Although high blood pressure (BP) is a strong risk factor of ischemic heart disease (IHD), lowering BP in patients with hypertension has not produced the expected reductions in morbidity and mortality from IHD. This paradox was highlighted by the results of the Hypertension Optimal Treatment (HOT) Study. In the HOT study, drug-treated hypertensive patients had the same risk of IHD during the study period whether they had a diastolic blood pressure (DBP) of 105 mm Hg or 75 mm Hg, and they basically had the same risk of IHD whether they had a systolic blood pressure (SBP) of 170 mm Hg or 120 mm Hg.

As a group, patients with high BP have the metabolic syndrome X, a cluster of multiple interrelated abnormalities in glucose and lipid metabolism that tend to increase their risk of IHD. It is believed that resistance to insulin-stimulated glucose uptake with compensatory hyperinsulinemia is the primary culprit in the metabolic syndrome X. It has been proposed that it is the presence of this cluster of risk factors for IHD in patients with hypertension that explains why interventions directed solely to the lowering of BP has had relatively little beneficial effect on risk of IHD. However, this hypothesis has not yet been tested in a prospective study.

In the Copenhagen Male Study (CMS), we found that the characteristic dyslipidemia seen in subjects with the metabolic syndrome X, that is, high plasma triglycerides (TG) and low HDL cholesterol, is an important risk factor of IHD. The present analysis was initiated to test the hypothesis that the level of BP would be less predictive of risk of IHD in those with high TG/low HDL cholesterol, the characteristic dyslipidemia in the metabolic syndrome X, than in those without.

Methods

Study Population

We have described the methods used in the CMS in greater detail elsewhere. The CMS began in 1970 as a cardiovascular study of 5249 men. From 1985 to 1986, a new baseline was established that was used for the present study. All survivors from the 1970 study were traced by means of the Danish Central Population Register. Between June 1985 and June 1986, all survivors (except 34 emigrants) from the original cohort were invited to take part in this study. Three thousand three hundred eighty-seven (75%) men agreed to participate in the study, and they gave informed consent. Their mean age was 63 years (range 53 to 74 years). Each subject was interviewed by a physician (H.O.H.) in regard to a previously completed questionnaire, and height, weight, and blood pressure measurements were performed. A venous blood sample for lipid measurements was taken after the subjects had fasted for 12 hours.

Men with a history of acute myocardial infarction (AMI), angina pectoris, stroke, or intermittent claudication were excluded from the follow-up study. Before the start of the study, hospital records were checked for all men who reported admission to a hospital because of AMI. Information on angina pectoris, stroke, and intermittent claudication was established from the questionnaire. Three hundred

Key Words: coronary disease ■ blood pressure ■ lipids ■ lipoproteins ■ risk factors
TABLE 1. Clinical, Lifestyle, and Other Characteristics According to Level of SBP in Men Taking No Drugs to Lower BP

<table>
<thead>
<tr>
<th>Variables</th>
<th>&lt;120 mm Hg, n=1399</th>
<th>120–140 mm Hg, n=967</th>
<th>&gt;140 mm Hg, n=253</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>6.43 (1.09)</td>
<td>6.55 (1.08)</td>
<td>6.55 (1.11)</td>
<td>0.006</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>4.42 (1.03)</td>
<td>4.42 (1.05)</td>
<td>4.39 (1.06)</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.37 (0.35)</td>
<td>1.37 (0.36)</td>
<td>1.38 (0.37)</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.38 (0.70)</td>
<td>1.62 (1.31)</td>
<td>1.65 (1.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combined high TG/low HDL-C</td>
<td>15.9%</td>
<td>19.4%</td>
<td>21.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use, beverages/wk</td>
<td>16.7 (13.4)</td>
<td>18.0 (13.7)</td>
<td>20.3 (15.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>63%</td>
<td>51%</td>
<td>47%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity, &lt;4 h/wk</td>
<td>45%</td>
<td>46%</td>
<td>48%</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical/paraclinical factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.9 (3.0)</td>
<td>25.9 (3.1)</td>
<td>26.4 (3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>107 (9)</td>
<td>128 (6)</td>
<td>150 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>66 (9)</td>
<td>76 (10)</td>
<td>82 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIDDM</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>Other characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low social class</td>
<td>51%</td>
<td>49%</td>
<td>52%</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>62.1 (5.0)</td>
<td>63.0 (5.2)</td>
<td>63.6 (5.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean (SD) or frequencies in percent. P values of test for linearity in ANOVA or Kendall’s Tau for trend.

