

# Recent Advances in Management of Stroke Risk Factors



Kwang-Yeol Park

Dep. of Neurology, Chung-Ang University, Seoul South Korea

## Stroke in Korea

### Hypertension and Stroke

J curve in Stroke?

BP Goal

SPRINT

HOPE-3

### Genetic variability

AF Genetic Risk

SVD Genetic Risk

Genetic Risk of Recurrent Stroke

### Summary

## Why $p = 0.05$ ?

In February 2014, George Cobb, Professor Emeritus of Mathematics and Statistics at Mount Holyoke College, posed these questions to an ASA discussion forum:

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- Q Why do so many people still use  $p = 0.05$ ?
- A Because that's what they were taught in college or grad school.

## Pre-requisite quiz

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- ▶ *If the p-value is less than the required significance level, we say the null hypothesis is rejected at the given level of significance.*
- ▶ What is the meaning of  $p > 0.05$  ?
- ▶ *If the p-value is not less than the required significance level, the test has no result. The evidence is insufficient to support a conclusion.*

**Absence of evidence is not evidence of absence.**

## Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble



Vassilis Kontis\*, James E Bennett\*, Colin D Mathers, Guangguan Li, Kyle Foreman, Majid Ezzati

### Summary

**Background** Projections of future mortality and life expectancy are needed to plan for health and social services and

*Lancet* 2012; 380: 1323–35

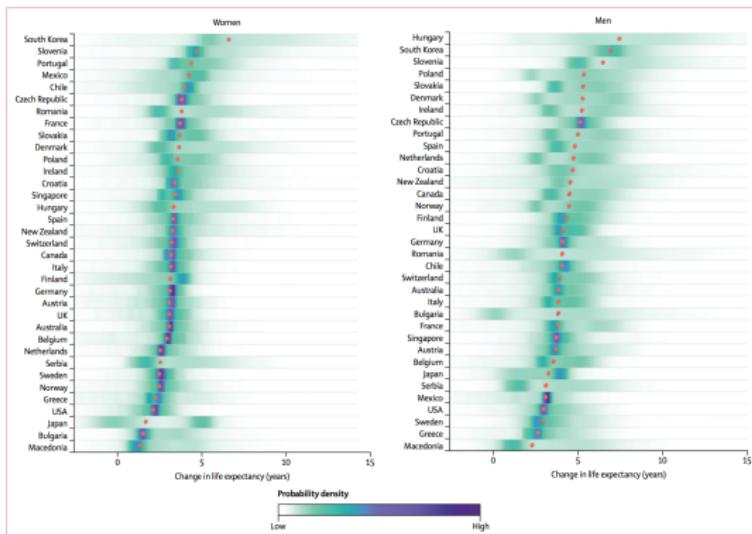
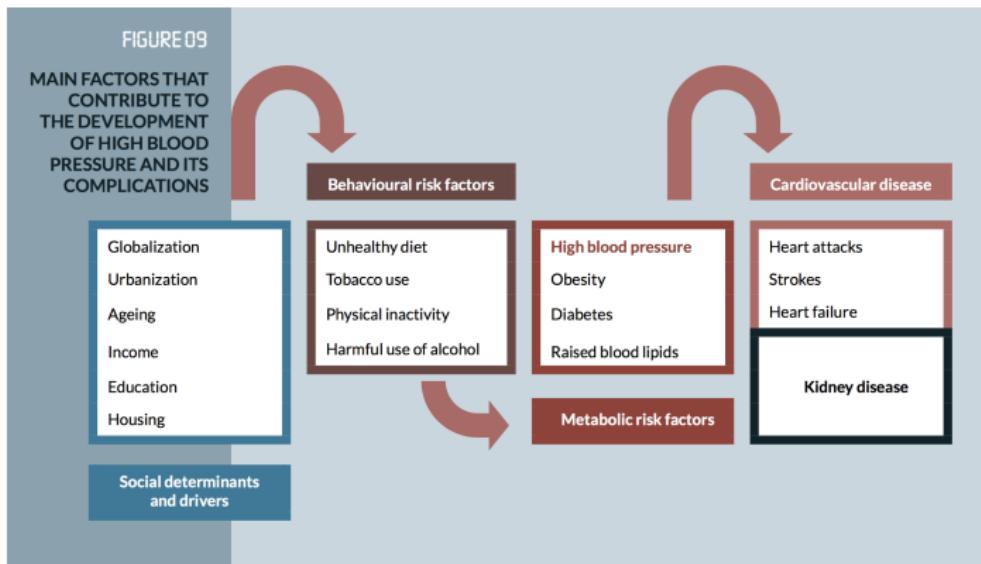


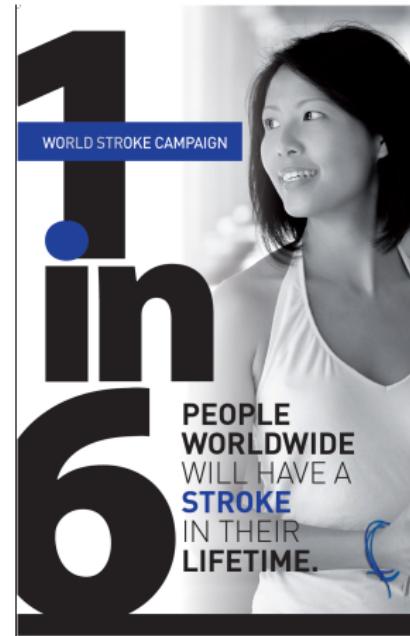
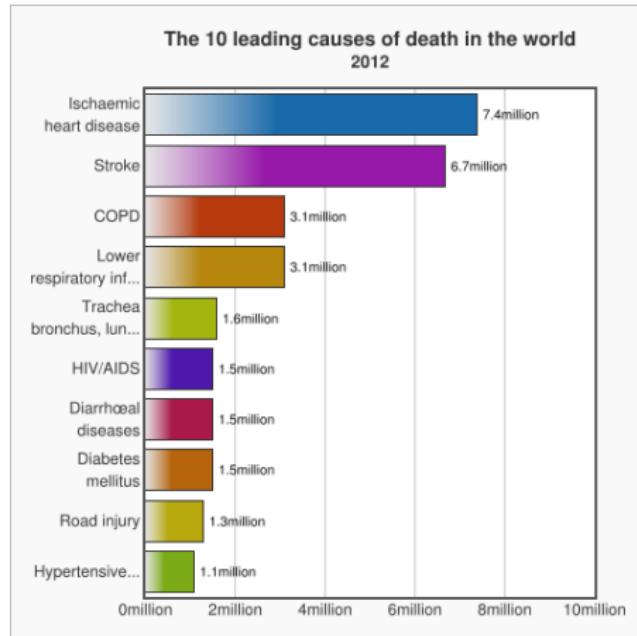
Figure 1: Posterior distribution of projected change in life expectancy at birth from 2010 to 2030  
Red dots show the posterior medians. Countries are ordered vertically by median projected increase from largest (at the top) to smallest (at the bottom).

There is a **90% probability that life expectancy at birth among South Korean women in 2030 will be higher than 86 · 7 years, and a 57% probability that it will be higher than 90 years.**

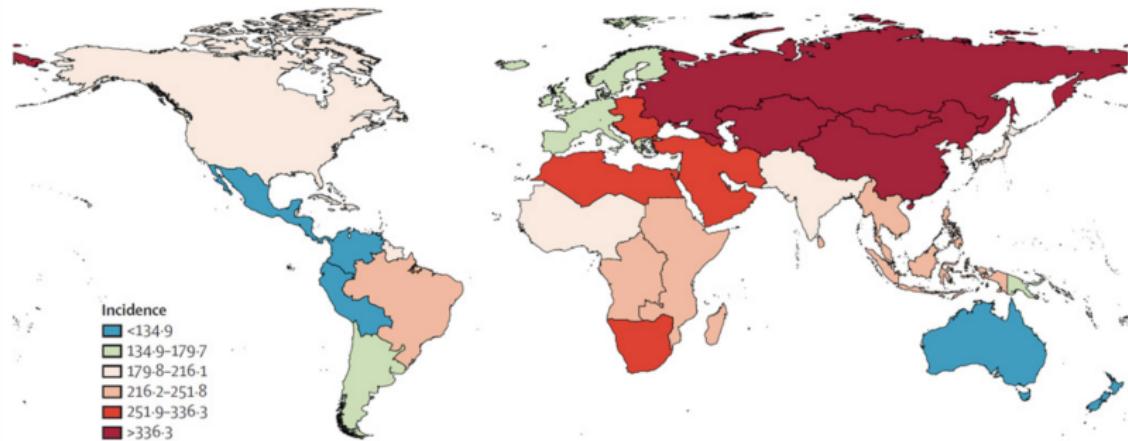
There is a **greater than 95% probability that life expectancy at birth among men in South Korea, Australia, and Switzerland will surpass 80 years in 2030, and a greater than 27% probability that it will surpass 85 years.**



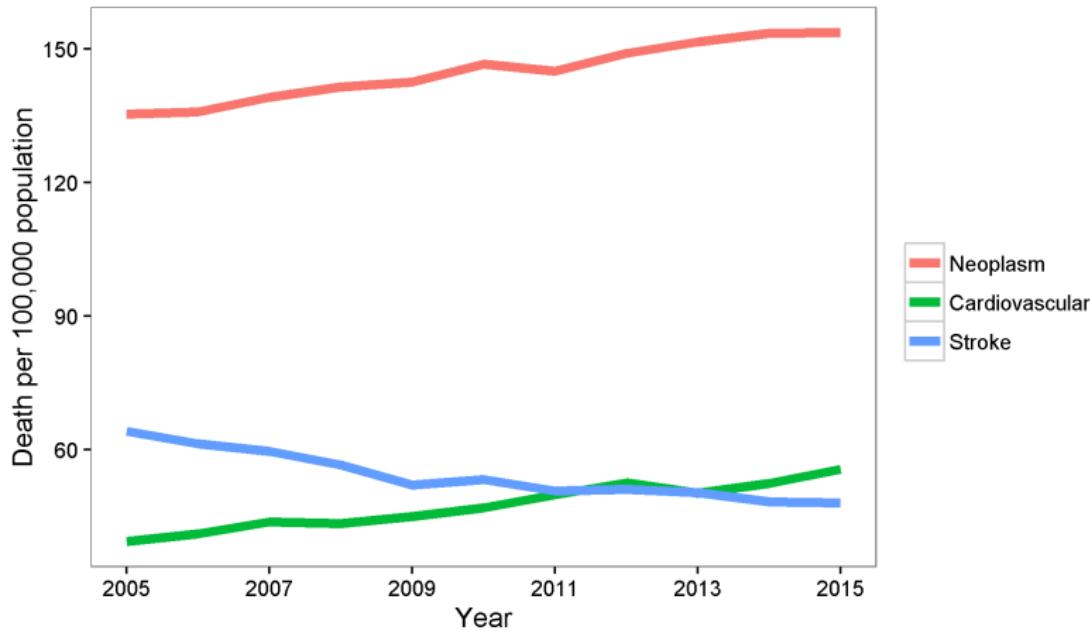
## Global burden of stroke



## Age-standardised stroke incidence per 100 000 person-years for 2010



## Secular trend of mortality in Korea



## Etiologies of stroke

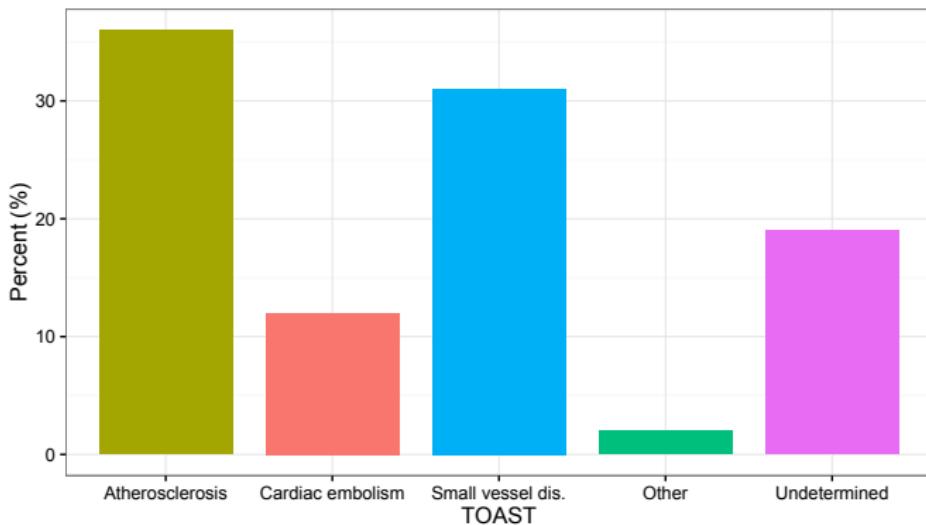
### Ischemic Stroke

- ▶ Atherosclerosis
- ▶ Small artery occlusion
- ▶ Cardiac disease causing embolism
- ▶ Other causes such as moyamoya disease

