Usefulness of Optic Fundus Examination With Retinography in Initial Evaluation of Hypertensive Patients

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BACKGROUND

Although international guidelines for management of hypertension recommend optic fundus examination in the initial evaluation of hypertensive patients, there have been no studies to evaluate the usefulness of retinography in this application.

METHODS

Two hundred and fifty consecutive new patients with hypertension but without known cardiovascular disease were studied. The average age was 57.2 years (s.d. 12.9) and 56% were men. The study was conducted in 14 primary care centers. Measurements included target organ damage (TOD) evaluation (electrocardiography, retinography, microalbuminuria, and serum creatinine) and blood pressure (BP) measurements. Outcome measurements were made to risk stratification according to 2003 World Health Organization and International Society of Hypertension (WHO–ISH) and 2007 European Society of Hypertension and European Society of Cardiology (ESH–ESC) guidelines, analyzed first without incorporating the retinography results and then reclassified using the retinography data.

RESULTS

Advanced retinopathy was detected in 10.8%. The risk stratification arrived at as per the WHO–ISH guidelines, and without the retinography data was: 11.4% low risk, 62.4% moderate risk, and 26.2% high risk. When retinography results were taken into account, 8% from the moderate-risk group were reclassified to the high-risk group (11.4, 54.4, and 34.2%, respectively; $P < 0.001$). Using ESH–ESC guidelines, the risk stratification without the retinography data was 0.9% reference, 11.3% low, 58.8% moderate, 21.7% high, and 7.3% very high risk. With retinography, 10% were reclassified from a lower to a higher risk group (0.9, 10.4, 51.1, 20.4, and 17.2%, respectively; $P < 0.001$).

CONCLUSIONS

As an alternative to optic fundus examination, retinography enables a more accurate cardiovascular risk stratification in the first evaluation after diagnosis of hypertension. When retinography is included in the assessment of cardiovascular risk, ~10% of patients are reclassified to a higher risk group.

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The image of the optic fundus obtained by retinography permits a direct view of the small vessels of the retina and may reveal the existence of a variety of lesions, some of which typically appear early in the course of arterial hypertension and are highly specific to this condition.[1–3]

The international guidelines continue to recommend optic fundus examination for initial evaluation of patients with hypertension, though with some variations. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure continues to consider retinopathy (in all its forms) as target organ damage (TOD).[4] The European Society of Hypertension/European Society of Cardiology (ESH–ESC, 2007) supports cardiovascular risk stratification, but takes into account only the advanced signs of damage (exudates, hemorrhages, or papilledema) as associated clinical conditions.[5] The World Health Organization/International Society of Hypertension (WHO–ISH, 2003) recommends the evaluation of the fundus to gather further data for risk stratification, so as to be able to quantify the prognosis and adopt a therapeutic approach, but these guidelines too consider only severe damage such as exudates, hemorrhages, or papilledema.[6] Also, these guidelines do not specifically address the use of retinography to gather TOD information.

Retinal images are extremely useful in the evaluation of the state of the retina, because they provide documentation and permit an estimate of retinal damage,[7] as well as a comparison, over time, of the changes produced in the retina. Moreover, retinography makes it possible to reproduce inter- and intra-observations of advanced signs of damage.[8]

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It is known that a significant percentage of patients diagnosed with arterial hypertension present with abnormalities that can be detected by retinography,[9] and that failure to carry out retinopathic examination denies patients an opportunity to avail treatment for this TOD.[10] Therefore an understanding of the state of the retina during the initial evaluation of hypertensive patients may modify the therapeutic approach. However, the usefulness of the information provided by optic fundus examination in patients with hypertension is being questioned.[11] Recent studies with retinography provide sufficient evidence clearly associating the detection of severe lesions at the optic fundus (hemorrhages, exudates, and papilledema) with a higher risk of morbidity and mortality, especially on account of stroke, regardless of other risk factors.[9,12,13]

This study assesses the usefulness of retinography and its impact on risk stratification in newly diagnosed patients with hypertension, who have no pre-existing cardiovascular disease or diabetes.

