
**International Task Force for Prevention
Of Coronary Heart Disease**



*Coronary heart disease and stroke:
Risk factors and global risk*

Slide Kit 2

Stroke

Ethiology and epidemiology of stroke

TABLE OF CONTENT

Slide 1: Definition of stroke	3
Slide 2: Major recognized mechanisms for ischemic stroke	4
Slide 3: Incidence of stroke and coronary events in 14 WHO MONICA populations	5
Slide 4: Incidence of stroke and coronary events in 14 WHO MONICA populations	6
Slide 5: Incidence of pathological types of stroke	7
Slide 6: Major risk factors for ischemic stroke	8
Slide 7: Major risk factors for hemorrhagic stroke	9
Slide 8: Investigation of the causes of stroke. The Prospective Studies Collaboration	10
Slide 9: The Prospective Studies Collaboration	11
Slide 10: The Prospective Studies Collaboration	12
Slide 11: Mortality from different pathological types of stroke by cholesterol levels	13
Slide 12: Non-hemorrhagic and hemorrhagic stroke in eastern Asia by diastolic blood pressure	14
Slide 13: Non-hemorrhagic and hemorrhagic stroke in eastern Asia by total cholesterol	15
Slide 14: Protective effect of HDL-cholesterol on ischemic stroke	16
Slide 15: Baseline characteristics of stroke cases and controls in the PROCAM Study	17
Slide 16: The PROCAM Coronary Risk Algorithm also predicts the incidence of stroke	18
Slide 17: Number of strokes per 100.000 per year during 7.2 years of follow-up in the PROCAM Study	19
Slide 18: Major risk factors for both ischemic and hemorrhagic stroke in 7.2 years of follow-up in the PROCAM Study	20
Slide 19: Midlife blood pressure and cholesterol predict development of Alzheimer's disease	21
Slide 20: Distribution of prothrombotic risk factors in children with stroke and controls	22
Slide 21: Candidate genes for heritable disorders of blood coagulation based on sub-set analysis from the PROCAM Study	23

Slide 1:

**Stroke:
Definition of stroke**



Definition of Stroke



The WHO defines stroke as

“rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin”

This definition includes signs and symptoms suggestive of

- **ischemic stroke**
- **hemorrhages (intracerebral or subarachnoid)**

Definition of stroke

This slide gives the definition of stroke established by the World Health Organization (WHO) in 1980.

Slide 2:

Stroke:

Major recognized mechanisms for ischemic stroke



Major Recognized Mechanisms for Ischemic Stroke



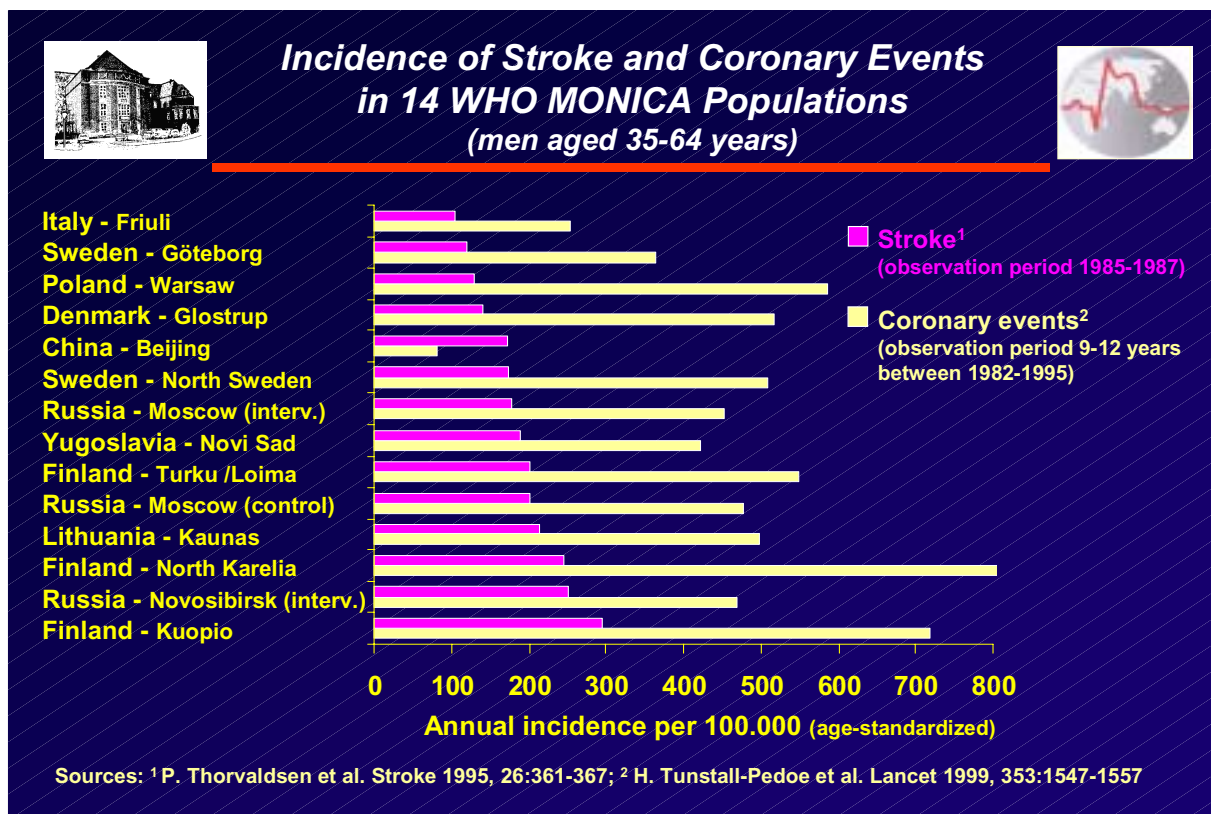
- **occlusion of small cerebral arteries in persons with hypertension**
- **embolism to the brain of cardiac or aortic origin**
- **artery to artery embolism from the extracranial and intracranial arteries**
- **rarely, perfusion failure due to severe extracranial arterial stenosis and occlusion**

Source: G Assmann et al.; NMCD 1998; 8:205-271

Major recognized mechanisms for ischemic stroke

This slide shows the major recognized mechanisms by which ischemic stroke occurs. In persons with high blood pressure the most common cause is occlusion of small cerebral arteries. Other common causes are emboli which may arise either in the heart or in the aorta or within the extracranial and intracranial arteries. In rare cases, ischemic stroke may be due to perfusion failure as a result of severe stenosis of the extracranial arteries.