### Hemorrhagic Stroke

- ▶ Hypertensive hemorrhage
- ▶ Cerebral amyloid angiopathy
- ▶ Arteriovenous malformations
- ▶ Subarachnoid hemorrhage

## Ischemic stroke in Korea: Analysis of 10,861 cases in Korean Stroke Registry



## Risk factors for Stroke

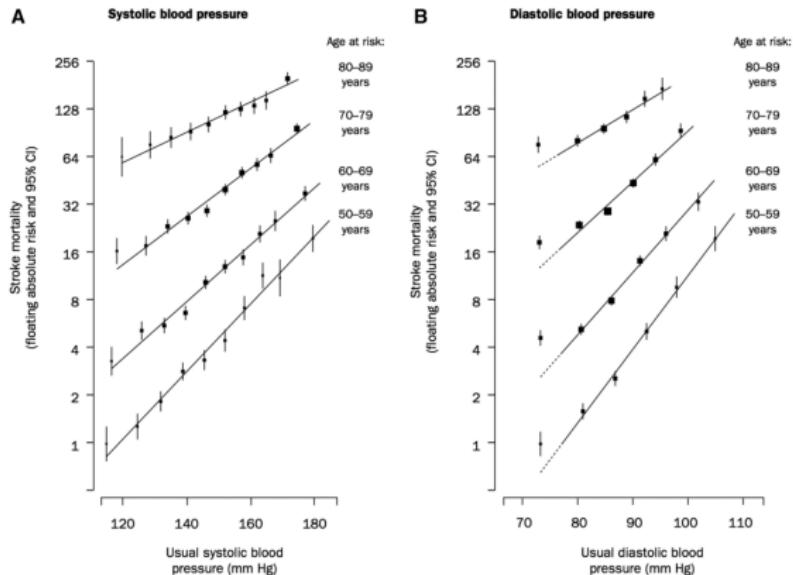
### Non-modifiable factors

1. Age
2. Sex
3. Race
4. Family history
5. **Genetic variability**

### Modifiable factors

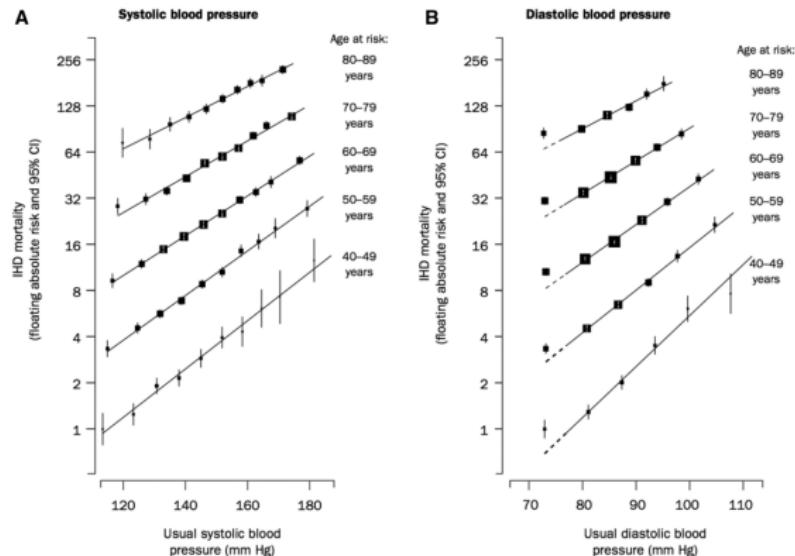
1. **Hypertension**
2. Diabetes
3. Dyslipidemia
4. Smoking
5. Carotid disease
6. Cardiac disease such as atrial fibrillation
7. Obesity
8. Inactivity

# Stroke and HT



**Figure 2. Stroke mortality in each decade of age vs usual blood pressure at the start of the decade.** CI indicates confidence interval.  
Adapted from the Prospective Studies Collaboration (Lewington et al<sup>12</sup>) with permission of the publisher. Copyright ©2002, Elsevier.

## IHD and HT



**Figure 1. Ischemic heart disease (IHD) mortality in each decade of age vs usual blood pressure at the start of the decade.**  
CI indicates confidence interval. Adapted from the Prospective Studies Collaboration (Lewington et al<sup>17</sup>) with permission of the publisher.

# IHD vs Stroke and SBP

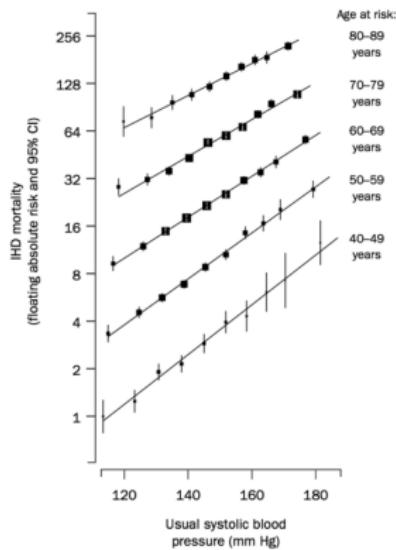


Figure 1. Ischemic heart disease (IHD) mortality

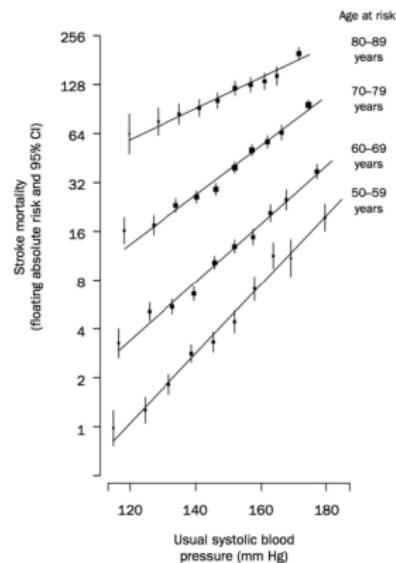
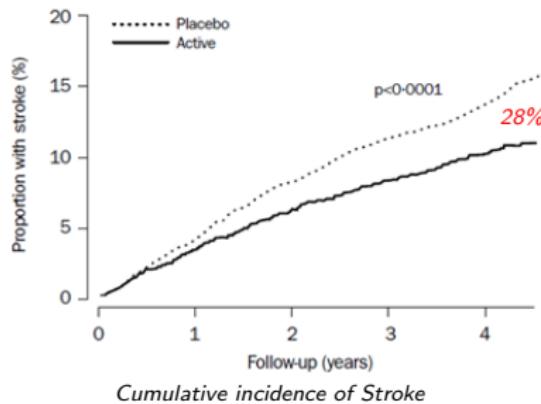
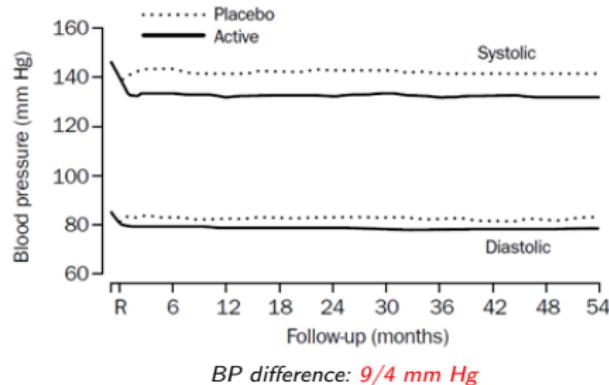


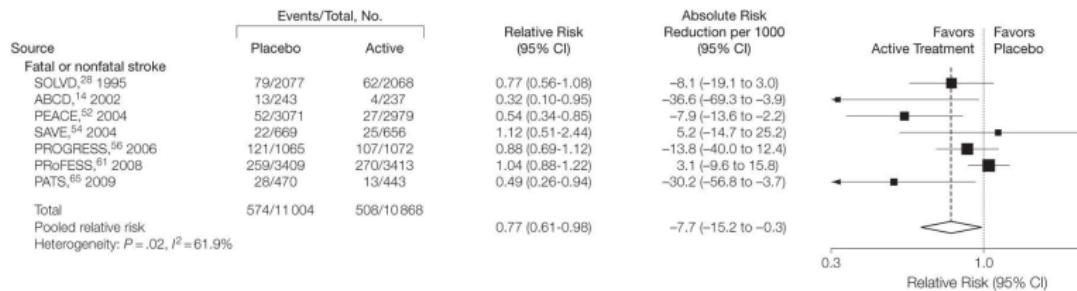
Figure 2. Stroke mortality

# PROGRESS

Randomized trial enrolling 6,105 patients with a history of TIA or stroke (ischemic or hemorrhagic) to perindopril+ indapamide or placebo



# Anti-HT Tx. and stroke

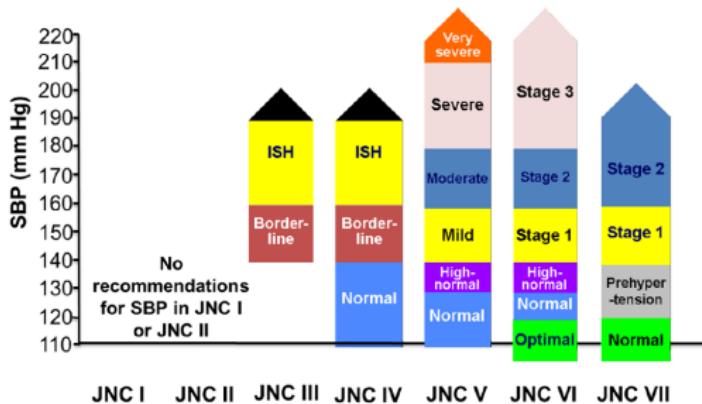


# Recent Advances in Stroke

## └ Hypertension and Stroke

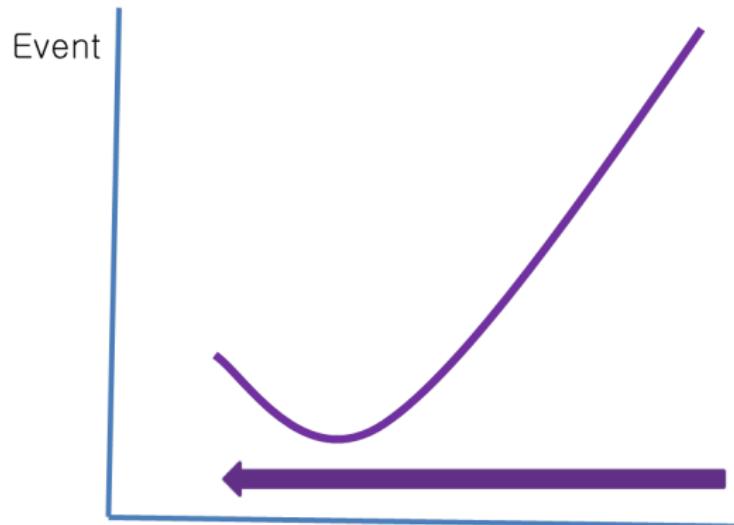
WASHINGTON, D.C. April 9, 1944			
9th	202/102	P.M.	196/96
10th	196/94	"	200/104
11th	192/96	"	204/100
12th	200/102	"	204/98
13th	196/100	"	202/96
14th	206/100	"	200/96
15th	206/102	"	196/100
16th	215/102	"	206/120
17th	216/120	"	206/116 (Dr.Bruen 6th sound)
18th	220/120	(4th sound)	Unicosp 1; XI $\neq$ x.t.i.d. ac.
19th	218/120	P.M.	204/104
20th	212/106	Noon	210/96 9:54 p.m. 190/100 (XI discontinued)
21st	9:05 a.m.	234/126; 10:15 a.m. (sitting)	210/116; 10:05 a.m. 218/120 (prone, both arms checked) 6:45 p.m. after outing 214/180; 9:50 p.m. 220/114.
22nd	9:30 a.m.	214/120; 11:30 a.m.	210/114; 6:30 p.m. (after boat trip) 206/110.
23rd	10:15 a.m.	214/118 (2 1/2 hr drive)	9:45 212/114.
24th	10:15 a.m.	222/122	10:30 p.m. 220/110
25th	10:05	224/116	10 p.m. 214/106 (after luncheon party).
26th	10. a.m.	214/112	10:30 p.m. 222/110
27th	10:15 a.m.	222/118;	9:45 p.m. 210/114
28th	224/124	P.M.	230/120 (one additional digit tablet Tuesday and Friday)
29th	9:15 a.m. (on swaying)	196/112; (sitting after breakfast)	10:10 226/120; (Prone, after E.E.) 220/118; 2:15 (after lunch) 226/112 (Thesodate discontinued); 9:30 p.m. 210/110
30th	8:45 (Prone, on swaying)	210/110; (after breakfast)	10:00 206/104; ; after lunch 206/114; 9:00 p.m. 224/120
May 1st. Prone 9:15 a.m. 220/116; Noon 210/110; 2 p.m. (after lunch 210/ 106; 10:30 p.m. 210/118.			

