CEREBRAL VENOUS THROMBOSIS

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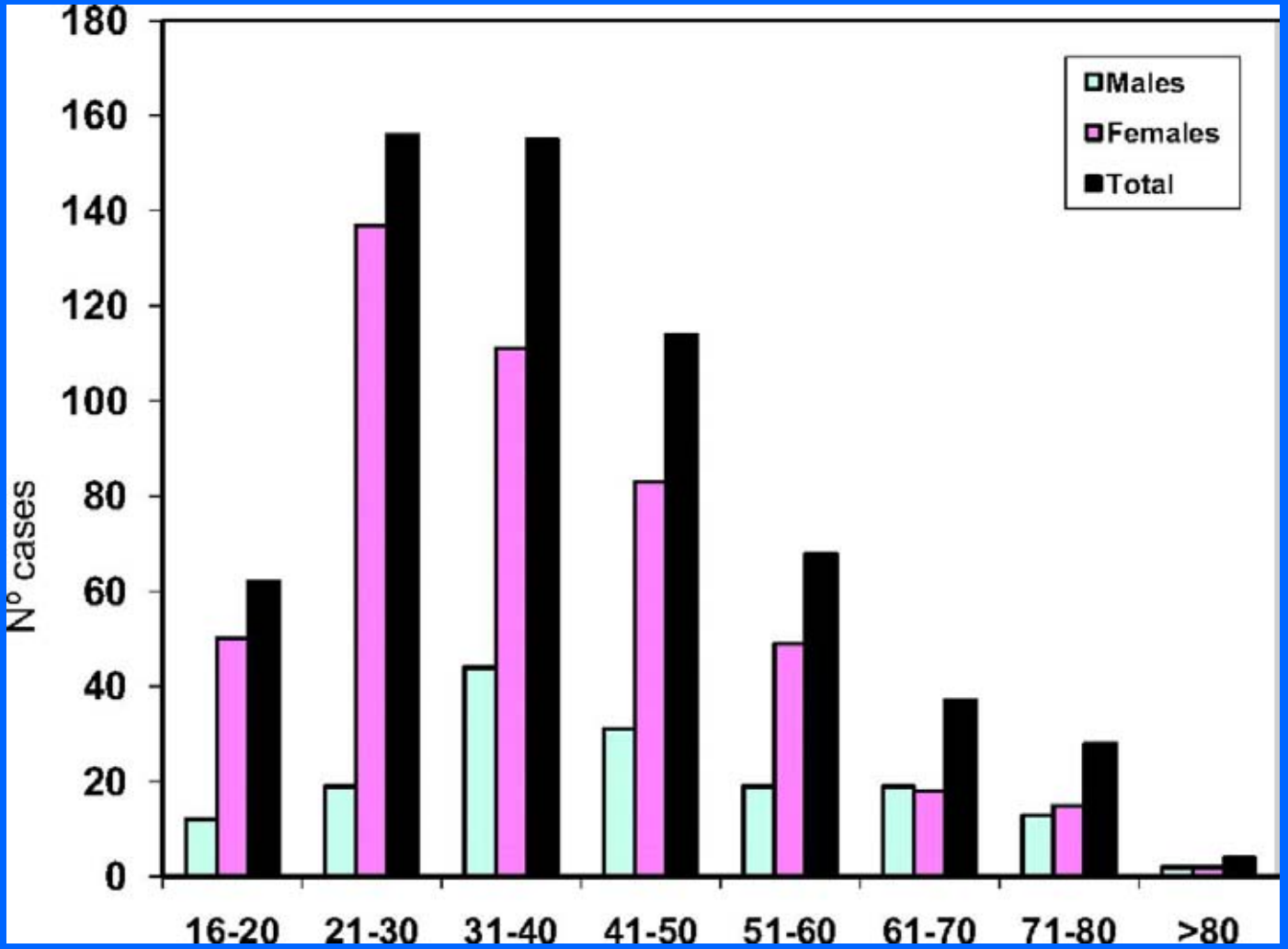
CEREBRAL VENOUS THROMBOSIS

- DISCLOSURES
  - none

CEREBRAL VENOUS THROMBOSIS: EPIDEMIOLOGY

- Incidence and prevalence
  - Autopsies: 1-9%
  - Hospital bases series
    - Portugal: 0.22/100 000/year (IC 95% = 0-47)
    - Isfahan, Iran: 1.23/100 000/year
    - Netherlands: 1.32/100 000/year
  - Stroke registries
    - Mexico: 3% of 2000 strokes; India: 6% of 1014 strokes
  - Pregnancy
    - 11.6/100 000 deliveries in USA
    - 136/240 (57%) pregnant women with stroke (Mexico)
  - Infants & children <18 years in Canada
    - 0.64/100 000

CVT: DEMOGRAPHY



Saposnik, G. et al. Stroke 2011;42:1158-1192; data from the ISCVT cohort

CVT: PRESENTING SYNDROMES

- Isolated intracranial hypertension syndrome
  - Headache, nausea/vomiting, papilloedema, visual disturbances, diplopia/VI nerve palsy, tinnitus
  - Isolated headache
- Focal syndrome
  - Focal deficits: mono/hemiparesis, aphasia
  - Seizures
- Encephalopathy
  - Multifocal signs
  - Seizures
  - Mental status changes
  - Decreased alertness, stupor/coma

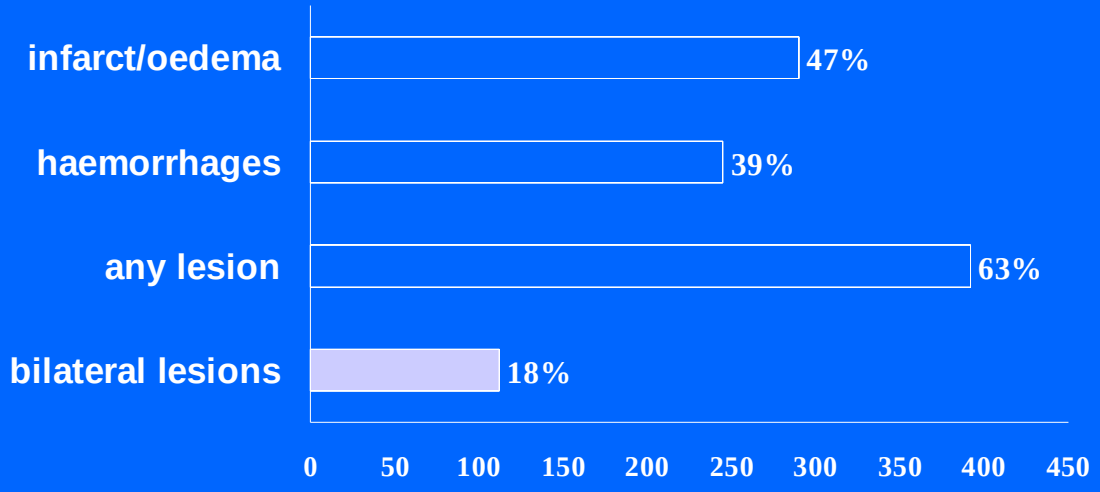
CVT: LESS COMMON PRESENTING SYNDROMES

- Cavernous sinus syndrome
- Clustering TIAs
- Subarachnoid haemorrhage
  - Generalised, basal
  - Localised, convexity
- Pulsating tinnitus
- Cranial nerve palsies
  - VII
  - Collet-Sicard syndrome

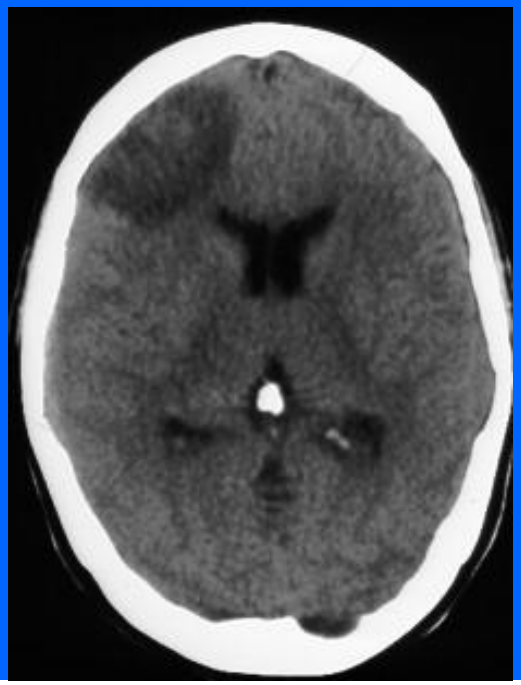
CVT: PRESENTING SYMPTOMS & SYNDROMES

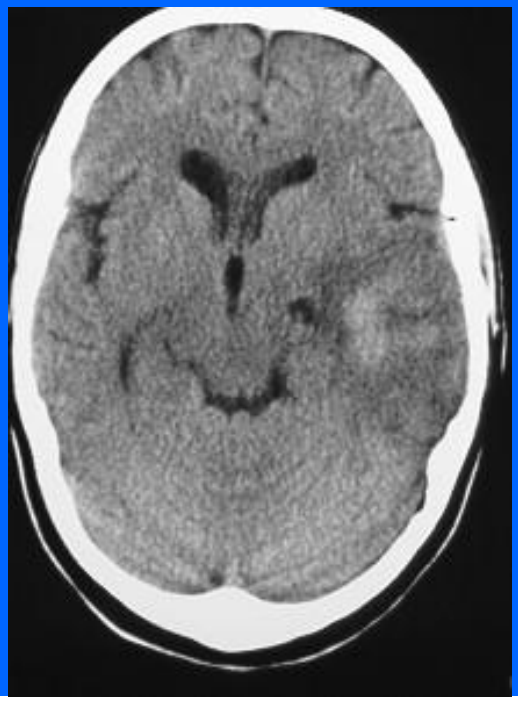
- Variable with:
  - Interval onset-presentation
  - Age of the patient
  - Gender of the patient
  - Location of vein or sinus occlusion
  - Parenchymal lesions
  - Underlying disease

