also note the degree of education, socioeconomic status, family history of heart disease and stroke and history of diabetes, smoking, alcohol use and other relevant life style indicators in the medical record.

Clearly, implementation of this strategy requires a change in attitude among primary care physicians and can only be achieved through targeted graduate and post-graduate education, and campaigns to increase awareness and motivation in the medical profession. The financial and logistic consequences need to be

worked out before widespread initiation, in order to improve the chances of succes. Also, direct preventive action, through changes in life style and drug treatment of high risk patients, may effectively be achieved through the primary health centers, which are government owned or subsidized, and headed by a physician as well as through the community based health-service post, which is headed by a midwife or nurse. Both institutions are widespread throughout Indonesia. Diagnostic work up of hypertensive patients should be standardized and guidelines for treatment should be issued and controlled. Primarily, known effective, non-expensive medication should be used, notably (potassium-sparing) diuretics and beta-blockers, so the people can afford it. It should be realized that most of the population is not medically insured. Physicians should be trained to support and motivate their patients and help patients to comply with medication also in social and economic circumstances where prevention of heart disease and stroke may seem a rather distant goal. Following this strategy in awareness, diagnosing and treating hypertension properly we will also reach the low socioeconomic class which is at the highest risk of stroke, and may invert the trend in morbidity and mortality from cardiovascular disease and stroke in Indonesia.

Directions for future research

Based on the results of our study, two broad categories of further research present itself. First, additional research is needed into the epidemiology of stroke in Indonesia and its determinants. Second, research is needed on effective preventive programmes and strategies for health education.

From our research, it has become clear that there is still lack of knowledge on the frequency of stroke in Indonesia and variation in stroke incidence across geographic areas and population groups. No reliable data are available on stroke incidence and mortality and case-fatality rates. Also, time trends can only be estimated crudely using central statistics data which are not complete nor sufficiently valid. The possibility for national or local stroke registries should be investigated and ways to improve the national death statistics explored.

Similarly, data on cardiovascular risk factors and trends in various age groups are needed. This will help to design and implement the most (cost-) effective preventive approaches. It appears useful to launch one or multiple population based cohort studies to generate some of the data described above and also to further stimulate and enable research into cardiovascular disease and stroke. Such studies could follow the design and methods worked out in the MONICA framework but should also include young adults and children. Risk factors and atherosclerosis in individuals develop over a lifetime and life styles are rooted in habits learned early in life. At the other end of the line, research into stroke treatment and secondary prevention is necessary. Too little is as yet known about the relative importance of different stroke types and diagnostic and therapeutic possibilities in most hospitals are still limited. With respect to stroke in young women, our study has demonstrated the importance of high blood pressure but the causes of blood pressure elevation in these patients could not be addressed in the present research. While obesity is important as a determinant of blood pressure level, this can hardly explain the relatively high frequency of hypertension observed in our population. Several environmental and genetic factors involved in blood pressure regulation have been proposed in recent years and merit examination in women in Indonesia and other Asian countries. A collaborative effort of clinicians, epidemiologists and basic researchers is needed. Apart from elevated blood pressure, the importance of other risk factors, including diabetes, warrants further attention. The specific risk factors for different stroke types are of interest and could lead the way to additional preventive and therapeutic improvements but require larger studies to be addressed in detail. One additional benefit of a stroke registry would be the possibility of recruitment of patients for case-control analyses.

Apart from etiologic and therapeutic research as outlined above, research is needed on effective preventive programmes and strategies for health education. The awareness of cardiovascular risk factors, including hypertension, is low both among lay people and the medical profession. Knowledge on diet and lifestyle in health and disease is poor and improvements are hindered by educational, social and economical factors. The most effective and financially

feasible strategies on a national and individual level need to be delineated. Importantly, education is needed of the population at large, and cardiovascular prevention and health education should become part of graduate and post-graduate medical training. Programmes developed in westernized countries may not be effective or feasible and dedicated strategies need to be designed matching the possibilities and limits inherent to a developing country such as Indonesia. The potential to incorporate para-medical personnel and even volunteers in the detection and management of cardiovascular risk needs to be considered.

