

1 Assessing the Cardiovascular Effects of Levothyroxine Use in an Ageing
2 United Kingdom Population with Subclinical Hypothyroidism: Emulated
3 Target Trial (ACEL-UK-ETT)

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59 **Abstract**

60 **Background:** Thyrotropin levels increase with age, but standard reference intervals do not account for this,
61 potentially leading to overdiagnosis of subclinical hypothyroidism (SCH) and overuse of levothyroxine in older
62 adults.

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64 **Methods:** Using data from The Health Improvement Network, this observational emulated target trial study
65 assessed 10-year outcomes in adults over 50 years with SCH (thyrotropin 4.1-10.0mU/L, free thyroxine 10.0–
66 24.0 pmol/L) who were prescribed levothyroxine versus those who were not. Subgroup analyses were limited to
67 patients with age-specific thyrotropin levels. The primary outcome was cardiovascular events (angina,
68 myocardial infarction, peripheral vascular disease, stent procedures, or stroke). Secondary outcomes included
69 bone events (fragility fractures or osteoporosis) and all-cause mortality. Hazard ratios, adjusted through inverse
70 probability of treatment weighting (IPTW) for age, sex assigned at birth, body mass index, Charlson
71 comorbidity index, total cholesterol, hypertension, thyrotropin, hormonal medications, and smoking, were
72 estimated.

73
74 **Findings:** Between January 1, 2006, and January 1, 2022, 22,621 patients (median age [IQR] 66 [59-75] years,
75 76.7% female) were identified; 62% received levothyroxine and 38% did not. Levothyroxine was associated
76 with reduced cardiovascular (IPTW-adjusted hazard ratio (aHR) 0.82; 95% CI: 0.74-0.91; p<0.0001) and all-
77 cause mortality (aHR: 0.71; CI: 0.67-0.75; p<0.0001), with no adverse effects on bone (aHR: 1.04; CI: 0.93-
78 1.17; p=0.45). Cardiovascular benefits were limited to patients with thyrotropin levels above the age-specific
79 range and after at least five years of treatment.

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81 **Interpretation:** Long-term levothyroxine use in older adults with SCH was associated with lower long-term
82 cardiovascular and all-cause mortality risks, with no significant harm to bone health. Age-specific thyrotropin
83 levels should guide treatment decisions.

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104 **Background**

105 The interpretation of thyrotropin (TSH) levels in older adults is debated, as conventional reference ranges (0.4–
106 4.0/4.5 mU/L) may not reflect age-related physiological changes. Studies show that TSH rises naturally with
107 age, despite normal free thyroxine (fT4).^{1–3} Longitudinal data suggests that the upper limit may reach 8.0 mU/L
108 in nonagenarians.^{4–6} This has led to recognition that age-adjusted thresholds may better define thyroid
109 dysfunction in older populations.³

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111 Large studies, including the Scottish Thyroid Epidemiology, Audit, and Research Study (TEARS) (n = 153,127)
112 and the United States National Health and Nutrition Examination Survey (n = 16,533), show the 97.5th
113 percentile of TSH increases with age, exceeding 5.9 mU/L in those >80 years.^{1,3} TSH concentrations exceeding
114 10.0 mU/L have consistently been linked to increased cardiovascular risk,⁷ while mild elevations (4.5–7.0
115 mU/L) have been associated with improved mobility and reduced mortality in older age groups.^{8,9}

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117 Given these findings, there is increasing debate about the appropriateness of initiating levothyroxine (LT4) in
118 older adults with mildly elevated, age-specific TSH levels. The role of LT4 in the treatment of subclinical
119 hypothyroidism (SCH), defined as elevated TSH with normal fT4, remains uncertain due to limited high-quality,
120 long-term evidence.¹⁰ In older adults, LT4 carries a recognised risk of overtreatment, which has been associated
121 with increased incidence of cardiovascular events and fractures.^{11,12} Despite this, LT4 is frequently prescribed in
122 this population, often resulting in suppressed TSH levels.¹³ Although European guidelines recommend LT4
123 initiation in adults with TSH concentrations exceeding 10 mU/L with symptoms,¹⁴ real-world adherence to this
124 is inconsistent.¹³

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126 Evidence on the cardiovascular and skeletal effects of LT4 treatment in older adults with SCH remains limited,
127 primarily due to a lack of adequately powered randomised controlled trials (RCTs). The Thyroid Hormone
128 Therapy for Older Adults with Subclinical Hypothyroidism (TRUST) trial aimed to investigate cardiovascular,
129 but was underpowered due to recruitment challenges and revised its primary outcome to quality of life.¹⁵ An
130 upcoming trial in China will evaluate LT4 in older adults with SCH using age-specific TSH reference ranges,
131 with 254 participants and a 48-week follow-up.¹⁶ Consequently, fundamental questions regarding the long-term
132 impact of LT4 in this population remain unresolved, with no registered trials addressing this gap. A recent
133 United Kingdom cohort study (n = 53,899) reported cardiovascular benefits of LT4 but increased risks to bone
134 health and all-cause mortality.¹⁷ Systematic reviews have also highlighted the absence of evidence on long-term
135 cardiovascular and bone health outcomes in older adults with SCH over 50 years, emphasising the need for
136 further research.^{18,19}

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138 To address this evidence gap, this emulated target trial was developed.²⁰ By emulating an RCT with
139 observational primary care data,²¹ this study aimed to provide more causally robust evidence than traditional
140 observational designs. Notably, the ACEL UK ETT study uniquely evaluated LT4 treatment in individuals with
141 age-specific mildly elevated TSH levels, as defined by the TEARS study, offering clearer insight into its effects
142 in this group.

144 **Materials and Methods**

145 *Study Design and Setting*

146 This study employed an emulated target trial design using observational data to replicate the randomisation and
147 prospective follow-up of an RCT. The study drew upon data from The Health Improvement Network (THIN),
148 which includes electronic healthcare records from approximately 6% of the UK population. THIN contains
149 clinical information such as diagnoses, laboratory test results, and prescription data, enabling longitudinal
150 tracking of patient health and treatments. This database has shown generalisability to the UK population.²² The
151 study adhered to the Hernan and Robins framework (Table 1) to ensure robustness, with the protocol published
152 in November 2023.²⁰

154 *Study Population*

155 Data were extracted from the THIN database for patients aged over 50 years on January 1, 2006, with at least
156 one TSH reading exceeding 4.1 mU/L between January 1, 2006, and January 1, 2022. The inclusion and
157 exclusion criteria were then applied to this dataset.

159 *Inclusion criteria:*

- 160 1. Adults registered on the THIN database aged 50 years or older as of January 1, 2006.
- 161 2. TSH level between 4.01 mU/L and 10.0 mU/L at baseline.
- 162 3. FT4 level between 10.0pmol/L and 24.0pmol/L at baseline.²³

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Exclusion criteria:

1. History of thyroid cancer, hyperthyroidism or pituitary disease.
2. Use of drugs affecting thyroid function (liothyronine, lithium, or amiodarone).
3. Previous thyroid surgery or radioiodine treatment.
4. Pre-existing cardiovascular conditions or bone disease, depending on the outcome assessment.

The population was subsequently divided into three cohorts based on the findings of the TEARS study's TSH levels (Table 2).³

1. Cohort 1: Patients with a mildly elevated TSH level.
2. Cohort 1a: Patients within Cohort 1 with an age-specific normal TSH level.
3. Cohort 1b: Patients within Cohort 1 with an age-specific mildly elevated TSH level.

Treatment Strategies

The two primary exposures in this emulated target trial were:

1. **LT4 treatment:** Participants in this group received LT4 at baseline.
2. **No treatment:** Participants in this group did not receive LT4 at baseline.

A trial emulation design using an intention-to-treat approach was employed to assess the effect of LT4 on the time to first outcome event or death. Patients who had not previously used LT4 were assigned to the treatment group at the time of their first LT4 prescription, and they simultaneously met the eligibility criteria. For patients in the comparison (no treatment) group, the index date was established when they met eligibility criteria, with follow-up starting at eligibility for both groups.

Patient follow-up occurred over a 10-year period, between January 1, 2006, and January 1, 2022. The follow-up period for each patient began at their respective index date and continued until one of the following occurred: outcome event, deregistration from the database, death, or completion of ten years of follow-up. There was no grace period or minimum follow-up period implemented in the study design.²⁴

Outcome Measures

The primary outcome of this study was cardiovascular events, which included angina, myocardial infarction, peripheral vascular disease, stent procedures, and stroke. Secondary outcomes included bone health-related events (osteoporosis and fragility fractures) and all-cause mortality. Composite outcomes were identified using the International Classification of Diseases, 10th Edition (ICD-10) and Read Codes (Supplementary Data, Table 1). Mortality was determined based on the recorded date of death. The first occurrence of any outcome event was considered the event of interest for each patient.

Statistical Analysis

Baseline covariates were balanced between treatment groups using inverse probability of treatment weighting (IPTW).^{25,26} Weights were calculated from logistic regression models predicting treatment assignment, then stabilised for overall exposure and truncated at the 1st and 99th percentiles to ensure robustness. Covariates included age, sex assigned at birth, body mass index (BMI), Charlson Comorbidity Index (CCI),²⁷ total cholesterol, hypertension, concomitant hormonal medications (oestrogen, testosterone), TSH, and smoking status. E-values were calculated to assess the impact of unmeasured confounding.²⁸ Ethnicity was excluded from the analysis due to >50% missing data (Supplementary Data, Table 2).

For raw outcome comparisons, frequencies and percentages were presented. The primary analysis used weighted Cox proportional hazard ratios (HRs) with 95% confidence intervals (CIs) to assess associations between LT4 exposure and outcomes. A significance level of 0.01 was selected, following a Bonferroni correction from an initial significance level of 0.05.²⁹ Kaplan-Meier survival curves visualised survival probability differences between treatment groups. Missing data were addressed using multiple imputations with predictive mean matching and polytomous regression, depending on variable type.

Sensitivity analyses used alternative upper limit TSH cutoffs (4.5 and 5.0 mU/L) to account for variations in levels and laboratory ranges.²³ Additionally, cholesterol was removed from IPTW models, given its potential role as a mediator between SCH and cardiovascular disease. Subgroup analyses examined age, sex assigned at birth, smoking status, and baseline fT4 (above or below the population median). All analyses were performed using R version 4.4.2.³⁰

222 Based on the Kaplan-Meier curves suggesting time-varying cardiovascular effects, post-hoc analyses evaluated
223 LT4 impacts over time: (1) piecewise Cox regression with a five-year split, (2) landmark analysis restricting
224 follow-up to patients event-free at five years, and (3) restricted mean survival time (RMST) comparing event-
225 free survival up to five years and between five and ten years. Stabilised IPTW weights were used; all analyses
226 were exploratory and not pre-specified.

227 *Ethical Approval*

228 This study was approved by the University of Sunderland Research Ethics Group (ID 011081) and the THIN
229 Scientific Review Committee (protocol 22-003). THIN database has Health Research Authority ethical approval
230 for research (reference 20/SC/0011).

231 *Data Sharing*

232 The data that supports the findings of this study are available from THIN, a wholly owned subsidiary of
233 Cegecim SA, which owns the proprietary rights to THIN data. Restrictions apply to the availability of these
234 data, which were used under license for the current study and are not publicly available. Data are, however,
235 available from the authors upon reasonable request and with the permission of THIN.