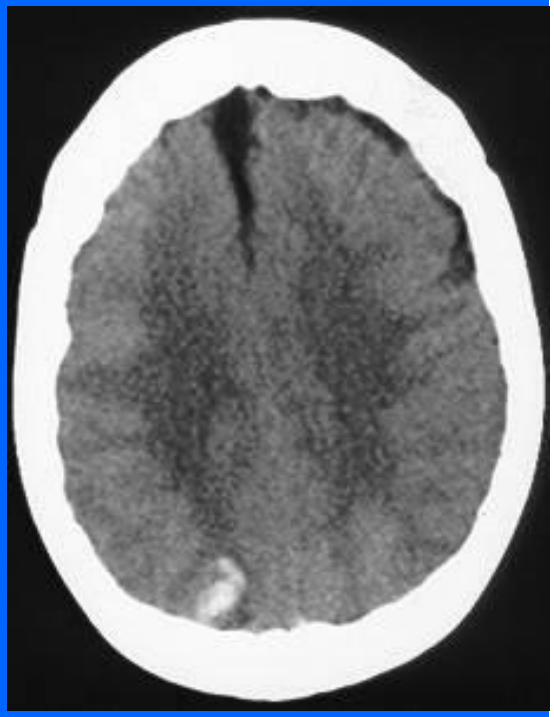
CVT: PARENCHYMAL LESIONS



ISCVT, 2004







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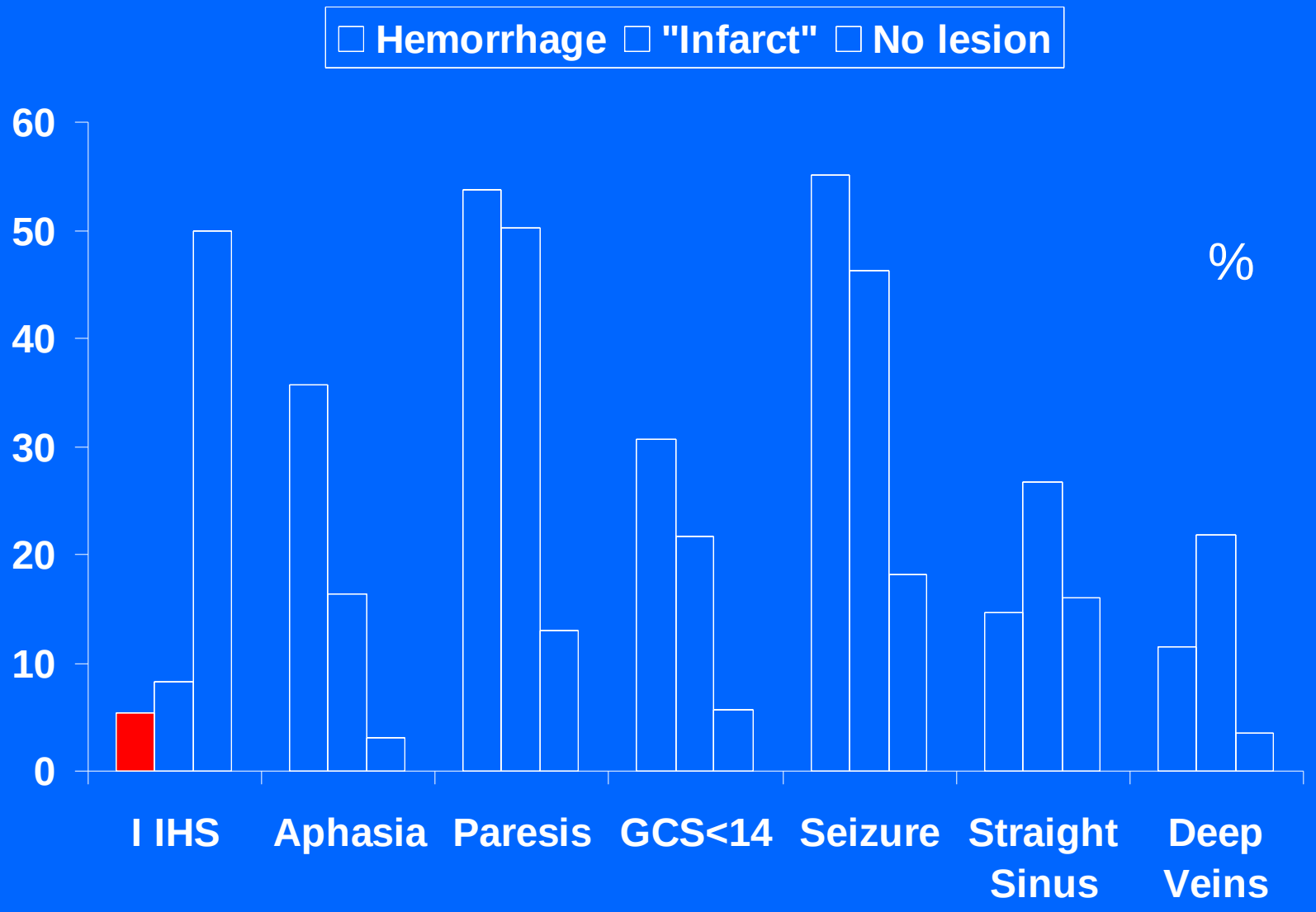
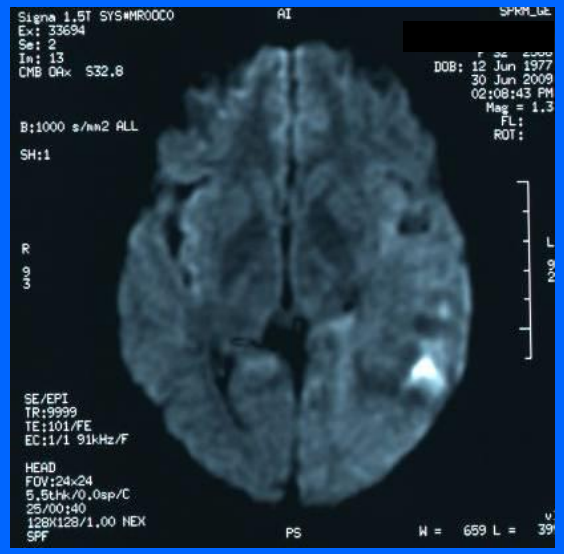


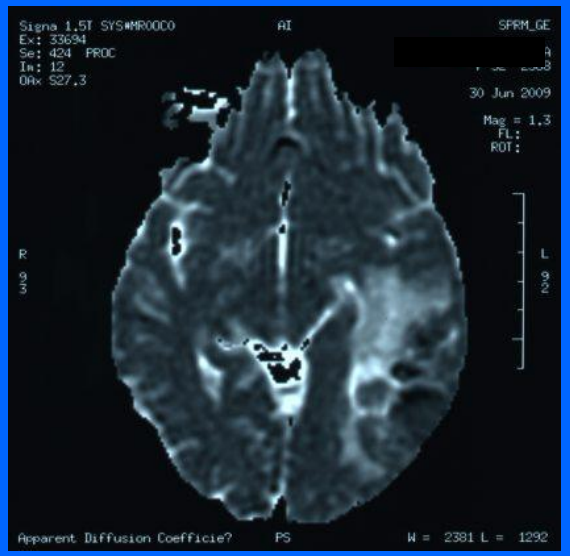
Ferro et al ESC 2009

VENOUS “INFARCTS”

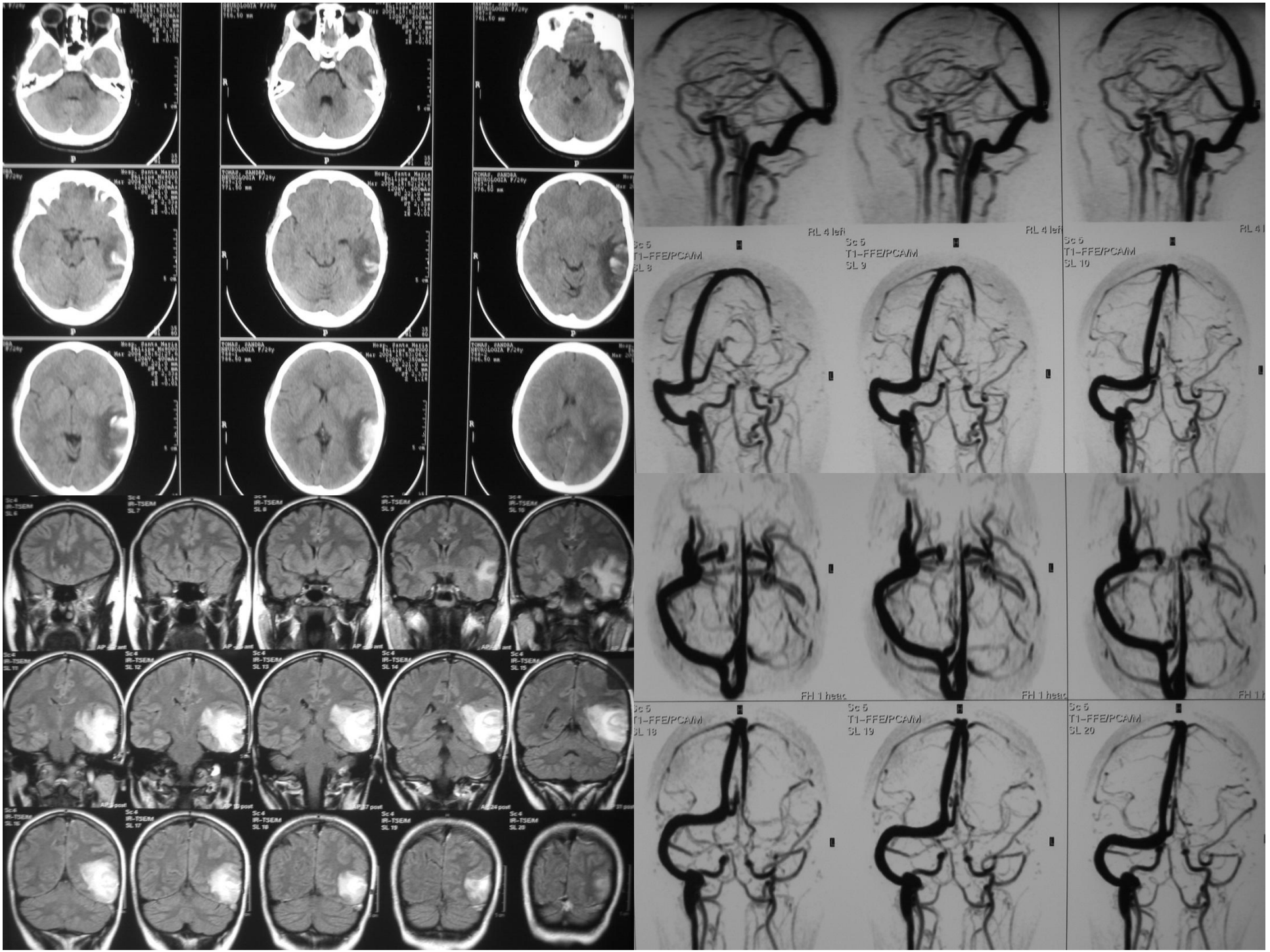
FLAIR



DWI

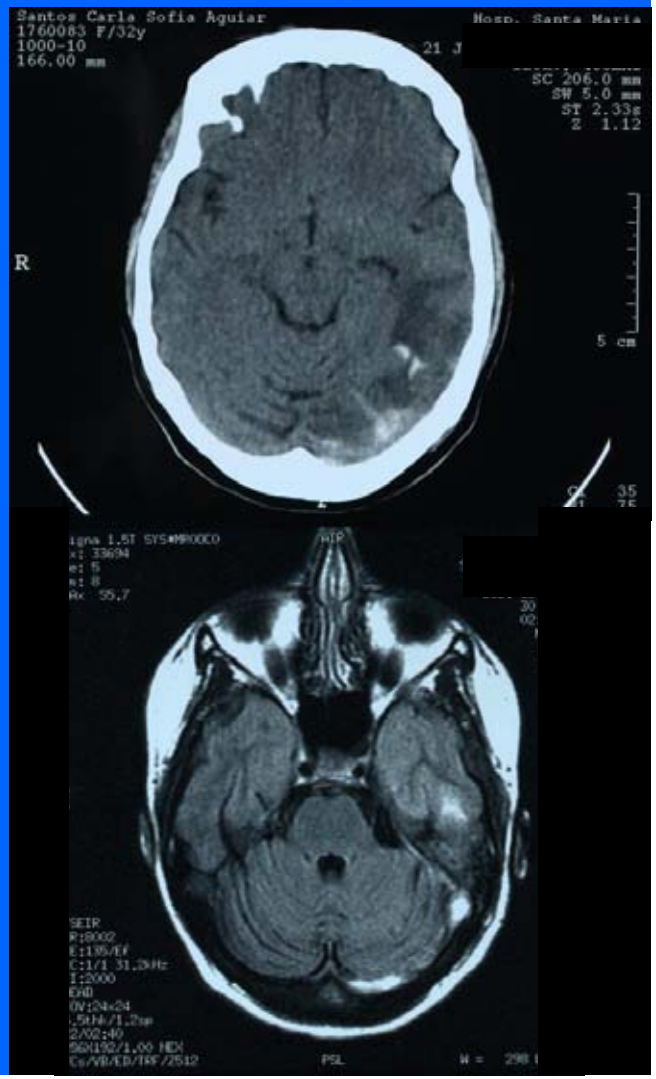


ADC


RL 4 left
Sc 5
T1-FFE/PCA/M
SL 8
Sc 5
T1-FFE/PCA/M
SL 9
Sc 5
T1-FFE/PCA/M
SL 10
FH 1 head
Sc 5
T1-FFE/PCA/M
SL 18
Sc 5
T1-FFE/PCA/M
SL 19
Sc 5
T1-FFE/PCA/M
SL 20