Slide 3:

Stroke:**Incidence of stroke and coronary events in 14 WHO MONICA populations****Incidence of stroke and coronary events in 14 WHO MONICA populations**

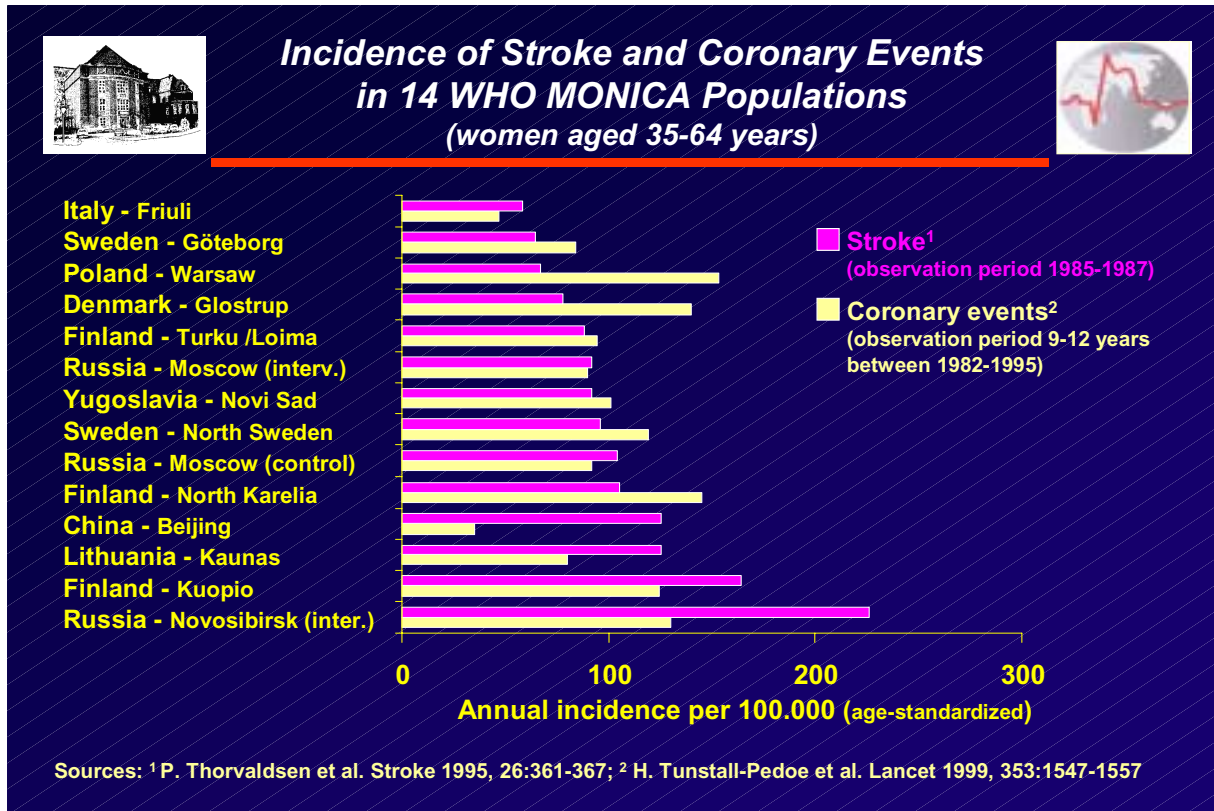
This slide compares incidences of stroke and coronary events assessed in men from 14 WHO MONICA populations. The WHO MONICA (World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease) Project was initiated in the early 1980s. The aim was to measure within defined populations over 10 years, the occurrence of coronary events and stroke and to analyze the relation between temporal trends in incidence and mortality rates and changes in major cardiovascular risk factors over time.

The present comparison includes 14 populations for which data on the incidence of both stroke and coronary events were available from two publications, though length of observation period differs. Stroke incidence rates were high among the men in Finland, Russia and Lithuania. In all centers but Beijing, China, the incidence of coronary event rates was much greater than that of stroke. This underlines the greater public health impact of coronary events in these centers, but is also due to the age range of 35-64 years, since approximately 75 % of all strokes occur after the age of 65.

Slide 4:

Stroke:

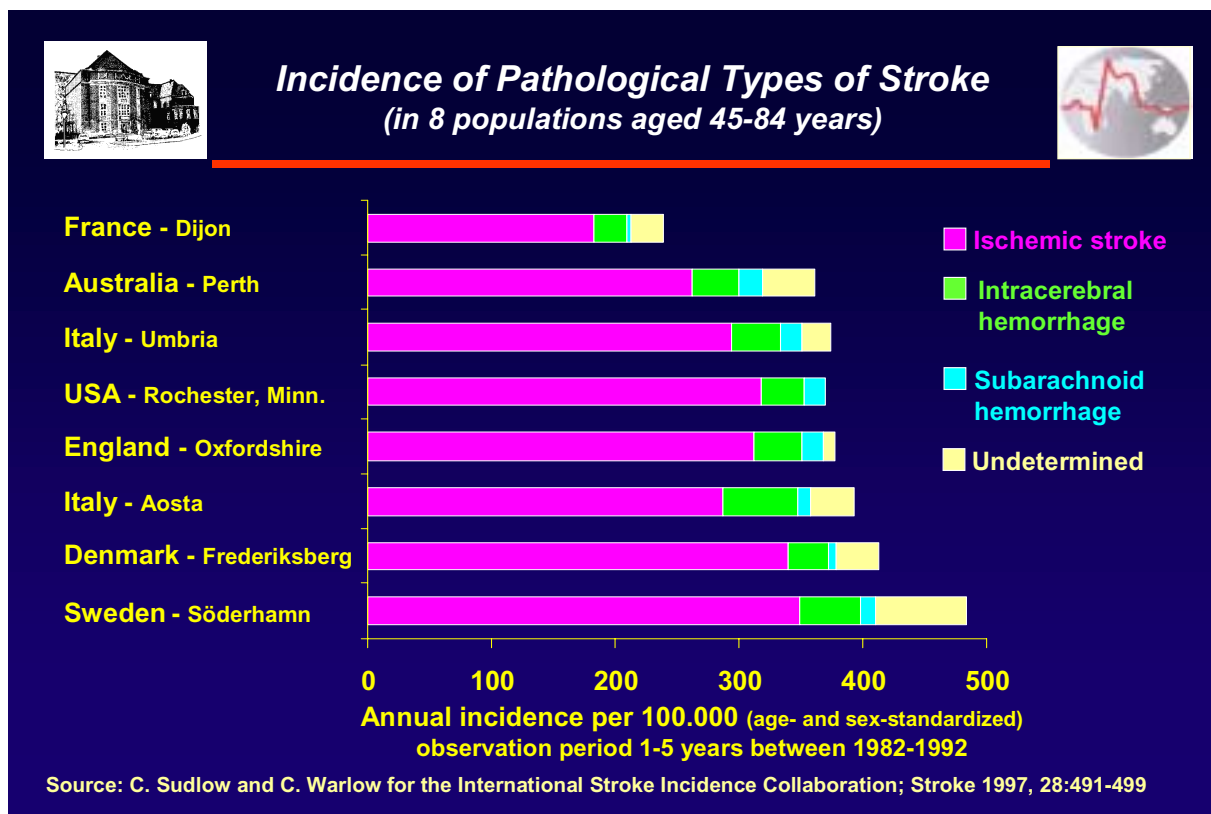
Incidence of stroke and coronary events in 14 WHO MONICA populations



Incidence of stroke and coronary events in 14 WHO MONICA populations

This slide compares the incidences of stroke and coronary events assessed in women from the 14 WHO MONICA cohorts. As expected overall incidence rates in women aged 35-64 years were lower than rates observed with men of the same age (Slide 3). However, among the populations of Chinese, Finnish, Russian and Lithuanian women stroke incidence rates were similar to or higher than rates of coronary events.

