Hypertensive retinopathy and incident coronary heart disease in high risk men

B B Duncan, T Y Wong, H A Tyroler, C E Davis, F D Fuchs

Background/aim: Although routine ophthalmoscopy is recommended in the evaluation of people with hypertension, the prognostic significance of retinopathy is unknown. The purpose of this study is to determine if hypertensive retinopathy predicts coronary heart disease (CHD).

Methods: A prospective cohort study involving 560 hypertensive, hyperlipidaemic, middle aged men enrolled in the Lipid Research Clinic’s Coronary Primary Prevention Trial. Signs of hypertensive retinopathy (generalised and focal arteriolar narrowing, arteriovenous nicking, widened arteriolar light reflex, retinal haemorrhage and exudates, microaneurysms, and disc swelling) were evaluated by direct fundoscopy during a baseline examination by study physicians. Incident CHD events were ascertained from hospital records, necropsy reports, and death certificates, and reviewed by a masked panel of cardiologists.

Results: There were 51 definite CHD events (definite CHD deaths or myocardial infarctions) during a median follow up of 7.8 years. After adjusting for age, blood pressure, electrocardiographic manifestations of left ventricular hypertrophy, cholesterol levels and treatment, glucose and creatinine levels, and smoking status in proportional hazards analysis, the presence of hypertensive retinopathy predicted a doubling of the risk of definite CHD events (relative risk 2.1; 95% confidence interval (CI) 1.0 to 4.2). The presence of either generalised or focal arteriolar narrowing predicted almost a tripling of the risk (relative risk 2.9; 95% CI 1.3 to 6.2). Associations were similar for stage 1 hypertension (systolic and diastolic blood pressures of 140–159 and 90–99 mm Hg, respectively) and for other CHD end points.

Conclusion: Hypertensive retinopathy predicts CHD in high risk men, independent of blood pressure and CHD risk factors. The data support the concept that retinal microvascular changes are markers of blood pressure damage and may be useful in risk stratification and in the tailoring of hypertension treatment decisions.

The purpose of this study was to investigate whether hypertensive retinopathy, as diagnosed by physicians using direct ophthalmoscopy, predicts the long term incidence of CHD, independent of blood pressure and other cardiovascular risk factors. Hypertensive men participating in the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) provided the basis for this investigation.

METHODS

Study population

The LRC-CPPT cohort and procedures have been described elsewhere. Briefly, between 1973 and 1976, a total of 3806 men aged 35–59 years with type II-a hyperlipidaemia (total cholesterol > 6.85 mmol/l or 265 mg/dl, low density lipoprotein cholesterol (LDL-cholesterol) > 4.91 mmol/l or 190 mg/dl, and triglycerides <3.39 mmol/l or 300 mg/dl), and without clinically apparent CHD were randomised into two treatment groups, one receiving cholestyramine resin and the other an inert placebo. Though recruitment involved both clinical and community based approaches, most participants were recruited through community based strategies. Additional exclusion criteria included blood pressure > 180/120 mm Hg at one of the four prerandomisation visits, or =160/105 mm Hg at more than one of the last three of these prerandomisation visits; the use of antihypertensive medication, a history of stroke or transient ischaemic attack; significant peripheral vascular disease (previous surgery or symptoms limiting treadmill examination); aortic aneurysm; diabetes mellitus (fasting glucose > 130 mg/dl or receiving insulin or oral hypoglycaemics); thyroid disease; nephrotic syndrome; the
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Definitions and statistical analysis

The primary end point in this analysis is a definite CHD event, defined as either a definite CHD death or a definite myocardial infarction. Additionally, the LRC classified suspected CHD events and any coronary event. \(^{21-24}\) Individual retinal lesions were analysed separately, and an aggregate variable, any retinopathy, was defined as the presence of any of the above mentioned specific retinal lesions. A separate aggregate retinopathy variable was created excluding a widened light reflex, because this was felt to be the most subjective of all the retinal signs. Cox proportional hazards regression models \(^{25}\) were constructed to estimate the relative risk (RR) of CHD, in the presence or absence of retinopathy, adjusting for (1) age, (2) age and hypertension indicators (systolic blood pressure, diastolic blood pressure, creatinine levels, and left ventricular hypertrophy score, based on electrocardiographic findings \(^{26}\)), and (3) age, hypertension indicators, and other CHD risk factors used in risk stratification of hypertensive individuals (total cholesterol, LDL-cholesterol, high density lipoprotein (HDL)-cholesterol, current or ex-smoking status, and fasting glucose levels at baseline) as well as cholesterol treatment status. These were selected for inclusion in the models as they are risk factors that might be already considered in the management decision to treat a hypertensive patient, based on current recommendations. \(^{27}\) Proportional hazards assumption was visually verified by plotting log of cumulative hazard function comparing presence or absence of any retinopathy over the 7.8 years of follow up. Next, analyses were repeated in men with stage 1 hypertension (defined as systolic blood pressure of 140–159 and diastolic blood pressure of 90–99 mm Hg) and for other CHD end points (definite CHD deaths, definite myocardial infarction, suspected and definite CHD, and any coronary event). Finally, the principal retinal variables were entered simultaneously in a model to evaluate whether the predictive ability of each retinal lesion was independent of that of the others.

