In search of the right word: a statement of the HEART Group on scientific language

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This editorial refers to ‘Statement on matching language to the type of evidence used in describing observational studies vs. randomized trials†, by the Editors of the Heart Group Journals, on page 20

Facts and precision

To improve language, means to improve thinking—nothing else! Friedrich Nietzsche (1844–1900)

For scientists, the world consists of facts, as the seminal philosopher Ludwig Wittgenstein put it almost a century ago.1 Facts are observed and measured by equipment and devices of ever greater precision, and eventually described using highly accurate and well-defined words—usually of Latin descent to give them greater weight. In any case, the expressions we use should match what they describe.2 Ever since its existence, science has stood for precision, both in quantifying phenomena and with regard to the language used. In contrast to fiction and poetry, where uncertainty, double-meaning, and symbolism are part of the art, scientific writing utilizes words with well-defined meanings. Widely accepted definitions—from the Latin word definere for restricting—are the basis of scientific communication, be it in logic, mathematics, physics, life sciences, or medicine.

Facts and causes

What is beyond the realm of fact does not exist in the world of science. This may sound rather restrictive, but it is not. Indeed, we have come very far by restricting ourselves to measurable facts. Impressively, in <500 years, we advanced from anatomy to physiology, and from early diagnostics to modern-day evidence-based medicine involving genetics, cell biology, large registries, and randomized trials.3

Undoubtedly, the words and expressions scientists used over time were part of the paradigms they used in their research. Accordingly, their meanings changed as concepts advanced to today’s science. At each stage of the scientific process, however, they were fundamental for proper communication and for the growth of knowledge.

The discovery of causality was essential for the advancement of science and medicine. If the cause of a disease was discovered, a remedy was in sight. The first physician to take this seriously was James Lind (1716–1794), a naval physician and native of Edinburgh, who developed the theory that citrus fruits could cure scurvy, a then major problem for the Royal Navy as well as the French and Spanish fleets when on the high seas. At sea, Lind divided 12 scurbutic sailors into six treatment groups. They all received the same diet but, in addition, group 1 was given a quart of cider daily, group 2, were given 25 drops of elixir of sulfuric acid, group 3 were give six spoons of vinegar, group 4 were given half a pint of seawater, group 5 were given oranges and lemon, and the last group were given a spicy paste plus barley water. The treatment of group 5 stopped after 6 days when they ran out of fruit, but by that time one sailor was fit for duty, while the other had almost recovered.5 While today, such a small sample size would lead to immediate rejection of such a study by any recognized journal, including the European Heart Journal,6 Lind made history with his experiments.

Today, such trials are usually based on experimental data and tested in much larger trials. For instance, Anitchkow’s seminal experiments with rabbits fed a high fat diet provided the experimental evidence for the cholesterol theory of atherosclerosis7 put forward already by Rudolf Virchow in the 19th century. But a rabbit is a rabbit, not a human. The Framingham study then provided epidemiological data that indeed showed that in apparently healthy humans, plasma cholesterol levels were predictive of the outcome, and specifically of the clinical consequences, of atherosclerosis such as myocardial infarction, stroke, and cardiovascular death.8

Associations and causes

However, as outlined by the statement of the HEART Group, an informal group of all editors of cardiovascular journals,9 associations—such as those provided by epidemiological studies—are not necessarily proof of causality. Indeed, up until the late 1980s, many eminent clinical scientist—among them, Sir Michael Oliver as one of the most outspoken10—put the cholesterol hypothesis in doubt and—based on the early trials with fibrates such as clofibrate—claimed that cholesterol lowering would lead to depression, suicide, accidents, and death, all events seemingly associated with low cholesterol in early studies.

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Things started to change as Michael Brown and Joseph Goldstein provided the understanding of cholesterol uptake and synthesis by the liver\textsuperscript{11} and when Akiro Endo isolated the first compounds inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A reductase pathway.\textsuperscript{12} Eventually the seminal 4S study involving 4444 patients with or at risk of cardiovascular disease\textsuperscript{13}—and thereafter many other large randomized trials\textsuperscript{14}—proved beyond reasonable doubt that lowering cholesterol with statins reduced major cardiac events.

As pointed out in table 1 of the HEART group statement published in this issue of the \textit{European Heart Journal},\textsuperscript{15} the appropriate description for epidemiological data would be ‘in subjects with lower cholesterol levels, a lower cardiovascular risk was observed’, while 4S and the later randomized trials showed that ‘statins reduce cardiovascular events’. While the former describes an association, the latter proves causality.

The importance of proper wording

This distinction is important for the proper practice of medicine: indeed, to the surprise of many clinicians, the CAST study showed that while antiarrhythmics suppressed extrasystoles effectively, the drugs increased mortality. Thus, markers of disease are not necessarily its cause and hence not always an appropriate target of therapy. Similar observations have been made with activators of cAMP in heart failure where the drugs improved physical performance of highly symptomatic patients, but increased mortality. Finally, homocysteine, while a highly predictive marker of outcome in primary prevention, proved not to be a therapeutic target since, in large intervention trials, a reduction of its plasma levels by chronic supplementation with folic acid had no effect on major cardiovascular events in the participating subjects.

Judgement and evidence

Hence, it became clear that only well-designed and properly performed randomized clinical trials comparing a novel remedy with placebo were able to provide convincing proof of causality—and this made them the basis of modern medicine and the guidelines we use.\textsuperscript{15} Obviously, we intuitively take associations frequently for causality. For instance, the change in the number of pairs of breeding storks and the millions of newborn babies in Europe show a strong correlation over time (Figure 1).\textsuperscript{16} Unfortunately, this does not confirm the popular fairy tale.

Nevertheless, observational studies and prospective registries are not without value (Table 1). Indeed, if properly performed, registries reflect the real-world situation much more closely than randomized trials since no or few inclusion criteria are used and treatments regimens are those of current clinical practice. Of note, event and mortality rates are considerably higher in registries than they are in randomized trials. Hence, data obtained under real-world conditions are more generalizable than those of randomized trials which may be applicable only to a highly defined group of patients. On the other hand, the results of registries are prone to unmeasured confounders. Additionally, data collection may be less complete and of lower quality as compared with randomized and well monitored trials. Therefore, while novel statistical

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<td>Inclusion criteria</td>
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<td>Exclusion criteria</td>
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<td>Standardized and blinded treatment</td>
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<td>Defined outcome measures</td>
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<td>Unbiased comparison of treatments groups</td>
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<td>Very expensive</td>
<td>Less expensive</td>
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Figure 1 Relationship between pairs of brooding storks and the number of newborn babies (in millions) over time (modified from Sies\textsuperscript{16}). Reprinted by permission from Macmillan Publishers Ltd: Nature ‘A new parameter for sex education’. © 1988.
methods such as multivariate and propensity analysis may partially account for confounding variables, results from registries must be interpreted with more caution.

Take-home message

What is the take-home message of these statements? We should be aware of what we say and what words we use to describe which propositions. Only generally accepted definitions will allow us to communicate results properly, and, hence, we should adhere to it. And what we cannot speak about, as Ludwig Wittgenstein stated at the end of his Tractatus Logico-Philosophicus, we must pass over in silence.\(^\text{17}\)

References