Long-term Mortality and Cardiometabolic Effects of Treatment for Hyperthyroidism: EGRET Study

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Objectives: Hyperthyroidism has been linked to long-term cardiovascular and metabolic morbidity and increased mortality. Current evidence indicates differential cardio-metabolic effects from antithyroid drugs (ATD) and definitive treatment options (radioiodine or thyroidectomy). We aimed to assess differences in mortality and cardiometabolic outcomes depending on treatment modality to better inform patient-clinician decision-making.

Methods: We identified 55,318 patients with newly diagnosed hyperthyroidism, treated with ATD, radioiodine or thyroidectomy from a UK population-based electronic health record database (>2,000 contributing primary care practices, >16M patients). Health records were linked with Office for National Statistics (ONS) mortality data, (Hospital Episode Statistics) HES, and Health Survey for England for background BMI comparison. All-cause mortality, major cardiovascular events (MACE: cardiovascular death, heart failure or stroke) and post-treatment obesity diagnosis were studied. A "target trial" approach was used to allow to elucidate causal effects from observational data; average treatment effects (ATE) were estimated. Confounding was controlled for using inverse-probability weights (IPW) with regression adjustment. Mortality was assessed as time-to-event; other outcomes were modelled as binary (funded by NIHR RfPB, NIHR200772).

Results: Patients treated with ATD comprised 77.6% of the cohort; 14.6% were treated with radioiodine, and 7.8% with thyroidectomy. The average follow-up was 12.1 years (SD 5.2). Estimated mean survival was 12.0 years with ATD treatment. Definitive treatment increased survival: radioiodine by 1.7y. (95%CI: 1.2-2.2; P<0.0001) and thyroidectomy by 1.1y. (0.1-2.0; P=0.03). The estimated risk of MACE if the population were treated with ATD was 10.2% (9.9-10.5), which significantly increased by an additional 1.3% (0.5-2.1; P=0.001) with radioiodine but not with thyroidectomy (0.1% [-1.1, 1.3], P=0.08). Compared with background population, thyroidectomy was associated with an increased likelihood of obesity in both men (OR=1.57 [1.29-1.91], P<0.0001), and women (1.27 [1.16-1.39], P<0.0001), while radioiodine increased obesity risk in women (1.13 [1.06-1.20], P=0.0002) but not in men (1.04 [0.93-1.16], P=0.5).

Conclusion: EGRET is the first large study using population-based linked community and hospital data to evaluate long-term consequences of treatment modalities for hyperthyroidism. We confirmed a decreased mortality in patients undergoing definitive treatment whereas a slightly increased risk of obesity was found in patients treated with radioiodine and surgery. Compared to medical treatment, a small increase in cardiovascular events was noted with radioiodine

Presentation Type: Oral Presentation Date: June 17 Presentation Time: 3:30 PM - 5 PM Location: Room W178A