Slide 5:

Stroke:**Incidence of pathological types of stroke****Incidence of pathological types of stroke**

In 8 populations from Europe, Australia and the United States compared in the International Stroke Incidence Collaboration (3.5 million person-years, 5575 strokes) most strokes were of ischemic origin. The similarities in stroke incidence and pathological types are perhaps not surprising given that all populations are Westernized and mainly white. In the Far East the proportion of intracerebral hemorrhages is presumably considerably higher. The International Stroke Incidence Collaboration included subjects aged 45-84 years, thus stroke incidence rates are higher than in the WHO MONICA Project.

Slide 6:

Stroke:

Major risk factors for ischemic stroke



Major Risk Factors for Ischemic Stroke



non-modifiable

- age
- male sex
- race (more common in blacks)
- inherited predisposition

modifiable

- hypertension
- diabetes mellitus
- cardiac diseases (atrial fibrillation, infective endocarditis, mitral stenosis, recent large MI, left ventricular hypertrophy)
- cigarette smoking
- overweight
- homocysteine ↑
- cholesterol ↑, especially in hypertensives

Source: G Assmann et al.; NMCD 1998; 8:205-271

Major risk factors for ischemic stroke

This slide shows the consensus opinion of the International Task Force for Prevention of Coronary Heart Disease on the main non-modifiable and modifiable risk factors for ischemic stroke.

Slide 7:

Stroke: Major risk factors for hemorrhagic stroke



Major Risk Factors for Hemorrhagic Stroke



intracerebral hemorrhage

- advanced age
- race (more common in ?)
- male sex

- high blood pressure
- heavy use of alcohol
- cocaine use
- anticoagulant or thrombolytic therapy
- amyloid angiopathy in the elderly (rare)

subarachnoid hemorrhage

- congenital
or acquired aneurysms
or arteriovenous malformations

- high blood pressure
- cigarette smoking

Source: G Assmann et al.; NMCD 1998; 8:205-271

Major risk factors for hemorrhagic stroke

It is becoming increasingly clear that hemorrhagic stroke and ischemic stroke are two distinct diseases with distinct risk factors. Among hemorrhagic stroke a distinction must be made between strokes due to intracerebral hemorrhage and those due to subarachnoid hemorrhage. Thus, high blood pressure is a risk factor for both types of hemorrhagic stroke, but cigarette smoking has only been shown to be a risk factor for stroke due to a subarachnoid hemorrhage. Subarachnoid hemorrhage is often due to a rupture of congenital aneurysms or vascular malformation in the subarachnoid space. The risk factors for intracerebral hemorrhage are distinct from those for subarachnoid hemorrhage and also to an extent distinct from those for ischemic stroke (see slide 7).

Slide 8:

Stroke:

Investigation of the causes of stroke. The Prospective Studies Collaboration



Investigation of the Causes of Stroke:
The Prospective Studies Collaboration



45 prospective observational cohort studies

450 000 individuals

mean 16 years of follow-up (range 5-30 years)

7.3 million person-years of observation

13 397 strokes

mostly fatal strokes (studies recorded only mortality)

only about one quarter of the studies included recorded both fatal and non-fatal strokes

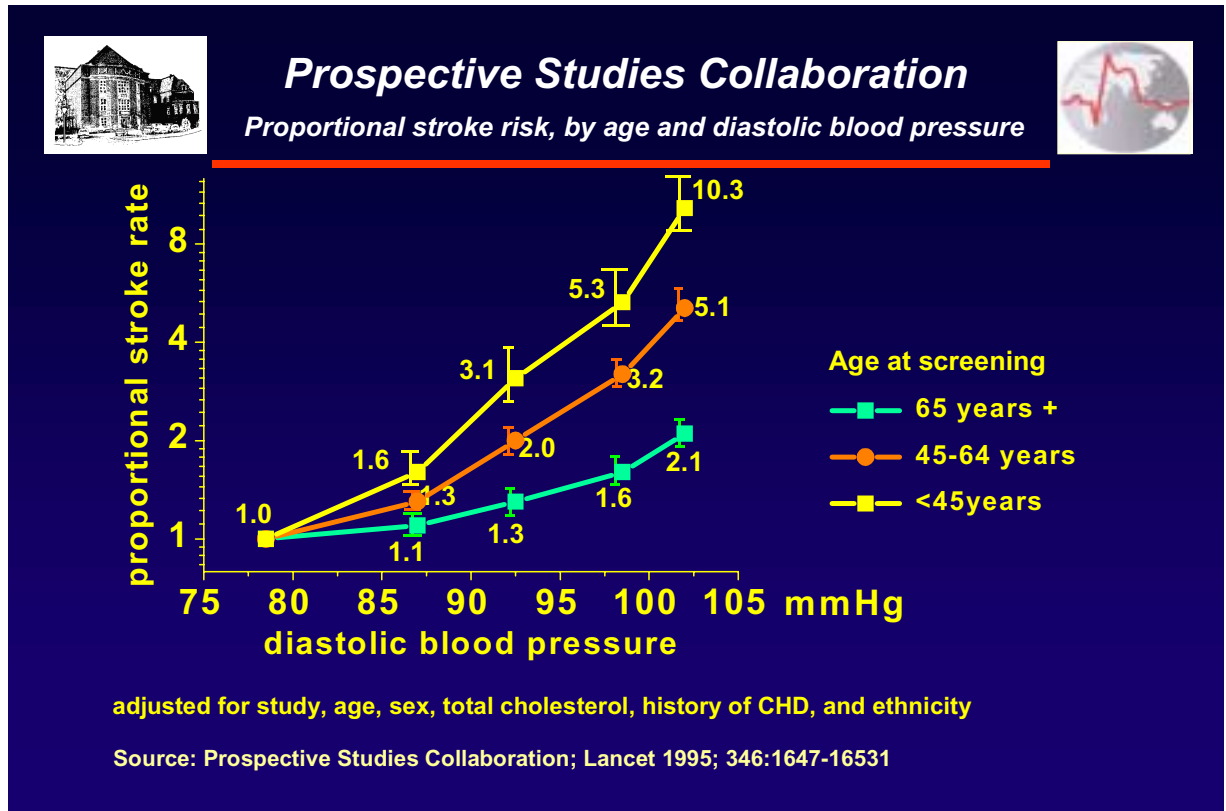
Source: Prospective Studies Collaboration; Lancet 1995; 346:1647-1653

Investigation of the causes of stroke. The Prospective Studies Collaboration

This slide summarizes the main features of a very large meta-analysis which was published in the Lancet in 1995. It includes information from the PROCAM Study. This is the largest such meta-analysis which exists. It includes 7.3 million person-years of observation and 13,397 strokes. An important limitation of the Prospective Studies Collaboration was that only about one quarter of the studies recorded both fatal and non-fatal strokes.

