Atherosclerotic cardiovascular disease prevention in rheumatoid arthritis

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Pathogenesis of ischaemic and non-ischaemic heart diseases in rheumatoid arthritis

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Cardiac involvement in RA

- ✓Patients with RA have approximately a 50% increased risk of incident cardiovascular events and cardiovascular death.
- ✓CVD events seem to occur at younger ages in patients with seropositive RA than in the general population.
- ✓the risk of CVD mortality might not increase until 7–10 years after the onset of RA symptoms.
- ✓Data of cardiac MRI and PET-CT in patients with RA with no diagnosis of CVD demonstrated that up to half showed signs of cardiac fibrosis or inflammation.
- ✓ These changes in the myocardium might be responsible for the observed increased left ventricular mass in patients with RA

Cardiac involvement in RA

✓Echocardiography studies revealed that RA is also associated with exceptionally

high rates of asymptomatic pericarditis and cardiac valvular involvement.

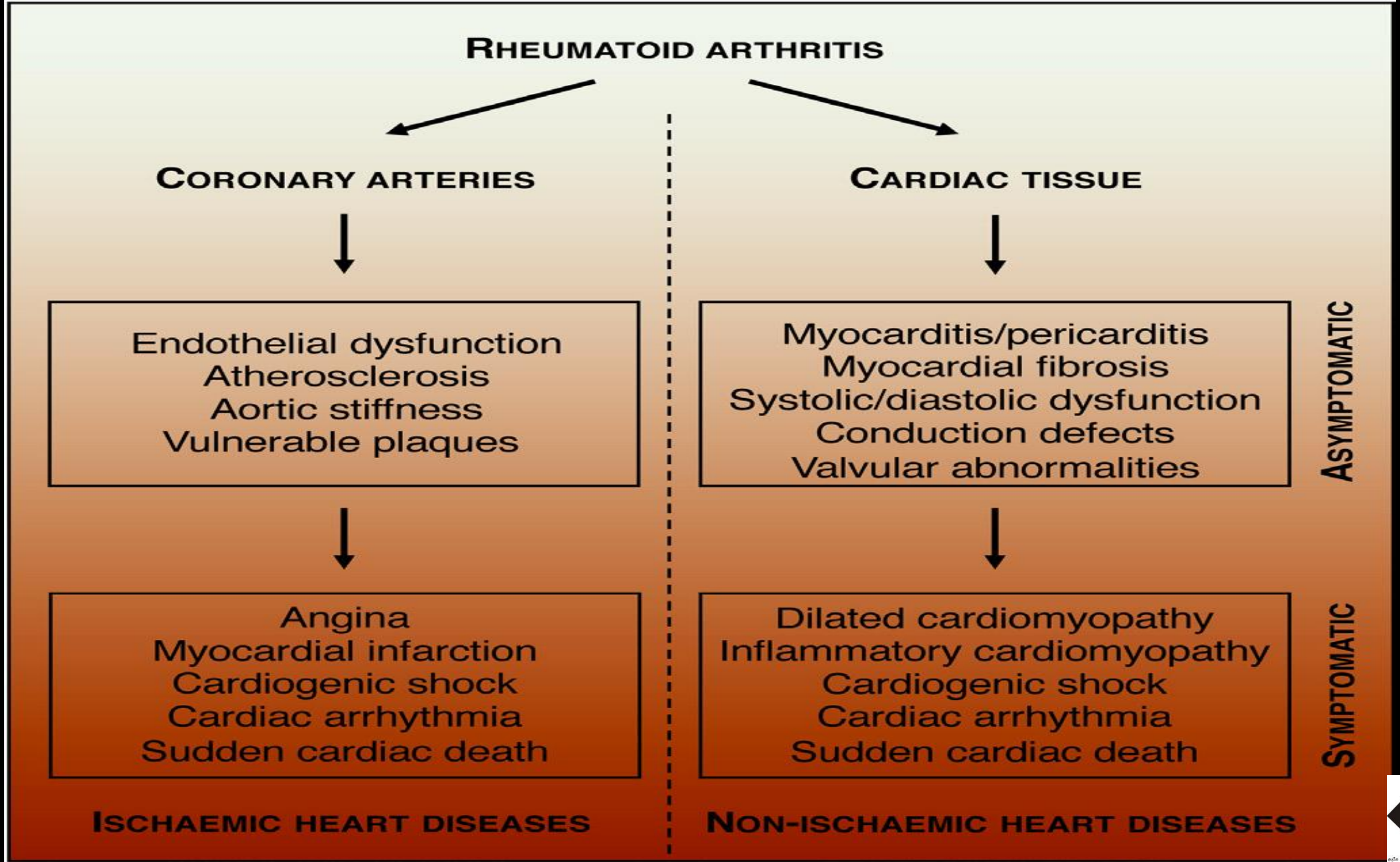
✓Several types of CVD-related morbidity are increase in patients with RA,including

❖myocardial infarction

❖stroke

❖atrial fibrillation

❖heart failure


RHEUMATOID ARTHRITIS
CORONARY ARTERIES
CARDIAC TISSUE
Endothelial dysfunction
Atherosclerosis
Aortic stiffness
Vulnerable plaques
Myocarditis/pericarditis
Myocardial fibrosis
Systolic/diastolic dysfunction
Conduction defects
Valvular abnormalities
ASYMPTOMATIC
Angina
Myocardial infarction
Cardiogenic shock
Cardiac arrhythmia
Sudden cardiac death
Dilated cardiomyopathy
Inflammatory cardiomyopathy
Cardiogenic shock
Cardiac arrhythmia
Sudden cardiac death
SYMPTOMATIC
ISCHAEMIC HEART DISEASES
NON-ISCHAEMIC HEART DISEASES

Clinical manifestations of CVD in RA

❑ ***Myocardial infarction***

✓ many studies have consistently reported a 1.5-fold to 2.0-fold increased risk of MI in patients with RA.

✓ Patients with RA are also less likely to report symptoms of angina

✓ and more likely to experience unrecognized (or 'silent') MI than the general population.

❑ ***Stroke and atrial fibrillation***

✓ patients with RA have an increased risk of valvular disease, which are known risk factors for AF and ischaemic stroke.

✓ the risk of recurrent stroke is 40% higher in patients with RA than in those without RA,particularly among smokers.

Clinical manifestations of CVD in RA

❑*Heart failure*

- ✓Patients with RF-positive RA had a 2.5-fold increased risk of heart failure.
- ✓heart failure in patients with RA is characterized by a preserved EF,
- ✓and patients with heart failure who have RA experience poorer outcomes than patients with heart failure who do not have RA.
- ✓Left ventricular diastolic dysfunction is also more common in patients with RA than in individuals without RA and is associated with RA disease activity
- ✓patients with RA progressively develop proarrhythmic QTc prolongation; however, this is not associated with cardiovascular mortality in these patients

Inflammation as a driving force for heart diseases in RA

- ✓CRP values and the ESR have also been linked with increased CVD morbidity in patients with RA.
- ✓The inflammatory biomarker high-sensitivity CRP can be used to independently predict future vascular events.
- ✓Statin therapy reduces high-sensitivity CRP concentrations in healthy individuals, patients with stable coronary disease and in those with acute coronary syndrome.
- ✓At the molecular level, proinflammatory cytokines:TNF-α, IL-1β, IL-6 , IL-17 have been associated with inflammation in RA and with pathogenesis of heart disea

Inflammation as a driving force for heart diseases in RA

❑Inflammation and ischaemic heart diseases

✓Clinical data further confirmed that elevated inflammatory markers as well as increased disease activity were associated with increased risk of acute coronary events in patients with RA.