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CHAPTER 8

SUMMARY

Stroke is generally considered as a disease of the old. In the last two decades, however, many publications point out that stroke is not so uncommon in the young. The proportion of strokes occurring at a young age appears to differ by geographical area, and may be larger in the developing countries. The main objective of the work presented in this thesis was to study the determinants of stroke risk in young women in Indonesia, as one of the developing countries.

After a brief introduction to the research presented in this thesis in Chapter 1, Chapter 2 presents a review of the epidemiology of stroke in the young. In the seventies in the United States of America and in some European countries the proportion of strokes occurring at a young age was estimated at only 3 to 5 %. However, in the last two decades the interest of stroke in the young has increased, and the estimates of its occurrence have been adjusted upwards to between 8 to 13 %. The importance of stroke at younger ages seems also to vary between different geographical areas. From two studies in Indonesia the occurrence was estimated at 11 to 14 %, while in other countries including India and Libya the proportion of strokes in the young may be as high as 19 to 30 %.

As in older subjects, most of the strokes in the young appear to be ischemic in nature, although findings in some studies from the USA, Europe and Japan, have suggested that hemorrhagic stroke is more common. A decline in overall stroke incidence and mortality has been described for most Westernized societies, but this decline has not been confirmed in young adults. The most common causes of ischemic stroke in the young are cardioembolism and atherosclerosis, although there is a wide variety of causes of some-times rare but often identifiable and treatable disorders. In spite of cerebral CT-scan and angiography etiology remains unknown in 7 to 45 % of cases, depending on methodology and the availability of diagnostic tools and the criteria used. The prognosis of young adults with ischemic stroke appears better than in the elderly. The annual recurrence rate of 0.5 % is much lower compared with 5 to 6 % in the older persons.

In Chapter 3 the design and methods of the research presented in this thesis are described. A hospital based case-control study was carried out in Jakarta, the capital city of Indonesia, covering both a rural and urban area with 8 million inhabitants, from January 1989 until May 1993. Fourteen hospitals within the city area of Jakarta participated in the study. This study formed part of a WHO multicenter (17 countries) case-control study of cardiovascular disease and steroid hormone contraceptive use. The research presented in this thesis concerns only the Indonesian component of the study. Cases were young women aged 20-44 years of age, admitted with first time stroke. The controls were age-matched, as many as possible up to a maximum of three per case. All cases and controls were interviewed in a standard fashion using the same WHO-questionnaire. Clinical findings were obtained from the medical record. Classification of stroke diagnoses was reconfirmed in the WHO coordinating center in London. Blood pressure was measured in all patients, and cholesterol levels in a subgroup of cases and controls.

Chapter 4 describes the main findings on risk factors for stroke in young women. The results obtained from 235 cases and 682 controls show the primary risk factors for stroke in young women to be largely similar as those established in older, male populations. However, due to the relatively low frequency of stroke and the absence of advanced atherosclerotic arterial disease in this age groupe, the relative risks for stroke observed for elevated blood pressure and diabetes mellitus are substantially higher than generally reported for older subjects. Total serum cholesterol levels, although higher in the cases in the univariate comparison, showed no independent association with stroke risk presumably because of confounding by hypertension. Other potential risk factors such as smoking and alcohol are as yet rare in this population, but may gain in importance as women become more emancipated and lifestyle changes towards that in more westernized societies.

In Chapter 5 emphasis is on social and economic determinants of stroke risk in young women. From a limited number of reports, it appears that stroke is

becoming more common in the developing world. Findings from this study indicate that risk of stroke is higher among lower social and economic classes. This notion, together with the observation that Asian women appear to be particularly at risk for stroke, emphasizes the importance to recognize social and economic factors in stroke prevention and treatment.

The prevalence, diagnosis and treatment of hypertension are described in Chapter 6. Our findings on blood pressure in the women who were recruited as a reference group for the case-control study, indicate that the frequency of hypertension is high given their relatively young age; 6.5% according to the WHO-criteria and 24.3% according to the criteria of the Fifth Report of the Joint National Committtee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V). Moreover, a large proportion of women with elevated blood pressure was unaware of their blood pressure status and among those with a previous diagnosis of hypertension less than half were on treatment with only a minority adequately controlled.

