# *Arteriel trombo-emboli kursus for DSTH*

Hotel Scandic – Vejle
4. – 6. oktober 2017
Ib Tønder Hansen
Reumatologisk Afd. U - AUH

# *Pt. case: Akral mummificering*

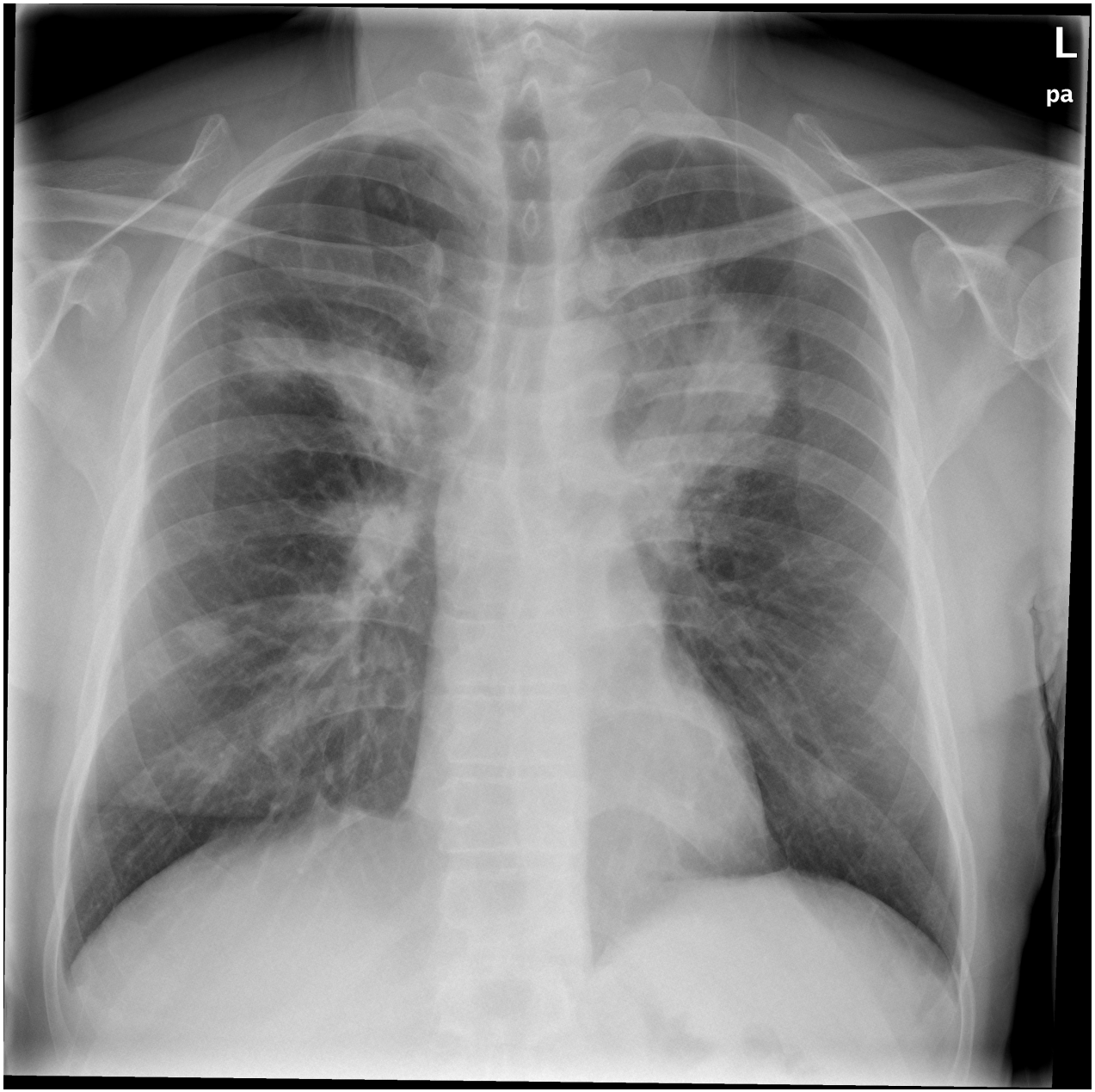
# *57 årig tidl. rask mand indlægges i MVA AUH*

- Adm. direktør i stort firma
- Luftvejssymptomer i to måneder
  - Snue, tæt i hovedet, åndenød ved aktivitet
- Antibiotika via egen læge uden den store effekt
- Tidligere ryger − ophørt for ca. 10 år siden
- Højresidig hævelse af knæ, ankel og MTP 1+2
- 8 kg vægttab, træthed, nattesved i en måned
- Feber op til 39$^{o}$
- Stet. pulm: Obs for afsvækket resp. apikalt sin.
- Ellers normal objektiv undersøgelse

# *Blodprøver*

- CRP 290, SR 88, Trombocyt 690 (145-350),
- Leukocytose 15 (3,5-10), neutrofil overvægt
- Albumin 18 (36-45), Hgb. 8 (8,3-10,5)
- ALAT 120 (10-70), Bas.phosf. 150 (35-105)
- Nyretal og elektrolytter inkl. $Ca^{2+}$ ion normale
- IgG+A+M normale
- Fibrin D-dimer 6,7 (<0,5), B2GP1 <7, kryoglob 0
- Mikrobiologi fra blod, urin og snot

# *CT-Thorax*




- Bilaterale infiltrater
- Supraklav. Glandel
- Hvad tænker man??

# *Principielle diagnostiske overvejelser*

- ***Infektion?***
  - Negative dyrkninger fra blod, urin og snot

- ***Malignitet?***
  - ***FNA*** supraclav. gldl: Inflammation
  - ***EBUS grovnål*** fra lungen: Svære reaktive forandringer, organiseret pneumoni, ingen malignitet

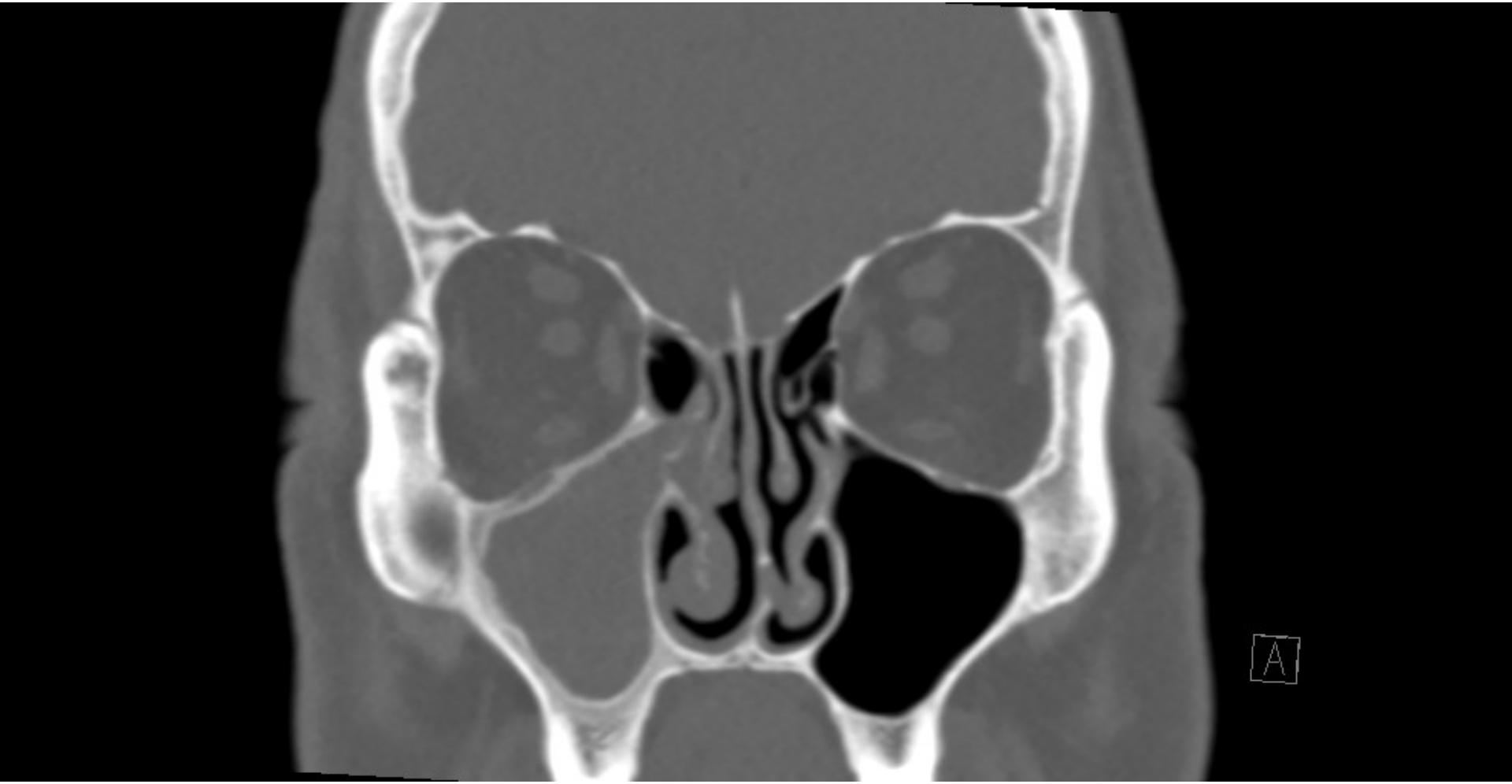
- ***Inflammatorisk sygdom?***
  - Led?
  - Bindevæv?
  - Vaskulit?

