Updated classification of hypertensive retinopathy: which role for cardiovascular risk stratification?

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Cardiac and extracardiac hypertensive target organ damage (TOD) is recognized as an intermediate step in the continuum of cardiovascular disease and a powerful independent predictor of cardiovascular morbidity, mortality and all-cause deaths. Furthermore, regression or reduction of TOD is increasingly regarded as a useful intermediate endpoint for assessing the efficacy of blood pressure (BP)-lowering medications [1]. A consistent body of evidence from different clinical settings conveys the concept that a variety of biomarkers of TOD such as electrocardiographic or echocardiographic left ventricular hypertrophy, carotid intima–media thickening or plaque, reduced glomerular filtration rate, microalbuminuria, increased pulse wave velocity (PWV) and advanced microvascular retinal lesions are associated with unfavourable cardiovascular prognosis independently of confounders and traditional risk factors [2–5]. On the contrary, controversial evidence is available about the prognostic value of early retinal abnormalities in the hypertensive setting.

In this issue of the *Journal of Hypertension*, Aissopou et al. [6] report the findings of a cross-sectional study aimed at investigating the correlation of microvascular retinal alterations (i.e. generalized arteriolar narrowing, focal narrowing and arteriovenous crossings, as assessed by digital retinal images) with TOD in nondiabetic normotensive and hypertensive patients free of overt cardiovascular disease. In particular, the authors examined the association of these vascular retinal abnormalities, classified according to the traditional Keith–Wagener–Barker or the simplified Wong–Mitchell grading, with carotid-ilemoral PWV, common carotid wall cross-sectional area (CCSA) and carotid plaques in the whole-population sample and in subgroups stratified for sex and age. Before addressing the strengths and limitations of the study, previous knowledge on this issue and related topics deserves to be summarized.

Hypertensive retinopathy is a complex vascular phenotype characterized by a wide spectrum of retinal vessels changes reflecting the severity and duration of BP elevation. Three physiopathological stages of hypertensive retinopathy have been described in systemic hypertension: an early constrictive stage characterized by generalized narrowing of arteriolar diameter; an intermediate stage characterized by focal and generalized arteriolar narrowing due to intimal thickening and medial hyperplasia, resulting in arteriovenous nicking and altered arteriolar light reflexes; an exudative stage characterized by isolated or multiple alterations such as microaneurysms, flame haemorrhages, hard exudates, cotton-wool spots and papilloedema. These advanced microvascular lesions reflect severe alterations of local circulation, such as increased vascular permeability, necrosis of capillary and precapillary arteriolar wall and retinal ischemia. From a historical point of view, hypertensive retinopathy was described for the first time by Markus Gunn at the end of the nineteenth century in a group of hypertensive patients with kidney disease. The first comprehensive classification of hypertensive retinopathy was provided by Keith, Wagener and Barker five decades later [7] and was defined by four grades of retinal damage: grade 1 (narrowing), grade 2 (arteriovenous crossings), grade 3 (haemorrhages and exudates) and grade 4 (papilloedema). In their pioneering longitudinal study, the authors were able to demonstrate the adverse prognostic impact of retinal vascular injuries in 209 patients with untreated hypertension. They showed that the presence of optic disk oedema (grade 4), haemorrhages and/or exudates (grade III) was related to a 5-year survival rate of 1 and 20%, respectively, as opposed to 70 and 50% of patients with grade 1 and 2 retinopathy at the initial evaluation, respectively. The original Keith–Wagener–Barker scale has been questioned in the last three decades as this classification is not sensitive enough to differentiate grade 1 from grade 2 in clinical practice. More importantly, the lower grades of retinopathy have not been shown to be closely related to office and out-of-office BP levels as well as validated markers of TOD. Furthermore, numerous studies have shown that detection and grading of early retinal microvascular alterations, the dominant features in current clinical practice, have a limited intraobserver and interobserver reproducibility, when assessed either by...
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of TOD after adjusting for age, family history of coronary artery disease, BMI, antihypertensive and statin treatment; in subgroups analyses, a significant adjusted relation between retinopathy, PWV and CCSA was found in men but not in women, in younger (<55 years) but not in older participants; and these results were unchanged when the analysis was restricted to hypertensive patients.

