UVA Health

2025 Heart Failure Symposium

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Inflammatory Heart Disease

Disclosures

The following disclosure relate to research support and consultancy/advisory work mostly outside the presented work.

Kiniksa	Consultant
Novo-Nordisk	Consultant
MonterosaTx	Consultant

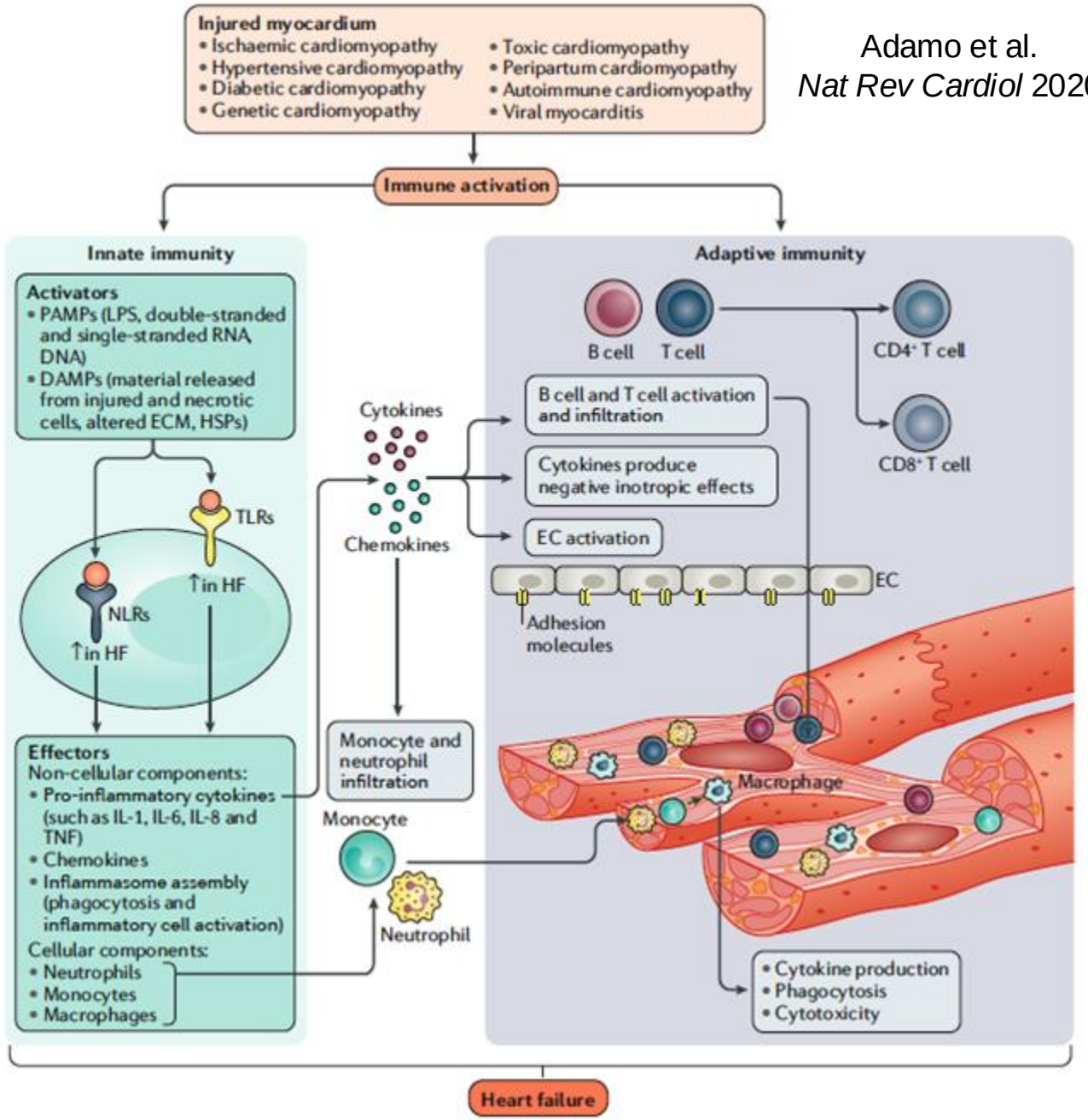
Significant >$5,000 per year; updated on 2/2/2024

LEARNING GOALS

1) Inflammation and cardiovascular diseases
2) Management of myocarditis
3) Management of pericarditis
4) Inflammatory component of the cardiovascular risk
5) Inflammatory component of heart failure

Why am I talking about inflammation at a heart failure symposium?

- Patients with cardiovascular risk factors and abnormal inflammatory biomarkers are at increased risk of developing HF
- Patients with HF and systemic inflammation have worse outcomes
- Patients with HF who show ‘resolving inflammation’ have better prognosis



Adamo et al.
Nat Rev Cardiol 2020

Why am I talking about inflammation at a heart failure symposium?

Am. Heart J.
April, 1956

A STUDY OF C-REACTIVE PROTEIN IN THE SERUM OF PATIENTS WITH CONGESTIVE HEART FAILURE

SAMUEL K. ELSTER, M.D.,* EUGENE BRAUNWALD, M.D.,** AND HARRISON F. WOOD, M.D.

NEW YORK, N.Y.

This study has demonstrated that C-reactive protein frequently is present in the course of congestive heart failure. This is particularly true in patients in whom there is a relatively recent increase of cardiac insufficiency. Of forty patients with congestive heart failure studied, thirty had C-reactive protein in their serum. From these thirty patients, seven patients in whom the C-reactive protein could be ascribed to other causes, i.e., possible rheumatic activity, acute myocardial infarction, and subacute bacterial endocarditis should be eliminated. This leaves twenty-three patients in whom there was no clinical evidence of disease processes, other than the congestive heart failure to which the presence of C-reactive protein could be attributed. In sixteen patients the C-reactive protein disappeared from the blood following recovery from the heart failure. The specific factors responsible for the appearance of C-reactive protein in congestive heart failure are not known. Several possibilities must be considered.

From the Departments of Medicine and Microbiology, The Mount Sinai Hospital, New York, Irvington House, Irvington-on-Hudson-New York, and the Department of Pediatrics, New York University College of Medicine.

Received for publication July 27, 1955.

*Rosenstock Foundation Fellow in Medicine.
**Postdoctoral Research Fellow of the National Heart Institute, U.S.P.H.S.

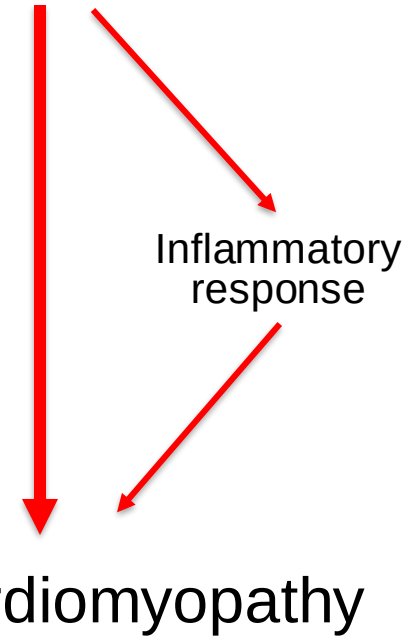
Role of inflammation in heart failure

Scenario #1

Injury — Ischemic/Toxic

Inflammation — Inflammatory response

Heart Failure — Cardiomyopathy



Inflammation amplifies the injury and worsens the cardiomyopathy

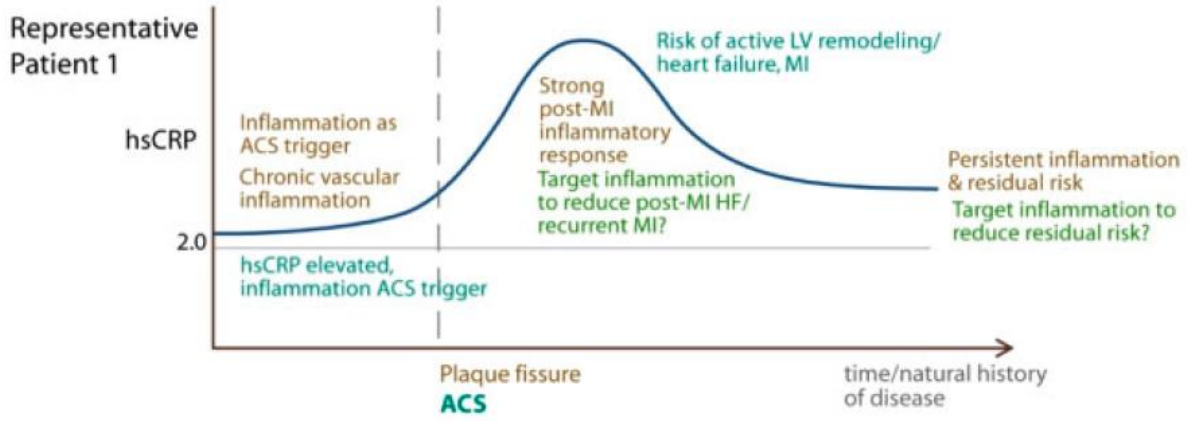
ESC European Society of Cardiology
European Heart Journal (2021) **42**, 113–131
doi:10.1093/eurheartj/ehaa099

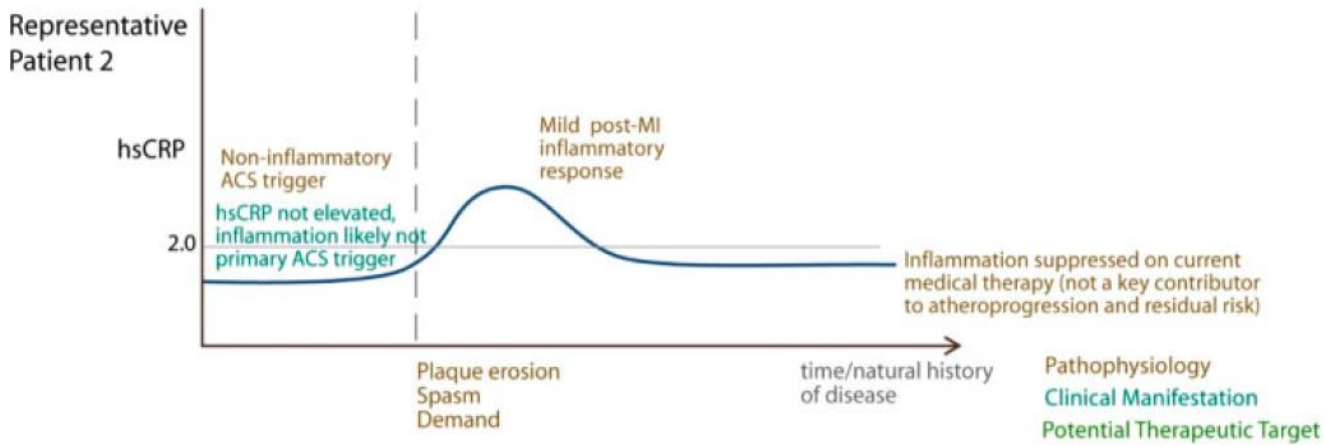
STATE OF THE ART REVIEW
Epidemiology and prevention

Targeting cardiovascular inflammation: next steps in clinical translation

Patrick R. Lawler [1,2,3]*, Deepak L. Bhatt [4], Lucas C. Godoy [1,5], Thomas F. Lüscher[6], Robert O. Bonow [7], Subodh Verma[3,8], and Paul M. Ridker [4,9]

Paul Ridker, MD





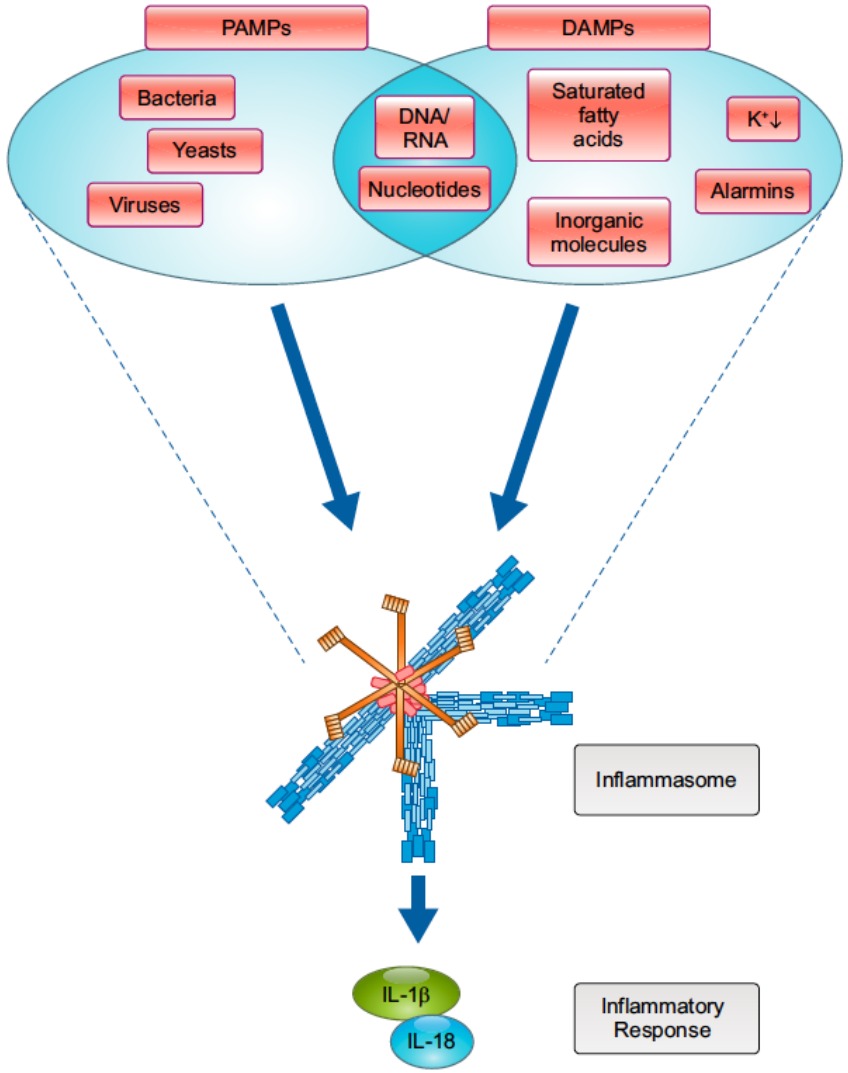
Inflammation as cause/trigger of acute coronary syndrome

Inflammation complicating acute myocardial infarction

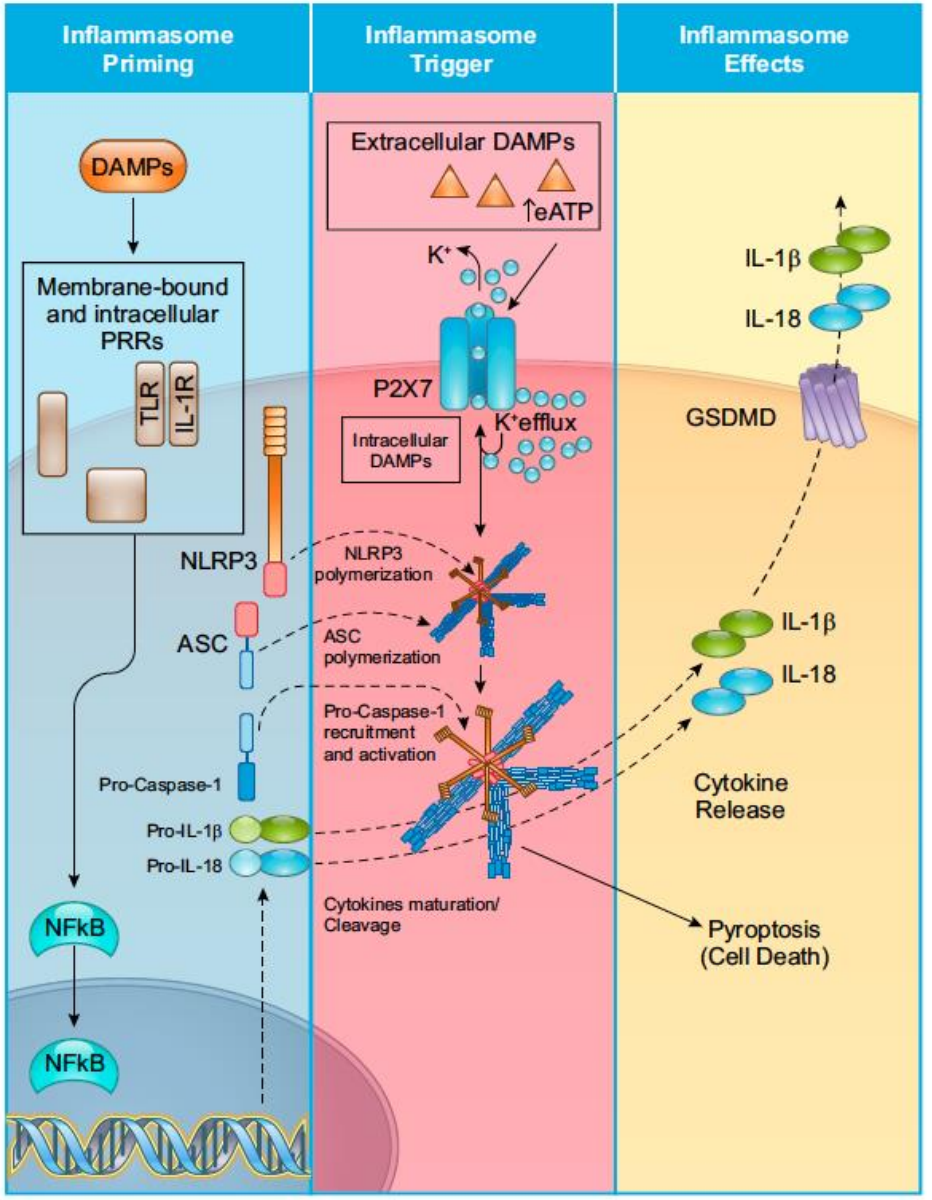
Inflammation promoting heart failure

Inflammation as residual risk

Interleukin-1 and the inflammasome

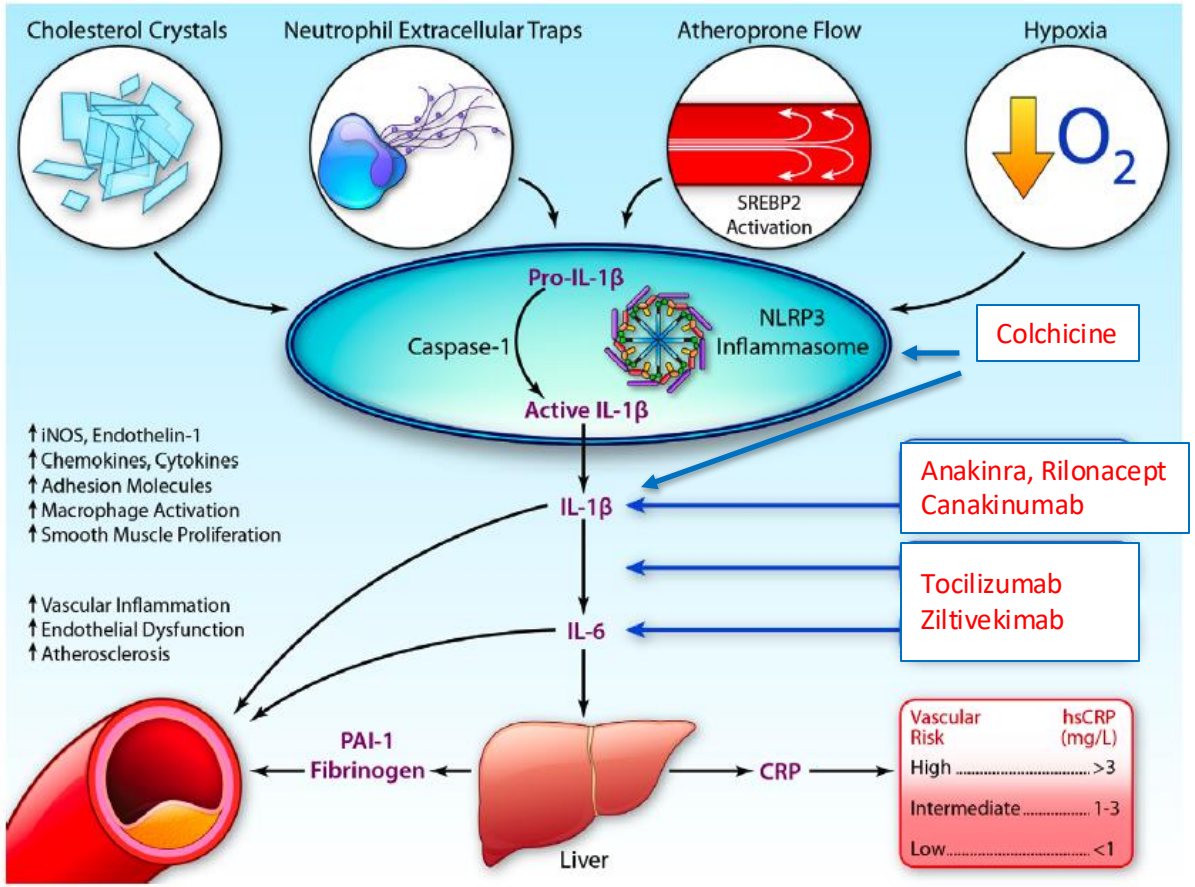


Stefano Toldo, PhD



Toldo ….. Abbate – *Am J Physiol* 2018

NLRP3 inflammasome

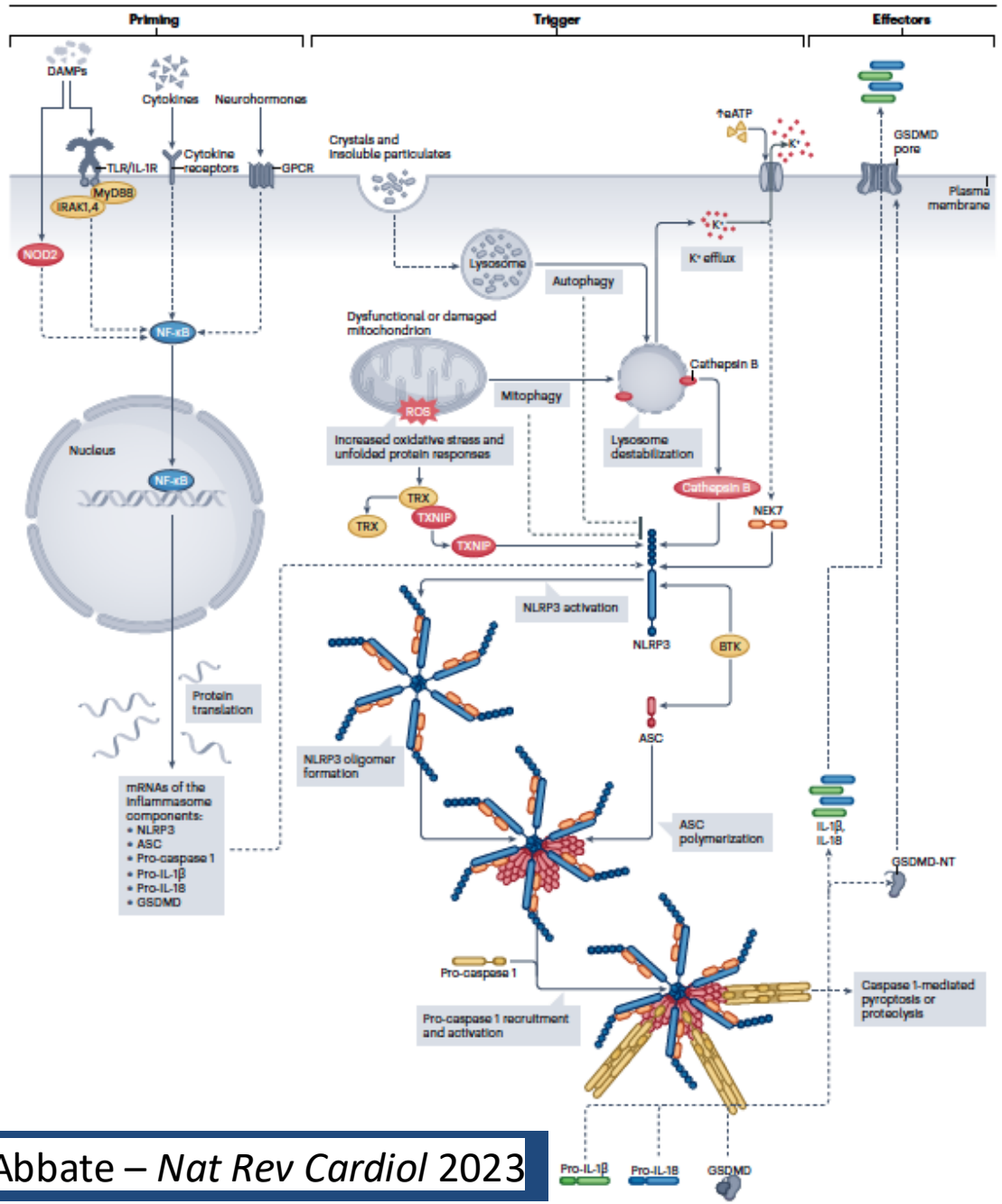


Modified from

From C-Reactive Protein to Interleukin-6 to Interleukin-1

Moving Upstream To Identify Novel Targets for Atheroprotection

Paul M Ridker



Toldo, Abbate – *Nat Rev Cardiol* 2023

Role of inflammation in heart failure

Scenario #1

Injury — Ischemic/Toxic

Inflammation — Inflammatory response

Heart Failure — Cardiomyopathy

Inflammation amplifies the injury and worsens the cardiomyopathy

Scenario #3

No injury to heart

Extracardiac injury (sepsis)

Inflammatory response

Cardiomyopathy

Cytokine mediated cardiac dysfunction

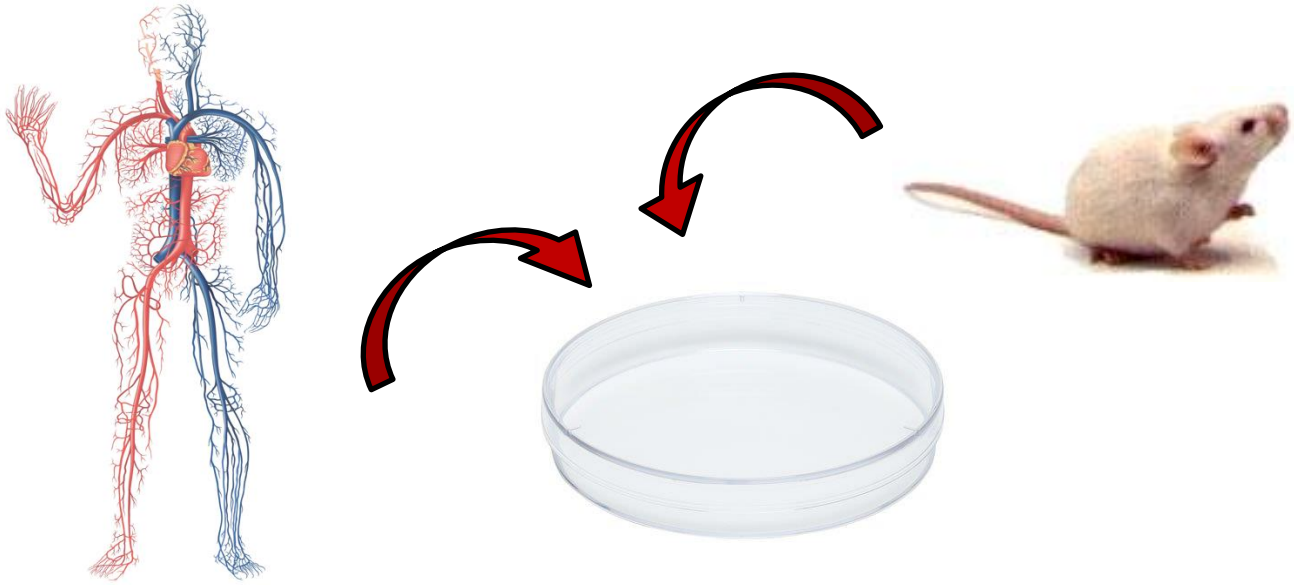
Soluble cardiodepressant substance(s)

A Circulating Myocardial Depressant Substance in Humans with Septic Shock

Septic Shock Patients with a Reduced Ejection Fraction Have a Circulating Factor That Depresses In Vitro Myocardial Cell Performance

Joseph E. Parrillo, Cynthia Burch, James H. Shelhamer, Margaret M. Parker, Charles Natanson, and William Schuette
Critical Care Medicine Department, Clinical Center, National Institutes of Health, Bethesda, Maryland 20205

J Clin Invest. 1985 Oct;76(4):1539-53.



Soluble cardiodepressant substance(s)

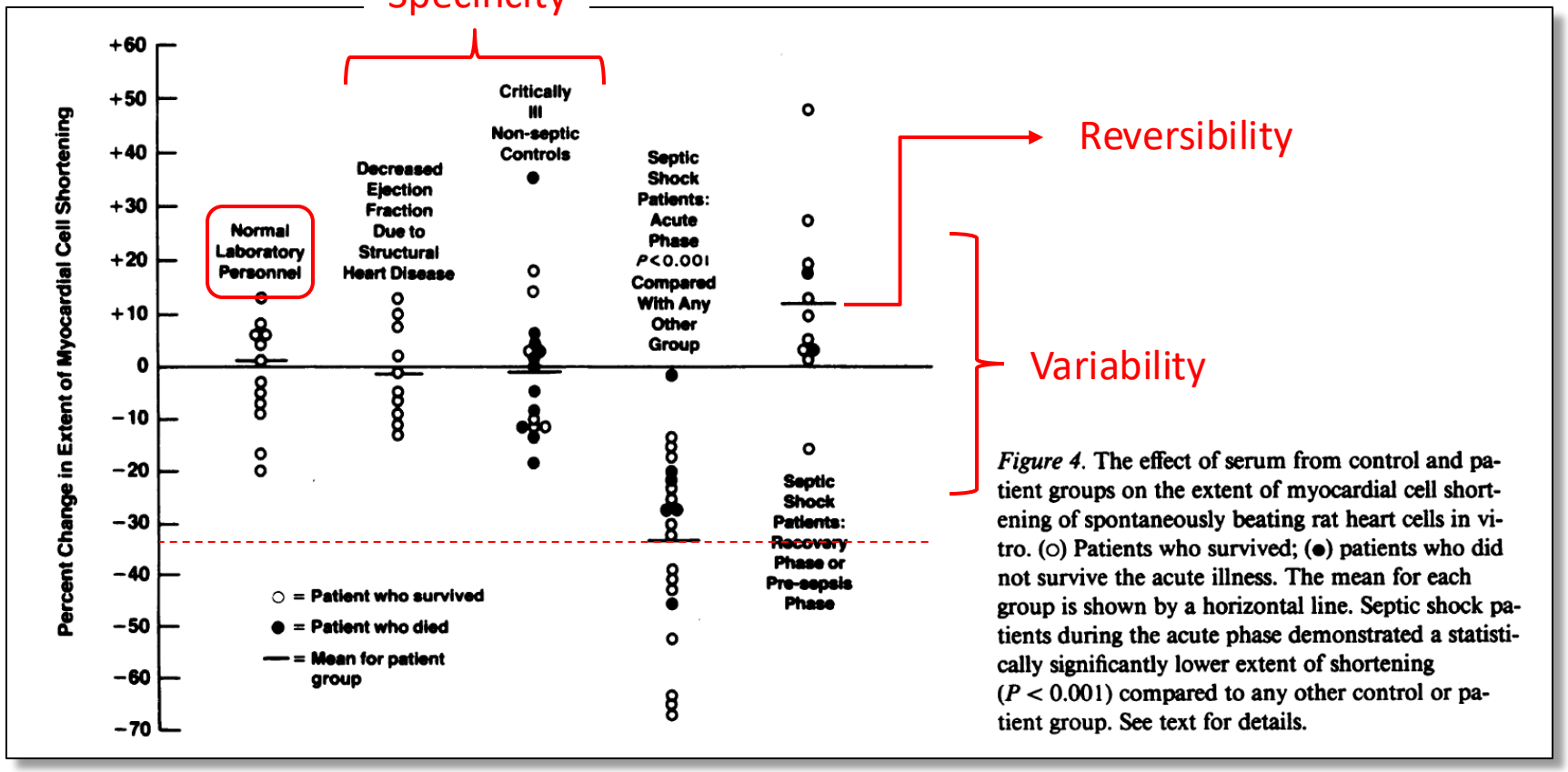


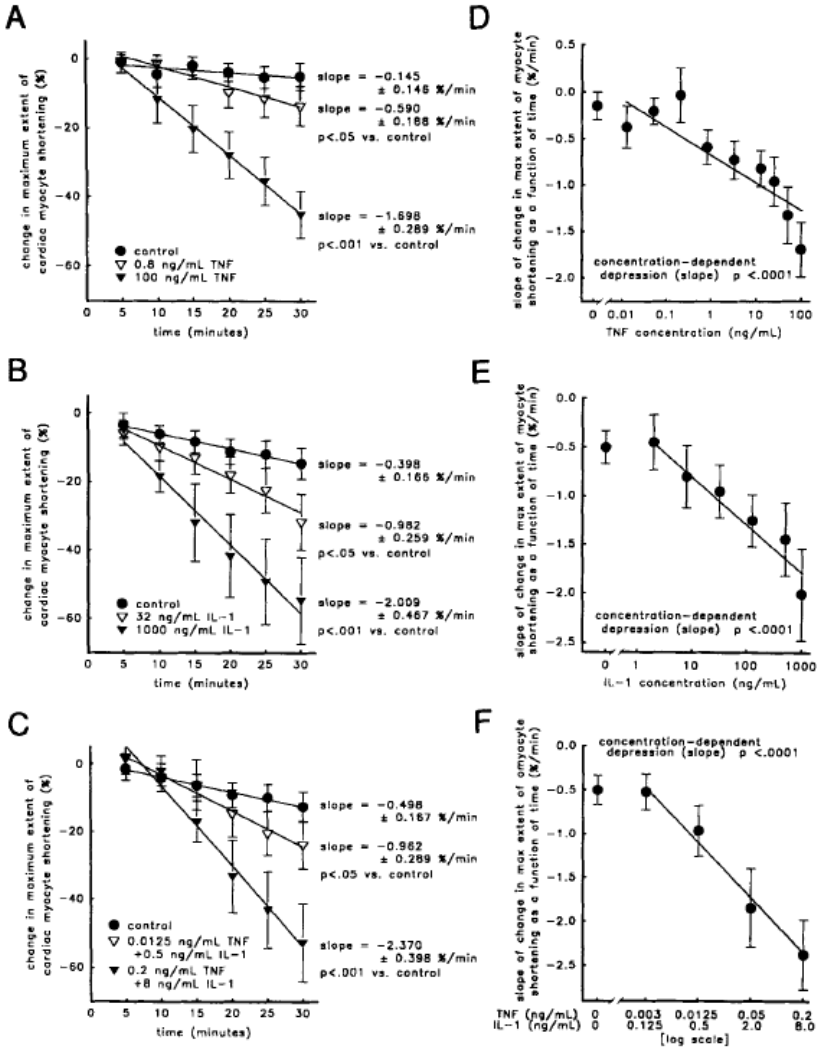
Figure 4. The effect of serum from control and patient groups on the extent of myocardial cell shortening of spontaneously beating rat heart cells in vitro. (○) Patients who survived; (●) patients who did not survive the acute illness. The mean for each group is shown by a horizontal line. Septic shock patients during the acute phase demonstrated a statistically significantly lower extent of shortening ($P < 0.001$) compared to any other control or patient group. See text for details.

J Clin Invest. 1985 Oct;76(4):1539-53.

