Therapy Escalation Following an Elevated HbA_{1c} in Adults Aged 45 Years and Older Living With Diabetes in Australia: A Real-World Observational Analysis

Diabetes Care 2020;43:e185–e187 | https://doi.org/10.2337/dc20-0269

*Ying Xie,[1,2] Jannah Baker,[2] Tamara Young,[2,3] Min Jun,[2,3] Louisa Sukkar,[2,4] Anna Campain,[2,3] Amy Kang,[2,3] Alan Cass,[5] Ji Hu,[1] David Peiris,[2,3] Carol Pollock,[6,7] Germaine Wong,[4,8] Sophia Zoungas,[2,9] Kris Rogers,[2,10] Meg Jardine,[2,3,11] and Carinna Hockham,[2,3] on behalf of the EXTEND45 Steering Committee**

Stepwise escalation of glucose-lowering therapy to more intensive regimens is an integral component of type 2 diabetes management (1). Early blood glucose control is associated with beneficial effects on long-term micro- and macrovascular outcomes (2). Understanding factors associated with time to therapy escalation following an elevated glycated hemoglobin (HbA_{1c}) may inform interventions to facilitate timely control. We used linked real-world data to examine time to therapy escalation following a recorded HbA_{1c} ≥8.0% (64 mmol/mol) and associated factors.

The EXamining ouTcomEs in chroNic Disease in the 45 and Up Study (EXTEND45 Study) is an Australian population-based linked data study in which participants of the 45 and Up Study have been linked to the Medicare Benefits Schedule (MBS), providing data on government-subsidized medical services, the Pharmaceutical Benefits Scheme (PBS), providing prescription claims data, and community laboratory databases (among others) (3). The 45 and Up Study comprises 267,153 individuals aged ≥45 years living in New South Wales (NSW), Australia, recruited between July 2006 and December 2009. Ethical approval for the EXTEND45 Study was obtained from the NSW Population & Health Services Research Ethics Committee (HREC/13/CIPHS/49).

In EXTEND45, 24,430 individuals with diabetes between 2006 and 2014 have been identified using multiple linked data sources (3). In the current study, therapy escalation was assessed during the 6 months following all linked HbA_{1c} results ≥8.0% occurring in non–treatment-naive, non–insulin-using individuals presumed to have type 2 diabetes. As a result, the unit of analysis was the elevated HbA_{1c}, with individuals able to contribute multiple results to the analysis. A threshold of 8.0% was used to reflect the typically higher HbA_{1c} targets recommended for older people (4). To ensure that all included HbA_{1c} results represented separate instances of an elevated HbA_{1c} in the same individual, those results ≥8.0% that occurred within 3 months after the end of the 6-month follow-up period were excluded.

Therapy escalation was determined using Anatomical Therapeutic Chemical classification codes to identify prescription claims for different glucose-lowering therapy regimens in the PBS data set. Regimens were categorized as monotherapy, dual therapy, triple/quadruple therapy, and temporary discontinuation (defined as a break of two or more standard coverage days). Escalation was defined as the addition of ≥1 oral glucose-lowering drug, a glucagon-like peptide 1 receptor agonist, or insulin to the individual's existing regimen.

Explanatory variables included age, HbA_{1c} result, glucose-lowering therapy regimen, number of general practitioner (GP) visits, and number of consultant (any specialty) visits in the previous 90

[1]*The Second Affiliated Hospital of Soochow University, Suzhou, China*
[2]*The George Institute for Global Health, Sydney, New South Wales, Australia*
[3]*Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia*
[4]*School of Public Health, University of Sydney, Sydney, New South Wales, Australia*
[5]*Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia*
[6]*Renal Division, Kolling Institute for Medical Research, Sydney, New South Wales, Australia*
[7]*University of Sydney, Sydney, New South Wales, Australia*
[8]*Centre for Transplant and Renal Research, Westmead Hospital, Sydney, New South Wales, Australia*
[9]*School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia*
[10]*Graduate School of Health, University of Technology Sydney, Sydney, New South Wales, Australia*
[11]*Concord Repatriation General Hospital, Sydney, New South Wales, Australia*

Corresponding author: Carinna Hockham, chockham@georgeinstitute.org.au

Received 6 February 2020 and accepted 7 August 2020

This article contains supplementary material online at https://doi.org/10.2337/figshare.12813428.

**A complete list of the EXTEND45 Steering Committee members can be found in the supplementary material online.*

days, assessed at the time of the elevated HbA_{1c}, as well as fixed demographic, socioeconomic, lifestyle, and clinical variables. To account for individuals contributing multiple HbA_{1c} results to the analysis, marginal Cox proportional hazards models were used, with variable selection performed using the Hosmer-Lemeshow method (5). For each included HbA_{1c} result, follow-up ended when therapy was escalated, the individual died, or after 6 months, whichever occurred first.

A total of 4,009 eligible HbA_{1c} results ≥8.0% among 2,456 individuals were identified, with 60% of individuals contributing a single HbA_{1c} result. The majority (59%) of included results occurred in female participants and 63.6% in participants aged 55–75 years. Forty-four percent of elevated HbA_{1c} results (n = 1,774) were met with a PBS dispensing indicating therapy escalation within 6 months (median time 45 days, interquartile range 14–101 days).

