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Cardiac Allograft Vasculopathy

Prevention and Treatment

Sudhir S. Kushwaha

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Rochester, MN

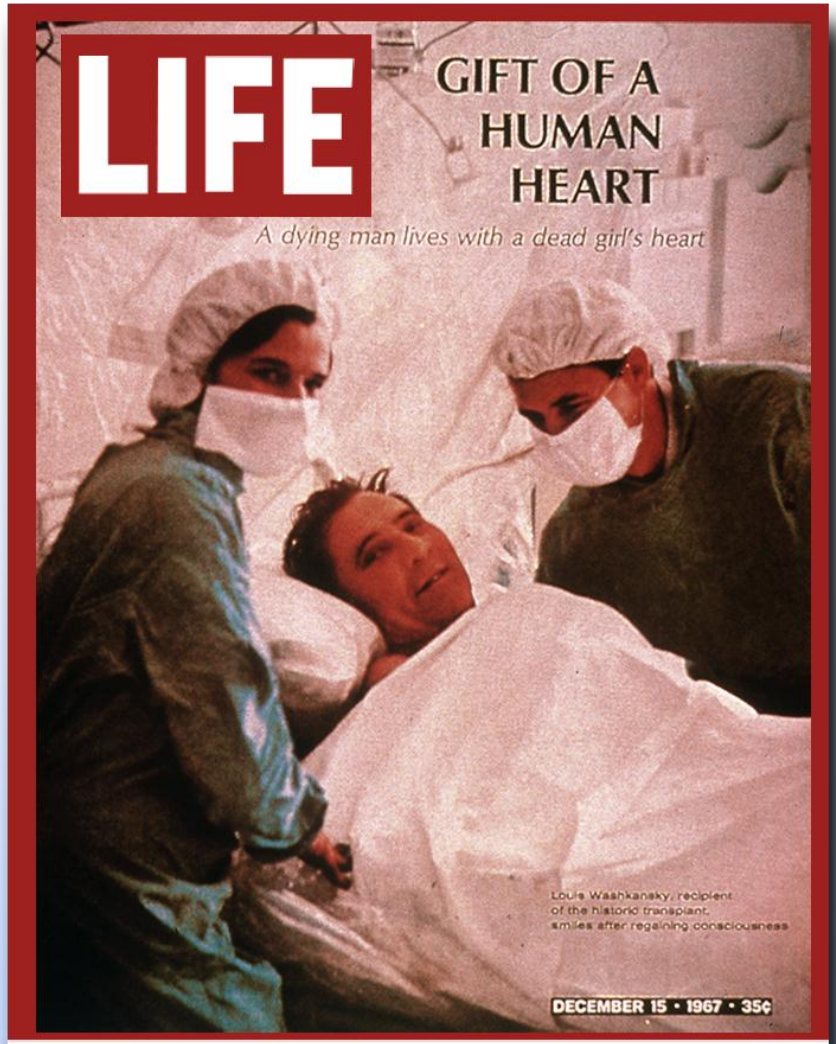

Photo by Cloete Breytenbach

December 15, 1967

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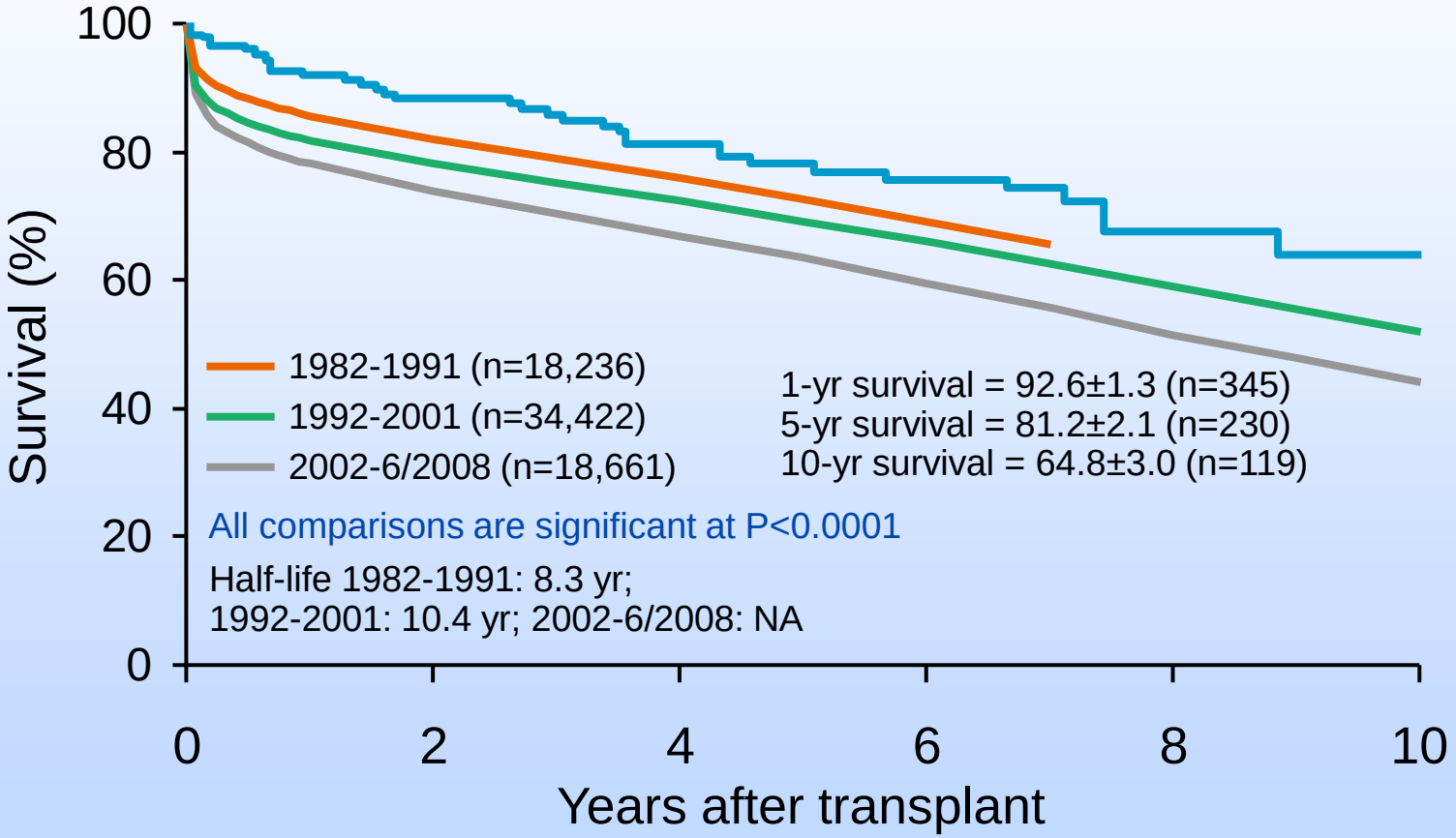
Mayo Clinic William J von Liebig Transplant Center

Cardiac Transplantation - Kaplan-Meier Survival

397 Patients Transplanted 06/01/88-04/26/11



J Heart Lung Transplant. 2010 Oct; 29 (10): 1083-1141, 2010

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Present Limitations to Survival

Problems with the graft

- Rejection
- Allograft vasculopathy

Other comorbidities

- Infection
- Renal dysfunction
- PTLD

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Post-Heart Transplant Morbidity for Adults

Cumulative Prevalence in Survivors at 1, 5 and 10 Years Post-Transplant (Follow-ups: April 1994-June 2009)

Outcome	Within 1 year	Total n with known response	Within 5 years	Total n with known response	Within 10 years	Total n with known response
Hypertension	73.2%	(n=24,229)	93.1%	(n=10,485)	97.4%	(n=2,238)
Renal dysfunction	26.8%	(n=25,524)	31.1%	(n=12,146)	36.8%	(n=3,681)
Abnormal creatinine <2.5 mg/dL	18.1%		21.0%		24.3%	
Creatinine >2.5 mg/dL	7.0%		7.3%		6.2%	
Chronic dialysis	1.5%		2.3%		4.8%	
Renal transplant	0.3%		0.5%		1.5%	
Hyperlipidemia	58.1%	(n=25,572)	87.8%	(n=11,800)	93.3%	(n=2,659)
Diabetes	27.4%	(n=25,292)	36.6%	(n=11,154)	38.5%	(n=2,401)
Cardiac allograft vasculopathy	7.8%	(n=22,853)	31.0%	(n=1,897)	51.8%	(n=1,830)

J Heart Lung Transplant. 2010 Oct; 29 (10): 1083-1141

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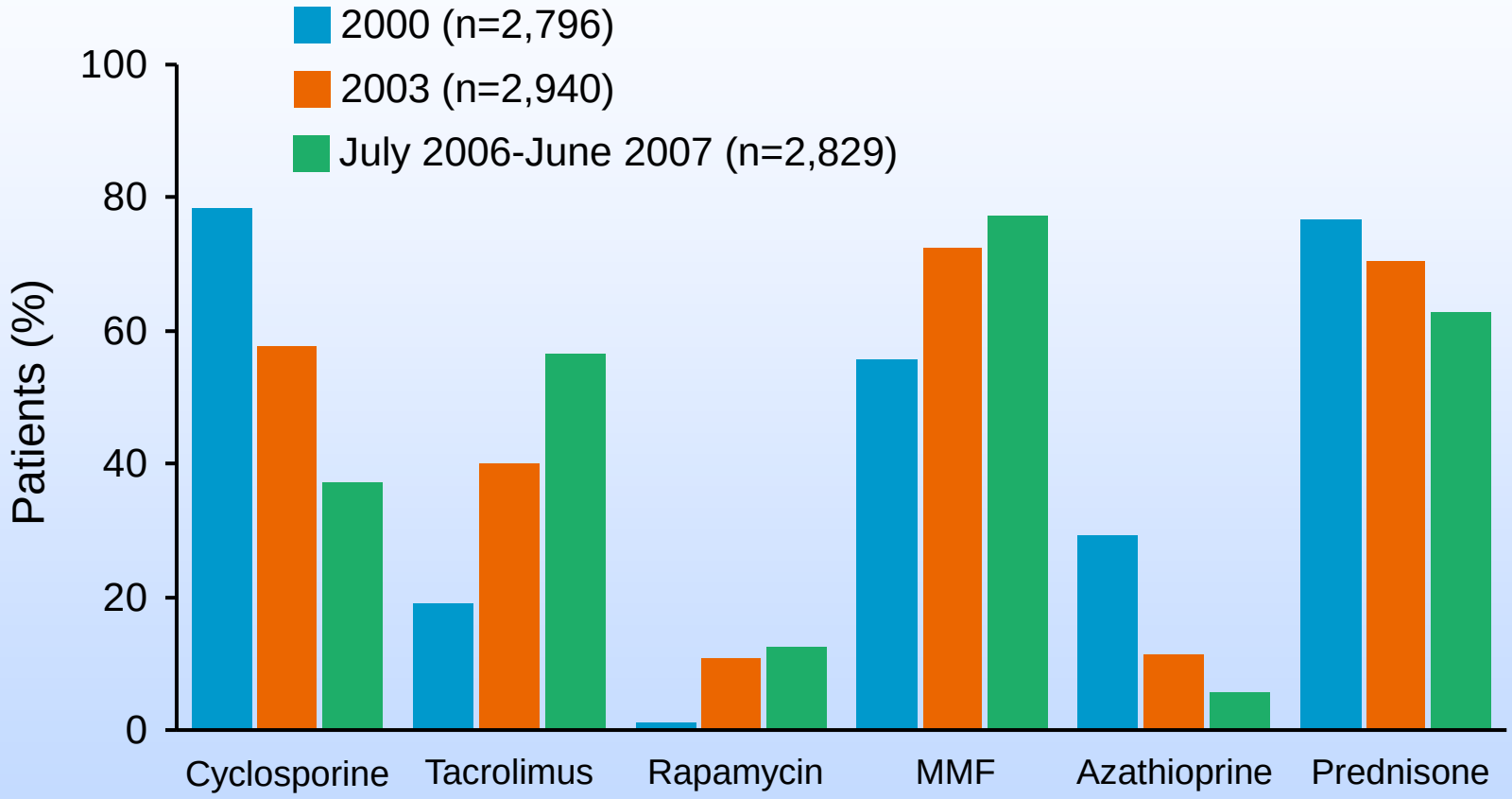
Adult Heart Recipients

Maintenance Immunosuppression at Time of 1-Year Follow-Up



Note: Different patients are analyzed in each time frame
Analysis is limited to patients who were alive at time of follow-up
ISHLT 2008; J Heart Lung Transplant 27:937, 2008

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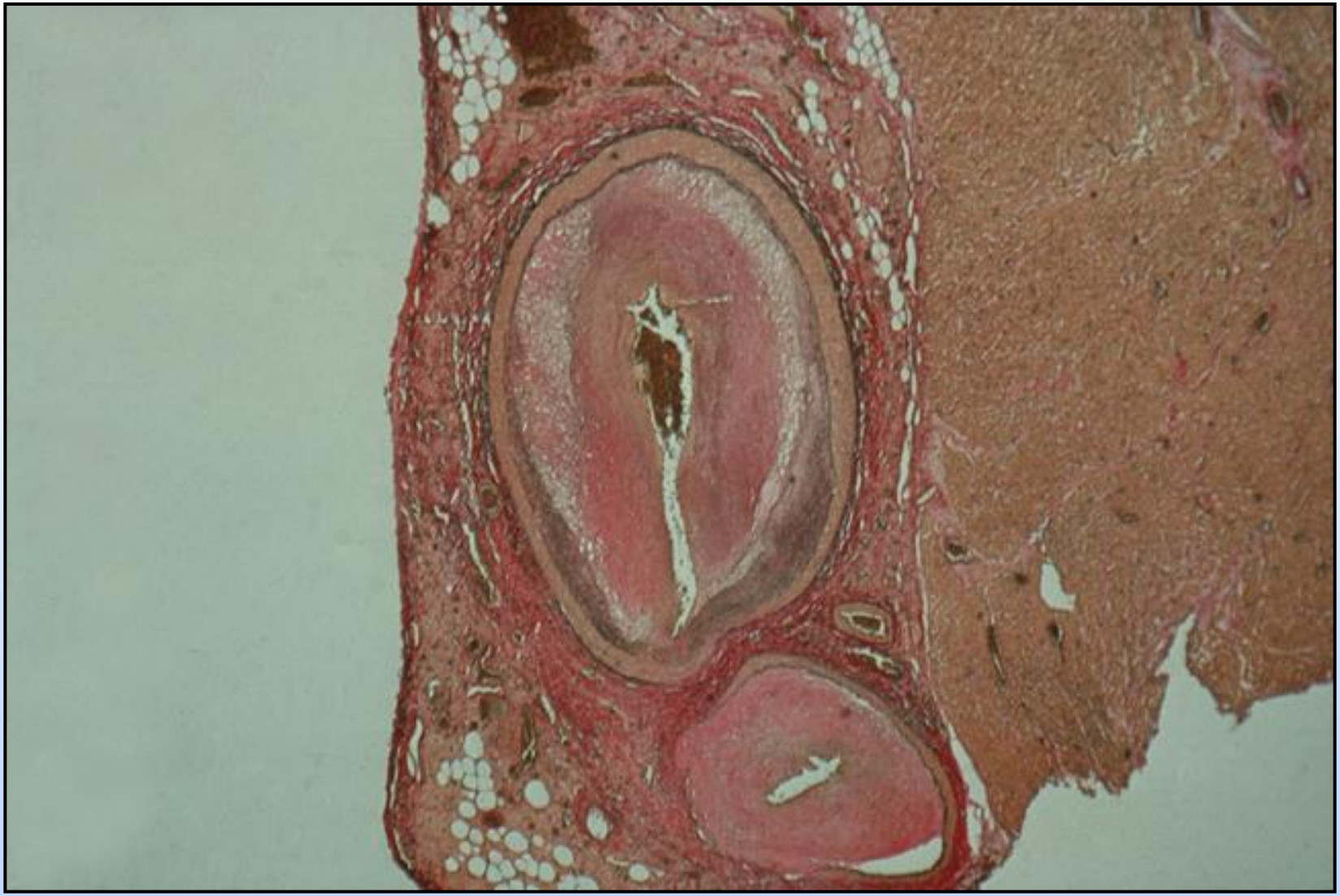