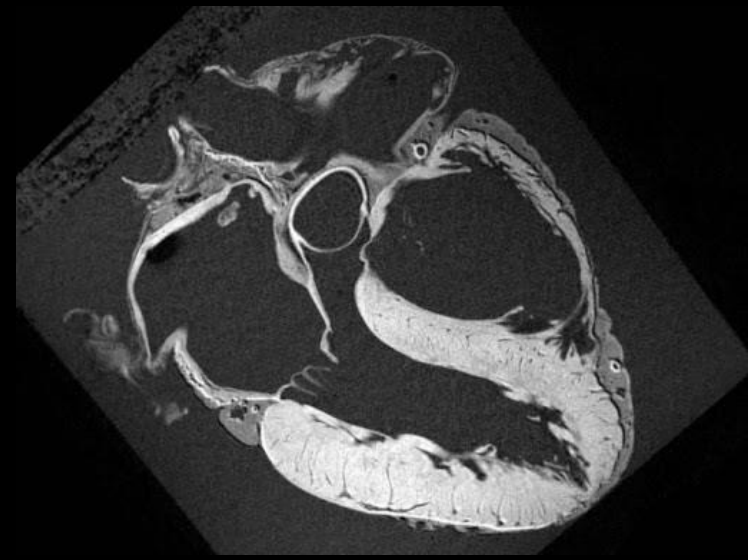
✓ more detailed analysis of carotid arteries by ultrasonography pointed to more unstable plaques in patients with RA with active disease.

✓ CT angiography analysis confirmed the presence of more vulnerable plaques in coronary arteries of patients with RA with more active disease.

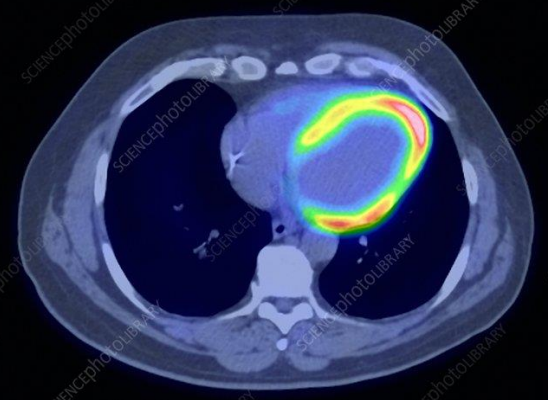
✓ Interestingly, the risk of MI in RA has not been associated with disease activity but with CRP level.

Inflammation as a driving force for heart diseases in RA

❑Inflammation and non-ischaemic heart diseases



- ✓Active inflammatory processes in the heart may lead to excessive myocardial fibrosis causing stiffening of the ventricles and thus contribute to systolic and diastolic dysfunctions and to cardiac arrhythmia.
- ✓Cardiac MRI and PET-CT data indeed confirmed a correlation between RA disease activity and increased myocardial inflammation and fibrosis.



- ✓High disease activity and elevated CRP levels were associated with increased prevalence of diastolic heart failure

CVD risk evaluation

CVD risk calculators

Imaging in CVD risk assessment

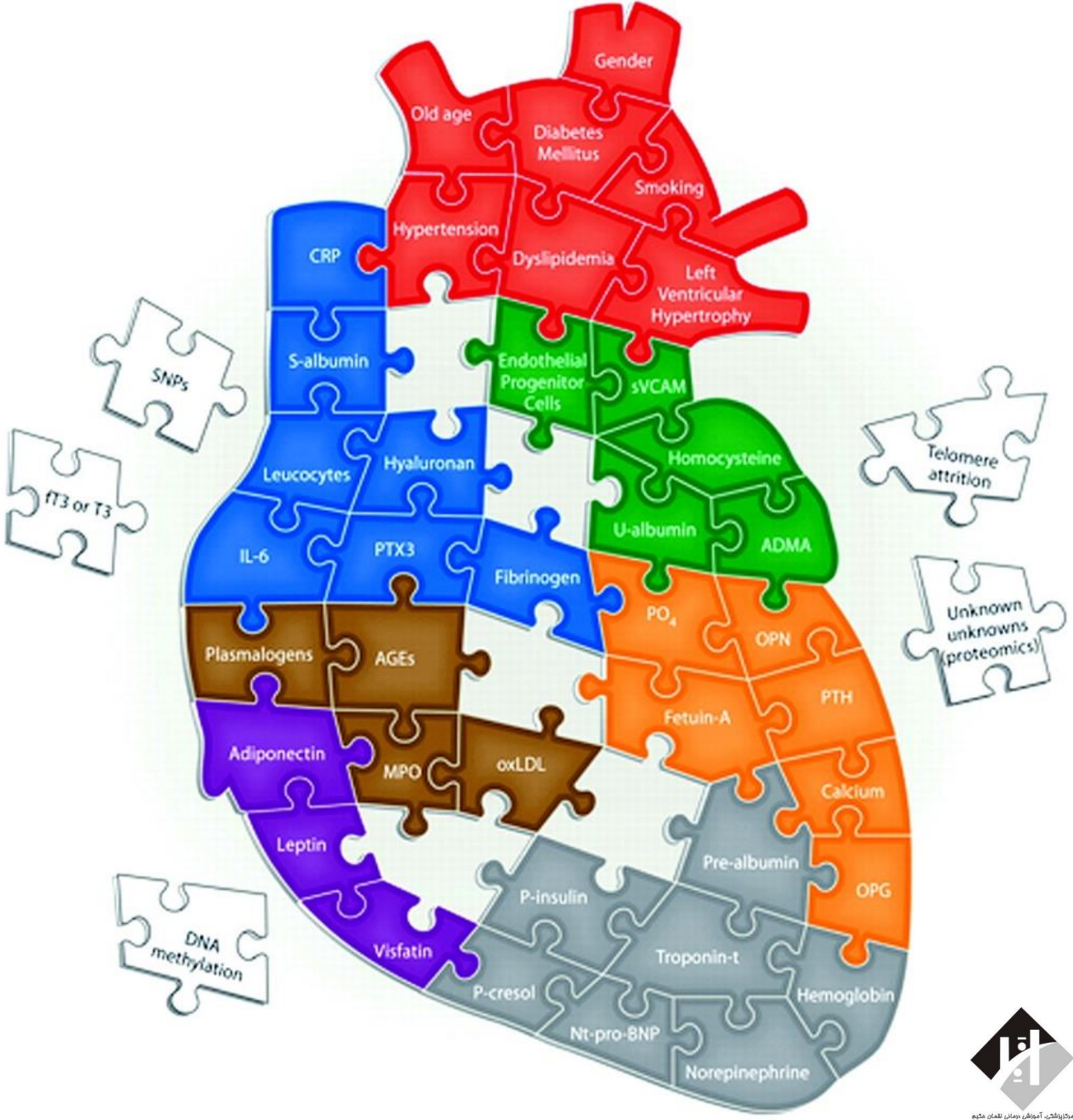


Table 1 | **Cardiovascular disease outcomes and treatment thresholds of various risk calculators**