In the general discussion (Chapter 7) selected inferences from our findings are discussed and suggestions for future research are given. Hypertension is an important risk factor for stroke in young women. Also, other risk factors for stroke appear to be largely similar to those reported for older and other populations. In contrast, the degree of detection and control of hypertension is inadequate and a reemphasis on hypertension prevention and treatment is needed.

For Indonesia, two prevention strategies, the macro (national) and the micro (patient oriented) strategy, may be distinguished. In the macro strategy, the Ministry of Health should work together with other ministries and prominent people in the community to arrive at a national strategy. The micro strategy is patient oriented and aims to improve the awareness, detection and treatment of hypertension properly through the Indonesian primary health centers. The emphasis is on case-finding among persons who visit primary health centers seeking treatment for any illness. Following this strategy the low socioeconomic

class will be reached, which is at particular risk for stroke.

There are several opportunities for future research, with two categories of particular importance. First, additional research is needed into the frequency of occurrence of stroke in Indonesia and its determinants. The possibility for national or local stroke registries should be investigated. Second, research is needed on effective preventive programmes and strategies for health education. Knowledge on diet and lifestyle in health and disease is poor and improvements are hindered by educational, social and economic factors. Programmes developed in westernized countries may not be effective or feasible and dedicated strategies need to be designed matching the possibilities and limites inherent to Indonesia.

CHAPTER 9

SAMENVATTING

Cerebrovasculair accidenten (CVA) worden gewoonlijk beschouwd als aandoeningen van de oudere mens. In de afgelopen twintig jaar hebben evenwel talrijke publicaties erop gewezen, dat ook op jonge leeftijd het optreden van een CVA geen ongewoon fenomeen is. Het aandeel dat CVA op jonge leeftijd inneemt verschilt van geografisch gebied tot geografisch gebied, maar lijkt in ontwikkelingslanden groter te zijn dan in Westerse landen. Het voornaamste doel van de studie beschreven in dit proefschrift was een onderzoek in te stellen naar determinanten van het risico op een cerebrovasculair accident bij jonge vrouwen uit een van die ontwikkelingslanden, Indonesië.

Na een korte inleiding in Hoofdstuk 1, wordt in Hoofdstuk 2 een overzicht van de literatuur gepresenteerd inzake de epidemiologie van CVA bij jonge mensen. In de jaren zeventig werd het aandeel van beroerte op jonge leeftijd in de Verenigde Staten van Amerika (VSA) en in Europese landen geschat op 3 tot 5 procent. In de afgelopen twintig jaar is de belangstelling voor CVA bij jonge mensen evenwel toegenomen en zijn deze schattingen bijgesteld tot 8 à 13 procent. Ondanks deze bijstelling lijken er ook nog aanzienlijke geografische verschillen in het vóórkomen van CVA te bestaan. In twee Indonesische onderzoeken wordt het aandeel van CVA op jonge leeftijd op 11 en 14% geschat, terwijl in landen als India en Libië deze proportie zelfs cijfers van 19 en 30 procent bereikt.

Evenals bij oudere mensen, blijken de meeste cerebrovasculaire accidenten op jonge leeftijd ischaemisch van karakter te zijn. Sommige onderzoeken uitgevoerd in de VSA, Europa en Japan hebben evenwel gesuggereerd, dat haemorrhagische accidenten meer voorkomen. In de meeste Westerse landen is zowel de incidentie van CVA als die van de sterfte als gevolg hiervan afgenomen, maar deze afname is niet bevestigd voor CVA op jonge leeftijd. De meest voorkomende oorzaken van ischaemisch CVA bij jonge mensen zijn cardioembolisme en atherosclerose, maar daarnaast bestaat er een grote verscheidenheid aan soms zeldzame maar behandelbare oorzakelijke aandoeningen. Ondanks de beschikbaarheid van nieuwe diagnostische

technieken, zoals computer-tomografie en angiografie, blijft afhankelijk van de diagnostische methoden en de beschikbare technieken, de oorzaak onbekend in 7 tot 45 procent van de patiënten met een CVA. De prognose van jong volwassenen met een ischaemisch CVA lijkt beter dan die van oudere patiënten. De jaarlijkse recidiefkans van 0.5 procent in jonge patiënten is aanzienlijk lager dan de 5 of 6 procent bij oudere mensen.