CVT DIAGNOSIS: CT, MRI & VENOGRAPHY

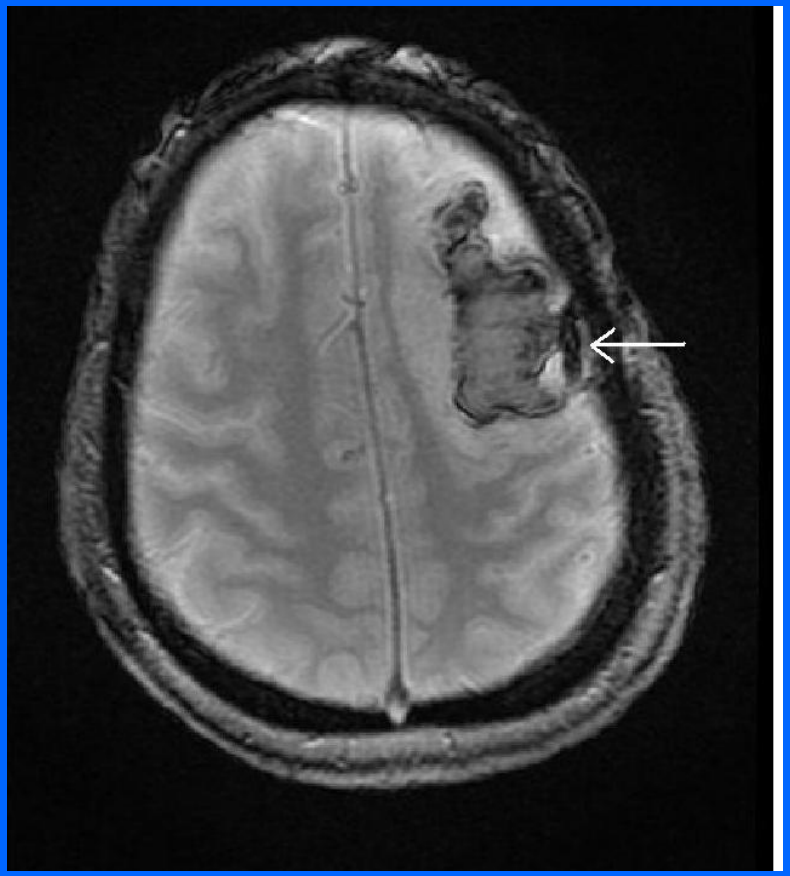
- CT
  - Low sensitivity
  - Morerate specificity of “typical” signs
- MR
  - T1 isointense and T2 hypointense thrombus in the 1st four days



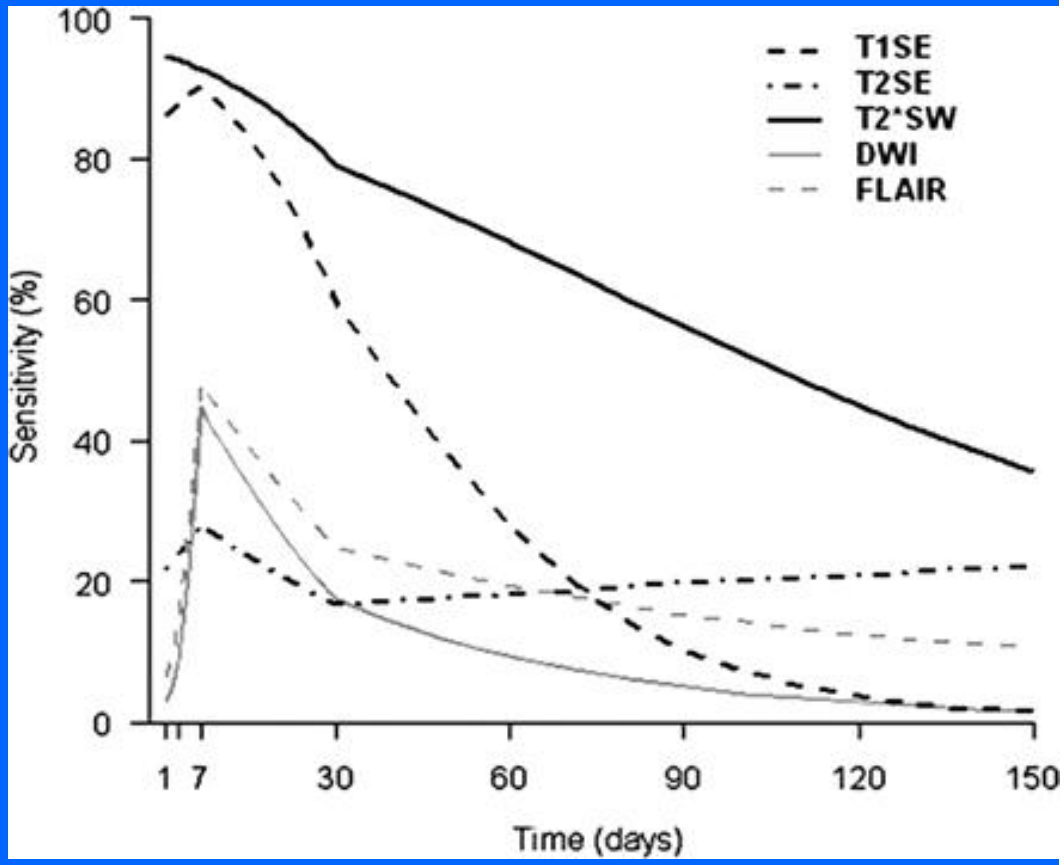
CVT DIAGNOSIS: CT, MRI & VENOGRAPHY

- MR Venography
  - Limited spatial resolution
  - Saturation of flow signal
- CT Venography
- IA Venography
  - Hypoplasia vs. Occlusion
  - High anatomical variability

DIAGNOSIS: MR SEQUENCES



T2*SW



Idbaih A et al Stroke 2006

TVC: D-DIMERS

- Are DD < 500 ng/mL a good screening test for CVT?
  - Meta-analysis of 14 studies with 1134 patients **
    - Sensitivity 93.9%; specificity 89.7%
    - Risk factors for false negative D-Dimers
      - Isolated headache
      - Limited extent of CVT
      - Longer duration of symptoms
  - Ongoing M Arnold´s study
    - D-dimers; FXIII-AP

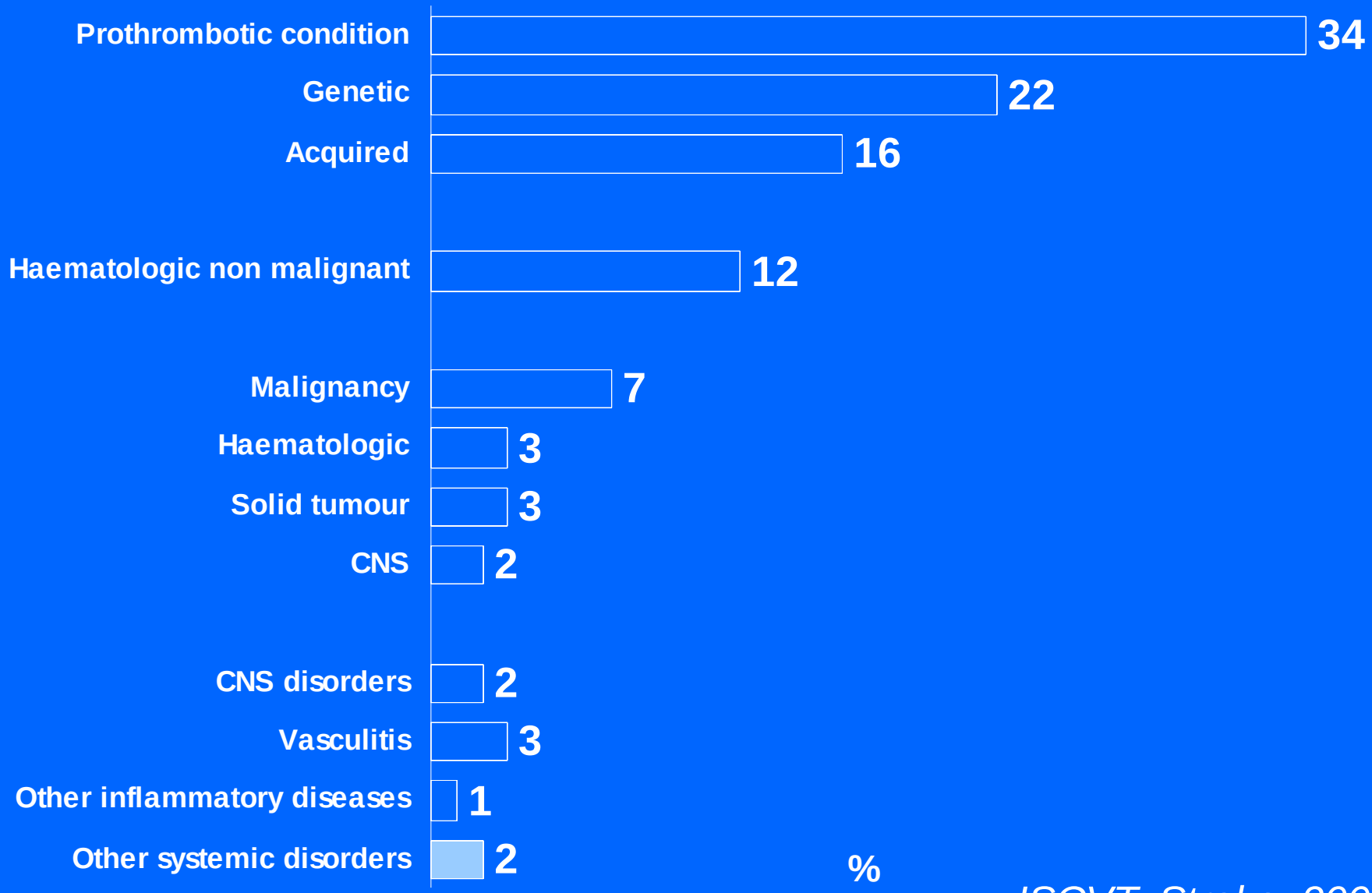
THE “CAUSES” OF CVT

- Associated conditions
  - Condition found in association with CVT
- Risk factors
  - Condition that increases the risk of CVT
- Cause
  - Causality requests are fulfilled
    - Necessary
    - Sufficient
    - *Contributory*

CVT ASSOCIATED CONDITIONS

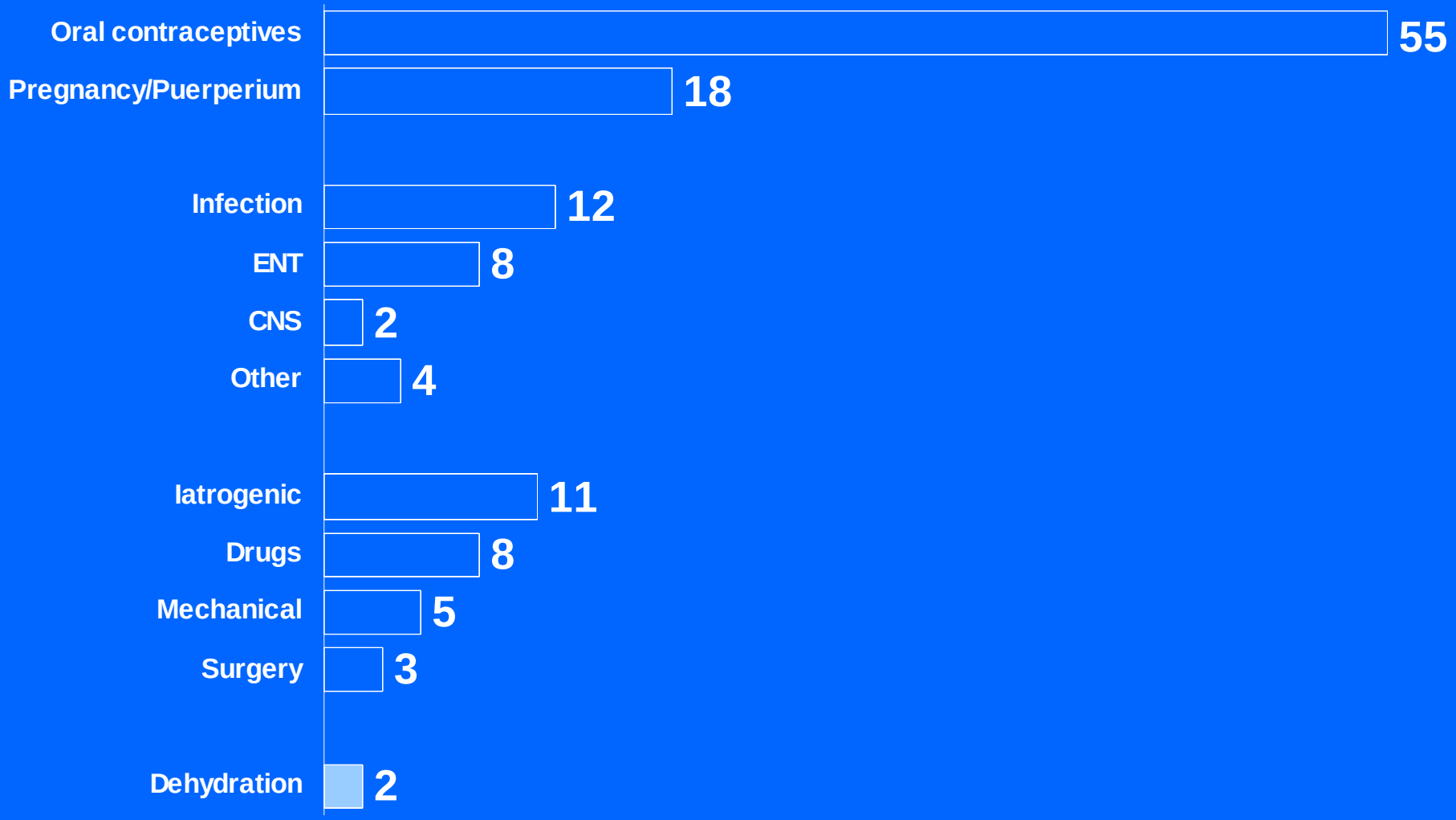
- Permanent
  - Hereditary thrombophilia
  - Chronic conditions associated with a prothrombotic state (e.g. APS, malignancy)
- Transient
  - Oral contraceptives
  - Pregnancy/puerperium
  - Infections
- Both permanent and transient
- None (cryptogenic CVT)

