Table 1. Independent Predictors of Death from All Causes among 29,244 Patients Referred for Symptom-Limited Exercise Testing.*

Variable	No. of Patients (%)	Adjusted Hazard Ratio (95% CI)	P Value
Age (10-yr increments)	—	2.3 (2.1–2.4)	<0.001
Physical fitness			
Poor	1,991 (7)	2.3 (2.0–2.7)	<0.001
Fair	5,987 (20)	1.7 (1.5–1.9)	<0.001
Heart-rate recovery (abnormal vs. normal)	6,487 (22)	1.5 (1.3–1.6)	<0.001
Tobacco (use vs. nonuse)	5,179 (18)	1.6 (1.4–1.8)	<0.001
Male sex	20,611 (70)	1.6 (1.4–1.8)	<0.001
Chronotropic incompetence without beta-blockade (presence vs. absence)	5,058 (17)	1.4 (1.3–1.6)	<0.001
Chronic lung disease (presence vs. absence)	717 (2)	1.7 (1.4–1.9)	<0.001
Diabetes treated with insulin (presence vs. absence)	909 (3)	1.7 (1.4–2.0)	<0.001
Frequent ventricular ectopy during recovery (presence vs. absence)	1,080 (4)	1.6 (1.3–1.9)	<0.001
Diabetes not treated with insulin (presence vs. absence)	2,210 (8)	1.3 (1.2–1.5)	<0.001
Left bundle-branch block (presence vs. absence)	353 (1)	1.7 (1.3–2.2)	<0.001
Dihydropyridine (use vs. nonuse)	2,284 (8)	1.3 (1.1–1.4)	<0.001
Resting heart rate (10-beat/min increments)	—	1.2 (1.1–1.3)	<0.001
Resting diastolic blood pressure (10–mm Hg increments)	—	0.8 (0.8–0.9)	<0.001
Aspirin (use vs. nonuse)	9,374 (32)	0.8 (0.7–0.9)	<0.001
Beta-blocker (use vs. nonuse)	5,096 (17)	1.2 (1.1–1.4)	0.006
Known coronary artery disease (presence vs. absence)	9,308 (32)	1.2 (1.0–1.4)	0.009

* Variables are listed in the order in which they were entered in the stepwise-selection Cox proportional-hazards model. Only the variables with a P value ≤0.01 are shown. CI denotes confidence interval, and dashes not applicable.

tween frequent ventricular ectopy during recovery and the type of recovery protocol used for the prediction of death (P for interaction, 0.97).

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Carcinoid Heart Disease

TO THE EDITOR: Møller et al. (March 13 issue)[1] addressed the topic of the progression of carcinoid heart disease. Serial echocardiographic studies were available for 71 of the 273 referred patients. The median level of urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion at base line in patients with carcinoid heart disease was 209 mg per 24 hours, and in those without carcinoid heart disease it was 110 mg per 24 hours; the median duration of the syndrome was relatively short, at 1.0 and 1.8 years, respectively. Remarkably, data on 5-HIAA levels during the course of this disease are scarce. We therefore studied 73 patients with the carcinoid syndrome who were referred between 1985 and 2002, in whom the 5-HIAA level was measured at one-year intervals. The median urinary 5-HIAA level gradually increased, reaching 110 mg per 24 hours only after more than seven years had passed (Fig. 1). The very high urinary 5-HIAA levels and the high incidence of carcinoid heart disease relative to that in another

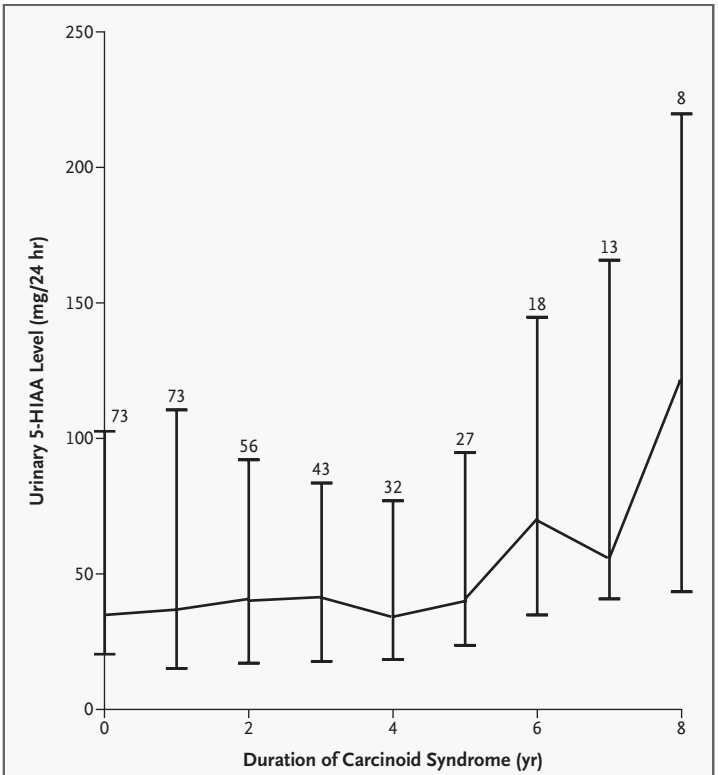

Figure 1. Median Urinary 5-Hydroxyindoleacetic Acid (5-HIAA) Levels over Time.
The values shown at each point are the numbers of patients. The I bars represent interquartile ranges.

recent study[2] suggest that Møller et al. studied a highly selected group. This underscores that although somatostatin analogues did not prevent carcinoid heart disease in their population, a beneficial effect is not precluded in less advanced disease.