End Points

In 1995, a register follow-up was performed on morbidity and mortality between 1985 to 1986 and December 31, 1993. All men who had taken part in the 1985 to 1986 examination were traced from registers. Information on hospital admissions and death certificate diagnoses within the follow-up period were obtained. We used the diagnoses from official national registers. IHD diagnoses accepted were codes 410 to 414 (International Classification of Diseases, 8th revision). Previous studies have demonstrated a high validity of Danish National registers.21–25

Statistical Analysis

Variables of interest were expressed as mean±SD or frequencies in percent. The study population was divided into various subgroups according to (1) SBP <120, 120 to 140, >140 mm Hg; (2) DBP <75, 75 to 90, >90 mm Hg; (3) presence of high TG/low HDL cholesterol, belonging to both the highest third of TG levels (>1.59 mmol/L) and lowest third of HDL cholesterol levels (<1.18 mmol/L) in the population; and (4) taking drugs to lower BP. Differences between groups were tested by ANOVA, Student’s t test, χ² test for heterogeneity, or Kendall’s Tau B test for trend when appropriate. The simultaneous contribution of several factors to the risk of IHD was analyzed with multiple logistic regression models and the maximum likelihood ratio method. All calculations were performed with the SPSSPC+ statistical software for Windows.26–27

A P≤0.05 was considered significant unless otherwise stated. The study was approved by the Ethics Committee for Medical Research in the county of Copenhagen.

Results

Of the 2906 men eligible for the study, 347 reported taking medication to lower BP. Nearly 67% of these men used diuretics, ≈34% used diuretics only, 20% used diuretics in
Lifestyle factors

- Alcohol use, beverages/wk
  - Men taking antihypertensive medication: 19.8 (16.4)
  - Others: 17.6 (13.8)
  - P < 0.001
- Smoking
  - Men taking antihypertensive medication: 41%
  - Others: 57%
  - P < 0.001
- Physical activity, <4 h/wk
  - Men taking antihypertensive medication: 55%
  - Others: 46%
  - P = 0.001

Clinical/paraclinical factors

- Body mass index, kg/m²
  - Men taking antihypertensive medication: 27.8 (4.2)
  - Others: 25.4 (3.1)
  - P < 0.001
- DBP, mm Hg
  - Men taking antihypertensive medication: 81 (12)
  - Others: 71 (11)
  - P < 0.001
- NIDDM
  - Men taking antihypertensive medication: 4%
  - Others: 2%
  - P = 0.003

Other characteristics

- Low social class
  - Men taking antihypertensive medication: 52%
  - Others: 50%
  - NS
- Age, y
  - Men taking antihypertensive medication: 63.6 (5.2)
  - Others: 62.7 (5.1)
  - P = 0.002

TABLE 3. Crude Cumulative Incidence (%) and Relative Risk of IHD According to Levels of SBP and Presence of High TG/Low HDL-C Versus Others in the Entire Population

<table>
<thead>
<tr>
<th>SBP, mm Hg</th>
<th>High TG/Low HDL-C</th>
<th>Others</th>
<th>High TG/Low HDL-C</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>12.5% (30/241)</td>
<td>5.2% (60/1162)</td>
<td>1†</td>
<td>1†</td>
</tr>
<tr>
<td>120–140</td>
<td>12.9% (33/255)</td>
<td>8.0% (72/901)</td>
<td>1.1 (0.6–1.9)</td>
<td>1.6 (1.1–2.4)‡</td>
</tr>
<tr>
<td>&gt;140</td>
<td>10.0% (8/80)</td>
<td>9.7% (26/267)</td>
<td>0.9 (0.4–2.2)</td>
<td>2.2 (1.4–3.6)‡</td>
</tr>
<tr>
<td>P=NS</td>
<td>(Trend test)</td>
<td>P=0.001</td>
<td>(Trend test)</td>
<td>(Trend test)</td>
</tr>
</tbody>
</table>

Measurements of high TG/Low HDL-C were triglycerides >1.59 mmol/L and HDL cholesterol <1.18 mmol/L.

