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Novel Approaches for Cardiac Recovery Following Ischemic Injury

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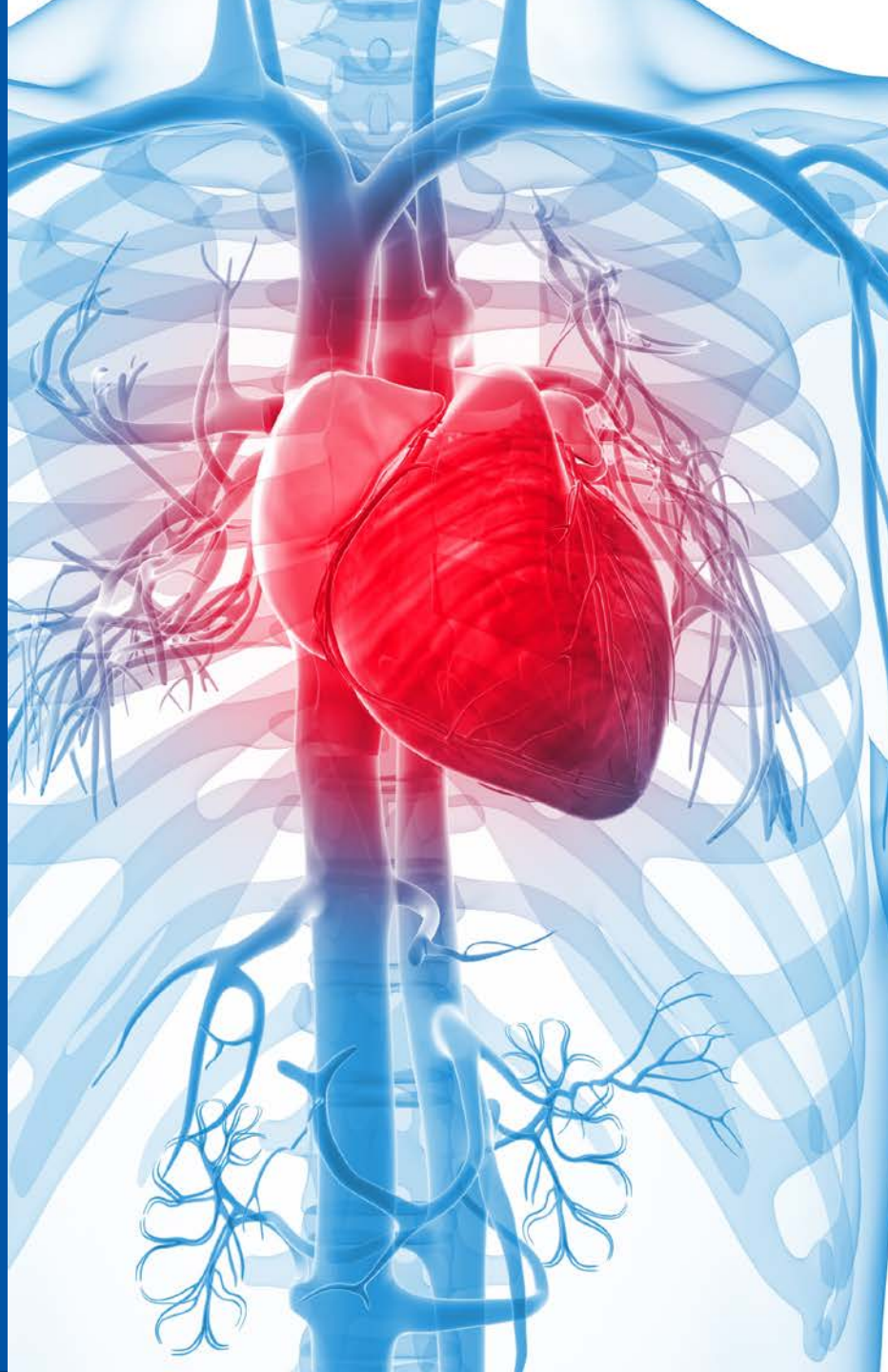

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Disclosures

None

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Education Need/Practice Gap

Acute myocardial infarction initiates multiple inflammatory and reparatory pathways that predict the damage and cardiac recovery after injury. The prognostic and therapeutic implications of these therapies are poorly understood. Novel therapeutic targets for these phenomena are being tested in clinical studies.

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Learning Objectives

Upon completion of this learning activity, you will be able to:

1. Review local and systemic changes following cardiac ischemic injury leading to heart failure and ischemic cardiomyopathy.

2. Describe emerging translational therapies targeting inflammation in patients with ischemic heart disease.

3. Discuss novel myocardial regenerative therapies for ischemic heart disease.

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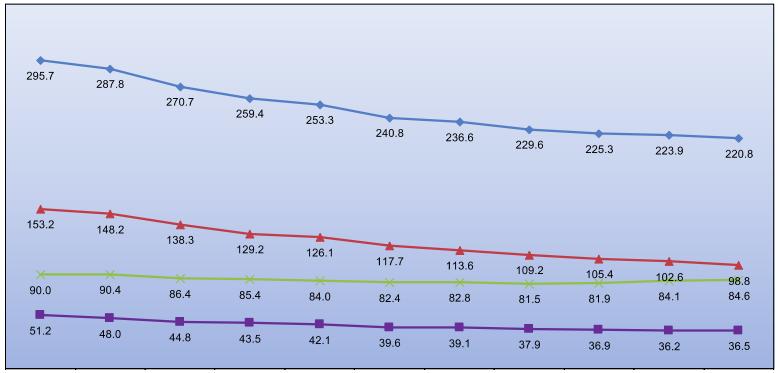
Expected Outcome

Understand the landscape of novel therapies for ischemic heart disease.

Ischemic Cardiomyopathy

- Cardiovascular disease remains the leading cause of mortality in the United States and world-wide
- With the aging population, ischemic cardiomyopathy is increasing in prevalence and adding more expenses to the health care system
- Heart failure is the leading cause of hospitalization in persons older than 65 years
- Available treatments are predominantly symptomatic with no available approved regenerative therapy



Hospital Discharges for Heart Failure

Circulat

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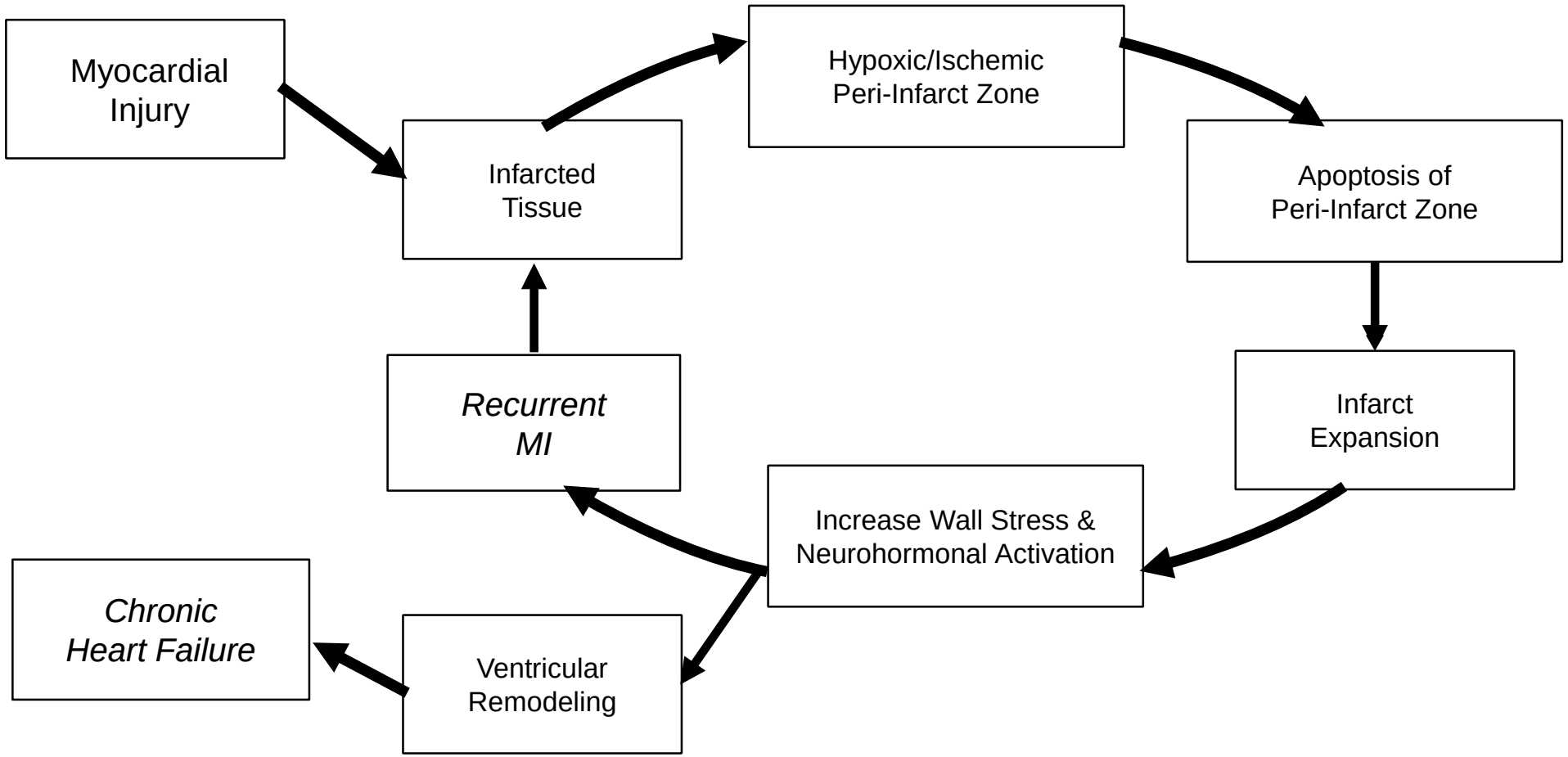
Benjamin, et al. Circulation, 2017; 135: e1-e458.

Post-MI cycle of risk: driven by infarct size, infarct expansion & remodeling



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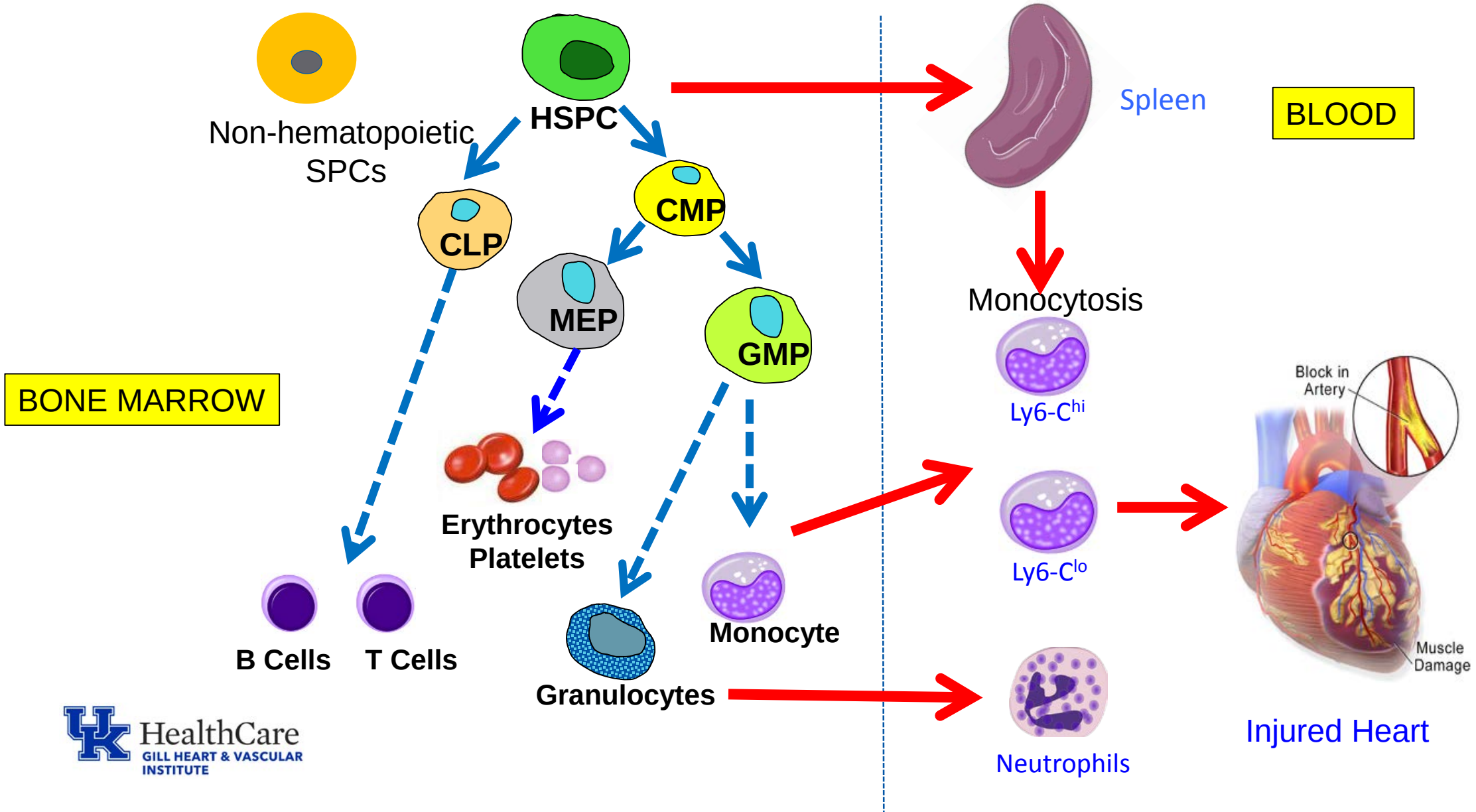
BM response after acute myocardial ischemia



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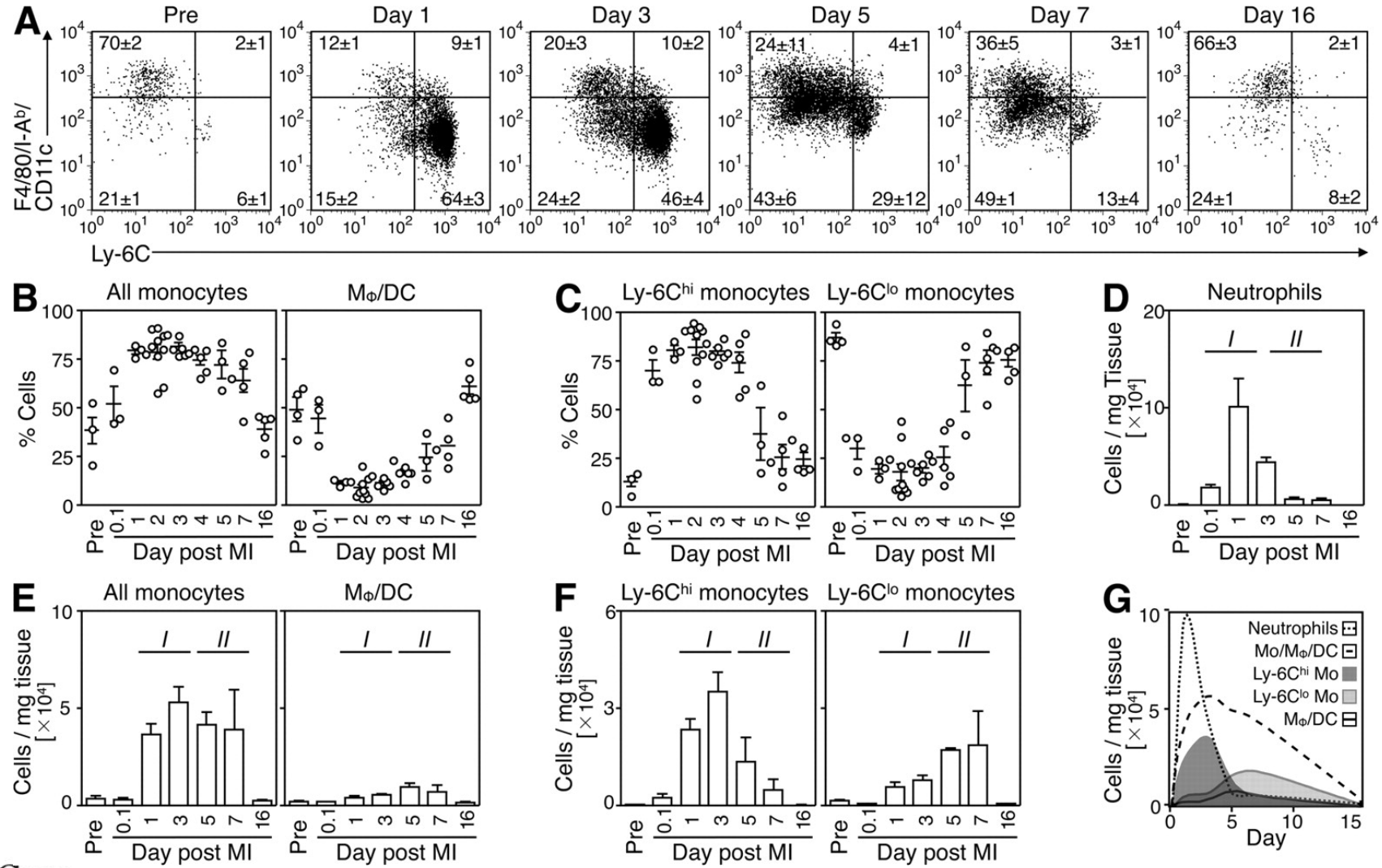
The healing myocardium sequentially mobilizes two monocyte populations with divergent and complimentary functions



