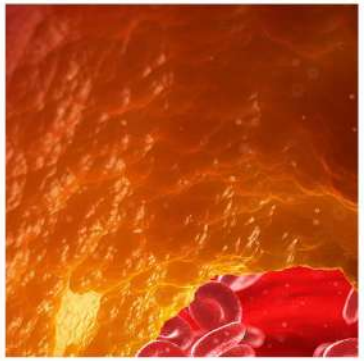
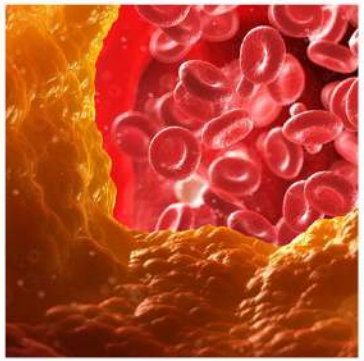
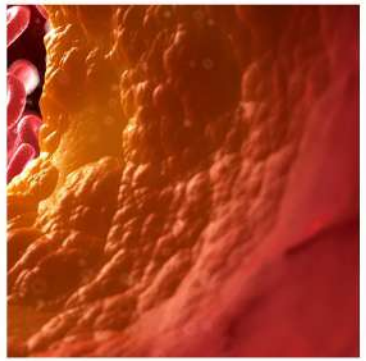
The 2019 EMEA Cardiometabolic Workshop







Saturday,
16 November 2019

Baku, Azerbaijan

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

Thyroid Hormones and Cardiovascular Disease

Salman Razvi

Salman Razvi
Institute of Genetic Medicine
International Centre for Life
Newcastle upon Tyne, United Kingdom

Disclosures

Have received speaker fees from Merck plc, Abbott Pharma Ltd., and Menarini Pharma – all makers of levothyroxine.
The views expressed in this presentation are those of the authors alone and not influenced by any external factors or agencies.

Learning objectives

- Illustrate the role of thyroid hormones on cardiovascular homeostasis
- Understand the impact of cardiovascular disease on the personalization of thyroid hormone therapy
- Manage subclinical hypothyroidism in patients at high cardiovascular risk

Format

1. Observational studies of Cardiovascular effects of Subclinical Hypothyroidism
2. Interventional studies of Treatment of Subclinical Hypothyroidism on the Cardiovascular system
3. Thyroid Function in cardiac disease
4. Thyroid Hormones in other cardiac conditions such as Heart Failure and Acute MI
5. Conclusions

Patient A

- 76 year old man with:

Angina

Hypertension

Type 2 Diabetes mellitus

Hyperlipidaemia

- Treated with aspirin, statin, metformin, lisinopril and bisoprolol.
- Routine tests performed

TSH **5.8** mU/L (0.3 – 4.5)

FT4 16.2 pmol/L (10 – 22)

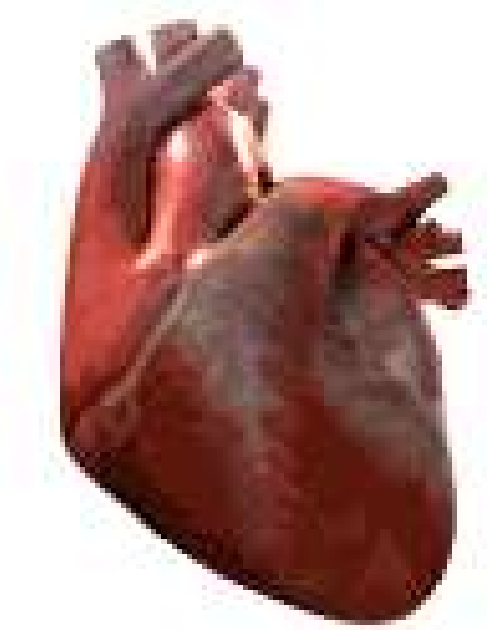
- Similar levels when repeated 3 months later

Thyroid hormones and the Heart

T4

↓

T3



Observational studies of cardiac disease in Subclinical Hypothyroidism

PRECLINICAL HYPOTHYROIDISM: A RISK FACTOR FOR CORONARY HEART-DISEASE*

P. A. BASTENIE
L. VANHAELST
M. BONNYNS
P. NEVE
M. STAQUET

Department of Medicine, Hôpital Universitaire Saint-Pierre, Brussels, Belgium

Lancet 1971; I: 203

Increased incidence of MI in population-based studies

Rotterdam (women >55 yrs)

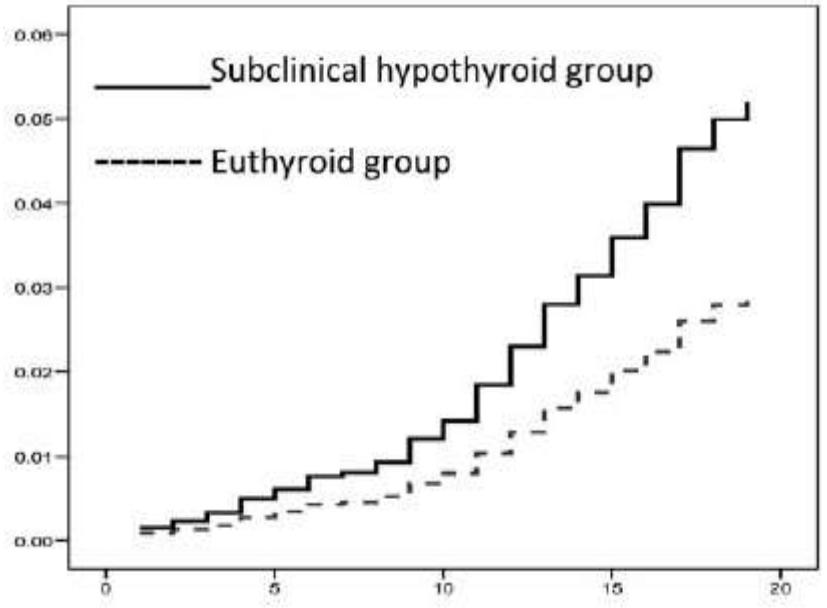
Table 4. Attributable Risk Percentages and Population Attributable Risk Percentages for Subclinical Hypothyroidism and Classic Risk Factors for Cardiovascular Disease Associated with Incident Myocardial Infarction in Women in the Rotterdam Study