Tumor Necrosis Factor α and Interleukin 1β Are Responsible for In Vitro Myocardial Cell Depression Induced by Human Septic Shock Serum

By Anand Kumar, Venkateswarlu Thota, Linda Dee, Jeanne Olson, Eugene Uretz, and Joseph E. Parrillo

J. Exp. Med. © The Rockefeller University Press
Volume 183 March 1996 949–958



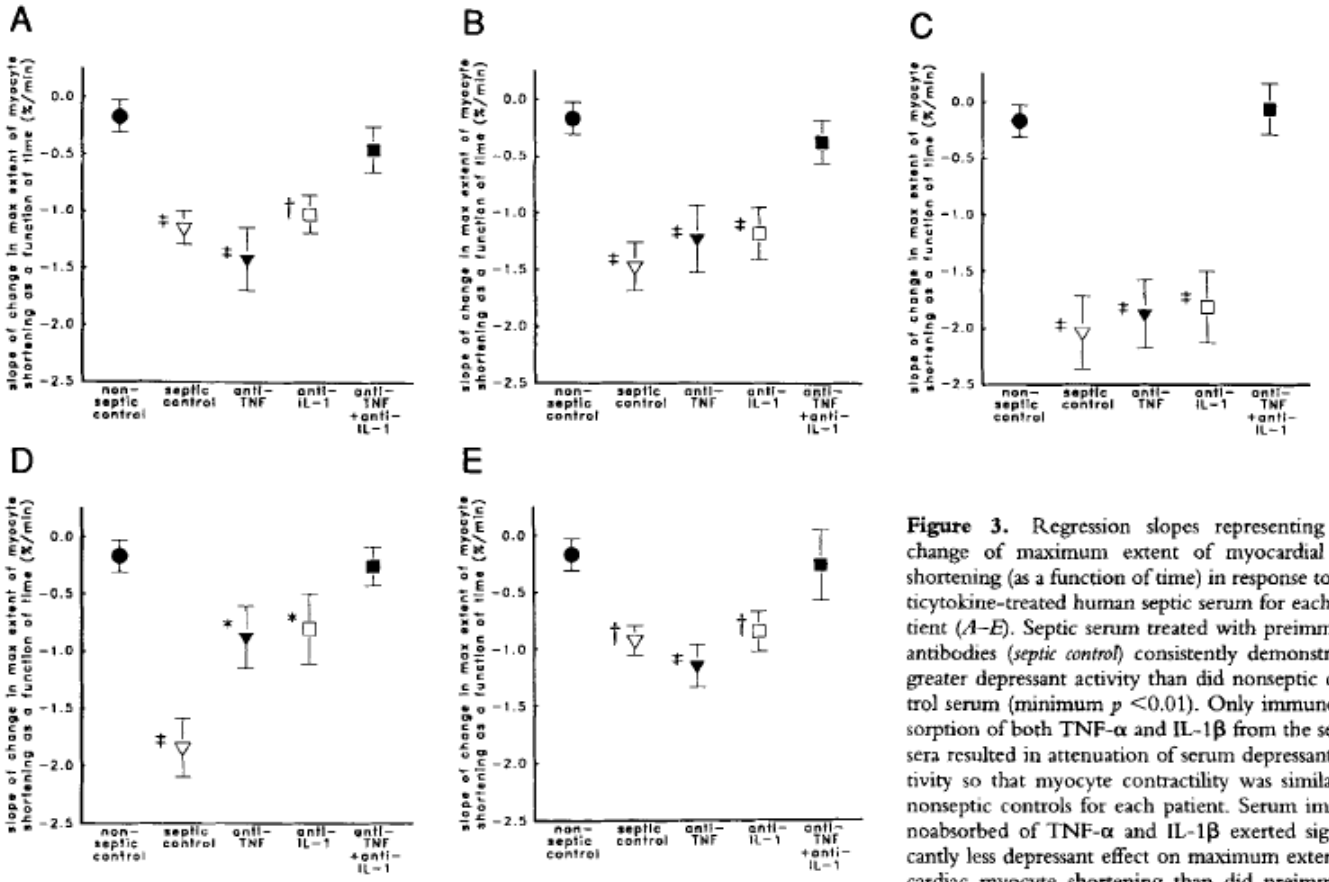
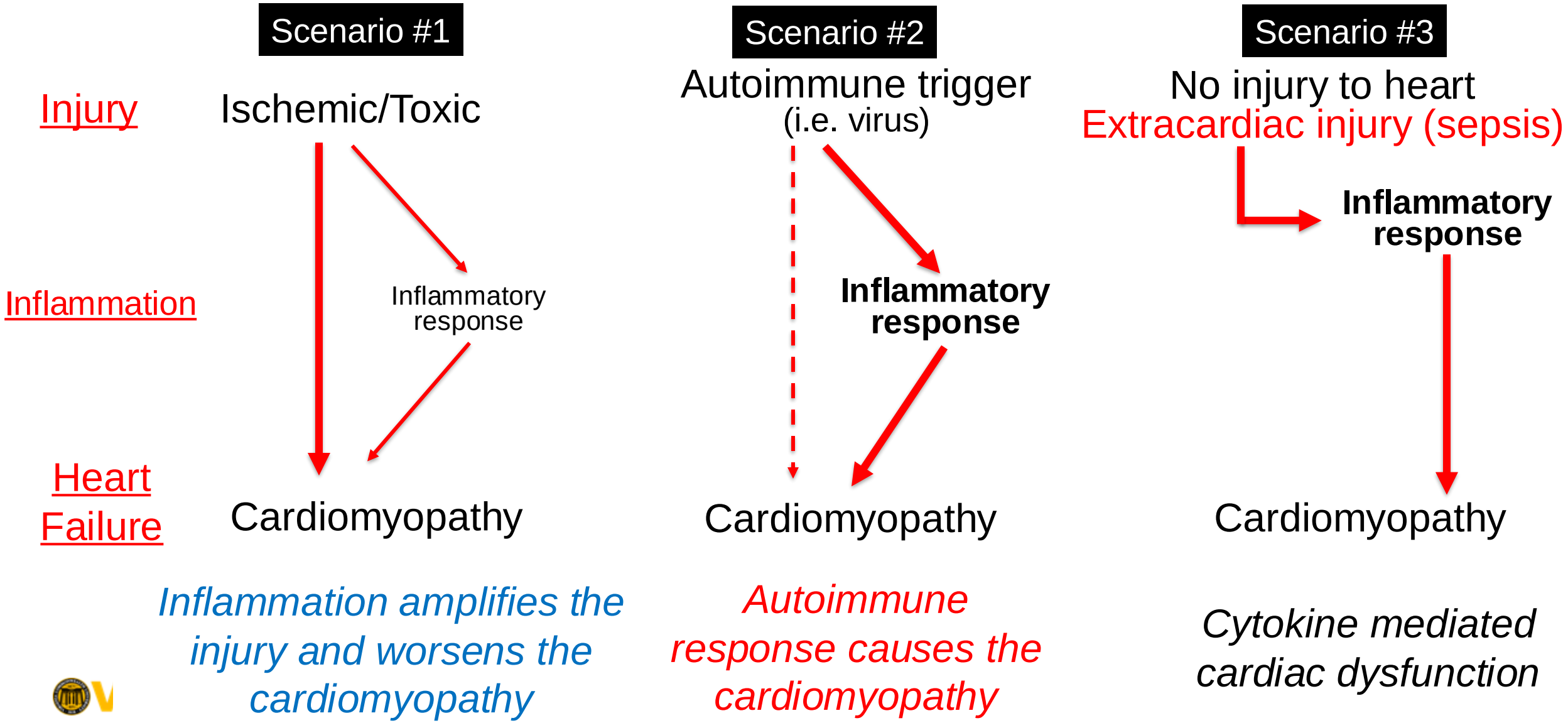


Figure 3. Regression slopes representing the change of maximum extent of myocardial cell shortening (as a function of time) in response to anticytokine-treated human septic serum for each patient (*A–E*). Septic serum treated with preimmune antibodies (*septic control*) consistently demonstrated greater depressant activity than did nonseptic control serum (minimum $p < 0.01$). Only immunoabsorption of both TNF-α and IL-1β from the septic sera resulted in attenuation of serum depressant activity so that myocyte contractility was similar to nonseptic controls for each patient. Serum immunoabsorbed of TNF-α and IL-1β exerted significantly less depressant effect on maximum extent of cardiac myocyte shortening than did preimmune antibody treated (*septic control*) samples (minimum $p < 0.01$). A Bonferonni adjustment for multiple comparisons was made so that each comparison was considered significant only if $p \leq 0.0125$. (*) $p < 0.05$; (†) $p < 0.01$; (‡) $p < 0.001$ vs. nonseptic control. Error bars, SEM.

Role of inflammation in heart failure



LEARNING GOALS

1) Inflammation and cardiovascular diseases
2) **Management of myocarditis**
3) Management of pericarditis
4) Inflammatory component of the cardiovascular risk
5) Inflammatory component of heart failure

Acute myocarditis

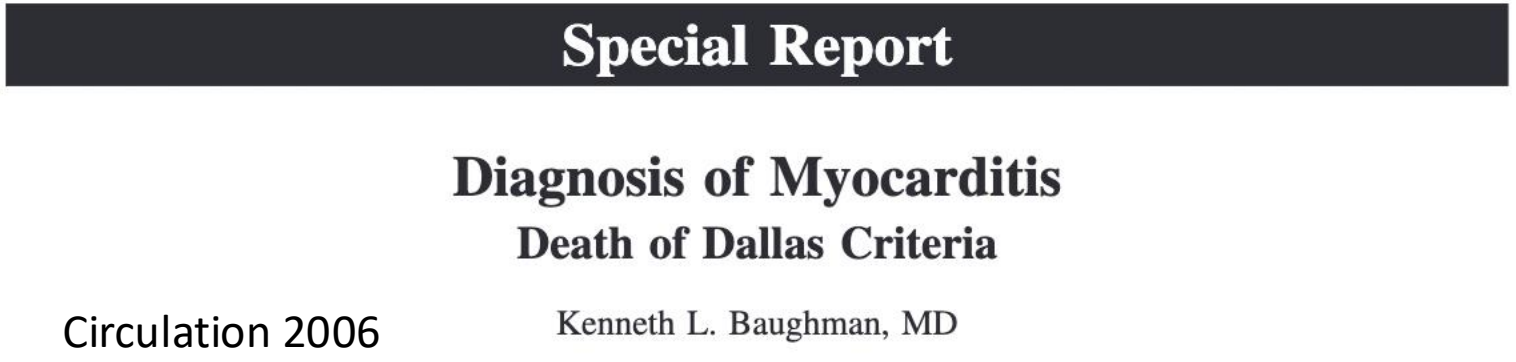
Definition:

- Injury to the myocardium
  - Elevated cardiac biomarkers (troponin I or T, CK-MB)
  - Endomyocardial biopsy (cell death)
  - Cardiac magnetic resonance (LGE)
  - ECG/Echocardiogram (indirect evidence)
- Inflammatory injury
  - Often diagnosis of exclusion
    - Not ischemic injury
    - Not toxic injury
    - Not physical injury
  - Associated with an infection or autoimmune disease

Acute myocarditis

Diagnosis:

- Definite diagnosis of m
  rarely performed
  - Dallas criteria for lympl
  - Giant cell myocarditis
  - Eosinophilic myocarditi



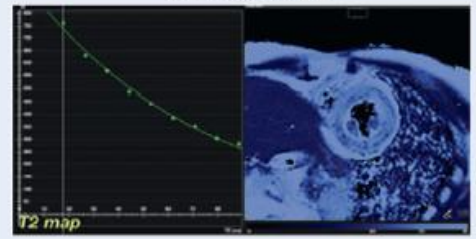
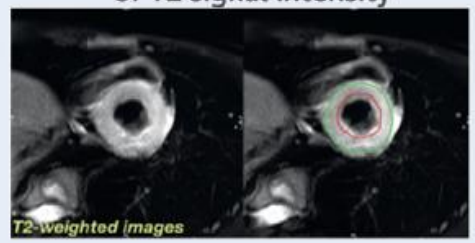
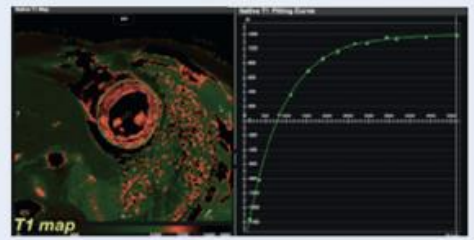
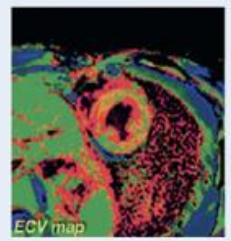
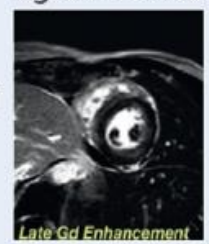
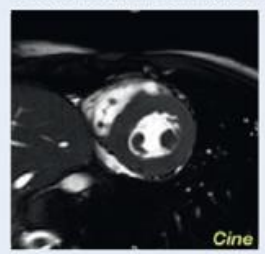
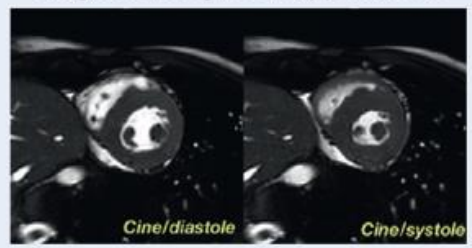
Circulation 2006

- Diagnosis of probable myocarditis is based on clinical scenario of myocardial injury considered to be secondary to an inflammatory (not ischemic) injury
- Growing role of cardiac MRI (Lake Louise criteria)

  → Injury - LGE (epicardial enhancement, patchy, non ischemic) or enhanced T1 signal

  → Edema- enhanced T2 signal

  - Additional criteria (regional WMA, pericardial effusion)

2018 Lake Louise Criteria		CMR Image Examples			
Main Criteria	**Myocardial Edema** (T2-mapping or T2W images)	Regional or global increase of native T2		or	Regional or global increase of T2 signal intensity 
	Non-ischemic Myocardial Injury (Abnormal T1, ECV, or LGE)	Regional or global increase of native T1		or	Regional or global increase of ECV  or Regional LGE signal increase 
Supportive Criteria	**Pericarditis** (Effusion in cine images or abnormal LGE, T2, or T1)	Pericardial effusion			
	Systolic LV Dysfunction (Regional or global wall motion abnormality)	Regional or global hypokinesis			

Ferreira, V.M. et al. J Am Coll Cardiol. 2018;72(24):3158-76.

ECV = extracellular volume; LGE = late gadolinium enhancement; T2W = T2-weighted.

Question #1: which of these is most consistent with acute myocarditis?

1) 40 yo male with chest pain, ST elevation lateral leads, subepicardial LGE at cardiac MRI
2) 22 yo with chest pain, non-specific ST-T changes on ECG, mild troponin I elevation, and small pericardial effusion at echocardiogram, 1 week after SARS-CoV2 vaccination
3) 67 yo F with metastatic melanoma on Keytruda (pembrolizumab) with syncope and 3rd AV block
4) 74 yo F with antibody-associated myositis symptomatic for palpitations and found to have runs of ventricular tachycardia at ECG monitoring
5) All of the above

Clinical case (1)

30 yo male

No past medical history

Chest pain for 2 days

Low grade fever

2^{nd} dose of Pfizer SARS-CoV2 mRNA vaccine 2 days prior

Vital signs normal

Exam normal

ECG – minor abnormalities

CRP and Troponin I minimally abnormal

Rest of labs normal, improving over 24h

No arrhythmias

Next diagnostic test?

Treatment?

Clinical case (2)

51 yo male

Mild hypercholesterolemia

Mild cold symptoms, test + for SARS CoV2, symptoms last 3-5 days

5-7 days later chest pain and shortness of breath

Progressive shortness of breath and fatigue

Seen in the ED

Hypotensive, tachycardic

Markedly abnormal ECG

CRP and Troponin I significantly elevated

Abnormal renal function and signs of shock

Arrhythmias noted

Patient started on norepinephrine and dobutamine

Transferred to tertiary center

Next diagnostic/therapeutic step?

JAMA | Review 2023

Diagnosis and Treatment of Acute Myocarditis
A Review

Enrico Ammirati, MD, PhD; Javid J. Moslehi, MD

Type of myocarditis	Median age and sex prevalence	Sample size and study design[a]	Characteristic findings	Associated conditions and risk factors	Typical clinical presentation	Outcome and frequencies of therapies based on registries
Classification based on clinical presentation						
Uncomplicated acute myocarditis[13]	33 y Male, 85%	Cohort of 325 patients Retrospective study	LVEF ≥50% on echocardiogram, no ventricular arrhythmias, hemodynamic stability	Associated autoimmune disorder such as SLE and eosinophilic granulomatosis with polyangiitis in 4.2%	Chest pain in 96.6% Dyspnea in 6.2% Prodromal symptoms in 80.1% Median LVEF of 60% on echocardiogram	No deaths at 5 y Immunosuppressive drugs used in 2.8% NSAIDs used in 67.6%
Acute myocarditis complicated by LVSD/AHF[13]	35 y Male, 69%	Cohort of 118 patients Retrospective study	LVEF <50% on echocardiogram Signs of AHF	Associated autoimmune disorders in 15.4%	Chest pain in 59.1% Dyspnea in 55.7% Prodromal symptoms in 81.7% Median LVEF of 35% on echocardiogram	Cardiac death or heart transplant during hospitalization of 11.9% and 14.7%, respectively, at 5 y Immunosuppressive drugs used in 37.2% NSAIDs used in 44.0%
Acute myocarditis complicated by ventricular arrhythmias[28]	44 y Male, 77%	Cohort of 156 patients Retrospective study	Onset characterized by the presence of SVT or VF	Family history of cardiomyopathy in 8% Risk factors associated with ventricular arrhythmia recurrence: SVT at presentation (HR, 2.90); fibrosis involving ≥2 myocardial segments on CMR (HR, 4.51); and absence of edema on CMR (HR, 2.59)	SVT at presentation in 67% VF at presentation in 33% Median LVEF of 50% on echocardiogram Lymphocytic myocarditis was the most frequent histology in 89%	37.2% had a recurrence of ventricular arrhythmias after a median follow-up of 23 mo Ventricular arrhythmia recurrence occurred after a median of 8 mo
Fulminant myocarditis[29]	42 y Male, 51%	Cohort of 165 patients Retrospective study	Cardiogenic shock requiring inotropes or mechanical circulatory supports	Associated autoimmune disorders in 17.7% Risk factors associated with cardiac death or heart transplant: need for temporary mechanical circulatory support other than intra-aortic balloon pump (HR, 3.27) Giant cell histology (HR, 3.03) QRS interval >120 ms (HR, 1.74)	Dyspnea in 66.6% Chest pain in 37.0% Syncope in 16.6% Median LVEF of 22% on echocardiogram Lymphocytic myocarditis was the most frequent histology in 72.7%	Cardiac death or heart transplant at 60 d of 28.0% and at 7 y of 47.7% Immunosuppressive therapy used in 66.8% Use of IV corticosteroids in 20.2% and IVIG in 7.3% No association between use of immunosuppressive drugs and risk of cardiac death or heart transplant (HR, 0.78 [95% CI, 0.46-1.31])
Classification based on histology/etiology						

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Myocarditis

Cristina Basso, M.D., Ph.D.

From the Cardiovascular Pathology Unit, Azienda Ospedaliera, Department of Cardiac, Thoracic, and Vascular Sciences and Public Health, University of Padua, Padua, Italy. Dr. Basso can be contacted at cristina.basso@unipd.it or at Cardiovascular Pathology, via Gabelli, 61, 35121 Padua, Italy.

N Engl J Med 2022;387:1488-500.
DOI: 10.1056/NEJMra2114478

CME

ACCORDING TO THE 1995 WORLD HEALTH ORGANIZATION TASK FORCE ON cardiomyopathies, myocarditis is an inflammatory disease of the myocardium that is diagnosed on the basis of established histologic, immunologic, and immunohistochemical criteria.[1] Since the introduction of the Dallas criteria in 1987,[2] endomyocardial biopsy has been considered the standard method of diagnosis.[3-7] Over the past two decades, however, the diagnostic workup has changed with the introduction of new tools, mainly highly sensitive troponin and cardiac magnetic resonance imaging (MRI)[8,9]; in routine clinical practice, a combination of symptoms and signs, laboratory testing, and imaging studies is often sufficient to establish the diagnosis.

Acute myocarditis

Clinical Presentations:

- ACS-like presentation *(most common and favorable prognosis of the different forms)*
  - chest pain,
  - troponin I or T (usually mild) elevation
  - regional WMA or mild global reduction in LVEF
- Myopericarditis
  - pericarditis dominates the presentation
- Cardiogenic shock / fulminant
  - Heart failure and shock as presentation
  - rare but can be fatal
- Arrhythmias *(consider giant cell myocarditis or immune check point inhibitors)*
  - AV block, ventricular or atrial tachyarrhythmias
- Incidental finding
  - asymptomatic Trop I/T elevation
- Hyper-inflammatory
  - cytokine storm (i.e. CAR-T)
  - MIS C/A (i.e COVID-19)

Acute myocarditis

Work up:

- ECG
  - Can be normal, but often abnormal
  - TWI common, STE common, ST depression rare
- Echocardiogram – can be normal
  - Regional WMA can be subtle (can be global dysfunction)
  - Pericardial effusion can be present
- Cardiac markers need to be elevated – although can be minimal
- Cardiac MRI usually diagnostic
- Pathology (biopsy) gold-standard for specificity, sensitivity suboptimal, uncommonly performed

Acute myocarditis

Work up:

- ECG
  - Can be normal, but often abnormal
  - TWI common, STE common, ST depression rare
- Echocardiogram – can be near normal
  - Regional WMA can be subtle (can be global dysfunction)
  - Pericardial effusion can be present
- Cardiac markers need to be elevated – although can be minimal
- Cardiac MRI usually diagnostic
- Pathology (biopsy) gold-standard for specificity, sensitivity suboptimal

Additional tests:

- Isolated (no extra-cardiac symptoms or signs)

→ commonly viral → no or limited w/u required

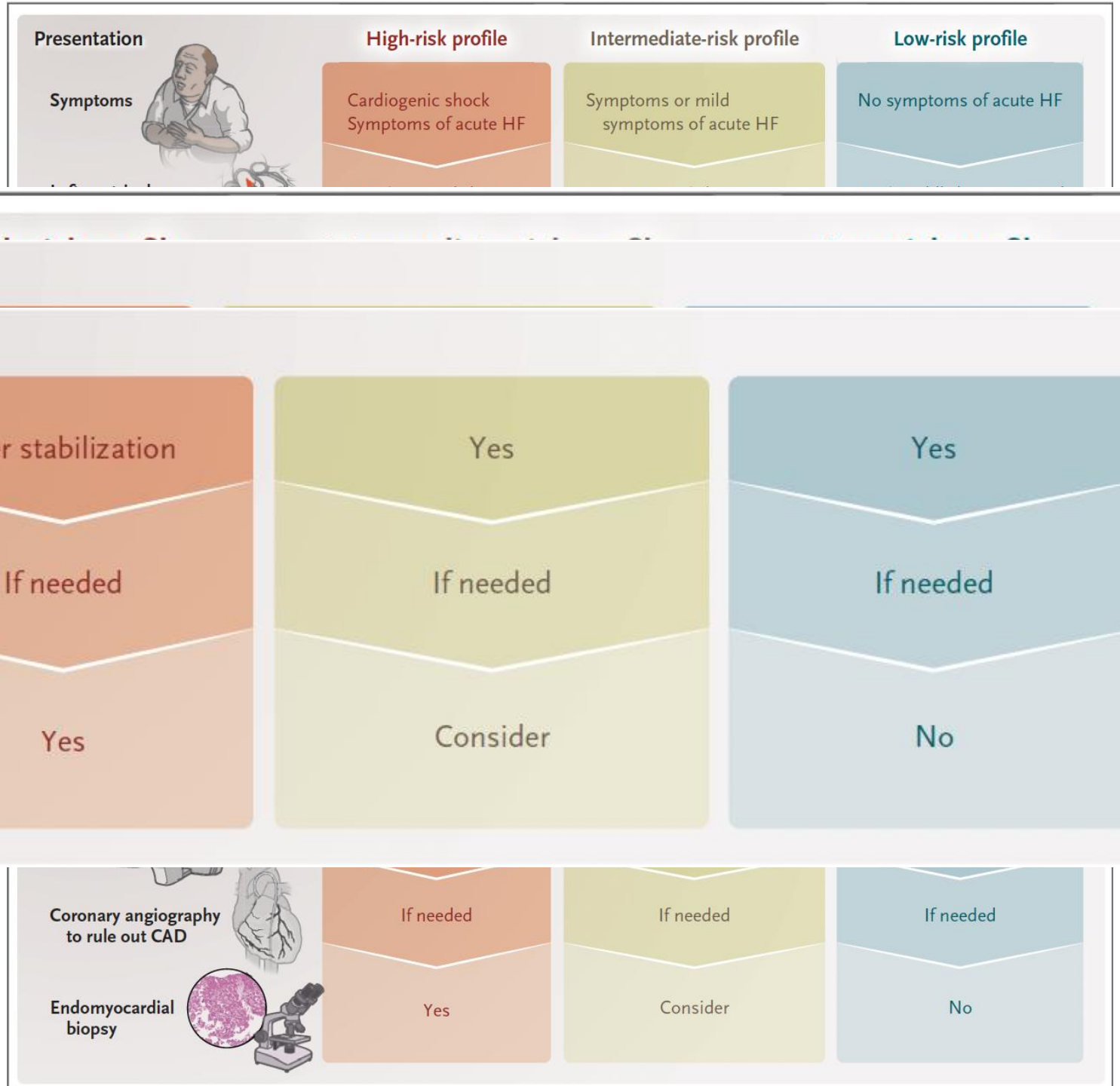
- Autoimmune – associated with rheumatologic symptoms → requires work up for SLE, RA, myositis, scleroderma, vasculitis, HIV, HCV
- Coronary angiogram - CTA/invasive, needed to rule out ACS, PET → sarcoid?
- Endomyocardial biopsy – rarely done (for arrhythmias, shock, refractory HF) due to risks (i.e. perforation)

Acute (viral) myocarditis

Treatment: mostly supportive care

- Treatment of LV systolic dysfunction and HF if present
- Treatment of pericarditis if associated
- Immunosuppressive drugs – selected cases
  - Immune check point inhibitors – cancer treatment (!!!)
  - Giant cell myocarditis *[treat first but then biopsy]*
  - Eosinophilic or drug-induced sensitivity *[consider biopsy]*
  - Fulminant / hemodynamically unstable (empiric therapy)
  - Hyper-inflammatory (high ferritin) → IL-1/IL-6 blockers
- Mechanical support for shock or arrhythmias

Cristina Basso, MD
N Engl J Med 2022

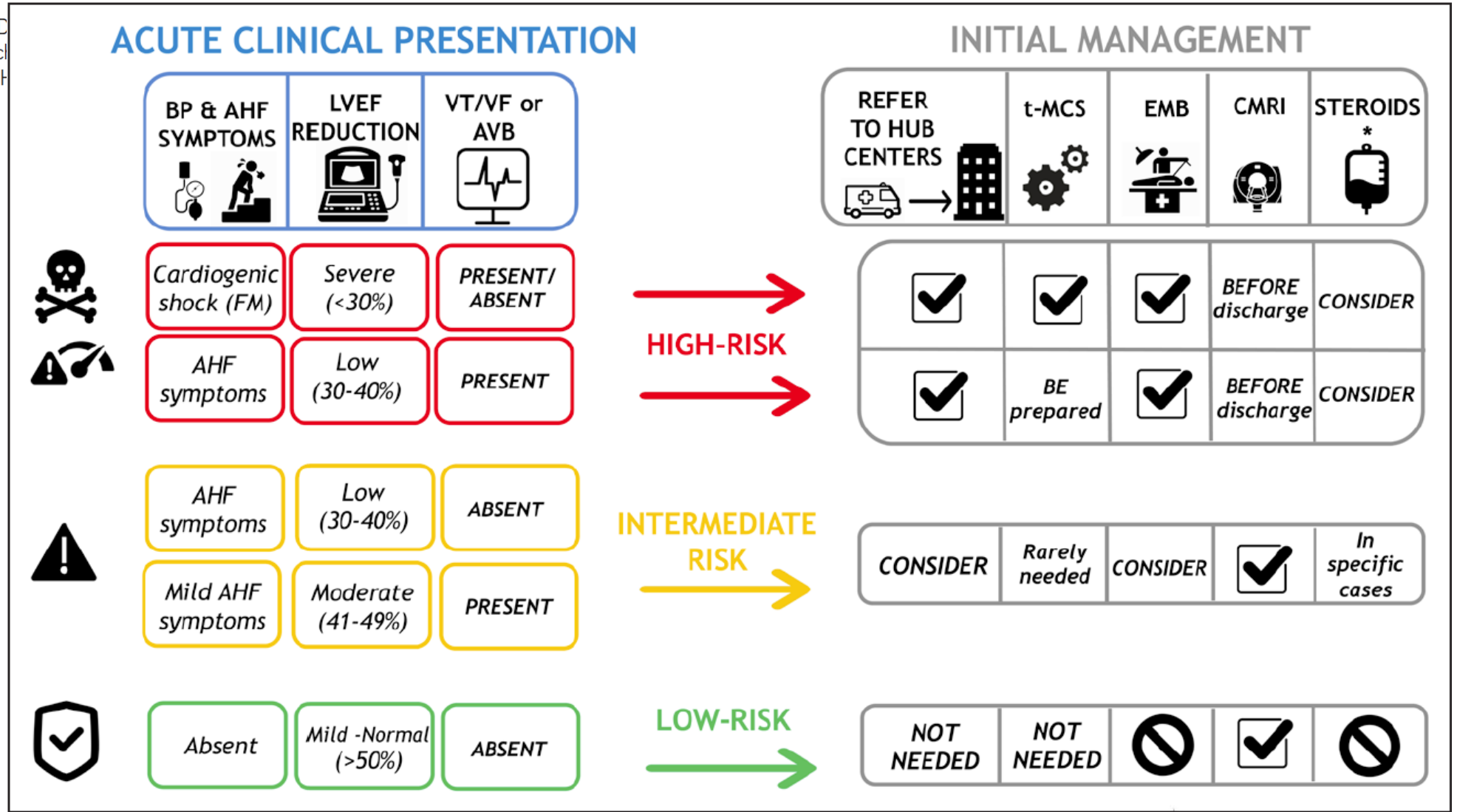


Circulation: Heart Failure

Management of Acute Myocarditis and Chronic Inflammatory Cardiomyopathy

An Expert Consensus Document

Enrico Ammirati, MD, PhD*; Maria Frigerio, MD
Michela Brambatti, MD, MS; Matthias G. Friedrich
Patrizia Pedrotti, MD; Ornella E. Rimoldi, MD; H
Paolo G. Camici, MD†



Diagnosis and Treatment of Acute Myocarditis

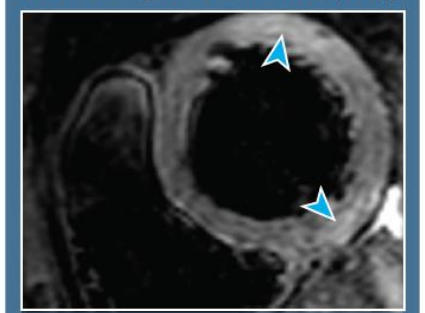
Patient presents with clinically suspected myocarditis

Abnormal electrocardiogram: elevation or depression of ST-T segments
Elevated troponin I or T
Abnormal echocardiogram: increased myocardial wall thickness and brightness with normal or nearly normal ventricular dimensions, segmental hypokinesia typically involving the inferior and lateral walls, diastolic dysfunction, and pericardial effusion

Uncomplicated presentation
- Chest pain
- No presence of LVEF<50%, no acute heart failure, no sustained ventricular arrhythmias, and no advanced conduction disturbances

Complicated presentation
- Left ventricular systolic dysfunction (LVEF<50%)
- Acute heart failure
- Ventricular tachycardia/ventricular fibrillation
- Second- or third-degree atrioventricular block (AVB)
- Cardiogenic shock

AHA/ACC recommendation 2B and C
Cardiac magnetic resonance (CMR)

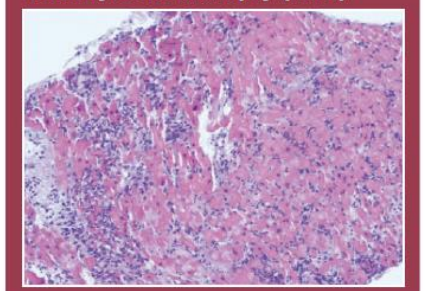


No

Hemodynamic instability (fulminant myocarditis)
High-degree AVB
Sustained or symptomatic ventricular tachycardia

Yes

AHA/ACC recommendation 1B
Endomyocardial biopsy (EMB)



Evolving toward a complicated phenotype
Peripheral eosinophilia
New atrial arrhythmias
Septal inflammation detected on CMR
Immune checkpoint inhibitors treatment
Suspected systemic autoimmune disorder

Nondiagnostic findings

Consider EMB

CMR

---

1 Patient presents with clinically suspected myocarditis

Symptoms: chest pain, dyspnea, fever, syncope, shock
Abnormal electrocardiogram (ECG): elevation or depression of ST-T segments
Elevated troponin: above the upper reference limit
Abnormal echocardiogram: increased myocardial wall thickness and brightness with normal or nearly normal ventricular dimensions, segmental hypokinesia typically involving the inferior and lateral walls, diastolic dysfunction, and pericardial effusion

Uncomplicated presentation
- Isolated chest pain
- LVEF >50% on echocardiogram

Complicated presentation
- Isolated left ventricular systolic dysfunction (LVSD)

Complicated presentation
- Ventricular arrhythmia (VA)/second- or third-degree atrioventricular block
- Acute heart failure
- Fulminant myocarditis

Admit to monitor ECG, troponin levels, and echocardiogram
Admission to cardiology ward is preferable

Admit to ICU/CICU
Consider transfer to centers with mechanical circulatory support (MCS) facility

Perform coronary angiography or angio CT to rule out acute coronary syndrome if
- Patient aged >45 y
- Cardiovascular risk factors present (eg, diabetes, smoking, hypertension, dyslipidemia, family history of coronary artery disease)
- ECG/echocardiogram abnormalities present (eg, ST segment changes, segmental hypokinesia)

Persistent chest pain: NSAIDs

Reduced LVEF and stable hemodynamics: heart failure (HF) therapies including angiotensin-converting enzyme inhibitors, β-blockers, mineralocorticoid recepter antagonists, angiotensin receptor-neprilysin inhibitors, and sodium-glucose co-transporter 2 inhibitors

Treatment for VA, inotropes, or MCS
Consider immunosuppression if
- Systemic autoimmune disorders
- Peripheral eosinophilia
- Multisystem inflammatory syndrome due to COVID-19
- Patient on VA-ECMO

EXPERT CONSENSUS DECISION PATHWAY

2024 ACC Expert Consensus Decision Pathway on Strategies and Criteria for the Diagnosis and Management of Myocarditis

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the Heart Failure Society of America, International Society of Cardiomyopathies, Myocarditis and Heart Failure, and the Myocarditis Foundation

FIGURE 2 Three Classic Presentations of Myocarditis

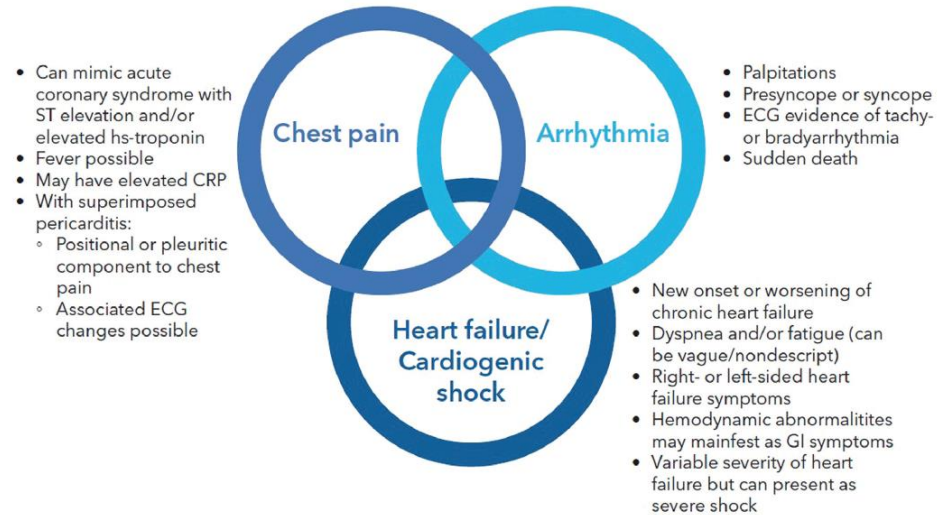
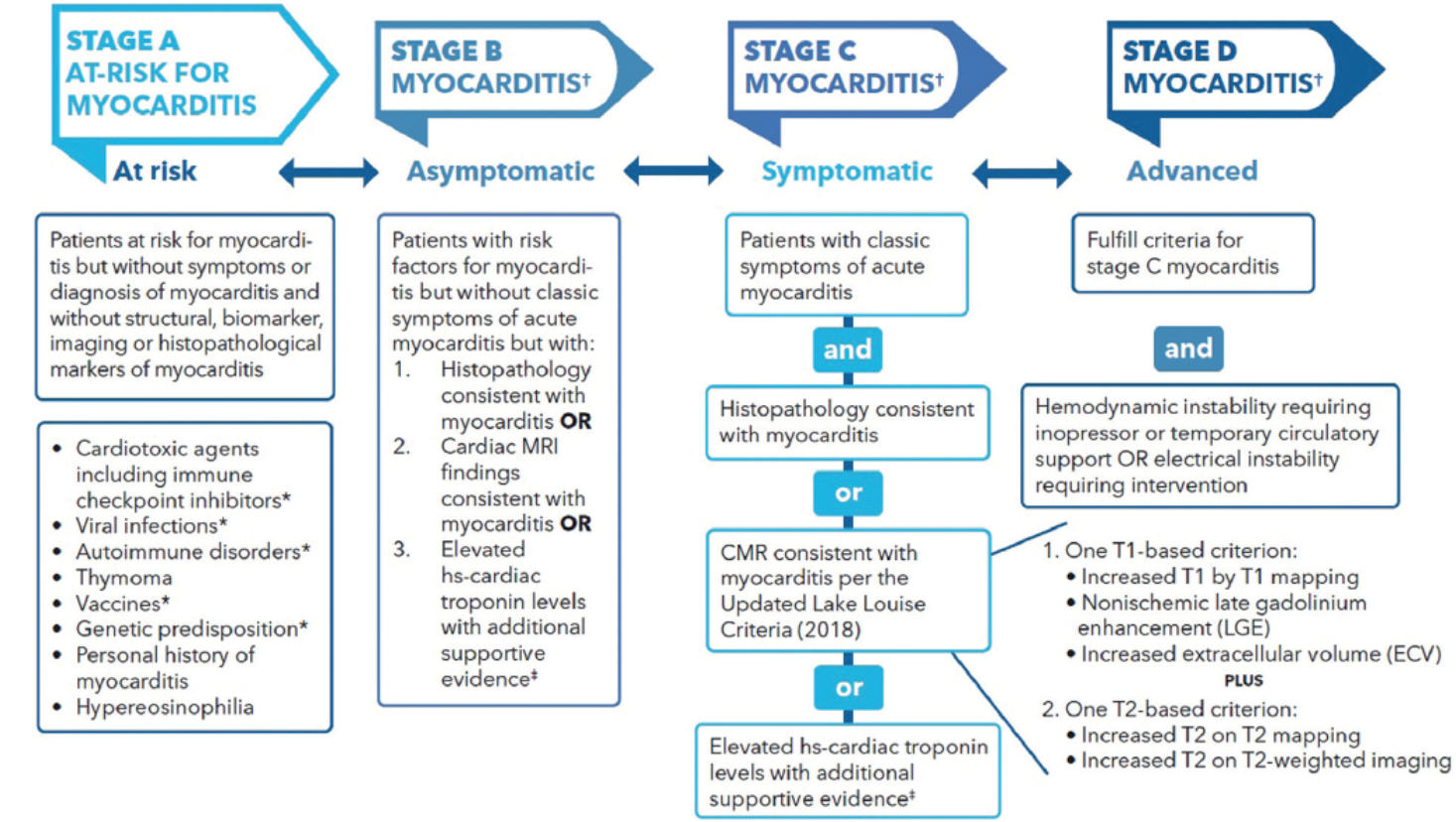


FIGURE 5 Proposed Stages of Myocarditis



The spectrum of myocarditis is described as 4 stages: A (at-risk); B (asymptomatic); C (symptomatic myocarditis); and D (advanced myocarditis). There are 2 pivotal tests to diagnose stages B-D myocarditis: EMB and CMR. EMB, including histopathology, immunohistochemistry, and molecular search for infectious agents, is the gold-standard diagnostic test for myocarditis, allowing characterization of histotype and specific etiologies (including viral). EMB is associated with some risks due to its invasive nature and limitations due to sampling error. CMR is an attractive noninvasive strategy although it too has limitations, including reduced sensitivity depending upon clinical presentation, a delayed timing after onset of symptoms, and technical challenges due to patient breath-holding and irregular heart rhythms. The specificity of CMR diagnosis of myocarditis is enhanced when both T_1 and T_2 criteria are met, although isolated T_1 or T_2 abnormalities may be seen at times. In the appropriate clinical context (eg, therapy with an immune checkpoint inhibitor), an acute rise in troponin can be consistent with the diagnosis of myocarditis but the specificity of an elevated troponin with most other stage A risk factors is not adequate to make the diagnosis and one of the two pivotal tests would be needed. Further, myocardial infarction needs to be excluded (eg, by coronary angiography or absence of ischemic LGE on CMR) as the basis of an elevated troponin level in most contexts when considering the diagnosis of myocarditis. Unlike the staging system in HFrEF, patients with myocarditis can move from higher to lower stages *Those known to be associated with myocarditis. †Pericarditis may complicate stages B-D ("myopericarditis"). ‡The level of supportive evidence depends upon the clinical context, including which stage A risk factor is present. CMR = cardiac magnetic resonance; EMB = endomyocardial biopsy; HFrEF = heart failure with reduced ejection fraction; hs = high sensitivity; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging.