Franklin D. Roosevelt Library

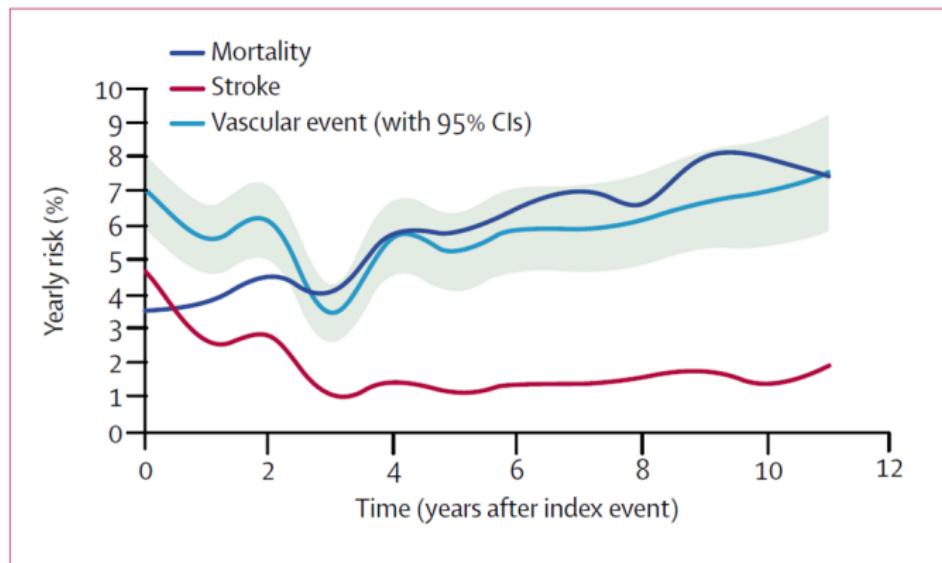


*JNC I. JAMA. 1977; JNC II. Arch Intern Med. 1980; JNC III. Arch Intern Med. 1984; JNC IV. Arch Intern Med. 1988; JNC V. Arch Intern Med. 1993; JNC VI. Arch Intern Med. 1997; JNC 7 Express*

## Hypertension: J curve ?



## Yearly Risk over Time in Dutch TIA trial



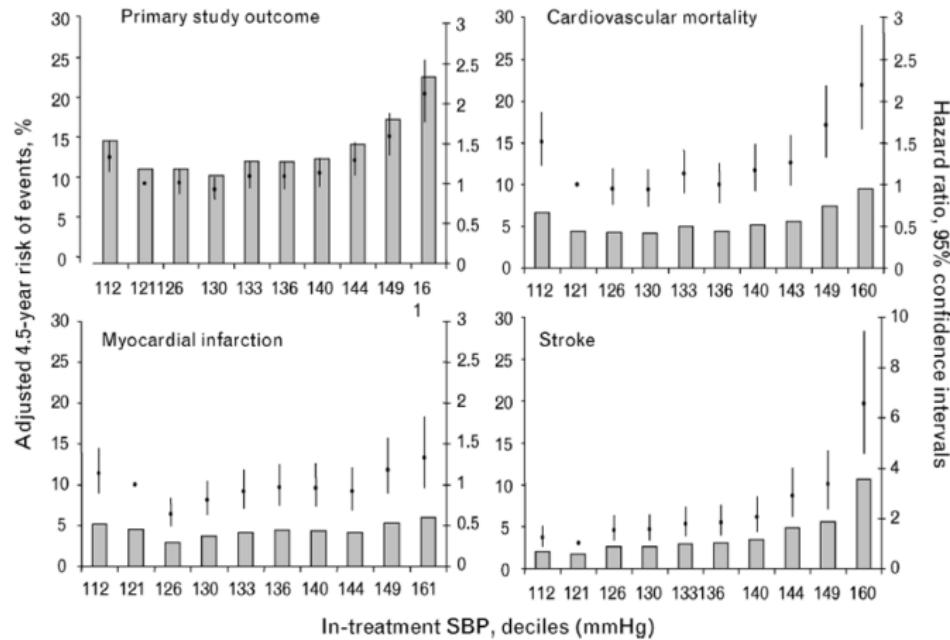
## Vascular events after stroke

### Risk of Myocardial Infarction and Vascular Death After Transient Ischemic Attack and Ischemic Stroke A Systematic Review and Meta-Analysis

Emmanuel Touzé, MD; Olivier Varenne, MD, PhD; Gilles Chatellier, MD, PhD;  
Séverine Peyrard, MSc; Peter M. Rothwell, MD, PhD, FRCP; Jean-Louis Mas, MD

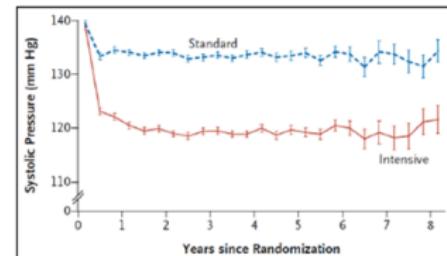
	Annual Risk
Nonstroke vascular death	2.1% (1.9 to 2.4)
Total MI	2.2% (1.7 to 2.7)
Nonfatal MI	0.9% (0.7 to 1.2)
Fatal MI	1.1% (0.8 to 1.5)

# Ontarget study



# The lower BP looks beneficial in stroke: ACCORD

- 4733 patients with type 2 DM
- SBP  
< 140 mm Hg vs. < 120 mm Hg



Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	%/yr	no. of events	%/yr		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03

ACCORD	
Population	4733 DM
Intervention	<120 vs. <140
Primary endpoint	MI, Stroke, CV death
SBP at 1yr	119 vs. 134
Outcome/yr	1.87% vs. 2.09%
All cause mortality/yr	1.28% vs. 1.19%
Stroke	0.32% vs. 0.53% *

**Special Communication**

## **2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults**

**Report From the Panel Members Appointed  
to the Eighth Joint National Committee (JNC 8)**

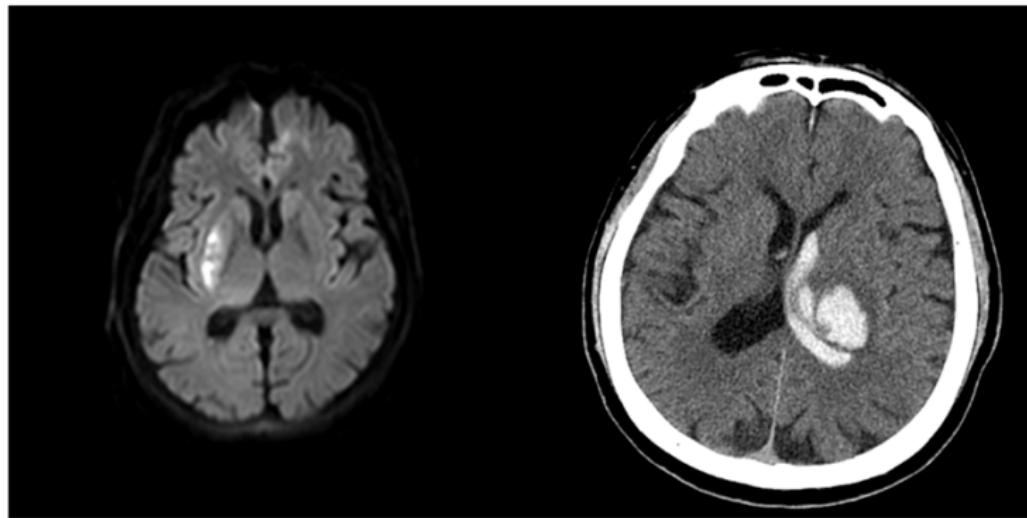
Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD;  
Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH;  
Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS;  
Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD;  
Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

### **Recommendation 1**

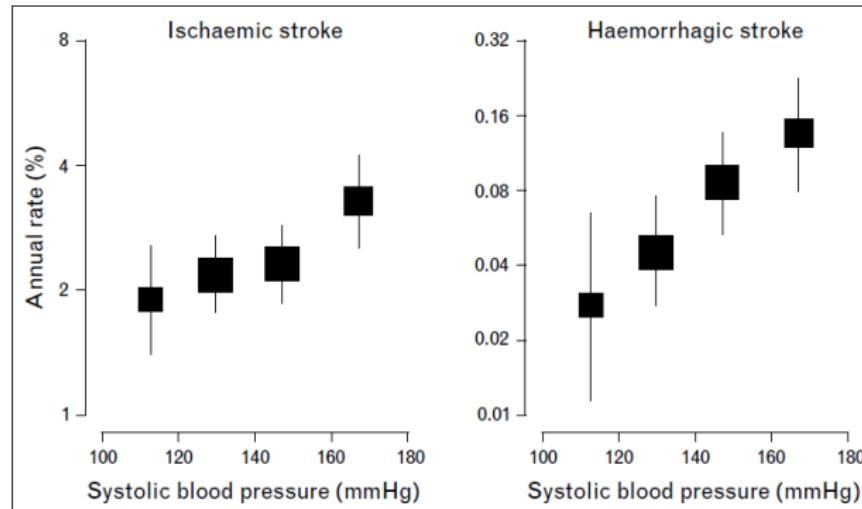
In the general population aged  $\geq 60$  years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP)  $\geq 150$  mm Hg or diastolic blood pressure (DBP)  $\geq 90$  mm Hg and treat to a goal SBP  $< 150$  mm Hg and goal DBP  $< 90$  mm Hg. (Strong Recommendation – Grade A)

### **Corollary Recommendation**

In the general population aged  $\geq 60$  years, if pharmacologic treatment for high BP results in lower achieved SBP (eg,  $< 140$  mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

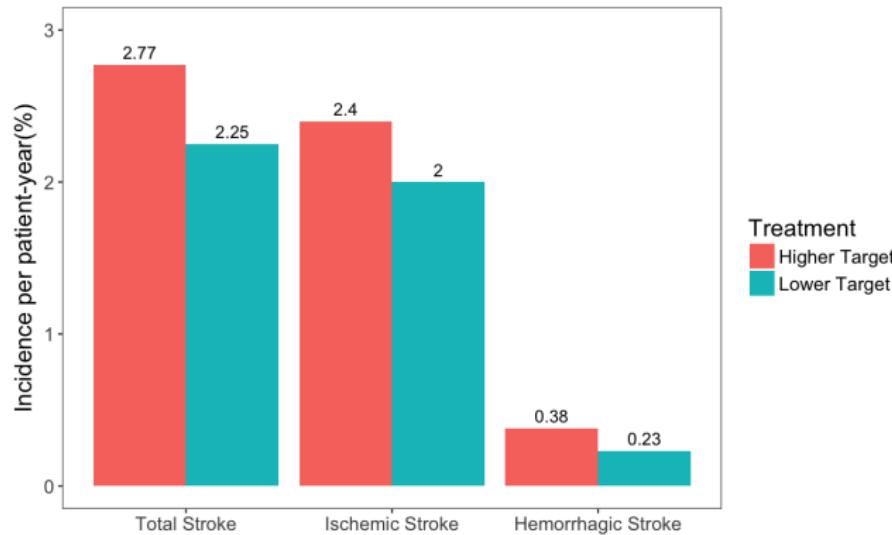


## Lower target BP for stroke prevention: PROGRESS



## BP targets in recent lacunar stroke: SPS3

3020 patients assigned to a SBP target of 130–149 or < 130 mm Hg.  
After 1 year, mean SBP was 138 mm Hg vs. 127 mm Hg.