In Hoofdstuk 3 worden het ontwerp van de studie en de gebruikte methoden beschreven. In Jakarta, de hoofdstad van Indonesië, werd een patiënt-controle onderzoek in ziekenhuispatiënten uitgevoerd. Deze patiënten waren afkomstig van zowel een stedelijk als een plattelands gebied met in totaal 8 millioen inwoners. De studie werd tussen januari 1989 en mei 1993 in 14 hospitalen binnen de stadsgrenzen van Jakarta verricht en maakte onderdeel uit van de multicenter patiënt-controle studie in 17 landen naar het verband tussen cardiovasculaire ziekten en hormonale contraceptiva van de Wereld Gezondheids Organisatie (WGO). Het onderzoek in dit proefschrift beschreven betreft alleen het Indonesische deel van de WGO-studie. Patiënten waren jonge vrouwen tussen de 20 en 44 jaar, die werden opgenomen met een eerste diagnose CVA. De controles betroffen in leeftijd passende andere patiënten. Voor iedere CVA patiënt werden zoveel mogelijk, met een maximum van drie, controlepatiënten geselecteerd. Alle CVA- en controlepatiënten werden op gestandaardiseerde wijze ondervraagd, waarbij gebruik werd gemaakt van dezelfde WGO-vragenlijst. De klinische bevindingen werden uit de medische status verkregen. De classificatie van CVA categorieën werd herbevestigd in het WGO-studie coördinatie centrum in Londen. Bij alle patiënten werd de bloeddruk gemeten, en totaal serumcholesterol werd in een deel van de CVA- en controlepatiënten bepaald.

In Hoofdstuk 4 wordt het voorkomen van CVA in relatie tot de voornaamste risicofactoren beschreven. Bij 235 CVA- en 682 controlepatiënten bleken de primaire risicofactoren op CVA bij jonge vrouwen grotendeels dezelfde te zijn als die bij oudere, mannelijke, patiëntenpopulaties werden gevonden. Indien de

betrekkelijk lage frequentie van CVA en het ontbreken van vergevorderde atherosclerotische arteriële afwijkingen in deze jonge leeftijdsgroep in aanmerking worden genomen, blijken de waargenomen relatieve risico's op CVA van een verhoogde bloeddruk en diabetes mellitus aanzienlijk groter te zijn dan worden vermeld voor oudere patiënten. Het gemiddelde totaal serumcholesterol bleek in de univariate analyse bij de CVA-patiënten significant hoger te zijn dan in de controlepatiënten. Bij multivariate analyse bleek deze significante samenhang, waarschijnlijk onder invloed van een gelijktijdig aanwezige verhoogde bloeddruk, te verdwijnen. Andere potentiële risicifactoren zoals het roken van sigaretten en alcoholgebruik waren zeldzaam in deze populatie van jonge vrouwen, maar kunnen aan belang winnen wanneer Indonesische vrouwen meer geëmancipeerd raken en hun levensgewoonten aanpassen aan die van hun Westerse soortgenoten.

In Hoofdstuk 5 ligt de nadruk op sociale en economische variabelen als risicofactoren voor CVA bij jongen vrouwen. Op grond van een beperkt aantal publicaties lijkt het vóórkomen van CVA in ontwikkelingeslanden toe te nemen. Uit de onderhavige studie komen aanwijzigen dat het risico op CVA groter is in de lagere sociale en economische lagen van de maatschappij. Deze bevinding, tesamen met de waarneming dat in het bizonder Aziatische vrouwen een verhoogd risico op CVA lopen, versterkt het belang van de onderkenning van sociale en economische factoren bij de behandeling en preventie van CVA.