Risk calculator	Target population	CVD outcome	Applicable age range (years)	Treatment threshold (%
Framingham risk score (Adult Treatment Panel III)	USA	Coronary heart disease including myocardial infarction	30–74	10
Framingham risk score for general CVD	USA	CVD events (fatal and non-fatal) including acute coronary syndrome (myocardial infarction and unstable angina pectoris), chronic ischaemic heart disease (stable angina pectoris), coronary revascularization (percutaneous coronary intervention and coronary artery bypass graft surgery), coronary death, other cardiovascular death, cerebrovascular events (ischaemic cerebrovascular accident and transient ischaemic attack), peripheral vascular events (non-coronary revascularization procedures and peripheral artery disease) and heart failure	30–74	20
ACC/AHA pooled cohort equation	USA	Atherosclerotic CVD events (defined as first occurrence of non-fatal myocardial infarction, coronary heart disease death, or fatal or non-fatal stroke)	40–79	7.5
Reynolds Risk Score	USA	Myocardial infarction, ischaemic stroke, coronary revascularization and cardiovascular death	50+	10
QRISK2	UK	Coronary heart disease, stroke and transient ischaemic attack	35–74	10
SCORE	EU	Fatal CVD events	40–79	5

Ultrasonography of carotid arteries

- which can be used to measure the:

1. carotid intima–media thickness (CIMT)
2. and to detect the presence of carotid plaques.

- However,the quality of ultrasonography is operator dependent.

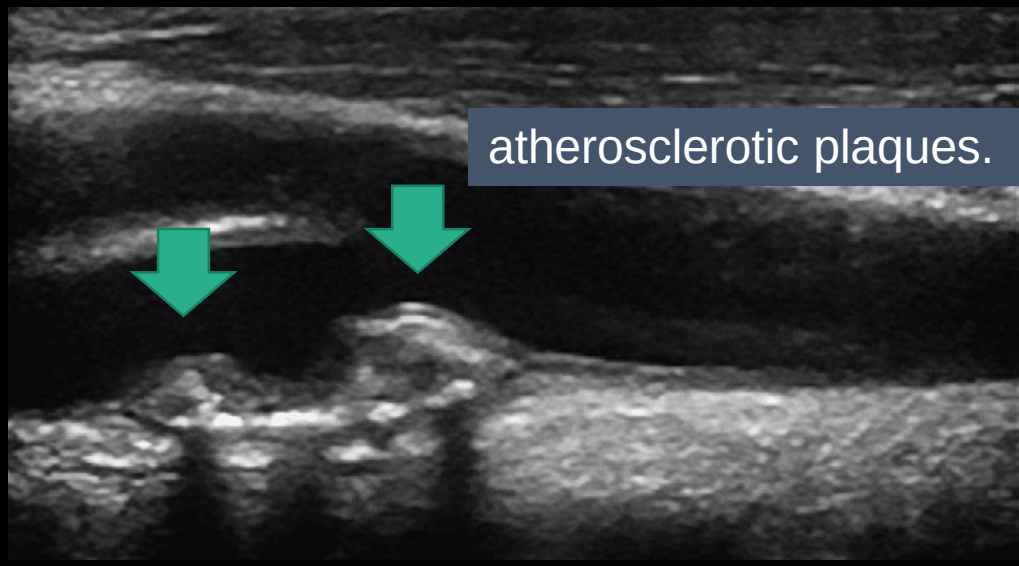
❑CIMT

✓screening of CIMT by carotid ultrasonography is not currently recommended for use in CVD risk evaluation for the general population or for patients with RA.

✓increased CIMT could both be associated with atherosclerosis formation

✓ and with smooth muscle cell hypertrophy, mainly caused by hypertension

Ultrasonography of carotid arteries



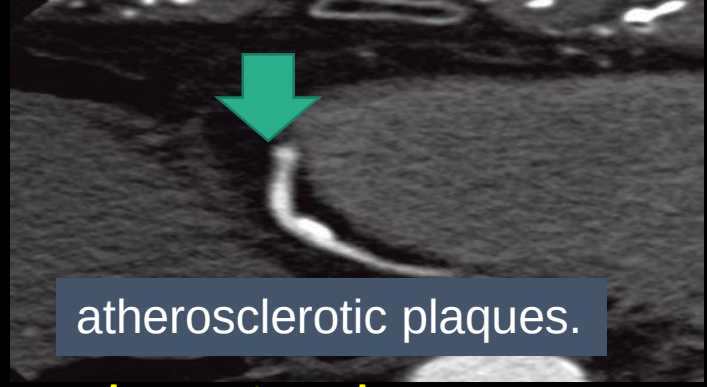
- carotid plaques

✓Carotid plaques are considered to be a coronary heart disease risk equivalent.

✓The indication for statin treatment should a carotid plaque be present,

✓EULAR recommends that screening for asymptomatic atherosclerotic plaques by carotid ultrasonography should be considered as part of CVD risk evaluation for all patients with RA.

Coronary CT angiography and calcium scoring



- CCTA also reveals the localization and morphology of atherosclerotic plaques.

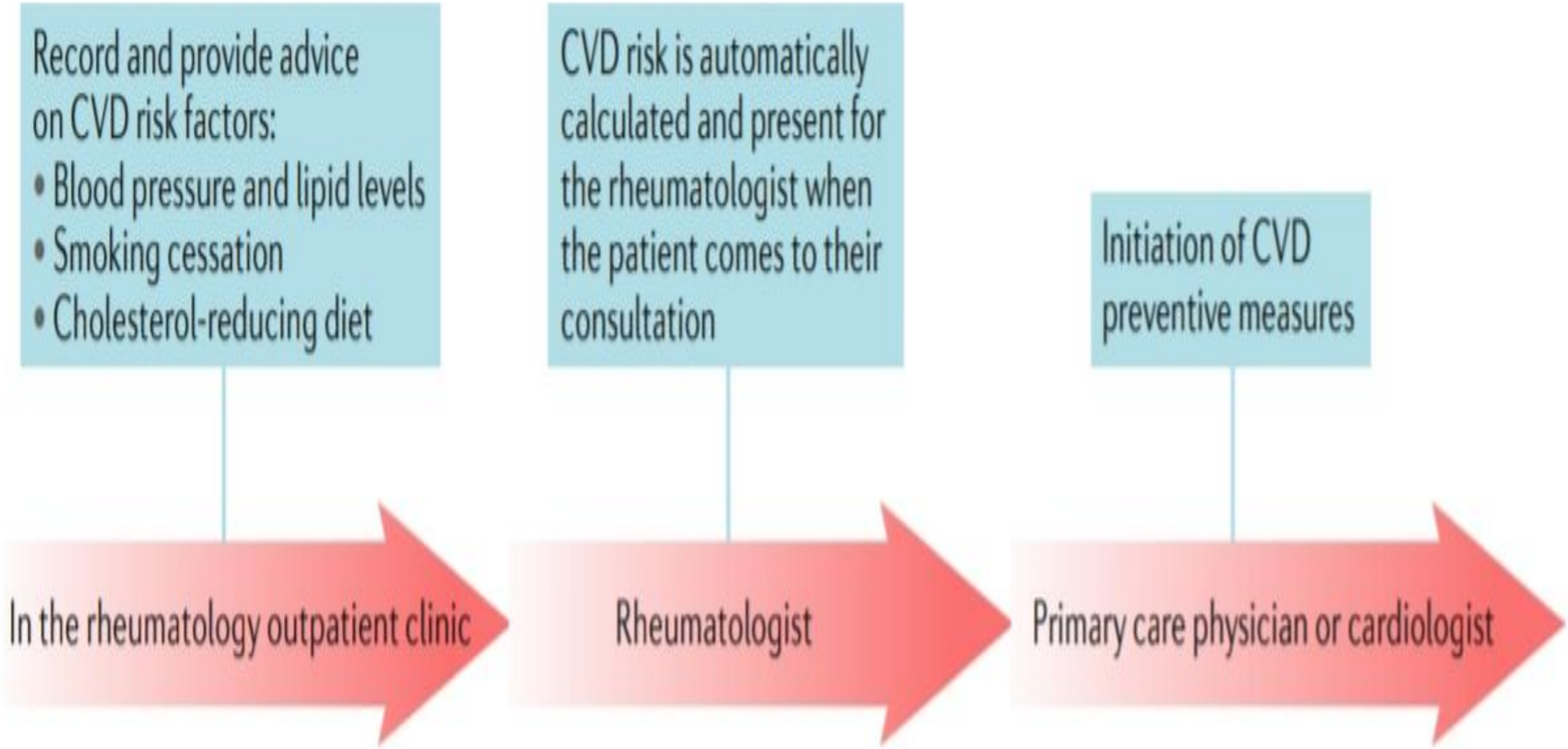
❑The coronary artery calcium (CAC)

