

# Autoimmune disease: diagnosis, treatment, cardiovascular disease, and mortality

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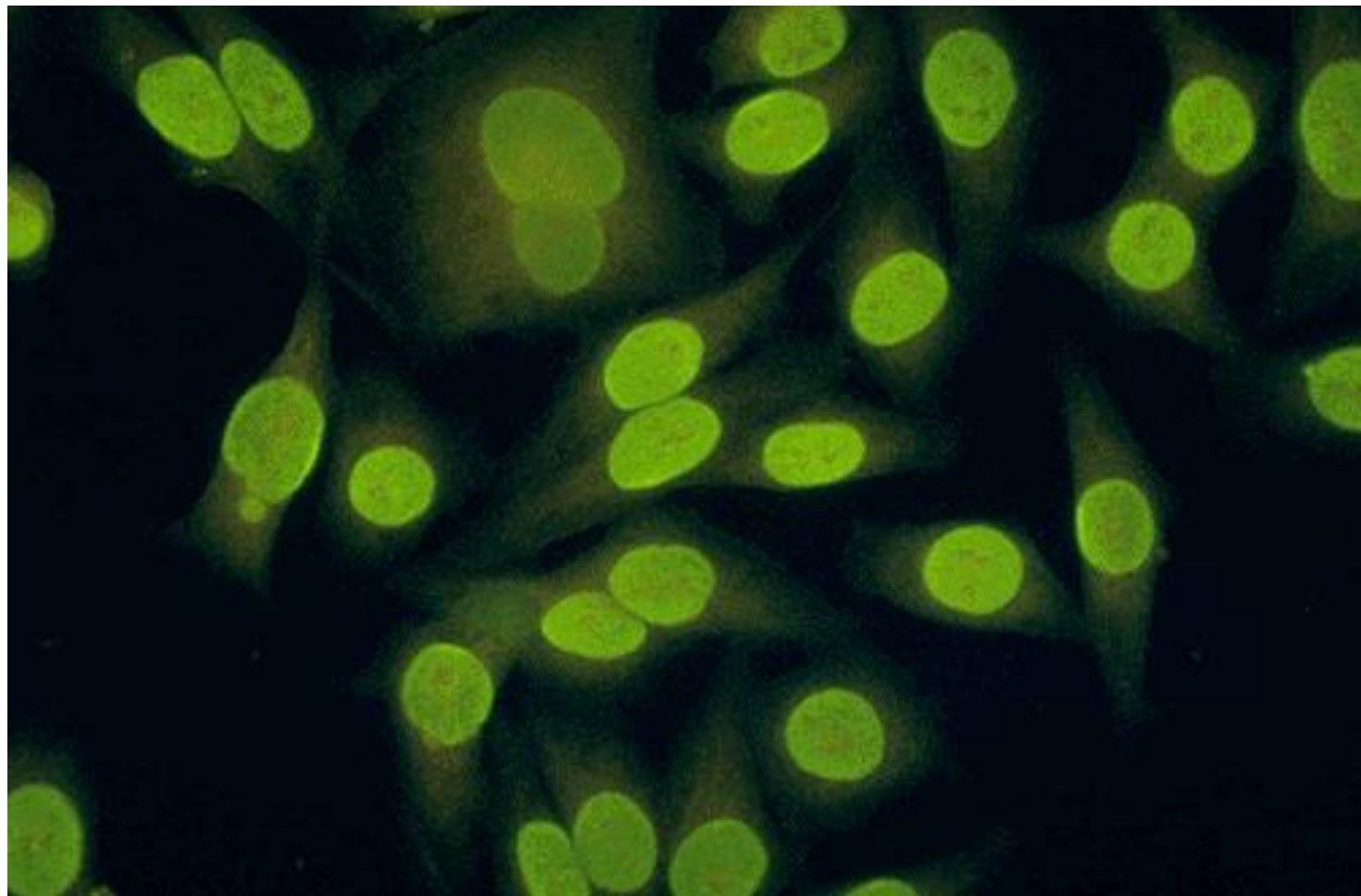
Medical University of South Carolina



# Objectives

- Serologies in autoimmune disease
- Newer biologics for connective tissue diseases
- Connective tissue disease as risk factor for atherosclerotic disease
- Predictors of mortality in CTD

