Stadtspital Zürich

Causes and prevention of stroke in the young adult

L'AVC du patient jeune et âgé: State of the Art
Lausanne, Jeudi, 30 septembre 2021

Marie-Luise Mono, Stadtspital Zürich

Stroke in the young adult

- Epidemiology
- Risk factors
- Etiology
- Diagnostic approach
- Management
- Outcome

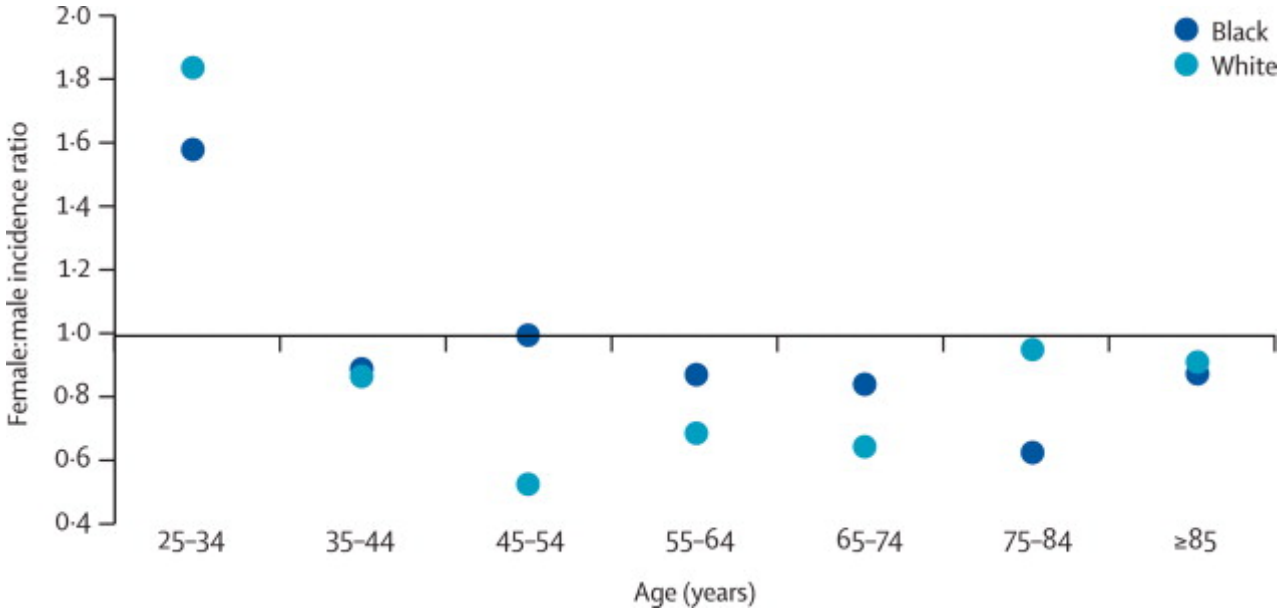
Ischemic stroke in young adults: What is different?

- Better chances to survive, better outcome than older individuals
- Superproportional burden due to longer life expectancy
- Wider range of risk factors (some exclusive to young adults)
- Broader differential diagnosis with potentially treatable causes
- Few large prospective studies

Jacobs BS et al. Stroke 2002; Rolfs A et al. Lancet. 2005; Knoflach et al. Neurology 2012; Rozenthul-Sorokin N et al. Stroke 1996

Epidemiology

- In white adults < 45y: annual incidence rates 3.4 -11.3/100.000
- In black adults < 45y: annual incidence rates 22.8/100.000



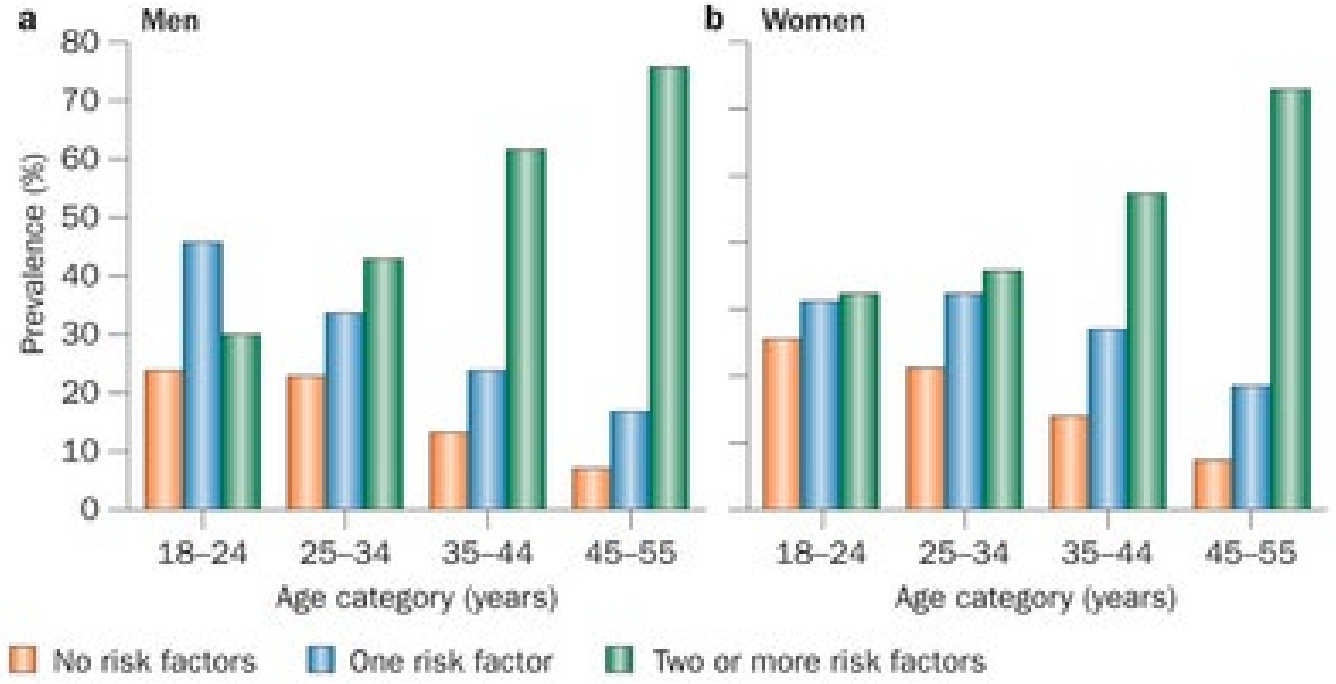
Female: male incidence ratios for stroke by age

Incidence of stroke at younger ages has been increasing and the prevalence among working adults doubled over the last decade

Nencini P et al Stroke 1988; Kittner SJ et al Stroke 1993; Kissela B et al Stroke 2004

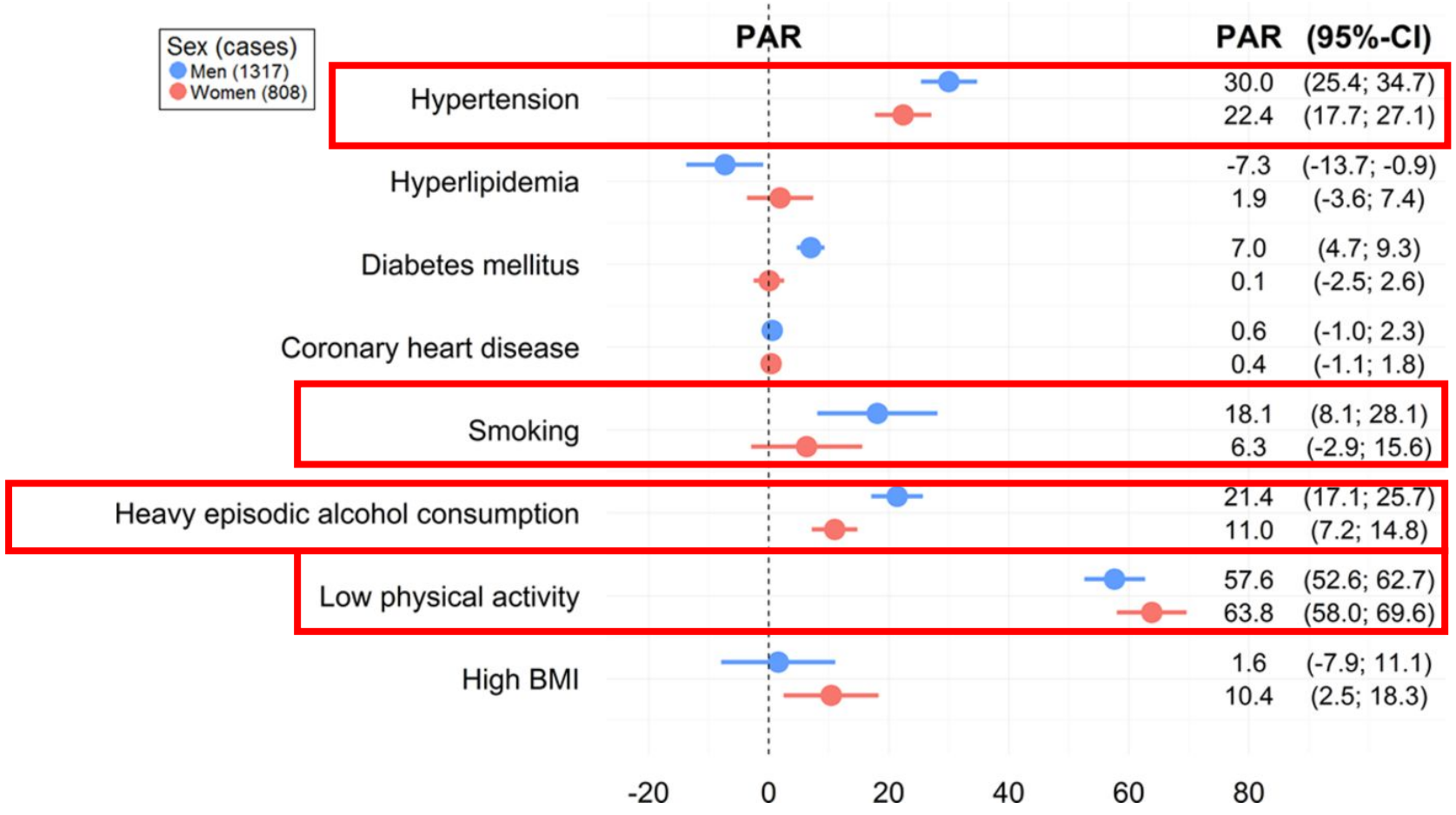
Age-specific proportions of patients with traditional vascular risk factors, stratified by sex

