What is the appropriate evaluation of cryptogenic stroke, and when is a hypercoagulability work-up needed?

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Within the past 12 months, I have had a financial affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	
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What is the underlying mechanism?

"Stroke is an observation not a diagnosis"

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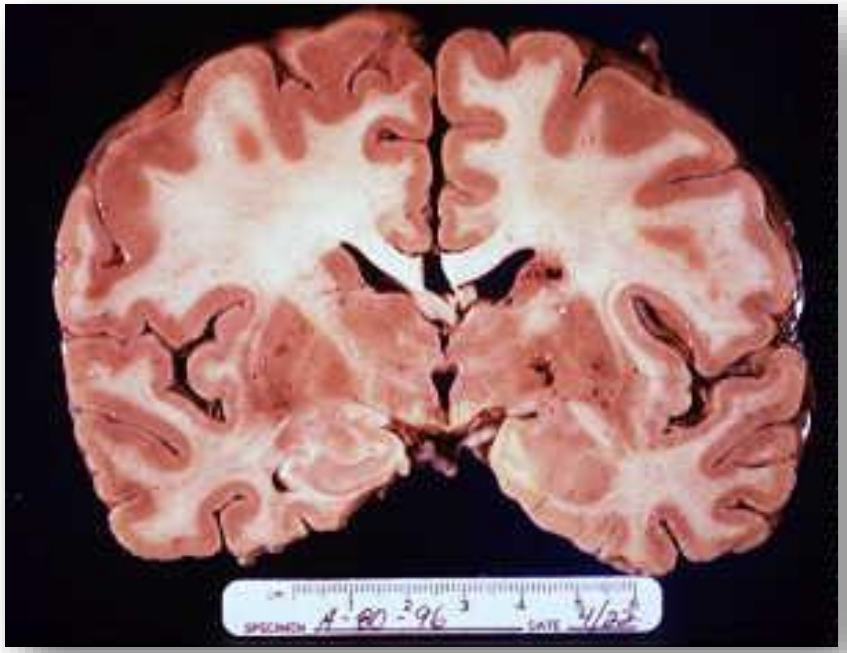
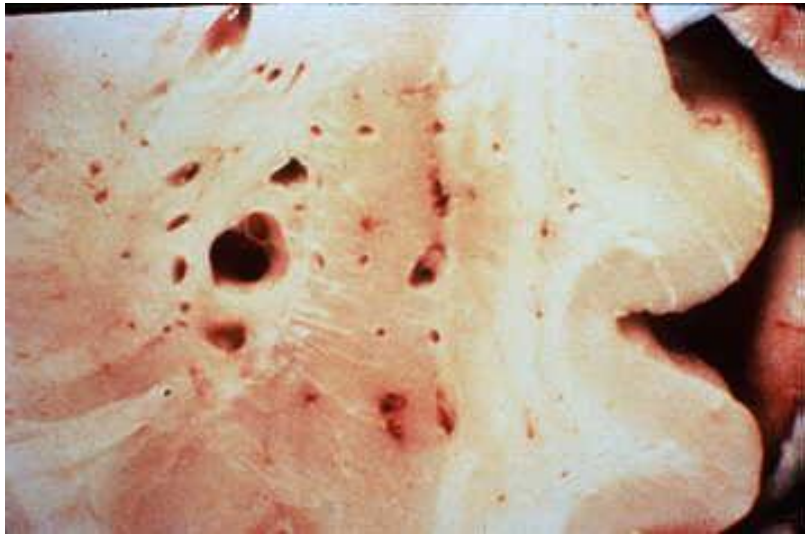
Common mechanisms of cerebral ischemia