Risk Factor	Age-Adjusted Relative Risk*	Attributable Risk	Population Attributable Risk
		%	
Subclinical hypothyroidism	2.5	60	14
Hypercholesterolemia	2.4	58	18
Hypertension	1.6	38	14
Smoking	2.0/1.2†	50/17‡	15
Diabetes mellitus	2.4	58	14

* Determined by using Cox proportional hazards regression analysis.
† Age-adjusted relative risk and attributable risk percentage for current compared with never smokers.
‡ Age-adjusted relative risk and attributable risk percentage for past compared with never smokers.

Hak et al, 2000

Whickham (men and women)



Razvi et al, JCEM 2010

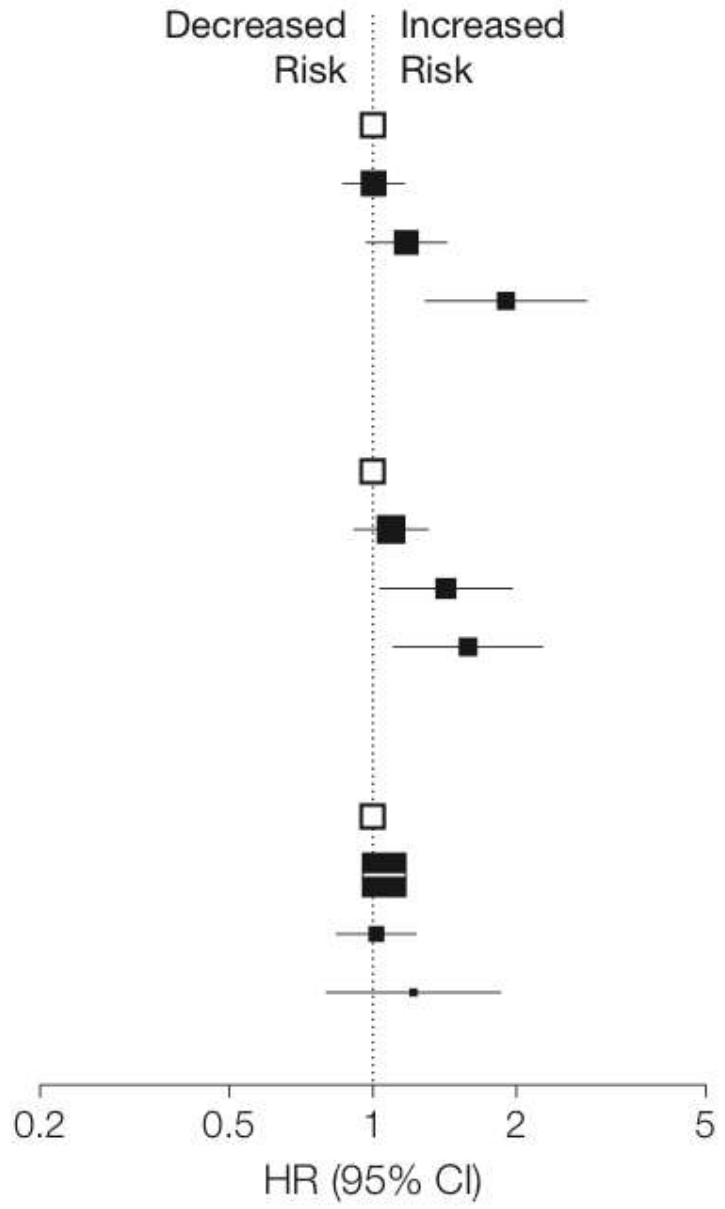
Patient level meta-analysis

- 55,287 participants; 3,450 with SCH (6.2%)
- Information derived from 11 studies
- 9664 deaths; 2168 from CHD
- SCH defined as TSH 4.5-19.99 mU/l (normal FT4)