Pooled data from the 15 Cities study, FUTURE study, and SIFAP1 study



Maaijwee NA et al Nature Reviews Neurology 2014

Population attributable risk of vascular risk factors



Aigner A et al Stroke 2017

The Lausanne Experience – Data from the ASTRAL registry

64 out of **746** (8.6%) acute ichemic stroke patients < 55y had no established vascular risk factor

Variable	Study cohort (N=746)	No EVRF (N=64)	Any EVRF (N=682)	OR	95% CI
Age	46.65	37.18 (17.6)	47.2 (11.4)	0.92	0.9-0.94
Female	263 (35.2%)	35 (54.7%)	228 (33.4%)	2.4	1.43-4.03
Comorbidities					
Migraine	89 (12%)	14 (21.9%)	75 (11.0%)	2.26	1.19-4.28
PFO	263 (35.2%)	35 (72.9%)	178 (41.5%)	3.8	1.95-7.38
Hormone replacement or contraceptive	68 (9.2%)	14 (21.9%)	534 (8.0%)	3.23	1.68-6.22

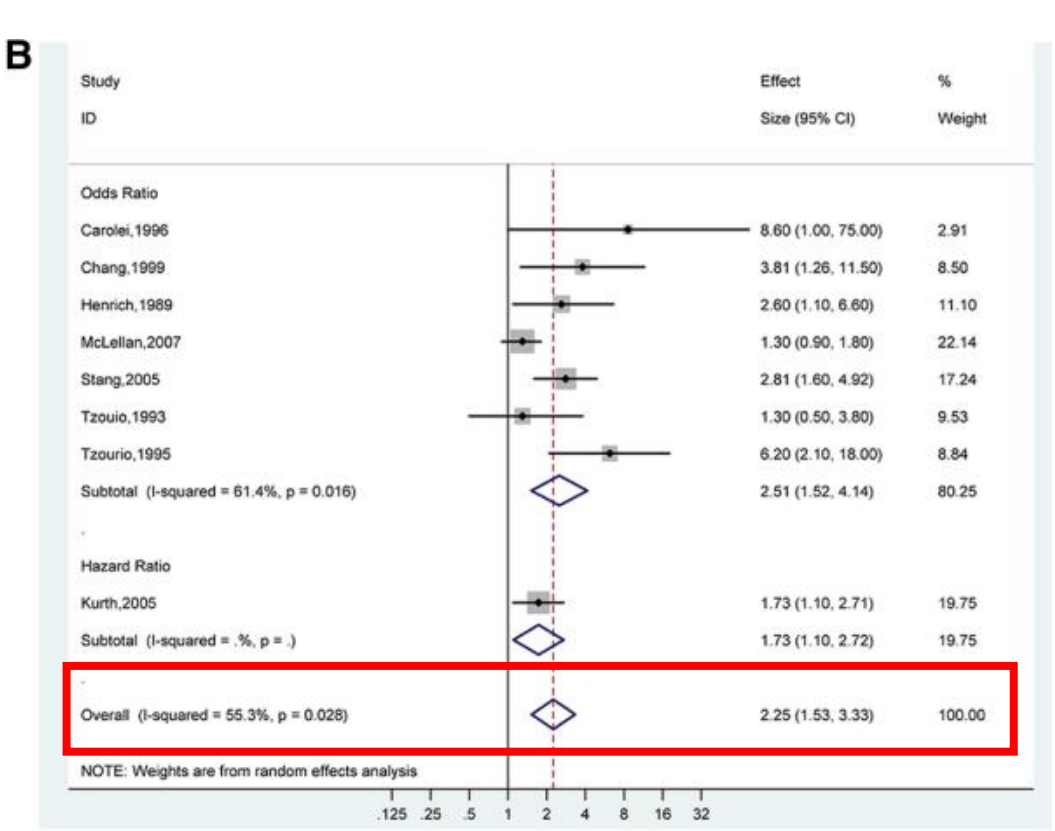
Nannoni S et al Eur J Neurol 2020

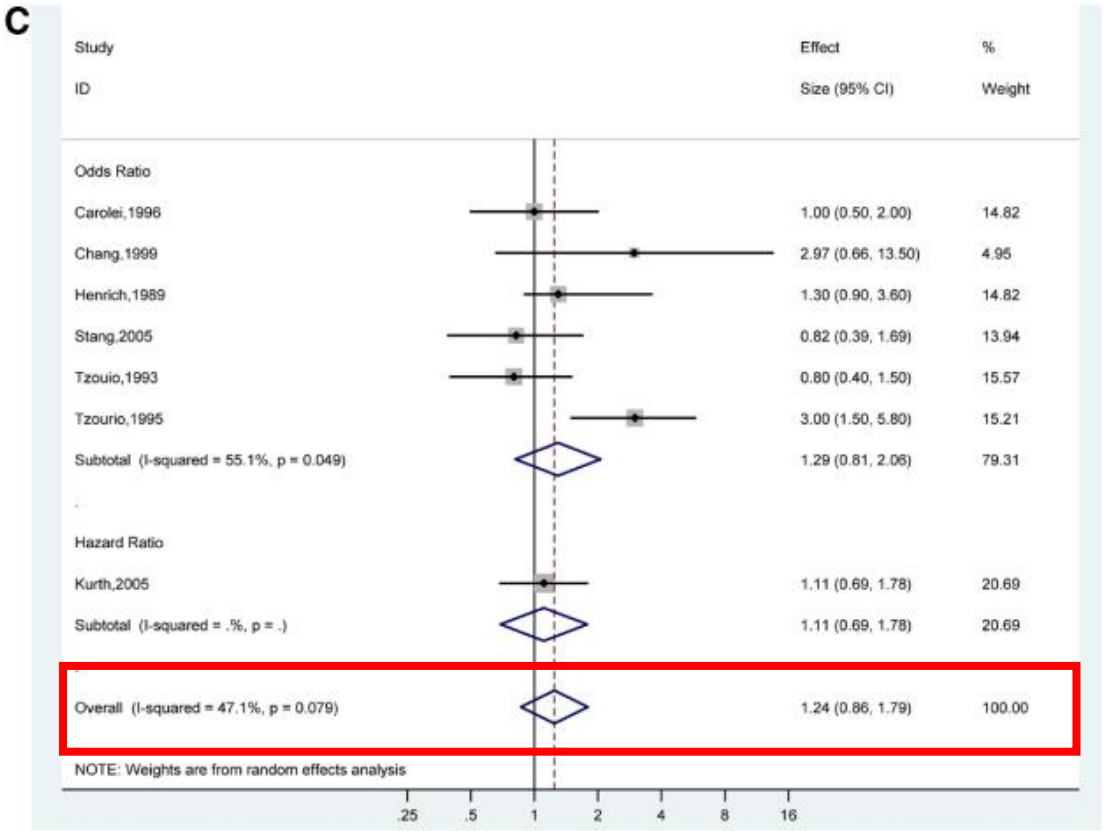
Migraine and stroke

Meta-analysis including 622`381 patients

Migraine with aura

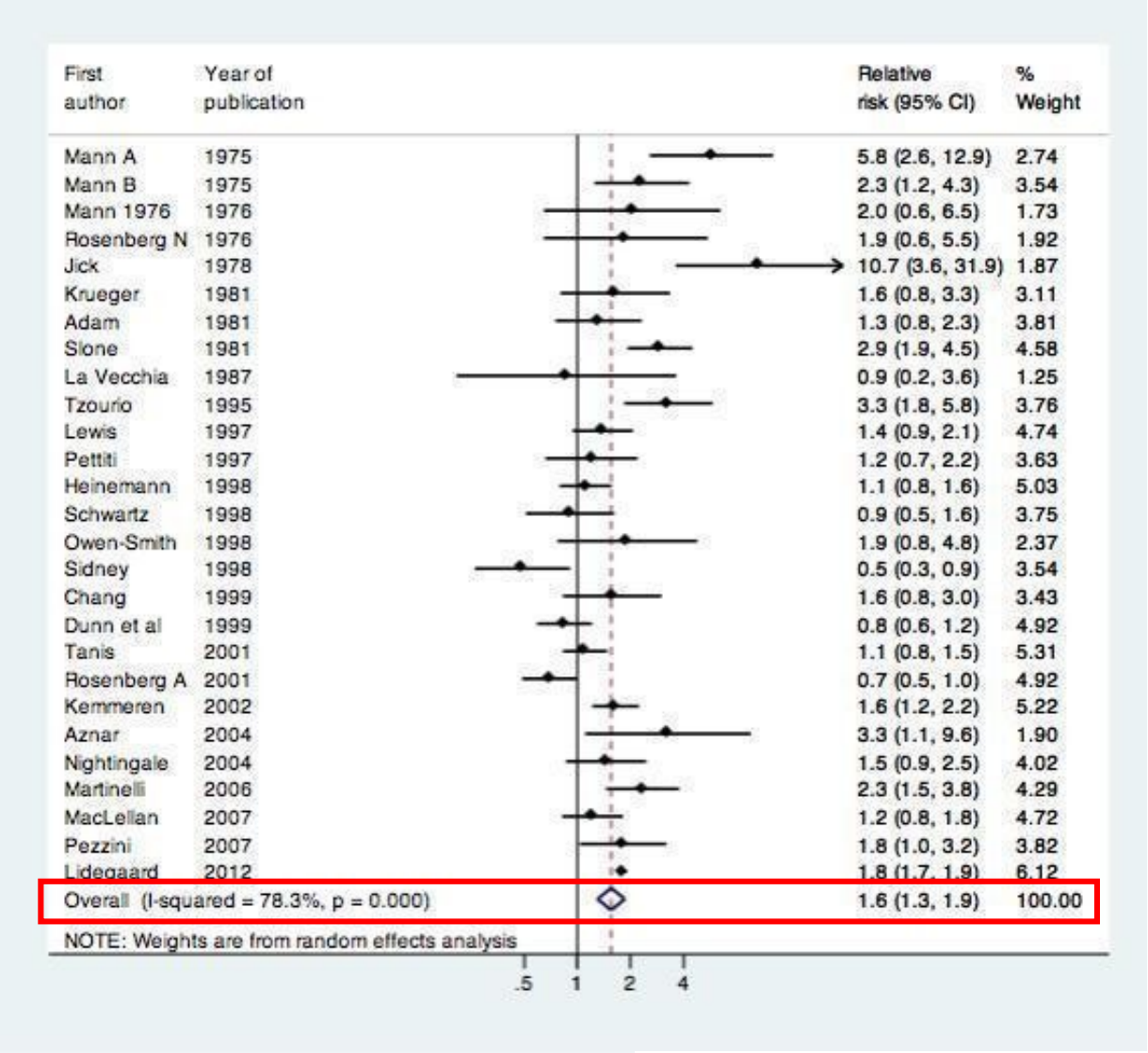
Migraine without aura





