

SPOTLIGHT COMMENTARY

Spotlight commentary: A role for real-world evidence to inform the clinical care of patients with diabetes mellitus

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Randomized trials are the gold standard for evaluating healthcare interventions because well-designed, well-executed, and appropriately analysed trials provide the strongest support for causality. While this robust experimental design is not without shortcomings, trial evidence is and should be a major driver of clinical practice. This is certainly true for the medical subspecialty of diabetology, a field rich with trial findings that directly inform treatment guidelines. More recently, there has been an interest in the potential for non-experimental findings from real-world data to serve as evidence. The objective of our commentary is to spotlight examples of how real-world evidence (RWE) can complement trials, for example, by helping *set a research agenda*, *generalize trial findings to real-world settings*, and *elucidate treatment effect heterogeneity*. Indeed, a recent review by Caparrotta et al.¹ in *Br J Clin Pharmacol* touches on these tenets while acknowledging the real but mitigable influence of bias and confounding in non-experimental studies. Despite this potential role, can RWE actually inform clinical practice in diabetes? Health professionals in the field have articulated their visions for RWE and/or offered pragmatic solutions to increase its adoption. Salvo and Faillie² make the case that a real-world assessment of antihyperglycaemic treatments is needed given the predominance of surrogate endpoints to study beneficial drug effects, the exclusion of older and/or multimorbid persons from trials, and the inability of trials to examine uncommon safety outcomes. Zaccardi et al.³ envision that RWE in diabetes can foster a path toward personalized medicine using newer and more powerful data-driven tools.

Blonde et al.⁴ held a roundtable to help healthcare professionals better understand the value and limitations of RWE relating to the provision of effective diabetes treatment in everyday clinical practice. Regulators have also offered perspectives, evidenced by 2020 U.K. Medicines and Healthcare products Regulatory Agency and 2019 U.S. Food and Drug Administration draft guidances in response to the congressional *21st Century Cures Act* and even relied on RWE to support an antihyperglycaemic drug labelling change.⁵ Given the potential importance of RWE to the field, we spotlight recent non-experimental research published in *Br J Clin Pharmacol* that may inform the clinical care of patients with diabetes mellitus.

Seong et al.⁶ (Ewha Womans University, South Korea) studied an effectiveness endpoint using 2011–2015 Korean Health Insurance Review & Assessment claims. Using an incident user cohort design, the authors examined the association between dipeptidyl peptidase-4 inhibitor (DPP-4i) initiation (vs. non-initiation) and new onset of select autoimmune diseases among patients with type 2 diabetes mellitus. In separate analyses, propensity score (PS) weighting and PS matching were used to address confounding. Cox proportional hazards regression was used to generate hazard ratios (HRs). Within a base cohort of ~1.1 million patients meeting inclusion criteria, the PS-weighted adjusted HR for DPP-4i initiation versus non-initiation was 0.82 (95% confidence interval [CI] 0.68–0.99). Among ~0.8 million PS-matched patients, the adjusted HR was 0.76 (0.62–0.76). Given the modest number of covariates included in the PSs, interpretability of findings

might have been helped by conducting a quantitative bias analysis and/or calculating an *E* value to assess the robustness of findings to unmeasured confounding. With this and other limitations in mind, these RWE findings suggest that DPP-4is could be repurposed for autoimmune disease treatment. While randomized data are likely needed, this and other observational work play a central role in demonstrating that such trials are justified and important,⁷ thus *guiding the research agenda* in diabetes mellitus.