✓score is used to indicate the total plaque burden in the coronary arteries and is measured by CCTA.

✓the CAC score was superior to carotid plaque burden for CVD risk prediction.

✓the guidelines from the USA suggest that non-smoking individuals without CAC would have a very low risk of an atherosclerotic CVD event in the next decade,

✓ whereas a CAC score of greater than the 75th percentile for age and sex or ≥100 measured by the Agatston method would support the initiation of statin therapy.



Model for cardiovascular disease risk evaluation in a rheumatology clinic.

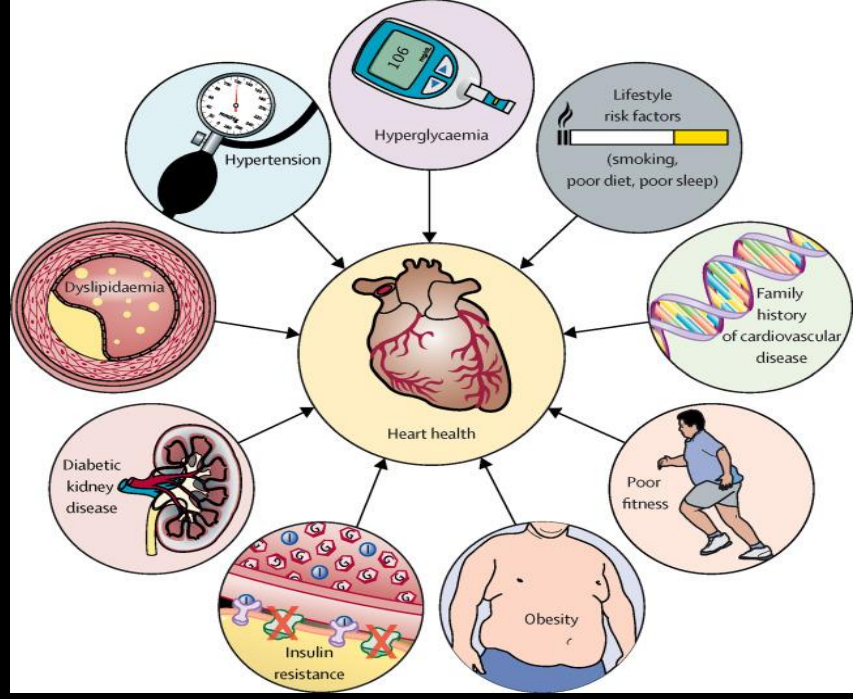
CVD risk assessment in the clinic

✓The rheumatologist evaluates the risk estimate, and if the patient has low or moderate CVD risk (<5%) then no further measures are taken,

✓ but a new CVD risk assessment should be performed after 5 years.

✓ Conversely,if the patient has a high or very high CVD risk (≥5%) then a referral note can be forwarded to the patient's primary care physician or cardiologist for the initiation of CVD preventive measures

Traditional cardiovascular risk factors in RA

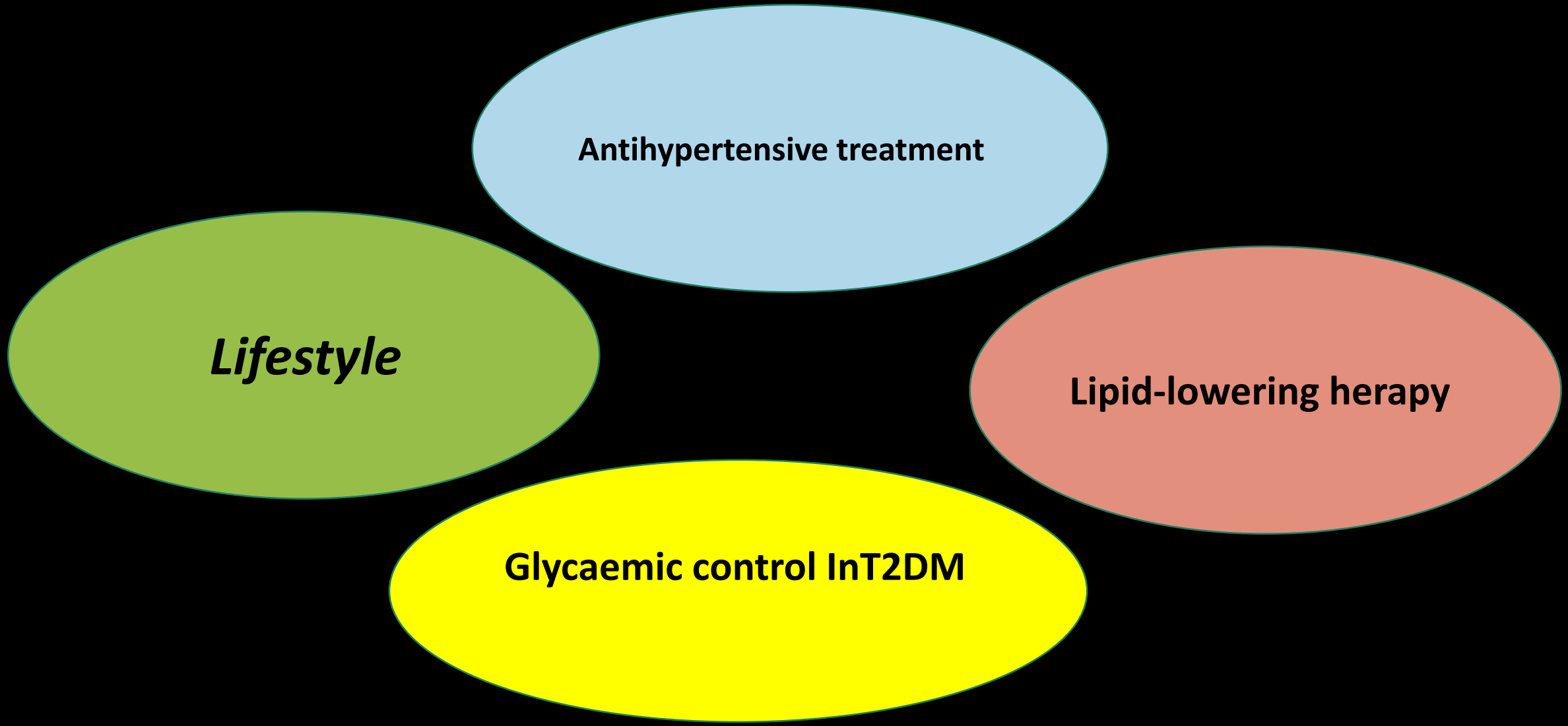


✓Diagnosed hypertension or type 2 DM is associated with a nearly twofold increased risk of cardiovascular morbidity in patients with RA.