Spector JT et al Am J Med 2010

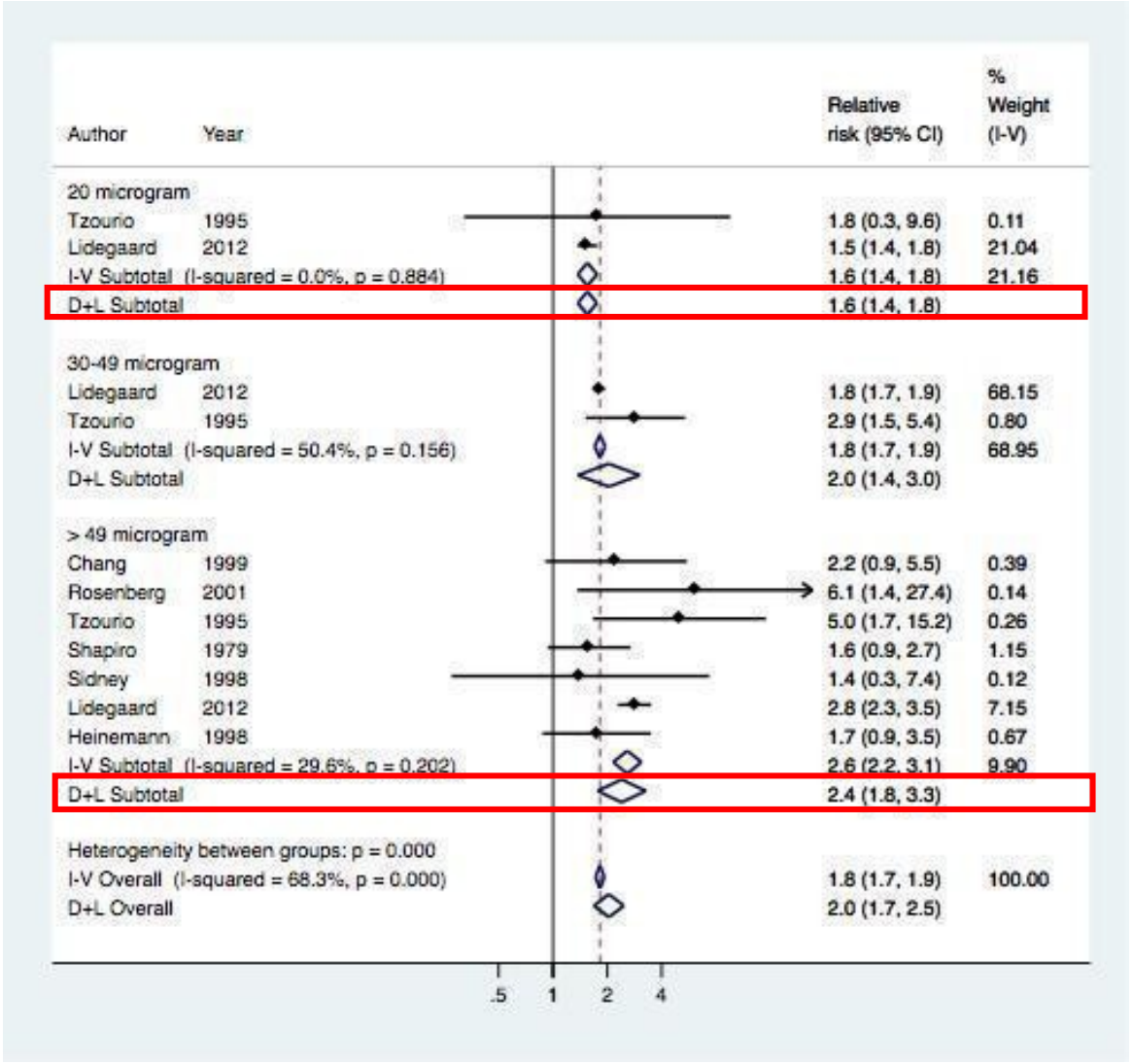
Oral contraceptives (OC) and stroke



Risk increase of MI or ischemic stroke 1.6

Roach RE Cochr Database Syst Rev 2015

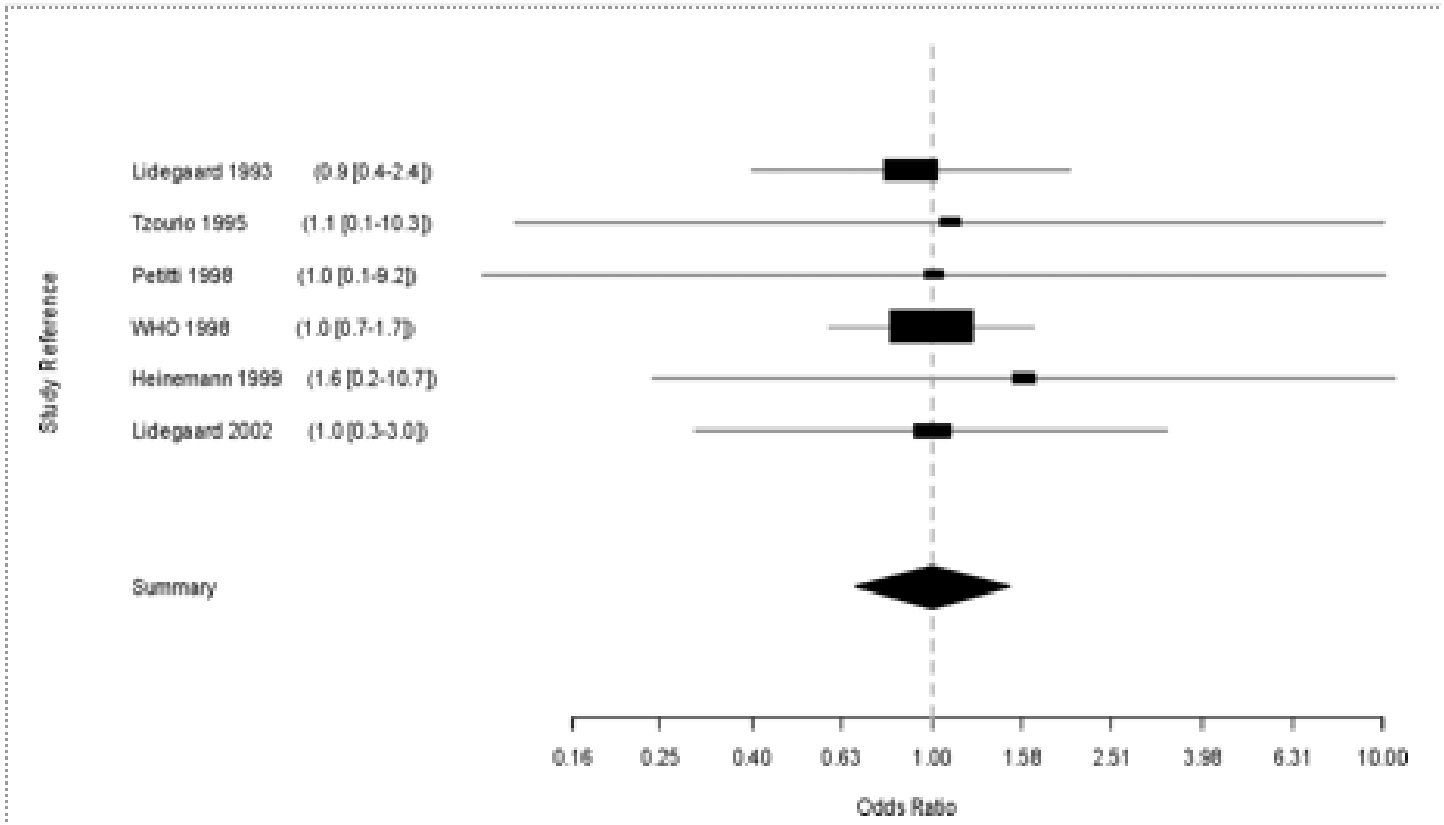
Dose-depending effect of estrogen dose



Risk increase of MI or ischemic stroke from 1.6 to 2.4

Roach RE Cochr Database Syst Rev 2015

Risk of stroke and progesterone-only contraceptives



Chakhtoura Z, et al Stroke 2009

The Lausanne experience : Data from the ASTRAL registry

57 of 179 (39.6%) women with ischemic stroke < 50y on contraception

Variables	Odds ratio	Confidence Interval
Stroke features		
Age	0.93*	0.89–0.98
Admission NIHSS	1.00	0.96–1.04
Risk factors and comorbidities		
Previous cerebrovascular events	0.33	0.09–1.08
Hyperlipidaemia	38.87*	3.84–393.2
Smoking	0.04*	0.00–0.37
Patent foramen ovale	1.21	0.27–5.35
Migraine with aura	0.05*	0.00–0.54
Stroke mechanism		
Undetermined	51.02*	6.66–391.44
Other determined (rare)	0.00*	0.00–0.06

*Significant values $p < 0.05$.