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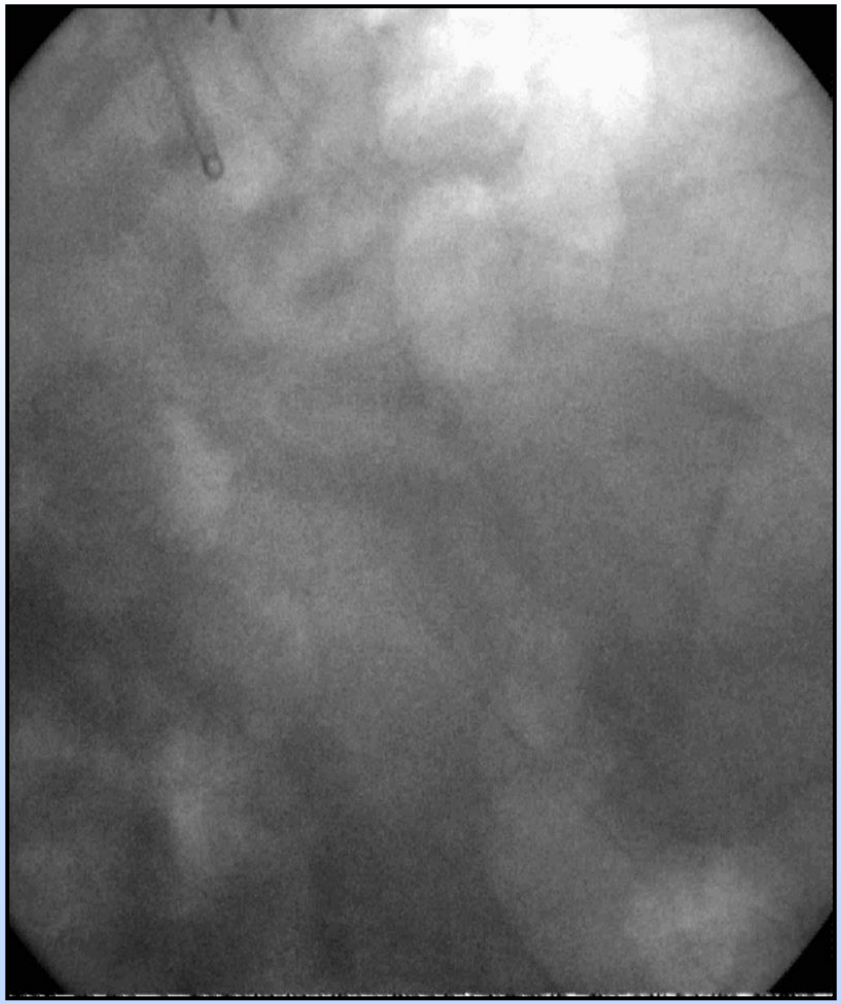
61-Year-Old Man
5 Years from Transplant



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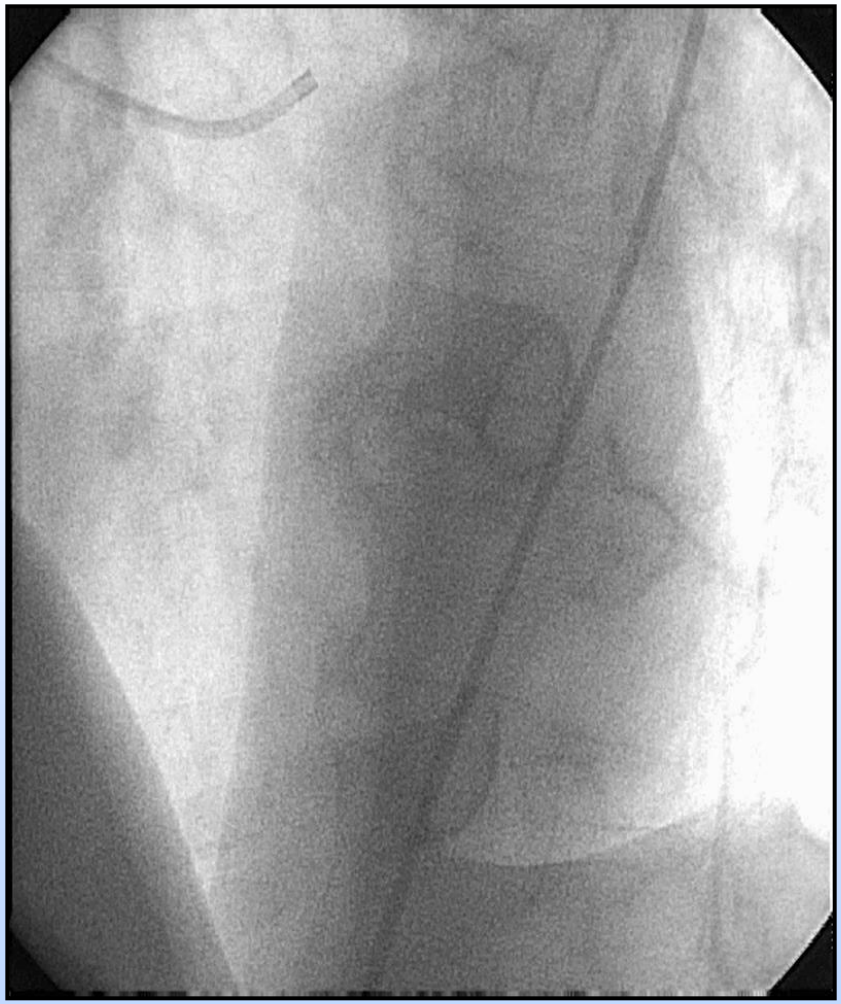
61-Year-Old Man
5 Years from Transplant



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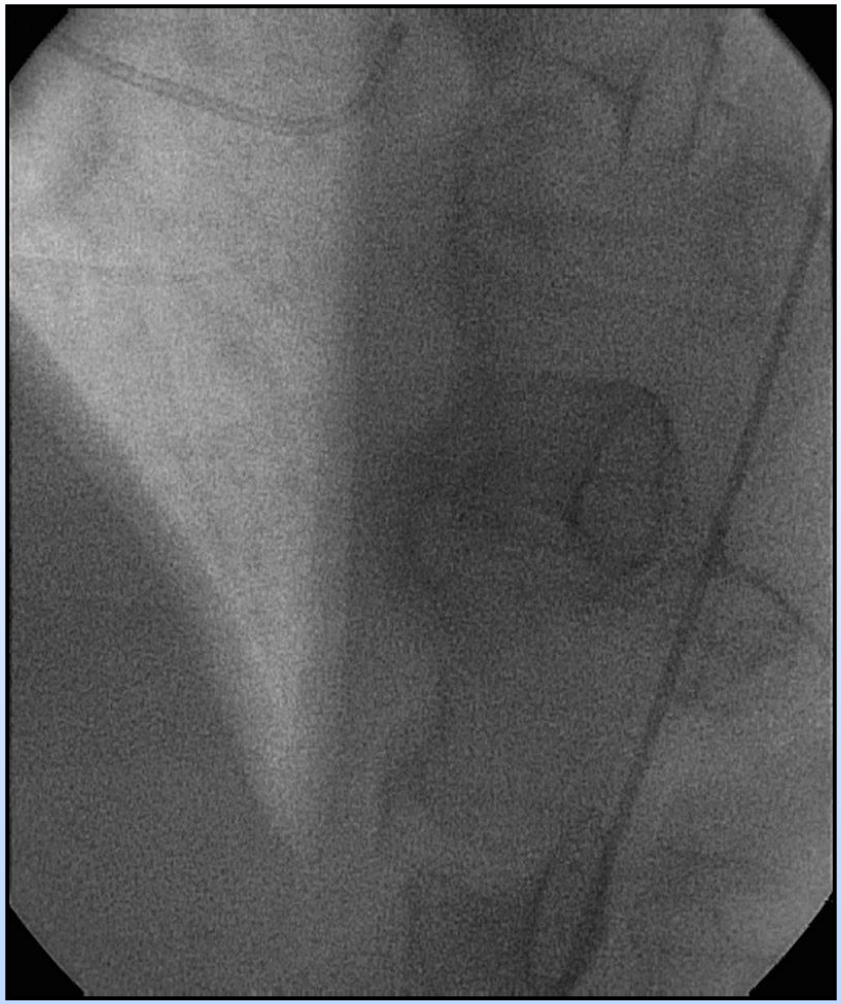
62-Year-Old Man

6 Years from Transplant



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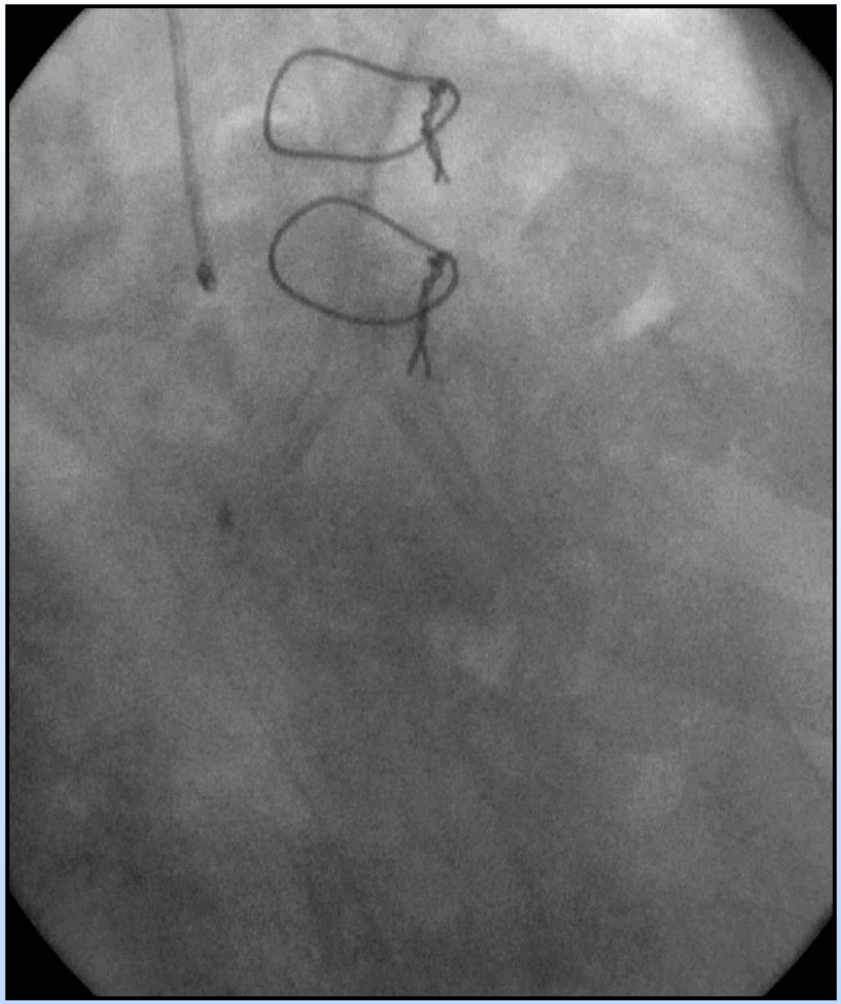
62-Year-Old Man

6 Years from Transplant



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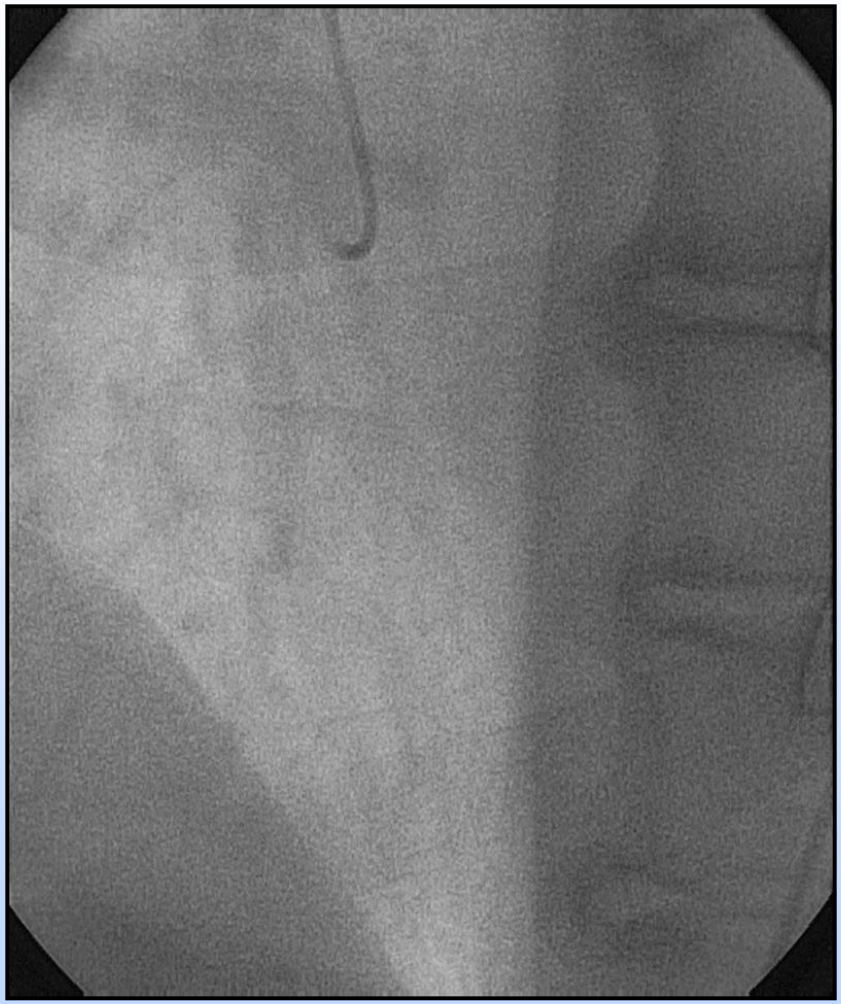