The next two studies demonstrate how RWE can help *generalize trial findings to real-world settings*. Lee et al.⁸ (National Cheng Kung University, Taiwan) examined cost-effectiveness and safety using 2004–2013 Taiwanese National Health Insurance Research Database claims. The authors quantified numbers needed to treat (NNTs) for new use of a long-acting insulin analogue (LAIA) compared with intermediate-long-acting human insulin (ILAHI) to prevent diabetes-related complications and hypoglycaemia among patients with type 1 diabetes mellitus. Potential differences in baseline patient characteristics by exposure status were addressed by PS matching. NNTs were calculated using absolute risk reductions, the latter defined as differences between insulin exposure groups in the cumulative incidence of the endpoint during time *t*. Relative to an ILAHI, 10, 12, and 9 patients would need to be treated with a LAIA for a mean of 3.6, 5.8, and 6.0 years to prevent an occurrence of a diabetes-related complication, hypoglycaemia requiring medical assistance, and outpatient hypoglycaemia, respectively. Interpretability of findings might have been helped by examining aggregated treatment benefits, for example, quality-adjusted life years. With this and other limitations in mind, these non-experimental findings suggest that greater costs associated with LAIAs for patients with type 1 diabetes mellitus could be substantially offset by savings from averted hypoglycaemia or diabetes-related complications.

Jensen et al.⁹ (Aalborg University, Denmark) examined hypoglycaemia using 1996–2017 Danish National Patient Register data linked to the National Pharmacological Database. Using a matched case–control design, the authors examined associations between different insulin regimens and hospital admission for hypoglycaemia among patients with type 1 diabetes mellitus. Measured confounding was addressed by adjusting for investigator-selected baseline covariates. Logistic regression was used to generate odds ratios (ORs). Approximately 6400 hypoglycaemia cases were matched to an equal number of controls. With a basal-bolus insulin regimen using human insulins as the reference category, exposure odds for a *basal insulin analogue + bolus insulin analogue* regimen was lower among cases versus controls (OR = 0.61, 0.54–0.68). Other regimens including analogue insulins (e.g., *basal human insulin + bolus insulin analogue*) were generally also associated with lower exposure odds, while exposure odds for *basal human insulin* and *mix human insulin* regimens were higher among cases versus controls (OR = 1.53, 1.31–1.80 and 2.10, 1.83–2.40, respectively). Interpretability of findings may be limited by the inclusion of only last hypoglycaemia events experienced by cases; a requirement for cases to have static insulin regimens in the 6 months prior to their event; and a lack of conditioning on matching in the logistic regression analysis. With this and other limitations in mind,

these non-experimental findings suggest that use of a basal-bolus insulin analogue regimen may be safer with respect to hypoglycaemia than use of a basal-bolus human insulin-only regimen. This work by Jensen et al.⁹ and previously discussed work by Lee et al.⁸ help *generalize trial findings to the real world*. It is reasonable to be concerned that clinical trial results showing the superiority of newer insulin analogues might not generalize to routine practice conditions. These two observational studies comparing newer to older insulin regimens both confirm that the advantages of the newer agents hold under real-world conditions, an essential “reality-check.”

Finally, Filion et al.¹⁰ (McGill University, Canada) examined cardiovascular (CV) safety using 1998–2014 U.K. Clinical Practice Research Datalink records. Using an active comparator incident user cohort design, the authors examined the association between sulfonylurea (vs. metformin) monotherapy and new onset myocardial infarction (secondary endpoints included ischaemic stroke, CV death, and all-cause death) among patients with type 2 diabetes mellitus. Confounding was addressed by matching on high-dimensional PS, a data-adaptive method that empirically identifies commonly occurring covariates likely to cause bias. Cox proportional hazards regression was used to generate HRs. Among ~0.1 million high-dimensional PS-matched patients, adjusted HRs for myocardial infarction, ischaemic stroke, CV death, and all-cause death were 1.04 (0.85–1.29), 1.25 (1.002–1.56), 1.25 (1.06–1.47), and 1.60 (1.45–1.76), respectively. The authors reported effect measure modification by age with sulfonylurea use (vs. metformin) and ischaemic stroke, CV death, and all-cause death; individuals <75 (vs. ≥75) years of age had increased relative rates. Interpretability of findings might have been aided by considering time-varying covariates, although a concern for residual confounding by dynamic factors may have been mitigated by the relatively short mean follow-up duration. With this and other limitations in mind, these findings suggest that among newly treated patients with type 2 diabetes mellitus, first-line use of sulfonylureas (vs. metformin) may not be associated with an increased rate of myocardial infarction, but may be associated with increased rates of ischaemic stroke, CV death, and all-cause death. Metformin has long been thought superior to sulfonylureas for CV outcomes based on a small trial that was not powered for subgroup analyses. The amply powered observational work by Filion et al offers the important insight that metformin's CV benefits may be greatest in individuals ≥75 years of age, thus *elucidating treatment effect heterogeneity* in a vulnerable subpopulation.