METHODS

Study population. A total of 250 patients between the ages of 15–75 years were recruited from 14 primary healthcare centers in Girona, Catalonia, Spain, between 2003 and 2005. The study included patients with clinical hypertension, defined as an average >139 mm Hg systolic blood pressure (BP) and/or >89 mm Hg diastolic BP from at least two BP measurements per visit (taken at 2-min intervals) on three consecutive days.[5] All subjects were newly diagnosed, had not received any antihypertensive treatment, and had no history of diabetes or cardiovascular disease.

The exclusion criteria were: (i) the patient's inability to perform self-monitoring of BP, in the opinion of the health professional; (ii) diabetes mellitus; (iii) secondary hypertension; (iv) prior cardiovascular disease; (v) renal or hepatic insufficiency; (vi) alcoholism or serious psychological illness; (vii) serious endocrine or hematological illness or other illness or limitation that the physician considered to be a motive for exclusion; (viii) patients who had clouded eyes or ophthalmologic diseases that could affect the interpretation of optic fundus; and (ix) lack of patient's consent.

This research is part of a validation study on self-monitoring of BP in isolated clinical hypertension (VAMPAHICA study). The details of the study have been published earlier.[14] (A list of the VAMPAHICA study researchers is provided in the **Supplementary Material** online.)

Diagnosis of clinical hypertension. Nurses conducted an initial BP measurement using OMRON 705 CP or OMRON 705 IT monitors with a cuff bladder adapted to the circumference of each patient's arm. International standard protocols were followed, and all devices were calibrated annually. Following 5 min of rest in a sitting position, two readings were taken at intervals of 2 min. If the difference between readings on the same day was >5 mm Hg, an additional measurement was taken. The BP value used in the study was the mean of all the measurements taken for each subject.

Evaluation of previous cases and TOD. The clinical variables recorded included age, gender, weight, height, body mass index, clinic BP, self BP monitoring, ambulatory BP monitoring, family and personal history, and hypertension history.

In order to achieve 24-h ambulatory BP monitoring, each participant was instructed by a nurse in the correct use of the Spacelab 90217 monitor, which was set to record BP every 20 min during the daytime (8 AM to 11 PM) and every 30 min during the night (11 PM to 8 AM).

Retinography was carried out using a non-mydriatic camera (CANON CR6-45NM, EOS D36), and retinal images were interpreted by an experienced physician who was unaware of the details relating to the patients in the study. This physician classified optic fundus lesions in the following categories: (i) alteration of the arterial vein ratio (>2/3; <2/3 and <1/2), (ii) arteriolar focal narrowing, (iii) hemorrhage, (iv) exudates (soft and/or hard), and (v) papilledema. Ambulatory BP monitoring and retinography were completed within 30 days.

The TOD variables measured were: serum creatinine (women >1.2 mg/dl, men >1.3 mg/dl), left ventricular hypertrophy (LVH) (electrocardiography criteria as per Cornell, modified by Dalfó,[15] and/or as per Sokolow–Lyon), microalbuminuria (women ≥31 mg/g, men ≥22 mg/g as per 2007 ESH/ESC guidelines),[5] and advanced optic fundus lesions (exudates, hemorrhages, and papilledema). Alteration in renal function was also calculated using the Cockroft formula, and expressed as glomerular filtrate (<60 ml/min).[16]

Microalbuminuria was determined by measuring the ratio of albumin to creatinine (milligrams of albumin/gram creatinine) in the first morning urine. A reactive strip was used for testing the urine. If the test was positive, the urine was analyzed, and the anomaly was treated. Microalbuminuria was tested for again after 15 days. A diagnosis was made when at least two out of three tests were positive.

All the patients or their legal representatives were asked to give informed consent. The study was approved by the Ethics Committee of the Girona Healthcare Institute (Spain).

Risk stratification. Patients were stratified on the basis of cardiovascular risk factors, TOD, and clinical conditions indicated in the 2003 guidelines from WHO–ISH and the 2007 guidelines of ESH–ESC. This was done first without incorporating the retinography results and then after incorporating them, reclassifying the risk strata as necessary. Finally, the number of patients whose risk assessment changed as a result of the reclassification was determined.

Statistical analysis. First, descriptive analyses were carried out for all the variables. Next we calculated the statistical significance of the change in the percentage of subjects in each risk group (according to 2003 WHO–ISH and 2007 ESH–ESC guidelines) when data provided by retinography (i.e., the presence of optic fundus damage) was subjected to bivariate nonparametric tests of equality of proportions (i.e., χ^2-tests).