Rodondi et al. JAMA 2010

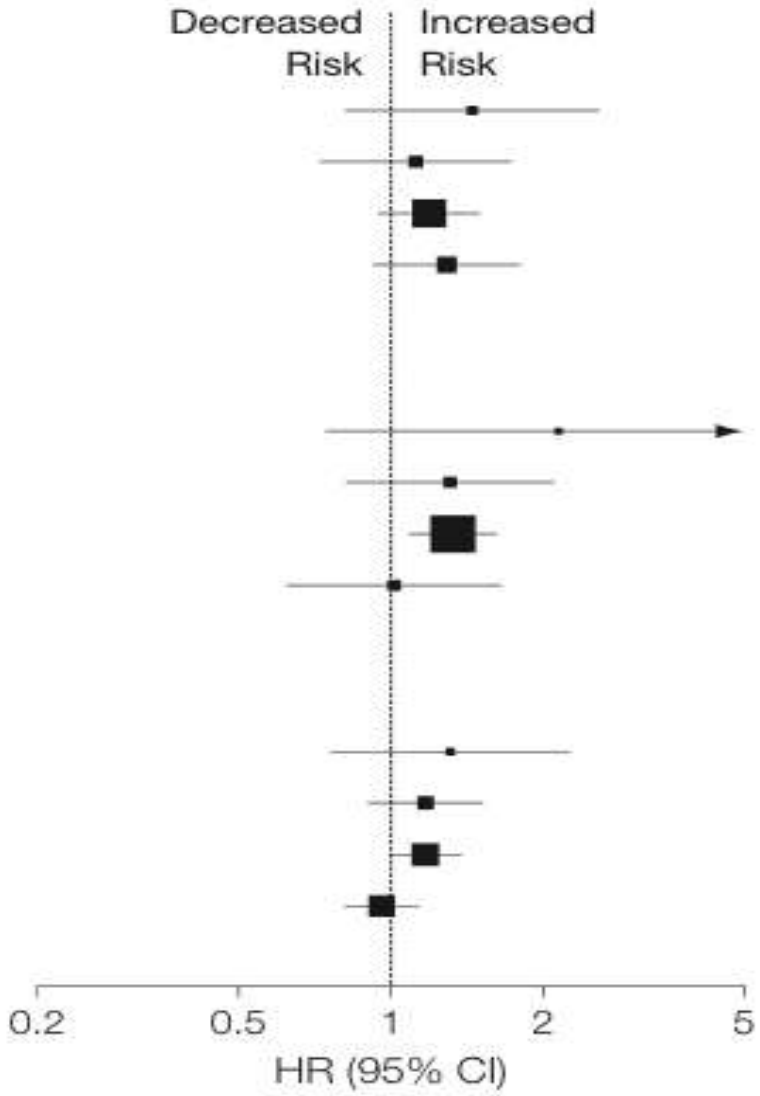
Patient level meta-analysis

	HR Ratio (95% CI)
CHD Events by TSH Level, mIU/L[b]	
0.5-4.49	1 [Reference]
4.5-6.9	1.00 (0.86-1.18)
7.0-9.9	1.17 (0.96-1.43)
10-19.9	1.89 (1.28-2.80)
	P<.001 for trend
CHD Mortality by TSH Level, mIU/L[c]	
0.5-4.49	1 [Reference]
4.5-6.9	1.09 (0.91-1.30)
7.0-9.9	1.42 (1.03-1.95)
10-19.9	1.58 (1.10-2.27)
	P =.005 for trend
Total Mortality by TSH Level, mIU/L[d]	
0.5-4.49	1 [Reference]
4.5-6.9	1.06 (0.96-1.17)
7.0-9.9	1.02 (0.84-1.24)
10-19.9	1.22 (0.80-1.87)
	P =.39 for trend



Patient level meta-analysis

	HR Ratio (95% CI)
CHD Events, by Age, y[b]	
18-49	1.46 (0.82-2.62)
50-64	1.13 (0.73-1.77)
65-79	1.20 (0.95-1.51)
≥80	1.30 (0.93-1.82)
	P = .78 for trend
CHD Mortality, by Age, y[c]	
18-49	2.13 (0.74-6.14)
50-64	1.30 (0.81-2.08)
65-79	1.32 (1.08-1.62)
≥80	1.01 (0.62-1.63)
	P = .22 for trend
Total Mortality, by Age, y[d]	
18-49	1.31 (0.76-2.26)
50-64	1.17 (0.90-1.51)
65-79	1.17 (0.99-1.39)
≥80	0.96 (0.81-1.12)
	P = .29 for trend



