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

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

* 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.

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
recent study\(^2\) suggest that Møller et al. studied a highly selected group. This underscores that 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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2. Zuetenhorst JM, Bonfrer JM, Korse CM, Bakker R, van Tinteren H, Taal BG. Carcinoid heart disease: the role of urinary 5-hydroxyindoleacetic acid 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 consec-
utive patients with carcinoid tumors who were re-
ferred 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 pa-
tients 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 lev-
els 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 represen-
tative 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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1. Denney WD, Kemp WJ Jr, Anthony LB, Oates JA, Byrd BF III.
Echocardiographic and biochemical evaluation of the development
and progression of carcinoid heart disease. J Am Coll Cardiol 1998;
32:1017-22.
2. Westberg G, Wängberg B, Ahlman H, Bergh CH, Beckman-
Suurkula M, Caidahl K. Prediction of prognosis by echocardiogra-
phy in patients with midgut carcinoid syndrome. Br J Surg 2001;88:
865-72.

Genetics of Colorectal Cancer

TO THE EDITOR: Lynch and de la Chapelle (March
6 issue)1 emphasize the screening of high-risk pa-
tients 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 fa-
miliar adenomatous polyposis is not noted. Congen-
ital 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 in-
volving the detection of an APC mutation and detec-
tion of congenital hypertrophy of retinal pigment
epithelium for presymptomatic diagnosis of familial
adenomatous polyposis is highly recommended.5

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retinal pigment epithelium and APC mutations in Chinese with famil-
of the retinal pigment epithelium in familial adenomatous polyposis:
novel criteria of assessment and correlations with constitutional ade-
4. Lam DSC, Kwok SPY, Kwok AKH, Liew CT, Lau JYW, Pang CC.
Incidence and predictive value of congenital hypertrophy of retinal
pigment epithelium in Chinese familial adenomatous polyposis
5. Pang CP, Lam DS. Differential occurrence of mutations causa-
tive of eye diseases in the Chinese population. Hum Mutat 2002;19:
189-208.

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 macrocephaly4 (with normal-
size ventricles). Typically, their birth weight is grea-
ter 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 pro-
cess affecting the proximal muscles is present.2

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