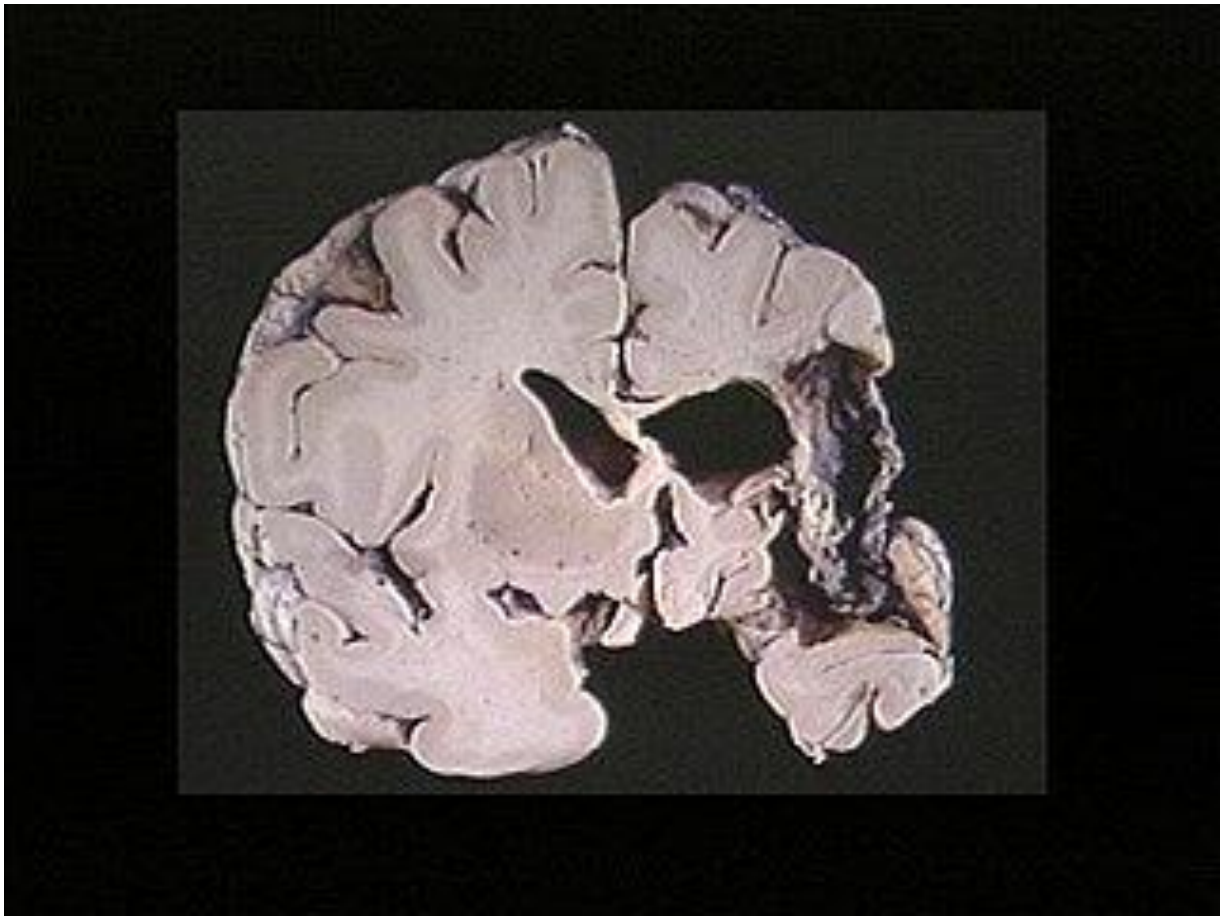
- "Small vessel disease," lacune (lipohyalinosis)
- Embolism
  - Artery-to-artery (carotid, aorta, other)
  - Cardiac source
  - Paradoxical
- Decreased perfusion through a fixed stenosis

Lacunar stroke (0.2-15mm^3)





Large, old stroke



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Other causes of cerebral ischemia

- **Vasculitis**
- **Collagen vascular diseases:** isolated angiitis of the CNS, temporal (giant cell) arteritis, polyarteritis nodosa, Wegener's granulomatosis, Takayasu's arteritis, syphilis
- **Meningitis**: tuberculosis, fungi, syphilis, bacteria, herpes zoster
- **Arterial dissection:** carotid, vertebral, basal intracranial arteries
- **Hematologic disorders:** polycythemia, thrombocytosis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, dysproteinemias, hemoglobinopathies (sickle cell disease)
- **Miscellaneous**: cocaine, amphetamines, moyamoya disease, fibromuscular dysplasia, CADASIL
- **Hypercoagulable states**: secondary to systemic disease, carcinoma (especially pancreatic), eclampsia, oral contraceptives, lupus, factor C or S deficiency, factor V mutation, etc.
- **Vasospasm**: following subarachnoid hemorrhage
- **Reversible cerebral vasoconstriction:** idiopathic, migraine, eclampsia, trauma
- **Venous**: Dehydration, pericranial infection, postpartum and postoperative states, systemic cancer