# *Reumatologisk tilsyn*

- Fordi der er hævede led

- Med tiden rå slimhinde og sår i næsen, næseblod
- Reaktiv artrit / artrit / bindevævssygdom????
- Urinundersøgelse:
- ANA, dsDNA RF, Anti-CCP, C3 og C4, ANCA
- CT-Bihuler, mellemøre, mastoid
- Patienten overflyttes til reumatologisk regi

# *CT bihuler, mellemøre og mastoid*



# *CT bihuler, mellemøre og mastoid*

# *Urin undersøgelse – glomerulonefrit?*

- ***Biokemi:*** Normale nyreparametre
- ***Stix*** uden blod eller protein
- ***Døgnurin:*** Clearence normal; Protein 50 mg/d
- ***Ingen røde cylindre***

# *Udvikling i klinikken – Reum. Afd. U*

- ***100 mg prednisolon behandling***
  - Eklatant effekt på AT og led
  - CRP falder brat
- ***Huden akralt på fingrene:***
  - Punktformige vaskulitforandringer/mikronoduli
  - Neglesplinters
- ***PNS:*** Nedsat sensibilitet sv.t. 4+5 finger sin
- ***ØNH-tilsyn:*** Vulnerabel, ulcererende slimhinde bilat. i næsen. Biopsi med akut og kron. inflammation
- ***TTE og TEE:*** Ingen kardiel embolikilde

# *Udvikling i klinik og behandling*

- ***Methylprednisolon*** 500 mg i.v. dagligt i 3 døgn, som gentages pga.:
  - Akral cyanose og nekrotisering 3-5 finger bilat.

- ***Iloprost*** behandling

# *Blodprøver – ANCA*

- MPO-ANCA < 3,5
- PR3-ANCA 5,9 (<2,0)
- GBM-Ab <7

# *Fingrene i fokus i behandlingen*

- Methylprednisolon 500 mg dagligt i 3 døgn pga de progredierende nekrotiske fingre
  - Akral cyanose og nekrotisering 3-5 finger bilat
  - Gentages fordi tilstanden progredierer

- Iloprost

# *Diagnose og behandling*

- Wegener diagnosen købes som eksklusionsdiagnose
  - Malignitet anses udelukket
  - Infektion anses udelukket
  - Relevant organinvolvering til WG / GPA

- ***Beskedent PR3-ANCA positiv, systemisk Wegener (granulomatose med polyangiit) med involvering af HNØ – lunger – PNS – Hud***
  - PR3-ANCA kommer til at stige til 70 da patienten er behandlet til remission.

# *Pt. case: Akral mummificering*

# *Wegener – småkarsvaskulit – hyppigste klinik*

- Øre-Næse-Hals regionen
- Lungerne
- Nyrerne
- Huden
- Perifere nervesystem

- ***Principielle differentaldiagnoser***
  - 1) Infektion
  - 2) Malignitet
  - 3) Inflammatorisk sygdom

# *Cavitating lung nodulus*

And now…….

To something completely different!

And then again……

# *Giant cell arteritis*

- ***Vasculitis in medium to large arteries:***
  - Temporal arteritis
  - Large vessel arteritis
  - Polymyalgia rheumatica???

- ***Arterial trombo-embolic complications:***
  - Blindness, Thrombosis, AA, emboli, AMI

- ***Great development in diagnosis and treatment***
  - Imaging modalities
  - Biologic treatment

# *GiACTA – 2017*

## (Giant-cell Arteritis Actemra)

## The effect of the interleukin-6 receptor alpha inhibitor tocilizumab on the rates of relapse during glucocorticoid tapering in patients with GCA

NEJM 377;4: 317-328

John Stone et al

# *Aortic vasculitis (AV) in GCA and PMR*

## *1) GCA intensity & 2) Methodology*

- ***Early GCA:*** 50 – 66% AV using FDG-PET[1] and CT-A[2]
- ***Necropsy pathology3***: 12/13 GCA ptts with AV (92,3%)
- ***Necropsy/surgical specimen pathology:*** 39% AV in ascending aorta among 72 GCA ptts.[4]
- ***Retrospective registry studies*** covering 20-50 years[5+6]
  - AA in 9,5 – 18% 3 – 6 years after GCA diagnosis
  - Risk (AA/AD) 18,7-18,9% pr 1000 person-years
- ***Cross-sectional imaging study*** of 54 ptts. (5,4 years GCA)
  - AA/AD in 12/54 (22%)[7]

1) BLOCKMANS: Arthritis Rheum 2006; 55: 131-7PRIETO-GONZÁLEZ S 2) ARGUIS P *et al.*: *Ann Rheum Dis* 2012; 71: 1170-6
*3) Ostberg G: Med Scand Suppl* 1972; 533: 135-59. 4) Lie JT: *Semin Ar- thritis Rheum* 1995; 24: 422-31
5)Nuenninghoff: *Arthritis Rheum* 2003; 48: 3522-31 6)Gonzales-Gay: *Medicine* (Baltimore) 2004; 83: 335-41
7) Garcia-Martinez:*Arthritis Rheum* 2008; 59: 422-30

# *GCA: Prevalence of non-aortic LVV*

- ***Frequency variability determinants***
  - Definition of disease activity
  - Technique used
  - Vascular segments studied

- ***Common: proximal aortic branches***
  - Subclavian-, axillary- and proximal brachial arteries
- ***Infrequent: abdominal aortic branches***
  - Arteries to gut, kidneys and lower extremities

Klein RG: Ann Intern Med 1975; 83: 806-12 Brack A: *Arthritis Rheum* 1999; 42: 311-7 Kermani TA: *J Rheumatol* 2009; 36: 2277-83

# Study design

- Randomized
- Double-blind
- Placebo-controlled
- Phase III study
- New / relapse ptts = 119 / 131