✓ Surprisingly, the impact of certain traditional risk factors (eg, male gender, smoking, personal cardiac history or physical inactivity) on major cardiovascular outcomes is lower in RA compared with non-RA cohorts.

✓ Furthermore,an increased cardiovascular incidence in patients with RA has been reported for traditional low-risk factors such as low cholesterol levels or low body mass index

CVD management in patients with RA



Lifestyle-related CVD risk factors

❑**tobacco smoking**

✓Patients with RA who smoke tobacco should receive smoking cessation advice.

✓Smoking cessation programmes should be implemented in rheumatology clinics.

❑**Body weight and composition**

✓Around 60% of patients with RA are either overweight or obese

✓Increased lean mass and reduced body fat percentage could have beneficial effects on cardiovascular disease risk in patients with RA.

Lifestyle-related CVD risk factors

❑Diet

✓The Mediterranean-style and Dietary Approaches to Stop Hypertension dietary patterns are two examples that include

✓ an increased intake of fruits, vegetables, whole grains, low-fat dairy products, lean meat, legumes, nuts,seeds, seafood and vegetable oils

✓and a reduced intake of dietary cholesterol, sugars, sodium,alcohol, saturated fat and *trans*-fatty acids.

❑*Exercise and physical activity*

✓The WHO recommends 30 min of moderate-to-intense activity five times per week,which is safe and advisable for patients with RA.

✓If symptoms of previously unrecognised angina pectoris or peripheral artery disease should occur during exercise,

✓proper medical evaluation must be sought before physical activity is resumed in patients with RA, as for the general population.

Blood pressure treatment targets in patients with rheumatoid arthritis

Age group (years)	Additional comorbidities	SBP targets	DBP targets
18–65	Hypertension	130 mmHg or lower if tolerated; not <120 mmHg	70–79 mmHg
	Diabetes mellitus		
	CAD		
	Stroke or TIA		
	CKD	<140 to 130 mmHg if tolerated	
Over 65	All comorbidities	130–139 mmHg if tolerated	

Antihypertensive treatment

Hypertensive patients with RA should be treated equally to hypertensive patients without RA

- ❑Monotherapy

✓with a single BP -lowering drug is suitable for low-risk patients with an SBP >140 mmHg but <150 mmHg and for frail elderly patients.

- ❑Two-drug combination

✓Initiation of antihypertensive treatment with a two-drug combination is advised

✓A RAS blocker in combination with either a CCB or a diuretic is the first drug of choice

✓Beta blockers are only indicated for HR control, angina, post-MI or CHF.

Management of hypertension

❑Triple therapy

✓(compromising an RAS blocker, a CCB and thiazide or a thiazide-like diuretic) is recommended for resistant hypertension.

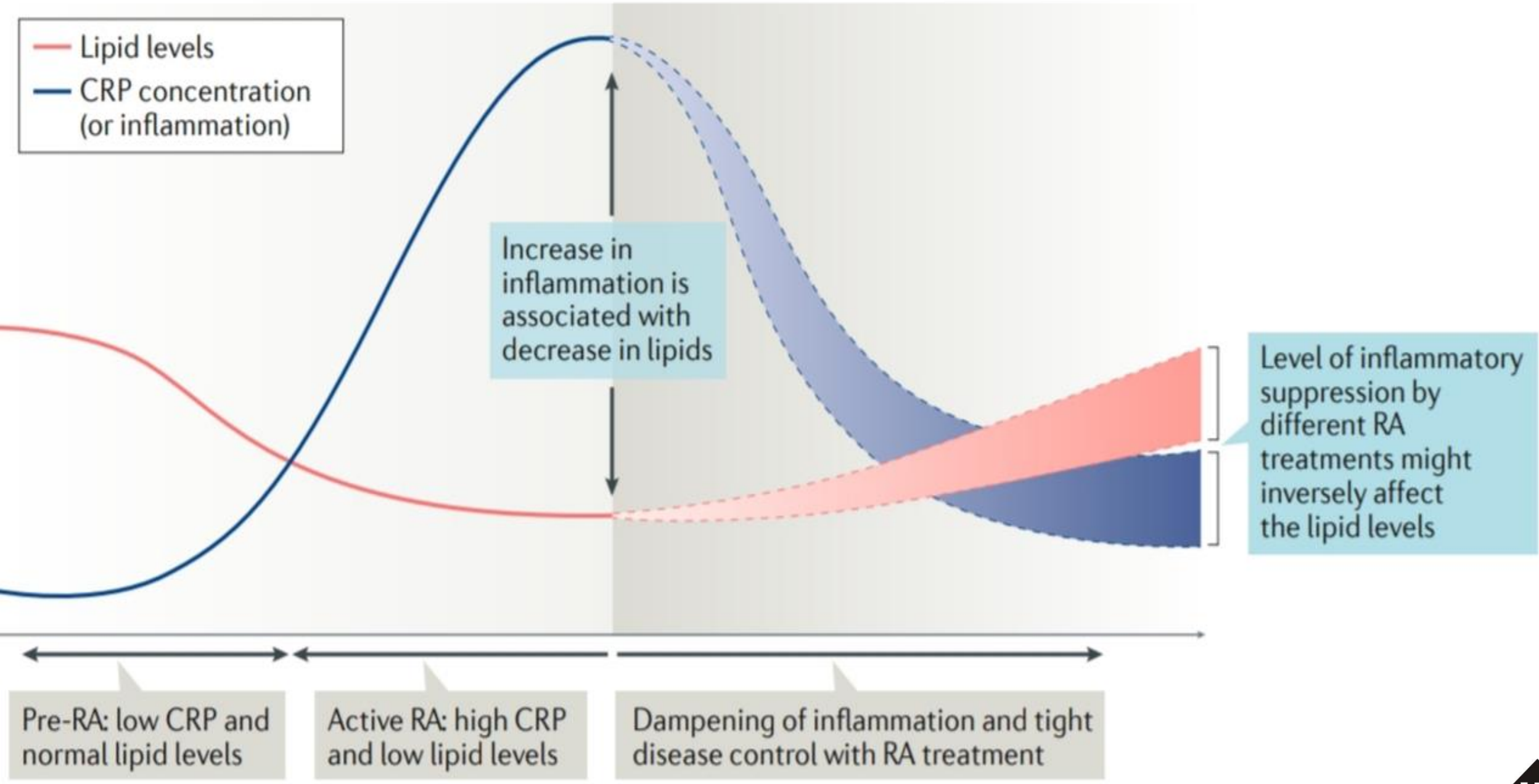
✓After the initiation of antihypertensive treatment, the BP lowering effect should be recorded within 2 months.