RESULTS

Of the 560 men included in this study, 498 (88.9%) had stage 1 hypertension (140–159/90–99 mm Hg) and 62 (11.1%) stage 2 (160–169/100–109 mm Hg) disease. At baseline, 65 (11.6%) participants had signs of retinopathy. Of the specific lesions detected, 32 (5.7%) had generalised arteriolar narrowing, eight (1.4%) focal arteriolar narrowing, arteriovenous nicking, widened arteriolar light reflex, retinal haemorrhage and exudates, microaneurysms and disc swelling. Hypertensive retinopathy was defined to include the presence of any one of the above lesions.

### Table 1 Baseline characteristics comparing men with definite CHD (n=51) versus those without definite CHD (n=509), participating in the Lipid Research Clinics Coronary Primary Prevention Trial

<table>
<thead>
<tr>
<th>Characteristic at baseline</th>
<th>Definite CHD</th>
<th>No definite CHD</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.3 (0.9)</td>
<td>48.9 (0.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>139.3 (1.3)</td>
<td>137.7 (0.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>92.2 (0.8)</td>
<td>92.7 (0.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>299.9 (4.6)</td>
<td>295.1 (1.4)</td>
<td>0.65</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>214.8 (4.4)</td>
<td>215.7 (1.4)</td>
<td>0.85</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>42.1 (1.6)</td>
<td>46.0 (0.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.03 (0.02)</td>
<td>1.03 (0.01)</td>
<td>0.83</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>98.9 (1.4)</td>
<td>100.5 (0.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Average cigarettes smoked‡</td>
<td>29.3 (2.9)</td>
<td>24.2 (1.2)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*SE = standard error.
†p Values are based on age adjusted comparison of mean values between men with versus without definite CHD (except for age).
‡Excluding never smokers.
Table 2  Age adjusted relative risk (RR) of coronary heart disease (CHD) death or myocardial infarction (MI), by the presence of retinal abnormalities, among hypertensive participants of the LRC-CPPT

<table>
<thead>
<tr>
<th>Retinal abnormalities</th>
<th>Death or MI</th>
<th>MI only</th>
<th>Death or MI in men with stage 1 hypertension</th>
<th>Definite or suspected CHD</th>
<th>Any coronary event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any retinopathy</td>
<td>2.2 (1.1 to 4.3)</td>
<td>2.1 (1.0 to 4.2)</td>
<td>2.0 (0.9 to 4.2)</td>
<td>1.9 (0.9 to 4.2)</td>
<td>2.1 (1.0 to 4.5)</td>
</tr>
<tr>
<td>Any retinopathy except widened light reflex</td>
<td>2.2 (1.0 to 4.6)</td>
<td>2.0 (1.0 to 4.3)</td>
<td>1.9 (0.8 to 4.3)</td>
<td>1.7 (0.7 to 4.1)</td>
<td>2.2 (1.0 to 5.0)</td>
</tr>
<tr>
<td>Arteriolar narrowing</td>
<td>3.3 (1.5 to 6.9)</td>
<td>2.9 (1.3 to 6.2)</td>
<td>2.8 (1.2 to 6.4)</td>
<td>2.4 (1.0 to 5.8)</td>
<td>3.1 (1.3 to 7.1)</td>
</tr>
<tr>
<td>Generalised only</td>
<td>2.8 (1.2 to 6.5)</td>
<td>2.5 (1.1 to 5.9)</td>
<td>2.2 (0.8 to 5.8)</td>
<td>1.9 (0.7 to 5.2)</td>
<td>2.5 (0.9 to 6.5)</td>
</tr>
<tr>
<td>Generalised focal</td>
<td>1.9 (0.6 to 6.2)</td>
<td>2.1 (0.6 to 6.9)</td>
<td>1.5 (0.4 to 6.3)</td>
<td>1.6 (0.4 to 6.9)</td>
<td>3.3 (1.0 to 10.9)</td>
</tr>
<tr>
<td>Widened light reflex</td>
<td>1.6 (0.5 to 5.3)</td>
<td>1.8 (0.5 to 6.1)</td>
<td>1.8 (0.6 to 6.0)</td>
<td>2.2 (0.6 to 7.6)</td>
<td>1.6 (0.5 to 5.2)</td>
</tr>
</tbody>
</table>

Figures are age adjusted RRs. Figures in parentheses denote 95% confidence intervals.

