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EDITORIAL

Standing firm—the *European Heart Journal*, scientific controversies and the industry

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The scientific process

Science is not a continuous process, but rather, one which advances in leaps and bounds, moving forward only to experience setbacks as unexpected, new information becomes available. Knowledge thus develops with conjectures and refutations as Karl R. Popper,[1] the eminent philosopher of science, once said. As Thomas H. Huxley put it, the tragedy of scientific inquiry is that a beautiful hypothesis may be slain by an ugly fact.[2] Knowledge therefore is never stable; in fact, even the most elegant theory may be disclaimed by surprising new data. All our assumptions, theories and concepts must continually withstand falsification attempts through novel insights and unexpected findings, and the longer they survive, the better and more useful they are.

Many concepts have been disproved by appropriately powered trials, one of the more prominent examples being the CAST trial[3] which falsified the assumption that suppression of premature ventricular beats will prevent sudden death. Similarly, in heart failure stimulation of left ventricular function with either catecholamines or their derivatives as well as stimulators of myocardial second messengers such as cAMP increased rather than decreased mortality, although symptoms and physical performance were improved.[4] The series of negative trials was just recently complemented by the ILLUMINATE trial[5] using torcetrapib, a cholesterol ester trans-protein inhibitor, to increase the plasma levels of protective high-density lipoproteins which unexpectedly led to increased mortality in the active treatment group.

However, it is not merely the efficacy of drugs, interventions, or devices which requires continual critical monitoring: safety has become the new efficacy as the scientific community has experienced surprising findings with molecules used for non-cardiovascular indications. In fact, while cyclooxygenase-2 inhibitors were increasingly used to the benefit of patients afflicted osteoarthritis or other conditions, the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial,[6] which was designed to expand the indication of this promising and novel class of drugs, revealed an unexpected increase in myocardial infarctions in the actively treated group. Together with a previously published secondary analysis of the VIGOR-trial,[7] this led to the withdrawal of rofecoxib or Vioxx[R] by Merck, its manufacturer, on 30 September 2004. Consequently, the safety of all other drugs in this class as well as all non-steroidal anti-inflammatory drugs was in question and new trials such as PRECISION were launched to test this very issue.[8]

The contribution of industry

The pharmaceutical industry has made immense investments in developing novel drugs—and obviously had and still has to deal with the risks involved. If a drug is proved to be effective, the efforts of industry were always rewarded by substantial sales, in most cases to the benefit of the respective company as well as the patients in need. It goes without saying that the pharmaceutical industry has contributed enormously to the impressive progress of medicine and cardiology in particular over the last 50 years: aspirin developed by Bayer, beta-blockers by ICI, ACE-inhibitors by Squibb, statins by Merck and Bristol, Myers & Squibb and thereafter many others such as angiotensin Type 2 receptor antagonists by Merck and later Takeda, Novartis and AstraZeneca are just a few of the most prominent examples that have changed our daily practice. Similarly, pacemakers, implantable defibrillators, balloons, and stents would not be part of our therapeutic armamentarium, had they not have been developed by innovative manufacturers in close collaboration with academic researchers.

Challenges and successes

With the increasing success of drug development, however, things became a bit more difficult, especially in cardiovascular medicine. Today, novel drugs not only have to prove better and better efficacy, but must also provide impeccable safety. This has made it increasingly difficult to introduce novel cardiovascular drugs into the market. The development of many molecules had to be stopped prematurely because of a less than perfect side effect profile or because of disappointing efficacy. For example, the promising adenosine type 1 receptors antagonist rolofylline which was expected to improve prognosis in acute heart failure

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by interfering the tubulo-glomerular feedback never saw the light of clinical practice because the pivotal trial could not confirm the results of the phase I and II studies. For the manufacturer, in this case Merck Inc., this proved to be a considerable setback. In fact, such events may significantly affect the future strategy of the company, its organization and the careers of many of its employees. Thus, along the road of research and development of pharmaceuticals and devices, the hopes and fears of scientists within industry and academia may create serious conflicts of interest.

Unmet needs

Despite the tremendous progress in cardiovascular medicine that we were fortunate enough to witness in recent decades, there are still many unmet needs, for instance in diabetes. Indeed, although aspirin, statins, and inhibitors of the renin–angiotensin system are effective in this patient population, risk remains high. This has led to development of several novel treatment strategies, among them the so-called thiazolidinediones or PPAR-y activators. These drugs exert an array of effects in the cardiovascular system as well as in lipid and glucose metabolism and hence created high hopes that the devastating natural history of diabetes could be favourably influenced.

Thiazolidinediones were thus promising from the start. However, troglitazone, which was marketed in 1998 in the USA and later in Europe, soon came under intense scrutiny because of a rare, yet potentially fatal hepatotoxicity.[9] The next available molecules of this class, rosiglitazone and pioglitazone, seemed to lack these side effects and were thus rapidly approved for clinical use by the FDA and the EMEA, while troglitazone was withdrawn from the market. Both drugs undoubtedly exerted beneficial effects on a variety of surrogate endpoints such as high density lipoproteins, markers of inflammation and plasma glucose levels. However, in the case of rosiglitazone, unfavourable signals were noted in several trials suggesting that the drug might be associated with water retention, an increased incidence of heart failure and possibly myocardial ischaemia. These concerns were discussed both by the registration agencies and clinical scientists, particularly after the meta-analysis of Nissen and Wolski[10] had been published. Nevertheless, the discussion continued due to the lack of a sufficiently large and adequately powered clinical trial.

The culprit

In a recent issue of the *European Heart Journal*, Komajda *et al.*[11] published another analysis on the cardiovascular effects of rosiglitazone reporting an increased incidence of congestive heart failure in the RECORD trial. The paper was accompanied by an editorial authored by Steve Nissen,[9] an acknowledged expert in the field. Editorials are meant to be provocative in order to stimulate scientific discourse. To this end, the *European Heart Journal* aims to foster open debate on scientific issues for its readership and regularly invites reviewers and key opinion leaders to elaborate on published articles. The journal also defines its position in this forum through the following disclaimer: 'The opinions expressed in this article are not necessarily those of the editors of the *European Heart Journal* or of the European Society of Cardiology'—they might, but they don't have to.

Unexpected mail

On 21 February 2010, the Editor-in-Chief of the *European Heart Journal* received a letter from Dr Moncef Slaoui, the chairman of research and development of GlaxoSmithKline, the manufacturers of rosiglitazone. In his communiqué, he urged the journal not to publish the online editorial in print. The journal's editorial board discussed the issue and unanimously agreed that such a demand was unacceptable. However, representatives of the manufacturer were invited to express their position in the journal, to allow for an open scientific debate. Obviously, such an offer also had to involve the editorialist, Steve Nissen, and thus the *European Heart Journal* is pleased to publish both the statement of GlaxoSmithKline as well as the response to their criticism by Steve Nissen.

Standing firm

Science is an interactive process and that is why journals are optimally positioned to promote this process. Communicative reasoning within the scientific community is *the hallmark* of the scientific process as Habermas[12] put it. Scientists know what a good argument is and will consider its merits and evidence, if put forward by knowledgeable colleagues, may they work in academia or in the industry. However, we cannot suppress concerns, data or divergent opinions—we must consider them and argue with data, numbers and plausibility. Only through such a discourse can progress evolve.

Conflict of interest: none declared.

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