MAYO CLINIC

Myositis and Heart Disease

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Disclosures

- Financial:
  - Dynavax – study adjudication committee
  - Pfizer – study steering committee
- Off-label use: No

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- Cynthia Crowson, M.S.

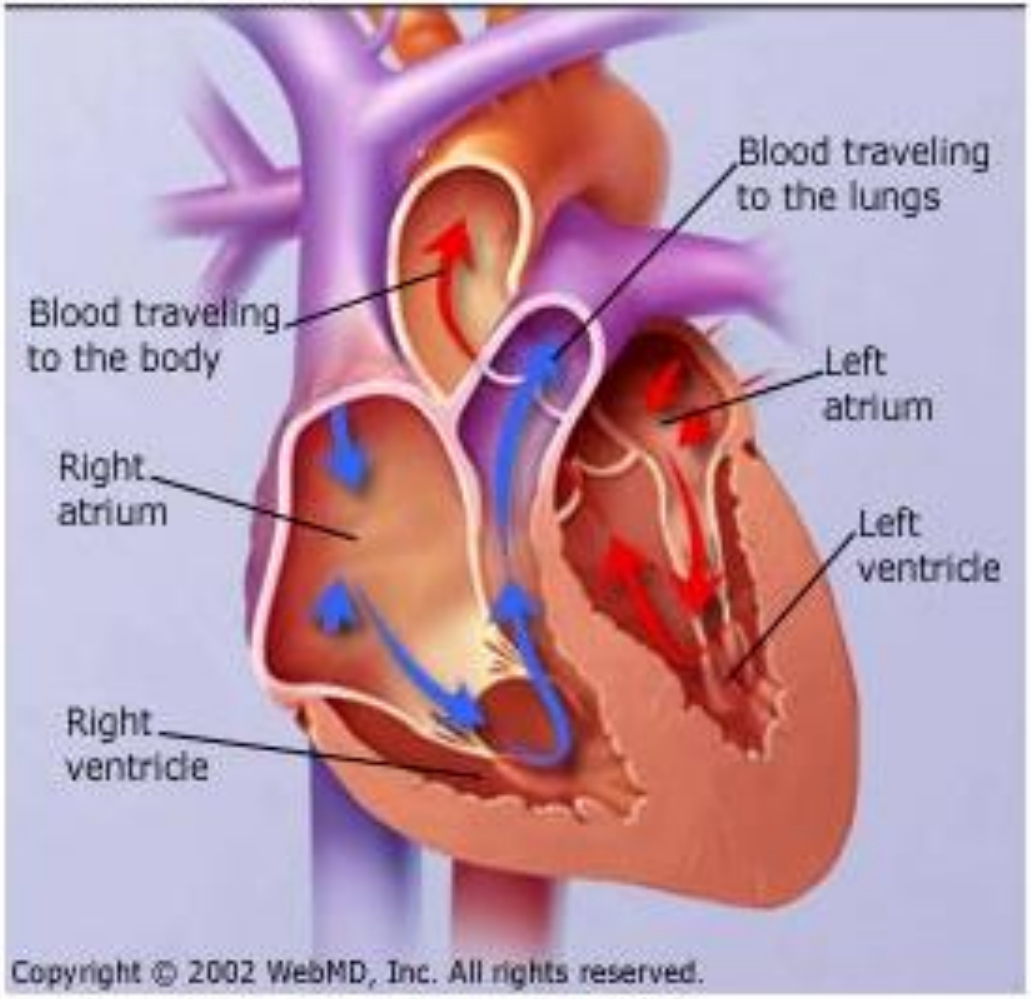
Heart Involvement in IIM

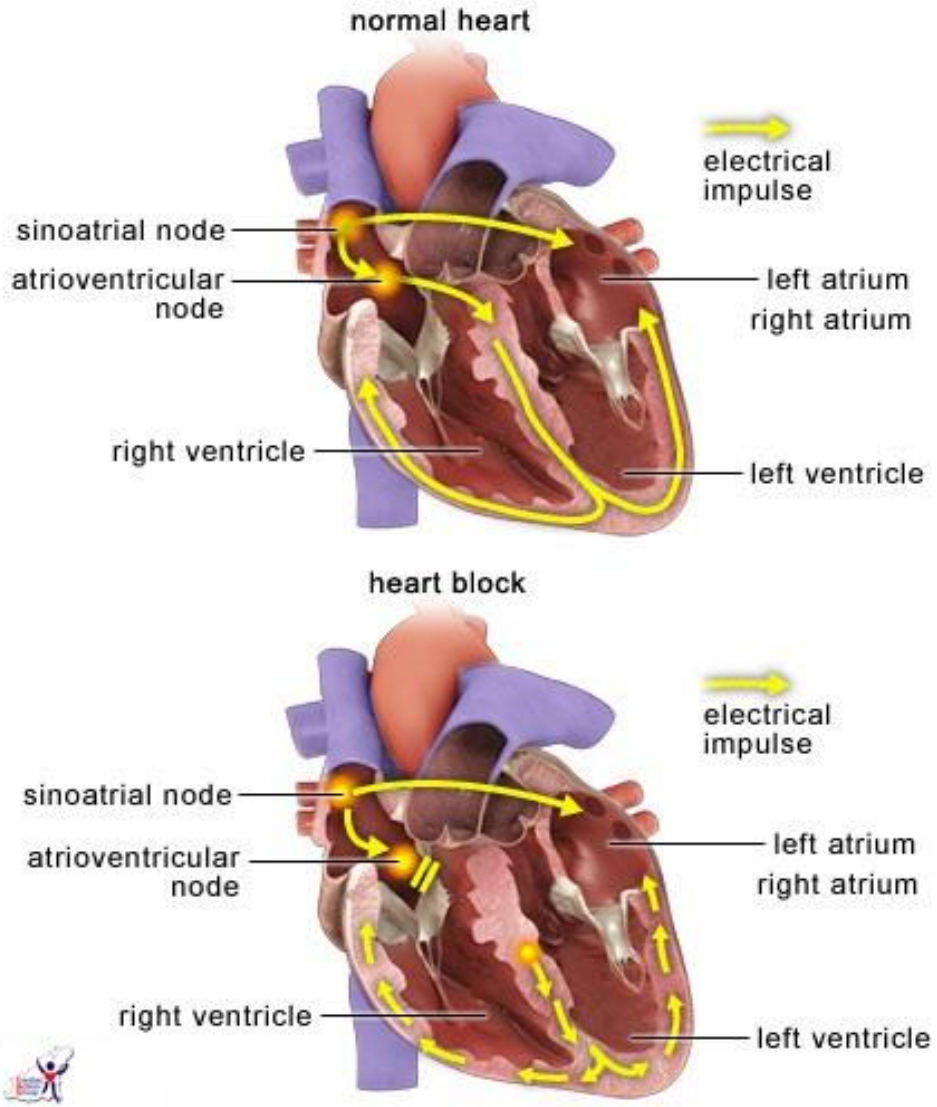
- Clinically manifest heart problems are relatively infrequent
  - CHF: 3 – 45%
  - LVDD: 12 – 42%