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Cryptogenic Stroke

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N Engl J Med 2016;374:2065-74.
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Table 1. Suggestive Findings on History and Physical Examination in Patients with Cryptogenic Stroke.*

Variable	Potential Clinical Implication
Historical feature	
Neck trauma or manipulation	Carotid or vertebral artery dissection
Migraine	Migrainous infarction or CADASIL
Intravenous drug use	Endocarditis, HIV infection, vasculitides, paradoxical emboli, or vasospasm
Dental procedure or systemic bacterial infection	Endocarditis, septic emboli, or coagulopathy
Airplane travel or Valsalva maneuver at stroke onset	Paradoxical embolism
Family history of early myocardial infarction or ischemic stroke	Genetic accelerated atherosclerosis
Pregnancy and peripartum	Cerebral venous thrombosis or eclampsia
Sickle-cell disease	Secondary moyamoya disease
Physical finding	
Asymmetric arm pressures	Coarctation of aorta, aortic dissection, Takayasu's disease, or premature atherosclerosis
Skin	
Needle tracks	Intravenous drug use or HIV infection
Livedo reticularis	Sneddon's syndrome, antiphospholipid antibody syndrome, or systemic lupus erythematosus
Xanthoma or xanthelasma	Hyperlipidemia
Adenopathy	HIV infection, sarcoid, or Tangier disease
Heart murmur	Endocarditis, ventral septal defect, or myxoma
Vessels	
Diminished pulses	Premature atherosclerosis, coarctation of aorta, aortic dissection, or Takayasu's disease
Bruit	Premature atherosclerosis, fibromuscular dysplasia, or arterial dissection
Venous thrombosis in the legs	Hypercoagulable state

* CADASIL denotes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and HIV human immunodeficiency virus.

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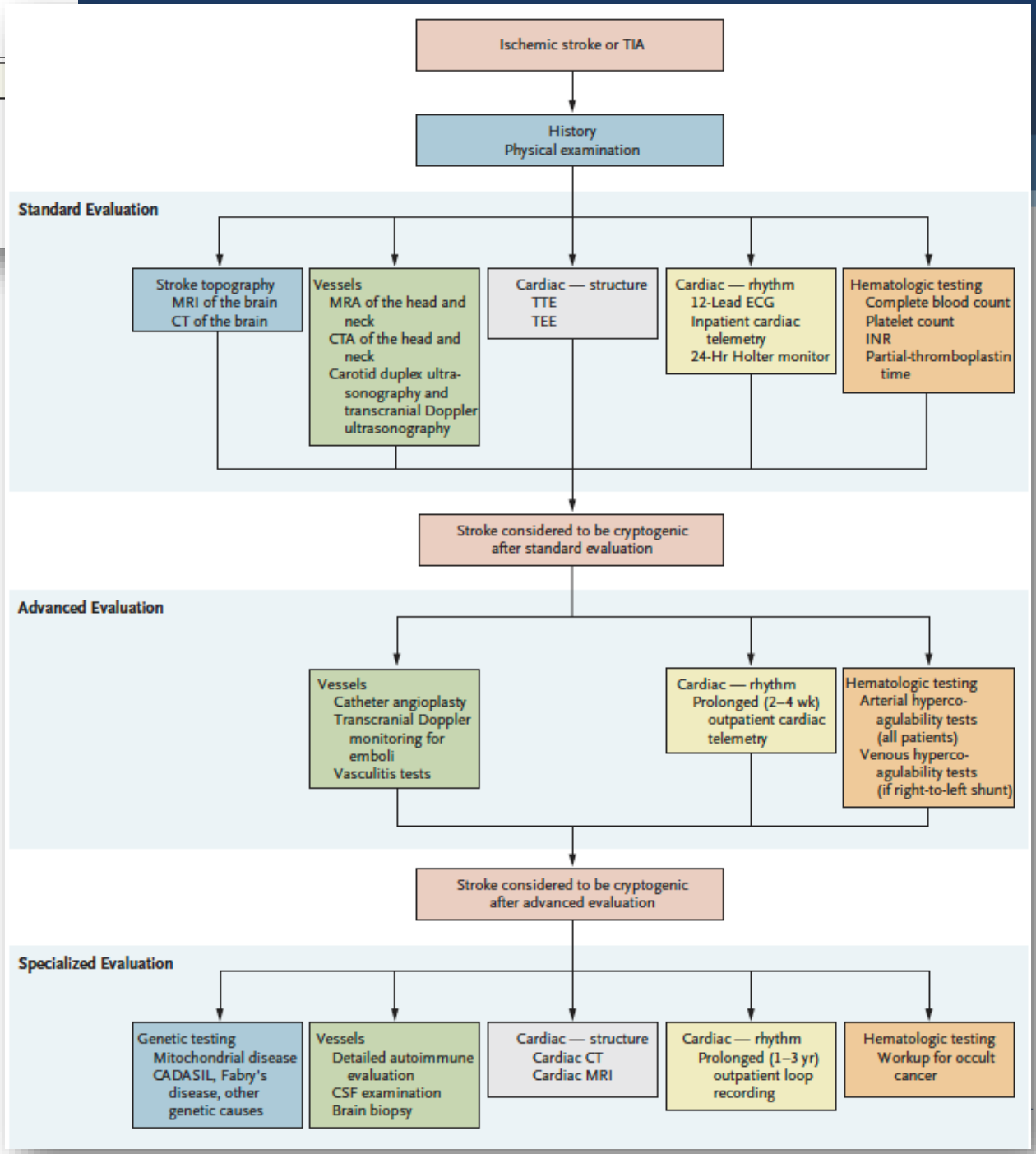