239 **Findings**

240 There were 282,036 initial patient records received from THIN. After applying the study criteria for
241 cardiovascular outcomes, 264,281 patients were removed (Supplementary Data, Figure 1). There were 22,621
242 patients included in the analyses for Cohort 1, with 14,064 (62.2%) taking LT4 and 8,557 (37.8%) receiving no
243 treatment. Cohort 1a comprised 4,951 patients, with 1,398 (28.2%) receiving treatment and 3,553 (71.2%) not.
244 Cohort 1b comprised 17,670 patients, with 12,666 (71.7%) prescribed LT4 and 5,004 (28.3%) not. The median
245 (interquartile range) follow-up for cardiovascular outcomes was 10.0 (10.0 – 10.0) years for all three groups.
246 Among treated patients in Cohort 1, the median baseline and follow-up LT4 dose was 50 [IQR 25–50] mcg/day.
247 At baseline, treated patients were more likely to have fT4 values below the cohort median compared with
248 untreated patients across cohorts (Cohort 1: 57.5% vs 33.9%; Cohort 1a: 50.7% vs 32.2%; Cohort 1b: 58.2% vs
249 35.1%), with untreated patients more frequently having fT4 values above the median. The study population had
250 a higher proportion of females than males, with the majority aged 61–70 years. Ethnicity was predominantly
251 White, with a small representation of Black patients (0.5%). Baseline characteristics were balanced after
252 weighting (Table 3), as presented by standardised mean differences less than 0.1 (Supplementary Data, Table 3).

253 For bone health outcomes, 256,984 patients were excluded based on the eligibility criteria, leaving 25,052
254 patients for weighting. Among these, 15,216 (60.7%) were prescribed LT4, while 9,836 (39.2%) were not,
255 comprising Cohort 1. Cohort 1a included 5,816 patients, with 27.7% treated and 72.2% untreated. Cohort 1b
256 consisted of 19,236 patients, of whom 70.7% were treated and 29.3% were untreated. All three groups had a
257 median (interquartile range) follow-up time of 10.0 (8.9–10.0) years for bone health outcomes.

258 A total of 254,773 patients were excluded based on the trial's exclusion criteria for all-cause mortality outcomes,
259 leaving 27,263 patients eligible for weighting. Of these, 60.9% were assigned to LT4, and 39.0% were not. In
260 Cohort 1a, out of 6,371 patients, 28.1% were prescribed LT4, and 71.9% were not. In Cohort 1b, out of 20,892
261 patients, 71% were prescribed LT4, and 29% were not. All three groups had a median (interquartile range)
262 follow-up time of 10.0 (10.0–10.0) years for all-cause mortality outcomes.

263 Cardiovascular outcomes: Across all three cohorts, the treatment group had lower cardiovascular event rates
264 than the control group (10.1% vs 13.0% in Cohort 1, 13.1% vs 15.0% in Cohort 1a, and 9.8% vs 11.6% in
265 Cohort 1b). Cohort 1 exhibited significantly reduced long-term cardiovascular risk when prescribed LT4
266 treatment (Table 4). Cohort 1a showed no association between LT4 treatment and cardiovascular outcomes.
267 Treatment with LT4 in cohort 1b demonstrated a beneficial effect.

268 Bone health outcomes: Across all three groups, there was a similar proportion of adverse bone health outcomes,
269 regardless of LT4 treatment. Cohort 1 revealed an IPTW-adjusted HR of 1.04 (95% CI 0.93–1.17; $p = 0.45$),
270 indicating no increased risk of osteoporosis or fragility fractures when prescribed LT4. Cohort 1a and Cohort 1b
271 displayed similar findings.

272 All-cause mortality: Cohort 1 and Cohort 1b had lower mortality in the treatment group compared to the control
273 group (23.8% vs. 30.0% in Cohort 1 and 18.3% vs. 25.0% in Cohort 1b); Cohort 1a showed similar proportions
274 (37.4% vs 36.5%) across both the LT4-treated and control groups. Cohort 1 indicated a significantly reduced
275 all-cause mortality risk associated with using LT4, presented by IPTW-adjusted HR's. Cohorts 1a and 1b
276 presented a similar association.

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282 IPTW-adjusted HRs were also calculated for various subgroups (Supplementary Data, Table 4). These
283 generally showed no significant associations across outcomes, likely due to limited sample sizes. An exception
284 was observed for all-cause mortality, where LT4 use was consistently associated with a favourable outcome,
285 other than Cohort 1a. Additionally, sensitivity analyses using varying TSH cutoffs (4.5 and 5.0 mU/L) yielded
286 results consistent with the primary HRs (Supplementary Data, Table 5). A third sensitivity analysis, excluding
287 cholesterol from the IPTW model, also produced consistent findings. E-values corresponding to the primary
288 HRs (up to 1.94) suggest that substantial unmeasured confounding would be needed to explain the observed
289 associations (Supplementary Data, Table 5).

290
291 The Kaplan-Meier plot for Cohort 1 suggests early and late effects of LT4 treatment, with non-significant
292 cardiovascular outcomes until approximately 2,000 days (Figure 1). Beyond this, the treatment group showed a
293 significantly higher survival rate. The Kaplan-Meier plot for Cohort 1b displayed similar findings. Conversely,
294 the Kaplan-Meier plot for Cohort 1a illustrated no difference in the survival probability, regardless of LT4 status
295 (Supplementary Data, Figure 2).

296 297 *Post-Hoc Analyses*

298 Visual inspection of Kaplan-Meier cardiovascular event-free survival curves (Figure 1) suggested differences
299 between LT4-treated and untreated groups, varying over time, with a trend toward improved cardiovascular
300 outcomes in the LT4 group after approximately five years. To assess this time-varying effect, we conducted
301 piecewise Cox regression, landmark, and RMST analyses. Piecewise Cox regression showed a non-significant
302 adverse effect of LT4 within the first five years (HR 1.08; 95% CI 0.94–1.25; $p = 0.25$), but a significant
303 protective effect from five to ten years (HR 0.54; 95% CI 0.44–0.66; $p < 0.001$), consistent across Cohorts 1a
304 and 1b (Supplementary Material, Table 7). Landmark analysis, restricted to patients event-free at five years,
305 confirmed reduced cardiovascular risk beyond five years of LT4 treatment (Cohort 1, HR 0.58; 95% CI 0.50–
306 0.68; $p < 0.001$, Cohort 1a, HR 0.59; 95% CI 0.43–0.80; $p < 0.001$, Cohort 1b, HR 0.58; 95% CI 0.49–0.69; p
307 < 0.001). RMST analysis further supported these findings, with LT4 patients experiencing ~21 fewer event-free
308 days in the first five years but gained ~24 event-free days between five and ten years. Together, these post-hoc
309 analyses suggest a delayed but significant cardiovascular benefit of LT4 treatment.

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311 **Discussion**

312 *Summary of the Main Findings*

313 In this emulated target trial using UK primary care data, LT4 in older adults with SCH was associated with
314 long-term reduced cardiovascular events and all-cause mortality. No cardiovascular benefit was observed among
315 those with age-specific TSH values, suggesting that modest TSH elevations in older adults may reflect
316 physiological ageing rather than clinically relevant thyroid dysfunction. Importantly, we also observed no
317 adverse effects on bone health associated with LT4 in the ageing SCH population. Post-hoc analyses showed
318 cardiovascular benefits of LT4 were not significant in the first five years of treatment but became substantial
319 between five and ten years of follow-up, specifically in individuals treated with an age-specific elevated TSH
320 level.

321 322 *Comparison with Other Literature*

323 This ETT confirms cardiovascular benefits of LT4 in older adults with SCH, reinforcing findings from a
324 previous cohort study involving over 53,000 patients.¹⁷ Notably, it demonstrates no adverse effects on bone
325 health and a significant reduction in all-cause mortality. These differences may be attributed to the superior
326 methodological design of the ETT, which effectively emulates a hypothetical RCT within a large dataset. In
327 contrast, the TRUST trial, a RCT involving just 737 participants, lacked statistical power to detect meaningful
328 cardiovascular outcomes and failed to demonstrate significant benefits. This underscores the limitations inherent
329 in clinical trials, specifically on ageing SCH patients. A recently published systematic review further emphasises
330 this study's relevance. The review revealed inconsistent evidence regarding long-term cardiovascular and bone
331 health effects of LT4 due to variations in sample sizes and follow-up periods.¹⁸ Through a large sample size,
332 decade-long follow-up, and rigorous methods, this ETT provides the most comprehensive real-world evidence
333 to date regarding LT4 outcomes in an ageing SCH population.

334 335 *Strengths and Weaknesses*

336 This study has notable strengths. To our knowledge, it is the most extensive and methodologically robust study
337 to evaluate the long-term effects of LT4 in ageing adults with SCH. With over 22,000 patients included and a
338 10-year follow-up, the study's size and duration considerably enhance the validity and reliability of its
339 findings.²¹ The ETT design, combined with IPTW and adjustment for multiple clinically relevant confounders,

340 enhances confidence in causal relationships.²⁶ Importantly, multiple sensitivity analyses confirmed the primary
341 results and provided plausible explanations for the observed effects. While both this ETT and our prior cohort
342 study demonstrated cardiovascular benefits of LT4, only the ETT found no adverse bone effects and a reduction
343 in mortality risk.¹⁷ These differences likely reflect the methodological superiority of the ETT, emulating a
344 hypothetical gold-standard RCT. Fundamentally, by utilising existing big data, this trial addresses the cost,
345 recruitment, and retention challenges that have limited prior RCTs, as highlighted in the recent systematic
346 review.¹⁸

347
348 There are several limitations to consider. Cause-of-death data were unavailable, which limited the interpretation
349 of mortality outcomes and potentially introduced selection bias. Although IPTW was employed, residual
350 confounding from unmeasured variables remains possible. Additionally, many patients had only a single
351 recorded TSH measurement and one LT4 prescription, restricting our ability to evaluate treatment adherence,
352 LT4 dose, and thyroid function control; however, this reflects the intention-to-treat design of the target trial
353 emulation. Defining SCH based on a single baseline TSH may have introduced misclassification bias, as some
354 individuals may have had transient TSH elevations that would normalise on repeat testing. The absence of
355 ethnic data further limited subgroup analyses. Lastly, while the THIN database is representative of the UK
356 population, the findings may not be generalisable to other healthcare settings or populations with different
357 characteristics.

358 359 *Implications for Practice and Research*

360 To our knowledge, this is the first long-term follow-up study describing the causal effects of LT4 in older adults
361 with SCH. As an observational emulated target trial, these findings may be affected by residual confounding and
362 health-care-seeking behaviour and should be interpreted with caution. RCTs in this population are unlikely, as
363 demonstrated by recruitment challenges in prior studies, including the underpowered TRUST trial, which
364 enrolled only 737 patients.¹⁵ In contrast, this study represents the largest observational emulated target trial to
365 date, involving over 22,000 patients. Given practical and financial barriers to conducting a trial of this scale,
366 high-quality emulated trials currently provide the most reliable available evidence. Our findings suggest
367 clinicians and guideline authors should consider the routine LT4 use in older adults with age-specific TSH
368 levels and a selective, risk-based treatment approach. Using standard TSH reference ranges risks over-diagnosis
369 and unnecessary intervention in adults over 50 years. Future research will likely rely on emulated target trials
370 with large, generalisable population datasets.

371 372 **Author Contribution**

373 Mia Holley: writing – original draft (lead); methodology (supporting); data curation (lead), formal analysis
374 (lead); writing – review and editing (equal). Salman Razvi: Conceptualisation (supporting); methodology
375 (supporting); formal analysis (supporting); writing – review and editing (equal). Ian Maxwell: methodology
376 (supporting); formal analysis (supporting); writing – review and editing (equal). Rosie Dew: methodology
377 (supporting); formal analysis (lead); writing – review and editing (equal). Scott Wilkes: Conceptualisation
378 (lead); funding acquisition (lead); methodology (lead); formal analysis (lead); writing – review and editing
379 (equal).

380 381 **Author Disclosure Statement**

382 Salman Razvi has received speaker fees from Meck KGaA and Berlin Chemie AG, makers of Levothyroxine.
383 All other authors declare that there were no conflicts of interest.

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392	List of Abbreviations	
393	ACEL-UK-ETT	Assessing the Cardiovascular Effects of Levothyroxine Use in an Ageing United
394		Kingdom Population: an Emulated Target Trial
395	aHR	Adjusted hazard ratio
396	ARC	Applied Research Collaboration
397	BMI	Body mass index
398	CCI	Charlson comorbidity index
399	CI	Confidence interval
400	ft4	Free thyroxine
401	HR	Hazard ratio
402	ICD-10	International Classification of Diseases, 10th Edition
403	IPTW	Inverse probability of treatment weighting
404	LT4	Levothyroxine
405	NIHR	National Institute for Health and Care Research
406	RCT	Randomised controlled trial
407	RMST	Restricted Mean Survival Time
408	SCH	Subclinical hypothyroidism
409	TEARS	Thyroid Epidemiology, Audit, and Research Study
410	THIN	The Health Improvement Network
411	TRUST	Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism
412	TSH	Thyrotropin
413	UK	United Kingdom

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488 **Table 1 Overview of the target trial and trial emulation study protocols to estimate the effect of levothyroxine on cardiovascular, bone health and mortality**
 489 **outcomes.**²⁰

Protocol Components	Target Trial (ideal randomised controlled trial)	Trial Emulation using observational data
Eligibility criteria	<ul style="list-style-type: none"> Adults aged >50 years and under 101 years on January 1, 2006. Patients with a baseline thyrotropin level between 4.01 mU/L and 10.0 mU/L. Patients with a baseline free thyroxine level between 10.0pmol/L and 24.0pmol/L. No previous thyroid cancer, pituitary disease, radioiodine treatment, thyroid surgery or hyperthyroidism history. No use of drugs that affect thyroid function (lithium, amiodarone, or lithium). No angina, myocardial infarction, peripheral vascular disease, stent, or stroke history (<i>cardiovascular outcome only</i>). No osteoporosis or fragility fracture history (<i>bone health outcome only</i>). 	Same as the target trial.
Treatment strategies	<ol style="list-style-type: none"> Patients who initiated levothyroxine. Patients who initiated the placebo. 	<ol style="list-style-type: none"> Patients who initiated levothyroxine. Patients who did not initiate levothyroxine.
Assignment procedures	Participants were randomly assigned to either strategy at baseline and were unaware of the strategy to which they were assigned.	Randomisation was emulated via inverse probability of treatment weighting (IPTW), using baseline confounders.
Follow-up period	Started at randomisation and ended at death, outcome event, administrative censoring, or ten years after follow-up began.	Similar: Started at assignment to treatment strategy and ended at death, outcome event, administrative censoring, or ten years after trial inception.
Outcome	Cardiovascular, bone health, or mortality event within ten years of baseline.	Same as the target trial.
Causal contrasts of interest	Intention-to-treat effect.	Observational analogue of the intention-to-treat principle.
Analysis plan	Cox proportional hazard models (one for each outcome event type: cardiovascular, bone health, and all-cause mortality).	Same as the target trial, except that Cox proportional hazard models were weighted through IPTW.

490 **Table 2 Categorisation of patient cohorts in the study, split by age and thyrotropin (TSH) levels.**
 491

Age, y	Cohort 1 TSH level (mU/L)	Cohort 1a TSH level (mU/L)	Cohort 1b TSH level (mU/L)
51-60	[4.01-10.00]	[4.01-4.40]	[4.41-10.00]
61-70	[4.01-10.00]	[4.01-4.60]	[4.61-10.00]
71-80	[4.01-10.00]	[4.01-5.00]	[5.01-10.00]
81-90	[4.01-10.00]	[4.01-5.50]	[5.51-10.00]
91-100	[4.01-10.00]	[4.01-5.90]	[5.91-10.00]

492

493 **Table 3 Baseline characteristics of participants.**

Characteristic, N (%)	Cohort 1, Treatment (n = 14,064)	Cohort 1, Control (n = 8,557)	Cohort 1a, Treatment (n = 1,398)	Cohort 1a, Control (n = 3,553)	Cohort 1b, Treatment (n = 12,666)	Cohort 1b, Control (n = 5,004)
Sex Assigned at Birth						
Female	10793 (76.7)	6086 (71.1)	1106 (79.1)	2537 (71.4)	9687 (76.5)	3549 (70.9)
Male	3271 (23.3)	2471 (28.9)	292 (20.9)	1016 (28.6)	2979 (23.5)	1455 (29.1)
Age (years)						
51-60	4085 (29)	2710 (31.7)	193 (13.8)	683 (19.2)	3892 (30.7)	2027 (40.5)
61-70	4696 (33.4)	2797 (32.7)	335 (24)	1059 (29.8)	4361 (34.4)	1738 (34.7)
71-80	3387 (24.1)	2303 (26.9)	435 (31.1)	1286 (36.2)	2952 (23.3)	1017 (20.3)
81-90	1654 (11.8)	689 (8.1)	369 (26.4)	482 (13.6)	1285 (10.1)	207 (4.1)
91+	242 (1.7)	58 (0.7)	66 (4.7)	43 (1.2)	176 (1.4)	15 (0.3)
Median [lower quartile, upper quartile]	66 [59, 75]	66 [58, 74]	74 [65, 82]	71 [62, 77]	66 [59, 74]	63 [57, 70]
Ethnicity						
Asian	434 (3.1)	240 (2.8)	36 (2.6)	99 (2.8)	398 (3.1)	141 (2.8)
Black	68 (0.5)	39 (0.5)	7 (0.5)	12 (0.3)	61 (0.5)	27 (0.5)
Mixed	4572 (32.5)	2825 (33)	432 (30.9)	1130 (31.8)	4140 (32.7)	1695 (33.9)
Other	132 (0.9)	77 (0.9)	21 (1.5)	34 (1)	111 (0.9)	43 (0.9)
White	8858 (63)	5376 (62.8)	902 (64.5)	2278 (64.1)	7956 (62.8)	3098 (61.9)
Location						
London	1000 (7.1)	571 (6.7)	83 (5.9)	209 (5.9)	917 (7.2)	362 (7.2)
Midlands and East	2364 (16.8)	1256 (14.7)	167 (11.9)	520 (14.6)	2197 (17.3)	736 (14.7)
North	2369 (16.8)	1943 (22.7)	195 (13.9)	782 (22)	2174 (17.2)	1161 (23.2)
Northern Ireland	957 (6.8)	381 (4.5)	110 (7.9)	185 (5.2)	847 (6.7)	196 (3.9)
Scotland	1609 (11.4)	805 (9.4)	200 (14.3)	362 (10.2)	1409 (11.1)	443 (8.9)
South	3518 (25)	1879 (22)	358 (25.6)	688 (19.4)	3160 (24.9)	1191 (23.8)
Wales	2247 (16)	1722 (20.1)	285 (20.4)	807 (22.7)	1962 (15.5)	915 (18.3)
Smoker status						
Smoker	1065 (7.6)	601 (7)	86 (6.2)	228 (6.4)	979 (7.7)	373 (7.5)
Past smoker	4491 (31.9)	2654 (31)	439 (31.4)	1095 (30.8)	4052 (32)	1559 (31.2)
Non-smoker	8508 (60.5)	5302 (62)	873 (62.4)	2230 (62.8)	7635 (60.3)	3072 (61.4)
Comorbidities						
Asthma	1328 (9.4)	647 (7.6)	112 (8)	242 (6.8)	1216 (9.6)	405 (8.1)
BMI, median [lower quartile, upper quartile]	28.1 [24.9, 32.2]	28.1 [24.8, 32.1]	27.7 [24.6, 32.0]	27.9 [24.7, 31.8]	28.1 [24.9, 32.2]	28.1 [24.8, 32.3]
Chronic kidney disease	1621 (11.5)	36 (0.4)	235 (16.8)	15 (0.4)	1386 (10.9)	21 (0.4)
Chronic obstructive pulmonary disease	1978 (14.1)	1020 (11.9)	170 (12.2)	403 (11.3)	1808 (14.3)	617 (12.3)
Dementia	160 (1.1)	17 (0.2)	37 (2.6)	14 (0.4)	123 (1)	3 (0.1)
Depression	2032 (14.4)	846 (9.9)	162 (11.6)	326 (9.2)	1870 (14.8)	520 (10.4)
Diabetes	168 (1.2)	178 (2.1)	19 (1.4)	75 (2.1)	149 (1.2)	103 (2.1)
Dyslipidaemia	1589 (11.3)	681 (8)	175 (12.5)	283 (8)	1414 (11.2)	398 (8)
Hormones	201 (1.4)	104 (1.2)	13 (0.9)	44 (1.2)	188 (1.5)	60 (1.2)
Hypertension	7071 (50.3)	4299 (50.2)	796 (56.9)	1941 (54.6)	6275 (49.5)	2358 (47.1)
Rheumatoid arthritis	445 (3.2)	205 (2.4)	57 (4.1)	96 (2.7)	388 (3.1)	109 (2.2)
Thyroid Hormone Levels						
Low-normal free thyroxine	8081 (57.5)	2900 (33.9)	709 (50.7)	1143 (32.2)	7372 (58.2)	1757 (35.1)
High-normal free thyroxine	5983 (42.5)	5657 (66.1)	689 (49.3)	2410 (67.8)	5294 (41.8)	3247 (64.9)

Characteristic, N (%)	Cohort 1, Treatment (n = 14,064)	Cohort 1, Control (n = 8,557)	Cohort 1a, Treatment (n = 1,398)	Cohort 1a, Control (n = 3,553)	Cohort 1b, Treatment (n = 12,666)	Cohort 1b, Control (n = 5,004)
TSH, median [lower quartile, upper quartile]	6.5 [5.5, 7.9]	4.8 [4.4, 5.6]	4.5 [4.3, 4.8]	4.3 [4.2, 4.5]	6.8 [5.8, 8.1]	5.4 [4.9, 6.1]

494 *Cohort 1: Patients aged over 50 years with a thyrotropin (TSH) level between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine (fT4) level.*

495 *Cohort 1a: Patients aged over 50 years with a thyrotropin level between 4.1 mU/L and the age-specific upper limit and a normal fT4 level.*

496 *Cohort 1b: Patients aged over 50 years with a thyrotropin level between the age-specific upper limit and 10.0 mU/L and a normal fT4 level.*

497 *Low-normal and high-normal fT4 levels are defined as above or below the median baseline fT4 level.*

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499 **Table 4 Outcomes of the 10-year follow-up cohort study represented by raw numbers and IPTW-adjusted hazard ratios (aHR), 95% confidence intervals (CI) and**
500 **p-values.**

Outcome	Cohort 1			Cohort 1a			Cohort 1b		
	N (%), Treatment	N (%), Control	aHR (95% CI), p-value	N (%), Treatment	N (%), Control	aHR (95% CI), p-value	N (%), Treatment	N (%), Control	aHR (95% CI), p-value
Cardiovascular	1426 (10.1)	1114 (13.0)	0.82 (0.74, 0.91), p < 0.0001	183 (13.1)	532 (15.0)	0.93 (0.78, 1.11), p = 0.42	1243 (9.8)	582 (11.6)	0.85 (0.75, 0.96), p = 0.011
Bone Health	1286 (8.5)	841 (8.6)	1.04 (0.93, 1.17), p = 0.45	185 (11.5)	419 (10.0)	1.14 (0.95, 1.37), p = 0.15	1101 (8.1)	422 (7.5)	1.03 (0.89, 1.18), p = 0.71
All-Cause Mortality	3951 (23.8)	3189 (30.0)	0.71 (0.67, 0.75), p < 0.0001	669 (37.4)	1671 (36.5)	0.8 (0.72, 0.89), p < 0.0001	981 (18.3)	1343 (25.0)	0.68 (0.63, 0.73), p < 0.0001

