COMMENTARY

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Controversy about the Cardiovascular Safety of Sibutramine

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Obesity is a major cause of morbidity and mortality, predominantly through cardiovascular diseases (CVD).[1] However, the current state of weight reduction in the prevention and treatment of CVD remains controversial, essentially because no long-term, large-scale study of intentional weight loss with medical (pharmacological) means has been adequately powered to examine CVD endpoints in overweight/obese individuals with or without diabetes mellitus.[2] Conventional risk-reduction measures, such as lifestyle modification, the use of aspirin (acetylsalicylic acid) – especially in patients with pre-existing CVD – and appropriate blood pressure- and lipid-lowering drugs, are of proven benefit in reducing CVD and saving lives in at-risk subjects, including overweight/obese individuals. However, for most of the glucose-lowering agents (except metformin and perhaps pioglitazone), there are few or no data to support benefit with regard to CVD. Furthermore, the evidence concerning the effects of specific weight-reducing agents (so-called anti-obesity agents) on CVD is almost absent and, if anything, limited and inconclusive.

Safety aspects are also critical in the management of overweight/obese persons, essentially because anti-obesity agents are known to be associated with adverse events, and several of them have been withdrawn from the market because of serious safety problems.[3,4] The concern about cardiovascular safety of drugs that are supposed to reduce cardiovascular risk was recently reactivated by the story of rosiglitazone, a medication acting as an insulin sensitizer and used as a glucose-lowering agent for the treatment of type 2 diabetes.[5] The safety alert was prompted by the results of a large meta-analysis of 42 randomized controlled trials, which reported that treatment with rosiglitazone resulted in a 43% ($p = 0.03$) significant increase in risk for myocardial infarction and a 64% ($p = 0.06$) non-significant increase in risk for cardiovascular death.[6] These data were particularly alarming because the metabolic effects of thiazolidinediones (including rosiglitazone) were widely presumed, although not proven, to reduce the risk for ischaemic heart disease. Subsequently, a number of additional reports using alternative meta-analyses, recently published results of new clinical trials, and observational studies have provided variable evidence regarding a negative/positive/neutral cardiovascular effect of this pharmacological class. In particular, large observational studies have examined the risk of ischaemic heart disease associated with rosiglitazone;[5] however, studies vary in their design and ability to overcome residual confounding and biases.

Sibutramine, a combined norepinephrine and serotonin reuptake inhibitor, is one of the few established and well proven agents for obesity, and may be considered effective in the management of patients requiring pharmacotherapy as part of a multi-modal approach to weight loss.[7,8] Early studies showed that sibutramine is generally well tolerated, with no induction of primary pulmonary hypertension or adverse effects on cardiac valves, which is in contrast to what

was previously reported with (dex)fenfluramine.[9] Soon after its launch, however, sibutramine was associated with several adverse effects, which has given rise to a debate that still endures today. Indeed, its action on the sympathetic nervous system has linked sibutramine to blood pressure and heart rate elevations.[7-9] This raised the possibility of increased CVD risk despite the favourable weight-reducing effect of the drug.[10] For that reason, the use of sibutramine was contraindicated in many countries, including Europe and New Zealand, in patients with uncontrolled hypertension, coronary heart disease, cardiac dysrhythmias, congestive heart failure or stroke. Furthermore, a long-term, large-scale, prospective trial (SCOUT [Sibutramine Cardiovascular Outcomes Trial]) has been designed to determine whether weight management with a novel lifestyle intervention plus either sibutramine (10–15 mg/day) or placebo in cardiovascular high-risk overweight and obese patients can impact upon CVD endpoints.[11] Initial observations during the first 6-week lead-in period of SCOUT were reassuring.[12] However, even though the final complete results of SCOUT are not yet available and caution is thus required,[13] an increased risk of non-fatal cardiovascular events was noticed in patients treated with sibutramine compared with patients receiving placebo. Because of this concern, the European Medicines Agency recommended that the marketing authorization for sibutramine should be suspended, while the US FDA requested that new contraindications for patients with a history of CVD should be added to the sibutramine label (as was already the case in Europe and New Zealand, for instance). However, important differences have to be pointed out between the characteristics of the population in SCOUT and those of the population of patients who are prescribed sibutramine in real-life postmarketing use. Of the 10 742 patients in SCOUT, only 8.1% patients met label criteria; 91.9%, the majority with CVD and/or blood pressure >145/90 mmHg, were nonconformers; 84% had diabetes.[12] Furthermore, sibutramine has been administered continuously at a daily dose of 10–15 mg in patients of SCOUT, whatever the impact of the drug on bodyweight, whereas the drug is generally stopped in the absence of significant weight loss in routine practice.

