Interessamento CV nelle malattie reumatiche

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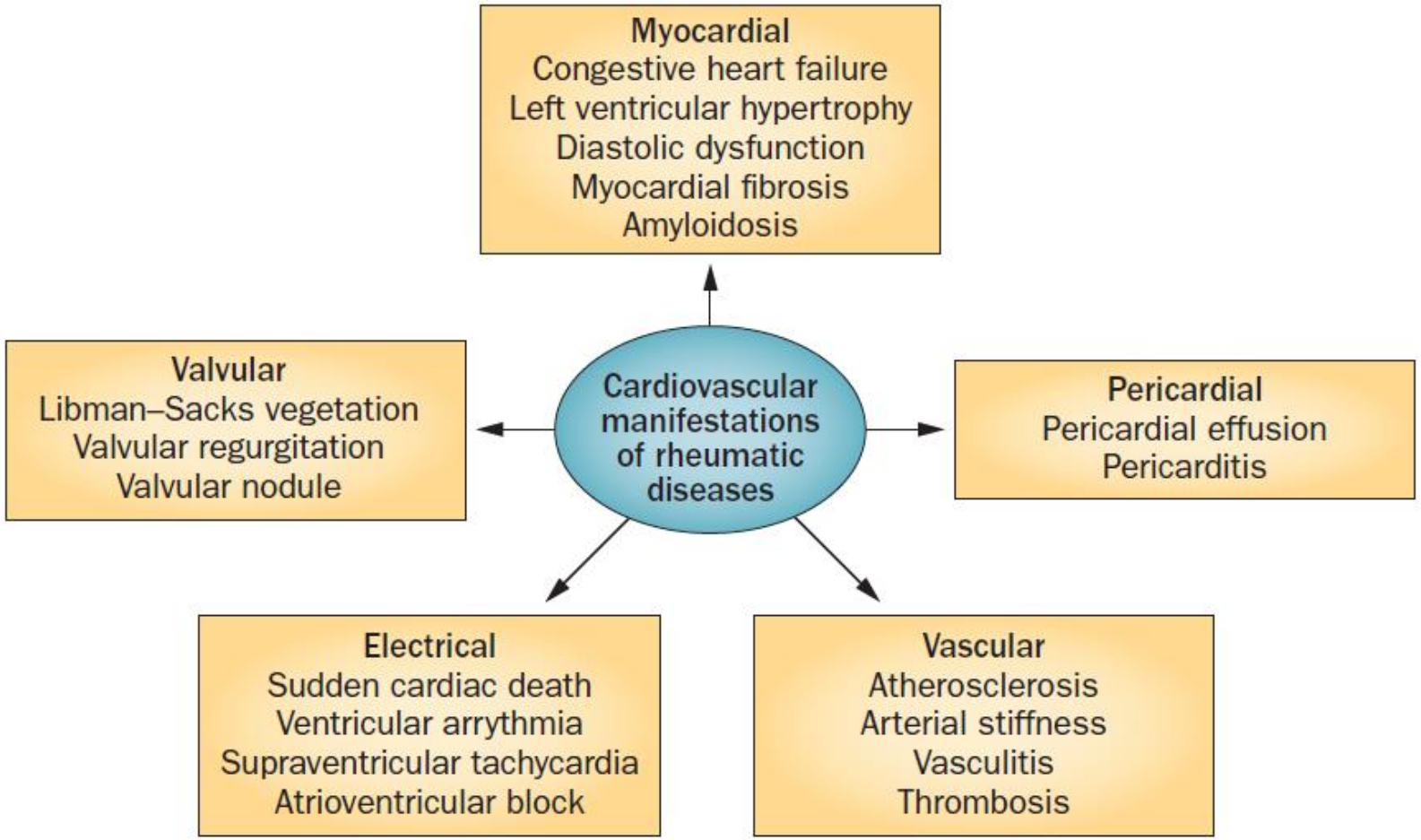
Cardio-Rheumatology



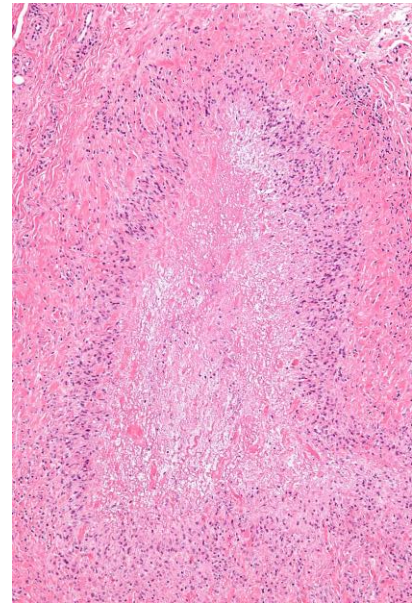
Rheumatic diseases

CARDIOVASCULAR INVOLVEMENT

Rheumatoid arthritis

Pericarditis

- 50% of patients at autopsy.
- Clinically apparent disease is far less common, with cardiac tamponade serving as a rare consequence.
- An exudative sample characterized by cellular infiltrate, high protein and LDH concentrations, and a low glucose and low pH.



Myocarditis

- rare but may be related to granulomatous disease or interstitial myocarditis.

Conduction defects

- Atrioventricular (AV) block is an unusual complication of RA, but if present is probably related to direct granulomatous involvement.
- Amyloidosis can result in both cardiomyopathy and conduction disturbances.

Endocardial inflammation

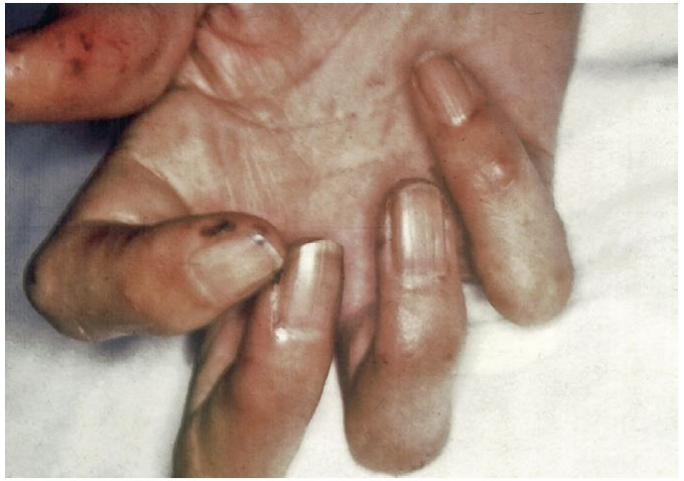
- Often asymptomatic, echocardiographic studies have demonstrated a high prevalence of mitral valve abnormalities in RA.

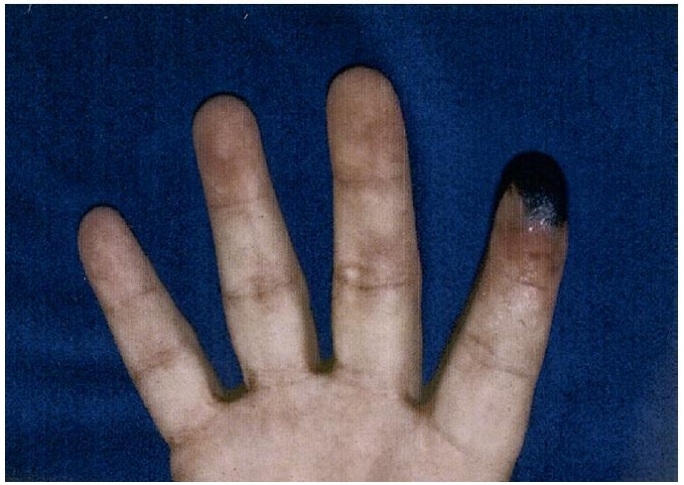
Granulomatous aortitis

- In severe RA, granulomatous disease of the endocardium can spread to the base of the aorta resulting in aortitis and valvular incompetency

Rheumatoid vasculitis

- Distal arteritis with splinter hemorrhages, nail-fold infarcts, and possible gangrene
- Cutaneous ulceration, including pyoderma gangrenosum
- Peripheral neuropathy with either a mononeuritis multiplex or a sensory-related stocking-glove polyneuropathy
- Palpable purpura
- Arteritis involving viscera, similar to polyarteritis nodosum
- Rheumatoid pachymeningitis (rare), confined to the dura and pia matter





Ankylosing Spondylitis

Ascending aortitis

- In rare situations, aortitis may precede other features of AS.

Aortic valve incompetence

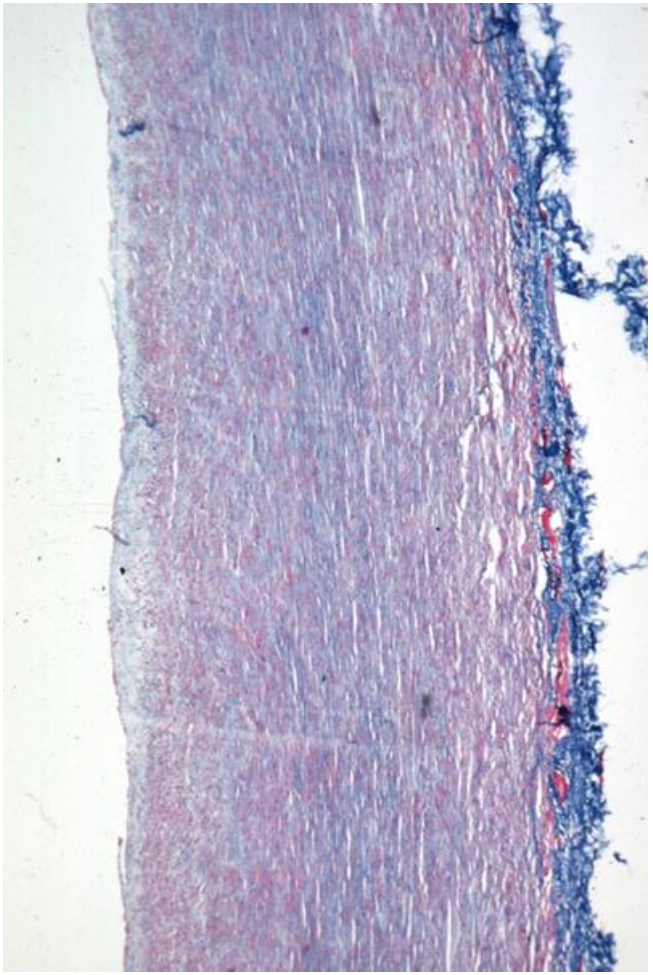
- 3.5% of patients who had the disease for 15 years and in 10% after 30 years
- Both aortic incompetence occur twice as often in patients with peripheral joint involvement

Conduction abnormalities

- 2.7% of those with disease of 15 years' duration and in 8.5% after 30 years

Cardiomegaly

Pericarditis



Systemic Lupus Erythematosus

Pericarditis

- Pericarditis, with or without an effusion, is the most common cardiac manifestation of SLE, occurring in more than 50% of patients with SLE at some point during the course of their disease.
- Pericardial effusions are usually small and asymptomatic and typically are detected on echocardiography performed for another indication

Myocarditis

- If myocarditis is suspected, an endomyocardial biopsy may be helpful in confirming the diagnosis and excluding other causes of cardiomyopathy such as hydroxychloroquine toxicity.
- The distinguishing pathologic finding of hydroxychloroquine toxicity is myocyte vacuolization in the absence of active myocarditis.
- Histopathologic findings of SLE myocarditis include perivascular and interstitial mononuclear cell infiltration and sometimes fibrosis and scar.

Valvular abnormalities

- valvular abnormalities of 61% in patients with SLE compared with 9% of controls, with vegetations present in 43% of patients with SLE compared with none of the controls.

Hypercoagulable states

- Stroke
- Myocardial infarction

Libman-Sacks endocarditis

Libman-Sacks endocarditis has been recognized in multiple pathologic studies as a characteristic valvular abnormality in SLE.

Libman-Sacks verrucae typically appear as pea-sized, flat or raised, granular lesions that occur most commonly on the ventricular aspects of the mitral valve posterior leaflet. The verrucae often extend onto the adjacent left ventricular mural endocardium and may lead to adherence of the leaflet and chordae tendineae to the ventricular mural endocardium, resulting in valvular regurgitation. All four valves may be involved, but recent studies suggest a predominance of left-sided lesions.

The lesions are frequently clinically silent because they are typically found on the undersurface of valve leaflets, surrounded by fibrous tissue.

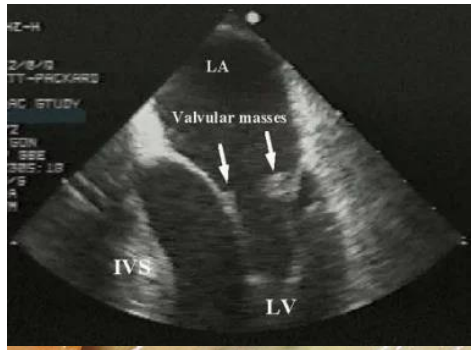
Histologically, two types of verrucae have been described:

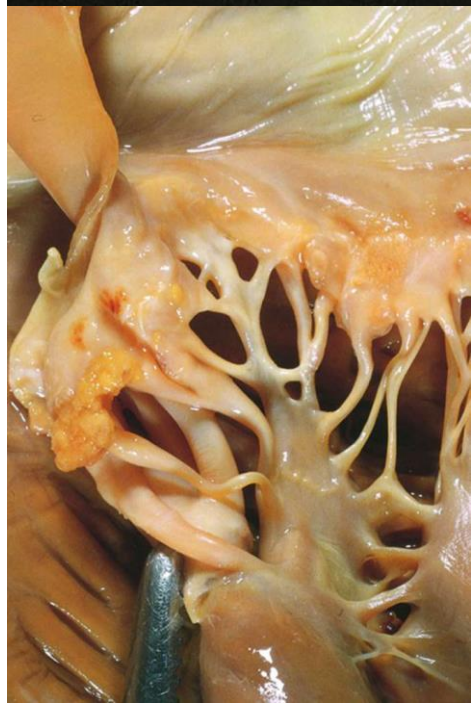
- (1) active lesions consisting of fibrin clumps with infiltrating lymphocytes and plasma cells, and
- (2) healed lesions consisting of dense vascularized fibrous tissue with or without calcification.

Immunopathologic studies have demonstrated immunoglobulin and complement deposition in a granular pattern at the base of the valve, along the valve leaflet, and within the verruca itself.

Systematic reviews have suggested that the presence of valvular abnormalities in SLE are associated with anti-phospholipid antibody.

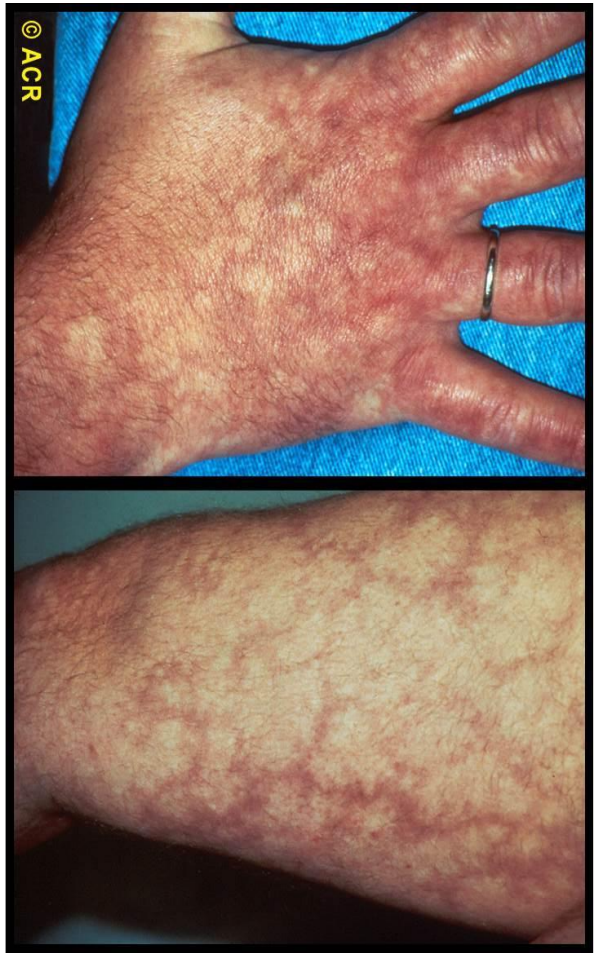
- One study of 1656 patients with SLE determined that the odds of valvular heart disease in patients with SLE with anti-phospholipid antibodies was three times higher than in SLE patients without antiphospholipid antibodies.