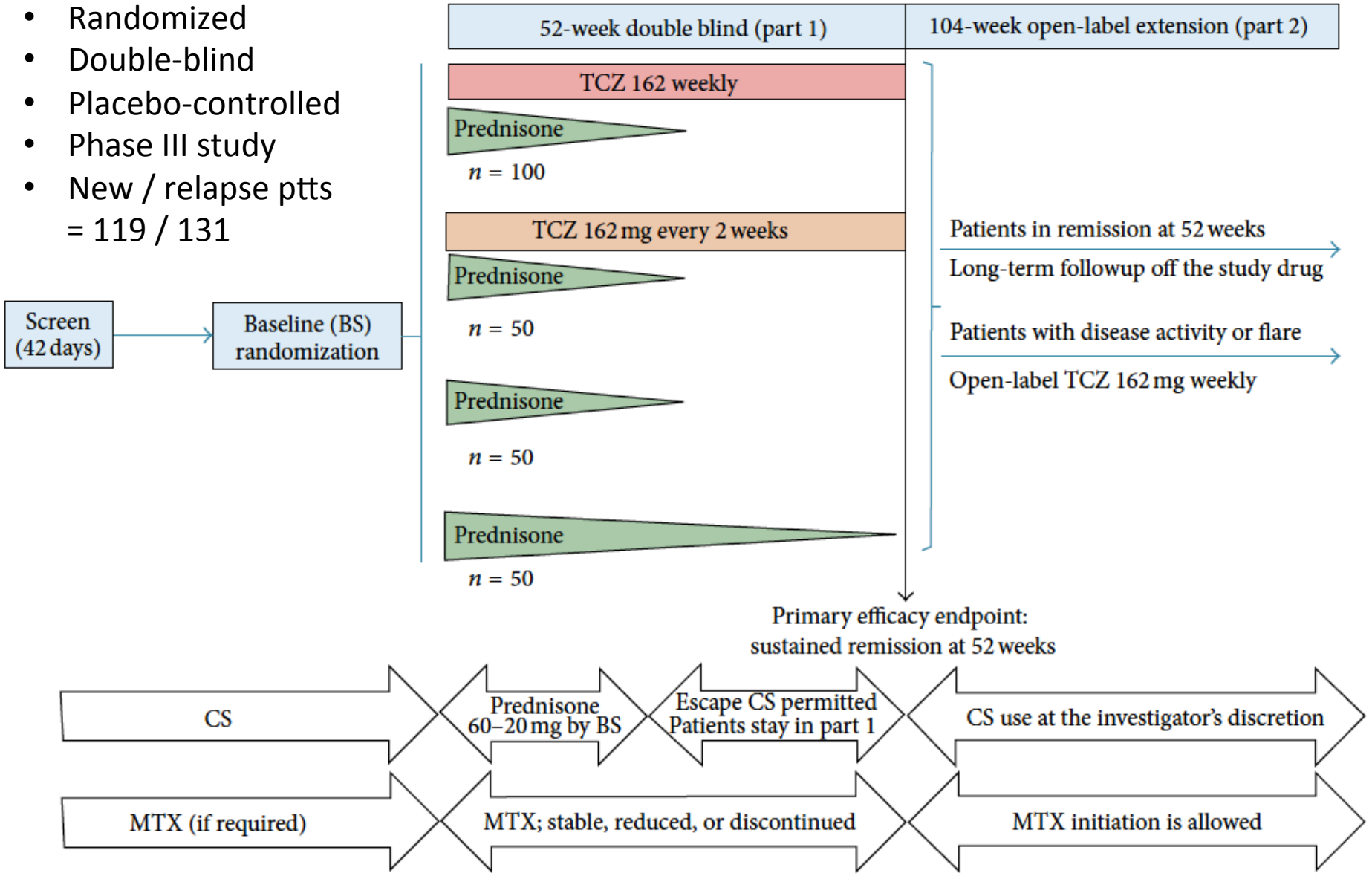



FIGURE 1: Study schema.

# *Results*

## *Primary endpoint: Sustained GC free remission rates at W52*

| TLZ 162 mg/w 26W GC taper | TLZ 162 mg eow 26W GC taper | 26 W GC taper TLZ placebo | 52 W GC taper TLZ placebo |
|---|---|---|---|
| 56% | 53% | 14% | 18% |

P<0.001 for any TLZ group versus any placebo group

## *52W Cumulative median prednisolone dose in mg*

| TLZ groups | 26W GC taper | 52W GC taper |
|---|---|---|
| 1862 (1582-1942) | 3296 (2730-4024) | 3818 (2818-4426) |

P<0.001 for TLZ groups versus any placebo group

P<0.001 both

# *GiACTA – Conclusions*

- ***52W sustained GC-free remission:***
  - TLZ ew or eow + 26W GC taper is superior to
  - 26W or 52W GC taper + placebo TLZ (P<0,001)

- ***Cumulative 52W GC dose*** 50% reduced in TLZ treatment

- ***TLZ ew or eow***
  - Superior to either Plcb regime, but
  - TLZ ew had better 50% reduced disease control (ptt's global VAS)

- ***Unanswered:*** Safety and efficacy of TLZ beyond 52W

# *CANTOS study*

## *The Canakinumab Anti-inflammatory Thrombosis Outcomes Study*

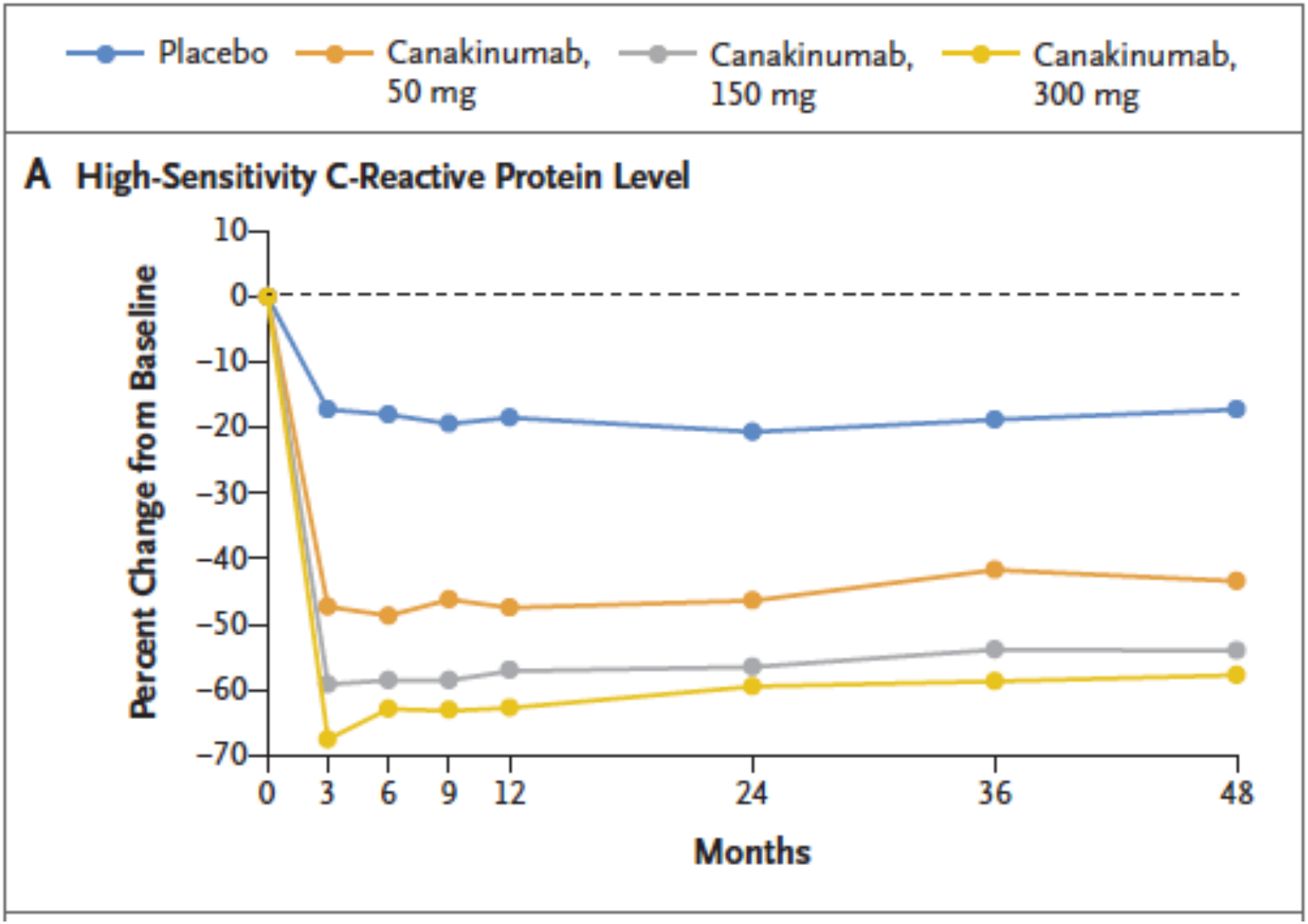
## *"Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease"*