Non-experimental studies generating RWE have well described limitations (including concerns for bias and confounding) and cannot replace randomized trials. But, by linking the idealized world of randomized trials to reality on the ground, thoughtfully designed and well conducted observational studies may ultimately play just as an important role in optimizing diabetes care.

COMPETING INTERESTS

We declare the following competing interests. Dr. Leonard is an Executive Committee Member of the University of Pennsylvania's Center for Pharmacoepidemiology Research and Training. The Center

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CONTRIBUTORS

All authors made substantial contributions to the conception of the work. C.E.L. drafted the work. All authors revised it critically for intellectual content. All authors gave final approval of the version to be published. C.E.L. agrees to be accountable for all aspects of this work.

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REFERENCES

1. Caparrotta TM, Dear JW, Colhoun HM, Webb DJ. Pharmacoepidemiology: using randomised control trials and observational studies in clinical decision-making. *Br J Clin Pharmacol.* 2019;85(9):1907-1924.

2. Salvo F, Faillie JL. Interest and challenges of pharmacoepidemiology for the study of drugs used in diabetes. *Therapie.* 2019;74(2):255-260.
3. Zaccardi F, Davies MJ, Khunti K. The present and future scope of real-world evidence research in diabetes: what questions can and cannot be answered and what might be possible in the future? *Diabetes Obes Metab.* 2020;22(Suppl 3):21-34.
4. Blonde L, Bailey T, Strong J, Levin P. Real-world evidence in diabetes: relevance to clinical practice. *J Fam Pract.* 2019;68(3 Suppl):jfp_68031.
5. Eichler HG, Bloechl-Daum B, Broich K, et al. Data rich, information poor: can we use electronic health records to create a learning healthcare system for pharmaceuticals? *Clin Pharmacol Ther.* 2019;105(4):912-922.
6. Seong JM, Yee J, Gwak HS. Dipeptidyl peptidase-4 inhibitors lower the risk of autoimmune disease in patients with type 2 diabetes mellitus: a nationwide population-based cohort study. *Br J Clin Pharmacol.* 2019;85(8):1719-1727.
7. Farag SS, Abu Zaid M, Schwartz JE, et al. Dipeptidyl peptidase 4 inhibition for prophylaxis of acute graft-versus-host disease. *N Engl J Med.* 2021;384(1):11-19.
8. Lee TY, Kuo S, Yang CY, Ou HT. Cost-effectiveness of long-acting insulin analogues vs intermediate/long-acting human insulin for type 1 diabetes: a population-based cohort followed over 10 years. *Br J Clin Pharmacol.* 2020;86(5):852-860.
9. Jensen MH, Hejlesen O, Vestergaard P. Association of insulin regimens with severe hypoglycaemia in patients with type 1 diabetes: a Danish case-control study. *Br J Clin Pharmacol.* 2020;86(8):1560-1566.
10. Filion KB, Douros A, Azoulay L, Yin H, Yu OH, Suissa S. Sulfonylureas as initial treatment for type 2 diabetes and the risk of adverse cardiovascular events: a population-based cohort study. *Br J Clin Pharmacol.* 2019;85(10):2378-2389.

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