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Strategies for the Prevention of Transplant Vasculopathy

- Early and aggressive statin use
- Aggressive control of lipids
- Treatment of patients at risk for CMV
- IVUS to identify early disease
- Rapamycin
- PCI (selected cases)

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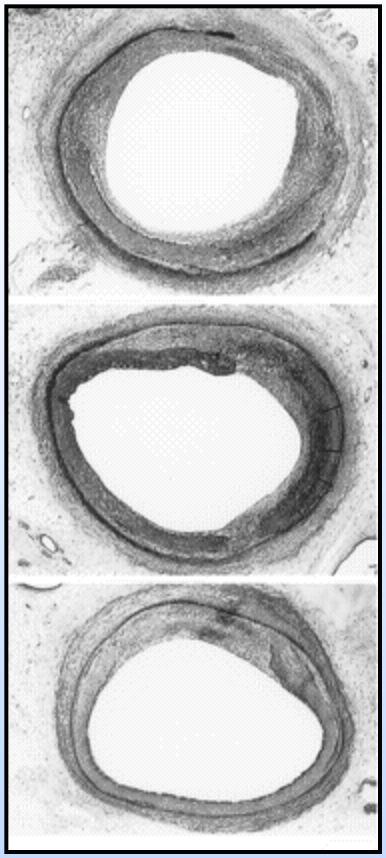
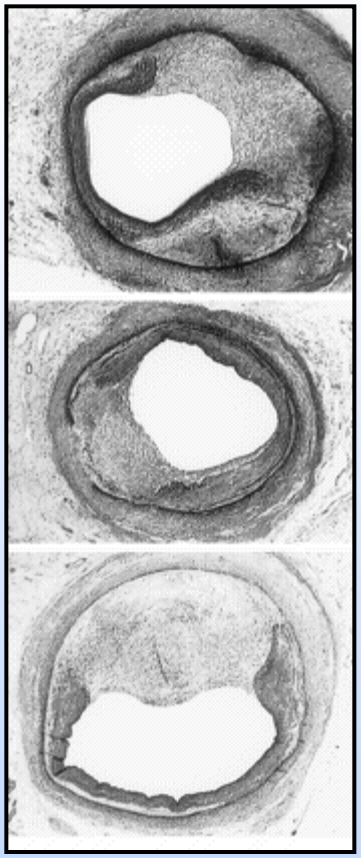
Rapamycin Inhibits Intimal Hyperplasia



Rapamycin treated



Control

Gallo R et al: Circulation 99:2164, 1998

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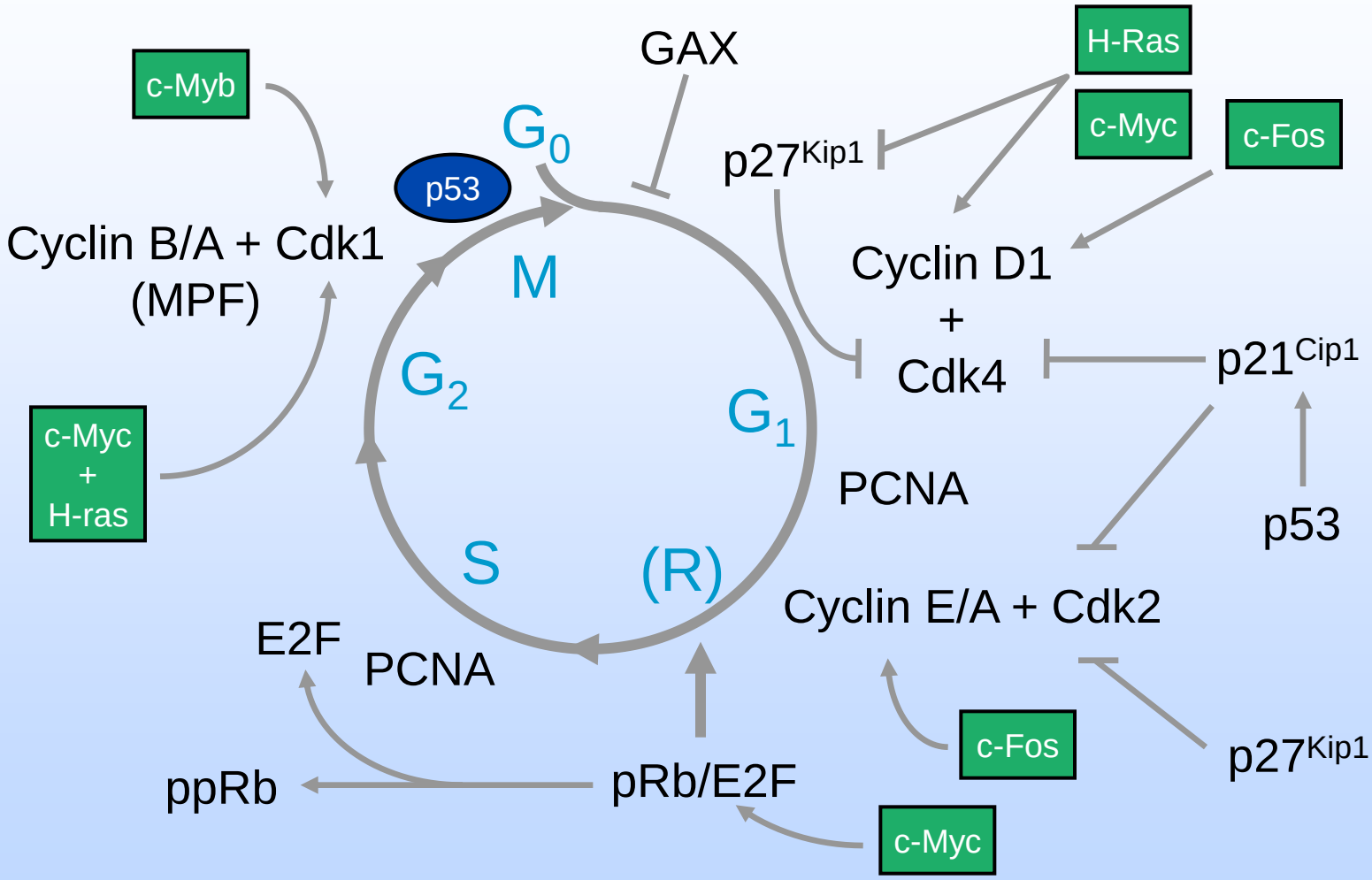
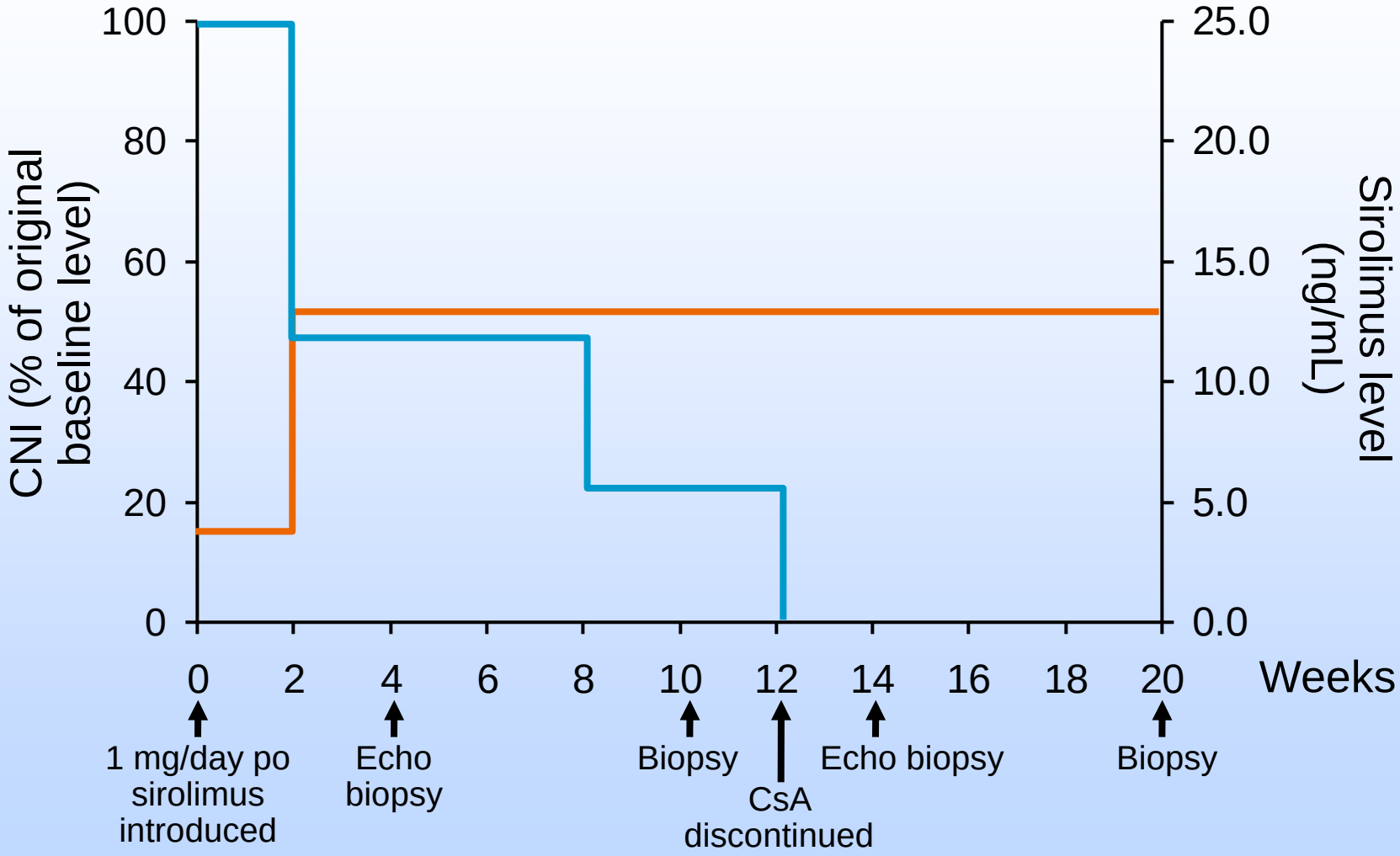
The Cell Cycle



Sirolimus Conversion Protocol



Kushwaha, JHLT 2005

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Sirolimus for CAV Prevention

- Retrospective nonrandomized single-center study
- 29 patients (SRL group) were enrolled 3.81±3.4 years following transplant
- 40 patients (CNI group) were enrolled 4.80±4.0 years following transplant

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Methods
IVUS

- IVUS performed at baseline
  - Before conversion in SRL
  - Time of study entry in CNI
- Repeat IVUS exam at 12 months
- Performed during routine angiogram
- Intracoronary NTG
- Mechanical pullback from mid-distal LAD to left main with subsequent
  off-line volumetric analysis

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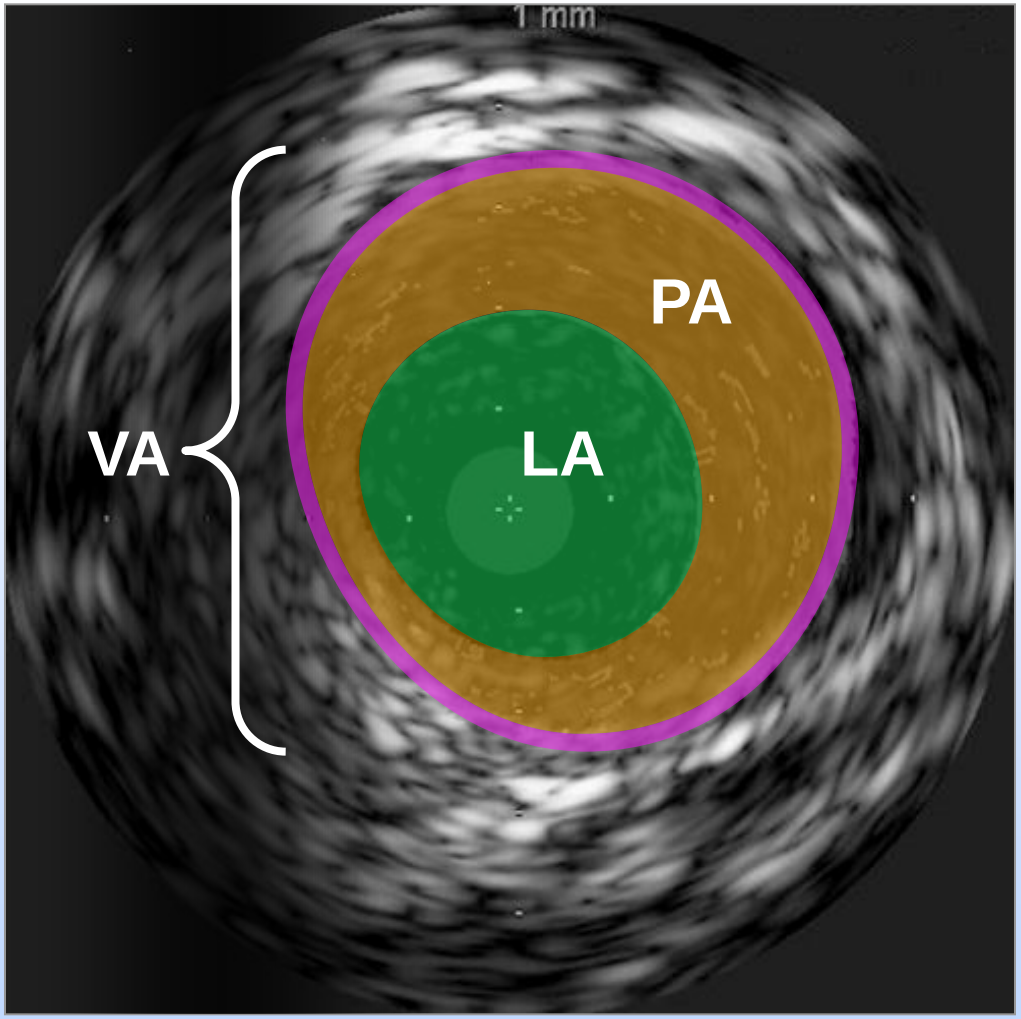