EXPERT CONSENSUS DECISION PATHWAY

2024 ACC Expert Consensus Decision Pathway on Strategies and Criteria for the Diagnosis and Management of Myocarditis

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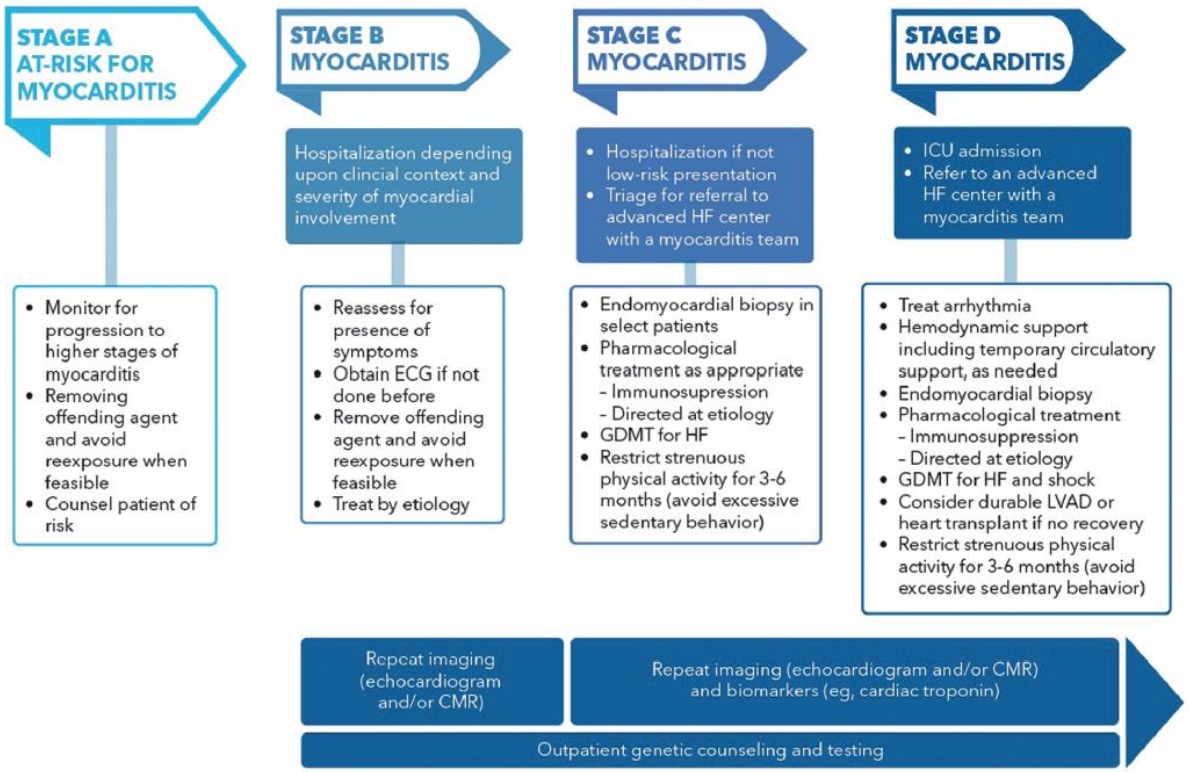
FIGURE 8 Surveillance and Treatment by Stage of Myocarditis



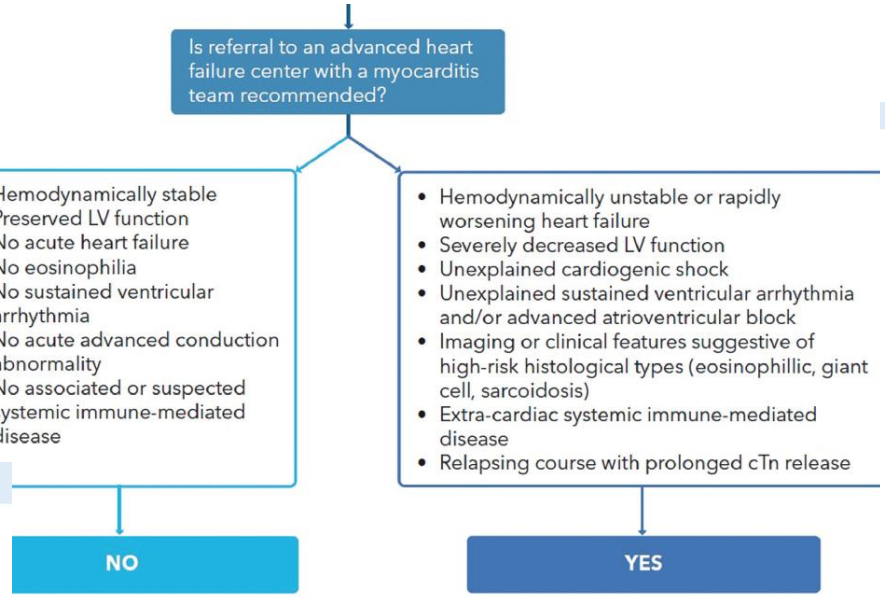


FIGURE 6 When to Perform EMB in Patients With Suspected Myocarditis

Stage B myocarditis
- In setting of ICI therapy

Stage C myocarditis with:
- LV dysfunction or
- Symptomatic heart failure or
- Arrhythmia
  - High-degree AV block
  - Frequent multifocal PVCs or VT or VF
- Or peripheral eosinophilla
- Or uncertain of diagnosis and unable to acquire CMR

Stage D myocarditis

Not all patients with myocarditis require immunosuppressive therapy

General consensus is to administer immunosuppressive therapy for the following conditions:
- Eosinophilic myocarditis
- Giant cell myocarditis
- Granulomatous myocarditis (sarcoid)
- Associated with immune checkpoint inhibitor therapy
- In setting of other autoimmune conditions

There remains lack of broad consensus but myocarditis experts from certain centers advise:
- Perform viral PCR on endomyocardial biopsy tissue to exclude active infection prior to initation of immunosuppressive therapy
- Treat chronic lymphocytic myocarditis (with negative viral PCR) with immunosuppressive therapy

Implementation of immunosuppressive therapy
- Typically start with methylprednisolone boluses (7-14 mg/kg per day for 3 days) followed by oral prednisone taper (start at 1 mg/kg)
- Giant cell myocarditis requires higher level of immunosuppression than IV steroids, typically including a calcineurin inhibitor (cyclosporine or tacrolimus)
- Involve other specialty experts in setting of autoimmune conditions (eg, systemic lupus, vasculitis) as immunosuppressive strategy may be altered based on other organ involvement.

IVIG can be considered in the setting of inflammatory, antibody-mediated, or autoimmune disorders

Type of myocarditis	Therapies based on cases series or recommendations based on experts' consensus[a]	Potential adverse effects of therapies (rates of adverse events)
Giant cell myocarditis[32,58]	Combination therapy with: IV pulses of methylprednisolone (1000 mg for 3 d) and maintenance at 1 mg/kg If hemodynamic instability: +IV ATG, 1 mg/kg, usually a single dose + oral cyclosporine twice a day (target trough levels, 150-250 ng/mL) Alternative therapy to ATG: IV alemtuzumab (anti-CD52 antibody), a single dose of 30 mg If hemodynamic stability: +oral cyclosporine twice a day (target trough levels, 150-250 ng/mL)	Methylprednisolone: hepatic function abnormalities (≥10%), malaise (≥10%), moon face (≥10%), risk of infections (≥10%), acne (≥10%), hyperglycemia (1%-10%), gastrointestinal upset (1%-10%), osteopenia (1%-10%), osteoporosis (1%-10%), insomnia (1%-10%), gastrointestinal bleeding (<1%), hypertension (<1%), febrile neutropenia (<1%), diabetes (<1%), glaucoma (<1%), and cataract (<1%)[b] ATG: risk of infections (≥10%), bone marrow suppression (≥10%), febrile neutropenia (1%-10%), gastrointestinal upset (1%-10%), risk of cancer (1%-10%), rash (1%-10%), hypotension (1%-10%), serum sickness (<1%) Cyclosporine: kidney toxicity (≥10%), risk for infection,[c] hypertension (≥10%), hyperlipidemia (≥10%), tremor (≥10%), hypomagnesemia (1%-10%), and hepatic function abnormalities (1%-10%) Alemtuzumab: neutropenia (≥10%), rash (≥10%), thyroid disorder ≥10%), infection (≥10%), herpes infection (≥10%), and infusion reactions (1%-10%)
Lymphocytic acute myocarditis (presenting with acute HF/fulminant presentation)	Based on case reports and case series of fulminant myocarditis[1,56,58,72]: initial IV pulses of methylprednisolone (500-1000 mg for 3 d) and maintenance at 1 mg/kg could be considered on individual bases MTT trial showed no benefit of prednisone + azathioprine or cyclosporine in patients with lymphocytic myocarditis with LVSD[73] MYTHS randomized trial is assessing efficacy of IV methylprednisolone, 1000 mg, for 3 d in this setting (NCT05150704)[74]	Methylprednisolone: see above

? – potential benefit

MYTHS trial now enrolling also at UVA
Pragmatic trial of high dose steroids vs no steroids

Anakinra ? – potential benefit

IVIG? Potential benefit

Eosinophilic acute myocarditis[30] (hypersensitivity reaction [ie, myocarditis associated with clozapine use], eosinophilic granulomatosis with polyangiitis, raw meat consumption [toxocariasis], and myeloproliferative variant of HES)	Corticosteroids are used as first-line therapy. Type and dosage range from prednisolone, 50 mg/d, tapered over 8 wk to methylprednisolone, 1000 mg for 3 d[30] Withdrawal of suspected drug in case of hypersensitivity reaction ± corticosteroids (generally used in case of complicated presentation) Additional drugs are used based on the associated conditions IV cyclophosphamide 600 mg/m^2 (BSA) at 1, 15, and 30 d Alternatively, anti-IL-5 agents: mepolizumab, 100-300 mg SC/4 wk, or benralizumab, 30 mg SC/4-8 wk Albendazole, 600-800 mg/d, for 2-8 wk[76] Imatinib, 100-400 mg/d, for 4-28 d (up to normalization of eosinophilic count)[77]	Corticosteroids: See methylprednisolone adverse effects Cyclophosphamide: bone marrow suppression (≥10%), alopecia (≥10%), urinary tract infection (≥10%), hematuria (≥10%), neutropenic fever (1%-10%), hemorrhagic cystitis (1%-10%), risk of infections (1%-10%), and infertility (1%-10%) Anti-IL-5 agents: headache (≥10%), risk of respiratory infections (1%-10%), urinary tract infections (1%-10%), hypersensitivity reactions (1%-10%), nasal congestion (1%-10%), and abdominal discomfort (1%-10%) Albendazole: hepatic function abnormalities (≥10%), gastrointestinal upset (1%-10%) headache (<1%), hypersensitivity reaction (<1%) Imatinib: bone marrow suppression (≥10%), gastrointestinal upset (≥10%), and hepatic function abnormalities (1%-10%)
Immune checkpoint inhibitor–associated acute myocarditis[1,78]	Withdrawal of immune checkpoint inhibitor therapy Initial IV pulses of methylprednisolone (500-1000 mg for 3 d) used in most of cases as first line Additional regimens in refractory to steroids cases based on case reports: IV abatacept (a CTLA-4 agonist), 10 mg/kg-25 mg/kg, on days 0, 5, and 12 IV ATG, 1 mg/kg, usually single dose or IV alemtuzumab (anti-CD-52 antibody), 30 mg, single dose or ruxolitinib, 10-15 mg, by mouth twice a day (usually treated for 2-4 wk)	Methylprednisolone: see above Abatacept: risk of respiratory infection (>10%), risk of urinary tract/herpetic infection (1%-10%), hypertension (1%-10%) ATG: see above Alemtuzumab: see above Ruxolitinib: risk of thrombocytopenia or anemia (>10%) and bruising (>10%)

ATRIUM trial now enrolling also at UVA
Randomized trial of Abatacept on top of steroids for ICI myocarditis

MYOCARDITIS - LEARNING GOALS

1) Diagnosis – *based on clinical, labs, imaging … biopsy*
2) Stratification – *essential! Identify high risk individuals*
3) Initial Management – *treat first in some cases*
4) Work up – *defining a (differential) diagnosis is important*
5) Special cases – *identify cases that need targeted therapy*
6) Consider enrolling in a clinical trial (if available)
7) Let's review the two initial cases

Clinical case (1)

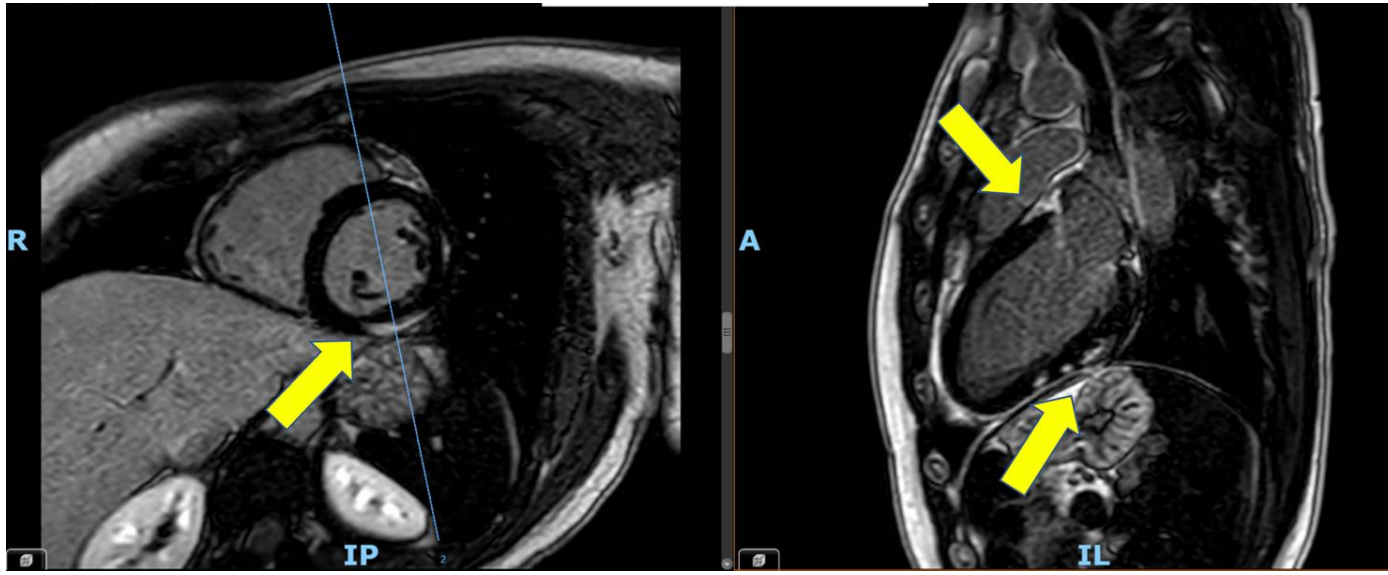
30 yo male
No past medical history
Chest pain for 2 days
Low grade fever

2nd dose of Pfizer SARS-CoV2 mRNA vaccine 2 days prior

Vital signs normal
Exam normal
ECG – minor abnormalities
CRP and Troponin I minimally abnormal
Rest of labs normal, improving over 24h
No arrhythmias

Next diagnostic test?

Treatment?



Resolution of symptoms over 72 hours
Restrictions for strenuous exercise for 6 months
No known long-term consequences, no Tx

Clinical case (2)

51 yo male

Mild hypercholesterolemia

Mild cold symptoms, test + for SARS CoV2, symptoms last 3-5 days

5-7 days later chest pain and shortness of breath

Progressive shortness of breath and fatigue

Seen in the ED

Hypotensive, tachycardic

Markedly abnormal ECG

CRP and Troponin I significantly elevated

Abnormal renal function and signs of shock

Arrhythmias noted

Patient started on norepinephrine and dobutamine

Transferred to tertiary center

LVEF 20% at echocardiogram

Immediate cardiac catheterization

Placement of percutaneous LVAD – Impella

High dose steroids, IVIG, colchicine

Improved at 72 hours

Discharged after 7 days

Recovered at 6 months

Asymptomatic 2 years later

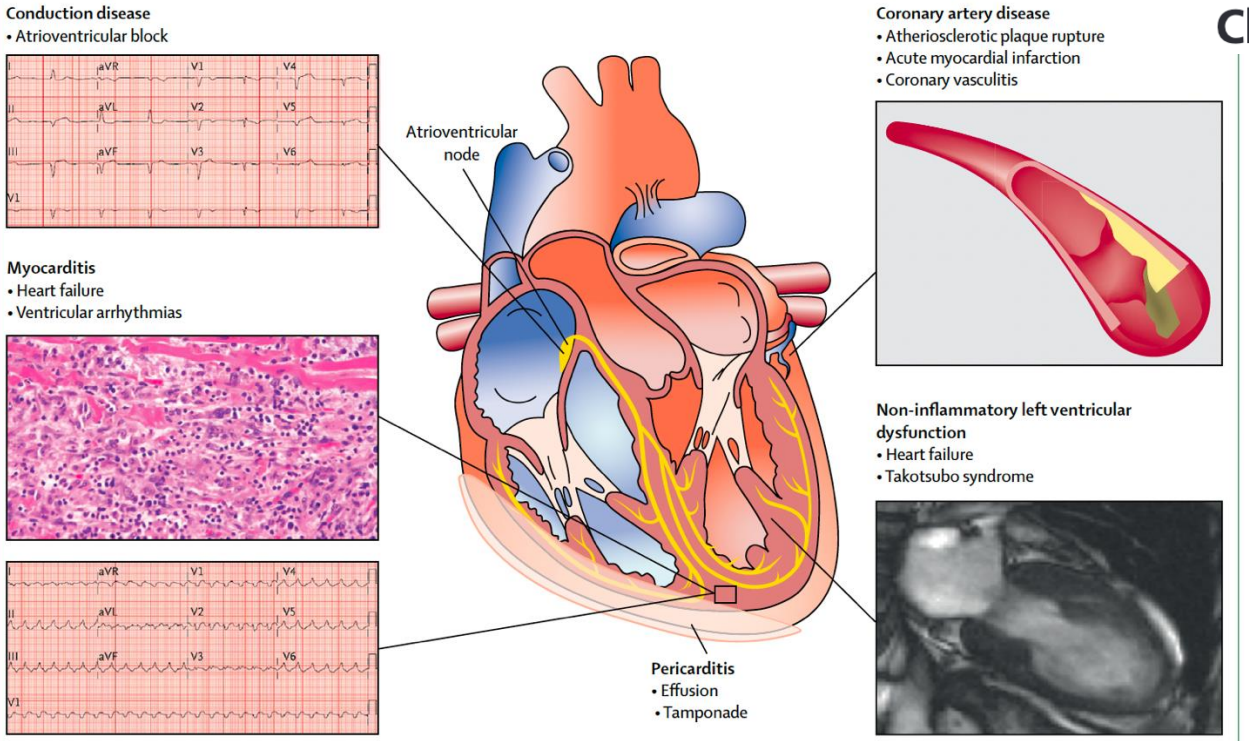
Five less common conditions you need to recognize:

Case #1: 65 yo M with metastatic lung cancer, admitted after a syncopal episode, found to have complete AV block, LVEF 50%, in cardiogenic shock

Immune checkpoint inhibitors and cardiovascular toxicity

Alexander R Lyon, Nadia Yousaf, Nicolò M L Battisti, Javid Moslehi, James Larkin

Lancet Oncol 2018



Panel 1: Potential risk factors for immune checkpoint inhibitor-related cardiotoxic effects

Treatment-related factors
- Dual immunotherapy (eg, ipilimumab and nivolumab)
- Combined immunotherapy and other cardiotoxic cancer therapy (eg, VEGF tyrosine kinase inhibitors)

Concurrent immune-related toxic effects
- Immune checkpoint inhibitor-related skeletal myositis

Previous cardiovascular disease with myocardial injury
- Myocardial infarction
- Heart failure
- Myocarditis
- Previous anthracycline chemotherapy
- Previous cancer therapy-induced left ventricular dysfunction

Previous autoimm
- Systemic lupus
- Rheumatoid art
- Sarcoidosis
- Dressler's syndr

Tumour-related fa
- Cardiac antigen
- Cardiac T-cell cl

Genetic factors
- Unknown

ESC European Society of Cardiology
European Heart Journal (2020) **41**, 1733–1743
doi:10.1093/eurheartj/ehaa051

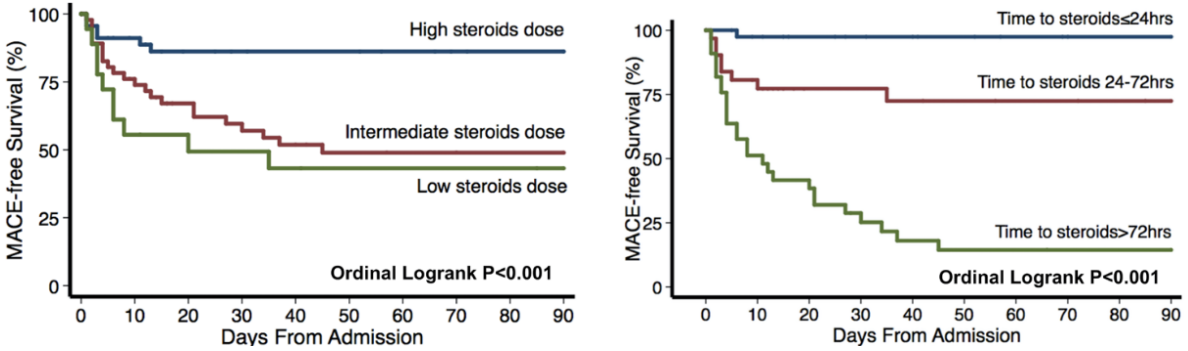
CLINICAL RESEARCH
Heart failure/cardiomyopathy

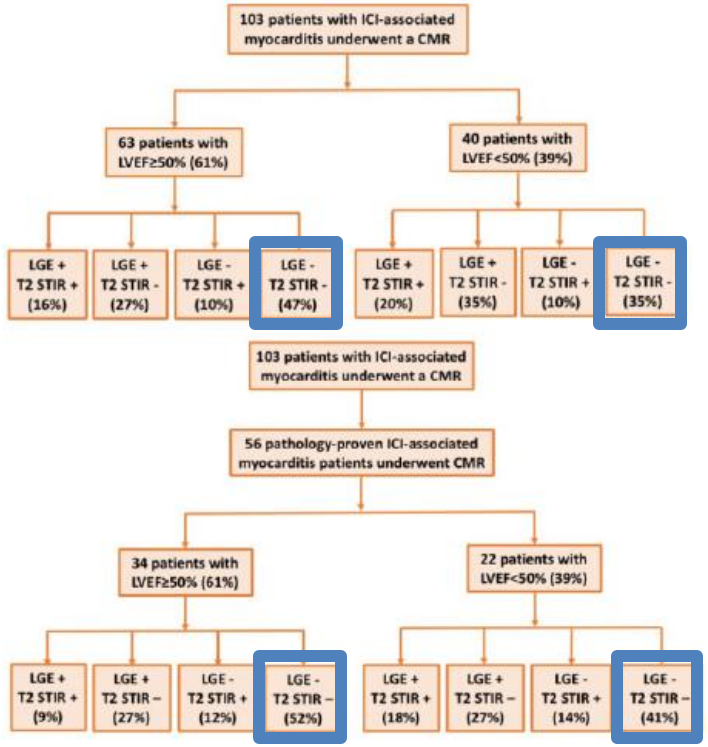
Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis

Lili Zhang [1,2], Magid Awadalla [1,2], Syed S. Mahmood [3], Anju Nohria [4], Malek Z.O. Hassan [1], Franck Thuny [5,6,7], Daniel A. Zlotoff [2], Sean P. Murphy [1], James R. Stone [8], Doll Lauren Alexandra Golden [1], Raza M. Alvi [1], Adam Rokicki [1,2], Maeve Jones-O'Connor [1], Justine V. Cohen [9],

RESEARCH LETTER Circulation

Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor–Associated Myocarditis





Five less common conditions you need to know:

Case #1: 65 yo M with metastatic lung cancer, admitted after a syncopal episode, found to have complete AV block, LVEF 50%, in cardiogenic shock

Immune checkpoint myocarditis

Take home messages:

1) Identify patients at risk (on treatment)
2) Recognize as high-risk for arrhythmias, shock and death
3) Use all clinical available data, don't rely on CMR or biopsy alone
4) Start high-dose steroids early
5) Look for other –it is as autoimmune manifestations
6) Enroll in clinical trials

Five less common conditions you need to know:

Case #2: 47 yo F with asthma presenting with chest pain and shortness of breath. On exam she has a diffuse maculopapular rash. ECG mildly abnormal, troponin mildly elevated, BNP severely elevated, LVEF normal, restrictive filling pattern at Doppler echocardiography.

Acute eosinophilic myocarditis

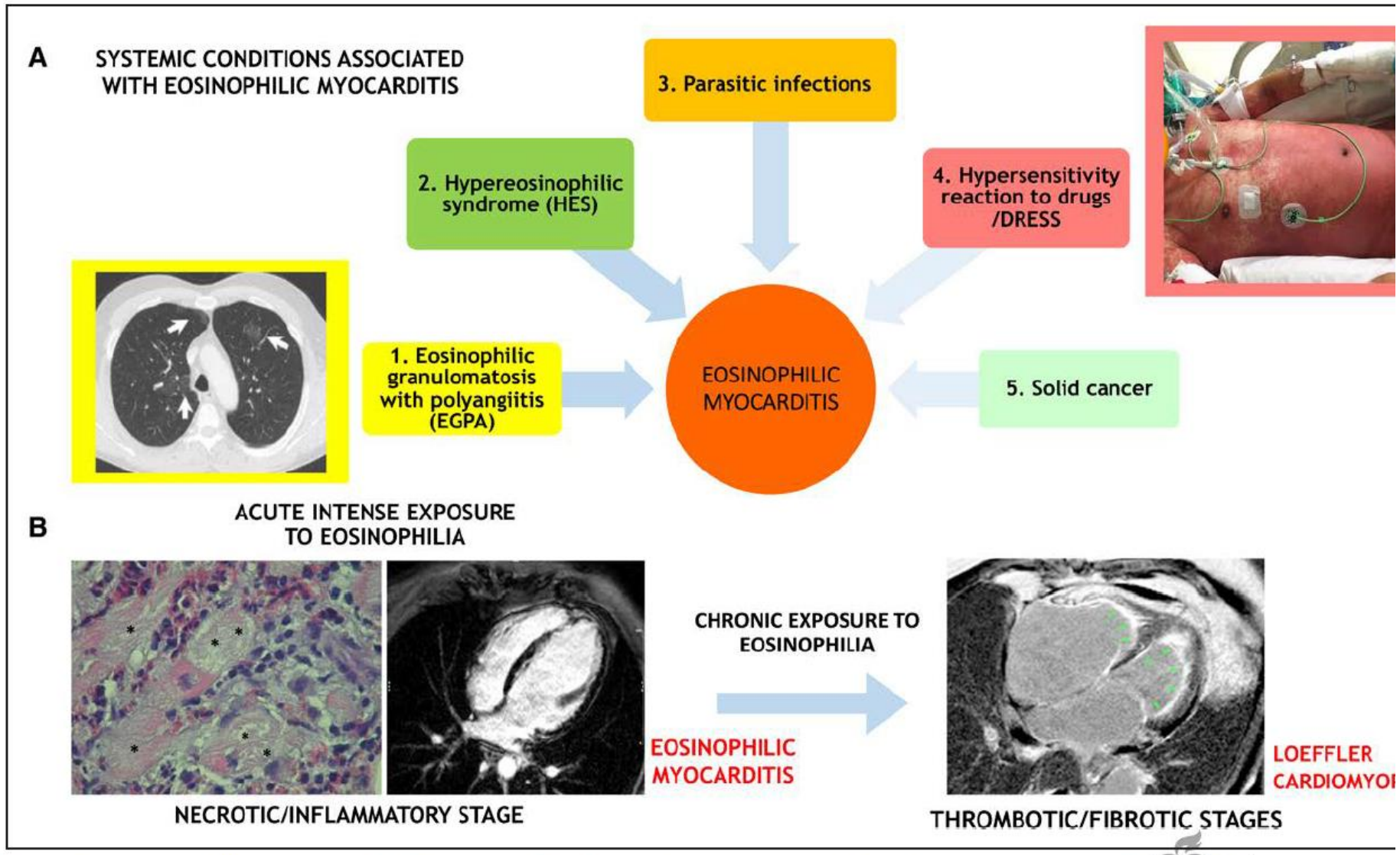


Figure 4. Eosinophilic myocardial injury: associated conditions and transition from acute myocarditis to inflammatory cardiomyopathy.