- ***10.061 patients:***
  - Previous myocardial infarction
  - hs-CRP >2 mg/L
- ***Intervention:***
  - Different dose-regimes of Canakinumab every 3M
- ***Primary endpoints:***

  1) Nonfatal AMI or 2) Nonfatal stroke or ) C-V death

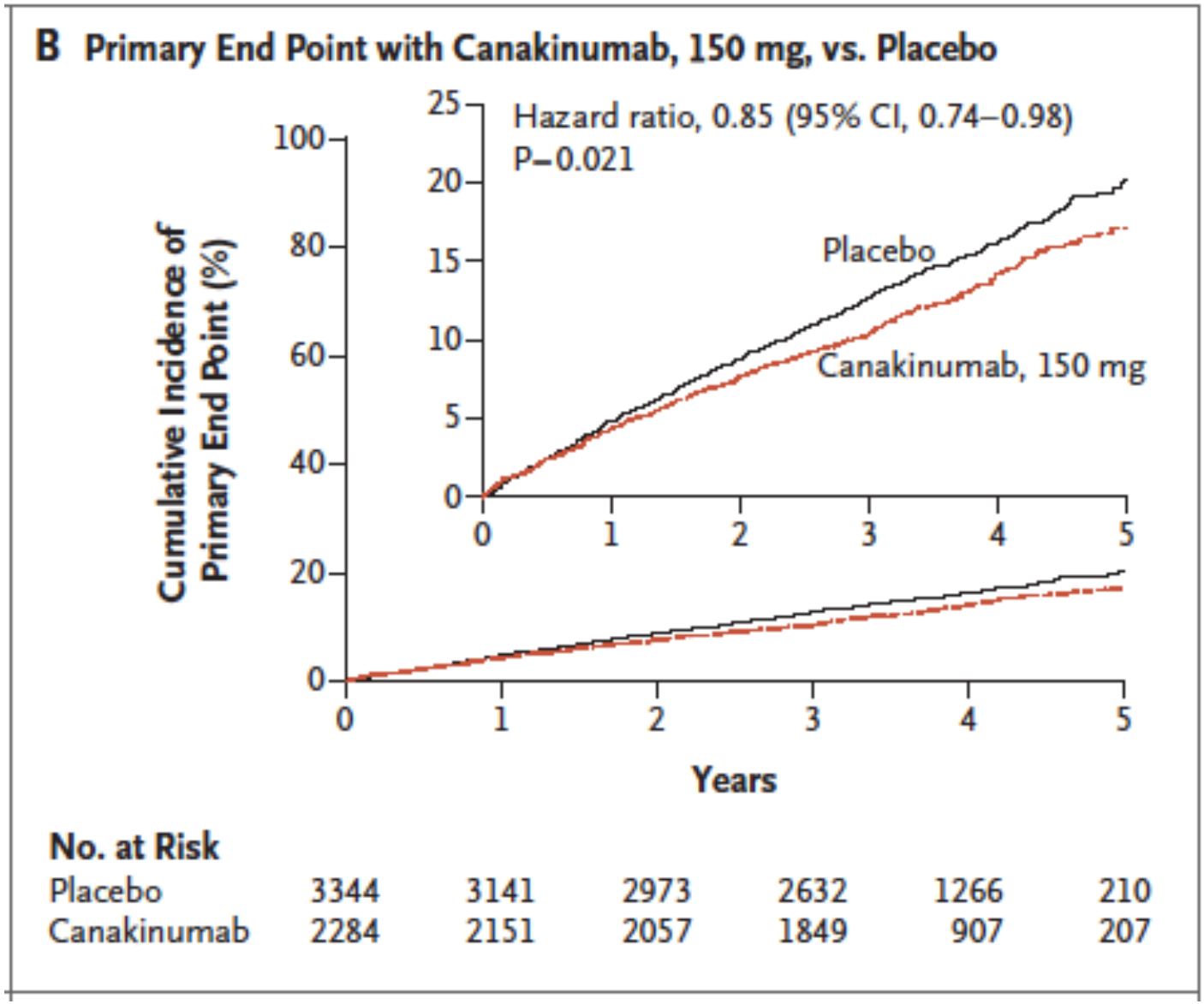
NEJM N Engl J Med 2017;377:1119-31.

# *CANTOS – results*




NEJM N Engl J Med 2017;377:1119-31.