Mortality in cardiac patients

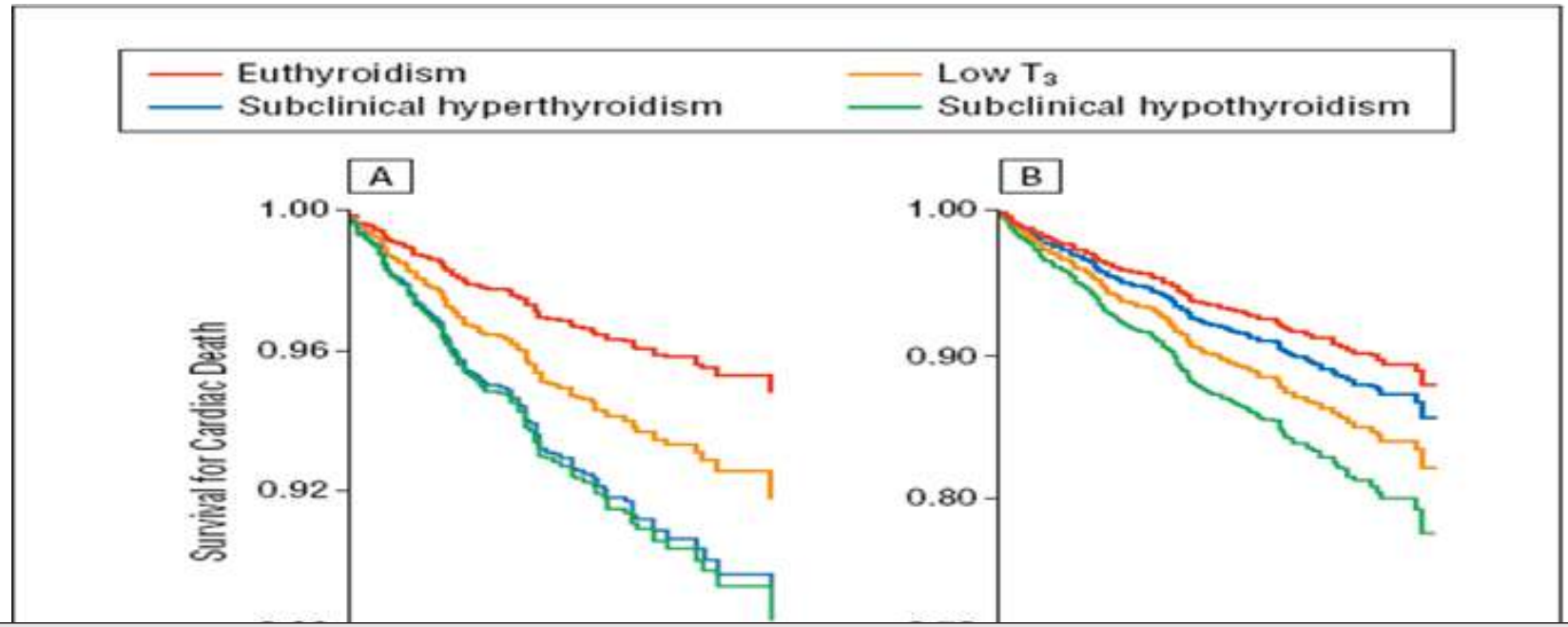
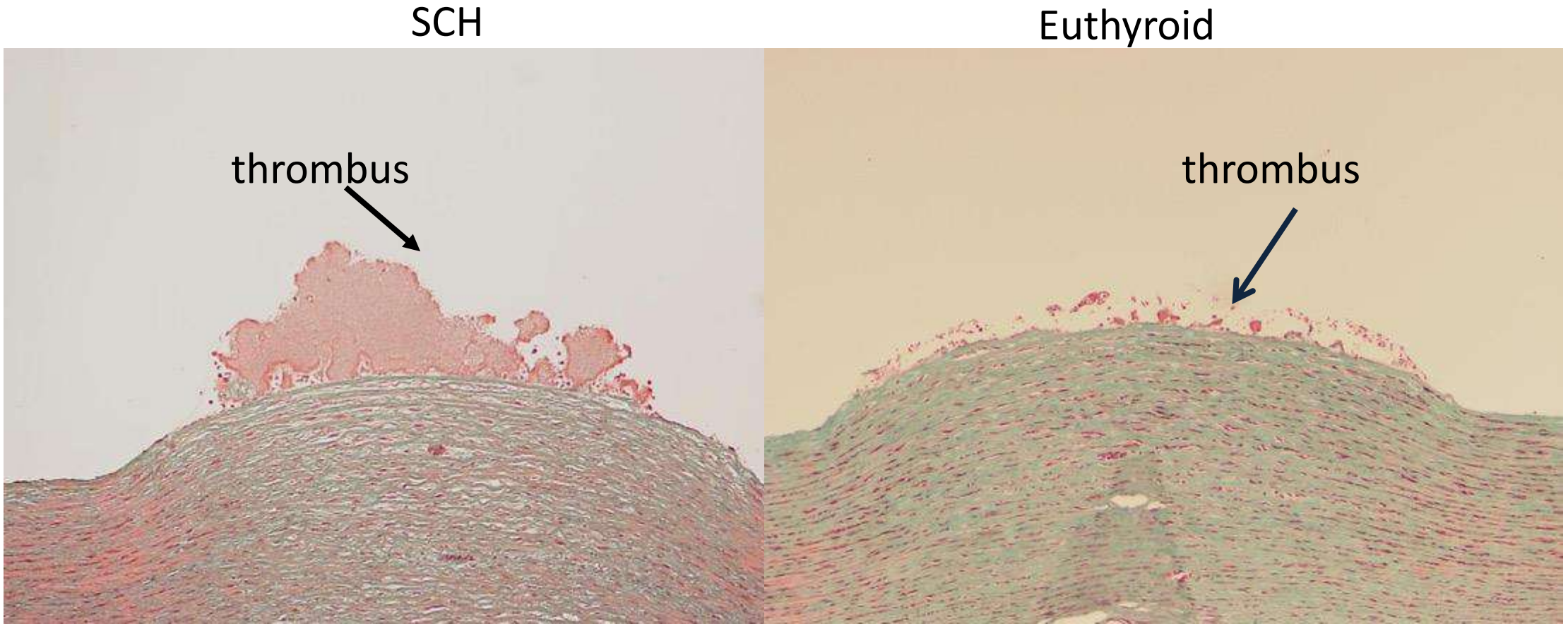


Table 3. Hazard Ratios for Cardiac and Overall Deaths by Thyroid Status[a]

Variable	Euthyroidism (n = 1905)	Subclinical Hypothyroidism (n = 208)	Subclinical Hyperthyroidism (n = 98)	Low T_3 (n = 910)
Cardiac deaths, No. (n = 147)	65	15	8	59
Hazard ratio (95% CI)	1 [Reference]	2.40 (1.36-4.21)	2.32 (1.11-4.85)	1.63 (1.14-2.33)
P value[b]		.02	.02	.007
Overall deaths, No. (n = 295)	140	27	9	119
Hazard ratio (95% CI)	1 [Reference]	2.01 (1.33-3.04)	1.22 (0.62-2.40)	1.57 (1.22-2.01)
P value		<.001	.56	<.001