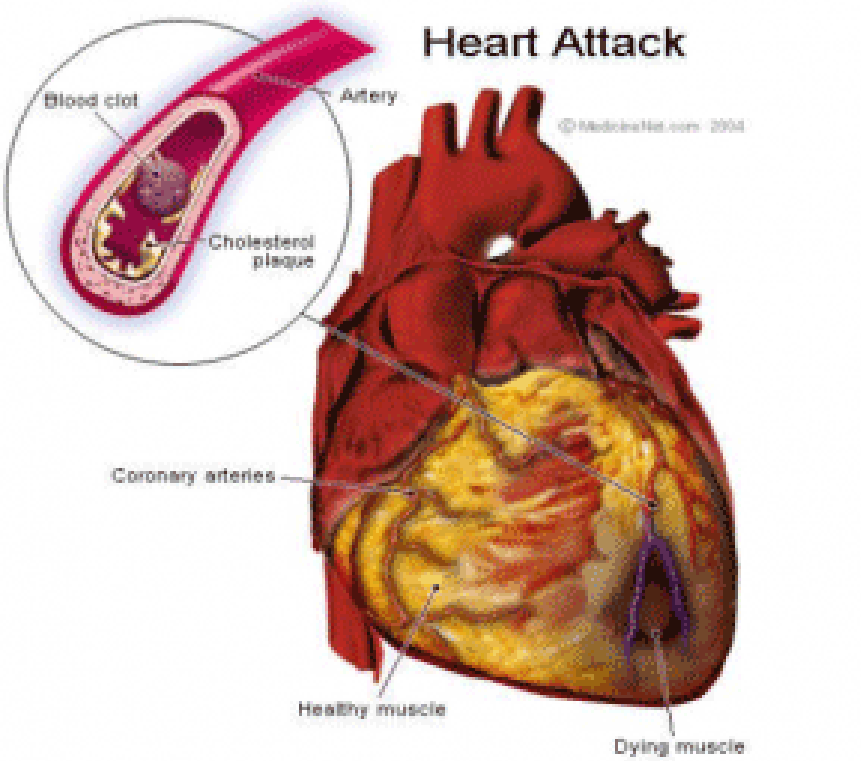
- Conduction abnormalities
- Pericarditis
- Myocarditis

Lundberg, Rheumatology 2006; 45: iv18-iv21

Normal Heart




normal heart
electrical impulse
sinoatrial node
atrioventricular node
left atrium
right atrium
right ventricle
left ventricle
heart block
electrical impulse
sinoatrial node
atrioventricular node
left atrium
right atrium
right ventricle
left ventricle


Heart Attack
Blood clot
Artery
Cholesterol plaque
Coronary arteries
Healthy muscle
Dying muscle

Effects of IIM on the Heart

- CV disease is often subclinical

  Lundberg, Rheumatology 2006; 45: iv18-iv21

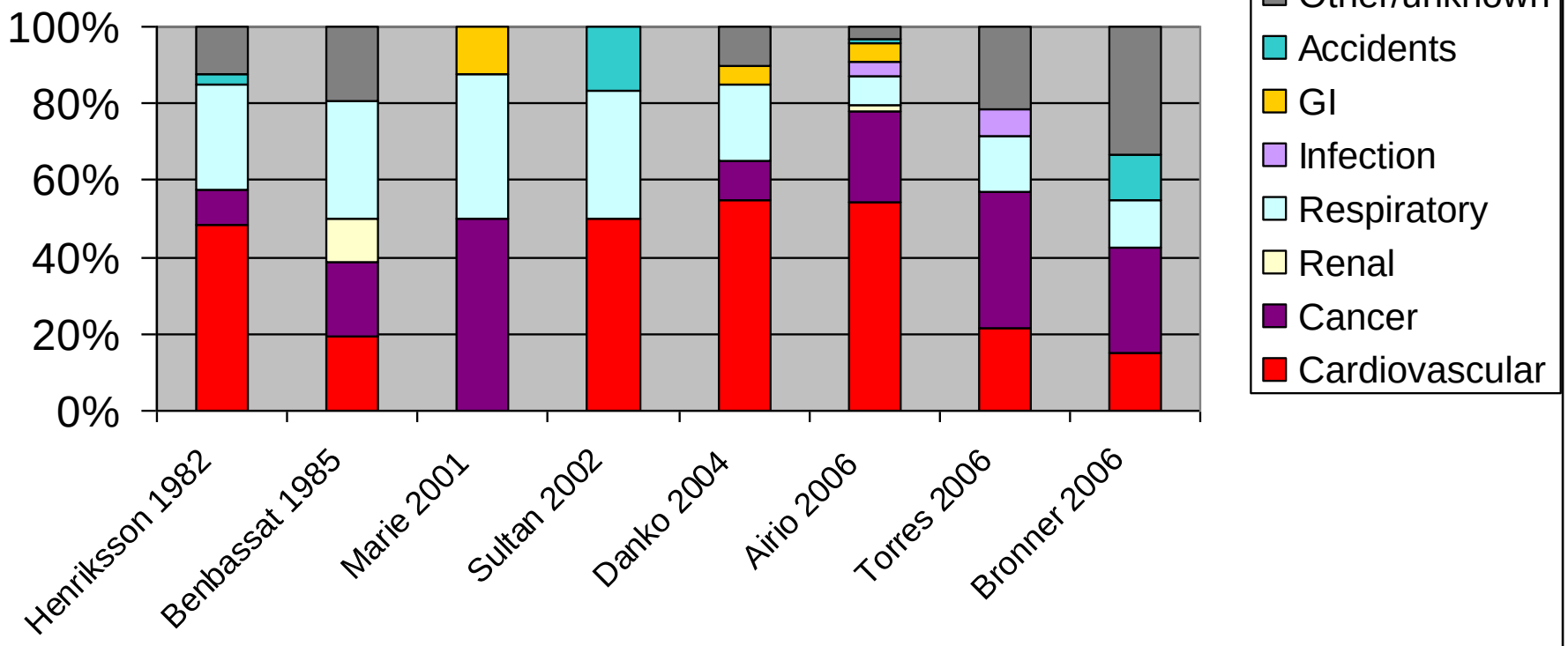
- CV disease among leading causes of death in patients with IIM, listed as cause of death in 15-60% of patients