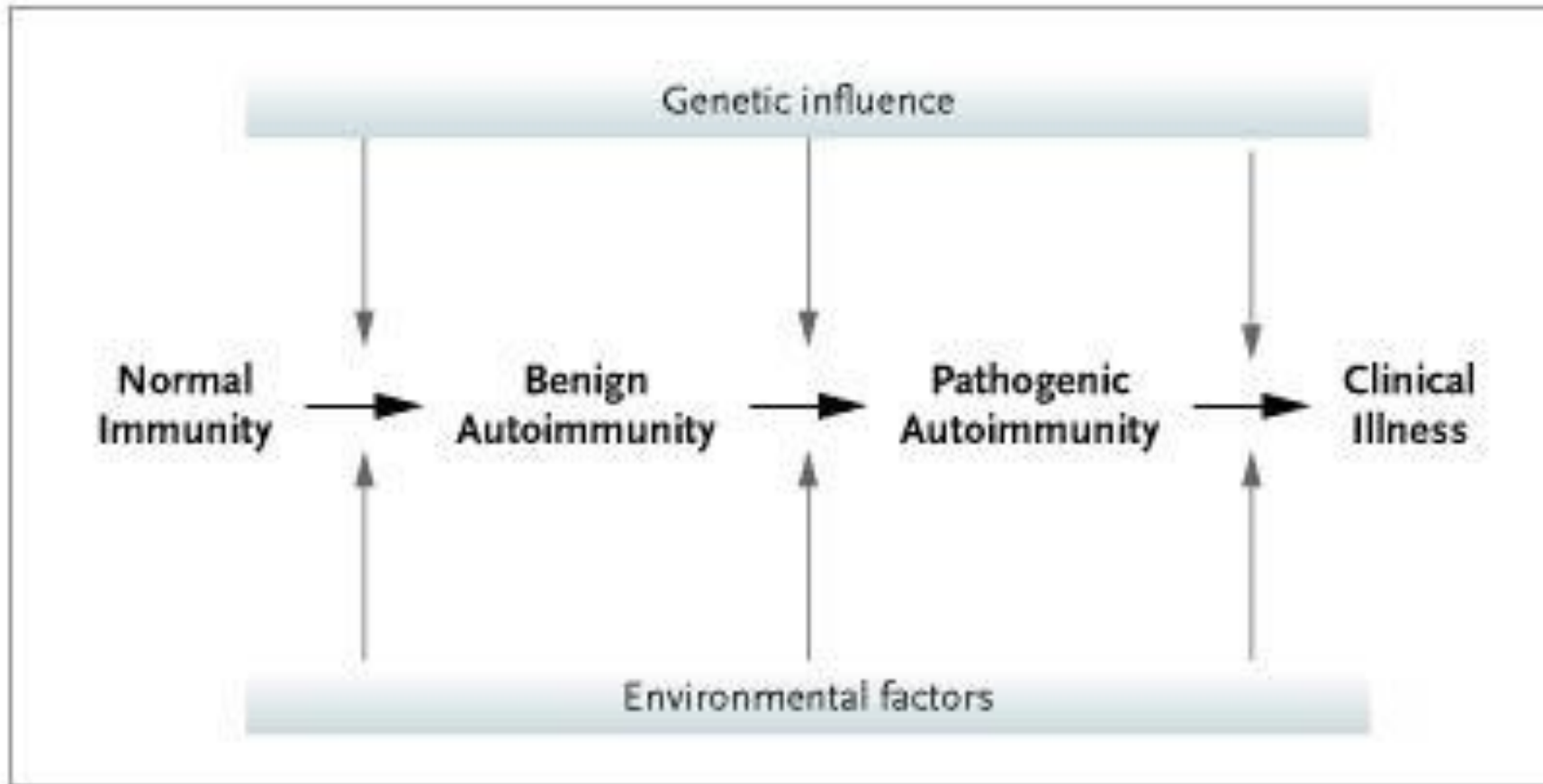
# Antinuclear Antibody

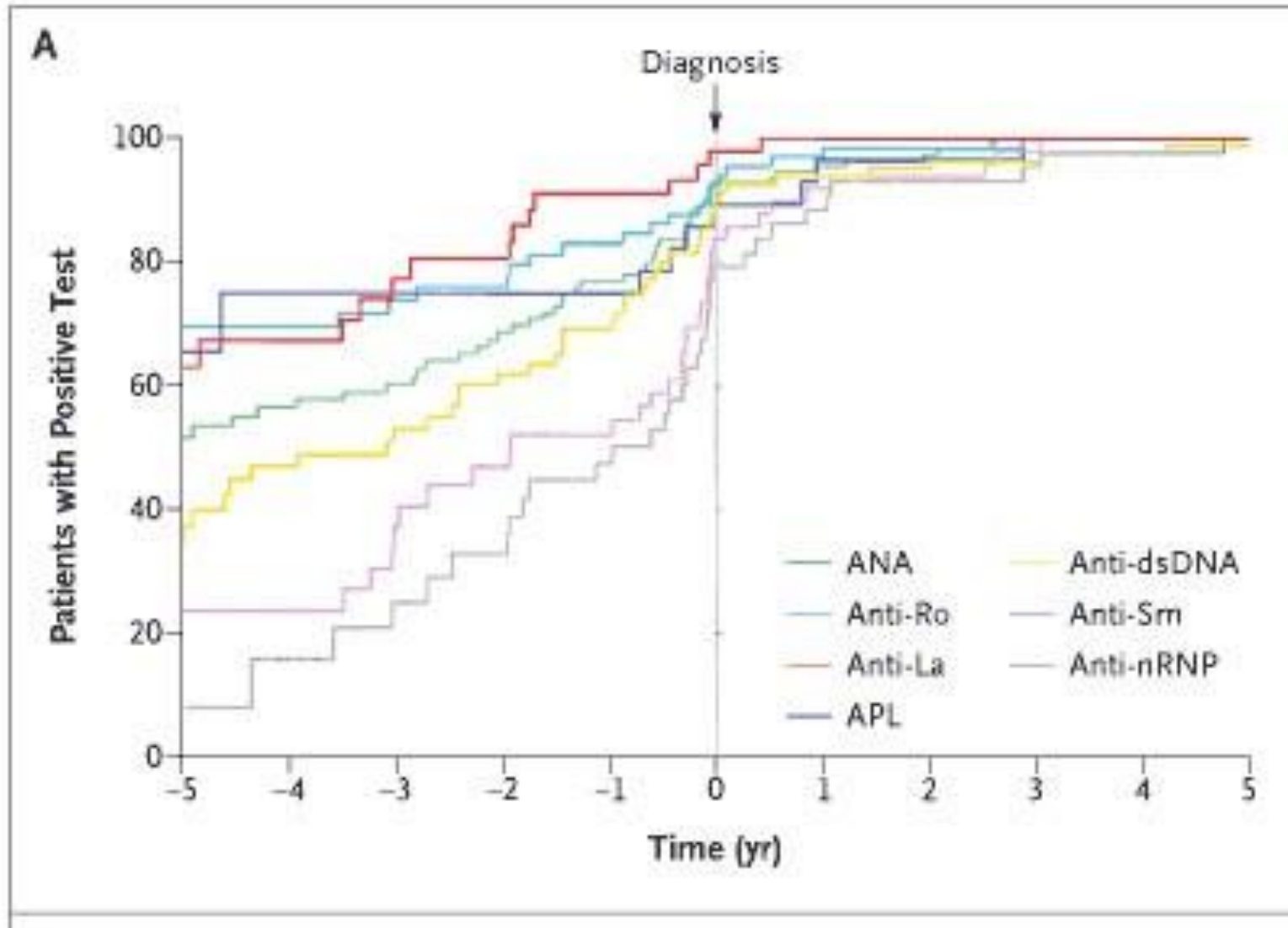


# ANA testing

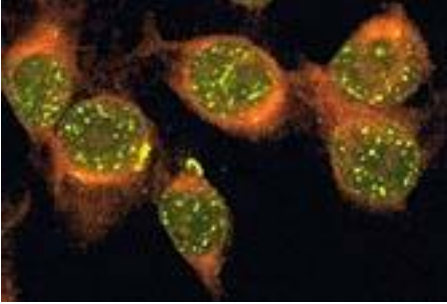
- 98% sensitive
- 95% specific at 1:160
- 20% of 1<sup>st</sup> degree relatives of SLE patients will be ANA positive, while only 5% will get SLE
- The prevalence of ANA increases with aging and infections