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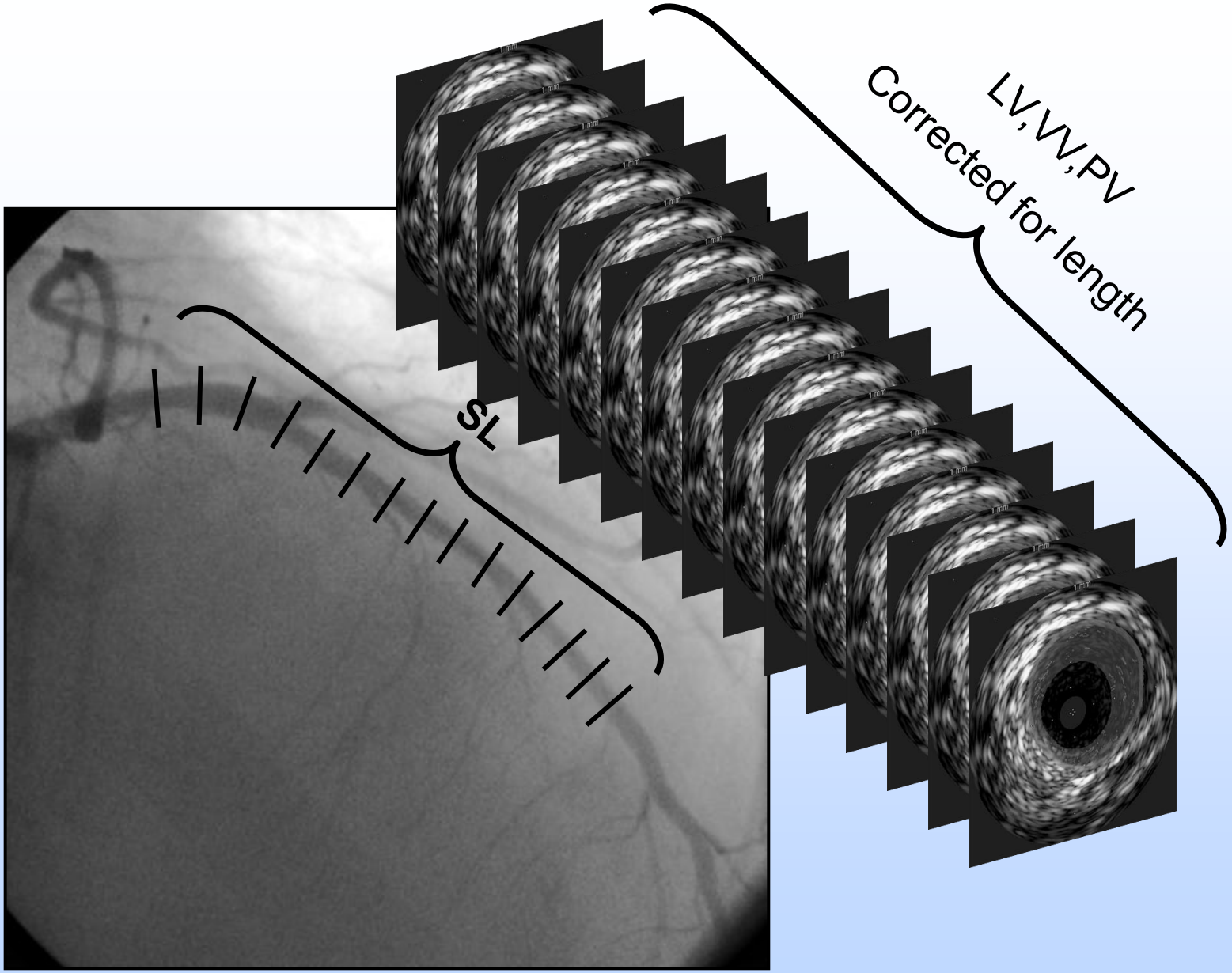

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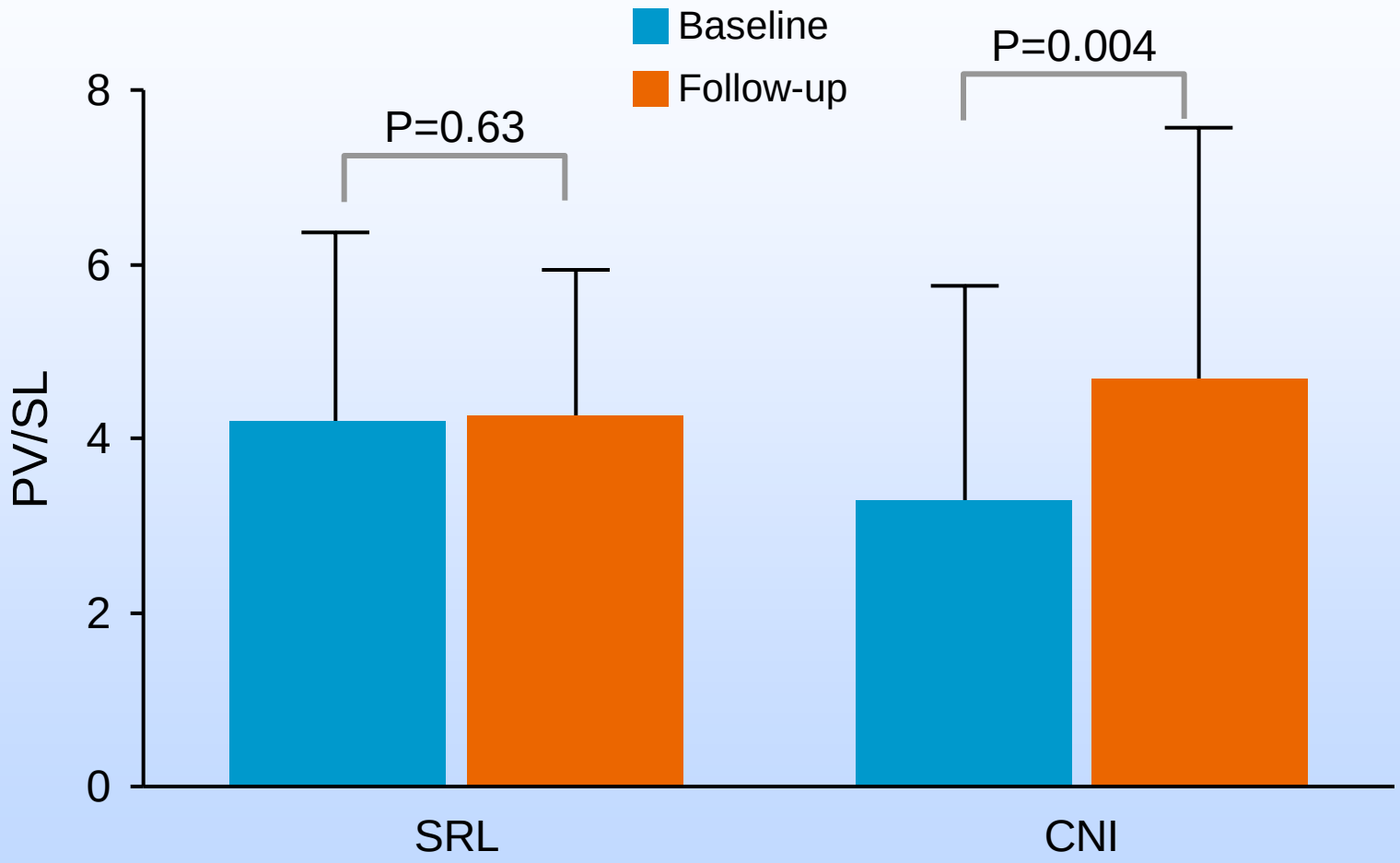
Plaque Volume in SRL and CNI Groups



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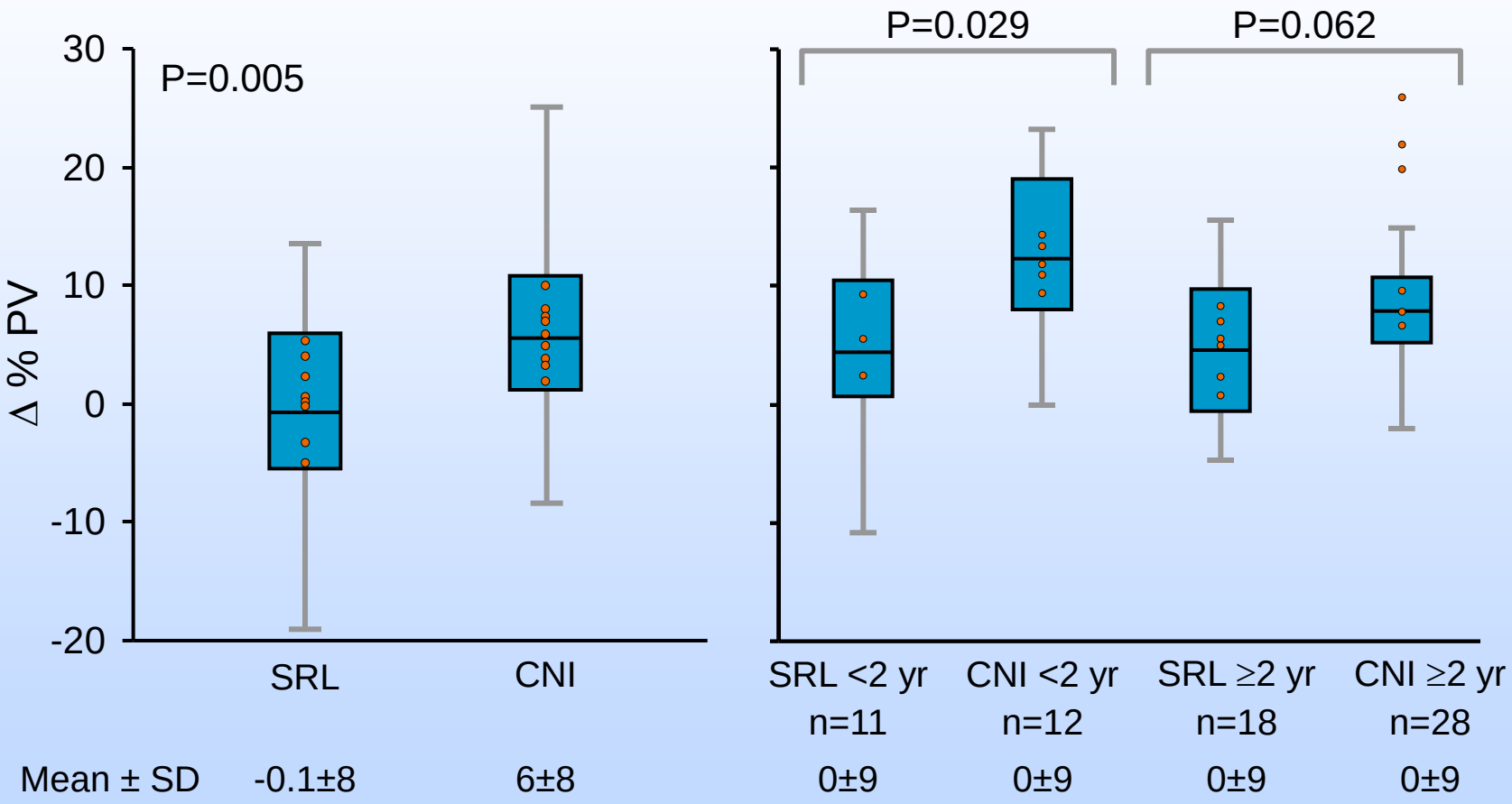
Conversion To SRL As Primary Immunosuppression Attenuates the Progression of Allograft Vasculopathy after Cardiac Transplantation



Raichlin E. et al. Circulation. 2007;116:2726-2733

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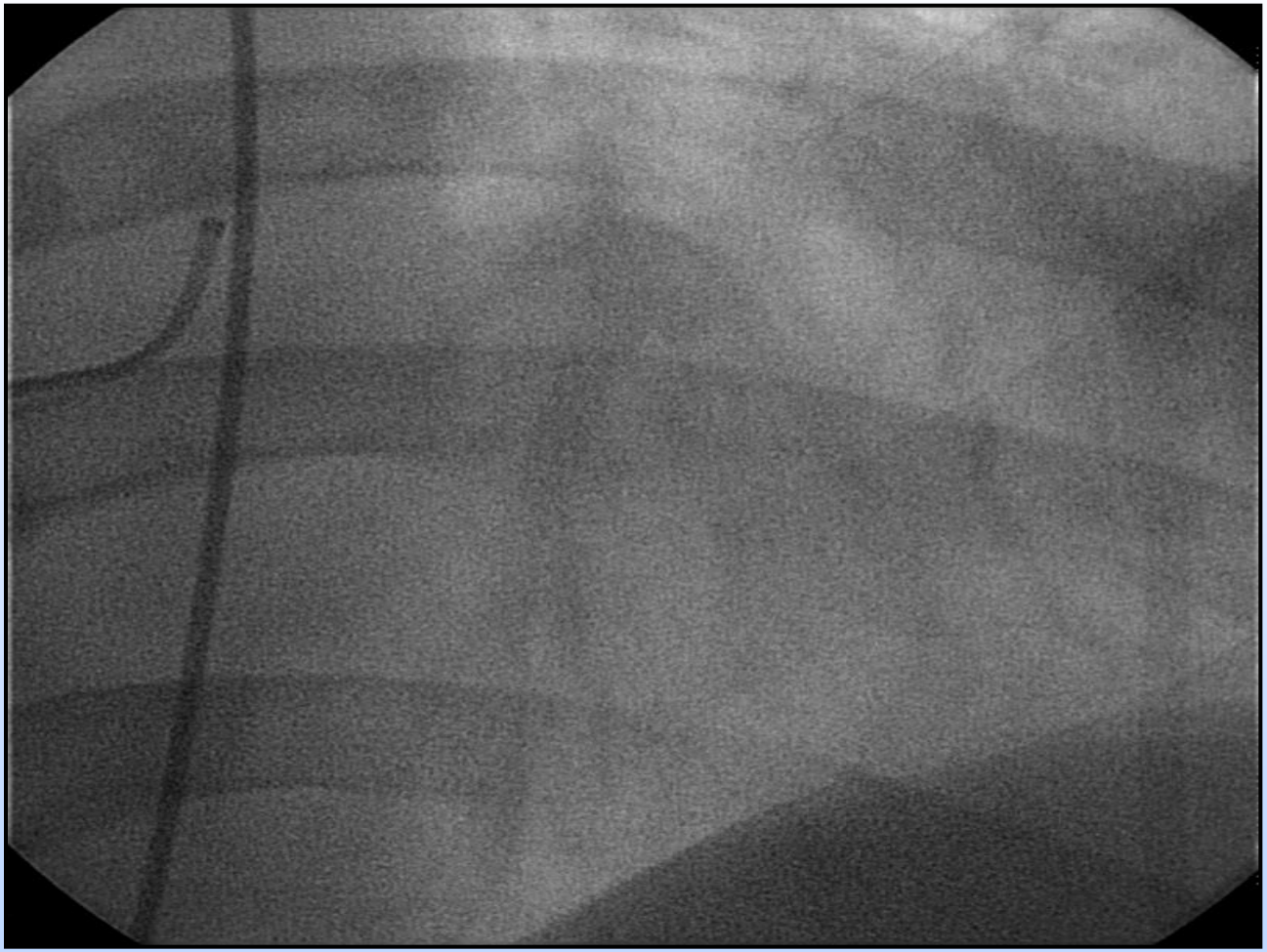
12 Months
Post-Transplant Angiogram