frontiers in Neurology

ORIGINAL RESEARCH
published: 21 August 2017
doi: 10.3389/fneur.2017.00421

Characteristics and Outcomes of Young Patients with First-Ever Ischemic Stroke Compared to Older Patients: The National Acute Stroke ISraeli Registry

Miri Lutski[1†], Inbar Zucker[1,2†], Tamy Shohat[1,2] and David Tanne[2,3]*

[1] The Israel Center for Disease Control, Ministry of Health, Ramat Gan, Israel, [2] Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel, [3] The Sagol Neuroscience Center, Sheba Medical Center, Tel-Hashomer, Israel

	Age groups (years)		*p* Value
	≤50 *N* = 336 *n* (%)	51–84 *N* = 3,243 *n* (%)	
Demographic data			
Gender			
Male	211 (62.8)	1,833 (56.5)	0.03
Female	125 (37.2)	1,410 (43.5)	
Population group			
Jews	232 (73.2)	2,605 (84.8)	<0.001
Arab	71 (22.4)	398 (13.0)	
Others	14 (4.4)	68 (2.2)	
Known risk factors and comorbidities			
Current smoking	159 (47.3)	702 (21.9)	<0.001
Hypertension	133 (39.7)	2,499 (77.3)	<0.001
Diabetes	76 (22.6)	1,410 (43.5)	<0.001
Dyslipidemia	161 (48.2)	2,007 (62.2)	<0.001
Obesity	73 (22.5)	644 (20.9)	0.5
Atrial fibrillation	9 (2.7)	548 (17.0)	<0.001
Congestive heart failure	12 (3.6)	391 (12.1)	<0.001
Chronic kidney disease	14 (4.2)	377 (11.7)	<0.001
Peripheral artery disease	7 (2.1)	191 (5.9)	0.004
Prior TIA	(3.6) 12	201 (6.3)	0.05
Known carotid stenosis >50%	2 (0.6)	79 (2.5)	0.03
Ischemic heart disease	33 (9.8)	891 (27.5)	<0.001
Family history of stroke	24 (7.4)	61 (2.0)	<0.001
APLS	6 (1.8)	12 (0.4)	<0.001
Known patent foramen ovale	14 (11.3)	18 (2.8)	<0.001
Prior disability (modified Ranking Scale ≥ 2)	12 (3.6)	612 (19.3)	<0.001
Score of modifiable vascular risk factors			
No	56 (17.4)	181 (5.9)	<0.001
1	90 (28.0)	628 (20.6)	
2	90 (28.0)	961 (31.6)	
3+	86 (26.7)	1,275 (41.9)	
Prior atherosclerosis			
No	283 (85.2)	2,053 (64.5)	<0.001
Yes	49 (14.8)	1,129 (35.5)	
Medications prior to event			
Statin	72 (21.8)	1,389 (44.0)	<0.001
ACE/ARB	61 (18.5)	1,405 (44.3)	<0.001
Antiplatelet	67 (20.1)	1,513 (47.8)	<0.001
Anticoagulants	15 (4.5)	276 (8.7)	0.009
Mode of arrival to emergency room			
Ambulance	102 (32.2)	1,454 (47.6)	<0.001
Private car	183 (57.7)	1,379 (45.2)	
Transfer from other hospital	17 (5.4)	43 (1.4)	
Other	15 (4.7)	177 (5.8)	
Time delay (h) from stroke onset to ER arrival and ER-CT[a] (mean ± SD)			
Stroke onset-ER time	5.55 ± 5.48	5.51 ± 5.54	0.72
ER-CT time	3.53 ± 4.48	3.39 ± 4.53	0.63
Revascularization			
Thrombolysis	17 (5.1)	159 (4.9)	0.89
Mechanical revascularization	8 (11.1)	24 (3.0)	<0.001