Some other aspects of this study deserve to be briefly commented. First, at difference from Wong–Mitchell classification, grades 1 and 2 retinopathy defined according to Keith–Wagener–Barker scale was unable to show an independent relation with PWV and CCSA in age and sex-based analysis. In particular, no differences in TOD were observed in participants with grade 2 as compared to those with grade 1 retinopathy. Second, although the intraobserver and interobserver reproducibility of Wong–Mitchell grading system (71 and 91%) was higher than that reported for Keith–Wagener–Barker classification (64 and 88%), the level of intraobserver variability in detecting mild retinopathy remains too elevated. From these figures, it can be calculated that approximately one-third of the sample was differently categorized by two observers. Third, carotid damage was assessed by the authors as the presence of discrete plaque (i.e. intima-media thickness >1.5 mm) and common carotid remodelling (CCSA). Carotid plaque, a robust predictor of cardiovascular disease, was not independently associated with mild retinopathy in the total population as well as in subgroups. Surprisingly, no information was provided about carotid intima-media thickness, a marker of TOD with proven prognostic value according to European Society of Hypertension/European Society of Cardiology guidelines and more commonly used for risk stratification in both clinical and research settings. The lack of data addressing the association between mild retinopathy and signs of cardiac and renal TOD represents a limitation of the present study, as an electrocardiogram and a search for microalbuminuria should be performed, according to guidelines, in all hypertensive patients at the initial evaluation. It should also be noted that about a half of patients enrolled by Aissopou et al. [6] were taking antihypertensive drugs that may have affected the relationship between retinal changes and TOD. There is evidence that antihypertensive treatment may promote regression of mild hypertensive retinopathy. Diffuse or focal arteriolar narrowing, reflecting the abnormal increase in peripheral vascular resistance in untreated or suboptimal treated hypertensive patients, is known to be potentially reversible. Furthermore, some classes of BP-lowering drugs may exert favourable effects on retinal vessels as compared with others, as reported in the Anglo-Scandinavian Cardiac Outcomes Trial [15]. In this trial, patients randomized to amiodipine-based therapy showed larger arteriolar diameters than those on atenolol-based therapy.

Nonetheless, the study by Aissopou et al. [6] provides interesting data on the link between mild retinopathy signs, as assessed by an updated and simplified classification, and vascular TOD in young people. These findings are in keeping with the notion that retinal microvascular changes such as arteriolar narrowing, arteriovenous crossing and increased arteriolar reflexes are more closely correlated to BP levels and TOD in younger than in older hypertensive

traditional ophthalmology or digital retinal imaging. Finally, only few studies provided reliable evidence that the likelihood of TOD and cardiovascular disease differs between grade 1 and 2 signs. The Ibaraki Prefectural Health Study, including 87,890 individuals (29,917 men and 57,973 women) aged from 40 to 79 years, documented that a mild hypertensive retinopathy (grades 1 and 2 according to Keith–Wagener–Barker classification) was an independent predictor of cardiovascular mortality among Japanese men and women, with or without hypertension [8]. The conclusions of this study, however, have been criticized and should be taken with caution for several reasons [9,10].

First, readers assigned to retinopathy evaluation were not blinded to critical baseline characteristics of participants; second, definite signs of grade 2 hypertensive retinopathy, such as focal arteriolar narrowing, arteriovenous crossings and exaggerated arterial light reflex were not taken into account; finally, the prognostic value of grade 1 retinopathy was not confirmed in the separate analysis of the non-hypertensive fraction of the population for any study outcomes.

In order to overcome the limitations of Keith–Wagener–Barker classification, a simplified grading of hypertensive retinopathy based on two/three grades has been proposed by different authors [11,12]. In these updated classifications, diffuse and focal arteriolar narrowing as well as arteriovenous crossings are grouped in a single entity (mild retinopathy), separated from alterations because of retinovascular leakage, vessel occlusion and disk oedema, which are more closely associated with severe or accelerated hypertension. Studies investigating the prognostic value of retinal abnormalities according to this simplified classification have demonstrated that mild retinopathy is associated with a modest but significantly increased risk of incident cardiovascular events. For instance, Wong et al. [13] reported that 7-year cumulative incidence of chronic heart failure was approximately 5% in patients with normal fundoscopic examination, 8% in those with mild retinopathy and 18% in those with moderate retinopathy (i.e. microaneurysm, haemorrhage and cotton-wool spots).

At the present time, the clinical value of retinal vessel examination, even assessed with updated instruments (i.e. computerized analysis of digital photographs, scanner laser Doppler flowmetry) remains disappointingly limited in cardiovascular risk stratification [14]. On the basis of available knowledge, the 2013 European Society of Hypertension and European Society of Cardiology guidelines did not consider mild retinopathy as a specific sign of TOD and excluded fundoscopy from the list of routine workup examinations recommended for the majority of hypertensive patients (grades 1 and 2 hypertensive patients).

The report by Aissopou et al. [6] provides a new piece of evidence to the discussion on the association between mild retinopathy (defined according to Wong–Mitchell classification) and macrovascular signs of TOD (as assessed by PWV and carotid ultrasonography) in a selected group of 107 apparently healthy normotensive and hypertensive (80%) individuals. The principal findings of this study can be summarized as follows: in the whole-sample population, mild retinopathy did not correlate with any markers of TOD after adjusting for age, family history of coronary artery disease, BMI, antihypertensive and statin treatment; in subgroups analyses, a significant adjusted relation between retinopathy, PWV and CCSA was found in men but not in women, in younger (<55 years) but not in older participants; and these results were unchanged when the analysis was restricted to hypertensive patients.
patients. As a consequence, the search for mild hypertensive retinopathy in the elderly fraction of the hypertensive population has a limited value in refining cardiovascular risk stratification, because of the impact of age on retinal vessels. Future larger studies are needed to assess whether retinal digital photography and a simplified classification of retinal vascular abnormalities will improve the prediction of cardiovascular risk in routine clinical practice [16].

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Conflicts of interest

There are no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES


