EASD 2014
Vienna . Austria
15 – 19 September 2014

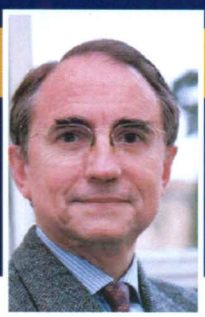
the MENARINI group

15th September
11.00 - 12.30
Sutherland Hall

Symposium on the occasion of the 50th Annual Meeting of the European Association for the Study of Diabetes

Cardiovascular management in your angina patients with Type 2 diabetes: a critical unmet need

Chairmen: E. Ferrannini (IT)
P. J. Grant (UK)



Juan Tamargo

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Universidad Complutense, Madrid, Spain

The late sodium current inhibition: effective approach in a large patients population

Ranolazine is a potent and selective inhibitor of the late sodium current (I_{NaL}). As a consequence, ranolazine prevents the increase in intracellular Na^+, reduces Na^+-dependent Ca^{2+} overload during myocardial ischaemia and preserves intracardiac ionic homeostasis (Figure 1).

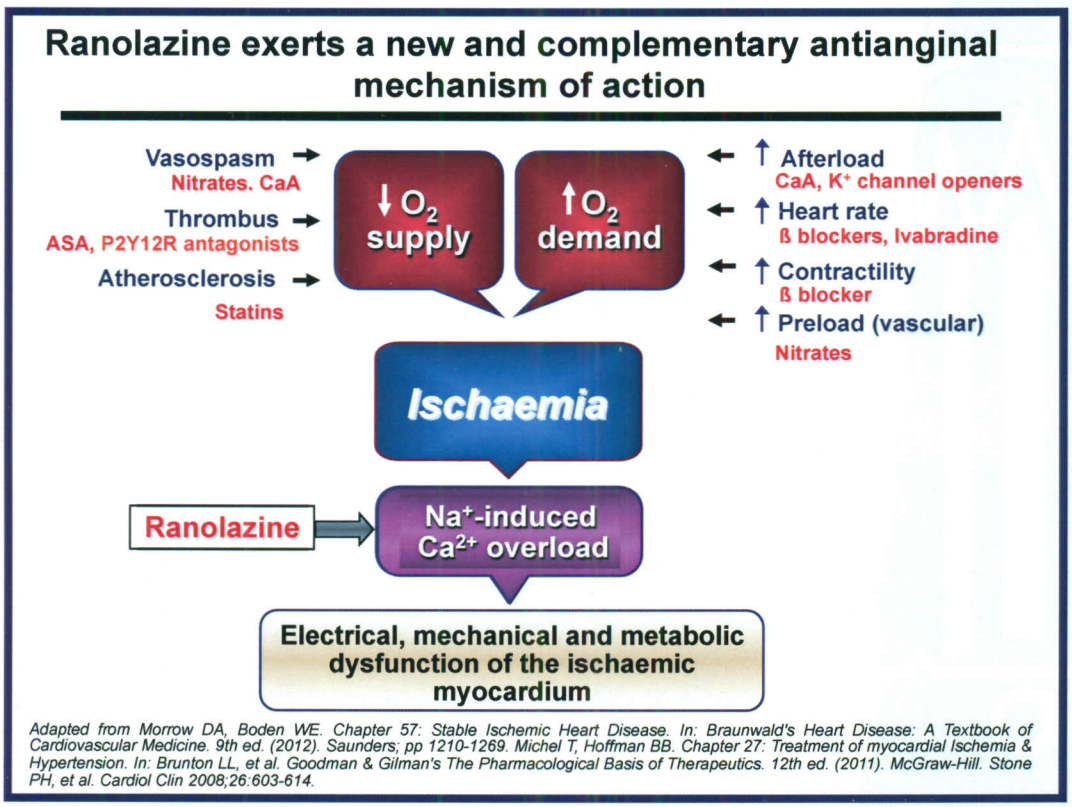


Figure 1. Ranolazine exerts a new and complementary antianginal mechanism of action.

The reduction of Na^+ and Ca^{2+} overload decreases left ventricular (LV) wall tension and myocardial oxygen demands and improves LV diastolic dysfunction. Additionally, the reduction in diastolic LV wall tension has the potential to reduce the compression of the intramural coronary vessels, increasing coronary O_2 supply to the ischaemic area. This distinct and complementary mechanism of ranolazine represents an alternative therapeutic approach in patients with chronic stable angina inadequately controlled by, or intolerant to, first-line agents (beta-blockers and/or calcium antagonists). Interestingly, the antianginal and anti-ischaemic effects of ranolazine appear at doses at which the drug has no effect on heart rate or blood pressure.

Patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) have more extensive disease and worse outcomes than those without T2DM. In addition to its anti-ischaemic and antianginal effects, ranolazine has been shown to lower haemoglobin A1c (HbA1c) in patients with CAD and T2DM in three clinical trials. In patients with T2DM, CAD and chronic stable angina who were symptomatic despite treatment with up to 2 antianginal agents, the Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) trial found that ranolazine reduced weekly angina frequency and sublingual nitroglycerin use, the effects being more pronounced in patients with higher baseline HbA1c[1]. In patients with chronic angina enrolled in the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial, ranolazine produced similar improvements in exercise parameters, nitroglycerin use, and angina

frequency in diabetic and non-diabetic patients. In a *post hoc* analysis of the CARISA trial, ranolazine (750 and 1,000 mg bid*) significantly reduced HbA_{1c} *vs.* placebo by 0.48 and 0.70%, respectively, regardless of concomitant insulin and/or oral hypoglycaemic therapy[2]. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial enrolling patients with recent non-ST-elevation acute coronary syndrome, ranolazine in addition to standard antidiabetes therapy reduced HbA1c (by 0.64%) in patients with T2DM and reduced the incidence of new fasting glucose >110 mg/dL or HbA1c ≥6% by 32% in patients without DM at baseline[3]. Consistent with the efficacy of other antidiabetes drugs, HbA1c lowering by ranolazine was greater in patients with more marked hyperglycaemia[4] (Figure 2).