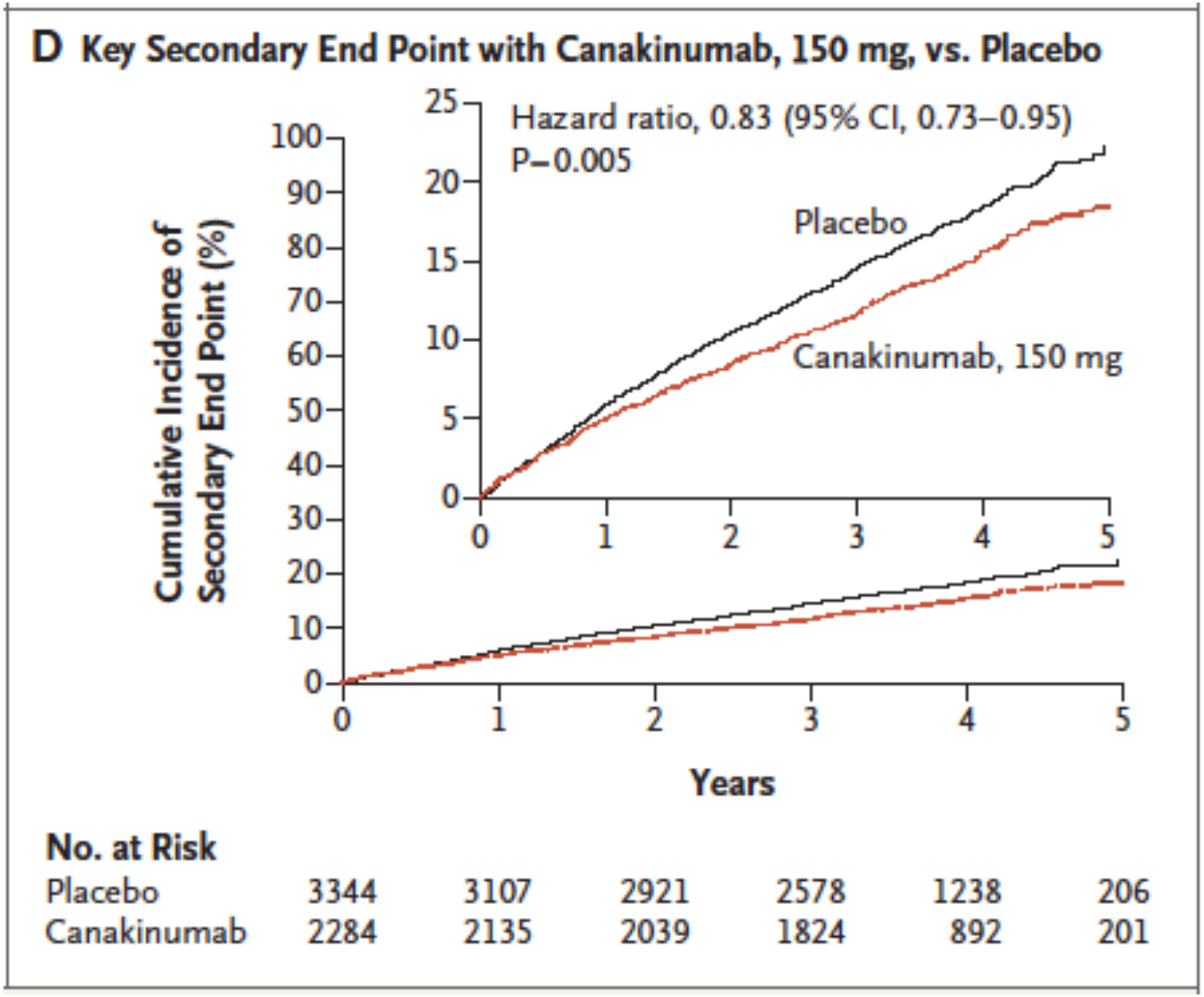
# *CANTOS – results*




NEJM N Engl J Med 2017;377:1119-31.

# CANTOS results

***Secondary endpoint: Prim. endpoint + UAP, hospitalization, urgent revascularization***




NEJM N Engl J Med 2017;377:1119-31

# *CANTOS – Conclusion*

***”Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering.”***

Sceneskift igen……

# *36 årig mand – Samtidig hånd- og fod iskæmi*

# *36 årig mand – Samtidig hånd- og fod iskæmi*

# *Leo Buerger – Publication 1908*

Buerger L, Am J Med Sci 1908

# ***Characteristics***

- Ischaemic disease in distal extremities
- Rare
- Tobacco
- Hen or eg: Thrombosis or vasculitis?
- Primarily a ***clinical diagnosis***
- Characteristic ***pathology***
- ***Lab. tests:*** No pathognomy − tellingly negative
- Unsettled pathogenesis
- Relatively unsettled treatment

# *Pathogenesis*

- ***Unsettled!!***
- Increased cellular immunity to collagen I and III[1]??
- AutoAbs against endothelial cells[2]??
- Prothrombin gene mutation 202105 association[3]?
- Anticardiolipin Abs 6 association[4]?

Adar R: N Engl J Med.1983;308:1113–1116. 2) Eichorn J: Am J Med Sci. 1998; 315:17–23. 3) Avcu F: Thromb Res. 2000;100:143–147 4) Maslowski: VascMed. 2002;7:259 –264

# *Epidemiology*

- ***Rare*** (ann. incidence 12.6 pr. 100.000 in USA)
- ***Worldwide***, esp. Mediteranean, Middle East, Far East
- 80% ***male***, 20% female[1]
- ***Young smokers*** (debut <40 – 45 years)

- Prevalence in peripheral arterial occlusive disease[2]:
  - Up to 5% in Western Europe
  - About 50% in India
  - 66% in Korea and Japan
  - 80% in Ashkenazi Jews

1) Mills et al, Am J Surg 1987, 154:123 2) Arkkila PE, Orphanet J Rare Dis 2006; 1:14

# *Tobacco and Buerger's disease*

- Initiation, maintenance and progression
- ***Cigarettes***, especially home made on raw tobacco
- Also seen: Cigars, marijuana (cannabis arteritis), snuff, chewing tobacco
- Typically heavy and longstanding smokers

- 2/3 ptts: severe periodontal disease, and chronic anaerobic periodontal infection??
  - Pos PCR in thrombus and mouth[1]

1) Iwai T: J Vasc Surg. 2005;42: 107–115

# *Clinical features*

- ***Ischemia*** of distal small extremity arteries and veins
- ***Proximalization*** with time
- ***Claudication***: hands, feet, legs, arms
- Progression to ischaemic ***rest pain***
- ***Ulceration*** in toes, feet, fingers
- Ultimately ***gangrene***
- Typically ***>2 limbs*** involved (arteriogram in all limbs?)
- ***Superficial thrombophlebitis***, may be migratory
  - Not in other vasculitides (seen in Behcet's)
- ***Raynaud's*** phenomenon

# *Cliveland Clinic Foundation: 112 BD ptt. population*

**TABLE 1.** DEMOGRAPHIC CHARACTERISTICS AND PRESENTING SYMPTOMS AND SIGNS OF 112 PATIENTS WITH THROMBOANGIITIS OBLITERANS, 1970 THROUGH 1987.*

| VARIABLE | VALUE |
|---|---|
| Mean age — yr | 42 |
| Male sex — no. (%) | 86 (77) |
| Intermittent claudication — no. (%) | 70 (62) |
| Pain at rest — no. (%) | 91 (81) |
| Ischemic ulcers — no. (%) | 85 (76) |
| Arm | 24 (21) |
| Leg | 39 (35) |
| Both | 22 (20) |
| Thrombophlebitis — no. (%) | 43 (38) |
| Raynaud's phenomenon — no. (%) | 49 (44) |
| Sensory findings — no. (%) | 77 (69) |
| Abnormal Allen-test result — no. (%) | 71 (63) |

*Data are from Olin et al.[11]

Jeffrey W, NEJM, 2000, Vol 343; 12: 864-69

# *Pathology in Buerger's*

- **Small/medium, distal extremity arteries and veins**
- Case reports: cerebral, coronary, renal, aorta arteries
- Segmental
- **Thrombus: Highly cellular, inflammatory, occlusive, relative IF sparing of the vessel wall**

# *3 pathology phases*

- ***Acute phase***
  - Occlusive a/v IF thrombus: Polymorphnuclear L, microabscesses, MuN-GC, no fibrinoid necrosis
  - Intact lamina elast. interna
  - Diagnostic biopsi of thrombophlebitic supercial vein
- ***Intermediate / subacute phase***
  - Thrombus organization, thrombus IF > vessel wall
- ***Chronic phase***
  - Organized thrombus and vascular fibrosis

# *3 phases in Buerger's disease*

Acute phase: thrombus including neutrophils and giant cells occludes the vessel lumen but spares the wall.

Subacute phase: progressive organization of the thrombus takes place.

Chronic phase: inflammation is no longer present and organized thrombus and vascular fibrosis remain.

