

Patients with hyperthyroidism treated with radioiodine may be at increased risk of long-term morbidity and hospitalization for arrhythmias and cardiovascular disease

Metso S, Auvinen A, Salmi J, Huhtala H, Jaatinen P. Increased long-term cardiovascular morbidity among patients treated with radioactive iodine for hyperthyroidism. *Clin Endocrinol (Oxf)* 2008;68:450-7.

SUMMARY

BACKGROUND Some long-term studies find an increase in cardiovascular disease (CVD) mortality in patients with hyperthyroidism treated with radioactive iodine (¹³¹I). However, hyperthyroidism itself may account for the increase in CVD mortality. The aim of this study was to compare the rate and causes of hospitalization in patients with hyperthyroidism that were treated with ¹³¹I with the general population.

METHODS This population-based case-control study comprised 2611 patients with hyperthyroidism treated with radioiodine (¹³¹I); 430 were men (16.5%) and 2181 were women (83.5%). Age and gender-matched controls were selected from a population registry. The causes and dates of hospitalization for each individual were obtained from a nationwide Finnish registry. The cause of hospitalization was classified into 13 general groups, which included infectious disease, gastrointestinal disease, and fracture, and CVD which was further subclassified as hypertension, coronary artery disease, pulmonary circulation disorders, arrhythmias, heart failure, cerebrovascular diseases, and diseases of other arteries and cerebrovascular diseases.

RESULTS The median age of study subjects and controls was 62 years (range, 49 to 72) and the median follow-up period was 9.0 years for the patient group and 9.1 years for the control group. For both groups, CVD was the most frequent cause of hospitalization. Still, the rate of hospitalization was higher in the patient group as compared with the control group (637.1 vs. 476.4 per 10,000 patient years, RR 1.12). The risk remained elevated for as long as 35 years after ¹³¹I therapy.

Among the causes of CVD, hospitalization was more common in the patient group than the control group for arrhythmia (RR, 1.22), atrial fibrillation (RR, 1.35), cerebrovascular disease (RR, 1.31), other artery and vein disease (RR, 1.22), hypertension (RR, 1.20), and heart failure (RR, 1.48 (Figure 1). Although coronary artery disease was the second most common cause of hospitalization, the rates were not significantly different between patients and controls. The third highest rate of hospitalization was for cerebrovascular disease, with rates of 160.2 in patients and 122.8 in controls per 10,000 person years (RR P<0.001, Fig. 1). Sixty percent

of the patients with CVD had Graves' disease and 40% had toxic multinodular goiter or toxic adenoma. Patients with nodular thyroid disease had higher hospitalization rates for CVD than controls (650.9 vs. 568 hospitalizations per 10,000 person-years) but the rates in patients with Graves' disease were not statistically significant.

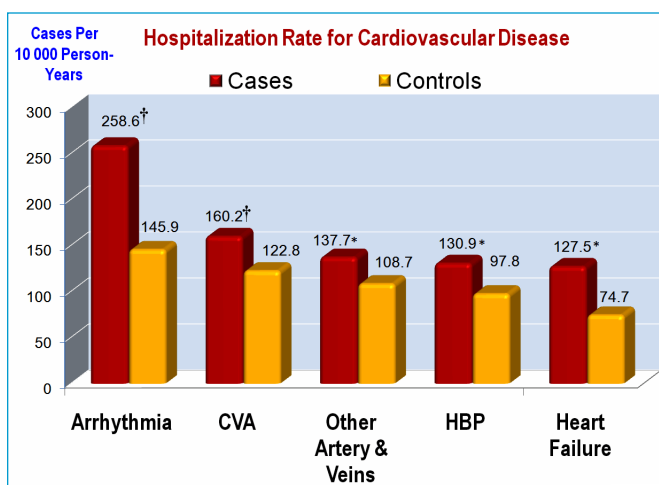


Figure 1. The rate of hospitalization for patients and controls with cardiovascular diseases. CVA denotes cerebrovascular accident, and HBP hypertension. †P = 0.001, and *P<0.05 comparing cases and controls. This figure is drawn from the data in Table 2 of Metso et al.