In a multivariable analysis, therapy escalation was more likely for HbA_{1c} results occurring in individuals who had a higher HbA_{1c} ($P < 0.0001$ for linearity), were receiving monotherapy at the time of the result, had visited their GP multiple times in the previous 90 days ($P < 0.0001$ for linearity), had visited a consultant physician in the previous 90 days, lived in Inner Regional Australia (areas classified by the Australian Bureau of Statistics as having some restrictions upon access to services due to geographic distance), or had self-reported anxiety on the 45 and Up Study baseline questionnaire (Fig. 1). Age was nonlinearly associated with therapy escalation ($P <$ 0.0001 for nonlinearity). Therapy escalation was less likely for elevated results occurring in individuals receiving dual therapy or triple/quadruple therapy,

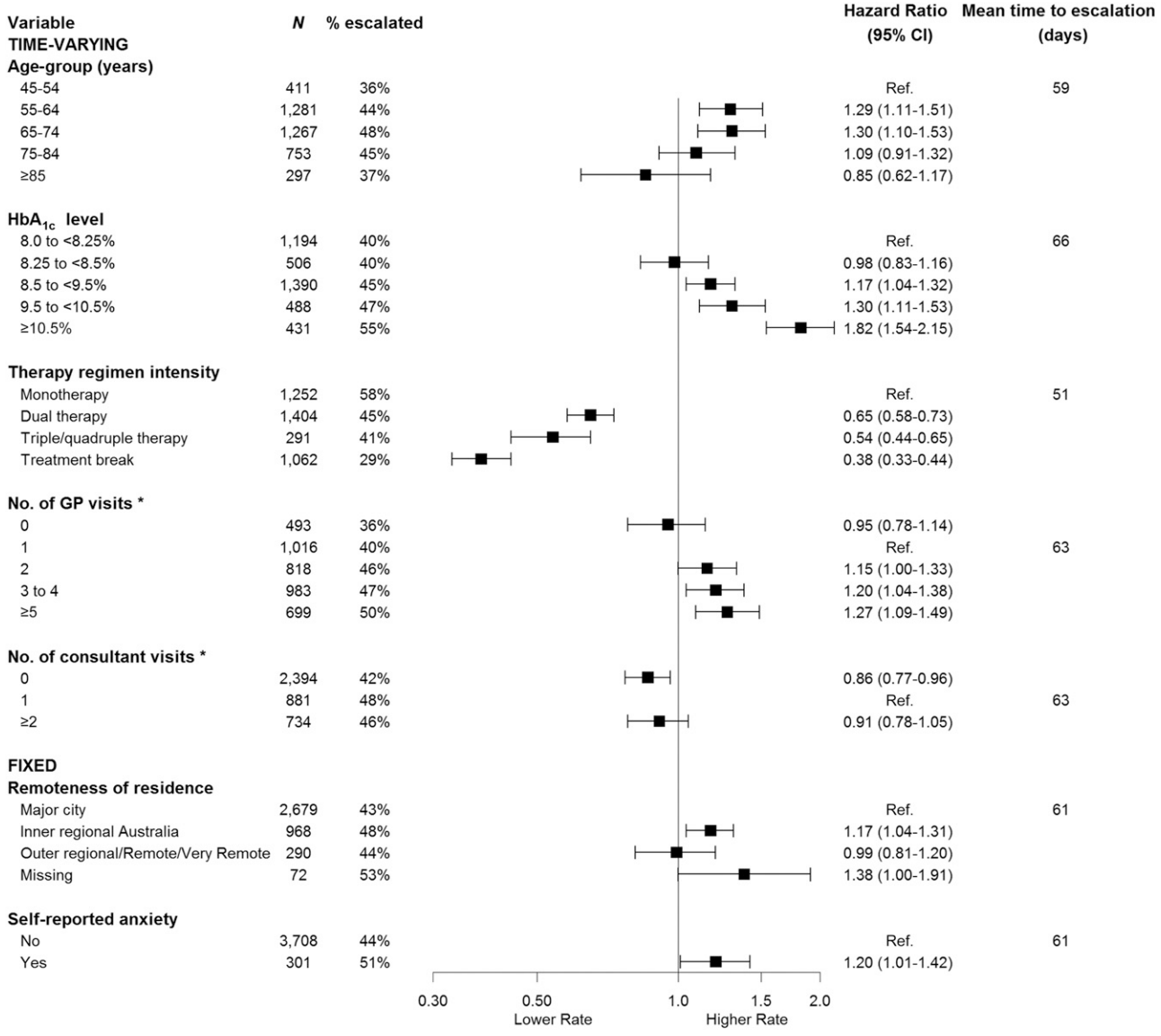

Figure 1—Results of a multivariable marginal Cox proportional hazards model showing the association between therapy escalation following an elevated HbA_{1c} and a range of factors. In Australia, remoteness of residence relates to the five Remoteness Areas defined by the Australian Bureau of Statistics to objectively categorize areas based on their relative access to services. *In the 90 days prior to the elevated HbA_{1c} result.

or who had temporarily discontinued therapy (Fig. 1).