Table 3  Multivariate relative risk (RR) of definite coronary heart disease (CHD) death or myocardial infarction (MI), by the presence of retinal abnormalities, adjusted for hypertension† and other CHD risk factors‡, among hypertensive participants of the LRC-CPPT

<table>
<thead>
<tr>
<th>Retinal abnormalities</th>
<th>Death or MI</th>
<th>MI only</th>
<th>Death or MI in men with stage 1 hypertension*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any retinopathy</td>
<td>3.1 (1.4 to 6.8)</td>
<td>2.7 (1.2 to 5.9)</td>
<td>2.6 (1.1 to 6.3)</td>
</tr>
<tr>
<td>Any retinopathy except widened light reflex</td>
<td>1.6 (0.5 to 5.3)</td>
<td>1.7 (0.5 to 5.8)</td>
<td>1.3 (0.4 to 4.5)</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>1.1 (0.3 to 3.7)</td>
<td>1.3 (0.4 to 4.7)</td>
<td>1.2 (0.3 to 5.3)</td>
</tr>
</tbody>
</table>

*Defined by systolic and diastolic blood pressure levels of 140–159 and 90–99 mm Hg, respectively.
†Adjusted for age, systolic and diastolic blood pressure, creatinine levels, and left ventricular hypertrophy score at baseline.
‡Adjusted for other cardiovascular risk factors (RR of 2.1, 95% CI 1.0 to 4.2) and was similar to that found for the subcategory definite myocardial infarction alone. Likewise, the associations did not change after excluding those with only a widened light reflex, and were stronger for arteriolar narrowing (multivariate RRs of 2.9 for any narrowing and 2.5 for generalised narrowing, respectively). When the analysis was confined to men with stage 1 hypertension, the associations were of similar strength.

Table 4  Multivariate relative risk (RR) of definite coronary heart disease (CHD) death or myocardial infarction (MI) by individual retinal abnormalities when adjusted simultaneously for other retinal abnormalities, for hypertension† and other CHD risk factors‡, among hypertensive participants of the LRC-CPPT

<table>
<thead>
<tr>
<th>Retinal abnormalities</th>
<th>Death or MI</th>
<th>MI only</th>
<th>Death or MI in men with stage 1 hypertension*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised or focal arteriolar narrowing</td>
<td>3.1 (1.4 to 6.8)</td>
<td>2.7 (1.2 to 5.9)</td>
<td>2.6 (1.1 to 6.3)</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>1.6 (0.5 to 5.3)</td>
<td>1.7 (0.5 to 5.8)</td>
<td>1.3 (0.4 to 4.5)</td>
</tr>
<tr>
<td>Widened light reflex</td>
<td>1.1 (0.3 to 3.7)</td>
<td>1.3 (0.4 to 4.7)</td>
<td>1.2 (0.3 to 5.3)</td>
</tr>
</tbody>
</table>

*Defined by systolic and diastolic blood pressure levels of 140–159 and 90–99 mm Hg, respectively.
†Adjusted for age, systolic and diastolic blood pressure, creatinine levels, and left ventricular hypertrophy score at baseline.
‡Adjusted for other factors plus total cholesterol, LDL-cholesterol, HDL-cholesterol, cholesterol treatment status, current or ex-smoking status, and fasting glucose levels at baseline. Figures in parentheses denote 95% confidence intervals.
Additional analyses were performed for other CHD end points, with similarly consistent results. For example, arterio-
lar narrowing predicted a higher risk of definite CHD deaths (age adjusted RR of 4.2; 95% CI 1.2 to 15.5) and any coronary
events (multivariate RR 1.7; 95% CI 1.0 to 2.8). On the other hand, for non-CHD deaths (n=13), no associations were
found. Finally, in models with all retinal variables entered simultaneously (Table 4), generalised or focal arteriolar
narrowing independently predicted a higher rate of definite CHD, other abnormalities predicting small, but not statisti-
cally significant, additional risk.

DISCUSSION

Hypertensive retinopathy consists of a spectrum of retinal vascular changes that are pathologically related to both tran-
sient and persistent microvascular damage from elevated blood pressure. The relation between blood pressure and
the presence and severity of these changes are well established, and confirmed in several large population based
studies. The important issue of the prognostic significa-
cance of this retinopathy, however, has remained unclear. Does it merely reflect blood pressure levels (thus, providing no
additional information for the management of hypertension over that obtained by measuring blood pressure); or does it offer important predictive information about cardiovascular health, beyond blood pressure measurement?