The risk of retinopathy, adjusted for confounding and modifying factors, was estimated by logistic regression. The probability of advanced retinopathy was assumed to be related to hypertension status, after adjusting for microalbuminuria, sex, age, obesity, LVH, and level of physical activity. With the exception of age and microalbuminuria, which were centered (subtracted from the mean and the values considered normal for sex, respectively), the rest of the explanatory variables were categorized: degree of hypertension (moderate or severe), gender (female or male), physical activity (yes or no) body mass index (within normal range or not), and LVH (yes or no).

All models were checked for goodness-of-fit and misspecification. Particular attention was paid to the presence of heteroscedasticity, i.e., residual variance larger than nominal, because this would be a symptom of uncontrolled confounding.

This study underwent review for ethical considerations by the Institut d'Assistència Sanitària (Healthcare Institute). Consent was specifically sought from every patient.

RESULTS

Table 1 shows the characteristics of patients included in the study. Of the 250 patients with hypertension included in the study, the analysis was limited to 214 patients; 36 subjects were excluded because of lack of sufficient data to achieve proper risk stratification. Global prevalence of retinopathy with exudates or hemorrhages was 10.8% of the patients.

Table 2 shows total TOD presented by all the patients in the study and describes the different types of organ lesions: 54.6% had at least one TOD.

The stratification of risk by category, in accordance with the 2003 WHO–ISH guidelines, with and without the information provided by retinography, is shown in **Table 3**. Retinography information produced a shift of 8.0% of the total number of patients from the moderate-risk category to the high-risk category (reference category 11.4%, $P < 0.001$). **Table 4** presents the 5-category 2007 ESH–ESC risk stratification. Using the newer ESH–ESC guidelines, and adding in retinography data, 10.0% of the patients had to be reclassified from a lower to a higher risk group (reference category 0.9%, $P < 0.001$).

In multivariate analysis, the additional cardiovascular risk associated with advanced retinopathy varied in relation to: (i) gender, with risk being higher for women (odds ratio (OR) = 3.17, $P = 0.008$; 95% confidence interval (CI): 1.22–8.22); (ii) BMI, (25–30 kg/m^2 vs. normal weight or >30 kg/m^2; OR = 0.30, $P = 0.03$, 95% CI: 0.08–0.94); and (iii) arterial hypertension, with risk being marginally higher for those with a higher range of BP (grade 1: 140–159/90–99 mm Hg vs. grade 2: 160–179/100–109 mm Hg, OR = 0.46, $P = 0.08$, 95% CI: 0.15–1.40). Advanced retinopathy posed no extra cardiovascular risk in relation to: (i) the level of physical activity (yes vs. no, OR = 0.97, $P = 0.4$, 95% CI: 0.34–2.74), (ii) LVH (yes vs. no, OR = 0.80, $P = 0.3$, 95% CI: 0.24–2.66), and (iii) microalbuminuria (subtracting the results of each patient (mg/g) from the normal value for gender, OR = 0.97, $P = 0.37$, 95% CI: 0.81–1.16).

Table 1 | Baseline characteristics of all patients studied

	Hypertensive patients ($n = 250$)
Men	56.0%
Age (years)	57.2 (12.9)
Weight (kg)	76.2 (17.9)
Height (m)	1.6 (0.3)
Body mass index	28.0 (6.0)
Tobacco	15.2%
Alcohol	19.2%
Physical activity	23.6%
Cholesterol total (mg/dl)	224.0 (38.1)
HDL (mg/dl)	66.3 (38.8)
LDL (mg/dl)	138.8 (32.7)
Creatinine (mg/dl)	0.9 (0.2)
Systolic clinic blood pressure (mm Hg)	152 (15)
Diastolic clinic blood pressure (mm Hg)	89 (11)
Systolic SBPM (mm Hg)	143 (14)
Diastolic SBPM (mm Hg)	85 (10)
SBPM heart rate	72 (10)
Daytime systolic ABPM (mm Hg)	138 (13)
Daytime diastolic ABPM (mm Hg)	88 (9)
24-h Systolic ABPM (mm Hg)	134 (12)
24-h Diastolic ABPM (mm Hg)	84 (8)
Signs of organ damage	
Left ventricular hypertrophy	26.0%
Microalbuminuria (mg/g)	4.8 (8.7)
Microalbuminuria (abnormal)[a]	2.4%
GF Cockroft–Gault (ml/min)	106.5
Advanced retinopathy[b]	10.8%

