19. Gasparini M, Regoli F, Ceriotti C, Galimberti P, Bragato R, De Vita S, Pini D, Andreuzzi B, Mangiavacchi M, Klersy C. Remission of left ventricular systolic dysfunction and of heart failure symptoms after cardiac resynchronization therapy: temporal pattern and clinical predictors. *Am Heart J* 2008;**155**:507–514.
20. Dittrich HC, Erickson JS, Schneiderman T, Blacky AR, Savides T, Nicod PH. Echocardiographic and clinical predictors for outcome of elective cardioversion of atrial fibrillation. *Am J Cardiol* 1989;**63**:193–197.
21. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold J, Malcolm O, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008;**358**:2667–2677.
22. Wilkoff BL. How to treat and identify device infections. *Heart Rhythm* 2007;**4**:1467–1470.
23. Israel CW, Barold SS. Cardiac resynchronization therapy in patients with atrial fibrillation: is atrial lead implantation necessary? *PACE* 2008;**31**:263–265.
24. Steinberg JS. Desperately seeking a randomized clinical trial of resynchronization therapy for patients with heart failure and atrial fibrillation. *J Am Coll Cardiol* 2006;**48**:744–746.

**CARDIOVASCULAR FLASHLIGHT**

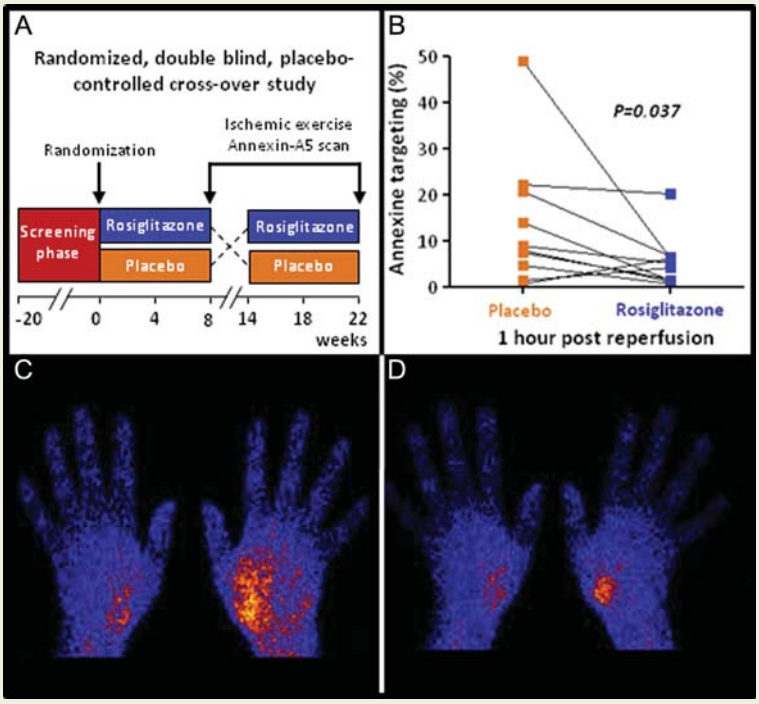
doi:10.1093/eurheartj/ehp562
Online publish-ahead-of-print 17 December 2009

# Rosiglitazone reduces ischaemia-reperfusion injury in patients with the metabolic syndrome

**Alexander J. Rennings[1]*, Patrick Meijer[2], Dominique J. van Uden[1], Cees J. Tack[3], Paul Smits[1,3], Otto C. Boerman[4], Wim J. Oyen[4], and Gerard A. Rongen[1,3]**

[1]Department of Pharmacology-Toxicology, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands; [2]Department of Anaesthesiology, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands; [3]Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands; and [4]Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen Centre for Evidence Based Practice and Institute for Genetic and Metabolic Disease, PO Box 9101, 6500 HB Nijmegen, The Netherlands

* Corresponding author. Tel: +31 24 361 4597, Fax: +31 24 361 4214, Email: a.rennings@pharmtox.umcn.nl




In animals, thiazolidinediones reduce ischaemia-reperfusion injury. A clinical meta-analysis raised suspicion that rosiglitazone increases the *incidence* of myocardial infarction (Nissen *et al.*, *N Engl J Med* 2007;356:2457–2471). However, human data on a possible benefit on infarct *size* (i.e. ischaemia-reperfusion injury) are not available. Therefore, we investigated the effect of rosiglitazone on ischaemia-reperfusion injury in 10 insulin resistant participants without hyperglycaemia. We used a thoroughly validated human *in vivo* model to quantify ischaemia-reperfusion injury in skeletal muscle by annexin-A5-scintigraphy (Rongen *et al.*, *Circulation* 2005;111:173–178). At the end of each treatment period (rosiglitazone 4 mg b.d. vs. placebo), the participants were subjected to 10 min of forearm ischaemia, combined with standardized intermittent handgripping. At reperfusion, 500 MBq $^{99m}$Tc-annexin-A5 was administered intravenously. Annexin-uptake (counts per pixel) was measured in thenar muscle 1 h post-reperfusion using a gamma camera. Ischaemia-reperfusion injury was quantified as the percentage difference in uptake between experimental and control side (annexin-targeting). Rosiglitazone reduced annexin-targeting from 8.4% (median; range 0.6–49%) to 4.7% (0.7–20%) ($P = 0.037$). We present the first human *in vivo* data on the beneficial effects of rosiglitazone on ischaemia-reperfusion injury. This observation puts the disputed elevation in myocardial ischaemic events during rosiglitazone treatment in perspective.

*Panel A.* Study design.

*Panel B.* Individual plots of the effects of rosiglitazone on $^{99m}$Tc-annexin-targeting in insulin resistant subjects.

*Panel C.* Typical $^{99m}$Tc-annexin-uptake one hour after reperfusion at the end of the placebo period. Left: control hand; right: post-ischaemic hand. Counts increase from blue to yellow.

*Panel D.* Same patient, but at the end of the rosiglitazone treatment period.