✓ Electrolytes and kidney function should be monitored if treatment with diuretics and/or RAS blockers is initiated

❑Adverse effects

✓Kidney failure: NSAID use results in a vasoconstriction of the afferent renal arteriole; RAS blockers cause efferent renal arteriolar vasodilatation;

✓ and diuretics can cause hypovolaemia



The interaction between lipids and inflammation in rheumatoid arthritis.

Cardiovascular disease risk classes, lipoprotein targets and interventions for patients with rheumatoid arthritis

CVD risk class[a]	Description	Target levels	Intervention
LDL cholesterol			
Low	CVD risk <1%	LDL cholesterol <3.0 mmol/l (<116 mg/dl)	Consider adding a lipid-lowering drug (a statin or ezetimibe) if LDL cholesterol is 3.0 to <4.9 mmol/l; add a statin if LDL cholesterol >4.9 mmol/l
Moderate	CVD risk ≥1% to <5% and LDL cholesterol 2.6 to <3 mmol/l (100 to <115 mg/dl)	LDL cholesterol <2.6 mmol/l (<100 mg/dl)	Consider adding a lipid-lowering drug (statins, statins and ezetimibe or ezetimibe monotherapy) if LDL cholesterol 2.6 to <4.9 mmol/l; add a statin if LDL cholesterol ≥4.9 mmol/l
High	CVD risk ≥5% and <10% and LDL cholesterol 1.8 to <2.6 mmol/l (70 to <100 mg/dl) and/or diabetes mellitus and/or a total cholesterol >8.1 mmol/l	LDL cholesterol <1.8 mmol/l (<70 mg/dl) or ≥50% reduction of baseline LDL	Statins; statins and ezetimibe; ezetimibe monotherapy; a statin and a PCSK9 inhibitor; PCSK9 inhibitor monotherapy
Very high	CVD risk >10% and LDL cholesterol >1.8 mmol/l (70 mg/dl) and/or established CVD	LDL cholesterol <1.4 mmol/l (<55 mg/dl) or ≥50% reduction of baseline LDL cholesterol	Statins; statins and ezetimibe; ezetimibe monotherapy; a statin and a PCSK9 inhibitor; PCSK9 inhibitor monotherapy

Lipid-lowering therapy

❑Statins

✓Statin initiation in patients with RA should be carried out in the same way as for the general population

✓Systemic inflammation (measured by CRP or ESR) or the use of any antirheumatic medication did not influence the dose of statin needed to obtain recommended LDL cholesterol goals.

✓ Overall, the CVD risk classes, recommended LDL cholesterol targets and interventions for CVD prevention in patients with RA might be the same as those for the general population.

Lipid-lowering therapy

❑*Statin use in elderly individuals*

✓To initiate statin therapy in patients older than 75 years, consider quality of life and whether life expectancy is >5 years

✓Statins can be considered in the elderly as part of symptom relief treatment for intractable angina pectoris

✓in elderly individuals, starting on a low-dose statin and titrating up to the maximum tolerated dose in relation to the recommended LDL cholesterol goal might be beneficial.

✓In general, treatment with statins is recommended for older people with atherosclerotic CVD in a similar way to that for younger patients.

Lipid-lowering therapy

❑Adverse effects

✓If a patient experiences myalgia with no increase in CPK (occurring in 5–10% of treated patients), statin treatment can be continued if the muscle pain is tolerable for the patient.

✓An increase of CPK<5 times the upper limit of normal in two blood samples is considered acceptable.

✓Myalgia: change to another statin or start with the lowest dose of a statin taken 2 to 3 times a week and increase by one tablet per week every 3–4 weeks until maximum tolerable dose is acquired

✓Liver: if the increase in liver enzymes is >3 times the ULN, discontinue statin treatment; if the increase in liver enzymes is <3 times the ULN, reduce the statin dose or stop or reduce methotrexate

✓No data are available on the risk of T2DM development in patients with RA who use statins.

Lipid-lowering therapy

❑Drug–drug interactions

- Simvastatin, lovastatin and, to a lesser extent, atorvastatin are metabolized by the hepatic isoenzyme CYP3A4 and often have drug–drug interactions,

✓Tocilizumab, an IL-6 inhibitor might reverse the suppression of CYP3A4 activity,

➢If a patient is taking tocilizumab, choose fluvastatin, pravastatin or rosuvastatin

➢Drugs that are metabolized by CYP3A4 potentially interact with statins, so care should be taken when using:

✓Calcium antagonists (e.g. amlodipine, diltiazem and verapamil);

✓anti-infective medications (e.g. erythromycin, clarithromycin,HIV proteases and antifungal agents);

✓and some other medications (e.g. amiodarone, gemfibrozil and cyclosporine)

Lipid-lowering therapy

- Although not a drug, grapefruit juice is also not recommended when using statins
- grapefruit juice can substantially increase the blood concentrations of statins metabolized by CYP3A4 (such as simvastatin and atorvastatin),
- and thus consumption of grapefruit juice is not recommended when using these drugs

Lipid-lowering therapy

❑Statins and ezetimibe

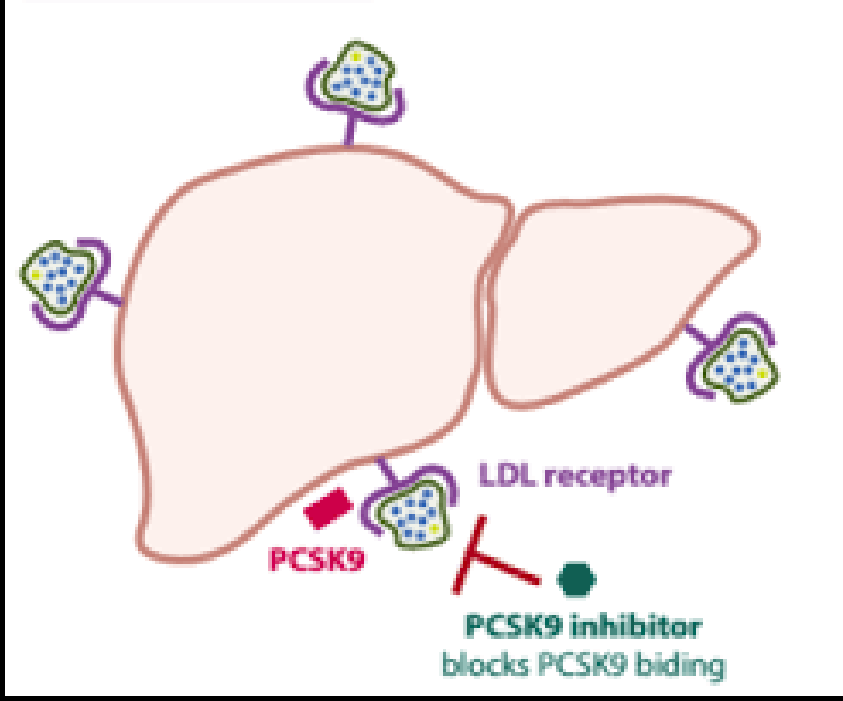
✓A trial in 2002 demonstrated an additional reduction in LDL cholesterol levels of 12–19% when ezetimibe was taken in addition to a statin by patients with primary Hypercholesterolaemia.