CVT: ASSOCIATED CONDITIONS PERMANENT



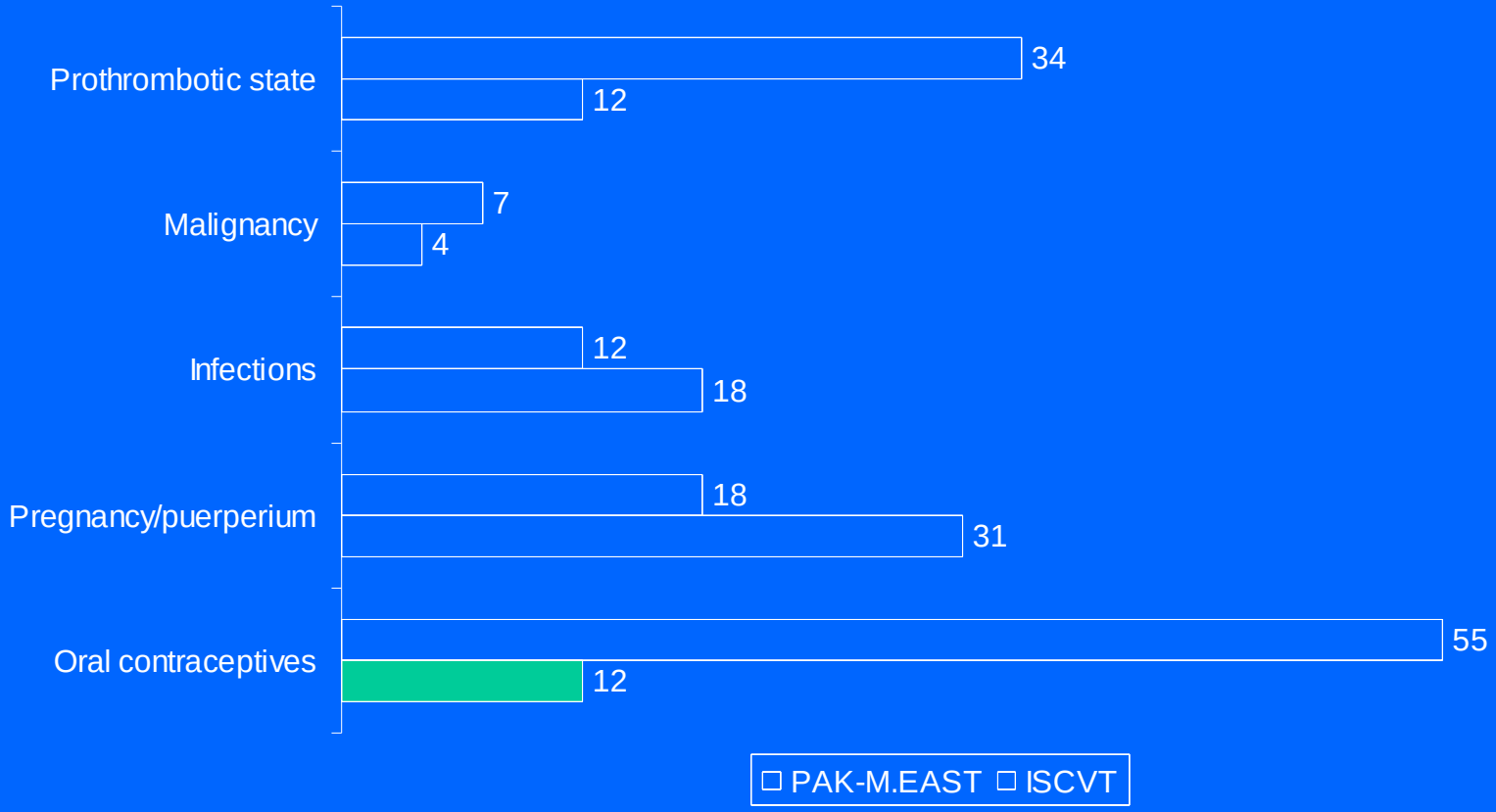
ISCVT, Stroke, 2004

CVT: ASSOCIATED CONDITIONS TRANSIENT



ISCVT, Stroke, 2004

CVT: ASSOCIATED CONDITIONS IN A PAKINSTAN-MIDDLE EAST COHORT



Khealani et al Stroke 2008

CONTRACEPTIVES (54%)

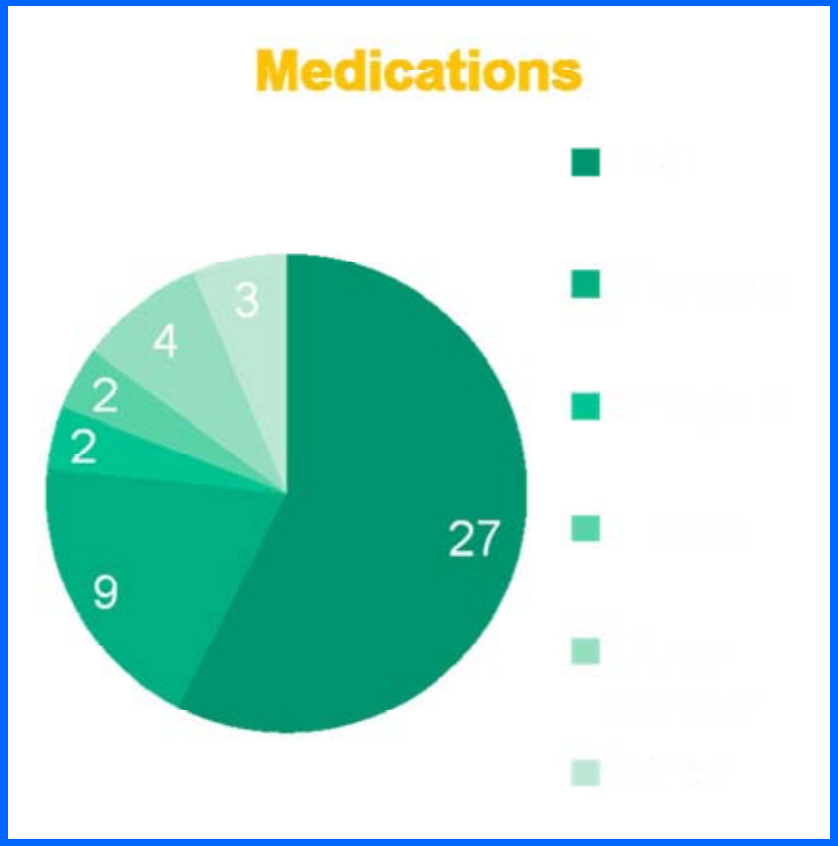
Estrogens		OR	5.59
	CVT	IR/100000/y	IRR
Levonorgestrel	2	0.7	1.0
Norgestimate	7	1.6	2.4
Desogestrel	5	2.7	4.0
Contraceptive patch	0	0	----

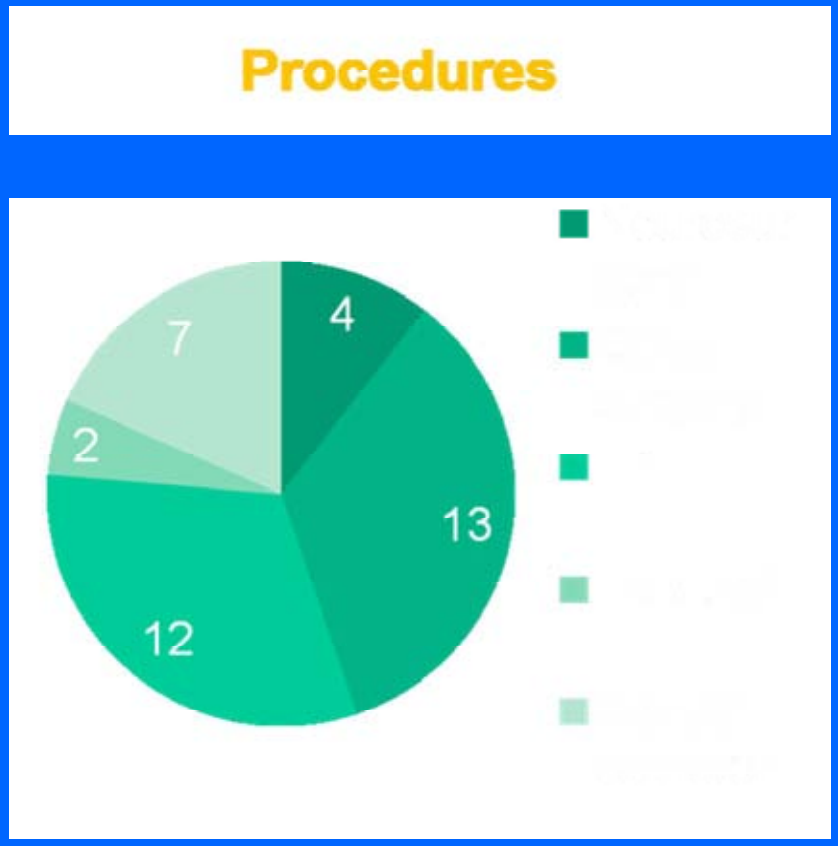
Dentali et al, 2006; Jick and Jick, 2006

OTHER GENDER SPECIFIC CAUSES

- Vaginal rings
  - Case reports
- Emergency (day after) contraception
  - Case report
- In-vitro fertilization
  - Case report
- Hormonal replacement therapy

IATROGENIC CVT: ISCVT (11%)