501 *Cohort 1: Patients aged over 50 years with a thyrotropin (TSH) level between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine (fT4) level.*

502 *Cohort 1a: Patients aged over 50 years with a TSH level between 4.1 mU/L and the age-specific upper limit and a normal fT4 level.*

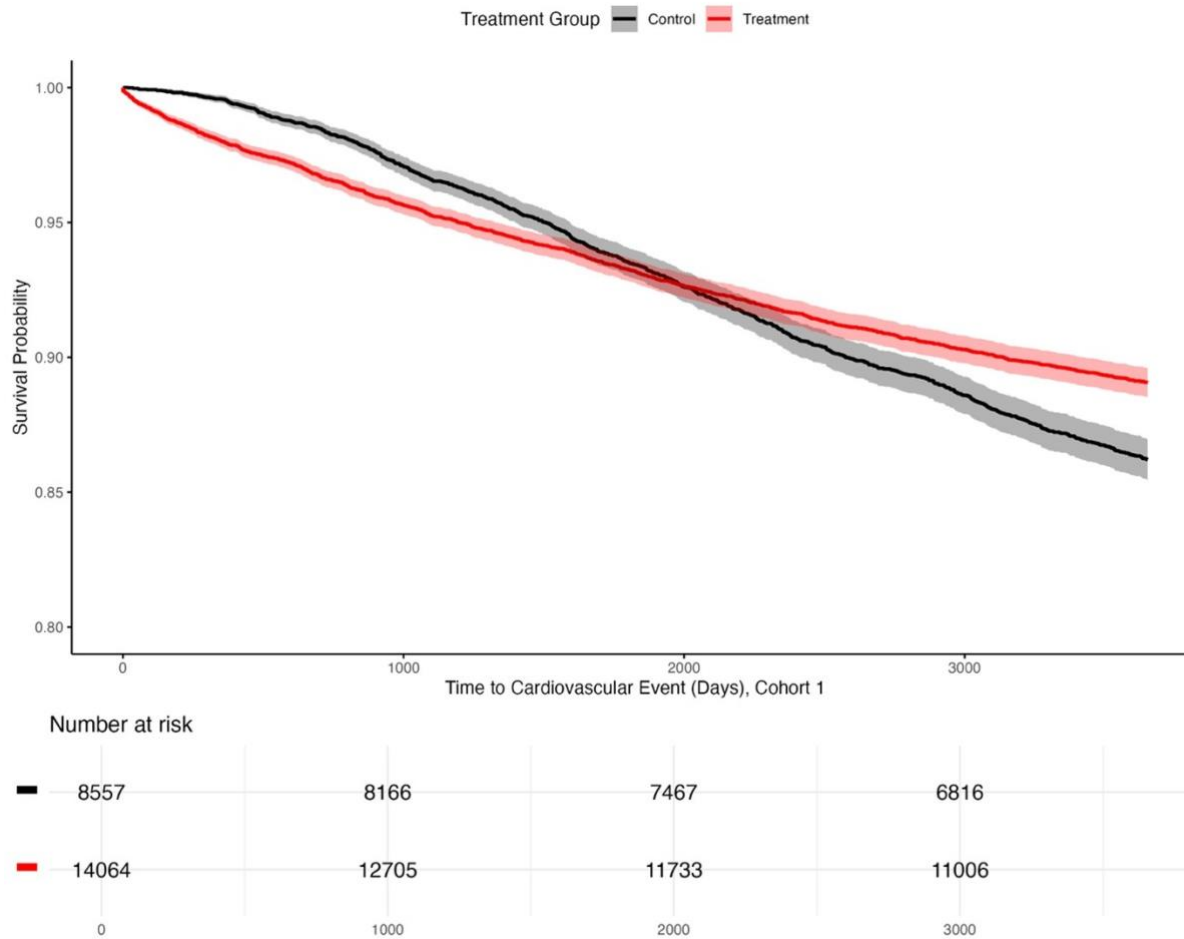
503 *Cohort 1b: Patients aged over 50 years with a TSH level between the age-specific upper limit and 10.0 mU/L and a fT4 level.*

504 Hazard ratios were adjusted through inverse probability of treatment weighting (IPTW) for age, sex assigned at birth, body mass index, Charlson comorbidity index, total
505 cholesterol, hypertension, thyrotropin, hormonal medications, and smoking.

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508 **Figure 1 Kaplan-Meier plots illustrating survival probabilities over time for cardiovascular outcomes.**
 509 *Cohort 1: Patients aged over 50 years with a thyrotropin level between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine level.*



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Supplementary Data
Table 1 Outcome International Classification of Diseases, 10th Edition (ICD-10) diagnosis codes.

Cardiovascular		Bone Health	
ICD-10 code	Diagnosis	ICD-10 code	Diagnosis
I60	H/O sub-arachnoid haemorrhage	M81·9	Osteoporosis
I70·8	Atherosclerotic retinopathy	M81·9	Osteoporosis, unspecified
I70·8	Arteriosclerotic retinopathy	M81·8	Senile osteoporosis
I70·8	Atheroscleritic retinopathy	M81·0	Postmenopausal osteoporosis
I21·9	Acute myocardial infarction	M81·5	Idiopathic osteoporosis
I21·9	Attack - heart	M81·2	Dissuse osteoporosis
I21·9	Coronary thrombosis	M81·4	Drug-induced osteoporosis
I21·9	Cardiac rupture following myocardial infarction (MI)	M81·1	Postophorectomy osteoporosis
I21·9	Heart attack	M81·3	Postsurgical malabsorption osteoporosis
I21·9	MI - acute myocardial infarction	M81·6	Localized osteoporosis - Lequesne
I21·9	Thrombosis - coronary	M81·9	Vertebral osteoporosis
I21·9	Silent myocardial infarction	M81·6	Osteoporosis localized to spine
I21·0	Acute anterolateral infarction	M81·4	Osteoporosis due to corticosteroids
I21·0	Other specified anterior myocardial infarction	M81·9	Osteoporosis NOS
I21·0	Acute anteroapical infarction	M84·4	Sponaneous fracture
I21·0	Acute anteroseptal infarction	M80·3	Postsurgical malabsorption osteoporosis with path fracture
I21·0	Anterior myocardial infarction NOS	M80·9	Fragility fracture due to unspecified osteoporosis
I21·1	Acute inferolateral infarction	M80·9	Minimal trauma fracture due to unspecified osteoporosis
I21·1	Acute inferoposterior infarction	M84·4	Fragility fracture
I21·2	Posterior myocardial infarction NOS	M84·4	Minimal trauma fracture
I21·2	Lateral myocardial infarction NOS	M81·2	Disuse atrophy of bone
I21·2	True posterior myocardial infarction	M81·8	[X]Other osteoporosis
I21·4	Acute subendocardial infarction	S32·0	Closed fracture lumbar vertebra

I21·4	Acute non-Q wave infarction	S32·0	Closed fracture lumbar vertebra, burst
I21·9	Acute non-ST segment elevation myocardial infarction	S32·0	Closed fracture lumbar vertebra, wedge
I21·1	Inferior myocardial infarction NOS	S32·0	Closed fracture lumbar vertebra, spondylolysis
I21·3	Acute Q-wave infarct	S32·0	Closed fracture lumbar vertebra, spinous process
I21·9	Mural thrombosis	S32·0	Closed fracture lumbar vertebra, transverse process
I21·2	Acute posterolateral myocardial infarction	S32·0	Closed fracture lumbar vertebra, posterior arch
I21·3	Acute transmural myocardial infarction of unspecif site	S32·0	Closed fracture lumbar vertebra, tricolunar
I21·9	Acute ST segment elevation myocardial infarction	S32·0	Open fracture lumbar vertebra
I21·9	Other acute myocardial infarction	S32·0	Open fracture lumbar vertebra, burst
I21·9	Acute atrial infarction	S32·0	Open fracture lumbar vertebra, wedge
I21·4	Acute papillary muscle infarction	S32·0	Open fracture lumbar vertebra, spondylolysis
I21·2	Acute septal infarction	S32·0	Open fracture lumbar vertebra, spinous process
I21·1	Other acute myocardial infarction NOS	S32·0	Open fracture lumbar vertebra, transverse process
I21·9	Acute myocardial infarction NOS	S32·0	Open fracture lumbar vertebra, posterior arch
I20·0	Preinfarction syndrome	S32·0	Open fracture lumbar vertebra, tricolunar
I20·0	Crescendo angina	S32·1	Closed fracture sacrum
I20·0	Impending infarction	S32·1	Closed compression fracture sacrum
I20·0	Unstable angina	S32·1	Closed vertical fracture of sacrum
I20·0	Angina at rest	S32·1	Open fracture sacrum
I20·0	Unstable angina	S32·1	Open compression fracture sacrum
I20·0	Angina at rest	S32·1	Open vertical fracture of sacrum
I20·0	Refractory angina	S32·8	Closed fracture pelvis, coccyx
I20·0	Worsening angina	S32·8	Open fracture pelvis, coccyx
I20·0	Acute coronary syndrome	S32	Fracture of lumbar spine and pelvis
I20·0	Preinfarction syndrome NOS	S32·0	Fracture of lumbar vertebra
I20	Angina pectoris	S32·1	Fracture of sacrum
I20·0	Angina decubitus	S32·2	Fracture of coccyx

I20·8	Nocturnal angina	S32·3	Fracture of ilium
I20·0	Angina decubitus NOS	S32·4	Fracture of acetabulum
I20·1	Prinzmetal's angina	S32·5	Fracture of pubis
I20·1	Variant angina pectoris	S32·7	Multiple fractures of lumbar spine and pelvis
I20·1	Coronary artery spasm	S32·0	Closed fracture of lumbar spine with spinal cord lesion
I20·9	Angina pectoris NOS	S32·0	Closed spinal fracture with unspecified lumbar cord lesion
I20·8	Status anginosus	S32·0	Closed spinal fracture with complete lumbar cord lesion
I20·8	Stenocardia	S32·0	Closed spinal fracture with anterior lumbar cord lesion
I20·8	Syncope anginosa	S32·0	Closed spinal fracture with central lumbar cord lesion
I20·8	Angina on effort	S32·0	Closed spinal fracture with posterior lumbar cord lesion
I20·9	Ischaemic chest pain	S32·0	Closed spinal fracture with cauda equina lesion
I20·9	Post infarct angina	S32·0	Open fracture of lumbar spine with spinal cord lesion
I20·9	New onset angina	S32·0	Open spinal fracture with unspecified lumbar cord lesion
I20·9	Stable angina	S32·0	Open spinal fracture with complete lumbar cord lesion
I20·9	Angina pectoris NOS	S32·0	Open spinal fracture with anterior lumbar cord lesion
I22	Subsequent myocardial infarction	S32·0	Open spinal fracture with central lumbar cord lesion
I22·0	Subsequent myocardial infarction of anterior wall	S32·0	Open spinal fracture with posterior lumbar cord lesion
I22·1	Subsequent myocardial infarction of inferior wall	S32·0	Open spinal fracture with cauda equina lesion
I22·8	Subsequent myocardial infarction of other sites	S32·0	Open spinal fracture with incomplete lumbar cord lesion NOS
I22·9	Subsequent myocardial infarction of unspecified site	S32·1	Closed fracture of sacrum with spinal cord lesion
I23	Certain current complication follow acute myocardial infarct	S32·1	Closed fracture of sacrum with unspec spinal cord lesion
I23·0	Haemopericardium/current comp folow acute myocardial infarct	S32·1	Closed fracture of sacrum with complete cauda equina lesion
I23·1	Atrial septal defect/curr comp folow acute myocardial infarct	S32·1	Closed fracture of sacrum with other cauda equina injury
I23·2	Ventric septal defect/curr comp fol acute myocardial infarctn	S32·1	Closed fracture of sacrum with other spinal cord injury
I23·3	Ruptur cardiac wall w/out haemopericard/cur comp fol ac MI	S32·1	Closed fracture of sacrum with spinal cord lesion NOS
I23·4	Ruptur chordae tendinae/curr comp fol acute myocardial infarct	S32·1	Open fracture of sacrum with spinal cord lesion
I23·5	Rupture papillary muscle/curr comp fol acute myocardial infarct	S32·1	Open fracture of sacrum with unspecified spinal cord lesion