In this cohort of hypertensive, hyperlipidaemic, middle aged US men, the presence of retinopathy, as detected through
a standard direct ophthalmoscopic examination performed by
non-ophthalmologists, was associated with a twofold higher
risk of CHD death or myocardial infarction, independent of systolic and diastolic blood pressure, left ventricular hypertro-
phy, creatinine levels, cholesterol levels and treatment, glucose
levels, and smoking status. In fact, arteriolar narrowing, whether generalised or focal, was independently associated
with a nearly three times higher risk of CHD. The higher risk
persisted with diverse CHD end points, including definite CHD
deaths, definite myocardial infarction, suspected and definite
CHD, and any coronary event. Perhaps more importantly, the higher risk was also seen when analyses were restricted to
those with only stage 1 hypertension, suggesting that retinal
lesions are useful predictors even in people without severe
hypertension. Although individual lesions had different strengths of association—strongest for arteriolar narrowing,
weaker (and statistically non-significant) for arteriovenous
narrowing independently predicted a higher rate of definite
CHD, other abnormalities predicting small, but not statisti-
cally significant, additional risk.

Risk in Communities Study.

The current literature provides limited and inconsistent data on the association between retinopathy and either cardio-
vascular disease or cardiovascular mortality. Some studies have indicated that retinal changes may be associated
with CHD even in people without hypertension. In a cross sec-
tional study of 70 non-diabetic and non-hypertensive subjects
undergoing coronary angiography, retinal lesions were associ-
ated with prevalent cardiovascular disease or cardiovascular mortality. Although numerous studies have docu-
mented associations between retinopathy and CHD in hypertensive individu-
als, these studies have significant limitations. These include possible inapplicability to current populations (for example, only one case in our cohort met the stage 3 hypertensive retinopathy definition proposed by Keith et al), inadequate evaluation of specific cardiovascular outcomes and lack of control for possible confounders. The current LRC study show that hypertensive/arteriosclerotic retinopathy is a predictor of CHD in high risk hypertensive men, independent of the increased risk associated with blood pressure level and other CHD risk factors.

A number of important limitations of this study should be mentioned. Firstly, it should be re-emphasised that the popu-
lation was non-randomly selected, having been derived from a multicentre clinical trial, and consisted of hyperlipidaemic,
middle age white men. Thus, caution should be taken when extending these findings to other segments of the popu-
lation—those without hyperlipidaemia, older and younger age groups, women, other ethnic groups, etc. However, the fact that the association was minimally confounded by the presence of other risk factors (lipid levels, smoking, etc) and that cross sectional associations in the Nhanes study were present in a representative sample of US males and, if anything, greater in a representative sample of US women, supports generalisation beyond those who par-
ticipated in the trial. Secondly, medical advances in the recog-
nition and treatment of hyperlipidaemia and hypertension, by altering the clinical course of these conditions, may have altered somewhat the predictive ability of retinal findings to current clinical practice. Thirdly, retinal assessment was performed using direct ophthalmoscopy or undilated eye by
non-ophthalmologists. Non-standardised direct ophthalmo-
scopic examination by physicians has been suggested to be less reliable, and to compare unfavourably with standard-
ised photographic retinopathy grading systems, such as those used in the Beaver Dam Eye Study and the Atherosclerosis Risk in Communities Study. Finally, even though subjects with prevalent cardiovascular disease, repeated blood pressure measurement 160/105 mm Hg, or using antihypertension medication were excluded from the study, study physicians did review blood pressure and perform a medical history ori-
ented toward cardiovascular disease immediately before the
retinal examination. This knowledge could have influenced their determination of retinal findings. However, that our findings remained significant after adjustment for blood pressure level and the presence of other cardiovascular risk factors makes a resultant measurement bias less likely.

Significant strengths of this study should also be empha-
sised. Firstly, while standardised photographic grading in epi-
demiological research studies are inherently more valid and
precise, they are currently not widely used for risk stratifica-
tion in hypertensive individuals. In this regard, the lack of
standardisation and quality control of the retinal examination
should make our results clinically more relevant to standard
medical practice. Secondly, cardiovascular outcomes in the
LRC-CPT study were rigorously validated and documented
throughout the trial and follow up. Blood pressure and
Nevertheless, these results are consistent with recent data that define their prognostic significance more precisely. In conclusion, in hypertensive, hyperlipidaemic men, the presence of hypertensive retinopathy was associated with a twofold higher risk of CHD developing over a median of 7.8 years, independent of blood pressure levels and other coronary risk factors. Further studies of retinal microvascular abnormalities, perhaps with more objective methods such as retinal photography, and in populations that are more representative of patients seen in current clinical practice, are indicated to define their prognostic significance more precisely. Nevertheless, these results are consistent with recent data that hypertensive retinal microvascular changes predict stroke, and support the current recommendation in the use of direct retinal examination for cardiovascular risk stratification.

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