New-onset diabetes in hypertensive patients and mortality: timing is everything

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This editorial refers to ‘Contrasting mortality risks among subgroups of treated hypertensive patients developing new-onset diabetes’, by S. Lip et al., on page 968.

Arterial hypertension and type 2 diabetes mellitus are well known cardiovascular (CV) risk factors, which are often associated.¹ In a large, prospective cohort study including 12 550 adults, the development of type 2 diabetes was almost 2.5 times as likely in patients with hypertension than in their normotensive counterparts. It is common knowledge that prevalent and new-onset diabetes in hypertensive patients are associated with a two- to three-fold higher risk of CV disease.² Furthermore, a recent analysis of the Framingham data showed that the population with prevalent hypertension at the time of diagnosis of diabetes mellitus had higher rates of all-cause and CV mortality, thus suggesting that much of this excess risk is attributable to co-existent hypertension.³ This strong piece of evidence led to the classification of hypertensive patients with diabetes mellitus automatically at very high CV risk by ESC/ESH Guidelines.⁴ For that reason, in the past years lower blood pressure (BP) targets had been recommended for this subgroup of patients,⁵ although no evidence from randomized clinical trials supported this suggestion. Indeed, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study failed to demonstrate a significant reduction in incidence of CV events when lowering systolic BP to ≏119 mmHg in comparison with 133 mmHg in diabetic patients.⁶ The added risk portended by diabetes on top of hypertension might be related to amplification of vascular damage; indeed, both conditions are characterized by increased arterial stiffness and endothelial dysfunction, with patients with both hypertension and diabetes mellitus having a stiffer aorta and a worse endothelial function as compared with hypertensive non-diabetic patients.⁷ Furthermore, endothelial dysfunction is a determinant of aortic stiffness in hypertensive diabetic patients but not in hypertensive patients without diabetes, suggesting a role for endothelium-related mechanisms.⁸ For this reason, a number of studies investigated possible differences in vasculoprotection exerted by different glucose-lowering therapeutic agents.

A complex cause–effect relationship might be hypothesized between hypertension and diabetes. Obesity, visceral adiposity, and insulin resistance are probably the main pathogenic factors favouring the development and co-existence of both conditions, activating a cascade of pathophysiological mechanisms: inappropriate activation of the renin–angiotensin–aldosterone system, oxidative stress, low-grade inflammation, increased sympathetic nervous system activation, dysfunctional immune responses, and abnormal renal handling of sodium.⁹ Furthermore, hypertension-associated endothelial dysfunction, remodelling of small arteries and/or chronic sympathetic activation, might induce insulin resistance and diabetes, by reducing insulin delivery to muscles or by causing pancreatic microvascular dysfunction. Finally, new-onset diabetes in hypertensive patients might be the consequence of treatment with some antihypertensive drugs, namely diuretics and beta-blockers. In turn, overt diabetes might favour systolic hypertension onset and maintenance, due to accelerated large artery stiffness and hypertension secondary to chronic kidney disease (Figure 1). Thus, the co-existence of hypertension and diabetes might actually correspond to at least two different phenotypes, characterized by different temporal trajectories, pathophysiological pathways, and, possibly, CV prognosis. This interesting hypothesis is, however, difficult to demonstrate, since it requires large prospective cohort studies with several time points for outcome assessment. Furthermore, in clinical practice, the actual time of onset of this type of chronic condition is difficult to determine with a sufficient degree of certainty, and thus this might remain a rather academic issue.

In this complex framework, the work of Lip and co-workers is worthy of consideration. In this issue of the journal, Lip et al. examined diabetes-related mortality in a cohort of 15 089 hypertensive patients attending the Glasgow blood pressure clinic, a tertiary centre for the treatment of hypertension, and followed up for up to 40 years.⁰ The authors confronted this intricate issue with a pragmatic approach: hypertensive diabetic patients were classified based on diabetes onset starting from first access to the Hypertension Unit