Data are mean and (standard deviation if not stated otherwise).
ABPM, ambulatory blood pressure monitoring; GF, glomerular filtrate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBPM, self blood pressure monitoring.
[a]Normal values: <22 mg/g in men and <31 mg/g in women. [b]Exudates, hemorrhages or papilledema.

DISCUSSION

The TOD information provided by the optic fundus permits more accurate cardiovascular risk stratification, resulting in a change in risk status in 8–10% of patients with hypertension. Advanced signs of optic fundus damage are detected in about 10.8% of newly diagnosed patients with hypertension. This study is the first to evaluate the usefulness of optic fundus retinography in the stratification of newly diagnosed hypertensive patient in accordance with current international guidelines. Patients included in this study had never been treated for arterial hypertension, had no history of diabetes or cardiovascular disease, and were enrolled consecutively. However, the study has certain limitations. First, although

Table 2 | Target organ damage: number and types in studied patients

TOD: number found	TOD type	Percentage
None		45.4
1 TOD		35.9
	LVH	50.6
	Microalbuminuria (abnormal)	3.9
	Renal lesion[a]	24.7
	AR	20.8
>1 TOD		18.7
	LVH + Microalbuminuria	4.8
	LVH + Renal lesion	38.1
	LVH + AR	19.0
	Microalbuminuria + Renal lesion	9.5
	Renal lesion + AR	23.8
	LVH + Microalbuminuria + AR	4.8

AR, advanced retinopathy (exudates, hemorrhages, or papilledema); LVH, left ventricular hypertrophy; TOD, target organ damage.
[a]Renal lesion: creatinine (women >1.2 mg/dl, men >1.3 mg/dl) or glomerular filtrate <60 ml/min.

Table 3 | Risk stratification according to the guidelines of the 2003 World Health Organization and the International Society of Hypertension

		Without data provided by retinography (%)	With data provided by retinography (%)	*P* value
Risk stratification	Low	11.4	11.4	—
	Moderate	62.4	54.4	<0.001
	High	26.2	34.2	<0.001

Table 4 | Risk stratification according to the 2007 European Society of Hypertension/European Society of Cardiology guidelines

		Without data provided by retinography (%)	With data provided by retinography (%)	*P* value
Risk stratification	Reference	0.9	0.9	—
	Low	11.3	10.4	0.158
	Moderate	58.8	51.1	<0.001
	High	21.7	20.4	0.180
	Very high	7.3	17.2	<0.001

good results have been obtained for advanced stages of damage by inter- and intra-observation studies of reproducibility,[8] this study's reliance on interpretation by only one observer may have resulted in a subjective evaluation. Second, it is important to note that the exclusion of patients with diabetes (to avoid confounding the interpretation of retinal damage) has undoubtedly influenced the results. The mere presence of diabetes bestows a high-risk label, making the retinography of little practical use for risk stratification of this group; however, it is useful in detecting the typical complications of the illness, such as proliferative retinopathy.[5] Finally, because our study was conducted in primary care centers, it is not a population study; therefore it is not clear whether it can be generalized to other populations. However, it must be borne in mind that the subjects studied belonged mainly to semi-urban areas where the majority of the population receives healthcare in these public centers.

The prevalence of TOD in never-treated patients with essential hypertension (26% LVH and 2.4% microalbuminuria) is similar to that reported in other studies.[8,17]

Risk of advanced retinopathy was associated with sex (women), weight (overweight inferior to obesity) and—only with a marginal statistically significant association—at the levels of hypertension. Other variables, such as physical activity, microalbuminuria and LVH, were not associated with increased risk of advanced retinopathy. The physiopathological mechanisms described for advanced retinopathy and for microalbuminuria differ. Clearly, advanced retinopathy would be related to important and transitory elevation of BP,[18] whereas microalbuminuria correlates better with sustained hypertension.[19] The low incidence of microalbuminuria detection (2.4%) may also have influenced the results.