Platelets

Erythrocyte

Circulation. 2010;121:1858-1861

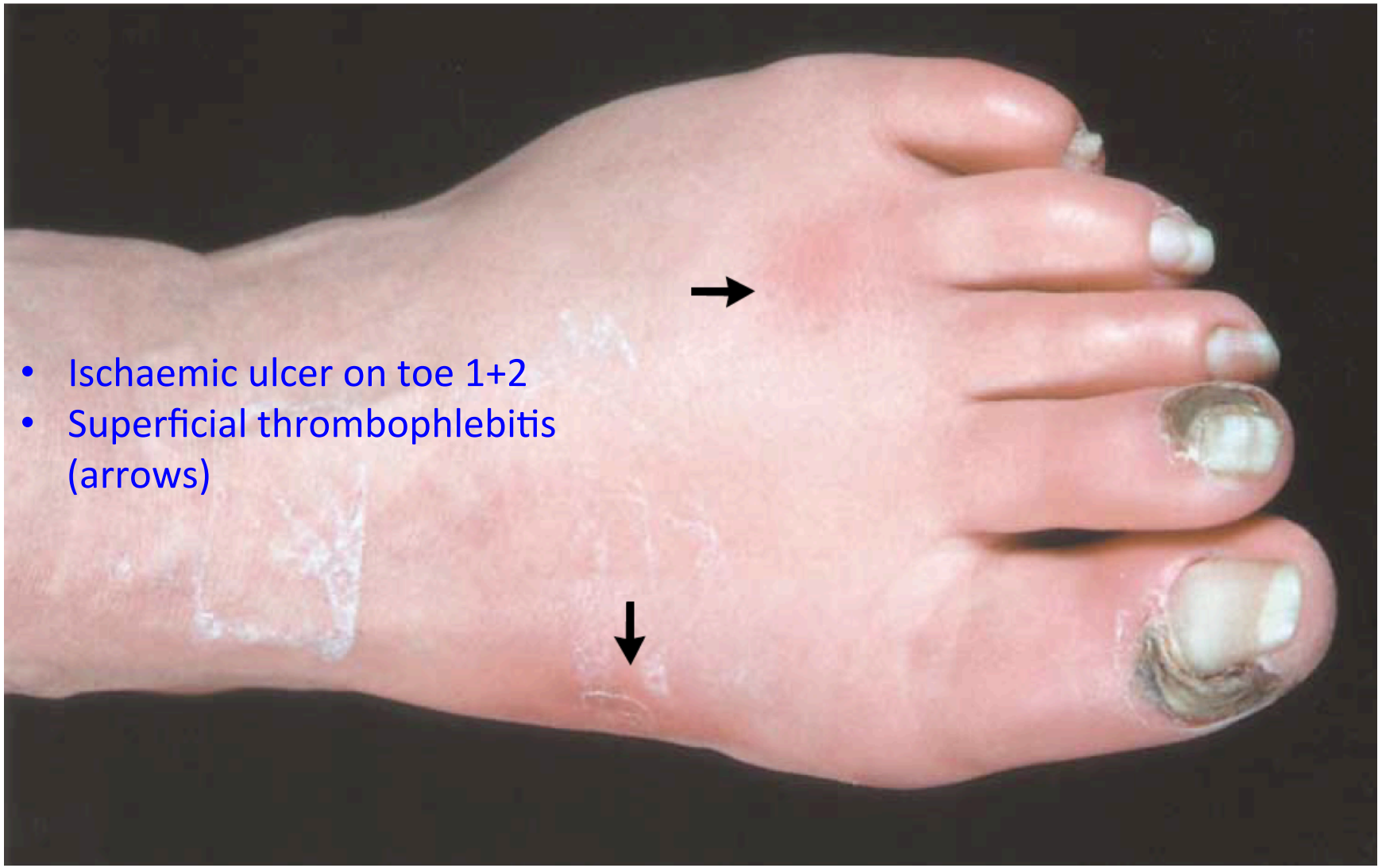
# *Clinical examination*

- Detailed history
- Thorough vascular examination
    - Peripheral pulses
    - Auscultation – arterial bruits
    - Ancle Brachial Index
    - Bilateral blood pressure
- Superficial thrombophlebitis (nodules, cords)
- Signs of ischemia in hands and feet
- Allen's test
- Neurologic sensory deficits (up to 70%)

# *"Diagnostic" criteria*

- Age <40 - 45 years
- Tobacco − current or recent
- Distal extremity ischemia
- Non-atherosclerotic
- Imaging and echo to detect embolic source
- I.v. contrast angiography > CT-A and MR-A
    - Distal small / medium size artery involvement
    - Corkscrew collaterals
    - Segmental occlusions
- Negative exclusion laboratory tests
    - Phase reactants
    - IJD, CTD, Scl and SVV serology
    - DM, Cholesterol prophile, thrombofilia
- Biopsy − from superficial thrombophlebitis

# *Buerger's foot*




Jeffrey W, NEJM, 2000, Vol 343; 12: 864-69

# *Allen's test*

1. Pt. clenches hand (empty for blod)
2. Doctor compresses ulnar and radial arteries
3. Pt. opens hand (relaxed open to avoid false positivity)
4. Doctor releases pressure on only ulnar artery
   - Hand paleness = ulnar artery occlusion (positive test)
5. Test repeated for occlusion of radial artery

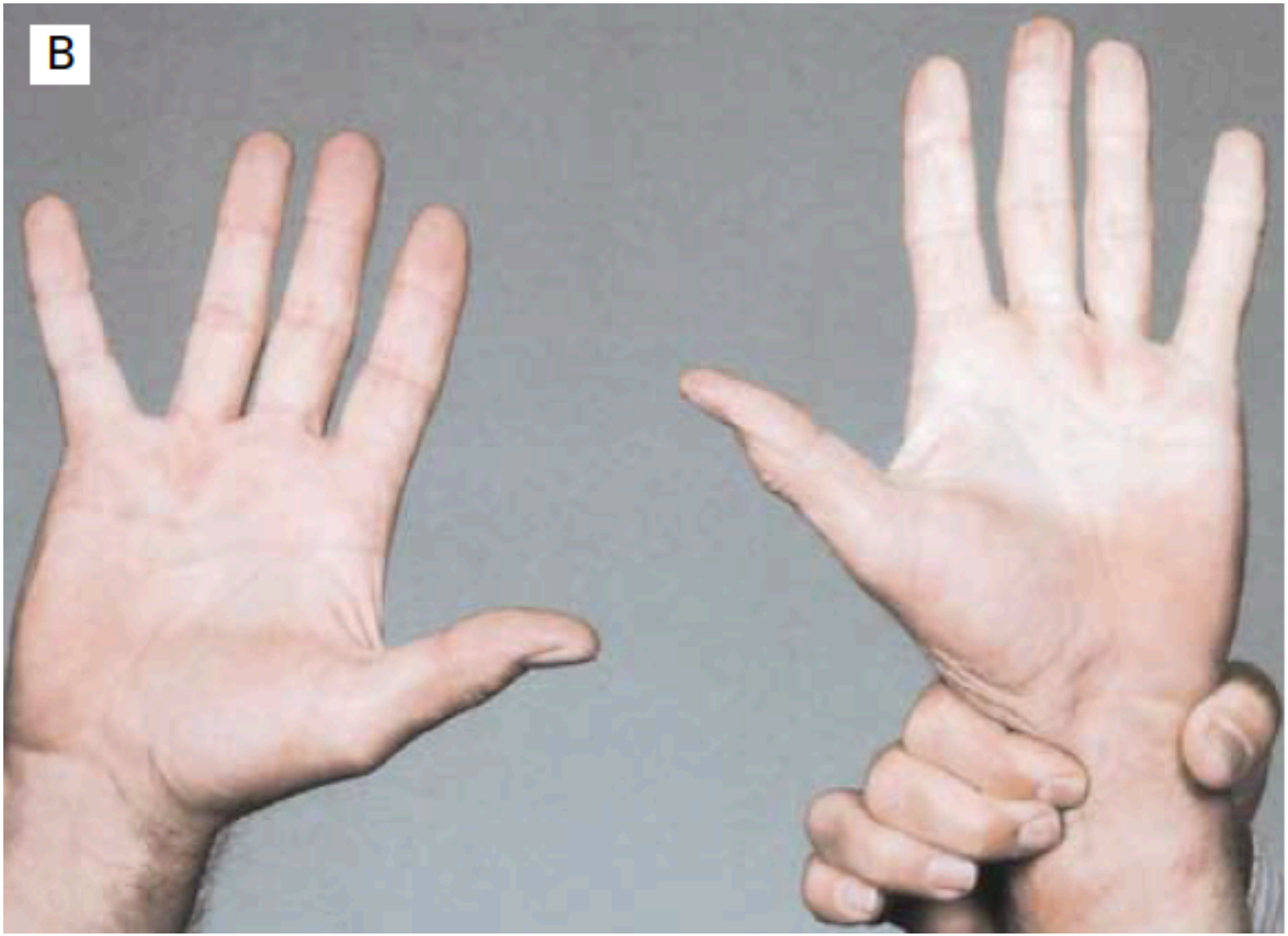
Allen's test is non-specific

- Buerger's disease
- Other SV occlusive disease: Scleroderma, CREST, hypercoagulable states, emboli, repetitive trauma, vasculitis

