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Interpreting differences in data from randomized controlled trials versus real-world evidence: Lessons from the Diuretic Comparison Project

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I. INTRODUCTION

Randomized clinical trials (RCTs) are considered the gold standard for clinical evidence generation. However, these trials are expensive and take a long time to complete. Thus, there are calls for alternative methods of evaluating the efficacy and safety of medical interventions.[1]

As defined by the US Food and Drug Administration (FDA), real-world data (RWD) "… are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources".[2] As highlighted during the COVID-19 pandemic, real-world evidence (RWE) is starting to play an increasing role in healthcare decisions in settings where RCT data are lacking. This raises the question of whether RWE can supplement RCT data or aid in clinical decision-making.[3]

With RWE there is an opportunity to accelerate therapy development and monitor the successes and failures of both newly approved and existing therapies. However, it is critical that stakeholders, including researchers, healthcare providers, regulators, administrators and patients, understand the limitations of RWE. RWE is primarily done with the question of clinical care in mind. Thus, the appropriate use of RWE must be driven by well-designed guidelines and regulations to ensure accurate, unbiased findings.[4]

Until recently, RWE has been used primarily to monitor drug safety and detect adverse events in post-marketing surveillance studies. RWE is particularly useful when the outcome of interest is rare, prolonged follow-up is required to assess outcomes, or it is difficult to perform an RCT (e.g. in pediatric or pregnant populations).[4] Any use of observational RWE to substitute for RCT data must be done with caution. Booth et al. stated that RWE should not replace clinical trials due to the inability to compare outcomes between non-randomized groups.[5]

Although, a real-world study can be done prospectively, with randomization and propensity score matching to construct comparable cohorts (pragmatic approach), it may still not be able to account for certain biases or confounding factors the way an RCT can do, due to its open-label nature. The RCT design is more equipped to compare two drugs as the patient population is homogeneous due to strict inclusion, exclusion criteria with randomization and use of double blinding, which ensures a level playing field to the two comparator drugs.

Thus, RWE should not replace RCTs in the approval process but can provide supplementary information to inform better understanding of treatment effectiveness and safety in real-world settings.[4]

The case of the Diuretic Comparison Project

There is a good body of RCT evidence for the superiority of chlorthalidone over hydrochlorothiazide for the prevention of cardiovascular events in patients with hypertension.[6] The real-world Diuretic Comparison Project (DCP) compared hydrochlorothiazide and chlorthalidone in an open-label, real world setting.[7] Adults aged ≥65 years who were being treated with hydrochlorothiazide 25 or 50 mg/day either continued therapy with hydrochlorothiazide or switched to chlorthalidone 12.5 or 25 mg/day. The primary outcome was a composite of nonfatal myocardial infarction, stroke, heart failure resulting in hospitalization, urgent coronary

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revascularization for unstable angina, and non-cancer-related death; safety was also assessed in the trial.[7] The rate of primary outcome events did not differ between the chlorthalidone and hydrochlorothiazide groups (10.4% vs. 10%; hazard ratio [HR] 1.04, 95% confidence interval [CI] 0.94–1.16; p=0.4).[7]

In contrast, no significant difference in HR for primary outcome was found between CTD and HCTZ in patients who had no history of MI and stroke[7] (HR 1.12; 95%CI, 1.00 to 1.26; p=0.0545[13]).

Although seeking to address a clinically relevant question in a pragmatic fashion, the DCP had several design limitations. In the high-risk group of individuals with a history of myocardial infarction (MI) and/or stroke (10.8% and 10.7% in the chlorthalidone and hydrochlorothiazide groups, respectively), the risk of the primary outcome was significantly lower in the chlorthalidone versus hydrochlorothiazide group (HR 0.73, 95% CI 0.57–0.94; p=0.0135); no such difference was seen in the lower risk group without a history of MI and/or stroke.[7] The study population was mostly composed ofwhite, male, old subjects with a mean age of 72 years and thus the results should not be extrapolated to other demographic groups. No information is given regarding the drugs prescribed in both groups in association to CTD or HCTZ, nor about the concomitant use of aspirin, statins and glucose-lowering drugs which might have a potential to influence the reported CV outcomes. Given that all DCP participants had been taking hydrochlorothiazide for an unknown period before randomization, switching to chlorthalidone for a median period of only 2.4 years did not appear to be sufficient to improve cardiovascular risk in the low-risk population. In contrast, this duration of therapy with chlortalidone seemed to be adequate to reduce risk compared with hydrochlorothiazide when the background level of risk was higher. Therefore, unequal exposure to the two drugs of interest before randomization was likely to be a critical issue.

Another issue was the drug dosages used in the DCP trial. Daily doses considered equivalent in this study were hydrochlorothiazide 25 mg/day and chlorthalidone 12.5 mg/day.[7] However, the starting dose of hydrochlorothiazide should be 12.5 mg/day in the elderly only and 25 mg/day in younger patients. For chlorthalidone, the starting dosage should be 6.25 mg/day in the elderly and 12.5 mg/day in younger patients.[8]

The American College of Cardiology/American Heart Association hypertension guidelines[9] state that the usual dosage of hydrochlorothiazide should be 25–50 mg/day, while the usual dosage of chlorthalidone is 12.5–25 mg/day. A 2018 meta-analysis noted that the equivalent dosages of hydrochlorothiazide and chlorthalidone have a 3:1 ratio.[10]

Furthermore, data from an ambulatory blood pressure monitoring study showed that reductions in 24-hour and nighttime blood pressure were greater with chlorthalidone 6.25 mg/day than with hydrochlorothiazide 12.5 mg/day.[11] The higher rate of hypokalemia in the chlorthalidone arm of the DCP study is also indicative of a mis-match in effective dosages used.[7]

About 15% of the participants who were randomly assigned to CTD reverted back to HCTZ; but, only 3.8% shifted from HCTZ to CTD.[7] This clearly shows the shortcomings of a RWE like DCP, due to an open label setting the physicians and patients were aware of the medications been taken and could have influenced the therapeutic management and increased the bias.

Implications of all available evidence

Most major RCTs comparing chlorthalidone with other antihypertensives have shown a reduction in cardiovascular events, but this is not the case for hydrochlorothiazide. One set of RWE reporting the two diuretics to be equivalent should therefore not negate five decades of data to the contrary from RCTs. It is ironic that the Multiple Risk Factor Intervention Trial (MRFIT)[12] was criticized for not being an RCT, but now the real-world DCP study is being used to claim that the chlorthalidone and hydrochlorothiazide equal with respect to cardiovascular outcomes.

II. CONCLUSION

The shortcomings of the DCP suggest that RWE is inappropriate for the head-to-head comparison of treatment options. However, RWE does have a role in confirming clinical effectiveness and safety in real-world settings. As such, RWE represents a complementary approach alongside RCTs, rather than an alternative. Therefore, until robust RCT data using equipotent dosages show that the two diuretics are equivalent, chlorthalidone should be considered superior to hydrochlorothiazide with respect to cardiovascular risk reduction in hypertension based on decades of RCT data generated in landmark studies.

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