*Confounders included age, total cholesterol, BMI, alcohol consumption, smoking, physical activity, NIDDM, and social class.
†Reference group in each category. ‡P<0.05 compared to reference group.
risks of IHD were independent of the level of DBP, although the relationship tended to resemble a U curve. In the rest of the study population, there was an increase in risk of IHD with increasing DBP that remained borderline significant after adjustment for the other major risk factors of IHD. Excluding subjects with ECG signs of LVH, strain, and silent ischemia did not change the results presented in the overall section of Table 5.

Table 6 shows the absolute risk of IHD according to DBP and presence of high TG/low HDL cholesterol in untreated men and in men taking antihypertensive medication, respectively. In untreated men, the results basically corresponded to the results from the entire study population. In drug-treated men with high TG/low HDL cholesterol, the absolute risk of IHD was substantially higher with a DBP <75 mm Hg, and this relationship remained significant after adjustment of the other major risk factors of IHD. In drug-treated men without high TG/low HDL cholesterol, the absolute risk of IHD was independent of the level of DBP.

In the entire study population, in subjects with high TG/low HDL cholesterol, the absolute risk of IHD was similar whether they had SBP >140 mm Hg and DBP >90 mm Hg or SBP <120 mm Hg and DBP <75 mm Hg, 11.1% versus 13.8%, respectively. In subjects without this dyslipidemia, the corresponding figures were 8.9% versus 4.9%.

Finally, we looked at the relationship between the lipid data from 1985 to 1986 and the BP values obtained from 1970 to 1971 when the CMS was initiated. Again, in men with high TG/low HDL cholesterol, the risk of IHD was not directly related to the level of SBP, whereas that was clearly the case in the rest of the study population (data not shown). With respect to DBP, men with high TG/low HDL cholesterol had a slightly higher risk of IHD with increasing DBP, but the relative increase in risk with increasing DBP from <80 to >90 mm Hg was ≈25% of the increase seen in men without high TG/low HDL cholesterol (data not shown).

**Discussion**

**Main Results**

The major new finding in our study of middle-aged and elderly white men who were free of overt cardiovascular diseases at baseline was that the risk of IHD in subjects with high TG/low HDL cholesterol was not directly related to the level of SBP or DBP and that the previously described U-curved relationship between risk of IHD and level of treated DBP was only found in men with high TG/low HDL cholesterol. Because in BP-lowering trials investigators have not looked for special treatment effects in subgroups of hypertensive patients with and without this dyslipidemia, our findings may offer a possible explanation of the apparent paradox that lowering BP has not produced the expected reduction in risk of IHD in patients with hypertension.

**Potential Bias and Study Limitations**

Could our findings be the result of bias? In a previous paper we discussed the importance of validity of data and reporting bias. In the present cohort, well-known contributing factors to high BP such as age, alcohol use, physical inactivity, obesity, and a history of NIDDM were also highly correlated

**TABLE 4. Crude Cumulative Incidence of IHD According to Levels of SBP and Presence of High TG/Low HDL-C Versus Others According to Medical Treatment for High BP**

<table>
<thead>
<tr>
<th>SBP, mm Hg</th>
<th>No Treatment</th>
<th>On Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High TG/low HDL-C</td>
<td>Others</td>
</tr>
<tr>
<td>&lt;120</td>
<td>11.6% (25/215)</td>
<td>5.1% (57/1124)</td>
</tr>
<tr>
<td>120–140</td>
<td>11.8% (22/186)</td>
<td>7.8% (61/781)</td>
</tr>
<tr>
<td>&gt;140</td>
<td>7.6% (4/53)</td>
<td>9.0% (18/200)</td>
</tr>
</tbody>
</table>

IHD is in percent. High TG/low HDL-C measurements were triglycerides >1.59 mmol/L and HDL cholesterol <1.18 mmol/L.