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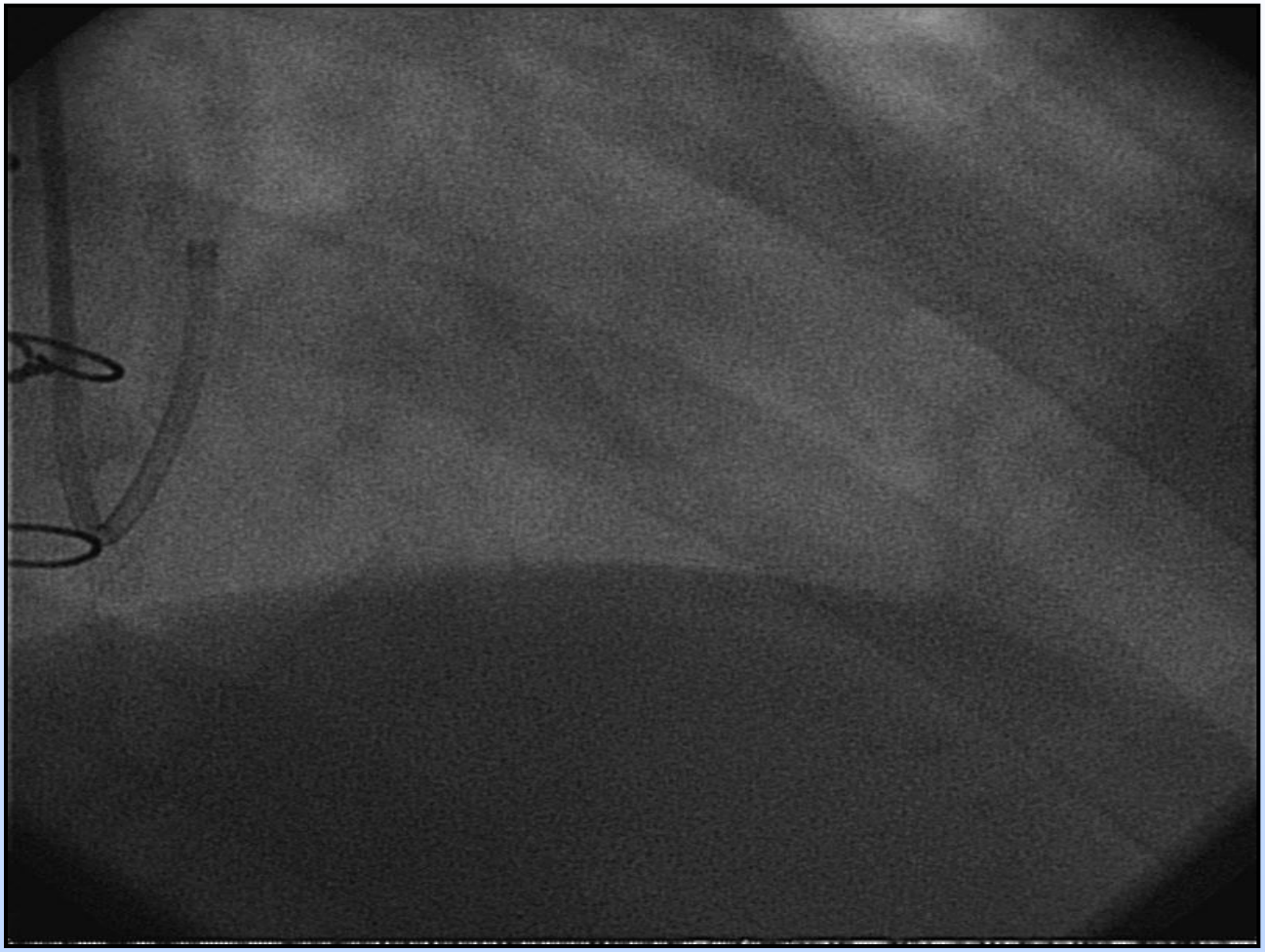
18-Month Angiogram – Following
6 Months of Sirolimus



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Conversion to Sirolimus as Primary Immunosuppression Attenuates the Progression of Allograft Vasculopathy After Cardiac Transplantation

Eugenia Raichlin, MD; Jang-Ho Bae, MD; Zain Khalpey, MD, MRCS; Brooks S. Edwards, MD; Walter K. Kremers, PhD; Alfredo L. Clavell, MD; Richard J. Rodeheffer, MD; Robert P. Frantz, MD; Charanjit Rihal, MD; Amir Lerman, MD; Sudhir S. Kushwaha, MD

Background—We investigated the potential of conversion to sirolimus (SRL) as a primary immunosuppressant in attenuating cardiac allograft vasculopathy progression.

Conclusions – Substituting CNI with SRL as primary immunosuppression attenuates cardiac allograft vasculopathy progression.

smaller in the SRL group (n=11) than in the CNI (n=12) group. In patients enrolled ≥2 years after transplantation, the increase in PI was less in the SRL group compared with the CNI group (0.1±6.5% versus 5±8%; *P*=0.033), but changes in PV did not differ significantly. Treatment with azathioprine or mycophenolate did not affect PV or PI in either the SRL group (PV: 0.22±0.66 versus 0.05±1.45 mm^3/mm, *P*=0.46; PI: 1.5±6% versus −1.6±8.5%, *P*=0.29) or the CNI group (PV: 1.42±1.39 versus 1.06±2.28 mm^3/mm, *P*=0.49; PI: 7.8±8.7% versus 4.8±7.3%, *P*=0.23).

Conclusions—Substituting CNI with SRL as primary immunosuppression attenuates cardiac allograft vasculopathy progression. (***Circulation*. 2007;116:2726-2733.**)

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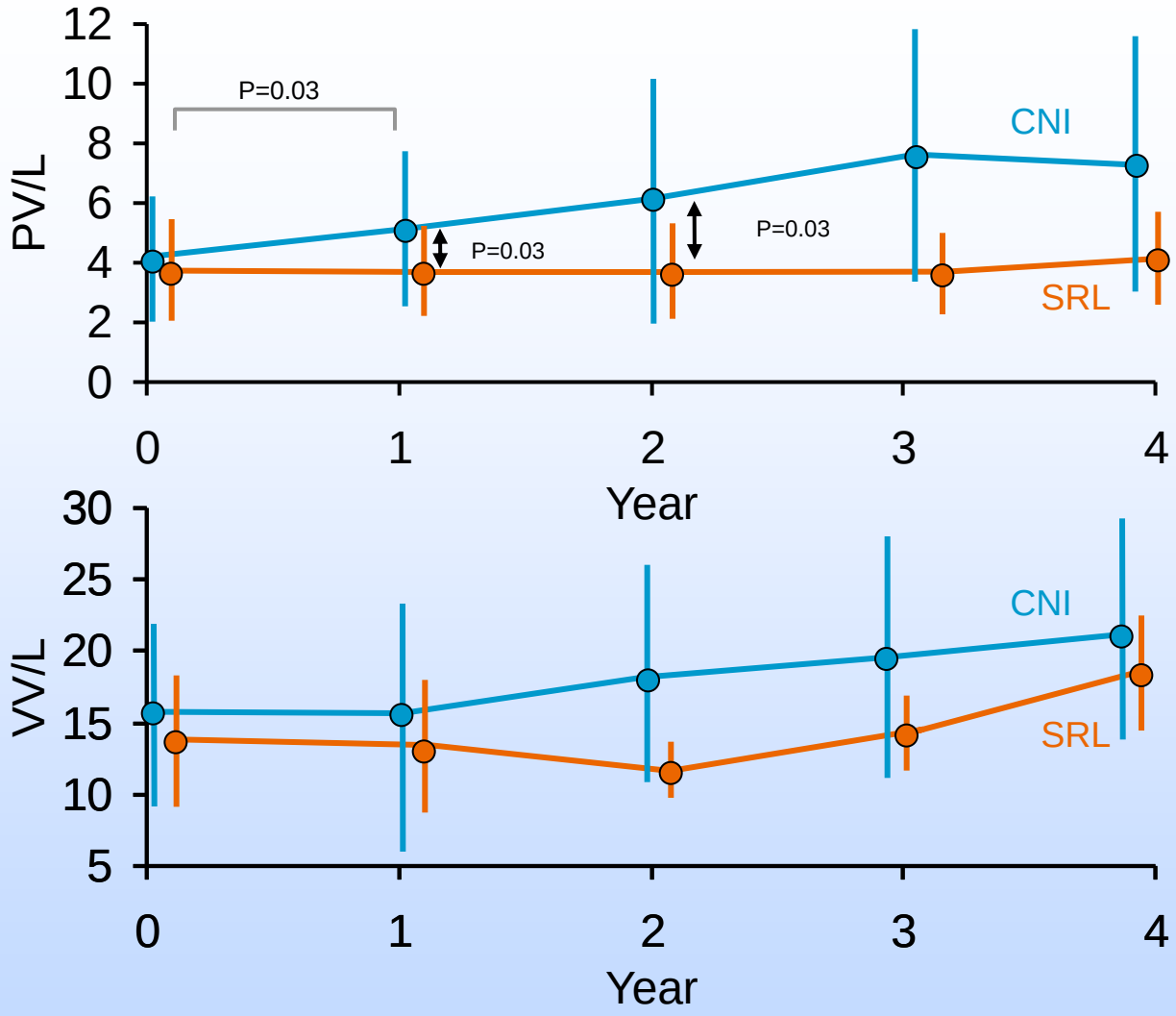

CNI	16	12	5	7	5
SRL	12	12	8	7	3

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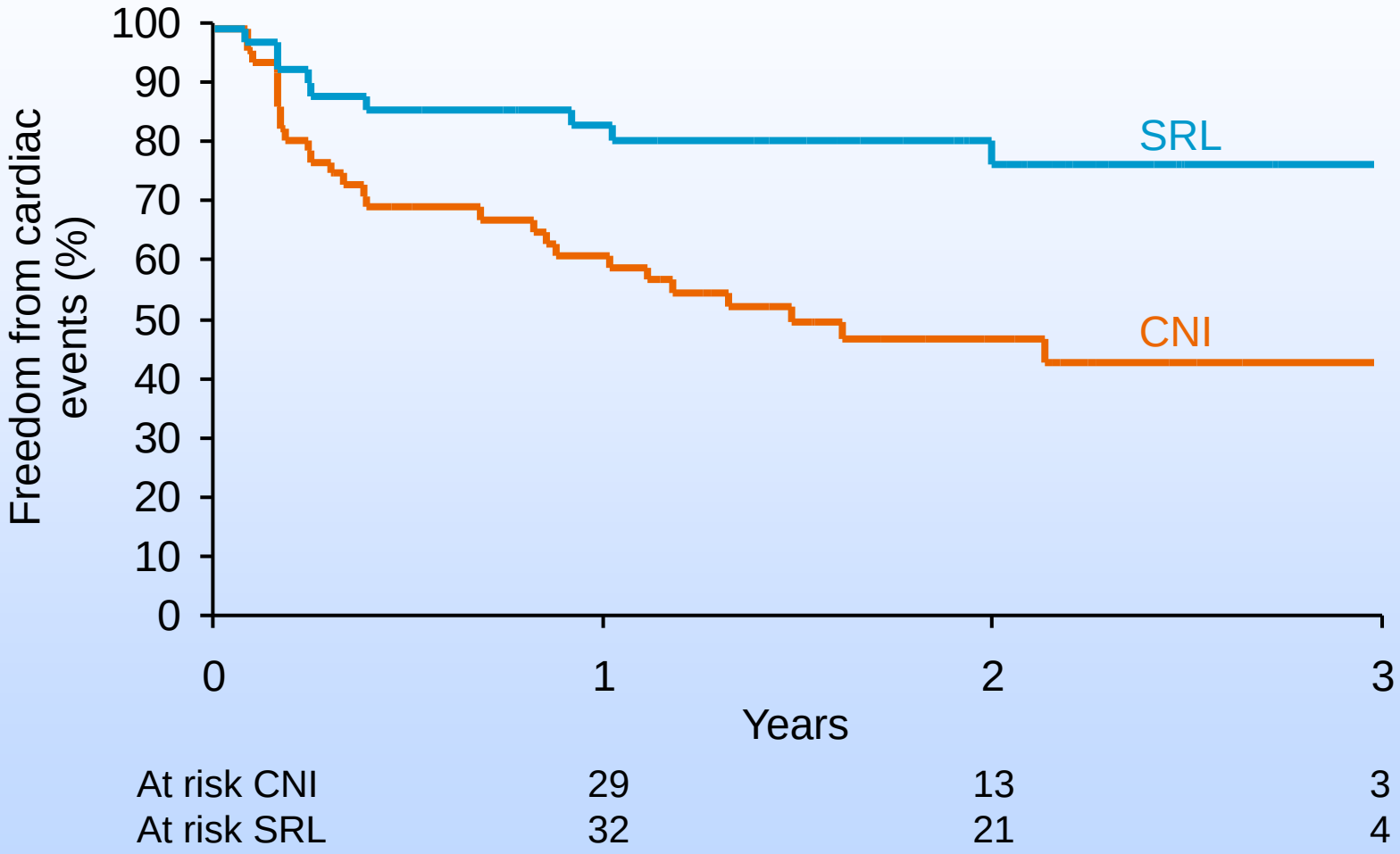
Freedom from Cardiac Events



