

The Impact of Diagnostic Stroke Tests on Final Etiologic Subtype Assignment in SiGN

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***Presenting on behalf of Hakan Ay, Murat Arsava, and the
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Introduction

- Clinicians often stop diagnostic investigations in stroke after a positive test
 - Graded practice patterns can be efficient
 - Failure to search for alternative etiologies can result in ignorance of causally-related pathologies
 - However currently available evidence on yield of diagnostic tests is inadequate
- Approximately one half of stroke patients with a major stroke etiology harbor another etiology.
- The presence of an etiology $\neq$ stroke cause.
- Determination of both phenotypic and causative stroke subtype can help determine the diagnostic yield of stroke tests in identifying another major etiology (potentially changing the causative subtype) by stroke phenotype

Aims

- To determine yield of diagnostic tests to identify a major alternative etiology in patients with a particular stroke phenotype.
- To determine yield of diagnostic tests in altering *the cause* of stroke in each stroke phenotype.

Causative Classification of Stroke (CCS)

■ PHENOTYPE SUBTYPES

- Documentation of abnormal test findings
- No weightings
- FOUR TYPES: LI, LAA, CE, other uncommon causes

■ CAUSATIVE SUBTYPE

- Integrates stroke presentation and test results
- FIVE TYPES: Supra-aortic LAA, cardio-aortic embolism, small artery occlusion, other uncommon, undetermined

Methods: Stroke Genetics Network Study (SiGN)

- Etiologic stroke subtypes determined using CCS system
- Restricted patients to:
 - Those with major phenotypic subtype
 - Those with complete evaluation:
 - Thorough clinical evaluation (neuro hx & exam)
 - Brain imaging (CT or MRI)
 - Cardiac evaluation: EKG, TTE or TEE
 - Both intra- and extra-cranial vascular imaging (any type)

Methods: Patients

- Total of 16,445 patients
 - 23 centers (12 US, 11 European)
 - 7,295 US patients; 9,150 European patients
 - 331-1487 subjects recruited at each study site
- 8,937 patients had ≥ 1 missing investigations.
 - Of the remaining 7,508 patients, 5,206 had a major stroke phenotype → target study population.

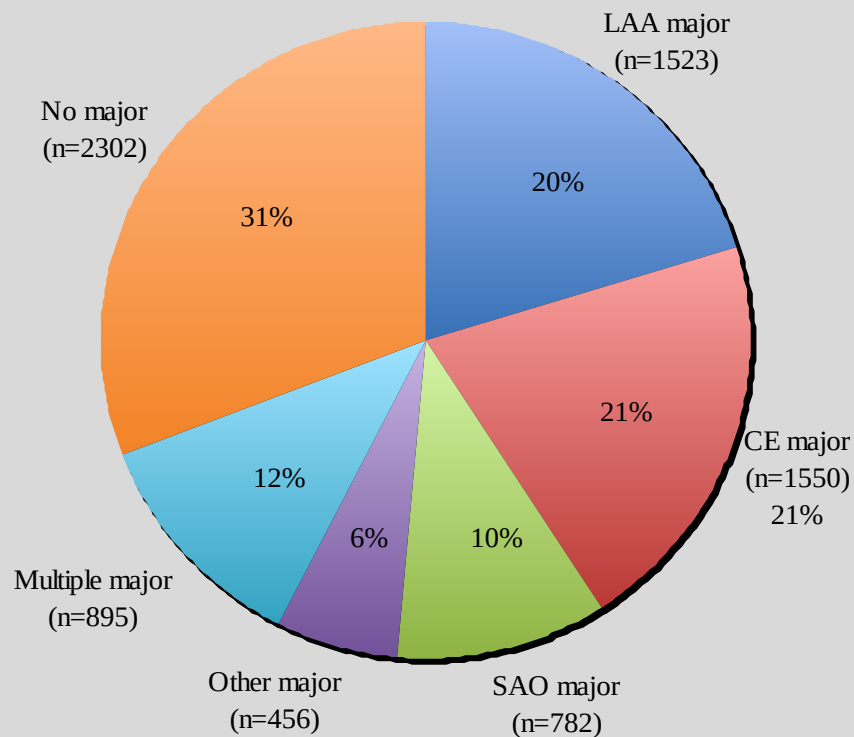
Methods: Completeness of investigations

- Varied by site: Range 5-97%
 - Mean 47%, median 40% (IQR 23-72%)
- Practice pattern driven
 - Some sites: no vascular imaging or echo if lacunar stroke – others with 100% studies regardless of phenotype
- Analysis was repeated for the subgroup of sites with complete investigation rate $\geq 80\%$ (5 sites)

