Table 1. Diagnostic Performance of Global Myocardial Edema, Global Relative Myocardial Enhancement, Late Gd Enhancement, and Lake Louise Criteria.

	Edema	RE	LGE	LLC
Sensitivity	91.7%	58.3%	58.3%	75.0%
Specificity	81.8%	63.6%	45.4%	72.7%
Accuracy	87.0%	60.9%	52.2%	73.9%

RE=myocardial enhancement; LGE=Late Gd Enhancement; LLC=Lake Louise Criteria.

Dr. Couri concluded that noninvasive imaging offers an efficient and safe means for acute management of patients. Cardiac MRI is the most versatile and powerful imaging modality for the comprehensive assessment of cardiac pathology. Despite its current success, however, cMRI in myocarditis remains a work in progress.

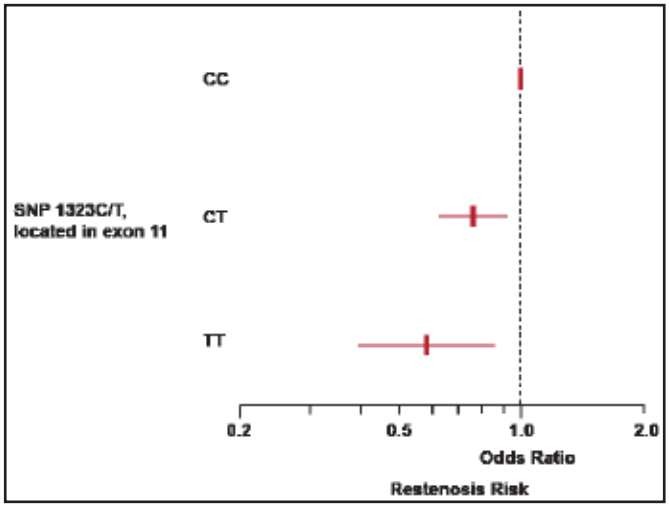
Inflammation and Vascular Injury

The focus of Dr. Daniel I. Simon's research at University Hospitals Harrington Heart & Vascular Institute, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA, is on a class of leukocyte adhesion molecules, leukocyte β_2-integrins, among which Mac-1 ($\alpha_M b_2$, CD11b/CD18) is the most common integrin on neutrophils. The leukocyte Mac-1 receptor interacts with the glyocoprotein Ibα (GPIbα) receptor on platelets, thereby regulating pro-inflammatory and pro-thrombotic bidirectional signals in both inflammatory cells and platelets. Dr. Simon has centered his research on the structure, function, and signaling of Mac-1, identifying the Mac-1 binding site for GPIbα and developing tools to disrupt leukocyte-platelet complexes that promote vascular inflammation.

The repair response following vascular injury is an inflammatory process in which neutrophils and monocytes are rapidly recruited to sites of arterial injury, including stented human blood vessels. Neutrophils appear within hours; monocytes/macrophages predominate at 7 days. Inflammatory cells are the most abundant cells in the stented human intima for months following injury. The inflammatory cells enter the blood vessel through a 2-step process, involving selectin-mediated rolling and then firm adhesion and diapedesis through the integrin Mac-1.

Inoue et al. [*J Am Coll Cardiol* 1996] observed that upregulation of the Mac-1 receptor on neutrophils predicts restenosis risk. Dr. Simon used Mac-1 knockout mice to prove the importance of the receptor in the vascular injury response [Simon DI et al. *J Clin Invest* 2000]. Following arterial injury, the wild-type mouse (Mac-1+/+) develops thick neointima while the Mac-1-/- mouse is protected from neointima growth. In stented rabbit arteries, brisk recruitment of inflammatory cells was disrupted by antibody targeting of the Mac-1 receptor, resulting in dramatically reduced restenosis [Rogers C et al. *Proc Natl Acad Sci U S A* 1998]. In humans, a single nucleotide polymorphism (SNP) in the CD18 locus of the β2 integrin is highly predictive of restenosis following stenting [Koch W et al. *Am J Cardiol* 2001] (Figure 1).

Figure 1. CD 18 Genetic Polymorphism Linked to Restenosis Risk.



Reproduced with permission from Elsevier. Koch W et al. Association of a CD18 gene polymorphism with a reduced risk of restenosis after coronary stenting. *Am J Cardiol* 2001;88(10):1120.

Mac-1 signaling via ligand engagement and clustering is important in amplifying the inflammatory response. Clustering of Mac-1 activates the master inflammatory transcription factor NFkB via a Toll/IL-1 receptor family-like signaling pathway [Shi et al. *Circulation Research* 2001]. Mac-1 signaling also regulates the expression of the transcription factor Foxp1 [Shi C et al. *J Clin Invest* 2004], which serves as a repressor of the gene encoding the M-CSF receptor. Mac-1 signaling downregulates the expression of Foxp1, thereby promoting monocyte differentiation and pro-inflammatory macrophage functions. Overexpression of Foxp1 specifically in monocytes/macrophages prevents monocyte maturation, resulting in reduced vascular inflammation and atherosclerosis.