Slide 9:

Stroke: The Prospective Studies Collaboration

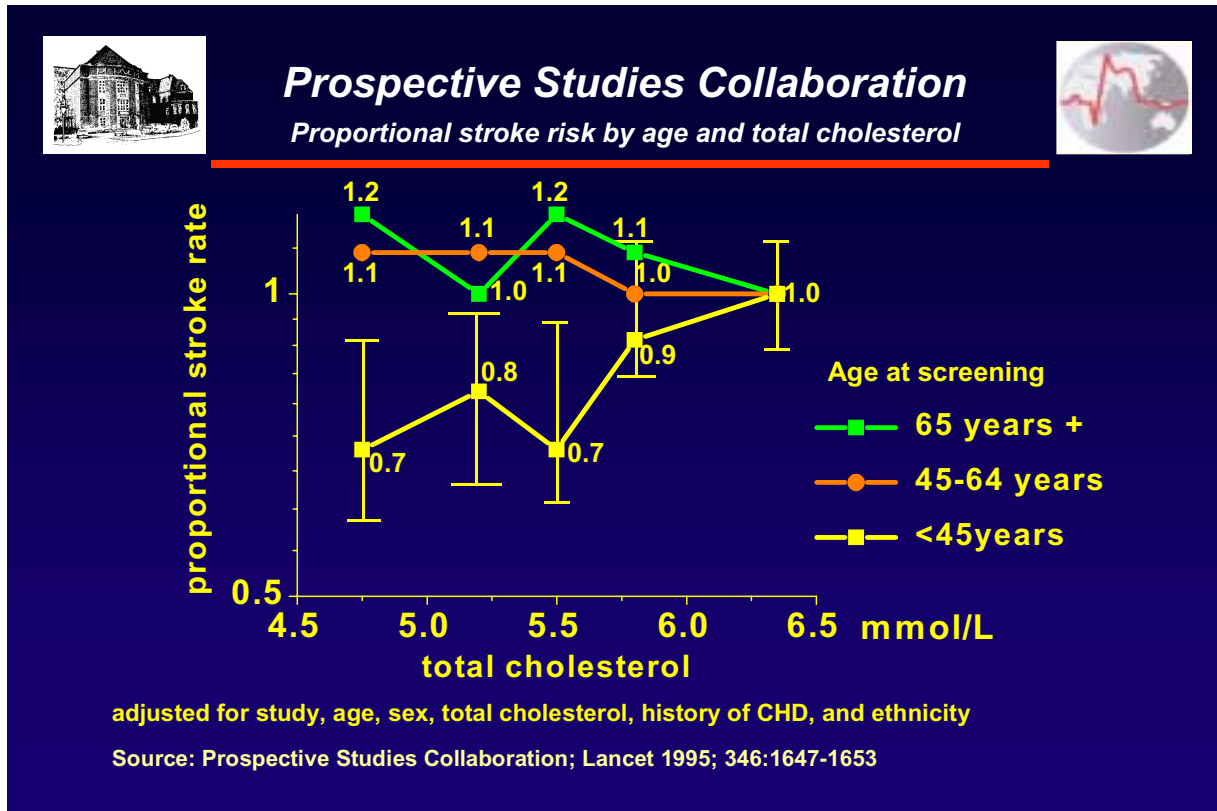


The Prospective Studies Collaboration

This slide from the Prospective Studies Collaboration shows the curvilinear relationship that exists between diastolic blood pressure and the incidence of stroke. The relevance of diastolic blood pressure to stroke varied substantially with age at baseline, the gradient being much steeper in the younger age categories. It is important to note that the relationship also holds at diastolic blood pressure within the normal range.

Slide 10:

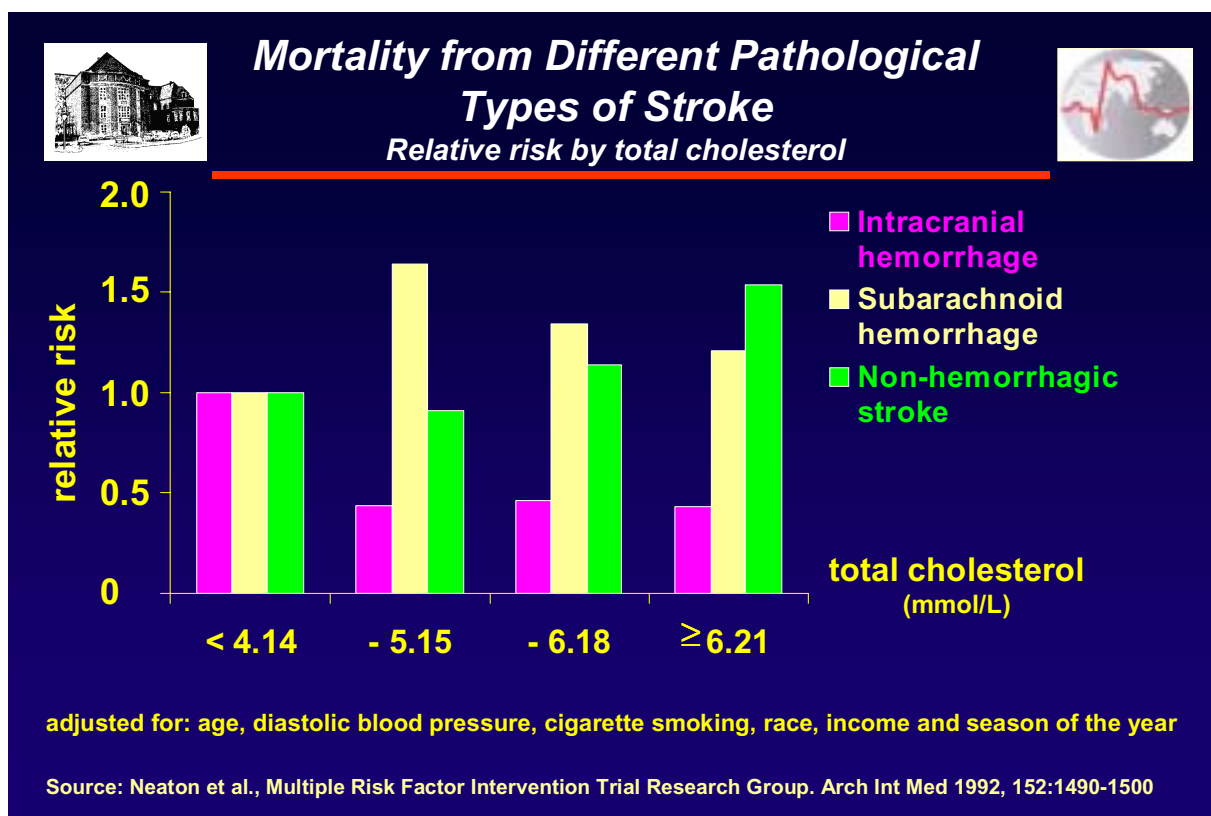
Stroke: The Prospective Studies Collaboration



The Prospective Studies Collaboration

This slide shows the relationship between total cholesterol and overall stroke incidence in various age groups. In younger age groups an increase in cholesterol is associated with an increase in overall stroke incidence but this relationship is lost in older age groups.