Results: Baseline characteristics of the study population

	Overall Study Population N=16,445	Complete Investigation N=7,508	Incomplete Investigation N=8,937
Age, yrs (mean, +/- SD)*	67.41 (14.93)	64.7 (15.7)	69.7 (13.8)
Female (%)*	49.3	45.0	53.0
Race (%)			
Asian	1.1	1.6	0.7
Black*	9.5	11.9	7.5
White	77.7	78.5	77.1
Other	11.7	8.0	14.7
Ethnicity			
Hispanic*	3.8	6.5	1.6
HTN (%)	68.0	66.4	69.4
DM (%)	25.2	25.9	24.6
AF (%)	21.6	23.0	20.3
CAD (%)	23.2	21.6	24.5
Current smoking (%)	24.2	25.0	23.5
*p<0.001 for comparison between complete and incomplete investigations			

Results: Distribution of phenotypic CCS subtypes



The 2302 patients without major etiology were excluded from yield analysis.

RESULTS: Diagnostic yield of stroke work-up in identifying an alternative major etiology in major stroke phenotype in the target population (n=5206)

Major Phenotypes	Diagnostic Yield of Cardiac Evaluation (%)			Diagnostic Yield of Vascular Evaluation (%)			Combined Diagnostic Yield of Cardiac and Vascular Evaluation (%)
	History/ EKG	TTE/T EE	Overall	ICI	ECI	Overall	
LAA (n=2253)	21.0*	1.8*	22.8	-	-	-	-
CE (n=2202)	-	-	-	9.9*	17.1*	23.3	-
LI (n=1087)	9.2*	1.7*	10.9	10.4**	8.6**	17.3	25.6
Other (n=614)	9.9*	2.0*	11.9	5.5***	9.0***	13.0	21.3

*p<0.001
 **p=0.164
 ***p=0.028

(data for one-size-fits-all practice pattern (n=1720) didn't vary)

RESULTS: Diagnostic yield of stroke work-up in identifying an alternative causative etiology in each major stroke phenotype in the target population (n=5206)

Major Phenotypes	Probability of Alternative Causative Subtype by Cardiac Evaluation (%)			Probability of Alternative Causative Subtype by Vascular Evaluation (%)			Probability of Alternative Causative Subtype by Cardiac and Vascular Evaluation (%)
	History/ EKG	TTE/T EE	Overall	ICI	ECI	Overall	
LAA (n=2253)	13.1	1.2	14.3	-	-	-	-
CE (n=2202)	-	-	-	8.4*	15.6*	21.2	-
LI (n=1087)	1.1	0.1	1.2	4.5**	2.9**	6.3	7.7
Other (n=614)	4.7	1.3	6.0	2.6***	6.2***	9.3	15.5

*p<0.001

**p=0.070

***p=0.004

(data for one-size-fits-all practice pattern (n=1720) didn't vary)

Results: The proportion of patients assigned to a causative subtype that was different from the phenotypic subtype

Phenotypic Subtype	Causative Subtype					
		LAA	CE	SAO	Other	Undetermined
	LAA (n=2253)	-	1%	5.3%	0.9%	16.9%
	CE (n=2202)	7.6%	-	4.8%	1.4%	14.9%
	LI (n=1087)	0	0	-	0	7.7%
	Other (n=614)	3.7%	0.5%	3.1%	-	11.2%

Discussion

- Weaknesses: TCD, test results not adjudicated centrally (could have variable definitions)
- Strengths: real-world data, rigorous subtype determination

Discussion

- Yield of echocardiography is quite low
- Yield of intracranial imaging is relatively high in all phenotypic categories - Changes causative subtype
- The impact of tests – even when they are positive -- in changing the causative subtype is low in LI.
- Future:
 - generate cost-efficient diagnostic strategies, based on phenotype
 - aid decisions regarding minimum required tests in multi-center consortia

Discussion

- Could be used to generate cost-efficient diagnostic strategies
- Could be useful to aid decisions regarding minimum required tests in multi-center consortia