Iervasi et al, Arch Intern Med 2007

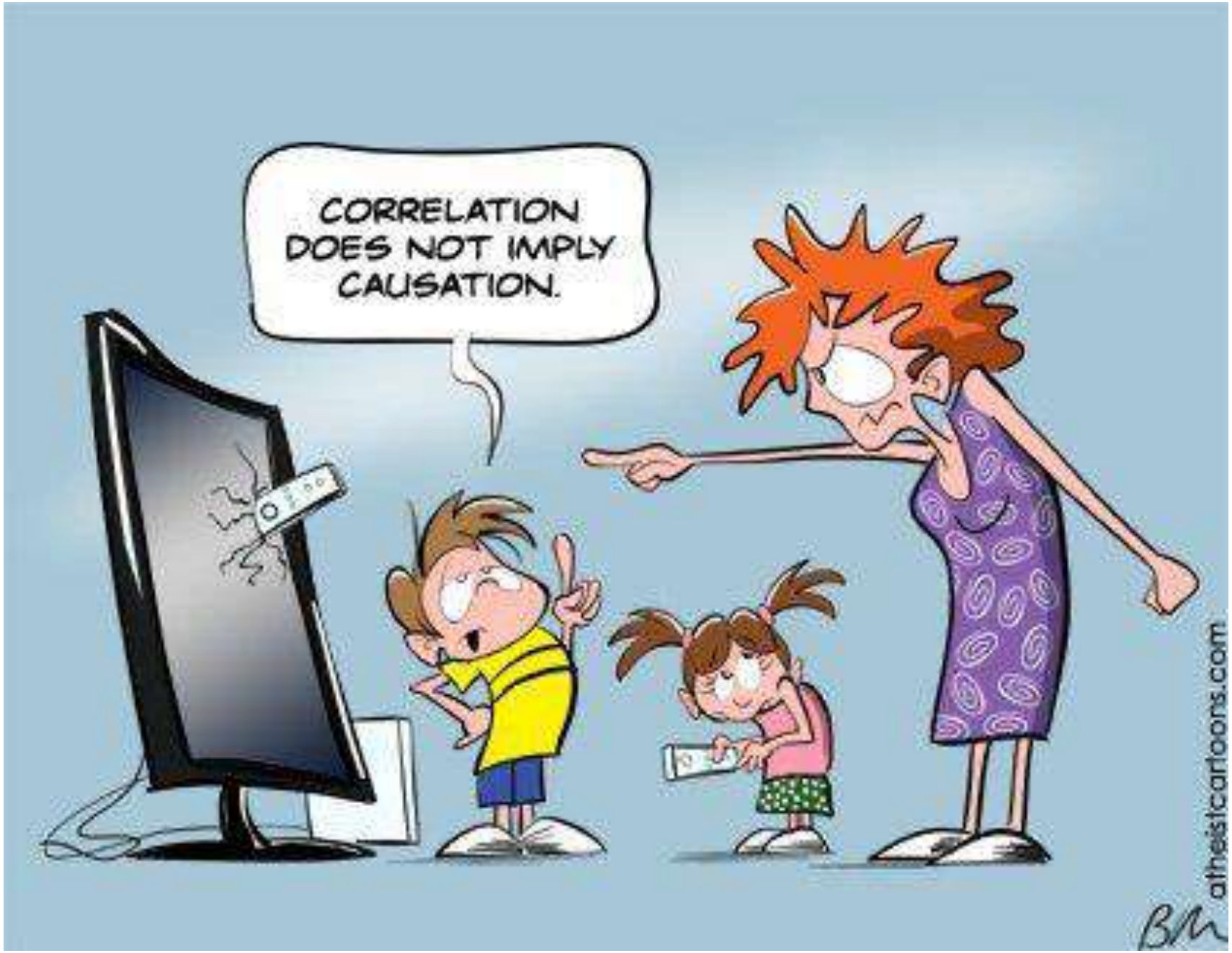
Thrombus Burden in acute NSTEMI



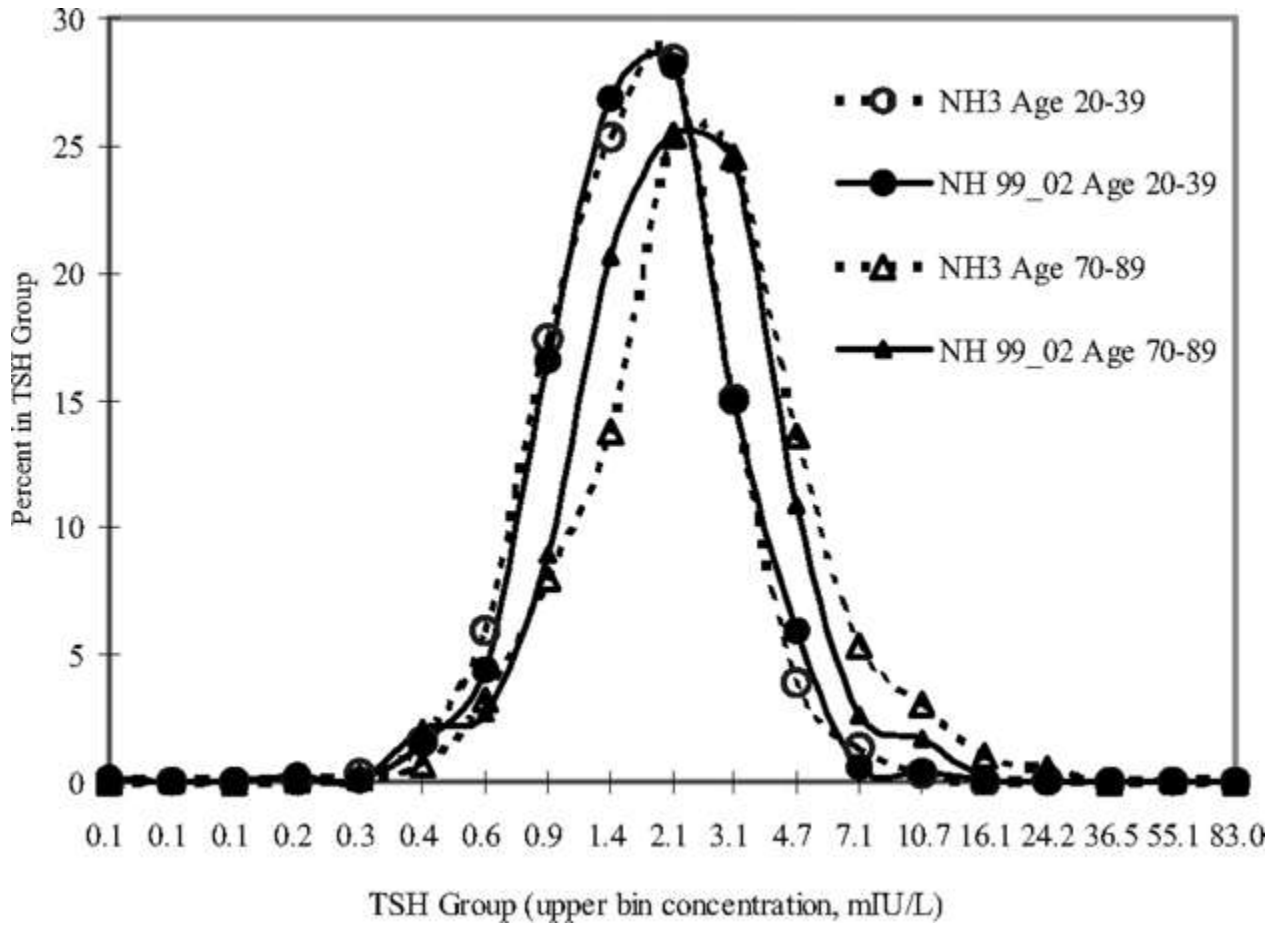
Modified Mason tri-chrome staining of thrombus in porcine aorta obtained from Badimon chamber