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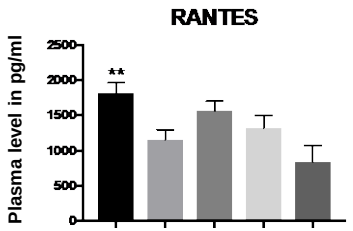
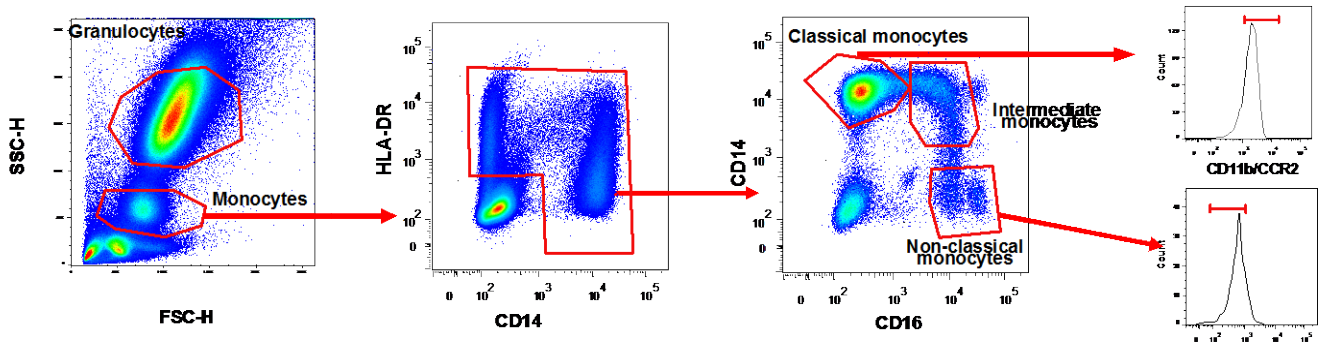
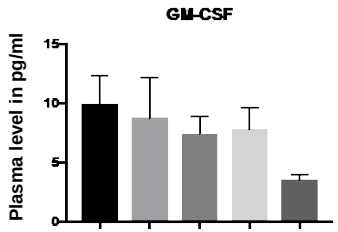
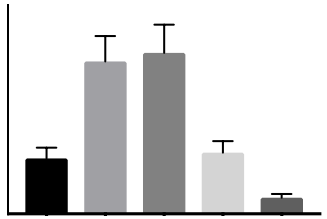
Nahrendorf, et al. J Exp Med, 2007: 204; 3037-3047.

Elevated inflammatory cells post-MI predict cardiac damage and cardiovascular outcomes









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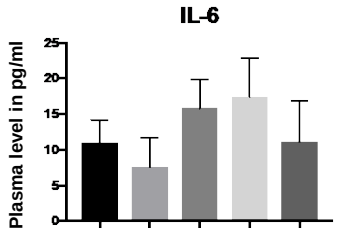

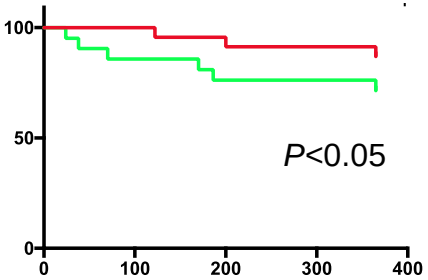

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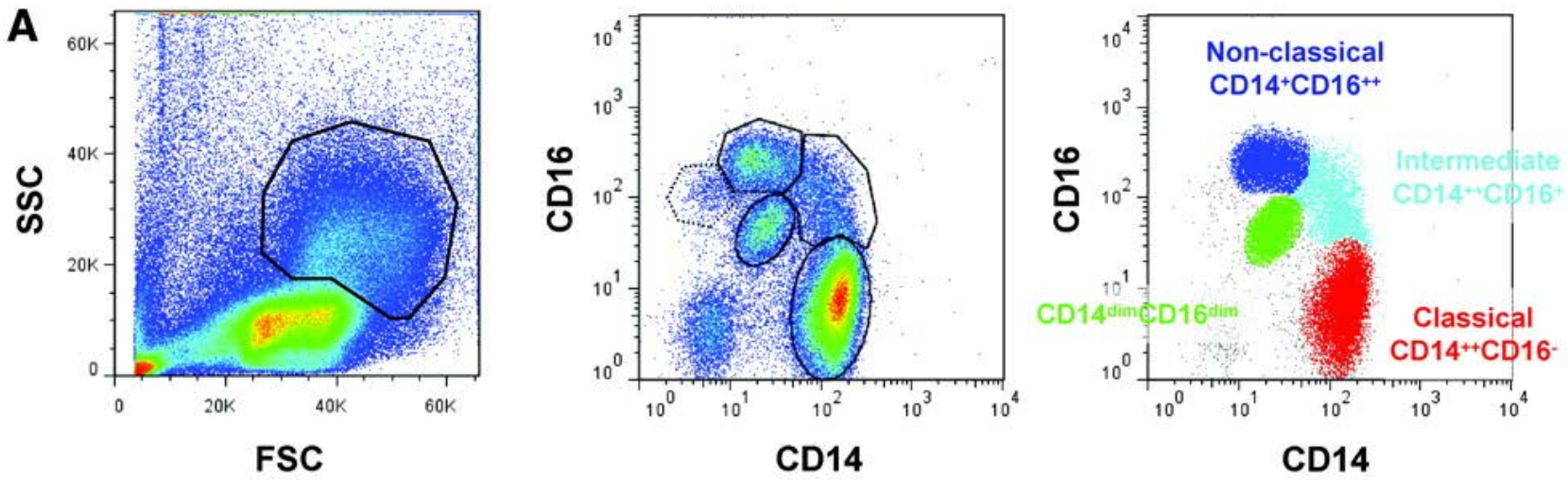
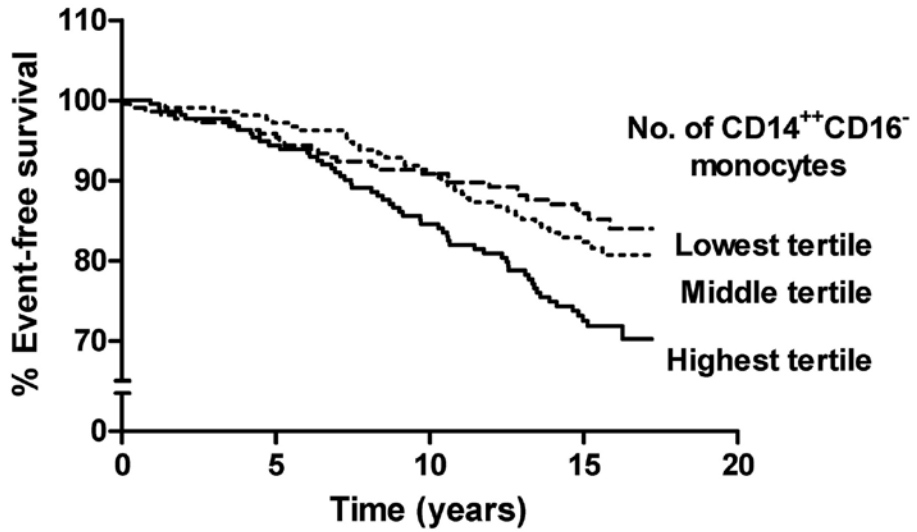
Elevated CD14++CD16+ (inflammatory) monocytes predict cardiovascular outcomes





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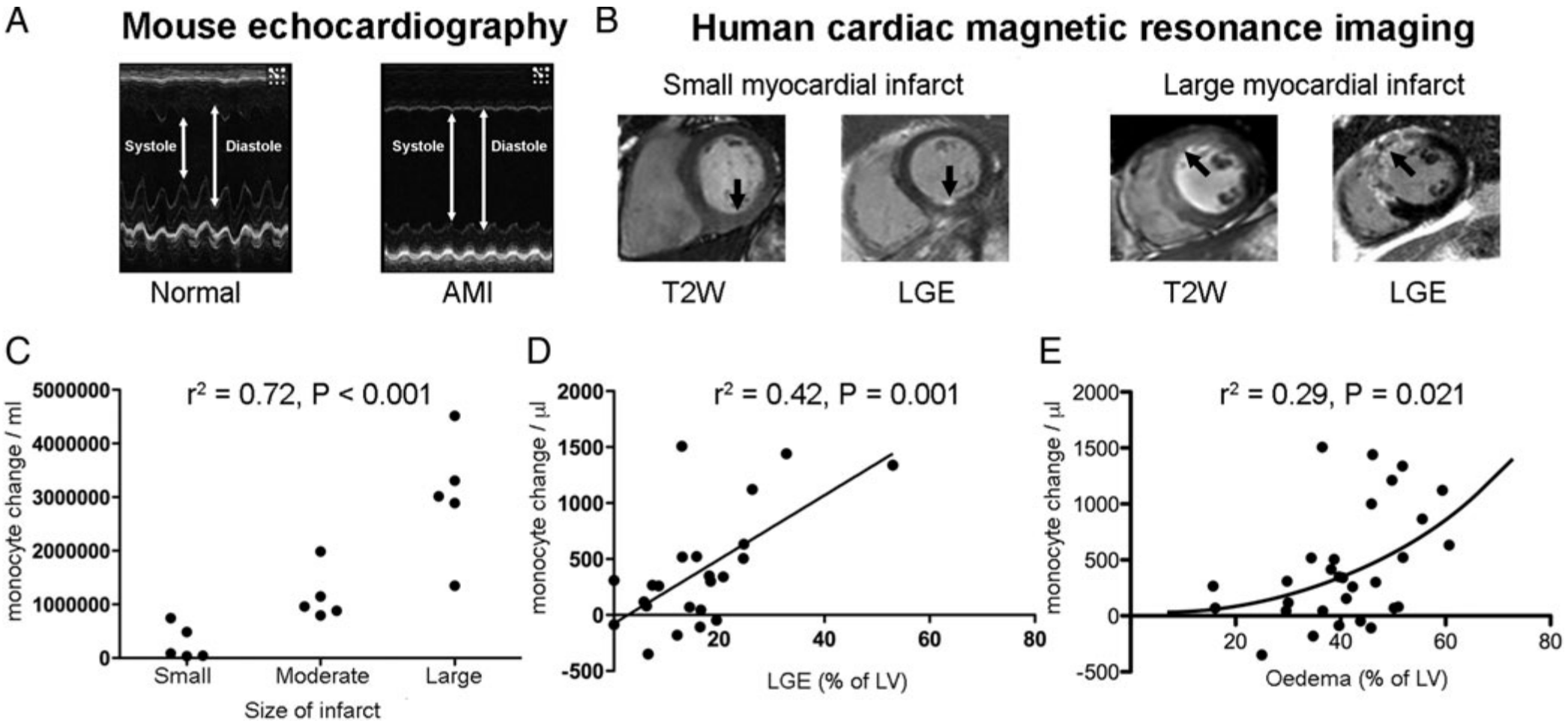
Berg, et al. Circ Cardiovasc Genet, 2012; 5: 122-131

Acute myocardial infraction activates monocytosis which increases cardiac damage



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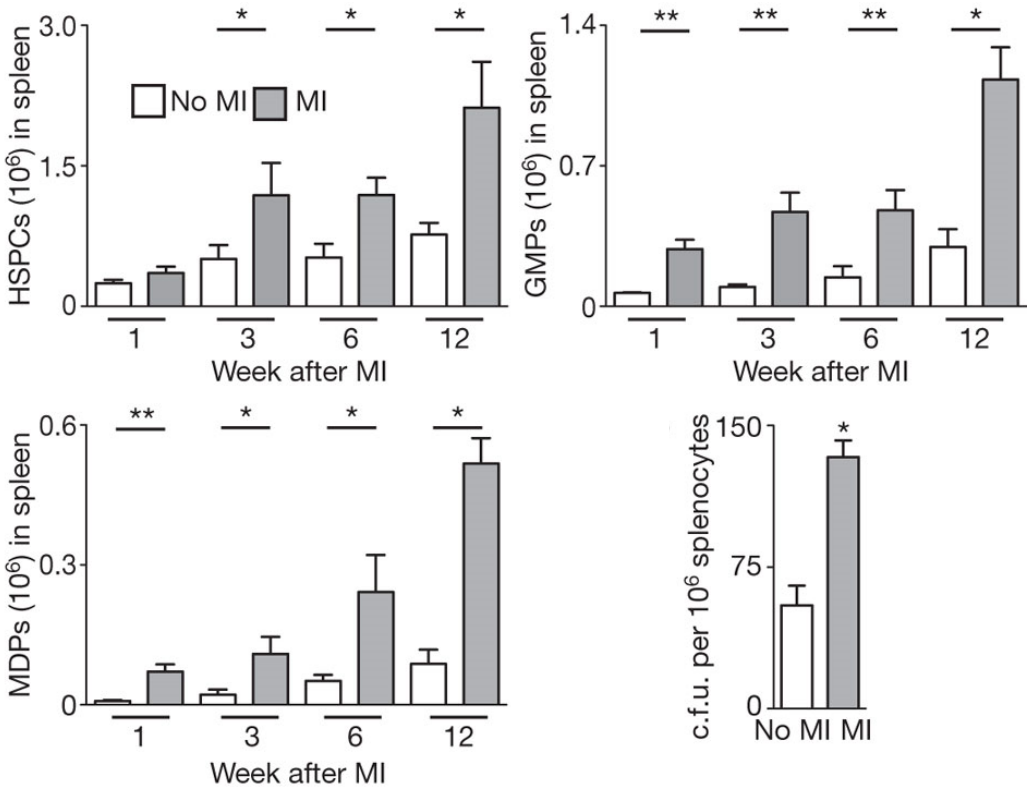
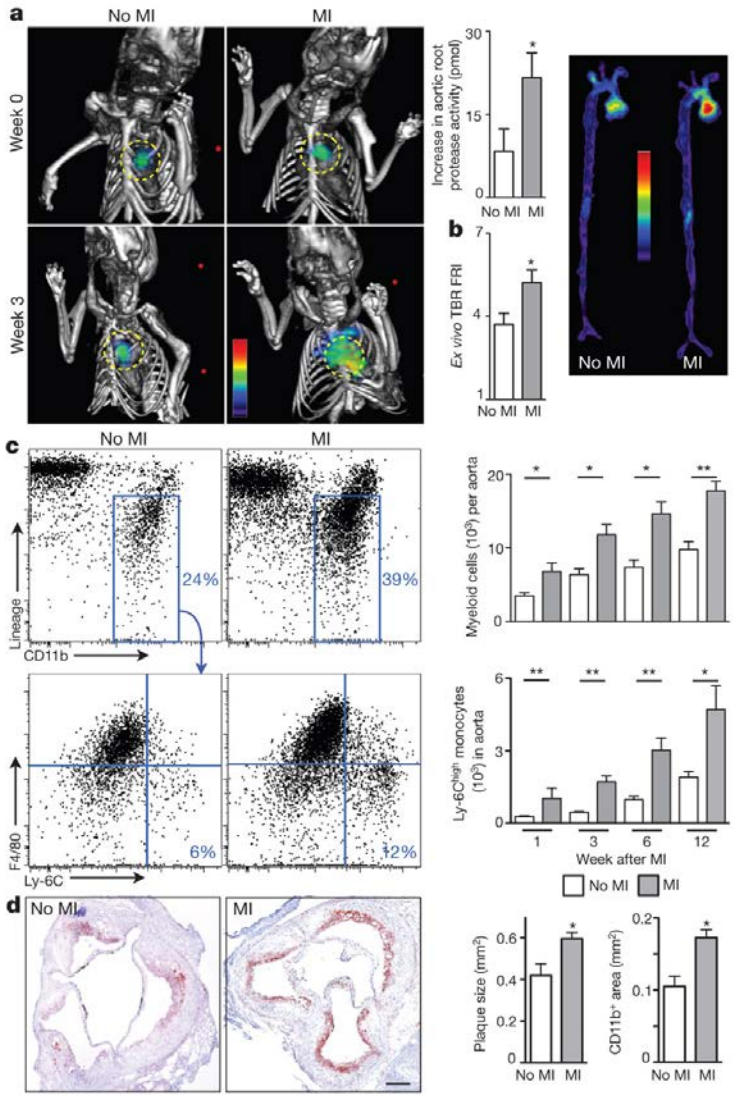
Ruparelia, et al. Eur Heart J, 2015