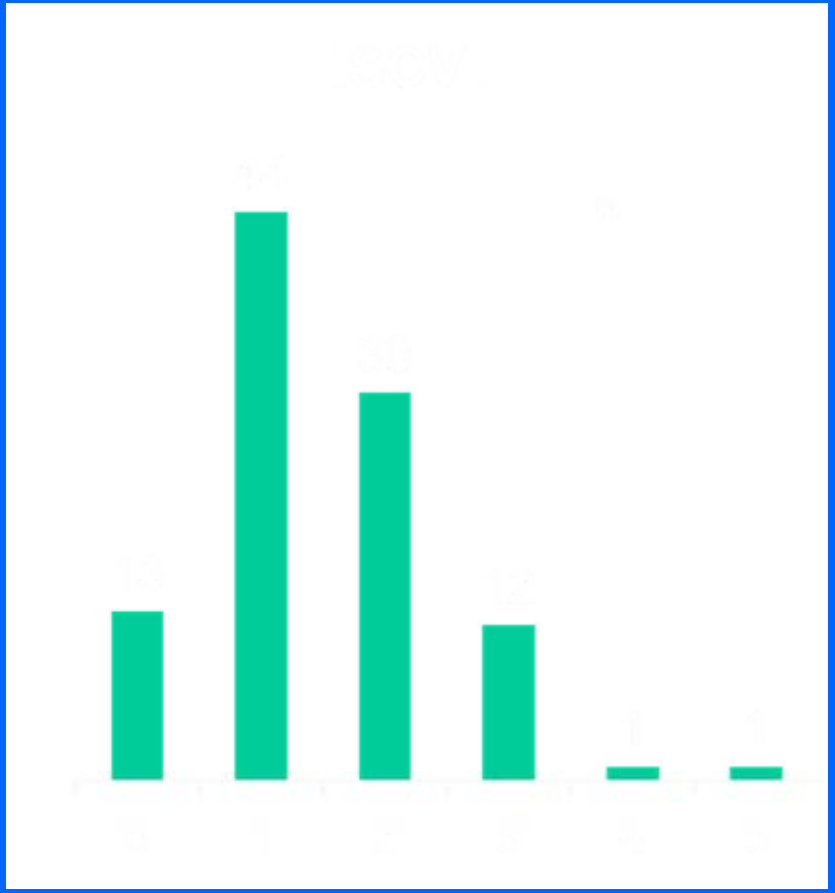




Ferro and Canhão, 2013

CVT ASSOCIATED CONDITIONS

- 13% no associated condition
- 44% > 1 associated condition
  - 41% - genetic prothrombotic mutation



Nº associated conditions

CVT: PROTHROMBOTIC MUTATIONS IN ADULTS

- Prothrombin G20210A 5.5 x
- Factor V Leiden 2.4 x
- MTHFR C677T 0.94 x
- PAI-1 0.93 x
- Protein Z/G79A 1.34 x
- JK-2/V617 not estimable

Gouveia and Canhão, 2010; Marjot et al Stroke 2011

THROMBOPHILIA SCREENING

- Lupus anticoagulant
- Anticardiolipine antibodies
- Anti-?Ⅱ glycoprotein antibodies
- Homocystinemia
- Protein S
- Protein C
- Antithrombin
- Factor V Leiden mutation
- Prothombin G20210A mutation
- Factor VIII

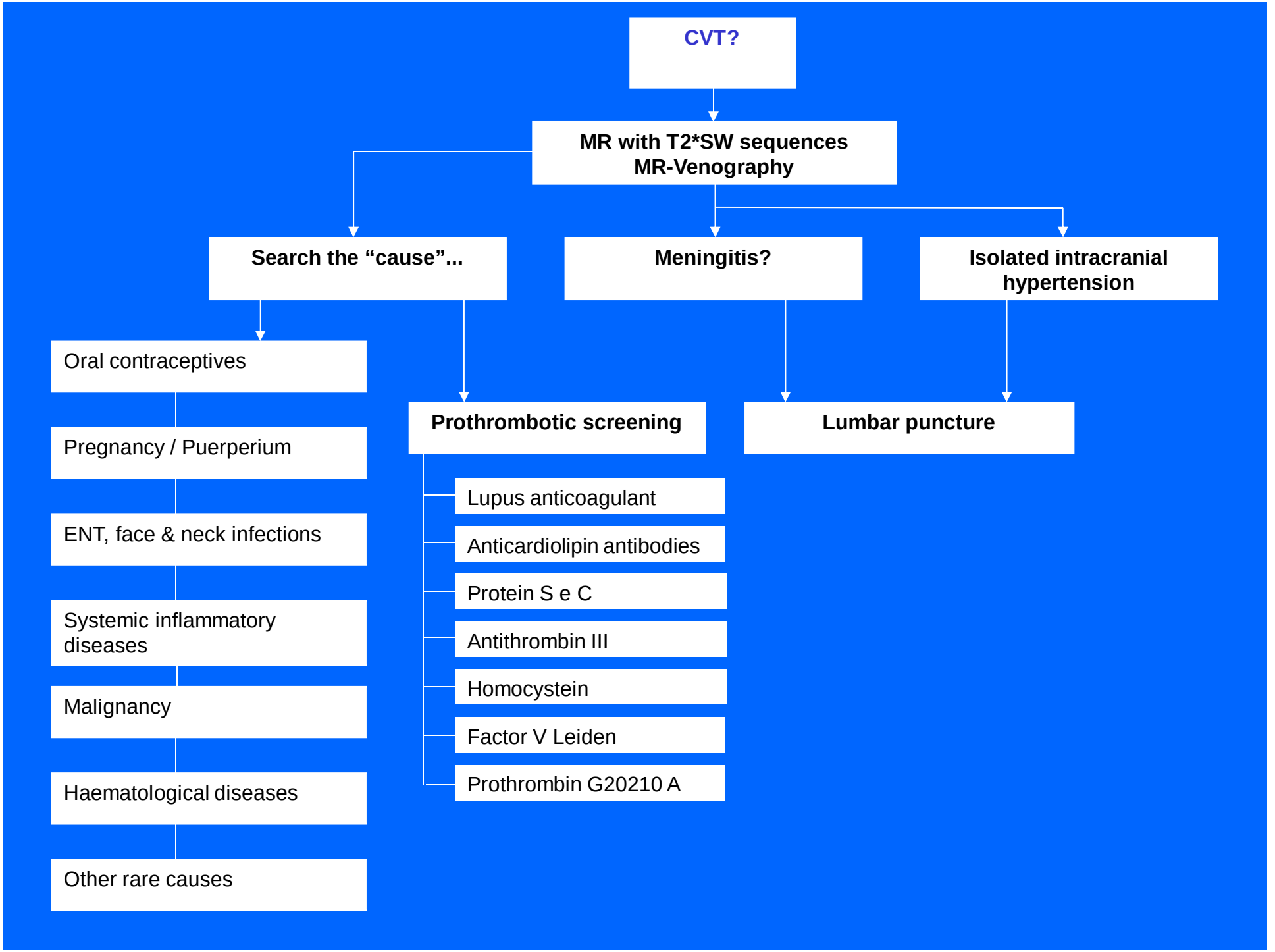
CVT: SCREENING FOR THROMBOPHILIA

- International Consensus Statement Guidelines (2005)
  - 1st VTE, VTE < 50 years, only risk factor oral contraceptives or pregnancy, recurrent VTE

- AHA/ASA Guidelines (2011)
  - Screening is recommended
    - in adults (Class I, level C)
    - In children (Class IIb, level B)

THROMBOPHILIA SCREENING operational aspects

- Protein S, C and antithrombin deficiencies
  - After at least 6 weeks after the acute phase
  - Not in patients on vitamin K antagonists
  - Confirmed with repeated testing
- APS
  - High titers of lupus anticoagulant, anticardiolipin antibody IgG or anti-?2-glicoprotein IgG
  - At least 2 occasions 12 weeks apart

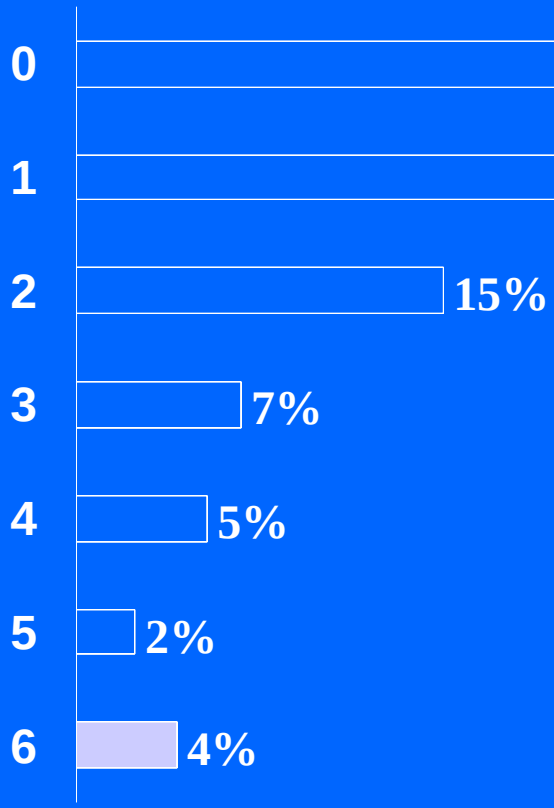

CVT?
MR with T2*SW sequences
MR-Venography
Search the “cause”...
Meningitis?
Isolated intracranial hypertension
Oral contraceptives
Pregnancy / Puerperium
ENT, face & neck infections
Systemic inflammatory diseases
Malignancy
Haematological diseases
Other rare causes
Prothrombotic screening
Lupus anticoagulant
Anticardiolipin antibodies
Protein S e C
Antithrombin III
Homocystein
Factor V Leiden
Prothrombin G20210 A
Lumbar puncture

CRYPTOGENIC CVT?

- 13% in ISCVT, 88% with complete prothrombotic screening

- CVT preciding a systemic disease
  - Anti-phospholip syndrome
  - Essential thrombocythemia and policythemia
  - Inflammatory diseases (IBD, B'D)
  - Malignancy

CVT: ACUTE PROGNOSIS



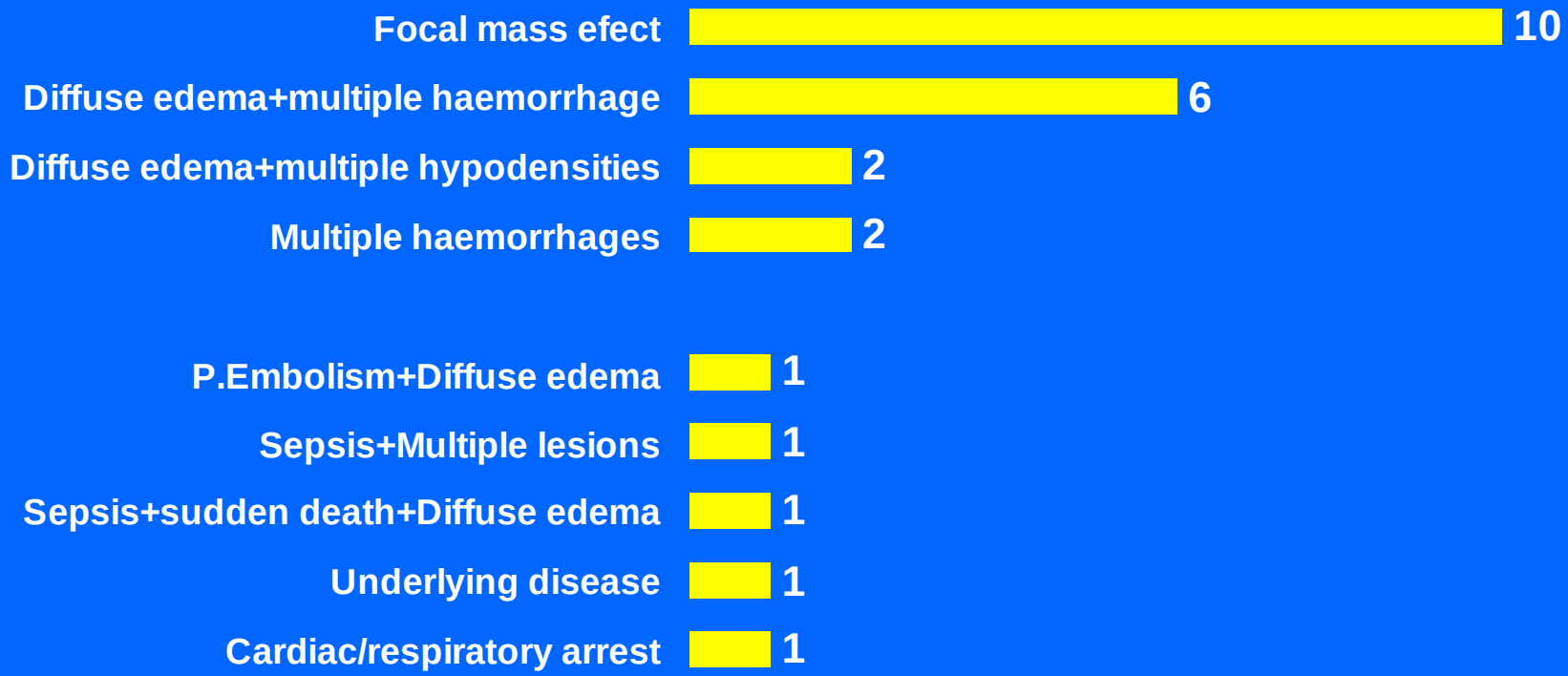
Complete recovery (Rankin 0/1)
N=410 66%