Viswanathan G et al, JCEM 2014

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

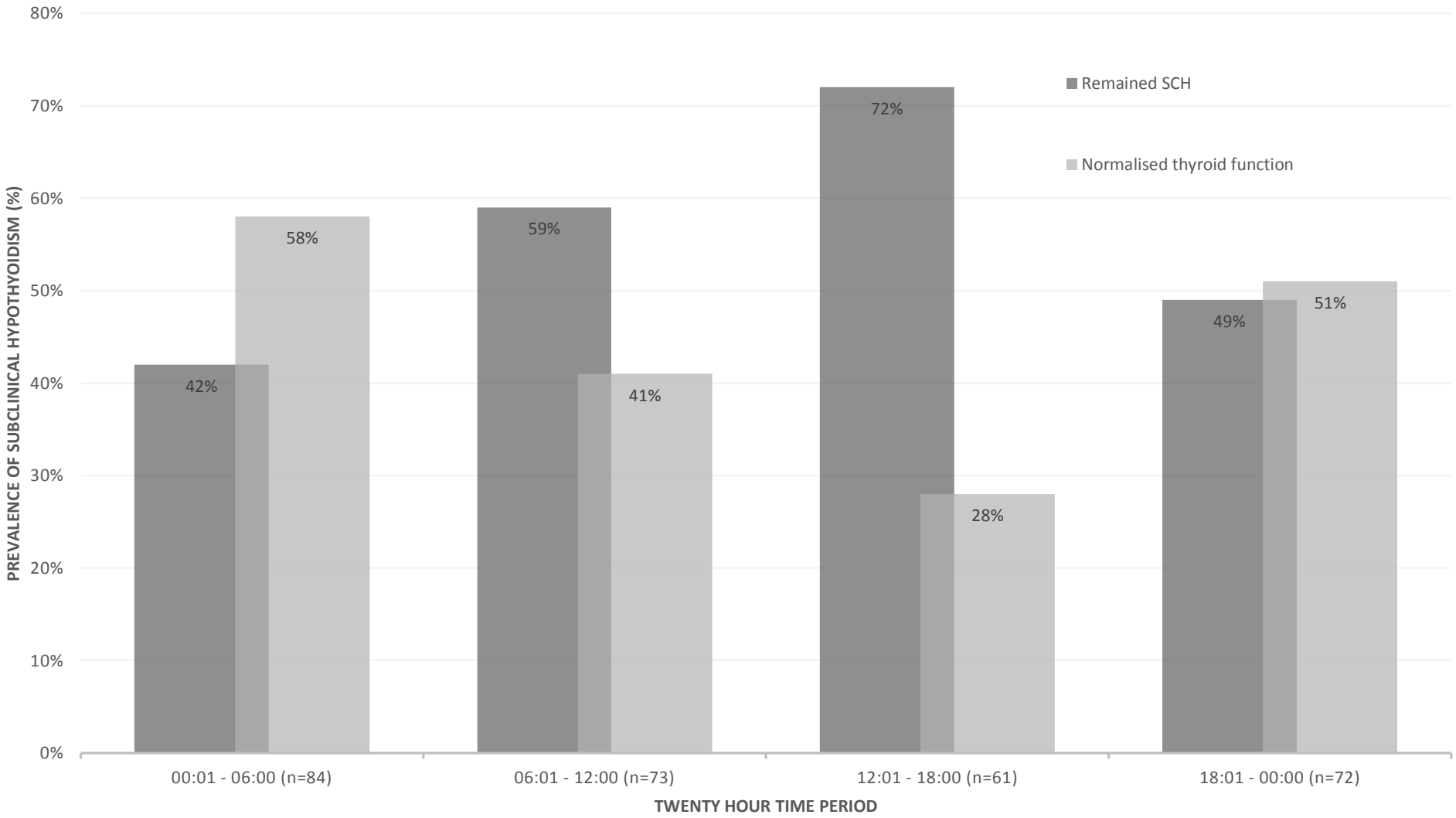


TSH and aging



Surks M, JCEM 2007

Time of sampling and the risk of remaining in subclinical hypothyroidism state after 7 – 10 days