Key factors:

- Systemic illness (usually)
- Eosinophilia (>1.5K/mm^3, can be transient or absent)
- Rash (frequent, can be mild)
- Drug-related (occasionally)
- Sub-endo LGE (classic) with thrombus (common)

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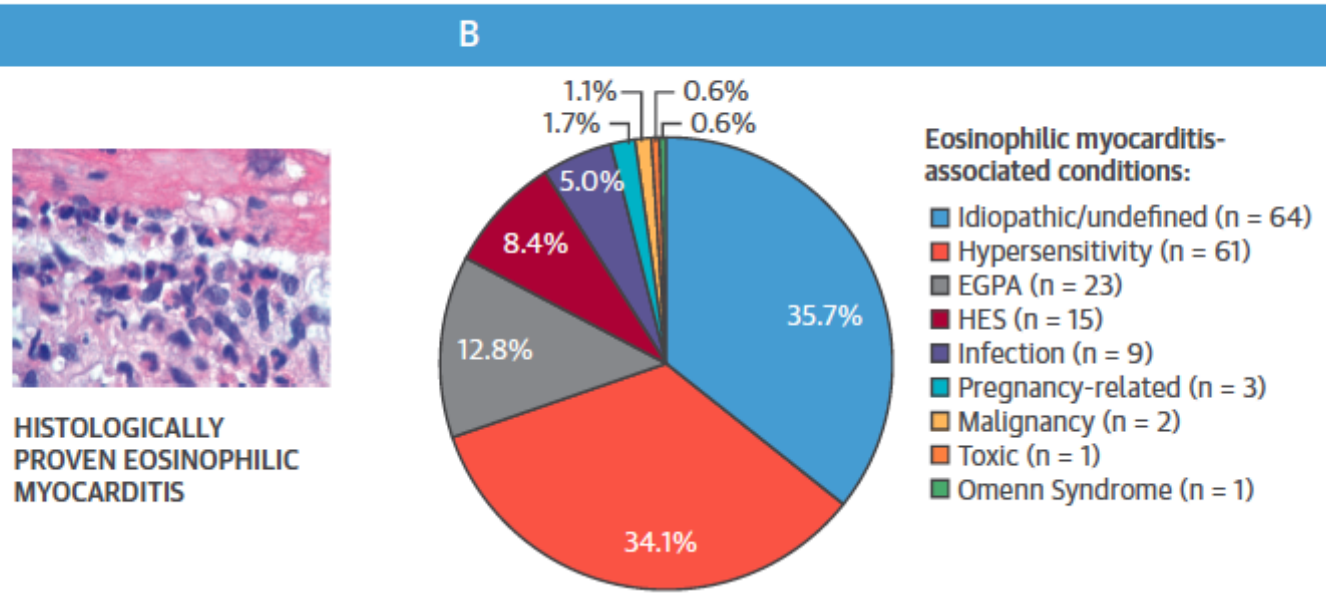
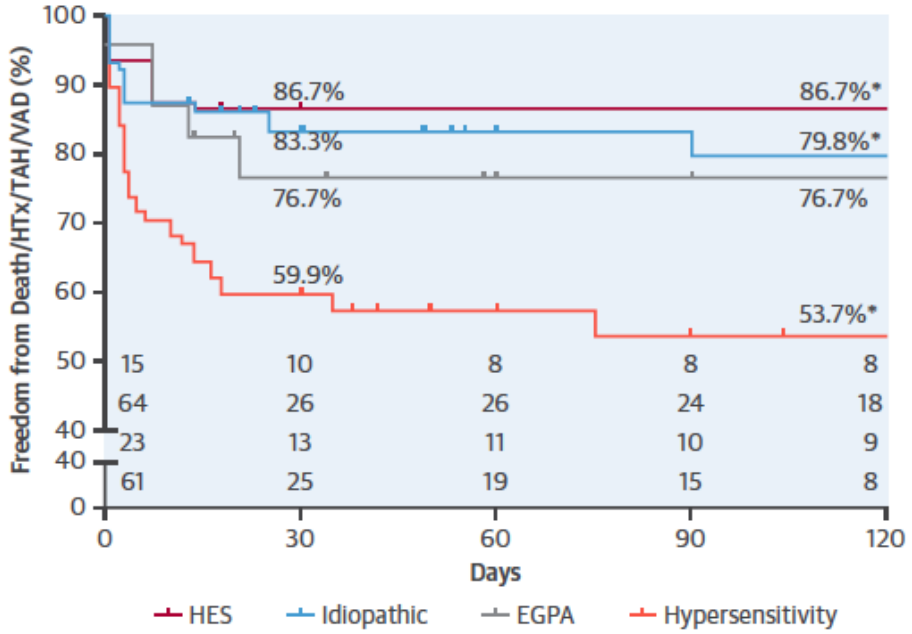
Eosinophilic Myocarditis

Characteristics, Treatment, and Outcomes

Michela Brambatti, MD,[a] Maria Vittoria Matassini, MD,[b] Eric D. Adler, MD,[a] Karin Klingel, MD,[c] Paolo G. Camici, MD,[d,e] Enrico Ammirati, MD, PhD[e,f]

CENTRAL ILLUSTRATION Prevalence and Outcome of Associated Systemic Conditions to Histologically Proven EM





Treatment: [no RCTs]

- Steroids
- Mechanical assist devices
- Targeted therapies
  - Mepolizumab
  - Imitanib

Five less common conditions you need to know:

Eosinophilic myocarditis

Case #2: 47 y
asthma prese
chest pain and
shortness of breath. On exam she has a diffuse rash. ECG mildly abnormal, troponin mildly elevated, BNP severely elevated, LVEF normal, restrictive filling pattern

Take home messages:
1) Identify patients at risk (eosinophilic diseases)
2) Look for peripheral eosinophilia (>1.5k)
3) Recognize as high-risk for complications
4) Consider EBM if unclear case
5) Start steroids early
6) Look for other manifestations
7) Consider targeted therapies (mepolizumab or imitanib)
8) Consider anticoagulants

Five less common conditions you need to know:

Eosinophilic myocarditis

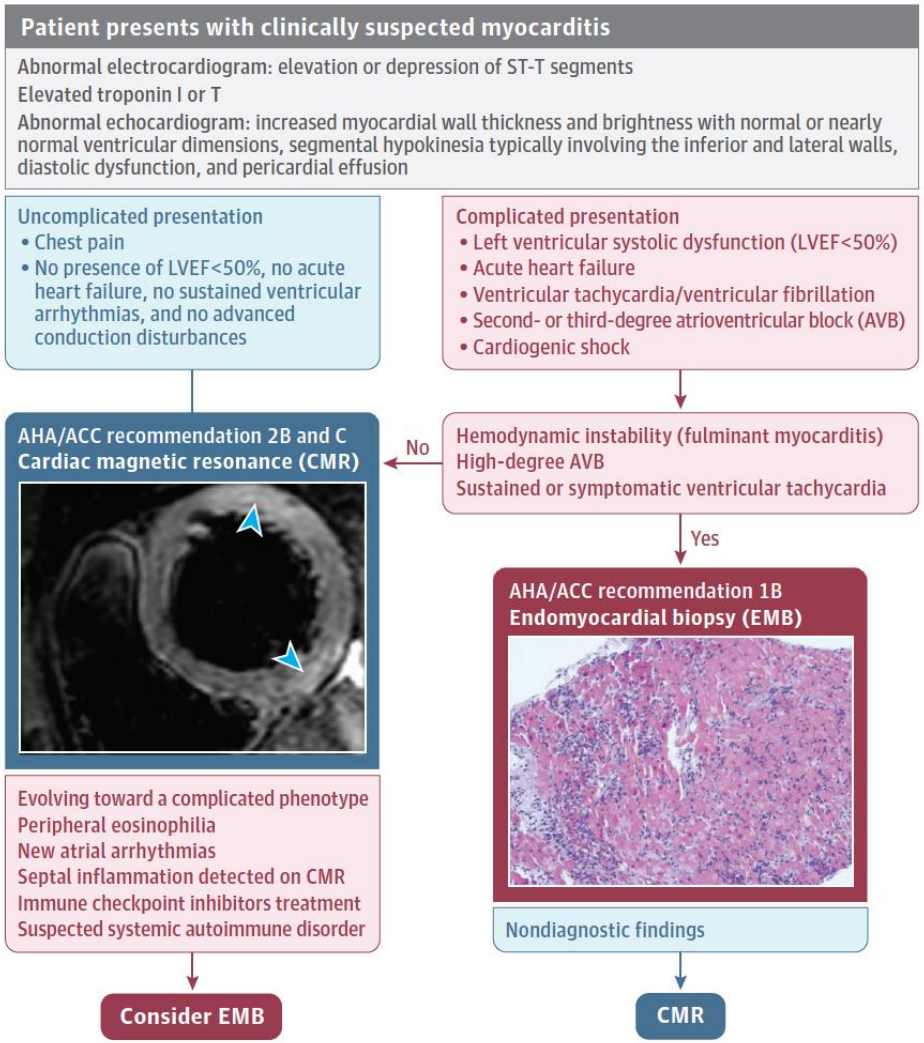
Immune checkpoint myocarditis

Case #3: 40 yo M presenting with new onset systolic heart failure and frequent non-sustained VTach. Shortly after the admission, he has an electrical storm and cardiac arrest, and he is now supported with VA-ECMO. The results of an endomyocardial biopsy arrive and a new treatment is started.

JAMA | Review

Diagnosis and Treatment of Acute Myocarditis
A Review

Enrico Ammirati, MD, PhD; Javid J. Moslehi, MD



The New England Journal of Medicine *N Engl J Med* 1997

IDIOPATHIC GIANT-CELL MYOCARDITIS — NATURAL HISTORY AND TREATMENT

LESLIE T. COOPER, JR., M.D., GERALD J. BERRY, M.D., AND RALPH SHABETAI, M.D.,
FOR THE MULTICENTER GIANT CELL MYOCARDITIS STUDY GROUP INVESTIGATORS*

Conclusions Giant-cell myocarditis is a disease of relatively young, predominantly healthy adults. Patients usually die of heart failure and ventricular arrhythmia unless cardiac transplantation is performed. Despite the possibility of fatal disease recurrence, transplantation is the treatment of choice for most patients. (N Engl J Med 1997;336:1860-6.)

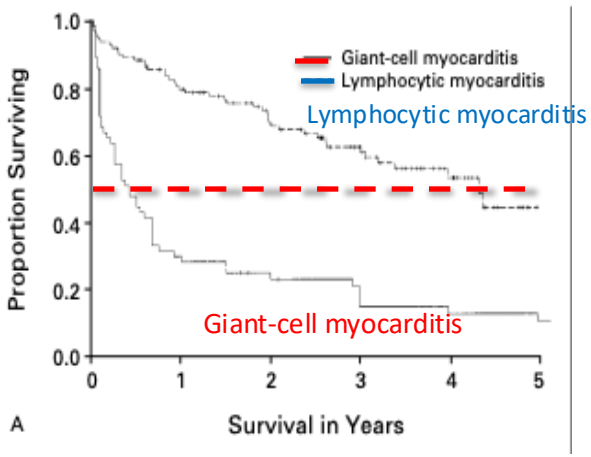


TABLE 2. THE EFFECT OF IMMUNOSUPPRESSION ON SURVIVAL IN PATIENTS WITH GIANT-CELL MYOCARDITIS.

PATIENT GROUP	NO. OF PATIENTS	MEDIAN SURVIVAL FROM SYMPTOM ONSET (MO)	P VALUE*
No immunosuppression	30	3.0	—
Corticosteroids alone	11	3.8	0.68
Corticosteroids plus azathioprine	11	11.5	0.025
Cyclosporine combination therapy†	10	12.6	0.003
All treatment groups except corticosteroids alone	22‡	12.3	0.001
All treatment groups including corticosteroids alone	33	8.2	0.014

†Cyclosporine was combined with corticosteroids (three patients), with corticosteroids and azathioprine (five patients), or with corticosteroids, azathioprine, and muromonab-CD3 (OKT3, two patients).

Five less common conditions you need to know:

Case #3: 40 yo M presenting with new onset systolic heart failure and frequent non-sustained VTach. Shortly after the admission, he has an electrical storm and cardiac arrest, and he is now supported with VA-ECMO. The results of an endomyocardial biopsy arrive and a new treatment is started.

Giant Cell Myocarditis

Take home messages:
1) Middle-age (both sexes)
2) Heart failure
3) Ventricular arrhythmias
4) Severely reduced LVEF
5) Diffuse LGE at CMR
6) Associated with autoimmune diseases or hematologic cancers
7) High mortality
8) Requires immuno-suppression (i.e. high dose steroids and cyclosporine or tacrolimus)

Five less common conditions you need to know:

Giant Cell Myocarditis

Eosinophilic myocarditis

Immune checkpoint myocarditis

Case #4: 55 yo F with shortness of breath and chest pain with deep breathing or lying flat. She reports also a rash on her cheeks, ulcers in her mouth, and diffuse joint pain. Her mother has systemic Lupus erythematosus and she is wondering if she has the same.

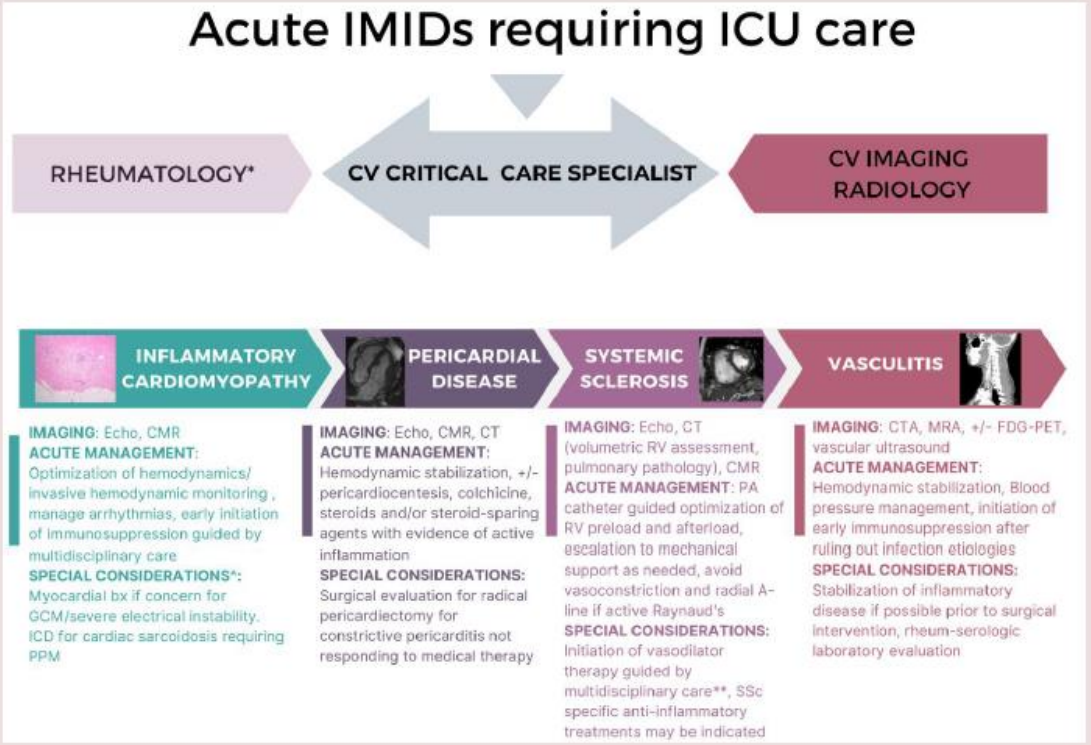
ESC European Society of Cardiology
European Heart Journal: Acute Cardiovascular Care (2023) **12**, 792–801
https://doi.org/10.1093/ehjacc/zuad096

EDUCATIONAL PAPER
General Intensive Care

Acute cardiovascular complications of immune-mediated systemic inflammatory diseases

Brittany N. Weber [1]*, Michael Garshick [2], Antonio Abbate[3], Taryn Youngstein [4], Garrick Stewart[1], Erin Bohula[1], Sven Plein [5], and Monica Mukherjee[6]

Graphical Abstract



Conceptual model of the role of multi-disciplinary care in patients with IMIDs who require ICU-level care. *If available, consider cardio-rheumatology consultation. **For pulmonary hypertension management, consider pulmonary vascular specialists as available. ^Advanced heart failure involvement for mechanical support and/or heart transplant evaluation.

Table 1 Acute cardiovascular manifestations of immune-mediated systemic inflammatory conditions: clinical biomarkers and immunosuppression

Cardiovascular manifestation	Laboratory markers	Medications/immunosuppression
Pericardial disease	hs-CRP, ESR, CBC with differential[a] *Disease-specific auto-antibodies:* •SLE: ANA[b], Smith, Ro/La (*SSA/SSB*), dsDNA, antiphospholipid antibodies[+] •RA: RF, anti-CCP •MCTD/SSc U1RNP, Scl-70, RNA polymerase III, Centromere antibodies or ANA in centromere pattern •EGPA: ANCA, myeloperoxidase, and proteinase 3 antibodies	*First-line*: high-dose NSAIDs, colchicine 0.6 mg BID •If refractory/recurrent and failed first-line: prednisone 0.2–0.5 mg/kg/day with a slow taper, IL-1 inhibition: anakinra 100 mg daily, rilonacept 320 mg loading × 1, then 160 mg weekly. *Autoimmune disease-specific* • methylprednisolone or prednisone 0.5–1 mg/kg, or pulse dose IV steroid for concomitant myocardial involvement or severe cases. • Steroid-sparing options: Azathioprine: start at 50 mg titrate to 1–2 mg/kg daily, MMF: 500 mg PO BID titrate to 1–1.5 g PO BID, IVIG: 2 g/kg over 3–5 days[5] **Caution for the use of steroids in SSc with pericarditis*
Inflammatory cardiomyopathy	hsTnT, NT-proBNP, hsCRP, ESR, CBC with differential *Cardiac sarcoidosis:* ACE level can be considered, but low sensitivity/specificity	*Cardiac sarcoid:* prednisone 0.5–1 mg/kg MTX 5–15 mg PO/weekly, or MMF dosing as above. Anti-TNF therapy (infliximab or adalimumab) is used for refractory disease or as steroid-sparing therapy. *Giant cell myocarditis:* Multidrug immunosuppression, typically high-dose corticosteroids with cyclosporine or tacrolimus. ATG or alemtuzumab for refractory disease. *EGPA:* High-dose corticosteroids, often with cyclophosphamide, MMF for maintenance therapy. Mepolizumab may be added for eosinophilic mediated manifestations[6]
Systemic sclerosis (Scleroderma)	Auto-antibodies: RNA polymerase III, Centromere antibodies, or ANA in centromere pattern	Immunosuppression guided by organ manifestations includes MTX, MMF, AZA, and cyclosporine. Steroids are avoided, given the increased risk of precipitating scleroderma renal crisis. *SSc Subtype:* • SSc-active Raynaud's, microvascular coronary disease: Amlodipine, Nifedipine +|– long-acting nitrates, Sildenafil • SSc-acute myocarditis: immunosuppressants +|– steroids • Group 1 SSc-PAH: upfront combination therapy (PDE5 + ERA) • Group 2 SSc-PVH: preliminary data for SGLT-2 and MRA in SSc-HFpEF, SSc-HFrEF without inflammation, standard GDMT • Group 3 SSc-ILD-PH: standard immunosuppressant therapy (MMF or cyclophosphamide) +|– biological and antifibrotic therapies
Vasculitis	hs-CRP, ESR, CBC with differential[a] [%] Disease-specific antibodies as above plus Immune complex: IgA, anti-GBM, IgG4 level, HLA B51 (Bechet's), cryoglobulins, complement, RF, hepatitis serologies	General management for most vasculitides includes medium to high-dose corticosteroids as induction therapy with the addition of DMARD/biologic for maintenance as guided by the disease. *Disease-specific treatments:* • ANCA-associated vasculitis: induction with steroids, cyclophosphamide (15 mg/kg), and rituximab with maintenance regimens defined by subtype.[7] • Kawasaki: IVIG 2 g/kg over 3–5 days[8]

Journal of the American Heart Association 2024

CONTEMPORARY REVIEW

Cardiac Involvement in Patients With Multisystem Inflammatory Syndrome in Adults

Giulia La Vecchia, MD*; Marco Giuseppe Del Buono, MD*; Aldo Bonaventura, MD, PhD; Alessandra Vecchiè, MD; Francesco Moroni, MD; Iside Cartella, MD; Gianluigi Saponara, MD; Michael J. Campbell, MD, PhD; Lorenzo Dagna, MD; Enrico Ammirati, MD, PhD; Tommaso Sanna, MD, PhD; Antonio Abbate, MD, PhD

Key points

- Infection active or recent, or suspected
- Hyperinflammatory syndrome
  - CRP, Ferritin, etc.. very high!!!
- Myocarditis (and/or pericarditis)

Box 1 Centers for Disease Control and Prevention case definition of multisystem inflammatory syndrome in adults

1. Documented fever (≥38°C) for ≥24 hours prior to hospitalisation or within first 3 days of hospitalisation.
2. Meet at least three clinical criteria (atleast one must be a primary clinical criterion).
   a. Primary clinical criteria
      1. Severe cardiac illness (ie, myocarditis, pericarditis, ejection fraction <50%).
      2. Rash and non-purulent conjunctivitis.
   b. Secondary clinical criteria
      1. New-onset neurological symptoms (ie, seizures, meningeal signs).
      2. Shock or hypotension.
      3. Abdominal pain, vomiting, diarrhoea.
      4. Thrombocytopenia (platelet count $<150\times10^9$/L).
3. Meet laboratory evidence criteria
   a. Elevated levels of atleast two of the following: C reactive protein, ferritin, interleukin-6, erythrocyte sedimentation rate, procalcitonin.
   b. A positive COVID-19 test via RT-PCR, serology or antigen detection.

Five less common conditions you need to know:

Giant Cell Myocarditis

Myocarditis as part of IMIDs

Eosinophilic myocarditis

Immune checkpoint myocarditis

#4: 55 yo F with
tness of breath and
t pain with deep

Take home messages:

1) Complete history and physical exam are necessary
2) Need to identify systemic inflammatory symptoms and signs
3) Requires rheumatological work-up for diagnosis and disease-specific management of the different organ involvement
4) Generally treated with prednisone or other glucocorticoids and steroid-sparing agents

Five less common conditions you need to know:

Giant Cell Myocarditis

Myocarditis as part of IMIDs

Eosinophilic myocarditis

Immune checkpoint myocarditis

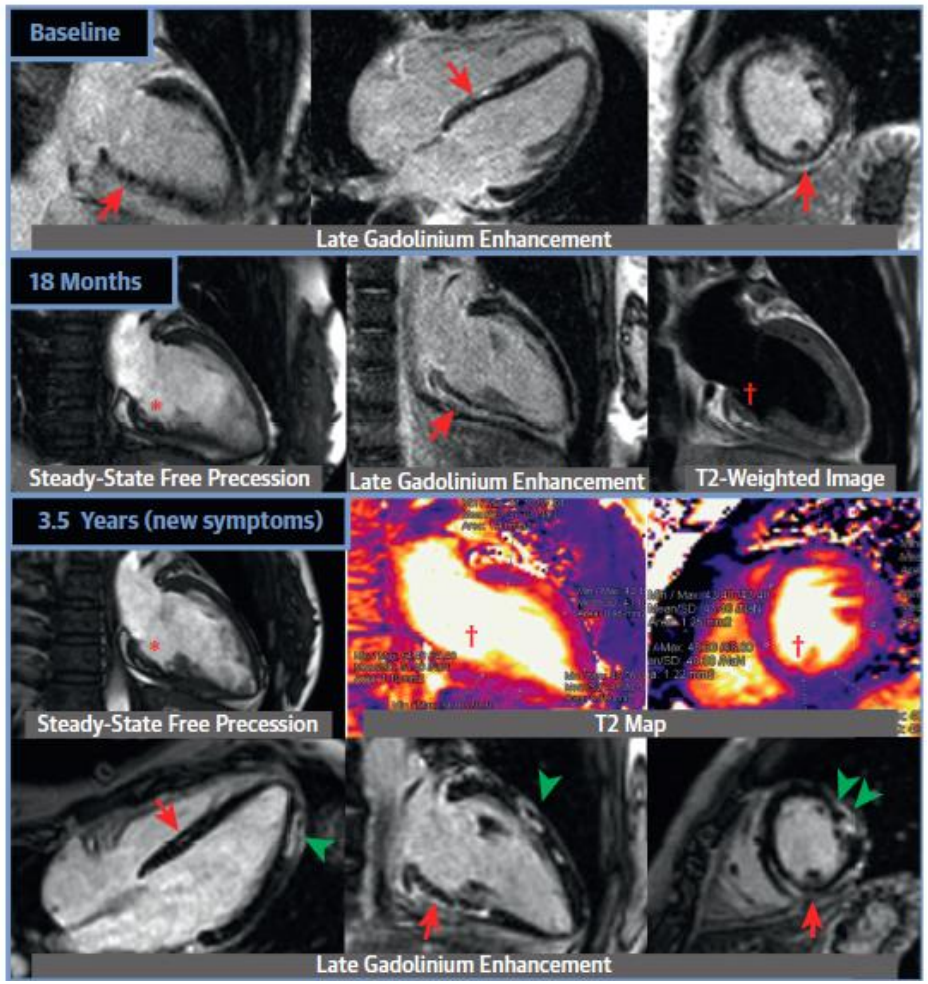
Case #5: 25 yo F with chest pain and shortness of breath after a presumed upper respiratory illness. She has low-grade fever, vitals otherwise normal, troponin I and BNP mildly elevated, LVEF 50% at echocardiogram, NSVT on telemetry, the CMR shows a ring-like mid-wall LGE.

Inflammatory Episodes of Desmoplakin Cardiomyopathy Masquerading as Myocarditis

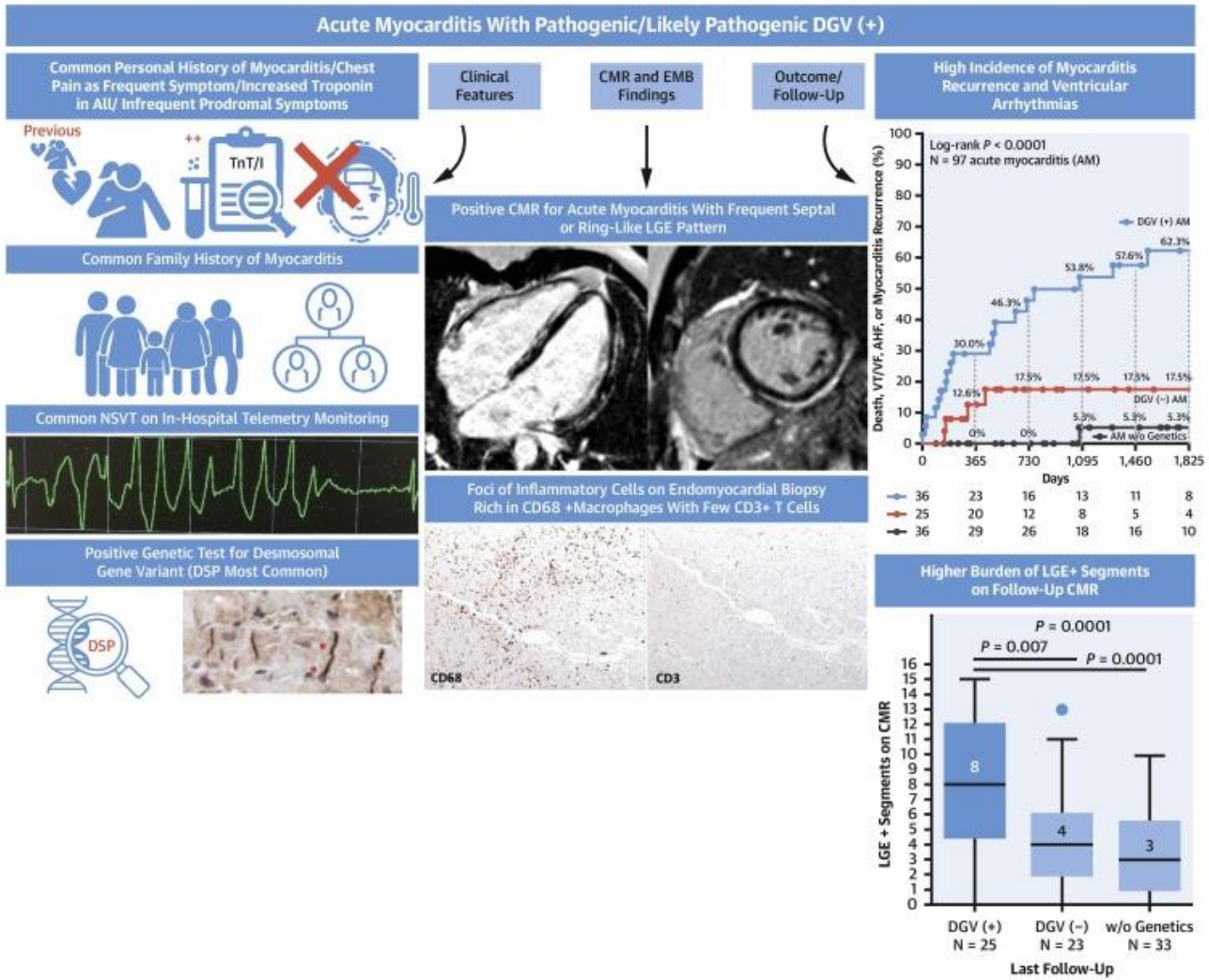
JACC Cardiovasc Imaging

Unique Features on Cardiac Magnetic Resonance Imaging

Reid Alley, MD,[a] John D. Grizzard, MD,[b] Krishnasree Rao, MD,[c] Roshanak Markley, MD,[c] Cory R. T



CENTRAL ILLUSTRATION: Myocarditis Recurrence and Ventricular Arrhythmias in Patients With Acute Myocarditis Associated With Desmosomal Gene Variants



Ammirati E, et al. J Am Coll Cardiol HF. 2022;10(10):714–727.

Five less common conditions you need to know:

Take home messages:

1) Young age, both sexes
2) Often recurrent, multiple episodes possibly triggered by (or presenting as) viral illnesses
3) Family history of myocarditis or cardiomyopathy can be present, but can be sporadic
4) Associated with ventricular arrhythmias and requires prophylactic ICD placement
5) Abnormal MRI – patchy or ring-like LGE
6) Often progressive and worsening at each flare
7) Possible role of anti-inflammatory treatments (i.e. prednisone, CellCept, IL-1 blockers)

Myocarditis associated with DSP mutations

Five less common conditions you need to recognize:

Giant Cell Myocarditis

Myocarditis as part of IMIDs

Eosinophilic myocarditis

Myocarditis associated with DSP mutations

Immune checkpoint myocarditis

Thanks for your attention – spread the word!

LEARNING GOALS

1) Inflammation and cardiovascular diseases
2) Management of myocarditis
3) **Management of pericarditis**
4) Inflammatory component of the cardiovascular risk
5) Inflammatory component of heart failure

QUESTION #1

A 65 yo M is seen in ED and diagnosed with acute pericarditis. He was treated with ibuprofen with improvement of symptoms. He is now seen in the cardiology clinic after 3 months with recurrent pericarditis. Which of the following treatment should be instituted?

a) NSAIDs and colchicine
b) NSAIDs, colchicine and steroids
c) Colchicine, steroids and IL-1 blockers
d) Colchicine and IL-1 blockers
e) All the combinations listed of the above

QUESTION #2

Which of the following **treatments** target the **inflammasome pathway** and have been shown to reduce pericarditis complications in **randomized clinical trials**?

a) NSAIDs and colchicine
b) NSAIDs, colchicine and steroids
c) Colchicine, steroids and IL-1 blockers
d) Colchicine and IL-1 blockers
e) All the combinations listed of the above

QUESTION #3

Same patient …
Starts colchicine and ibuprofen, but continues to have pain
The ECG shows minor abnormalities, the echocardiogram shows a small effusion, CRP is 1.5 mg/dl (n.v. < 0.3), a cardiac MRI shows pericardial LGE:
Which treatment next?

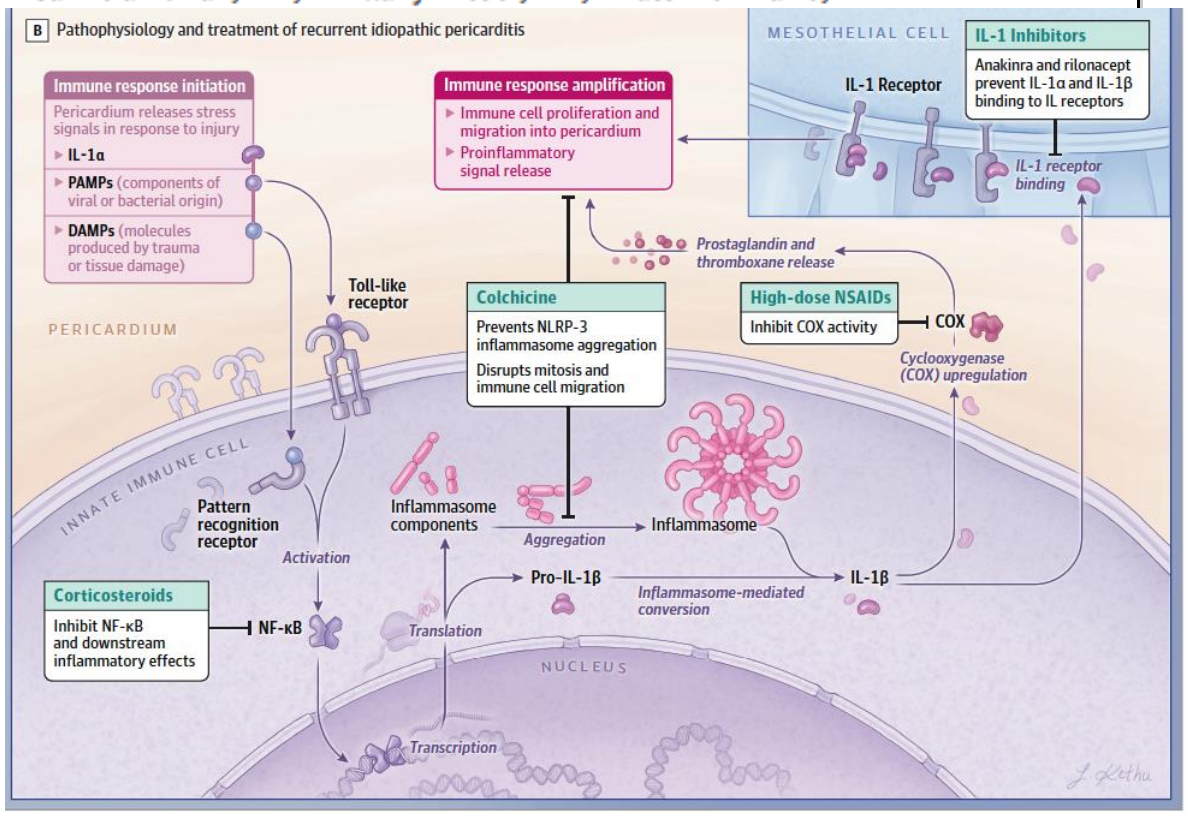
a) Continue NSAIDs and colchicine
b) Continue NSAIDs, colchicine and add steroids
c) Stop other meds and add steroids
d) Continue colchicine and add IL-1 blockers
e) None of the combinations above

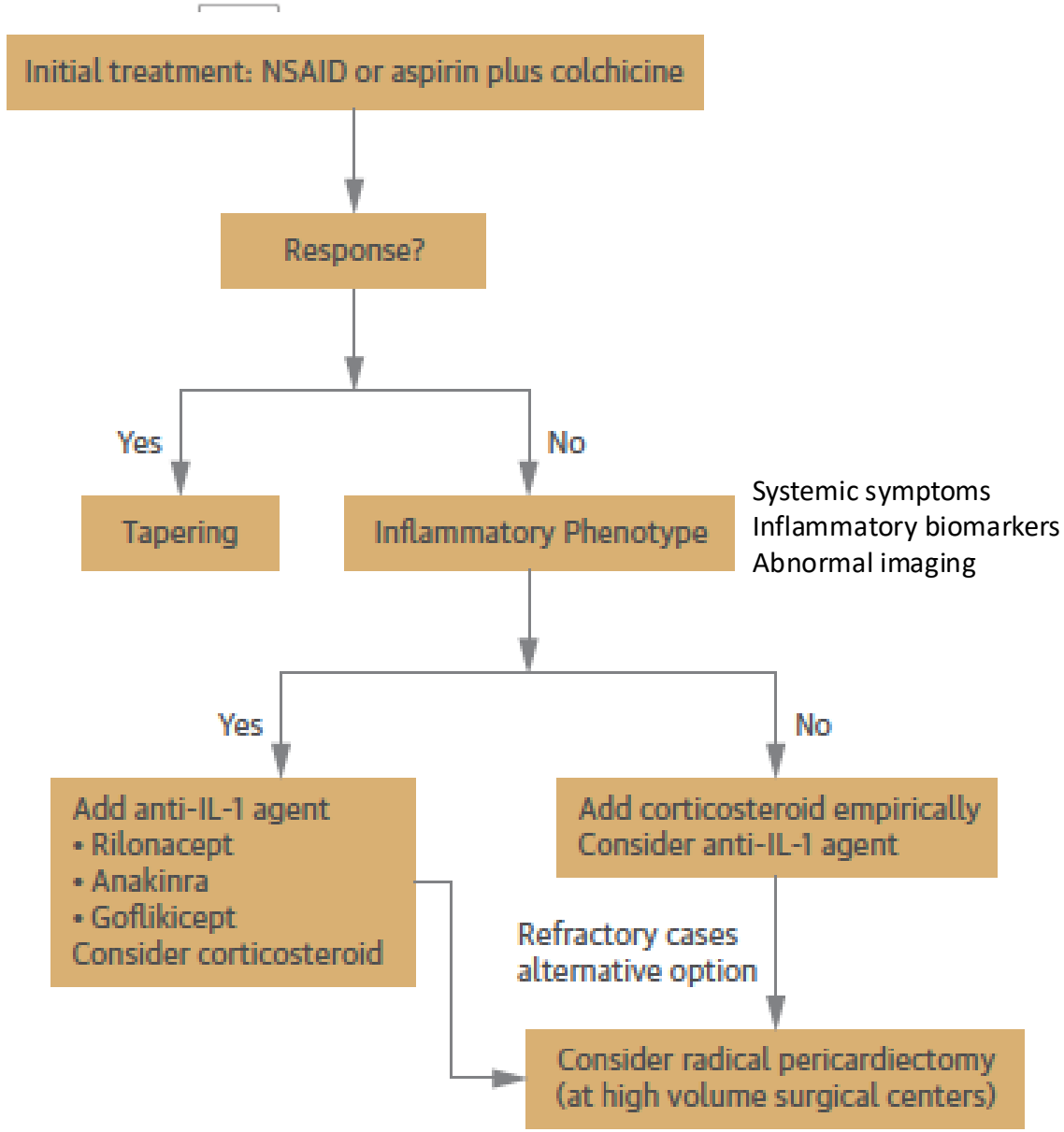
Pericardial Diseases

International Position Statement on New Concepts and Advances in Multimodality Cardiac Imaging

Endorsed by American College of Cardiology Imaging Council and Society of Cardiac M

Allan L. Klein, MD,[a,*] Tom Kai Ming Wang, MBChB, MD,[a,*] Paul C. Cremer, MD,[b,*] A
Yehuda Adler, MD,[d] Craig Asher, MD,[e] Antonio Brucato, MD,[f] Michael Chetrit, MD,[g]
Christine L. Jellis, MD, PhD,[a] Deborah H. Kwon, MD,[a] Martin LeWinter, MD,[i] David Li
Vartan Mardigyan, MD,[l] Jae K. Oh, MD,[k] Karen G. Ordovas, MD,[m] E. Rene Rodriguez,
Carmela D. Tan, MD,[n] Brittany Weber, MD,[p] Massimo Imazio, MD[q,r,*]