ACE/ARB, angiotensin-converting-enzyme inhibitor/angiotensin II receptor antagonists.
[a] Data missing for approximately 30% of cases. Patients with in-hospital events and

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TABLE 1 | Characteristics and health-related conditions of stroke patients, by age group.

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	≤50 N = 336 n (%)	51–84 N = 3,243 n (%)	
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Known carotid stenosis >50%	14 (11.3)		
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APLS		181 (6.9)	
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Score of modifiable vascular risk factors	90 (28.0)	1,275 (41.9)	
No	90 (28.0)		<0.001
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Other			
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- Arterial hypercoagulable testing
  - Lupus anticoagulant
  - Anticardiolipin Ab
  - Beta-2 glycoprotein
  - Homocysteine

If venous infarction or R-L shunt identified

- Arterial hypercoagulable testing
  - Lupus anticoagulant
  - Anticardiolipin Ab
  - Beta-2 glycoprotein
  - Homocysteine

- Venous hypercoagulable testing
  - Protein C, protein S, anti-thrombin III (RARE!)
  - Prothrombin gene mutation
  - Factor V Leiden (activated protein C resistance)
  - Factor VIII

If venous infarction or R-L shunt identified

- Arterial hypercoagulable testing
  - Lupus anticoagulant
  - Anticardiolipin Ab
  - Beta-2 glycoprotein
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If unexplained BILATERAL embolic infarcts…

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If venous infarction or R-L shunt identified

- Arterial hypercoagulable testing
  - Lupus anticoagulant
  - Anticardiolipin Ab
  - Beta-2 glycoprotein
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  - Factor VIII

If unexplained BILATERAL embolic infarcts…

…cancer?

