

Cardiac and Polyvascular Investigations in Acute Stroke Patients



허지회

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Why do we evaluate stroke patients?

Determination of etiology



Outcome prediction
Prevention strategy

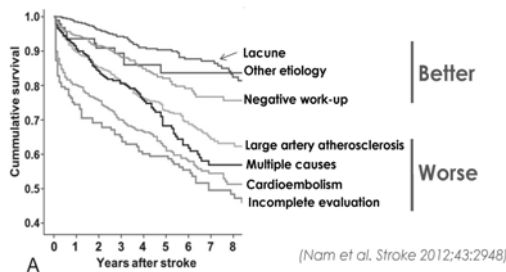
Stroke etiologic mechanisms

- Large artery atherosclerosis
- Cardioembolism
- Lacunar infarction (small vessel occlusion)
- Undetermined causes
 - Multiple causes
 - Negative work-up
 - Incomplete evaluation
- Other etiology

Different outcome according to different stroke mechanism

3278 patients followed for median 3.4 yrs

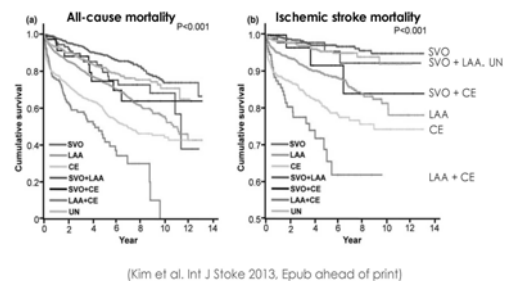
Mortality | 30-day 3.8%
1 year cumulative 10.5%
3 year cumulative 18.4%



Different long term mortality in patients with multiple mechanisms

3533 patients mean follow-up for 3.9 years

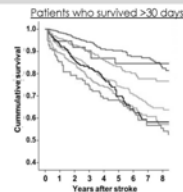
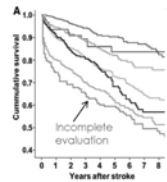
- Coexisting LAA and CE showed the worst outcome
- Outcome of coexisting lacune and LAA or CE group was not significantly different from that of lacune



Poor outcome in patients with incomplete evaluation

Very high long-term mortality when stroke evaluation is incomplete during admission

- Too sick to undergo studies during hospitalization
- Increased risk of recurrent stroke (cardioembolic, large artery atherosclerosis-related)
- Poor compliance to treatment



(Nam et al. Stroke 2012;43:2948)

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Editorials

What Is Certain When the Stroke Etiology Is Uncertain?

Gustavo Saposnik, MD, MSc, FAHA, FRCPC

“We should make the effort in completing the necessary investigations to determine the stroke mechanism, hopefully before patients are discharged.”

‘Essential’ or ‘necessary’ evaluations in stroke patients

- Brain imaging (CT/MRI)
- Cerebral angiography (CTA, MRA, or DSA)
- ECG

What else?

Cardiac evaluation

**Continuous ECG monitoring
Echocardiography**

Cardioembolic sources of embolism

High-risk sources	N (%)	Medium-risk sources	N (%)
Atrial fibrillation (AF)	293 (64)	Patent foramen ovale	108 (28)
Mitral stenosis with AF	58 (13)	Spontaneous echo contrast	107 (28)
LA/appendage thrombus	24 (5)	Congestive heart failure	69 (17)
Mechan. prosthetic valve	23 (5)	Lone AF	31 (8)
Dilated cardiomyopathy	15 (3)	Hypokinetic LV segment	28 (7)
Akinetic LV segment	13 (3)	Mitral stenosis without AF	14 (4)
MI within 4 weeks	10 (2)	4 weeks < MI < 6 months	9 (2)
Sick sinus syndrome	10 (2)	Bioprosthetic heart valve	7 (1.5)
LV thrombus	7 (1)	Atrial septal aneurysm	6 (1.5)
Infective endocarditis	4 (1)	Atrial flutter	5 (1)
Atrial myxoma	3 (1)	Mitral valve prolapse	4 (1)
		Nonbacterial endocarditis	3 (0.8)
		Mitral annular calcification	1 (0.2)
Total	458(100)	Total	392 (100)

2482 patients from YSR

(Han et al. Cerebrovasc Dis. 2007;24:463)