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instead of from hypertension onset, leading to surprising results. The main finding of the study is that individuals with prevalent diabetes (diabetes diagnosis before or within 2 years after the first clinic visit), with early new-onset diabetes (NOD) (2–10 years) and late diabetes (diabetes diagnosis before or within 2 years after the first clinic visit, the higher the mortality. Indeed, the two groups, early and late NOD, exhibit relevant differences in terms of clinical characteristics, thus confirming the hypothesis of two distinct phenotypes. The early NOD group, whose prognosis is more similar to that of hypertensive patients with an established diabetes history at the first clinic visit, is characterized by higher body mass index (BMI), and lower renal function and blood glucose levels at enrolment, well before diabetes onset: these patients develop diabetes at a younger age than the late NOD group. The late NOD group is characterized by leaner individuals with a lesser degree of metabolic abnormalities at enrolment: they seem to develop diabetes at an older age and access the blood pressure clinic at a younger age, suggesting a longer hypertension duration before NOD in comparison with early NOD. One important factor is obviously that early NOD individuals, developing diabetes at a younger age, are exposed for a longer time to the hyperglycaemic environment and are more prone to develop diabetic macrovascular and microvascular complications: a longer diabetes duration is associated with higher death rates for all causes and for CV disease, regardless of age.10 However, considering only this explanation might be too simplistic: we suggest another explanation, which may connect the present observational data with pathophysiology. Early NOD patients might coincide with the ‘insulin resistance phenotype’ depicted above: these individuals might be predisposed to hypertension and diabetes onset, develop both conditions almost simultaneously, and, according to the findings of Lip et al., have a reduced life expectancy in comparison with euglycaemic hypertensive patients. Conversely, late NOD patients develop hypertension earlier in life, while diabetes occurs after a long duration of hypertension: this phenotype might correspond to a ‘hypertension-induced diabetes’, according to the above-mentioned vascular hypothesis for insulin resistance. In these individuals, diabetes might be considered as a consequence of extensive hypertensive organ damage, with global prognosis dominated by hypertension burden rather than diabetes itself. This hypothesis, suggested in a pioneering article by Anderson and Mark, is in keeping with the findings of Izzo et al., who recently demonstrated that incident diabetes in hypertensive patients is higher in patients with left ventricular hypertrophy and/or carotid atherosclerosis.

The definition of two hypertensive diabetic phenotypes might have relevant implications for their clinical management. In hypertensive patients with prevalent diabetes or early NOD, hypertension specialists should aim at achieving a tight blood glucose control and, more generally, implement a strategy to reduce global CV risk aggressively and increase life expectancy. In contrast, late NOD might not confer an added risk for CV events on top of hypertension; thus intensive glucose-lowering treatment would not be necessary. The optimal therapeutic strategy would then be an early and aggressive BP control, while intensive glucose-lowering strategies might be expensive and harmful, leading to a higher rate of hypoglycaemia and other adverse events. BP-lowering and glucose-lowering drugs with vasculoprotective effects should be preferred in these patients, while waiting for the development of drugs specifically targeting and able to reverse vascular damage.

Conflict of interest: none declared.

References


Figure 1 Complex cause–effect relationship between hypertension and diabetes. SNS, sympathetic nervous system; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species.
Abdominal aortic aneurysm and lumbar plexus palsy

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An 82-year-old man was found to have a 6 cm infra-renal abdominal aortic aneurysm (AAA) (Panel A, white arrow). Elective AAA surgery was postponed due to incidental finding of a hepatocellular carcinoma (Panel A inset, red arrow), for which he underwent successive catheter-directed embolization to good result (Panel B inset, red arrow). He lived on his own and maintained an independent lifestyle. He was therefore re-assessed for the suitability of surgical repair for AAA. Repeat imaging revealed the incidental finding of a ruptured AAA, with a large haematoma encasing the left psoas muscle along the third to fifth lumbar vertebrae (Panels B and C, yellow arrow). His abdominal examination was entirely normal.

Upon further questioning, he recalled an episode of violent coughing ~12 weeks prior. Within hours, he experienced sudden onset of intense hyperesthesia in his left scrotum. Over the following weeks, he noticed persistent numbness over the left groin and anterior upper thigh. He was referred by his GP to the neurology clinic for the assessment of this peculiar neuropathy in the interim.

In the presence of an AAA, sudden onset lumbar plexus palsy should alert the clinicians of a differential diagnosis of AAA rupture. His symptoms were due to haematoma compressing branches of the lumbar plexus, including the genital-femoral nerve which emerges onto the anteromedial surface of psoas muscle and supply the scrotal skin (genital branch) and skin of femoral triangle (femoral branch), the lateral femoral cutaneous nerve, and ilio-inguinal nerve (both emerges lateral to the psoas muscle and supply the skin of the corresponding thigh).

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