Myocardial infarction accelerates atherosclerosis





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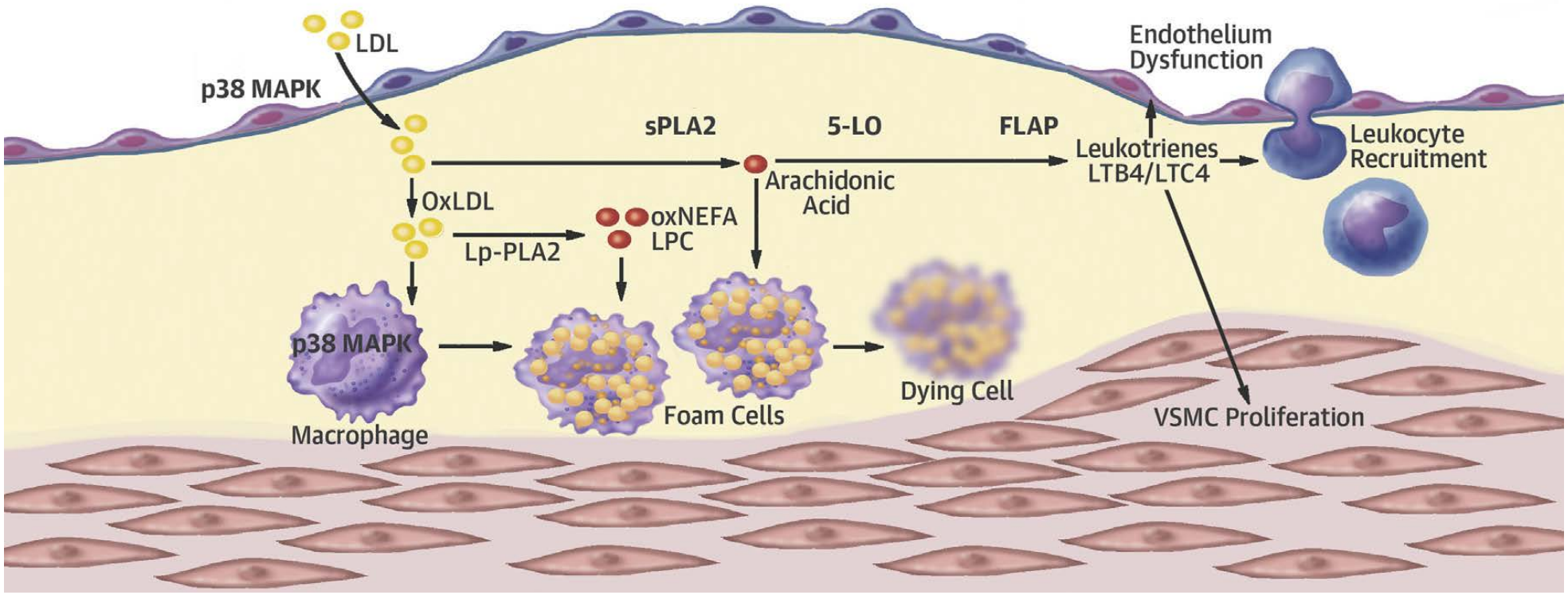
Dutta, et al. Nature, 2012; 487: 325-329.

Systemic inflammation in CAD patients



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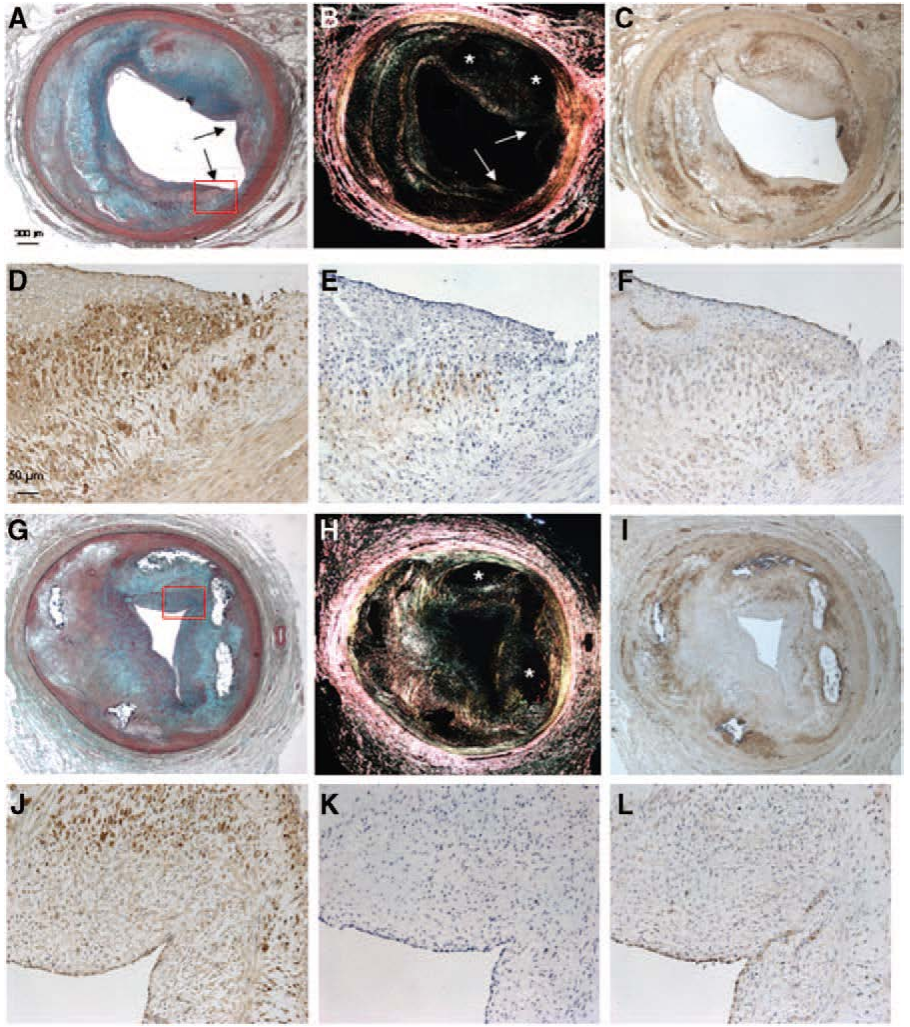
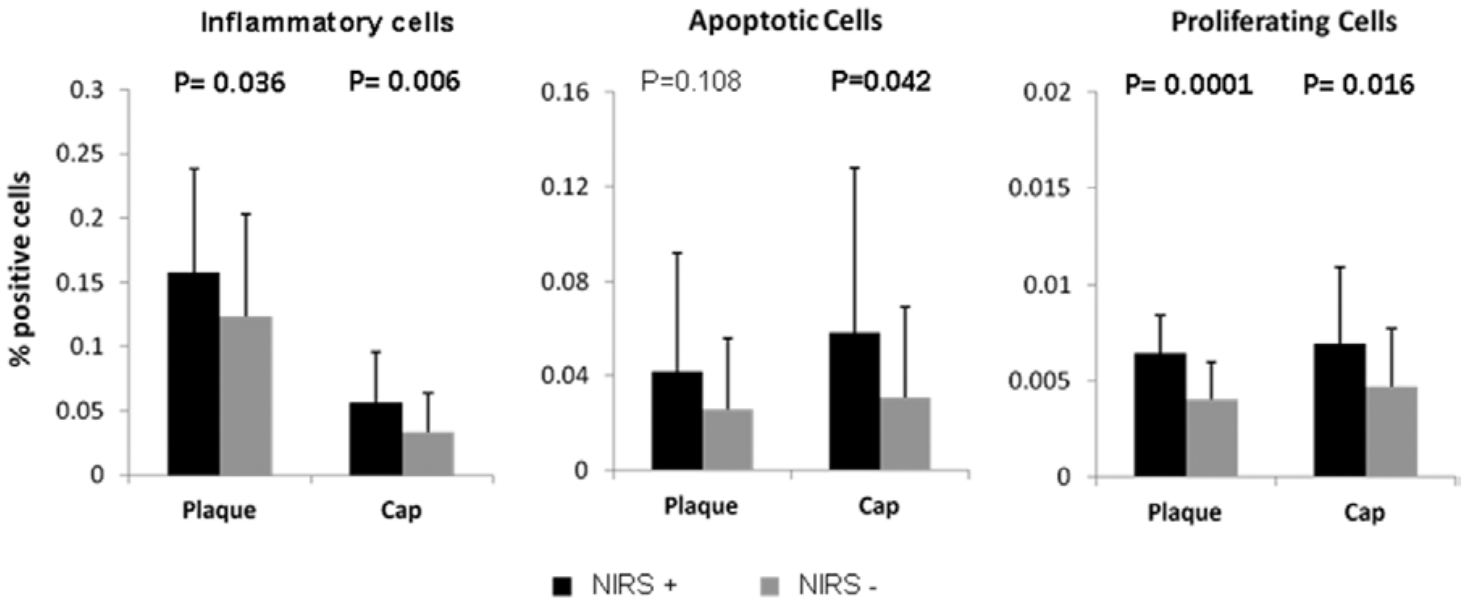
Zhao, et al. JACC, 2019: 73; 1691-1706.

Inflammatory cells correlate with plaque progression





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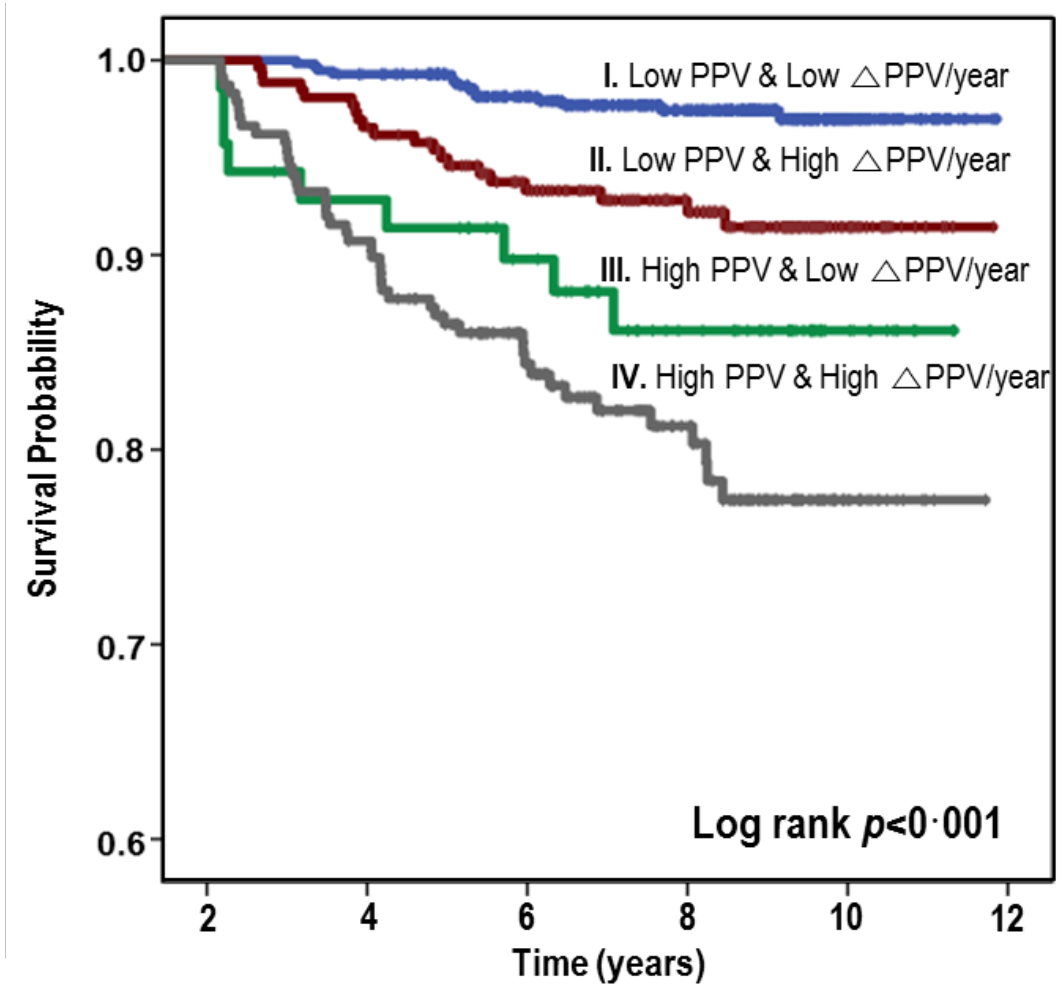
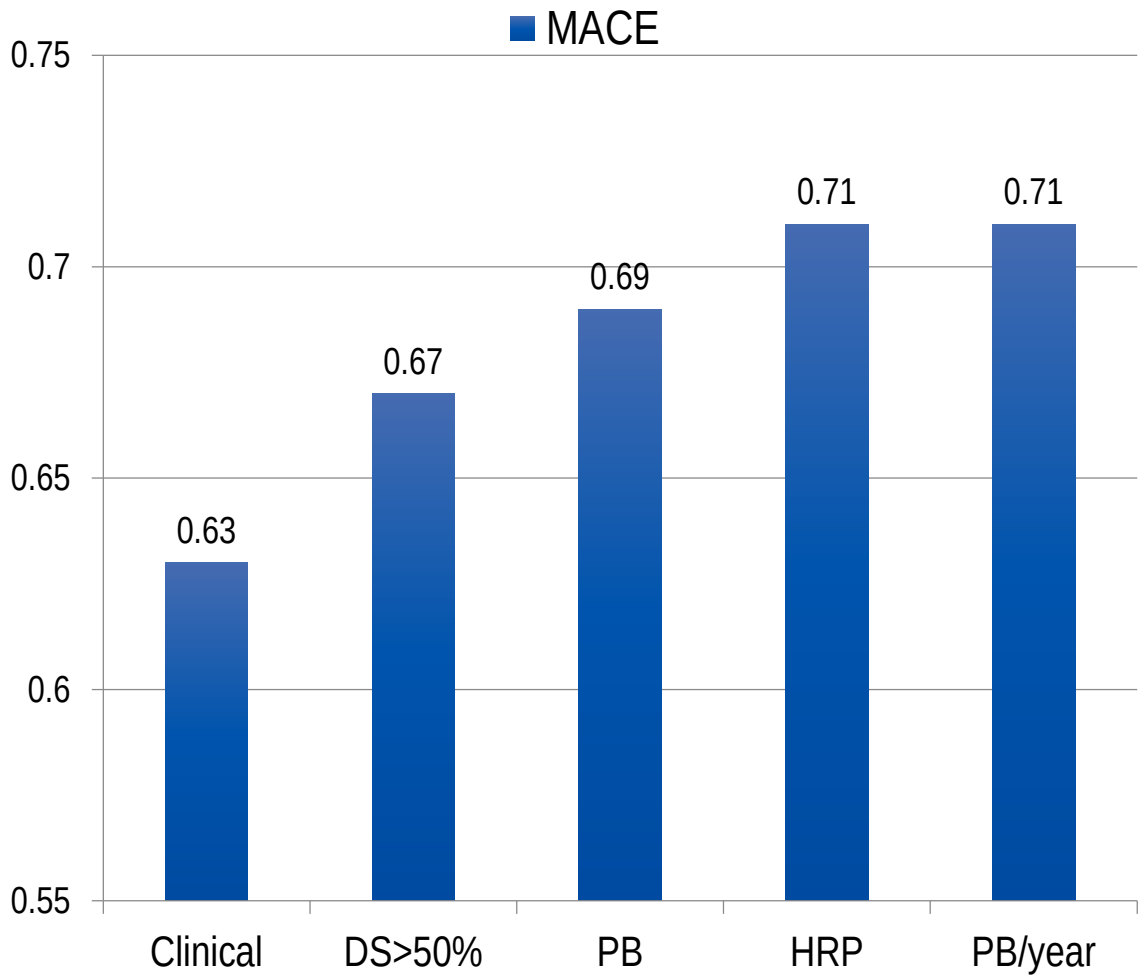
Patel, et al. ATVB, 2013; 33: 347-53.