**TABLE 5. Crude Cumulative Incidence (%) and Relative Risk of IHD According to Levels of DBP and Presence of High TG/Low HDL-C Versus Others in the Entire Population**

<table>
<thead>
<tr>
<th>DBP, mm Hg</th>
<th>Crude Cumulative Incidence of IHD</th>
<th>Adjusted Relative Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High TG/low HDL-C</td>
<td>Others</td>
</tr>
<tr>
<td>&lt;75</td>
<td>13.7% (37/270)</td>
<td>6.1% (86/1417)</td>
</tr>
<tr>
<td>75–90</td>
<td>10.6% (27/255)</td>
<td>7.5% (58/771)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>13.7% (7/51)</td>
<td>9.9% (14/142)</td>
</tr>
</tbody>
</table>

P=NS (Trend test) P=0.06 (Trend test)

Measurements of high TG/low HDL-C were triglycerides >1.59 mmol/L and HDL cholesterol <1.18 mmol/L.

*Confounders included age, total cholesterol, BMI, alcohol consumption, smoking, physical activity, NIDDM, and social class.

†Reference group in each category.

‡P<0.05 compared to reference group.
with the level of BP and a diagnosis of hypertension.\textsuperscript{28,29} Thus our study population does not appear to be unusual, and the overall reporting appears to be precise. In Denmark, diagnoses from official national registers are known to have a high validity.\textsuperscript{21–25} and it seems unlikely that men with high TG/low HDL cholesterol would be treated differently than others with respect to a diagnosis of IHD in the present study. Because we had reasonably similar results whether we used BP measurements from 1970 to 1971 or from 1985 to 1986, our findings do not appear to be the result of a selection bias. In our study, treated hypertensive subjects with high TG/low HDL cholesterol had the highest risk of IHD. Could it be possible that this observation was due to severe hypertension being treated with drugs that raise TG and lower HDL cholesterol? This does not appear to be the case. There were no statistically significant differences in the number of drugs or the groups of drugs being used between subjects with high TG/low HDL cholesterol and others, and in medical literature, raised TG levels that are associated with drug treatment do not seem to have any impact on risk of IHD.\textsuperscript{26}

At first sight, our results appear to be in contrast with the medical literature. Other cohort studies that have examined the relation of lipids and BP to the risk of IHD have generally found graded relationships between lipids, BP, and risk of IHD.\textsuperscript{29,31,32} However, none of these studies\textsuperscript{29,31,32} focused on the characteristic dyslipidemia seen in subjects with the metabolic syndrome X, high TG/low HDL cholesterol, a circumstance that may explain the discrepancy between their findings and our findings. On the other hand, a manuscript by Sheu et al\textsuperscript{33} provides substantial support for the notion that the increased risk of IHD in patients with hypertension is related to the metabolic syndrome X, with insulin resistance and its consequences. Sheu et al\textsuperscript{33} showed in a cross-sectional study design that patients with hypertension and evidence of IHD by ECG criteria were insulin resistant, hyperinsulinemic, with higher TG and lower HDL cholesterol concentrations as compared with individuals who were equally hypertensive but had normal ECGs.

In the CMS, we have no measurements of plasma insulin or glucose, and simply basing the metabolic syndrome X on lipid criteria may not be adequate for some readers. However, although most readers probably would consider fasting insulin to be a better surrogate for insulin resistance in large-scale cohort studies, carefully conducted metabolic ward studies have found a similar relationship between fasting TG levels and insulin resistance ($r=0.65$) to that between fasting insulin levels and insulin resistance ($r=0.47$).\textsuperscript{34,35} Thus, we believe it is justified to discuss the metabolic syndrome X on the basis of TG and HDL cholesterol levels. 2 lipid measurements readily available for most physicians, which makes our observations easy to apply in clinical medicine. Also, in the CMS, the men appeared to have lower BPs than expected. We used the manometer developed by the London School of Hygiene,\textsuperscript{12} an instrument that compared with other BP recorders has been shown to give lower BPs.\textsuperscript{36} therefore the actual level of BPs in our study population may have been higher than the values presented.