✓No difference in efficacy and safety in patients with RA from what is reported for the general population

✓If a patient with RA is intolerant to statins, monotherapy with ezetimibe can be considered

Lipid-lowering therapy

❑PCSK9 inhibitors(alirocumab and evolocumab)



- Monoclonal antibodies against PCSK9 are available:

✓ for high-risk individuals with atherosclerotic CVD

✓or familial hypercholesterolaemia

✓ who are already taking the maximally tolerated statin therapy but who require greater LDL cholesterol reduction.

✓In combination with a statin,a PCSK9 inhibitor reduces LDL cholesterol by 40-60%

✓and reduces CVD events by 15–20%

✓Drug interactions or other adverse effects could theoretically occur when a patient uses a bDMARD and a PCSK9 inhibitor, but this effect has not been evaluated

Cardiovascular disease risk classes, lipoprotein targets and interventions for patients with RA

Triglycerides	Description	target levels	Intervention
Normal	Triglyceride level <1.7 mmol/l (<150 mg/dl)	No target level, but a triglyceride level <1.7 mmol/l (<150 mg/dl) indicates lower risk	Exercise; avoiding sugar and refined carbohydrates; optimization of glucose control in diabetes mellitus; withdrawal of oestrogen therapy; weight loss; choose healthier dietary fats; moderate alcohol intake
Borderline high	Triglyceride level 1.8 to 2.2 mmol/l (150 to 199 mg/dl)		
High	Triglyceride level 2.3 to 5.6 mmol (200 to 499 mg/dl)		
Very high	Triglyceride level ≥5.7 mmol/l (≥500 mg/dl)		Fibrates, niacin and omega-3 fatty acids can be used when triglyceride levels are >10 mmol/l to prevent pancreatitis

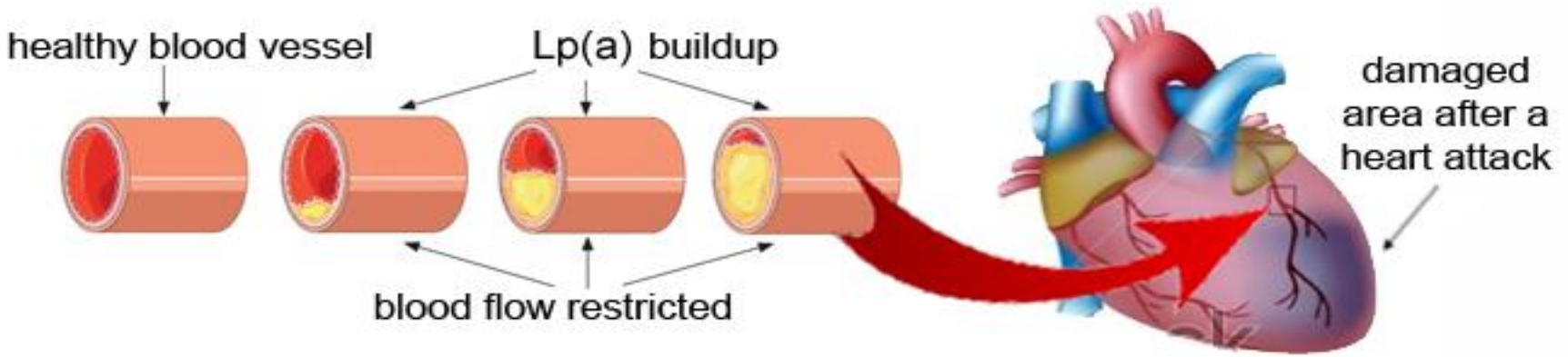
Management of hypertriglyceridaemia

- ✓The recommendations for patients with RA do not differ from those for the general population
- ✓Exercise; avoiding sugar and refined carbohydrates; optimization of BS control in DM

withdrawal of oestrogen therapy; weight loss;choose healthier dietary fats; moderate alcohol intake

- ✓If a fibrate(Gemfibrozil) is combined with a statin(simvastatin and lovastatin)the fibrate should be taken in the morning and the statin in the evening to reduce the risk of myopathy.
- ✓Caution should be taken when combining fibrates and statins, especially if kidney or liver disease is present.
- ✓Fibrates, niacin and omega-3 fatty acids(2–4 g daily) can be used when TG are > 900 mg/dl to prevent pancreatitis

Management of high lipoprotein(a)



- ✓High levels of lipoprotein(a) are associated with an increased risk of CVD.
- ✓Lipoprotein(a) seems to be a weaker CVD risk factor than LDL cholesterol
- ✓In contrast to statins, PCSK9 inhibitors reduce lipoprotein(a) levels by 30–40%,
- ✓there are no recommendations for lowering elevated lipoprotein(a), either in the general population or in patients with RA.
- ✓ The present approach to managing high lipoprotein(a) levels in patients with RA is to reduce other CVD risk factors

Cardiovascular disease risk classes, lipoprotein targets and interventions for patients with RA

HDL cholesterol	Description	target levels	Intervention
Increased risk	HDL cholesterol <1.0 mmol/l (<40 mg/dl) in men and <1.2 mmol/l (<45 mg/dl) in women	No target HDL cholesterol level, but recommended HDL cholesterol >1.0 mmol/l (>40 mg/dl) in men and >1.2 mmol/l (>45 mg/dl) in women	Exercise; diet; weight loss; moderate alcohol intake

Management of low HDL cholesterol

- Low HDL cholesterol levels (<1.0 mmol/l for men; <1.2 mmol/l for women) are common in metabolic syndrome
- Low HDL cholesterol levels can be raised by: a change in diet to contain more free fatty acids; exercise; moderate alcohol intake; smoking cessation; and weight loss

Glycaemic control in T2DM

- ✓patients with RA might be at increased risk of developing :
  - insulin resistance
  - and T2DM owing to physical inactivity,
  - glucocorticoid treatment
  - and a high degree of disease activity,
- ✓if an individual has both RA and T2DM,the risk of CVD is increased 2.6-fold compared with someone who does not have RA and T2DM.
- ✓The first drug of choice for initiation of antiglycaemic treatment in T2DM is metformin
- ✓Patients with T2DM and atherosclerotic CVD or who are at high risk of CVD should be offered treatment with an SGLT2 inhibitor (such as empagliflozin)or a GLP1-RA

Recommended glycaemic and lipid targets in patients with rheumatoid arthritis and diabetes mellitus

Patient population	Recommendation	Treatment targets
Most patients (adjusted according to duration of diabetes mellitus, age and comorbidities)	Glycaemic control	Glycated haemoglobin <7.0% (<53 mmol/mol)
Very high CVD risk	Lipid-lowering therapy	LDL cholesterol <1.4 mmol/l (<55 mg/dl) and LDL cholesterol lowering >50%
High CVD risk	Lipid-lowering therapy	LDL cholesterol <1.8 mmol/l (<70 mg/dl) and LDL cholesterol lowering >50%
Moderate CVD risk	Lipid-lowering therapy	LDL cholesterol <2.6 mmol/l (<100 mg/dl)

Antirheumatic treatment and CVD risk

Antirheumatic treatment and CVD risk

❑NSAIDs

✓ have long been associated with an increased risk of CVD in patients with RA.