## 2014 AHA/ASA 2ndary Prevention of Stroke Guideline

**For patients with a recent lacunar stroke, it might be reasonable to target an SBP of <130 mmHg (Class IIb; Level of Evidence B). (Revised recommendation)**

# The NEW ENGLAND JOURNAL of MEDICINE

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## A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group\*

### ABSTRACT

#### BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

#### METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N., B.S.N., M.A., Kayce M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Rebourdin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C. Cush-

## SPRINT: Demographics

	Intensive Tx.	Standard Tx.
Number	4678	4683
Age	67.9 ± 9.4	67.9 ± 9.5
Female	1684 (36.0%)	1648 (35.2%)
CVD	940 (20.1%)	937 (20.0%)
CKD	1330 (28.4%)	1315 (28.1%)
GFR	71.8 ± 20.7	71.7 ± 20.5
Initial BP	139.7/78.2 mm Hg	139.7/78.0 mm Hg
Mean SBP	121.5 mm Hg	134.6 mm Hg

## SPRINT: Primary outcome

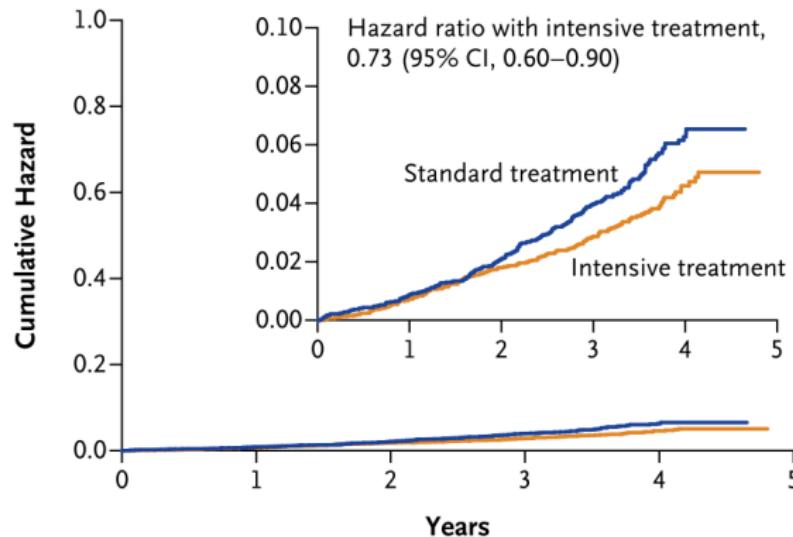
The first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.

**Table 2.** Primary and Secondary Outcomes and Renal Outcomes.\*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per year	no. of patients (%)	% per year		
<b>All participants</b>	<b>(N=4678)</b>		<b>(N=4683)</b>			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005

## SPRINT: All cause mortality

Death from Any Cause



# Data sharing and SPRINT

# SPRINT and ACCORD

	ACCORD	SPRINT
Population	4733 DM	9631 non-DM
Intervention	<120 vs. <140	<120 vs. <140
Primary endpoint	MI, Stroke, CV death	+ HF, other ACS
SBP at 1yr	119 vs. 134	121 vs. 136
Outcome/yr	1.87% vs. 2.09%	1.65% vs. 2.19% *
All cause mortality/yr	1.28% vs. 1.19%	1.03% vs. 1.40% *
Stroke	0.32% vs. 0.53% *	0.41% vs. 0.47%

# SPRINT and ACCORD

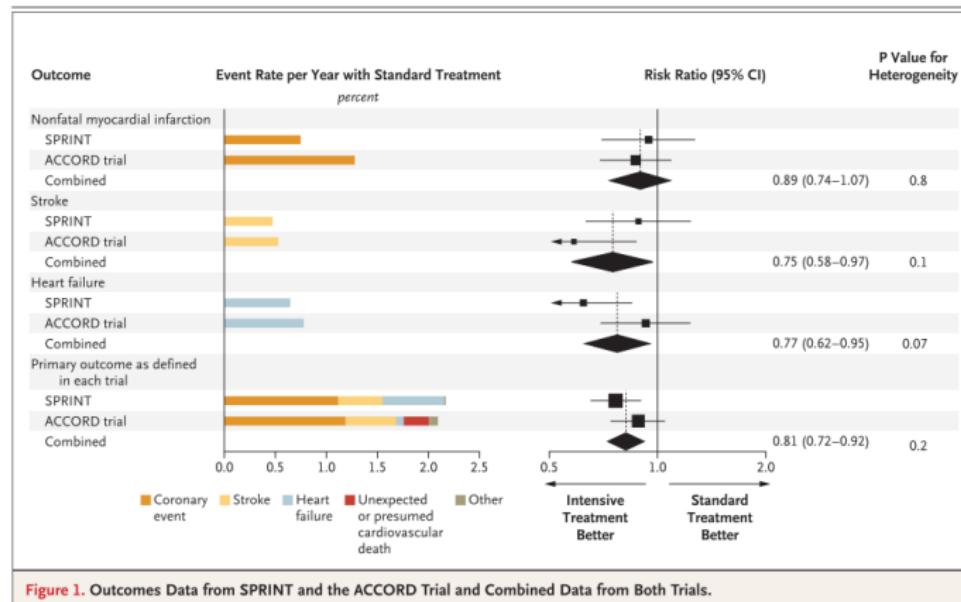
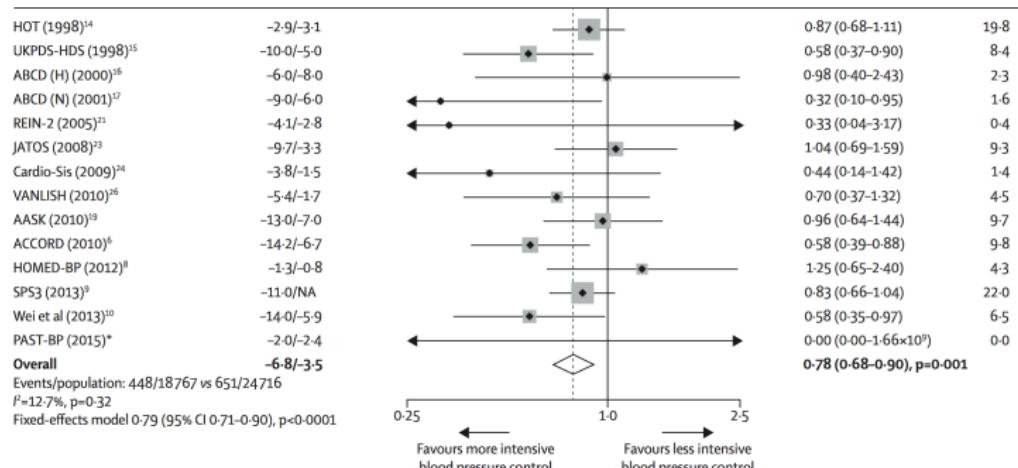


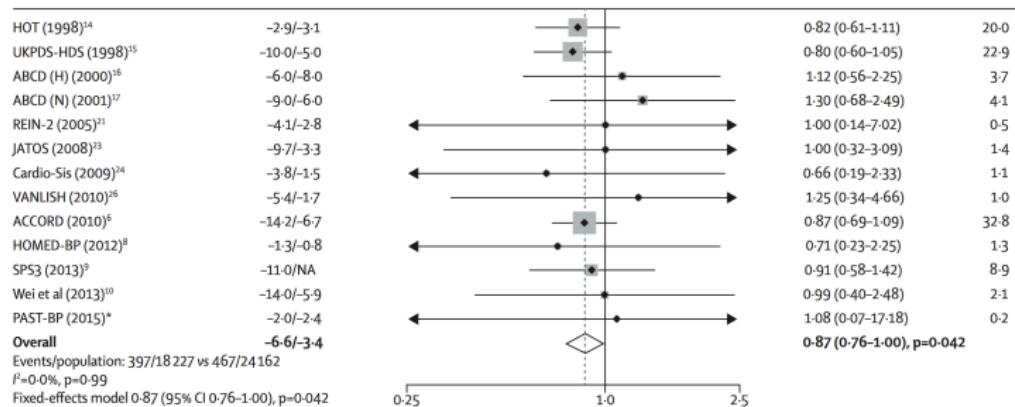
Figure 1. Outcomes Data from SPRINT and the ACCORD Trial and Combined Data from Both Trials.

# Effect of intensive BP lowering on Stroke



133/76 mm Hg vs. 140/81 mm Hg

# Effect of intensive BP lowering on MI



133/76 mm Hg vs. 140/81 mm Hg

Recent Advances in Stroke

└ Hypertension and Stroke

└ BP Goal

## HOPE-3

# The NEW ENGLAND JOURNAL of MEDICINE

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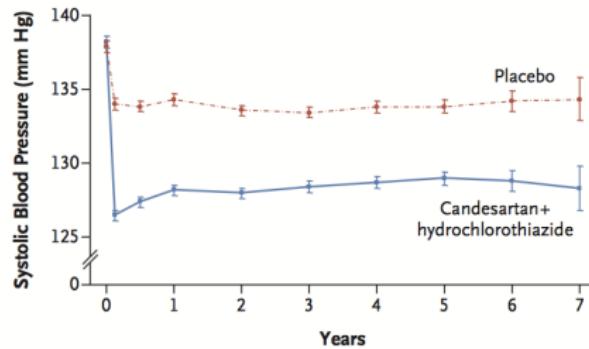
## Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D.,

# HOPE-3

Characteristic	Candesartan + Hydrochlorothiazide (N=6356)	Placebo (N=6349)
Age — yr	65.7±6.4	65.8±6.4
Female sex — no. (%)	2910 (45.8)	2964 (46.7)
Cardiovascular risk factor — no. (%)		
Elevated waist-to-hip ratio	5511 (86.7)	5523 (87.0)
Recent or current smoking	1782 (28.0)	1742 (27.4)
Low concentration of HDL cholesterol	2297 (36.1)	2291 (36.1)
Impaired fasting glucose or impaired glucose tolerance	799 (12.6)	817 (12.9)
Early diabetes mellitus	386 (6.1)	345 (5.4)
Family history of premature coronary heart disease	1668 (26.2)	1667 (26.3)
Early renal dysfunction	184 (2.9)	166 (2.6)
Hypertension	2398 (37.7)	2416 (38.1)
Blood pressure — mm Hg		
Systolic	138.2±14.7	137.9±14.8
Diastolic	82.0±9.4	81.8±9.3

# HOPE-3

**No. at Risk**

Candesartan+hydro-chlorothiazide	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

# ACCORD, SPRINT, and HOPE-3

	ACCORD	SPRINT	HOPE-3
Population	4733 DM	9631 non-DM	12705
Intervention	<120 vs. <140	<120 vs. <140	drug vs. placebo
Primary outcome	MI, Stroke, CV death	+ HF, other ACS	= ACCORD
SBP at 1yr	119 vs. 134	121 vs. 136	≈ 128 vs. ≈ 134
Outcome/yr	1.87% vs. 2.09%	1.65% vs. 2.19% *	4.1% vs. 4.4%
All cause death/yr	1.28% vs. 1.19%	1.03% vs. 1.40% *	5.4% vs. 5.5%
Stroke	0.32% vs. 0.53% *	0.41% vs. 0.47%	1.2% vs. 1.5%

HOPE-3: event rates during follow-up (median f/u 5.6year)

## Guidelines Debate

### Is It Time to Reappraise Blood Pressure Thresholds and Targets?

A Statement From the International Society  
of Hypertension—A Global Perspective

Michael A. Weber, Neil R. Poulter, Aletta E. Schutte, Louise M. Burrell, Masatsugu Horiuchi,  
Dorairaj Prabhakaran, Agustin J. Ramirez, Ji-Guang Wang, Ernesto L. Schiffrin, Rhian M. Touyz

Taking into consideration the global target population of interest to the International Society of Hypertension, together with evidence derived from SPRINT and other recent meta-analyses and clinical trials, the practical message from the International Society of Hypertension is to strive for a systolic blood pressure target of 130 mmHg in most patients with hypertension. This is especially important considering that

# We want something like this in genetics

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ORIGINAL CONTRIBUTION

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## Association of *BRCA1* and *BRCA2* Mutations With Survival, Chemotherapy Sensitivity, and Gene Mutator Phenotype in Patients With Ovarian Cancer

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Da Yang, PhD

---

Sofia Khan, PhD

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Yan Sun, MD, PhD

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Kenneth Hess, PhD

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Ilya Shmulevich, PhD

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Anil K. Sood, MD

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Wei Zhang, PhD

INCREASED SURVEILLANCE OF *BRCA1/2*  
normal tissue mutation carriers is a non-

**Context** Attempts to determine the clinical significance of *BRCA1/2* mutations in ovarian cancer have produced conflicting results.