  Lundberg & Forbess, Clin Exp Rheumatol 2008; 26: S109-114

  Airio, et al., Clin Rheumatol 2006; 25: 234-239

- Increased risk of heart disease in patients with RA and SLE

Causes of Death in Patients with Myositis (% Total Deaths)



Arterial Events in IIM

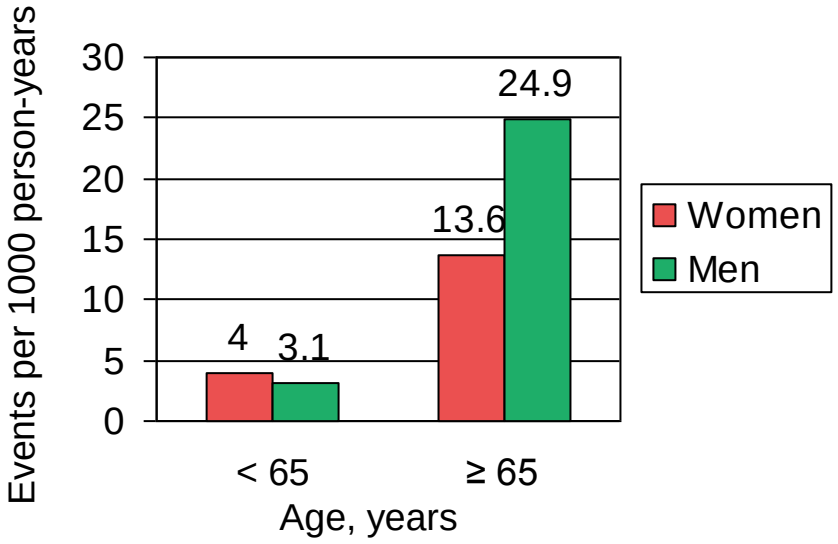
- Administrative databases in Quebec province, 1994-2003
  - ≥ 1 hospital discharge diagnosis of PM or DM, or
  - ≥ 2 outpatient billing codes of PM or DM, at least 8 weeks apart with at least 1 from a rheumatologist, neurologist, dermatologist, immunologist, or internist
- Cohort subjects followed until: outcome event, death, or end of study (12/31/2003)
- Comorbidities determined with similar criteria, prior to index date
- Drug exposure defined by ≥ 1 prescription for the given drug between cohort entry and index date

Tisseverasinghe, et al. J Rheumatol 2009; 36: 1943-6

Arterial Events in IIM

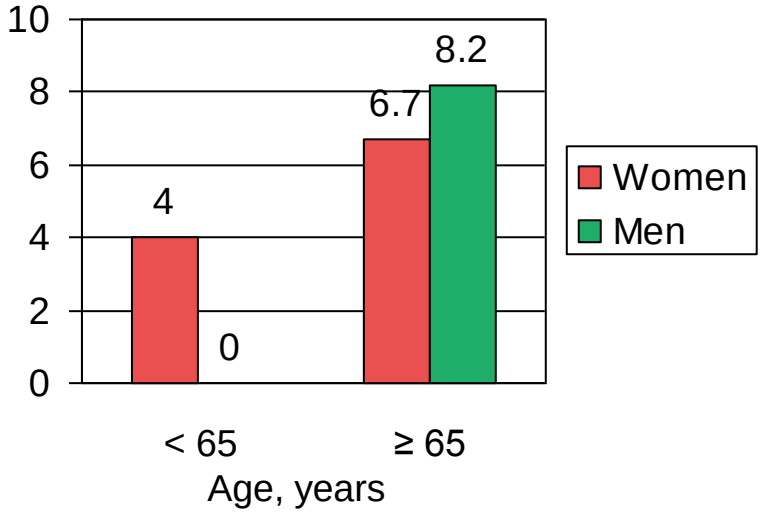
- 124 arterial events in 80 subjects (66% F)
- Average 2.9 ± 2.9 years after cohort entry
- Mean age at incident event = 60 ± 18 years

Acute myocardial infarction



SIR = 1.95 [1.35, 2.72]

Atherosclerotic cerebrovascular disease



Tisseverasinghe, et al. J Rheumatol 2009; 36: 1943-6

Atherosclerotic Cardiovascular Disease in Dermatomyositis

- National Inpatient Sample survey
  - Sample of 20% US community hospitals
  - 1993-2007, 7 million hospitalizations/yr
  - Primary dx and up to 14 secondary dx
- Search
  - Patients ≥ 18 yo
  - DM code
  - CV disease and/or procedure code
  - Matched 10 non-DM cases for each DM

