We read with interest the excellent report by Mitchell et al. (1) in this issue of JACC: Heart Failure. In brief, the investigators conducted a subset analysis of the SCD-HeFT (Sudden Cardiac Death in Heart Failure) trial that was originally published in 2005. They looked at the subset of patients with evidence of thyroid hormone dysfunction at the beginning of the trial and those who developed evidence of thyroid hormone dysfunction during the trial. The investigators found that evidence of abnormal thyroid function in patients with heart failure portends a poor prognosis and is associated with increased mortality. The study is based on clinical trial data, with a protocol for follow-up measures that should minimize bias. Various subgroup analyses were conducted that, if sufficiently powered, raise the question of whether the thyroid abnormalities have a causal relationship to mortality.

For instance, patients treated for hypothyroidism were found to have risk that was apparently not significantly different from those untreated. Furthermore, the increased mortality risk was reported to be similar for hyperthyroidism and hypothyroidism. Might the thyroid test abnormalities be only a marker for an underlying condition that is the actual causal factor for increased mortality? Unfortunately, the investigators present only p values, not confidence intervals, which would have assisted with interpretation as to whether there was a nonsignificant trend and its direction.

An important aspect of this report is that treatment with an implantable cardioverter-defibrillator (ICD) was not associated with more benefit in patients with abnormal thyroid function data. If ventricular arrhythmias are the main reason that thyroid abnormalities are associated with increased mortality, then ICD use has the potential to decrease mortality associated with thyroid abnormalities. Because ICD use did not improve mortality in those with thyroid abnormalities over those without thyroid abnormalities, ventricular arrhythmias may not be the main mechanism for thyroid abnormality–associated increased mortality. However, further benefit may not have been detected, because the analysis of the thyroid abnormality subgroup within the ICD subgroup may not have had enough power to exclude benefit.

The issue of whether we should aggressively treat low triiodothyronine or mild thyroid abnormalities in patients with heart failure has not been settled. As pointed out by Mitchell et al. (1), the associations among abnormal thyroid function, hypothyroidism, and increased mortality in heart failure have been known for years. Although only thyroid-stimulating hormone (TSH) was measured in this study, as noted, low triiodothyronine is common in patients with heart failure. Through the years, investigators have tried to treat patients with heart failure using supplemental thyroid hormone replacement, with disappointing results. Although one can achieve beneficial therapeutic effects in the short term, longer treatment results in manifestation of the systemic effects of thyroid hormone (2,3). This has led us and other investigators to develop thyroid hormone analogues to treat heart failure. Unfortunately, in the only randomized multicenter trial of the use of a thyroid hormone analogue, we showed that although left ventricular function improved, the side effects were such that the analogue was poorly tolerated (4).

Clinicians should still look for and treat classic thyroid disease in patients with heart failure. Furthermore, many clinicians favor treatment of subclinical thyroid disease, especially in "severe" subclinical disease (5). The present findings of increased risk for mortality and a high prevalence of thyroid abnormalities with the use of amiodarone can be combined with other findings of increased adverse outcomes associated with thyroid abnormalities to influence the diagnosis and treatment of thyroid disease. They are also consistent with the current emphasis on case finding with TSH and free thyroxine (FT4) for the diagnosis of thyroid disease rather than universal screening. Clinicians should continue to measure TSH and FT4 in patients with symptoms compatible with thyroid disease, such as fatigue, weight changes, tachycardia, bradycardia, and fluid retention, symptoms often found in those with heart failure. They should also be measured in patients at increased risk for thyroid abnormalities, including those using amiodarone, and in those with illnesses that may not tolerate thyroid abnormalities, including those with heart failure.

These findings also support strict maintenance of normal TSH as a goal of therapy for classic thyroid disease, because TSH values outside the reference range may confer risk for
several poor outcomes, including mortality. Thus, for those with classic hyperthyroidism, TSH < 0.1 mU/l and elevated FT4, and for those with classic hypothyroidism, TSH > 10 mU/l and decreased FT4, should have normal TSH as the treatment goal.

Treatment of patients with subclinical thyroid disease, typically defined as an abnormal TSH level and concurrent FT4 in the normal range, is controversial. The controversy stems from the lack of randomized controlled trial data showing efficacy for the treatment of subclinical thyroid disease. However, many clinicians treat “severe” subclinical thyroid disease. For example, patients with normal FT4 and TSH > 10 mU/l and symptoms compatible with hypothyroidism often are considered to have “severe” subclinical hypothyroidism and are treated. Patients with TSH higher than the upper limit of normal, typically > 5 but < 10 mU/l, have “mild” subclinical hypothyroidism and are less likely to be treated. Likewise, those with TSH < 0.1 mU/l and normal FT4 (“severe” subclinical hyperthyroidism) are more likely to be treated than those with “mild” subclinical hyperthyroidism, with TSH > 0.1 mU/l but less than the lower limit of normal, often 0.4 mU/l. Those in favor of treating patients with subclinical thyroid disease despite the lack of randomized controlled trial data cite the association of untreated disease with an increase in serious outcomes, the low cost of therapy, the ability to monitor TSH to guide therapy, and a low likelihood of serious side effects of therapy. Thus, many clinicians will diagnose and treat subclinical thyroid disease, including patients with heart failure. Others will note the present post hoc analysis, consider it hypothesis generating rather than demonstrating causality, and wait to treat “mild” subclinical thyroid disease until randomized controlled trials demonstrate efficacy.

Treatment of subclinical thyroid disease in those taking amiodarone deserves special consideration. Because amiodarone can block the effects of thyroid hormone, some patients develop mild increases in TSH, usually < 10 mU/l, and mild increases in FT4. These increases may compensate for the blocking effects of amiodarone and may be required to maintain normal tissue activity of thyroid hormone. Thus, most clinicians will not treat mild elevations in TSH or FT4 in patients taking amiodarone.

Reprint requests and correspondence: Dr. Steven Goldman, Tucson VA Hospital, Cardiology 111C, Cardiology Division, S. Sixth Avenue, 111C, Tucson, Arizona 85723-0001. E-mail: steven.goldman@va.gov.

REFERENCES

Key Words: amiodarone • heart failure • ICD • thyroid disease.