I23·6	Thrombosis atrium,auric append&vent/curr comp foll acute MI	S32·1	Open fracture of sacrum with complete cauda equina lesion
I20·8	Cardiac syndrome X	S32·1	Open fracture of sacrum with other cauda equina injury
I20·8	Coronary microvascular disease	S32·1	Open fracture of sacrum with other spinal cord injury
I23·8	Post infarction pericarditis	S32·1	Open fracture of sacrum with spinal cord lesion NOS
I60·9	Subarachnoid haemorrhage	S32·2	Closed fracture of coccyx with spinal cord lesion
I60·7	Ruptured berry aneurysm	S32·2	Closed fracture of coccyx with unspec spinal cord lesion
I60·0	Subarachnoid haemorrhage from carotid siphon and bifurcation	S32·2	Closed fracture of coccyx with complete cauda equina lesion
I60·1	Subarachnoid haemorrhage from middle cerebral artery	S32·2	Closed fracture of coccyx with other cauda equina injury
I60·2	Subarachnoid haemorrhage from anterior communicating artery	S32·2	Closed fracture of coccyx with other spinal cord injury
I60·3	Subarachnoid haemorrhage from posterior communicating artery	S32·2	Closed fracture of coccyx with spinal cord lesion NOS
I60·4	Subarachnoid haemorrhage from basilar artery	S32·2	Open fracture of coccyx with spinal cord lesion
I60·5	Subarachnoid haemorrhage from vertebral artery	S32·2	Open fracture of coccyx with unspecified spinal cord lesion
I60·7	Subarachnoid haemorrh from intracranial artery, unspecif	S32·2	Open fracture of coccyx with complete cauda equina lesion
I60·9	Subarachnoid haemorrhage NOS	S32·2	Open fracture of coccyx with other cauda equina injury
I61	Intracerebral haemorrhage	S32·2	Open fracture of coccyx with other spinal cord injury
I61	CVA - cerebrovascular accid due to intracerebral haemorrhage	S32·2	Open fracture of coccyx with spinal cord lesion NOS
I61	Stroke due to intracerebral haemorrhage	S32·8	Fracture or disruption of pelvis
I61·1	Cortical haemorrhage	S32·4	Closed fracture acetabulum
I61·0	Internal capsule haemorrhage	S32·4	Closed fracture acetabulum, anterior lip alone
I61·0	Basal nucleus haemorrhage	S32·4	Closed fracture acetabulum, posterior lip alone
I61·4	Cerebellar haemorrhage	S32·4	Closed fracture acetabulum, anterior column
I61·3	Pontine haemorrhage	S32·4	Closed fracture acetabulum, posterior column
I61·3	Bulbar haemorrhage	S32·4	Closed fracture acetabulum, floor
I61·0	External capsule haemorrhage	S32·4	Closed fracture acetabulum, double column transverse
I61·5	Intracerebral haemorrhage, intraventricular	S32·4	Closed fracture acetabulum, double column unspecified
I61·6	Intracerebral haemorrhage, multiple localized	S32·4	Other specified closed fracture acetabulum
I61·1	Lobar cerebral haemorrhage	S32·4	Closed fracture acetabulum NOS

I61·2	Intracerebral haemorrhage in hemisphere, unspecified	S32·4	Open fracture acetabulum
I61·2	Left sided intracerebral haemorrhage, unspecified	S32·4	Open fracture acetabulum, anterior lip alone
I61·2	Right sided intracerebral haemorrhage, unspecified	S32·4	Open fracture acetabulum, posterior lip alone
I61·9	Intracerebral haemorrhage NOS	S32·4	Open fracture acetabulum, anterior column
I62	Other and unspecified intracranial haemorrhage	S32·4	Open fracture acetabulum, posterior column
I62·1	Extradural haemorrhage - nontraumatic	S32·4	Open fracture acetabulum, floor
I62·0	Subdural haemorrhage - nontraumatic	S32·4	Open fracture acetabulum, double column transverse
I62·0	Subdural haematoma - nontraumatic	S32·4	Open fracture acetabulum, double column unspecified
I62·0	Subdural haemorrhage NOS	S32·4	Other specified open fracture acetabulum
I62·9	Intracranial haemorrhage NOS	S32·4	Open fracture acetabulum NOS
I63·0	Cerebral infarct due to thrombosis of precerebral arteries	S32·5	Closed fracture pubis
I63·1	Cerebral infarction due to embolism of precerebral arteries	S32·5	Closed fracture pelvis, single pubic ramus
I63·8	Infarction - cerebral	S32·5	Closed fracture pelvis, multiple pubic rami - stable
I63·5	Stroke due to cerebral arterial occlusion	S32·5	Closed fracture pelvis, multiple pubic rami - unstable
I63·3	Cerebral infarction due to thrombosis of cerebral arteries	S32·5	Other specified closed fracture pubis
I63·4	Cerebral infarction due to embolism of cerebral arteries	S32·5	Closed fracture pubis NOS
I63·9	Cerebral infarction NOS	S32·5	Open fracture of pubis
I63·9	Brainstem infarction NOS	S32·5	Open fracture pelvis, single pubic ramus
I63·9	Cerebellar infarction	S32·5	Open fracture pelvis, multiple pubic rami - stable
I63·9	Brainstem infarction	S32·5	Open fracture pelvis, multiple pubic rami - unstable
I63·9	Left sided cerebral infarction	S32·5	Other specified open fracture of pubis
I63·9	Right sided cerebral infarction	S32·5	Open fracture of pubis NOS
I63·9	Infarction of basal ganglia	S32·8	Other or multiple closed fracture of pelvis
I64	Intermittent cerebral ischaemia	S32·3	Closed fracture of ilium, unspecified
I64	Stroke and cerebrovascular accident unspecified	S32·8	Closed fracture pelvis, ischium
I64	CVA unspecified	S32·7	Closed multiple disruptions of pelvis
I64	Stroke unspecified	S32·8	Closed fracture pelvis, ischial tuberosity

I64	CVA - Cerebrovascular accident unspecified	S32·3	Closed fracture pelvis, anterior superior iliac spine
I64	Left sided CVA	S32·3	Closed fracture pelvis, anterior inferior iliac spine
I64	Right sided CVA	S32·3	Closed fracture pelvis, iliac wing
I64	Cerebral palsy, not congenital or infantile, acute	S32·3	Closed vertical fracture of ilium
I72·8	Vertebral artery dissection	S32·8	Other or multiple closed fracture of pelvis NOS
I63·6	Cereb infarct due cerebral venous thrombosis, nonpyogenic	S32·8	Other or multiple open fracture of pelvis
I63·2	Cereb infarct due unsp occlus/stenos precerebr arteries	S32·3	Open fracture of ilium, unspecified
I63·5	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrts	S32·8	Open fracture pelvis, ischium
I79·8	Arterial, arteriole and capillary disease	S32·7	Open multiple disruptions of pelvis
I78·9	Capillary disease	S32·8	Open fracture pelvis, ischial tuberosity
I70	Atherosclerosis	S32·3	Open fracture pelvis, anterior superior iliac spine
I70	Arteriosclerosis	S32·3	Open fracture pelvis, anterior inferior iliac spine
I70·0	Aortic atherosclerosis	S32·3	Open fracture pelvis, iliac wing
I70·0	Aorto-iliac disease	S32·3	Open vertical fracture of ilium
I70·1	Renal artery atherosclerosis	S32·8	Other open fracture of pelvis
I70·1	Atherosclerotic renal artery stenosis	S32·7	Other/multiple open fracture of pelvis NOS
I70·1	ARAS - Atherosclerotic renal artery stenosis	S32·8	Closed complete rupture of pelvic ring
I70·2	Extremity artery atheroma	S32·5	Closed complete rupture pubic symphysis
I70·2	Monckeberg's medial sclerosis	S32·8	Open complete rupture of pelvic ring
I70·2	Extremity artery atheroma NOS	S32·5	Open complete rupture pubic symphysis
I70·1	Acquired renal artery stenosis	S32·8	Closed fracture of pelvis NOS
I70·8	Other specified artery atheroma	S32·8	Open fracture of pelvis NOS
I70·8	Carotid artery atherosclerosis	S52·5	Closed Colles' fracture
I70·8	Carotid artery disease	S52·5	Smith's fracture - closed
I70·9	Arteriosclerotic vascular disease NOS	S52·5	Closed fracture of the distal radius, unspecified
I71·9	Aortic aneurysm	S52·5	Dupuytren's fracture, radius - closed
I71·0	Dissecting aortic aneurysm	S52·5	Closed Smith's fracture

I71·1	Thoracic aortic aneurysm which has ruptured	S52·5	Closed Galeazzi fracture
I71·1	Ruptured thoracic aortic aneurysm	S52·5	Closed volar Barton's fracture
I71·2	Thoracic aortic aneurysm without mention of rupture	S52·5	Closed volar Barton's fracture-dislocation
I71·3	Abdominal aortic aneurysm which has ruptured	S52·5	Closed volar Barton fracture-subluxation
I71·3	Ruptured abdominal aortic aneurysm	S52·5	Closed dorsal Barton's fracture
I71·3	Ruptured suprarenal aortic aneurysm	S52·5	Closed dorsal Barton's fracture-dislocation
I71·4	Abdominal aortic aneurysm without mention of rupture	S52·5	Closed dorsal Barton fracture-subluxation
I71·4	AAA - Abdominal aortic aneurysm without mention of rupture	S52·5	Closed fracture radial styloid
I71·4	Juxtarenal aortic aneurysm	S52·5	Closed fracture distal radius, intra-articular, die-punch
I71·4	Inflammatory abdominal aortic aneurysm	S52·5	Closed fracture distal radius, extra-articular, other type
I71·4	Infrarenal abdominal aortic aneurysm	S52·5	Closed fracture distal radius, intra-articular, other type
I71·4	Aneurysm of suprarenal aorta	S52·5	Closed Barton's fracture
I71·8	Ruptured aortic aneurysm NOS	S52·5	Greenstick fracture of distal radius
I71·5	Thoracoabdominal aortic aneurysm, ruptured	S52·5	Open Colles' fracture
I71·9	Aortic aneurysm without mention of rupture NOS	S52·5	Smith's fracture - open
I71·6	Thoracoabdominal aortic aneurysm, without mention of rupture	S52·5	Open fracture of the distal radius, unspecified
I71·3	Leaking abdominal aortic aneurysm	S52·5	Dupuytren's fracture, radius - open
I71·1	Abscess of aortic root	S52·5	Open Smith's fracture
I71·2	Aortic root dilatation	S52·5	Open Galeazzi fracture
I71·9	Aortic aneurysm NOS	S52·5	Open volar Barton's fracture
I72	Other aneurysm	S52·5	Open volar Barton fracture-dislocation
I72·1	Aneurysm of artery of arm	S52·5	Open volar Barton fracture-subluxation
I72·1	Aneurysm of brachial artery	S52·5	Open dorsal Barton's fracture
I72·1	Aneurysm of radial artery	S52·5	Open dorsal Barton's fracture-dislocation
I72·1	Aneurysm of ulnar artery	S52·5	Open dorsal Barton's fracture-subluxation
I72·1	Aneurysm of arm artery NOS	S52·5	Open fracture radial styloid
I72·2	Aneurysm of renal artery	S52·5	Open fracture distal radius, intra-articular, die-punch

