



RESPONSE TO COMMENT ON PONGRAC BARLOVIC ET AL.

## The Association of Severe Diabetic Retinopathy With Cardiovascular Outcomes in Long-standing Type 1 Diabetes: A Longitudinal Follow-up. *Diabetes Care* 2018;41:2487–2494

*Diabetes Care* 2019;42:e49–e50 | <https://doi.org/10.2337/dci18-0058>

*Drazenka Pongrac Barlovic*,<sup>1,2</sup>  
*Valma Harjutsalo*,<sup>3,4,5,6</sup> and  
*Per-Henrik Groop*<sup>3,4,5,7</sup>

We are thankful for the response from Camoin et al. (1) to our article (2) showing the association of severe diabetic retinopathy (SDR) with cardiovascular disease, including peripheral artery disease, in long-standing type 1 diabetes. Importantly, the association was present even in the absence of DKD, a well-established risk factor for cardiovascular events and premature mortality (3). Results from the French cohort of patients with type 1 diabetes further strengthen the importance of SDR as a risk factor for lower-extremity ischemia, foot ulcers, and amputations. In their cohort ( $n = 204$ ) they were able to show an association between SDR and foot ulcers after adjustment for the presence of DKD and other cardiovascular risk factors, even with shorter diabetes duration ( $21 \pm 13$  years) and shorter follow-up (7 years). Moreover, they propose that the association is mediated through peripheral neuropathy, since it was more prevalent in their patients with SDR. However, they do not present data on the association between peripheral neuropathy and cardiovascular disease, myocardial infarction, and stroke.

Similarly, data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study

reported an independent association between cardiac autonomic neuropathy and cardiovascular events, also after adjustment for albuminuria, but not specifically between peripheral neuropathy and cardiovascular events (4). In addition, data from the Joslin Diabetes Center's cohort of patients with very long type 1 diabetes duration also do not point to the association of peripheral neuropathy and cardiovascular events (5). Interestingly, however, recently published data from the Canadian Study of Longevity in Type 1 Diabetes cohort ( $n = 69$ ) show that coronary artery calcium scores were higher in patients with sensory polyneuropathy and diabetic retinopathy, but not with DKD or autonomic neuropathy (6). However, since coronary calcification scores cannot differentiate between stable and vulnerable plaques, they could not reliably predict incident acute cardiovascular events.

Associations of SDR or peripheral neuropathy with cardiovascular disease in the absence of DKD are important, as they suggest the need for continued vigilance to reduce cardiovascular risk even in the absence of DKD and in long-standing diabetes (2). Since both microvascular and macrovascular disease share similar risk factors in long-standing

diabetes (4), the independent association of isolated sensory polyneuropathy with cardiovascular disease would be of no surprise, but it has not yet been shown. Until more longitudinal and mechanistic data become available, SDR should be regarded as an independent risk factor for critical limb ischemia and foot ulcers, as well as for other types of cardiovascular disease. Therefore, regular diabetic foot screening tests in this population are of the utmost importance.

**Funding.** This research was funded by grants from the Folkhälsan Research Foundation, Academy of Finland, Wilhelm and Else Stockmann Foundation, Liv och Hälsa Society, Novo Nordisk Foundation (grant number NNF14SA0003), The Diabetes Research Foundation, and Päävikki and Sakari Sohlberg Foundation. D.P.B. was supported by the European Association for the Study of Diabetes Albert Renold Fellowship, generously offered by the European Foundation for the Study of Diabetes.

**Duality of Interest.** D.P.B. reports receiving lecture honoraria from Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Eli Lilly, Merck, Merck Sharp & Dohme, Krka, and Servier Pharma and being an advisory board member for Boehringer Ingelheim, AstraZeneca, and Novo Nordisk. P.-H.G. reports receiving lecture honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, ELO Water, Genzyme, Merck Sharp & Dohme, and Novartis and being an advisory

<sup>1</sup>University Medical Center Ljubljana, Ljubljana, Slovenia

<sup>2</sup>Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

<sup>3</sup>Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland

<sup>4</sup>Abdominal Center Nephrology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

<sup>5</sup>Diabetes and Obesity, Research Programs Unit, University of Helsinki, Helsinki, Finland

<sup>6</sup>The Chronic Disease Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland

<sup>7</sup>Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia

Corresponding author: Per-Henrik Groop, [per-henrik.groop@helsinki.fi](mailto:per-henrik.groop@helsinki.fi)

© 2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

board member for AbbVie, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

### References

1. Camoin M, Delyfer M-N, Korobelnik J-F, et al. Comment on Pongrac Barlovic et al. The association of severe diabetic retinopathy with cardiovascular outcomes in long-standing type 1 diabetes: a longitudinal follow-up. *Diabetes Care* 2018;41:2487–2494 (Letter). *Diabetes Care* 2019;42:e48. DOI: 10.23337/dc18-2202
2. Pongrac Barlovic D, Harjutsalo V, Gordin D, et al.; FinnDiane Study Group. The association of severe diabetic retinopathy with cardiovascular outcomes in long-standing type 1 diabetes: a longitudinal follow-up. *Diabetes Care* 2018;41:2487–2494
3. Groop P-H, Thomas M, Feodoroff M, Forsblom C, Harjutsalo V; FinnDiane Study Group. Excess mortality in patients with type 1 diabetes without albuminuria—separating the contribution of early and late risks. *Diabetes Care* 2018;41:748–754
4. Pop-Busui R, Braffett BH, Zinman B, et al.; DCCT/EDIC Research Group. Cardiovascular autonomic neuropathy and cardiovascular outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. *Diabetes Care* 2017;40:94–100
5. Tinsley LJ, Kupelian V, D'Eon SA, et al. Association of glycemic control with reduced risk for large-vessel disease after more than 50 years of type 1 diabetes. *J Clin Endocrinol Metab* 2017;102:3704–3711
6. Lovshin JA, Bjornstad P, Lovblom LE, et al. Atherosclerosis and microvascular complications: results from the Canadian Study of Longevity in Type 1 Diabetes. *Diabetes Care* 2018;41:2570–2578