Contraceptive group with significantly lower adjusted stroke and transient ischemic attack recurrence rate over 12 months

Correia P et al Eur Stroke J 2021

Pregnancy/puerperium and stroke

- Incidence of ischemic stroke <20 per 100.000 deliveries
- Mostly in third trimester, around delivery and puerperium
- The cause of stroke remains unknown in many cases
- Possible mechanism may include hypercoagulable state, peripartum cardiomyopathy or amniotic fluid embolism
- Eclampsia is the main pregnancy-specific disorder and may be associated with reversible cerebral vasoconstriction syndrome and stroke-like episodes (vasogenic oedema)

Swartz RH, Int J Stroke 2017

Patent foramen ovale (PFO)

- In cryptogenic strokes, a PFO can be found in up to 50%
  - Up to 70% in patients without vascular risk factors
- PFO is an incidental finding in 33% of all stroke patients with PFO (52% in patients > 55 y, and 20% in patients < 55y)
- The RopE Score is helpful to estimate the probability of a pathogenic PFO

Less risk factors and younger age
- higher probability of pathogenic PFO

	Cryptogenic stroke (n = 3,023)		
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI)[a]	PFO-attributable fraction, % (95% CI)[a]
0-3	613	23 (19-26)	0 (0-4)
4	511	35 (31-39)	38 (25-48)
5	516	34 (30-38)	34 (21-45)
6	482	47 (42-51)	62 (54-68)
7	434	54 (49-59)	72 (66-76)
8	287	67 (62-73)	84 (79-87)
9-10	180	73 (66-79)	88 (83-91)

Kent et al. Neurology 2013

Stroke etiology in young adults

- Etiologies typically seen in older patients are considerably less common in young adults
- Etiology remains undetermined (cryptogenic) in up to 39.7% (age-dependent)
  - Of them, high proportion with PFO
- More than 150 rare etiologies of ischemic stroke can be considered in younger adults
  - underlie up to 21.5% of ischemic strokes in large series
  - The most frequent singular cause of ischemic stroke in young adults is cervical artery dissection, causing up to 20% of all events in the largest series

Yesilot N et al Eur J Neurol 2013; Yesilot N et al Curr Vasc Pharmacol 2017; Rolfs A et al Stroke 2013; Nannoni et al Eur J Neurol 2020

Stroke etiology in young adults – Data from the ASTRAL registry

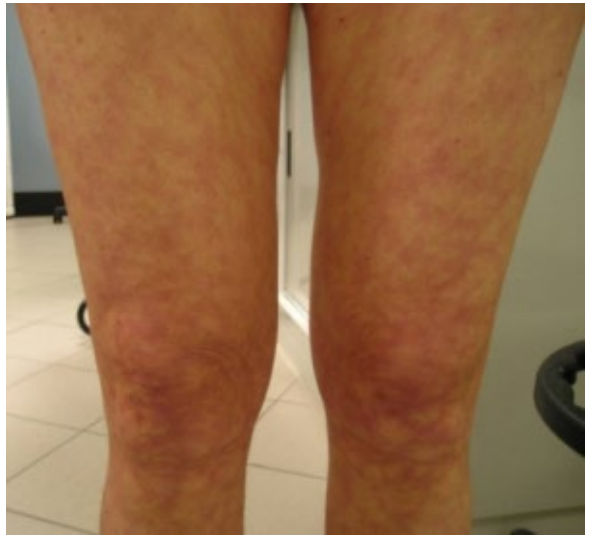
Stroke etiology	**Study cohort** (N=746)	**No EVRF** (N=64)	**Any EVRF** (N=682)	**OR**	**95% CI**
Atherosclerosis	64 (8.7%)	1 (1.6%)	63 (9.4%)	0.15	0.02 - 1.12
Cardioembolism	85 (11.5%)	4 (6.2%)	81 (12%)	0.49	0.17 - 1.37
Lacunar	59 (8.0%)	0 (0%)	59 (8.8%)	0.08	0.00 - 1.34
Dissection	140 (19.0%)	18 (28.1%)	122 (18.1%)	1.76	0.99 - 3.15
ESUS	105 (14.3%)	6 (9.4%)	99 (14.7%)	0.60	0.25 - 1.43
PFO	130 (17.7%)	27 (42.2%)	103 (15.3%)	4.03*	2.35 - 6.91
Undetermined, and/or incomplete workup	64 (8.7%)	3 (4.7%)	61 (9.1%)	0.49	0.15 - 1.62
Other determined, rare cause	81 (11%)	5 (7.8%)	76 (11.3%)	0.66	0.26 - 1.71
Multiple/coexisting causes from the TOAST	8 (1.1%)	0 (0%)	8 (1.2%)	0.61	0.03 - 12.62

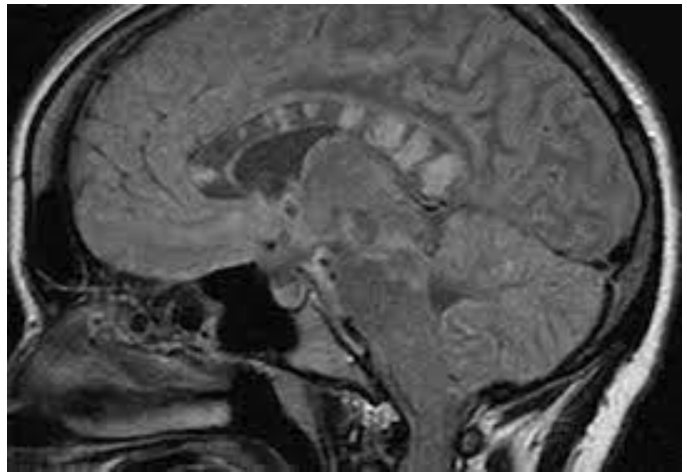
Nannoni et al Eur J Neurol 2020

Cause	Specific Clinical Characteristics and Red Flags	Diagnostic Workup	Treatment
Antiphospholipid syndrome	Recurrent venous and/or arterial thrombosis; miscarriages; eclampsia; placental failure	Lupus anticoagulant, anticardiolipin antibodies, anti-2-glycoprotein-I antibodies in at least 2 time points at least 12 weeks apart	Vitamin K antagonists with or without antiplatelets
Behçet disease	Brainstem involvement; recurrent oral and/or genital ulcers, uveitis; retinal vasculitis; erythema nodosum, arthritis; cerebral venous thrombosis; Mediterranean, Middle East, or Asian ethnic origin	Clinical criteria; no specific tests aid in diagnosis	Symptomatic; interferon alfa and tumor necrosis factor inhibitors being tested in clinical trials
Cervical artery dissection	Trauma to head or neck; neck or facial pain; Horner syndrome; lower cranial nerve palsies	CT angiography (CTA)/ magnetic resonance angiography (MRA), digital subtraction angiography (DSA): irregular stenosis, an occlusion or a dissecting aneurysm, intimal flap, double lumen; axial fat-saturated T1-weighted MRI sequences of the neck to show intramural hematoma	Anticoagulation or antiplatelets for 6–12 months; long-term treatment in selected patients after repeat imaging
Illicit drug use	History of drug use; marks of injection	Urine toxicology screening	Cessation of drug use; no specific treatment unless other comorbid conditions, such as endocarditis or cerebral vasoconstriction, are present
Intracranial artery dissection	Headache	CTA/MRA, DSA: intramural hematoma, intimal flap, double lumen, stenosis, occlusion, or aneurysm; CT/MRI: ischemic stroke and/or subarachnoid hemorrhage	Antiplatelets; if aneurysm progressively enlarges, endovascular or surgical repair can be considered
Malignancy	History of malignancy; symptoms suggestive of malignancy (eg, weight loss, unexplained fatigue)	Screening investigations in high suspicion, eg, chest and abdomen CT	Treatment of underlying malignancy; anticoagulation (often with low-molecular-weight heparins) or antiplatelets
Migrainous infarction	Known migraine with aura; ischemic stroke associated with a typical aura (for that patient) persisting >60 min	No specific diagnostic tests; apply International Headache Society criteria	No specific treatment; triptans and ergotamines should be avoided
Moyamoya disease or syndrome	Migrainelike headache; seizures; recurrent ischemic events; events triggered by hypoperfusion or hyperventilation; intracerebral hemorrhage; choreiform movements (in children)	CTA/MRA, DSA: distal internal carotid artery narrowing and collateral formation	Antiplatelets, calcium channel blockers, revascularization surgery (bypass)