❑Glucocorticoid

✓high doses might be detrimental in relation to CVD risk in patients with RA.

✓The risk of adverse events was higher with increasing cumulative and average daily glucocorticoid doses.

✓Of note, even short-term(1-year) treatment with corticosteroids in patients with new-onset RA significantly increased the risk of non-ischaemic heart failure.

❑sulfasalazine

✓was associated with a lower cardiovascular risk compared with patients with RA who never used sulfasalazine ;HCQ or MTX.

Antirheumatic treatment and CVD risk

❑Antimalarial drugs (particularly HCQ) and MTX

✓are cardioprotective in most studies.

✓In some cases, antimalarials can induce cardiomyopathies in patients with RA.

✓The vascular effects of MTX may be somewhat controversial:

❖MTX itself increase the production of the proatherogenic homocysteine.

Homocysteine is toxic for endothelial cells and stimulates LDL oxidation.

❖On the other hand, MTX controls systemic inflammation and thus may exert beneficial cardiovascular effects.

❑Leflunomide

- Was associated with a significantly lower rate of MI.
- leflunomide may, however, increase BP and aggravate hypertension.

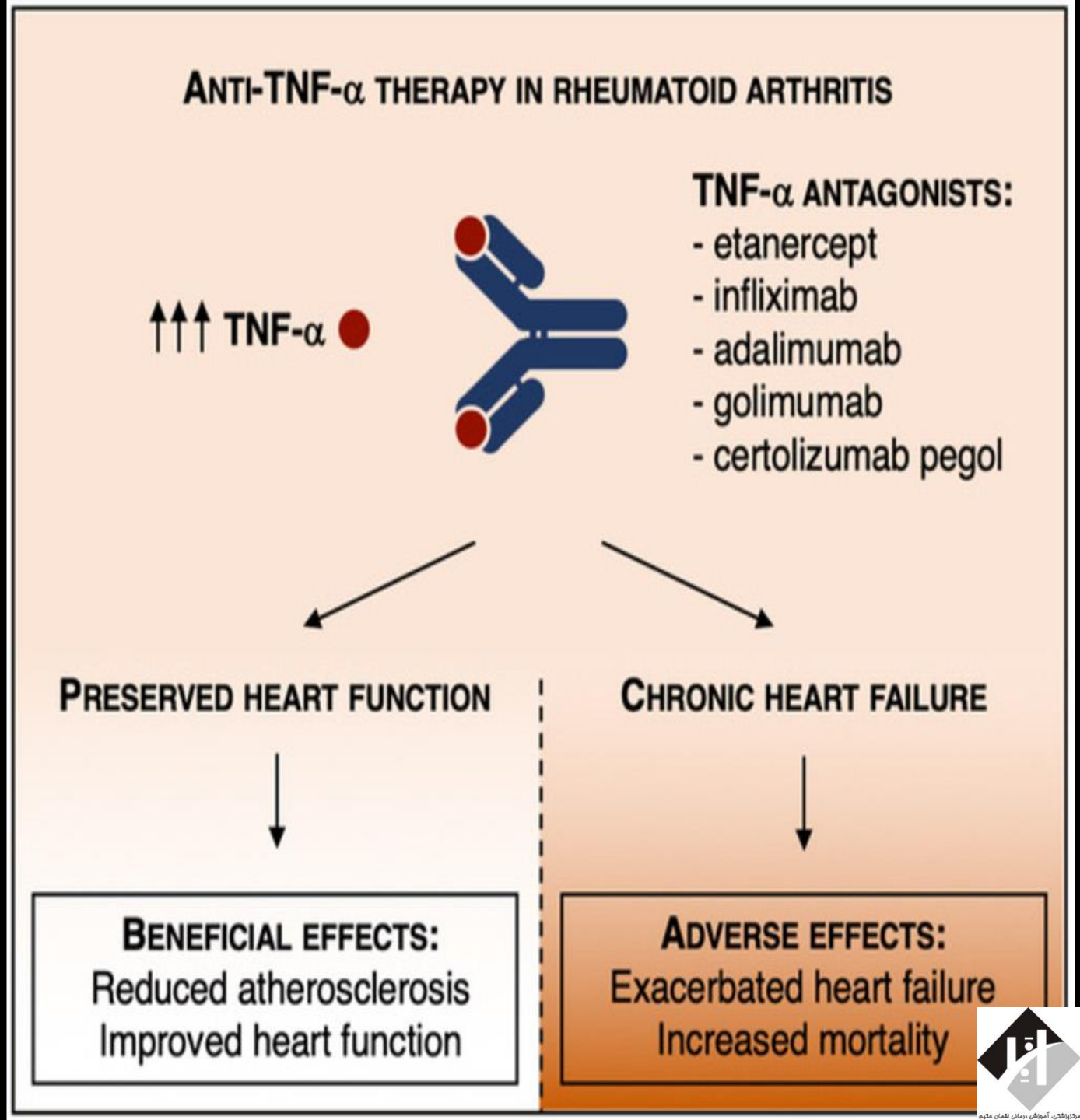
❑ ANTI-TNF- α

TNF-α therapies effectively suppress inflammation and prevent progression of RA and there by reduce the risk of CVD episodes.

✓ It seems that in patients with RA without heart failure, TNF- α increases the risk of CVD by promoting systemic inflammation.

✓ In the failing heart, instead, TNF-α might play a cardioprotective role,

✓ but the underlaying mechanisms remain unknown.



Antirheumatic treatment and CVD risk

- ❑Abatacept
- ✓Is prescribed to patients with RA with a worse CVD profile.
- ✓it does not affect the risk of developing heart failure compared with etanercept.
- ❑Rituximab
- ✓was shown to improve vascular pathophysiology in RA.
- ❑tocilizumab
- ✓A 2019 meta-analysis showed that treatment with the IL-6 inhibitor tocilizumab might be associated with a reduced risk of CVD events compared with treatment with TNF inhibitors.
- ❑Canakinumab(selective monoclonal antibody against IL-1β)
- ✓found a reduction in major adverse cardiovascular events without an effect on LDL cholesterol.
- ✓Three doses of canakinumab were tested (50 mg, 150 mg and 300 mg);
- ✓however, only the 150 mg dose showed a protective effect against future CVD.

Antirheumatic treatment and CVD risk

❑JAK inhibitors

✓Some patients with RA receive tsDMARDs JAK inhibitors tofacitinib or baricitinib.

✓Both JAK inhibitors have been shown to worsen the plasma lipid profile.

✓high-dose tofacitinib (10 mg twice daily) have an increased risk of pulmonary embolism and death.

✓initiation of statin therapy in patients with RA who were treated with baricitinib or tofacitinib substantially reduced the LDL cholesterol levels.

✓however,data from clinical studies and databases do not suggest an increased CVD risk in patients with RA treated with these drugs.

Conclusions

✓Awareness of the high CVD risk in patients with RA is low among the patients themselves and among health personnel.

✓The overarching goal should be that patients with RA have a structured system for CVD prevention equal to that of other high-risk patient populations.

✓Future studies should be more focused on targeted, cardioprotective therapies tailored for these patients with RA with high disease activity .

Thank you for your patience and attention