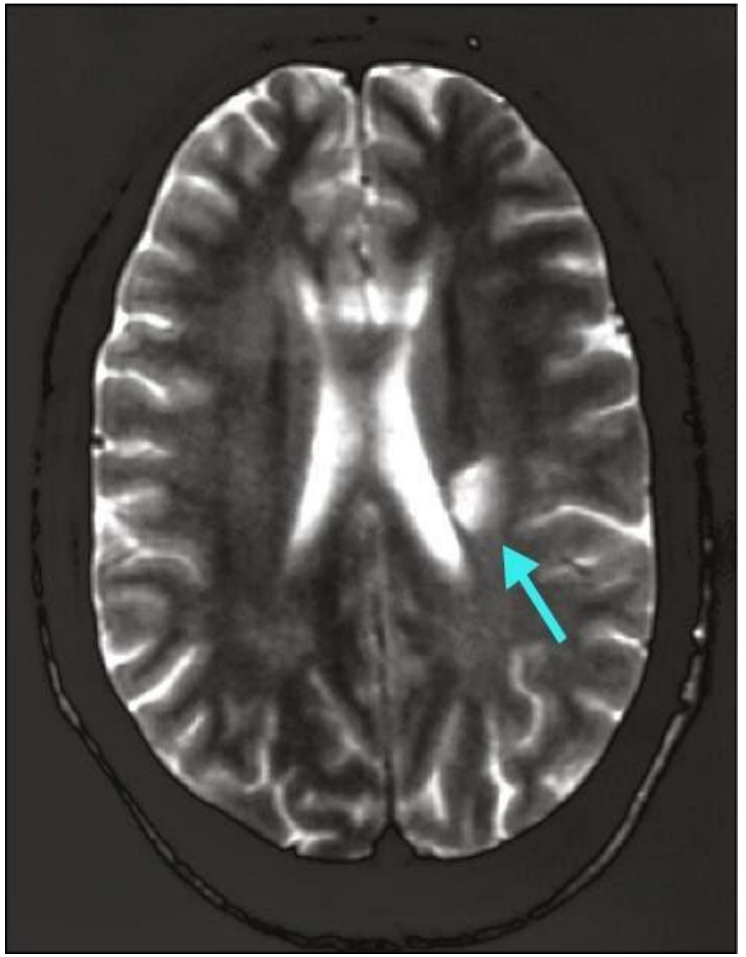




Antiphospholypid syndrome

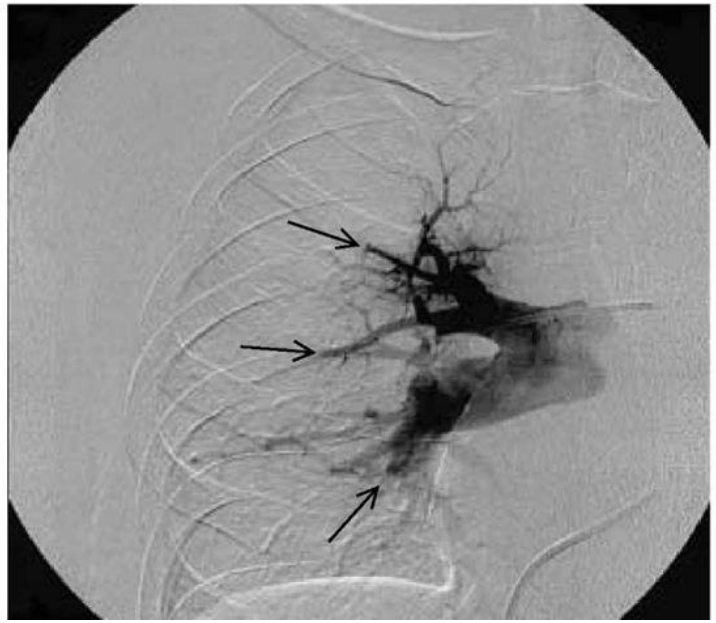
SNEDDON SYNDROME



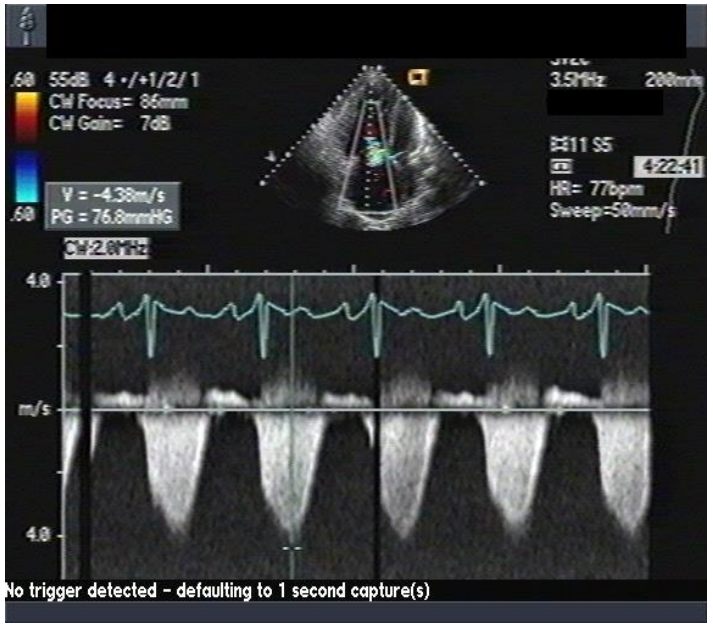


APS - cardiopulmonary

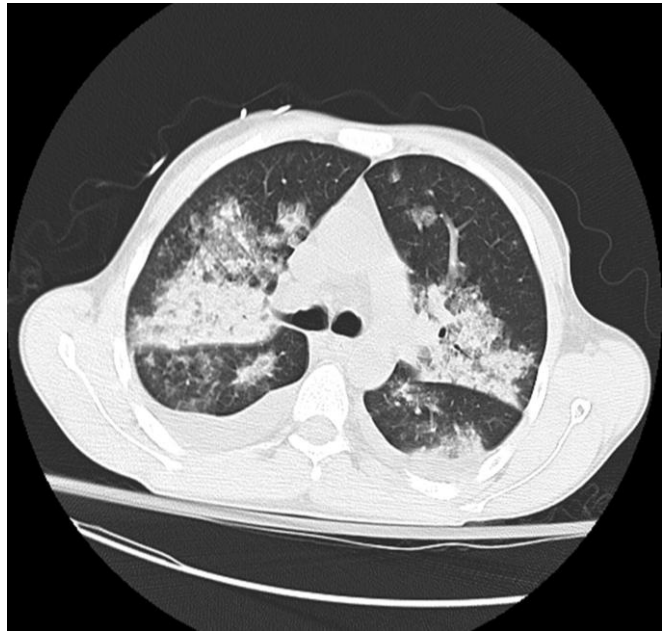
TROMBOEMBOLIA



IPERTENSIONE POLMONARE

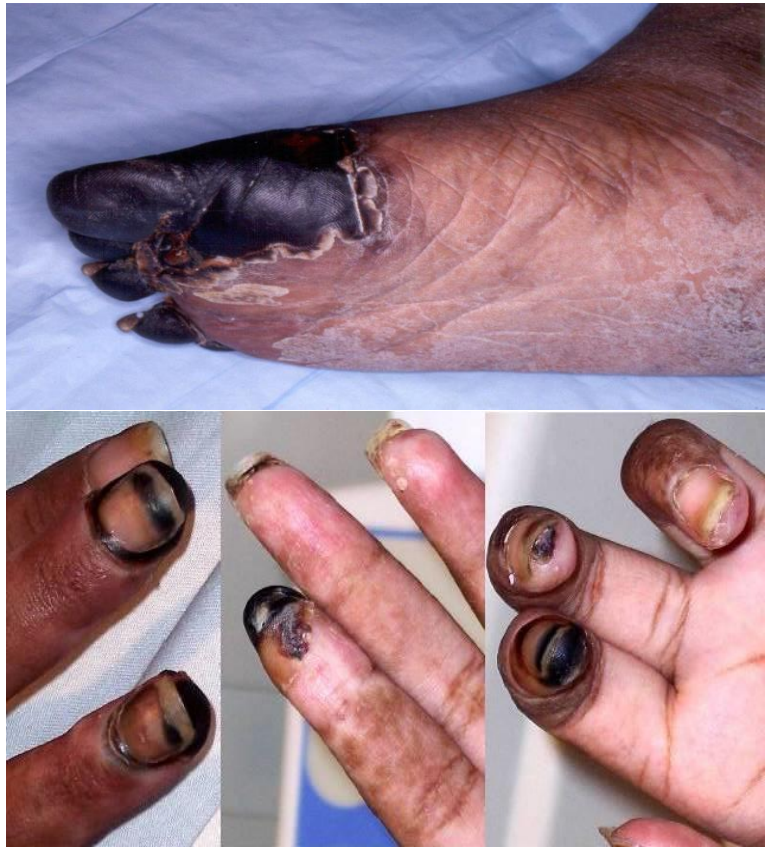


EMORRAGIA ALVOLARE

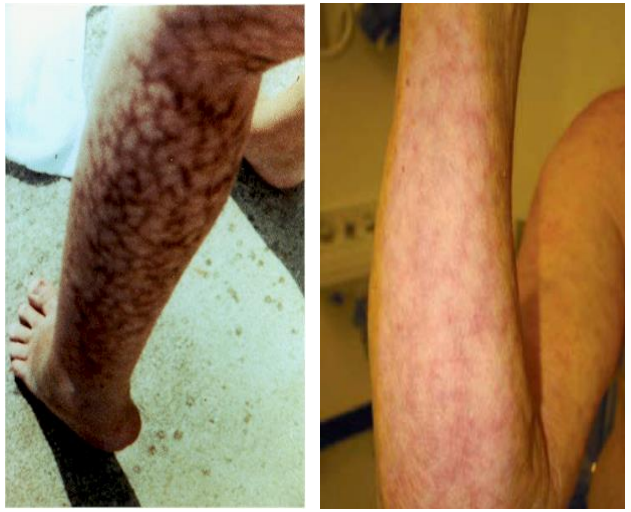


APS – microvascular involvement

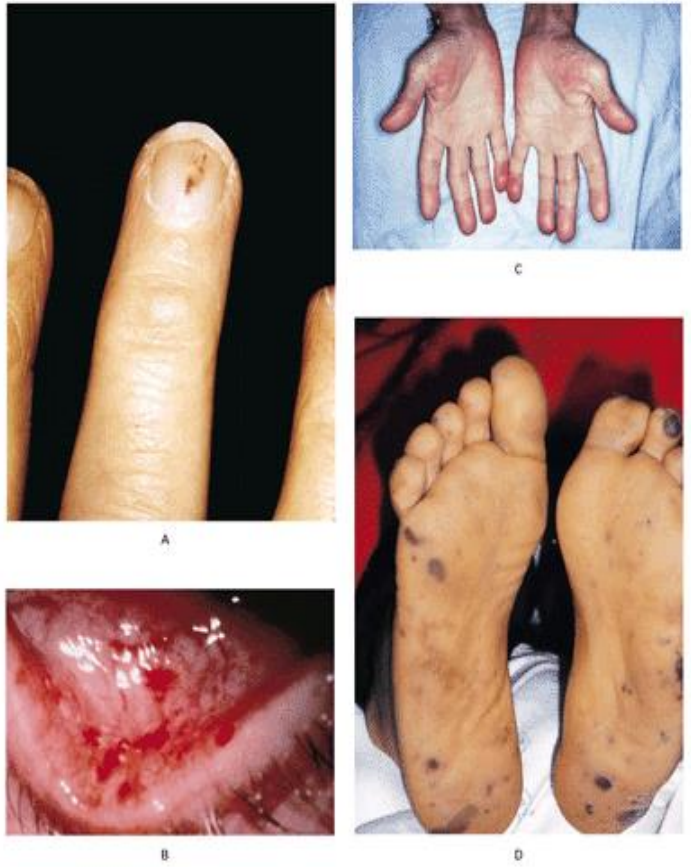
GANGRENE



LIVEDO RETICULARIS



SPINTER HEMORRAGES



Systemic sclerosis

Epidemiology

- The clinical manifestations of heart disease are highly variable, ranging from clinically silent cardiac involvement to frank heart failure. The reported prevalence of heart disease varies from 10% to more than 50%, depending on the diagnostic method used, but in general it tends to be underestimated.
- One study found that 25% of deaths could be directly related to heart disease (mostly heart failure and arrhythmias). In a large meta-analysis, cardiac involvement was associated with increased mortality (hazard ratio, 2.8; 95% CI, 2.1 to 3.8) after adjustments for age and gender.

Risk factors

- male gender, age, digital ulcerations, myositis, and no use of calcium channel blockers were independent factors associated with left ventricular dysfunction

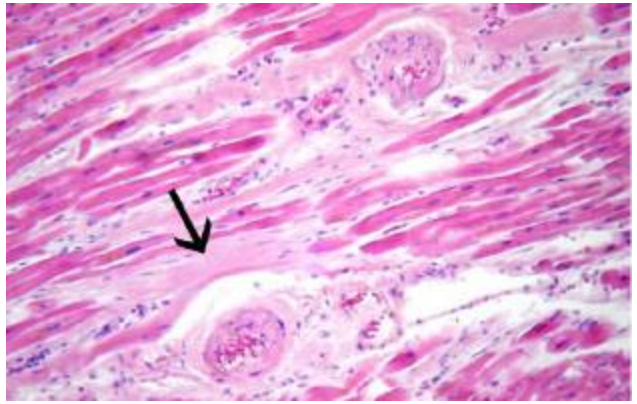
Pericarditis

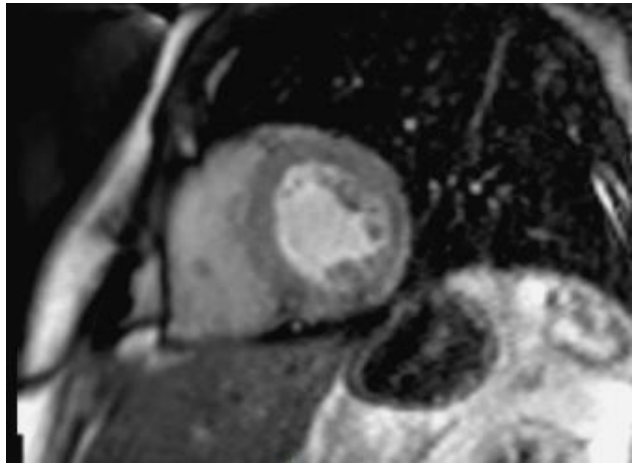
- Clinically overt pericarditis is uncommon, but asymptomatic and hemodynamically benign pericardial effusions are frequently detected by ECHO. In a controlled study, significant pericardial effusion was found in about 15% of patients compared with 4% of control subjects
- Pathologic studies have shown that some degree of pericardial involvement is detectable in 33% to 77% of patients with scleroderma, usually with evidence of a fibrinous pericarditis with adhesions and chronic inflammatory cell infiltrates.

Systemic sclerosis

Myocardiopathy

- Focal myocardial fibrosis is the hallmark of established primary heart involvement in scleroderma
- The fibrotic lesions in the hearts of patients with scleroderma are patchy, involve the myocardium of both ventricles, and usually are accompanied by evidence of microvascular disease with concentric intimal hypertrophy associated with fibrinoid necrosis of the intramural coronary arteries and arterioles. This phenomenon results in reduced coronary flow reserve even with normal epicardial coronary arteries and in the absence of clinically manifested cardiac dysfunction.
- myocardial fibrosis may be associated with reversible vasospasm of the microvascular coronary circulation and that vasodilating agents such as calcium channel blockers may have the capacity to improve coronary flow and prevent further cardiac damage.





Polymyositis/Dermatomyositis

Clinically evident heart involvement is **rare**.

Subclinical manifestations are **frequently discovered** when patients with PM or DM are evaluated.

The most frequently reported subclinical manifestations are **conduction abnormalities and arrhythmias** detected by electrocardiogram (ECG), and **subclinical cardiomyopathies** are common when cardiac MRI is performed, even in patients thought to be in remission.

The underlying pathophysiologic mechanisms that can lead to cardiac manifestations in patients with PM or DM are **myocarditis and coronary artery disease**, as well as involvement of the small vessels of the myocardium.

Serum tests such as **CK-myocardial band** (CK-MB) to detect cardiac involvement are unreliable in patients with inflammatory myopathies because CK-MB can be released from regenerating skeletal muscle fibers, a common feature in biopsies from patients with PM or DM. The **CK-MB/total CK ratio** may be greater than 3%, a threshold value that is used to define myocardial damage.

A more specific marker for myocardial damage in myositis patients is increased serum levels of cardiac isoform **troponin I**. The other cardiac troponin isoforms, troponin C and troponin T, are less specific and are also expressed in adult skeletal muscle

Granulomatosi eosinofila

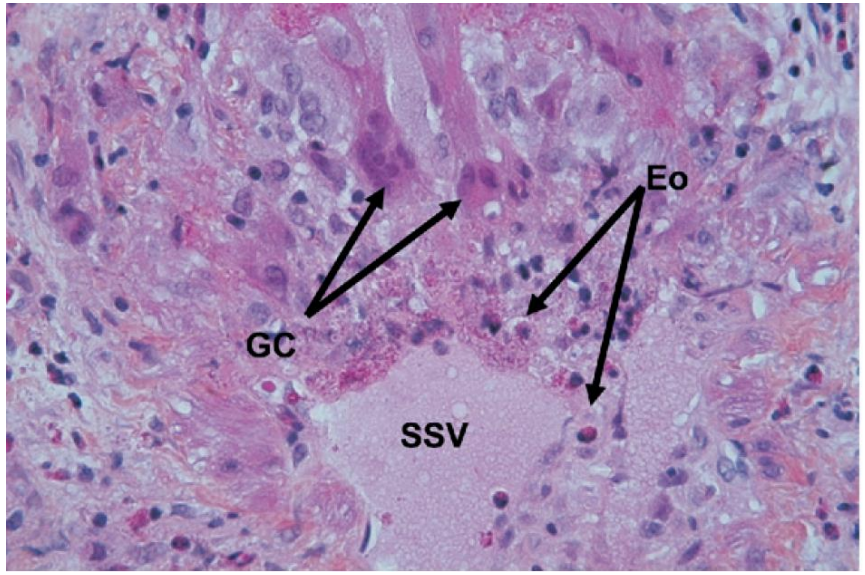
Cardiac involvement is one of the more serious manifestations of EGPA, accounting for approximately one-half of deaths attributable to EGPA

Clinical manifestations include clinical signs of heart failure or pericarditis and cardiac rhythm abnormalities

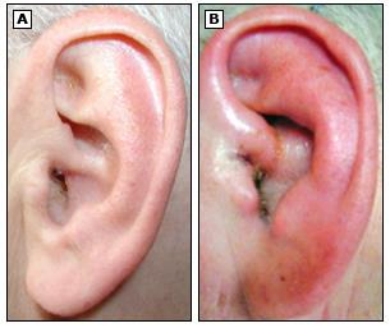
Patients with cardiac involvement typically have a shorter duration of EGPA related symptoms than those without.

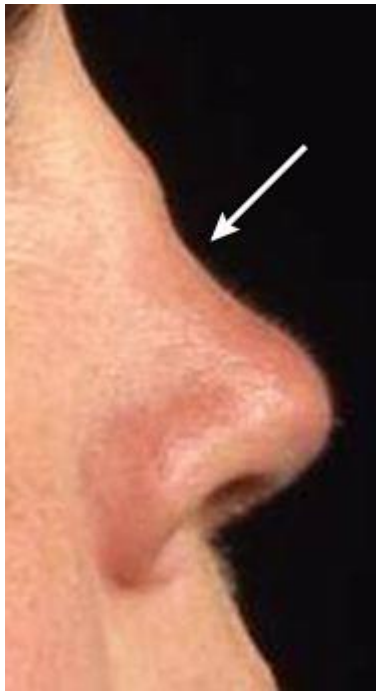
Cardiac involvement is more frequent in patients with higher eosinophil counts at the time of diagnosis

Patients with cardiac involvement were less likely to have a positive antineutrophil cytoplasmic antibody (ANCA) and more likely to have higher peripheral blood eosinophil counts than other EGPA patients.



Relapsing polychondritis





Auricular chondritis

Arthritis

Nasal chondritis

Ocular inflammation

Laryngotracheal symptoms

Reduced hearing

Vestibular dysfunction

Microhaematuria

Saddle nose

Cutaneous

Laryngotracheal stricture

Vasculitis

Elevated creatinine

Aortic or mitral regurgitation

Aneurysm

- Clinically significant **aortic or mitral valvular disease** occurs in approximately **10 percent** of patients.
- Less frequent cardiac manifestations of RPC include pericarditis, heart block, and **myocardial infarction** due to **coronary arteritis**.
- **Aortic regurgitation** can result from the destruction of valvular cusps, aortic ring dilatation, or dilatation or thickening of the aortic root.
- **Valvular disease** may appear within months of the onset of other RPC symptoms or may be delayed for more than a decade.
- In addition, one case of chondritis complicated by rapidly fatal **giant cell myocarditis** and myositis has been reported.

Behcet's disease

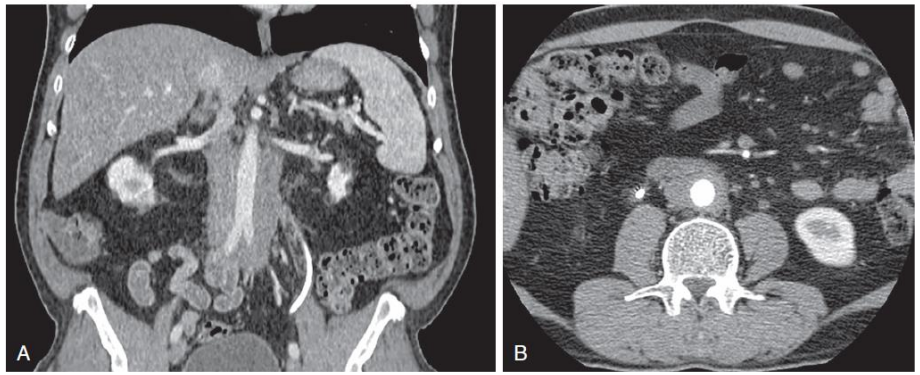
	Number of patients
Venous disease	
Deep venous thrombosis	221
Subcutaneous thrombophlebitis	205
SVC occlusion	122
IVC occlusion	93
Cerebral sinus thrombosis	30
Budd-Chiari syndrome	17
Other venous occlusion*	24
Arterial disease	
Pulmonary artery occlusion or aneurysm	36
Aortic aneurysm	17
Extremity arterial occlusion or aneurysm	45
Other arterial occlusion or aneurysm¶	42
Right ventricular thrombus	2

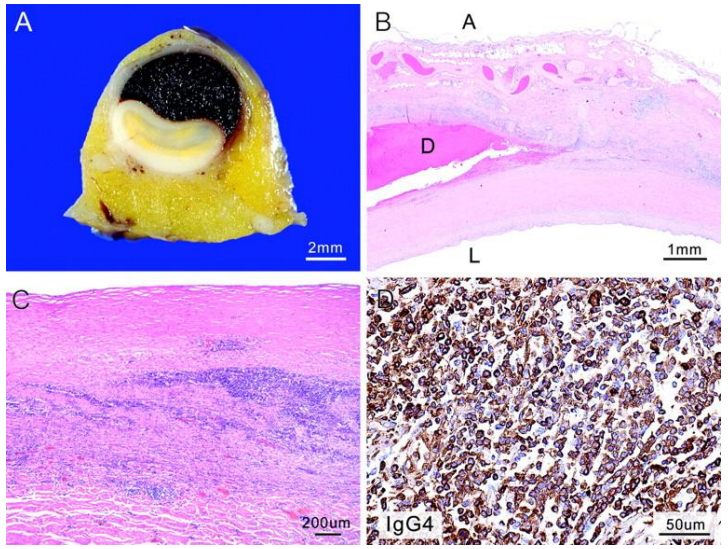
Symptomatic cardiac disease is uncommon in Behçet syndrome.

