BIG DATA: BRIDGING THE GAP BETWEEN REAL-WORLD AND TRIAL EVIDENCE

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The potential of the analysis of big data to improve health care and the understanding of diseases is impressive. How to use real-world evidence to support the approval of new indications for old drugs or for postapproval matters is currently a hot topic of discussion. At the 15th Global Cardiovascular Clinical Trialists Forum held on November 29–December 1, 2018 in Washington, DC, US, trialists, regulators, payers, industries, practitioners, and patients provided different perspectives about the use of big data to support drug development.

REAL-WORLD DATA

Real-world data consist of electronic health records, product and disease registries, patient-generated data, and, overall, all the data on patient health status and health care utilization collected by different sources. Analysis of real-world data leads to real-world evidence. Real-world data analyses and trials are not opposites, but provide complementary evidence. Indeed, randomized clinical trials (RCTs) allow the efficacy of treatments to be tested, but enroll selected populations, and are useless without effective implementation strategies to maximize the utilization of the new treatments. On the other hand, analyses of real-world data cannot be used to test treatment efficacy because of confounding factors and bias, but allow for the assessment of the association between drug use and the risk of outcomes. Compared with trials, real-world data analyses are cheaper and more generalizable (ie, less inclusion/exclusion criteria, meaning that they reflect real-world practice). Due to the large sample size, they foster the identification of the occurrence of rare clinical events, which may be underestimated in a trial population. Thus, real-world data may be key for the investigation of safety, tolerability, ease of use, cost, effectiveness, and implementation of treatments in daily clinical practice, aspects that are as important as efficacy in the development journey of a new drug. The importance of real-world evidence has been well recognized by regulators. In the 21st Century Cures Act, the FDA announced a new drug-development modernization plan. Although RCTs are considered gold standards to support medical product approval decisions, their limitations are acknowledged. Regulators aim that real-world evidence may be the key to answer

most of the critical questions unanswered by RCTs, particularly those about the effects of a drug in broader populations and over a more extended period of time than in the RCTs.[1] The FDA is actively working to integrate real-world evidence into the process of medical product development.[1]

Registry-based randomized clinical trials

Real-world evidence and randomization can be integrated to provide a novel study design, namely prospective, registry-based RCTs (RRCTs), which allows the advantage of conducting an RCT, ie, randomization, with all the pros of using real-world data, such as large clinical registries (ie, less selected populations, real-world practice settings, larger number of events and potential for identifying rare events, lower costs) to be combined.[2] In an RRCT, a registry is used to identify eligible patients who are randomized to receive the treatment or the control after attaining consent to participate, and to collect patients' baseline characteristics. A registry can also be used to collect key outcomes, making it possible to follow-up patients longer, but at a lower cost than in RCTs. When appropriate, open-label randomization, limited monitoring procedures, and no centralized event adjudication may be adopted, which further contributes to simplifying the study design and reduce costs, but have well-known limitations.[2]

Observational studies based on real-world data cannot assess efficacy of a treatment due to the limitation of a lack of randomization, but can provide important hypotheses to test in subsequent interventional RCTs. An analysis of the SCAAR registry, which is part of the SWEDEHEART registry, showed that the use of thrombectomy as an adjunct to percutaneous coronary intervention in patients with STEMI was associated with an increased risk of death after adjustment for several potential confounders.[3] This real-world evidence inspired the investigators to test the same hypothesis in a randomized setting.

Thus, the RRCT TASTE[4] was designed to test manual thrombus aspiration on top of primary percutaneous coronary intervention vs percutaneous coronary intervention alone in patients with STEMI. An open-label design was adopted and the primary end point was mortality at 30 days. The SCAAR registry enrolls all consecutive patients undergoing coronary intervention in Sweden and Iceland and allowed for the identification of eligible patients for the TASTE trial. Inclusion criteria were very few, such as diagnosis of STEMI with percutaneous coronary intervention planned after coronary angiography. All baseline and procedural data were entered directly into the registry. Randomization was performed by an online randomization module within the SCAAR registry. An initial oral consent was requested before randomization and the agreement to participate had to be confirmed by written informed consent within 24 hours. Data for the primary end point (mortality at 30 days) were obtained by linking SCAAR with the national

population registry, whereas those for the secondary end points (30-day hospitalization for MI, stent thrombosis, target-vessel revascularization, target-lesion revascularization, composite of death or MI) were extracted from SWEDEHEART and the Swedish national patient registry. Linkage between Swedish disease health registries and governmental health and statistical registries was done using the 10-digit personal identity number assigned at birth (or immigration) to every Swedish resident. The TASTE trial randomized 7244 patients, 3621 were assigned to thrombus aspiration and 3623 to conventional percutaneous coronary intervention. The cost of this RRCT was around 400 000 USD (beyond the ordinary costs of the registry), which is extremely low when compared with the expenditures required for running an industry-funded RCT (around 10 million USD for an RCT of equivalent size). The TASTE trial did not show any benefit in terms of a reduction in 30-day mortality in patients randomized to thrombus aspiration before percutaneous coronary intervention vs percutaneous coronary intervention alone in patients with STEMI. Real-world data also allow the implementation of trial evidence in clinical practice to be verified. Indeed, after the publication of the TASTE RRCT, an analysis of SCAAR/SWEDEHEART reported a sudden decrease in the use of thrombus aspiration in the setting explored in the trial, highlighting a successful implementation of the TASTE findings in clinical practice.

Several RRCTs have followed the TASTE trial, with most of them testing invasive procedures or short-term pharmacological treatments. The SPIRRIT-HFPEF trial is the first RRCT testing a chronic treatment in heart failure and is currently enrolling patients (end of enrollment planned for 2020, end of the follow-up planned for 2022).[5] Briefly, it is a phase 4, randomized, multicenter, safety/efficacy, parallel assignment, intention-to-treat, open-label treatment, event-driven interventional trial testing spironolactone (or eplerenone) on top of usual care vs usual care alone in patients with heart failure with an ejection fraction >40%. SPIRRIT-HFPEF is sponsored and managed by the nonprofit academic research organization Uppsala Clinical Research center. The Swedish Heart Failure Registry, which is linked to other national health registries, such as the Patient Registry, the Dispensed Drug Registry, and the LISA registry, by the Swedish personal identity number, provide baseline and outcome data. The primary outcome is cardiovascular death. Cause of death is adjudicated by an independent clinical end point committee. A short and simple written consent form has to be signed at the time of randomization. During the course of the study, patients are followed up according to the routine care and provide serum/plasma creatinine and potassium assessments on 5 occasions.

CONCLUSIONS

The "big data" session at the 2018 Cardiovascular Clinical Trialists Forum has clearly highlighted the potential of using real-world data to improve health care. Real-world data may actively contribute to improve the process of developing new treatments and the implementation of their use in medical practice. Real-world data is a friend, rather than an enemy, of RCTs, and they complement one another. A coordinated effort by all stakeholders is needed to implement the use of real-world data in the evidence-generation process. ■

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