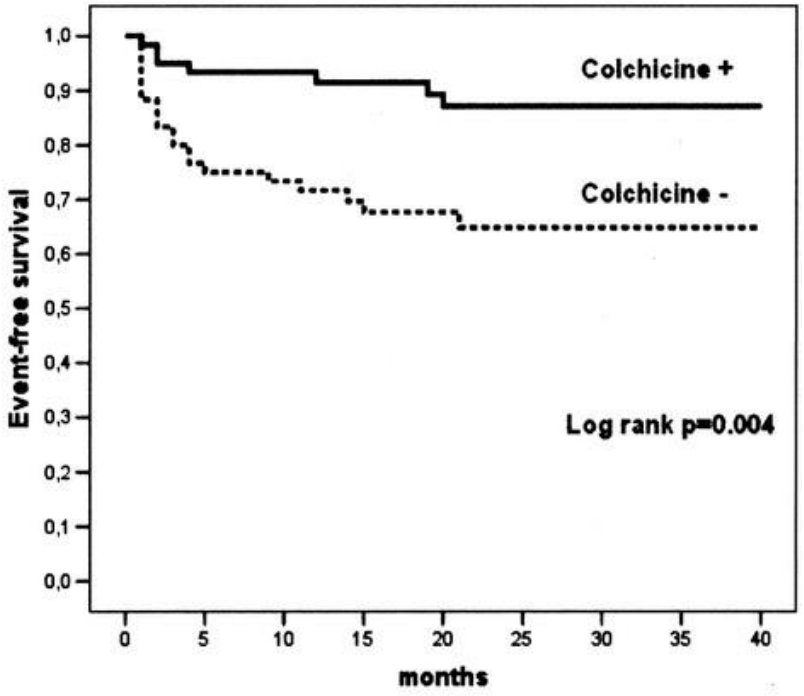




Colchicine for treatment and 1st line for acute pericarditis

COPE trial

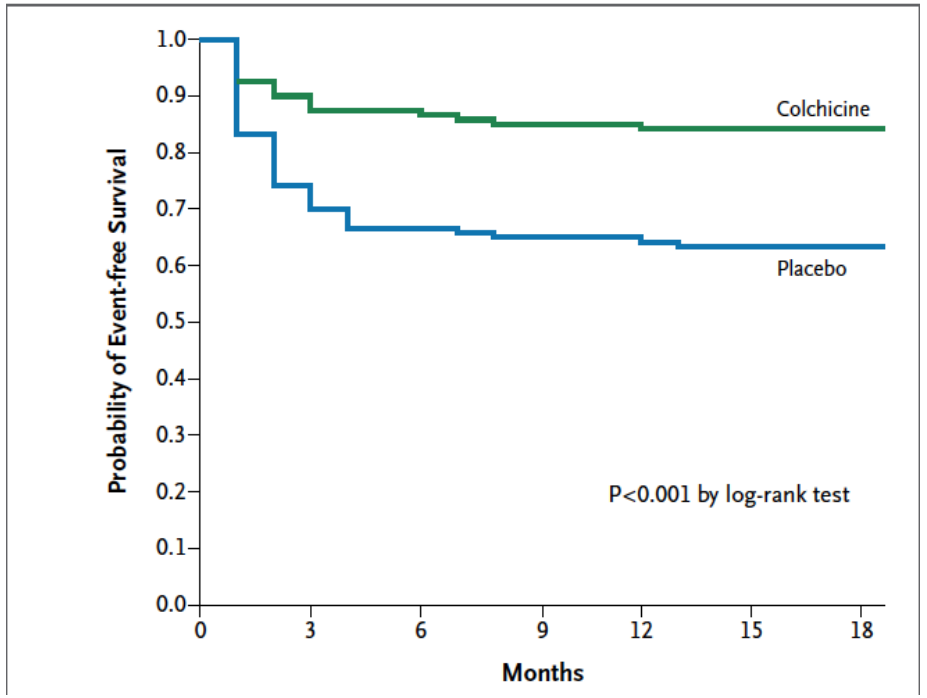
120 patients at first episode of acute pericarditis (idiopathic, viral, post-cardiac injury, connective tissue disease) randomized to Aspirin vs Aspirin + Colchicine 1.0-2.0 mg for the first day and then 0.5-1 mg for 3 months



Imazio. *et al.*, Circulation 2005

ICAP trial

240 patients at first episode of acute pericarditis (idiopathic, viral, post-cardiac injury, connective tissue disease) randomized to Colchicine 0.5-1 mg or placebo daily for 3 months on top of standard of care

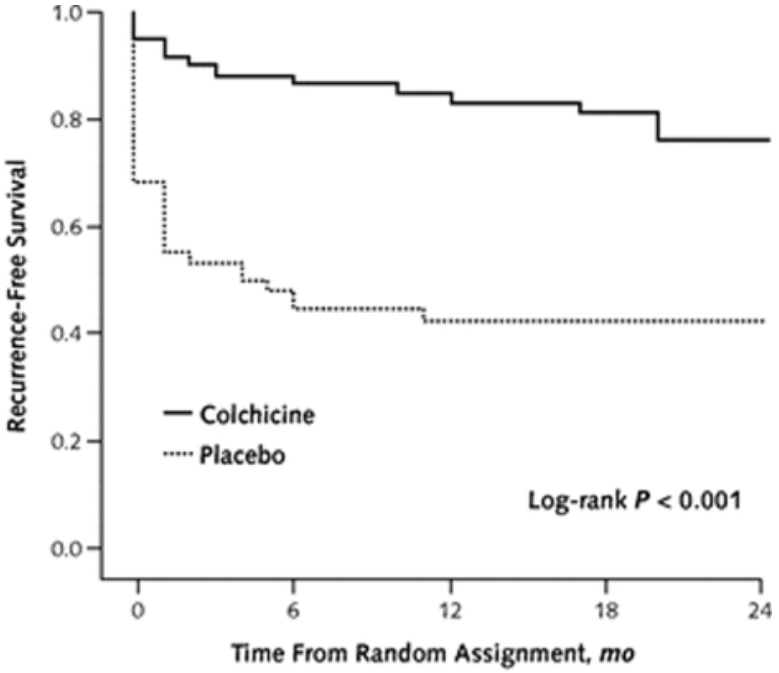


Imazio. *et al.*, N Engl J Med 2013

Colchicine for treatment and 1st line for recurrent pericarditis

CORP trial

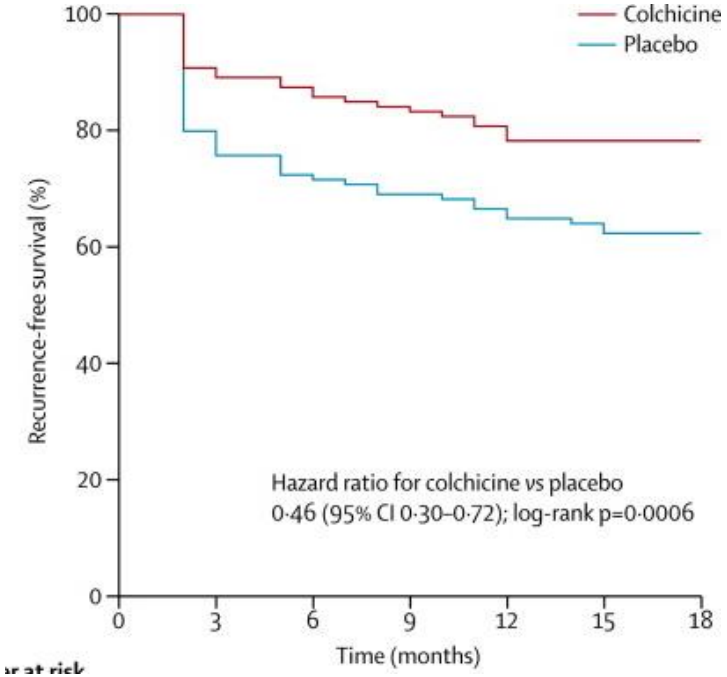
120 patients at first recurrence of acute pericarditis (idiopathic, viral, post-cardiac injury, connective tissue disease) randomized to conventional NSAIDs treatment alone vs the addition of Colchicine 1.0-2.0 mg for the first day and then 0.5-1 mg for 6 months



Imazio. *et al.*, Ann Intern Med 2011

CORP2 trial

120 patients with multiple recurrence of acute pericarditis (idiopathic, viral, post-cardiac injury, connective tissue disease) randomized to conventional NSAIDs treatment alone vs the addition of Colchicine 1.0-2.0 mg for the first day and then 0.5-1 mg for 6 months

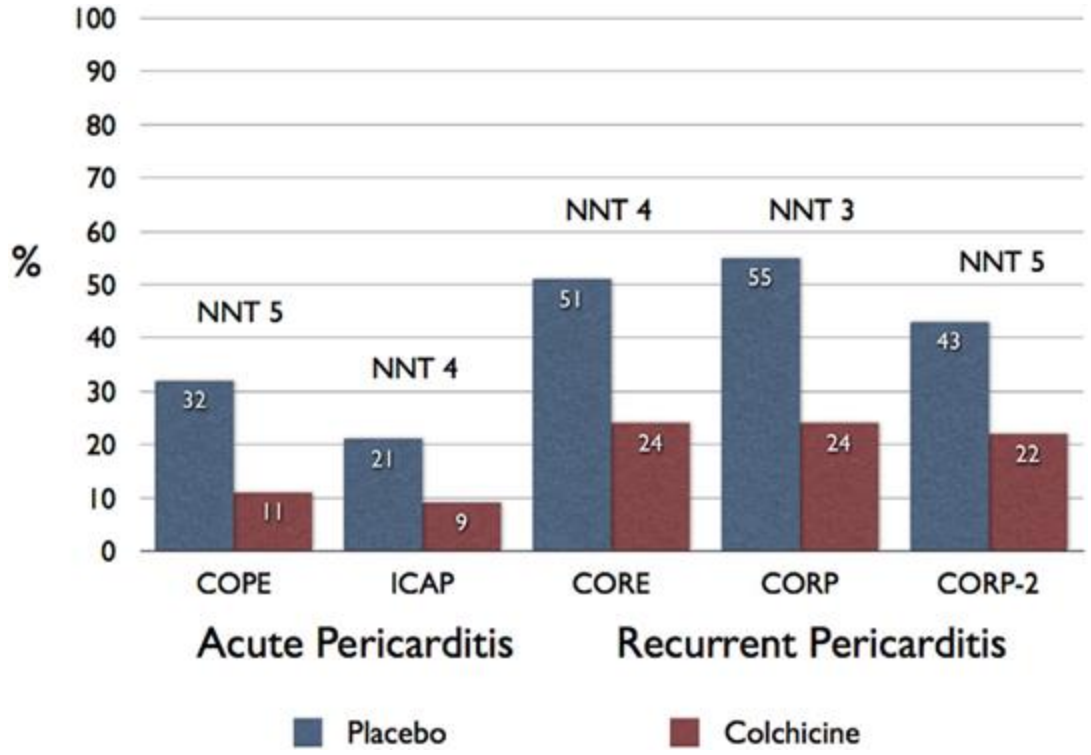


Imazio. *et al.*, Lancet 2014

Colchicine is central to the treatment of acute and recurrent pericarditis

While pericarditis pain improves with **NSAIDs** in most patients, NSAIDs alone are an insufficient treatment for acute pericarditis

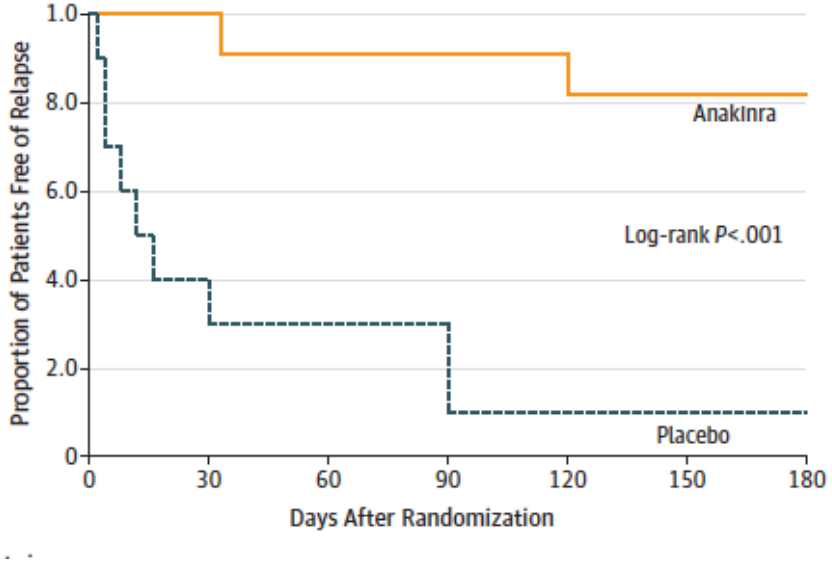
Colchicine, an old anti-inflammatory drug considered to act by inhibiting the polymerization of microtubules and aggregation of the NLRP3 inflammasome has shown to drastically reduce the risk of pericarditis recurrence and complications



IL-1 blockers to treat recurrent pericarditis and prevent recurrences

AIRTRIP trial

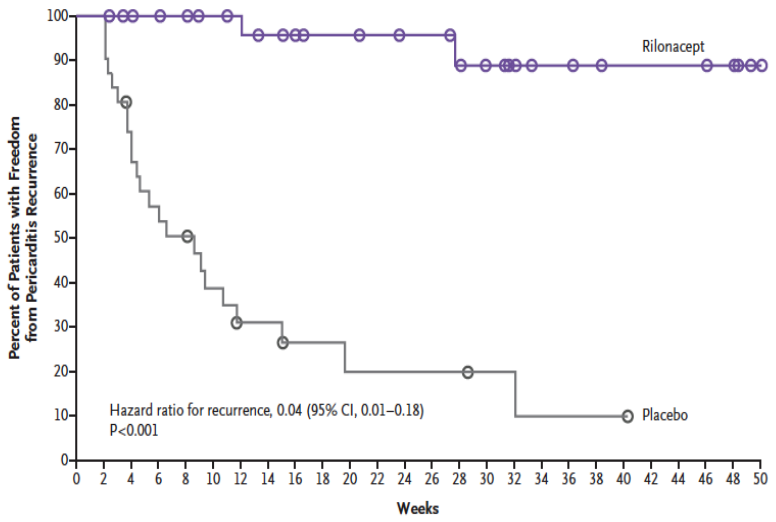
21 patients with recurrent pericarditis, resistant to colchicine and corticosteroid – dependent, treated with anakinra 100 mg daily and then when in remission randomized to continuation of anakinra or placebo



Brucato et al. *JAMA* 2016

RHAPSODY trial

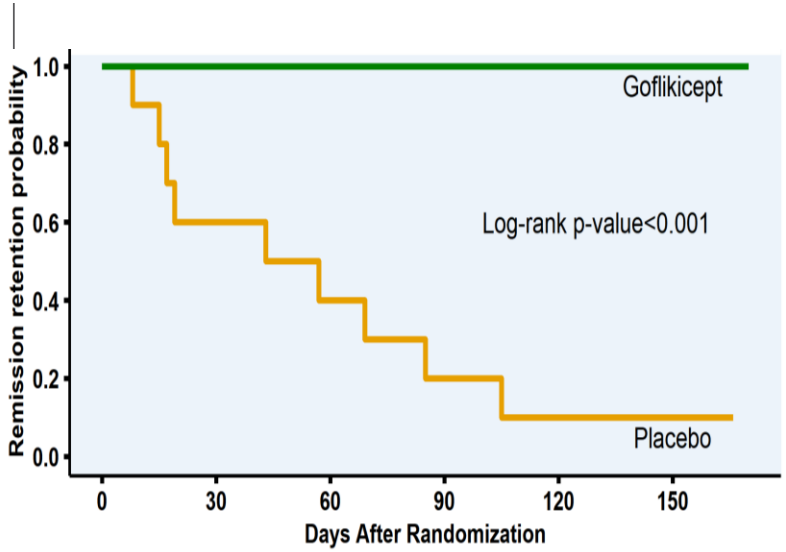
61 patients with recurrent pericarditis, treated with rilonacept 320 mg load and then 160 mg weekly and then when in remission randomized to continuation of rilonacept or placebo



Klein et al. *N Engl J Med* 2021

Goflikicept trial

20 patients with recurrent pericarditis, treated with goflikicept load and maintenance and then when in remission randomized to continuation of goflikicept or placebo



Myachikova et al. *J Am Coll Cardiol* 2023

As of 2021, Rilonacept is FDA approved for the treatment of recurrent pericarditis

- Treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years and older (1.3, 14.3)

QUESTION #1

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LEARNING GOALS

1) Inflammation and cardiovascular diseases
2) Management of myocarditis
3) Management of pericarditis
4) **Inflammatory component of the cardiovascular risk**
5) Inflammatory component of heart failure

QUESTION #1

Which of the following biomarkers predict atherothrombotic complications in patients with suspected acute coronary syndromes?

a) Low-density lipoprotein cholesterol (LDLc)
b) Cardiac specific troponin (cTn)
c) C reactive protein (CRP)
d) All of the above

How many of you measure CRP in patients with acute coronary syndromes?

QUESTION #2

Which of the following anti-inflammatory drugs are FDA-approved to reduce recurrent cardiovascular events in secondary prevention?

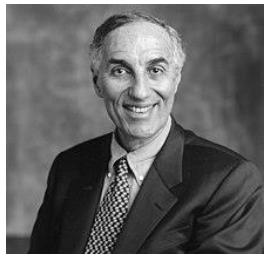
a) Statins
b) Colchicine
c) Steroids
d) Canakinumab
e) A and B

How many of you use colchicine to prevent recurrent events?

Atherosclerosis: an inflammatory disease

Russell Ross – *N Engl J Med* 1999

quoted >33,000 times



The New England Journal of Medicine

TABLE 1. CHARACTERISTICS OF ATHEROSCLEROSIS AND OTHER CHRONIC INFLAMMATORY DISEASES.*

DISEASE	MONOCYTES AND MACROPHAGES	LYMPHOCYTES	GRANULOCYTES	CONNECTIVE-TISSUE CELLS	EXTRACELLULAR MATRIX	PATHOGENETIC MECHANISMS	STUDIES
Atherosclerosis	+	+	−	Smooth-muscle cells	Collagen types I, III, and IV, elastin, fibronectin, proteoglycan	Endothelial-cell injury and dysfunction; fibrous cap; new matrix formation and degradation; necrotic core	Ross,[9] Libby and Hansson,[109] Ross and Fuster[110]
Cirrhosis	+	+	−	Fibroblasts, Ito cells	Collagen types I and III	Parenchymal-cell injury; new matrix and scarring replacing necrotic parenchyma	Maher,[111] Anthony et al.[112]
Rheumatoid arthritis	+	+	+/−	Synovial fibroblasts	Collagen types I and III, fibronectin, proteoglycan	Synovial-cell injury; erosion of cartilage; new matrix scarring (pannus)	Sewell and Trentham,[113] Harris [114]
Glomerulosclerosis	+	+	−	Mesangial cells	Collagen types I and IV, fibronectin	Epithelial- and endothelial-cell injury and dysfunction; decrease in glomerular filtration; new matrix formation	Johnson,[115] Magil and Cohen[116]
Pulmonary fibrosis	+	+	+/−	Smooth-muscle cells, fibroblasts	Collagen types III and IV, fibronectin	Inflammatory exudate in alveoli and bronchi, organized by extensive matrix deposition and scarring	Kuhn et al.,[117] Lukacs and Ward,[118] Brody et al.[119]
Chronic pancreatitis	+	+	−	Fibroblasts	Collagen, fibronectin, proteoglycan	Epithelial (ductal) injury; periductal inflammation; interstitial fat necrosis; new matrix formation	Sarles et al.,[120] DiMagno et al.[121]

*Plus signs denote the presence of a cell type, and minus signs its absence.

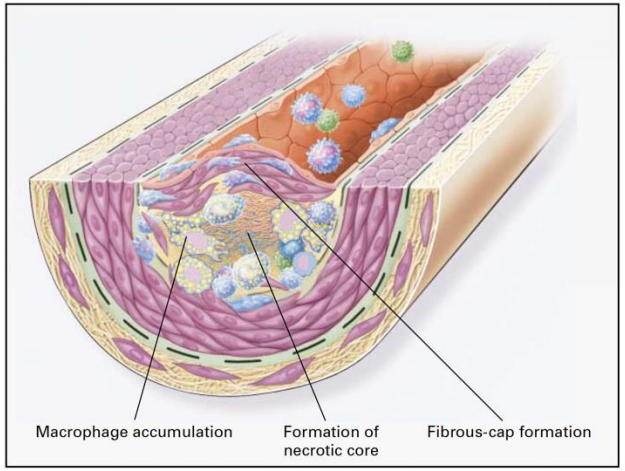


Figure 3. Formation of an Advanced, Complicated Lesion of Atherosclerosis.

As fatty streaks progress to intermediate and advanced lesions, they tend to form a fibrous cap that walls off the lesion from the lumen. This represents a type of healing or fibrous response to the injury. The fibrous cap covers a mixture of leukocytes, lipid, and debris, which may form a necrotic core. These lesions expand at their shoulders by means of continued leukocyte adhesion and entry caused by the same factors as those listed in Figures 1 and 2. The principal factors associated with macrophage accumulation include macrophage colony-stimulating factor, monocyte chemotactic protein 1, and oxidized low-density lipoprotein. The necrotic core represents the results of apoptosis and necrosis, increased proteolytic activity, and lipid accumulation. The fibrous cap forms as a result of increased activity of platelet-derived growth factor, transforming growth factor β, interleukin-1, tumor necrosis factor α, and osteopontin and of decreased connective-tissue degradation.

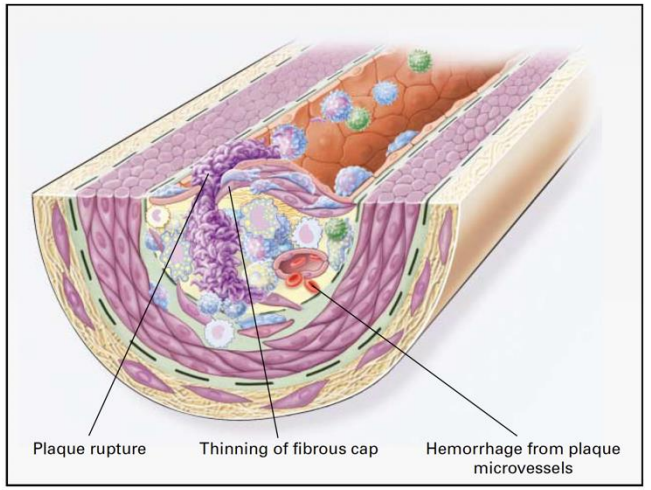


Figure 4. Unstable Fibrous Plaques in Atherosclerosis.

Rupture of the fibrous cap or ulceration of the fibrous plaque can rapidly lead to thrombosis and usually occurs at sites of thinning of the fibrous cap that covers the advanced lesion. Thinning of the fibrous cap is apparently due to the continuing influx and activation of macrophages, which release metalloproteinases and other proteolytic enzymes at these sites. These enzymes cause degradation of the matrix, which can lead to hemorrhage from the vasa vasorum or from the lumen of the artery and can result in thrombus formation and occlusion of the artery.

The NLRP3 inflammasome provides the link between atherogenesis and atherothrombosis

- Cholesterol crystals induce the NLRP3 inflammasome which in turns activates IL-1β
- IL-1β promotes local and systemic inflammatory changes favoring atherothrombosis

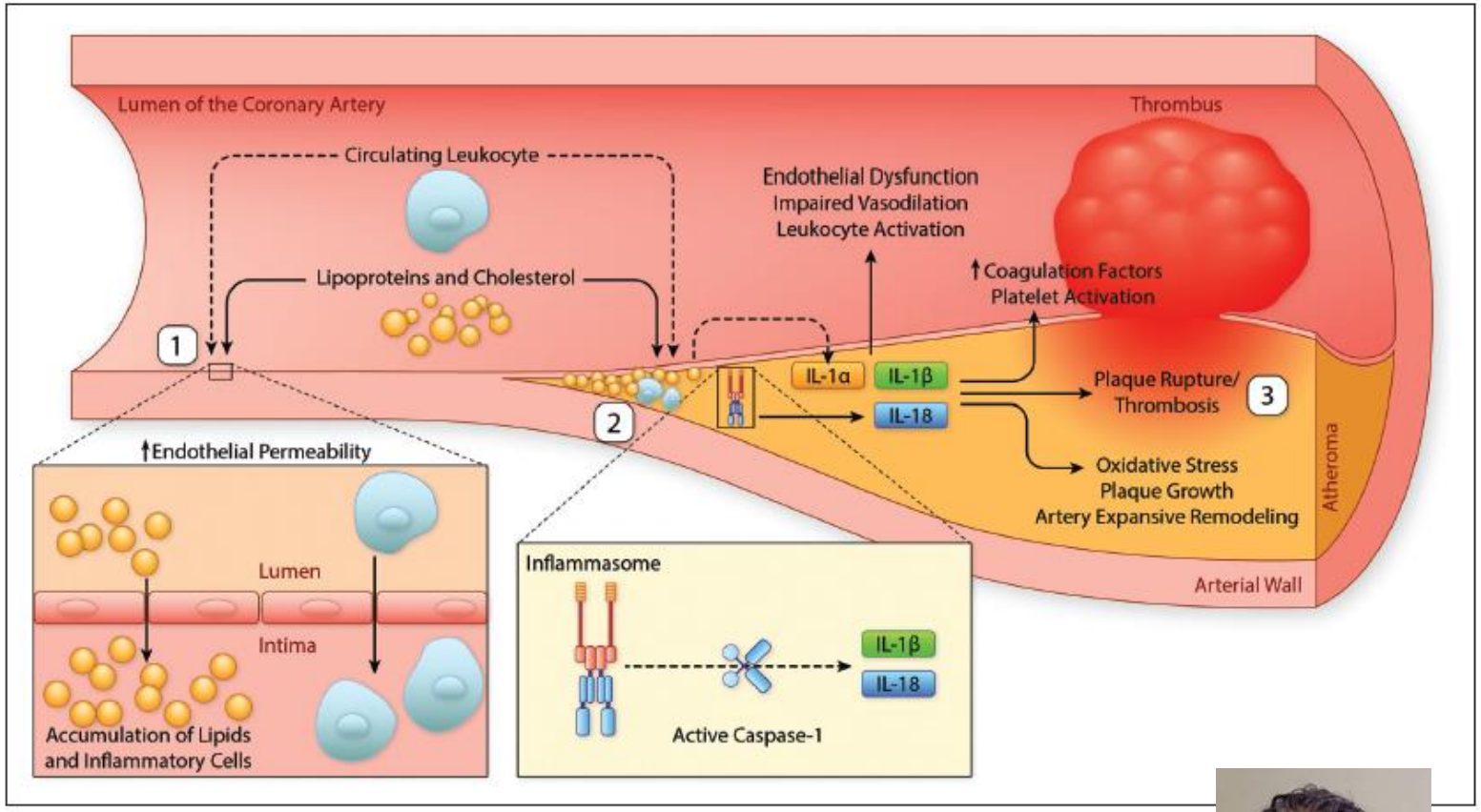


Figure 3. IL (interleukin)-1, inflammasome, and atherothrombosis.

Circulation Research

Circ Res 2020;126:1260

ATHEROSCLEROSIS COMPENDIUM

Interleukin-1 and the Inflammasome as Therapeutic Targets in Cardiovascular Disease

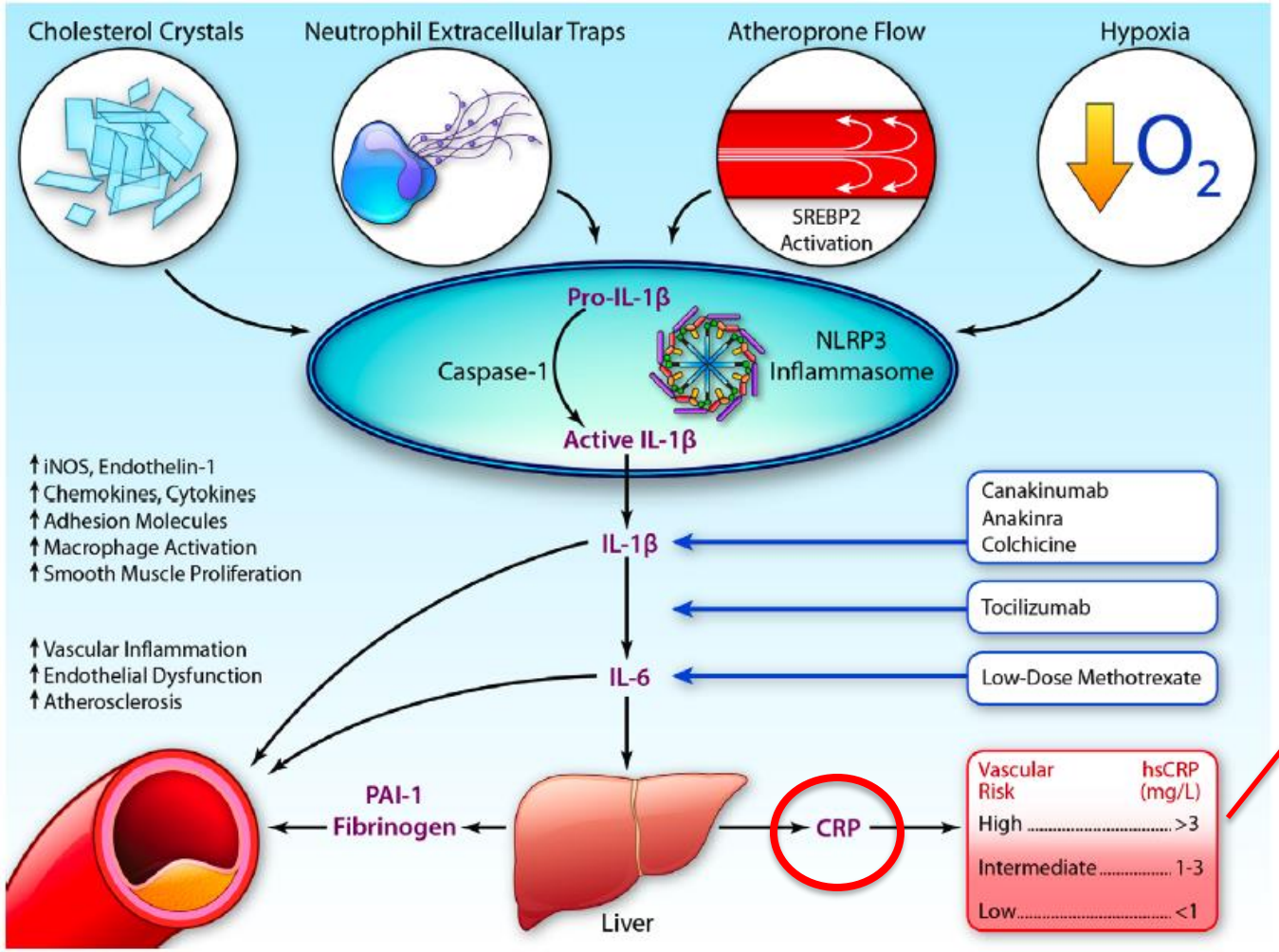
Antonio Abbate, Stefano Toldo, Carlo Marchetti, Jordana Kron, Benjamin W. Van Tassell, Charles A. Dinarello

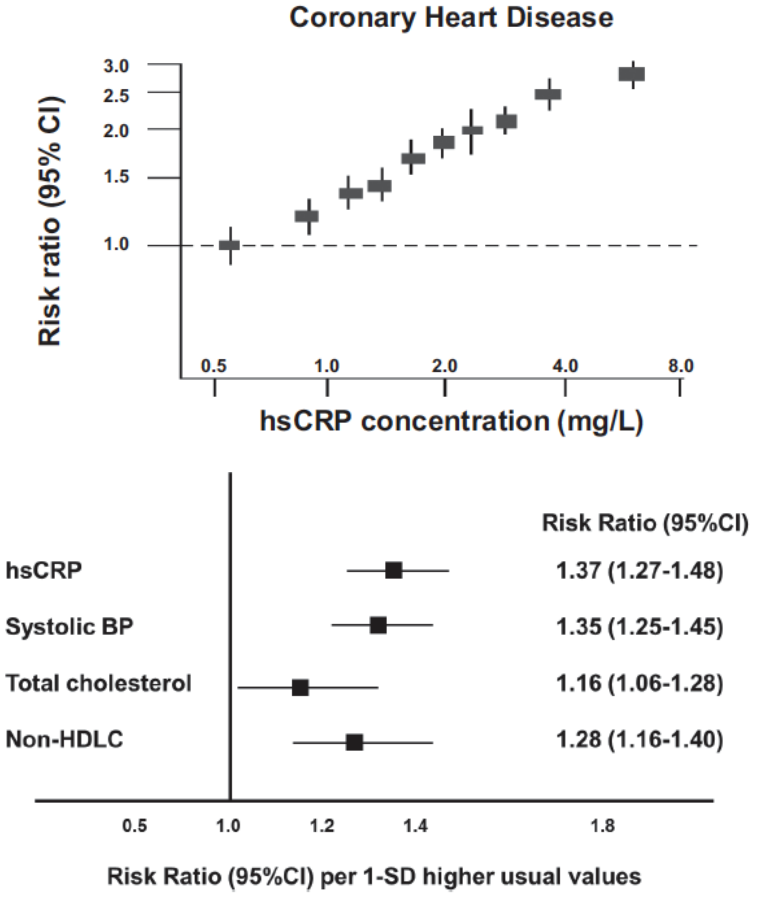
Stefano Toldo, PhD

From C-Reactive Protein to Interleukin-6 to Interleukin-1

Moving Upstream To Identify Novel Targets for Atheroprotection

Paul M Ridker *Circ Res* 2016





Secondary prevention

Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials

Paul M Ridker, Deepak L Bhatt, Aruna D Pradhan, Robert J Glynn, Jean G MacFadyen, Steven E Nissen, on behalf of the PROMINENT, REDUCE-IT, and STRENGTH Investigators

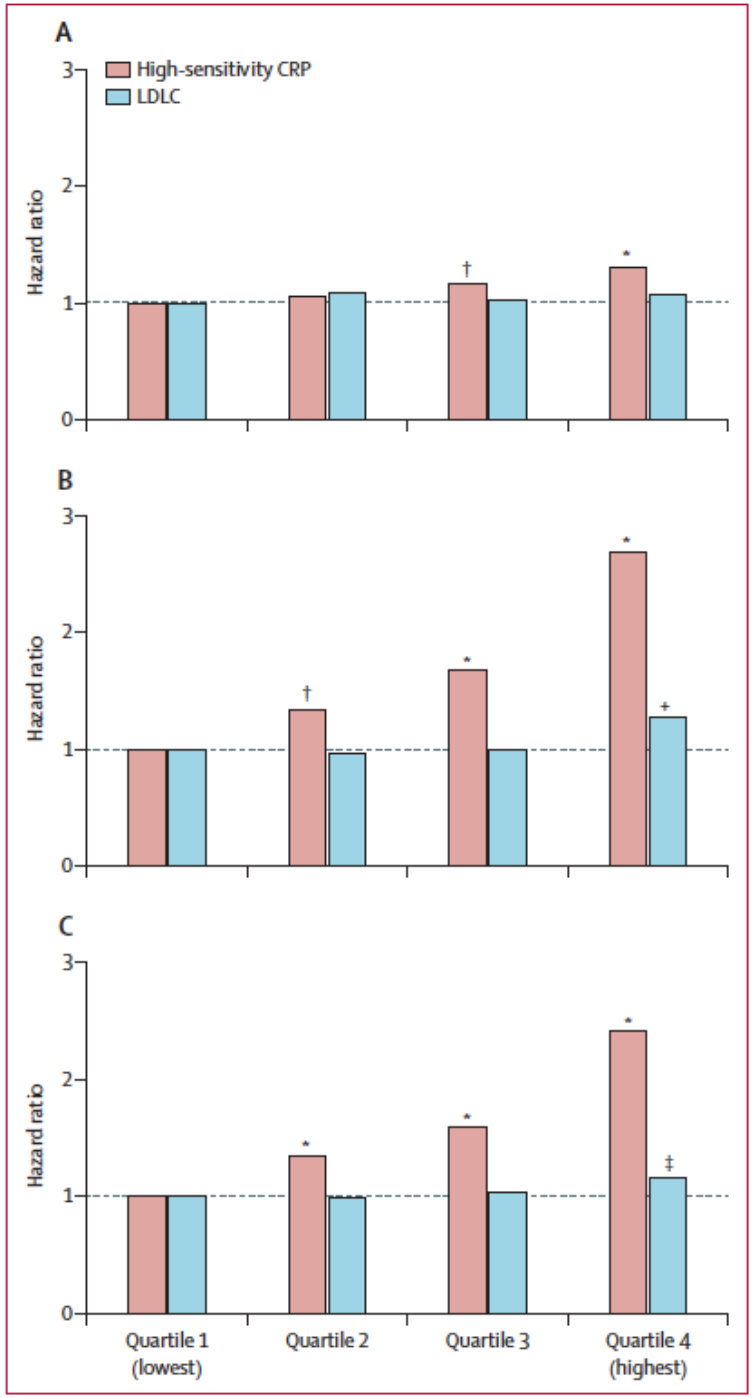
THE LANCET

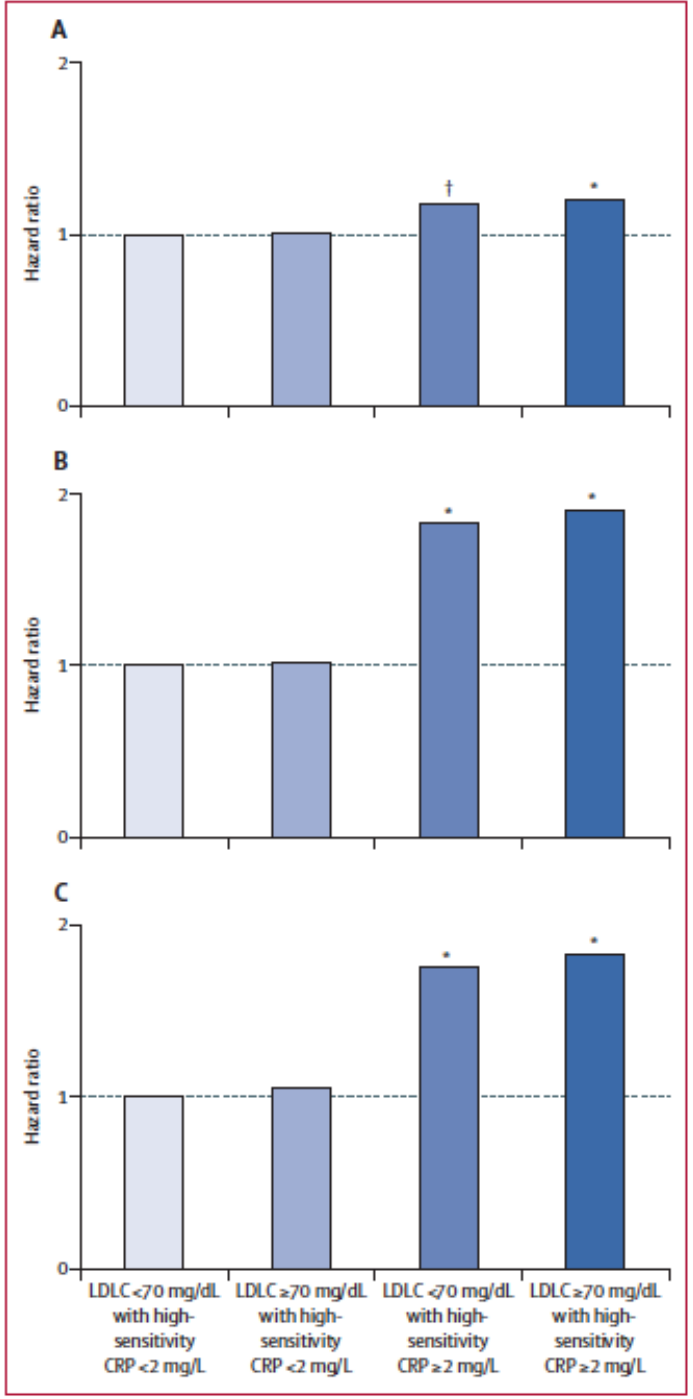
	Quartile 1 (lowest)	Quartile 2	Quartile 3	Quartile 4 (highest)
High-sensitivity CRP, mg/L				
PROMINENT	<1·2	1·2–2·3	2·4–4·8	>4·8
REDUCE-IT	<1·1	1·1–2·1	2·2–4·5	>4·5
STRENGTH	<1·1	1·1–2·0	2·1–4·2	>4·2
LDLC, mg/dL				
PROMINENT	<60	60–78	79–102	>102
REDUCE-IT	<62	62–75	76–89	>89
STRENGTH	<56	56–75	76–99	>99

CRP=C-reactive protein. LDLC=low-density lipoprotein cholesterol.