**Objective** To determine the relationships between *BRCA1/2* deficiency (ie, mutation and promoter hypermethylation) and overall survival (OS), progression-free survival (PFS), chemotherapy response, and whole-exome mutation rate in ovarian cancer.

**Design, Setting, and Patients** Observational study of multidimensional genomic and clinical data on 316 high-grade serous ovarian cancer cases that were made public between 2009 and 2010 via The Cancer Genome Atlas project.

**Main Outcome Measures** OS and PFS rates (primary outcomes) and chemotherapy response (secondary outcome).

Yang, D., et al. (2011). "Association of *BRCA1* and *BRCA2* mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer." *JAMA* 306(14): 1557-1565.

# In the era of precision medicine,



The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS

## patient education **Fact Sheet**

PFS007: BRCA1 and BRCA2 Mutations MARCH 2015

### **BRCA1 and BRCA2 Mutations**

Cancer is a complex disease thought to be caused by several different factors. A few types of cancer run in families. These types, called "hereditary" or "familial" cancer, have been linked to changes in genes that can be passed from parents to children. Changes in genes are called **mutations**.

**Hereditary breast and ovarian cancer syndrome** is a type of familial cancer. It most commonly is linked to mutations in two genes called **BRCA1** and **BRCA2**. Inheriting one of these mutations increases the risk of getting breast cancer, ovarian cancer, and other types of cancer. About 10% of cases of ovarian cancer and 3–5% of cases of breast cancer are due to mutations in **BRCA1** and **BRCA2**.

**Table 1.** Breast Cancer and Ovarian Cancer Risk for Women With **BRCA** Mutations

Type of Cancer	Risk for the General Population	Risk With <b>BRCA1</b> Mutation	Risk With <b>BRCA2</b> Mutation
Breast	12%	55–65%	45%
Ovary	1.4%	39%	11–17%

## In stroke,

Table 3. Selected Genetic Causes of Stroke

Disease	Mode of Inheritance	Gene/Protein	Mechanism of Stroke	Common Clinical Manifestations
<b>Single gene disorders that primarily cause stroke</b>				
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal dominant	NOTCH3/GAD1013	Small vessel disease	Ischemic stroke, leukoencephalopathy, migraines, pectoral manifestations, and dementia
Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy	Autosomal dominant	HTSM1/-/HTSA serine peptidase-1	Small vessel disease	Ischemic stroke, leukoencephalopathy, premature baldness, and speech loss
Familial amyloid angiopathy	Autosomal dominant	APPbeta-precursor protein	Bursture of small cortical vessels	Lobar hemorrhage, intracysts, leukoencephalopathy, dementia, and aneurysm spills
Collagen 4 (COL4A1) mutations	Autosomal dominant	Col4A1/col4A1 chain of collagen type 4	Bursture of cortical and subcortical vessels	Superficial and deep hemorrhages, intracranial aneurysms, hematuria, and cystic kidney disease
<b>Genetic disorders that include stroke as manifestations</b>				
Ehlers-Danlos type 4	Autosomal dominant	Col3A1/type II procollagen	Aneurysm dissection	Anthrax, epicanthic fold, dislocated scapulae, arachnoidoceles, myxomas, viscera and muscle dislocation, and uterine rupture during pregnancy
Fabry disease	X-linked	GAL $\alpha$ -galactosidase A	Large and small artery disease	Ischemic stroke and neuroangiopathy, angiokeratoma, corneal opacities and cataracts, neuropathy (especially peripheral), and progressive renal failure
Marfan syndrome	Autosomal dominant	FBN1/fibrillin 1	Aneurysm dissection and cardiac embolism	Ischemic stroke, arterial dissection, ectopia, pericarditis, aortic dilatation, valvular dysfunction/heart failure, and ectopia lens
Mitochondrial encephalopathy with lactic acid and stroke-like episodes	Maternal	Mitochondrial DNA (MT-III) (mitochondrially encoded phosphoenolpyruvate carboxykinase 1 (LNU42); others)	Energy failure and metabolic stroke	Ischemic stroke that does not observe vascular boundaries, short stature, developmental delay, atrophy, vision loss, hypoglycemia, and diabetes mellitus.
Sickle cell disease	Autosomal recessive	HBB/HBZ-globin (hemoglobin subunit)	Large and small vessel disease and moyamoya syndrome	Ischemic stroke, painful crises, vascular crises, and bacterial infections
Smooth muscle $\alpha$ -actin mutation-associated disorders	Autosomal dominant	ACTA2/smooth muscle $\alpha$ -actin	Moyamoya syndrome	Ischemic stroke, coronary artery disease, thoracic aortic aneurysms, and moyamoya syndrome
<b>Common genetic variants</b>				
TPH2	Common variant	TPH2/tryptophan-2 hydroxylase	Vascular development and arteriosclerosis	Large vessel ischemic stroke
PDK2	Common variant	PDK2/ortholog transcription factor	Small vessel disease; smooth muscle cell and pericyte coverage of central vessels	All strokes, small vessel stroke, and pneumonia and edema while water disease
ABO	Common and rare variants	ABO/blood group protein	Theoretical	Thrombosis and ischemic stroke
AGAT	Common and rare variants	AGAT/platelet desmosinase	Abnormalities	Large vessel ischemic stroke
PTG2	Common and rare variants	PTG2	Smooth muscle development and regulation of ion channels; modulation of surface receptors, and atrial fibrillation	Cardioembolic ischemic stroke and atrial fibrillation
ZFAT	Common and rare variants	ZFAT	Atrial fibrillation	Cardioembolic ischemic stroke and atrial fibrillation

## Etiologies of stroke are diverse

### Ischemic Stroke

- ▶ Atherosclerosis
- ▶ Small artery occlusion
- ▶ Cardiac disease causing embolism
- ▶ Other causes such as moyamoya disease

### Hemorrhagic Stroke

- ▶ Hypertensive hemorrhage
- ▶ Cerebral amyloid angiopathy
- ▶ Arteriovenous malformations
- ▶ Subarachnoid hemorrhage

# Terminology

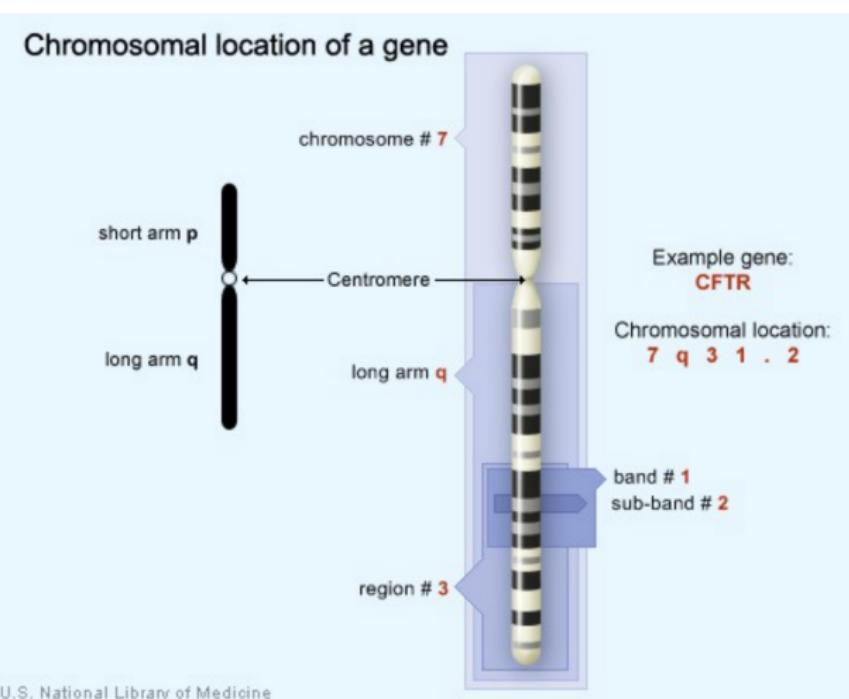
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RESEARCH ARTICLE

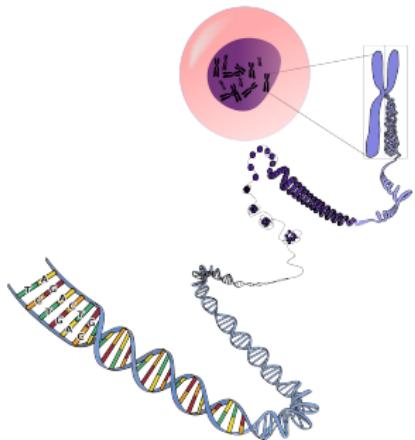
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## Genetic Variation at 16q24.2 Is Associated With Small Vessel Stroke

Matthew Traylor,<sup>1</sup> Rainer Malik,<sup>2</sup> Mike A. Nalls,<sup>3</sup> Ioana Cotlarciuc,<sup>4</sup>  
Farid Radmanesh,<sup>5,6,7</sup> Gudmar Thorleifsson,<sup>8</sup> Ken B. Hanscombe,<sup>1</sup>  
Carl Langefeld,<sup>9</sup> Danish Saleheen,<sup>10</sup> Natalia S. Rost,<sup>6</sup> Idil Yet,<sup>11</sup> Tim D. Spector,<sup>11</sup>  
Jordana T. Bell,<sup>11</sup> Eilis Hannon,<sup>12</sup> Jonathan Mill,<sup>12,13</sup> Ganesh Chauhan,<sup>14,15</sup>



# Location of DNA variation

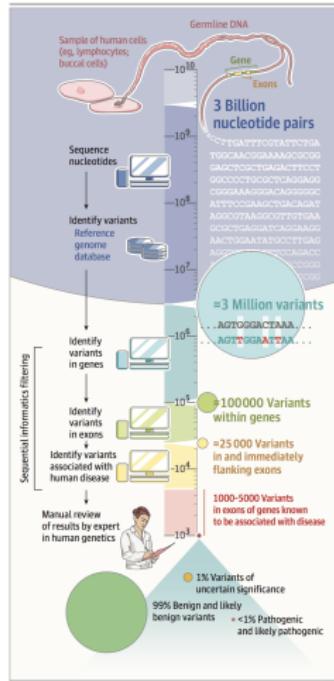


- | Cytogenetic changes  | Molecular genetic changes  |
|--|--|
| <ul style="list-style-type: none"> <li>• Whole chromosomal and whole genome changes: ~1-6 billion bp           <ul style="list-style-type: none"> <li>- Aneuploidy (abnormal number of chromosomes)</li> <li>- Aneusomy (fewer or more copies than 2 of a chromosome)</li> <li>- Interchromosomal translocations</li> <li>- Ring chromosomes</li> </ul> </li> <li>• Microscopic to submicroscopic           <ul style="list-style-type: none"> <li>- Segmental aneusomy</li> <li>- Chromosomal deletions</li> <li>- Chromosomal insertions</li> <li>- Chromosomal inversions</li> <li>- Intrachromosomal translocations</li> <li>- Chromosomal abnormality</li> <li>- Fragile sites</li> </ul> </li> <li>• 1 kb to submicroscopic           <ul style="list-style-type: none"> <li>- Copy number variants (CNVs)</li> <li>- Segmental duplications</li> <li>- Inversions, translocations</li> <li>- CNV regions</li> <li>- Microdeletions</li> <li>- Microduplications</li> </ul> </li> <li>• 2 bp to 1,000 bp           <ul style="list-style-type: none"> <li>- Microsatellites, minisatellites</li> <li>- Insertion-deletions (Indels)</li> <li>- Inversions</li> <li>- Di-, tri-, tetra-nucleotide repeats</li> <li>- Variable number tandem repeats e.g. microsatellites</li> </ul> </li> <li>• Single nucleotide 1 bp           <ul style="list-style-type: none"> <li>- Indels</li> <li>- SNPs</li> </ul> </li> </ul> | <p>bp indicates base pairs; SNP single nucleotide polymorphisms.</p> |