# Progression to clinical autoimmunity

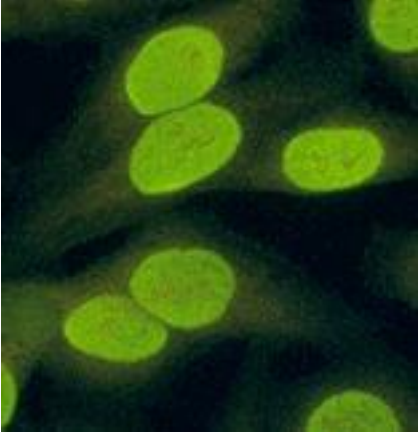




# ANA patterns



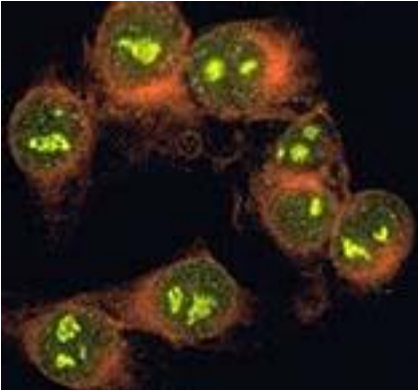
speckled



homogeneous

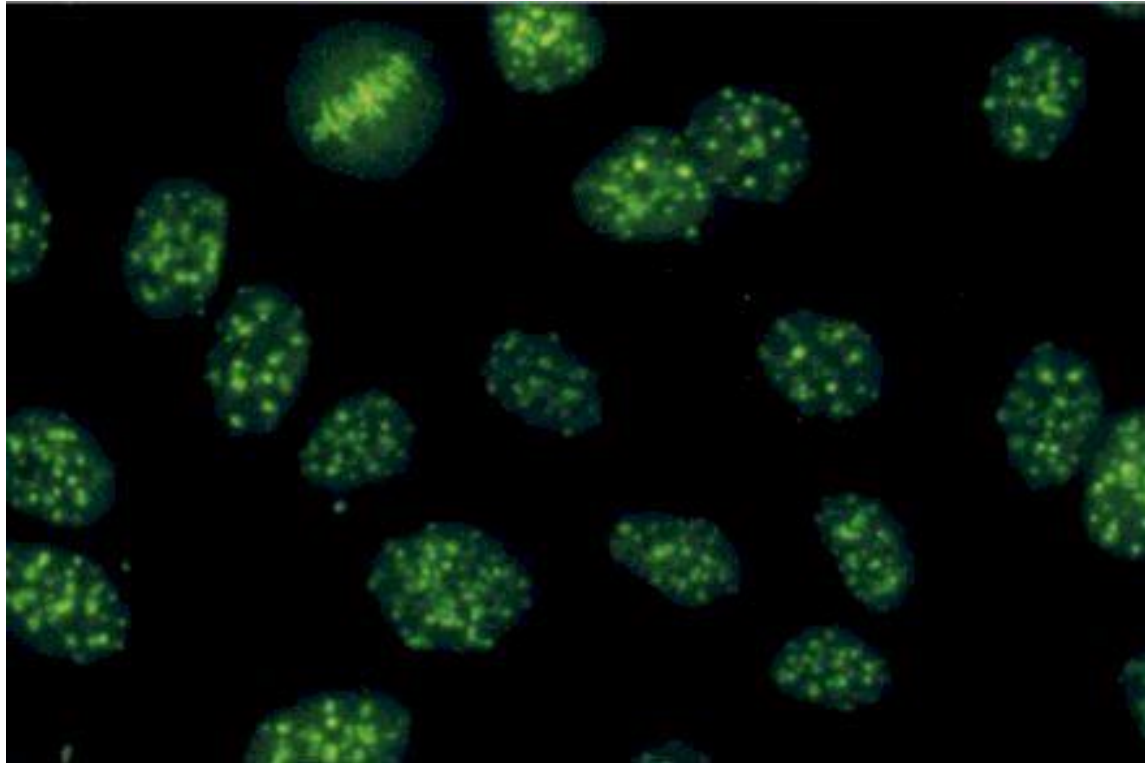


rim



nucleolar

# Centromere



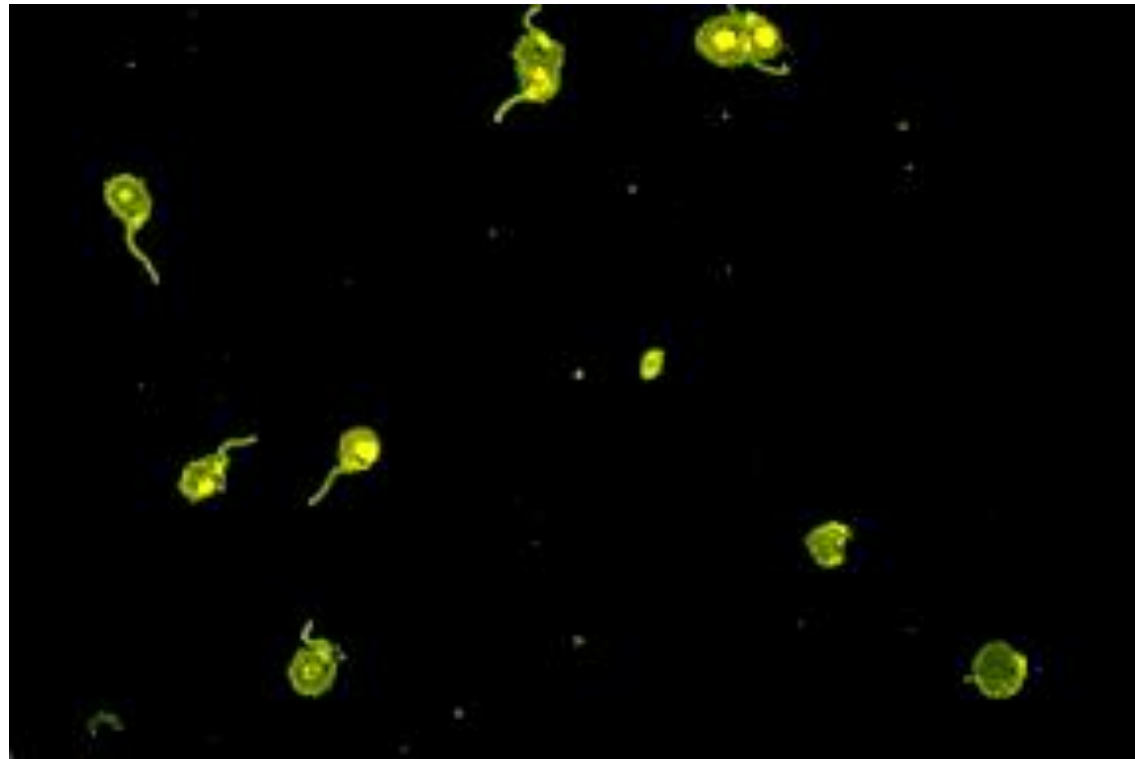


# What do the patterns mean?

- Speckled - Seen in lupus, overlap syndromes
- Rim - dsDNA. Specific for SLE.
- Homogenous - Seen in drug-induced lupus.
- Nucleolar - Seen in scleroderma
- Centromere - Seen in CREST syndrome