Linos, et al. Arthritis Res Ther 2013; 15:87

ASCVD in DM: Overall Characteristics

Characteristic	DM	Controls
Total number in sample	10,156	76,440
Mean age, years	58.3	58.5
Female %	73.2	73.4
Mean LOS, days	8.0	5.1
Mean total charges, $	28,545	33,853
Comorbidity index	1.4	1.2
Overall death rate, %	5.65	2.40

Linos, et al. Arthritis Res Ther 2013; 15:87

ASCVD in DM: Cardiovascular Characteristics (%)

Characteristic	DM	Controls
Any CV diagnosis	20.4	21.1
MI or acute CAD	4.4	5.7
Angina	2.5	2.8
Congestive heart failure	11.8	9.9
CABG	0.4	0.01
Cardiac catheterization	2.9	0
Angioplasty	0.8	0

Linos, et al. Arthritis Res Ther 2013; 15:87

ASCVD in DM: Outcomes 1

Table 2 Odds ratio for death, comparing patients with dermatomyositis and cardiovascular disease diagnoses with dermatomyositis patients without cardiovascular disease

Cardiovascular diagnoses	Odds ratio (95% CI)	*P* value
Any cardiovascular diagnosis	2.04 (1.71-2.45)	< 0.001
Myocardial infarction	1.57 (1.11-2.22)	0.01
Angina	0.34 (0.14-0.83)	0.02
Congestive heart failure	2.28 (1.85-2.80)	< 0.001
Coronary artery bypass grafting	-	-
Coronary catheterization	0.51 (0.26-1.01)	0.053
Percutaneous angioplasty	0.47 (0.12-1.94)	0.30

CI, confidence interval.

Linos, et al. Arthritis Res Ther 2013; 15:87

ASCVD in DM: Outcomes 2

Table 3 Odds ratio for in-hospital death, comparing patients with dermatomyositis and cardiovascular disease with controls with cardiovascular disease

Model	Odds ratio (95% CI)	*P* value
Univariate model[a]	2.11 (1.80-2.48)	< 0.001
Multivariate model[b]	1.98 (1.57-2.48)	< 0.001

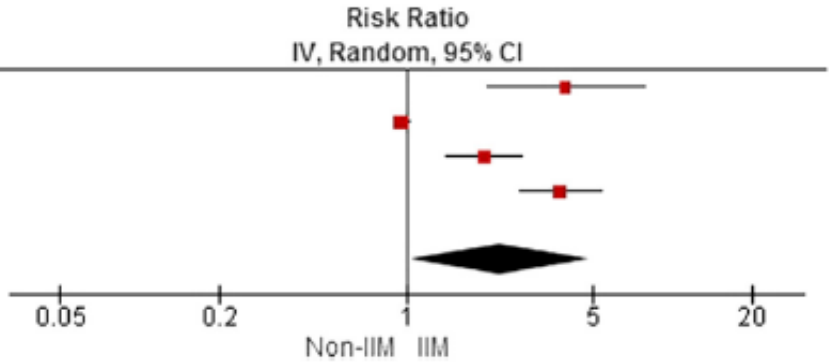
[a]Adjusted for age and gender only; [b]adjusted for age, gender, Charlson comorbidity index, number of diagnoses (to control for severity of admission), and type of admission (elective versus emergency). CI, confidence interval.

Linos, et al. Arthritis Res Ther 2013; 15:87

CHD in IIM: Meta-analysis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Lai et al.	1.38	0.35	22.3%	3.97 [2.00, 7.89]
Linos et al.	-0.04	0.03	26.8%	0.96 [0.91, 1.02]
Tisseverasinghe et al.	0.67	0.17	25.6%	1.95 [1.40, 2.73]
Zoller et al.	1.34	0.18	25.4%	3.82 [2.68, 5.43]
Total (95% CI)			100.0%	2.24 [1.02, 4.92]

Heterogeneity: Tau² = 0.60; Chi² = 87.45, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.02 (P = 0.04)



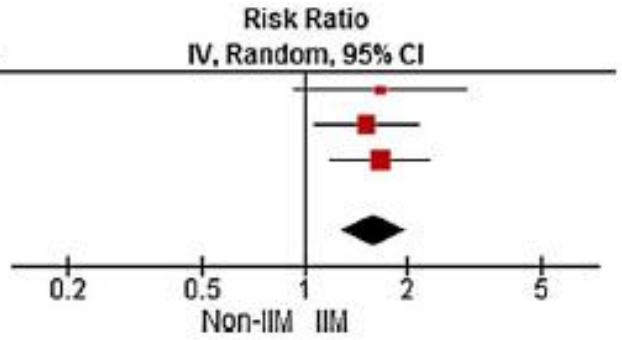
Ungprasert, et al. Semin Arthritis Rheum 2014; 44: 63-7

Stroke in IIM: Meta-analysis

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Tisseverasinghe et al.	0.517257	0.297911	14.9%	1.68 [0.94, 3.01]	2009
Zoller et al.	0.41871	0.180442	40.6%	1.52 [1.07, 2.16]	2012
Lai et al.	0.512824	0.172499	44.5%	1.67 [1.19, 2.34]	2013
Total (95% CI)			**100.0%**	**1.61 [1.28, 2.02]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.17$, df = 2 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 4.13 (P < 0.0001)



Ungprasert, et al. Rheumatol Int 2014

Cardiac Dysfunction in JDM

- DM by Bohan/Peter criteria; onset < 18 yo, duration ≥ 24 mos, age ≥ 6 yrs at inclusion
- Inception cohort diagnosed 1/1970 – 6/2006 in Norway
- 66 met criteria; 4 died; 59/62 (95%) participated
- Age- and sex-matched controls
- Patients and controls examined 2005-2009
- JDM patient characteristics