Table 2: **Trial-specific cutpoints for baseline high-sensitivity CRP and baseline LDLC**

hsCRP median 2.0-2.3 mg/L
LDLc median 75-78 mg/L





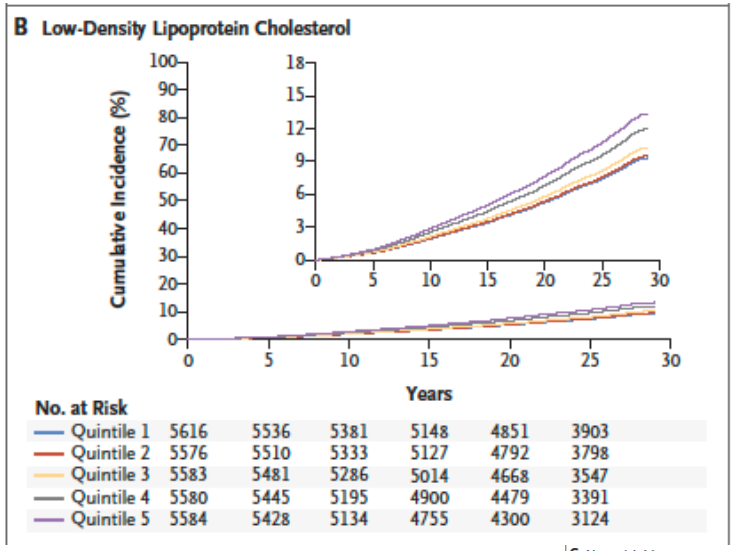
The NEW ENGLAND JOURNAL of MEDICINE 2024

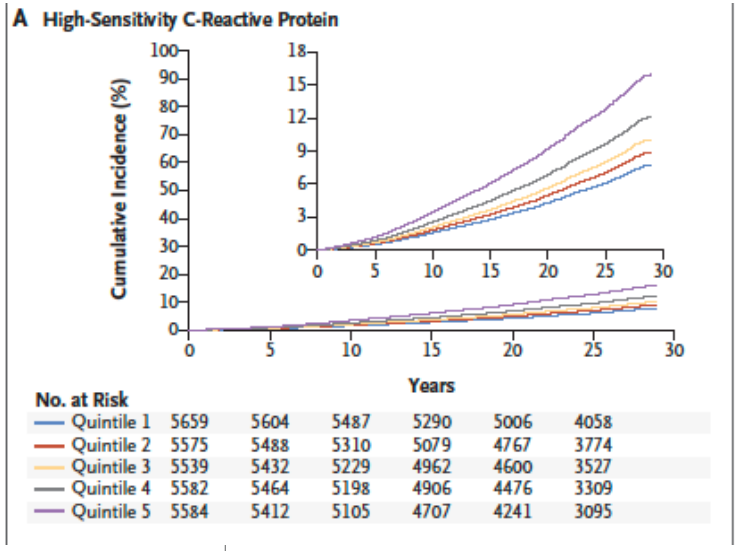
Primary prevention

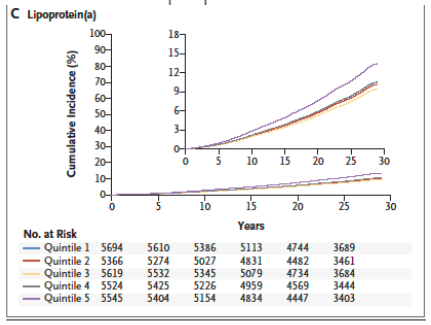
ORIGINAL ARTICLE

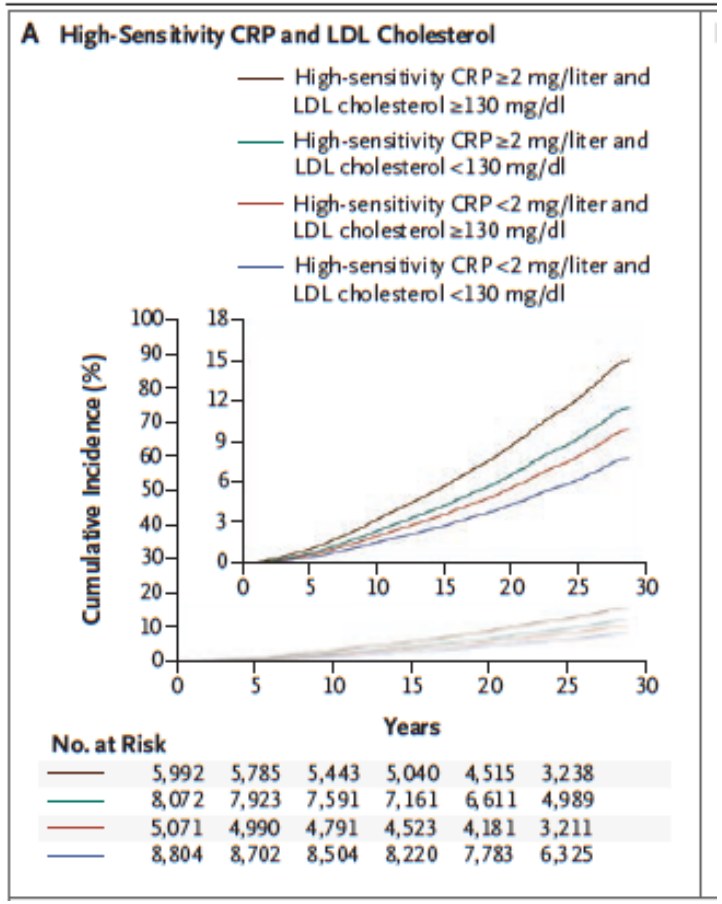
Inflammation, Cholesterol, Lipoprotein(a), and 30-Year Cardiovascular Outcomes in Women

Paul M Ridker, M.D., M. Vinayaga Moorthy, Ph.D., Nancy R. Cook, Sc.D., Nader Rifai, Ph.D., I-Min Lee, Sc.D., and Julie E. Buring, Sc.D.









ESC European Society of Cardiology
European Heart Journal (2024) **45**, 3415–3537
https://doi.org/10.1093/eurheartj/ehae177

2024 ESC Guidelines for the management of chronic coronary syndromes

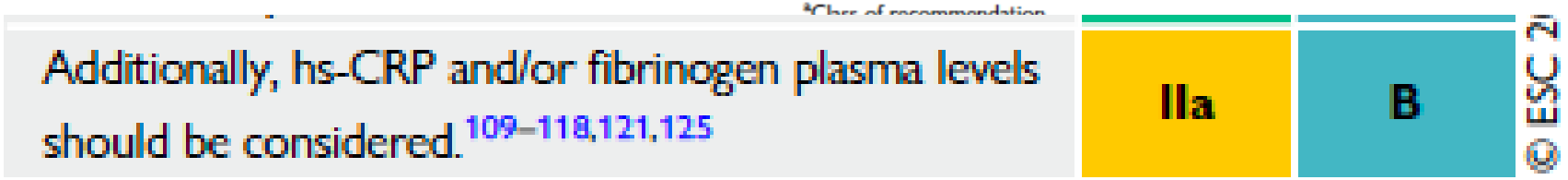
Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACT

Recommendation Table 2 — Recommendations for basic biochemistry in the initial diagnostic management of individuals with suspected chronic coronary syndrome (see also Evidence Table 2)

Recommendations	Class[a]	Level[b]
The following blood tests are recommended in all individuals to refine risk stratification, diagnose comorbidities, and guide treatment:		
• lipid profile including LDL-C;[64,128]	I	A
• full blood count (including haemoglobin);[129–133]	I	B
• creatinine with estimation of renal function;[134]	I	B
• glycaemic status with HbA1c and/or fasting plasma glucose.[16,86,135,136]	I	B
In patients with suspected CCS, it is recommended to assess thyroid function at least once.[137,138]	I	B
Additionally, hs-CRP and/or fibrinogen plasma levels should be considered.[109–118,121,125]	IIa	B

CCS, chronic coronary syndrome; HbA1c, glycated haemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.
[a]Class of recommendation



Hypothetical case:

52 yo M, family history of premature CAD,
No hypertension, diabetes, tobacco
Physical active 2-3 times/week, BMI 26
LDL 115 mg/dl, HDL 45 mg/dl, Lp(a) 11 nmol/L
hsCRP 3.0 mg/L, CAC score 0

Is this patient at increased risk for CV events?

How many measure hsCRP? and Lp(a)?

What can he do to reduce risk?

Aspirin?

Rosuvastatin?

Colchicine?

Other?

The New England
Journal of Medicine

VOLUME 336 APRIL 3, 1997 NUMBER 14

INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

PAUL M. RIDKER, M.D., MARY CUSHMAN, M.D., MEIR J. STAMPFER, M.D., RUSSELL P. TRACY, PH.D., AND CHARLES H. HENNEKENS, M.D.

INFLAMMATION, ATHEROSCLEROSIS, AND ISCHEMIC EVENTS — EXPLORING THE HIDDEN SIDE OF THE MOON

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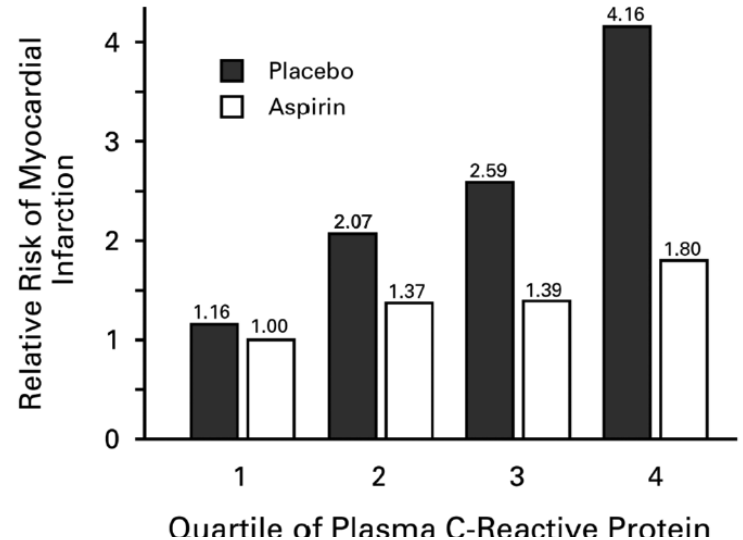
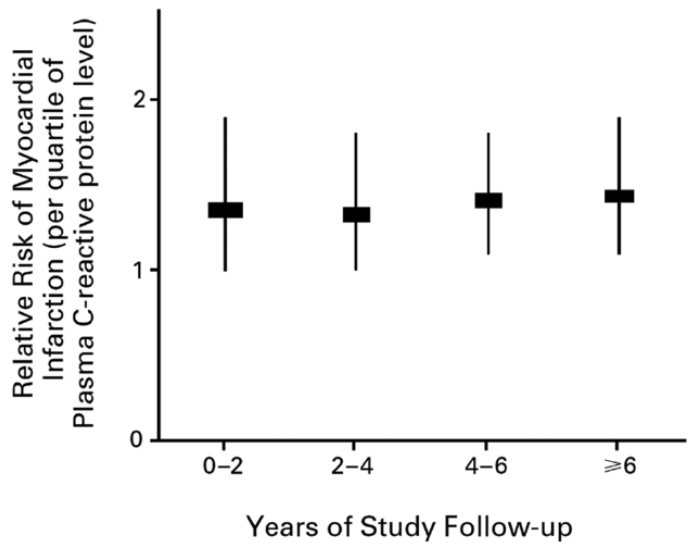
Ridker





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2008 VOL. 359 NO. 21

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

JUPITER trial

Paul Ridker, MD

Median age 66
(inclusion 50 yo M; 60 yo F)
Males 62%
White 71%
BP 134 [124-145]/80 [75-87]
LDL 108 [94-119]
HDL 49 [40-60]
Glucose 94 [87-102]
HbA1c 5.7% [5.4-5.9]
HsCRP 4.2 [2.8-7.1]

Primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes – median f/u 1.9 years

Table 1. Baseline Characteristics of the Trial Participants, According to Study Group.*

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Age — yr		
Median	66.0	66.0
Interquartile range	60.0–71.0	60.0–71.0
Female sex — no. (%)	3426 (38.5)	3375 (37.9)
Race or ethnic group — no. (%)†		
White	6358 (71.4)	6325 (71.1)
Black	1100 (12.4)	1124 (12.6)
Hispanic	1121 (12.6)	1140 (12.8)
Other or unknown	322 (3.6)	312 (3.5)
Body-mass index‡		
Median	28.3	28.4
Interquartile range	25.3–32.0	25.3–32.0
Blood pressure — mm Hg		
Systolic		
Median	134	134
Interquartile range	124–145	124–145
Diastolic		
Median	80	80
Interquartile range	75–87	75–87
Current smoker — no. (%)	1400 (15.7)	1420 (16.0)
Family history of premature CHD — no. (%)§	997 (11.2)	1048 (11.8)
Metabolic syndrome — no. (%)¶	3652 (41.0)	3723 (41.8)
Aspirin use — no. (%)	1481 (16.6)	1477 (16.6)
High-sensitivity C-reactive protein — mg/liter‖		
Median	4.2	4.3
Interquartile range	2.8–7.1	2.8–7.2
LDL cholesterol — mg/dl		
Median	108	108
Interquartile range	94–119	94–119
HDL cholesterol — mg/dl		
Median	49	49
Interquartile range	40–60	40–60
Triglycerides — mg/dl		
Median	118	118
Interquartile range	85–169	86–169
Total cholesterol — mg/dl		
Median	186	185
Interquartile range	168–200	169–199
Glucose — mg/dl		
Median	94	94
Interquartile range	87–102	88–102

The NEW ENGLAND JOURNAL of MEDICINE

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Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

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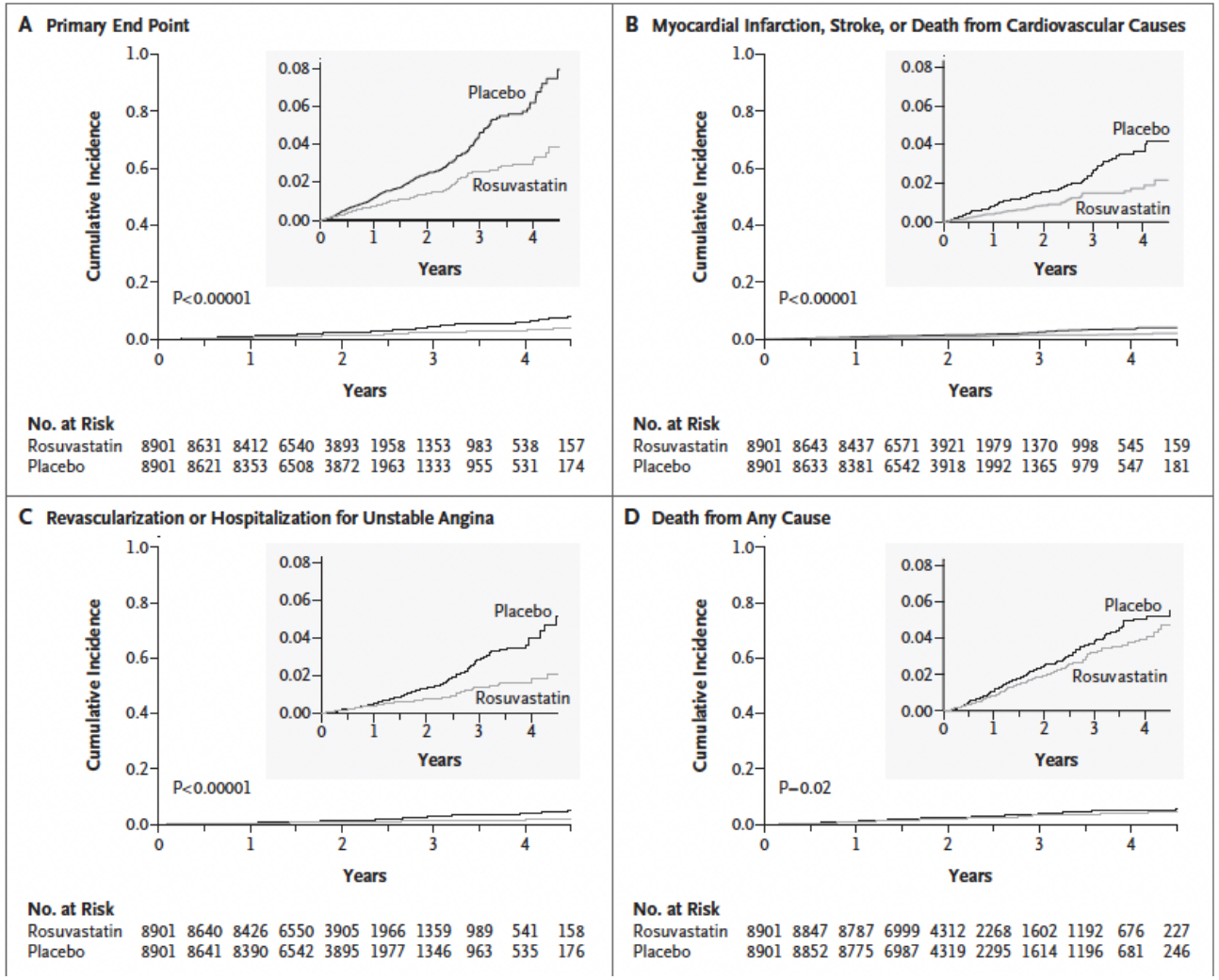
Table 2. Lipid and High-Sensitivity C-Reactive Protein Levels during the Follow-up Period, According to Study Group.*

Level	12 Mo		24 Mo		36 Mo		48 Mo	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo
High-sensitivity C-reactive protein (mg/liter)								
Median	2.2	3.5	2.2	3.5	2.0	3.5	1.8	3.3
Interquartile range	1.2–4.4	2.0–6.2	1.2–4.3	2.0–6.1	1.1–3.9	1.8–6.0	1.1–3.7	1.7–6.1
LDL cholesterol (mg/dl)								
Median	55	110	54	108	53	106	55	109
Interquartile range	44–72	94–125	42–69	93–123	42–69	90–121	44–70	94–124
HDL cholesterol (mg/dl)								
Median	52	50	52	50	50	49	50	50
Interquartile range	43–64	41–61	44–65	42–61	41–62	40–59	41–61	42–60
Triglycerides (mg/dl)								
Median	99	119	99	116	106	123	99	118
Interquartile range	74–137	87–167	73–134	83–165	77–148	90–173	74–140	87–164



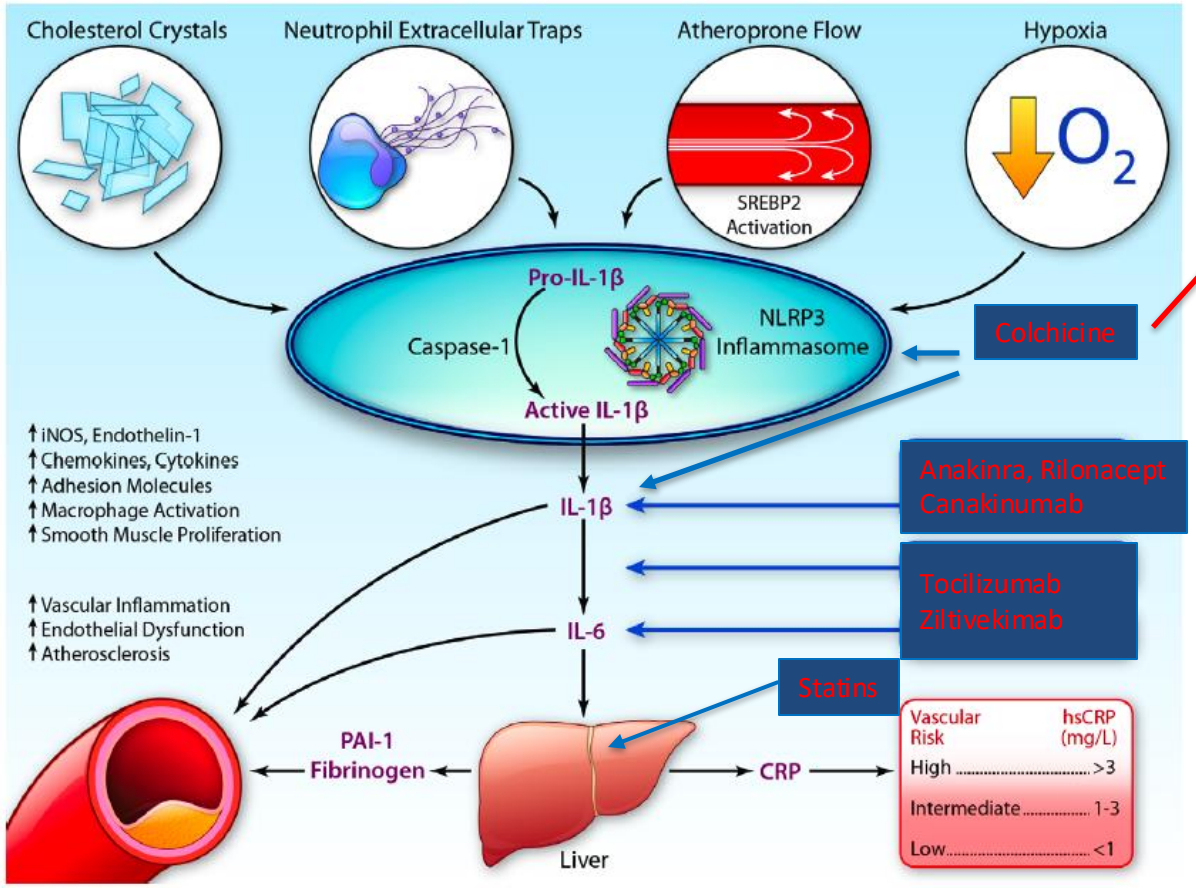
Primary endpoint: 0.77% and 1.36% per year in the rosuvastatin and placebo groups, respectively (absolute difference 0.59%; hazard ratio for rosuvastatin 20 mg was 0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001)

As of 2010, Rosuvastatin is FDA approved for the primary prevention of cardiovascular disease (independent of LDL levels)

1.6 Primary Prevention of Cardiovascular Disease

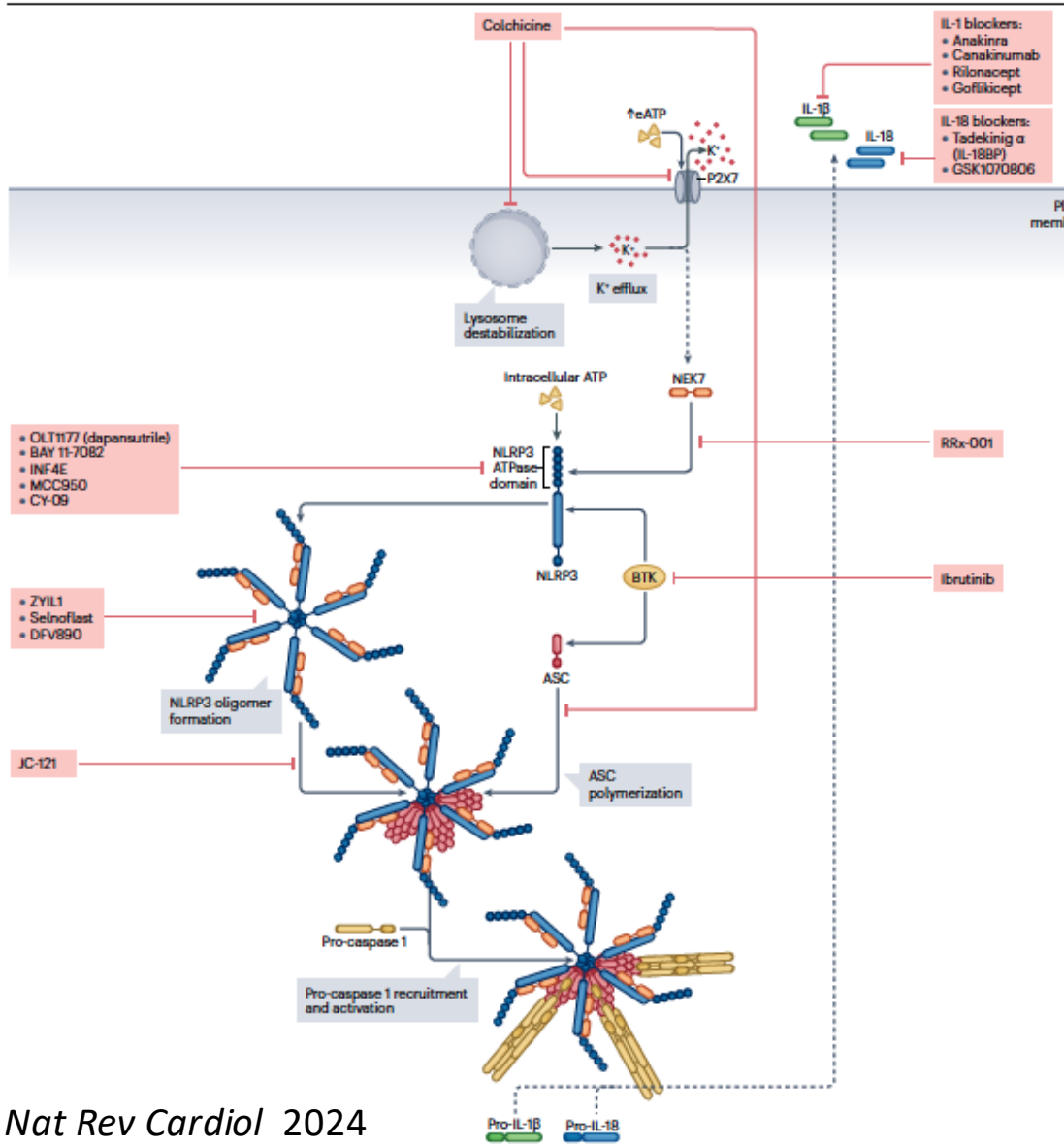
In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age $\geq$ 50 years old in men and $\geq$ 60 years old in women, hsCRP $\geq$ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization procedures



Colchicine

(non-specific inflammasome inhibitor)



Toldo & Abbate – *Nat Rev Cardiol* 2024

Colchicine and atherothrombosis

LODOCO2 trial

ORIGINAL ARTICLE

Nidorf SM – *N Engl J Med* 2020

Colchicine in Patients with Chronic Coronary Disease

5,522 pts with stable CAD randomized to colchicine or placebo

66 yrs
F 14.1-16.5%

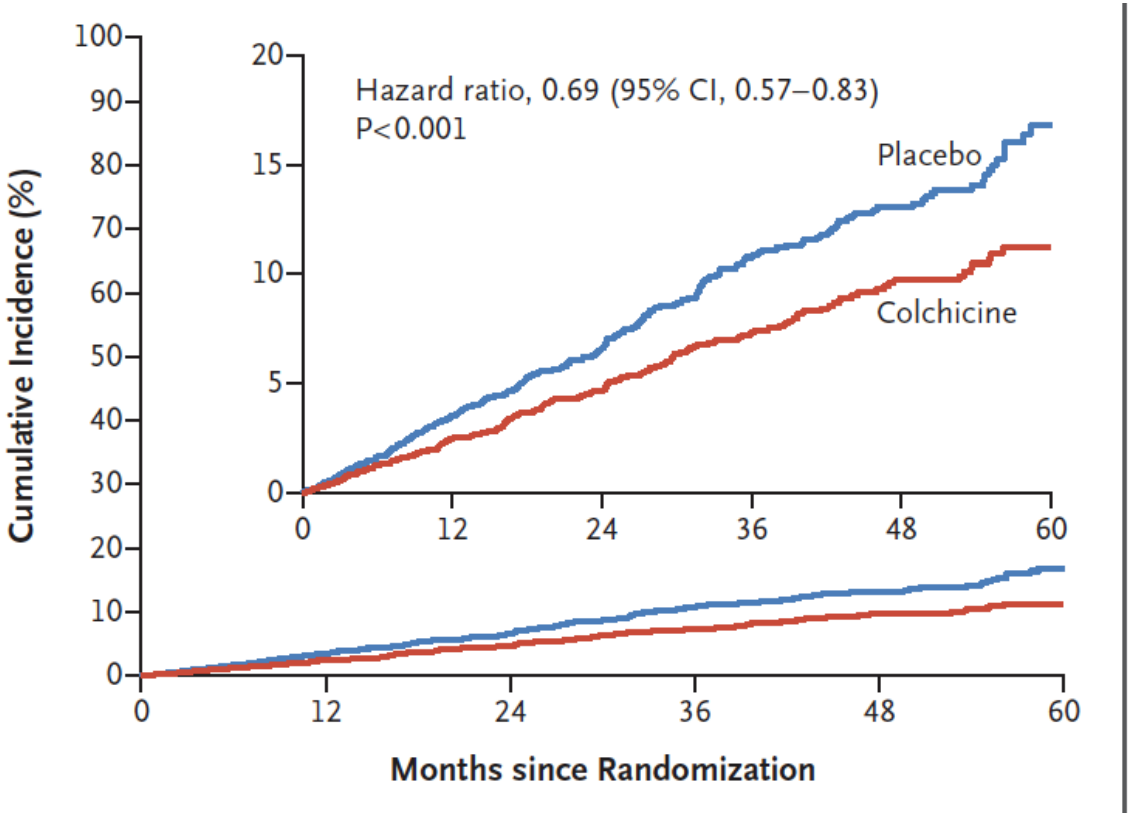
DM 17.8-18.7%

Prior ACS 84%

Statin 94%

Table 1. Characteristics of the Trial Patients at Baseline.*

Characteristic	Colchicine (N=2762)	Placebo (N=2760)
Age — yr	65.8±8.4	65.9±8.7
Female sex — no. (%)	457 (16.5)	389 (14.1)
Country — no. (%)		
Australia	951 (34.4)	953 (34.5)
The Netherlands	1811 (65.6)	1807 (65.5)
Current smoker — no. (%)†	318 (11.5)	330 (12.0)
Hypertension — no. (%)	1421 (51.4)	1387 (50.3)
Diabetes — no. (%)		
Patients receiving any treatment for diabetes	492 (17.8)	515 (18.7)
Patients dependent on insulin	140 (5.1)	147 (5.3)
Renal function — no. (%)‡		
Stage 1 or 2	2614 (94.6)	2602 (94.3)
Stage 3a	148 (5.4)	158 (5.7)
Prior acute coronary syndrome — no. (%)	2323 (84.1)	2335 (84.6)
Time since last acute coronary syndrome — no. (%)		
≤24 mo	753 (27.3)	726 (26.3)
>24 mo	1570 (56.8)	1609 (58.3)
Prior coronary revascularization — no. (%)	2301 (83.3)	2320 (84.1)
Coronary-artery bypass grafting	319 (11.5)	391 (14.2)
Percutaneous coronary intervention	2100 (76.0)	2077 (75.3)
History of atrial fibrillation — no. (%)	332 (12.0)	317 (11.5)
History of gout — no. (%)	220 (8.0)	226 (8.2)
Medication use — no. (%)		
Single antiplatelet therapy	1849 (66.9)	1852 (67.1)
Dual antiplatelet therapy	638 (23.1)	642 (23.3)
Anticoagulant	342 (12.4)	330 (12.0)
No antiplatelet agent or anticoagulant	4 (0.1)	11 (0.4)
Statin	2594 (93.9)	2594 (94.0)



Primary endpoint: 6.8% and 9.6% per year in the colchicine and placebo groups, respectively (absolute difference 2.8% per year; hazard ratio for colchicine 0.5 mg was 0.69, 95% confidence interval [CI], 0.57–0.83; P=0.02)

Colchicine and atherothrombosis

COLCOT trial ORIGINAL ARTICLE

Tardif JC – *N Engl J Med* 2019

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

4,745 pts with recent MI randomized to colchicine or placebo

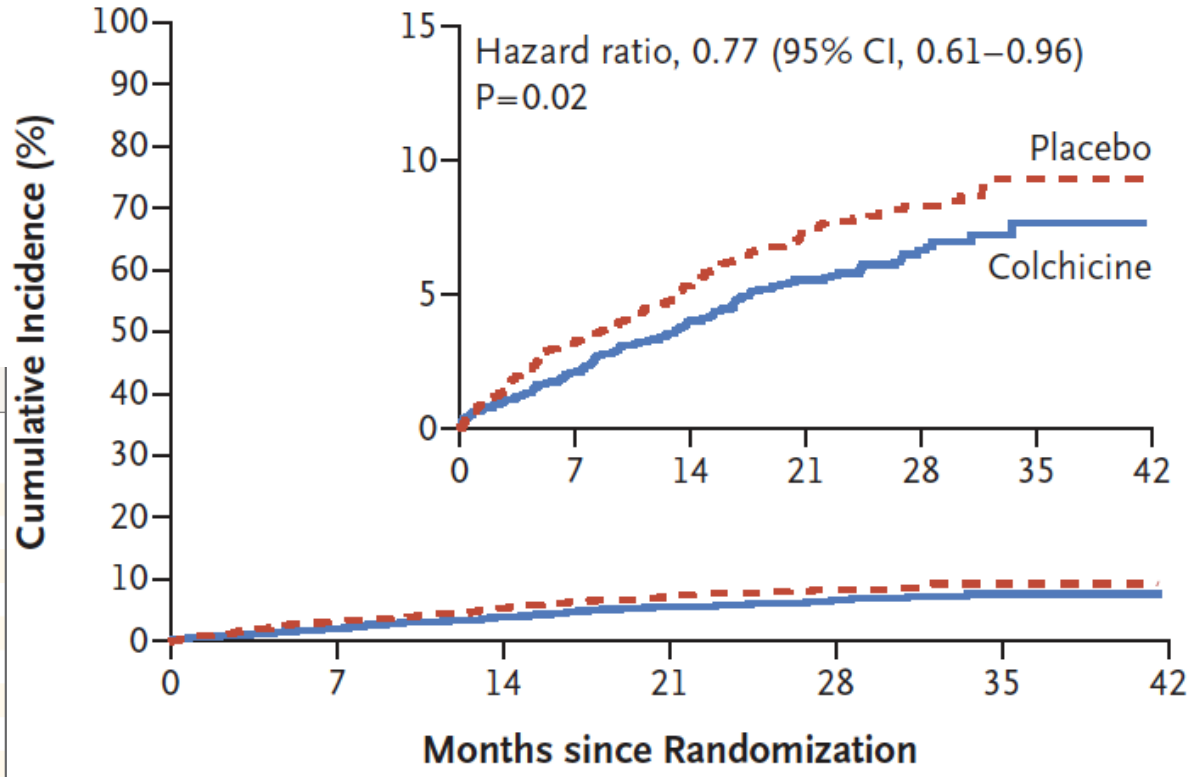
61 yrs
F 18.4-19.9%

DM 19.5-20.9%

13.5 days after MI

Table 1. Characteristics of the Patients.*

Characteristic	Colchicine (N=2366)	Placebo (N=2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375 (93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)



Primary endpoint: 5.5% and 7.1% in the colchicine and placebo groups at 42 months, respectively (absolute difference 0.48% per year; hazard ratio for colchicine 0.5 mg was 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02)

FDA approves colchicine, the first anti-inflammatory drug for treating cardiovascular disease

Dave Fornell | *June 20, 2023* | *Cardiovascular Business* | *Pharmaceutics*

The indication is similar to statins

The dose is 0.5 mg daily

Do NOT use with strong CYP3A4 or P-gp inhibitors (statins not a concern)
Do NOT use in renal failure (GFR<60 ml/min/m2), severe liver dysfunction, or blood dyscrasia

Consider GI side effects (usually mild)
Consider blood dyscrasias and neuro-muscular toxicity

to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease (1).