# Extractable Nuclear Antigens (ENA) and autoantibodies

- Anti-Smith, Ro, La, RNP, Scl-70 antibodies
- anti-double stranded DNA antibodies
- lupus anti-coagulant/ anti-cardiolipin antibodies



# ENA (extractable nuclear antigen) antibodies

- Smith – specific to SLE, 25% sensitive
- Ro (SSA) – 30% sensitive, seen in Sjögren's syndrome (50%), neonatal lupus, congenital heart block, subacute cutaneous lupus
- La (SSB) - 10% of SLE, more specific for Sjögren's
- RNP – 30-40% of SLE; in isolation seen in overlap syndromes with scleroderma, rheumatoid arthritis, and myositis
- Scl-70 – 30% sensitive, 95% specific for scleroderma

# Take Home Points

- Lupus is a clinical not a laboratory diagnosis
- Treat what you see
  - Prevent damage
  - Improve quality of life

# Serologies in RA

- Rheumatoid Factor (RF)
  - Positive test in ~75% of patients with RA
  - Occasionally occurs in other inflammatory diseases (Hepatitis C, TB, chronic infections)
  - Also seen in 5% of the population
  - Associates with erosions, damage, nodules, pulmonary fibrosis
- Anti-CCP antibodies
  - Anti-cyclic citrullinated peptide antibodies
  - Highly specific for RA (90%)
  - Correlates well with disease progression (erosions, systemic features)

# Markers of inflammation

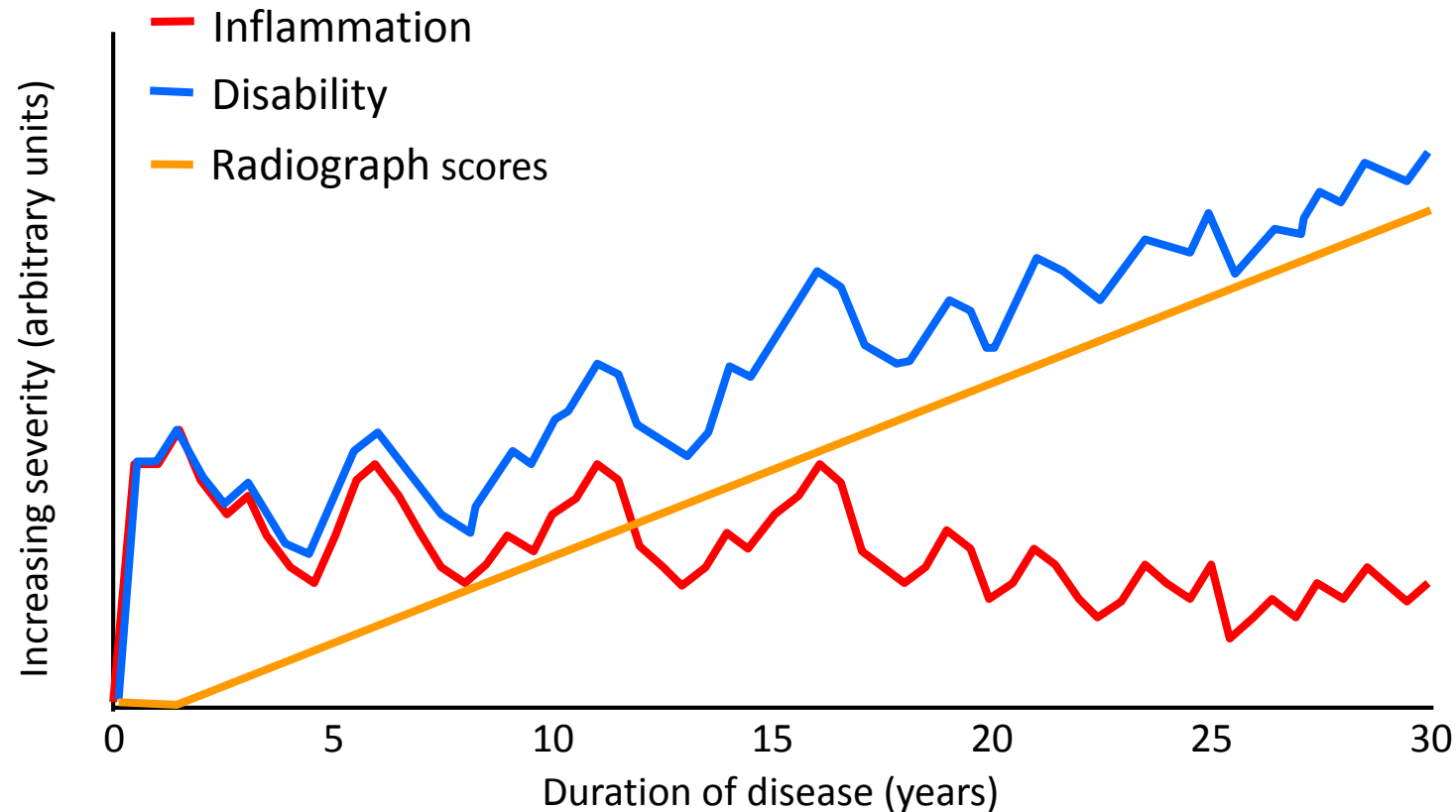
- Erythrocyte sedimentation rate (ESR)
  - Measures how rapidly red blood cells settle
  - Useful to monitor disease course
- C-reactive protein (CRP)
  - Serum protein that increases rapidly after tissue injury, indicating acute inflammation (typically  $>0.7$  mg/dL)
  - May be used to monitor disease course

**90% of the joints involved in RA are affected within the first year**

SO TREAT IT EARLY

# Relationship of Radiographic Joint Damage to Disability

Model of joint disease progression



Kirwan JR. *J Rheumatol* 2001;28:881-6.