Diagnosis of AF is important

- Anticoagulation is highly effective for prevention of stroke in patients with AF
- Better prevention is expected by introduction of new oral anticoagulants

The NEW ENGLAND
JOURNAL of MEDICINE

Direct thrombin inhibitor : Dabigatran (2009;361:1139)

Factor Xa inhibitors : Rivaroxanan (2011;365:883)

Apixaban (2011;365:981)

Edoxaban (2013;369:2093)

Paroxysmal AF

- A self-terminating recurrent form of AF
- 25-62% of AF
- Stroke risk in patients with PAF determined by surface ECG tracing is similar to that observed in chronic/persistent AF
- Paroxysmal AF may remain underdiagnosed in stroke and TIA on routine 12-lead ECG, which may result in underuse of OA
- Continuous ECG monitoring is helpful for diagnosis of PAF

Continuous ECG monitoring

Noninvasive

Continuous hospital telemetry
Holter monitor
Event-triggered ECG recorder
Mobile cardiovascular telemetry

Invasive

Implantable loop recorder
Pacemaker and defibrillator

New-onset AF in unselected stroke patients

Table 2. Detection of New-Onset Atrial Fibrillation in Unselected Populations of Stroke and Transient Ischemic Attack Patients

Study, Year	Study Population	Mean Age, y	Detection Methods	Eligible Patients After Excluding Established AF, n	Patients Diagnosed With New AF, n	Detection Rate of New AF, %
Shafiqi et al., 2004 ⁴¹	Stroke	67	Ambulatory ECG (24 h)	210	5	2.4
Yu et al., 2009 ⁴²	Stroke	75	Ambulatory ECG (24 h)	96	9	9.4
Douven et al., 2008 ⁴³	Stroke	NM	Inpatient serial ECG (72 h) + ambulatory ECG (72 h)	144	20	13.9
Koudstaal et al., 1986 ⁴⁴	TIA	61	Ambulatory ECG (24 h)	96	1	1.0
Shaw et al., 2004 ⁴⁵	Stroke/TIA	67	Ambulatory ECG (24 h)	404	9	2.2
Athadramy et al., 2010 ⁴⁶	Stroke/TIA	65	Ambulatory ECG (24 h)	413	11	2.7
Vivanco Hidalgo et al., 2009 ⁴⁸	Stroke/TIA	79	Inpatient continuous ECG (55 h)	465	16	3.4
Sposato et al., 2011 ⁴⁹	Stroke/TIA	67	Inpatient continuous ECG (5 d)	155	21	13.5
Rem et al., 1985 ⁵¹	Stroke/TIA	66	Inpatient continuous ECG (48 h) + ambulatory ECG (24 h)	171	6	3.5
Stahrenberg et al., 2010 ⁵²	Stroke/TIA	68	Ambulatory ECG (7 d)	220	28	12.7
Lazaro et al., 2011 ⁵³	Stroke/TIA	63	Inpatient continuous ECG (48 h) + ambulatory ECG (24 h)	133	8	6.0
Combined				2507	134	5.3

about **5%**

(Seet et al. Circulation 2011;124:477)

New-onset AF in selected stroke patients

Table 3. Detection of New-Onset Atrial Fibrillation in Selected Populations of Stroke and Transient Ischemic Attack Patients

Study, Year	Study Population	Mean Age, y	Method of Patient Selection	Detection Methods	Eligible Patients After Excluding Established AF, n	Patients Diagnosed With New AF, n	Detection Rate of New AF, %
Schuchert et al., 1999 ⁴⁴	Stroke	61	Suspected embolic etiology	Ambulatory ECG (72 h)	82	4	4.9
Dion et al., 2010 ⁴⁵	Stroke	49	Cryptogenic stroke + negative 24-h ECG	Implantable loop recorder (14.5 mo)	24	0	0
Jabaudon et al., 2004 ⁴³	Stroke/TIA	67	Negative 24-h ECG	Ambulatory ECG (7 d)	88	5	5.7
Rizzo et al., 2010 ⁴⁶	Stroke/TIA	72	Age >60 y	Inpatient continuous ECG (48 h) + ambulatory ECG (24 h)	136	29	21.3
Gaillard et al., 2010 ⁴⁸	Stroke/TIA	64	Negative 24-h ECG	Ambulatory ECG (transtelephonic) (30 d)	98	9	9.2
Tayal et al., 2008 ⁴⁸	Stroke/TIA	66	Negative 24-h ECG	Ambulatory ECG (MCOIT) (21 d)	56	3	5.3*
Eljwich et al., 2009 ⁴⁷	Stroke/TIA	68	Cryptogenic only	Automatic event recorder (30 d)	20	4	20
Bartelemy et al., 2003 ⁴⁸	Stroke/TIA	64	Cryptogenic stroke + negative 24-h ECG	Automatic event recorder (4 d)	28	4	14.3
Combined					532	58	10.9