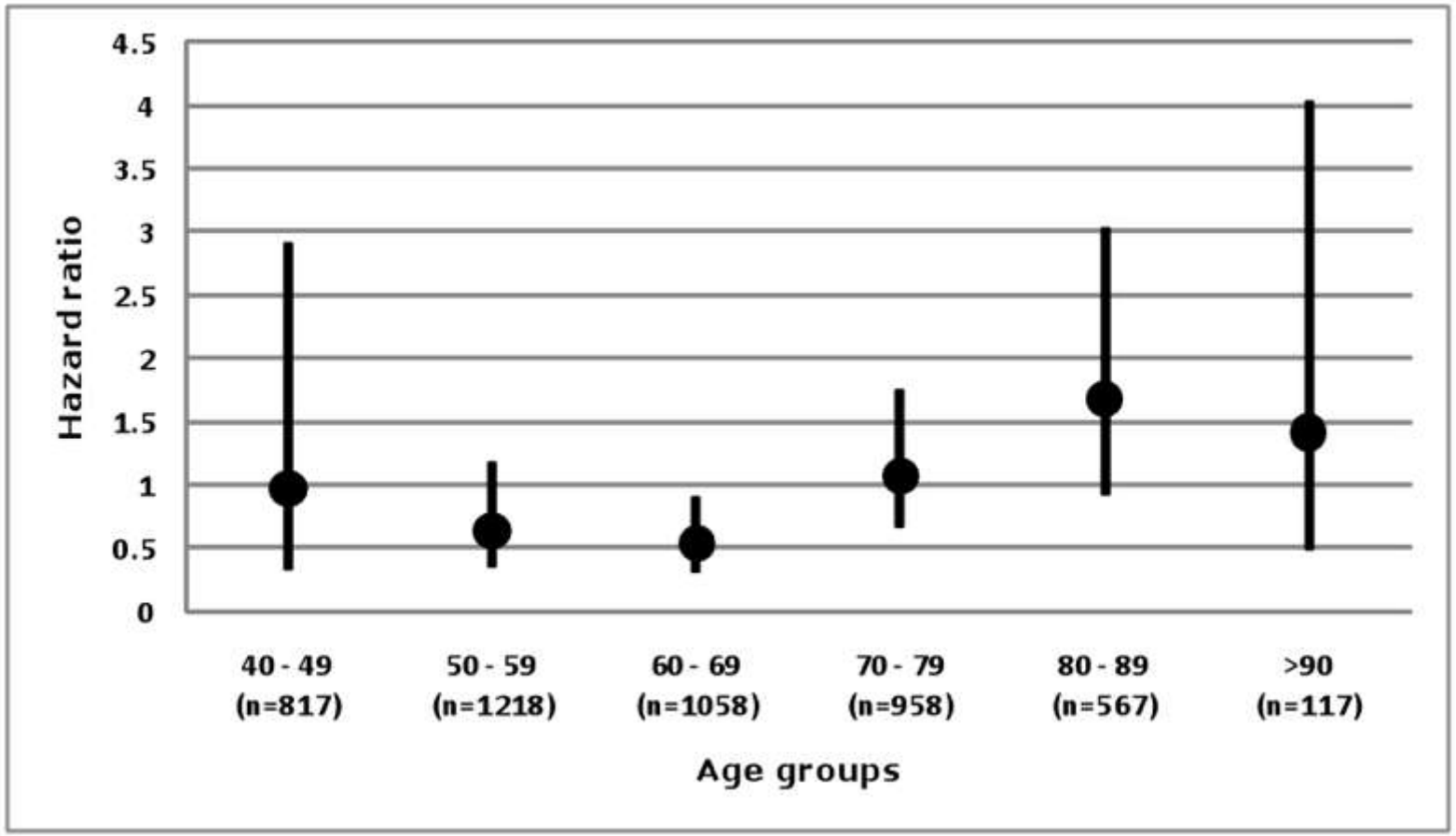
Razvi S et al, JCEM 2019, in press

Interventional studies in Subclinical Hypothyroidism

UK General Practice Research Database

LT4 vs untreated; Fatal + non fatal CV events

Event rate stratified by age



Razvi et al, Arch Intern Med 2012

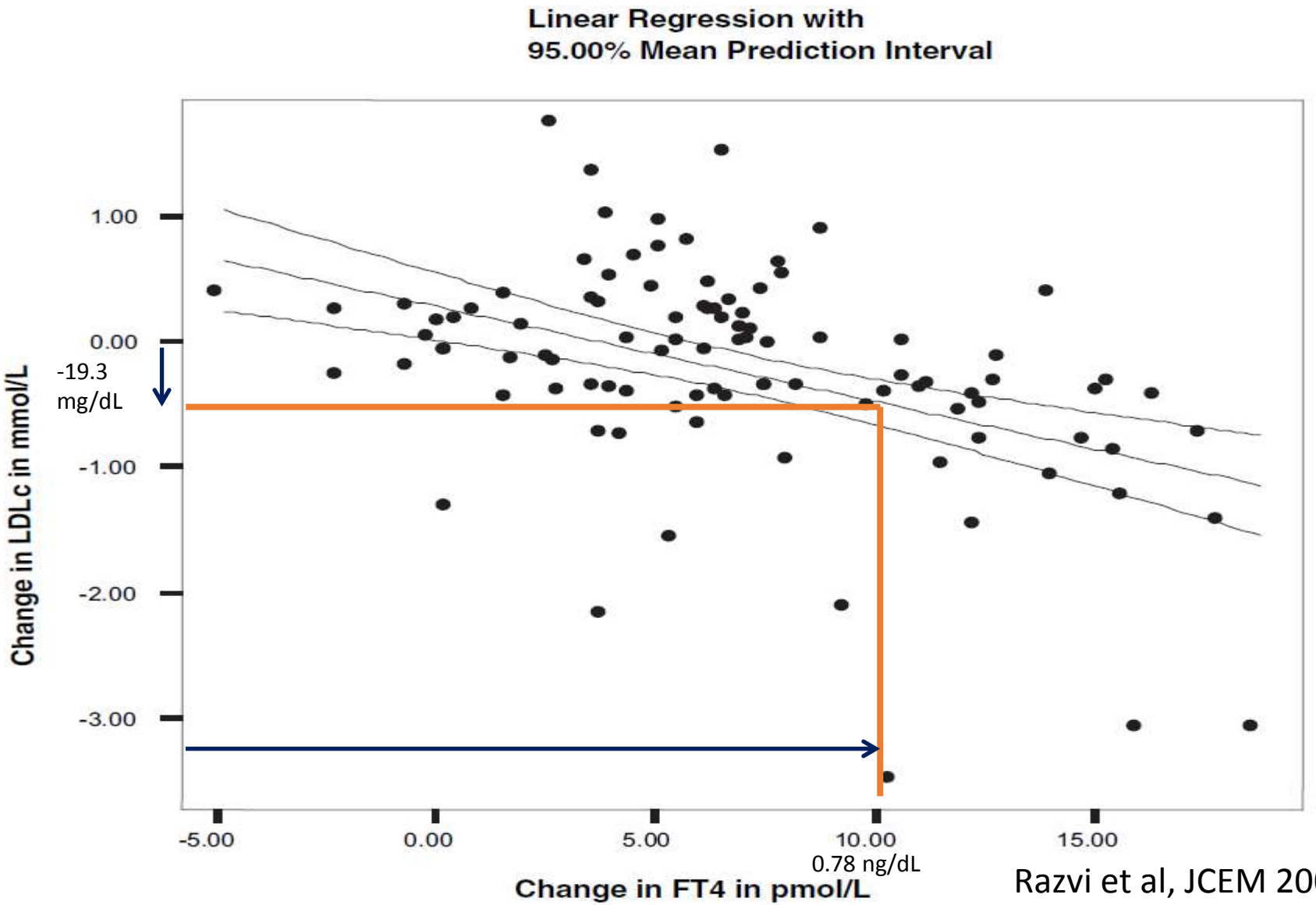
LT4 in SCH and CIMT

TABLE 2. Clinical features of sHT patients at baseline and after 6 months of stable euthyroidism or placebo

	Baseline		After therapy	
	sHT-LT_4 (n = 23)	sHT-placebo (n = 22)	sHT-LT_4 (n = 23)	sHT-placebo (n = 22)
BMI (kg/m^2)	24.3 ± 3.6	25.0 ± 3.5	23.7 ± 3.5	24.9 ± 3.8
SBP (mm Hg)	117 ± 15	112 ± 13	112 ± 15	114 ± 13
DBP (mm Hg)	72 ± 11	71 ± 9	69 ± 9	72 ± 8
TSH (mIU/liter)	6.03[a] (3.65–15.00)	5.68 (3.66–12.60)	1.32[c] (0.34–2.59)	6.01 (3.67–14.5)
FT_4 (pg/ml)	8.8 ± 1.9[a]	8.5 ± 2.0	10.8 ± 2.4[c]	8.4 ± 1.9
FT_3 (pg/ml)	3.1 ± 0.7	3.0 ± 0.5	3.2 ± 0.5	3.0 ± 0.6