# Clinical and Radiographic Symptoms of RA



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# Drugs for RA

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Disease-modifying anti-rheumatic drugs (DMARDs)
  - Synthetic
  - Biologic
- Glucocorticoids

# DMARDs

## Disease Modifying Anti-Rheumatic Drugs

- Reduce swelling & inflammation
- Improve pain
- Improve function
- Have been shown to reduce radiographic progression (erosions)

# Synthetic DMARDs (traditional)

- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Leflunomide
- Azathioprine

# Common DMARD Combinations

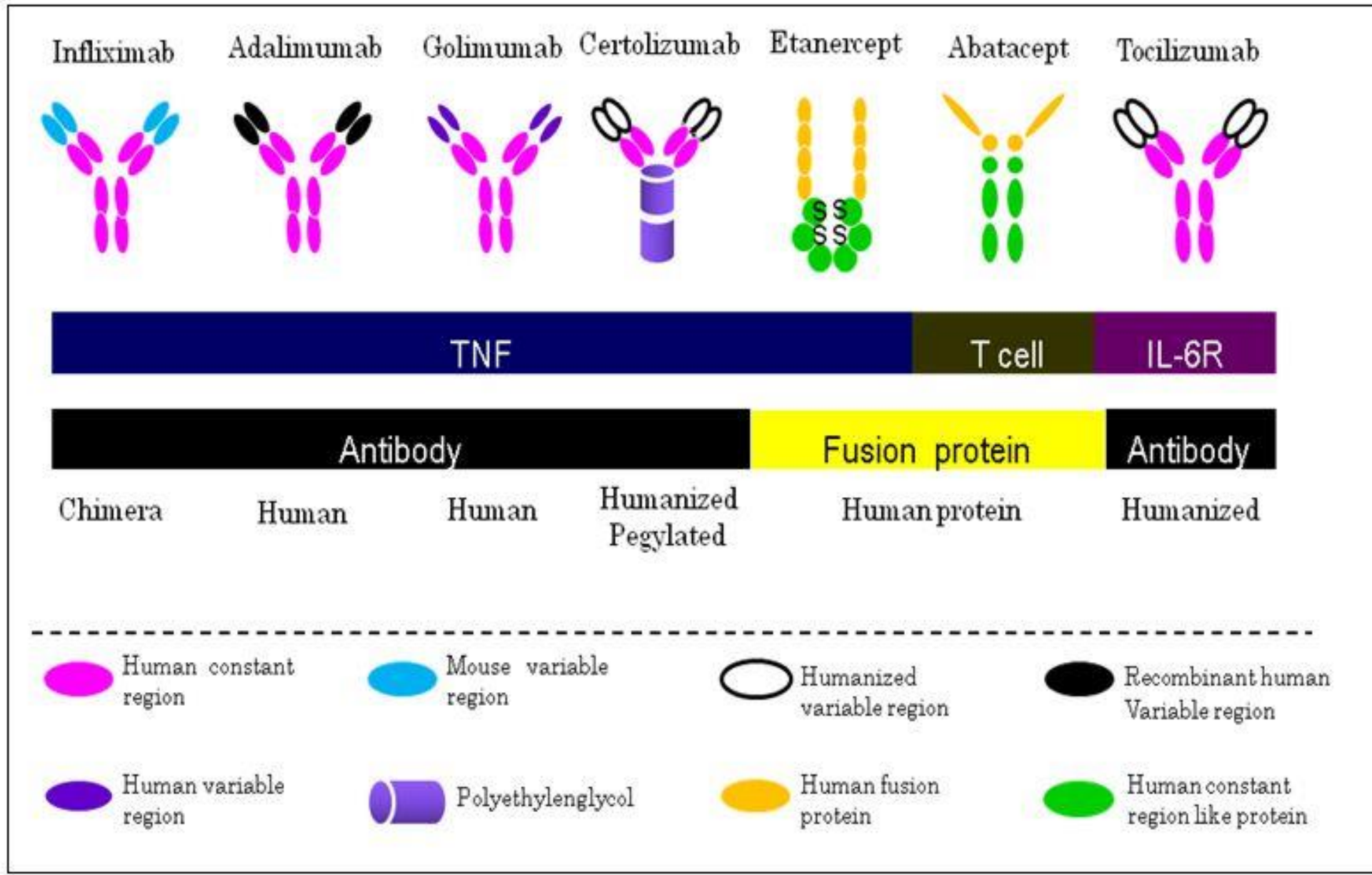
- Triple Therapy
  - Methotrexate, Sulfasalazine, Hydroxychloroquine
- Double Therapy
  - Methotrexate & Leflunomide
  - Methotrexate & Sulfasalazine
  - Methotrexate & Hydroxychloroquine
  - Sulfasalazine & Hydroxychloroquine

# Biologic Therapy

- Complex protein molecules
- Created using molecular biology methods
- Produced in prokaryotic or eukaryotic cell cultures
- Naming
  - “imab” = chimeric monoclonal (has mouse bits)
  - “umab” = humanized monoclonal
  - “cept” = fusion protein with Fc receptor