about **11%**

(Seet et al. Circulation 2011;124:477)

Subclinical tachyarrhythmia and risk of stroke in patients with pacemaker and defibrillator

ASSERT trial

- ≥ 65 yrs with hypertension, no history of AF
- Pacemaker for SA or AV node disease or implantable cardioverter defibrillator
- 2580 patients, Mean follow-up for 2.5 y
- Monitor for 3 m to detect subclinical tachyarrhythmia (atrial heart rate >190/min for more than 6 min)
- Subclinical tachyarrhythmias were detected in **10.1%** (261 patients)
- Ischemic stroke developed in 10/261 patients (1.54%/yr)
- Subclinical tachyarrhythmias were associated with increased risk of stroke (HR 2.50, 95% CI 1.28-4.85)

(Healey et al. NEJM 2012;366:120)

Holter versus continuous ECG monitoring in stroke unit

■ 496 patients with ischemic stroke or TIA and no AF on admission

- Holter monitoring
- Continuous ECG monitoring, when AF is suspected from the monitor trace by a SU staff, then, 12-lead ECG
- Continuous ECG monitoring data were analyzed automatically

■ Detection of PAF: 41 patients (8.3%)

aCEM > CEM > Holter

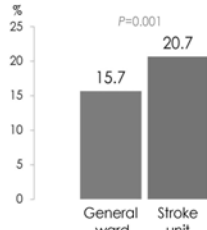
(92.7%) (65.9%) (34.1%)

(Stroke 2012;42:2689)

Detection of PAF by continuous ECG monitoring in SU

GW 2002 SU 2003-2008

Atrial fibrillation diagnosis



increased identification of AF by 5% after continuous EEG monitoring with monitor trace by a staff in SU

(Choi et al. Yonsei Med J 2013; 54:301)

2013

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

“Cardiac monitoring should be performed for at least the first 24 hours in stroke or TIA patients (Class I, Level of evidence B) “

New-onset AF in cryptogenic stroke patients

event-triggered recording

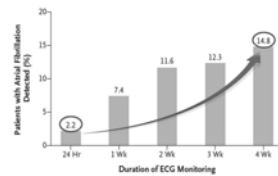
Cryptogenic stroke or TIA within the previous 6 m ≥ 55 y
572 patients
30-day event-triggered recording vs 24-h Holter monitoring

AF with duration ≥ 30 sec within 90 d

16.1% vs 3.1%

95% CI 12.9 (8.0-17.6)

Detection of AF increased with increasing duration of ECG monitoring



(Gladstone et al. NEJM 2014;370:2467)

New-onset AF in cryptogenic stroke patients

Insertable cardiac monitor

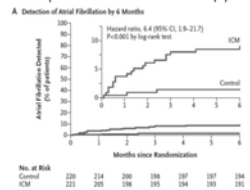
Cryptogenic stroke or TIA within the previous 90 d ≥ 40 y
(after 24-h Holter & TEE)
441 patients

Insertable cardiac monitor for 6 m vs Control (conventional follow-up)

AF with duration ≥ 30 sec within 6 m

**6 M : 8.9% vs 1.4%,
HR 6.4 95% CI (1.9-21.7)**

**12 M: 12.4% vs 2.0%,
HR 7.3 95% CI (2.6-20.8)**



(Sanna et al. NEJM 2014;370:2478)

In Cryptogenic stroke

- 24 h Holter monitoring may not be good enough.
- Prolonged ECG monitoring should be considered

Cardiac evaluation

Echocardiography

Transthoracic echocardiography (TTE)
Transesophageal echocardiography (TEE)

TTE versus TEE

TTE

Non-invasive
Cheaper
Easier to perform

TEE

Invasive
More expensive
Takes longer to perform

Diagnostic yield?