# Amount of data

- ▶ Interpretation of information
  - ▶ 3,000,000,000 base pairs
  - ▶ 3,000,000 SNPs
  - ▶ 100,000 variants in exon
- ▶ significance level in GWAS:  
 $5 * 10^{-8} = 0.05 * 10^{-6}$
- ▶ rs\*\*\*\*\*\*(number):  
 Reference SNP cluster ID

Figure. Informatic and Human Analysis Required for Finding Rare Pathogenic Variants in a Human Genome

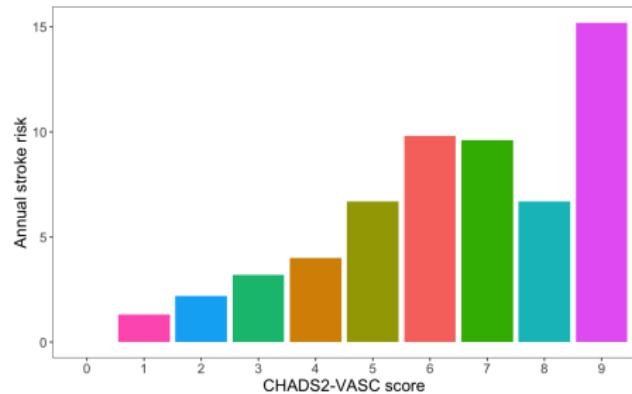


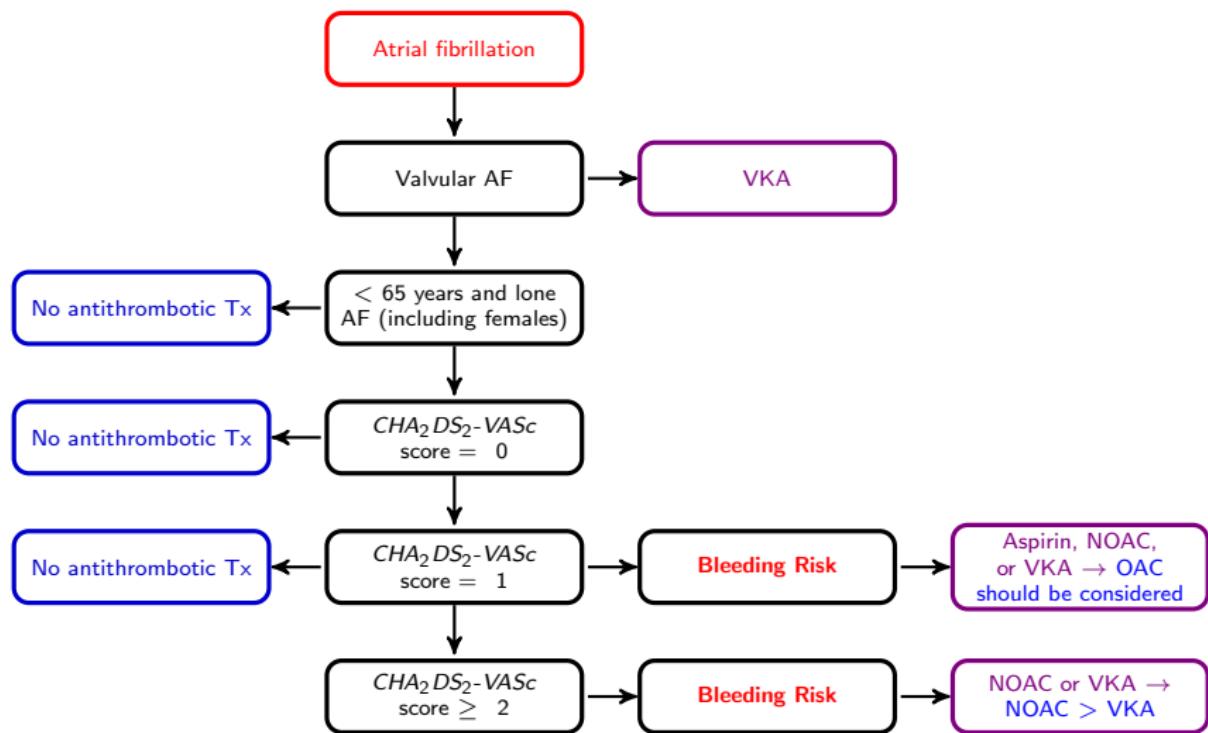
## Genetic causes of stroke

- ▶ Specific rare single gene disorder:
  - CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
  - Sickle cell anemia
- ▶ Common and rare variants of genetic polymorphism:
  - PITX2 (AF)
  - ABO (Thrombosis)

## Thromboembolic risk of AF

<i>CHA<sub>2</sub>DS<sub>2</sub>-VASc</i> criteria	Score
CHF	1
Hypertension	1
Age $\geq$ 75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease	1
Age 65-74 years	1
Sex category (female)	1





## Frequently,

- ▶ AF is diagnosed after the development of large infarction.
- ▶ AF is asymptomatic.
- ▶ AF is paroxysmal.
- ▶ Stroke mechanism can not be determined in some patients.

Genetic marker of AF can be helpful in these situations.

**ORIGINAL RESEARCH ARTICLE**

# Genetic Risk Prediction of Atrial Fibrillation

ORIGINAL RESEARCH  
ARTICLE

**Editorial, see p 1321**

**BACKGROUND:** Atrial fibrillation (AF) has a substantial genetic basis. Identification of individuals at greatest AF risk could minimize the incidence of cardioembolic stroke.

**METHODS:** To determine whether genetic data can stratify risk for development of AF, we examined associations between AF genetic risk scores and incident AF in 5 prospective studies comprising 18 919 individuals of European ancestry. We examined associations between AF genetic risk scores and ischemic stroke in a separate study of 509

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Henry J. Lin, MD  
Matthew Kolek, MD  
J. Gustav Smith, MD, PhD  
Stella Trompet, PhD  
Michiel Rienstra, MD, PhD  
Natalia S. Rost, MD, MPH  
Pedro L. Teixeira, PhD  
Peter Almgren, MSc  
Christopher D. Anderson, MD, MMSc  
Lin Y. Chen, MD, MS  
Gunnar Engström, MD, PhD  
Ian Ford, MD, PhD  
Karen L. Furie, MD, MPH  
Xiaojing Guo, PhD  
Martin G. Larson, ScD

**Table 1.** Characteristics of Participants Included in Analyses of Incident Atrial Fibrillation

	MDCS	MESA	PREVEND	PROSPER*	BioVU
Total, n	8226	2451	1624	5212	1388
Incident AF, n	190	76	34	503	229
Age, y	59±7	63±10	58±8	75±3	60±11
Women, n (%)	4275 (52)	1321 (52)	770 (47)	2716 (52)	678 (49)
Height, cm	169±9	169±10	172±9	165±9	171±11
Weight, kg	75±14	79±16	80±14	73±13	86±22
Systolic blood pressure, mm Hg	145±20	124±20	135±21	155±22	131±20
Diastolic blood pressure, mm Hg	87±10	75±10	77±10	84±11	75±30
History of smoking, n (%)	2513 (31)	1401 (55)	671 (41)	1388 (27)	619 (45)
Antihypertensive medication, n (%)	1799 (22)	840 (33)	362 (22)	3854 (74)	1339 (96)
History of diabetes mellitus, n (%)	542 (7)	151 (6)	98 (6)	540 (10)	359 (26)
History of heart failure, n (%)	39 (0.5)	NA	4 (0.2)	NA	161 (12)
History of myocardial infarction, n (%)	487 (9)	NA	71 (4)	697 (13)	284 (20)

Data are presented as mean±SD when appropriate. AF indicates atrial fibrillation; BioVU, Vanderbilt University Deidentified DNA Biobank; MDCS, Malmö Diet and Cancer Study; MESA, Multi-Ethnic Study of Atherosclerosis; PREVEND, Prevention of Renal and Vascular Endstage Disease; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk.

\*Maximum follow-up in PROSPER was 4 years.

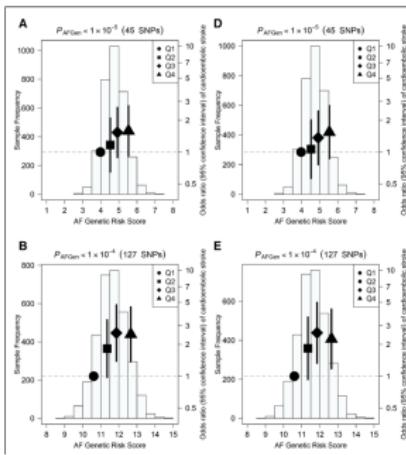
**Table 2. Characteristics of Participants of European Ancestry Included in Analyses of Ischemic Stroke From MGH-GASROS (Massachusetts General Hospital Genes Associated With Stroke Risk and Outcomes Study) and Referents**

	Cases	Referents
Total, n	509	3028
Age, y	66.9±14.4	42.3±7.8
Women, n (%)	214 (24.2)	732 (42.0)
AF	87 (17)	...

Data are presented as mean±SD when appropriate. AF indicates atrial fibrillation.

Stroke etiologic subtype: cardioembolic ( $n=202$ , 39%), large artery ( $n=114$ , 22%), small vessel/facuna ( $n=62$ , 12%), other ( $n=124$ , 24%), and undetermined ( $n=7$ , 1%).

$P < 0.001$  for comparison of age and sex between cases and referents.



**Figure 2. Risk of cardioembolic stroke in MGH-GASROS (Massachusetts General Hospital Genes Associated With Stroke Risk and Outcomes Study) according to atrial fibrillation (AF) genetic risk.**

Odds ratios for cardioembolic stroke in relation to AF genetic risk scores among cardioembolic stroke cases and 3028 referents. Blue histograms show distributions of genetic risk scores among cases and referents. Black dots indicate odds ratios for stroke for each quartile of genetic risk scores (bars indicate 95% confidence intervals). For A through C, genetic risk scores were based on 45 (A), 127 (B), and 701 (C) single nucleotide polymorphisms (SNPs) among 202 cardioembolic stroke cases (including 70 with known AF) and referents. For D through F, genetic risk scores were based on 45

AF genetic risk was strongly associated with cardioembolic stroke, suggesting that elevated AF genetic risk might serve as a surrogate for thromboembolism from AF.

## Atrial Fibrillation Genetic Risk and Ischemic Stroke Mechanisms

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Christopher D. Anderson, MD, MMSc; Emelia J. Benjamin, MD, ScM; Rainer Malik, PhD;  
Lu-Chen Weng, PhD; Martin Dichgans, MD; Cathie L. Sudlow, MD, PhD;  
Peter M. Rothwell, MD, PhD; Jonathan Rosand, MD, MSc; Patrick T. Ellinor, MD, PhD;  
Hugh S. Markus, DM; Matthew Traylor, PhD;  
on behalf of the WTCCC2, International Stroke Genetics Consortium, and AFGen Consortia

**Background and Purpose**—Atrial fibrillation (AF) is a leading cause of cardioembolic stroke, but the relationship between AF and noncardioembolic stroke subtypes are unclear. Because AF may be unrecognized, and because AF has a substantial genetic basis, we assessed for predisposition to AF across ischemic stroke subtypes.