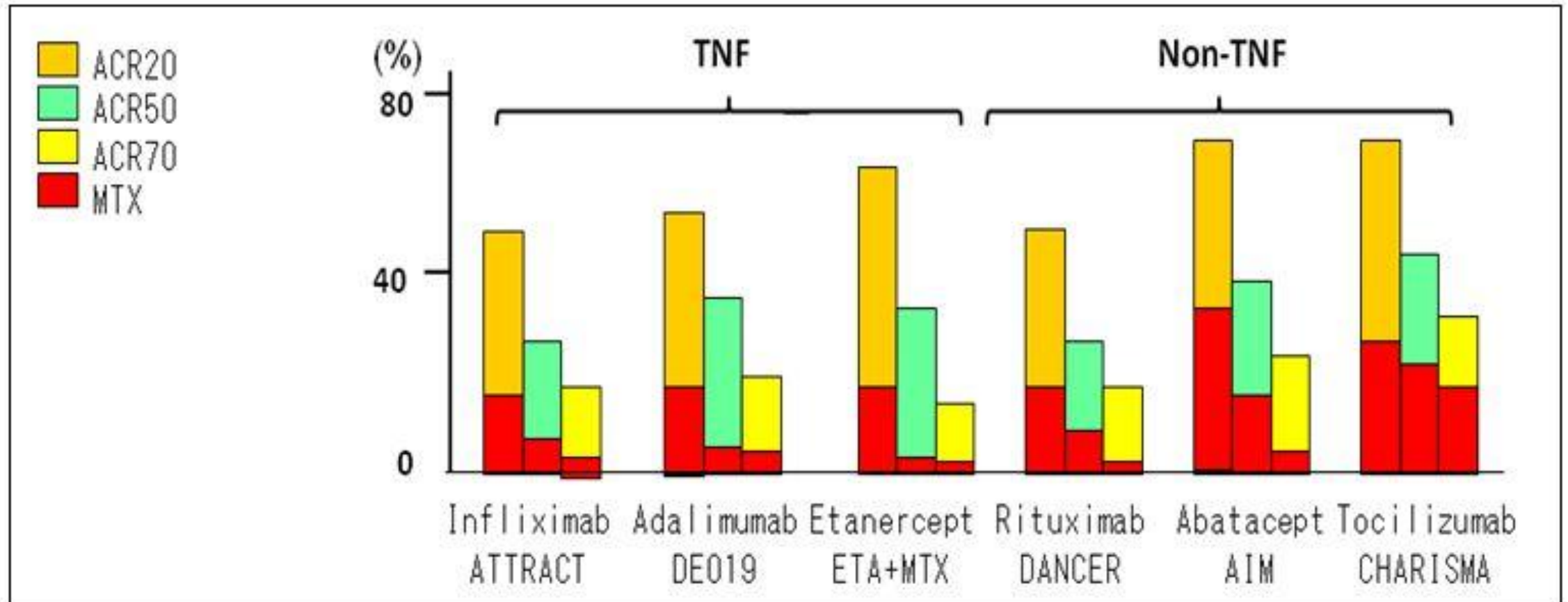
# Concerns in biologic therapy

- Slight increased risk for infection vs. placebo
- However, reduces over time due to replacement of prednisone
  - RR from 4.8 to 2.2 over 3 years
  - RR prednisone 7.5–14 mg/day,  $IRR_{adj}$  2.1
  - Prednisone  $\geq 15$  mg/day,  $IRR_{adj}$  4.7
  - TNF $\alpha$  inhibitors  $IRR_{adj}$  1.8



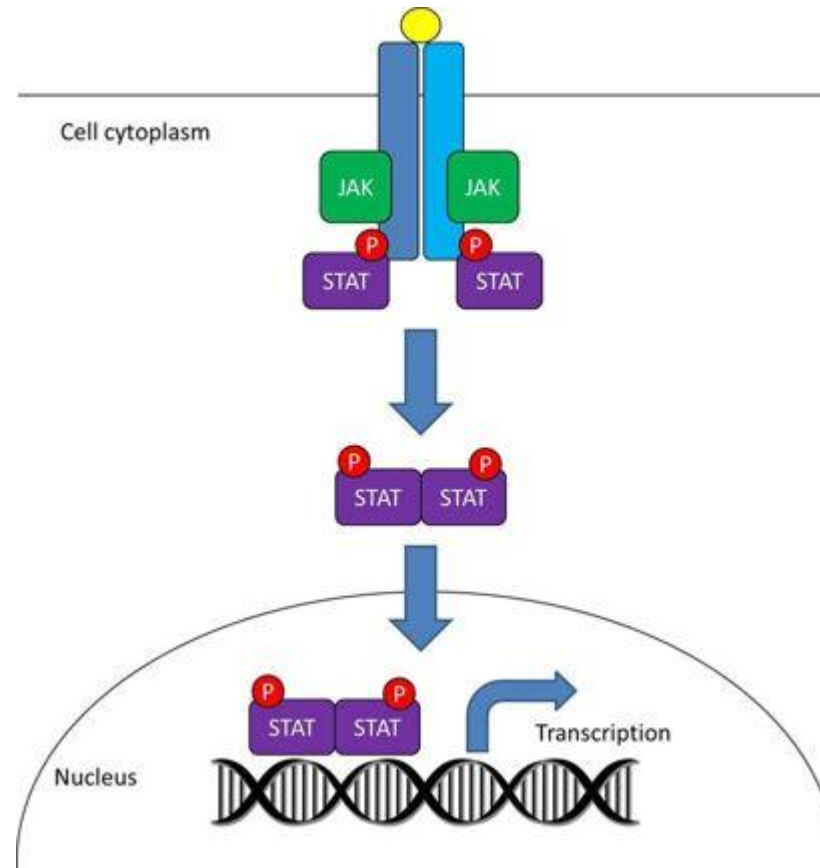


# Clinical responses to biologics vs. methotrexate



# Small molecule inhibitors

- Jak inhibitors (downstream of cytokine receptor signaling)
  - Tofacitinib
  - Baricitinib
  - Upadacitinib



# Glucocorticoids

- Potent anti-inflammatory drugs
- Serious adverse effects with long-term use
- To control the disease
- Indications
  - As a bridge to effective DMARD therapy
  - Systemic complications (e.g. vasculitis)
- Increases risk of infection by 67%

# Prednisone

- Sodium retention, Fluid retention , [Congestive heart failure](#) in susceptible patients, Potassium loss, Hypokalemic [alkalosis](#), [Hypertension](#)
- Muscle weakness, [Steroid myopathy](#), Loss of muscle mass, [Osteoporosis](#), [Tendon rupture](#), particularly of the [Achilles tendon](#), Vertebral [compression](#) fractures, [Aseptic necrosis](#) of [femoral](#) and humeral heads, [Pathologic fracture](#) of long bones
- [Peptic ulcer](#) with possible perforation and [hemorrhage](#), [Pancreatitis](#), [Abdominal distention](#), Ulcerative [esophagitis](#), Increases in [alanine](#) transaminase ([ALT](#), [SGPT](#)), aspartate transaminase ([AST](#), [SGOT](#)) and [alkaline phosphatase](#) have been observed following [corticosteroid](#) treatment. These changes are usually small, not associated with any clinical syndrome and are reversible upon discontinuation.
- Impaired wound healing, Thin fragile [skin](#), [Petechiae](#) and ecchymoses, Facial [erythema](#), Increased [sweating](#), May suppress reactions to skin tests
- Negative [nitrogen](#) balance due to [protein catabolism](#)
- Increased intracranial pressure with [papilledema](#) (pseudo-tumor cerebri) usually after treatment, Convulsions, [Vertigo](#), Headache
- [Menstrual](#) irregularities, Development of [Cushingoid](#) state, Secondary adrenocortical and [pituitary](#) unresponsiveness, particularly in times of stress, as in [trauma](#), surgery or illness  
Suppression of growth in children, Decreased carbohydrate tolerance, Manifestations of latent [diabetes mellitus](#), Increased requirements for [insulin](#) or oral [hypoglycemic](#) agents in diabetics
- Posterior subcapsular cataracts, Increased [intraocular pressure](#), [Glaucoma](#), [Exophthalmos](#)
- Atypical and typical infections