Detection of PCSE by TTE and TEE

TABLE 1. Potential Cardiac Sources of Embolism in 231 TIA or Stroke Patients Assessed by TTE or TEE

Potential Cardiac Source	TTE	TEE
Major risk factor		
LA cavity thrombus	0	1 (1%)
LA appendage thrombus	1 (1%)	38 (16%)
LV thrombus	2 (1%)	1
Aortic thrombus	0	1
Dilated cardiomyopathy (LVEF <35%)	5 (2%)	1
Mitral valve stenosis	0	1
Minor risk factors		
Mitral valve prolapse	4 (2%)	1
Mitral annular calcification	4 (2%)	1
Calcified aortic stenosis	8 (3%)	1
Patient foramen ovale	3 (1%)	12 (5%)
Spontaneous echo contrast	2 (1%)	5 (2%)
Atrial septal aneurysm	5 (2%)	8 (3%)
LV aneurysm	1 (1%)	1
Aortic aneurysm	0	1
False lumen	0	1
Aortic plaques	1 (1%)	69 (30%)
Other	2 (1%)	1

- PCSE was detected in **55%**
- In **39%**, PCSE was only identified on TEE
- Almost all PCSE detected on TTE were also detected on TEE

"This findings support the routine use of TEE in all patients with TIA or stroke of unknown origin"

(de Bruijn et al. Stroke 2006;37:2531)

TEE in patients with normal sinus rhythm & no cardiac disease history

● Detection of hidden causes

17.6% Cardioembolic sources

27.4% Aortic plaques

● Potential changes in treatment strategies

1.8% Medication changes

1.6% PFO closure (recurrent cryptogenic stroke and PFO)

Table 2 Findings of transesophageal echocardiography in 1833 patients with normal sinus rhythm and no cardiac disease history

Findings	No (%)
High-risk potential cardiac sources of embolism	45 (2.5)
Left atrial thrombus	10 (0.5)
Dilated cardiomyopathy	10 (0.5)
Akinetic left ventricular segment	9 (0.5)
Left ventricular thrombus	8 (0.4)
Infective endocarditis	4 (0.2)
Atrial myxoma	4 (0.2)
Medium-risk potential cardiac sources of embolism	310 (16.9)
Patient foramen ovale	223 (12.2)
Left atrial swelling	33 (1.8)
Hypokinetic left ventricular segment	23 (1.3)
Mitral stenosis without atrial fibrillation	1 (0.1)
Atrial septal aneurysm	9 (0.5)
Mitral valve prolapse	3 (0.2)
Mitral annular calcification	4 (0.2)
Non-bacterial endocarditis	2 (0.1)
Lambl excrescences	6 (0.3)
Atrial septal defect	6 (0.3)

(Cho et al. J Neurol Neurosurg Psychiatry 2010;81:412)

Do we need TEE in patients with AF

266 patients with AF and who had undergone TEE

68% at least one concomitant PCSE

Patients with concomitant PCSE

- Initially severe stroke median NIHSS 6 vs 3
- Larger infarct size

Table 1 Concomitant potential cardiac sources of embolism in all 266 patients.

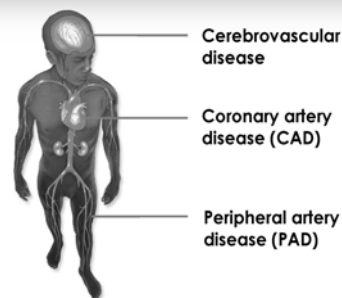
Concomitant potential cardiac sources of embolism	Number (%)
High-risk potential cardiac sources of embolism	80 (30.1)
Left atrial thrombus	42 (15.8)
Mitral stenosis with atrial fibrillation	31 (11.7)
Mechanical prosthetic valve	13 (4.9)
Left ventricular thrombus	4 (1.5)
Sick sinus syndrome	2 (0.8)
Dilated cardiomyopathy	2 (0.8)
Myocardial infarction within 4 weeks	1 (0.4)
Infective endocarditis	1 (0.4)
Medium-risk potential cardiac sources of embolism	154 (57.9)
Spontaneous echo contrast	122 (45.9)
Congestive heart failure	47 (16.2)
Patient foramen ovale	17 (6.4)
Bioprosthetic valve	4 (1.5)
Hypokinetic left ventricular segment	5 (1.9)
Mitral valve prolapsed	3 (1.1)
Mitral annular calcification	3 (1.1)
Atrial flutter	3 (1.1)
Nonbacterial endocarditis	1 (0.4)