I72·2	Acquired renal artery aneurysm	S52·5	Open fracture distal radius, extra-articular other type
I72·3	Aneurysm of iliac artery	S52·5	Open fracture distal radius, intra-articular other type
I72·3	Aneurysm of common iliac artery	S52·5	Open Barton's fracture
I72·3	Aneurysm of external iliac artery	S52·5	Fracture of lower end of radius
I72·3	Aneurysm of internal iliac artery	S62·1	Fracture of carpal bone
I72·3	Aneurysm of iliac artery NOS	S62·1	Closed fracture of carpal bone
I72·4	Aneurysm of leg artery	S62·1	Closed fracture of carpal bone, unspecified
I72·4	Aneurysm of femoral artery	S62·0	Closed fracture of the scaphoid
I72·4	Aneurysm of popliteal artery	S62·1	Closed fracture lunate
I72·4	Aneurysm of anterior tibial artery	S62·1	Closed fracture triquetral
I72·4	Aneurysm of dorsalis pedis artery	S62·1	Closed fracture pisiform
I72·4	Aneurysm of posterior tibial artery	S62·1	Closed fracture trapezium
I72·4	Ruptured popliteal artery aneurysm	S62·1	Closed fracture trapezoid
I72·4	Aneurysm of leg artery NOS	S62·1	Closed fracture capitate
I72·9	Arterial false aneurysm	S62·1	Closed fracture hamate
I72·9	False aneurysm	S62·1	Closed fracture hamate, hook
I72·1	Dissection of artery of upper extremity	S62·0	Closed fracture scaphoid, proximal pole
I72·1	Dissection of artery of arm	S62·0	Closed fracture scaphoid, waist, transverse
I72·2	Dissection of renal artery	S62·0	Closed fracture scaphoid, waist, oblique
I72·3	Dissection of iliac artery	S62·0	Closed fracture scaphoid, waist, comminuted
I72·4	Dissection of artery of lower extremity	S62·0	Closed fracture scaphoid, tuberosity
I72·4	Dissection of artery of leg	S62·0	Closed fracture carpal bones, multiple
I72·5	Aneurysm and dissection of precerebral artery	S62·1	Closed fracture of other carpal bone
I72·8	Dissection of other specified arteries	S62·1	Closed fracture of carpal bone NOS
I72·9	Dissection of artery	S62·1	Open fracture of carpal bone
I72·9	Ruptured aneurysm of dialysis vascular access	S62·1	Open fracture of carpal bone, unspecified
I72·9	Aneurysm of dialysis arteriovenous fistula	S62·0	Open fracture of the scaphoid

I72·9	Aneurysm of superficialised artery of dialysis AV fistula	S62·1	Open fracture lunate
I72·9	Aneurysm of needle site of dialysis arteriovenous fistula	S62·1	Open fracture triquetral
I72·9	Aneurysm of anastomotic site of dialysis AV fistula	S62·1	Open fracture pisiform
I72·9	Aneurysm of dialysis vascular access	S62·1	Open fracture trapezium
I72·8	Aneurysm of other artery	S62·1	Open fracture trapezoid
I72·0	Aneurysm of common carotid art	S62·1	Open fracture capitate
I72·0	Aneurysm of external carotid artery	S62·1	Open fracture hamate
I72·0	Aneurysm of internal carotid artery	S62·1	Open fracture hamate, hook
I72·0	Aneurysm of neck artery NOS	S62·0	Open fracture scaphoid, proximal pole
I72·1	Aneurysm of subclavian artery	S62·0	Open fracture scaphoid, waist, transverse
I72·8	Aneurysm of splenic artery	S62·0	Open fracture scaphoid, waist, oblique
I72·1	Aneurysm of axillary artery	S62·0	Open fracture scaphoid, waist, comminuted
I72·8	Aneurysm of coeliac artery	S62·0	Open fracture scaphoid, tuberosity
I72·8	Aneurysm of superior mesenteric artery	S62·1	Open fracture carpal bones, multiple
I72·8	Aneurysm of inferior mesenteric artery	S62·1	Open fracture of other carpal bone
I72·8	Aneurysm of hepatic artery	S62·1	Open fracture of carpal bone NOS
I72·8	Aneurysm of other visceral artery	S62·0	Fracture of scaphoid
I72·6	Vertebral artery aneurysm	S62·1	Fracture of carpal bone NOS
I72·9	Other aneurysm NOS	S62·8	Fracture-dislocation or subluxation of wrist
I72·9	Aneurysm NOS	S62·8	Closed fracture dislocation of wrist
I73	Other peripheral vascular disease	S62·1	Closed fracture-dislocation mid carpal
I73	Peripheral ischaemic vascular disease	S62·1	Closed fracture-dislocation lunate (volar)
I73	Ischaemia of legs	S62·1	Closed fracture-dislocation peri-lunate (dorsal)
I73	Peripheral ischaemia	S62·1	Closed fracture-dislocation peri-lunate trans-scaphoid
I73·1	Thromboangiitis obliterans	S62·1	Closed fracture-dislocation other carpal
I73·1	Buerger's disease	S62·8	Open fracture dislocation wrist
I73·1	Presenile gangrene	S62·1	Open fracture-dislocation mid carpal

I73·1	Thromboangiitis obliterans NOS	S62·1	Open fracture-dislocation lunate (volar)
I73·9	Ischaemic foot	S62·1	Open fracture-dislocation peri-lunate (dorsal)
I73·9	Peripheral arterial disease	S62·1	Open fracture-dislocation peri-lunate trans-scaphoid
I73·8	Other specified peripheral vascular disease	S62·1	Open fracture-dislocation other carpal
I79·2	Peripheral angiopathic disease EC NOS	S62·8	Closed fracture-subluxation of the wrist
I73·8	Acrocyanosis	S62·1	Closed fracture-subluxation mid carpal
I73·8	Acroparaesthesia - Schultze's type	S62·1	Closed fracture-subluxation lunate (volar)
I73·8	Schultze's simple acroparaesthesia	S62·1	Closed fracture-subluxation peri-lunate (dorsal)
I73·8	Acroparaesthesia - Nothnagel's type	S62·1	Closed fracture-subluxation peri-lunate trans-scaphoid
I73·8	Nothnagel's vasomotor acroparaesthesia	S62·1	Closed fracture-subluxation other carpal
I73·8	Acroparaesthesia - unspecified	S62·8	Open fracture-subluxation of the wrist
I73·8	Erythrocyanosis	S62·1	Open fracture-subluxation mid carpal
I73·8	Erythromelalgia	S62·1	Open fracture-subluxation lunate (volar)
I73·8	Erythralgia	S62·1	Open fracture-subluxation peri-lunate (dorsal)
I73·8	Other specified peripheral vascular disease NOS	S62·1	Open fracture-subluxation peri-lunate trans-scaphoid
I73·9	Peripheral vascular disease NOS	S62·1	Open fracture-subluxation other carpal
I73·9	Intermittent claudication	S32·8	Closed fracture-dislocation of pelvis
I73·9	Claudication	S32·8	Open fracture-dislocation of pelvis
I73·9	Vascular claudication	S32·8	Closed fracture-subluxation of pelvis
I73·9	Spasm of peripheral artery	S32·8	Open fracture-subluxation of pelvis
I73·9	Peripheral vascular disease NOS	S32·8	[X]Fract of other and unspec parts of lumbar spine & pelvis
I74·9	Arterial embolism and thrombosis	S62·1	[X]Fracture of other carpal bone(s)
I74·9	Arterial embolus and thrombosis		
I74·9	Thrombosis - arterial		
I74·9	Arterial embolic and thrombotic occlusion		
I74·0	Embolism and thrombosis of the abdominal aorta		
I74·0	Aortic bifurcation syndrome		

I74·0	Aortoiliac obstruction
I74·0	Leriche's syndrome
I74·0	Saddle embolus
I74·1	Embolism and thrombosis of the thoracic aorta
I74·4	Embolism and thrombosis of an arm or leg artery
I74·2	Embolism and thrombosis of the brachial artery
I74·2	Embolism and thrombosis of the radial artery
I74·2	Embolism and thrombosis of the ulnar artery
I74·2	Embolism and thrombosis of an arm artery NOS
I74·3	Embolism and thrombosis of the femoral artery
I74·3	Embolism and thrombosis of the popliteal artery
I74·3	Embolism and thrombosis of the anterior tibial artery
I74·3	Embolism and thrombosis of the dorsalis pedis artery
I74·3	Embolism and thrombosis of the posterior tibial artery
I74·3	Embolism and thrombosis of a leg artery NOS
I74·4	Peripheral arterial embolism and thrombosis NOS
I74·1	Embolism and thrombosis of other and unspec parts aorta
I74·8	Embolism and thrombosis of other specified artery
I74·5	Embolism and/or thrombosis of the common iliac artery
I74·5	Embolism and/or thrombosis of the internal iliac artery
I74·5	Embolism and/or thrombosis of the external iliac artery
I74·5	Embolism and thrombosis of the iliac artery unspecified
I74·2	Embolism and thrombosis of the subclavian artery
I74·8	Embolism and thrombosis of the splenic artery
I74·2	Embolism and thrombosis of the axillary artery
I74·8	Embolism and thrombosis of the coeliac artery
I74·8	Embolism and thrombosis of the hepatic artery

I74·9	Embolism and thrombosis of other arteries NOS
I74·9	Arterial embolism and thrombosis NOS
I77	Other disorders of arteries and arterioles
I77·0	Acquired arteriovenous fistula
I77·1	Stricture of artery
I77·2	Rupture of artery
I77·2	Aorto-duodenal fistula
I77·8	Hyperplasia of renal artery
I77·4	Coeliac artery compression syndrome
I77·4	Marable's syndrome
I77·5	Necrosis of artery
I77·6	Arteritis unspecified
I77·6	Aortitis
I77·8	Other disorders of arteries and arterioles
I77·3	Fibromuscular hyperplasia of arteries NOS
I77·3	Arterial fibromuscular dysplasia
I77·8	Other disorders of arteries and arterioles NOS
I77·1	Arterial insufficiency
I77·6	Vasculitis
I77·9	Disorders of arteries and arterioles NOS
I77·9	Iliac artery occlusion
I77·9	Femoral artery occlusion
I77·9	Popliteal artery occlusion
I78·9	Diseases of capillaries
I78·8	Other and unspecified diseases of capillaries
I78·8	Capillary haemorrhage
I78·8	Capillary hyperpermeability