Slide 11:

Stroke:**Mortality from different pathological types of stroke by cholesterol levels****Mortality from different pathological types of stroke by cholesterol levels**

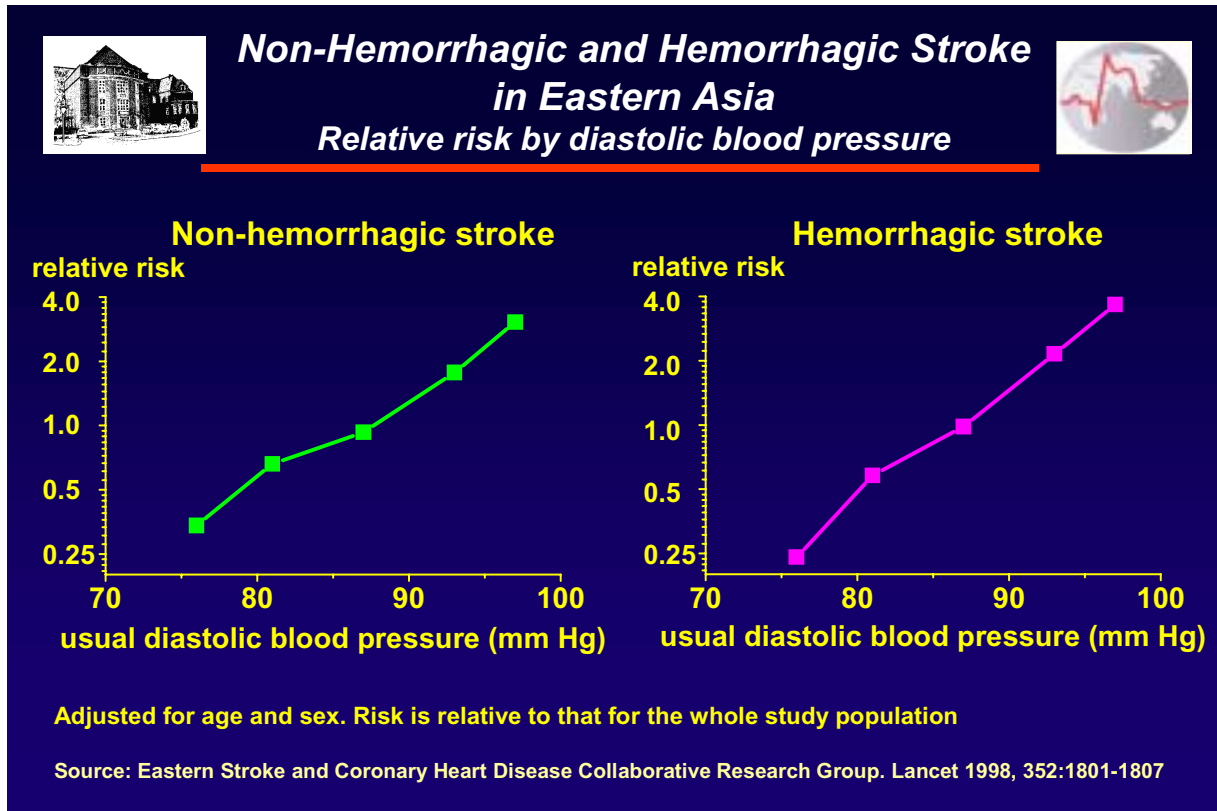
The lack of a consistent association between total cholesterol and stroke rate may partly be due to different relationships of serum cholesterol level with intracranial hemorrhage and non-hemorrhagic stroke.

In men screened in the Multiple Risk Factor Intervention Trial the relative risk for a fatal non-hemorrhagic stroke over the 12-year follow-up period increased with higher cholesterol levels while the relative risk for a fatal intracranial hemorrhage was greatest in those with cholesterol levels less than 4.14 mmol/L (< 160 mg/dl). Note, however, that most stroke were of non-hemorrhagic origin (see also slide 5).

Slide 12:

Stroke:

Non-hemorrhagic and hemorrhagic stroke in eastern Asia by diastolic blood pressure



Non-hemorrhagic and hemorrhagic stroke in eastern Asia by diastolic blood pressure

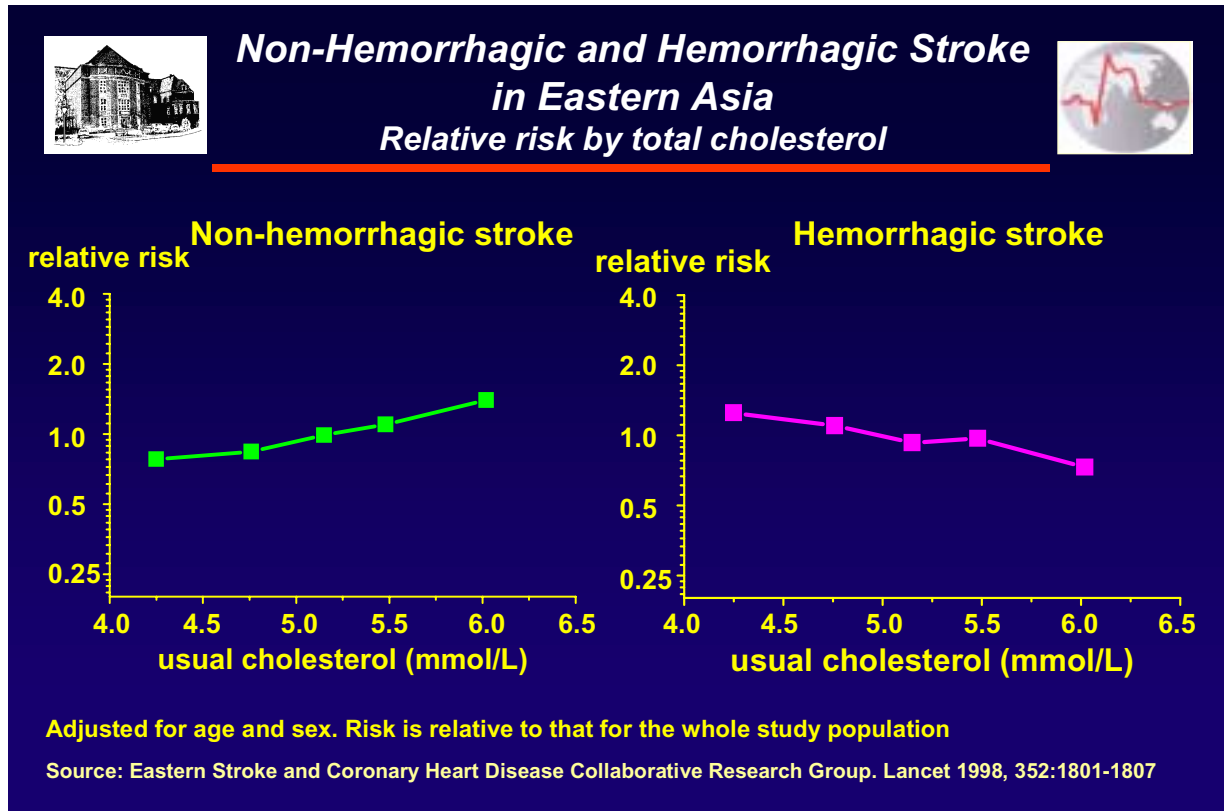
This slide shows a strong continuous association between usual diastolic blood pressure and the risk of both hemorrhagic and non-hemorrhagic stroke in 18 cohorts from China and Japan included in the Eastern Stroke and Coronary Heart Disease Collaborative Research Group (124 774 participants, 837 214 person-years, 1 798 strokes). The association is substantially stronger than relations observed in North American and European populations.

A decrease of 5 mmHg in usual diastolic blood pressure is associated with a 44 % decrease in risk of stroke compared with a 27 % lower stroke risk in the Prospective Studies Collaboration (Slide 9).