(Kim et al. J Neurol Sci 2010;298:23)

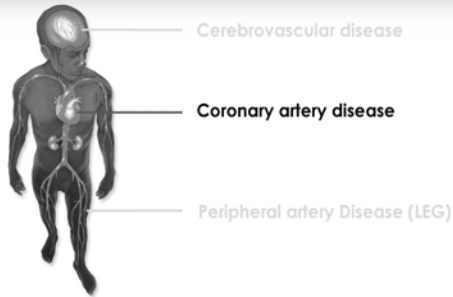
Echocardiography in stroke

- TEE is superior to TTE in detecting cardioembolic sources
- Etiology can be determined in many cryptogenic stroke patients
- Therapeutic yield is not high based on current guidelines
 - In the future ?
 - NOAC

Anything we are missing?



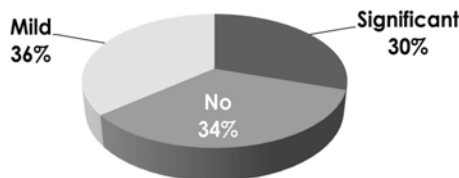
Anything we are missing?



CHD is a major cause of death after ischemic stroke

Meta-analysis	65,996 patients. Mean follow-up for 3.5 yrs Annual fatal MI 1.1% (Total MI 2.2%) (Touzé et al. Stroke 2005;36:2748)
Northern Manhattan Study	655 patients. Median follow-up for 4 yrs 5-yr fatal cardiac events 6.4% (Fatal stroke 3.7%) (Dhamoon et al. Neurology 2006;66:641)
SPARCL	4731 patients. Mean follow-up for 4.9 yrs Major coronary events 5.1% (cardiac death, nonfatal MI, resuscitated cardiac arrest): (Amarenco et al. Stroke 2010;41:426)
YSR	3278 patients. Mean follow-up for 3.4 yrs Fatal Ischemic heart disease 3.3% (Fatal stroke 12.3%) (Nam et al. Stroke 2012;43:2948)
About 1% of stroke or TIA patients died of CHD every year	

Frequency of asymptomatic CAD in stroke patients



Diagnostic tool	Patient No.	any CAD	≥50% stenosis	
Autopsy	188	68.2%	29.3%	Gongora-Rivera et al. Stroke 2007;38:1203
Coronary CTA	71		25.4%	Ser et al. Eur Neurol 2008;59:292
Coronary CTA	274	48%	18%	Calat et al. Circulation 2010;121:1623
Coronary angiography	315	61.9%	25.7%	Amarenco et al. Stroke 2011;42:22
Coronary CTA	1304	70.4%	33.1%	Yoo et al. Cerebrovasc Dis. 2012;33:286

Different relationship of cerebral atherosclerosis with CAD between cerebral arteries

	Cerebral artery atherosclerosis		OR, 95% CI	P-value
	No CAD (n=679)	CAD (n=377)		
Extracranial carotid	54 (8.0)	71 (18.8)	2.685 (1.838 - 3.925)	<.001
Intracranial carotid	28 (4.1)	33 (8.8)	2.230 (1.326 - 3.753)	0.002
Extracranial vertebral	108 (15.9)	80 (21.2)	1.624 (1.033 - 1.994)	0.031
Intracranial vertebral	43 (6.3)	55 (14.6)	2.524 (1.458 - 3.948)	<.001
Basilar	24 (3.5)	28 (7.4)	2.190 (1.252 - 3.855)	0.005
Middle cerebral	149 (21.9)	83 (22.0)	1.024 (0.741 - 1.361)	0.978
Anterior cerebral	34 (5.0)	22 (5.8)	1.176 (0.677 - 2.041)	0.565
Posterior cerebral	77 (11.3)	37 (9.8)	0.851 (0.542 - 1.287)	0.444

Reasons of different relationship of coronary atherosclerosis with different cerebral arteries

Lack of vasa vasorum in intracranial arteries
Similarity between coronary and extracranial arteries