Female	36 (61%)	
Age at disease onset, yrs	7.8	(1.4-17.3)
Age at diagnosis, yrs	8.9	(2.1-19.2)
Duration of disease at F/U, yrs	16.8	(2.0-38.1)
Age at F/U, yrs	21.5	(6.7-55.4)

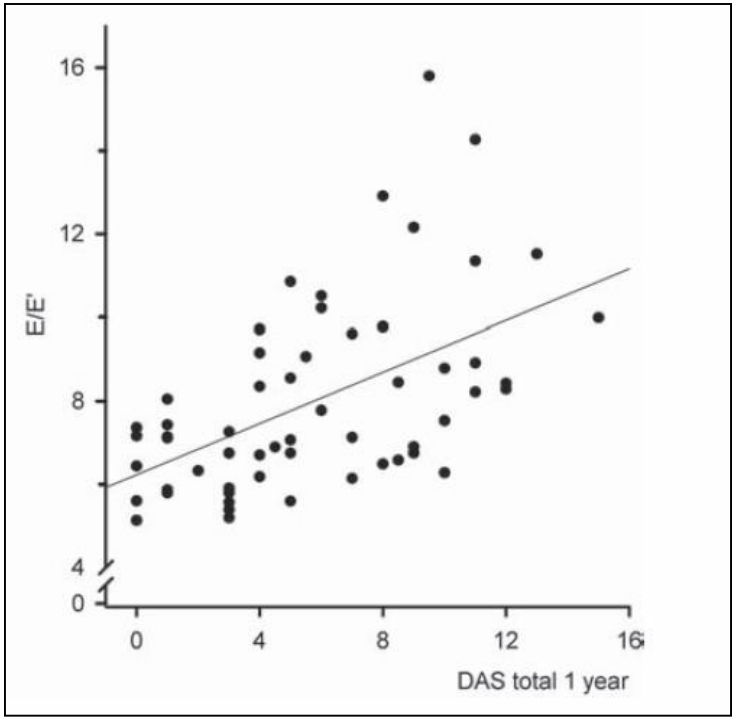
Schwartz, et al. Ann Rheum Dis 2011; 70: 766-71

Cardiac Dysfunction in JDM

Table 5 Correlations between cardiac outcome at follow-up and disease variables at 1 year

	E/E′		Pathological ECG	
	r_{sp}	p Value	r_{sp}	p Value
DAS muscle	0.41	0.001	0.12	0.371
DAS skin	0.55	<0.001	0.26	0.047
DAS total	0.56	<0.001	0.24	0.066
MDI	0.22	0.09	0.18	0.169

DAS, disease activity score; E, early diastolic transmitral flow; E′, early diastolic tissue velocity; ECG, electrocardiography; MDI, Myositis Damage Index; r_{sp}, Spearman correlation coefficient.