**Methods**—We examined associations between AF genetic risk and Trial of Org 10172 in Acute Stroke Treatment stroke subtypes in 2374 ambulatory individuals with ischemic stroke and 5175 without from the Wellcome Trust Case-Control Consortium 2 using logistic regression. We calculated AF genetic risk scores using single-nucleotide polymorphisms associated with AF in a previous independent analysis across a range of preselected significance thresholds.

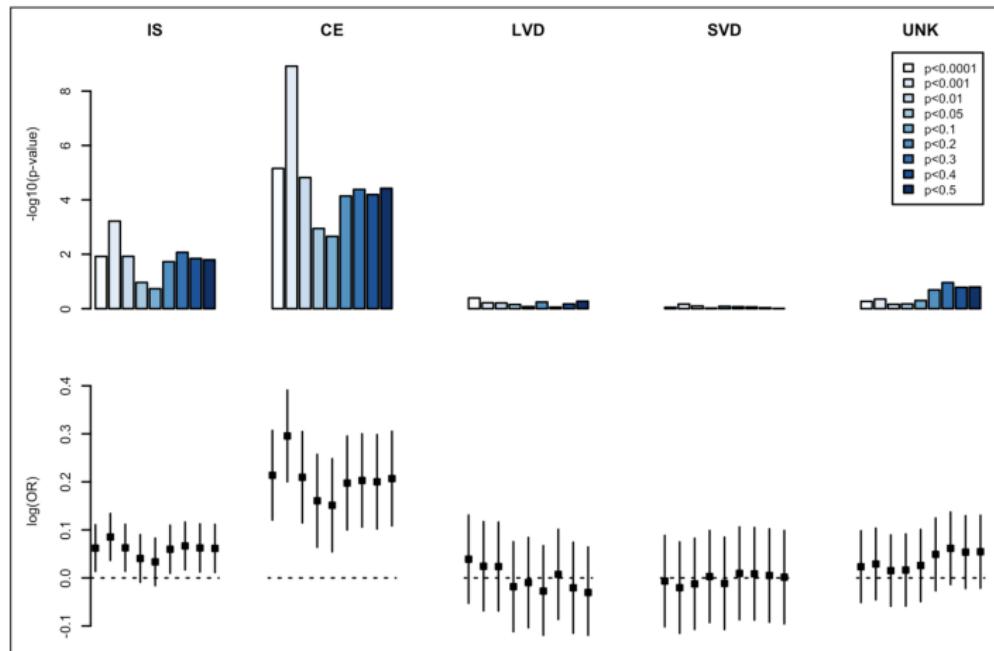
**Results**—There were 460 (19.4%) individuals with cardioembolic stroke, 498 (21.0%) with large vessel, 474 (20.0%) with small vessel, and 814 (32.3%) individuals with strokes of undetermined cause. Most AF genetic risk scores were associated with stroke, with the strongest association ( $P=6\times 10^{-4}$ ) attributed to scores of 944 single-nucleotide polymorphisms (each associated with AF at  $P<1\times 10^{-3}$  in a previous analysis). Associations between AF genetic risk and stroke were enriched in the cardioembolic stroke subset (strongest  $P=1.2\times 10^{-9}$ , 944 single-nucleotide polymorphism score). In contrast, AF genetic risk was not significantly associated with noncardioembolic stroke subtypes.

**Conclusions**—Comprehensive AF genetic risk scores were specific for cardioembolic stroke. Incomplete workups and subtype misclassification may have limited the power to detect associations with strokes of undetermined pathogenesis. Future studies are warranted to determine whether AF genetic risk is a useful biomarker to enhance clinical discrimination of stroke pathogeneses. (*Stroke*. 2017;48:1451-1456. DOI: 10.1161/STROKEAHA.116.016198.)

**Table 1.** Characteristics of Wellcome Trust Case-Control Consortium 2 Participants Included in the Analysis

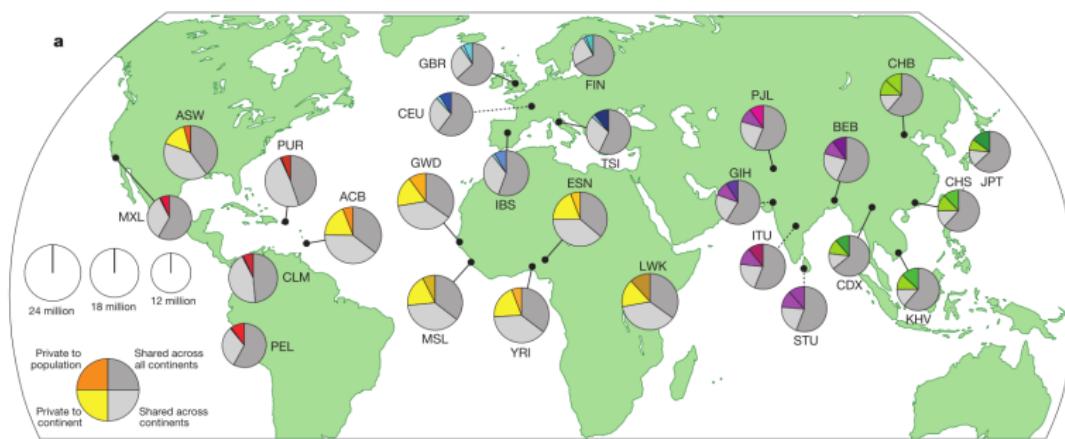
	n (%)	Age, y	Men, %	History of AF, n (%)	History of IHD, n (%)	MRI, n (%)	Echocardiogram, n (%)	Extracranial Imaging, n (%)
All ischemic stroke	2374	72.2±12.5	53.8	479 (20.1)	552 (23.3)	881 (37.1)	847 (35.7)	2176 (91.7)
Cardioembolic	460 (19.4)	75.4±12.5	62.1	362 (78.7)	141 (30.7)	113 (24.6)	259 (56.3)	393 (85.4)
Large vessel disease	498 (20.1)	68.2±10.8	66.2	2 (0.4)	136 (27.3)	196 (39.4)	133 (26.7)	487 (98.2)
Small vessel disease	474 (20.0%)	69.6±11.7	52.3	10 (2.1)	76 (16.0)	285 (60.1)	139 (29.1)	455 (96.0)
Unknown	814 (34.3)	70.8±13.8	45.7	26 (3.2)	153 (18.8)	248 (30.5)	248 (30.5)	726 (89.2)
Referents	5175	...	49.5	...	...	...	...	...

Data presented as mean±SD or n (%) unless otherwise specified. A further 128 (5.4%) individuals had stroke of tandem pathogenesis and were not included in any subgroup analyses. All patients underwent computed tomographic imaging and an ECG. Extracranial cerebral arterial imaging includes carotid and vertebral artery ultrasound, or computed tomographic angiography, or MRI. AF indicates atrial fibrillation; IHD, ischemic heart disease; and MRI, magnetic resonance imaging.



**Figure.** Association between atrial fibrillation genetic risk and ischemic stroke subtypes. **Top,** The strength of association between genetic risk scores comprised atrial fibrillation genetic markers and ischemic stroke subtypes are displayed. Separate scores were calculated corresponding to differences in the strength of association between each variant and atrial fibrillation in a prior independent analysis.<sup>32</sup> **Bottom,** The magnitude of association per 1-U change in each genetic risk score is displayed. CE indicates cardioembolic stroke; IS, all ischemic stroke; LVD, large vessel disease stroke; OR, odds ratio; SVD, small vessel disease stroke; and UNK, stroke of unknown pathogenesis.

# A global reference for human genetic variation



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RESEARCH ARTICLE

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# Genetic Variation at 16q24.2 Is Associated With Small Vessel Stroke

Matthew Taylor,<sup>1</sup> Rainer Malik,<sup>2</sup> Mike A. Nalls,<sup>3</sup> Ioana Cotlarciuc,<sup>4</sup>  
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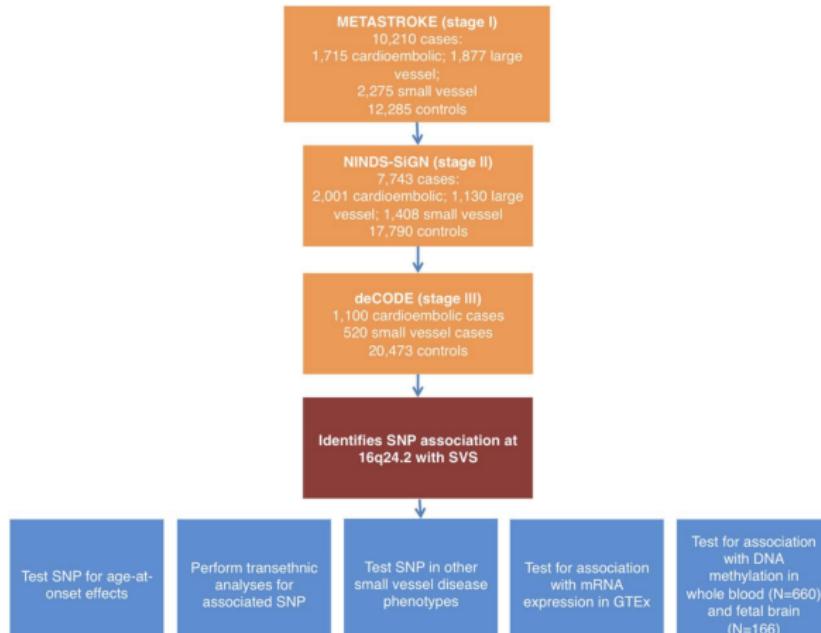


FIGURE 1: Flow chart of analyses performed. GTEx = Genotype-Tissue Expression; mRNA = messenger RNA; SNP = single-nucleotide polymorphism; SVS = small vessel stroke; [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

# Recent Advances in Stroke

## └ Genetic variability

### └ SVD Genetic Risk

TABLE 1. Ischemic Stroke Study Participants

Population	IS	CE	LAS	SVS	Controls	% Cases With MRI	Age of Cases (mean (SD))
Stage I populations							
ASGC	1,162	240	421	310	1,244	43.0	72.9 (13.2)
WTCCC2-Germany	1,174	330	346	106	797	83.0	66.7 (12.9)
WTCCC2-UK	2,374	474	498	460	5,175	37.2	72.2 (12.5)
Milano	366	64	73	25	407	86.7	57.4 (15.6)
DNA-lacunar/GENESIS	1,287	80	64	1,012	970	100.0	59.6 (12.0)
LSS	455	157	70	55	455	89.0	67.7 (14.5)
ISGS/SWISS	1,014	235	217	187	1,370	83.0	66.5 (13.6)
BRAINS	361	29	120	97	444	30.8	74.4 (14.2)
MGH-GASROS	294	106	68	23	376	60.0	66.7 (14.5)
VISP	1,723	—	—	—	1,047	47.0	68.0 (10.7)
Total (discovery)	10,210	1,715	1,877	2,275	12,285		
Stage II populations							
NINDS Stroke Genetics Network	7,743	2,001	1,130	1,408	17,970	62.0	66.3 (14.8)
Stage III populations							
deCODE	—	1,100	—	520	20,473	NA	72.7 (11.6)
Total	17,953	4,816	3,007	4,203	50,728		

IS = all ischemic stroke; CE = cardioembolic stroke; LAS = large artery stroke; SVS = small vessel stroke; ASGC = Australian Stroke Genetics Collaborative; WTCCC2 = Wellcome Trust Case Control Consortium 2; LSS = Leuven Stroke Study; BRAINS = Bio-repository of DNA in stroke; MGH-GASROS = The MGH Genes Affecting Stroke Risk and Outcome Study; VISP = The Vitamin Intervention for Stroke Prevention Trial; NA = information not available.