Slide 13:

Stroke:

Non-hemorrhagic and hemorrhagic stroke in eastern Asia by total cholesterol



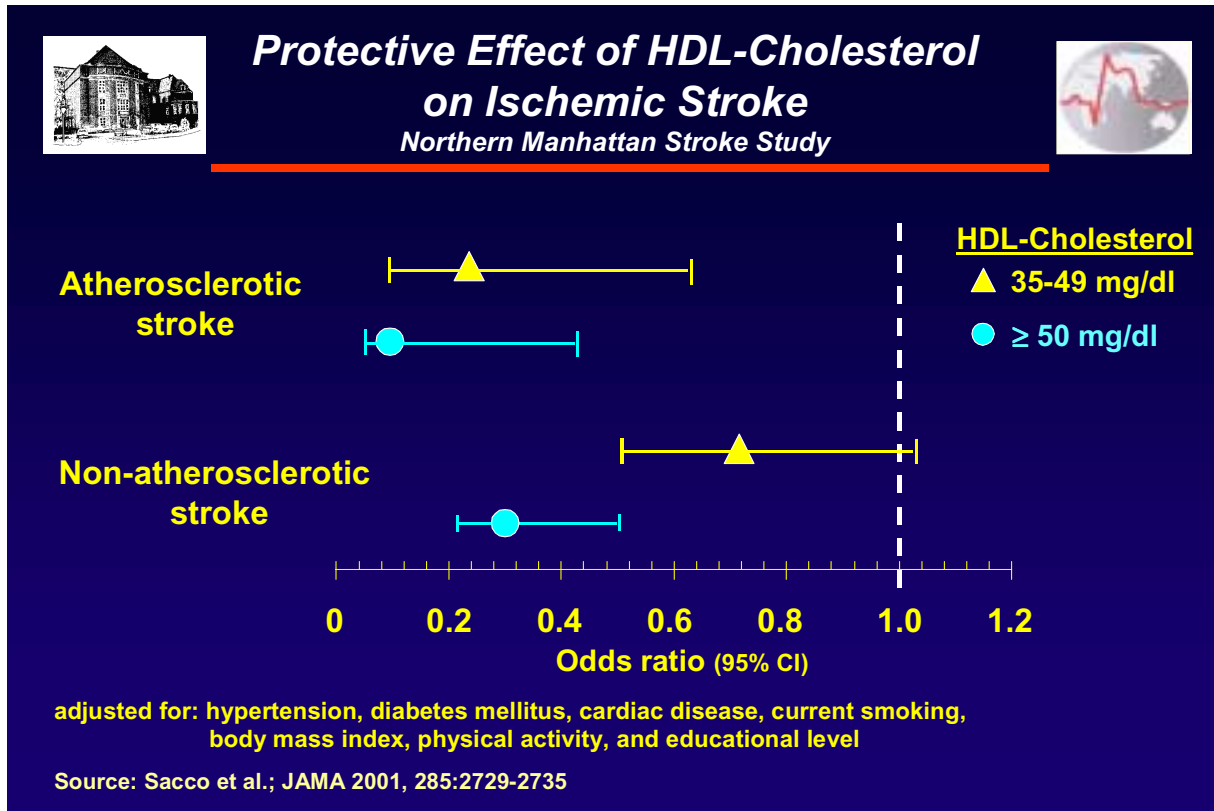
Non-hemorrhagic and hemorrhagic stroke in eastern Asia by total cholesterol

Differences in the directions of associations of cholesterol concentration with non-hemorrhagic and hemorrhagic stroke were also found in the cohorts from eastern Asia (see slide 11). The slide shows that with decreasing cholesterol concentrations there were trends towards a decrease in risk of non-hemorrhagic stroke and an increase in risk of hemorrhagic stroke.

Slide 14:

Stroke:

Protective effect of HDL-cholesterol on ischemic stroke



Protective effect of HDL-cholesterol on ischemic stroke

The Northern Manhattan Stroke Study, a population-based, incident case-control study (539 cases, 905 controls), found a reduced risk of ischemic stroke associated with higher HDL-cholesterol levels in the elderly and among different racial or ethnic groups. This slide shows a protective effect of a higher HDL-cholesterol level as compared to a HDL-cholesterol level below 35 mg/dl (reference) particularly for the atherosclerotic stroke subtype, but also for non-atherosclerotic brain infarction.

Slide 15:

Stroke:

Baseline characteristics of stroke cases and controls in the PROCAM Study

PROCAM (Münster Heart Study): Risk for Stroke		Baseline characteristics of participants (men aged 30-65 years)	
Variable	Controls (non-cases) (n=12827)	Total stroke (cases) (n=39)	p
Age	44.7 (8.6)	51.7 (7.8)	<0.001
Systolic blood pressure (mm Hg)	130.3 (17.8)	149.5 (22.3)	<0.001
Diastolic blood pressure (mm Hg)	84.4 (10.9)	93.3 (12.0)	<0.001
Known hypertension (%)	14.6	43.6	<0.001
Blood pressure ≥ 160/95 mm HG (%)	23.8	37.5	<0.05
Body Mass Index (kg/m ²)	26.0 (3.1)	27.3 (3.1)	0.02
Alcohol consumption (g/d)*	17.4 (14.4)	25.2 (19.7)	n.s.
Current cigarette smoker (%)	33.6	48.7	0.05
Cholesterol (mg/dl)	221.4 (42.7)	238.5 (46.5)	0.03
HDL cholesterol (mg/dl)	46.1 (12.2)	46.2 (15.8)	n.s.
LDL cholesterol (mg/dl)	145.9 (37.6)	156.8 (43.0)	n.s.
Triglycerides (mg/dl)	155.4 (140.4)	181.8 (115.5)	n.s.
Fasting blood glucose (mg/dl)	101.1 (19.7)	106.1 (26.1)	n.s.
Uric acid (mg/dl)	5.8 (1.2)	5.7 (1.3)	n.s.
Known diabetes mellitus (%)	2.4	7.7	0.07
Family history of stroke (%)	15.2	25.6	0.07

* n=10511 controls, 19 cases
 Values are mean and standard deviation (in brackets) unless otherwise indicated
 Source: Berger K et al.; Stroke, 1998; 29:1562-1566