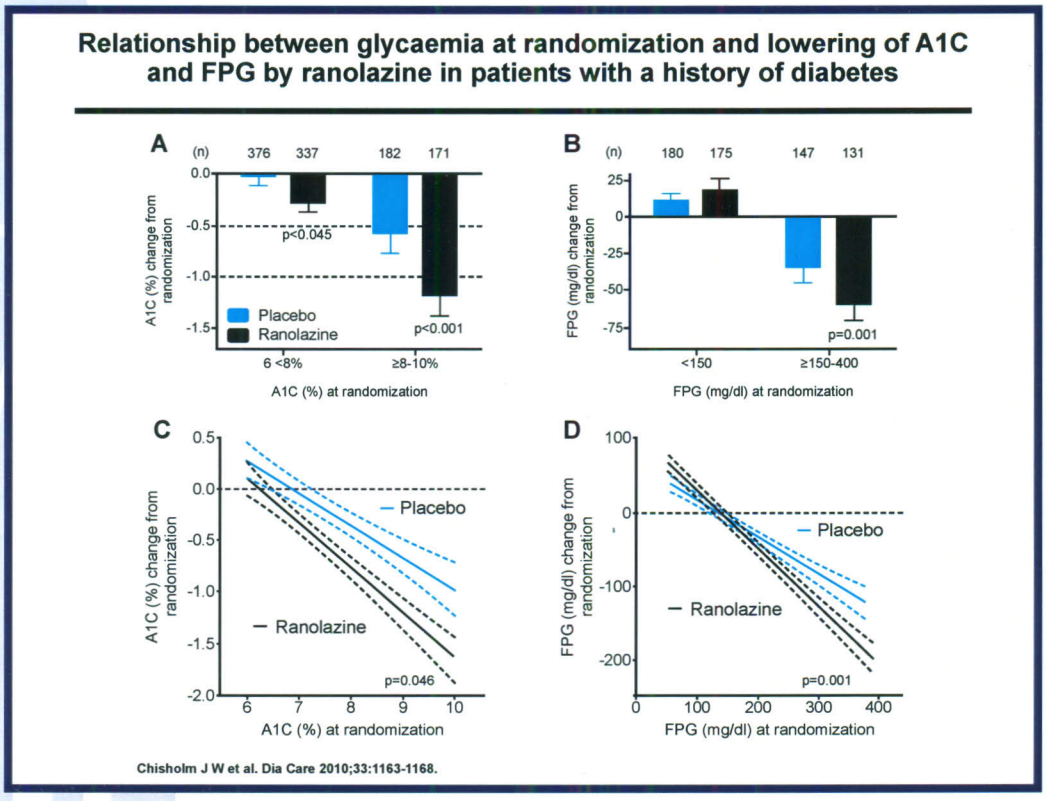


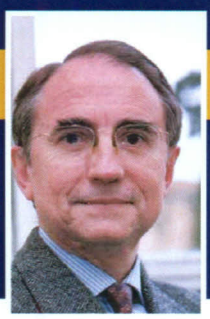
Figure 2. Relationship between glycaemia at randomization and lowering of A1C and FPG by ranolazine in patients with a history of diabetes. A: In a cell means model, with parameters for combinations of treatment, A1C category, and diabetes. B: In a cell means model, with parameters for combinations of treatment, FPG category, and diabetes. C: Relationship between A1C at randomization and the change in A1C at month 4. D: Relationship between FPG at randomization and the change in FPG at month 4. FPG, fasting plasma glucose; A1C, haemoglobin A1c.

In fact, the placebo-corrected decrease in HbA1c with ranolazine was 0.28% for the HbA1c 6 to <8% group and 0.59% for patients with HbA1c 8–10%[4]. Thus, ranolazine when added to concurrent antidiabetes treatment, lowers HbA1c in patients with CAD, chronic stable angina and poorly controlled T2DM, an effect that is not observed with first-line antianginal agents.

In this talk, first I shall review the possible mechanisms of action of ranolazine that can explain the antianginal effect and the reduction in HbA1c, including the blockade of the cardiac I_{NaL}, a decrease in postprandial and basal glucagon levels via the blockade of voltage-gated Na^+ (Nav1.3) channels in pancreatic α-cells, an increase in glucose-dependent insulin secretion, the inhibition of ion currents (I_{Na} and I_{Kr}) that play a role in insulin secretion in β-cells, and/or an improvement in pancreatic β-cell morphology and mass due to reduced apoptosis in pancreatic islets. Then, I shall analyze the pharmacological properties of ranolazine and, finally, its possible interactions with other antidiabetes drugs.

1. *Kosiborod M, et al. Evaluation of ranolazine in patients with type 2 diabetes mellitus and chronic stable angina: results from the TERISA randomized clinical trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina). J Am Coll Cardiol 2013; 61(20):2038-2045.*
2. *Timmis AD, et al. Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes. Eur Heart J 2006;27:42-48.*
3. *Morrow DA, et al. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. Circulation 2009;119:2032-2039.*
4. *Chisholm JW, et al. Effect of ranolazine on A1C and glucose levels in hyperglycemic patients with non-ST elevation acute coronary syndrome. Diabetes Care 2010;33:1163-1168.*

** Note: in the European Union ranolazine is recommended, at a maximum dose of 750 mg bid, as add-on therapy for patients with stable angina.*



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Juan Tamargo is Professor of Pharmacology in the School of Medicine of the University Complutense of Madrid (Spain).

He graduated as physician, obtained his PhD in Pharmacology and a Master degree in Clinical Pharmacology.

He completed his postgraduate training in Upstate Medical Center and Downstate Medical Centers (New York, EEUU) and the Universität des Saarlandes (Germany).

He is Member of the Royal National Academy of Pharmacy and of the Spanish Institute of Spain. He has received the Galien National Award to the excellence in Pharmacological Research and the Lilly National Award for Basic Sciences.

His primary research interest is cardiovascular pharmacology, with a focus on cardiac electrophysiology and arrhythmias.

He acts as an editorial board member for a number of scientific journals including the Spanish J Cardiology, Drug Development Research, Drug Update, Drugs in Context, Recent Patents on Cardiovasc Drug Discovery, Basic & Clinical Pharmacol & Toxicol, J Pharmacological Sciences, Arrhythmia and Electrophysiology Review, Cardiovascular Drugs and Therapy, Arrhythmia and Electrophysiology, World J Pharmacol, European Heart Journal – Cardiovascular Pharmacotherapy and Cardiovascular Research. He has published more than 350 original research papers and reviews.