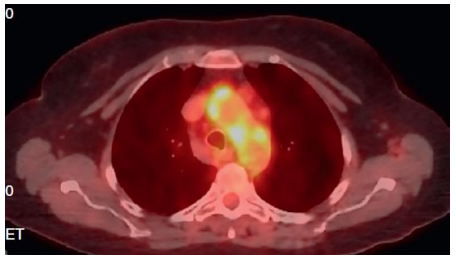
- pericarditis
- myocarditis
- coronary arteritis with or without myocardial infarction
- coronary artery aneurysm
- atrial septal aneurysm
- conduction system disturbances
- ventricular arrhythmias
- endocarditis
- endomyocardial fibrosis
- mitral valve prolapse
- intracardiac thrombosis
- valvular insufficiency

IgG4-related diseases

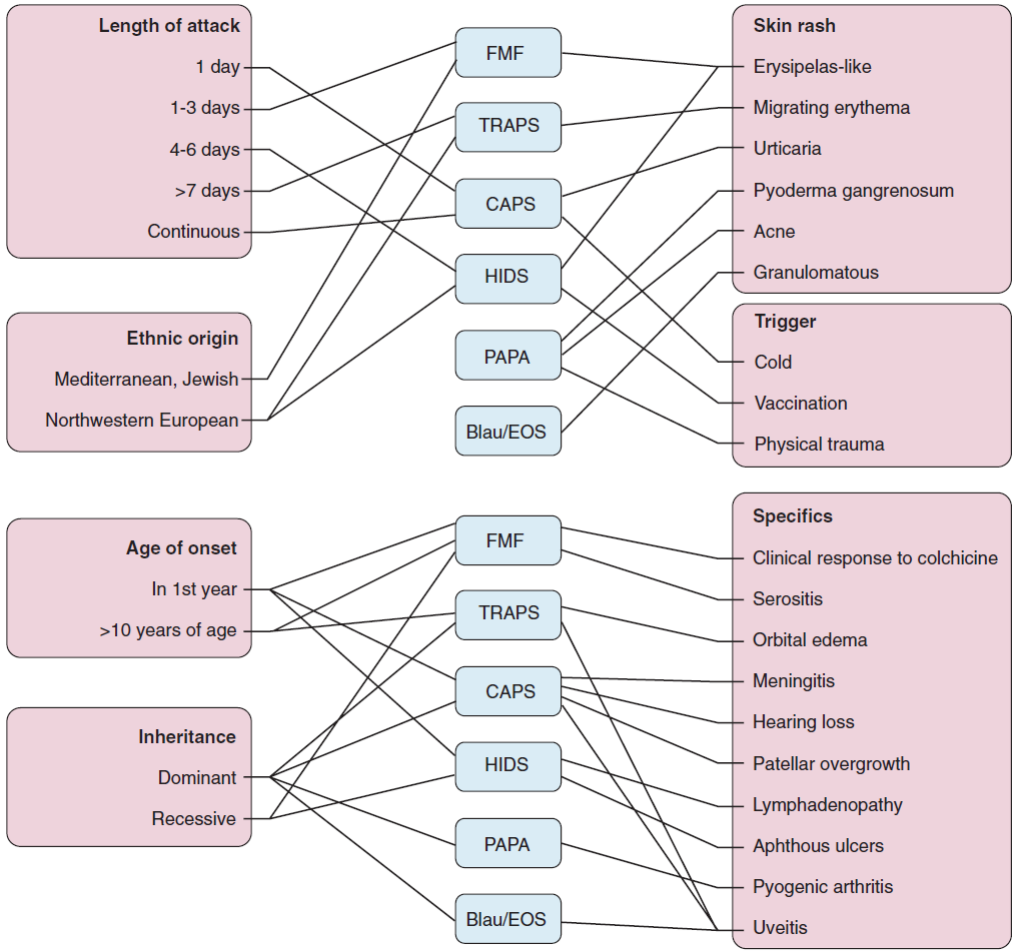
Mikulicz's disease (affecting the salivary and lacrimal glands)
Küttner's tumor (affecting the submandibular glands)
Riedel's thyroiditis
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Lymphomatoid granulomatosis, grade 1 (commonly affecting the lungs)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues/organs)
Lymphoplasmacytic sclerosing pancreatitis/autoimmune pancreatitis
Inflammatory pseudotumor (affecting the orbits, lungs, kidneys, and other organs)
Mediastinal fibrosis
Retroperitoneal fibrosis
Sclerosing mesenteritis
Periaortitis/periarteritis
Inflammatory aortic aneurysm
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits



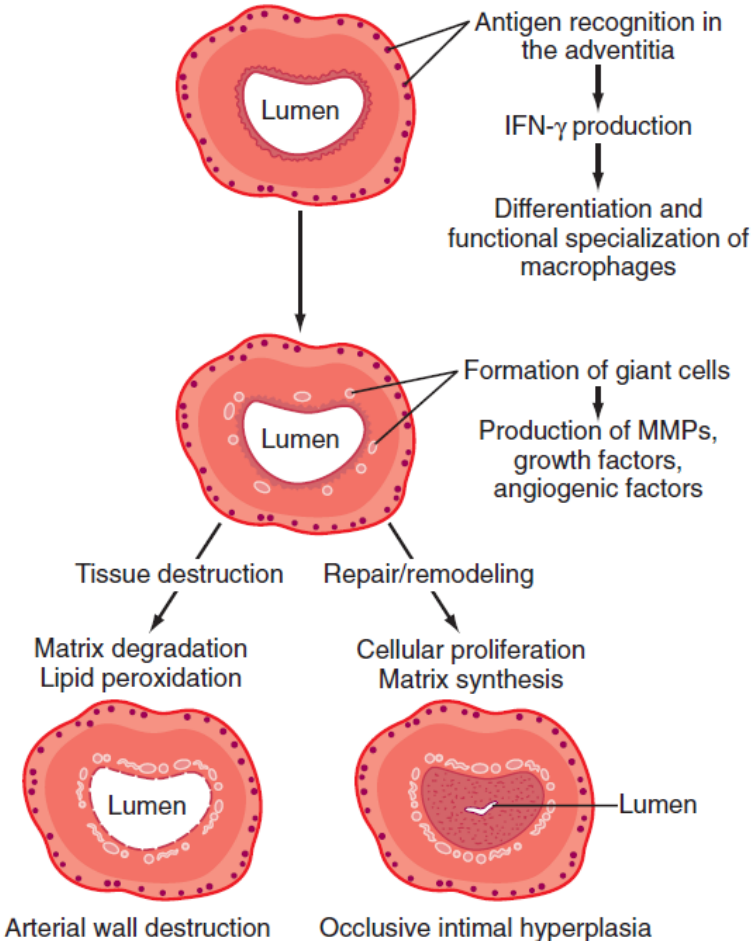


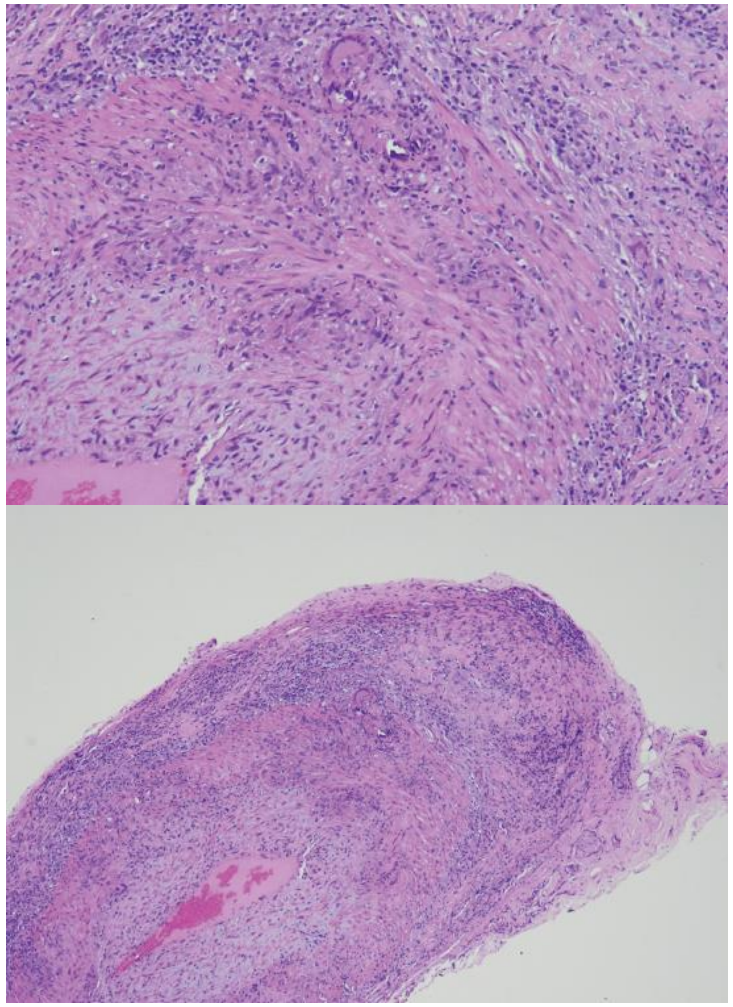


Auto-inflammatory diseases

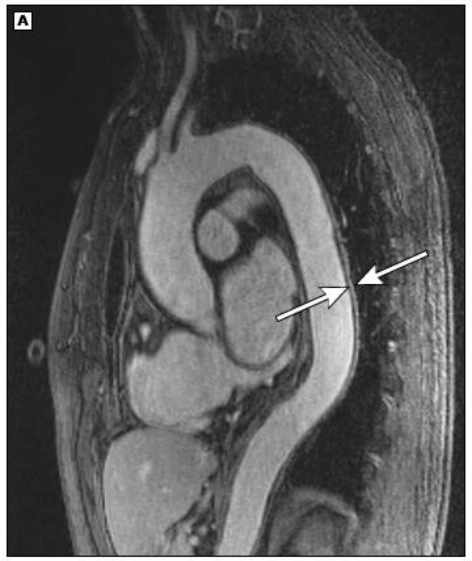


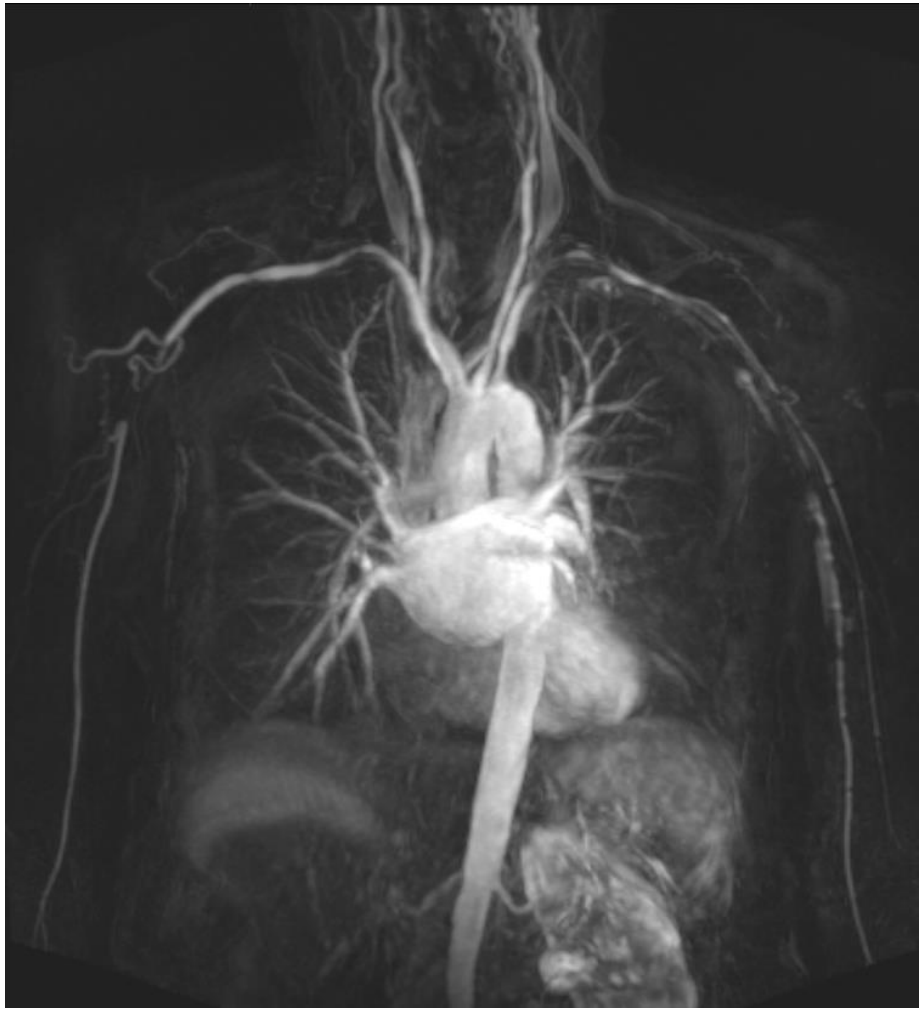
Giant cell arteritis

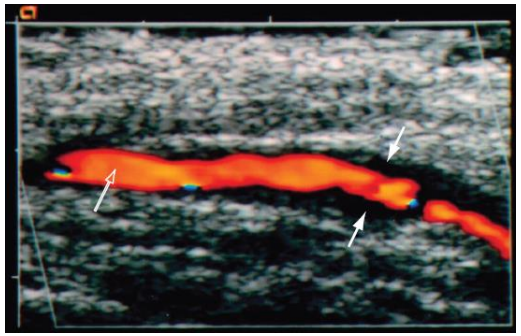


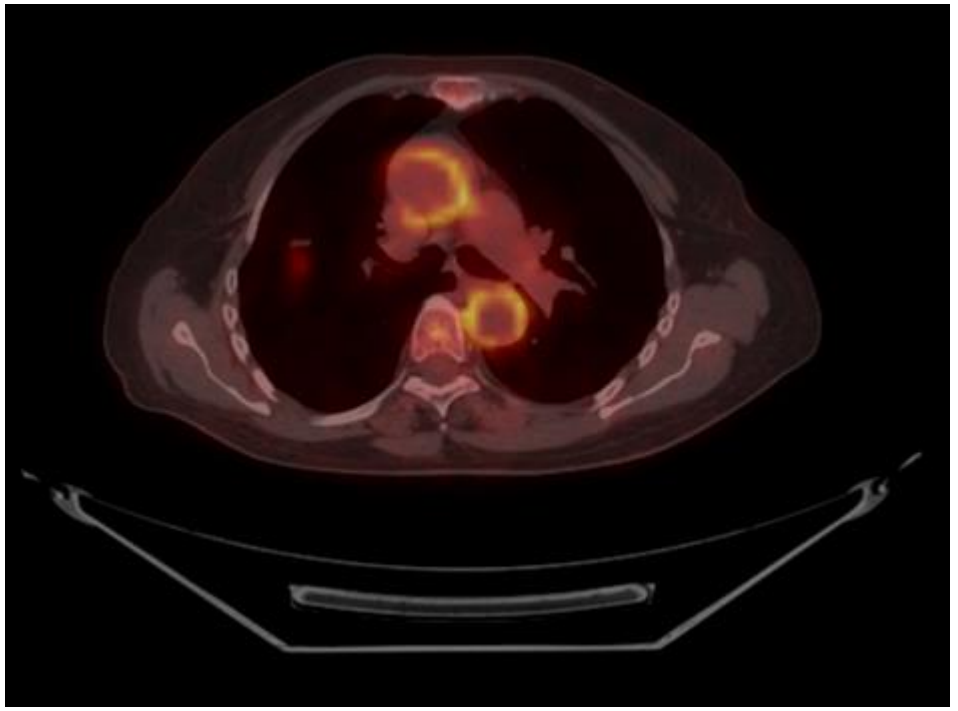


Giant cell arteritis









Takayasu's arteritis

Feature	At Presentation (%)	Ever Present (%)
Vascular	50	100
Bruit		80
Claudication (upper extremity)	30	62
Claudication (lower extremity)	15	32
Hypertension	20	33
Unequal arm blood pressures	15	50
Carotidynia	15	32
Aortic regurgitation		20
Central nervous system	30	57
Lightheadedness	20	35
Visual abnormality	10	30
Stroke	5	10
Musculoskeletal	20	53
Chest wall pain	10	30
Joint pain	10	30
Myalgia	5	15
Constitutional	33	43
Malaise	20	30
Fever	20	25
Weight loss	15	20
Cardiac	15	38
Aortic regurgitation	8	20
Angina	2	12
Congestive heart failure	2	10

Feature	Giant Cell Arteritis	Takayasu's Arteritis
Female-male ratio	2:1	8:1
Age range	≥50 yr	<40 yr
Average age of onset	72 yr	25 yr
Visual loss	10%-30%	Rare
Involvement of aorta or its major branches	25%	100%
Histopathology	Granulomatous arteritis	Granulomatous arteritis
Pulmonary artery involvement	No	Occasionally
Renal hypertension	Rare	Common
Claudication	Uncommon	Common
Ethnic groups with highest incidence	Scandinavian	Asian
Corticosteroid responsive	Yes	Yes
Bruits present	Minority	Majority
Surgical intervention needed	Rare	Common

Causes of aortic regurgitation

Primary cause of aortic regurgitation	Valve disease	Aortic root dilation
Calcific aortic valve disease	X	
Myxomatous degeneration	X	
Congenital heart disease		
Bicuspid aortic valve	X	X
High ventricular septal defect (infundibular or membranous)	X	
Sinus of valsalva aneurysm		X
Fenestrated leaflet*		
Rheumatic heart disease	X	
Genetic syndromes		
Marfan syndrome		X
Familial thoracic aneurysm		X
Ehlers-Danlos syndrome		X
Osteogenesis imperfecta		X
Pseudoxanthoma elasticum	X	
Systemic rheumatic disorders		
Giant cell arteritis		X
Takayasu arteritis		X
Ankylosing spondylitis	X	X
Rheumatoid arthritis	X	
Systemic lupus erythematosus	X	
Antiphospholipid syndrome	X	
Drug-induced valve disease (eg, fenfluramine-phentermine)	X	
Infection		
Endocarditis	X	
Infectious aortitis (eg, syphilis)		X
Aortic dissection	X	X
Hypertension		X
Trauma (causing aortic dissection or aortic valve injury)	X	X
Other genetic and acquired causes of annuloaortic ectasia		X

* Aortic leaflet fenestration or perforation may also be seen with myxomatous degeneration or endocarditis.