Putaala J et al Cerebrovas Dis 2020

Cause	Specific Clinical Characteristics and Red Flags	Diagnostic Workup	Treatment
Postradiation vasculopathy	History of radiation therapy to head, neck, or cervical spine	CTA/MRA: narrowing of distal internal carotid artery with or without development of collaterals	Antiplatelets
Primary central nervous system vasculitis	Headache; progressive cognitive impairment; encephalopathy; seizures; multifocal ischemic and/or hemorrhagic lesions at various stages; no signs of systemic disease	MRI: multiple acute and old infarctions in different vascular territories; MRA/DSA: focal or multifocal segmental narrowing of medium and small intracranial arteries; CSF analysis (pleocytosis, elevated protein), brain biopsy	Immunosuppression (prednisone followed by cyclophosphamide)
Reversible cerebral vasoconstriction syndrome	Recurrent thunderclap headaches; reversible edema; subarachnoid hemorrhage in the convexity	CTA/MRA, DSA: string-of-beads–like segmental narrowing of intracerebral arteries	Elimination of precipitating factors (eg, cocaine, amphetamines); nimodipine; avoid steroids and antiplatelets
Sneddon syndrome (livedo reticularis and stroke)[a]	Livedo reticularis; small infarctions in deep white matter and pons	Skin biopsy; screening for antiphospholipid antibodies; DSA	Vitamin K antagonists; antiplatelets in patients without antiphospholipid antibodies
Susac syndrome (retinocochleocerebral arteriopathy)	Encephalopathy; focal deficits; sensorineural hearing loss; visual disturbances; corpus callosum lesions on MRI	Retinal fluorescein angiography	Immunosuppression
Systemic vasculitis	Malaise, fever, weight loss, rash; neurologic symptoms as in primary central nervous system vasculitis; variable organ affliction depending on disease	CTA/MRA, DSA, aortic positron emission tomography (PET); skin, nerve, or muscle biopsy; full blood cell count, erythrocyte sedimentation rate, C-reactive protein; specific autoantibodies (perinuclear antineutrophil cytoplasmic antibodies/ myeloperoxidase, cytoplasmic antineutrophil cytoplasmic antibodies/ proteinase-3); CSF analysis (pleocytosis, elevated protein)	Immunosuppression

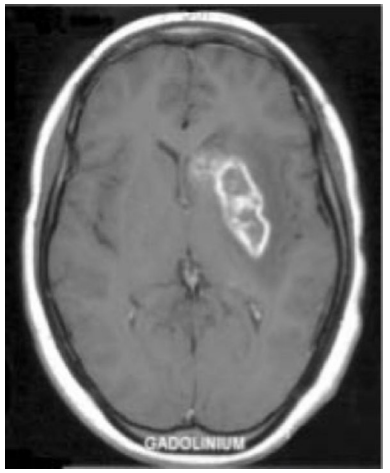


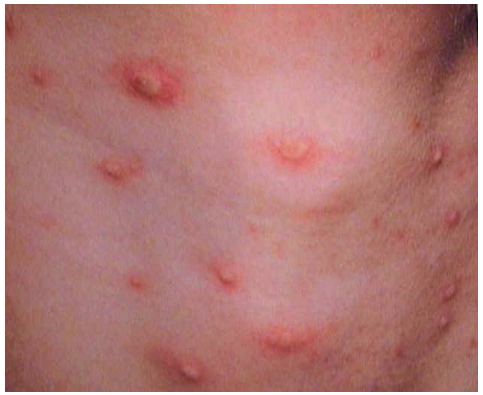


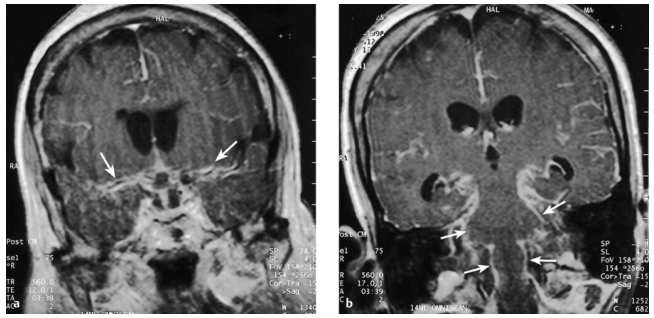
Putaala J et al Cerebrovas Dis 2020

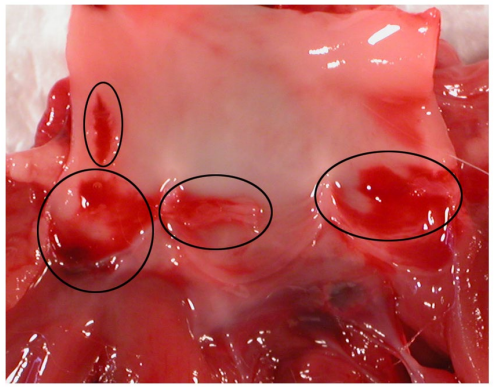
Infectious etiologies

- HIV
- Varicella zoster virus
- Neurosyphilis
- Neuroborreliosis
- Tuberculous meningitis
- Neurocysticercosis
- Bacterial meningitis
- Endocarditis









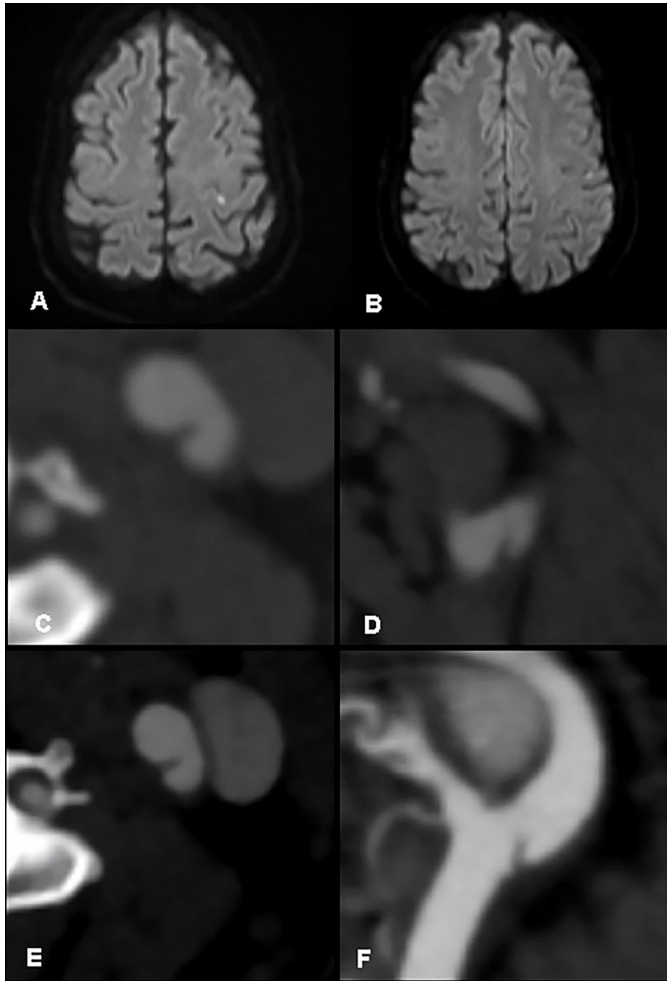
Smajlović D et al Vasc Health and Risk Management 2015

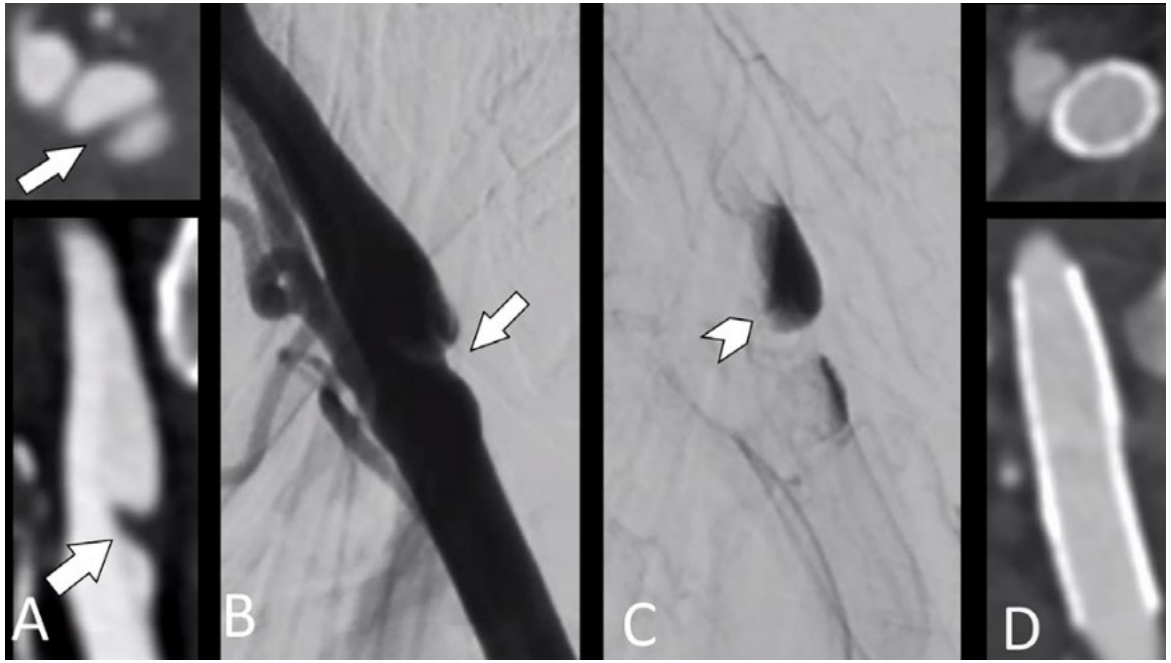
The carotid web

- The carotid web is a proposed stroke mechanism, particularly in younger patients without vascular risk factors
- Shelf-like projection into the lumen of the proximal internal carotid artery without evidence of calcification
- It is pathologically defined as intimal fibromuscular dysplasia
- Recirculation of blood distal to the web because of disruption of normal laminar flow which increases risk of platelet aggregation and thrombus formation
- Gold standard for the diagnosis is the CT angiography (CTA) of the neck

Mac Grory B et al JNNP 2020

Carotid web





Epidemiology of the carotid web

- Only few population-based study to date on prevalence of a carotid web
- In one study, the incidence of cryptogenic stroke associated with carotid web was 3.8/100 000 person years (3.2 in men and 4.3 in women)
- A post-hoc analysis of the MR-CLEAN trial found that 2.5% of patients had a carotid web ipsilateral to the large vessel occlusion
- Patients with carotid web are younger, more often female and have less cardiovascular risk factos