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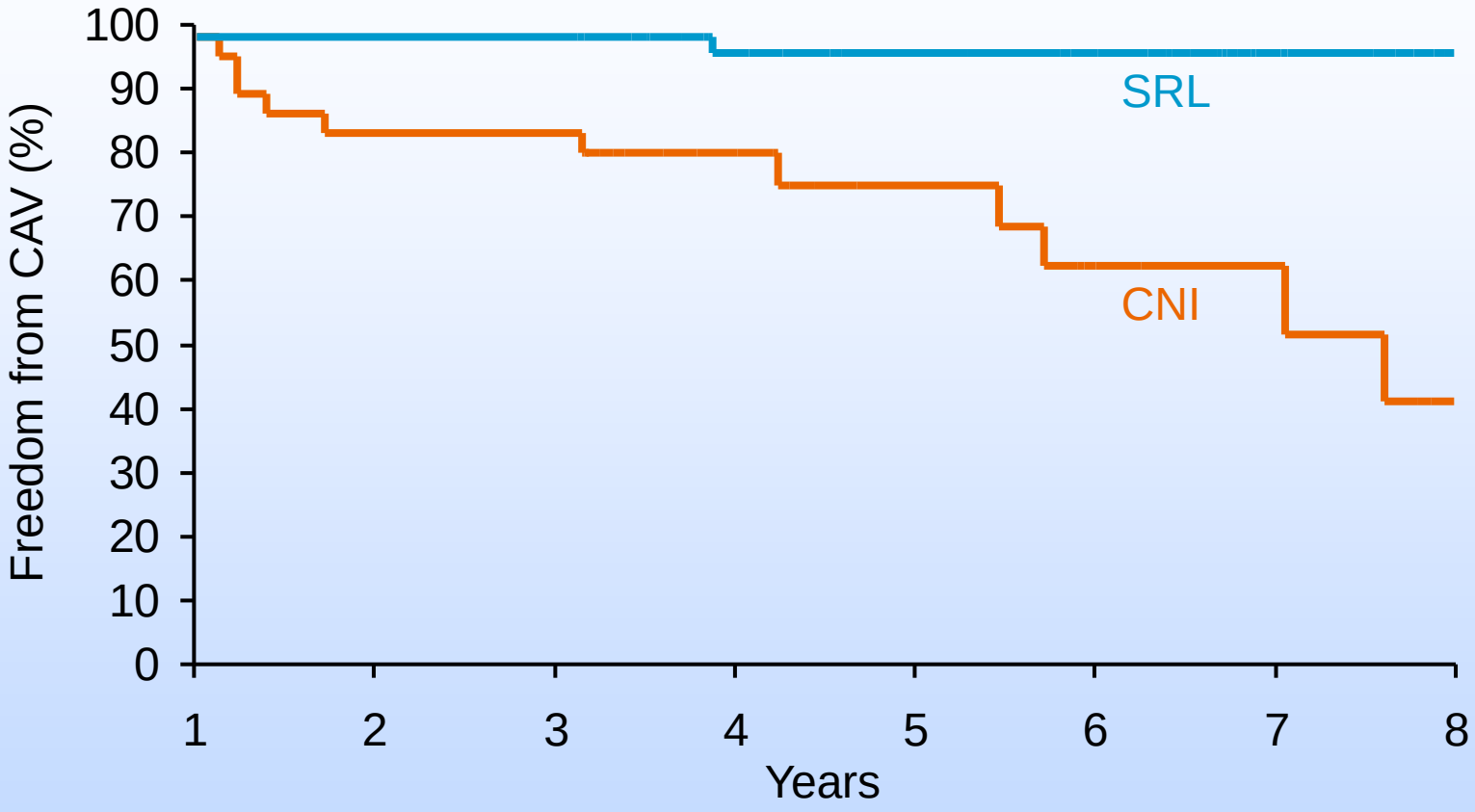
Freedom from CAV



At risk CNI	29	28	19	12	9	6
At risk SRL	50	50	39	33	31	19

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Summary

- SRL is effective as a primary immunosuppressant
- SRL has long term properties mitigating CAV progression by reducing intimal hyperplasia and delaying vessel remodeling
- The geometric vascular changes are translated to improved survival and less CAV related adverse outcomes

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Summary

- The beneficial effects are more pronounced if conversion to SRL takes place within the first two years following transplant but persist even in later phases
- Conversion to SRL should be considered as early as possible for primary immunosuppressive therapy after cardiac transplantation

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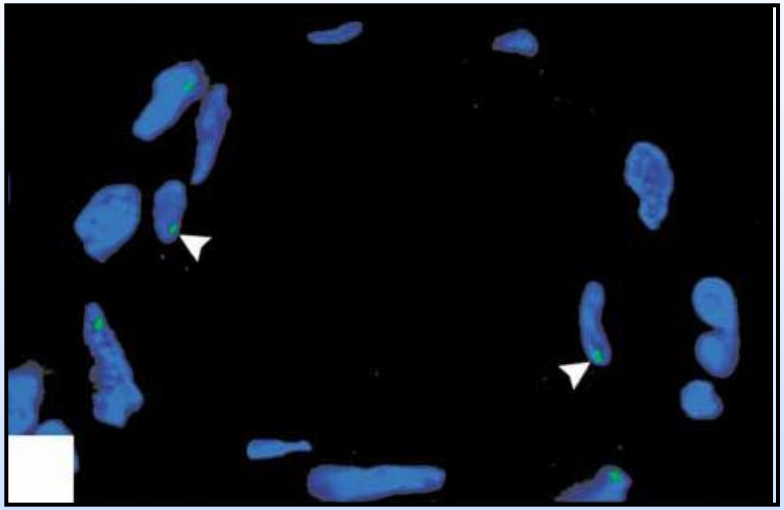
The New England
Journal of Medicine

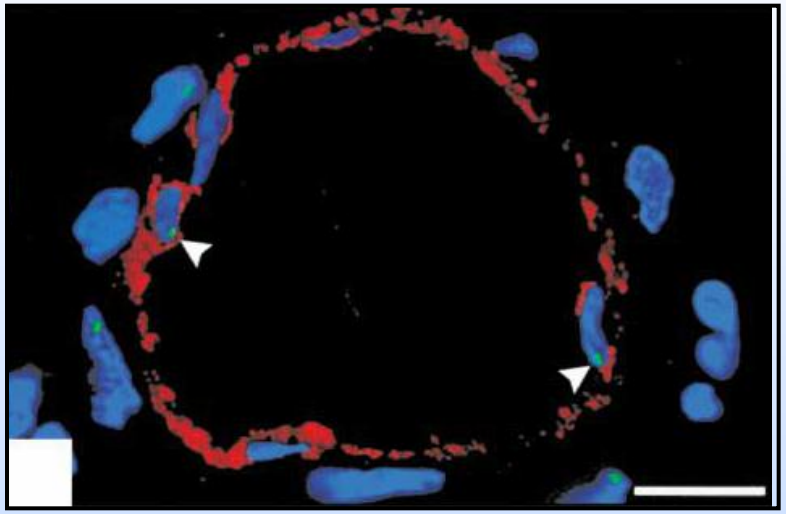
VOLUME 346 JANUARY 3, 2002 NUMBER 1

CHIMERISM OF THE TRANSPLANTED HEART

FEDERICO QUAINI, M.D., KONRAD URBANEK, M.D., ANTONIO P. BELTRAMI, M.D., NICOLETTA FINATO, M.D., CARLO A. BELTRAMI, M.D., BERNARDO NADAL-GINARD, M.D., PH.D., JAN KAJSTURA, PH.D., ANNAROSA LERI, M.D., AND PIERO ANVERSA, M.D.

Endothelial Cell Chimerism in the Transplanted Heart





Quaini: NEJM, 2002

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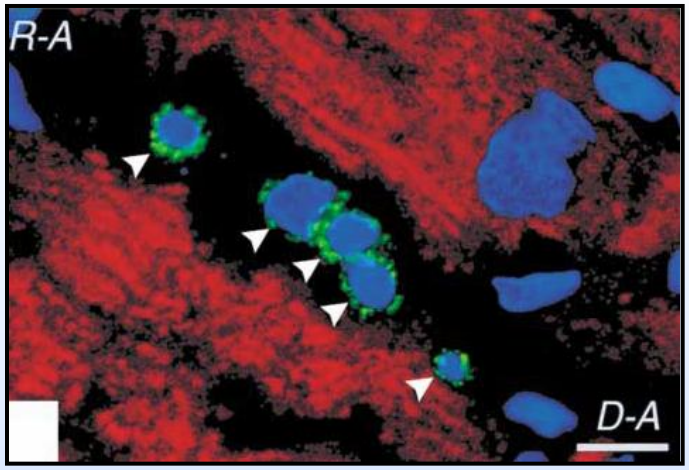
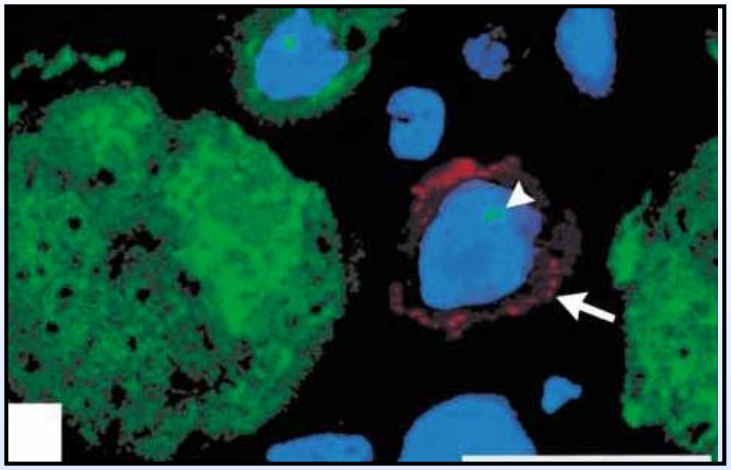
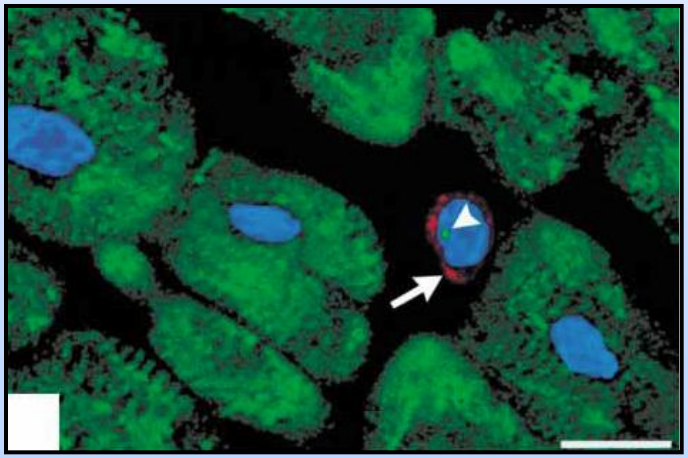
Presence of Stem Cell Markers







Quaini: NEJM, 2002

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Role of Stem Cells in Vascular Biology

- The heart and vascular system are not terminally differentiated organs, and possess resident stem cells

Beltrami AP et al: N Engl J Med 344:1750, 2001
Urbanek K et al: Proc Natl Acad Sci USA 102:8692, 2005
Ingram DA et al: Blood 105:2783, 2005
Zengin E et al: Development 133:1543, 2006

- Circulating progenitor and stem cells of bone marrow origin may play a role in endogenous vascular and cardiac repair mechanisms

Rehman J et al: Circulation 107:1164, 2003
Bautz F et al: Exp Hematol 28:700, 2000
Hildbrand P et al: Blood 104:2010, 2004

- Stem cells may play both an etiologic, but also a potentially therapeutic role in cardiovascular disease

Janssens S et al: Lancet 367(9505):113, 2006
Lunde K et al: N Engl J Med 355(12):1199, 2006
Schachinger V et al: Eur Heart J 27(23):2775, 2006
Strauer BE et al: J Am Coll Cardiol 46(9):1651, 2005

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Role of Circulating Progenitor Cells in Coronary Disease

- CD34+ progenitor cells reported to circulate in blood
- Include HPCs, possibly EPCs
- Numbers of CD34+ progenitor cells shown to be decreased in established CAD
- Numbers also decreased with increased CV risk

Hill JM et al: N Engl J Med 348:593, 2003
Valgimigli M et al: Circulation 110:1209, 2004
Werner N et al: N Engl J Med 242:999, 2005

Role of Stem Cells in Pathogenesis of CAV

- The migration of bone marrow derived progenitor cells into regions of vascular injury in the transplanted heart has been demonstrated
- These progenitor cells have been shown to differentiate into smooth muscle and endothelial cells

Hillebrands JL et al: J Clin Invest 107:1411, 2001
Hu Y et al: Circulation 108:3122, 2003

- Circulating progenitor cells are reduced in number in patients with CAV, with increased proportion of endothelial cells of recipient origin present at post-mortem studies

Simper D et al: Circulation 108:143, 2003

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Endothelial Progenitor Cells Are Decreased in Blood of Cardiac Allograft Patients With Vasculopathy and Endothelial Cells of Noncardiac Origin Are Enriched in Transplant Atherosclerosis

David Simper, MD*; Shaohua Wang, MD*; Arjun Deb, MD; David Holmes, MD;
Christopher McGregor, MD; Robert Frantz, MD; Sudhir S. Kushwaha, MD; Noel M. Caplice, MD, PhD

Background—Recent studies in animals suggest that circulating recipient endothelial precursors may participate in the biology of transplant vasculopathy. It is currently unknown whether a similar interaction between recipient endothelial cells and the vessel wall occurs in human subjects undergoing allogeneic cardiac transplantation.

Methods and Results—Circulating endothelial cells and endothelial progenitor cells (EPCs) were quantified in 15 cardiac transplantation subjects with and without angiographic evidence of vasculopathy. In a separate series of experiments, the origin (donor or recipient) of transplant plaque endothelial cells was assessed in subjects who had undergone a gender-mismatched cardiac transplantation and had histological evidence of severe vasculopathy at the time of heart explantation. Circulating EPC outgrowth colonies in peripheral blood were significantly reduced in subjects with transplant vasculopathy compared with those without angiographic evidence of disease (EPC colony-forming units [CFU_{EPC}]: 4.5 ± 1.9 versus 15.1 ± 3.7, $P < 0.05$). There was no significant difference in circulating endothelial cell numbers as defined by day 4 culture acetylated LDL/lectin assay in either of these patient groups. In a separate group of 5 subjects who underwent gender-mismatched cardiac transplantation, there was a significant seeding of recipient endothelial cells (range: 1% to 24% of all luminal endothelial cells) in large-vessel lumen and adventitial microvessel lumen of arteriopathic vessels. No opposite-sex chimeric cells were observed in control gender-matched transplantation scenarios.