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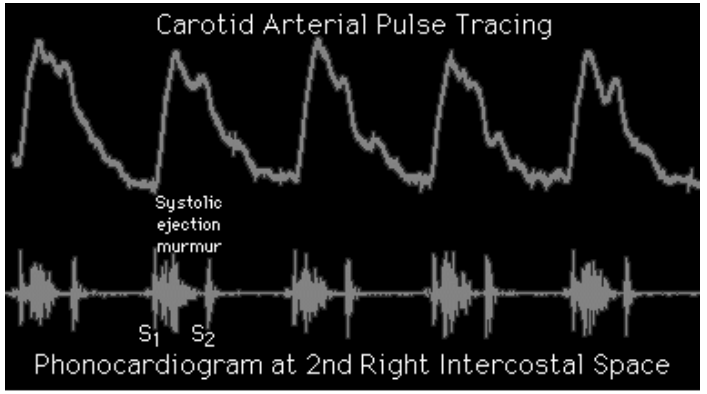
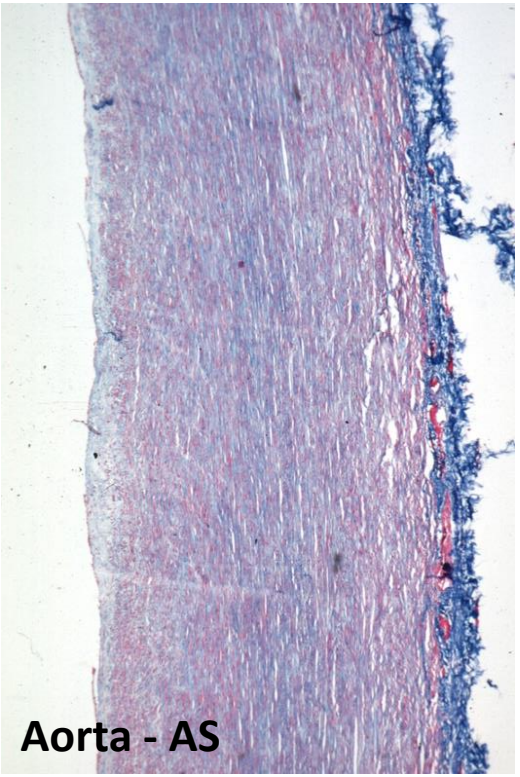
Insufficienza aortica



Aortic regurgitation Carotid artery pulse tracing and phonocardiogram of aortic regurgitation as heard at the second right intercostal space. S1 (mitral and tricuspid valve closure) is followed by a systolic ejection murmur due to the large stroke volume seen in aortic regurgitation. After S2 (aortic and pulmonic valve closure) there is a faint and short diastolic "blowing" murmur of aortic regurgitation. (Provided by John M Criley, MD, The Physiological Origins of Heart Sounds and Murmurs, Little, Brown, Boston, 1996, 1-800-527-0145. This program contains a complete interactive tutorial integrating over 200 heart sounds and murmurs with cineangiographic, echo-Doppler, and hemodynamic motion picture sequences.)



Case report

PMCID: PMC3662630

History

A 26-year-old Portuguese woman presented to the emergence department with a 48 hour history of progressive dyspnoea, generalized oedema and left lower chest pain with non-productive cough.

The patient had a 6 months history of inflammatory polyarthralgia involving initially interphalangeal joints, evolving, at some time later, the knees and elbows bilaterally. After ongoing rheumatologist evaluation, she started prednisolone 10 mg qd and hydroxychloroquine 400 mg qd, while waiting laboratory results.

12 days before admission, she had had symptoms of a urethritis episode, associated with unexplained anorexia and asthenia, which led her to suspend the therapeutic, even against medical advice.

Physical examination

On examination, patient was feeling very ill, afebrile, with tachycardia (144 bpm), tachypnoea (34/min), blood pressure 143/82 mmHg, peripheral oxygen saturation of 94% on 40% oxygen and raised jugular venous pressure.

Intermittently she presented dizziness.

Aside a diffuse moderate oedema and a livedoid skin discoloration, an erythematous rash over the cheeks and nasal bridge was noted.

On auscultation heart sounds were found to be diminished and **diffuse** coarse crackles were noted on both lungs, with depressed vocal transmission in right basal thorax. Abdominal examination revealed moderate hepatomegaly and ascites.

Ipotesi diagnostiche	Dispnea - Meccanismo	Esami richiesti
1. LES 2. …	1. Tromboembolia 2. Pericardite, tamponamento cardiaco 3. Versamento pleurico 4. Ascite 5. Interstiopatia 6. Polmonite acuta 7. Miocardite 8. Anemia	1. Emocromo…D-dimero, enzimi cardiaci, pro-BNP 2. Fx renale, elettroliti 3. P. Epatico 4. EGA 5. ECG 6. Ecocardio 7. Rx torace 8. aPL 9. ANA test reflex

Causes of pericardial disease

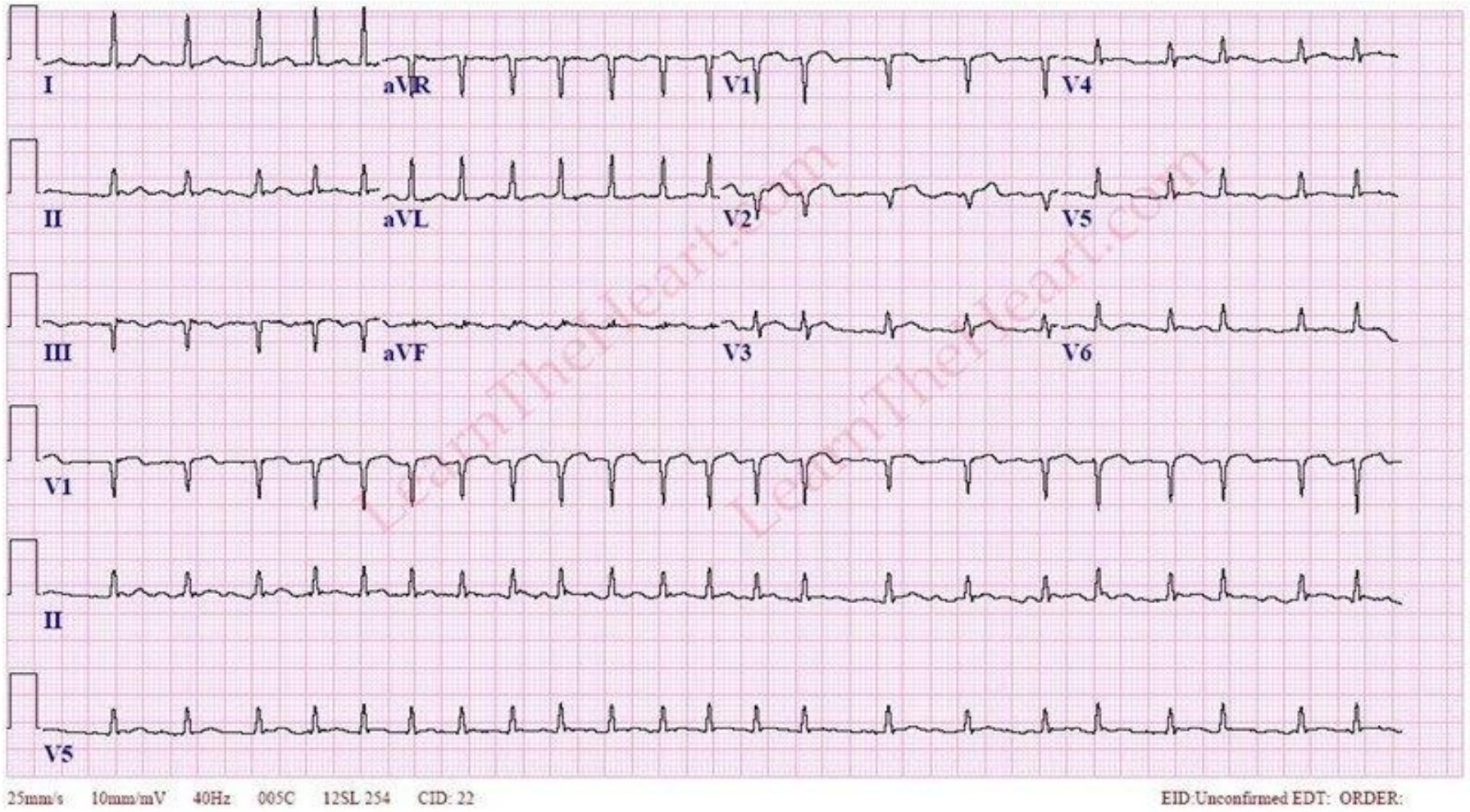
Idiopathic (presumed to be viral, postviral, or immune-mediated)
In most case series, the majority of patients are not found to have an identifiable cause of pericardial disease. Frequently such cases are presumed to have a viral or autoimmune etiology.
Infectious
Viral - Coxsackievirus, echovirus, adenovirus, Epstein-Barr virus, cytomegalovirus, influenza, varicella, rubella, HIV, hepatitis B, mumps, parvovirus B19, vaccina (smallpox vaccine)
Bacterial - *Mycobacterium tuberculosis* (most common cause in countries where tuberculosis is endemic), *Staphylococcus, Streptococcus, Haemophilus, Neisseria* (*N. gonorrhoeae or N. meningitidis*), *Chlamydia* (*C. psittaci or C. trachomatis*), *Legionella, Salmonella, Borrelia burgdorferi* (the cause of Lyme disease), *Mycoplasma, Actinomyces, Nocardia, Tropheryma whippelii, Treponema, Rickettsia*
Fungal - *Histoplasma, Aspergillus, Blastomyces, Coccidioides, Candida*
Parasitic - *Echinococcus*, amebic, *Toxoplasma*
Infective endocarditis with valve ring abscess
Noninfectious
Autoimmune and autoinflammatory
Systemic inflammatory diseases, especially lupus, rheumatoid arthritis, scleroderma, Sjögren syndrome, vasculitis, mixed connective disease
Autoinflammatory diseases (especially familial Mediterranean fever and tumor necrosis factor associated periodic syndrome [TRAPS], IgG4-related disease)
Postcardiac injury syndromes (immune-mediated after cardiac trauma in predisposed individuals)
Other - Granulomatosis with polyangiitis (Wegener's), polyarteritis nodosa, sarcoidosis, inflammatory bowel disease (Crohn's, ulcerative colitis), Whipple's, giant cell arteritis, Behçet's disease, rheumatic fever
Neoplasm
Metastatic - Lung or breast cancer, Hodgkin's disease, leukemia, melanoma
Primary - Rhabdomyosarcoma, teratoma, fibroma, lipoma, leiomyoma, angioma
Paraneoplastic
Cardiac
Early infarction pericarditis
Late postcardiac injury syndrome (Dressler's syndrome), also seen in other settings (eg, post-myocardial infarction and post-cardiac surgery)
Myocarditis
Dissecting aortic aneurysm
Trauma
Blunt
Penetrating
Iatrogenic - Catheter and pacemaker perforations, cardiopulmonary resuscitation, post-thoracic surgery
Metabolic
Hypothyroidism - Primarily pericardial effusion
Uremia
Ovarian hyperstimulation syndrome
Radiation
Drugs (rare)
Procainamide, isoniazid, or hydralazine as part of drug-induced lupus
Other - Cromolyn sodium, dantrolene, methysergide, anticoagulants, thrombolytics, phenytoin, penicillin, phenylbutazone, doxorubicin

Causes of exudative pleural effusions

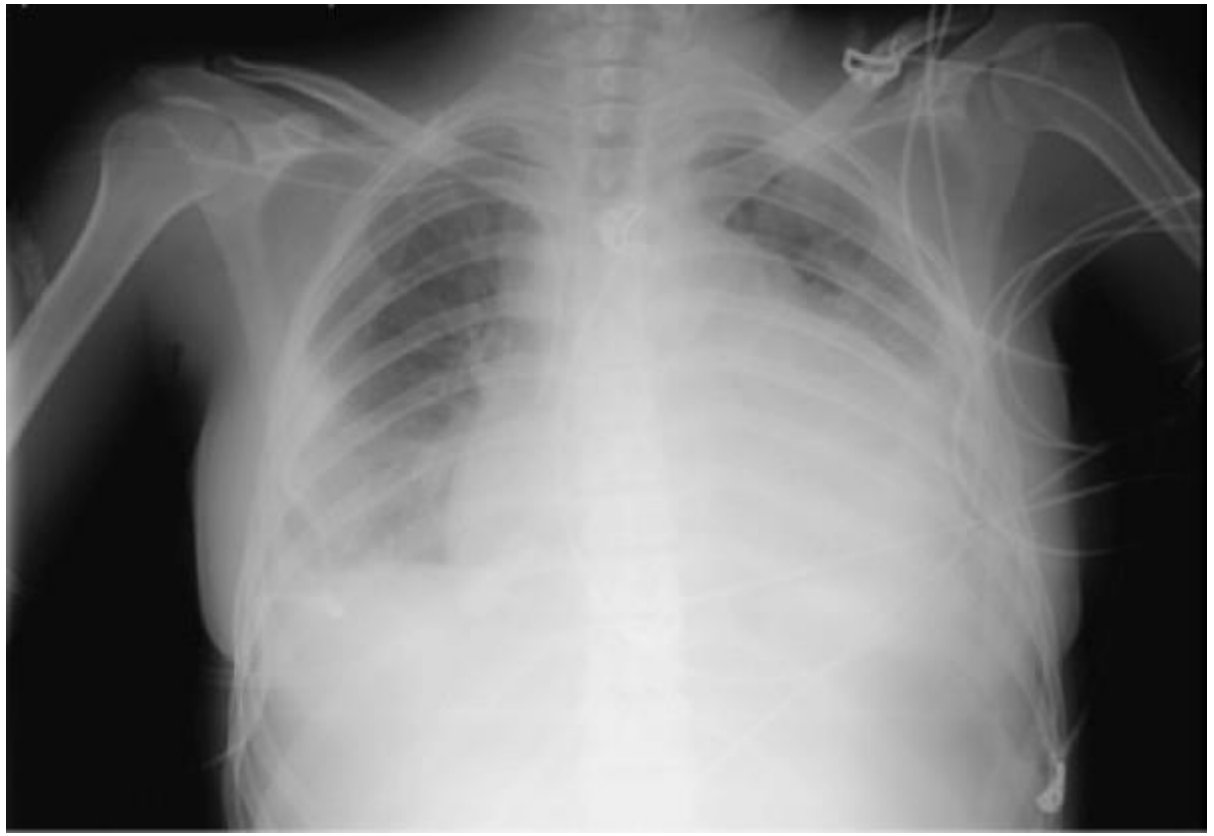
Infectious
Bacterial pneumonia
Tuberculous pleurisy
Parasites
Fungal disease
Atypical pneumonias (viral, mycoplasma)
Nocardia, Actinomyces
Subphrenic abscess
Hepatic abscess
Splenic abscess
Hepatitis
Spontaneous esophageal rupture
Iatrogenic
Central venous catheter misplacement/migration
Drug-induced
Esophageal perforation
Esophageal sclerotherapy
Enteral feeding tube in pleural space
Radiofrequency ablation of pulmonary neoplasms
Malignancy-related
Carcinoma
Lymphoma
Mesothelioma
Leukemia
Chylothorax
Paraproteinemia (multiple myeloma, Waldenstrom's macroglobulinemia)
Other inflammatory disorders
Pancreatitis (acute, chronic)
Benign asbestos pleural effusion
Pulmonary embolism
Radiation therapy
Uremic pleurisy
Sarcoidosis
Postcardiac injury syndrome
Hemothorax
Acute respiratory distress syndrome (ARDS)

Increased negative intrapleural pressure with accompanying pleural malignancy or inflammation
Lung entrapment
Cholesterol effusion
Connective tissue disease
Lupus pleuritis
Rheumatoid pleurisy
Mixed connective tissue disease
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Granulomatosis with polyangiitis (Wegener's)
Familial mediterranean fever
Endocrine dysfunction
Hypothyroidism
Ovarian hyperstimulation syndrome
Lymphatic abnormalities
Malignancy
Chylothorax
Yellow nail syndrome
Lymphangioleiomyomatosis
Lymphangiectasia
Movement of liquid from abdomen to pleural space
Pancreatitis
Pancreatic pseudocyst
Meigs' syndrome
Chylous ascites
Malignant ascites
Subphrenic abscess
Hepatic abscess (bacterial, amebic)
Splenic abscess, infarction

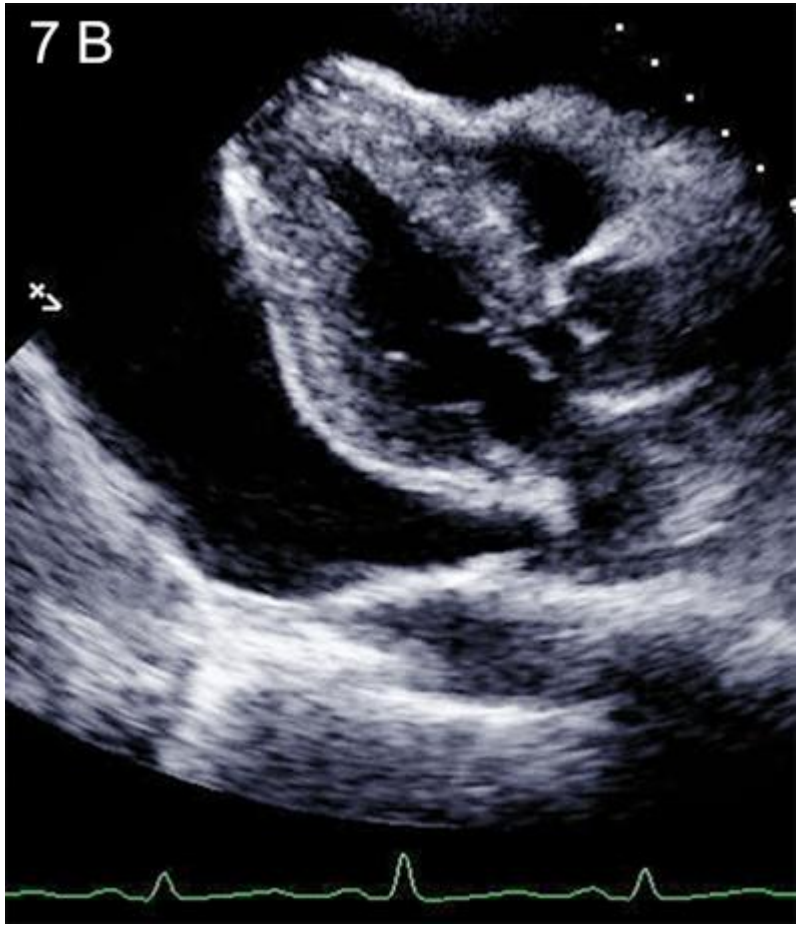
ECG


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5
25mm/s 10mm/mV 40Hz 005C 12SL 254 CID: 22
EID Unconfirmed EDT: ORDER:

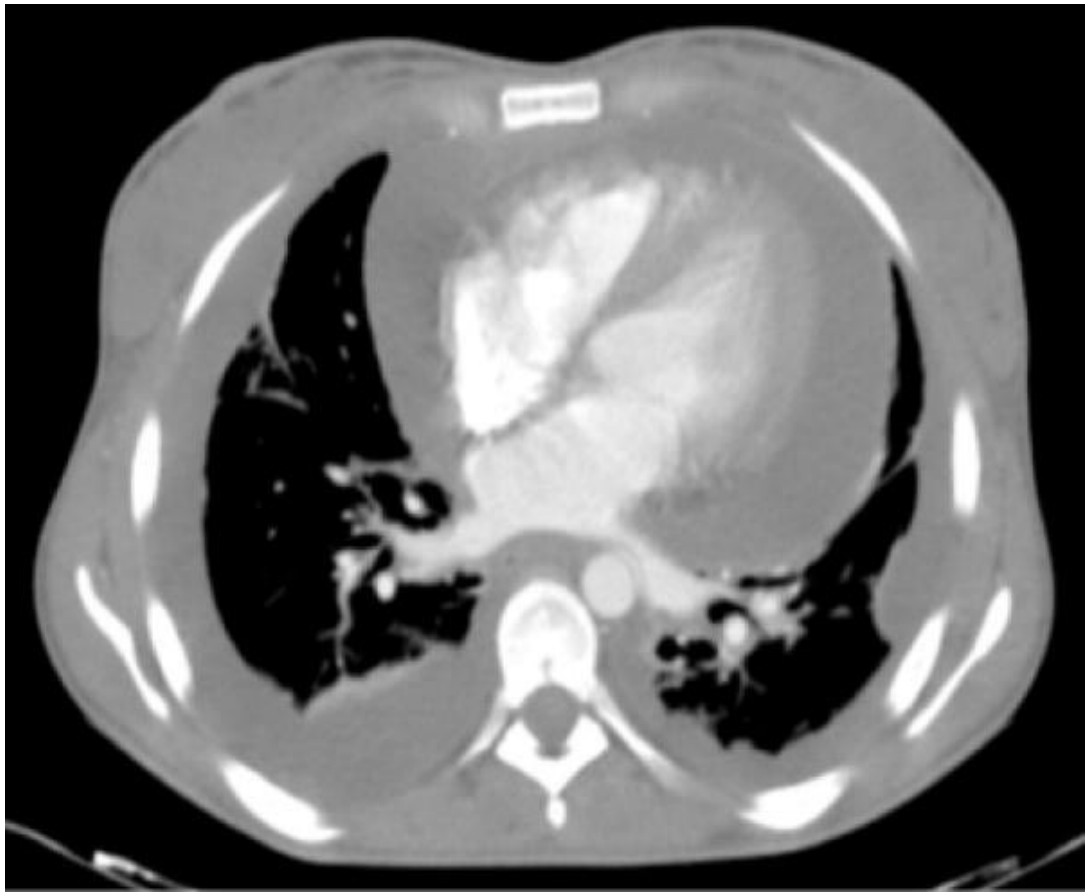
Chest X-Ray

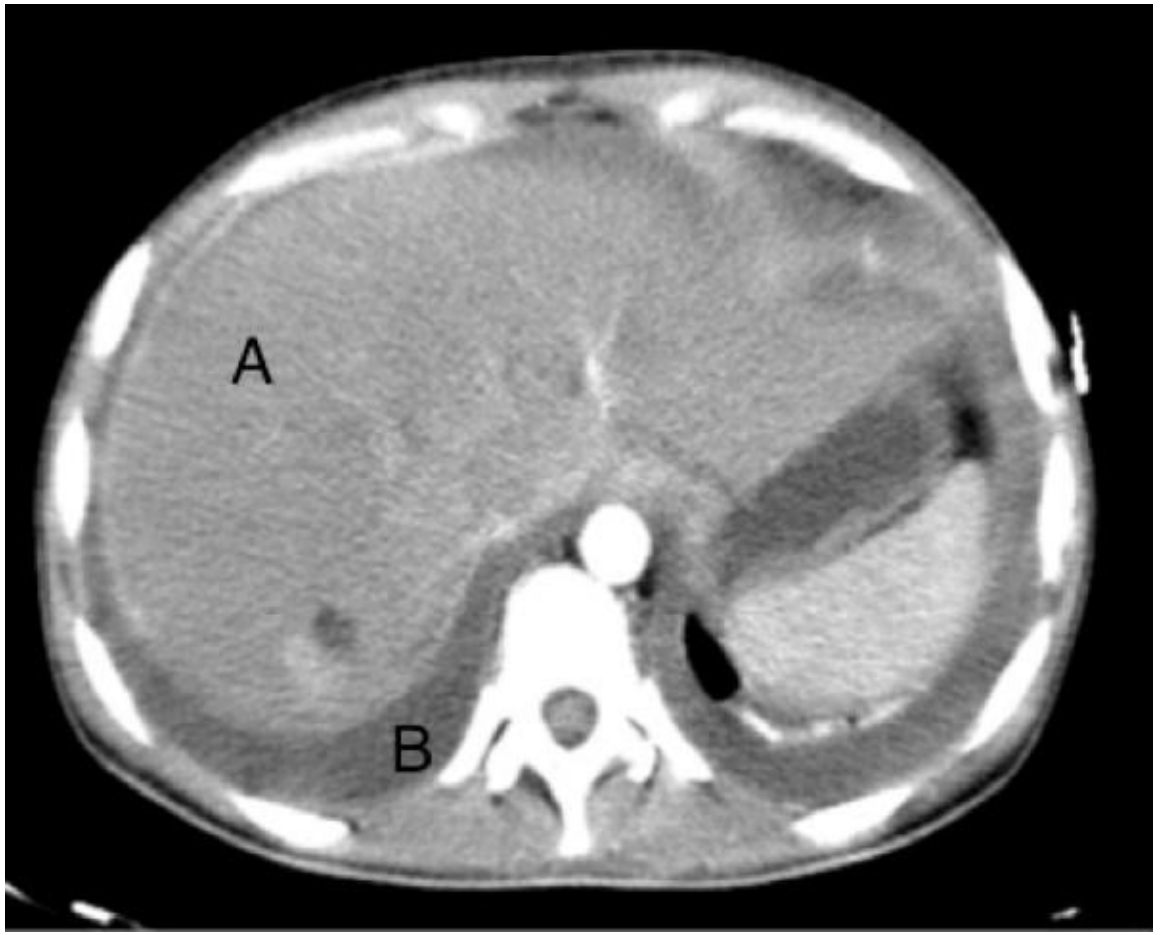


Ecocardiography



CT Scan





Laboratory

Arterial blood gas analysis

- pH 7.134
- PCO_2 18 mm Hg
- PO_2 85 mm Hg
- HCO_3 6 mEq/L

Laboratory

- WBC of 5.300 cells/mm3, with 70% PMNs
- platelet count of 417.000 per mm3
- haemoglobin 7.8 g/dL
- INR 2.4.
- sodium 131 mmol/L
- creatinine 1.4 mg/dL,
- total bilirubin 0.62 mg/dL,
- AST 401 U/L, ALT 85 U/L, and ALP 128 U/L.
- C reactive protein 160 mg/l and ESR 87 mm/h.

Urine analysis

- > 50 leucocytes per high-power field
- >40 erythrocytes per high-power field
- proteinuria > 75 mg/dL
  - A 24 hour urine: 2.1 g

Microbiologic tests

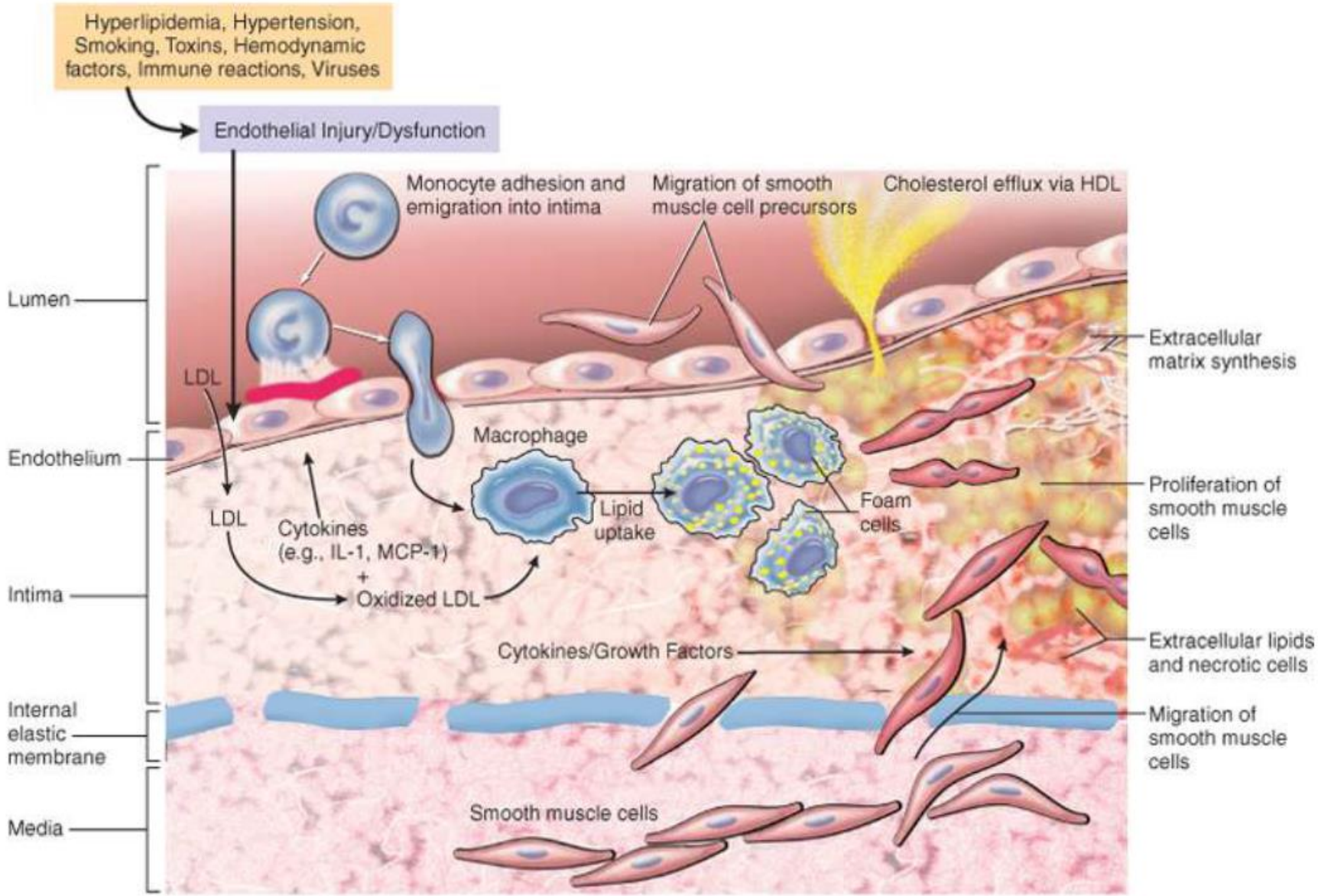
- Negative blood, pleural fluid and urine cultures became negative

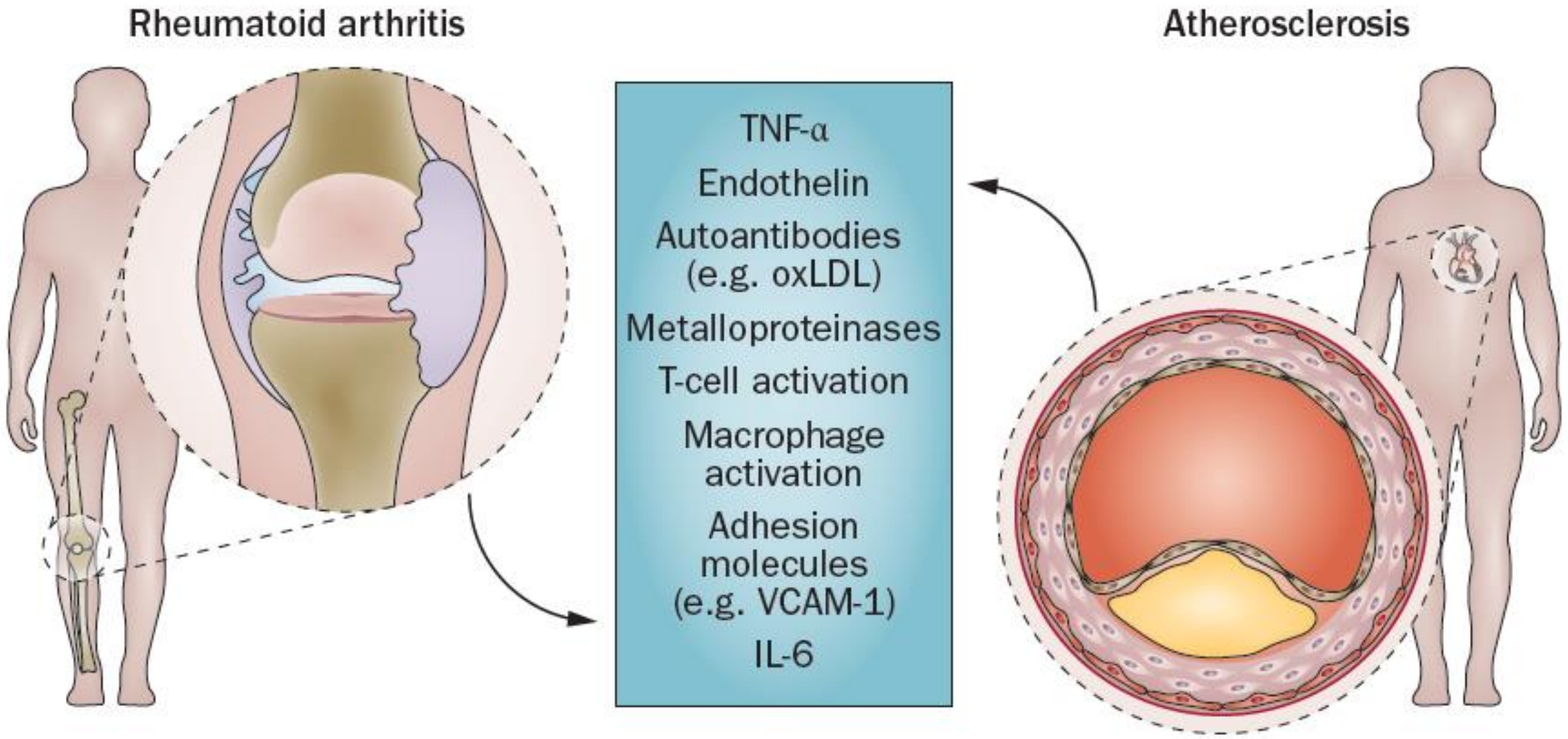
Immunological tests

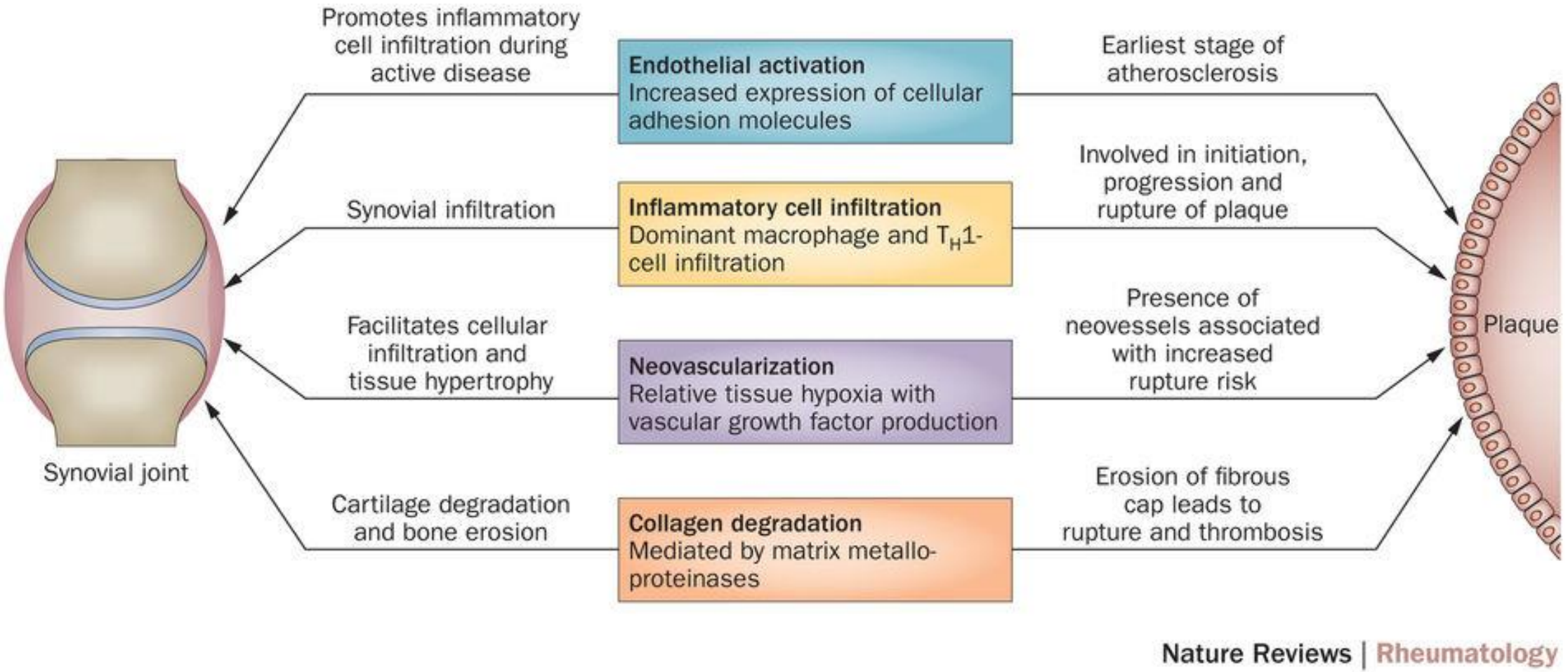
- ANA (1:320), anti-dsDNA antibodies (175 UI/mL) with anti SSA, SSB and Histone
- C3 <1 UI; C4 – 9 UI; CH50 <10 UI
- hypergammaglobulinemia
- direct positive Coombs test.