Vasa vasorum is associated with atherosclerosis

Initiation of plaque formation

Responsible for transporting inflammatory cells into the adventitia, which progresses inward

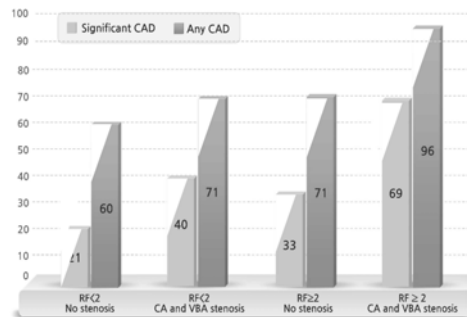
Progression and instability of plaques

Intraplaque hemorrhage is caused by rupture of fragile vasa vasorum



Who are at risk of CAD?

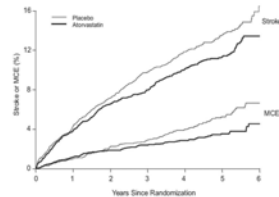
More than 2 risk factors
Carotid and VBA stenosis



(Yoo et al. Cerebrovasc Dis. 2012;33:286)

Detection of preclinical CAD can change outcome?

CHD risk can be substantially reduced by atorvastatin in patients with stroke or TIA



(Amarenco et al. Stroke 2010;41:426)

Figure 1. Stroke and major coronary event estimated failure curves. MCE, major coronary event (cardiac death, nonfatal myocardial infarction [MI], or resuscitated cardiac arrest).

One of every 16 patients received major interventional treatment

(Yoo et al. Cerebrovasc Dis 2012;33:286)

Heart CT versus TEE for detecting cardiac sources of embolism

Most PCSE detected on TEE can be also detected by Heart CT

137 Patients who underwent both Heart CT and TEE

Heart CT for detecting cardiac sources of embolism

Sensitivity 89%
Specificity 100%

(Hur et al. Stroke 2009;40:2073)

Table 2. Potential Cardiac Sources of Embolism in 137 Stroke Patients Assessed by CT and TEE

Findings	CT	TEE
High-risk sources		
Thrombus*		
LAA	11	11
LA	1	1
LV	0	0
Cardiac tumor	0	0
Valvular vegetation	1	2
Infective endocarditis	0	0
Aortic atheroma (AA or arch)	31	33
Medium risk sources		
Circulatory stasis/SEC†	15	15
PFO/ASD	17 (14/3)	22 (19/3)
ASA	8	11
Mitral annular calcification	5	5
No abnormality	57	46

AA indicates ascending aorta.

*Includes thrombus combined with circulatory stasis.

†Includes circulatory stasis without thrombus.

‡Includes 4 PFO combined with ASA.

Heart CT versus TEE

Can Heart CT replace TEE?

Anything we are missing?



Cerebrovascular disease

Coronary artery disease

Peripheral artery disease (LEG)

Frequency of PAD



31%

(204 patients with infarction or TIA, Busch et al. Stroke 2009;40:3700)

19.8%

(653 patients with ischemic stroke, Eur J Neurol 2013 online)

27%

(1131 patients with ischemic stroke, Manzano et al. Atherosclerosis 2012;223:219)

14.8%

(176 patients with infarction or TIA, Tsigoulis et al. Atherosclerosis 2012;220:407)

33%

(755 patients with ischemic stroke, Agnelli et al. J Thromb Hemostasis 2006;4:2599)



10.1%

(798 patients with infarction excluding malignancy, SOD [Kim et al. Atherosclerosis 2012;224:113])

7.4%

(1147 patients with infarction, Lee et al. Eur J Neurol 2012;19:892)

High mortality in patients with PAD in legs

1147 patients
at 1 Y
16.3% vs. 4.7%
HR 2.328

(Lee et al. Eur J Neurol 2012;19:892)

653 patients,
median 34 M follow-up
18.2% vs. 5.9%
HR 2.55

(Eur J Neurol 2013; online)

More frequent stroke recurrence?
Initially severe stroke?

Is stroke recurrence rate higher in patients with PAD in legs?

