Cardiovascular Disease and Mortality in Older Adults with Small Abdominal Aortic Aneurysms Detected by Ultrasonography: The Cardiovascular Health Study

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Abdominal aortic aneurysms (AAA) are a common condition found in at least 3% of the population aged over 50 years and, in this study, 9% of those over 65. The mortality of AAA rupture is significant and up to one half of the perioperative deaths are due to myocardial infarctions.

The Cardiovascular Health Study was designed to identify risk factors for development and progression of cardiovascular disease, including AAA in older adults. The primary goal of this study was to evaluate whether the risks for mortality and cardiovascular disease associated with abdominal aneurysms were related to higher levels of risk factors and greater extent of vascular disease on noninvasive testing. The Cardiovascular Health Study was a random, multicenter study of men and women older than 65. Patients were excluded if they were considered disabled, were institutionalized, or had cancer. The risk for mortality and incident cardiovascular events was assessed over a 4.5-year period. AAA were defined as an infrarenal aorta diameter of >3.0 centimeters, or an infrarenal:suprarenal ratio of >1.2. Risk factors for cardiovascular disease included cigarette smoking, hypertension, diabetes, sibling history of myocardial infarction or stroke, and lipid levels. The extent of vascular disease was assessed noninvasively by carotid ultrasound, ankle:arm index, and standard 12-lead electrocardiogram (ECG). Outcomes measured were total mortality from cardiac and noncardiac causes, incident cardiovascular disease, recurrent cardiovascular disease, and repair or rupture of AAA. Cardiovascular disease morbidity and mortality included any death or incident related to cardiovascular disease.
AAA were detected in 8.8% of participants and almost 90% were <3.5 cm in diameter. Patients with AAA present were similar in age (75 vs 74) to those without aneurysms. In the aneurysm group, patients were more likely to be men (61% vs 39%), smokers (15% vs 9%), and have a history of cardiovascular disease (41% vs 27%). They also had slightly higher low-density lipoprotein levels and lower high-density lipoprotein levels. On noninvasive testing, there was a marked increase in carotid wall thickness and a higher percentage of ankle:arm index readings <0.9 (24% vs 12%). There was no statistical significance between the 2 groups in the number of participants with diabetes mellitus, hypertension, or ECG abnormalities.

CARDIOVASCULAR DISEASE AND MORTALITY

Mortality rates were significantly higher in patients with AAA present. After adjustment for age, sex, ethnicity, height, and weight, the relative risk for death was 1.73. Adding the additional factors of smoking, lipid levels, family history, and a history of cardiovascular events, the relative risk was still increased at 1.47. The adjusted risk was similar for men and women. With adjustments for carotid wall thickness, ECG abnormalities present, and low ankle:arm index, the relative risk was 1.32. The risk for incident cardiovascular disease was higher in those participants with aneurysms present. This remained markedly elevated after adjustment in all of the multivariate models. Rates of recurrent cardiovascular disease were high in both groups.

MORTALITY AND ANEURYSM SIZE

The risk of death was markedly increased in men who had an abdominal aortic aneurysm >3.5 cm in diameter. In women, the increase in mortality began with AAA >3.0 cm in diameter. In the group of women with AAA of 3.0–3.5 cm, the relative risk of mortality was 4× that of women without AAA present, even after adjusting for age, height, weight, and ethnicity.

DISCUSSION

Consistent with other studies, the rates for total mortality, cardiovascular disease mortality, and incident cardiovascular disease were higher in patients with AAA present. These risks were independent of age, sex, other cardiovascular disease risk factors, and the extent of atherosclerosis by noninvasive testing (carotid ultrasound, ankle:arm index, ECG). The risk for mortality was markedly increased for women with aneurysms >3.0 cm and for men with aneurysms >3.5 cm. The risk of AAA rupture was small and not detectable in patients with aneurysms < 4.0 cm. This study is consistent with the opinion that aneurysms represent not only a local vasculopathy but also that they are markers of systemic disease.
Diabetes and All-Cause and Coronary Heart Disease Mortality Among US Male Physicians