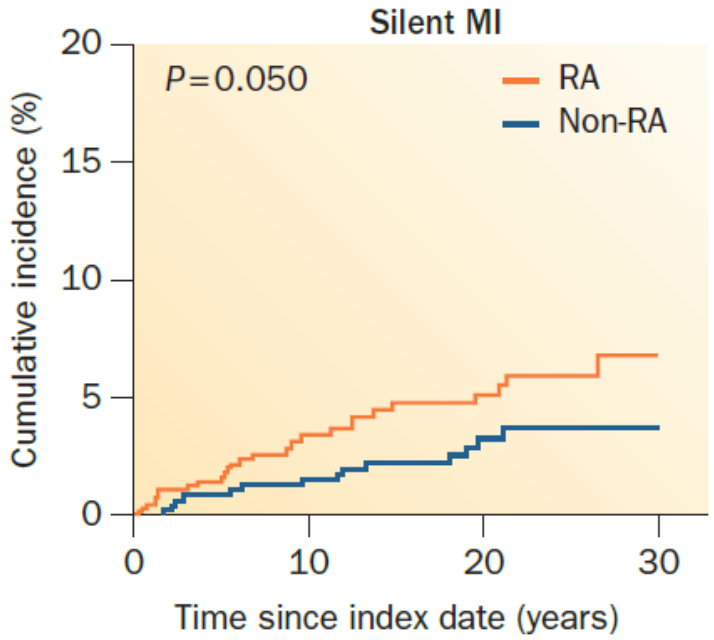
Accelerated atherosclerosis

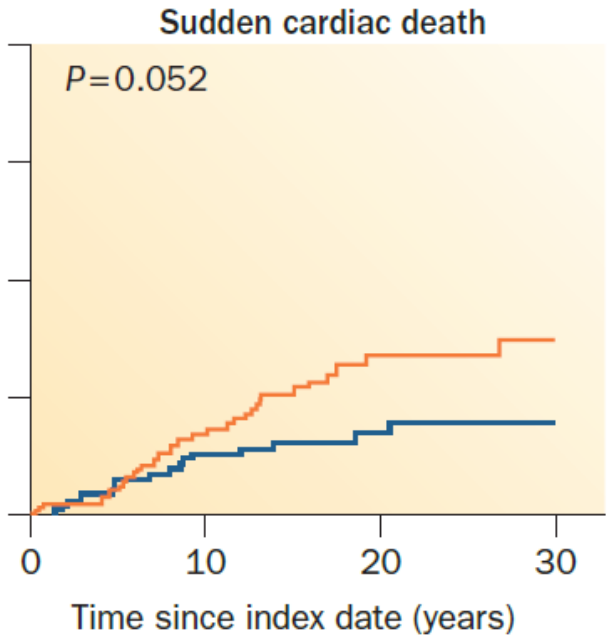
RHEUMATOID ARTHRITIS

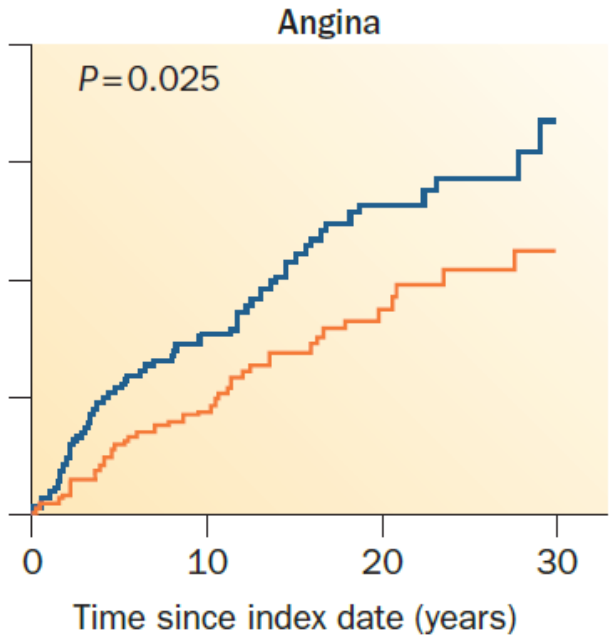

Hyperlipidemia, Hypertension, Smoking, Toxins, Hemodynamic factors, Immune reactions, Viruses
Endothelial Injury/Dysfunction
Monocyte adhesion and emigration into intima
Migration of smooth muscle cell precursors
Cholesterol efflux via HDL
Lumen
Endothelium
Intima
Internal elastic membrane
Media
LDL
LDL
Cytokines (e.g., IL-1, MCP-1) + Oxidized LDL
Macrophage
Lipid uptake
Foam cells
Extracellular matrix synthesis
Proliferation of smooth muscle cells
Extracellular lipids and necrotic cells
Migration of smooth muscle cells
Cytokines/Growth Factors
Smooth muscle cells

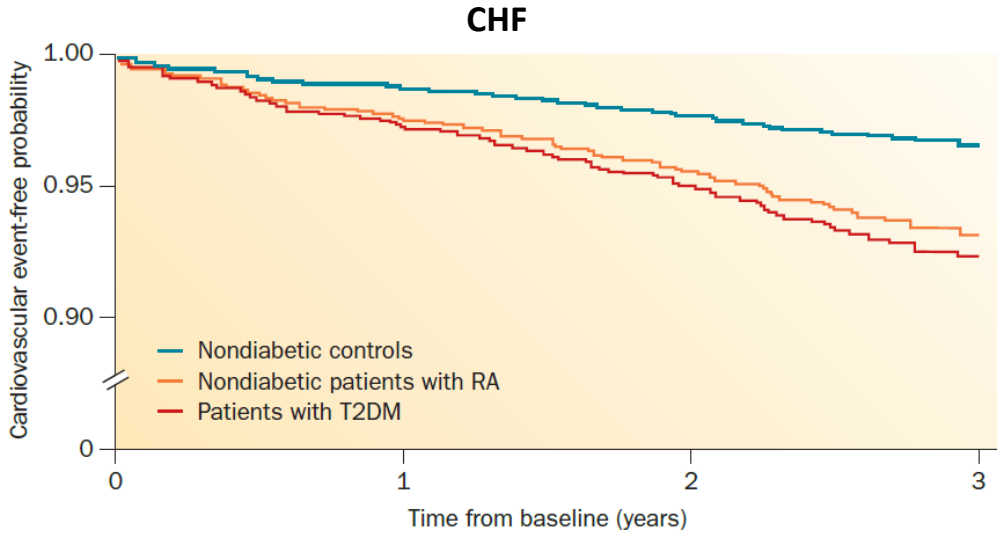

Rheumatoid arthritis
Atherosclerosis
TNF-α
Endothelin
Autoantibodies (e.g. oxLDL)
Metalloproteinases
T-cell activation
Macrophage activation
Adhesion molecules (e.g. VCAM-1)
IL-6


Promotes inflammatory cell infiltration during active disease
Endothelial activation
Increased expression of cellular adhesion molecules
Earliest stage of atherosclerosis
Synovial infiltration
Inflammatory cell infiltration
Dominant macrophage and T_H1-cell infiltration
Involved in initiation, progression and rupture of plaque
Facilitates cellular infiltration and tissue hypertrophy
Neovascularization
Relative tissue hypoxia with vascular growth factor production
Presence of neovessels associated with increased rupture risk
Cartilage degradation and bone erosion
Collagen degradation
Mediated by matrix metallo-proteinases
Erosion of fibrous cap leads to rupture and thrombosis
Synovial joint
Plaque
Nature Reviews | Rheumatology

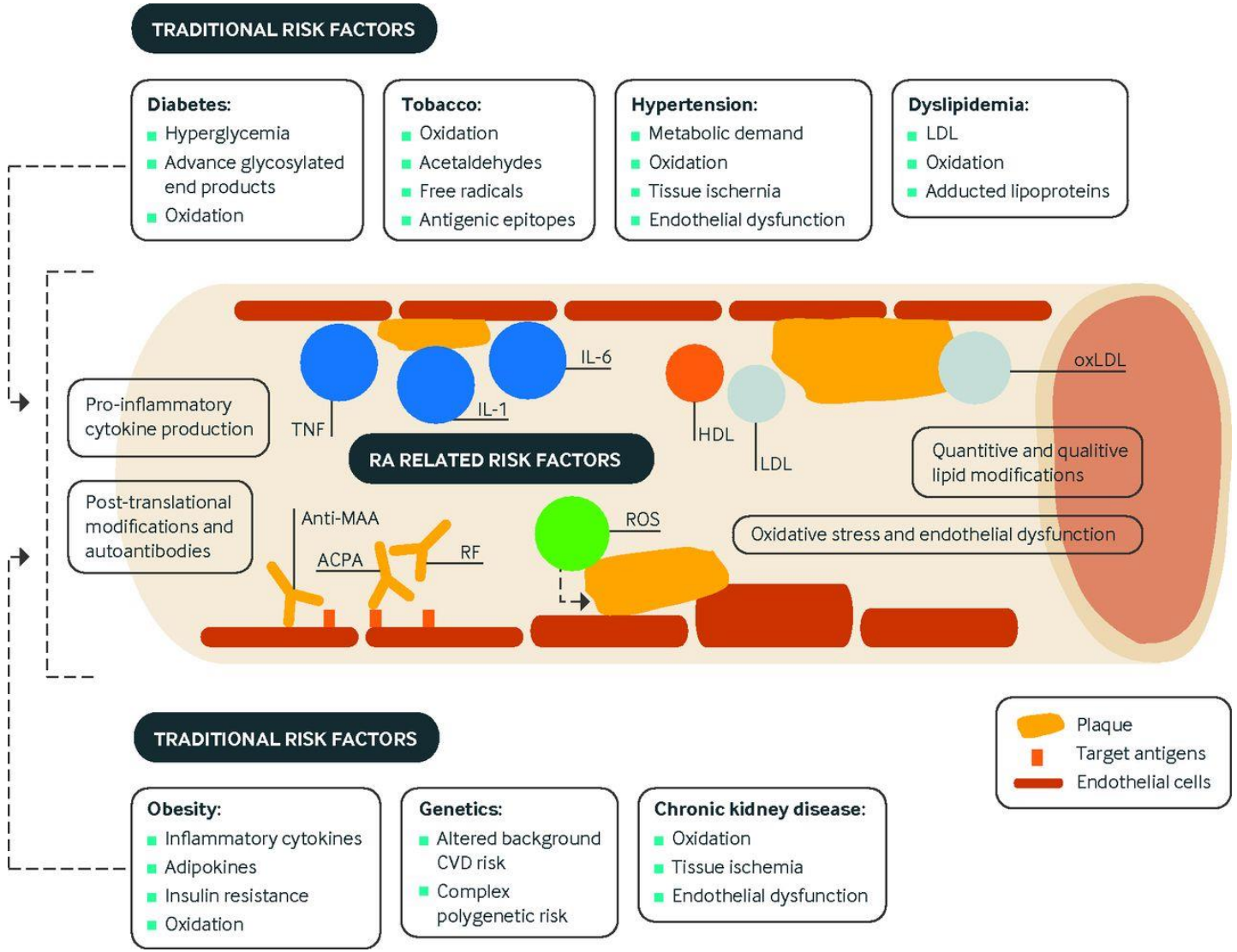

Silent MI
P=0.050
RA
Non-RA
Cumulative incidence (%)
20
15
10
5
0
0
10
20
30
Time since index date (years)


Sudden cardiac death
P=0.052
0
10
20
30
Time since index date (years)


Angina
P=0.025
0
10
20
30
Time since index date (years)

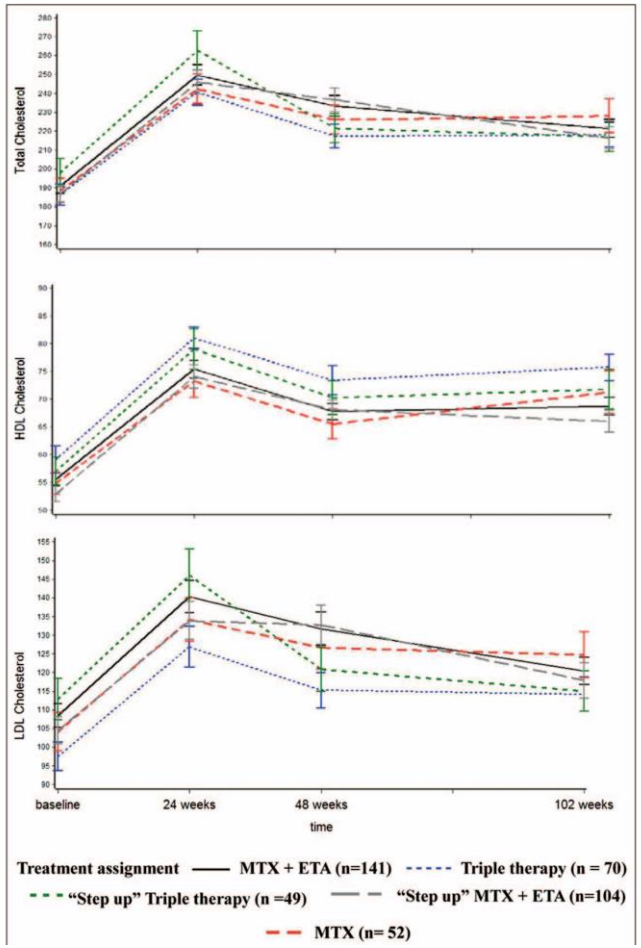

CHF
Cardiovascular event-free probability
1.00
0.95
0.90
0
Nondiabetic controls
Nondiabetic patients with RA
Patients with T2DM
0
1
2
3
Time from baseline (years)

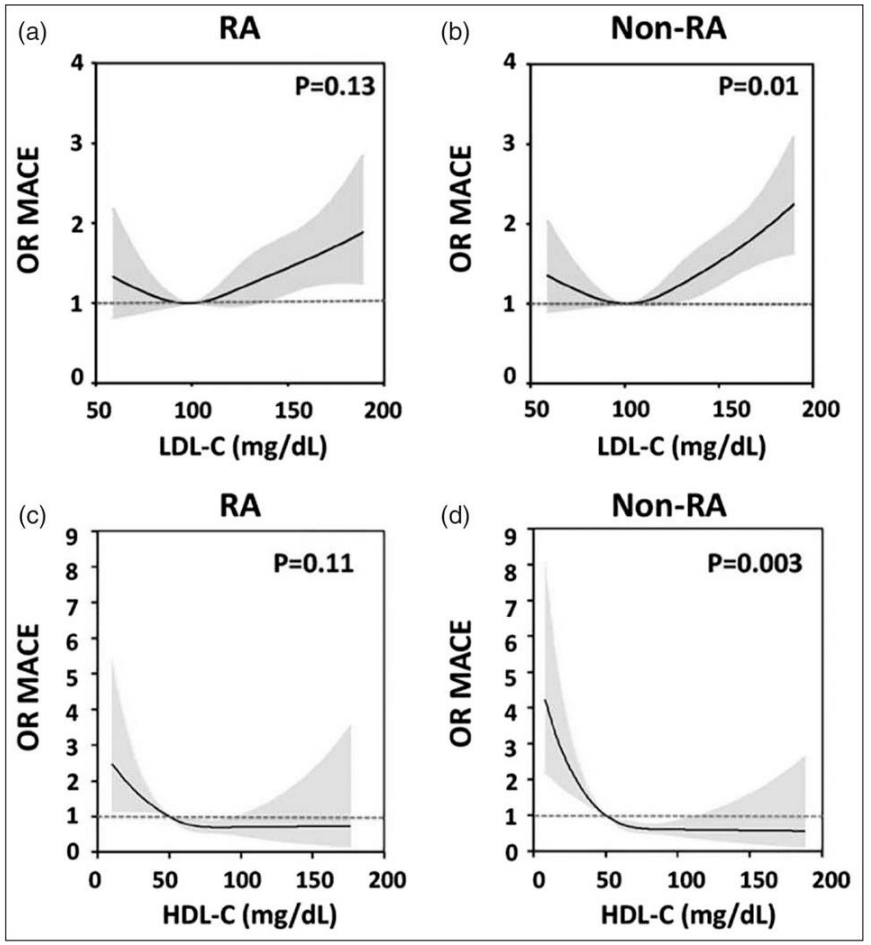
Overview of mechanisms of cardiovascular disease (CVD) in rheumatoid arthritis (RA).

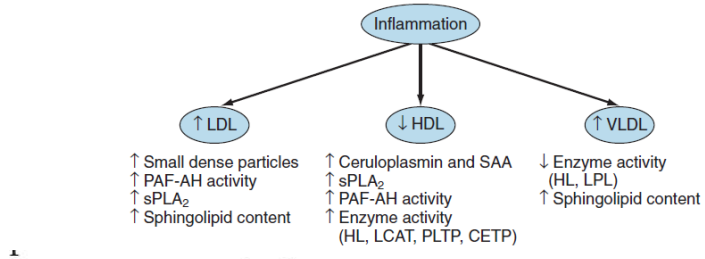


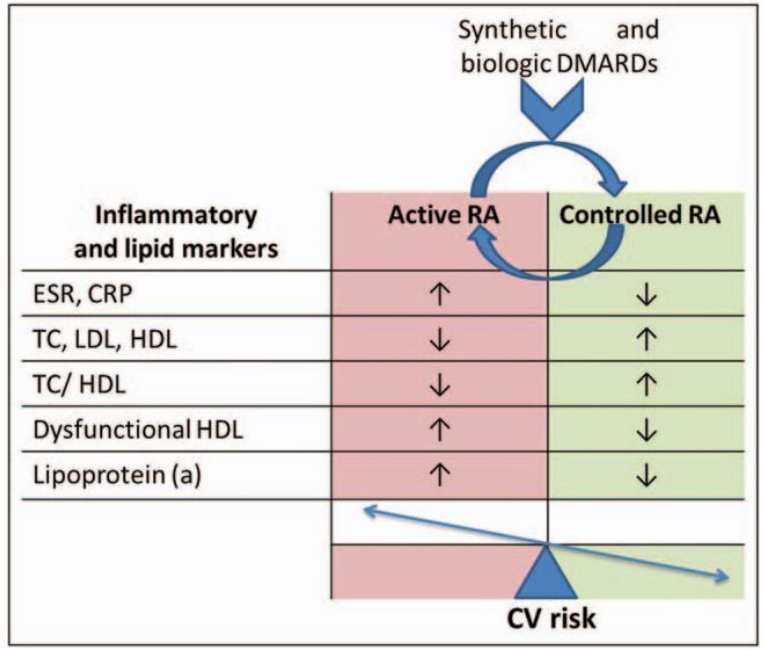
Bryant R England et al. BMJ 2018;361:bmj.k1036