De prevalentie, diagnose en behandeling van verhoogde bloeddruk bij de 682 jonge vrouwen, die gerecruteerd werden als referenten in het patiënt-controle onderzoek, worden beschreven in Hoofdstuk 6. Onze resultaten laten zien, dat de frequentie van hypertensie in deze relatief jonge groep vrouwen hoog is, namelijk 6,5% volgens de WGO-criteria en 24,3% volgens de criteria van het Vijfde Rapport van de Gezamelijke Commissie inzake Ontdekking, Evaluatie en Behandeling van Hoge Bloeddruk (Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure - JNC-V). Bovendien was een groot deel van deze vrouwen niet op de hoogte van haar

bloeddruk status en van diegenen, die eerder als hypertensief bekend waren geworden, bleek slechts de helft onder behandeling te zijn. Van hen die onder behandeling waren was slechts bij een minderheid de bloeddruk adequaat onder controle.

In Hoofdstuk 7 wordt een aantal gevolgtrekkingen uit onze bevindingen besproken en suggesties voor toekomstig onderzoek gedaan. Hypertensie is een belangrijke risicofactor op CVA bij jonge vrouwen. Ook andere risicofactoren bekend uit onderzoek bij oudere en andere patiëntenpopulaties blijken bij jonge vrouwen grotendeels dezelfde te zijn. Daar staat tegenover, dat de mate van ontdekking en controle van bestaande hypertensie in deze Indonesische patiëntengroep onvoldoende was en dat de preventie en behandeling van hypertensie op het niveau van de bevolking extra aandacht verdient.

Voor Indonesië worden twee preventie strategieën voorgesteld, de macro (= nationale) strategie en de micro (= op de patiënt gerichte) strategie. Bij de macro strategie moet in samenwerking tussen het Ministerie van Volksgezondheid, andere ministeries en prominenten uit de gemeenschap, een nationale aanpak ontwikkeld worden. De micro strategie richt zich op de patiënt en beoogt de bewustwording, ontdekking en behandeling van verhoogde bloeddruk te verbeteren door tussenkomst van de primaire gezondheids-centra. Hier ligt de nadruk op opsporing (case-finding) van verhoogde bloeddruk bij patiënten die het gezondheidscentrum bezoeken voor alle mogelijke aandoeningen. Door deze strategie wordt met name het laag sociaal-economisch deel van de bevolking, dat een verhoogd risico op het krijgen van een CVA heeft, bereikt.

Er zijn meerdere mogelijkheden voor toekomstig onderzoek. Hierbij springen twee categorieën in het oog. Ten eerste is aanvullend onderzoek nodig om een beter inzicht te verkrijgen in het vóórkomen van CVA in Indonesië en van de determinanten die daarbij een rol spelen. Daarbij moet de mogelijkheid om nationale of locale CVA-registraties op te zetten worden onderzocht. Op de tweede plaats is onderzoek noodzakelijk in het kader van preventieve

programma's en strategieën gericht op gezondheidsvoorlichting. De kennis over dieet- en levensgewoonten in ziekte en gezondheid is schaars en verbeteringen in deze gewoonten worden belemmerd door opvoedkundige, sociale en economische factoren. Programma's zoals die in de Westerse wereld zijn ontwikkeld, zijn mogelijk niet effectief of uitvoerbaar. Strategieën die toegespitst zijn op de mogelijkheden en beperkingen van de Indonesische maatschappij dienen derhalve te worden ontwikkeld.

CHAPTER 10

RINGKASAN

Pada umumnya strok dianggap sebagai penyakit orang tua. Namun dalam dua dasawarsa terakhir ini, banyak publikasi yang memberitakan tidak jarangnya strok ditemukan pada dewasa muda. Proporsi terjadinya strok pada dewasa muda agaknya berbeda tergantung dari letak geografis, dan kemungkinan lebih banyak dijumpai di negara berkembang. Tujuan utama dari penelitian yang dituangkan dalam disertasi ini adalah meneliti determinan dari beberapa faktor risiko strok pada wanita muda di Indonesia, sebagai salah satu negara yang sedang berkembang.