Death or dependency (Rankin 3-6)
N=118 19%

ISCVT, Stroke, 2004

MECHANISMS OF DEATH

Transtentorial herniation



Canhão et al Stroke 2005

CVT OUTCOME

DEATH OR DEPENDENCY AT THE END OF THE FOLLOW-UP: DATA FROM PROSPECTIVE STUDIES WITH LONG-TERM FOLLOW UP

Study	Follow-up Mean time (months)	Death/dependency yes/no	%	95% CI	Weight%
Rondepierre	6	8/18	44,4	24,6 - 66,3	1.9
Preter	78	18/85	21,2	13,8 - 31,0	9.1
DeBruijn	19	11/55	20	11,6 - 32,4	5.9
VENOPORT	22	8/91	8,8	4,5 - 16,4	9.7
Breteau	36	10/55	18,2	10,2 - 30,3	5.9
Cakmak	3	2/16	12,5	3,5 - 36,0	1.7
ISCVT	18	84/616	13,6	11,2 - 16,6	65.8
Total		141/936	15,1	12,9 - 17,5	100.0
Wasay	6	18/79	22.8	14.6 - 33.8	
Narayan	33	143/428	33.4	29.1 – 30.1	

LAST FOLLOW UP
DEATH/DEPENDENCY (n=32)

PROGNOSTIC FACTOR	HR	95%CI
CNS infection	3.3	2.0-17.2
Any malignancy	2.9	1.6-5.1
Deep venous system thrombosis	2.9	1.7-5.0
Haemorrhage on CT/MR	1.9	1.2-3.0
GCS score <9	2.6	1.4-4.6
Mental status disorder	2.0	1.2-3.1
Age > 37	2.0	1.2-3.3
Male gender	1.6	1.0-2.5

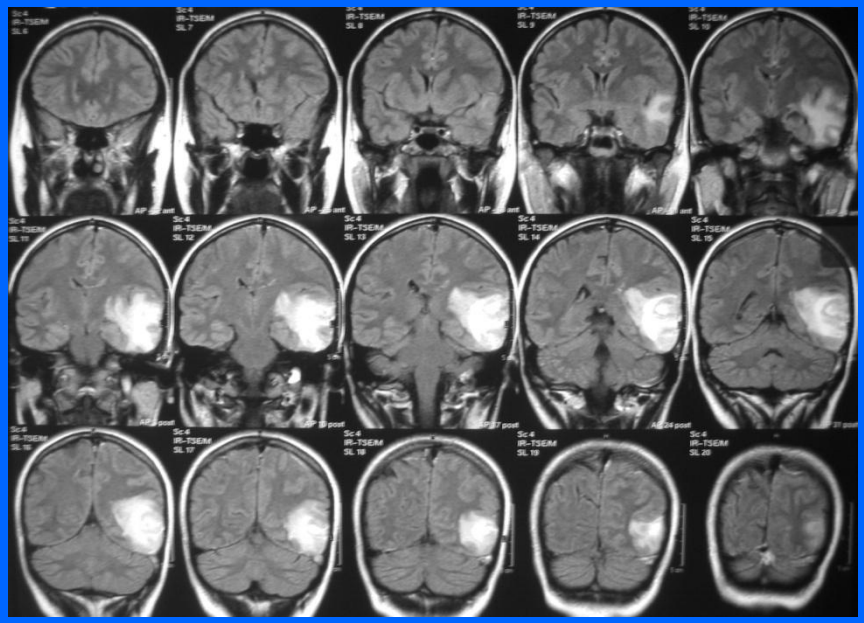
Accuracy: 85% area under the ROC curve 0.79

CVT PROGNOSIS

- Prognostic scale
  - Malignancy 2
  - Thrombosis of the deep venous system 2
  - Coma 2
  - Mental status dist. 1
  - IC haemorrhage 1
  - Male gender 1

Women 38 years, oral contraceptives, alert, aphasia

lateral sinus and jugular vein



Score: 1/9 – good prognosis

Ferro et al Cerebrovasc Dis 2009

ANTI-THROMBOTIC TREATMENT

Meta-analysis of heparin trials

Einhaupl et al, 1991; IV heparin, 20 patients

De Bruijn et al, 1999; nadroparin, 59 patients

2 trials excluded: Nagaraja, 1995; Maiti, 1997

	Relative risk	95% CI
Death	0.33	0.08 - 1.21
Death or dependency	0.46	0.16 - 1.31

Absolute risk reduction for death or dependency 13%

Including excluded trials

Death	0.33	0.14 - 0.78

Stam J et al, Cochrane Database of Systematic Reviews 2012

CVT: COMPLICATIONS OF HEPARIN TREATMENT

- Low risk of intracranial haemorrhage (8%)
- Low risk of systemic haemorrage (1.8%)
- Such haemorrages do not influence outcome

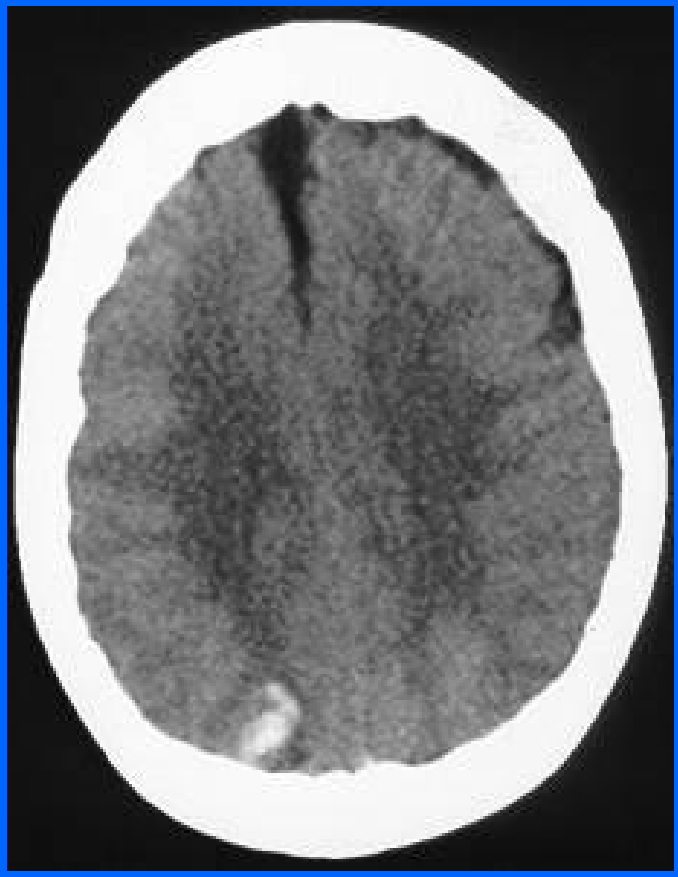
- Safe to use in patients with intracranial haemorrhages, either intracerebral or subarachnoid

ANTICOAGULATION IN THE ACUTE PHASE

- EFNS Guideline (2010)
  - Patients with CVT without contraindications for anticoagulation should be treated eather with body weigth adjusted LMWH or adjusted dose IV heparin – *Level B*
- AHA/ASA Guideline (2011)
  - Initial anticoagulation with adjusted dose UFH or LMWH is reasonable - *Class IIa, level of evidence B*

ANTICOAGULATION IN THE ACUTE PHASE

- EFNS Guideline (2010)
- AHA/ASA Guideline (2011)
  - Intracerebral hemorrhage is not a contraindication for anticoagulation

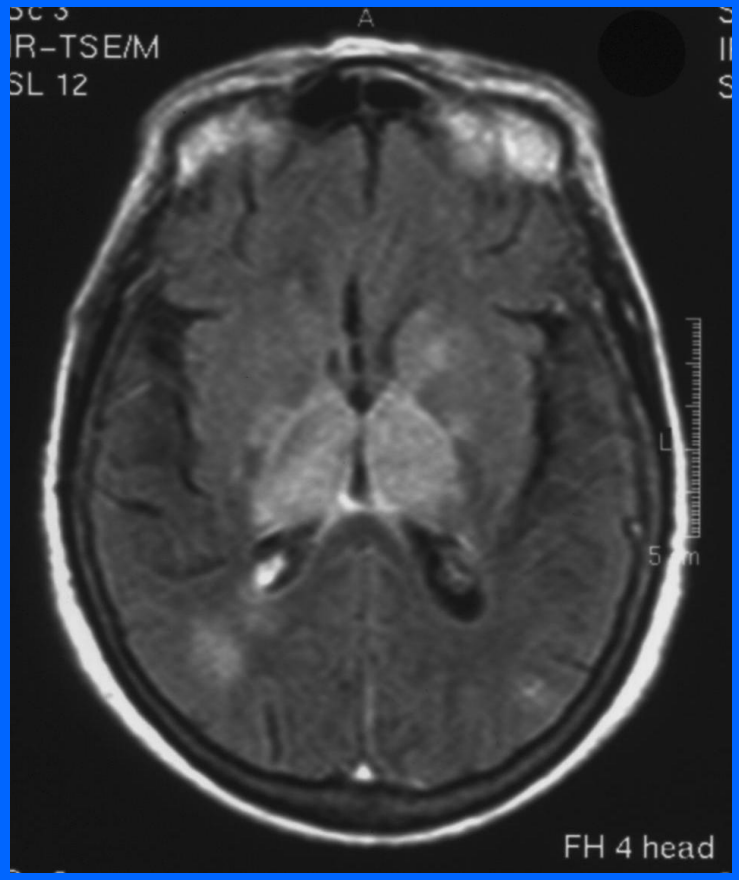


IV UFH or LMW Heparin?

- ISCVT*
  - LMW Heparin - 119 (28%) vs IV heparin – 302 (72%)
  - In favour of LMWH (after adjusting for prognostic factors)
    - More patients independent at 6 months
      - OR 2.4 (95% CI 1.0 to 5.7)
    - Less new intracerebral hemorrhages
      - OR 0.29 (95% CI 0.07 to 1.3)
  - No difference in complete recovery and mortality
- RCT in India
  - 32 IV heparin vs 34 LMWH
  - Death – 6 vs 0, Complete recovery – 20 vs 30
- LMWH seems preferable over IV UF heparin

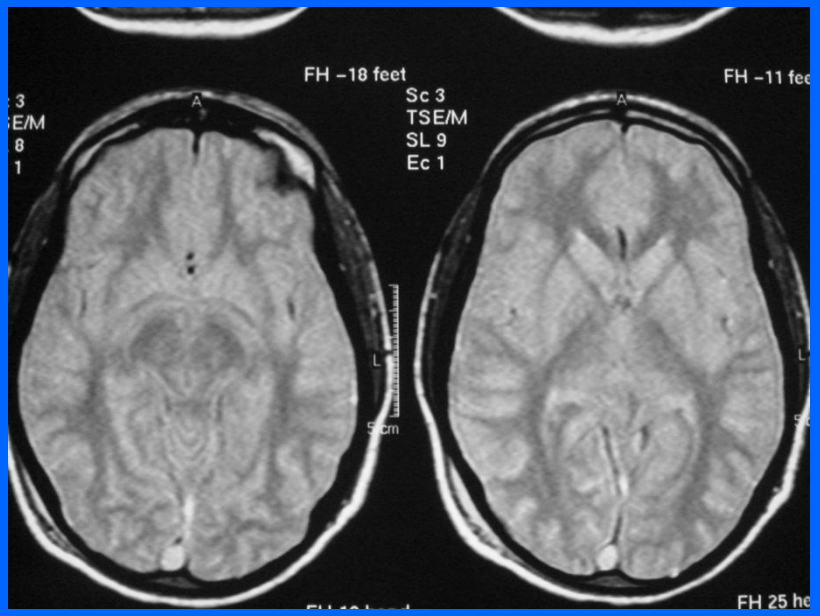
Coutinho et al (ISCVT) Stroke 2010; Misra et al 2012