Coronary Atherosclerosis (PARADIGM): What predicts MACE?





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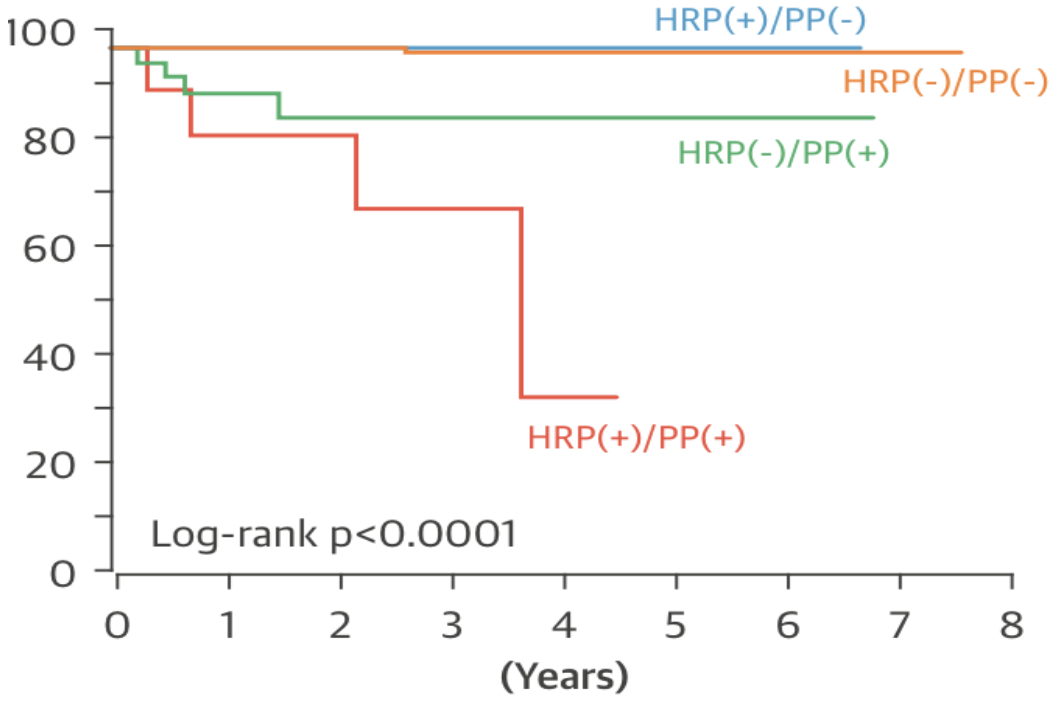
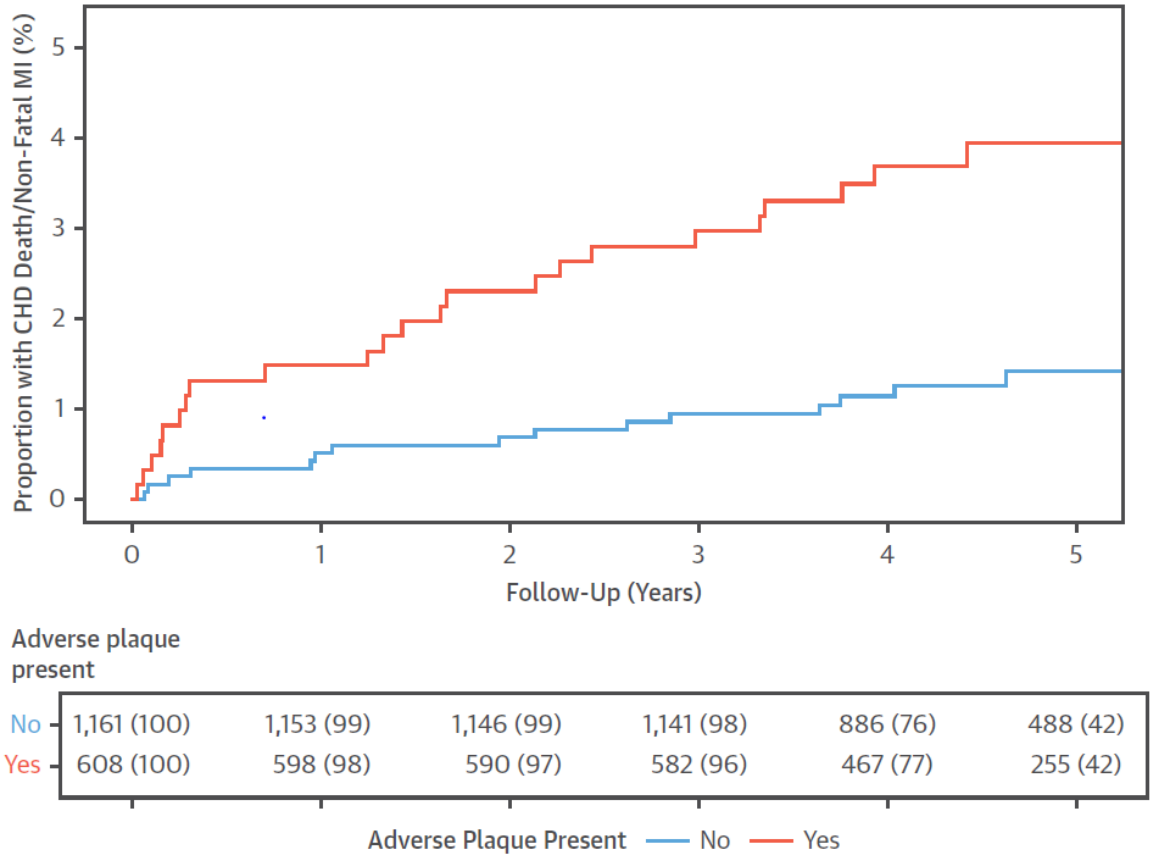
Source: PARADIGM, Preliminary Data

Plaque progression and morphology are key predictors of adverse cardiac events





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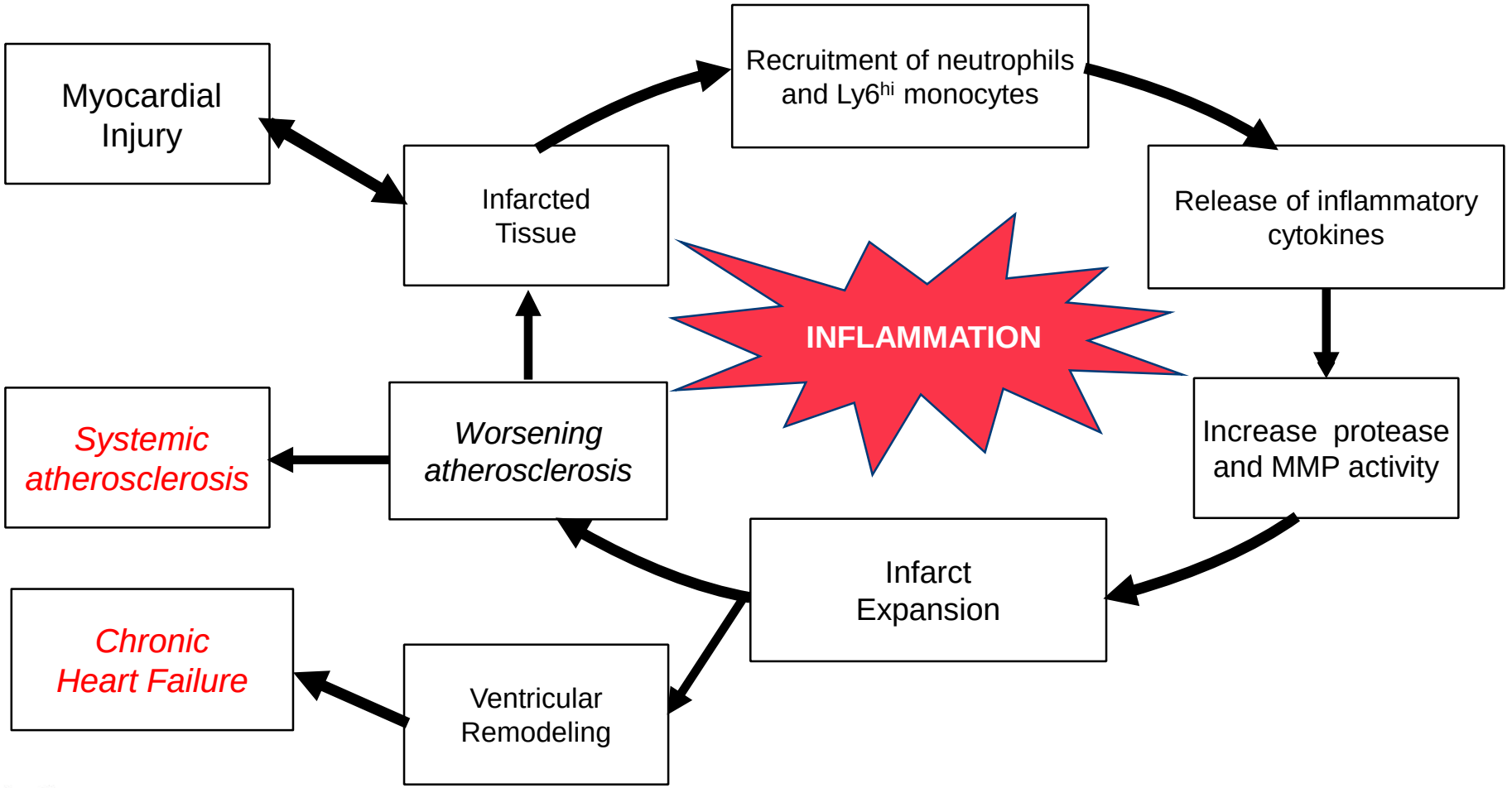
Williams, et al. JACC, 2019; 73: 291-301.

Post-MI Cycle of Risk: Driven by the immune response



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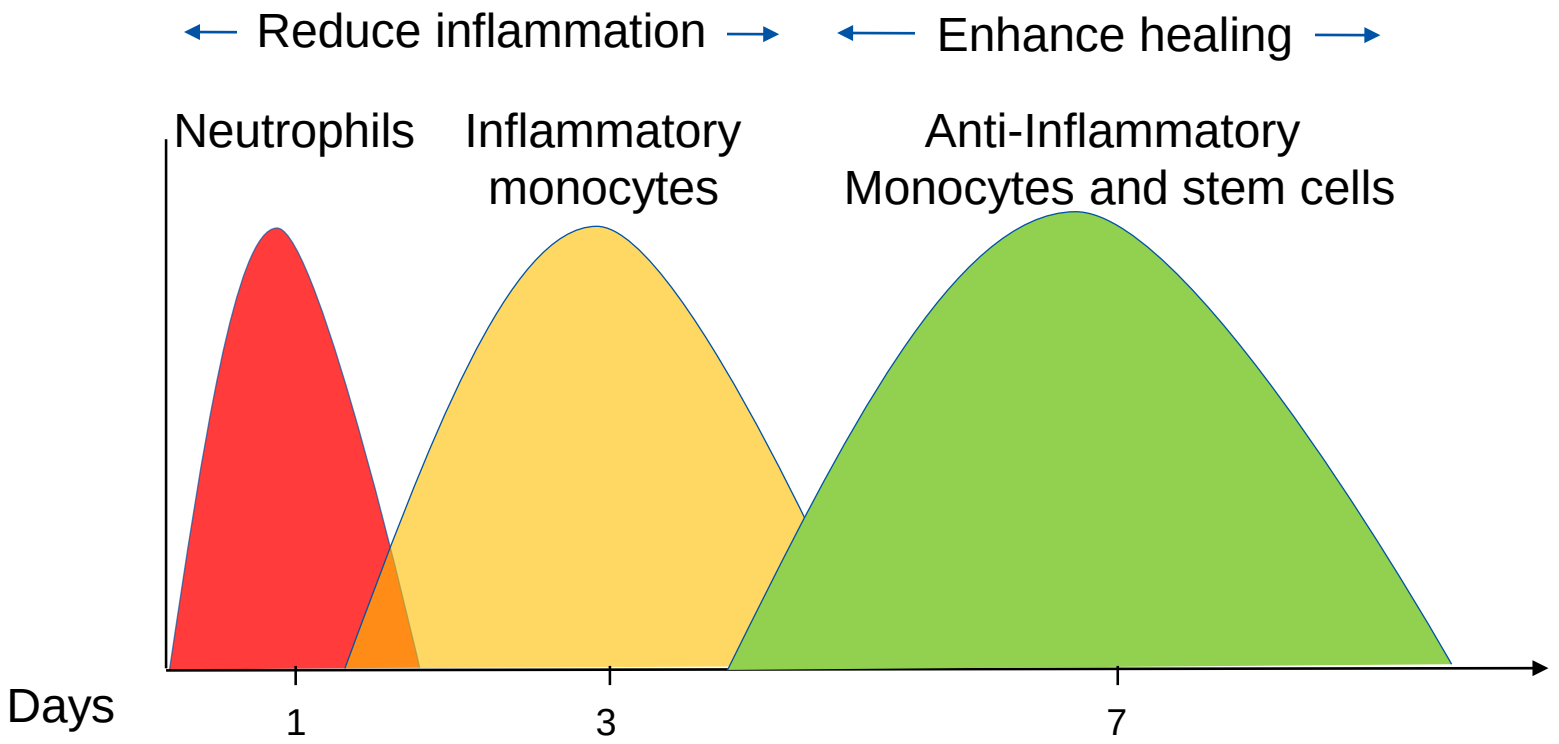
Bone marrow cells in the heart following myocardial infarction



	Neutrophils	Inflammatory monocytes	Anti-inflammatory monocytes and stem cells
Pros	Clean up of damaged tissue/cells	Release of proteolytic enzymes and phagocytosis	Initiate the healing process leading to collagen deposition and angiogenesis
Cons	Exacerbated inflammation can lead to infarct expansion	Infarct expansion and initiates atherosclerosis	Limited number of cells with limited healing