# *Allen's test*


Jeffrey W, NEJM, 2000, Vol 343; 12: 864-69

# *Allen's test of ulnar artery*




Jeffrey W, NEJM, 2000, Vol 343; 12: 864-69

# *Laboratory tests*

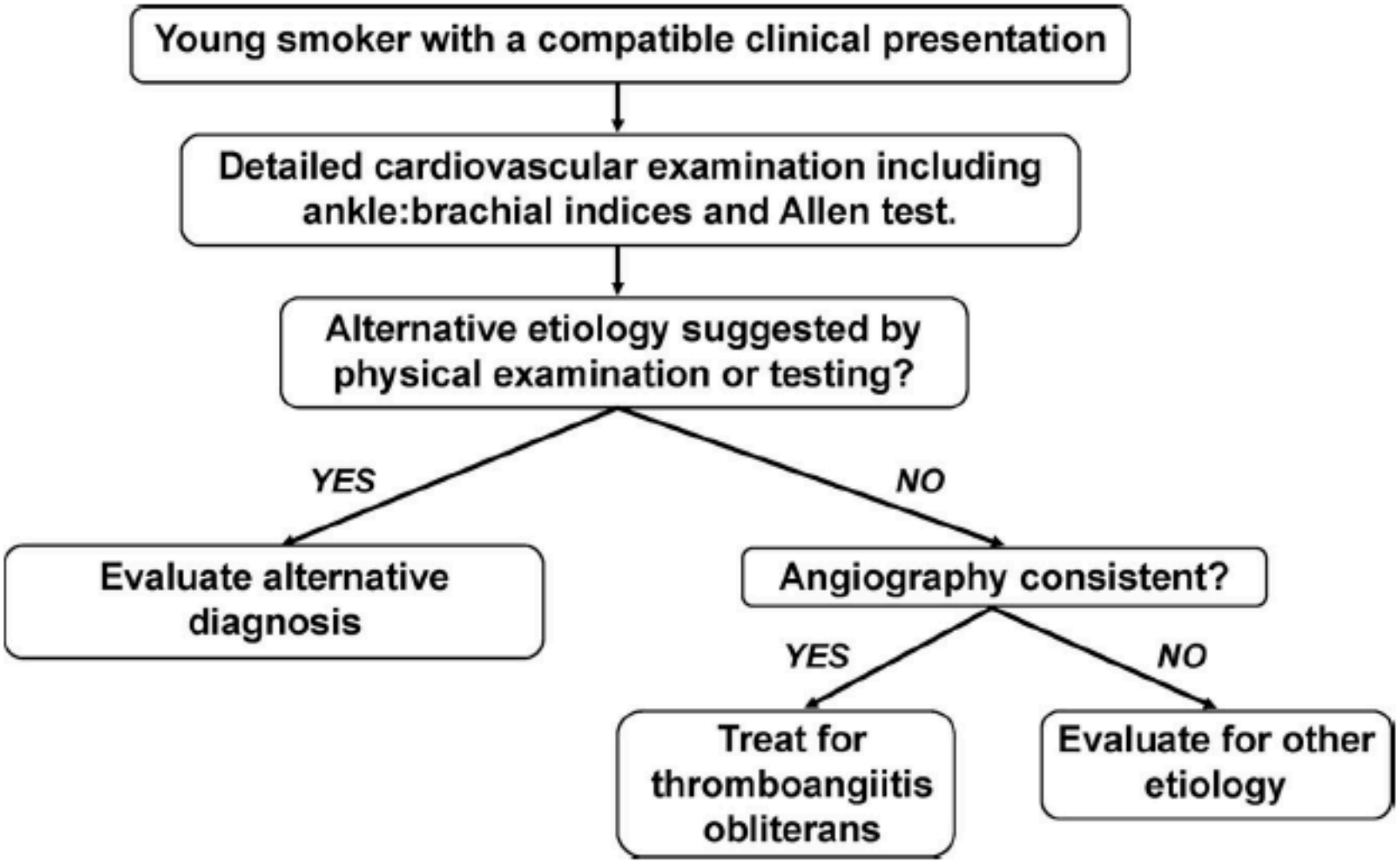
- NO specific tests

- Differential diagnosis
  - CRP and ESR
  - L+D
  - Coagulation tests, cryoglobulins
  - Serology: ANA, RF, ANCA, anti-centromer Ab, scl-70 Ab, C3+C4

# *Imaging*

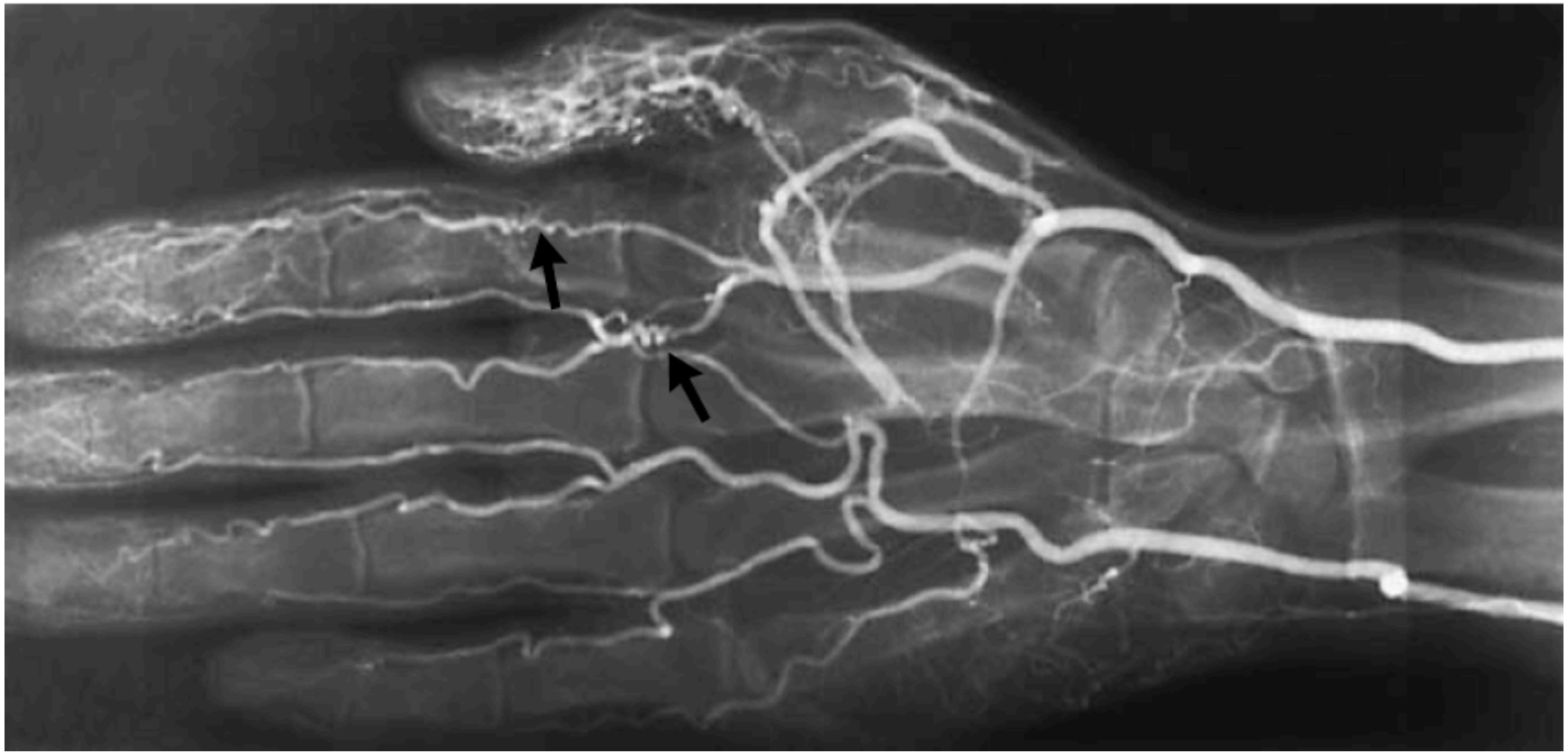
- Echocardiography – rule out embolism
- CT-A or MR-A or US?
- Arteriography? (Suggestive, not pathognomonic)
  - Small/medium arteries/veins
  - Palmar, plantar, tibial, peroneal, radial, ulnar arteries and the digital arteries of the fingers and toes
  - Segmental occlusive lesions (diseased arteries interspersed with normalappearing arteries);
  - More severe disease distally, and normal proximal arteries
  - No evidence of atherosclerosis
  - Collaterals around areas of occlusion (corkscrew)
  - No source of emboli
  - BD: distal to popliteal and brachial arteries
  - Same results: scleroderma, CREST, SLE, MCTD, RA, APS