Bab 1 dari disertasi ini adalah mengenai pendahuluan singkat mengenai penelitian, Bab 2 memberi sari kepustakaan mengenai epidemiologi strok pada dewasa muda. Dalam tahun tujuh puluhan di Amerika Serikat dan beberapa negara di Eropa, proporsi dari strok pada dewasa muda diperkirakan hanya 3 sampai 5%. Namun dalam dua dasawarsa terakhir ini, perhatian terhadap strok pada dewasa muda bertambah, dan perkiraan terjadinya meningkat antara 8 hingga 13%. Strok pada dewasa muda agaknya berbeda tingkat kepentingannya pada tiap negara, tergantung dalam letak geografis di mana penelitian dilakukan. Dari dua penelitian yang dilakukan di Indonesia angkanya adalah 11 dan 14%, sedangkan di negara lain seperti India dan Libya angkanya lebih tinggi lagi yaitu antara 19 hingga 30%.

Seperti juga pada penderita yang lebih tua, kebanyakan strok pada dewasa muda ditemui bentuk iskemik, meskipun dari beberapa penelitian di Amerika Serikat, Eropa dan Jepang, mengisyaratkan bahwa strok hemoragik lebih banyak dijumpai. Penurunan dari insiden dan angka kematian akibat strok secara keseluruhan banyak diuraikan di masyarakat dunia Barat, tetapi penurunan ini tak dapat dikonfirmasi pada dewasa muda. Penyebab terbanyak pada strok iskemik pada dewasa muda adalah emboli kardial dan aterosklerosis, meskipun ada keaneka ragaman penyebab yang jarang dijumpai tetapi jika dicari dengan lebih teliti sering dapat dikenali dan merupakan kelainan yang dapat ditangani. Meskipun dilakukan CT-sken serebral dan angiografi namun masih ada penyebab yang tetap tak diketahui sebanyak 7 sampai 45% kasus, tergantung

dari metodologi dan tersedianya alat diagnostik dan kriteria yang dipakai. Prognosa pada dewasa muda dengan strok iskemik lebih baik dibandingkan pada kelompok tua. Strok ulangan tiap tahunnya adalah sebesar 0.5%, jauh di bawah angka 5 sampai 6% yang didapati pada orang tua.

Dalam Bab 3 diuraikan bahan dan metoda dari penelitian yang menjadi bahan dari disertasi ini. Suatu penelitian kasus-kontrol di beberapa rumah sakit telah dilakukan didaerah Jakarta, ibu kota Indonesia, dengan 8 juta penduduk yang mendiami daerah pinggiran dan dalam kota, sejak Januari 1989 sampai Mei 1993. Empat belas rumah sakit yang tersebar di daerah Jakarta ikut serta dalam penelitian ini. Penelitian ini merupakan sebagian dari penelitian kasus-kontrol WHO dari beberapa sentra (17 negara) mengenai penyakit kardiovaskuler dan pemakaian kontrasepsi hormon steroid. Penelitian yang diajukan dalam disertasi ini hanya mengenai penelitian di Indonesia saja. Kasus ialah wanita muda berumur 20-44 tahun, yang dirawat untuk strok pertama kali. Kontrol diambil dari kelompok umur yang sama, sebanyak mungkin dengan maksimal tiga per kasus. Semua kasus dan kontrol diwawancarai dengan satu bentuk wawancara WHO yang baku. Hasil klinik didapatkan dari status medik. Klasifikasi diagnosa strok dikonfirmasi kembali oleh pusat koordinator WHO di London. Tekanan darah diukur pada semua penderita, dan kadar kolesterol dalam darah pada suatu sub-kelompok kasus dan kontrol.

Bab 4 menguraikan faktor risiko untuk strok pada wanita dewasa muda. Hasil dari penelitian kasus-kontrol yang terdiri dari 235 kasus dan 682 kontrol menunjukkan bahwa faktor risiko untuk strok pada wanita muda pada dasarnya ialah sama dengan kelompok pria tua, namun disebabkan oleh relatip rendahnya strok dan tak adanya penyakit aterosklerotik yang lanjut pada kelompok usia ini, maka risiko relatip untuk strok yang didapati pada hipertensi dan kencing manis adalah lebih tinggi dari yang telah dilaporkan pada kelompok umur tua. Kadar kolesterol total dalam darah, meskipun lebih tinggi pada kasus dalam perbandingan univariat, ternyata tak ada asosiasi yang independen dengan strok yang kemungkinan disebabkan terancu oleh darah tinggi. Faktor risiko lain yang

potensial seperti perokok dan peminum alkohol jarang ditemukan dalam penelitian ini, tetapi dapat menjadi penting dikemudian hari oleh karena adanya emansipasi dan perubahan gaya hidup kebarat-baratan.