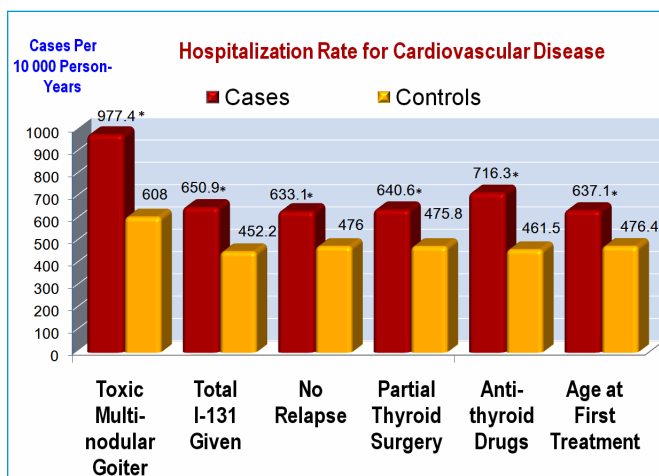


Figure 2. The hospitalization rates for cardiovascular diseases are shown in cases and controls. *P<0.05 comparing cases and controls. This figure is drawn from data in the text and Table 3 of Metso et al.

A total of 2106 patients (80.7%) were given a single ¹³¹I treatment, 397 (15.2%) were given two treatments, and 71 (2.7%) received three treatments. A mean of 304 MBq (8.2 mCi) of ¹³¹I was administered (range, 55 to 2664 MBq [1.5 to 72 mCi]). Hospitalization rates for CVD were elevated only among patients treated with a cumulative of 259 to 369 MBq of ¹³¹I (7 to 10 mCi), and were 650.9 in patients and 452.2 per 10,000 person-years in controls, (RR, 1.20; Figure 2). The risk of hospitalization due to CVD was lower in patients who did not undergo subtotal thyroidectomy or did not develop hypothyroidism or recurrence after ¹³¹I therapy. Patients treated with antithyroid drugs for less than 3 months or for more than 2 years were at increased risk of hospitalization due to CVD as compared with controls (Figure 2). Age at the time of first treatment predicted an increased risk of hospitalization in patients compared with controls (6.37 vs.

476.5 per 10,000 patient-years) and was greatest in patients aged 60 to 98 years.

The clinical factors predicting hospitalization for CVD were toxic multinodular goiter, older age at first ¹³¹I treatment, cumulative ¹³¹I dose, and duration of antithyroid drug therapy. Treatment with ¹³¹I was associated with an increased risk of hospitalization for infectious disease (RR, 1.23), gastrointestinal disease (RR, 1.23), and fracture (RR, 1.18), which was more common in women aged 50 years of age or older or in women younger than 50 or in men.

CONCLUSION The rate of hospitalization for cardiovascular diseases, especially cerebrovascular disease and arrhythmia, may be increased in patients with hyperthyroidism treated with radioiodine

COMMENTARY

Patients treated with ¹³¹I for hyperthyroidism have been reported to be at increased risk for death, but it is not clear whether this is due to hyperthyroidism itself or to the effect of ¹³¹I therapy. A similar study by Metso et al. (1) of 2793 patients treated with ¹³¹I for hyperthyroidism showed, after a median follow-up of 9 years, that all-cause mortality was increased in patients as compared with controls (453 vs. 406 deaths per 10,000 person-years; RR, 1.12). Cerebrovascular diseases accounted for most of the increased mortality (RR, 1.40), although mortality from cancer increased as well (RR, 1.29). As in the current study, mortality increased with the cumulative amount of administered ¹³¹I and with multinodular goiter, but did not increase in patients with Graves' disease. Also similar to the current study, mortality increased by ¹³¹I treatment of hyperthyroidism (RR, 1.56) and age (RR, 1.10) at the time of treatment; however, the development of hypothyroidism reduced mortality significantly. Based on these findings the authors conclude that hyperthyroidism itself probably accounted for the increased cerebrovascular mortality after ¹³¹I treatment.

The most striking finding of the current study by Metso et al. is the increased rate of CVD morbidity that persisted for as long as 35 years after ¹³¹I therapy. As a practical matter, this suggests that patients should undergo careful long-term follow-up with the usual surveillance for CVD. Also, the findings that gastrointestinal disease and fractures are increased in older women suggest that primary care physicians should perform the usual surveillance for loss of bone density in older women and be aware that occult gastrointestinal disease, especially gastric cancer, is a possibility in these patients (2). In an editorial on this article, Burman (3) opined that there are several deficits in the two Metso studies, including ascertainment bias resulting from the fact that only hospitalized patients were studied and that the multiple conclusions in the studies are difficult to apply to clinical practice, and that it is particularly difficult to understand how ¹³¹I therapy would increase the infectious disease rates. I agree with this opinion and find it difficult to understand how this risk might last as long as 35 years. Nonetheless, patients should be made aware of these findings and should also know the potential weaknesses of the observations.

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References

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3. Burman KD. Does radioiodine therapy for hyperthyroidism increase long-term morbidity? *Nat Clin Pract Endocrinol Metab* 2008;4:252-3.