# Oral disease modifying therapies in SLE

- Hydroxychloroquine \*  $\phi$
- Azathioprine
- Mycophenolate
- Methotrexate
- Leflunomide
- Cyclophosphamide
- Dapsone
- Glucocorticoids  $\phi$

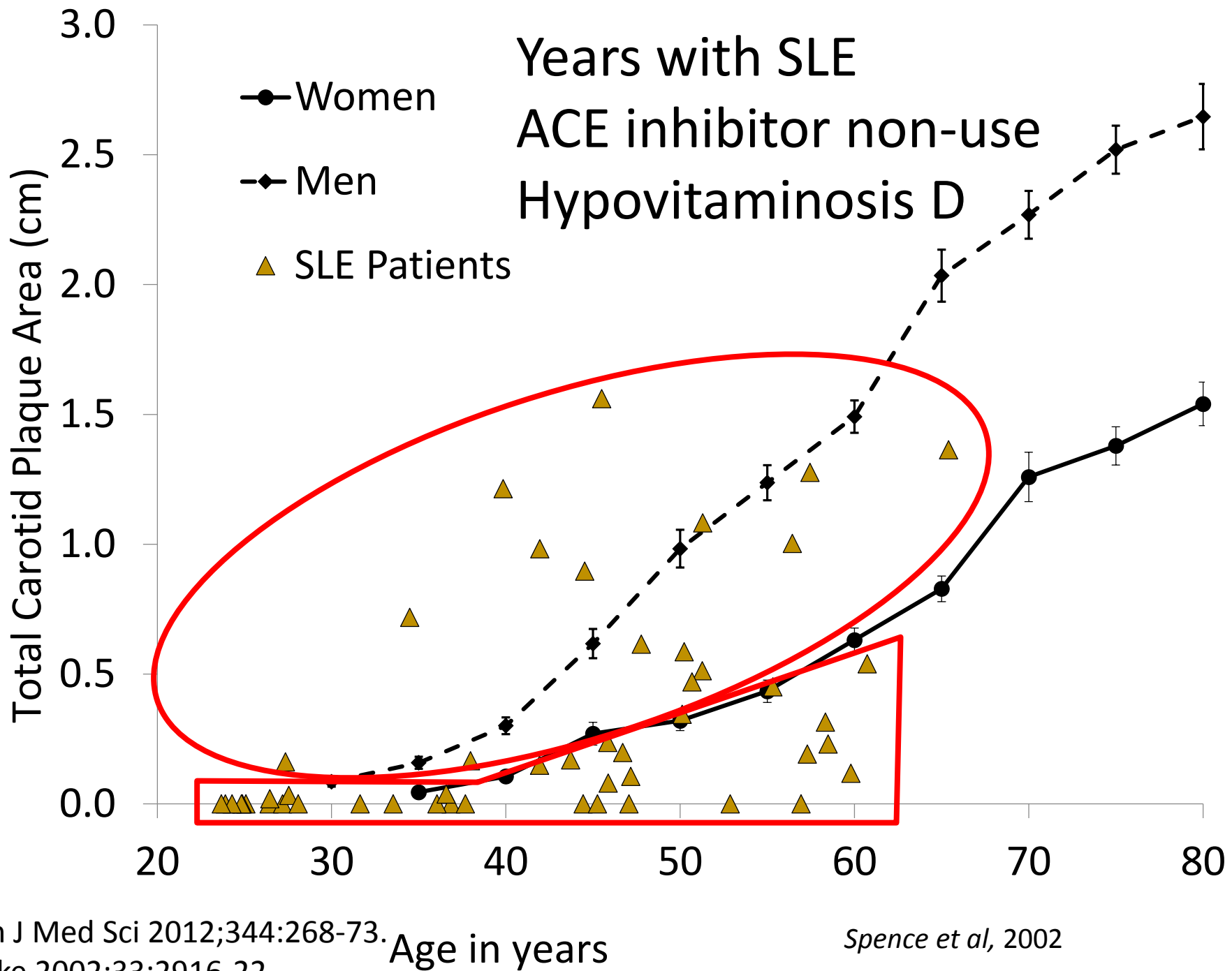
# Biologics in SLE

- Belimumab\*
- Rituximab
- Abatacept
- Anifrolumab – pending FDA review
- Tocilizumab

# Cardiovascular disease in SLE

**TABLE 4. Comparison of risk factors between women who had systemic lupus erythematosus with and without cardiovascular events, University of Pittsburgh, 1980–1993**

Risk factors	Cardiovascular event* (n = 33)		No event (n = 465)		P value†	RR‡	95% CI‡
	No	%	No.	%			
Non-Caucasian	6	18	93	20	0.97	0.57	0.23–1.42
Renal disease	10	30	101	21	0.35	1.51	0.69–3.32
Pericarditis	6	18	51	11	0.33	0.92	0.37–2.25
Hypertension	24	72	295	63	0.37	1.16	0.52–2.57
Hypercholesterolemia	6	18	21	4	0.003	3.35	1.34–8.36
Diabetes	4	12	27	5	0.28	1.98	0.69–5.71
Family history of cardiovascular disease	12	36	150	32	0.76	1.64	0.79–3.39
Postmenopause	16	48	138	29	0.03	0.77	0.24–2.46
Corticosteroid use	29	87	383	82	0.56	0.57	0.19–1.67
Duration of use§					0.002	0.98	0.94–1.03
Maximum dose¶					0.59	1.00	0.99–1.01
Tobacco							
Use	19	57	248	53	0.77	1.33	0.66–2.70
Pack-years#					0.33	1.01	0.99–1.03
	Cardiovascular event (mean years)	No event (mean years)			P value	RR	95% CI
Age at lupus diagnosis	39	34			0.02	1.21	1.09–1.35
Lupus disease duration	13	10			0.01	0.83	0.74–0.92



Ravenell RL, et al. Am J Med Sci 2012;344:268-73.

Spence JD, et al. Stroke 2002;33:2916-22.