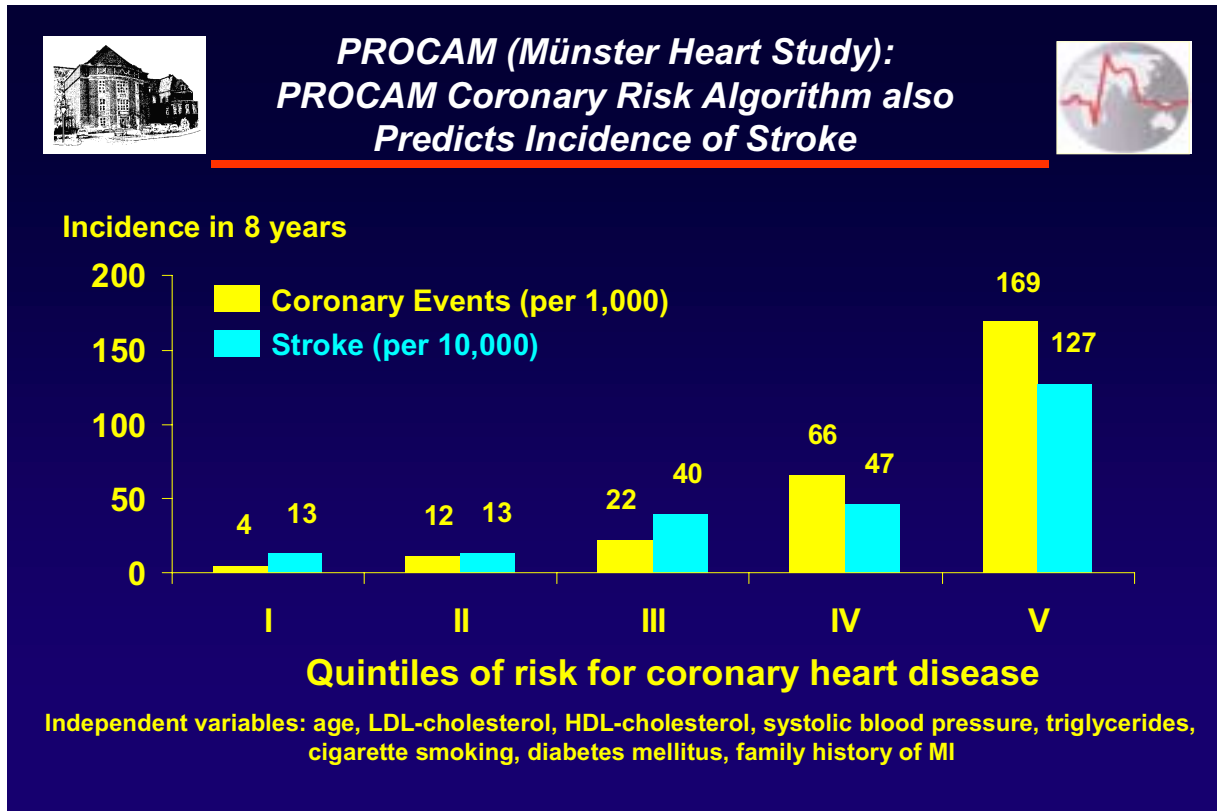
Baseline characteristics of stroke cases and controls in the PROCAM Study

This slide shows the baseline characteristics of a variety of atherosclerosis risk parameters among the middle aged men who suffered a stroke in the PROCAM Study. The values in the middle aged men who did not suffer a stroke (controls) are shown for comparison. Stroke patients were older, had a higher diastolic blood pressure and/or a history of hypertension, they tended to be overweight and had higher cholesterol levels.

Slide 16:

Stroke:

The PROCAM Coronary Risk Algorithm also predicts the incidence of stroke



The PROCAM Coronary Risk Algorithm also predicts the incidence of stroke

This slide shows the incidence of stroke expressed in events per 10.000 of population in 8 years of follow-up in each quintile of coronary heart disease (CHD) risk estimated by the PROCAM algorithm. The increasing incidence of stroke in the higher CHD risk groups is clear.

Slide 17:

Stroke:

Number of strokes per 100.000 per year during 7.2 years of follow-up in the PROCAM Study

**PROCAM (Münster Heart Study):
Number of Strokes per 100 000 Person-Years
during 7.2 Years of Follow-Up**

Parameter	No. of Cases	Rate per 100 000 person-years
Total cholesterol, mg/dL		
< 200	7	31.0
200-249	16	37.8
≥ 250	15	64.4
Triglycerides, mg/dL		
< 100	9	31.1
100-199	16	38.9
≥ 200	13	68.1
Systolic blood pressure, mmHg		
≥ 120	3	8.0
121-140	14	35.6
> 140	22	86.2
Diastolic blood pressure, mmHg		
≥ 80	7	17.3
81-90	15	42.6
> 90	17	92.6
Body Mass Index, kg/m²		
< 27.8	27	39.8
≥ 27.8	12	48.1
Smoking		
Never smoked/ex-smoker	20	30.5
Current smoker	19	71.0
Family history of stroke		
No	29	38.9
Yes	10	61.7
Rates adjusted to age distribution of non cases by the direct method		

Source: Berger K et al.; Stroke,1998; 29:1562-1566


Number of strokes per 100.000 per year during 7.2 years of follow-up in the PROCAM Study

This slide shows the adjusted stroke incidence for several risk factors in the PROCAM Study. The incidence of stroke increased with higher cholesterol levels, higher triglyceride levels, higher diastolic and systolic blood pressure, smoking, obesity and in persons with a family history of stroke. This slide underlines the concordance of risk factors that exist between coronary heart disease and stroke.


Slide 18:

Stroke:

Major risk factors for both ischemic and hemorrhagic stroke in 7.2 years of follow-up in the PROCAM Study



**PROCAM (Münster Heart Study):
 Major Risk Factors for Both Ischemic and Hemorrhage Stroke During 7.2 Years of Follow-Up**



Risk Factor	Total Stroke RR (95% CI)	p for Trend
Systolic blood pressure, mm Hg		
≤ 120	1.00 Reference	0.004
121-140	2.99 (0.85-10.49)	
> 140	5.56 (1.56-19.88)	
Smoking status		
Never smoked/Previous smoker	1.00 Reference	<0.001
≤ 20 cigarettes/day	1.65 (0.62-4.42)	
>20 cigarettes/day	3.56 (1.78-7.15)	
History of High blood pressure*		
No	1.00 Reference	
Yes	2.37 (1.20-4.71)	
Diabetes mellitus**		
No	1.00 Reference	
Yes	2.21 (1.00-4.87)	

Risk factors adjusted for age and variables listed here.