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TO THE EDITOR: Møller et al. reported that a high peak level of urinary 5-HIAA excretion is a predictor of carcinoid heart disease. However, the duration of exposure to elevated serotonin levels might be an even more important factor in the development of valvular fibrosis. The serotonin load can be assessed as the area under the curve for urinary 5-HIAA excretion. In our series of 37 consecutive patients (19 women and 18 men) with carcinoid heart disease,[1] the median interval between the diagnosis and cardiac ultrasonography was 28 months (range, 2 to 121). There was a significant correlation between the presence of carcinoid heart disease and the median level of urinary 5-HIAA excretion during the interval between diagnosis and cardiac ultrasonography (5-HIAA level, 576 μmol per 24 hours in the patients with carcinoid heart disease, as compared with 233 μmol per 24 hours in those without it; $P=0.02$). However, there was an even stronger relation between carcinoid heart disease and the serotonin load over time (i.e., the area under the curve for urinary 5-HIAA excretion during this interval) ($P<0.001$). This finding supports the theory that total exposure to serotonin is even more important than the level of serotonin in the development of carcinoid heart disease.

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THE AUTHORS REPLY: Drs. Zuetenhorst and Taal raise a pertinent question regarding the relative importance of the duration of exposure to elevated serotonin levels as compared with the peak level of serotonin in the development and progression of carcinoid heart disease. If the area under the curve is going to be compared between groups, serotonin excretion should be assessed at fixed time points at similar stages in the development of the disease. Not infrequently, patients with the carcinoid syndrome have carcinoid heart disease at the time of diagnosis or a long history of symptoms of the carcinoid syndrome preceding the date of diagnosis. Meaningful assessment of the area under the curve would be impossible in these circumstances. Thus, we related the peak values of urinary 5-HIAA to changes in the cardiac score (a score based on valvular anatomy and function and right ventricular function) during follow-up.

Dr. van der Horst-Schrivers and colleagues raise a potential issue regarding selection bias. The pop-

ulation in our study was selected from 273 consecutive patients with carcinoid tumors who were referred for echocardiography because of suspected carcinoid heart disease. Thus, a high frequency of carcinoid heart disease and high 5-HIAA excretion would be expected. However, we did not find any difference in peak 5-HIAA levels between the patients who were included in the study (median, 222 mg per 24 hours; interquartile range, 148 to 345) and those who were excluded (median, 238 mg per 24 hours; interquartile range, 131 to 362) (P=0.79). In contrast to the data presented by van der Horst-Schrivers and colleagues, we found that 5-HIAA levels decreased during follow-up, probably as a result of an aggressive therapeutic strategy. The 5-HIAA levels in our study were similar to those measured in previous studies of similar populations.[1,2] Thus, we believe that the population we studied is representative of patients with clinically significant carcinoid heart disease.

It is possible that somatostatin analogues may slow the progression of carcinoid heart disease. However, the available data indicate that current methods of treatment are inadequate to prevent the development and progression of carcinoid heart disease. Larger, prospective studies are needed to define the optimal treatment strategy.

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Genetics of Colorectal Cancer

TO THE EDITOR: Lynch and de la Chapelle (March 6 issue)[1] emphasize the screening of high-risk patients who have a mutation in the adenomatous polyposis coli (*APC*) gene or who have one or more first-degree relatives with familial adenomatous polyposis. However, the importance of ophthalmic examination in screening for and diagnosis of familial adenomatous polyposis is not noted. Congenital hypertrophy of retinal pigment epithelium is the most prominent extracolonic manifestation of familial adenomatous polyposis and is present in about 90 percent of patients.[2-4] This condition can be identified by noninvasive methods even in infants and young children by simple fundus examination with the pupils dilated. A combined approach involving the detection of an *APC* mutation and detection of congenital hypertrophy of retinal pigment epithelium for presymptomatic diagnosis of familial adenomatous polyposis is highly recommended.[5]

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TO THE EDITOR: In Table 3 of the review article by Lynch and de la Chapelle, microcephaly is listed as one of the phenotypic features of the Bannayan–Ruvalcaba–Riley syndrome. In fact, patients with this syndrome have macrocephaly[1] (with normal-size ventricles). Typically, their birth weight is greater than 4 kg and their birth length above the 97th percentile, but their final height as adults is within the normal range.[2] In addition, 50 percent of the patients have hypotonia, delayed gross motor or speech development, or mental retardation.[2] In about 60 percent of the patients, a myopathic process affecting the proximal muscles is present.[2]

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