Joux J et al Stroke 2016; Compagne KCJ Radiology 2018

Detecting monogenetic causes of stroke

- The incidence of monogenic disorders causing stroke might be as high as 7% when clinical prescreening algorithms are applied
- The presence of vascular risk factors does not exclude a diagnosis of monogenic disorders
- A positive family history was the only significant factor predicting a positive genetic diagnosis in one of the studies
- Many of the disorders show progressive cerebral small vessel disease pathology defined as MRI white matter hyperintensities
- Currently, genetic testing of monogenic disorders should be guided by positive family history and suggestive clinical phenotype

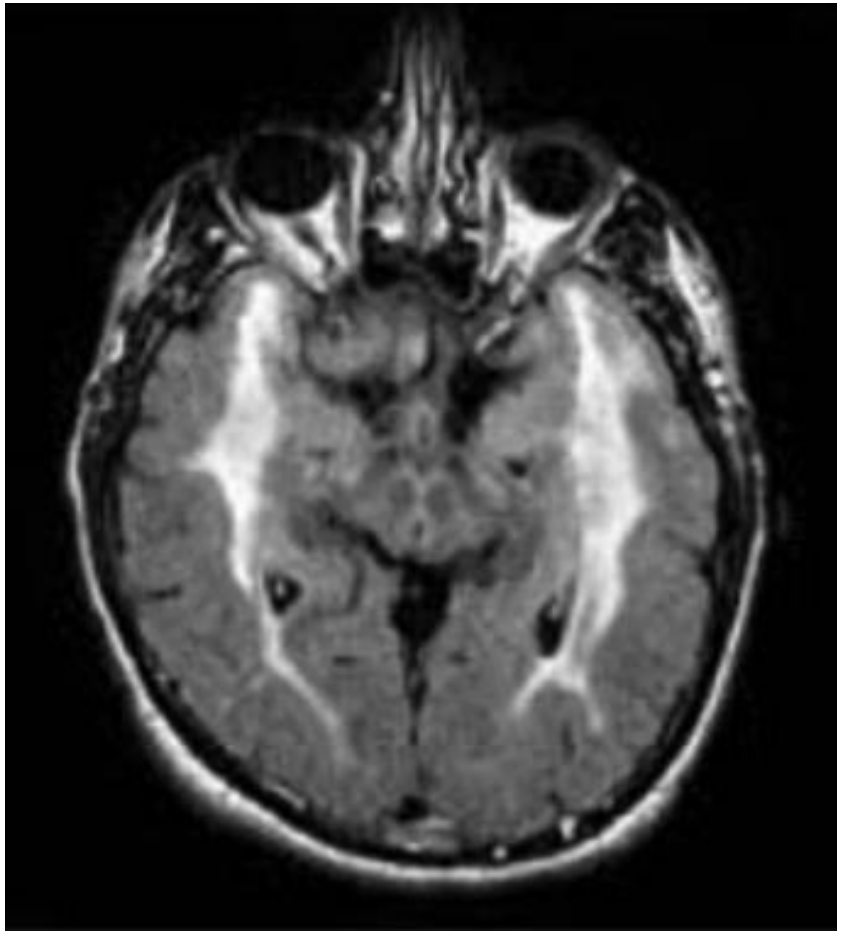
Yesilot Barlas N et al Eur J Neurol 2013; Bersano A et a Stroke 2016; Tatlisumak T et al J Neurol 2016

Some monogenetic causes of stroke

Disorder	Gene
CADASIL (AD)	NOTCH-3
CARASIL (AR)	HTRA-1
COL4A1 disorders (AD)	COL4A1
Deficiency of adenosine deaminase 2 (DADA2)-associated polyarteritis nodosa vasculopathy; (AR)	ADA2
Familial moyamoya; AD or AR	ACTA2, MTCP1, RNF213
Retinal vasculopathy with cerebral Leukodystrophy (RCVL); AD	TREX1
Fabry diseasea; X-linked recessive	GLA
MELAS	Several, mitochondrial; transfer RNA-Leu. most common
Neurofibromatosis type 1; AD	NF1

CADASIL

(Cerebral autosominal dominant arteriopathy with subcortical infarcts and leukencephalopathy)



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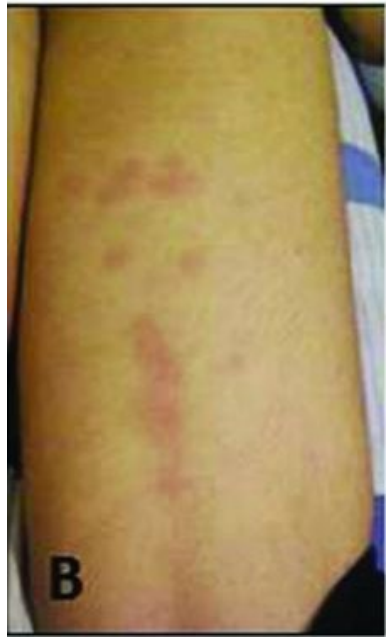
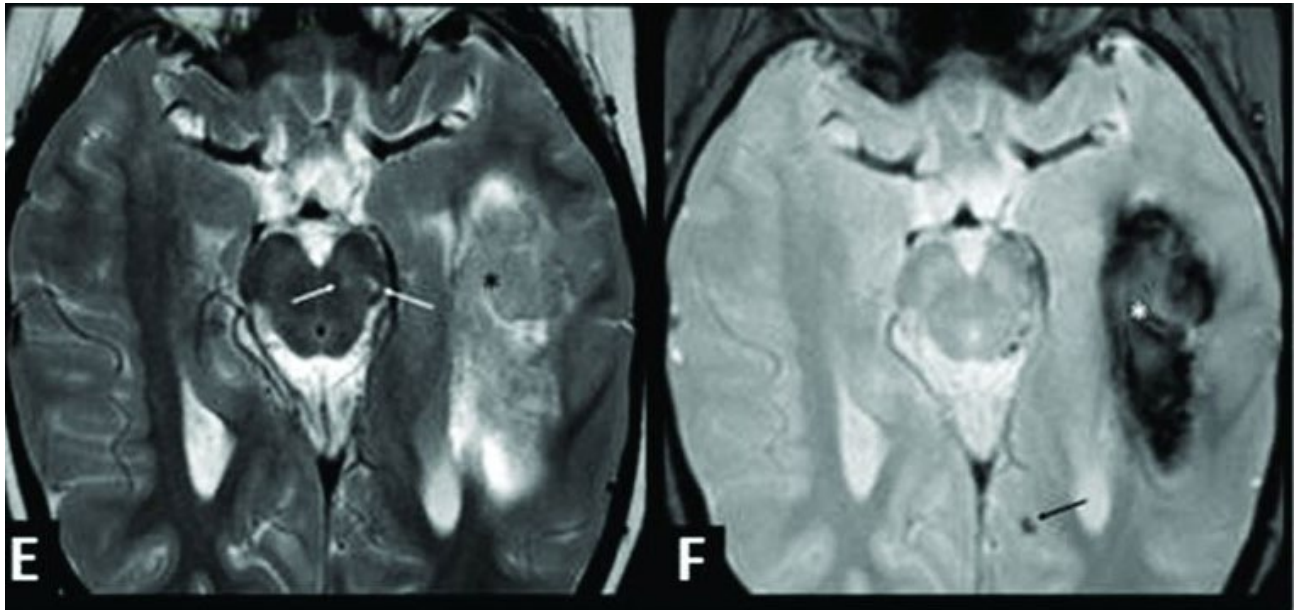
Deficiency of adenosine deaminase 2 (DADA2) associated polyarteriitis nodosa vasculopathy





Zhou Q et al N Engl J Med 2014

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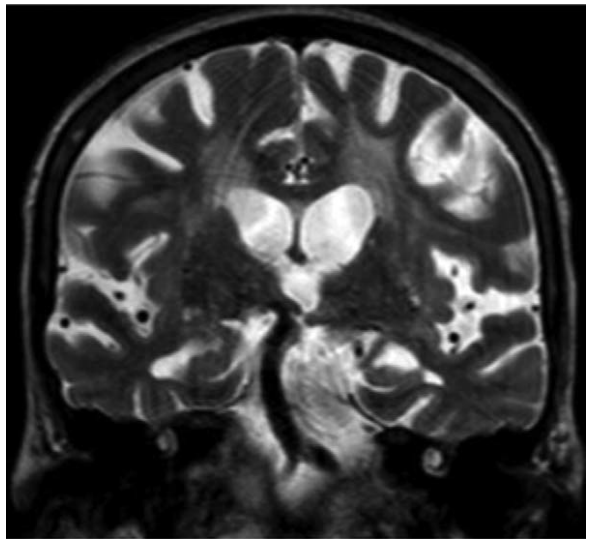
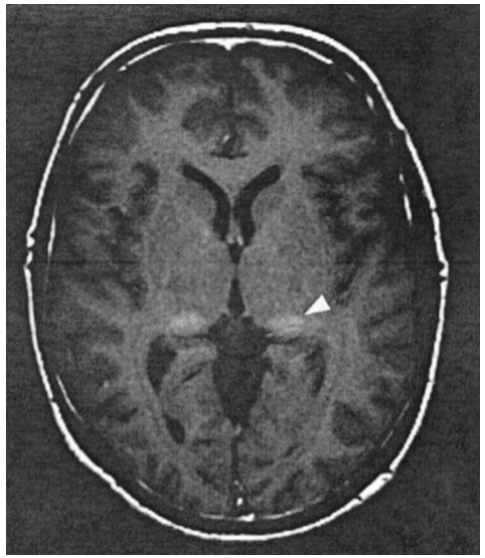
Fabry`s disease