Anti-inflammatory drugs in patients with chronic coronary syndrome—*Section 4*		
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.	IIa	A

The NEW ENGLAND JOURNAL of MEDICINE

CLEAR-Synergy Trial

Jolly SS et al – *N Engl J Med* 2024

ORIGINAL ARTICLE

Colchicine in Acute Myocardial Infarction

S.S. Jolly, M.-A. d'Entremont, S.F. Lee, R. Mian, J. Tyrwhitt, S. Kedev, G. Montalescot, J.H. Cornel, G. Stanković, R. Moreno, R.F. Storey, T.D. Henry

7,026 pts with Acute MI (mostly STEMI) randomized to colchicine or placebo (or spironolactone in 2x2 factorial design)

61 yrs
F 20%

DM 18%

95% STEMI

100% DES
100% P2Y12inh
98% DAPT

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Colchicine (N=3528)	Placebo (N=3534)
Demographic characteristics		
Mean age — yr	60.6±10.3	60.7±10.3
Age >75 yr — no. (%)	301 (8.5)	270 (7.6)
Female sex — no. (%)	725 (20.5)	713 (20.2)
Race or ethnic group — no. (%)†		
American Indian or Alaskan Native	7 (0.2)	3 (0.1)
Asian	95 (2.7)	89 (2.5)
Black	24 (0.7)	23 (0.7)
Native Hawaiian or other Pacific Islander	9 (0.3)	9 (0.3)
White	3233 (91.6)	3249 (91.9)
Other	153 (4.3)	159 (4.5)
Geographic region — no. (%)		
North America	1010 (28.6)	1012 (28.6)
Europe	2356 (66.8)	2359 (66.8)
Other	162 (4.6)	163 (4.6)
Clinical characteristics		
Killip class ≥II — no. (%)‡	25 (0.7)	24 (0.7)
NSTEMI at presentation — no. (%)	165 (4.7)	184 (5.2)
STEMI at presentation — no. (%)	3363 (95.3)	3350 (94.8)

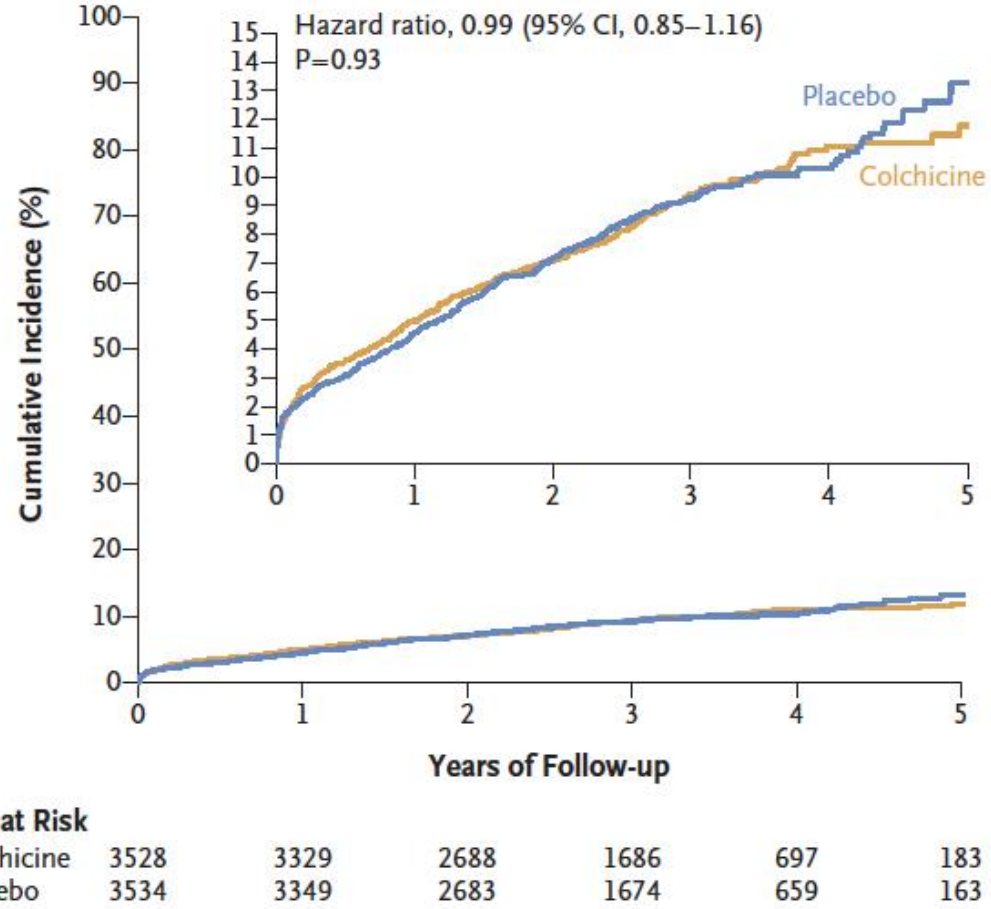


Figure 1. Kaplan–Meier Event Curves for Death from Cardiovascular Causes, Recurrent Myocardial Infarction, Stroke, or Ischemia-Driven Revascularization.

The inset shows a magnified version of the graph.

The NEW ENGLAND JOURNAL of MEDICINE

CLEAR-Synergy Trial Jolly SS et al – *N Engl J Med* 2024

ORIGINAL ARTICLE

Colchicine in Acute Myocardial Infarction

S.S. Jolly, M.-A. d'Entremont, S.F. Lee, R. Mian, J. Tyrwhitt, S. Kedev, G. Montalescot, J.H. Cornel, G. Stanković, R. Moreno, R.F. Storey, T.D. Henn

7,026 pts with Acute MI (mostly STEMI) randomized to colchicir or placebo (or spironolactone in 2x2 factorial design)

61 yrs
F 20%

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95% STEMI

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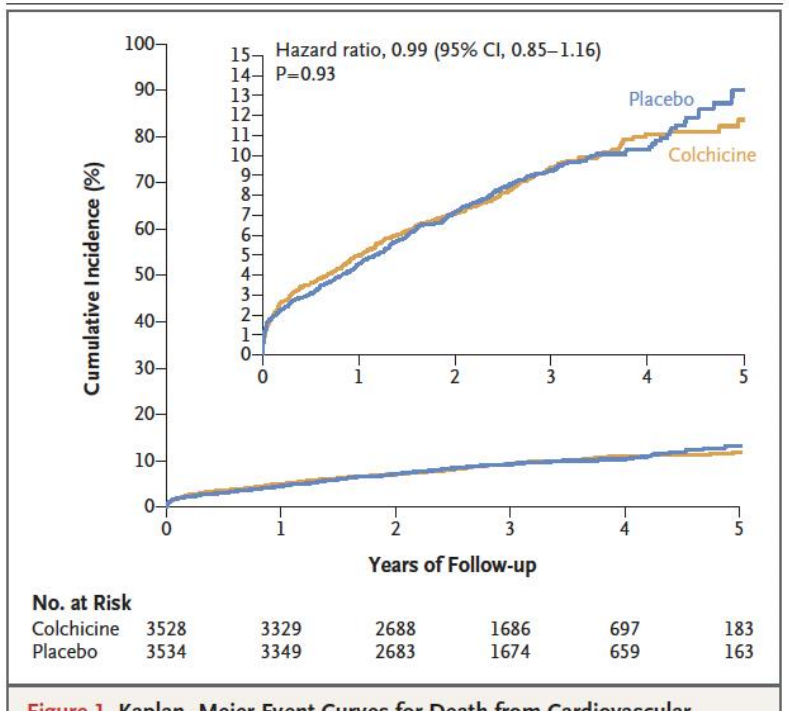
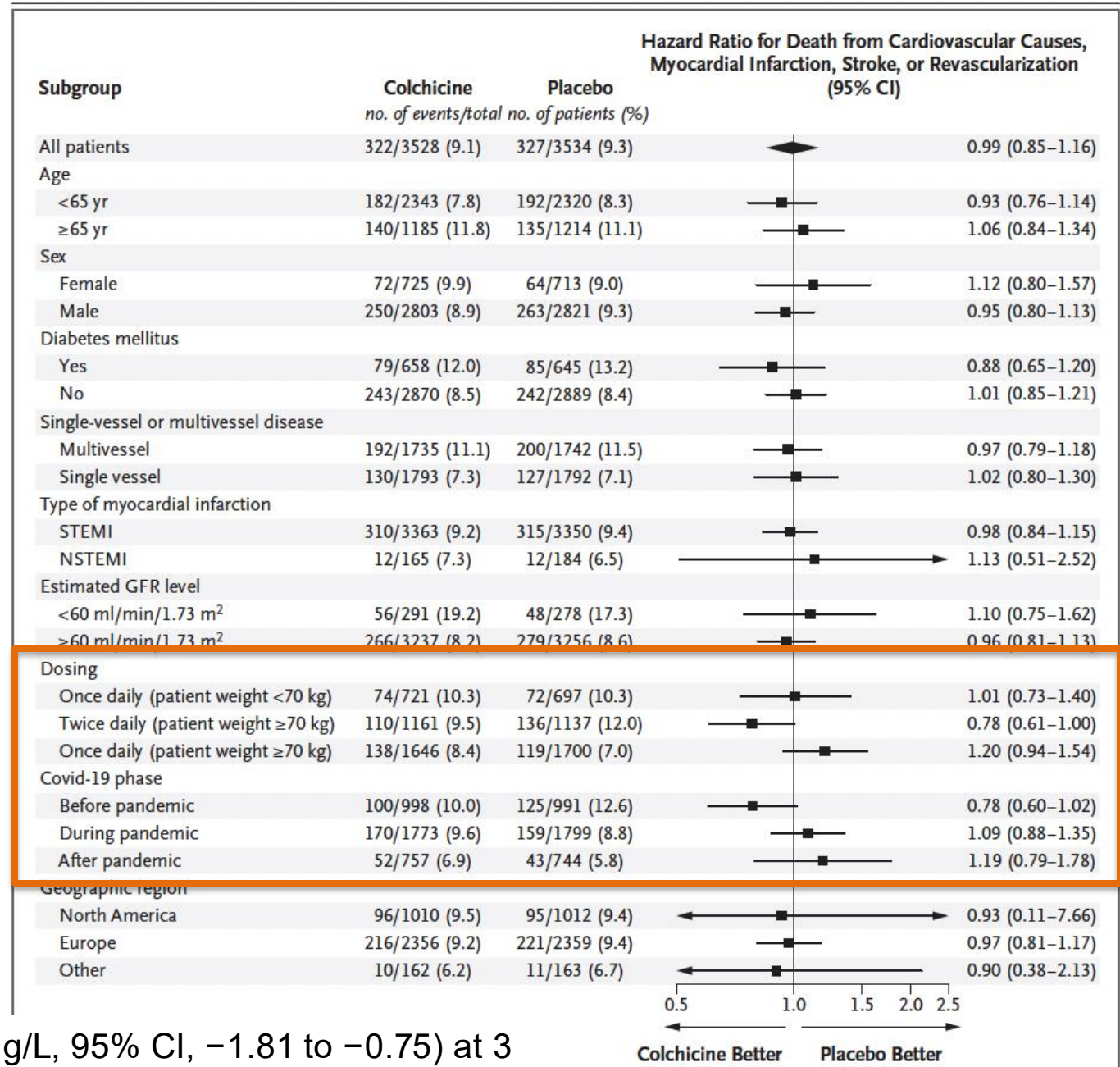


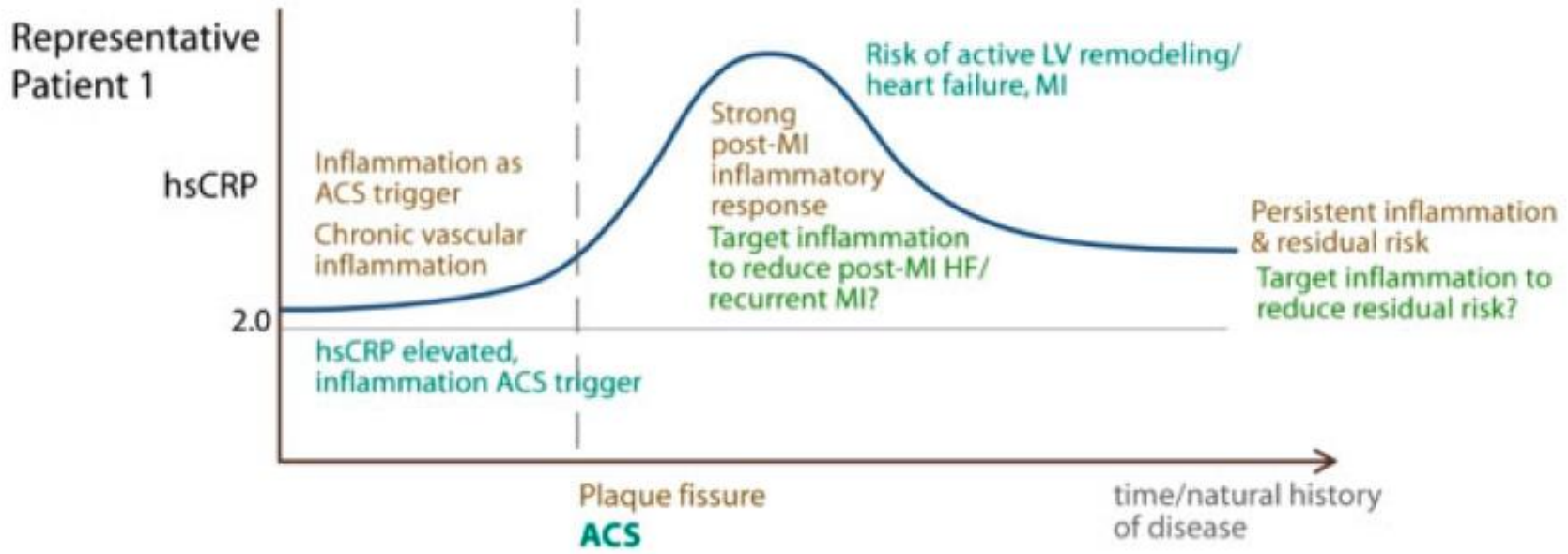
Figure 1. Kaplan–Meier Event Curves for Death from Cardiovascular



Subgroup	Colchicine no. of events/total	Placebo no. of patients (%)	
All patients	322/3528 (9.1)	327/3534 (9.3)	0.99 (0.85–1.16)
Age			
<65 yr	182/2343 (7.8)	192/2320 (8.3)	0.93 (0.76–1.14)
≥65 yr	140/1185 (11.8)	135/1214 (11.1)	1.06 (0.84–1.34)
Sex			
Female	72/725 (9.9)	64/713 (9.0)	1.12 (0.80–1.57)
Male	250/2803 (8.9)	263/2821 (9.3)	0.95 (0.80–1.13)
Diabetes mellitus			
Yes	79/658 (12.0)	85/645 (13.2)	0.88 (0.65–1.20)
No	243/2870 (8.5)	242/2889 (8.4)	1.01 (0.85–1.21)
Single-vessel or multivessel disease			
Multivessel	192/1735 (11.1)	200/1742 (11.5)	0.97 (0.79–1.18)
Single vessel	130/1793 (7.3)	127/1792 (7.1)	1.02 (0.80–1.30)
Type of myocardial infarction			
STEMI	310/3363 (9.2)	315/3350 (9.4)	0.98 (0.84–1.15)
NSTEMI	12/165 (7.3)	12/184 (6.5)	1.13 (0.51–2.52)
Estimated GFR level			
<60 ml/min/1.73 m²	56/291 (19.2)	48/278 (17.3)	1.10 (0.75–1.62)
≥60 ml/min/1.73 m²	266/3237 (8.2)	279/3256 (8.6)	0.96 (0.81–1.13)
Dosing			
Once daily (patient weight <70 kg)	74/721 (10.3)	72/697 (10.3)	1.01 (0.73–1.40)
Twice daily (patient weight ≥70 kg)	110/1161 (9.5)	136/1137 (12.0)	0.78 (0.61–1.00)
Once daily (patient weight ≥70 kg)	138/1646 (8.4)	119/1700 (7.0)	1.20 (0.94–1.54)
Covid-19 phase			
Before pandemic	100/998 (10.0)	125/991 (12.6)	0.78 (0.60–1.02)
During pandemic	170/1773 (9.6)	159/1799 (8.8)	1.09 (0.88–1.35)
After pandemic	52/757 (6.9)	43/744 (5.8)	1.19 (0.79–1.78)
Geographic region			
North America	96/1010 (9.5)	95/1012 (9.4)	0.93 (0.11–7.66)
Europe	216/2356 (9.2)	221/2359 (9.4)	0.97 (0.81–1.17)
Other	10/162 (6.2)	11/163 (6.7)	0.90 (0.38–2.13)

C-reactive protein (CRP) levels modestly reduced (−1.28 mg/L, 95% CI, −1.81 to −0.75) at 3 months and no CRP assessment beyond 3 months was performed.

Colchicine in CV risk reduction trials



LODOCO 2

CLEAR - SYNERGY

COLCOT

LODOCO 2

Colchicine in coronary artery disease:

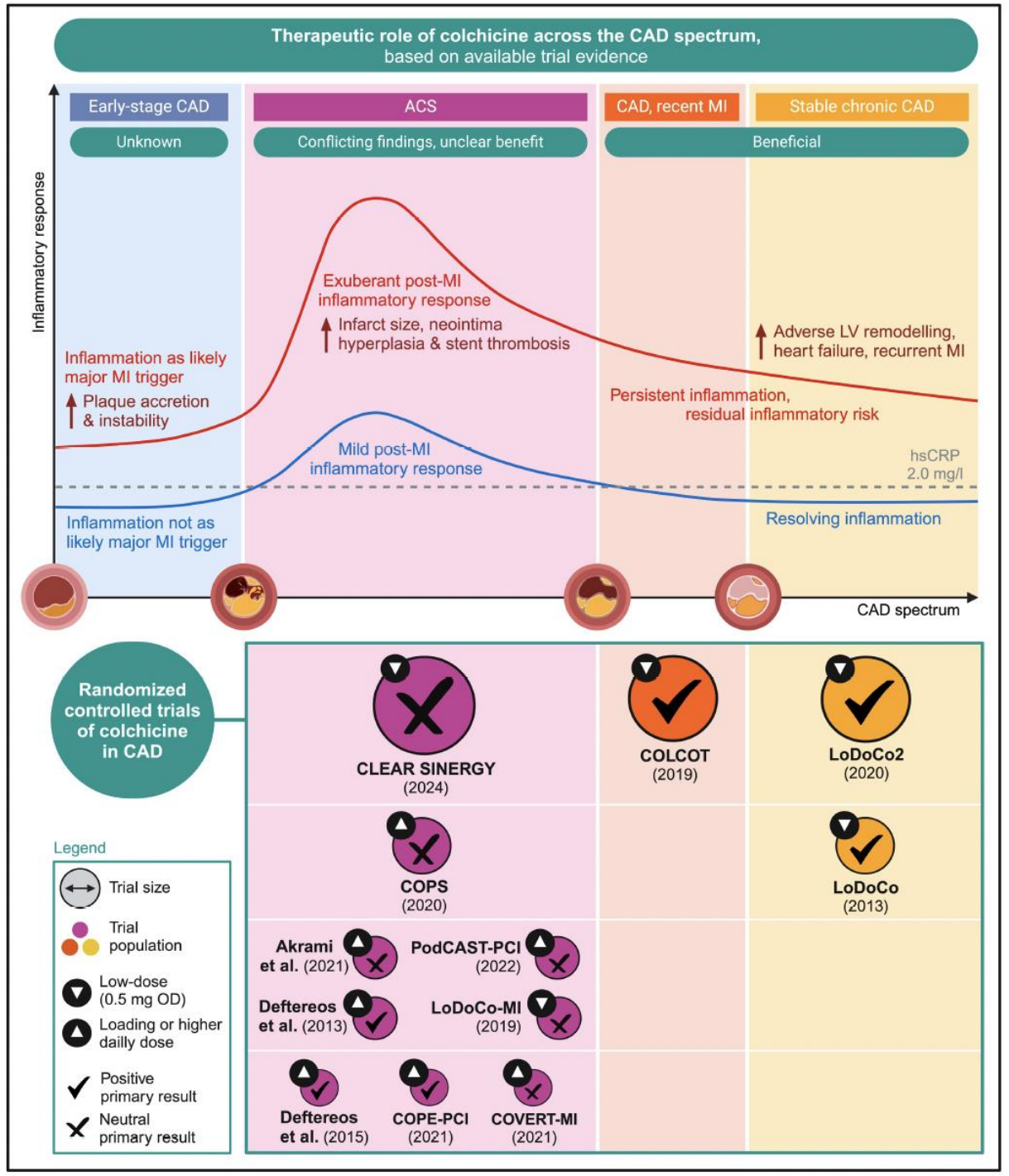
Where do we stand?

Aldo Bonaventura, MD, PhD[1]; Luca Liberale, MD, PhD[2,3];Simon Kraler, MD, PhD[4,5]; Brittany W Weber, MD, PhD[6]; Antonio Abbate, MD, PhD[7]

Journal of Cardiovascular Pharmacology - 2025

Take-home messages:

- Low-dose colchicine is safe
- Low-dose colchicine may be more efficacious in stable or sub-acute coronary syndromes
- Whether higher doses of colchicine would be better than low-dose in acute coronary syndromes is not known
- Other targeted therapy may be better suited for acute coronary syndromes



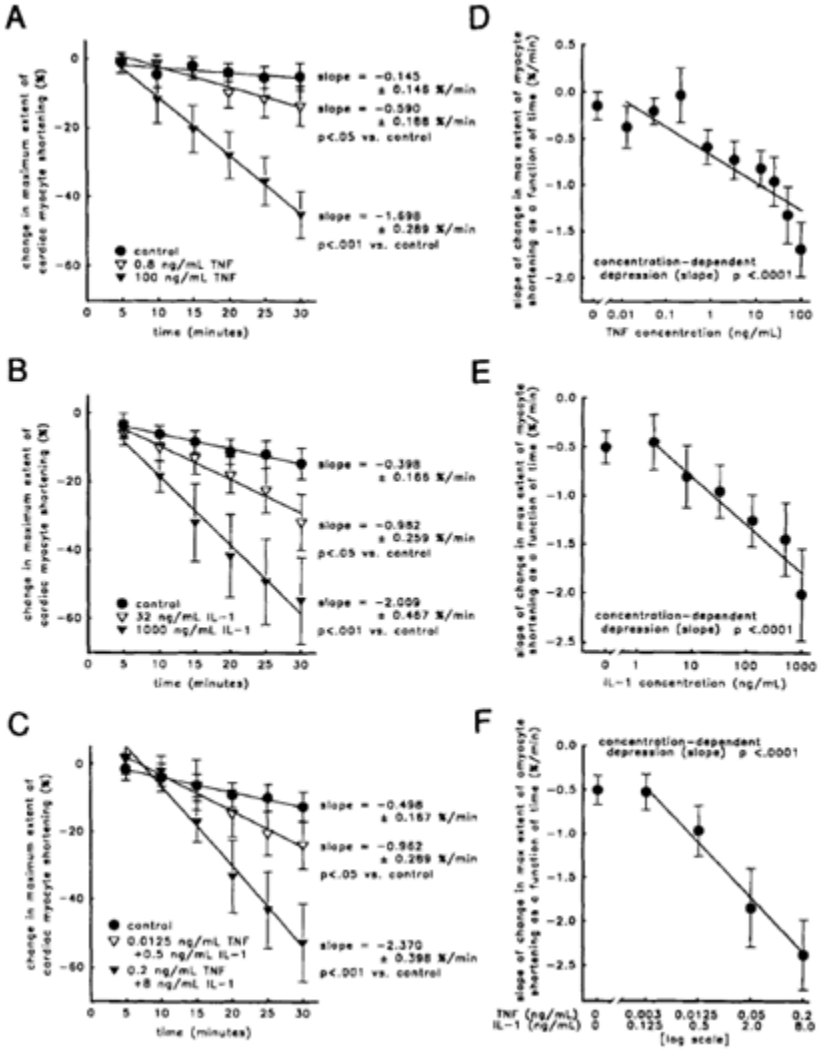
LEARNING GOALS

1) Inflammation and cardiovascular diseases
2) Management of myocarditis
3) Management of pericarditis
4) Inflammatory component of the cardiovascular risk
5) **Inflammatory component of heart failure**

Tumor Necrosis Factor α and Interleukin 1β Are Responsible for In Vitro Myocardial Cell Depression Induced by Human Septic Shock Serum

By Anand Kumar, Venkateswarlu Thota, Linda Dee, Jeanne Olson, Eugene Uretz, and Joseph E. Parrillo

J. Exp. Med. © The Rockefeller University Press
Volume 183 March 1996 949–958



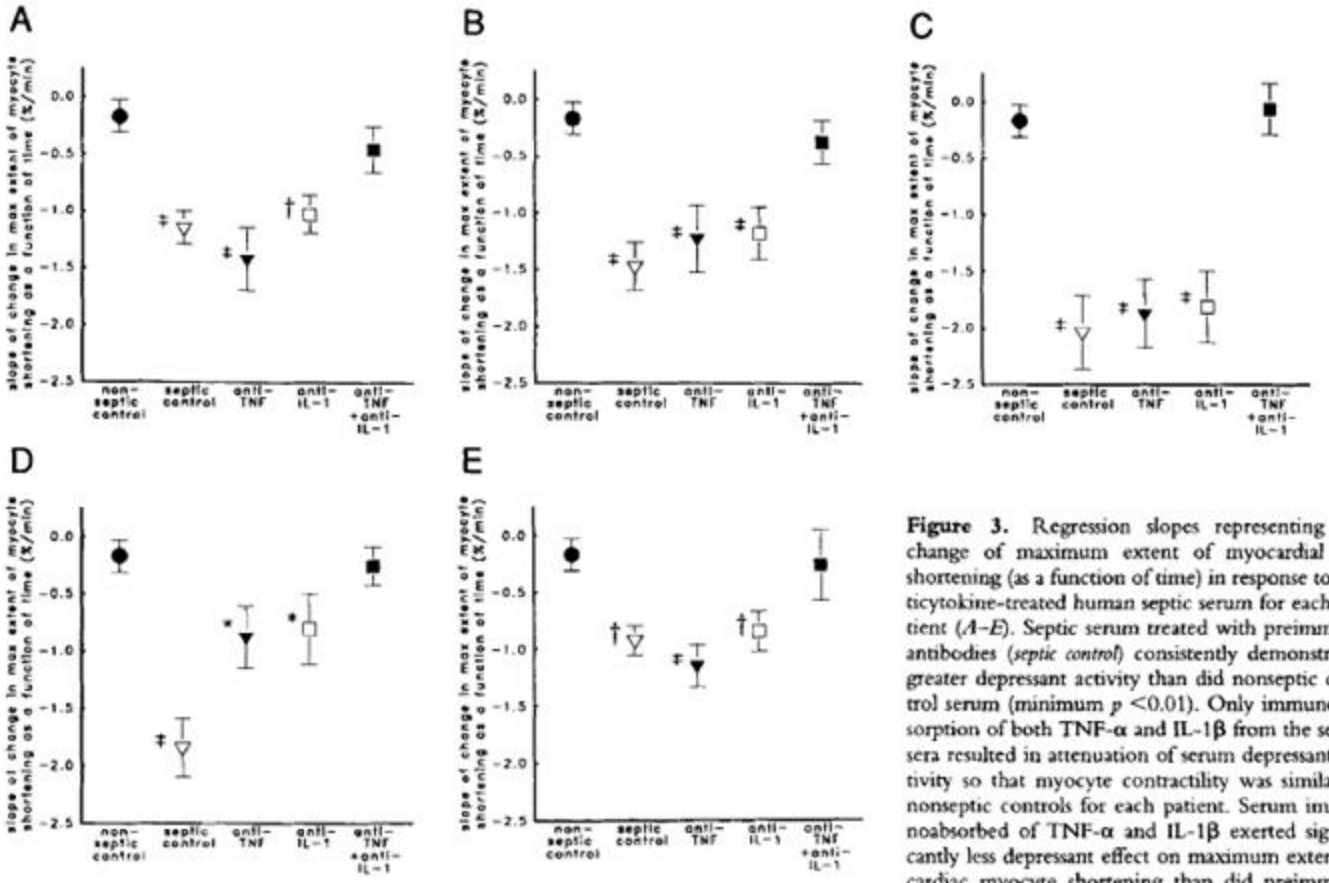


Figure 3. Regression slopes representing the change of maximum extent of myocardial cell shortening (as a function of time) in response to anticytokine-treated human septic serum for each patient (*A–E*). Septic serum treated with preimmune antibodies (*septic control*) consistently demonstrated greater depressant activity than did nonseptic control serum (minimum $p < 0.01$). Only immunoabsorption of both TNF-α and IL-1β from the septic sera resulted in attenuation of serum depressant activity so that myocyte contractility was similar to nonseptic controls for each patient. Serum immunoabsorbed of TNF-α and IL-1β exerted significantly less depressant effect on maximum extent of cardiac myocyte shortening than did preimmune antibody treated (*septic control*) samples (minimum $p < 0.01$). A Bonferonni adjustment for multiple comparisons was made so that each comparison was considered significant only if $p \leq 0.0125$. (*) $p < 0.05$; (†) $p < 0.01$; (‡) $p < 0.001$ vs. nonseptic control. Error bars, SEM.

Targeted cytokine inhibitors in HF

- TNF inhibitors

Supported by a strong rationale:

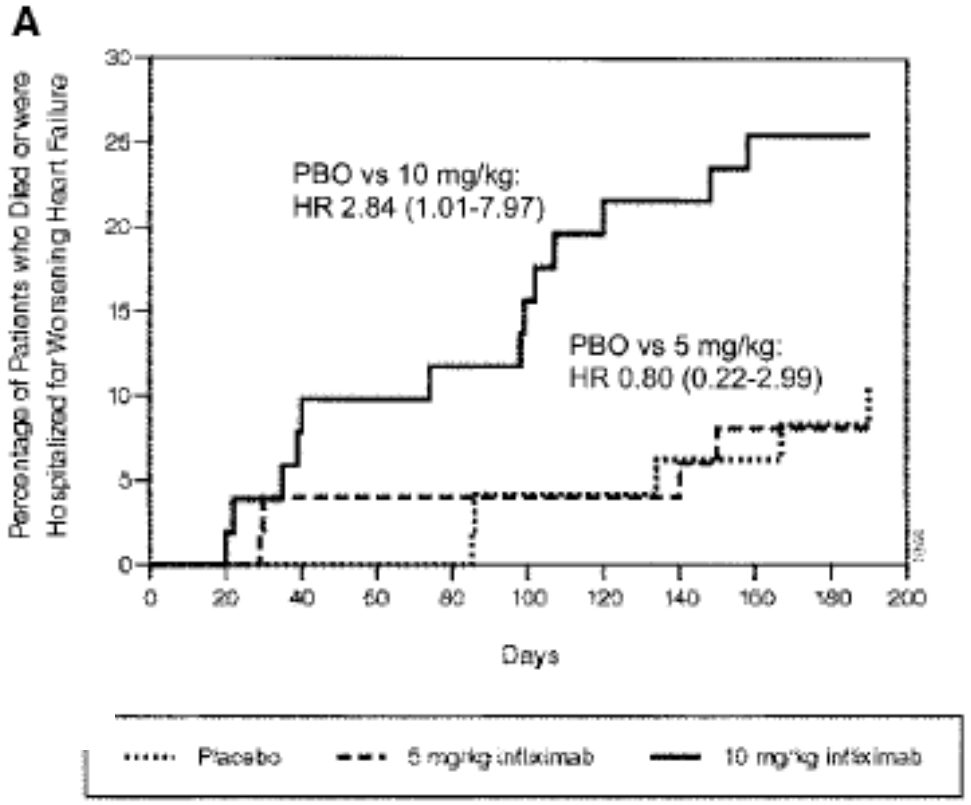
- TNF is a soluble cardiodepressant factor
- TNF levels are elevated in patients with HF
- Overexpression of TNF in the mouse leads to HF

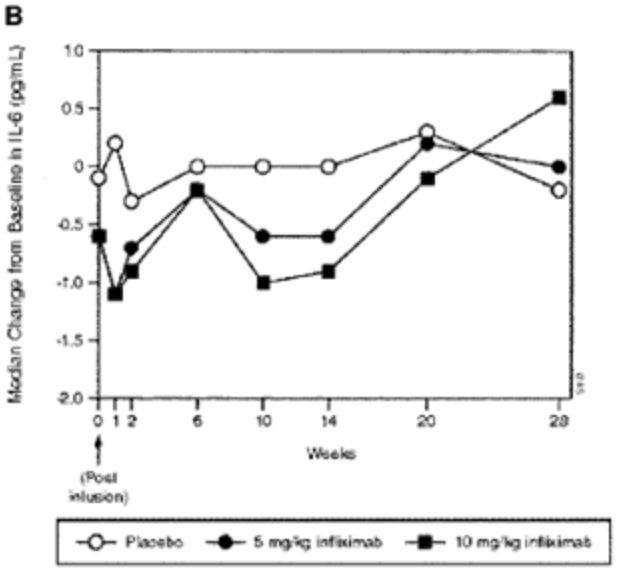
Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor-α, in Patients With Moderate-to-Severe Heart Failure

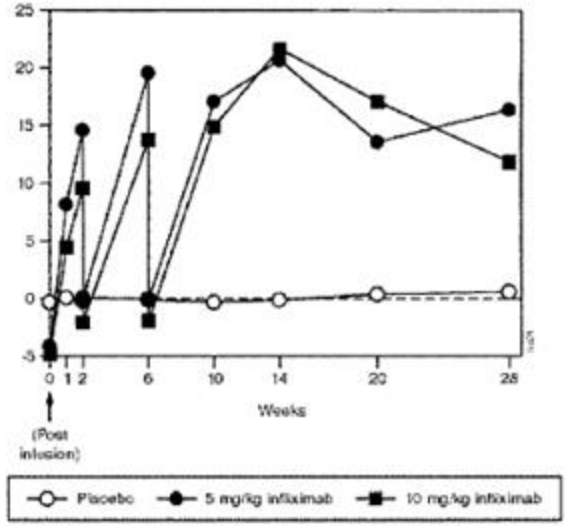
Results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) Trial

Eugene S. Chung, MD; Milton Packer, MD; Kim Hung Lo, PhD; Adedigbo A. Fasanmade, PhD; James T. Willerson, MD; for the ATTACH Investigators*

- Infliximab – TNF antibody
- 150 patients with NYHA III-IV systolic HF
- Randomized 1:1:1 to low dose, high dose or placebo
- Infusion at day 0, week 2 and 6







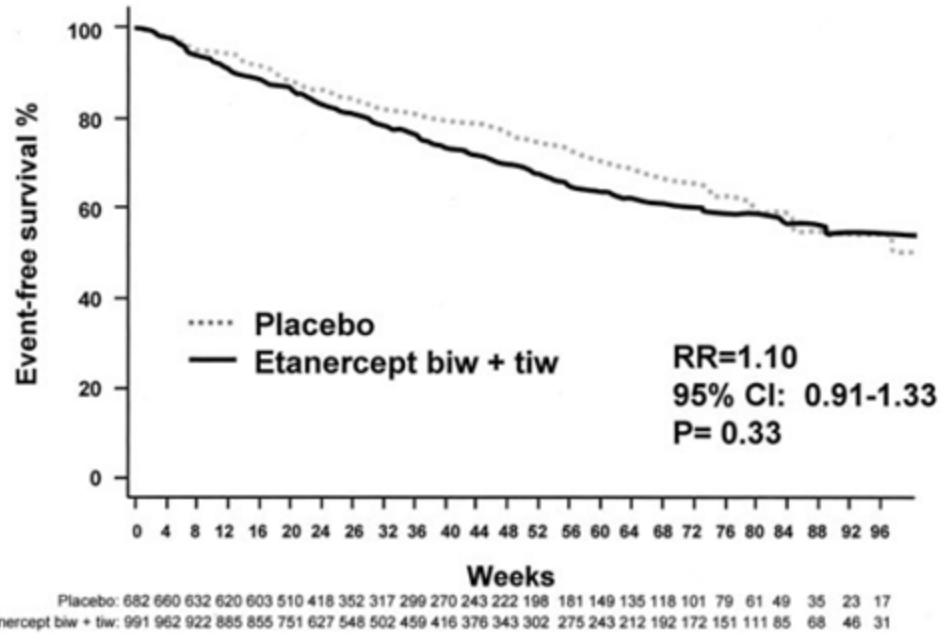
Chung et al. *Circulation* 2003

Targeted Anticytokine Therapy in Patients With Chronic Heart Failure

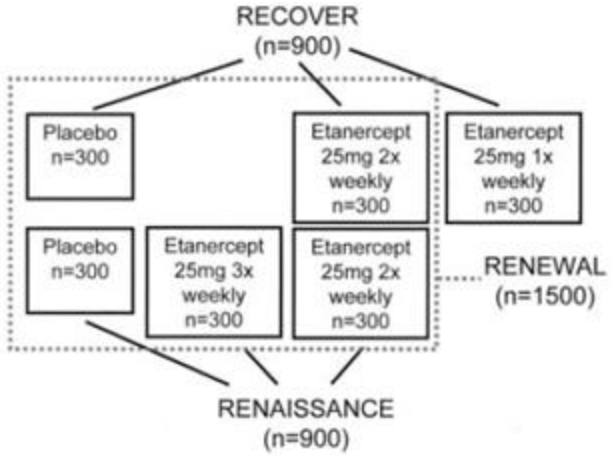
Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)

Douglas L. Mann, MD; John J.V. McMurray, MD, FRCP, FESC; Milton Packer, MD; Karl Swedberg, MD, PhD, FESC; Jeffrey S. Borer, MD; Wilson S. Colucci, MD; Jacques Djian, MD, FESC; Helmut Drexler, MD; Arthur Feldman, MD, PhD; Lars Kober, MD Henry Krum, MD, PhD, FRACP; Peter Liu, MD; Markku Nieminen, MD, PhD; Luigi Tavazzi, M Dirk Jan van Veldhuisen, MD, PhD; Anders Waldenstrom, MD, PhD; Marshelle Warren, MD Arne Westheim, MD; Faiez Zannad, MD, PhD; Thomas Fleming, PhD

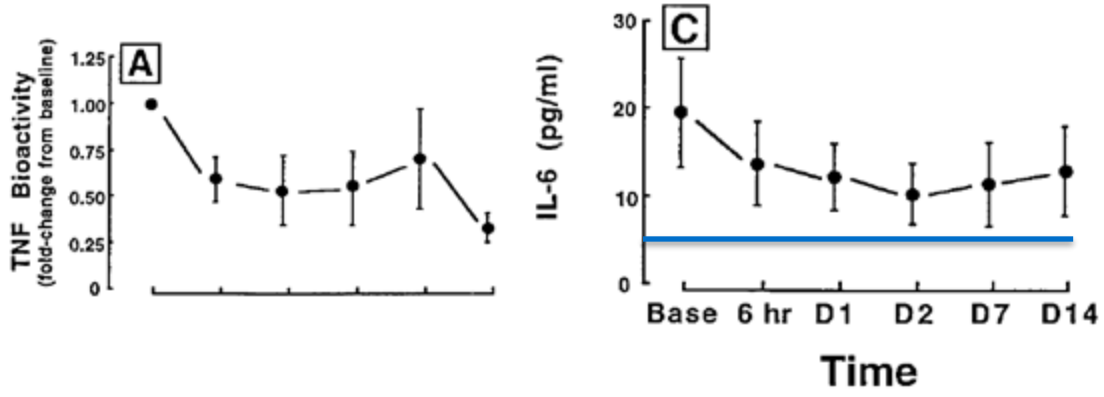
Mann et al. *Circulation* 2004



- Etanercept – TNF soluble receptor
- RENEWAL study included 1,500 patients treated with Etanercept of placebo from 2 trials



No data provided in the RENEWAL program re. IL-6 or CRP. Data from a pilot study on 18 NYHA III patients showed a modest reduction in IL-6 levels.