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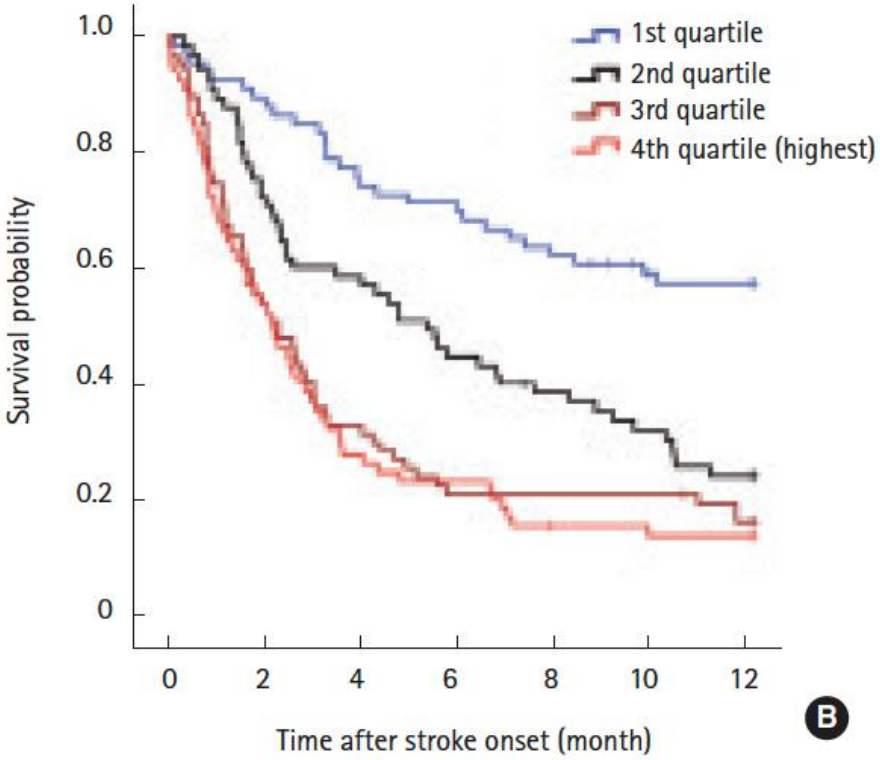
Stroke, cancer, d-dimer, and mortality

Baseline d-dimer and mortality



Hypercoagulability and Mortality of Patients with Stroke and Active Cancer: The OASIS-CANCER Study

Mi Ji Lee,[a] Jong-Won Chung,[a] Myung-Ju Ahn,[b] Seonwoo Kim,[c] Jin Myoung Seok,[a] Hye Min Jang,[a] Gyeong-Moon Kim,[a] Chin-Sang Chung,[a] Kwang Ho Lee,[a] Oh Young Bang[a]
Departments of [a]Neurology and [b]Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[c]Biostatistics Team, Samsung Biomedical Research Institute, Samsung Medical Center, Seoul, Korea

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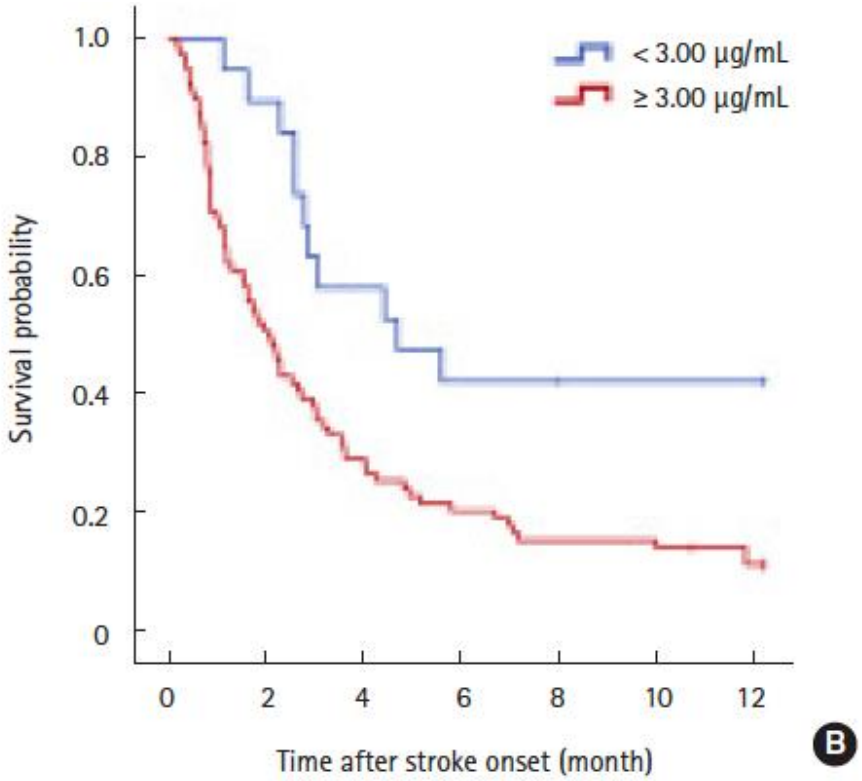
Treated d-dimer and mortality



CONCLUSIONS

- Rely on neurology to make a stroke diagnosis
- Tailor testing to individual patient characteristics
- Making a diagnosis ***is*** ”changing management”

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