* Known history of hypertension (treated or untreated) at baseline

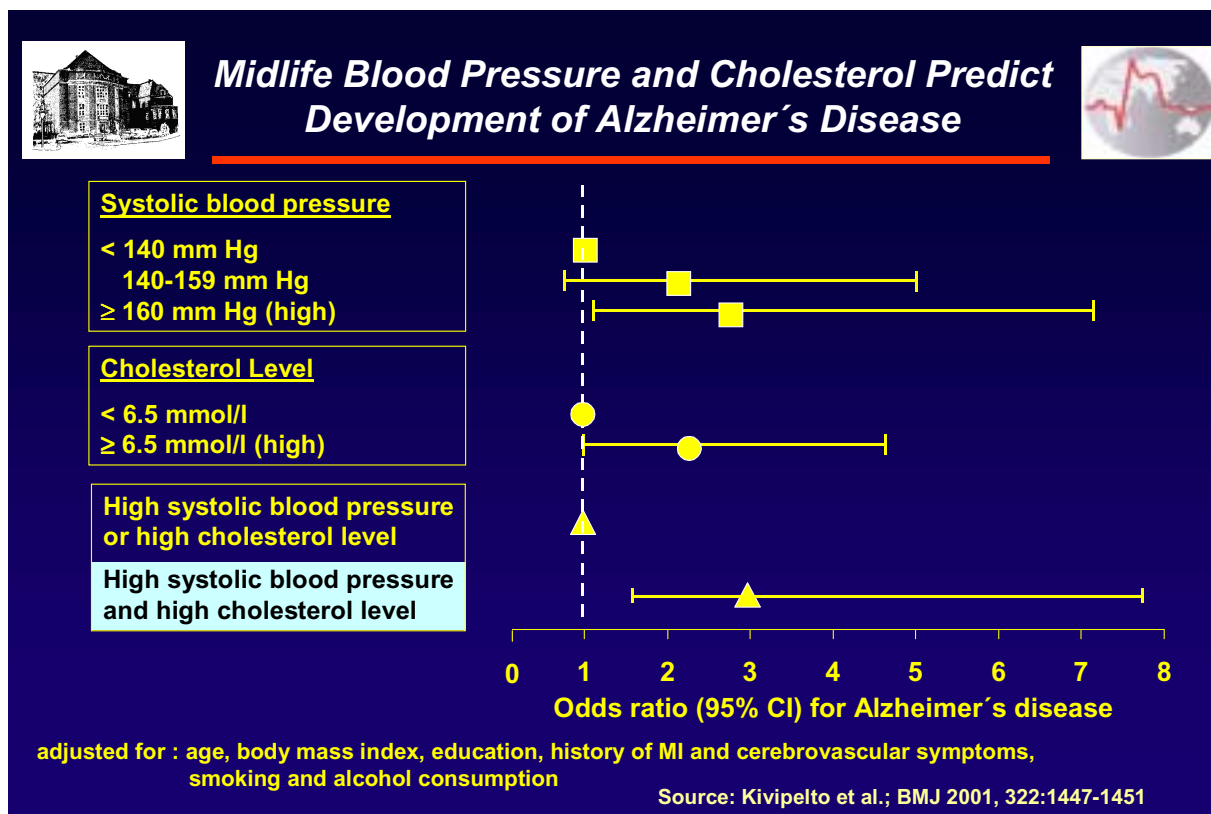
** Known history of diabetes mellitus (treated or untreated) or fasting blood glucose level >120 mg/dL at baseline

Source: Berger K et al.; Stroke, 1998; 29:1562-1566

Major risk factors for both ischemic and hemorrhagic stroke in 7.2 years of follow-up in the PROCAM Study

As shown in slide 17, there is a large degree of overlap between the risk factors for coronary heart disease and those for stroke. This slide underlines this point by showing that the incidence of overall (ischemic + hemorrhagic) stroke is greater at higher levels of systolic blood pressure or in persons with a history of hypertension, in those who smoke and in persons with diabetes mellitus.

Slide 19:



Stroke:**Midlife blood pressure and cholesterol predict development of Alzheimer's disease****Midlife blood pressure and cholesterol predict development of Alzheimer's disease**

This slide shows that a concordance of risk factors also exists between stroke and Alzheimer's disease. In a prospective, population-based study in eastern Finland raised blood pressure and high serum cholesterol levels, and in particular the combination of these risks, in midlife increase the risk of Alzheimer's disease in later life.

Slide 20:

Stroke:

Distribution of prothrombotic risk factors in children with stroke and controls

**Distribution of Prothrombotic Risk Factors
in Children with Stroke and Controls**

	Risk Factors	Controls (n=296)	Patients (n=148)	OR (CI)	χ^2 p value
Single risk factor	Lp(a) > 30 mg/dl	14 (4.7%)	39 (26.4%)	7.2 (3.8-13.8)	<0.0001
	FV G 1691A (+/-)	12 (4%)	30 (20.2%)	6 (2.97-12.1)	<0.0001
	Protein C deficiency	2 (0.67%)	9 (6%)	9.5 (2-44.6)	0.001*
	PT G20210A	4 (1.3%)	9 (6%)	4.7 (1.4-15.6)	0.01*
	MTHFR TT677 genotype	31 (10.4%)	35 (23.6%)	2.64 (1.53-4.5)	<0.0001
Combined risk factors	FV G1691A + Lp(a) > 30 mg/dl	1 (0.3%)	11 (7.4%)	23.6 (3-185)	<0.0001*
	FVG1691A + MTHFR TT677	-	5 (3.3%)	-	0.004*
Combinations (total)	FV G1691A + Lp(a) > 39 mg/dl or MTHFR TT677	1 (0.3%)	16 (10.8%)	35.75 (4.7-272)	<0.0001*

*Fischer's exact test

Source: Nowak-Gottl U et al., Circulation 1999; 100: 743-748

Distribution of prothrombotic risk factors in children with stroke and controls

This slide shows that various prothrombotic risk factors are more prevalent in children with stroke than in controls. The factors investigated in this multicentre study encompassing almost 150 children with stroke were a raised Lp(a) level, presence of the Factor V Leiden mutation (FV G 1691 A), protein C deficiency, a mutation at position 2021 in the prothrombin gene, and a polymorphism in the methylene tetrahydrofolate reductase (MTHFR) gene. The most striking aspect of this study, however, was that the coincidence of elevated Lp(a) with other risk factors was associated with a huge increase in risk. For example, the combination of Factor V Leiden and an elevated Lp(a) was associated with a relative stroke risk of 23.6, and the combination of Factor V Leiden and an elevated Lp(a) or a mutation in MTHFR was associated with a 36-fold increase in risk for stroke.

Slide 21:

Stroke:
Candidate genes for heritable disorders of blood coagulation based on sub-set analysis from the PROCAM Study

Gene Symbol	Name	cytogenetic location
F3	Tissue factor	1p22-p21
F5	Factor V	1q23
AT3	Antithrombin	1q23-q25
F13B	Factor XIII;B	1q31-q32.1
PROC	Protein C	2q13-q14
TFPI	Tissue Factor Pathway Inhibitor	2q31-q32
PROS1	protein S	3p11.1-q11.2
HRG	Histidine Rich Glycoprotein	3q28-q29
FGA, FGB, FGG	Fibrinogen	4q31
F11	Factor XI	4q35
F12	Factor XII	5q33-qter
F13A1	Factor XIII; A1	6p25-p24
PLG	Plasminogen	6q26
LPA	Lipoprotein (a)	6q26
PLANH1	Plasminogen Activator Inhibitor I	7q21.3-q22
PLAT	Tissue Plasminogen Activator	8p12-q11.2
PLAU	Urokinase Plasminogen Activator	10q24-qter
F2	Prothrombin	11p11-q12
VWF	Von Willebrand Factor	12p13
F10	Factor X	13q34
F7	Factor VII	13q34
APOH	beta 2-glycoprotein	17q23-qter
PLI	alpha-2-antiplasmin	17p13
PAI2	Plasminogen Activator Inhibitor II	18q21.3
KLK1, KLK2	Kallikrein 1, and 2	19q13.3
THBD	Thrombomodulin	20p11
HCF2	Heparin cofactor II	22q11
F9	Factor IX	Xq26.3-q27.1
F8c	Factor VIII	Xq28

Source: Koeleman et al., Thromb Haemost 1997, 77:873-878

Candidate genes for heritable disorders of blood coagulation based on sub-set analysis from the PROCAM Study

This slide shows the very wide range of genes which have been shown to be associated with an inherited pro-coagulatory state. It is likely that several of these polymorphisms contribute to the familial risk of stroke although the magnitude of this contribution and the effects of gene-gene or gene-environment interactions are not yet known.