Deswal et al. *Circulation* 1999

Targeted cytokine inhibitors in HF

- TNF inhibitors
  - Why did it not work?
    - Wrong biology? *unknown*
      - Was inflammation inhibited? *NOT*
    - Wrong dose/duration? *unlikely*
      - Wrong strategy? *possibly*
    - Side effects of treatment? *significant*

Targeted cytokine inhibitors in HF

- TNF inhibitors
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    - Wrong dose/duration? *unlikely*
      - Wrong strategy? *possibly*
    - Side effects of treatment? *significant*

- IL-1 blockers

Supported by a strong rationale:

- IL-1 is a soluble cardiodepressant factor
- IL-1 levels are elevated in patients with HF
- IL-1 blockade is protective in mouse models of HF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

- Canakinumab – IL-1β antibody
- 10,016 patients with prior MI
- Randomized 1:1:1:1.5 to canakinumab 50 mg, 150 mg, 300 mg, or placebo quarterly
- 15% reduction in the primary endpoint: CV death, non-fatal MI or stroke
- Largest cytokine study ever

Ridker PM et al. *N Engl J Med* 2017

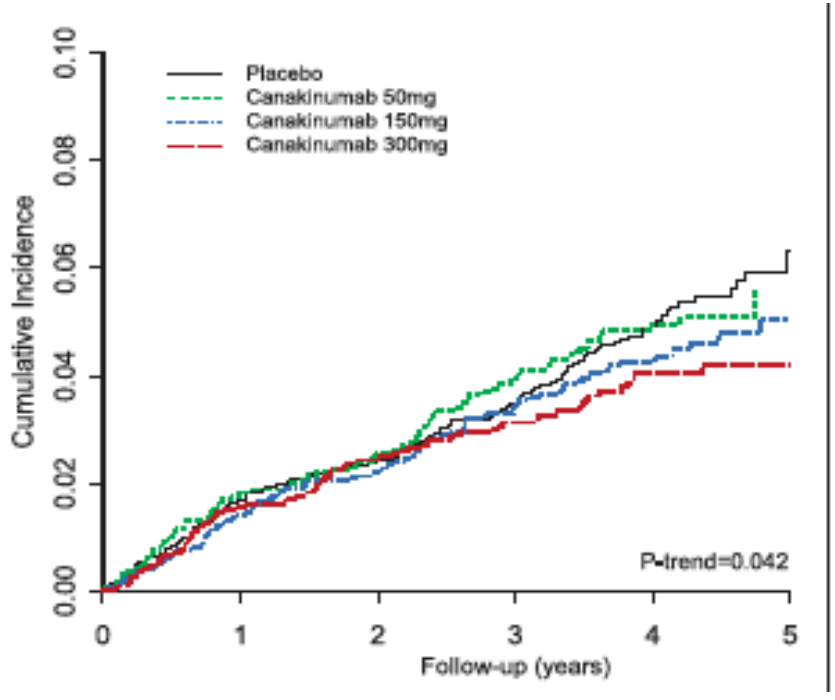
Circulation

Everett B et al. *Circulation* 2019

ORIGINAL RESEARCH ARTICLE

Anti-Inflammatory Therapy With Canakinumab for the Prevention of Hospitalization for Heart Failure

- Canakinumab treatment was associated with a dose—dependent trend in reduction in HF hospitalization or HF-related death

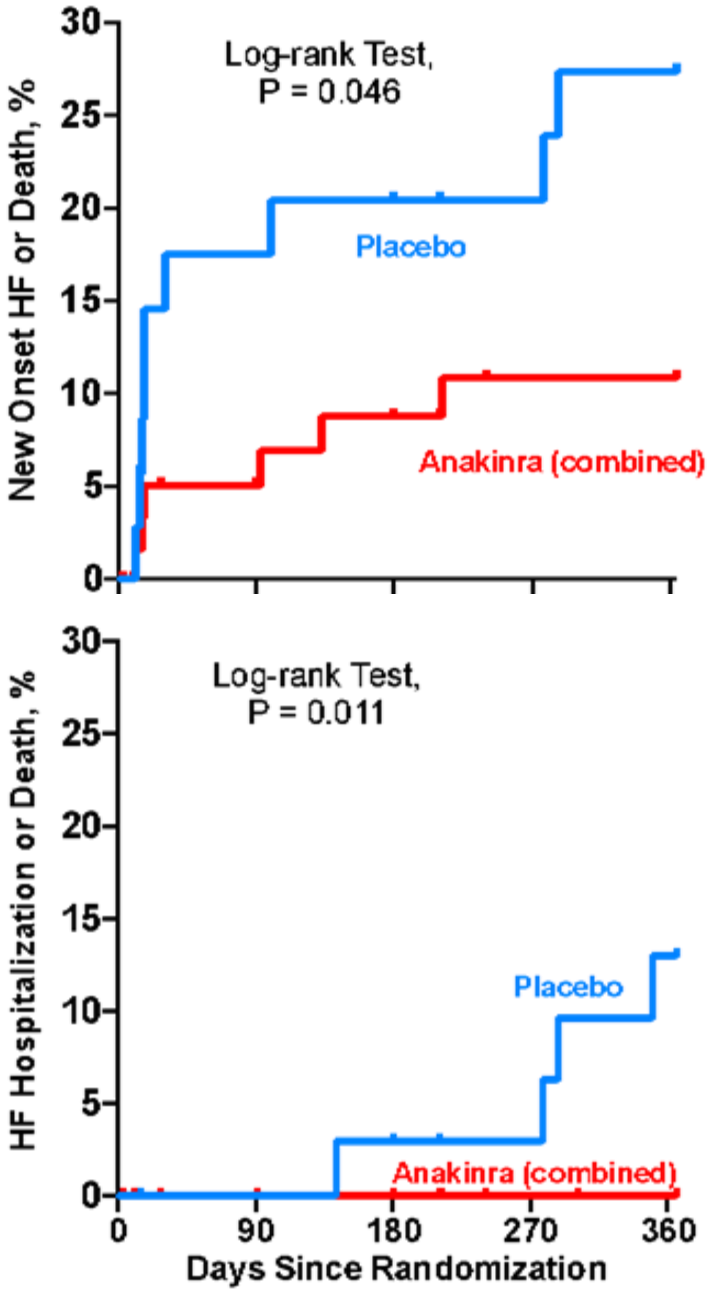


Interleukin-1 Blockade Inhibits the Acute Inflammatory Response in Patients With ST-Segment–Elevation Myocardial Infarction

Antonio Abbate, MD, PhD; Cory R. Trankle, MD; Leo F. Buckley, PharmD; Michael J. Lipinski, MD, PhD; Darryn Appleton, MD; Dinesh Kadariya, MD; Justin M. Canada, PhD; Salvatore Carbone, PhD; Charlotte S. Roberts, NP; Nayef Abouzaki, MD; Ryan Melchior, DO; Sanah Christopher, MD; Jeremy Turlington, MD; George Mueller, DO; James Garnett, MD; Christopher Thomas, MD; Roshanak Markley, MD; George F. Wohlford, PharmD; Laura Puckett, RN; Horacio Medina de Chazal, MD; Juan G. Chiabrando, MD; Edoardo Bressi, MD; Marco Giuseppe Del Buono, MD; Aaron Schatz, MD; Chau Vo, MD; Dave L. Dixon, PharmD; Giuseppe G. Biondi-Zoccai, MD, MStat; Michael C. Kontos, MD; Benjamin W. Van Tassell, PharmD

- Anakinra – IL-1 receptor antagonist
- 99 patients with ST-segment elevation MI (STEMI)
- Randomized 1:1:1 to anakinra 100 mg daily, 100 mg twice daily, or placebo for 14 days
- Primary endpoint: acute inflammatory response (AUC for CRP at 14 days)
- Secondary endpoints: new onset heart failure (adjudicated by independent committee)

- Anakinra (both doses) significantly reduced AUC for CRP at 14 days and reduced new onset HF and HF hospitalizations



Abbate et al. *J Am Heart Assoc* 2020

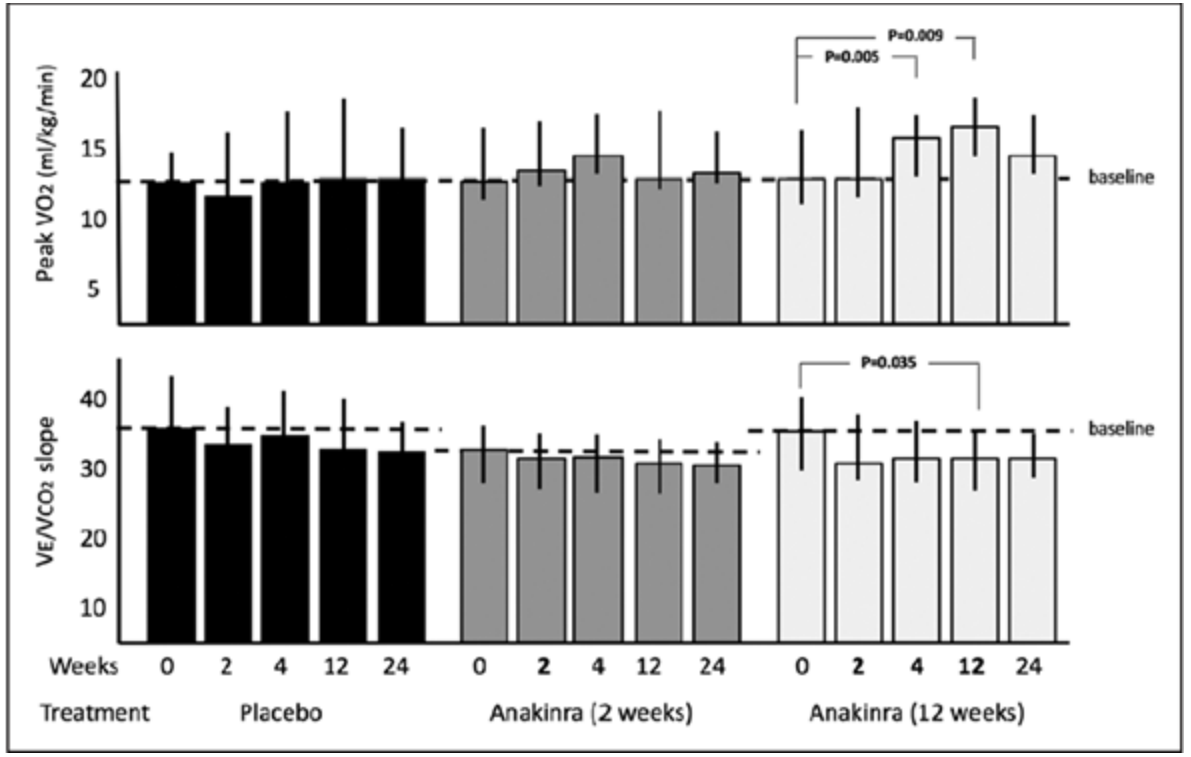
Interleukin-1 Blockade in Recently Decompensated Systolic Heart Failure

Results From REDHART (Recently Decompensated Heart Failure Anakinra Response Trial)

- Anakinra – IL-1 receptor antagonist
- 60 patients with recently decompensated HFrEF (within 2 weeks of hospital discharge)
- Randomized 1:1:1 to anakinra 100 mg daily for 2 weeks, 100 mg daily for 12 weeks, or placebo
- Primary endpoint: peak VO2 and VE/VCO2
- Secondary endpoints: heart failure hospitalization (adjudicated by independent committee)

- Peak VO2 and VE/VCO2 were significantly improved in the 12-week anakinra treatment group
- Readmission for HF was lowers in the anakinra 12-week group (P=0.10 – not significant)

Van Tassell et al. *Circ Heart Fail* 2017



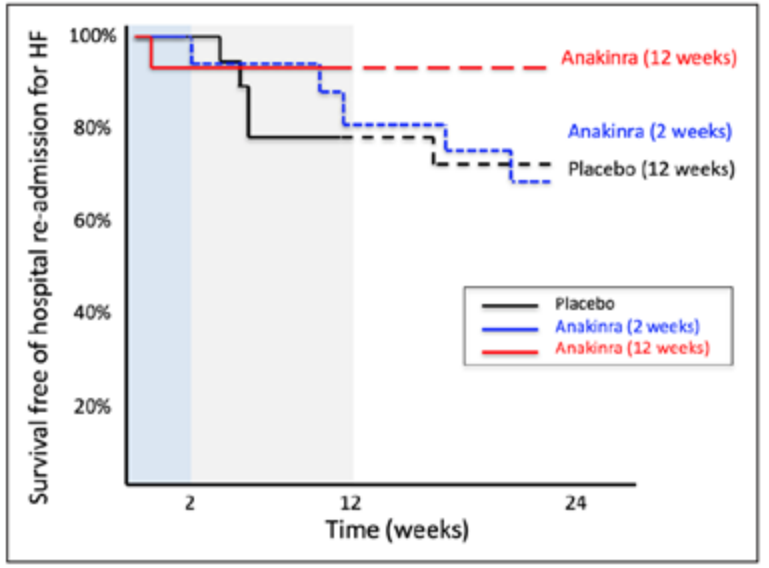


Figure 6. Effects of treatment on survival free of hospital readmission for heart failure (HF).
The incidence of death or readmission for HF at 24 wk was 30% in the placebo group, 31% in the group treated with anakinra for 2 wk, and 6% in the group treated with anakinra 12 wk (log-rank *P* test *P*=0.10).

Targeted cytokine inhibitors in HF

- TNF-α inhibitors
  - Why did it not work?
    - Wrong biology? *unknown*
      - Was inflammation inhibited? *NOT*
    - Wrong dose/duration? *unlikely*
      - Wrong strategy? *possibly*
    - Side effects of treatment? *significant*

- IL-1 blockers
  - Did it work?
    - Biological signal? *present*
      - Was inflammation inhibited? *Yes*
    - Dose/duration appropriate? *unsure*
      - Best strategy? *unsure*
    - Side effects of treatment? *significant in some cases*

Arteriosclerosis, Thrombosis, and Vascular Biology

2024

***ATVB* IN FOCUS:**
Immune Dysfunction and Cardiometabolic Disease

Series Edito

Novel Therapeutics and Upcoming Clinical Trials Targeting Inflammation in Cardiovascular Diseases

Nicola Potere, Aldo Bonaventura, Antonio Abbate

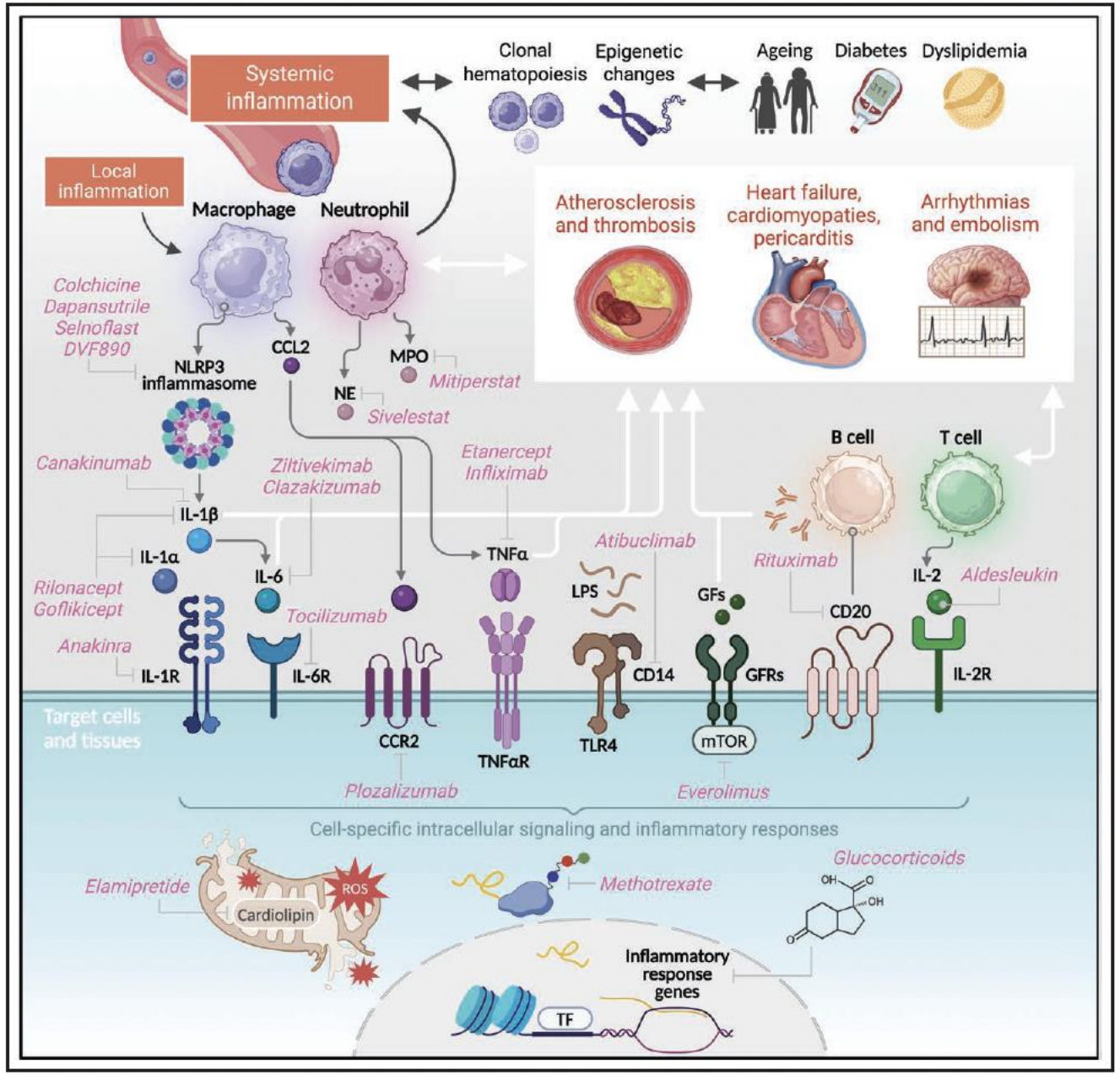


Figure. The growing anti-inflammatory drug armamentarium to combat cardiovascular diseases.

IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled, phase 2 trial

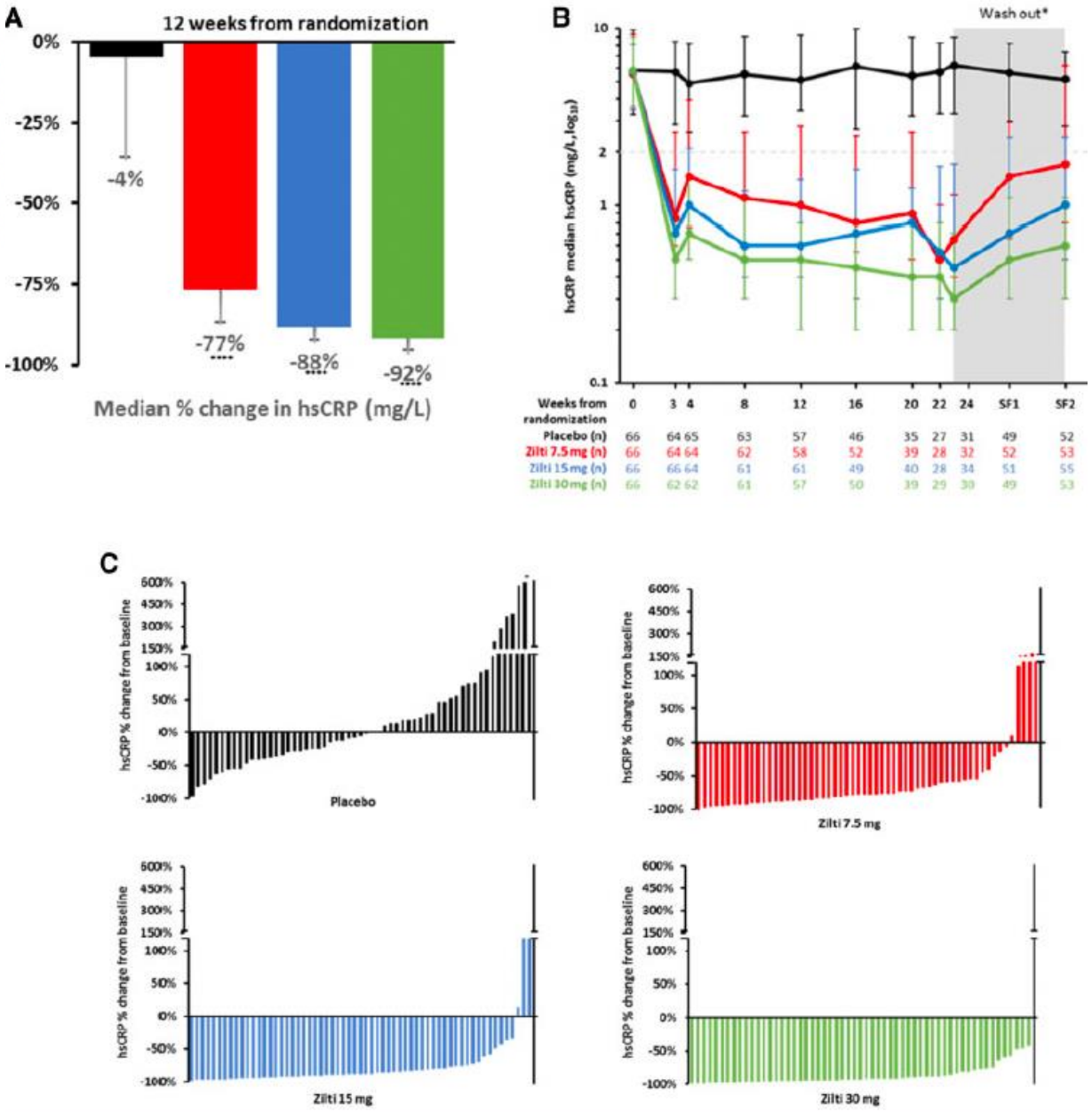
*Paul M Ridker, Matt Devalaraja, Florian M M Baeres, Mads D M Engelmann, G Kees Hovingh, Milana Ivkovic, Larry Lo, Douglas Kling, Pablo Pergola, Dominic Raj, Peter Libby, Michael Davidson, on behalf of the RESCUE Investigators**

Lancet 2021

	Placebo (n=66)	Ziltivekimab 7·5 mg (n=66)	Ziltivekimab 15 mg (n=66)	Ziltivekimab 30 mg (n=66)
Age, years	66·0 (60·0–74·0)	70·0 (60·0–74·0)	65·5 (59·0–74·0)	68·0 (61·0–76·0)
Gender				
Female	29 (44%)	32 (48%)	36 (55%)	32 (48%)
Male	37 (56%)	34 (52%)	30 (45%)	34 (52%)
Race				
White	50 (76%)	48 (73%)	49 (74%)	52 (79%)
Black or African American	16 (24%)	18 (27%)	12 (18%)	14 (21%)
Other	0	0	5 (8%)	0
Body-mass index, kg/m²	35·90 (29·20–39·50)	32·70 (27·50–40·20)	34·40 (29·60–38·90)	34·85 (31·30–39·80)
Diabetes*	50 (76%)	41 (62%)	48 (73%)	48 (73%)
Hypertension†	62 (94%)	60 (91%)	60 (91%)	60 (91%)
Atherosclerotic cardiovascular disease	37 (56%)	29 (44%)	27 (41%)	33 (50%)
Statin use	45 (68%)	44 (67%)	45 (68%)	45 (68%)
Chronic kidney disease stage‡				
3a	19 (29%)	16 (24%)	23 (35%)	19 (29%)
3b	23 (35%)	30 (45%)	29 (44%)	26 (39%)
4	17 (26%)	16 (24%)	10 (15%)	17 (26%)
5	5 (8%)	3 (5%)	4 (6%)	3 (5%)
eGFR, mL/min per 1·73 m²	38·00 (26·33–48·33)	35·33 (26·00–45·33)	37·33 (31·33–50·33)	37·17 (27·67–45·67)
High-sensitivity CRP, mg/L	5·80 (3·25–9·85)	5·53 (3·50–9·25)	5·70 (3·45–8·10)	5·80 (3·65–8·90)
IL-6, pg/mL§	5·24 (3·60–7·62)	4·85 (3·06–8·28)	5·11 (3·79–9·44)	6·63 (4·07–9·01)

Data are median (IQR) or n (%). eGFR=estimated glomerular filtration rate. *Includes patients with glycated haemoglobin >6·5%, those with a history of diabetes at baseline, or those on diabetes medication at baseline; diabetes history of patients was identified using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. †Includes patients with a history of hypertension at baseline or those on medication for hypertension at baseline, identified using MedDRA. ‡Baseline chronic kidney disease value based on laboratory results and calculated as the average of all eGFR assessments before the first dose. Chronic kidney disease stages 3a and 3b indicate stage 3 patients with baseline GFR of 45–59 mL/min per 1·73 m² (stage 3a) and 30–44 mL/min per 1·73 m² (stage 3b). §Baseline IL-6 measurements missing for some patients: placebo n=48, ziltivekimab 7·5 mg n=48, ziltivekimab 15 mg n=52, ziltivekimab 30 mg n=54.

Table 1: **Baseline characteristics of the RESCUE trial population**



A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Heart Failure and Inflammation (HERMES)

ClinicalTrials.gov Identifier: NCT05636176

Recruitment Status : Not yet recruiting
First Posted : December 5, 2022
Last Update Posted : April 4, 2023

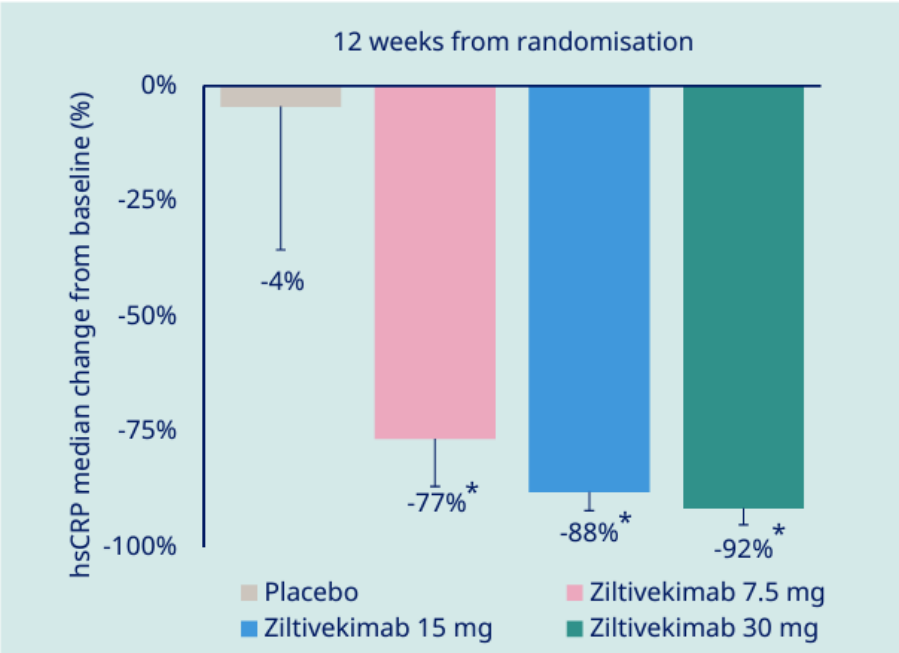
See Contacts and Locations

Inclusion Criteria:

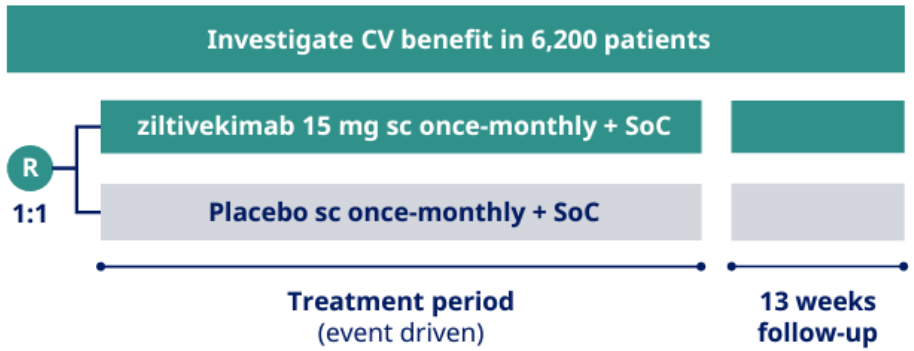
- Serum high-sensitivity C-reactive protein (hs-CRP) greater than equal to 2 milligrams per liter (mg/L) at screening (visit 1) Disease specific - cardiovascular
- At least one of the following:
    1. N-terminal-pro-brain natriuretic peptide (NT-proBNP) greater than equal to 300 picograms per milliliter (pg/mL) at screening (Visit 1) for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at screening (visit 1), NTproBNP must be greater than equal to 600 pg/mL.
    2. Hospitalisation or urgent/unplanned visit with a primary diagnosis of decompensated heart failure which required intravenous loop diuretic treatment, within the last 9 months prior to screening (visit 1) in combination with NT-proBNP greater than equal to 200 pg/mL at screening (Visit 1) for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at screening (visit 1), NT-proBNP must be greater than equal to 600 pg/mL.
- Diagnosis of heart failure (New York Heart Association [classification] [NYHA] Class II-IV).
- Left ventricular ejection fraction (LVEF) greater than 40 percentage (%) documented by echocardiography within 12 months prior to or at screening (visit 1). The LVEF must be documented in medical records and the most recent measurement must be used to determine eligibility with no interim event signalling potential deterioration in ejection fraction (e.g., myocardial infarction [MI] or heart failure [HF] hospitalisation).
- Structural heart disease and/or functional heart disease documented by echocardiography within 12 months prior to or at screening (visit 1) showing at least one of the following:
- Left atrial (LA) volume index greater than 34 milliliter per meter square (mL/m^2).
- LA diameter greater than equal to 3.8 centimeter (cm).
- LA length greater than equal to 5.0 cm.
- LA area greater than equal to 20 cm square.
- LA volume greater than equal to 55 milliliters (mL).
- Intraventricular septal thickness greater than equal to 1.1 cm.
- Posterior wall thickness greater than equal to 1.1 cm.
- Left ventricular (LV) mass index greater than equal to 115 grams per meter square (g/m^2) in men or greater than equal to 95 g/m^2 in women.
- E/e' (mean septal and lateral) greater than equal to 10.
- e' (mean septal and lateral) less than 9 centimeter per second (cm/s).
- No heart failure hospitalisations or urgent heart failure visits between screening (visit 1) and randomisation (visit 2).

ZEUS trial with ziltivekimab aims to validate the link between hsCRP and major adverse cardiovascular events

Results from the phase 2 trial RESCUE with ziltivekimab



Phase 3 CVOT trial ZEUS with ziltivekimab



Primary endpoint

- Time to the first occurrence of 3-point MACE[1]

Secondary endpoints

- Time to first occurrence of expanded MACE[1]
- Number of hospitalisations for HF or urgent HF visit
- Time to occurrence of all-cause mortality
- Time to first occurrence of a composite CKD endpoint

6200 pts
Event-driven

Inclusion Criteria:

- Chronic kidney disease defined by one of the below:
  1. Estimated glomerular filtration rate (eGFR) greater than or equal to (>=) 15 and below 60 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation)
  2. Urinary albumin-to-creatinine ratio (UACR) >= 200 milligrams per gram (mg/g) and eGFR >= 60 mL/min/1.73 m2 (using the CKD-EPI creatinine equation)
- Serum high-sensitivity C-reactive protein (hs-CRP) greater than or equal to 2 milligram per liter (mg/L)
- Evidence of atherosclerotic cardiovascular disease (ASCVD) by one or more of the following:

  a) Coronary heart disease defined as at least one of the following: i. Documented history of MI ii. Prior coronary revascularisation procedure iii. greater than or equal to 50% stenosis in major epicardial coronary artery documented by cardiac catheterisation or CT coronary angiography b) Cerebrovascular disease defined as at least one of the following: i. Prior stroke of atherosclerotic origin ii. Prior carotid artery revascularisation procedure iii. greater than or equal to 50% stenosis in carotid artery documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound.

  c) Symptomatic peripheral artery disease (PAD) defined as at least one of the following: i. Intermittent claudication with an ankle-brachial index (ABI) below or equal to 0.90 at rest ii. Intermittent claudication with a greater than or equal to 50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, MR angiography, CT angiography or Doppler ultrasound iii. Prior peripheral artery (excluding carotid) revascularisation procedure iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g. trauma or osteomyelitis).

ClinicalTrials.gov

Go to the classic website

NOT YET RECRUITING

ARTEMIS - A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With a Heart Attack (ARTEMIS)

ClinicalTrials.gov ID NCT06118281

Sponsor Novo Nordisk A/S

Information provided by Novo Nordisk A/S (Responsible Party)

Last Update Posted 2023-12-26