# *Overall diagnostic algorithm*




Circulation. 2010;121:1858-1861

# *Angiogram of hand in Buerger's*



- Occlusions of digital arteries
- Corkscrew collaterals (arrows)

Jeffrey W, NEJM, 2000, Vol 343; 12: 864-69

# *Angiography*

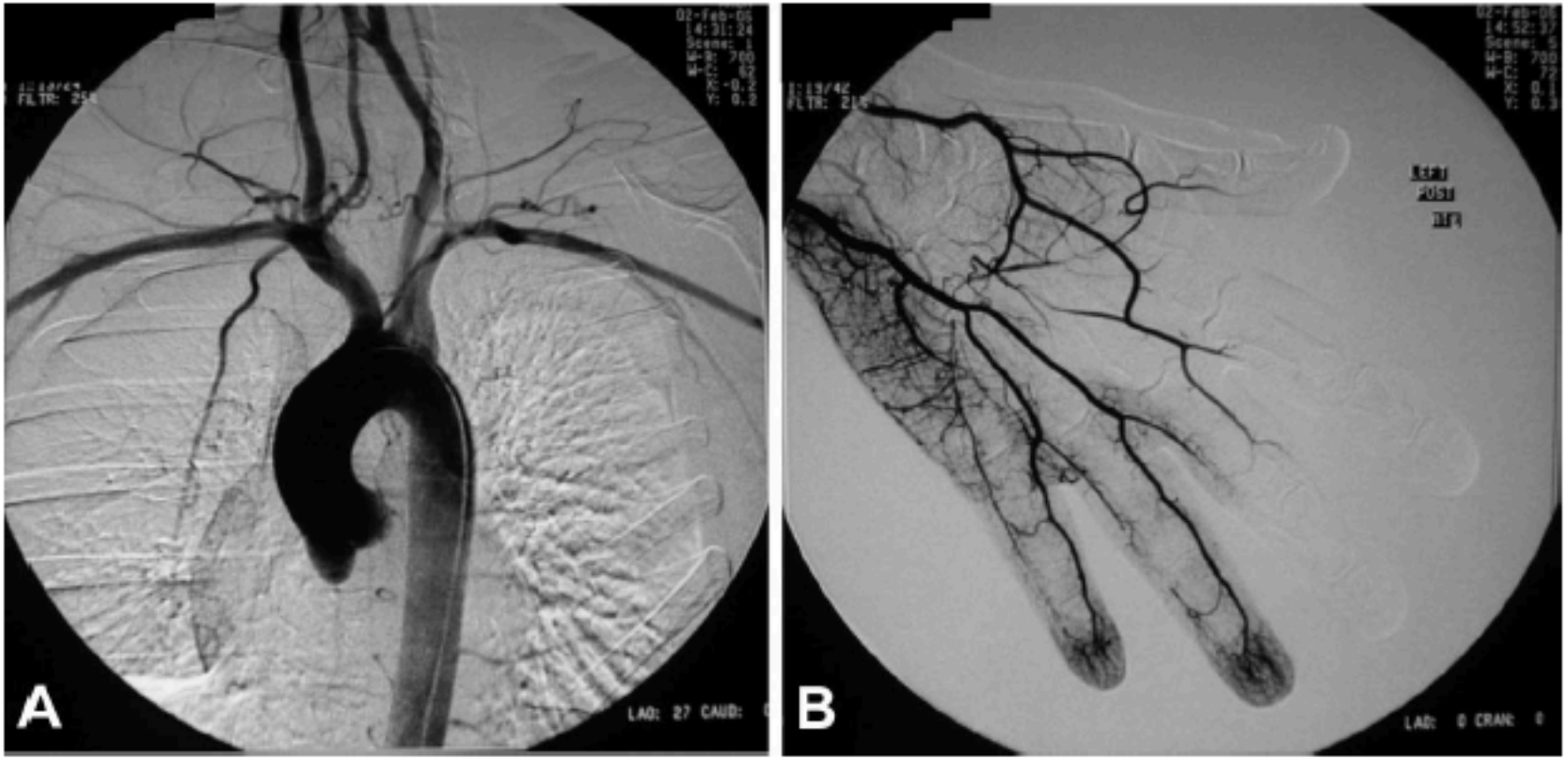



**Figure 3.** Invasive contrast angiography in a 28-year-old female smoker with thromboangiitis obliterans, severe secondary Raynaud's phenomenon, and digital ischemia culminating in gangrene of her left index finger. Her aortic arch and proximal upper-extremity arteries are free of atherosclerosis (A). However, angiography of her left hand demonstrates numerous digital artery occlusions and an incomplete palmar arch (B).

Circulation. 2010;121:1858-1861

# *Prognosis*

- Tobacco discontinuation dependent

- 110 ptt cohort
  - 43% underwent 118 amputations
  - 19% of continued smokers major amputations
  - No smoke quitters had amputations

# *Treatment*

- Tobacco abstinence − even a few cigarettes
  - Avoid nicotine replacement
- Surgical revascularization usually not feasible
  - Distal and diffuse character of BD
  - Suboptimal outcomes after 1Y, 5Y and 10Y[1]
    - » Primary patiency rates: 41%, 32%, 30%
    - » Secondary ditto: 54%, 47%, 39%
    - » 50% lower rates under continued smoking[2]
- Endovascular procedure[3]
    - » 95% successfull i Grazianis study
    - » Sustained clinical improvement i 16/19 limbs. 100% salvage

1) Ohta T: J Vasc Surg. 2004;39:176 –180. 2) Sasajima T: Eur J Vasc Endovasc Surg. 1997;13:186–192
3) Graziani L: Ann. Vasc. Surg. 26 (2012) 387e395.

# *Treatment – continued*

- Prostaglandin/Iloprost[1]
  - » Better healing rate than lumbar sympathectomi
  - » Complete healing rate PG/symp = 62% /41% at 4W and 85%/52% at 24W
- Bosentan (dual Endothelin-1 R antagonist − oral adm.)?
  - » PAH and digital ulcer treatment in systemic sclerosis
- Growth factors
  - » Increased angiogenic factors in ischaemic tissue
- Sympathectomy
- Spinal cord stimulation

1) Bozkurt: Int. Angiol. 25 (2006) 162-168

***TAK FOR OPMÆRKSOMHEDEN!!***