



Workshop on CV prevention with a focus on metabolic syndrome and surrogate markers

Taskforce 1 of the Cardiovascular Round Table, European Society of Cardiology: Executive Summary Report

Michaël G.L. Hertog* on behalf of Taskforce 1

European Society of Cardiology, Sophia Antipolis, France

Received 29 August 2005; accepted 22 September 2005; online publish-ahead-of-print 17 October 2005

On 9–10 June 2005, the European Society of Cardiology invited experts from academia, industry, and regulatory agencies to discuss the development of drugs in metabolic syndrome and the use of surrogate endpoints in clinical cardiovascular research. The metabolic syndrome is a relatively new clinical entity, resulting from the clustering of a number of processes, such as hypertension, glucose intolerance, and dyslipidaemia, linked to abdominal obesity, i.e. visceral fat excess. However, its definition remains debated. The IDF has issued a new definition, which requires the presence of abdominal obesity; at the same time, the threshold used for defining abdominal obesity has been considerably lowered, which results in a large proportion of the population classified as having the metabolic syndrome. Although the concept of metabolic syndrome is attractive for practising physicians to easily recognize high-risk patients, there is currently limited evidence that its predictive value for CV events adds much to that of its individual components or of established scores of CV risk. Metabolic syndrome has therefore not yet been considered a well-established endpoint by itself in clinical research, at least for regulatory purposes. In future clinical trials, evolution of the metabolic syndrome will need to be studied in conjunction with the occurrence of morbidity (new onset of diabetes and CV events) and mortality. Selecting patients with metabolic syndrome as a target population also seems appropriate, but the issue of background therapy will then be particularly important. It is proposed that pharmaceutical companies and academia collaborate in a global effort to validate the IDF definition by harmonizing relevant aspects of clinical trial protocols and by sharing clinical trials data and expertise.

The use of surrogate endpoints and biomarkers in clinical research is promising as it provides a science-driven approach and it may considerably simplify drug development. Markers need to be sensitive and specific, and assessment techniques must be readily available to treating physicians. Biomarkers assessing target-organ damage such as IMT/IVUS are particularly attractive. As new requirements

to clinical research are regularly added, there is indeed a concern that in a few years, clinical research will become unaffordable. Ways of making clinical trials simpler and less costly need to be urgently investigated. Identification of high-risk patient (groups) through biomarkers could reduce the number of patients needed to demonstrate efficacy in outcomes trials. From a regulatory perspective, this is attractive because it can identify the patients most likely to benefit, although this will obviously limit the indication given. Many questions remain, however, notably about the validation and (quantifiable) relation of surrogates with clinical efficacy and safety endpoints. Changes in target-organ damage are difficult to relate to improvements in clinical outcomes, and outcome studies gathering more data are needed to validate these associations. As a next step, a consensus/discussion meeting should be organized by the ESC between cardiology experts, EMEA, FDA, and industry on standards for development of biomarkers in imaging focusing, for instance, on the role of IMT/IVUS in assessing atherosclerosis development and progression.

The full report of this meeting is available on the ESC website www.escardio.org.

List of attendees

We thank the participants of this workshop who all contributed to the ideas explored in this report. All views expressed in this report are personal views and do not necessarily represent official views of the agencies, ESC, or the industries.

Eric Abadie, AFSSAPS (Paris, France); Juergen Ambrecht, Novartis (Switzerland); Guy de Backer, University Hospital (Gent, Belgium); David Bilheimer, Merck (USA); David Bregman, Merck (USA); Gonzalo Calvo Rojas, Agencia Espanola del Medicamento (Madrid, Spain); Bernard Charbonnel, UFR Médecine (Nantes, France); Nicolas Danchin, Hôpital Européen Georges Pompidou (Paris, France); Jacques Djian, Novartis (Switzerland); Milou Daniel Drici, UFR Médecine (Nice, France); Pieter de Graeff, Medicines Evaluation Board (The Netherlands); Philip Harris, Pfizer (UK); Peter Held, AstraZeneca (Sweden); Michaël Hertog,

* Corresponding author. E-mail address: mhertog@escardio.org

European Society of Cardiology (France); Alan Kerr, Sanofi Aventis (France); Susan Longman, GlaxoSmithKline (UK); Clemens Mittman, BfArM (Bonn, Germany); Thierry Nebout, Servier (France); Fausto Pinto, Lisbon Cardiovascular Institute (Lisbon, Portugal); Adriaan Potgieter, European Society of Cardiology (France); Isolde Puschmann, Bristol-Myers Squibb (Belgium); Amit Rakhit, Bristol-Myers Squibb (France); Murray Stewart, GlaxoSmithKline (UK); Luigi Tavazzi, Policlinico San Matteo (Pavia, Italy); Mia Van

Petegem, EMEA (London, UK, attended as observer during day 1 only); David Wood, Charing Cross Hospital (London, UK).

Acknowledgement

The workshop was supported by the European Society of Cardiology. We are grateful to Florence Bakry, ESC for the organization of this meeting.