Schwartz, et al. Ann Rheum Dis 2011; 70: 766-71

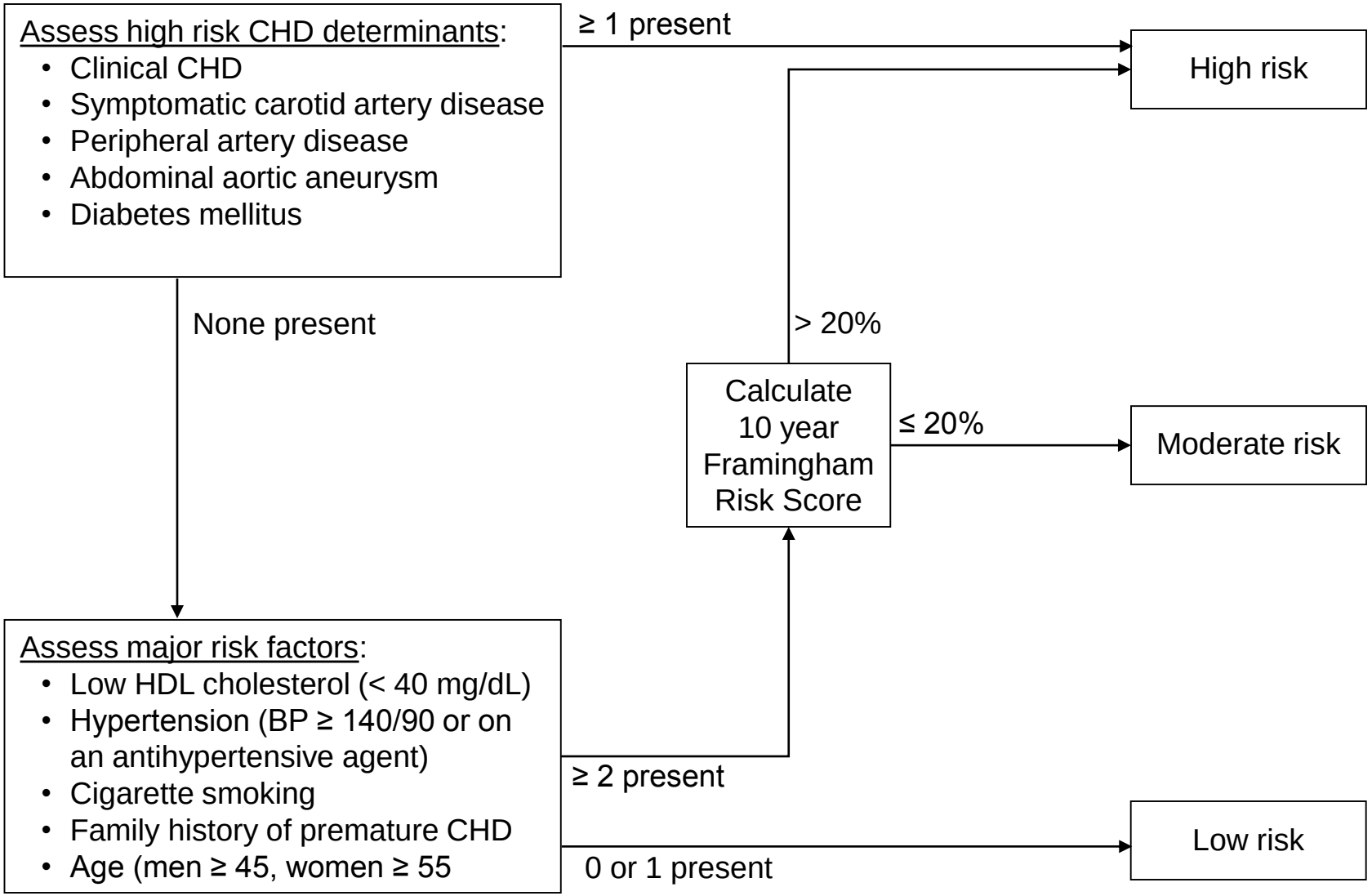
CV Risk in PM and DM

- Retrospective cross-sectional study
- All patients seen in Division of Rheumatology at Mayo Clinic Rochester, 2/08 – 2/09 with probable or definite PM or DM
- Age ≥ 18 yrs
- PM, DM or overlap with CTD; excluded IBM and patients with malignancy
- N = 156
  - Excluded for various analyses
    - Insufficient data to calculate CV risk – 2
    - Age ≥ 80 yrs – 6
- CV risk: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III-revised, ATP III-R)

CV Risk in PM and DM Patient Characteristics

N	156
Age, yrs, mean ± SD	55.0 ± 15.9
Sex % (F/M)	66/34
Myositis type, n (%)	
DM	81 (52)
PM	56 (36)
Overlap	19 (12)
Disease duration, yrs, median (IQR)	5 (2-8)
Activity % (Active/Stable)	30/70

