Trends in non-coronary arterial outcomes in people with type 1 or type 2 diabetes mellitus

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Type 1 and type 2 diabetes mellitus are both associated with an increased risk of cardiovascular disease.[1–3] In this Issue of *the Lancet Regional Health—Europe*, two cohort studies investigated trends in non-coronary arterial complications in people with either type 1 (N = 34,263)[4] or type 2 diabetes mellitus (N = 655,250)[5] based on the Swedish National Diabetes Register (NDR) between 2001 and 2019. In addition, up to five age-, sex-, and county-matched individuals functioned as a general population comparison cohort.

In both studies, the authors report significant decreases in incidences of extracranial large artery disease, lower extremity artery disease, and diabetic foot disease in people with type 1 or type 2 diabetes mellitus (Table 1). Yet, both types of diabetes mellitus remain strongly associated with higher incidences of extracranial large artery disease and lower extremity artery disease compared with controls. The authors also report incidences of aortic aneurism and aortic dissection, which in general were low and stable over time in people with diabetes. Furthermore, the authors examined the relative prognostic impact of cardiometabolic risk factors and elegantly demonstrated that each cardiometabolic risk factor within target was associated with a reduced relative risk of outcomes. In summary, the two papers add valuable insights to our current understanding of the risk of non-coronary arterial complications in patients with diabetes and the prognostic importance of modifiable risk factors. However, there are two main potential limitations related to the methodology used in both studies that need to be acknowledged.

First, participants were allowed to contribute observation time for several calendar periods if they did not experience an event. Thus, a person with diabetes entered into the Swedish NDR in 2001 could contribute observation time in the 2001–2002 study period and, if not censored due to an event, would continue to contribute with observation time in the 2003–2004, 2005–2006, etc, calendar periods if no events occurred. As acknowledged by the authors, this leads to "a sequential accumulation of healthier individuals in each period. As a result, this may result in a cohort that progressively comprise individuals at lower risk."[4] This issue is likely more influential for people with type 1 diabetes mellitus who were much younger when entering the Swedish NDR than people with type 2 diabetes mellitus (mean age 33 years for the former vs 64 years for the latter).[4,5] Well-treated, compliant people with type 1 diabetes mellitus have a low risk for many years and such patients will likely contribute observation time for many of the examined calendar periods. In contrast, non-compliant people with type 1 diabetes mellitus will have a high risk of events and thus a lower risk of contributing observation time to several calendar periods. Thus, it is unclear how much of the reported lower incidence of outcomes over time that may be due to the study design. It is noteworthy that the incidences of extracranial large artery disease and lower extremity artery disease also decreased in the matched controls. Consequently, the reported decline in both types of

	Age- and sex standardized incidence rates per 100,000 person-years	
	2001–2002	2016/7–2019[a]
Extracranial large artery disease		
T1DM	87[b]	84
Controls	68	28
T2DM	170	84
Controls	80	44
Lower extremity artery disease		
T1DM	456	311
Controls	66	53
T2DM	338	190
Controls	155	61
Diabetic foot disease		
T1DM	814	77
T2DM	309	226

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. [a]For patients with T2DM, the calendar period for extracranial large artery disease and lower extremity disease is 2016–2019, for all other groups the calendar period is 2017–2019. [b]Reported as 296.5 in the paper concerning type 1 diabetes mellitus, which corresponds to the calendar period 2003-2004.[3] The standardized incidence rate was highest in 2003–2004 and declined gradually afterwards.

Table 1: **Non-coronary arterial outcomes in the first and last calendar periods.**

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artery diseases could possibly either reflect the accumulation of healthier individuals or be due to a general risk reduction in both people with diabetes and the matched controls. This should be addressed in future studies with adequate study designs.

Second, the studies included participants with large variations in the duration of diabetes rather than starting follow-up when diagnosed with diabetes.[6–8] The Swedish NDR was established in 1996. Initially, this register comprised mainly people receiving care at hospital clinics, with later expansion to include an increasing number of people managed by general practitioners. People with diabetes entered early in the register were thus selected in a different way than those enrolled later. E.g., the mean age of people with type 1 diabetes mellitus was 38 years in 2001–2002, which declined to 26 years in 2013–2014, with corresponding diabetes durations being 18 years and 8 years, respectively. This is an inherent bias caused by the way the Swedish NDR was constructed. This bias can be circumvented, for example by using registries to identify people with newly diagnosed diabetes.[6–8]

The most important and valid clinical implication of these two Swedish NDR papers is that non-arterial outcomes can be reduced by optimizing treatment of modifiable risk factors. Future studies should examine whether early initiation of available cardiovascular protective antidiabetic drugs, such as sodium-glucose cotransporter 2 inhibitors and particularly glucagon-like peptide 1 agonists, can further reduce the risk of noncoronary arterial outcomes. These drugs combine weight loss and glucose-lowering effects, and they have the potential to inhibit or delay the development type 2 diabetes as well as reduce the diabetes-associated risk of coronary and non-coronary arterial outcomes.[1,2,9] Moreover, we need additional temporal studies to confirm the observed findings accounting for the above-mentioned limitations.

Contributors

Dr. Maeng drafted this commentary, which subsequently was revised in collaboration with Dr. Gyldenkerne.

Declaration of interests

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