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Diabetes has long been linked with an increased risk of coronary heart disease (CHD). Past studies have shown that men with diabetes mellitus (DM) are 2–3 times more likely to die of CHD, and women have an even higher risk. This study addresses the question whether or not the mortality risk associated with diabetes-related CHD rivals the excess risk associated with a prior myocardial infarction (MI). The US Physicians’ Health Study (PHS) enrollment cohort provided an opportunity to study the relationship of diabetes and history of CHD to all-cause and CHD mortality. Four subsets of participants were compared: men free of diabetes and CHD at baseline, men diagnosed with diabetes without CHD, men diagnosed with CHD without diabetes, and men diagnosed with both diabetes and CHD.

METHODS

The study cohort was part of the Physicians Health Study, a randomized, double-blind, placebo-controlled trial testing the benefits and risk of aspirin and beta carotene in the prevention of cardiovascular disease and cancer. Information was obtained for the PHS by questionnaire. The authors noted that previous studies of health professionals determined self-reporting diabetes and CHD is reliable. This study included a reference group of 82,247 men without a history of CHD or diabetes, 2317 men reporting a history of diabetes but not CHD, 5906 men who reported a history of CHD (previous MI or angina pectoris) but not diabetes, and 815 men who reported a diagnosis of both diabetes and CHD. A subset of the cohort (approximately 25%) was randomized into the trial. End points were all deaths and death caused by CHD. The mean follow-up period was 5 years. Cox proportional hazard analysis was used to calculate the age-adjusted and multivariate-adjusted relative risk for each category compared with the reference group. The multivariate analysis was adjusted for age,
body mass index, smoking, exercise, and alcohol consumption. Hypertension and high cholesterol were not included in the adjustment in the primary models. It was thought they were potential intermediates in the causal pathway because diabetes increases the risk of these conditions. A secondary model assessed whether hypertension or hypercholesterolemia mediated the effect of diabetes, but it was found that the results were similar to those of the primary multivariate model.

**RESULTS**

During the mean follow-up period of 5 years, 4% of the study cohort died; 46% of the deaths were considered to be due to cardiovascular diseases (excluding stroke). Compared to the reference group, those without either CHD or DM, the age-adjusted relative risk of all-cause mortality was similar for subjects with a history of diabetes but not CHD, relative risk (RR) 2.3 (2.0–2.6), and subjects with a history of CHD but not diabetes, RR 2.2 (2.0–2.4). All-cause mortality was higher among those with both diabetes and CHD at baseline, RR 4.7 (4.0–5.4). The age-adjusted CHD mortality was threefold higher for those with diabetes, but no CHD: RR 3.3 (2.6–4.1); fivefold higher for those with CHD but not diabetes: RR 5.6 (4.9–6.2); and 12-fold higher for those with both diabetes and CHD: RR 12.0 (9.9–14.6). The multivariate analysis with adjustment for age, body mass index, smoking status, exercise, or alcohol intake did not materially affect the results for any group. During analysis, participants were categorized into 3 age strata (40–54, 55–69, and 70–84 years).

Excess mortality risks associated with diabetes or CHD, or both, were observed in all age groups and was most dramatic in the youngest age group. Those with both DM and CHD diagnoses at baseline had a RR of 36.8 (18.3–74.1) for death due to CHD (See Figure 1—confidence intervals have not been included).