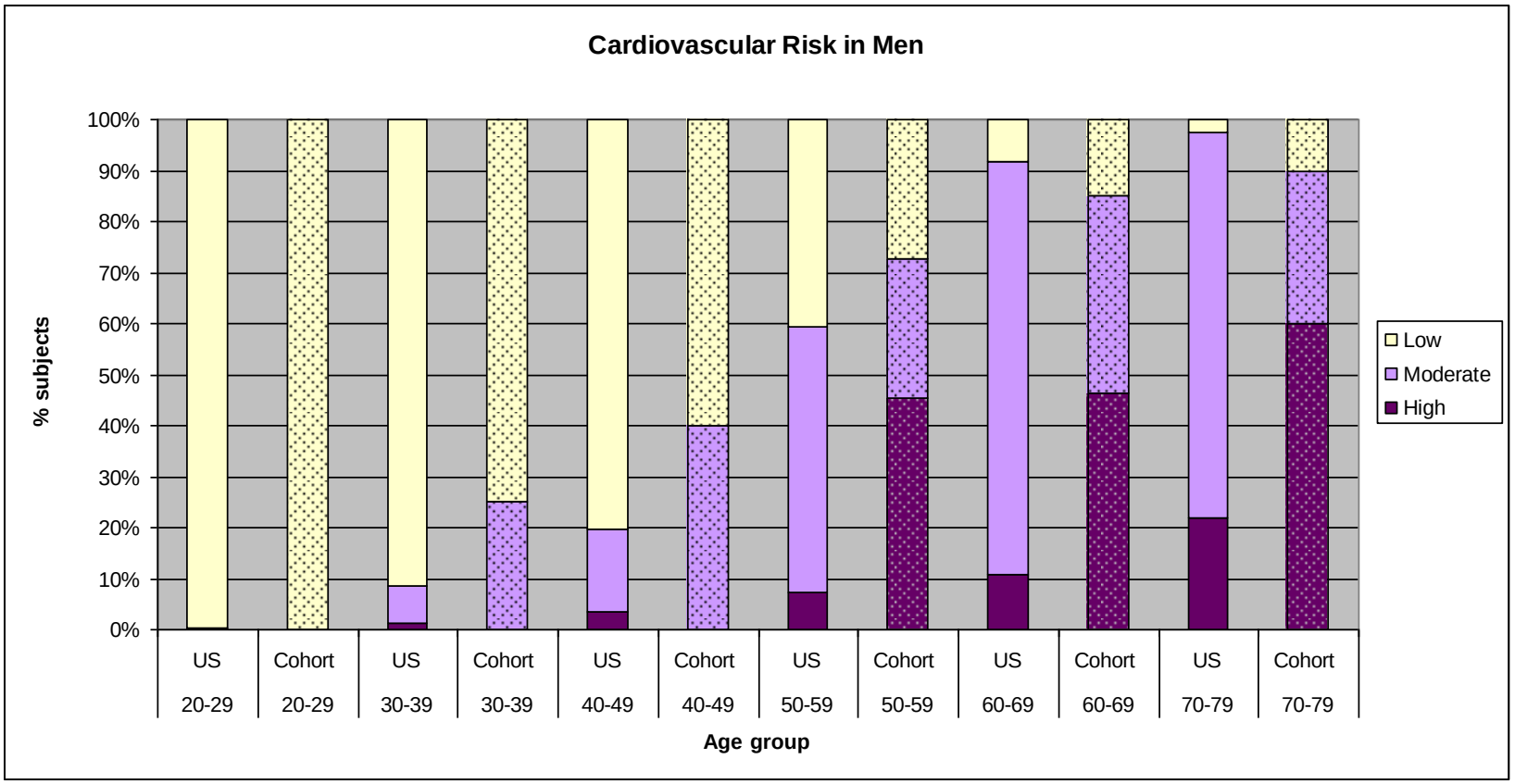
ATP-III R CV Risk Calculation



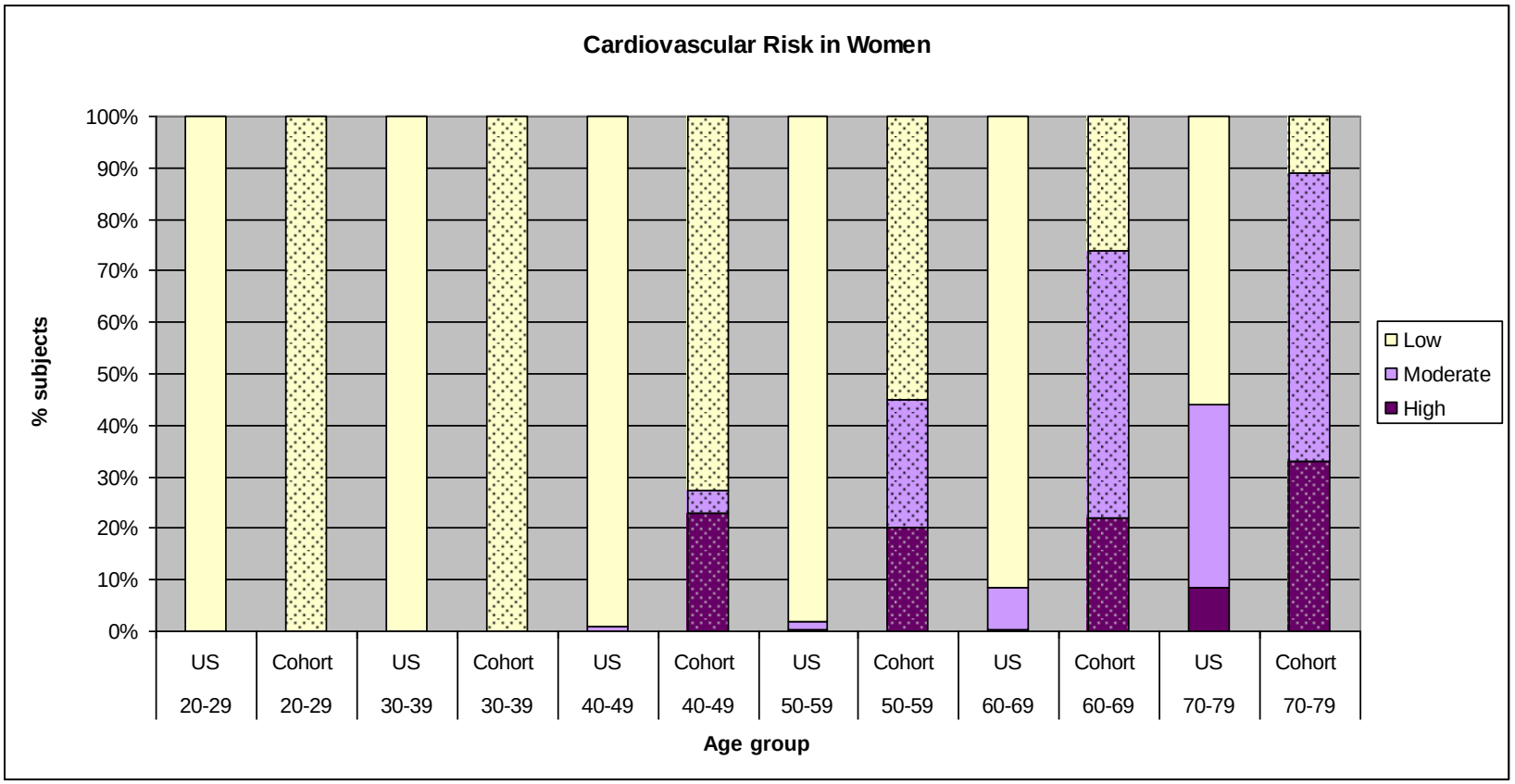
Framingham cardiovascular event risk groups

	Framingham Risk of Cardiovascular Event in 10 Years			
Patients	**Low risk**	**Moderate risk**	**High risk**	**Total**
Total				
Observed, n (%)	68 (46)	43 (29)	37 (25)	148(100)
Expected, n (%)	106.9 (74)	33.7 (23)	6.4 (4.4)	
Rate ratio (95% CI)	0.6 (0.5,0.8)	1.2 (0.9,1.7)	5.8 (4.1,8.0)	
Male				
Observed, n (%)	17 (23)	15 (33)	17 (46)	49 (32)
Expected, n (%)	16.5 (25)	24.9 (59)	4.6 (12)	
Rate ratio (95% CI)	0.9 (0.5,1.5)	0.6 (0.3,0.9)	3.7 (2.1,5.9)	
Female				
Observed, n (%)	51 (77)	28 (66)	20 (54)	99 (68)
Expected, n (%)	90.4 (90)	8.8 (8)	1.7 (2)	
Rate ratio (95% CI)	0.6 (0.4,0.7)	3.2 (2.1,4.6)	11.6 (7.1,17.9)	

CV Risk in Men with IIM



CV Risk in Women with IIM



Specific risk factors present

	Framingham risk of CV event in 10 years				
Framingham risk factor	**Low *(n = 68)***	**Moderate *(n = 46)***	**High *(n = 40)***	**Total *(n = 154)***	**p value**
Age, yrs, mean ± sd	63.9 ± 12.4	44.9 ± 14.0	63.0 ± 11.7		<0.0001
Hypertension, %	6	78	73	49	<0.0001
Hyperlipidemia, %	24	52	70	44	<0.0001
Current tobacco use, %	4	11	2	6	0.21
Family history CHD, %	4	22	25	15	0.009
Other CV risk factors					
BMI, median (IQR)	25.5 (21.6 – 30.3)	26.9 (23.6 – 30.7)	28.3 (25.0 – 32.1)		0.06
Chronic kidney dis, %	4	14	14	10	0.47

Risk factors for being “high risk”