Advanced stages of optic fundus damage (exudates and hemorrhages) were present in 10.8% of the patients, which approximates to the finding of 7–9.9% prevalence reported in a recent, systematic review of literature.[11] International guidelines (the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, ESH–ESC 2007, and WHO–ISH 2003) continue to recommend optic fundus examination as a source of additional data for establishing global cardiovascular risk in hypertensive patients. Advanced stages of optic fundus damage can be considered as being the equivalent of cardiovascular disease and are an indication that treatment is mandatory.[9] However, in practice, evaluation of the extent of retinal damage is rarely carried out. In fact, the incorporation of data provided by eye fundus visualization with an ophthalmoscope is exceptional in normal clinical practice,[20] given the skill and time involved in this examination. Retinography can be a valid alternative. This technique yields objective information about abnormalities in the retinal vessels.[7] It is a quick, noninvasive, accessible, and inexpensive technique that can be carried out by hospital staff (nurses or technicians) with minimal added training. Non-mydriatic retinography does not require the use of pharmaceuticals that, even though they may permit a better view of the fundus of the eye, have potential disadvantages such as more time spent per test and possible patient discomfort and/or secondary effects.

Although its effectiveness in relation to evaluating arterial hypertension has not been established, evidence exists that photographic funduscopy with a non-mydriatic camera is an effective method of screening for diabetic retinopathy.[21] This suggests that it could also be used effectively in arterial

hypertension. Given the trend in many countries of having a retinographer in clinics, adding retinography to the initial evaluation of hypertensive patients need not represent an excessive added financial burden. Because this is a painless procedure without secondary effects, the only inconvenience to the patient would be the possible need to travel to another location for the examination.

Our study clearly demonstrates the role of fundus examination in assigning patients to the most appropriate risk group. Using the 2003 WHO–ISH guidelines, the addition of data provided by retinography changed the stratification of the moderate- and high-risk groups from 62.4 and 26.2%, respectively, to 54.4 and 34.2%, representing a significant increase in the higher risk group. Using the 2007 ESH–ESC, the reference risk groups are not modified and the high-risk group shows only a minor change when optic fundus is taken into consideration. The significant shift, however, is the reduction in the moderate-risk group (from 58.8 to 51.1%) and a resulting increase in the "very high" risk category (from 7.3 to 17.2%). Treatment for patients considered at "moderate" risk without the retinography findings would probably have been deferred when, in fact, pharmaceutical treatment should already have been started for 17 patients (under the WHO–ISH guidelines) or for 22 patients (using ESH–ESC guidelines).

The classification of high-risk patients during initial evaluation of all diagnosed patients with hypertension is, therefore, influenced by TOD[22] and, among these considerations, an evaluation of optic fundus damage is indispensable. It is true that if TOD tests with higher sensitivity and specificity are used, the usefulness of the retinography exam would be lessened. For example, echocardiography would detect LVH more effectively than the electrocardiogram; ultrasonography could detect carotid intima-media thickness, which was not included in our study. However, given their high cost, these techniques are not routinely available in current clinical practice and even less so in primary care settings. On the other hand, retinography is readily available to primary care physicians because of its routine use in screening for diabetic retinopathy. In any case, our findings show that, in the absence of more sensitive—and more expensive—techniques, a diagnosis that does not include optic fundus is too limited for classifying cardiovascular risk correctly.

Systems are now being developed that permit computerized representation of artery-vein diameters, thereby facilitating a more objective classification of retinal damage caused by hypertension.[23–25] Future developments may result in the evaluation of optic fundus damage by means of retinography with computer modeling of the damage in patients with hypertension. Computerized measurement removes all subjectivity from the interpretation of images. Although our study does not compare retinography with standard funduscopy, our findings suggest that it can be an alternative to funduscopy in the future for initial evaluation of patients with hypertension.

On the basis of these findings, it seems useful to recommend optic fundus examination, if possible with non-mydriatic retinography, in the initial evaluation of patients with hypertension. The information from such an examination would enable clinicians to detect advanced stages of optic fundus damage (equivalent to cardiovascular disease). It would also enable a more accurate cardiovascular risk stratification which, in turn, can guide treatment decisions in clinical practice.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ajh

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