In this issue of *Drug Safety*, an observational prospective cohort study evaluated the risk of fatal and non-fatal cardiovascular adverse events in a general population of New Zealand who were prescribed sibutramine in 'real-life' use.[14] Sibutramine postmarketing safety was monitored by the New Zealand Intensive Medicines Monitoring Programme (IMMP) between February 2001 and March 2004, and follow-up questionnaires were also sent to doctors for patients with a first prescription of sibutramine. In the latter intensively followed-up cohort, the most frequent non-fatal cardiovascular events were hypertension, palpitations, hypotensive events and tachycardia, all of which are known adverse events associated with sibutramine therapy.[7-10] As a comparison, in a cohort of 12 336 patients (mean age 45 years, 80% females) prescribed sibutramine by general practitioners in the UK, clinical events significantly associated with taking sibutramine included CNS effects, nausea/vomiting, palpitation and sweating, and the most common reason for stopping the drug was hypertension (1.6% of patients).[15] In the study from New Zealand,[14] the rate of death from a cardiovascular event in the overall cohort was 0.07 per 100 treatment-years sibutramine exposure and the rate of death from all causes was 0.13 per 100 treatment-years sibutramine exposure. The latter level was considered lower than that reported in other overweight/obese populations. However, an important limitation of this study is that there was no direct comparator group because New Zealand national statistics available for the general population are stratified by age and sex, but not by bodyweight or body mass index (BMI). The authors referred to a prospective cohort study of BMI and mortality in more than 1 million adults.[16] However, this study was performed in the US and published in 1999. Therefore, it is difficult to compare the figures, also taking into consideration that there has been a longitudinal trend to decreased CVD mortality because of a better management of risk factors during the last two decades.[17] Analysis of

five cross-sectional, nationally representative surveys in the US showed that except for diabetes, CVD risk factors have declined considerably over the past 40 years in all BMI groups.[18] Although obese individuals still have higher risk factor levels than lean individuals, the levels of these risk factors are much lower than in previous decades.[18,19] This may explain, at least partially, the paradox of declining cardiovascular mortality but increasing obesity.[20] Even though the overall trends are still decreasing, a worrying levelling off of the previously falling rates of death from CVD among young adults has recently been reported.[21] This development could be in response to the obesity epidemic, with young people the most susceptible to this particular trend.[20]

Passive postmarketing surveillance systems (such as MedWatch in the US) currently monitor for untoward drug effects. Despite a lack of uniformity in reporting, these systems can be useful for detecting rare events. However, with inherent underreporting, the lack of a comparator group and the absence of randomization, passive surveillance is unlikely to reveal much about conditions commonly associated with the disease being treated, such as cardiovascular events in overweight/obese patients or in patients with diabetes. Active postmarketing surveillance, using large, linked patient registries from insurance or provider networks (such as the IMMP in New Zealand), appears to be more promising. Although these investigations are also limited by their nonrandomized design and the incompleteness of information on potential confounders, they do provide a defined population for evaluation and offer the major advantage of risk assessment in real-life conditions. Yet only outcome trials provide randomization, with its absence of bias, systematic and reliable capture of events, timely adjudication, retention for targeted duration of follow-up, and achievement of the proper dose and duration of use for assessment of the risk-benefit ratio of any drug, including sibutramine or diabetes therapies.[22] However, as previously mentioned regarding the SCOUT trial, the target population might be completely different from that commonly followed in clinical practice, which of course raises further debate and controversy.[13]

In my opinion, the possible explanation, proposed by Harrison-Woolrych and colleagues,[14] for the lower mortality rate in the IMMP cohort from New Zealand, that sibutramine may lower the risk of death in an overweight/obese general population (after exclusion of patients at high CVD risk) remains purely speculative. As already emphasized, caution must be observed in drawing definitive conclusions from observational studies because of the possibility of bias and confounding, which may lead to erroneous conclusions. We have to wait for the final complete results of SCOUT and of other postmarketing surveillance systems before drawing definite conclusions and further recommendations. Thus, the initial debate about cardiovascular safety of sibutramine still endures today and will undoubtedly continue. This debate is also likely to surround newly developed glucose-lowering agents, in light of the recent requirement by the FDA for a two-step procedure to demonstrate cardiovascular safety of any new antidiabetic agent for the management of type 2 diabetes.[22]

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