The interaction between Mac-1 and platelet GPIbα broadly regulates inflammation in diverse animal models, including restenosis, vasculitis, glomerulonephritis, and demyelinating diseases. Dr. Simon is using these model systems to develop anti-inflammatory drugs for this diverse disease subset. Using chimeric integrins, his laboratory identified the 16-amino acid sequence within the I-domain of Mac-1 that is necessary and sufficient for Mac-1 binding to GPIbα. A peptide (M2) corresponding to this sequence or an antibody targeting

this sequence (anti-M2) block Mac-1 binding to GPIbα but not to other Mac-1 ligands, including fibrinogen, ICAM-1, and JAM-3. Two of these amino acids, threonine 213 and arginine 216, are critical for binding GPIbα [Ehlers R et al. *J Exp Med* 2003].

The first approach to disrupting platelet binding to leukocytes *in vivo* was leveraging the anti-M2 antibody. Anti-M2 reduced neointimal thickening 28 days after injury and attenuated tissue injury responses in models of glomerulonephritis [Hirahashi J et al. *Circulation* 2009]. and demyelinating disease [Langer HF et al. *Circulation Research* 2012]. These and other studies strongly suggest that virtually all inflammation is platelet-dependent.

Understanding the molecular mechanisms of inflammatory cell recruitment and monocyte differentiation provides insights necessary to develop anti-inflammatory strategies for broadly modulating vascular injury.

Antiplatelet Therapy: Risks Versus Benefits

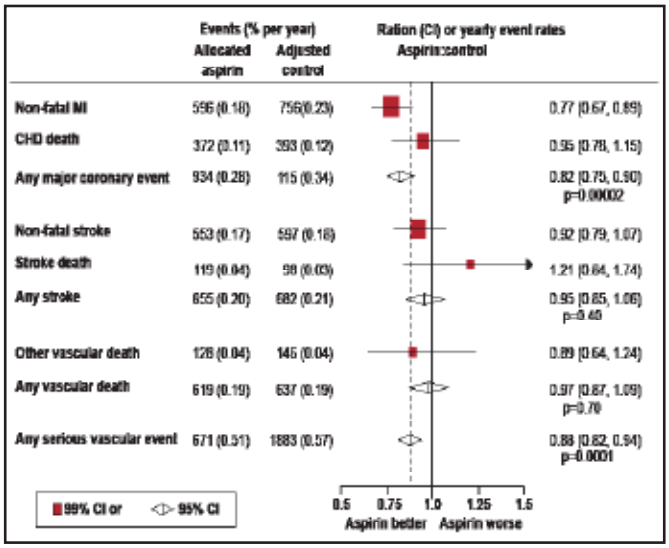
Louise Bowman, MBBS, MRCP, University of Oxford, Oxford, United Kingdom, reviewed evidence from the past 20 years on the benefits and risks of antiplatelet therapy for primary and secondary prevention of vascular events. The landmark ISIS-2 trial [ISIS-2 Collaborative Group. *Lancet* 1988] compared vascular mortality rates in patients after suspected acute myocardial infarction. Investigators reported vascular mortality rates of 13% in patients who received routine hospital care alone, 11% in those treated with aspirin only, 10% in those treated with streptokinase only, and 8% in those who received routine care plus aspirin and streptokinase.

An analysis of 25 secondary prevention trials (25,000 patients) found that antiplatelet therapy reduced the incidence of serious vascular events by about 25% among patients at risk for occlusive vascular disease [Antiplatelet Trialists' Collaboration. *Br Med J* (Clin Res Ed) 1988]. However, researchers noted that the balance of risks and benefits might be different for primary prevention in low-risk individuals. A 1994 meta-analysis [Antiplatelet Trialists' (ATT) Collaboration. *BMJ* 1994] of 145 trials of 70,000 high-risk and 30,000 low-risk subjects receiving antiplatelet therapy versus control and 10,000 high-risk subjects receiving different antiplatelet regimens found a significant benefit from antiplatelet therapy. The study provided no clear evidence on the balance of risks and benefits for primary prevention in low-risk subjects.

The ATT Collaboration evaluated the effects of antiplatelet therapy on vascular events in 212,000 high-risk patients from 287 trials [*BMJ* 2002]. The investigators found a significant odds reduction in most subgroups of individuals treated with antiplatelet therapy versus control, except diabetes patients, in whom the benefit was not clear. Despite this uncertainty, most guidelines recommend antiplatelet therapy for diabetes patients.

The absolute risk of bleeding with aspirin is increased in the elderly, men, diabetes patients, and smokers. Aspirin is associated with a 30% increased risk of intracranial bleeding and a 50% increase in extracranial bleeding. The ATT Collaboration analyzed 6 primary prevention trials of aspirin versus control involving 95,456 patients [*Lancet* 2009]. The meta-analysis showed that aspirin reduced the odds for major coronary events and any serious vascular event but showed no clear benefit in stroke reduction (Figure 1). Patients at higher risk of vascular events (the elderly, men, diabetes patients, and smokers) also had a 1.6- to 2.2-fold higher risk of bleeding with aspirin. Several ongoing clinical trials are evaluating aspirin therapy in patients with diabetes, cardiovascular disease risk, and the elderly.

Figure 1. Proportional Effects of Aspirin on Serious Vascular Events in Primary Prevention Trials.



CHD=coronary heart disease; MI=myocardial infarction.

Reproduced with permission from Elsevier. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Antithrombotic Trialists' Collaboration. *The Lancet* 2009;373(9678): 1849-1860.

Dr. Bowman concluded that the benefits of using antiplatelet therapy for secondary prevention outweigh the risks. Questions remain about the suitability of antiplatelet therapy for primary prevention. Ongoing trials will help to answer some of these questions in the next few years.