Dalam bab 5 penekanan lebih banyak diarahkan pada peranan sosial dan ekonomi sebagi risiko untuk strok pada wanita muda. Dari laporan yang terbatas, ternyata strok lebih banyak ditemukan di negara berkembang. Hasil dari penelitian ini menunjukkan bahwa risiko untuk strok lebih tinggi pada golongan sosial dan ekonomi rendah. Adanya penemuan ini, serta observasi bahwa wanita Asia nampaknya lebih berisiko untuk terserang strok, menggaris bawahi pentingnya peranan sosial dan ekonomi sebagi risiko.

Prevalensi, diagnosa dan pengobatan darah tinggi diuraikan dalam Bab 6. Hasil pengukuran darah tinggi yang didapatkan pada kelompok wanita sebagi kontrol pada penelitian kasus-kontrol ini memperlihatkan tingginya frekwensi tekanan darah tinggi mengingat usia mereka yang masih muda: yaitu 6.5% jika menggunakan pedoman WHO dan 24.3% menurut kriteria Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC-V). Apalagi, kebanyakan dari wanita dengan tekanan darah yang tinggi tidak mengetahui keadaan tekanan darahnya, dan di antara yang sebelumnya telah didiagnosa sebagi penderita darah tinggi, kurang dari separohnya mendapat pengobatan dan hanya sebagian kecil mendapat pengobatan yang memadai.

Dalam diskusi umum (Bab 7) hasil yang ditemukan didiskusi dan diberikan anjuran untuk penelitian dikemudian hari. Tekanan darah tinggi merupakan faktor risiko yang penting untuk strok pada wanita dewasa muda. Juga faktor risiko lain untuk strok agaknya juga sama dengan faktor risiko pada usia tua. Hanya kadar deteksi dan kontrol tekanan darah tinggi adalah tak memadai, dan penekanan kembali pada pencegahan dan pengobatan terhadap tekanan darah tinggi diperlukan.

Untuk Indonesia, strategi pencegahan sebaiknya dibedakan antara strategi makro

(nasional) dan mikro (orientasi pada penderita). Dalam strategi makro, Kementerian Kesehatan seyogyanya bekerja sama dengan kementerian lain dan pemuka masyarakat untuk sampai pada konsensus strategi nasional. Strategi mikro berorientasi pada penderita dan bertujuan untuk memperbaiki kesadaran, deteksi dan pengobatan darah tinggi dengan benar melalui Pusat Kesehatan Masyarakat (Puskesmas). Dititik beratkan pada penemuan kasus di antara orang-orang yang datang berobat ke Puskesmas untuk penyakit lain. Melalui pendekatan strategi ini, diharapkan golongan sosio ekonomi rendah dapat terjangkau, yaitu mereka yang termasuk golongan dengan risiko terkena strok.

Beberapa kemungkinan untuk penelitian dikemudian hari dapat dibagi dalam dua bagian. Pertama, penelitian tambahan diperlukan untuk mengetahui frekwensi kekerapan strok di Indonesia dan faktor faktor yang mempengaruhinya. Kemungkinan untuk mengadakan pendataan secara nasional maupun lokal perlu dikaji. Kedua, penelitian diperlukan untuk mengadakan suatu program pencegahan yang efektip dan strategi untuk pendidikan kesehatan. Pengetahuan mengenai diet dan gaya hidup pada yang sehat dan yang sakit adalah sedikit dan perbaikan agaknya terhalang oleh faktor pendidikan, sosial dan ekonomi. Program yang dikembangkan dinegara barat belum tentu cukup efektip dan dapat dipakai disini, sehingga diperlukan perencanaan suatu strategi yang sesuai dengan kondisi di Indonesia.

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Jahja Kisjanto was born in Brebes, Indonesia on September 3, 1931. He graduated from the High School in Jakarta in 1952. From there he entered the Faculty of Medicine at the University of Indonesia, Jakarta, where he graduated as medical doctor in 1959. Thereafter he worked for 4 years as a compulsory Army medical doctor.

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