Meta-analysis and moderation

The difference between the conclusions of a meta-analysis and those of a long-term randomized controlled trial both investigating the safety of a widely used bronchodilator highlights the importance of moderation in the presentation of meta-analyses that raise concerns about the risk–benefit profile of medicines.

The debate about the cardiovascular risks of rosiglitazone (Avandia; GlaxoSmithKline) continued to capture headlines in September; for example, with the UK's Medicines and Healthcare products Regulatory Agency reportedly stating that the drug no longer has a place on the UK market. Less prominent, however, was the wider debate on the merits and limitations of the different types of studies that form the scientific basis for making such decisions.

Broadly speaking, key evidence on one side of the rosiglitazone debate is provided by the influential meta-analysis[1] published in 2007 that highlighted the potential cardiovascular risks of the drug. And, on the other side, a randomized active-controlled trial known as RECORD (funded by GSK) to investigate the cardiovascular safety profile of rosiglitazone indicated that it did not increase the risk of cardiovascular hospitalization or mortality[2]. Both studies have important limitations, and the difficulties that the regulators have faced in making a decision on the future of rosiglitazone illustrate the uncertainty about the strength of the evidence on both sides of the debate. With regard to the impact on doctors, patients and the public, however, it is clear that the influence of the meta-analysis has been much greater; for example, the prescriptions of rosiglitazone dropped rapidly soon after its publication.

The extent to which such effects might represent a strong positive outcome for public health may be hard to establish with complete confidence, particularly if an ongoing trial known as TIDE, which is comparing the cardiovascular safety of rosiglitazone and the other drug in the same class, pioglitazone (Actos; Takeda), is terminated. However, a recent article[3] from authors at the US Food and Drug Administration (FDA) discussing the regulatory conclusions on another drug — tiotropium bromide (Spiriva; Boehringer Ingelheim/Pfizer) — over which major safety concerns were raised by a meta-analysis, provides a valuable illustration of the possible risks of making decisions on the basis of such studies alone.

Potential signals that tiotropium, a long-acting anticholinergic bronchodilator that is widely used to treat patients with chronic obstructive pulmonary disease (COPD), might increase the risk of major cardiovascular events were first reported to the FDA in 2007 by the manufacturer, initiating a regulatory investigation. Then, in September 2008, an independent meta-analysis of 17 studies of tiotropium (corresponding to ~4,600 patient-years of exposure to this drug) and the short-acting anticholinergic bronchodilator ipratropium was published[4]. The conclusion was that: "Inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI [myocardial infarction], or stroke among patients with COPD"[4].

By contrast, however, a 4-year randomized placebo-controlled trial of tiotropium known as UPLIFT involving ~6,000 patients (corresponding to ~9,200 patient-years of exposure to the drug) published shortly afterwards did not show an increased risk of MI, death from cardiovascular causes, or death from any cause[5]. At an FDA advisory committee meeting convened in 2009 to discuss the disparities between the conclusions of the two studies, it was almost unanimously voted that the UPLIFT study addressed the potential cardiovascular risk concerns for tiotropium[3]. In addition to the strength of the design of the UPLIFT study, a number of important limitations of the meta-analysis, including potentially biased study selection and the combination of long-acting and short-acting anticholinergic agents in the main analysis, were highlighted[3].

It is interesting to consider whether, in the absence of convincing clinical trial results contradicting the findings of the meta-analysis soon after its publication, patients would have halted a valuable treatment for a serious disease owing to the severity of the safety concerns raised by the meta-analysis and the apparent strength of its conclusions to non-experts. Indeed, as the FDA authors note, the publication of such meta-analyses commonly results in urgent calls for regulatory action, without acknowledgement of potential pitfalls in the interpretation of data from such studies[3]. Heeding their conclusion[3] — "We must use measured restraint during our evaluations to ensure that safe drugs remain on the market and that their use is not restricted in a way that unnecessarily denies beneficial interventions to patients who need them" — should be a high priority.

1. Nissen, S. E. *et al. N. Engl. J. Med.* **356**, 2457–2471 (2007).
2. Home, P. D. *et al. Lancet* **373**, 2125–2135 (2009).
3. Michele, T. M. *et al. N. Engl. J. Med.* **363**, 1097–1099 (2010).
4. Singh, S. *et al. JAMA* **300**,1439–1450 (2008).
5. Tashkin, D. P. *et al. N. Engl. J. Med.* **359**, 1543–1554 (2008).