I78·8	Capillary thrombosis
I78·8	Capillaritis
I78·9	Disease of capillaries NOS
I77·8	Occlusion of artery
I77·8	Occlusion of artery of upper limb
I77·8	Occlusion of radial artery
I77·8	Occlusion of brachial artery
I77·8	Occlusion of ulnar artery
I77·8	Occlusion of artery of lower limb
I77·8	Occlusion of dorsalis pedis artery
I77·8	Occlusion of anterior tibial artery
I77·8	Occlusion of posterior tibial artery
I77·8	Steal syndrome of hand
I79·8	Other specified arterial, arteriole or capillary disease
I79·8	Arterial, arteriole and capillary diseases NOS
I70·9	Vascular calcification
I20	[X]Ischaemic heart diseases
I20·8	[X]Other forms of angina pectoris
I23·8	[X]Other current complicatns following acute myocard infarct
I21·3	[X]Acute transmural myocardial infarction of unspcif site
I22·8	[X]Subsequent myocardial infarction of other sites
I22·9	[X]Subsequent myocardial infarction of unspecified site
I60·6	[X]Subarachnoid haemorrhage from other intracranial arteries
I60·8	[X]Other subarachnoid haemorrhage
I61·8	[X]Other intracerebral haemorrhage
I63·5	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrts
I63·8	[X]Other cerebral infarction

I60·7	[X]Subarachnoid haemorrh from intracranial artery, unspecif
I61·2	[X]Intracerebral haemorrhage in hemisphere, unspecified
I63·2	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
I79	[X]Diseases of arteries, arterioles and capillaries
I70·8	[X]Atherosclerosis of other arteries
I71·8	[X]Aortic aneurysm of unspecified site, ruptured
I71·9	[X]Aortic aneurysm of unspecified site, nonruptured
I72·8	[X]Aneurysm of other specified arteries
I73·8	[X]Other specified peripheral vascular diseases
I74·8	[X]Embolism and thrombosis of other arteries
I77·8	[X]Other specified disorders of arteries and arterioles
I78·8	[X]Other diseases of capillaries
I79·0	[X]Aneurysm of aorta in diseases classified elsewhere
I79·1	[X]Aortitis in diseases classified elsewhere
I79·2	[X]Peripheral angiopathy in diseases classified elsewhere
I79·8	[X]Oth disorders/arteries,arterioles+capillaries/diseases CE
	Transluminal balloon angioplasty of coronary artery
	Percutaneous balloon coronary angioplasty
	Percut transluminal balloon angioplasty one coronary artery
	Percut translum balloon angioplasty mult coronary arteries
	Transluminal balloon angioplasty of coronary artery OS
	Transluminal balloon angioplasty of coronary artery NOS
	Percutaneous transluminal laser coronary angioplasty
	Percut transluminal coronary thrombolysis with streptokinase
	Rotary blade coronary angioplasty
	Insertion of coronary artery stent
	Insertion of drug-eluting coronary artery stent

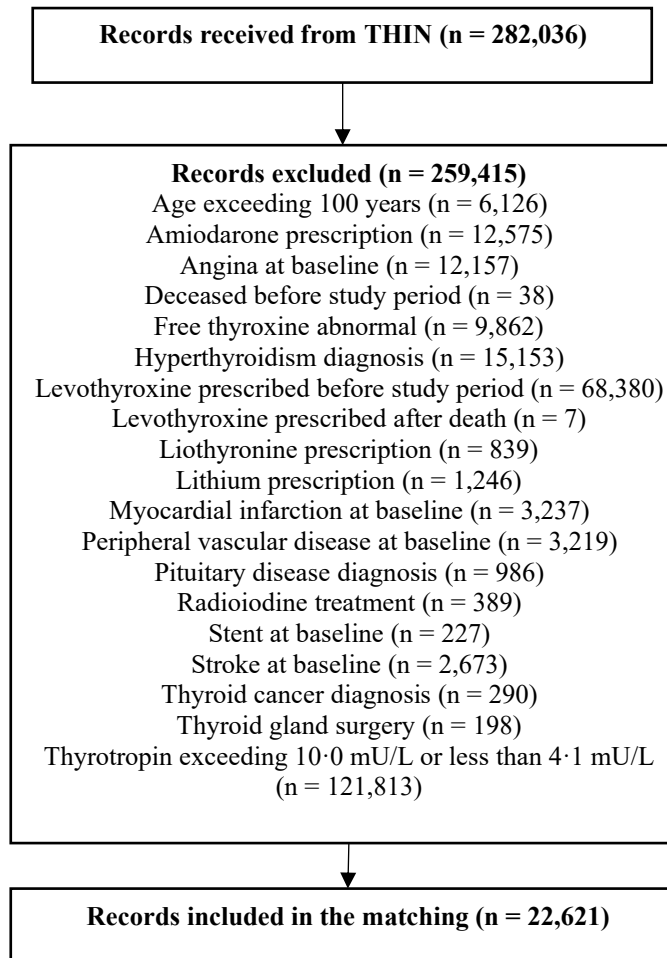
	Other therapeutic transluminal op on coronary artery OS
	Other therapeutic transluminal op on coronary artery NOS
	Perc translumin balloon angioplasty stenting coronary artery
	Perc translum ball angio insert 1-2 drug elut stents cor art
	Perc tran ball angio ins 3 or more drug elut stents cor art
	Perc translum balloon angioplasty insert 1-2 stents cor art
	Percutaneous cor balloon angiop 3 more stents cor art NEC
	OS perc translumina balloon angioplast stenting coronary art
	Perc translum balloon angioplasty stenting coronary art NOS

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Table 2 Proportion of missing data before imputation and weighting.

Covariate, %	Cohort 1	Cohort 1a	Cohort 1b
Cardiovascular			
Ethnicity	11931 (52.7)	2873 (58)	9058 (51.3)
Body mass index	7421 (32.8)	1663 (33.6)	5758 (32.6)
Cholesterol	2391 (10.6)	402 (8.1)	1989 (11.3)
Smoker status	34 (0.2)	12 (0.2)	22 (0.1)
Bone Health			
Ethnicity	13344 (53.3)	3370 (57.9)	9974 (51.9)
Body mass index	8238 (32.9)	1942 (33.4)	6296 (32.7)
Cholesterol	2460 (9.8)	425 (7.3)	2035 (10.6)
Smoker status	35 (0.1)	11 (0.2)	24 (0.1)
All-Cause Mortality			
Ethnicity	14615 (53.6)	3711 (58.2)	10904 (52.2)
Body mass index	9115 (33.4)	2171 (34.1)	6944 (33.2)
Cholesterol	2760 (10.1)	487 (7.6)	2273 (10.9)
Smoker status	37 (0.1)	13 (0.2)	24 (0.1)

516 *Cohort 1: Patients aged over 50 years with a thyrotropin (TSH) level between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine (fT4) level.*
517 *Cohort 1a: Patients aged over 50 years with a TSH level between 4.1 mU/L and the age-specific upper limit and a normal fT4 level.*
518 *Cohort 1b: Patients aged over 50 years with a TSH level between the age-specific upper limit and 10.0 mU/L and a normal fT4 level.*
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Figure 1 Patient exclusion flow chart of the cardiovascular target trial emulation study.

522 **Table 3 Standardised mean differences for confounders between treatment groups before and after weighting.**

Confounding Variable	Standardised Mean Differences					
	Cohort 1, Before Weighting	Cohort 1, After Weighting	Cohort 1a, Before Weighting	Cohort 1a, After Weighting	Cohort 1b, Before Weighting	Cohort 1b, After Weighting
Age	0.12	0.024	0.36	0.018	0.30	0.028
Sex assigned at birth	-0.056	-0.011	-0.077	-0.014	-0.056	-0.0094
Smoking Status	-0.015	-0.00038	-0.0032	-0.00036	-0.011	0.00035
Hypertension	0.00038	0.00042	0.023	0.0035	0.024	0.0010
TSH	1.20	0.069	0.53	0.025	1.0	0.060
Total cholesterol	-0.024	0.014	0.0072	-0.0092	-0.070	-0.013
Hormones	0.0021	0.0011	-0.0031	0.000081	0.0029	0.0014

523 *Cohort 1: Patients aged over 50 years with a thyrotropin (TSH) level between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine (fT4) level.*

524 *Cohort 1a: Patients aged over 50 years with a thyrotropin level between 4.1 mU/L and the age-specific upper limit and a normal fT4 level.*

525 *Cohort 1b: Patients aged over 50 years with a thyrotropin level between the age-specific upper limit and 10.0 mU/L and a normal fT4 level.*

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527 **Table 4 Hazard ratios (HR) and their 95% confidence intervals (CI) and p-values, categorised by subgroup and outcome.**

Outcome	HR (95% CI), p-value		
	Cohort 1	Cohort 1a	Cohort 1b
Cardiovascular			
Female	0.78 (0.68, 0.89), p = 0.00032	0.95 (0.77, 1.17), p = 0.65	0.80 (0.67, 0.94), p = 0.0071
Male	0.95 (0.81, 1.12), p = 0.56	0.97 (0.71, 1.32), p = 0.83	1.01 (0.84, 1.21), p = 0.93
51-60	0.79 (0.62, 1.01), p = 0.56	0.54 (0.27, 1.11), p = 0.094	0.89 (0.70, 1.13), p = 0.32
61-70	0.74 (0.62, 0.89), p = 0.0011	0.70 (0.46, 1.08), p = 0.11	0.72 (0.59, 0.87), p = 0.001
71-80	0.87 (0.73, 1.04), p = 0.12	1.00 (0.77, 1.31), p = 0.97	0.85 (0.67, 1.07), p = 0.17
81-90	0.90 (0.67, 1.19), p = 0.45	0.97 (0.71, 1.34), p = 0.85	0.92 (0.59, 1.44), p = 0.72
91+	1.50 (0.60, 3.75), p = 0.38	1.66 (0.68, 4.07), p = 0.27	1.79 (0.44, 7.38), p = 0.42
Non-smoker	0.84 (0.73, 0.98), p = 0.021	0.94 (0.75, 1.18), p = 0.60	0.90 (0.76, 1.08), p = 0.26
Past smoker	0.77 (0.65, 0.91), p = 0.0018	0.86 (0.65, 1.14), p = 0.29	0.82 (0.67, 1.00), p = 0.046
Smoker	0.89 (0.62, 1.27), p = 0.51	1.45 (0.72, 2.91), p = 0.30	0.75 (0.51, 1.1), p = 0.13
Low-normal fT4	0.84 (0.70, 1.01), p = 0.067	1.00 (0.77, 1.30), p = 0.99	0.85 (0.68, 1.07), p = 0.17
High-normal fT4	0.84 (0.73, 0.96), p = 0.0090	0.91 (0.72, 1.16), p = 0.46	0.88 (0.75, 1.03), p = 0.11
Bone Health			
Female	1.00 (0.89, 1.13), p = 0.99	1.15 (0.94, 1.39), p = 0.17	0.97 (0.84, 1.12), p = 0.68
Male	1.23 (0.9, 1.68), p = 0.20	0.95 (0.55, 1.65), p = 0.86	1.39 (0.92, 2.11), p = 0.12
51-60	1.00 (0.77, 1.3), p = 0.99	1.01 (0.50, 2.05), p = 0.98	1.01 (0.77, 1.32), p = 0.96
61-70	1.17 (0.94, 1.45), p = 0.17	1.56 (1.07, 2.26), p = 0.021	1.08 (0.84, 1.39), p = 0.54
71-80	1.00 (0.83, 1.19), p = 0.97	1.07 (0.8, 1.43), p = 0.66	0.98 (0.78, 1.23), p = 0.86
81-90	1.18 (0.88, 1.57), p = 0.28	1.17 (0.84, 1.65), p = 0.35	1.21 (0.76, 1.92), p = 0.41
91+	1.91 (0.78, 4.69), p = 0.16	0.83 (0.25, 2.8), p = 0.77	2.65 (0.59, 11.8), p = 0.20
Non-smoker	1.01 (0.89, 1.16), p = 0.83	1.17 (0.94, 1.47), p = 0.16	0.98 (0.83, 1.16), p = 0.80
Past smoker	1.02 (0.82, 1.27), p = 0.87	1.01 (0.71, 1.43), p = 0.96	1.03 (0.79, 1.35), p = 0.83
Smoker	1.46 (0.98, 2.16), p = 0.063	1.46 (0.73, 2.92), p = 0.29	1.49 (0.92, 2.41), p = 0.11
Low-normal fT4	0.92 (0.77, 1.1), p = 0.36	1.02 (0.78, 1.35), p = 0.86	0.90 (0.72, 1.12), p = 0.35
High-normal fT4	1.18 (1.02, 1.37), p = 0.022	1.28 (1.00, 1.64), p = 0.054	1.16 (0.97, 1.39), p = 0.098
All-Cause Mortality			
Female	0.65 (0.61, 0.70), p < 0.0001	0.75 (0.66, 0.85), p < 0.0001	0.61 (0.56, 0.67), p < 0.0001
Male	0.84 (0.76, 0.93), p < 0.0001	0.94 (0.78, 1.14), p = 0.55	0.82 (0.73, 0.92), p = 0.00078
51-60	0.58 (0.47, 0.72), p < 0.0001	0.73 (0.40, 1.3), p = 0.28	0.56 (0.44, 0.70), p < 0.0001
61-70	0.52 (0.46, 0.60), p < 0.0001	0.54 (0.39, 0.73), p = 0.0010	0.52 (0.44, 0.60), p < 0.0001
71-80	0.71 (0.64, 0.78), p < 0.0001	0.80 (0.67, 0.96), p = 0.015	0.67 (0.60, 0.76), p < 0.0001
81-90	0.81 (0.73, 0.89), p < 0.0001	0.84 (0.71, 0.99), p = 0.036	0.78 (0.69, 0.89), p < 0.0001
91+	2.12 (1.63, 2.76), p < 0.0001	2.50 (1.73, 3.62), p < 0.0001	2.01 (1.40, 2.87), p < 0.0001
Non-smoker	0.72 (0.66, 0.78), p < 0.0001	0.80 (0.70, 0.92), p = 0.0021	0.68 (0.61, 0.75), p < 0.0001
Past smoker	0.71 (0.64, 0.78), p < 0.0001	0.82 (0.69, 0.98), p = 0.030	0.67 (0.60, 0.75), p < 0.0001
Smoker	0.69 (0.57, 0.83), p < 0.0001	0.71 (0.49, 1.04), p = 0.081	0.69 (0.55, 0.86), p = 0.0011
Low-normal fT4	0.69 (0.63, 0.76), p < 0.0001	0.84 (0.72, 0.98), p = 0.027	0.64 (0.57, 0.72), p < 0.0001
High-normal fT4	0.77 (0.71, 0.83), p < 0.0001	0.82 (0.71, 0.95), p = 0.0067	0.74 (0.68, 0.82), p < 0.0001