**DISCUSSION**

In this selected cohort of adult male physicians, the increased risk of CHD and all-cause mortality in diabetics is striking. This group likely represents a best-case scenario given the access to medical insurance and medical care in the PHS population. The data from this study suggest that diabetes is associated with an increased risk of CHD and all-cause mortality regardless of the presence or absence of other risk factors.
LITERATURE REVIEW

Urine Detection of Survivin and Diagnosis of Bladder Cancer

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Apoptosis is the last act of a living cell by which suicidal enzymes are released, causing the death and destruction of the cell. Prevention of apoptosis would seem like the start of finding the fountain of youth. However, a recent discovery of an inhibitor of this process has shown just the opposite. Survivin, an inhibitor of apoptosis, is thought to abnormally prolong a cell’s life, thus increasing the odds of mutations and subsequent cancers. In this study conducted by the Yale School of Medicine, a total of 109 subjects were divided into 5 study groups to see if elevated levels of urinary survivin could be correlated to genitourinary cancers. The 5 groups consisted of:

- Group 1—Normal, healthy volunteers; mean age 47.6 years old.
- Group 2—Patients with nonneoplastic urinary tract disease or hematuria; mean age 60.0.
- Group 3—Patients with a history of genitourinary cancer (excluding bladder cancer); mean age 71.5.
- Group 4—Patients with the diagnosis of new onset or recurrent bladder cancer; mean age 69.7.
- Group 5—Patients who had undergone or were currently receiving treatment for bladder cancer but had a negative cystoscopy on the day of urine collection; mean age 76.1.

Urine was collected from the members of each group and analyzed for the presence or absence of survivin. The results are summarized in the following table.

**DISCUSSION**

From the table it is clear that detection of survivin correlates very well with the presence or absence of bladder cancer. It does not
appear to be elevated with other genitourinary cancers, nor does it tend to be elevated once the disease has been eradicated. Interestingly, of the 4 patients of group 2 who were survivin positive, 2 were later found to have developed bladder cancers.

Although this is a very small study, it does indicate that the presence of survivin, an inhibitor of apoptosis, may indicate the presence of bladder cancer. Larger studies with closer aged-matched controls may later prove this to be a simple and accurate screening tool for bladder cancer.

<table>
<thead>
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<th>Group</th>
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LITERATURE REVIEW

Long-Term Outcome in Asymptomatic Men With Exercise-Induced Premature Ventricular Depolarizations

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The Paris Prospective Study I examined and followed 7746 males, employed by the French Civil Service, aged between 42 and 53 years. They represented 93.4% of all men employed in 1967, the year of inception of the study. After exclusion for known or suspected cardiovascular disease, systolic BP > 180 at rest, or any abnormality on 12-lead resting electrocardiogram (ECG) including polymorphic premature ventricular contractions (PVCs), 6565 men underwent exercise testing. Of these, 6101 had complete data and follow-up for analysis in this study.

During exercise, 138 (2.3%) had frequent PVCs, defined as a run of 2 or more, or >10% of all beats in any 30 second interval. After 23 years of follow-up, both ischemia and PVCs led to increased cumulative mortality as shown in the table.

The authors determined relative risk of death after analysis, which revealed that both ischemia and PVCs independently affect prognosis. Multivariate Cox proportional hazards, with adjustment for age, body mass index, resting heart rate, systolic BP, tobacco use, physical activity, diabetes, total cholesterol, and PVCs prior to exercise or during recovery, yielded relative risk (95% confidence interval) of 2.6 (1.9-3.6) for ischemia and 2.5 (1.6-3.9) for ventricular dysrhythmia.

Frequent PVCs during exercise confer a mortality risk equivalent to ischemia in this population of middle-aged healthy men. The excess total cumulative mortality derives entirely from cardiac causes, lending more credence to the observation. In the accompanying editorial, Calkins emphasizes that the risk related to PVCs may not represent another method for detection of coronary artery disease: "It is conceivable that exercise testing..."
identifies a subgroup of patients with otherwise clinically occult cardiomyopathy." He and the study authors urge additional testing, namely echocardiography, and more careful follow-up for patients with exercise induced PVCs.

This study imitates screening exercise ECG testing of life insurance applicants: they are working and were screened to exclude most known disease. We can generalize these results to underwriting. Frequent PVCs during exercise in such people confers excess risk. Since the risk is independent of ischemia, additional testing to exclude ischemia (nuclear perfusion or angiography) does not negate the risk. Echocardiography can refine the risk assessment by exclusion of many forms of cardiomyopathy.

**REFERENCE**