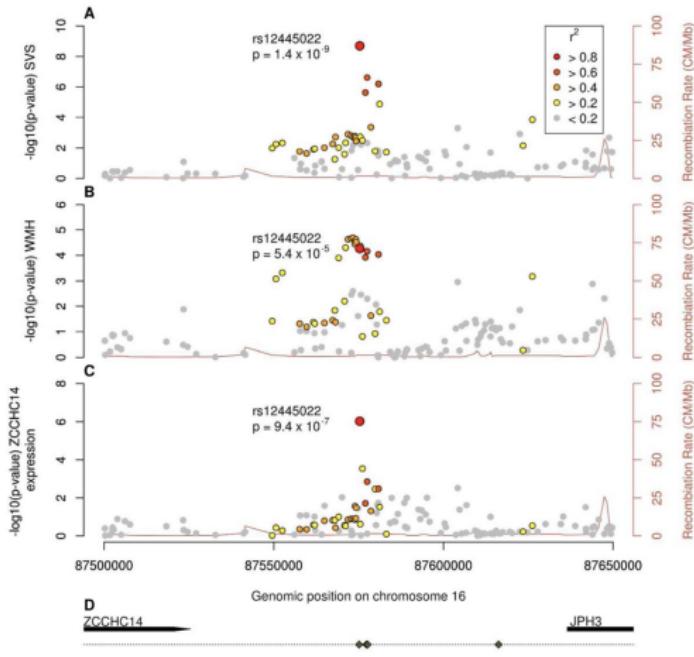


FIGURE 2: Associations at 16q24.2 with (A) small vessel stroke, (B) cerebral white matter hyperintensities, (C) mRNA expression of ZCCHC14, and (D) gene locations and associations of the locus with DNA methylation. mRNA = messenger RNA; SVS = small vessel stroke; WMH = white matter hyperintensities; ZCCHC14 = zinc finger CCHC domain-containing 14; JPH3 = junctophilin 3; meQTL = methylation quantitative trait locus. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

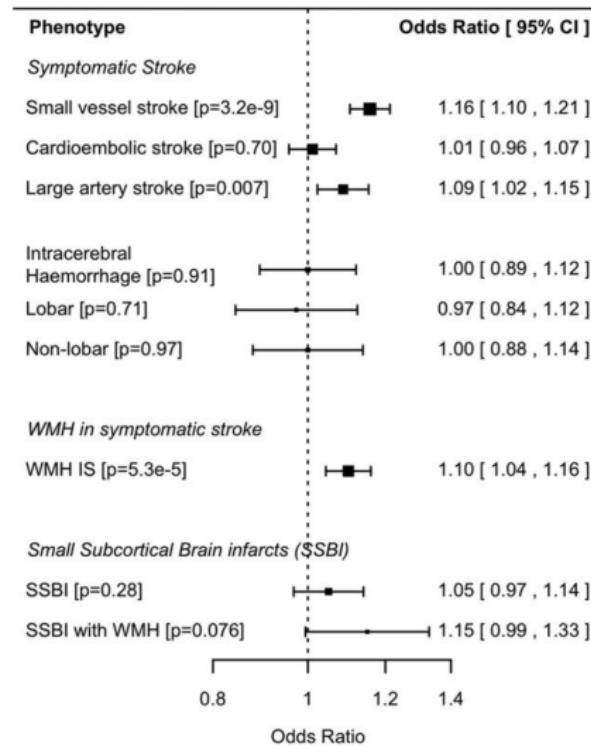


FIGURE 5: Associations with rs12445022 for stroke and

# GRECOs Project (Genotyping Recurrence Risk of Stroke)

## The Use of Genetics to Predict the Vascular Recurrence After Stroke

**Background and Purpose**—Vascular recurrence occurs in 11% of patients during the first year after ischemic stroke (IS) or transient ischemic attack. Clinical scores do not predict the whole vascular recurrence risk; therefore, we aimed to find genetic variants associated with recurrence that might improve the clinical predictive models in IS.

**Methods**—We analyzed 256 polymorphisms from 115 candidate genes in 3 patient cohorts comprising 4482 IS or transient ischemic attack patients. The discovery cohort was prospectively recruited and included 1494 patients, 6.2% of them developed a new IS during the first year of follow-up. Replication analysis was performed in 2988 patients using SNPlex or HumanOmni1-Quad technology. We generated a predictive model using Cox regression (GRECOs score [Genotyping Recurrence Risk of Stroke]) and generated risk groups using a classification tree method.

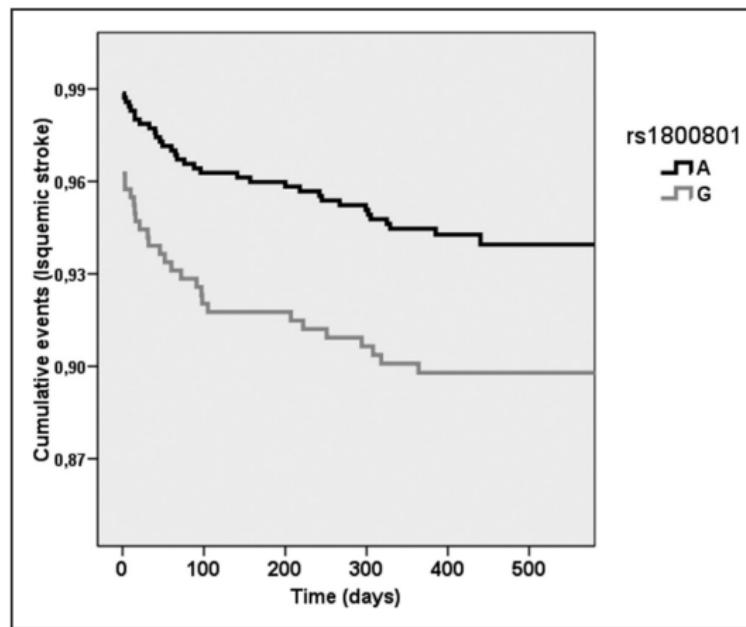
**Results**—The analyses revealed that rs1800801 in the *MGP* gene (hazard ratio, 1.33;  $P=9\times10^{-03}$ ), a gene related to artery calcification, was associated with new IS during the first year of follow-up. This polymorphism was replicated in a

Spanish cohort ( $n=1.305$ ); however, it was not significantly associated in a North American cohort ( $n=1.683$ ). The GRECOs score predicted new IS ( $P=3.2\times10^{-09}$ ) and could classify patients, from low risk of stroke recurrence (1.9%) to high risk (12.6%). Moreover, the addition of genetic risk factors to the GRECOs score improves the prediction compared with previous Stroke Prognosis Instrument-II score ( $P=0.03$ ).

**Conclusions**—The use of genetics could be useful to estimate vascular recurrence risk after IS. Genetic variability in the *MGP* gene was associated with vascular recurrence in the Spanish population. (*Stroke*. 2017;48:1147-1153. DOI: 10.1161/STROKEAHA.116.014322.)

- ▶ 256 polymorphisms from 115 candidate genes in 3 patient cohorts comprising 4482 IS or transient ischemic attack patients
- ▶ The discovery cohort was prospectively recruited and included 1494 patients, 6.2% of them developed a new IS during the first year of follow-up.
- ▶ Replication analysis was performed in 2988 patients

- ▶ rs1800801 in the MGP gene (hazard ratio, 1.33;  $P=9\times10^{-3}$ ), a gene related to artery calcification, was associated with new IS during the first year of follow-up.
- ▶ This polymorphism was replicated in a Spanish cohort ( $n=1,305$ );
- ▶ however, it was not significantly associated in a North American cohort ( $n=1,683$ ).



**Figure 1.** Kaplan-Meier curves of rs1800801 and time of recurrent ischemic stroke event. x axis: time (days) from first stroke or transient ischemic attack to recurrent ischemic stroke,  $P$  value=9×10<sup>-3</sup>. y axis: cumulative events (ischemic strokes). Data

## In-Depth Review

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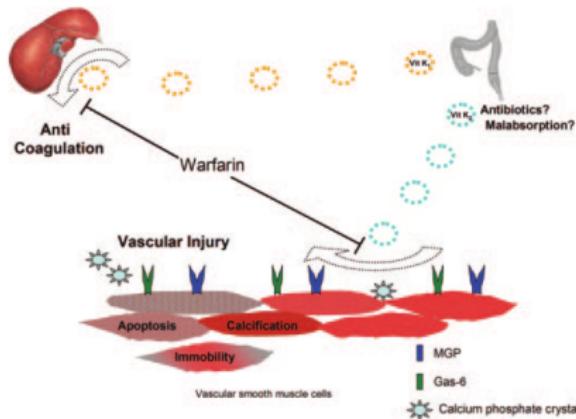
# Vitamin K-dependent Proteins, Warfarin, and Vascular Calcification

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Vitamin K-dependent proteins (VKDPs) require carboxylation to become biologically active. Although the coagulant factors are the most well-known VKDPs, there are many others with important physiologic roles. Matrix Gla Protein (MGP) and Growth Arrest Specific Gene 6 (Gas-6) are two particularly important VKDPs, and their roles in vascular biology are just beginning to be understood. Both function to protect the vasculature; MGP prevents vascular calcification and Gas-6 affects vascular smooth muscle cell apoptosis and movement. Unlike the coagulant factors, which undergo hepatic carboxylation, MGP and Gas-6 are carboxylated within the vasculature. This peripheral carboxylation process is distinct from hepatic carboxylation, yet both are inhibited by warfarin administration. Warfarin prevents the activation of MGP and Gas-6, and in animals, induces vascular calcification. The relationship of warfarin to vascular calcification in humans is not fully known, yet observational data suggest an association. Given the high risk of vascular calcification in those patients with chronic kidney disease, the importance of understanding warfarin's effect on VKDPs is paramount. Furthermore, recognizing the importance of VKDPs in vascular biology will stimulate new areas of research and offer potential therapeutic interventions.

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**Warfarin inhibits hepatic and peripheral carboxylation.** Warfarin prevents vitamin K from participating in the carboxylation process, inhibiting both hepatic and peripheral production of VKDPs. The well-known therapeutic effect is anticoagulation. However, warfarin also inhibits activation of MGP and Gas-6, interrupting the protective mechanisms of these proteins. Vascular smooth muscle cells are unable to respond to injury in a normal manner, and potentially, cell death and eventual calcification ensue.

## Viewpoints

### A Strategy for Genomic Research on Common Cardiovascular Diseases Aiming at the Realization of Precision Medicine

#### Personal Insights and Perspectives

Hiroyuki Morita, Issei Komuro

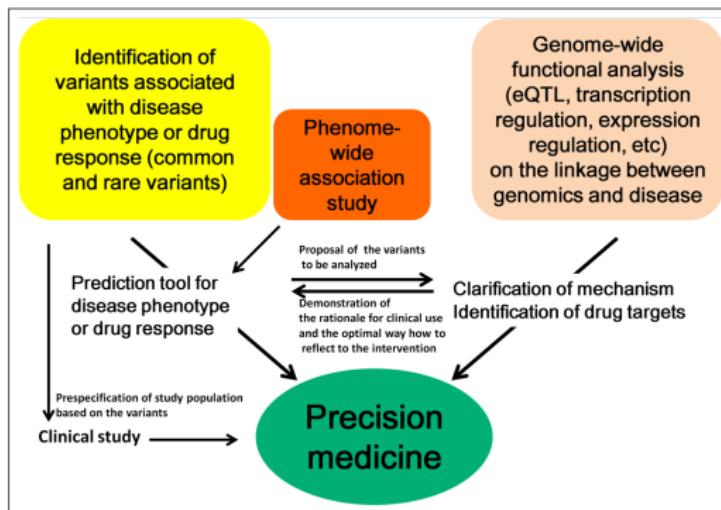


Figure. Schematic representation of genomic research on common diseases toward the realization of precision medicine.

## Take-Home Message: Hypertension

- ▶ Stroke and Hypertension are big health issues in rapidly aging societies like Korea.
- ▶ Therapeutic target of BP in patients with stroke should be individualized.
- ▶ The practical therapeutic goal of SBP in patients with hypertension might be **130 mm Hg**.

## Take-Home Message: Genetic variability

- ▶ Precision medicine will be our future
- ▶ Genetic variation might be useful in differentiating stroke mechanism and predicting vascular recurrence
- ▶ Specific genetic variation associated with disease might be different among races