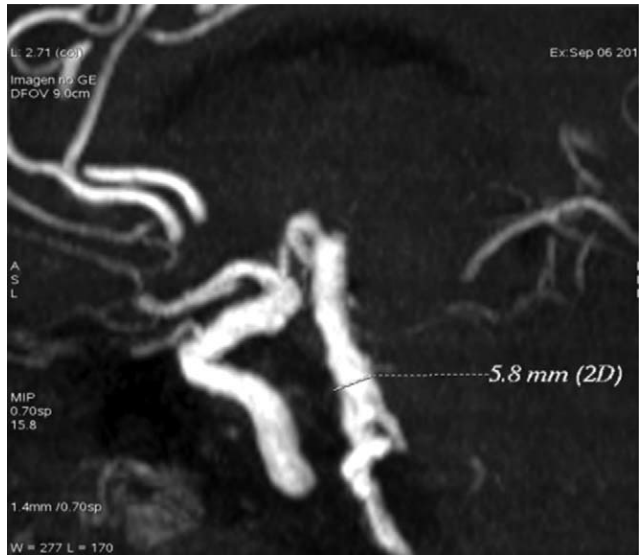
- Lysosomal storage disease with x-chromosomal inheritance (defect im glycosphingolipid metabolism)
- Mutations in the GLA gene lead to malfunction of lysosomal α-galactosidase A enzyme
- Classic symptoms include acroparesthesias, angiokeratomas, hypohidrosis, corneal opacity, gastrointestinal and ear symptoms
- Vertebrobasilar dolichoectasia and the coexistence of large-vessel and small-vessel disease are suggestive of Fabry's disease
- The diagnosis in symptomatic men can be made by deficit in serum α-galactosidase, but usually genetic testing ist needed, especially in women

Fabry`s disease MRI

- Progressive white matter lesions
- Hyperintensity of pulvinar thalami
- Vertebrobasilar dolichoectasia







Fabry`s disease

- In large multicentre studies, pathogenic mutations were recorded in 0.5-2% ischemic stroke patients
- Pathogenic mutations were more frequent in patients with evidence of small-vessel disease (lacunes or leukoaraiosis; 4.5%), even more if they were not hypertensive (7%), and in normotensive patients with posterior circulation strokes (12 ·5%)
- Effective enzyme substitution therapy (α-galactosidase) available
- Stroke frequently is the first manifestation of Fabry's disease and in the absence of other clinical findings

Goeggel-Simonetti B et al; J Neurol 2015; Baptista MV et al Stroke 2010; Brouns R et al Stroke 2010; Sims K et al Stroke 2009; Rolfs A et al Stroke 2013

General diagnostic approach in young stroke patients

- Specific validated diagnostic algorithms are not available for young patients
- Full clinical and family history and detailed history of drug use should be obtained
- Complete examination with attention to the cardiovascular system, skin, mucous membranes, and eyes, as well as stature and deformities
- Imaging of the brain:
  - MRI and MRA as goldstandard including diffusion-weighted, fluid-attenuated inversion recovery (FLAIR), and T2*/susceptibility-weighted sequences
  - axial neck MRI with fat-saturated T1-weighted to demonstrate arterial wall hematoma in cervical artery dissection

Diagnostic approach in young stroke patients

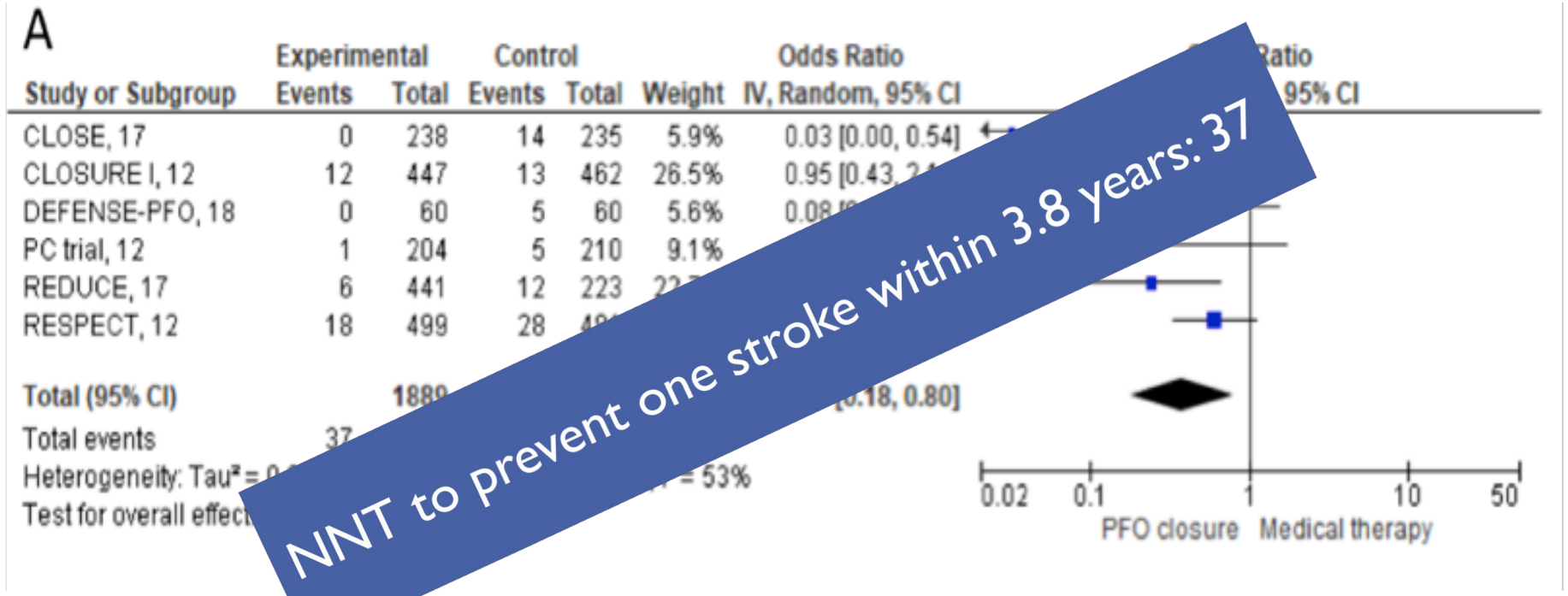
- 12-lead ECG and prolonged ECG-monitoring
- TTE and TEE (PFO)
- In special cases cardiac MRI/CT
- Laboratory test:
  - full blood cell count, lipid panel, blood glucose, kidney function tests as routine evaluation
  - systematic urine screening for illicit drugs
  - Although its utility in general is uncertain, screening for acquired and genetic thrombophilia should be considered in all young patients in whom initial diagnostic tests fail to identify a definite cause
  - When rarer causes are suspected a wider range of blood and CSF analyses should be carried out

Management of young stroke patients

- No specific guidelines for management of ischemic stroke in young adults
- General recommendations and target values for treatment of established cardiovascular risk factors
- Illicit drug use, combined oral contraceptives, and hormone replacement therapy should be discontinued and excessive alcohol intake reduced
- In patients with migraine, triptans and ergotamines should be avoided because of their vasoconstrictive effects
- Adherence to medical treatment or lifestyle changes might be challenging to maintain