### Biological Plausibility

Are our findings biologically plausible? High BP and high TG/low HDL cholesterol are components of the metabolic syndrome X,\textsuperscript{37,38} a constellation of interrelated metabolic changes that are believed to be major factors in the causes of IHD.\textsuperscript{37,38} The metabolic syndrome X with high TG/low HDL cholesterol includes an increased amount of atherogenic lipoproteins such as small, dense LDL particles\textsuperscript{39,40} and smaller TG-rich lipoproteins.\textsuperscript{34,41} The metabolic syndrome X with high TG/low HDL cholesterol includes higher levels of plasminogen activator inhibitor-1,\textsuperscript{38,42} which leads to a state of deficient fibrinolysis, and the metabolic syndrome X with high TG/low HDL cholesterol also includes hyperinsulinemia and hyperglycemia.\textsuperscript{37,38} 2 other changes that are known to be important risk factors of IHD.\textsuperscript{33,44} Thus, when high TG/low HDL cholesterol is present, several other important risk factors will also frequently be present to increase the risk of IHD independent of the actual level of BP and use of antihypertensive medications. Consequently, it is possible that in the hypertensive subject with the metabolic syndrome X, a substantial part of the risk associated with high BP is in fact caused by the other components in the syndrome and not high BP per se. In this context, it is interesting to note that in our cohort, the presence of high TG/low HDL cholesterol was a much stronger risk factor of IHD than the level of SBP and DBP.\textsuperscript{8}

In the medical literature, there is evidence that in subjects with a high risk of AMI, such as patients with established IHD or hypertensives with LVH, the expected direct relationship between level of BP and risk of IHD is not always found.\textsuperscript{45,46} and even a negative relation between both untreated and treated DBP has been reported in several studies,\textsuperscript{45,46} such as the controversial J- or U-curved phenomenon.\textsuperscript{3,45} The J-curve is thought to be a consequence of

### TABLE 6. Crude Cumulative Incidence of IHD (%) According to Levels of DBP and Presence of High TG/Low HDL-C Versus Others According to Medical Treatment for High BP

<table>
<thead>
<tr>
<th>DBP, mm Hg</th>
<th>High TG/low HDL-C</th>
<th>Others</th>
<th>High TG/low HDL-C</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75</td>
<td>11.1% (27/243)</td>
<td>5.8%</td>
<td>37.0% (10/27)</td>
<td>10.8%</td>
</tr>
<tr>
<td>75–90</td>
<td>11.0% (20/182)</td>
<td>7.3%</td>
<td>9.6% (7/73)</td>
<td>9.2%</td>
</tr>
<tr>
<td>&gt;90</td>
<td>13.8% (4/29)</td>
<td>9.9%</td>
<td>13.6% (3/22)</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Measures of high TG/low HDL-C were triglycerides $>1.59$ mmol/L and HDL cholesterol $<1.18$ mmol/L.
underlying heart disease (eg, a fall in coronary flow reserve) and not the cause of IHD.45

On the basis of the observation described above, in high-risk subjects the risk of IHD is not necessarily directly related to the level of BP,45 thus we think our findings are biologically plausible. Because subjects with high TG/low HDL cholesterol have a series of atherogenic and thrombogenic changes, they have a high risk of IHD, and therefore they tend to resemble other high-risk populations. In addition, their risk of IHD will not be directly related to level of BP.

Clinical Implications

Our findings may have important clinical implications. Our results suggest that in hypertensive subjects with high TG/low HDL cholesterol, it may be more important to normalize high TG/low HDL cholesterol and the other components in the metabolic syndrome X to lower risk of IHD than to normalize BP. However, although lowering BP in some groups may have less than the expected effect on IHD, it should be pointed out that it is also still very important to lower BP in subjects with high TG/low HDL cholesterol to reduce the risk of stroke.2 In addition, the medical literature suggests that a multiple risk factor intervention strategy may be more important to lowering the risk of IHD in hypertensive patients than a strategy directed solely to the lowering of BP. In a prospective population-based observational study of 686 treated hypertensive men followed for 2 decades, the risk of IHD was still very high and the risk of IHD was not related to entry or in study BP but to lipid levels.47 In addition, post hoc subgroup analyses from randomized, placebo-controlled trials have suggested that lipid-lowering therapy may be useful in lowering the risk of IHD in subjects with hypertension.48,49

Acknowledgments

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High Triglycerides and Low HDL Cholesterol and Blood Pressure and Risk of Ischemic Heart Disease
Jørgen Jeppesen, Hans Ole Hein, Poul Suadicani and Finn Gyntelberg

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