Evident should support or refute theories and hypotheses and be designed with sufficient scientific rigor to allow precise methods of observations, measurements, experiments and conclusions. Advancement of scientific knowledge relies on several tiers of evidence collection, aiming to deduce mechanisms and infer treatments. Thus we study the effect of a particular exposure on an outcome of interest, in populations or individuals. Although epidemiological observations are necessary to drive medical and scientific advancement, causality cannot be drawn from clinical observations alone.  

**Mortality with tiotropium**

Let us consider a real life example that has led to a degree of controversy as well as causing us to review which conclusions can be drawn from available data.  

Tiotropium bromide (Spiriva) is a long-acting antimuscarinic agent used worldwide for the treatment of COPD; it improves lung function, increases exercise capacity and reduces exacerbation rates. In 2008 a meta-analysis was published that showed that in COPD there was an increased cardiovascular mortality with anticholinergic drugs. This raised concerns within the respiratory community and further detailed systematic reviews were performed. The original meta-analysis was criticised for including several anticholinergic compounds, of double counting some patients and being heavily weighted by one particular study.  

The subsequent meta-analyses and systematic reviews came to differing conclusions, with several finding no increased cardiovascular or overall mortality in patients using tiotropium. A large four-year prospective study (UPLIFT) of tiotropium versus usual care in COPD demonstrated an 11 per cent reduction in all-cause mortality with tiotropium and a reduction in cardiovascular events.  

In a further posthoc pooled analysis increased mortality was observed in patients using the tiotropium Respimat device but not the HandiHaler; however, no plausible pharmacological or physiological explanation was advanced, leaving many perplexed.  

**Respimat vs HandiHaler**

As the controversy rumbled on, the makers of tiotropium, Boehringer Ingelheim, performed a definitive randomised control study (RCT) to answer this question. The Tiotropium Safety and Performance in Respimat Trial (TIO SPIR) is the largest RCT ever performed in COPD (over 17 000 patients over a mean follow-up period of 2.3 years) and compared mortality in patients using the Respimat and HandiHaler devices. Importantly, no difference in mortality between the two devices was observed, with similar safety and efficacy.  

Remarkably, the week before the TIO SPIR data were released a further large, observational, primary-care database study was published. Here mortality data were collected from patients receiving prescriptions for either device, the study concluding that Respimat was associated with a 30 per cent increased risk of mortality compared to the HandiHaler.  

**Interpreting the data**

So, what conclusions can we draw? In interpreting data one must seek to understand the depth of the evidence presented and utilise the strengths and limitations of each. At the European Respiratory Society annual conference in September 2013 both TIO SPIR and the Verhamme study (www.ers-education.org/events/annual-congress.aspx?idParent=130632) were reviewed followed by a critique of research methodology. Care is warranted when drawing conclusions from either meta-analyses or observational population studies, and an appropriately designed and powered RCT that studies the population of interest is the superior method for answering the specific question of whether there is increased mortality in COPD with tiotropium.  

One must note that meta-analyses will always be limited by the data available; posthoc pooled analysis may result in erroneous statistical conclusions, and observational epidemiological database studies cannot infer causality. Observational cohort studies, reflecting case-control, cross-sectional and longitudinal studies, gather evidence for associations in individuals and may permit a measure of the strength of association between exposure and outcome (odds ratio) but not an attributable risk.  

**Conclusion**

It is clear that one must use all data available in a critical manner and commit to the use of the right method to draw the correct conclusions. Have many hours of analysis been wasted in answering the HandiHaler vs Respimat question? We do not believe so as we have all learnt to address these questions better in the future.  

One question remains unanswered, though: by drawing erroneous conclusions from incorrect studies, have any patients come to harm?  

**References**


Declaration of interests
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