Conclusions—These data suggest that the human cardiac transplant arteriopathy is associated with reduction in circulating endothelial precursors and with seeding of recipient-derived endothelial cells at the site of plaque development. (***Circulation*. 2003;107:143-149.**)

Key Words: blood cells ■ endothelium ■ transplantation

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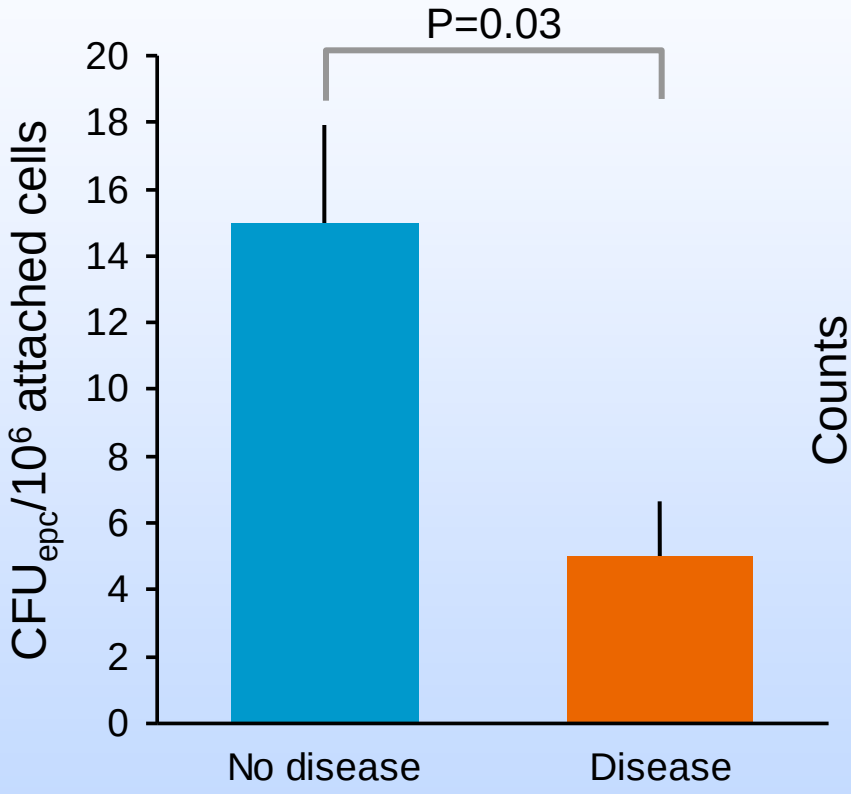
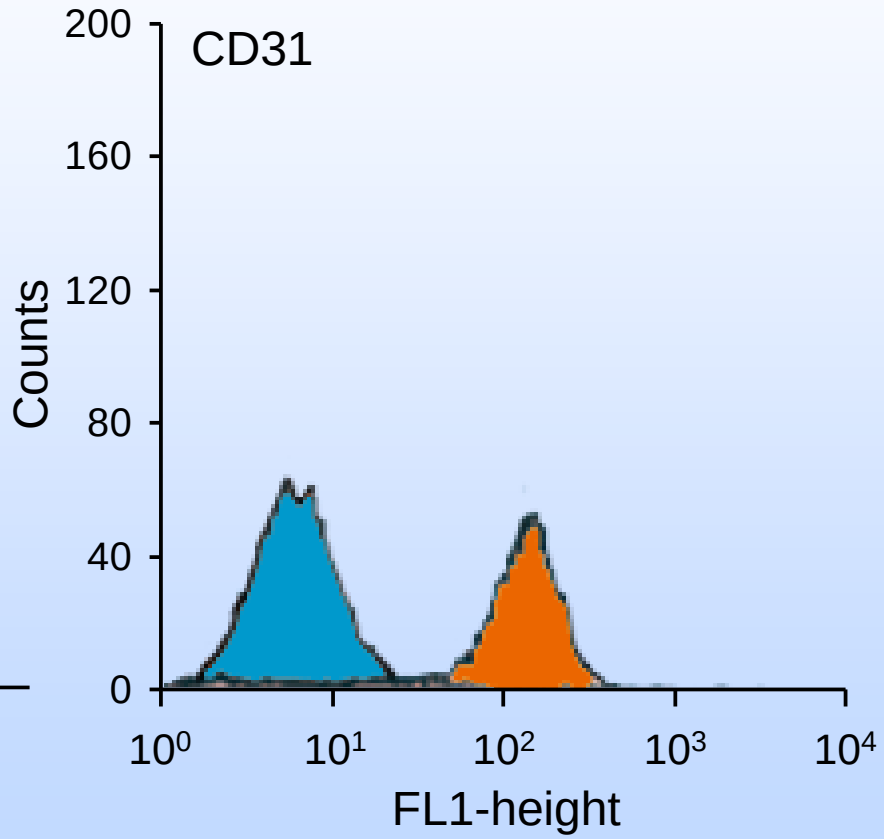
Circulating EPC Colonies Reduced in CAV





Simper: Circulation, 2003

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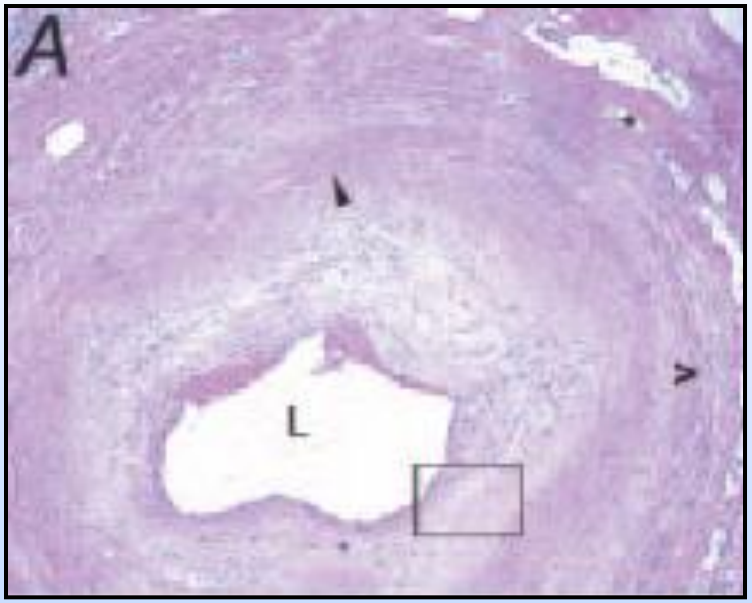
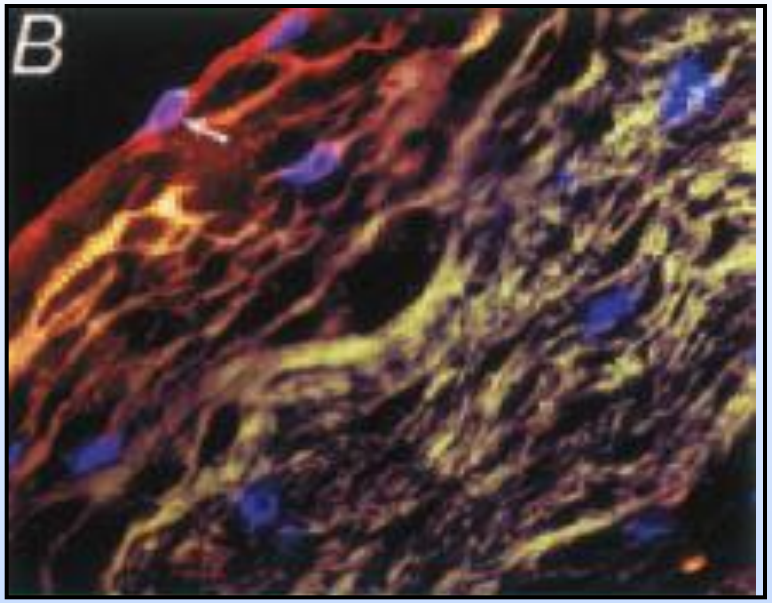
Recipient Endothelial Cells in CAV





Simper: Circulation, 2003

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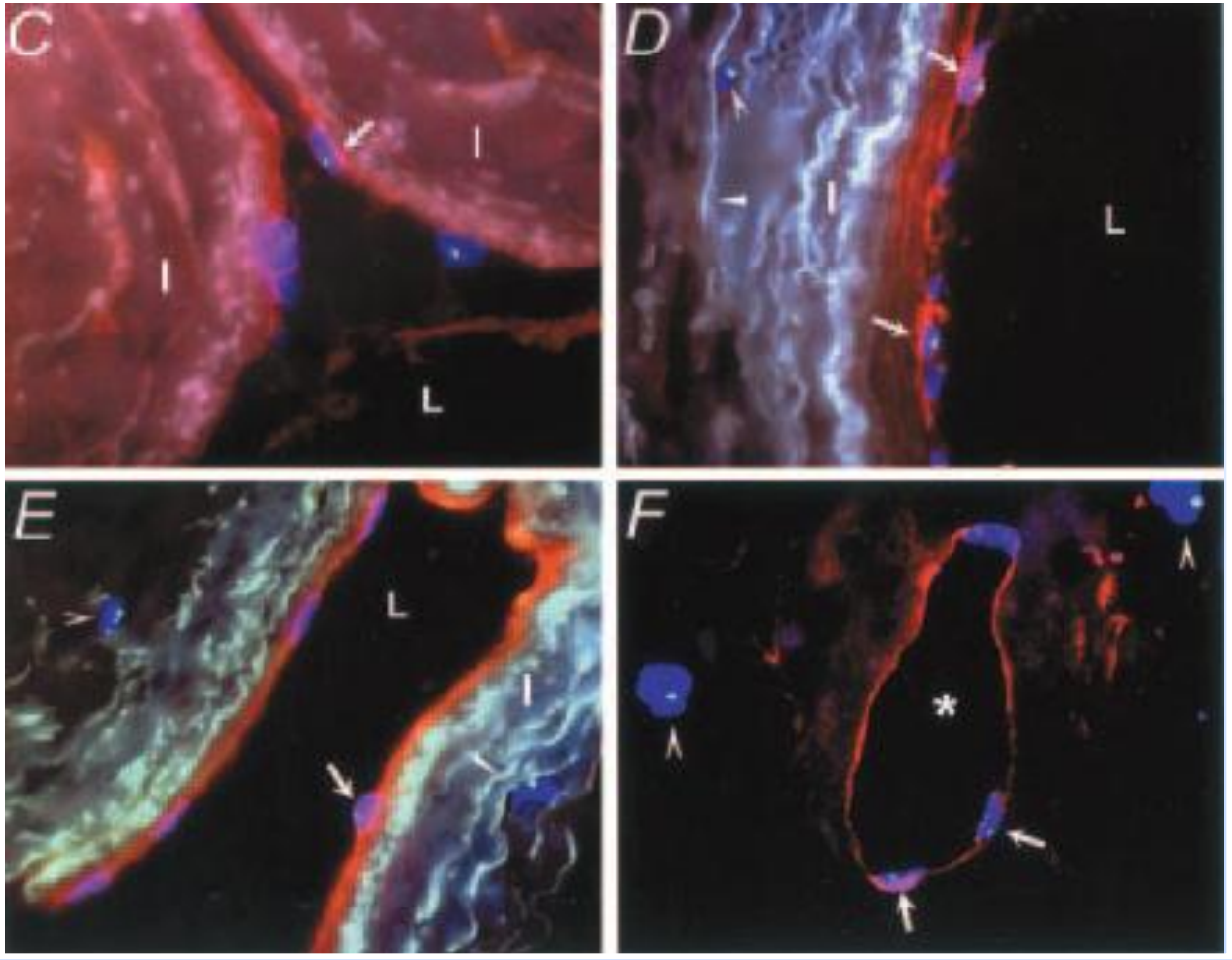
Recipient Endothelial Cells in CAV



Simper: Circulation, 2003

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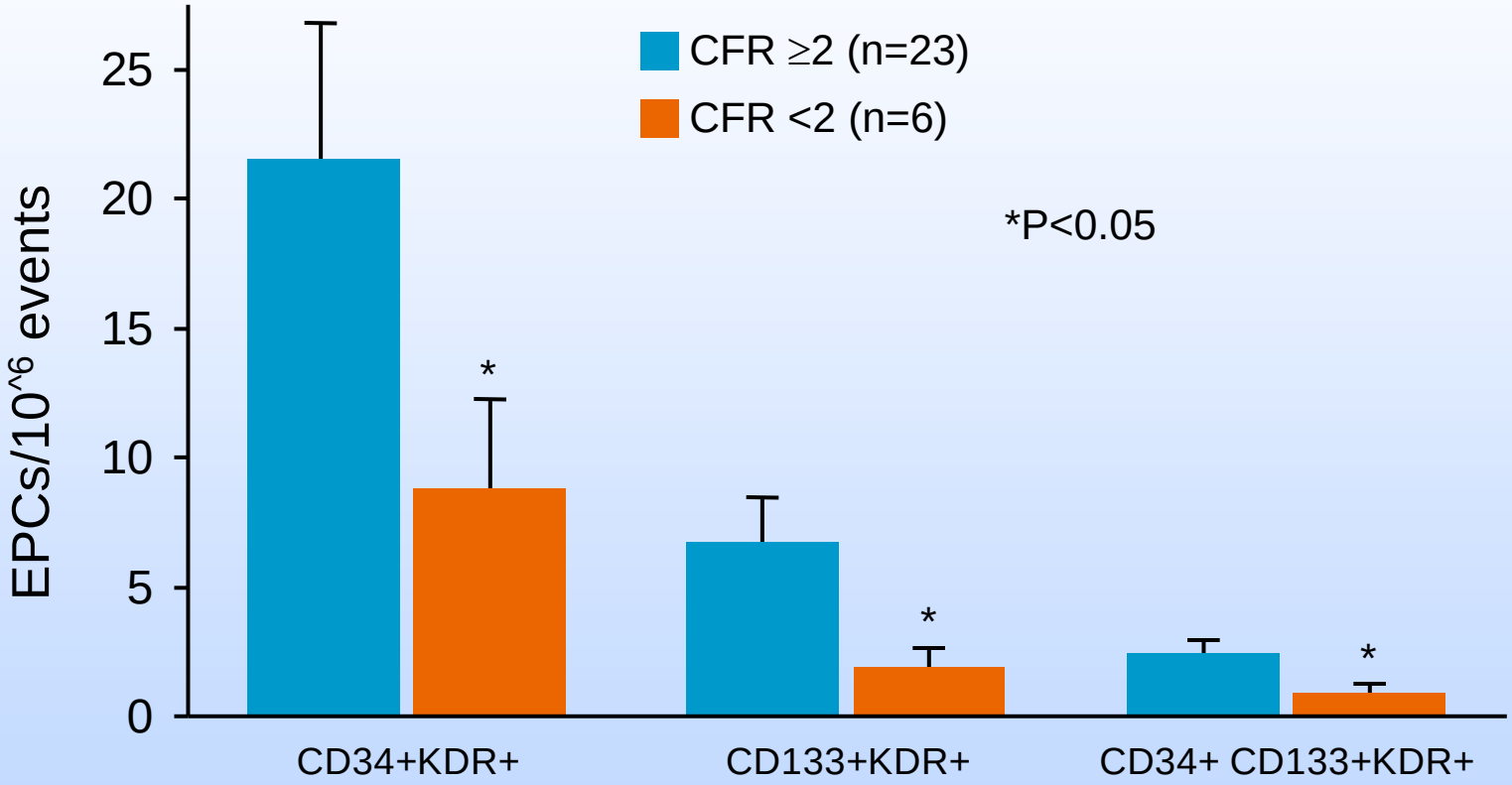
EPCs and Flow Reserve



