identify such patients and thereby avoid unnecessary and costly invasive procedures.

With regard to the randomized cohort, the comparable reduction in scintigraphic ischemia among the 2 strategies led to similar 1-year event rates. The crossover rates are similar to those reported in other acute coronary syndrome trials and were comparable between the two strategies. Although INSPIRE was underpowered to categorically assess differences in event rates between strategies, it provides event rate estimates for designing an adequately powered outcome trial. The main INSPIRE trial results give strong support for the premise that the presence and extent of scintigraphic ischemia predict risk and are surrogate markers for cardiac events.

Medical therapy is appropriate in all post-AMI patients, but it is usually not maximized. In INSPIRE, most patients in both randomized strategies received antiplatelet agents, beta-blockers, and statins. However, INSPIRE was unique in mandating maximally tolerated doses of all classes of anti-ischemic medications to patients in the medical-therapy limb. The objective was to minimize scintigraphic ischemia—a goal achieved in the majority of patients.

Both INSPIRE (1,2) and other recently published trials (3,4) provide new evidence that a conservative approach of early risk stratification through noninvasive imaging is not only reasonable but appropriate in the majority of patients post-AMI so as to identify those most likely to benefit from coronary revascularization. Finally, INSPIRE also shows that in patients with ischemia and preserved left ventricular function, intensive medical therapy is an excellent initial treatment option.

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doi:10.1016/j.jacc.2007.03.023

**Hyperthyroidism and Mortality**

Hyperthyroidism is associated with systemic inflammation (1) atrial fibrillation (2), and vascular and left ventricular hypertrophy (3,4). It is therefore reasonable to assume an increased mortality in patients with overt hyperthyroidism compared to euthyroid subjects. The effects of hyperthyroidism on all-cause and circulatory mortality, however, are a matter of debate and subject to ongoing controversy. Some investigations demonstrated increased mortality in hyperthyroid compared to euthyroid subjects (5,6), but others did not confirm this finding (7–9). One study even revealed lower mortality in hyperthyroid compared to euthyroid elderly subjects (10).

In a previous issue of JACC, Osman et al. (11) analyzed mortality of 393 patients with overt hyperthyroidism and 393 age- and gender-matched euthyroid subjects. During the 66.6 months of follow-up, 26 patients died, 7 of them from circulatory causes, whereas 12 euthyroid subjects died, 4 of them from circulatory causes. Unfortunately, risk estimates, including levels of statistical significance, were not given.

As correctly stated by Osman et al. (1), interpretation of their results is hampered by the low number of deceased subjects. Further limitations, however, should be considered and discussed. First, a number of potential factors confound the association between hyperthyroidism and mortality. Osman et al. (11) controlled for gender and age by study design. In addition, imbalances between hyperthyroid and euthyroid subjects with regard to smoking (29% vs. 15%, p < 0.0001) and diabetes mellitus (6% vs. 3%, p = 0.1) will have strong effects on the group-specific mortality risk in their study. Thus, analyses should also be controlled for at least these 2 factors.

Second, the outcome in patients who undergo a specific treatment depends upon various characteristics, including risk factors for the disease, the disease itself, comorbidities influencing the choice of a specific therapy, and desired and undesired treatment effects. Increased mortality in patients with hyperthyroidism seen in the study by Osman et al. (11) might therefore be explained at least hypothetically by, for example, the type of and the indication for a specific antithyroid therapy and the status of thyroid function following treatment.

Third, Osman et al. (11) recruited patients with hyperthyroidism from a university hospital, whereas euthyroid subjects were selected either from staff members working at the hospital or from a community center. Patients referred to university hospitals more often exhibit (not only cardiovascular) comorbidities than do ambulatory-treated patients or patients referred to general hospitals. Thus, patients with overt hyperthyroidism recruited for this investigation (11) are probably not representative of hyperthyroid patients living in the study region. Likewise, with regard to control subjects, medical staff might in general behave healthier than the rest of the population. As a result, excess mortality among cases compared to controls might be explained by selection bias.

Taken together, the association between overt hyperthyroidism and mortality found in the study of Osman et al. (11) likely results from bias and confounding and should not necessarily be interpreted as a biological, causal relationship.
We thank Dr. Völzke for his comments on our recent publication describing the cardiovascular manifestations of hyperthyroidism before and after antithyroid therapy (1). This age- and gender-matched case-control study of a consecutive series of 393 subjects presenting with overt hyperthyroidism aimed to define the cardiovascular manifestations of hyperthyroidism and to compare results with euthyroid control subjects. After a mean follow-up period of 5.5 years after presentation, 26 hyperthyroid subjects had died compared with 12 age- and gender-matched controls (p = 0.01). We state in our discussion that "the number of deaths remained too small to determine whether excess mortality [not a primary end point of our study] was specifically vascular in nature." We agree that the higher prevalence of smoking in our hyperthyroid subjects may be a confounder in terms of the mortality observed; however, there was no significant difference in prevalence of diabetes between subjects and controls. Whereas Dr. Völzke asserts that our hyperthyroid subjects may have been selected because they were seen in a university hospital setting, we consider this unlikely as our hospital serves as the general referral site for hyperthyroidism, rather than as a specialist referral center.

In summarizing previous reports examining the relationship between hyperthyroidism and mortality, Dr. Völzke failed to make the critical distinction between studies of overt hyperthyroidism and those examining subclinical hyperthyroidism (defined biochemically as low serum thyrotropin with normal circulating thyroid hormone concentrations). We have previously reported in 2 large cohort studies that overt hyperthyroidism is associated with excess all-cause and vascular mortality (2,3) findings in accord with a large cohort study in the U.S. (4) and together providing good evidence that the cardiovascular complications of overt thyroid hormone excess (1) translate into excess vascular mortality. Unsurprisingly, results are less clear-cut for subclinical hyperthyroidism, which represents a much lesser degree of thyroid hormone excess. Increasing evidence from several large studies supports a link between subclinical hyperthyroidism and atrial fibrillation (5-7). We have previously reported that a low serum thyrotropin result is, in turn, associated with increased mortality after follow-up of 10 years (8) however, a higher rate of coronary heart disease and all-cause mortality observed by Cappola et al. during follow-up of subclinical hyperthyroidism was not significant (5). Likewise, Walsh et al. (9) found no adverse outcomes in a prospective study of subclinical hyperthyroid subjects (9).

A very different study in subjects aged 73 to 94 years by van den Beld et al. (10)—incorrectly cited by Dr. Völzke as evidence against an association between subclinical hyperthyroidism and mortality—examined the relationship between circulating thyroid hormone concentrations and physical performance scores, other markers of muscle function, and bone density. That study revealed an association between higher serum T4 and reduced physical performance score. Gussekloo et al. (11) studied very elderly subjects from the Leiden cohort (85 to 89 years) and reported increased hazard ratios for mortality for increasing increments of serum-free T4, as well as reduced mortality associated with subclinical hypothyroidism, not hyperthyroidism as suggested by Dr. Völzke.

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