Pezzini A et al Circulatio 2014; von Dongen MME et al Ann Med 2019

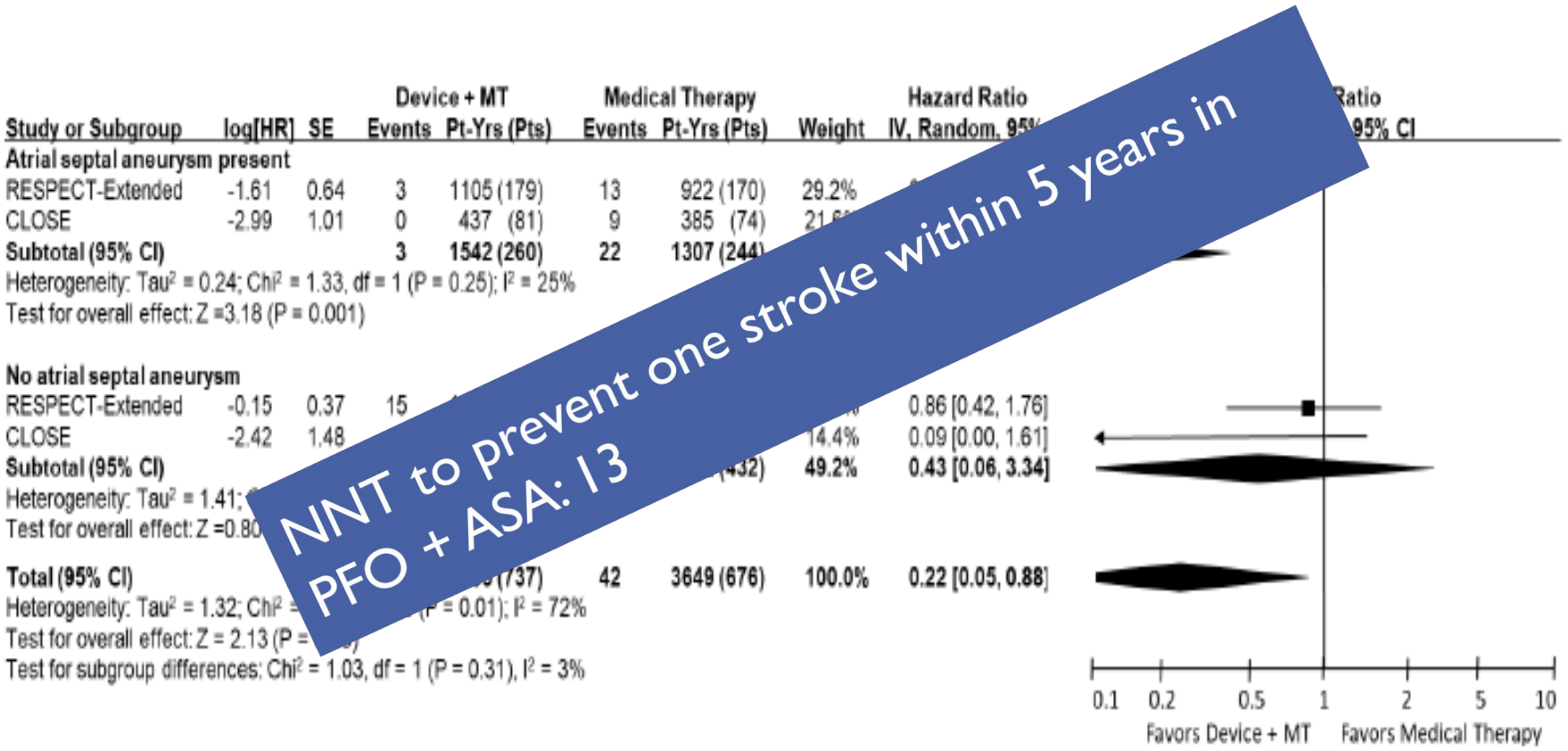
Efficacy of PFO Closure – overall



NNT to prevent one stroke within 3.8 years: 37

Saver JL et al Stroke 2018

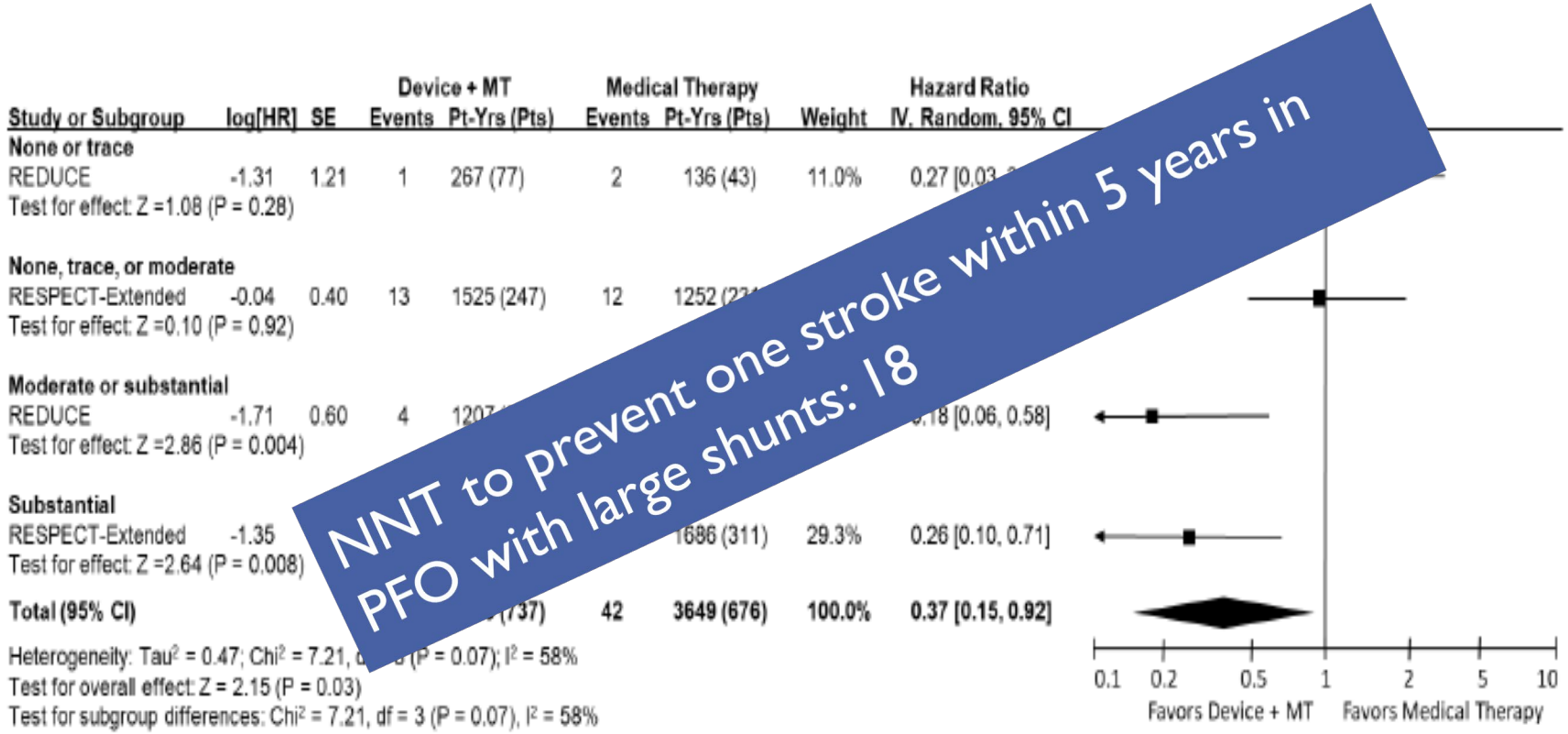
Efficacy of PFO Closure – ASA



NNT to prevent one stroke within 5 years in PFO + ASA: 13

Saver JL et al Stroke 2018

Efficacy of PFO Closure – Shunt size



Saver JL et al Stroke 2018

Management – carotid web

- Insufficent evidence to make recommendation for the optimal secondary prevention
- Antiplatelet therapy remains the standard of care as in cryptogenic stroke in general
- Anticoagulation might be pathophysiologically more appropriate for reducing thrombus formation, but this has not been studied yet
- The recurrence rate in patients with stroke associated with carotid web is high with rates of recurrent stroke reported between 24% and 40%
- Therefore, a more aggressive secondary prevention strategy might be reasonable and carotid endarterectomy or carotid artery stenting appear to be at low risk in this group

Joux J et al Stroke 2014; Haussen DC et al Stroke 2017; Sajedi P et al Neurology 2017; Haussen DC et al Interv Neurol 2018

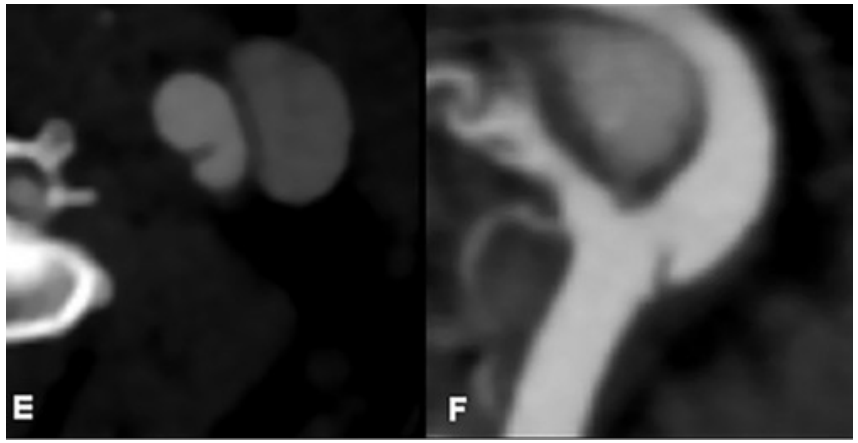
Poststroke outcome

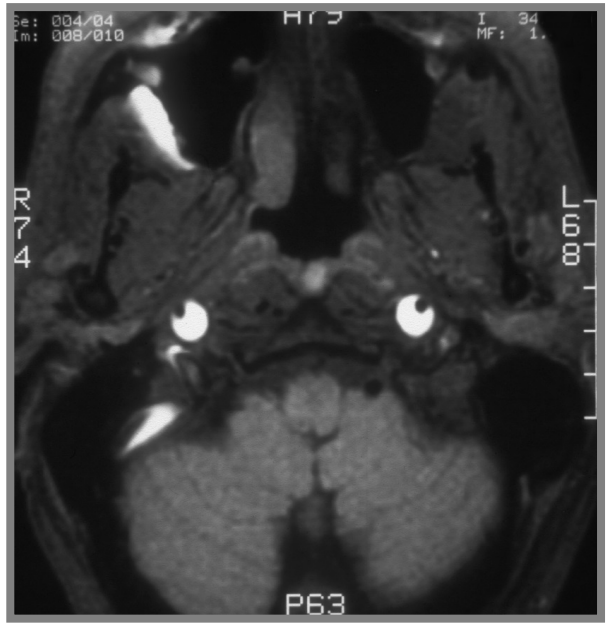
- In outcome studies, approximately 2 of 5 of young patients with ischemic stroke recovered completely or almost completely (modified Rankin scale, 0 to1), and almost 9 of 10 were able to live independently (modified Rankin scale, 0 to 2)
- Fatality 3-6%
- High risk of recurrence for years with cumulative risk for stroke around 10% at 5 years and 15% at 10 years
- Up to 50% of the patients have a decline in their cognitive skills even if the motor symptoms are mild
- A substantial proportion of young patients with ischemic stroke are not able to return to work, and this proportion increases over time (37.6% at 1 year, 47% at 5 years)

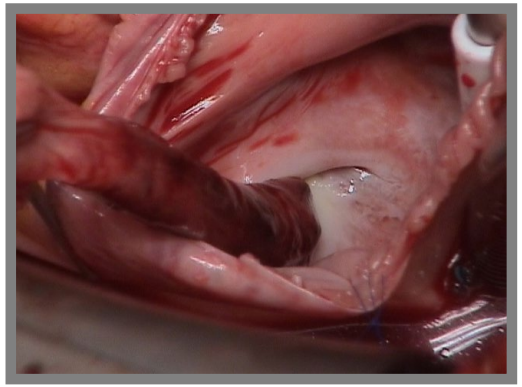
Goeggel Simonetti B et al J Neurol 2015; Putaala J et al Stroke 2009; Schaapsmeerders P et al Stroke 2013; Putaala J et al Stroke 2012; Nannoni et al Eur J Neurol 2020

Take home messages

- Recent studies demonstrated an increasing incidence of ischemic stroke in young adults worldwide
- Younger stroke patients have a wider range of risk factors, including age-specific factors, such as pregnancy/puerperium and combined oral contraceptive use
- Young adults with stroke are more frequently diagnosed with rare etiologies or monogenic causes underlying their strokes
- PFOs and dissection are the most common etiologies in young stroke patient
- The carotid web is a recently established cause of stroke in young adults
- The risk of mortality and stroke recurrence remains elevated for years after the event with a considerable socioeconomic impact







Thank you for your attention!