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Arrhythmias and the athlete: mechanisms and clinical significance: reply

We would like to thank Dr Whyte and his coworkers for their interest in our study¹ and their critical reflection on the cause and effect relationship between right ventricular (RV) dysfunction and ventricular arrhythmias (VA).

Tachycardia-induced cardiomyopathy is indeed a well-known entity, mainly as the result of incessant supraventricular tachyarrhythmias. A few reports have described reversible cardiomyopathy related to repetitive or persistent VA or very frequent ventricular ectopy.²⁻⁴ It is important to note, however, that these reversible cardiomyopathies were invariably associated with left ventricular dysfunction, whereas athletes with VA in our study had a normal left ventricular ejection fraction, which was comparable with athletes without VA. Moreover, all athletes in our study had paroxysmal and symptomatic episodes of VA. None had incessant VT or very frequent ventricular ectopy, which could explain a tachycardia-induced cardiomyopathy. Therefore, we think that the third hypothesis that Whyte and coworkers present for our findings is unlikely.

We concur that the mechanism of complex VA in endurance athletes is not yet elucidated and that it is always ambiguous to conclude that RV outflow tract ectopy is 'idiopathic' and benign. We previously highlighted the role of an electrophysiological study for risk stratification in athletes with VA, with induction of sustained ventricular tachycardia or ventricular fibrillation and a re-entry mechanism implicating a worse prognosis.⁵ On the basis of the current study, RV ejection fraction could be used as an additional and early risk stratification tool. The outcome of endurance athletes with complex VA was not the object of the present study, but our previous data⁵ noted the development of a major arrhythmic event in 18 of 46 high-level endurance athletes (sudden death in nine) presenting with complex VA after a median follow-up of 4.7 years. On the basis of these data and derived risk-stratification tools, 11 of 22 athletes with VA in the current study were treated with an implantable cardioverter-defibrillator, five of whom received at least one appropriate shock since implantation.

Concerning the possible mechanisms underlying RV dysfunction and/or arrhythmias, recent data have shown increased pulmonary artery pressures, increased RV dimensions, and decreased RV function

(correlating with the release of cardiac troponin T) in recreational athletes completing the Boston marathon.⁶ The hypothesis that such life-long, repetitive bouts of physical activity could lead to myocardial fibrosis, cardiac dysfunction, and arrhythmias remains certainly to be proven. The finding of myocardial fibrosis as described in the case of a marathon runner by Whyte and coworkers can be non-specific, possibly due to other causes (like the late stage of myocarditis). The observation of acute RV dysfunction and the release of cardiac troponins after endurance-athletic events are nevertheless intriguing in the light of our findings and will definitely stimulate further research in this area.

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Rimonabant as an adjunct therapy in overweight/obese patients with type 2 diabetes

We read with interest the extensive guidelines on diabetes, pre-diabetes, and cardiovascular diseases.¹ However, we were surprised by the very low emphasis put on weight management and abdominal obesity and its association with increased risk of type 2 diabetes and cardiovascular disease.^{2,3} According to the Task Force, 'increasing weight with a central distribution' plays a crucial role in the complex pathophysiology of type 2 diabetes. Furthermore, 'the recognition of the underlying insulin resistance with increased visceral adiposity is a key factor for an appropriate therapy, not only of hyperglycaemia but also of hypertension and dyslipidaemia'. However, if non-pharmacological lifestyle therapy was considered to improve metabolic control (class I, level A), drugs aiming to promote weight reduction and reduce abdominal adiposity were not considered.

In the recent RIO-Diabetes trial evaluating rimonabant, a selective CB1 receptor blocker,⁴ 1047 overweight/obese type 2 diabetes patients on monotherapy with metformin or sulfonylurea and with a mean baseline HbA_{1c} of 7.3%, was given a mild hypocaloric diet and randomized to placebo or rimonabant 5 or 20 mg for 1 year. Weight loss was significantly greater with rimonabant 20 mg (-5.3 vs. -1.4 kg for placebo; $P < 0.0001$). Rimonabant 20 mg improved HbA_{1c} levels in the overall population (-0.6 vs. +0.1% for placebo; $P < 0.0001$) and in the subgroup with baseline HbA_{1c} $\geq 8\%$ (-1.1 vs. -0.3%; $P = 0.001$). Other cardiometabolic risk factors, i.e. waist circumference, HDL cholesterol, triglycerides, insulin resistance, systolic blood pressure, and C-reactive protein levels, also improved significantly with rimonabant 20 mg.

The 6-month SERENADE trial confirmed in drug-naive patients with recently diagnosed type 2 diabetes a significant HbA_{1c} reduction (primary endpoint: -0.8% with rimonabant 20 mg vs. -0.3% with placebo; $P = 0.0002$), especially in the subgroup with baseline HbA_{1c} $\geq 8.5\%$ (-1.9% vs. -0.7; $P = 0.0009$).⁵ In addition, rimonabant was associated with significant reductions in

weight, waist, insulin resistance, and triglycerides and increases in HDL cholesterol and adiponectin levels.

New trials are currently evaluating the potential of rimonabant in the prevention of diabetes in overweight/obese patients with impaired glucose tolerance (prediabetes) ('RAPSONDI') or in the management of insulin-treated patients with type 2 diabetes ('ARPEGGIO'). Finally, the ongoing 'CRESCENDO' (Comprehensive Rimonabant Evaluation Study of Cardiovascular End-points and Outcomes) study will assess whether rimonabant 20 mg can reduce the risk of major cardiovascular events in 17 000 abdominally obese patients with clustering risk factors (at least half with type 2 diabetes) followed for 5 years.

Rimonabant 20 mg is recognized in Europe 'as an adjunct to diet and exercise for the treatment of obese patients (BMI \geq 30 kg/m²) or overweight patients (BMI $>$ 27 kg/m²) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia'. Furthermore, half of the observed improvements on HbA_{1c}, as well as HDL cholesterol and triglycerides, was recognized to occur beyond weight loss, in agreement with direct peripheral metabolic effects.⁴ Even if we agree that lifestyle intervention is essential, the potential role of rimonabant, a drug targeting multiple cardiometabolic risk factors, in overweight/obese patients with type 2 diabetes and high-risk cardiovascular disease deserves consideration.

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Rimonabant as an adjunct therapy in overweight/obese patients with type 2 diabetes: reply

Thank you for forwarding the letter of the distinguished colleagues, Andre Scheen and Luc Van Gaal, and the opportunity to respond.

The potential of rimonabant, the first representative of a new class of drugs, the CB1-receptor blocker, to induce weight loss and beneficial metabolic effects in support of a healthier lifestyle are undoubtedly impressive (references 3 and 4 of the letter). Guidelines, however, are to be based on available evidence in the form of published, full papers at the time they are consented. In view of this pre-condition, we regret that the rimonabant data in patients

with diabetes were published after the complex work of the guideline-producing process had been terminated. Moreover, some of these data are still available in the abstract format only (reference 5 of the letter).

When time comes to update the Joint ESC/EASD Guidelines on Diabetes, Prediabetes and Cardiovascular Diseases, we certainly foresee the need to consider also the state of affair in terms of rimonabant. By that time, it would be rather helpful if the weight-reducing and metabolic effects in high-risk patients with type 2 diabetes could be shown to indeed translate into a reduction of major cardiovascular events or appropriate surrogate markers.

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