Lypid paradox

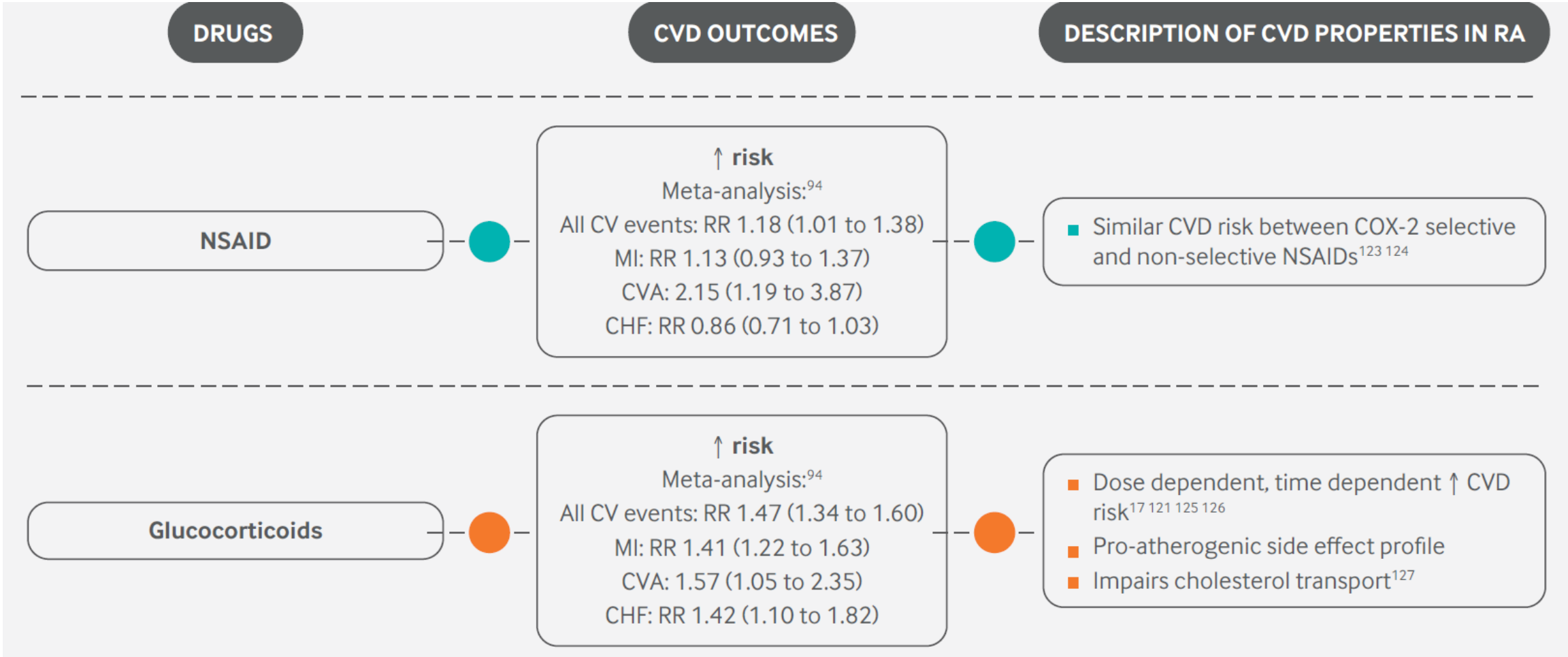




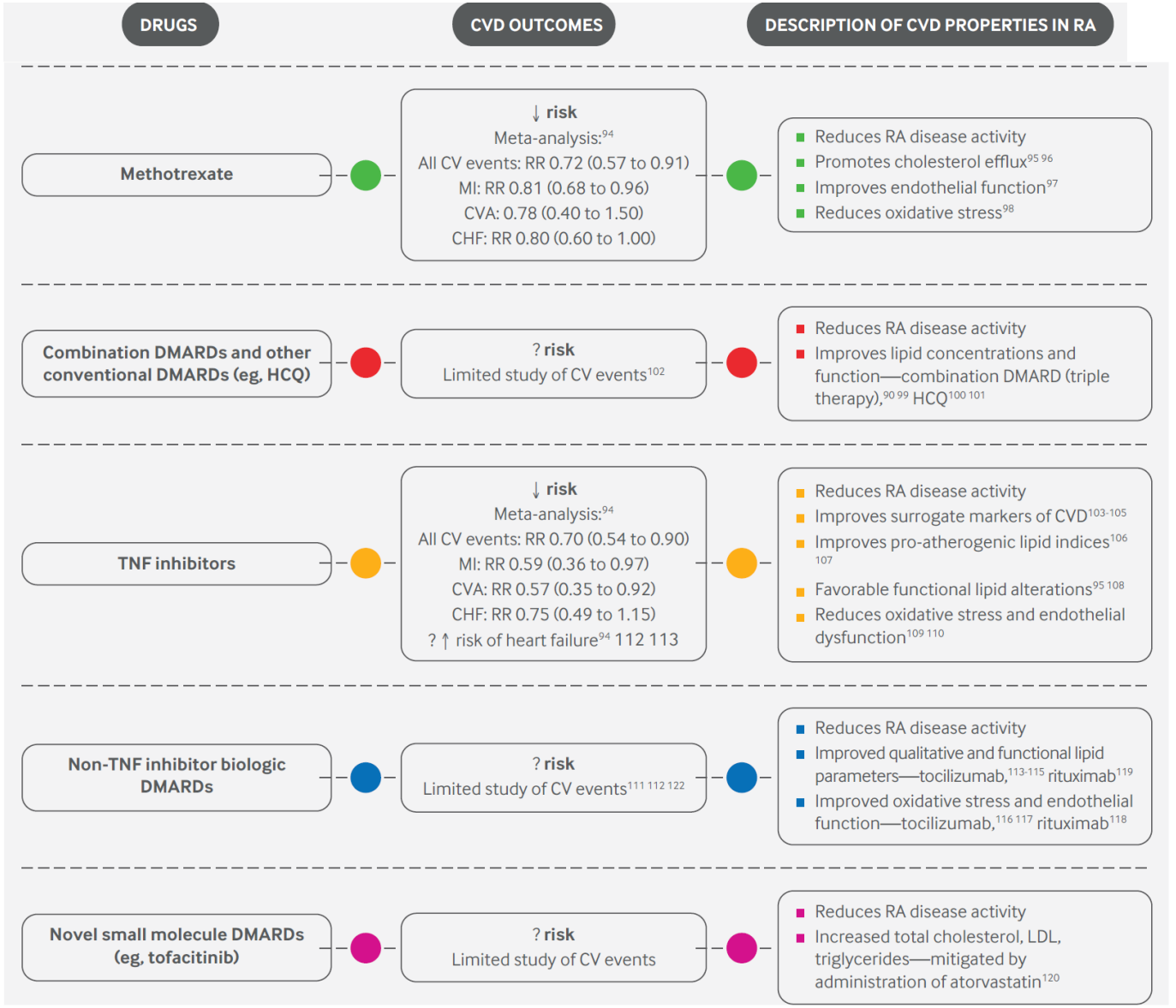




DOI: 10.1097/BOR.0000000000000378



Bryant R England et al. BMJ 2018;361:bmj.k1036



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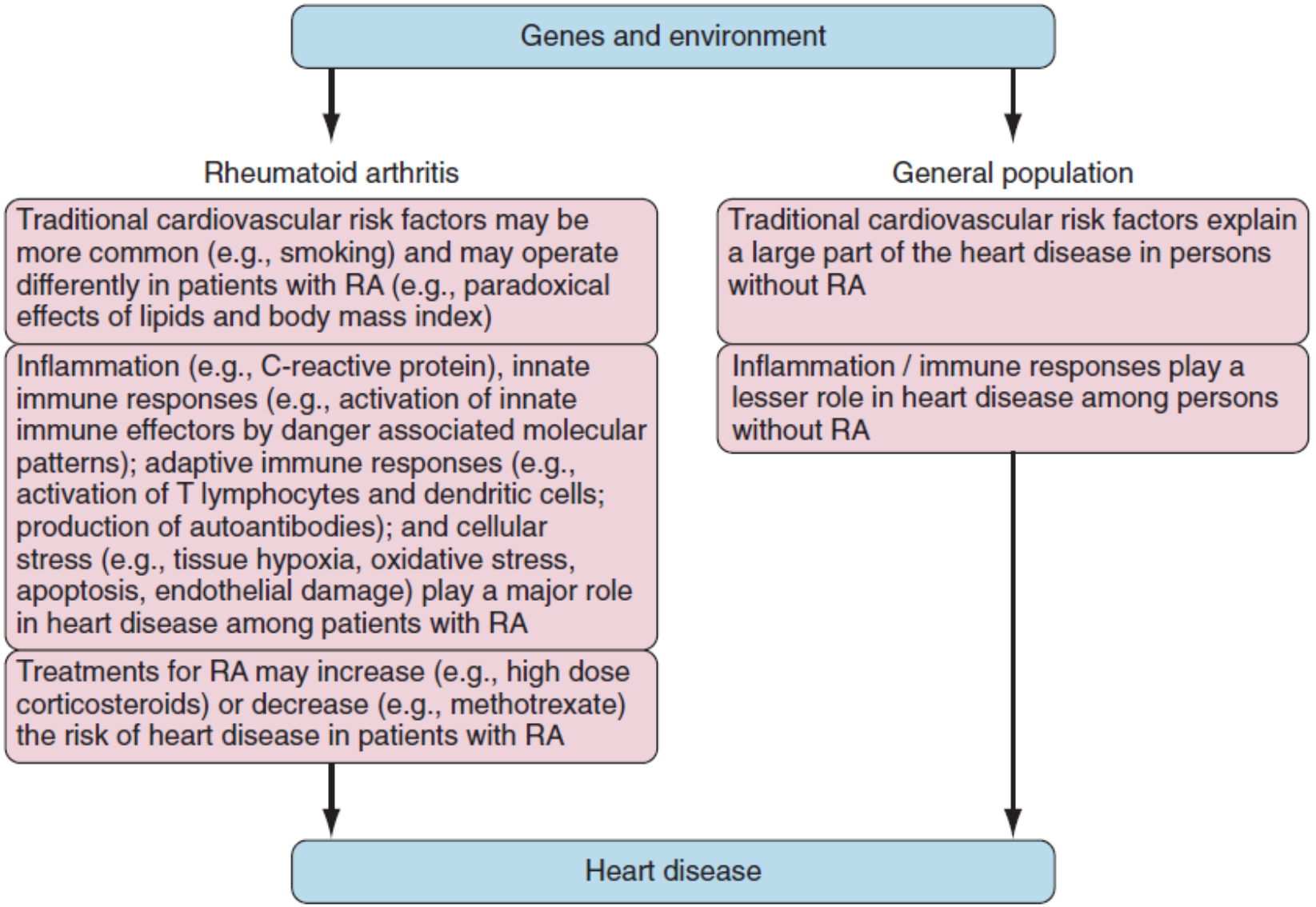
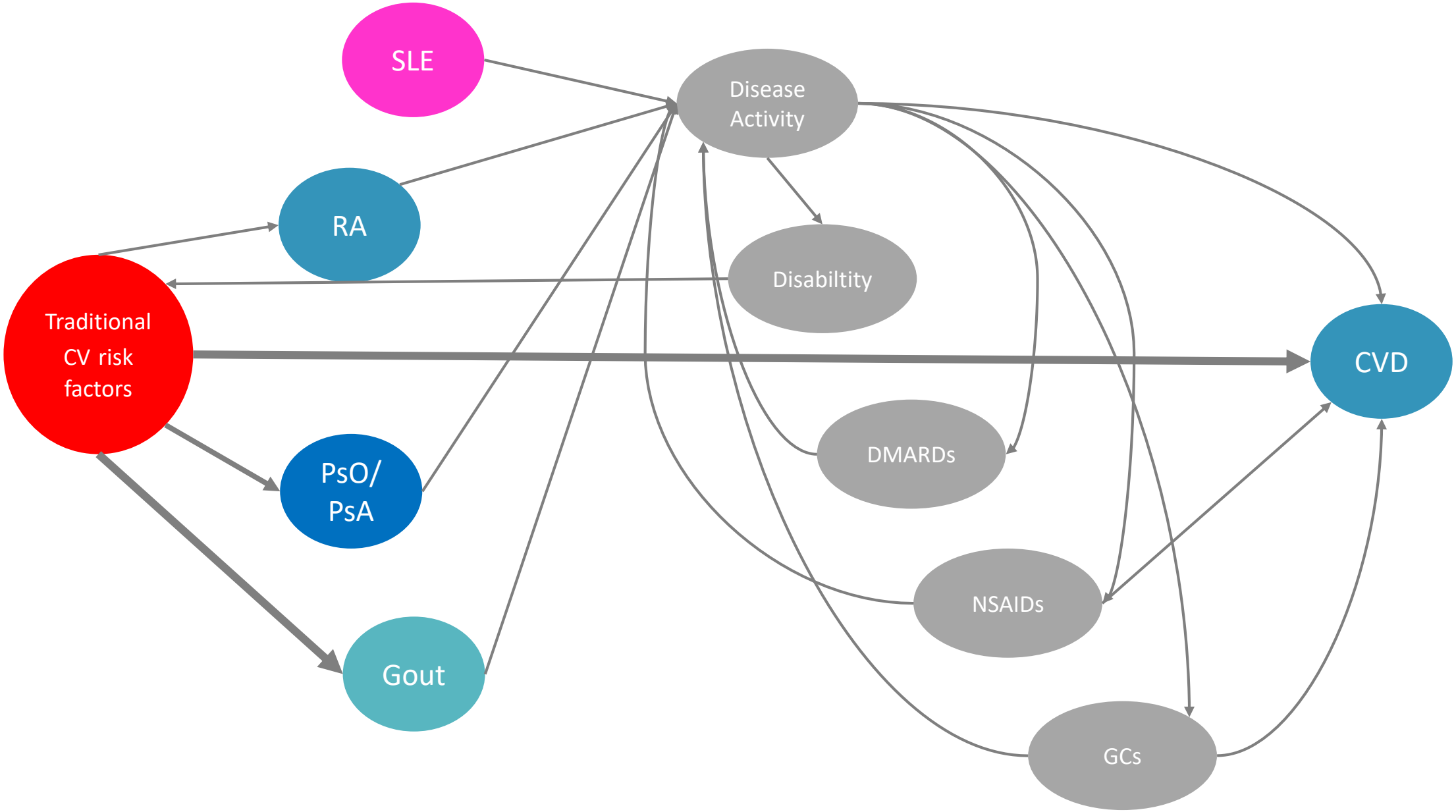
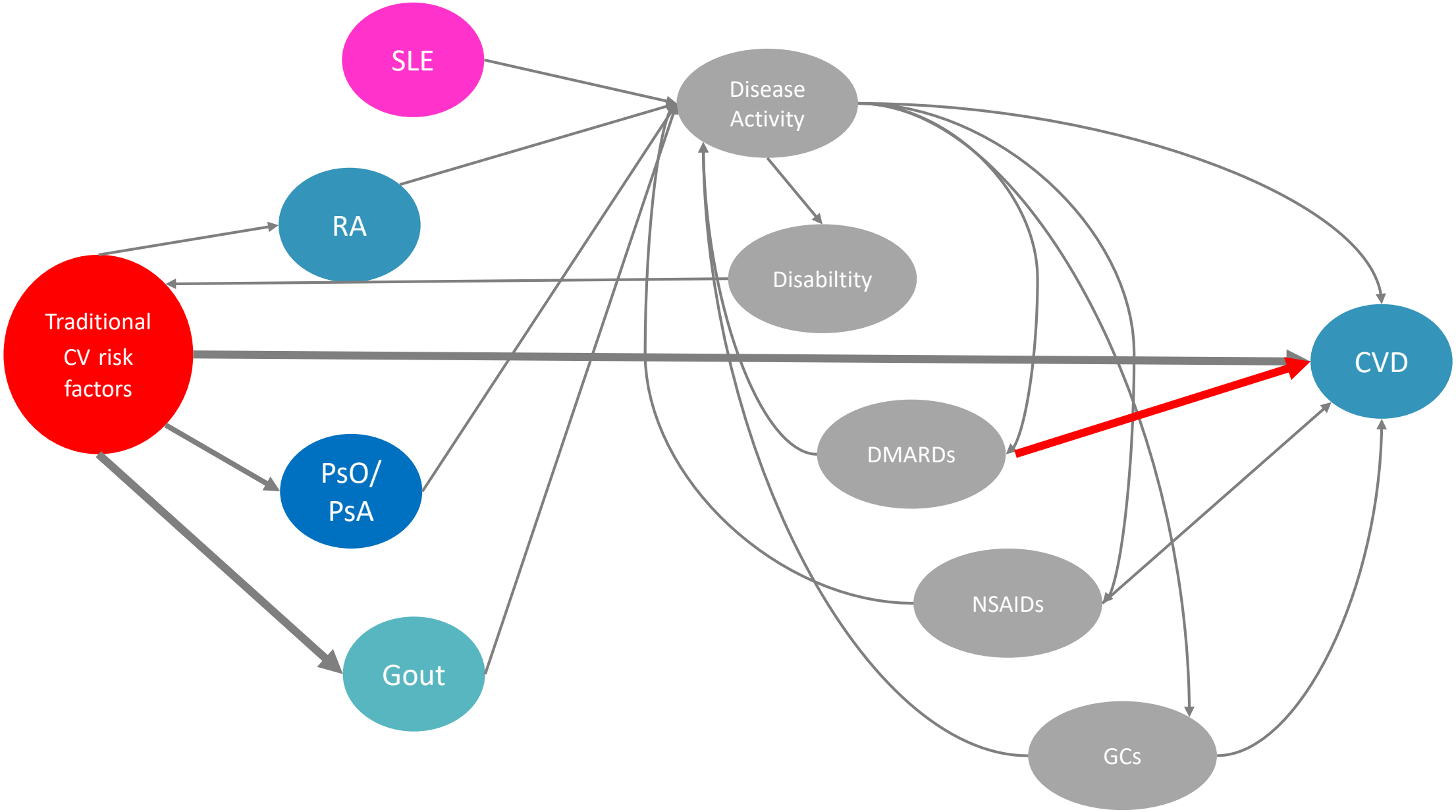

Genes and environment
Rheumatoid arthritis
General population
Traditional cardiovascular risk factors may be more common (e.g., smoking) and may operate differently in patients with RA (e.g., paradoxical effects of lipids and body mass index)
Traditional cardiovascular risk factors explain a large part of the heart disease in persons without RA
Inflammation (e.g., C-reactive protein), innate immune responses (e.g., activation of innate immune effectors by danger associated molecular patterns); adaptive immune responses (e.g., activation of T lymphocytes and dendritic cells; production of autoantibodies); and cellular stress (e.g., tissue hypoxia, oxidative stress, apoptosis, endothelial damage) play a major role in heart disease among patients with RA
Inflammation / immune responses play a lesser role in heart disease among persons without RA
Treatments for RA may increase (e.g., high dose corticosteroids) or decrease (e.g., methotrexate) the risk of heart disease in patients with RA
Heart disease

Targeting cardiovascular disease (CVD) risk reduction in rheumatoid arthritis (RA).

Bryant R England et al. BMJ 2018;361:bmj.k1036


SLE
Disease Activity
RA
Disabiltity
Traditional CV risk factors
CVD
PsO/ PsA
DMARDs
NSAIDs
Gout
GCs


SLE
Disease Activity
RA
Disabiltity
Traditional CV risk factors
CVD
PsO/ PsA
DMARDs
NSAIDs
Gout
GCs

RECORD Study

Rheumatoid arthritis (RA) is associated with an increased incidence of atherosclerosis leading to myocardial infarction and stroke, accounting for a 35-50% excess mortality.

Biologic disease-modifying anti-rheumatic drugs (DMARDs) targeting tumour necrosis factor (TNF)-α or interleukin (IL)-6 may influence the RA-associated cardiovascular (CV) risk, but available data are limited by the events low incidence, limiting the feasibility of prospective studies.

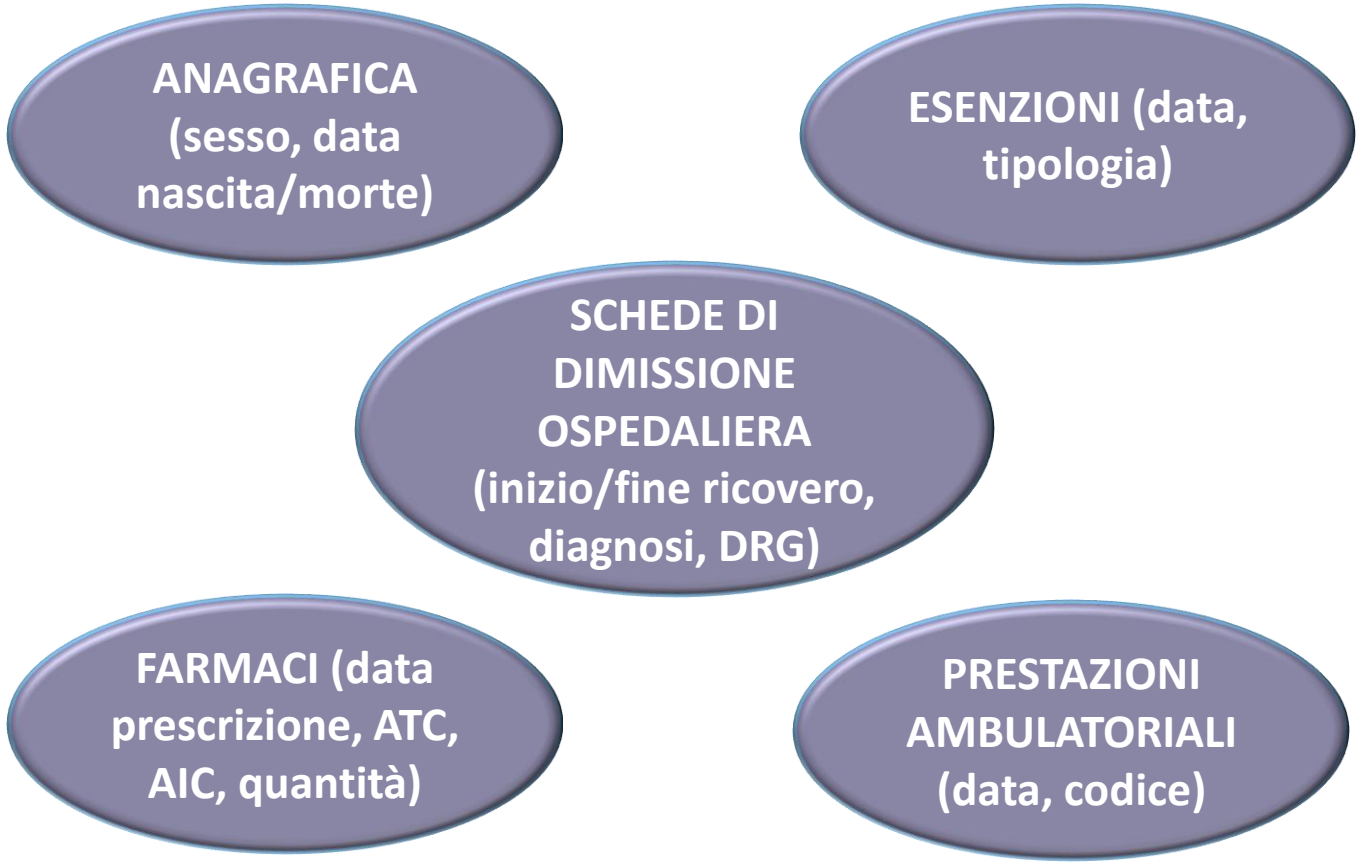
While coronary heath disease (CHD) genetic studies and experimental models suggest that IL-6 is pivotal in atherosclerosis and CV disease development, suggesting that IL-6 blockade might reduce CV risk, tocilizumab (TCZ) was associated with an increase in plasma lipid levels, suggesting a potential increase in CV risk.