Spence et al, 2002



# Predictors of CVD in SLE

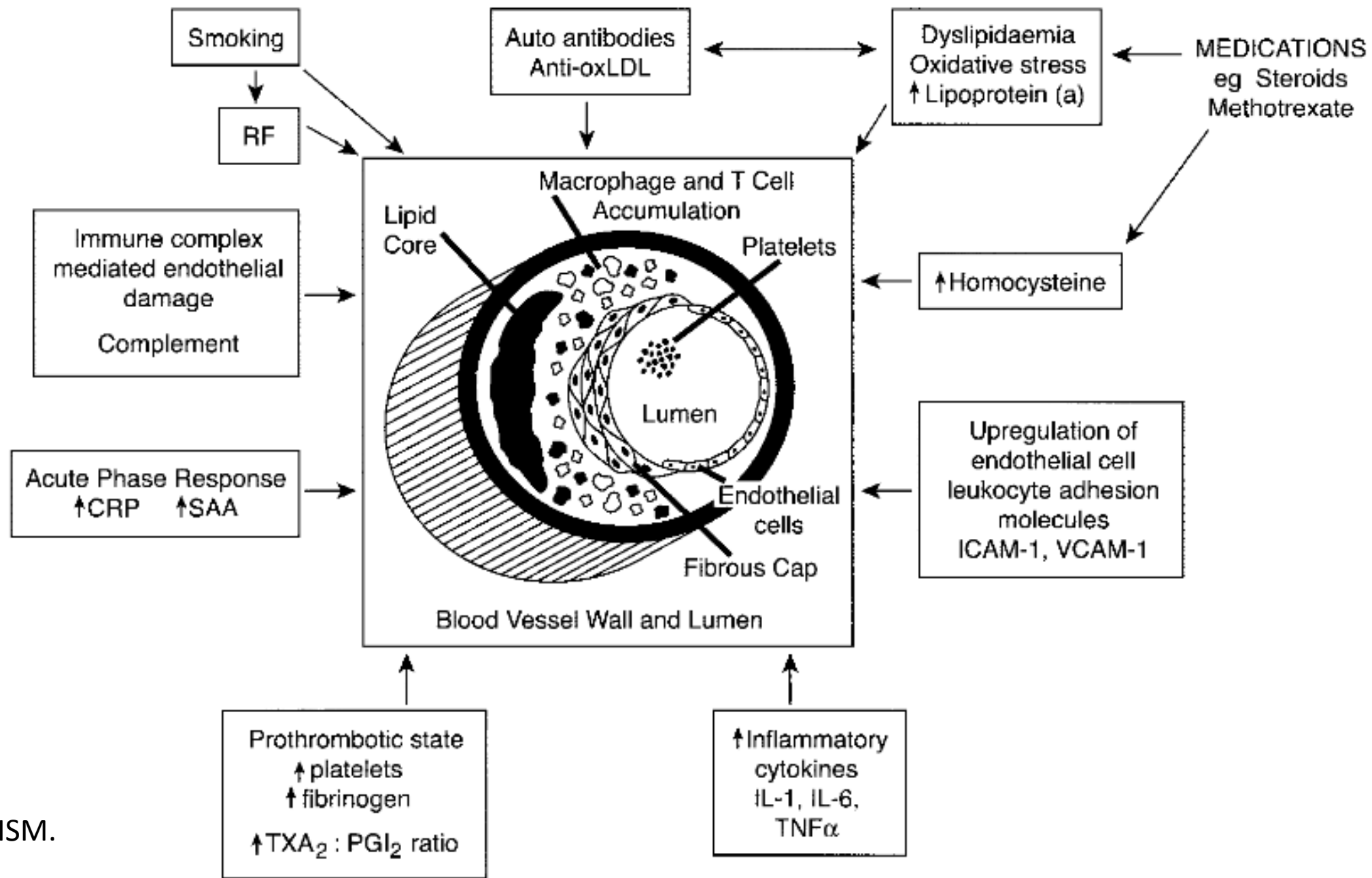
- Age
- Sex
- SBP
- Total cholesterol
- HDL
- SLEDAI (mean over time)
- Low C3
- Lupus anticoagulant
- If all of the above, 10 year risk = 45%

# Medication and risk for CVD in SLE

- Dose and duration of prednisone use
  - Mean daily prednisone  $\geq 7.5$  mg = higher risk of CVD (HR 1.54)
  - Mean daily prednisone  $\geq 7.5$  mg = higher risk osteoporotic fracture (2.41)
- Hydroxychloroquine protective

# Vascular disease in RA

- 50% of CVD in RA not accounted for by Framingham risk factors
- CRP predictive of future events
- Standardized mortality ratio 0.9 to 3.0 in RA with 34-40% due to CVD



# Predictors of Mortality in RA

- Health Assessment Questionnaire
  - 1 standard deviation – OR 2.31 (50% of model)
  - severely impaired functional status has been compared 3-vessel coronary artery disease or stage 4 Hodgkin's disease
- Global disease severity
  - 1 standard deviation – OR 1.83 (30% of model)
- 50% increase in death due to CVD in RA
  - Traditional risks increased by over 50%
- Presence of rheumatoid factor

Best Pract Res Clin Rheumatol 2007;21:871–83

Arthritis Rheum. 2003 Jun;48(6):1530-42.

Arthritis Rheum. 2008 Dec 15;59(12):1690-7.



# CVD and our therapies

- Lower mortality on TNF $\alpha$  inhibitors IF patients respond to therapy at 6 months
- Risk of MI accounted for by traditional risk factors plus
  - Use of corticosteroids

# Therapy and mortality in RA

- Methotrexate associated with 60% reduction in mortality
- Methotrexate non-responders had 5.6-fold increase in mortality over the general population



# RA mortality aside from CVD

- Infection, particularly pneumonia
- COPD, pulmonary fibrosis
- Non-Hodgkin's lymphoma
- Lung cancer (linked to smoking)

# Demographic predictors of mortality in RA

- Age
- Male gender

# Predictors of mortality in SLE

- Age > 50 at diagnosis (HR 5.9)
- Male gender (RH 2.4)
- Annual family income < \$25k
- Low complement during the first year
  
- Bimodal distribution of mortality in SLE
  - Active disease and infection early
  - Cardiovascular disease late

# Bottom line

- Effective therapy reduces mortality and CVD
  - Supports “treat-to-target” approaches
- Glucocorticoids increase mortality
- Traditional and disease-related factors contribute to CVD in RA and SLE
  - Supports “treat to target” approach
  - Supports aggressive management of traditional risk factors

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- Newer biologics for connective tissue diseases
- Connective tissue disease as risk factor for atherosclerotic disease
- Predictors of mortality in CTD