Osto, JHLT 2011

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Role of Stem Cells in Pathogenesis of CAV

- Animal studies have demonstrated recipient origin of neointimal cells in heterotopic mouse and rat transplant models, implicating a circulating smooth muscle cell progenitor

Hillebrands JL et al: J Clin Invest 107:1411, 2001
Saiura A et al: Nat Med 7:382, 2001
Hillebrands JL et al: Nat Med 8:194, 2002

- The recipient origin of smooth muscle in human gender mismatched transplants has also been demonstrated

Minami E et al: Circulation 112:2951, 2005

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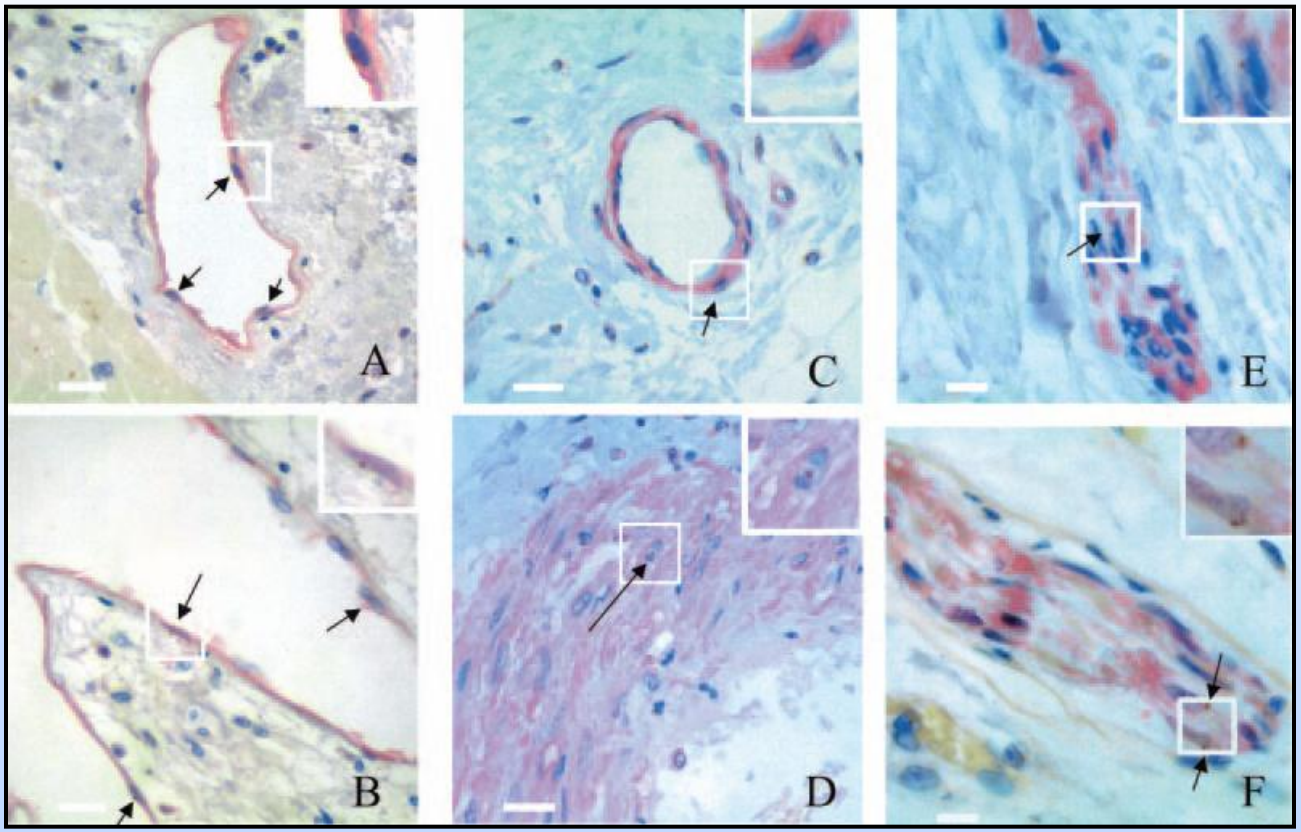
Extracardiac Progenitor Cells in Sex-Mismatched Heart Transplants

Endothelium (CD 31)

Smooth muscle (α-actin)

Schwann cells (S-100)



Minami: Circulation, 2005

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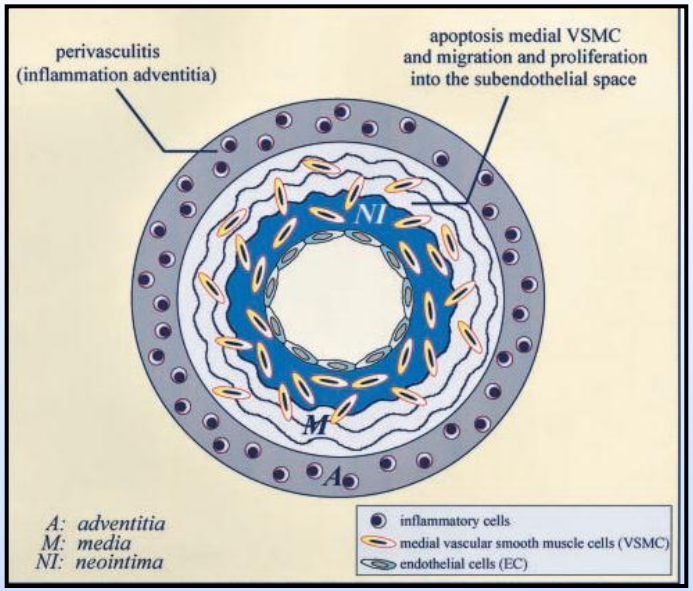
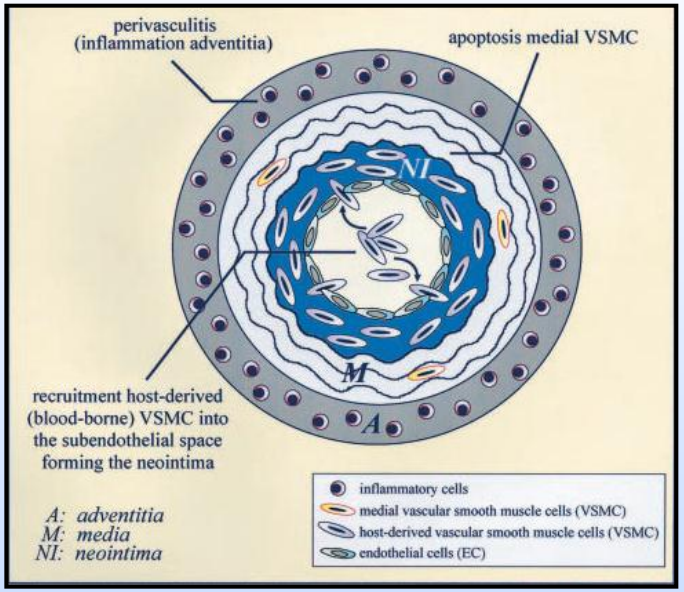
Recipient or Donor Derived?





Hillebrands: ATVB, 2003

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Role of TREGs

- TREGs are specialized T lymphocytes which suppress immune activation and maintain immune tolerance to self-antigens
- In vitro activation of TREGs by donor APCs, and then co-administration of donor HSCs by bone marrow transplantation prevents acute rejection in animal models
- If TREGs are also activated in vitro by recipient APCs, chronic rejection is also prevented

Lechler RI et al: Nat Med 11:604, 2005
Joffre O et al: Nat Med 14:88, 2008

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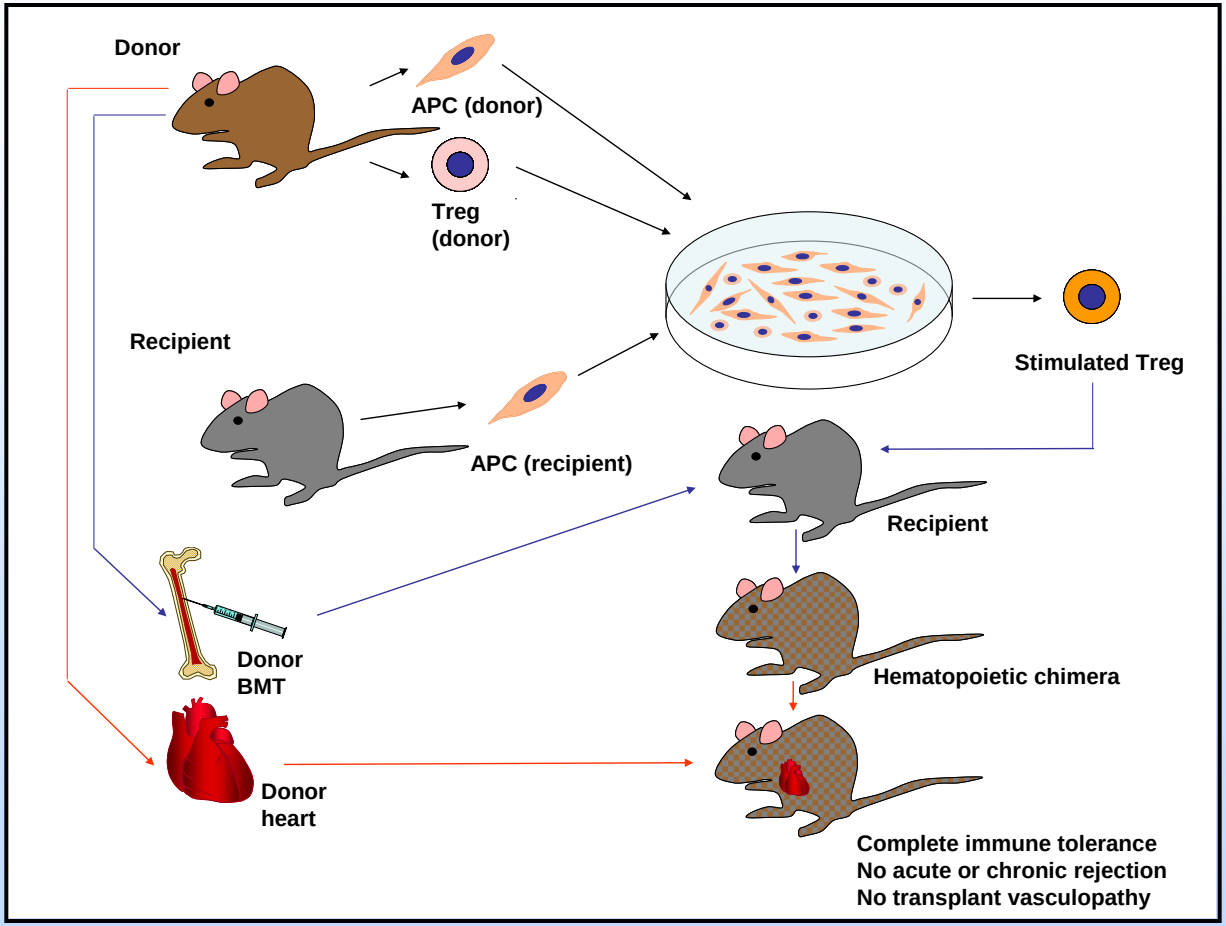
TREGs, APCs and Immune Tolerance



Boilson BA et al: Minerva Cardioangiologica 57(2):233, 2009

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Role of Sirolimus

- Sirolimus therapy has been demonstrated to attenuate the progression of CAV

Raichlin E et al: Circulation 116:2726, 2007

- Sirolimus has antiproliferative effects on smooth muscle progenitor cells, and also decreases interferon-γ production in animal models

Fukuda D et al: Circulation 111:926, 2005
Tellides G et al: Circ Res 100:622, 2007

- The number and function of TREGs is maintained by sirolimus compared to other T cell subsets (unlike cyclosporine)

Coenen JJ et al: Bone Marrow Transplant 39:537, 2007
Zeiser R et al: Blood 111:453, 2008

- Sirolimus also renders APCs more tolerogenic, and maintains the "stemness" of HSCs

Reichardt W et al: J Immunol 181:4770, 2008
Chen C et al: J Exp Med 205:2397, 2008

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Role of Statins

- The progression of CAV is attenuated by statin therapy

  Kobashigawa JA et al: N Engl J Med 333:621, 1995
  Weis M et al: J Am Coll Cardiol 38:814, 2001
  Wenke K et al: Circulation 107:93, 2003
  Kobashigawa JA et al: J Heart Lung Transplant 24:1736, 2005

- Statins reduce neointimal progression and have an antiproliferative effect on smooth muscle progenitor cells

  Werner N et al: Arterioscler Thromb Vasc Biol 22:1567, 2002
  Kusuyama T et al: J Pharmacol Sci 101:344, 2006

- Statins mobilize bone marrow derived stem cells, and facilitate their homing to sites of tissue injury, where they may have direct paracrine effects in promoting endogenous repair

  Werner N et al: Arterioscler Thromb Vasc Biol 22:1567, 2002
  Walter DH et al: Circulation 105:3017, 2002
  Suzuki G et al: Circ Res, 2008

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Conclusions

- Treatment options for CAV are limited
- EPCs and HSCs likely have a beneficial or reparative role
- The beneficial effects of statins and mTOR inhibitors may be related to effects on circulating and resident stem and progenitor cells
- Understanding the rapidly evolving field of stem cell biology may lead to the development of novel therapeutic strategies for the prevention and treatment of CAV

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Future Expectations

- Newer immunosuppressive approach will limit development of
  - CNI-induced renal failure
  - Allograft vasculopathy
- Improvement in long-term survival to 20-25 years
- Increased transplantation of patients with multiple comorbidities
- Increased use of LVADs

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