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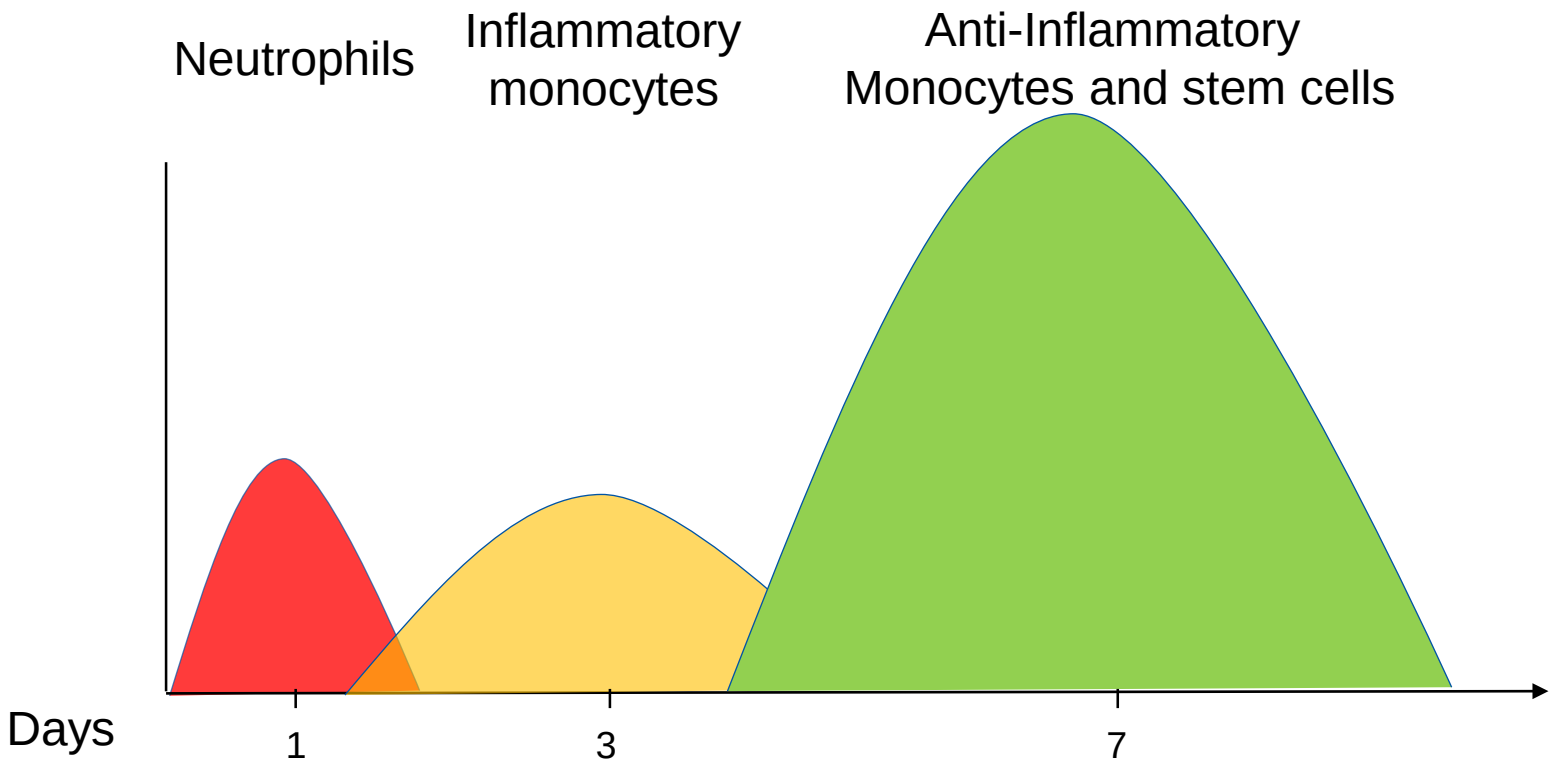

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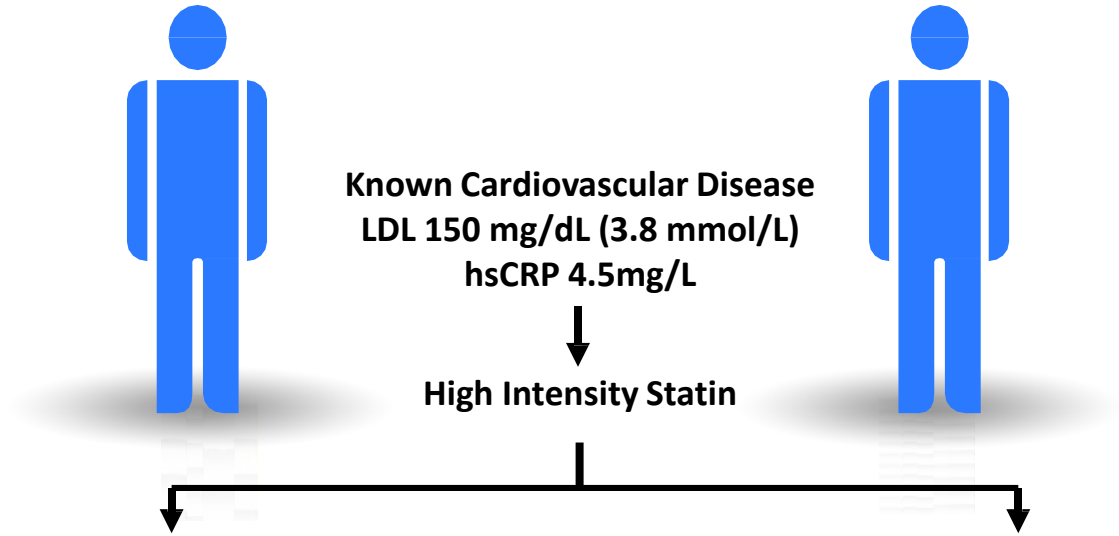
Residual Inflammatory Risk

- Plasma levels of inflammatory biomarkers including hsCRP and IL-6 robustly predict first and recurrent cardiovascular events, independent of lipid levels.
- Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDLC, but who also lower hsCRP.
- In primary prevention, the JUPITER trial demonstrated that those with elevated hsCRP but low levels of LDLC markedly benefit from statin therapy.



"Residual Cholesterol Risk"

LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

Additional
LDL Reduction

IMPROVE-IT : Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

"Residual Inflammatory Risk"

LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

Additional
Inflammation Reduction

Emerging therapeutic field

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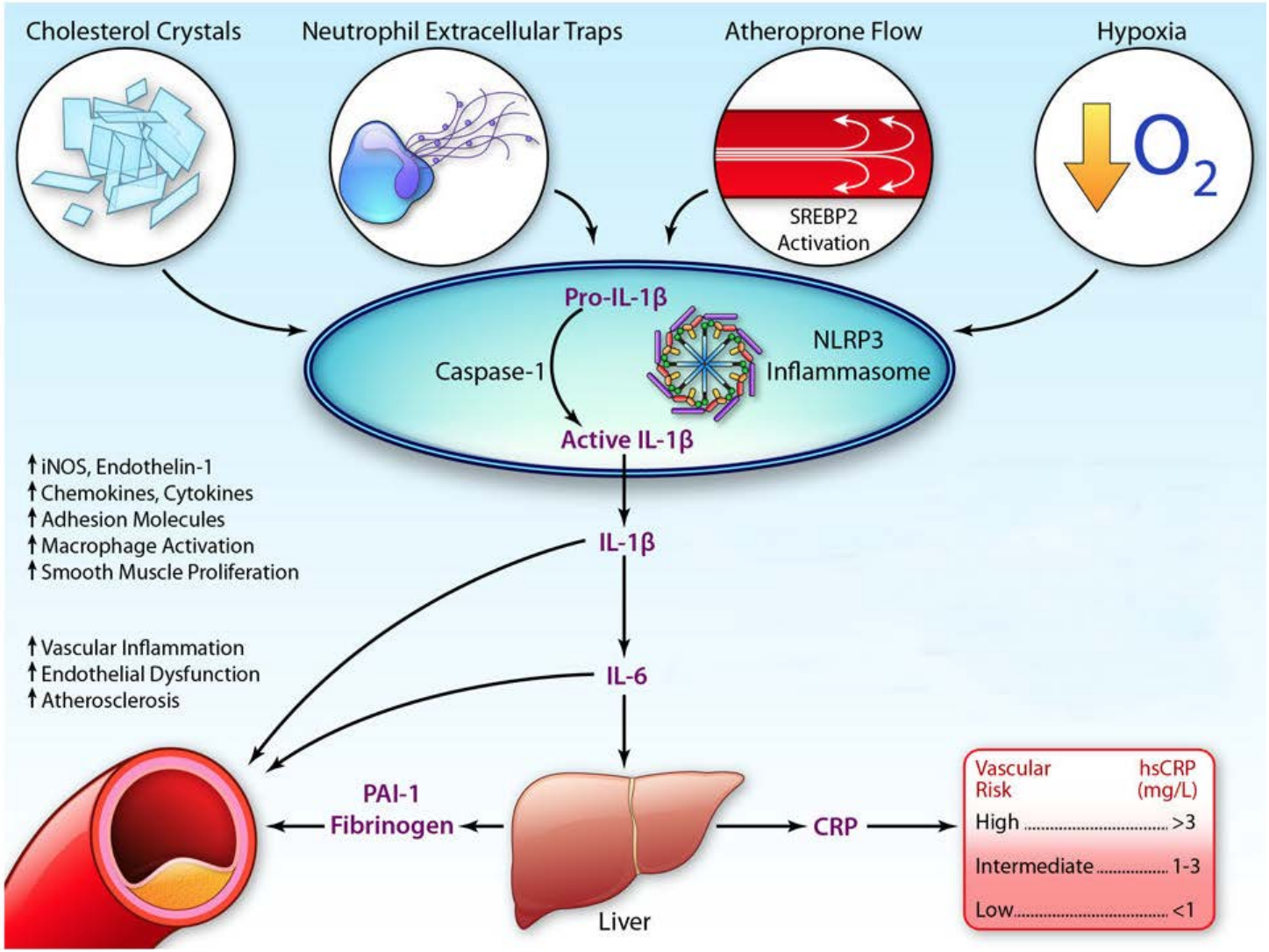
Ridker PM. Eur Heart J 2016;37:1720-22

Targeting upstream signaling molecules to enhance atheroprotection



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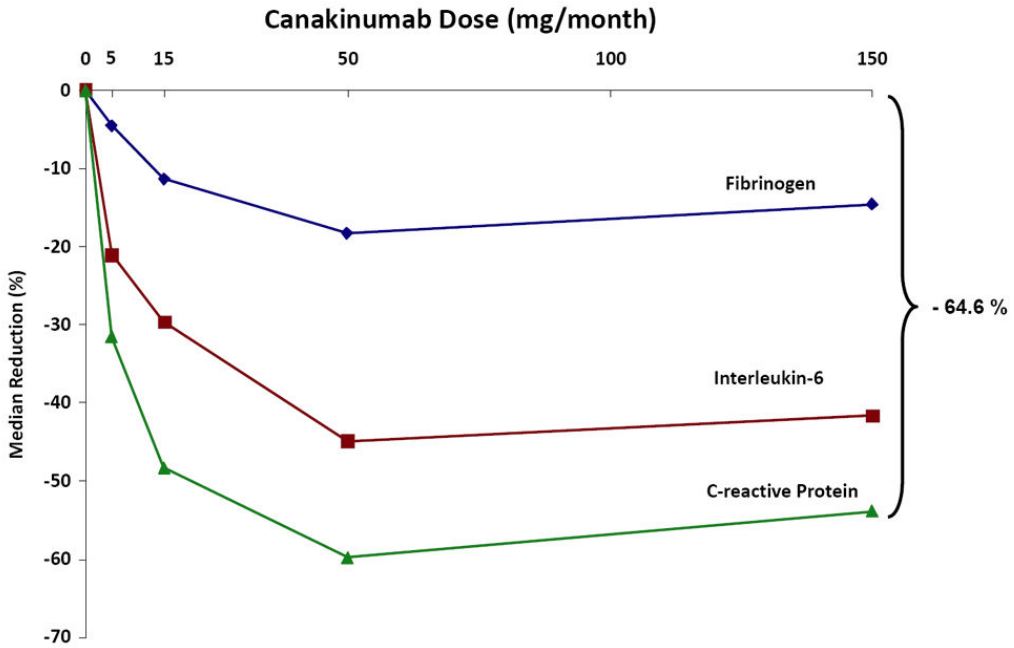
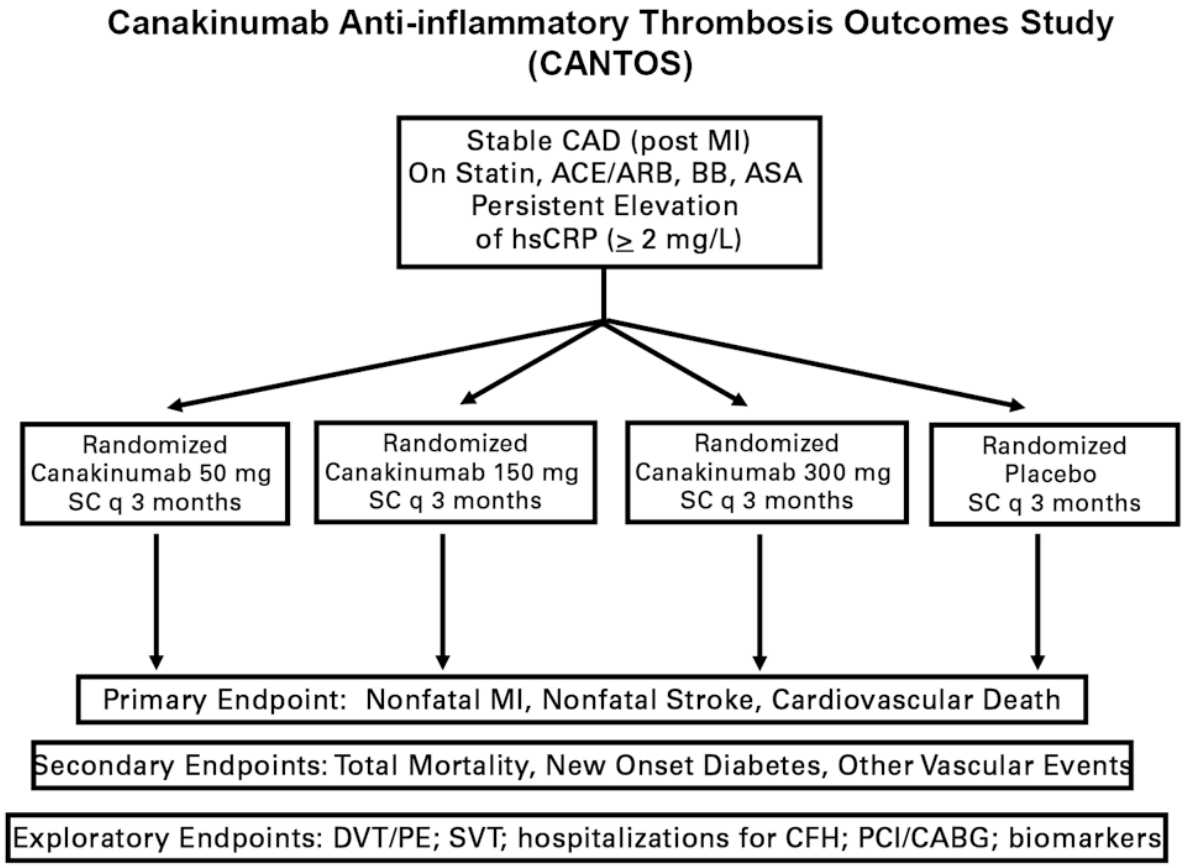
Ridker PM. Circ Res 2016;118:145-156.

Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease





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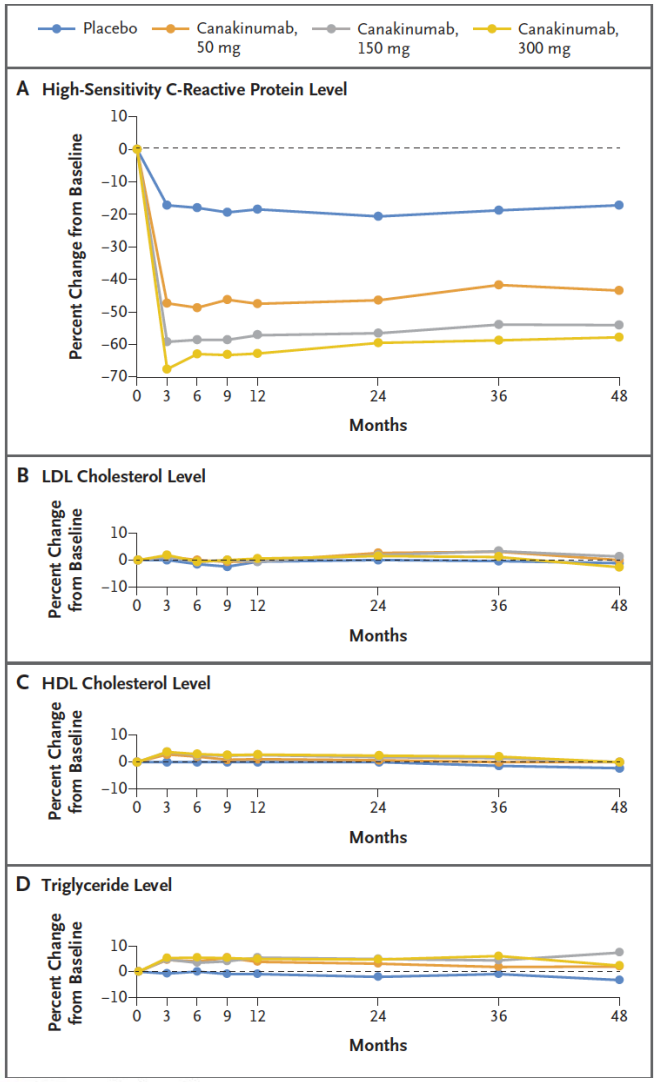
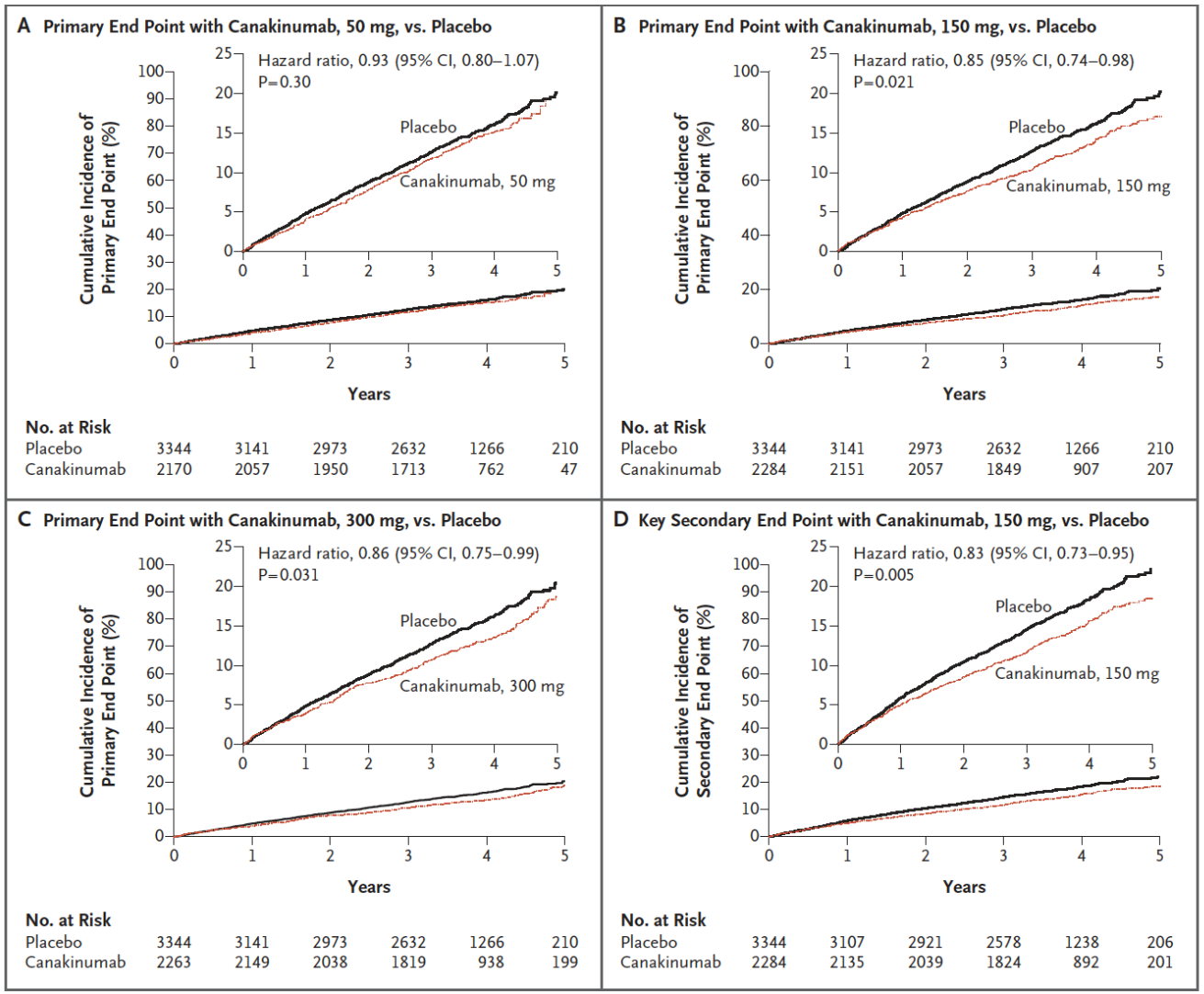
Ridker PM, et al; Circ Res 2016; 118: 145-156

Modulating inflammation improves outcomes in CAD patients





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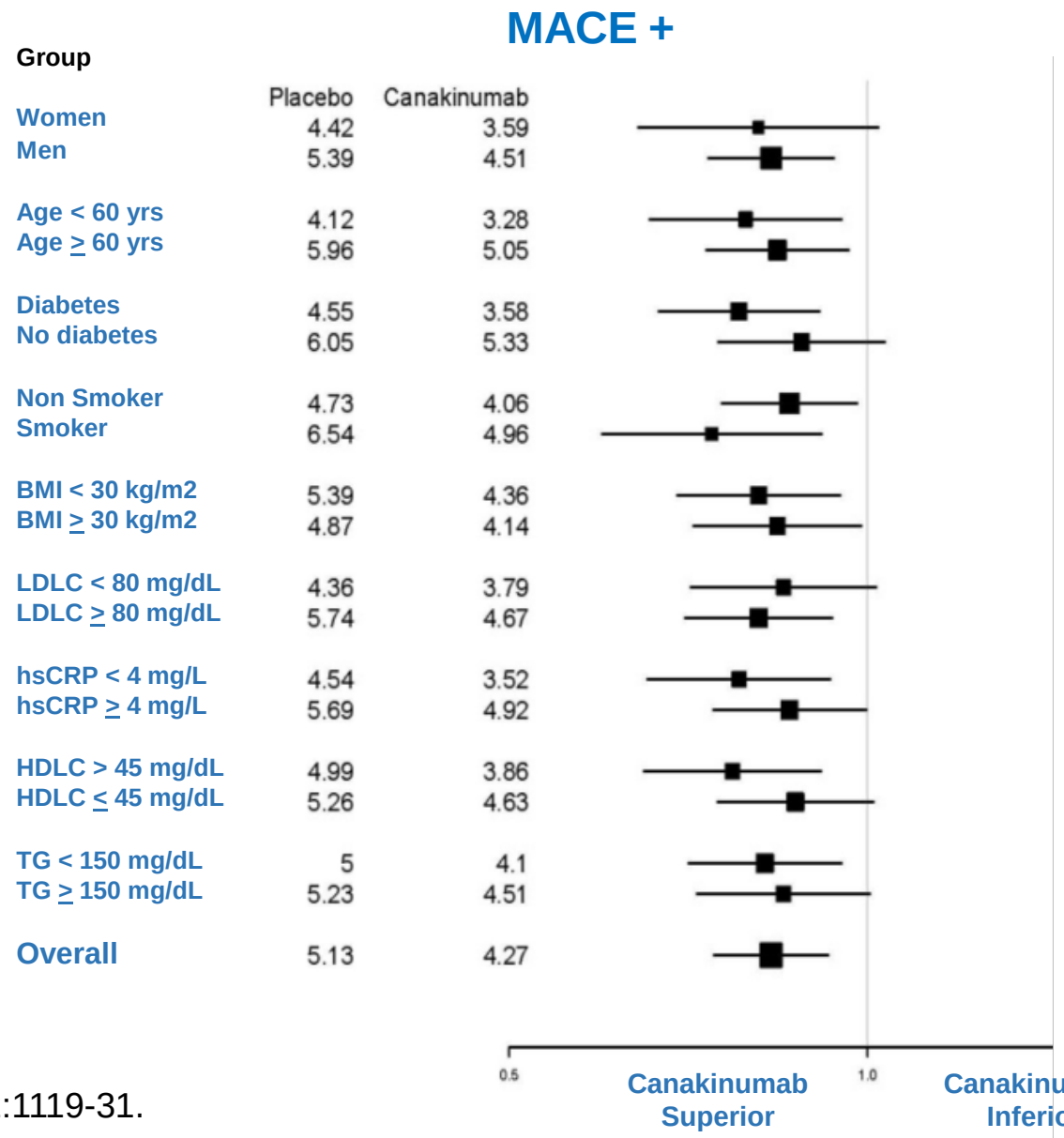
Ridker et al, et al, NEJM 2017; 377; 12:1119-31.

CANTOS: Consistency of HRs across endpoints and study

		Canakinumab SC q 3 months			
Endpoint	**Placebo (N=3347)**	**50 mg (N=2170)**	**150 mg (N=2284)**	**300 mg (N=2263)**	**P-trend**
Primary	1.00	0.93	0.85	0.86	0.020
Secondary	1.00	0.90	0.83	0.83	0.002
Myocardial Infarction	1.00	0.94	0.76	0.84	0.028
Urgent Revascularization	1.00	0.70	0.64	0.58	0.005
Any Coronary Revascularization	1.00	0.72	0.68	0.70	<0.001
Stroke	1.00	1.01	0.98	0.80	0.17
Cardiac Arrest	1.00	0.72	0.63	0.46	0.035
CV Death	1.00	0.89	0.90	0.94	0.62
All Cause Mortality	1.00	0.94	0.92	0.94	0.39



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Ridker et al, et al, NEJM 2017; 377; 12:1119-31.

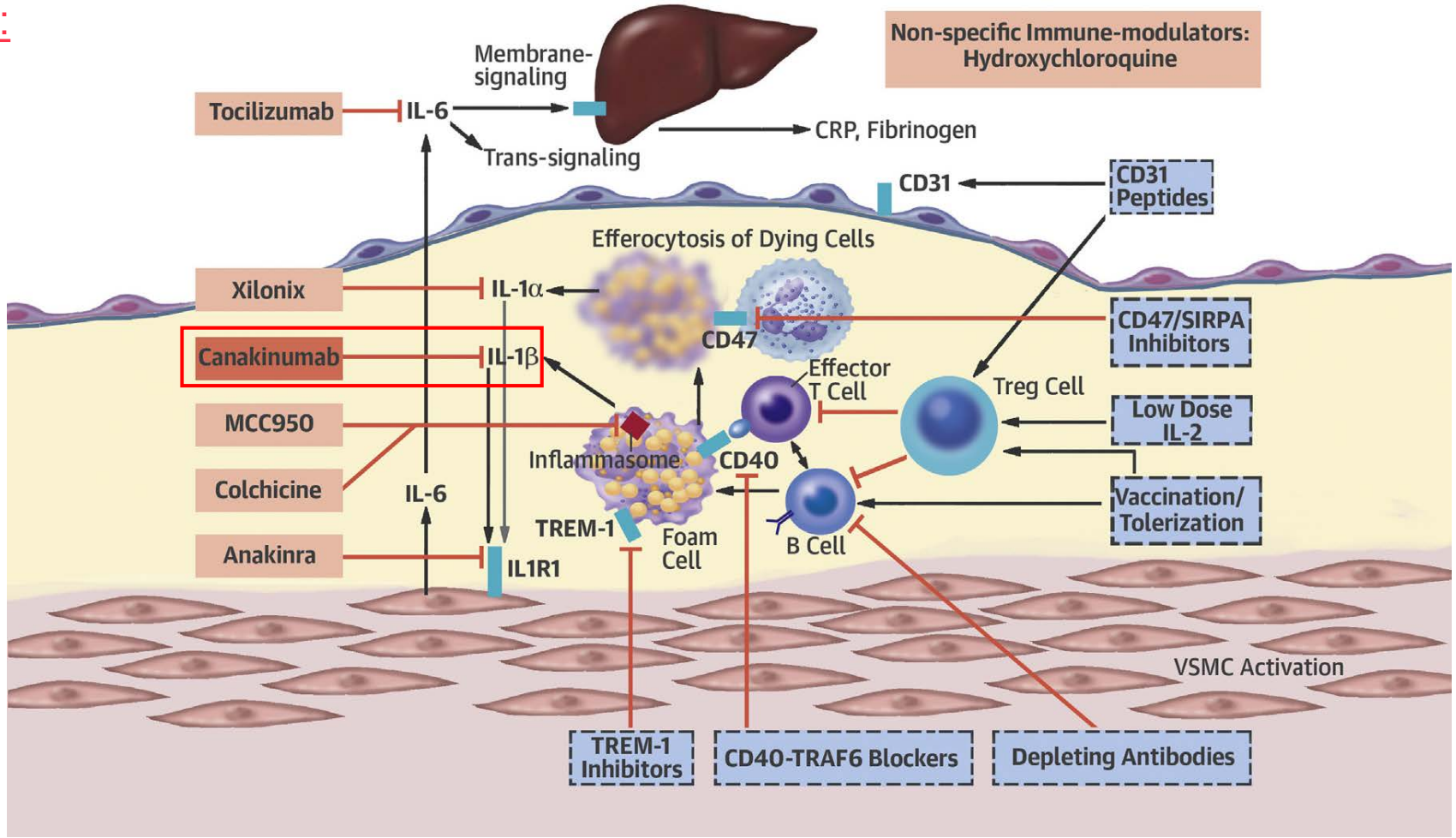
Targeting inflammation in CAD patients

Off target anti-inflammatory therapies:

1. Statins
2. ACEI and ARB
3. BB
4. Aspirin
5. Proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies

Current and future specific therapies:

1. IL-1β blockade
2. Targeting NLRP3
3. Targeting IL6
4. Colchicine
5. IL-1α blockade



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Zhao, et al. JACC, 2019: 73; 1691-1706.