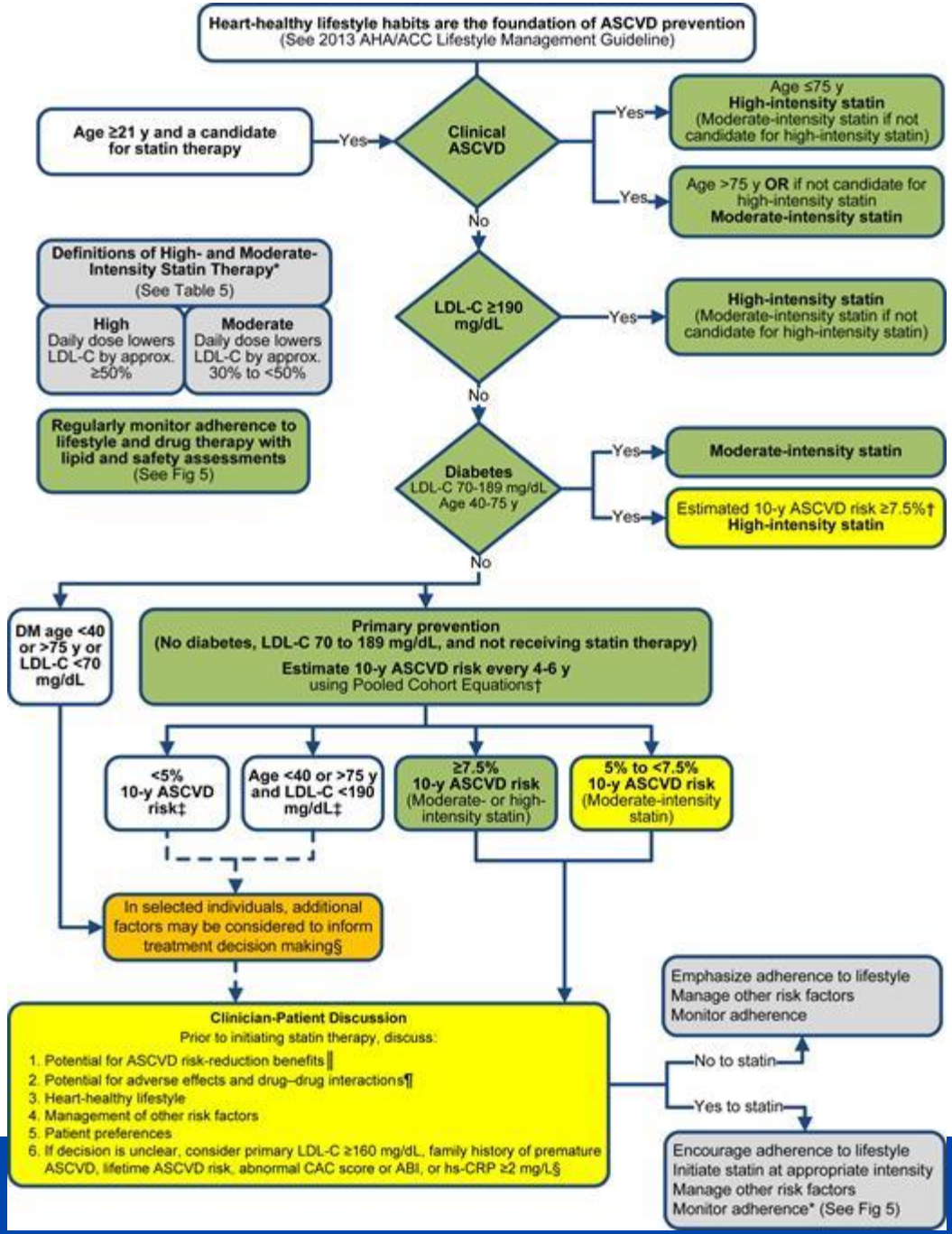
Risk factor	OR	(95% CI)
Hypertension	4.6	(1.9, 10.9)
Hyperlipidemia	2.6	(1.1, 5.9)
Male gender	2.3	(1.0, 5.3)

Myositis factors and CV risk

Myositis variable	Framingham risk of CV event in 10 years: Low *(n = 68)*	Moderate *(n = 46)*	High *(n = 40)*	Total *(n = 154)*	p value
Myositis type					
DM, n (%)	43 (54)	23 (29)	14 (18)	80	
PM , n (%)	18 (32)	17 (30)	21 (38)	56	0.07
Overlap , n (%)	7 (38)	6 (33)	5 (28)	18	
Disease duration, yrs, median (IQR)	5 (2-8)	4 (2-7)	6.5 (2-7.5)		0.37
Prednisone dose, mg/d, median (IQR)	2.25 (0.25-7.0)	2.75 (1.0-6.25)	4.5 (1.0-6.0)		0.85
Stable disease, n (%)	47 (69)	30 (65)	30 (77)		0.49

ATP-III Recommendations on Statin Use

Risk Category	LDL goal (mg/dL)	LDL level at which drug therapy recommended (mg/dL)
High risk	< 100	≥ 130 (Optional: 100 – 129 plus ≥ 2 risk factors)
Moderate risk 10-20% < 10%	<130	 ≥ 130 ≥ 160
Low risk	< 160	≥ 190 (Optional 160 – 189 plus ≥ 1 risk factor)



Stone, et al. J Am Coll Cardiol 2014; 63: 2889-2893

Treatment of modifiable risk factors

	Framingham risk of CV event in 10 years				
Framingham risk factor	**Low *(n = 68)***	**Moderate *(n = 46)***	**High *(n = 40)***	**Total *(n = 154)***	**p value**
Hypertensive patients with SBP < 130, n (%)	0/4 (0)	17/35 (49)	11/29 (38)	28/68 (41)	
Patients on aspirin, n	3	14	19	36	
Eligible for lipid-lowering therapy, n	5	13	19	37	

Lipid-lowering agent use	**n**
Statin	19
Ezetimibe	5
Nicotinic acid	2

Treatment of Lipid Abnormalities in Patients with IIM

- Online survey of IMACS members
- 63 respondents from 23 countries
- 76% reported using lipid-lowering agents in IIM patients
- Statins most commonly used class
- Among 300 patients treated with statin, 36 cases of worsening myositis reported; may improve with cessation of the statin

Charles-Schoeman, et al. Clin Rheumatol 2012; 31: 1163-8

Bottom Line

- Control disease activity
- Treat modifiable risk factors
- Worry about what to do with statins lacking firm evidence