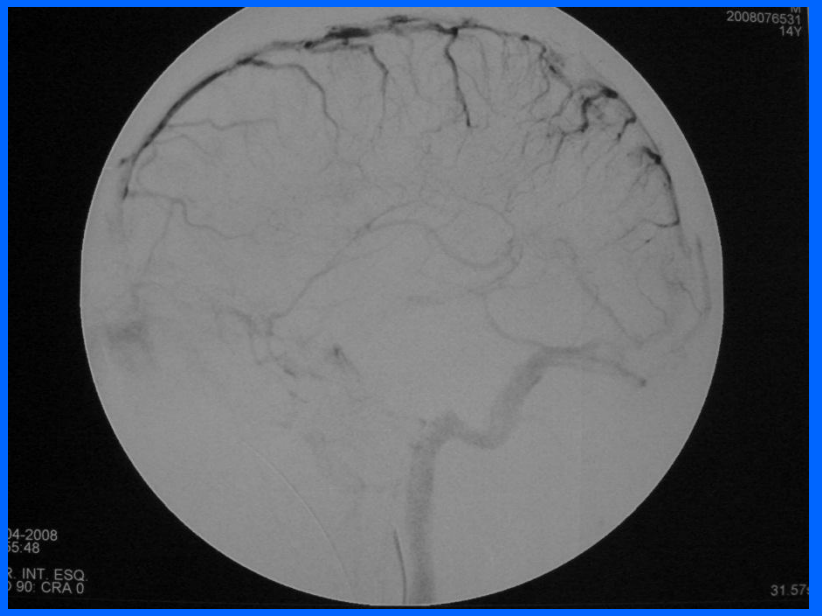
LOCAL THROMBOLYSIS IN CVT



14 year old boy with nephrotic syndrome treated with steroids and cyclosporine. Headache, coma and seizures

LOCAL THROMBOLYSIS IN CVT





Total recovery after being treated with local IV rtPA

Costa et al , 2010

THROMBOLYSIS IN CVT SYSTEMATIC REVIEW

- No RCT
- 15 studies (14 local, 1 systemic), 156 patients
- Death – 12 patients (9.2%)
- Major bleeding complications – 15 (9.8%)
  - Intracranial hemorrhages – 12 (7.6%)
  - Fatal intracranial hemorrhages - 7 (58.3%)

- Thrombolysis in CVT is associated with a non-negligible incidence of major bleeding complications

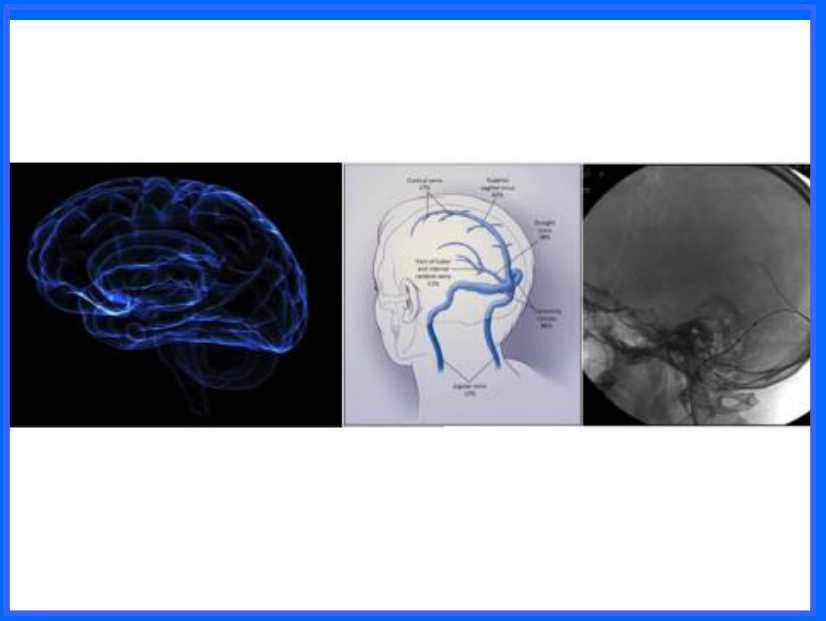
Dentali et al, Thromb Haemost 2010

TO-ACT TRIAL

Severe acute CVT
Mental status disorder
Coma
IC hemorrhage
Deep venous system

Standard anticoagulation
IV heparin or sc.LMWH

Local thrombolysis
rtpA or urokinase
+/- mechanical



PRIMARY ENDPOINT – mRS at 12 months

Safety endpoints – intra & extracranial bleedings

Sample size: 164 pt

Status September 2013

Centers -11
Countries – 2 (+3)
Included patients - 22

TVC: LOCAL IV THROMBOLYSIS

- Efficacy and safety may be less favourable in current practice than reported in publications
- Still an experimental treatment
- Must be reserved for patients in severe condition, diffuse brain edema, bilateral thrombosis of the deep venous system or worsening despite medical treatment
- Include patients in the TO- ACT trial

TREATMENT OF INTRACRANIAL HIPERTENSION

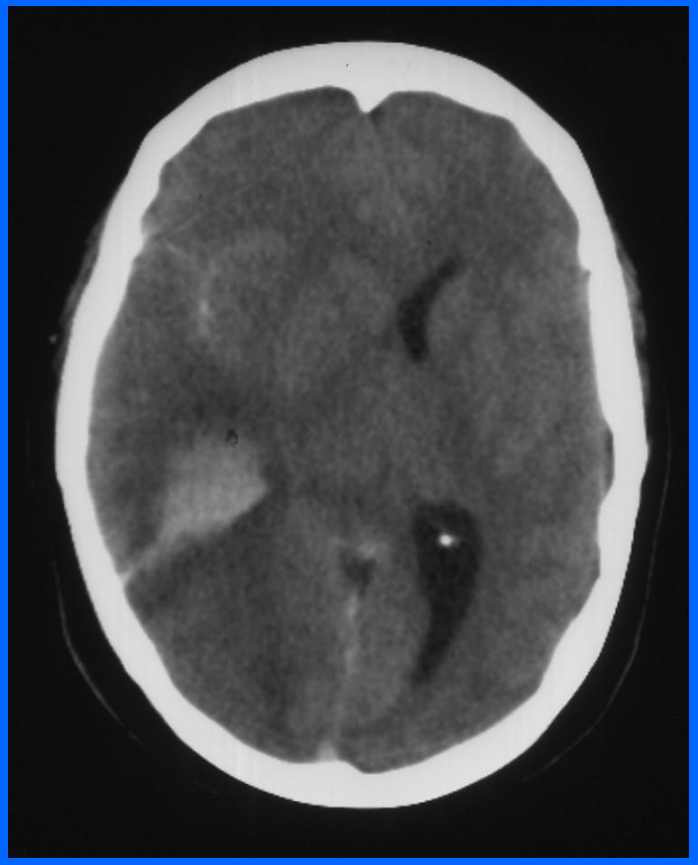
- Medical
  - Lumbar punctures
  - Osmotherapy (mannitol, glycerol)
  - Corticosteroids (no)
  - Dieuretics (furosemide, acetazolamide)
- Intensive
  - Sedation, ventilation
- Surgical
  - Hemicraniectomy
  - Haematoma evacuation
  - Shunt (external, ventricular, lumbar)
  - Optic nerve fenestration

ARE STEROIDS USEFUL?

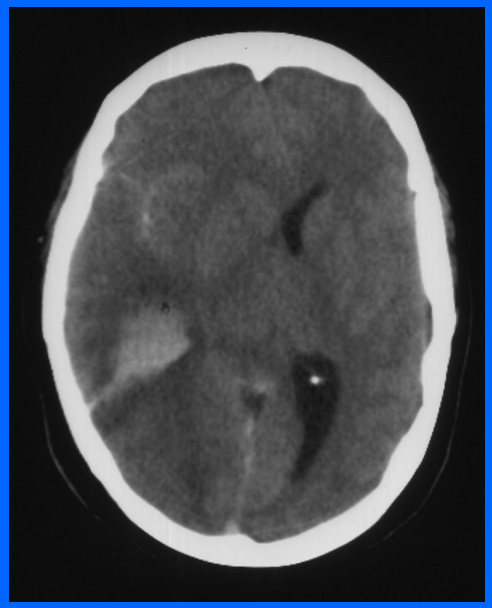
- Whole ISCVT cohort
  - no effect on outcome OR=1.5 95%CI=0.9-2.4
- Case-control design matched by prognostic factors
  - no effect on outcome OR=1.7 95%CI=0.9-33.3
- Stratification by nº of prognostic factors
  - No difference in any strata
- Sensitivity analysis by underlying condition
  - Similar results

Canhão et al, 2004

HEMICRANIECTOMY IN CVT

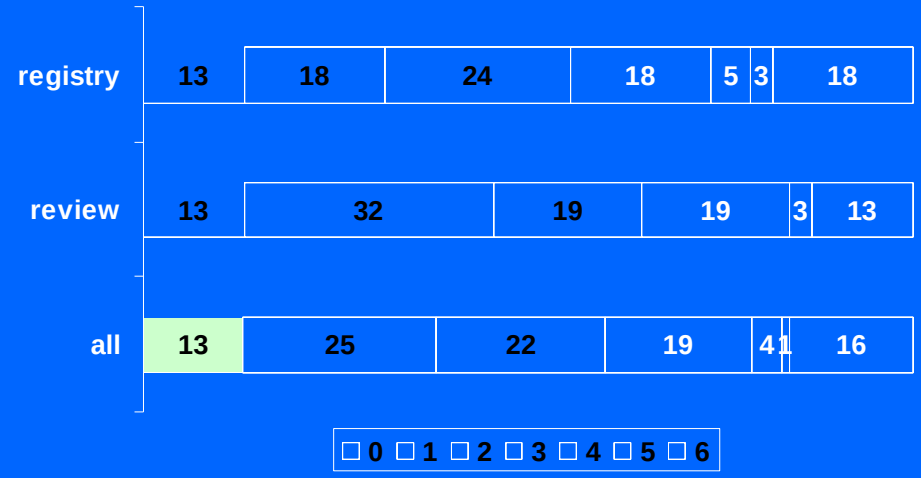


DECOMPRESSIVE SURGERY



Retrospective registry - 38

Systematic review - 31



In CVT patients with large brain lesions causing herniation, decompressive surgery was life-saving and often resultes in good functional outcome, even in pts. with severe clinical conditions