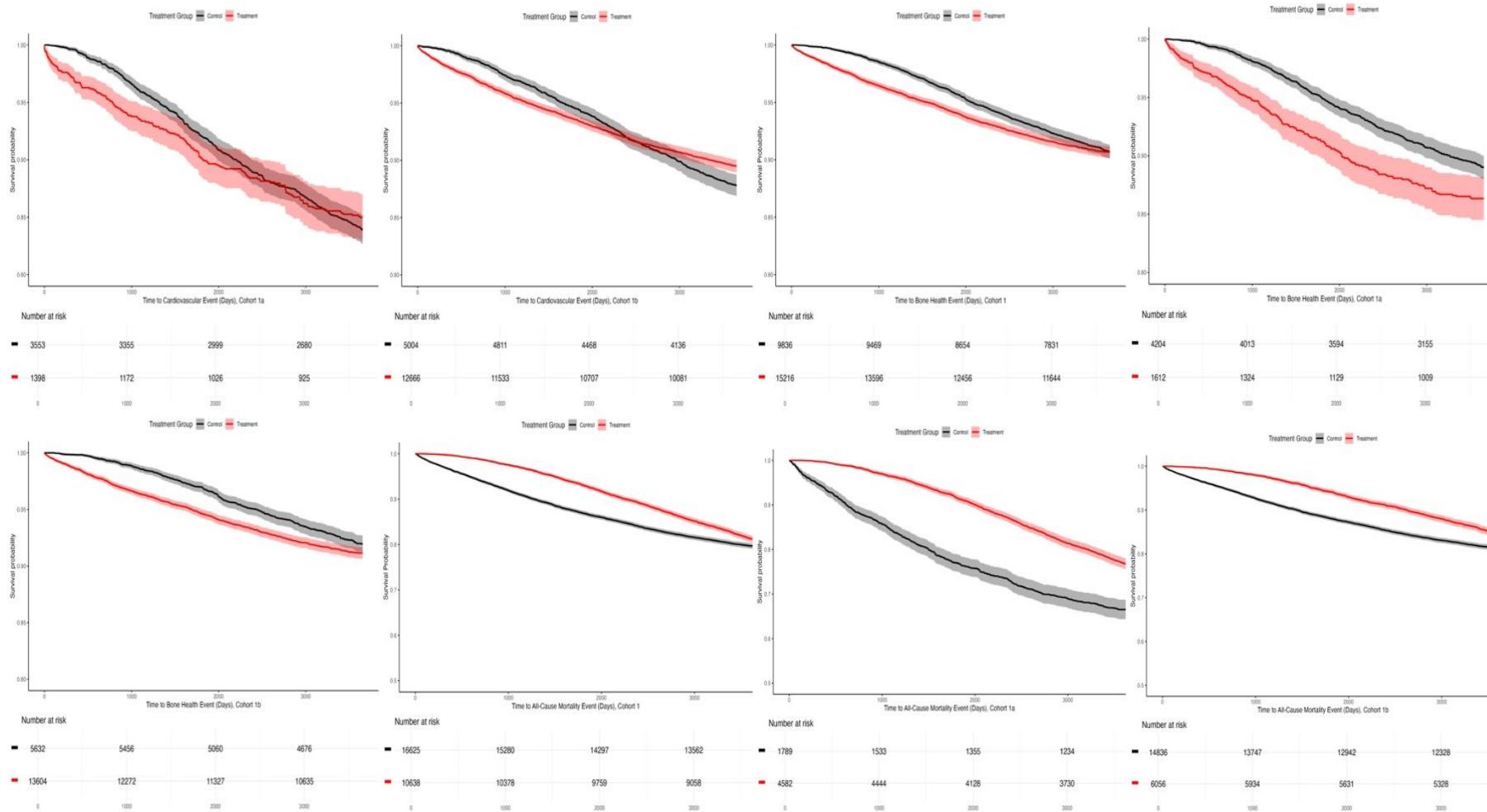
528 Cohort 1: Patients aged over 50 years with a thyrotropin (TSH) level between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine (fT4) level.

529 Cohort 1a: Patients aged over 50 years with a TSH level between 4.1 mU/L and the age-specific upper limit and a normal fT4 level.

530 Cohort 1b: Patients aged over 50 years with a TSH level between the age-specific upper limit and 10.0 mU/L and a normal fT4 level.

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Figure 1 Kaplan-Meier plots illustrating survival probabilities over time of all three outcomes.
Cohort 1: Patients aged over 50 years with a thyrotropin level (TSH) between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine (fT4) level.
Cohort 1a: Patients aged over 50 years with a TSH level between 4.1 mU/L and the age-specific upper limit and a normal fT4 level.
Cohort 1b: Patients aged over 50 years with a TSH level between the age-specific upper limit and 10.0 mU/L and a normal fT4 level.

538 **Table 5 Sensitivity analysis hazard ratios (HR) and their 95% confidence intervals (CI) and p-values.**

	Outcome		
	Cardiovascular	Bone Health	All-Cause Mortality
Sensitivity 1			
Cohort 1	0.84 (0.74, 0.95), p = 0.0061	1.04 (0.91, 1.18), p = 0.55	0.69 (0.65, 0.74), p < 0.0001
Cohort 1a	1.14 (0.89, 1.46), p = 0.30	1.18 (0.9, 1.55), p = 0.23	0.83 (0.72, 0.95), p = 0.0069
Cohort 1b	0.84 (0.74, 0.96), p = 0.0081	1.03 (0.89, 1.18), p = 0.71	0.67 (0.63, 0.72), p < 0.0001
Sensitivity 2			
Cohort 1	0.82 (0.71, 0.96), p = 0.015	1.03 (0.89, 1.2), p = 0.70	0.7 (0.65, 0.75), p < 0.0001
Cohort 1a	1.07 (0.63, 1.81), p = 0.81	0.86 (0.49, 1.5), p = 0.59	0.9 (0.72, 1.13), p = 0.36
Cohort 1b	0.82 (0.71, 0.94), p = 0.0058	1.02 (0.88, 1.19), p = 0.75	0.67 (0.62, 0.72), p < 0.0001
Sensitivity 3			
Cohort 1	0.83 (0.75, 0.92), p < 0.0001	1.04 (0.94, 1.36), p = 0.438	0.71 (0.67, 0.75), p < 0.0001
Cohort 1a	0.89 (0.74, 1.07), p = 0.215	1.13 (0.94, 1.36), p = 0.209	0.8 (0.72, 0.89), p < 0.0001
Cohort 1b	0.82 (0.73, 0.93), p = 0.0016	1.03 (0.9, 1.18), p = 0.676	0.67 (0.63, 0.72), p < 0.0001

539 *Cohort 1: Patients aged over 50 years with a thyrotropin (TSH) level between 4.1 mU/L and 10.0 mU/L and a normal free thyroxine (fT4) level.*

540 *Cohort 1a: Patients aged over 50 years with a TSH level between 4.1 mU/L and the age-specific upper limit and a normal fT4 level.*

541 *Cohort 1b: Patients aged over 50 years with a TSH level between the age-specific upper limit and 10.0 mU/L and a normal fT4 level.*

542 Sensitivity 1: cutoff TSH level of 4.5mU/L rather than 4.0 mU/L.

543 Sensitivity 2: cutoff TSH level of 5.0 mU/L rather than 4.0 mU/L.

544 Sensitivity 3: cholesterol removed from weighting.

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548 **Table 6 E-values corresponding to the primary Hazard Ratios (HR).**

Outcome	Cohort	HR	E-value
Cardiovascular	Cohort 1	0·82	1·56
Cardiovascular	Cohort 1a	0·93	1·28
Cardiovascular	Cohort 1b	0·85	1·48
Bone Health	Cohort 1	1·04	1·2
Bone Health	Cohort 1a	1·14	1·42
Bone Health	Cohort 1b	1·03	1·17
All-Cause Mortality	Cohort 1	0·71	1·85
All-Cause Mortality	Cohort 1a	0·8	1·61
All-Cause Mortality	Cohort 1b	0·68	1·94

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550 **Table 7 Piecewise Cox regression Hazard Ratios (HR) and corresponding 95% confidence intervals (CI) and p-values, for cardiovascular outcomes.**

Cohort	Time Period	H R (95% CI)	p-value
Cohort 1	0-5 years	1.08 (0.94–1.25)	0.25
Cohort 1	5-10 years	0.54 (0.44–0.66)	<0.001
Cohort 1a	0-5 years	1.17 (0.93–1.47)	0.18
Cohort 1a	5-10 years	0.50 (0.34–0.74)	0.0005
Cohort 1b	0-5 years	1.07 (0.90–1.27)	0.42
Cohort 1b	5-10 years	0.54 (0.42–0.69)	<0.001

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