To understand the effect of TCZ on the RA-associated CV risk in clinical practice and to test the hypothesis that TCZ is associated with an increased risk of acute CV events compared with etanercept (ETN), we analysed administrative healthcare databases (AHD) of a Northern Italian region.

Generali, Elena, Greta Carrara, Carlo Selmi, Suzanne M. M. Verstappen, Antonella Zambon, Alessandra Bortoluzzi, Ettore Silvagni, and Carlo Alberto Scire. "Comparison of the Risks of Hospitalisation for Cardiovascular Events in Patients with Rheumatoid Arthritis Treated with Tocilizumab and Etanercept." *Clinical and Experimental Rheumatology*, December 28, 2017.

Administrative healthcare databases

Dalle banche dati sanitarie della regione Regione Lombardia, si sono estratti dal 2004 al 2013 dati relativi ai **registri**:

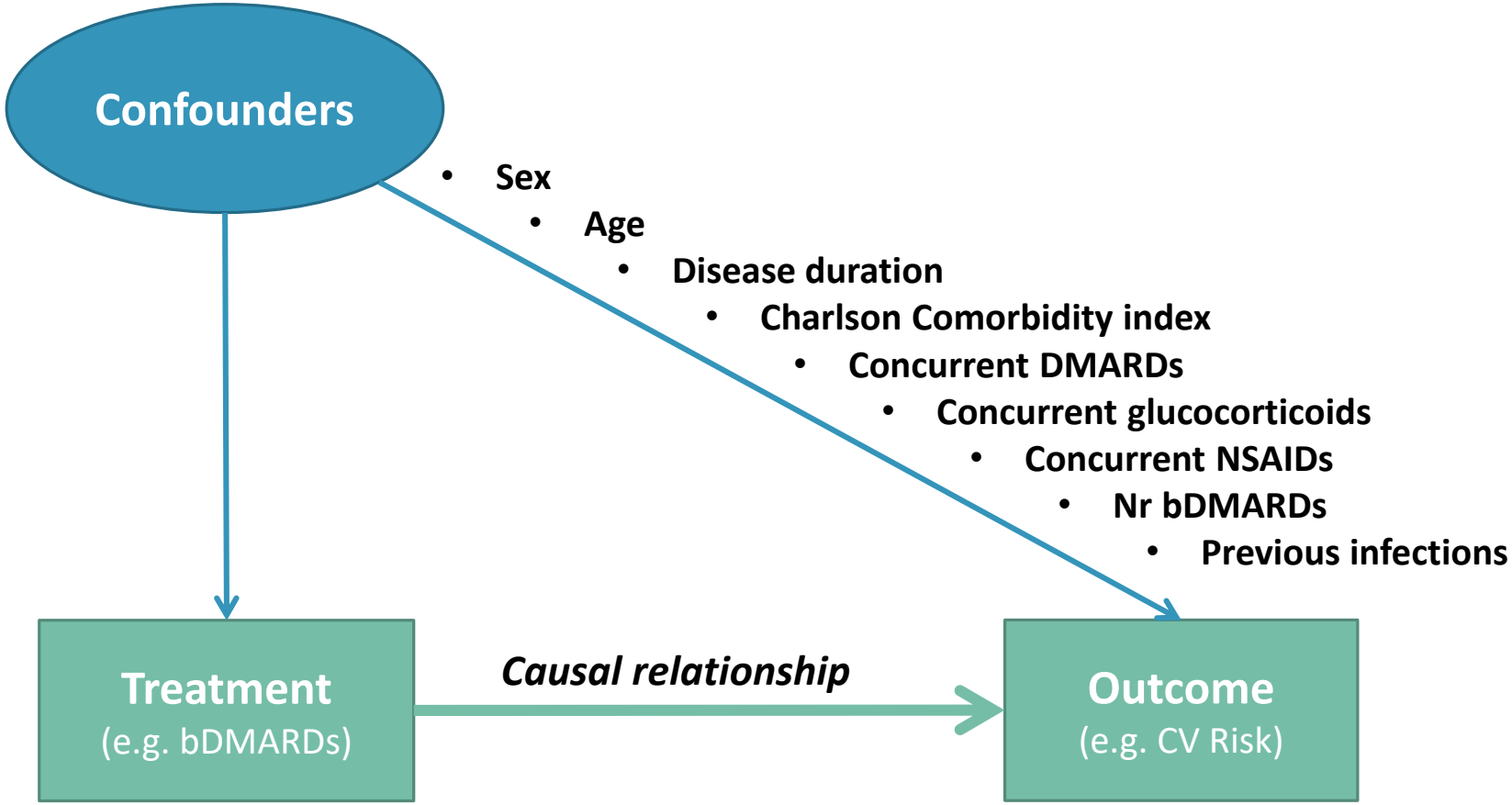


RECORD Study

	Etanercept (n= 1086)	Tocilizumab (n= 666)	p value
Female, n (%)	767 (70.6%)	545 (81.8%)	<0.001
Age mean, years (SD)	55.3 (13.2)	56.8 (12.6)	0.027
Disease Duration, <1 year, n (%)	92 (8.5%)	71 (10.7%)	<0.001
Disease Duration, 1-2years, n (%)	254 (23.4%)	101 (15.2%)	
Disease Duration, 3-5 years, n (%)	158 (14.5%)	84 (12.6%)	
Disease Duration, >5 years, n (%)	582 (53.6%)	410 (61.6%)	
Previous Biologic Therapy* median, (IQR)	0 (0-1)	1 (0-2)	<0.001
NSAIDs use, n (%)	690 (63.5%)	485 (72.8%)	<0.001
Concurrent MTX use at start, n (%)	623 (57.4%)	365 (54.8%)	0.294
Oral steroids use, n (%)	639 (58.8%)	478 (71.8%)	<0.001
Hypertension **, n (%)	188 (17.3%)	126 (18.9%)	0.394
Diabetes **, n (%)	98 (9%)	54 (8.1%)	0.509
Dyslipidemia**, n (%)	173 (15.9%)	125 (18.8%)	0.125
Previous Myocardial Infarction, n (%)	28 (2.6%)	12 (1.8%)	0.291
Previous Stroke, n (%)	17 (1.6%)	17 (2.6%)	0.146
Previous acute CV event (other), n (%)	55 (5.1%)	54 (8.1%)	0.010
Any previous CV event, n (%)	69 (6.4%)	62 (9.3%)	0.022

Generali, Elena, Greta Carrara, Carlo Selmi, Suzanne M. M. Verstappen, Antonella Zambon, Alessandra Bortoluzzi, Ettore Silvagni, and Carlo Alberto Scire. "Comparison of the Risks of Hospitalisation for Cardiovascular Events in Patients with Rheumatoid Arthritis Treated with Tocilizumab and Etanercept." *Clinical and Experimental Rheumatology*, December 28, 2017.

Confounding



Biological DMARDs – Efficacy & Safety

	Etanercept (n= 1086)	Tocilizumab (n= 666)	P value
Female, n (%)	767 (70.6%)	545 (81.8%)	p<0.001
Age mean, years (SD)	55.3 (13.2)	56.8 (12.6)	p=0.027
Disease Duration, <1 year, n (%)	92 (8.5%)	71 (10.7%)	p<0.001
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NSAIDs use, n (%)	690 (63.5%)	485 (72.8%)	p<0.001
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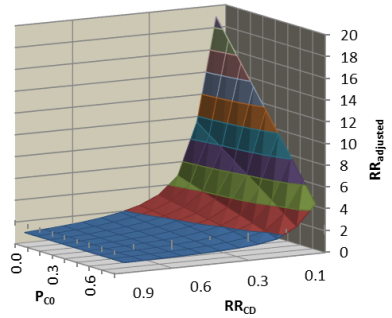

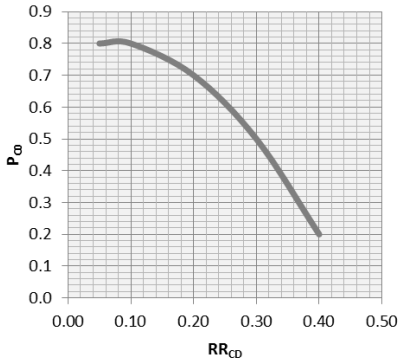

TCZ vs ETN (reference)	Crude ~~S~~HR	p value	Adj ~~S~~HR *	p value	Adj SHR **	p value
Any acute CV event	1.05 (0.62-1.78)	0.848	1.09 (0.63-1.87)	0.767	0.95 (0.54-1.66)	0.860
Myocardial Infarction	0.43 (0.14-1.27)	0.127	0.41 (0.13-1.27)	0.122	0.39 (0.15-1.06)	0.065
Stroke	2.53 (0.61-10.52)	0.202	2.22 (0.62-7.99)	0.223	1.45 (0.28-7.40)#	0.691
Other CV event	1.18 (0.68-2.03)	0.564	1.22 (0.70-2.14)	0.480	1.07 (0.59-1.92)	0.823

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EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update

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EULAR reccomendations CV risk management

Overarching principles

A. Clinicians should be aware of the higher risk for CVD in patients with RA compared with the general population. This may also apply to AS and PsA.
B. The rheumatologist is responsible for CVD risk management in patients with RA and other IJD.
C. The use of NSAIDs and corticosteroids should be in accordance with treatment-specific recommendations from EULAR and ASAS

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	Level of evidence	Strength of recommendation	Level of agreement (SD)
Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)

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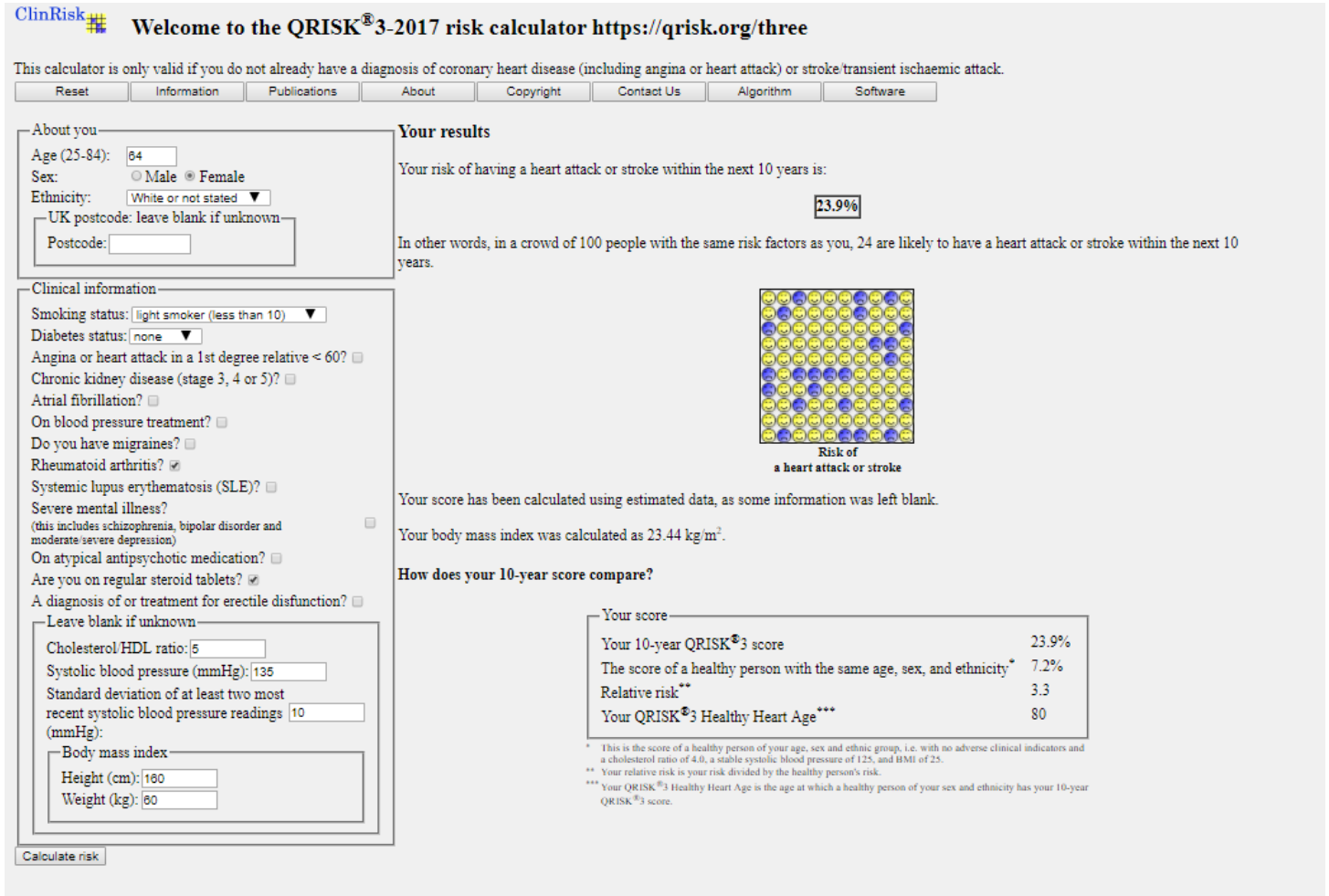
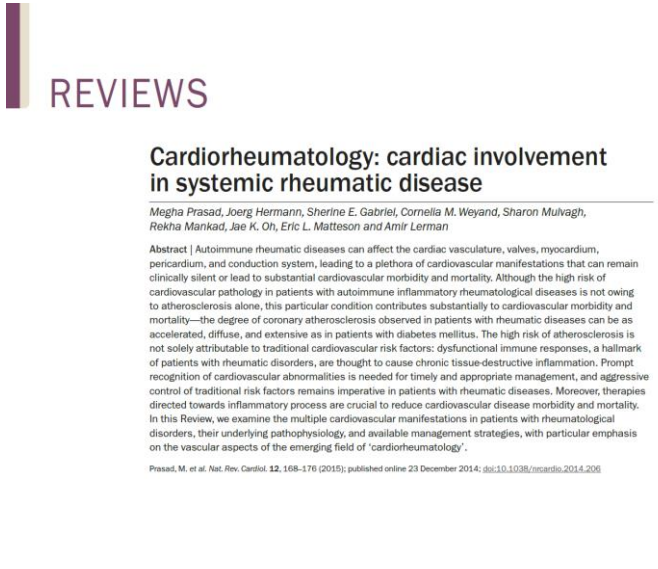
QRISK 3.0 - https://qrisk.org/three/index.php





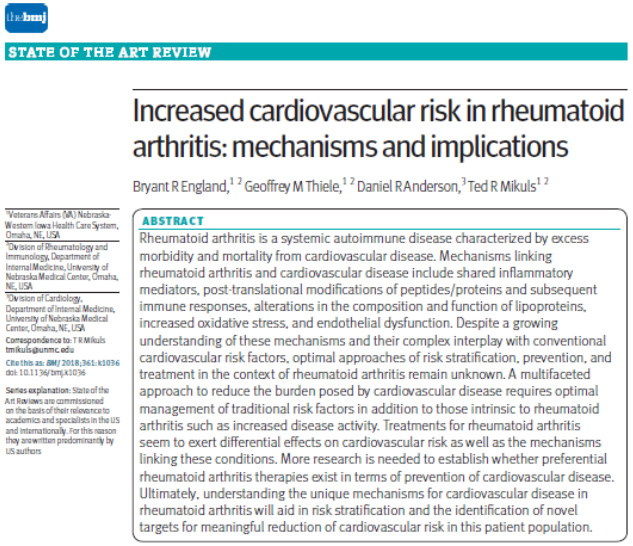
REVIEWS

Cardiorheumatology: cardiac involvement in systemic rheumatic disease

Megha Prasad, Joerg Hermann, Sherine E. Gabriel, Cornelia M. Weyand, Sharon Mulvagh, Rekha Mankad, Jae K. Oh, Eric L. Matteson and Amir Lerman

Abstract | Autoimmune rheumatic diseases can affect the cardiac vasculature, valves, myocardium, pericardium, and conduction system, leading to a plethora of cardiovascular manifestations that can remain clinically silent or lead to substantial cardiovascular morbidity and mortality. Although the high risk of cardiovascular pathology in patients with autoimmune inflammatory rheumatological diseases is not owing to atherosclerosis alone, this particular condition contributes substantially to cardiovascular morbidity and mortality—the degree of coronary atherosclerosis observed in patients with rheumatic diseases can be as accelerated, diffuse, and extensive as in patients with diabetes mellitus. The high risk of atherosclerosis is not solely attributable to traditional cardiovascular risk factors: dysfunctional immune responses, a hallmark of patients with rheumatic disorders, are thought to cause chronic tissue-destructive inflammation. Prompt recognition of cardiovascular abnormalities is needed for timely and appropriate management, and aggressive control of traditional risk factors remains imperative in patients with rheumatic diseases. Moreover, therapies directed towards inflammatory process are crucial to reduce cardiovascular disease morbidity and mortality. In this Review, we examine the multiple cardiovascular manifestations in patients with rheumatological disorders, their underlying pathophysiology, and available management strategies, with particular emphasis on the vascular aspects of the emerging field of 'cardiorheumatology'.

Prasad, M. *et al. Nat. Rev. Cardiol.* **12**, 168–176 (2015); published online 23 December 2014; doi:10.1038/nrcardio.2014.206



the bmj

STATE OF THE ART REVIEW

Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications

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Cite this as: *BMJ* 2018;361:k1036 doi: 10.1136/bmj.k1036

Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

ABSTRACT

Rheumatoid arthritis is a systemic autoimmune disease characterized by excess morbidity and mortality from cardiovascular disease. Mechanisms linking rheumatoid arthritis and cardiovascular disease include shared inflammatory mediators, post-translational modifications of peptides/proteins and subsequent immune responses, alterations in the composition and function of lipoproteins, increased oxidative stress, and endothelial dysfunction. Despite a growing understanding of these mechanisms and their complex interplay with conventional cardiovascular risk factors, optimal approaches of risk stratification, prevention, and treatment in the context of rheumatoid arthritis remain unknown. A multifaceted approach to reduce the burden posed by cardiovascular disease requires optimal management of traditional risk factors in addition to those intrinsic to rheumatoid arthritis such as increased disease activity. Treatments for rheumatoid arthritis seem to exert differential effects on cardiovascular risk as well as the mechanisms linking these conditions. More research is needed to establish whether preferential rheumatoid arthritis therapies exist in terms of prevention of cardiovascular disease. Ultimately, understanding the unique mechanisms for cardiovascular disease in rheumatoid arthritis will aid in risk stratification and the identification of novel targets for meaningful reduction of cardiovascular risk in this patient population.

References