15% vs 10%, 1 yr follow-up

(1131 patients with ischemic stroke,
Manzano et al. Atherosclerosis
2012;223:219)

19.2% vs 3.3%, 1 month follow-up

(176 patients with infarction or TIA,
Tsigoulis et al. Atherosclerosis
2012;220:407)

6.8 % vs 4.4% (p=0.3)

(204 patients with infarction or TIA,
Busch et al. Stroke 2009;40:3700)

10.9 % vs 9.4% (p=0.6), 2.3 yrs follow-up

(653 patients with ischemic stroke,
Eur J Neurol 2013 online)

OR 1.5 (0.85-2.26)

(755 patients with ischemic stroke,
Agnelli et al. J Thromb Hemostat
2006;4:2599)

yes

No

PAD in legs and Functional outcome and initial stroke severity

Functional
outcome

775 patients

Poor functional outcome (mRS>2) at 3 months
HR = 2.523, 95% CI 1.330-4.785

(Kim et al. Atherosclerosis 2012;224:113)

Initial stroke
severity

1147 patients

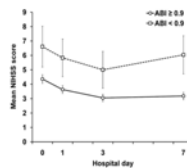
Initially severe stroke

NIHSS 6.6 vs 4.4

More severe leg weakness

(1.22 ± 1.459 vs. 0.63 ± 1.032, <0.001)

(Lee et al. Eur J Neurol 2012;19:892)



PAD in arms

834 patients

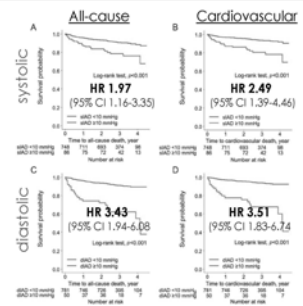
Measured interarm difference of
BP (IAD) using ABI
Mean follow-up for 2.96 ± 0.95 yrs

10% systolic IAD ≥ 10 mmHg

6.0% diastolic IAD ≥ 10 mmHg

**Large IAD was associated with
increased risk of all-cause and
cardiovascular mortality**

(Kim et al. Neurology 2013;80:1457)



- Blood pressures should be measured bilaterally to diagnosis and treat hypertension properly
- PAD either in arms or legs is associated with increased risk of mortality

Anything we are missing?



Cerebrovascular disease

Peripheral artery disease (ARM)

Coronary artery disease

Peripheral artery disease (LEG)

'Essential' or 'necessary' evaluations in stroke patients

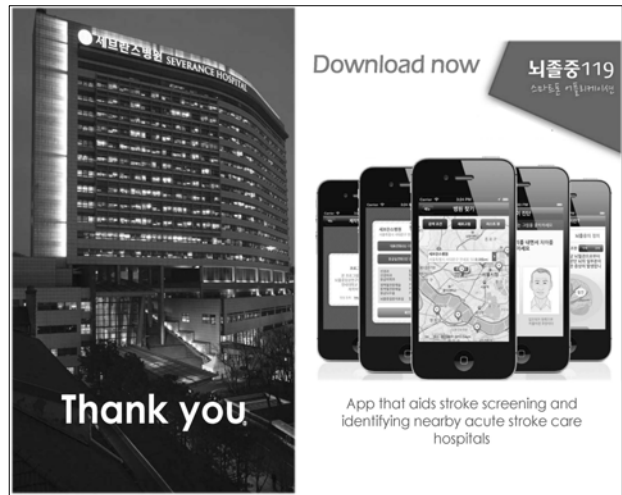
- Brain imaging (CT/MRI)
- Cerebral angiography (CTA, MRA, or DSA)
- ECG

What else?

- Continuous ECG monitoring
- Echocardiography
- Heart CT
- Ankle-Brachial index

Take home messages

- We should make every effort to determine stroke mechanism
- Continuous ECG monitoring should be performed in all patients without previous AF
- Paroxysmal AF is common in cryptogenic stroke
- TEE is superior to TTE for detecting cardiac sources, but therapeutic yield of TEE is low
- Coronary artery disease should be evaluated, particularly in patients with multiple risk factors and/or carotid and VB artery stenosis.
- Heart CT may be alternatively used instead of TEE
- PAD is associated with initially severe stroke, less recovery, poor functional outcome and high long term mortality
- ABI is useful for screening PAD
- Interarm difference of blood pressures (PAD in arms) should be concerned. Blood pressures should be measured bilaterally



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Thank you

App that aids stroke screening and identifying nearby acute stroke care hospitals