Targeting inflammation in CAD patients

TABLE 2 Therapies Currently in Clinical Trials, Their Pathways and Potential Pros and Cons for Their Future Development and Progress

Drug Name	Pathway	Trial Reference– Patient Population– Primary Trial Endpoint	Pro	Con
Colchicine	NLRP3 inflammasome inhibitor	NCT01709981–undergoing coronary angiography– IL6 level NCT02594111–undergoing coronary angioplasty–Peri-procedural MI (troponin) NCT02551094–acute MI- composite of major cardiovascular events NCT01906749–ACS–composite of major cardiovascular events	Licensed small-molecule drug. Has reduced a composite endpoint of CV events in a small randomized, observer-blinded trial	Significant side effects, especially gastrointestinal
MCC950	NLRP3 inflammasome inhibitor	N/A	Small molecule and specific inhibitor of NLRP3. Positive results in preclinical models	More specific inhibitors being developed
Anakinra	IL-1 receptor antagonist	NCT01950299–STEMI patients–CRP levels	Early phase studies show decrease in inflammation in the short-term	Rebound effect of CRP and IL-6 on stopping of unknown significance. Genetic studies of *IL1RN* (encoding IL-1Ra) are not supportive
Xilonix	Anti-IL-1α antibody	Sayed El et al. (88)–patients needing percutaneous revascularization–composite of major cardiovascular events	May target senescence and necrosis-dependent inflammation. Well tolerated	Did not decrease CRP and limited clinical data available
Tocilizumab	Anti-IL-6R antibody	NCT03004703–STEMI–myocardial salvage on MRI	Licensed drug Supportive genetic studies	Non-specific blocker of both membrane and trans IL-6 signaling. Alteration of lipid parameters
Hydroxychloroquine	Multiple	NCT02874287-CAD–change in CRP NCT02648464–NSTEMI–composite of major cardiovascular events	Licensed small-molecule drug. Supportive retrospective epidemiological data	Long-term inhibition of TLR7 and TLR9 may be detrimental
IL-2 (low-dose)	Treg cells expansion	Zhao et al. (114)-ACS–patient safety and vascular inflammation on ^{18}F-FDG/PET	Licensed drug, effective in other human inflammatory disease models. Supportive preclinical data	More selective Treg promoters being developed

ACS = acute coronary syndrome; CAD = coronary artery disease; CRP = C-reactive protein; FDG-PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography; IL = interleukin; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; Treg = regulatory T cells; TRL = toll like receptors.

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Zhao, et al. JACC, 2019: 73; 1691-1706.

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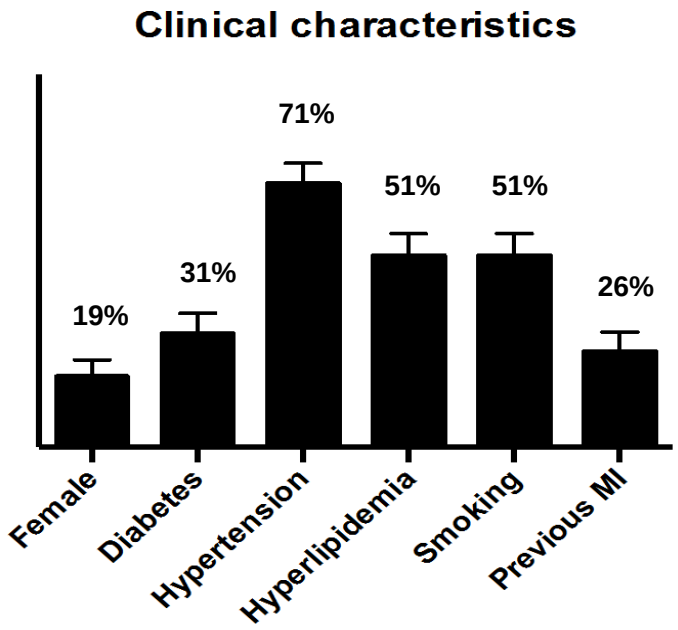
Bone marrow derived stem cells and cardiac recovery

Stem cell mobilization in STEMI patients



Clinical and Imaging Variables	
Age (years)	58.1 ± 1.5
Anterior STEMI (%)	41 ± 0.06
Baseline LVEF	44 ± 1.4
Baseline LVEDV	150 ± 7
Baseline LVESV	82 ± 6
Scar size (%)	22 ± 0.02
Scar mass (g)	32 ± 4
Troponin I (ng/ml)	14 ± 1.9
CK (IU/L)	1764 ± 150
NT pro-BNP (pg/ml)	2057 ± 216
Median follow up (days)	324

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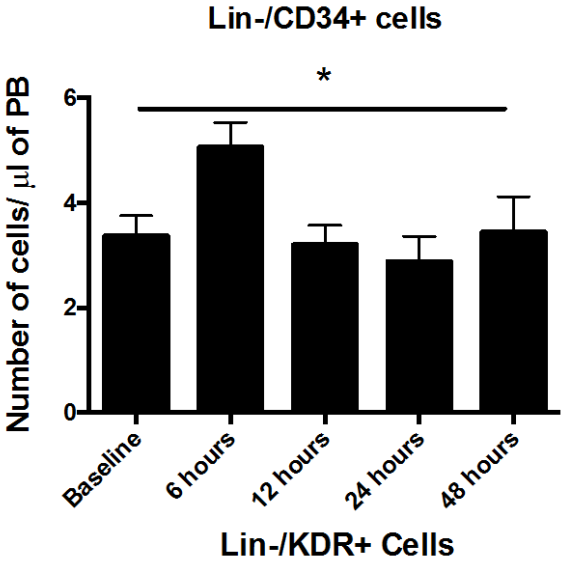
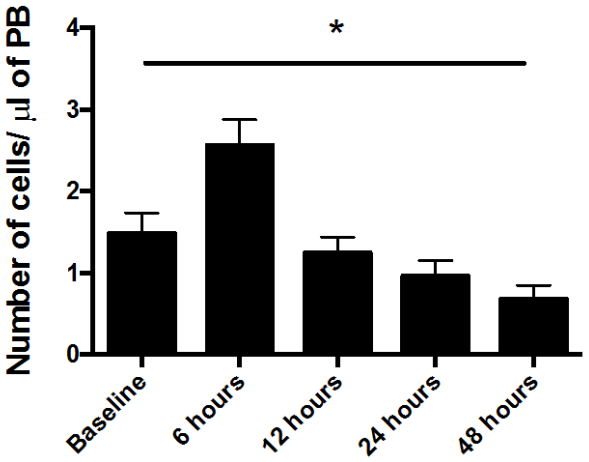
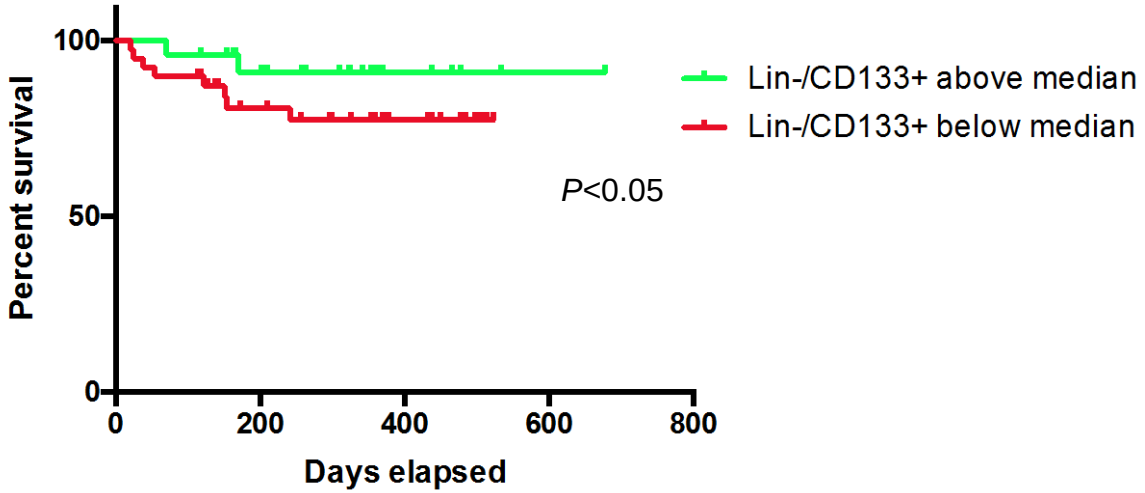
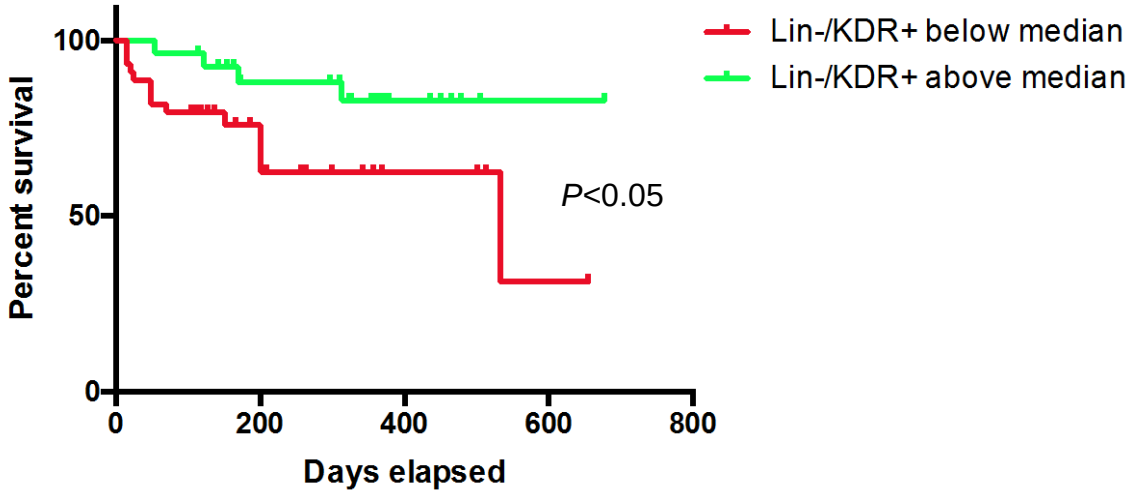
Stem cell mobilization predict outcomes in STEMI patients









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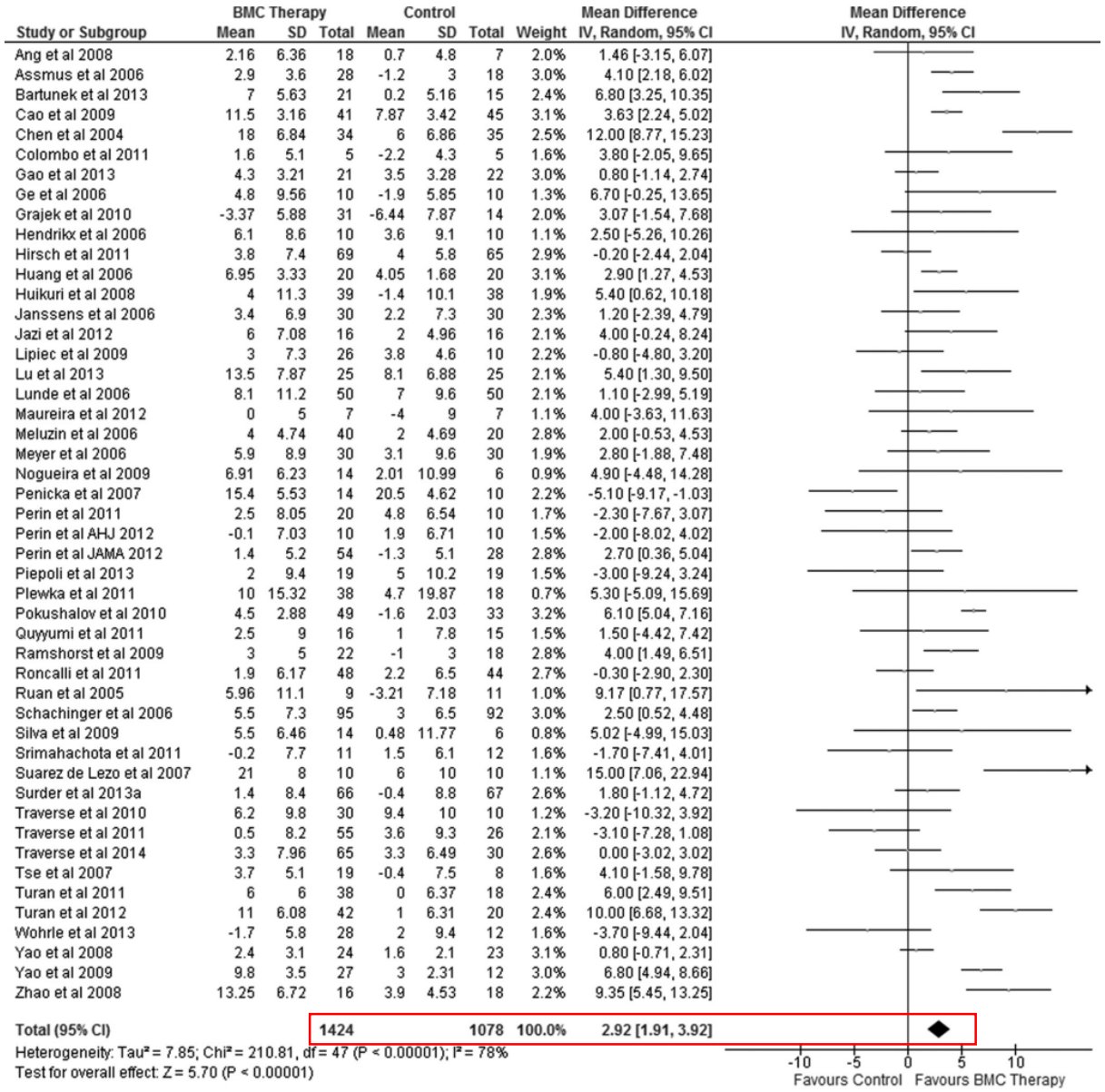
Bone marrow cells for myocardial regeneration (Clinical data)