To our knowledge, this study is the first to examine therapy escalation and clinical and sociodemographic associations in an Australian population using real-world data. Through the inclusion of a range of longitudinal data sources, we have been able to incorporate time-varying risk factors, such as HbA_{1c} level and therapy regimen intensity, into our analysis, better reflecting the longitudinal nature of diabetes management. Moreover, we examined a range of existing therapy regimens, including temporary discontinuation, increasing the generalizability of our findings to all individuals with type 2 diabetes aged ≥45 years. However, we were not able to assess dose up-titration or examine individuals' adherence to their existing regimens.

Measuring time to therapy escalation in response to an elevated HbA_{1c} is a useful indicator of quality of care of people with diabetes, and our findings can be used as a baseline for assessing future changes. The factors identified in this study can be used to identify potential interventions for promoting therapy escalation in patients with diabetes, but these should be investigated further. In addition, future studies should examine the clinical and patient-reported outcomes of therapy escalation.

Acknowledgments. The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW and partners the National Heart Foundation of Australia (NSW Division), NSW Ministry of Health, NSW Government Family and Community Services—Ageing, Carers, and the Disability Council NSW, and the Australian Red Cross Blood Service. The authors thank the many thousands of people participating in the 45 and Up Study. In addition, the authors thank Services Australia (formerly Department of Human Services) for their supply of MBS and PBS data and the private pathology companies who have contributed their data to this study. Data linkage was performed by the Sax Institute and the Centre for Health Record Linkage (CHeReL) (https://www.cherel.org.au).

Funding and Duality of Interest. The EXTEND45 Study is in part funded through peer-reviewed, unconditional grants, including an NSW Cardiovascular Research Network Development Project Grant from the National Heart Foundation of Australia (award no. 100720), a seeding GENESIS grant supported by Roche Products Pty Ltd. (grant no. FR-MIR-0095), and a Rebecca L. Cooper Grant (grant no. REB002). In addition, the EXTEND45 Study has received unconditional research grants from Eli Lilly (Australia) Pty Ltd. (grant no. PO4100294024), Merck Sharp & Dohme (Australia) Pty Ltd. (grant no. MSD_EXTEND45), and Amgen (Australia) Pty Ltd. (grant no. Amgen01). Y.X. received funding from the National Natural Science Foundation of China (grant no. 81670742) and Suzhou Municipal Science and Technology Bureau (grant ref. szxk201804) to conduct this research project. M.Ju. has received unrestricted grant support from VentureWise (a wholly owned commercial subsidiary of NPS MedicineWise) to conduct a commissioned project funded by AstraZeneca. C.P. is the current chair of the following: Kidney Health Australia, NSW Bureau of Health Information, and the NSW Cardiovascular Research Network; is a member of the international advisory board for AstraZeneca; is a member of local advisory boards for Vifor, Merck Sharp & Dohme, Boehringer Ingelheim, and Otsuka; serves on the scientific advisory board of Pharmaxis; has received travel and accommodation support from Amgen, AstraZeneca, and Roche; and has received speaker support from Amgen, AstraZeneca, Novartis, and Vifor. S.Z. has participated in the advisory board, expert committees, or educational meetings for Boehringer Ingelheim, Eli Lilly, Sanofi, Servier, AstraZeneca, Novo Nordisk, and Merck Sharp & Dohme on behalf of Monash University, with no direct financial compensation. M.Ja. is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Gambro, Baxter, CSL Behring, Amgen, Eli Lilly, and Merck; has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim, and Vifor; and has spoken at scientific meetings sponsored by Janssen, Amgen, and Roche, with any consultancy, honoraria, or travel support paid to her institution. No other potential conflicts of interest relevant to this article were reported.

Data Availability. The data sets generated during this study are not publicly available because of ethical restrictions. However, upon reasonable request, and with permission of the relevant data custodians, data may be accessed through the Secure Unified Research Environment (SURE). The appropriate steps for becoming a SURE user and accessing SURE will need to be undertaken. Readers can visit the relevant page on the 45 and Up Study website for more information.

Author Contributions. Y.X., M.Ja., and C.H. were responsible for the study concept and design. Y.X. and C.H. drafted the manuscript. All authors gave critical revision of the manuscript for important intellectual content and interpreted the data. J.B. and K.R. provided statistical analysis. M.Ja. and C.H. supervised the manuscript. C.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379

2. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (the Diabetes & Aging Study). Diabetes Care 2019; 42:416–426

3. Foote C, Hockham C, Sukkar L, et al. EXamining ouTcomEs in chroNic Disease in the 45 and Up Study (the EXTEND45 Study): protocol for an Australian linked cohort study. JMIR Res Protoc 2020;9:e15646

4. American Diabetes Association. 6. Glycemic targets: *Standards of Medical Care in Diabetes—2020*. Diabetes Care 2020;43(Suppl. 1):S66–S76

5. Hosmer D, Lemeshow S. *Applied Logistic Regression*. John Wiley & Sons, Inc., 2015