Ferro et al, Stroke 2011

DECOMPRESSIVE SURGERY

Ferro et al, Stroke 2011

DECOMPRESSIVE SURGERY

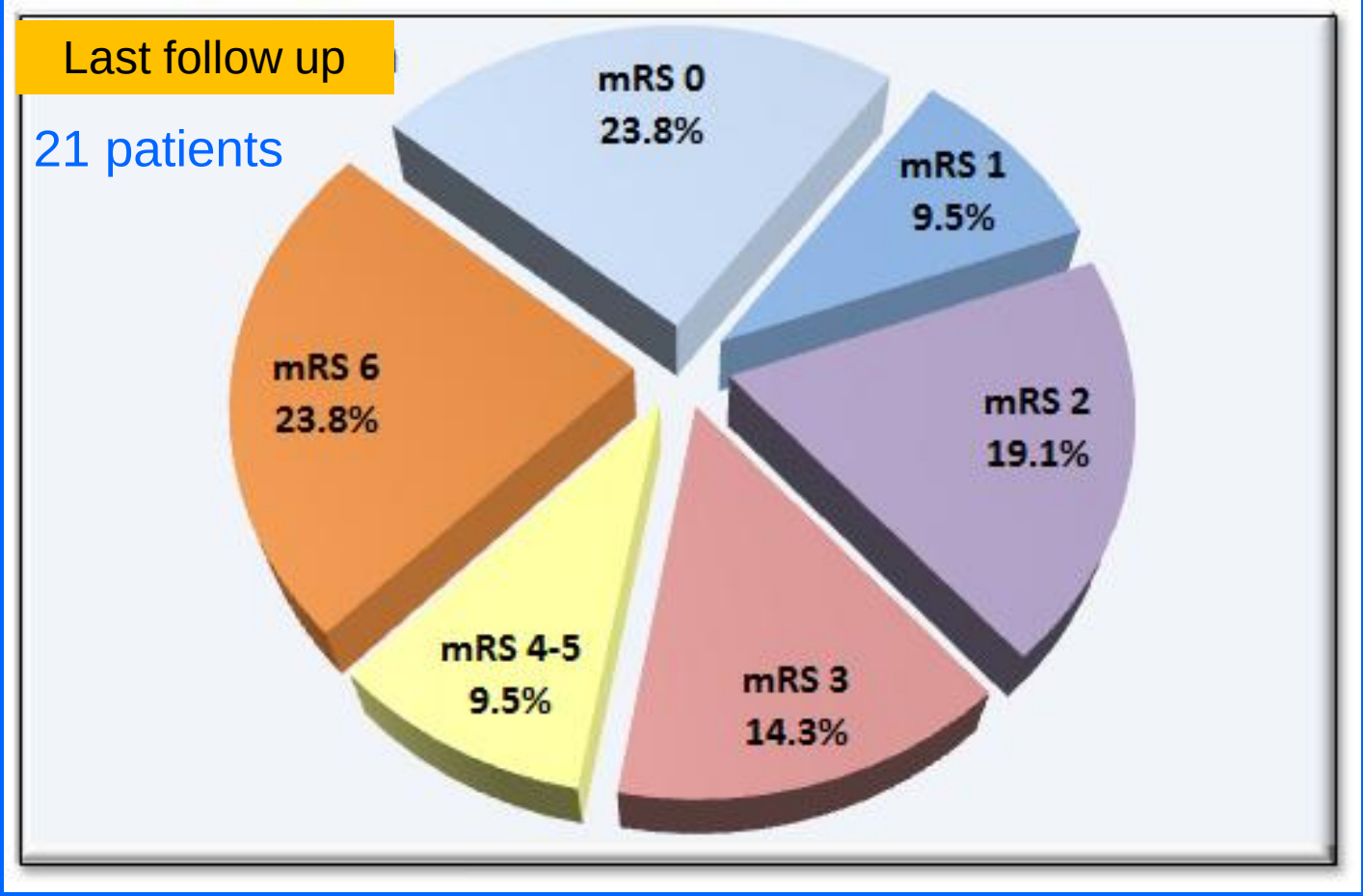
- Amsterdam (2006-2010) - 10 patients
  - Deaths - 2
    - edema, enlarging hemorrhagic infarcts
  - mRS 5 - 1
  - mRS 0-1 - 5

Zuurbier et al, J Neurol 2012

- Bangalore (2006-2008) – 34 patients
  - Deaths - 6
  - mRS 5 - none
  - mRS 0-1 - 28

Thirupathi et al J Neurosurg 2012

SHUNTING



Shunting does not prevent death or severe disability

Lobo S et al ESC 2012

ANTIEPILEPTICS AND EARLY SEIZURES

- ~30% have seizures from day 0-15
- Risk of status epilepticus
- Risk of death, including sudden death
- More likely to occur in patients with
  - Presenting seizures
  - Parenchymal lesions (infarcts or hemorrhages)

Ferro et al Stroke 2008

ANTIEPILEPTICS AND EARLY SEIZURES

- No supratentorial lesion, no presenting seizure
  - No AEs 197 early seizure 5 (2.5%)
  - AEs 11 early seizure 0
- No supratentorial lesion, presenting seizure
  - No AEs 14 early seizure 1 (7.1%)
  - AEs 35 early seizure 0
- Supratentorial lesion, no presenting seizure
  - No AEs 134 early seizure 11 (8.2%)
    OR=0.3
  - AEs 35 early seizure 1 (2.9%)
- Supratentorial lesion, presenting seizure
  - No AEs 47 early seizure 24 (51.0%)
    OR=0.006
  - AEs 148 early seizure 1 (0.7%)

Ferro et al Stroke 2008

CVT: ANTIEPILEPTICS

- EFNS guideline 2010
  - AED in patients with focal neurological defects and supratentorial lesions (GPP)
- AHA/ASA (2011)
  - routine use of AED is not indicated to prevent seizures (III, C)
  - single seizure with parenchymal lesions (I, B)
  - single seizure without parenchymal lesions (IIa, C)
- Optimal duration of treatment is unknown
  - Use general rules for AED selection and discontinuation

EVENTS DURING FOLLOW UP

EVENT	n	%
• **Death**	25	4.0
– related to the underlying condition	11	
• **Recurrent sinus thrombosis**	14	2.2
• **Other thrombotic events**	27	**4.3**
– deep venous thrombosis	16	2.5
– pulmonary embolism	3	0.5
– stroke	2	0.3
– TIA	2	0.3
– acute limb ischemia	4	0.7
• **Seizures**	66	**10.6**
• **Severe headache**	88	14.1
• **Severe visual loss**	4	0.6

HEADACHES

- Mostly primary headaches, unrelated to CVT
- If severe or persistent
  - MR or CT venography
  - Compare with previous venography
- Management
  - Paracetamol
  - Acetazolamide
  - Lumbar punctures
  - Shunt (ventricular, lumbar)

RISK OF REMOTE SEIZURES

- 67 (10.7%) had remote (> 2 weeks after diagnosis) seizures
  - Until 6 month: 36
  - Until 1 year: 55
  - Until 2 year: 66
  - > 1 seizure (epilepsy): 29 (4.6%)
- Risk factors for remote seizures
  - IC haemorrhage (HR=2.62), early seizure (HR=2.42), paresis (HR=2.22)
- Risk factors for epilepsy
  - IC haemorrhage (OR=6.76), early seizure (OR=3.99), paresis (OR=2.75)

Ferro et al presented at ESC 2007; abstract in Cerebrovasc Dis

PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM

- Risk of recurrence of venous thrombotic events
  - CVT: 2-12%
    - 0.5-1.5 per 100 person-years
  - Other VT: 7-15%
    - 2.0-4.1 per 100 person-years
- Risk factors for recurrence of venous thrombotic events in adults
  - Male gender
  - Policythemia/thrombocythemia
  - Severe thrombophilia (DVT and PE)
  - Previous VTE

- EFNS and AHA/ASA Guidelines
  - 3 months (transient risk factors) to lifetime, depending on thrombophilia grading
- International survey
  - 3 months -13%
  - 6 months – 64%
  - 12 months – 20%

Miranda et al Stroke 2010; Martinelli et al Circulation 2010; Dentali et al 2012

Coutinho et al, 2011

SEVERITY OF THROMBOPHILIA & RECURRENT VTE

- Antiphospholip antibody syndrome
- Cancer
- High D dimers (?) after discontinuation of anticoagulation

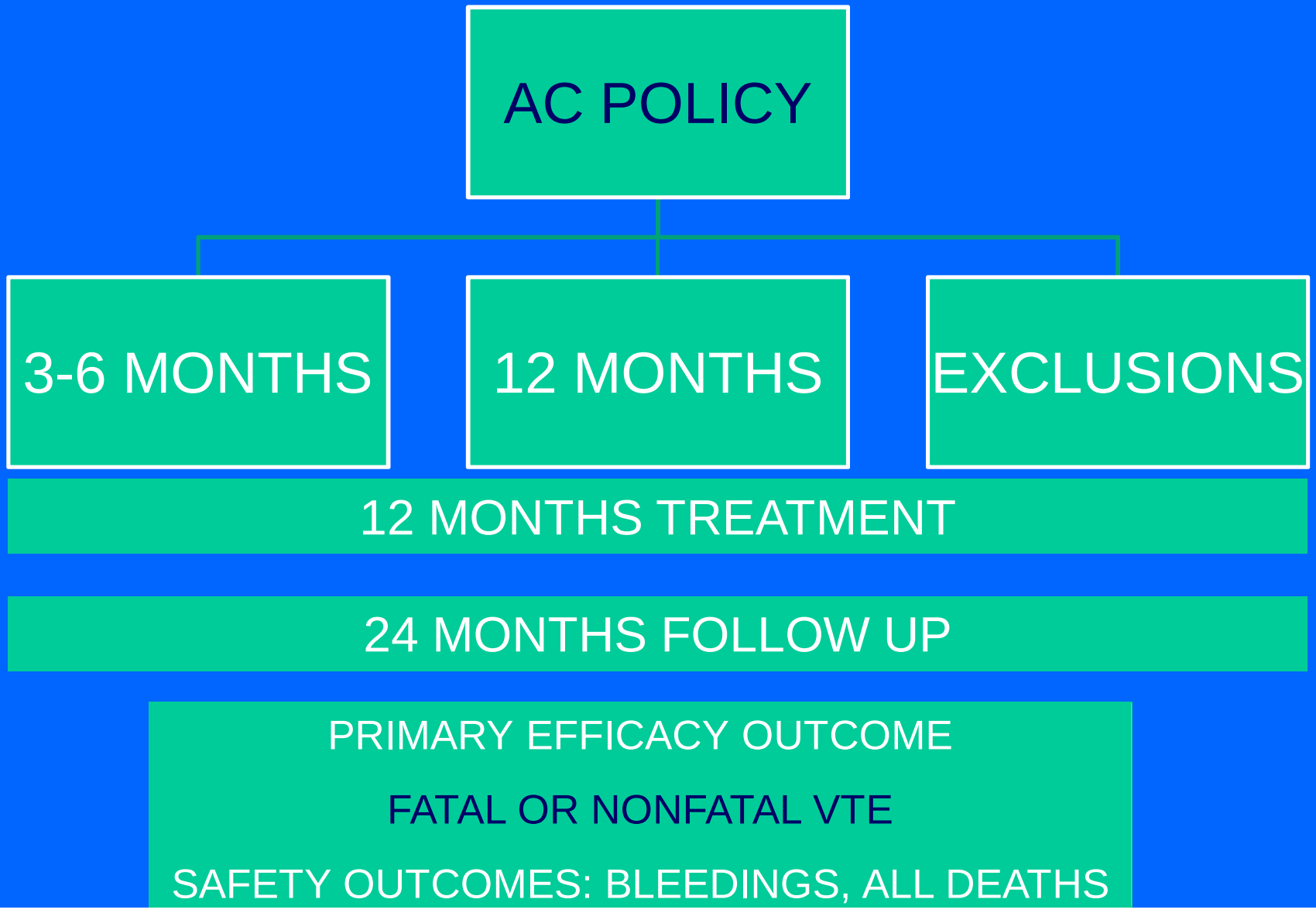
Thrombophilic defect	Annual risk of first DVT	Relative risk (compared to community controls)	Risk of recurrence
Antithrombin deficiency Protein C deficiency Protein S deficiency	1.52-1.90%	15-19x	At 5 yrs – 40% At 10 yrs – 55%
Factor V Leiden Prothrombin 20210A High FVIII	0.34-0.49%	3-5x	At 5 yrs – 11% At 10 yrs – 25%
High FIX High FXI High TAFI Hyperhomocysteinemia	Not independent risk factors for venous thrombosis. Risk associated with high FVIII		

Makris M Blood 2009 (evidence form DVT)

PREVENTION OF RECURRENT VENOUS THROMBOEMBOLISM

- CVT related to a transient risk factor – 3 or 3-6 months
- CVT idiopathic or related to “mild” thrombophilia – 6-12
- CVT related to “combined”, “severe” thrombophilia or recurrent CVT– permanent
- EFNS guideline (Eur J Neurol 2010)
  - Good practice point
- AHA/ASA guideline (Stroke 2011)
  - Class IIb, level of evidence C

EX-COA TRIAL
clustered randomised trial



CVT: GOOD POINTS FOR CLINICAL PRACTICE

- High suspiction rate
- Confirm diagnosis by MR/MR angio
- Prothombotic screening in all patients
- Anticoagulants for almost all patients in the acute phase
- Hemicraniectomy or local thrombolysis in selected severe cases
- Antiepileptic drugs for patients with seizures and supratentorial lesions

- Join ongoing registries and trials