LVEF



Study or Subgroup	BMC Therapy Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ang et al 2008	2.16	6.36	18	0.7	4.8	7	2.0%	1.46 [-3.15, 6.07]
Assmus et al 2006	2.9	3.6	28	-1.2	3	18	3.0%	4.10 [2.18, 6.02]
Bartunek et al 2013	7	5.63	21	0.2	5.16	15	2.4%	6.80 [3.25, 10.35]
Cao et al 2009	11.5	3.16	41	7.87	3.42	45	3.1%	3.63 [2.24, 5.02]
Chen et al 2004	18	6.84	34	6	6.86	35	2.5%	12.00 [8.77, 15.23]
Colombo et al 2011	1.6	5.1	5	-2.2	4.3	5	1.6%	3.80 [-2.05, 9.65]
Gao et al 2013	4.3	3.21	21	3.5	3.28	22	3.0%	0.80 [-1.14, 2.74]
Ge et al 2006	4.8	9.56	10	-1.9	5.85	10	1.3%	6.70 [-0.25, 13.65]
Grajek et al 2010	-3.37	5.88	31	-6.44	7.87	14	2.0%	3.07 [-1.54, 7.68]
Hendrikx et al 2006	6.1	8.6	10	3.6	9.1	10	1.1%	2.50 [-5.26, 10.26]
Hirsch et al 2011	3.8	7.4	69	4	5.8	65	2.9%	-0.20 [-2.44, 2.04]
Huang et al 2006	6.95	3.33	20	4.05	1.68	20	3.1%	2.90 [1.27, 4.53]
Huikuri et al 2008	4	11.3	39	-1.4	10.1	38	1.9%	5.40 [0.62, 10.18]
Janssens et al 2006	3.4	6.9	30	2.2	7.3	30	2.3%	1.20 [-2.39, 4.79]
Jazi et al 2012	6	7.08	16	2	4.96	16	2.1%	4.00 [-0.24, 8.24]
Lipiec et al 2009	3	7.3	26	3.8	4.6	10	2.2%	-0.80 [-4.80, 3.20]
Lu et al 2013	13.5	7.87	25	8.1	6.88	25	2.1%	5.40 [1.30, 9.50]
Lunde et al 2006	8.1	11.2	50	7	9.6	50	2.1%	1.10 [-2.99, 5.19]
Maureira et al 2012	0	5	7	-4	9	7	1.1%	4.00 [-3.63, 11.63]
Meluzin et al 2006	4	4.74	40	2	4.69	20	2.8%	2.00 [-0.53, 4.53]
Meyer et al 2006	5.9	8.9	30	3.1	9.6	30	1.9%	2.80 [-1.88, 7.48]
Nogueira et al 2009	6.91	6.23	14	2.01	10.99	6	0.9%	4.90 [-4.48, 14.28]
Penicka et al 2007	15.4	5.53	14	20.5	4.62	10	2.2%	-5.10 [-9.17, -1.03]
Perin et al 2011	2.5	8.05	20	4.8	6.54	10	1.7%	-2.30 [-7.67, 3.07]
Perin et al AHJ 2012	-0.1	7.03	10	1.9	6.71	10	1.5%	-2.00 [-8.02, 4.02]
Perin et al JAMA 2012	1.4	5.2	54	-1.3	5.1	28	2.8%	2.70 [0.36, 5.04]
Piepoli et al 2013	2	9.4	19	5	10.2	19	1.5%	-3.00 [-9.24, 3.24]
Plewka et al 2011	10	15.32	38	4.7	19.87	18	0.7%	5.30 [-5.09, 15.69]
Pokushalov et al 2010	4.5	2.88	49	-1.6	2.03	33	3.2%	6.10 [5.04, 7.16]
Quyyumi et al 2011	2.5	9	16	1	7.8	15	1.5%	1.50 [-4.42, 7.42]
Ramshorst et al 2009	3	5	22	-1	3	18	2.8%	4.00 [1.49, 6.51]
Roncalli et al 2011	1.9	6.17	48	2.2	6.5	44	2.7%	-0.30 [-2.90, 2.30]
Ruan et al 2005	5.96	11.1	9	-3.21	7.18	11	1.0%	9.17 [0.77, 17.57]
Schachinger et al 2006	5.5	7.3	95	3	6.5	92	3.0%	2.50 [0.52, 4.48]
Silva et al 2009	5.5	6.46	14	0.48	11.77	6	0.8%	5.02 [-4.99, 15.03]
Srimahachota et al 2011	-0.2	7.7	11	1.5	6.1	12	1.6%	-1.70 [-7.41, 4.01]
Suarez de Lezo et al 2007	21	8	10	6	10	10	1.1%	15.00 [7.06, 22.94]
Surder et al 2013a	1.4	8.4	66	-0.4	8.8	67	2.6%	1.80 [-1.12, 4.72]
Traverse et al 2010	6.2	9.8	30	9.4	10	10	1.2%	-3.20 [-10.32, 3.92]
Traverse et al 2011	0.5	8.2	55	3.6	9.3	26	2.1%	-3.10 [-7.28, 1.08]
Traverse et al 2014	3.3	7.96	65	3.3	6.49	30	2.6%	0.00 [-3.02, 3.02]
Tse et al 2007	3.7	5.1	19	-0.4	7.5	8	1.6%	4.10 [-1.58, 9.78]
Turan et al 2011	6	6	38	0	6.37	18	2.4%	6.00 [2.49, 9.51]
Turan et al 2012	11	6.08	42	1	6.31	20	2.4%	10.00 [6.68, 13.32]
Wohrle et al 2013	-1.7	5.8	28	2	9.4	12	1.6%	-3.70 [-9.44, 2.04]
Yao et al 2008	2.4	3.1	24	1.6	2.1	23	3.1%	0.80 [-0.71, 2.31]
Yao et al 2009	9.8	3.5	27	3	2.31	12	3.0%	6.80 [4.94, 8.66]
Zhao et al 2008	13.25	6.72	16	3.9	4.53	18	2.2%	9.35 [5.45, 13.25]
Total (95% CI)			1424			1078	100.0%	2.92 [1.91, 3.92]

Heterogeneity: Tau² = 7.85; Chi² = 210.81, df = 47 (P < 0.00001); I² = 78%
Test for overall effect: Z = 5.70 (P < 0.00001)

Mean Difference IV, Random, 95% CI
-10 -5 0 5 10
Favours Control Favours BMC Therapy

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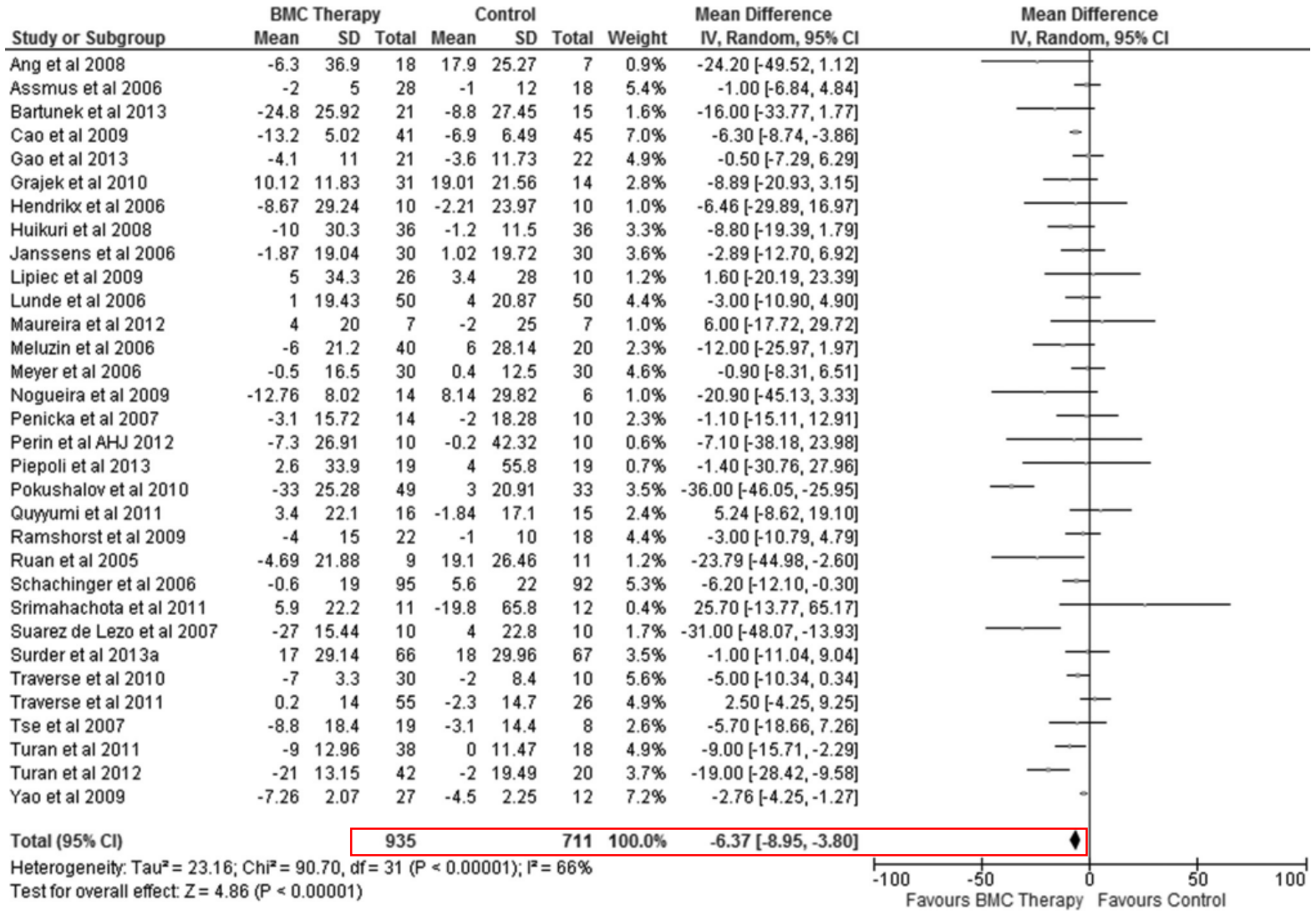
Bone marrow cells for myocardial regeneration (Clinical data)

LVESV



Study or Subgroup	BMC Therapy Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ang et al 2008	-6.3	36.9	18	17.9	25.27	7	0.9%	-24.20 [-49.52, 1.12]
Assmus et al 2006	-2	5	28	-1	12	18	5.4%	-1.00 [-6.84, 4.84]
Bartunek et al 2013	-24.8	25.92	21	-8.8	27.45	15	1.6%	-16.00 [-33.77, 1.77]
Cao et al 2009	-13.2	5.02	41	-6.9	6.49	45	7.0%	-6.30 [-8.74, -3.86]
Gao et al 2013	-4.1	11	21	-3.6	11.73	22	4.9%	-0.50 [-7.29, 6.29]
Grajek et al 2010	10.12	11.83	31	19.01	21.56	14	2.8%	-8.89 [-20.93, 3.15]
Hendrikx et al 2006	-8.67	29.24	10	-2.21	23.97	10	1.0%	-6.46 [-29.89, 16.97]
Huikuri et al 2008	-10	30.3	36	-1.2	11.5	36	3.3%	-8.80 [-19.39, 1.79]
Janssens et al 2006	-1.87	19.04	30	1.02	19.72	30	3.6%	-2.89 [-12.70, 6.92]
Lipiec et al 2009	5	34.3	26	3.4	28	10	1.2%	1.60 [-20.19, 23.39]
Lunde et al 2006	1	19.43	50	4	20.87	50	4.4%	-3.00 [-10.90, 4.90]
Maureira et al 2012	4	20	7	-2	25	7	1.0%	6.00 [-17.72, 29.72]
Meluzin et al 2006	-6	21.2	40	6	28.14	20	2.3%	-12.00 [-25.97, 1.97]
Meyer et al 2006	-0.5	16.5	30	0.4	12.5	30	4.6%	-0.90 [-8.31, 6.51]
Nogueira et al 2009	-12.76	8.02	14	8.14	29.82	6	1.0%	-20.90 [-45.13, 3.33]
Penicka et al 2007	-3.1	15.72	14	-2	18.28	10	2.3%	-1.10 [-15.11, 12.91]
Perin et al AHJ 2012	-7.3	26.91	10	-0.2	42.32	10	0.6%	-7.10 [-38.18, 23.98]
Piepoli et al 2013	2.6	33.9	19	4	55.8	19	0.7%	-1.40 [-30.76, 27.96]
Pokushalov et al 2010	-33	25.28	49	3	20.91	33	3.5%	-36.00 [-46.05, -25.95]
Quyyumi et al 2011	3.4	22.1	16	-1.84	17.1	15	2.4%	5.24 [-8.62, 19.10]
Ramshorst et al 2009	-4	15	22	-1	10	18	4.4%	-3.00 [-10.79, 4.79]
Ruan et al 2005	-4.69	21.88	9	19.1	26.46	11	1.2%	-23.79 [-44.98, -2.60]
Schachinger et al 2006	-0.6	19	95	5.6	22	92	5.3%	-6.20 [-12.10, -0.30]
Srimahachota et al 2011	5.9	22.2	11	-19.8	65.8	12	0.4%	25.70 [-13.77, 65.17]
Suarez de Lezo et al 2007	-27	15.44	10	4	22.8	10	1.7%	-31.00 [-48.07, -13.93]
Surder et al 2013a	17	29.14	66	18	29.96	67	3.5%	-1.00 [-11.04, 9.04]
Traverse et al 2010	-7	3.3	30	-2	8.4	10	5.6%	-5.00 [-10.34, 0.34]
Traverse et al 2011	0.2	14	55	-2.3	14.7	26	4.9%	2.50 [-4.25, 9.25]
Tse et al 2007	-8.8	18.4	19	-3.1	14.4	8	2.6%	-5.70 [-18.66, 7.26]
Turan et al 2011	-9	12.96	38	0	11.47	18	4.9%	-9.00 [-15.71, -2.29]
Turan et al 2012	-21	13.15	42	-2	19.49	20	3.7%	-19.00 [-28.42, -9.58]
Yao et al 2009	-7.26	2.07	27	-4.5	2.25	12	7.2%	-2.76 [-4.25, -1.27]
Total (95% CI)			**935**			**711**	**100.0%**	**-6.37 [-8.95, -3.80]**

Heterogeneity: Tau² = 23.16; Chi² = 90.70, df = 31 (P < 0.00001); I² = 66%
Test for overall effect: Z = 4.86 (P < 0.00001)

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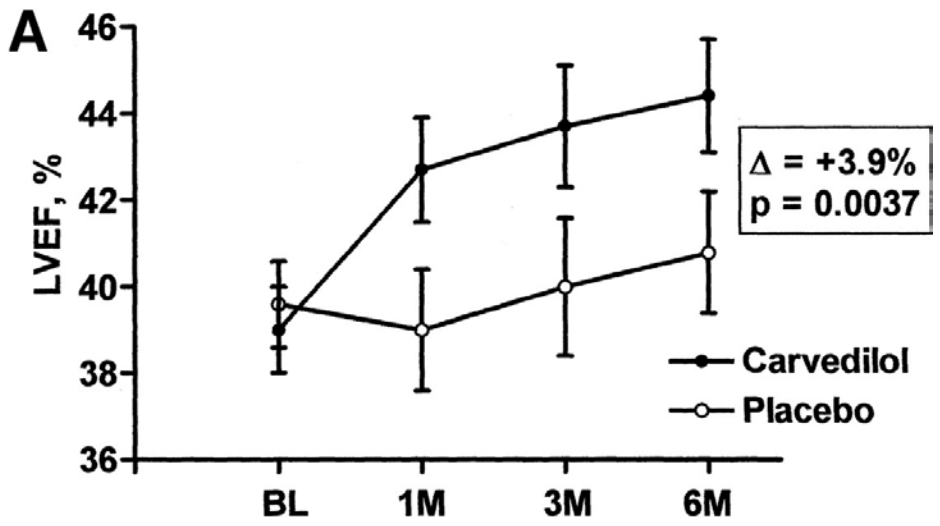
Drugs that increase ejection fraction modestly….



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Doughty R N et al. Circulation 2004;109:201-206

Bone marrow cells for myocardial regeneration (Clinical data)

Table 8. Clinical Outcomes in BMC-Treated Patients Compared With Patients Receiving Standard Therapy

Outcome	Patients With IHD				Patients With AMI				Patients With CIHD			
	BMC (n)	Control (n)	Peto OR (95% CI)	*P* Value	BMC (n)	Control (n)	Peto OR (95% CI)	*P* Value	BMC (n)	Control (n)	Peto OR (95% CI)	*P* Value
All-cause mortality	1397	980	0.55 (0.34–0.89)	0.01	1053	741	0.77 (0.41–1.44)	0.40	344	239	0.35 (0.16–0.73)	0.005
Cardiac deaths	970	666	0.52 (0.24–1.13)	0.10	712	496	0.58 (0.25–1.38)	0.22	258	170	0.36 (0.07–1.86)	0.22
Recurrent MI	1159	799	0.50 (0.27–0.92)	0.03	912	634	0.52 (0.27–1.01)	0.05	247	165	0.34 (0.05–2.19)	0.26
Heart failure	1027	761	0.62 (0.37–1.05)	0.08	841	626	0.77 (0.42–1.42)	0.40	186	135	0.36 (0.11–1.14)	0.08
Stent thrombosis	599	458	0.48 (0.21–1.09)	0.08	527	407	0.51 (0.22–1.18)	0.12	72	51	0.13 (0.00–6.54)	0.31
In-stent restenosis	432	332	0.92 (0.55–1.54)	0.75	383	284	0.91 (0.53–1.57)	0.74	49	48	0.97 (0.13–7.10)	0.97
TVR	866	606	0.84 (0.59–1.21)	0.36	778	546	0.83 (0.57–1.21)	0.33	88	60	1.00 (0.32–3.11)	1.00
CVA	640	462	0.25 (0.08–0.81)	0.02	491	355	0.47 (0.11–1.95)	0.30	149	107	0.07 (0.01–0.55)	0.01
VT/VF	481	419	0.45 (0.22–0.93)	0.03	264	209	0.38 (0.17–0.85)	0.02	217	210	0.95 (0.19–4.79)	0.95

AMI indicates acute myocardial infarction; BMC, bone marrow cell; CI, confidence interval; CIHD, chronic ischemic heart disease; CVA, cerebrovascular accident; MI, myocardial infarction; n, number of patients in each group; OR, odds ratio; TVR, target vessel revascularization; VF, ventricular fibrillation; and VT, ventricular tachycardia.

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