TC (mg/dl)	214.2 ± 37.5[a]	213.0 ± 48.7	191.6 ± 32.5[d]	219.6 ± 48.9
HDLc (mg/dl)	56.5 ± 11.7	56.8 ± 10.6	54.7 ± 7.4	57.8 ± 11.6
LDLc (mg/dl)	138.9 ± 32.3[a]	137.2 ± 40.2	119.2 ± 27.8[d]	141.3 ± 38.6
Triglyceride (mg/dl)	94.0 ± 31.9	95.0 ± 57.6	88.1 ± 30.0	102.7 ± 53.1
$ApoA_1$ (mg/dl)	166 ± 24	165 ± 25	152 ± 38	169 ± 29
ApoB (mg/dl)	107 ± 32	117 ± 53	98 ± 24	118 ± 49
Lp(a) (mg/dl)	13.0 (9.0–83.0)	16.5 (9.0–162.0)	10.7 (9.0–65.0)	15.5 (9.0–160.0)
Homocysteine (μmol/liter)	15.2 ± 19.2	10.1 ± 3.2	13.6 ± 9.3	9.8 ± 3.1
Vit. B_{12} (pg/ml)	315 ± 164	280 ± 123	306 ± 122	290 ± 139
Folate (ng/ml)	11.8 ± 7.5	10.7 ± 4.8	11.1 ± 6.6	11.3 ± 5.2
Maximal IMT (mm)	0.95 ± 0.34[b]	0.89 ± 0.20	0.85 ± 0.32	0.91 ± 0.18
Mean IMT (mm)	0.76 ± 0.14[a]	0.74 ± 0.13	0.67 ± 0.13[d]	0.77 ± 0.14

Monzani, JCEM 2004

Effect of increasing FT4 on LDLc

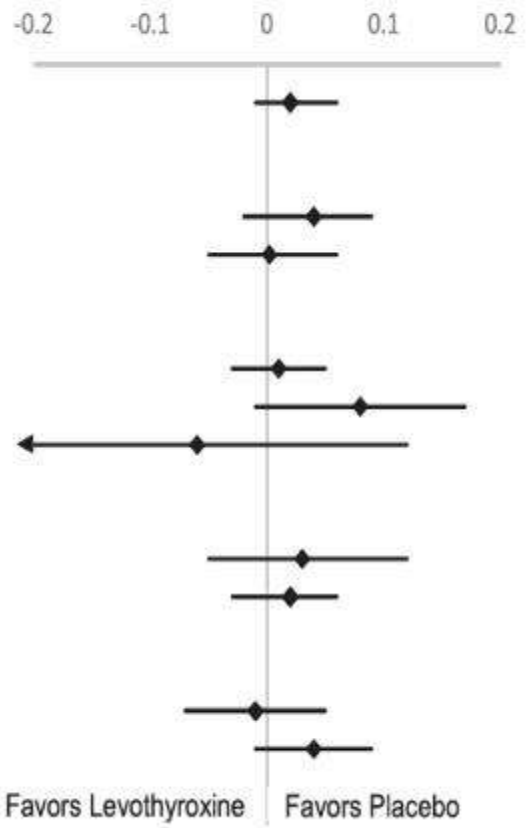


Razvi et al, JCEM 2007

Subgroup analysis of the TRUST trial

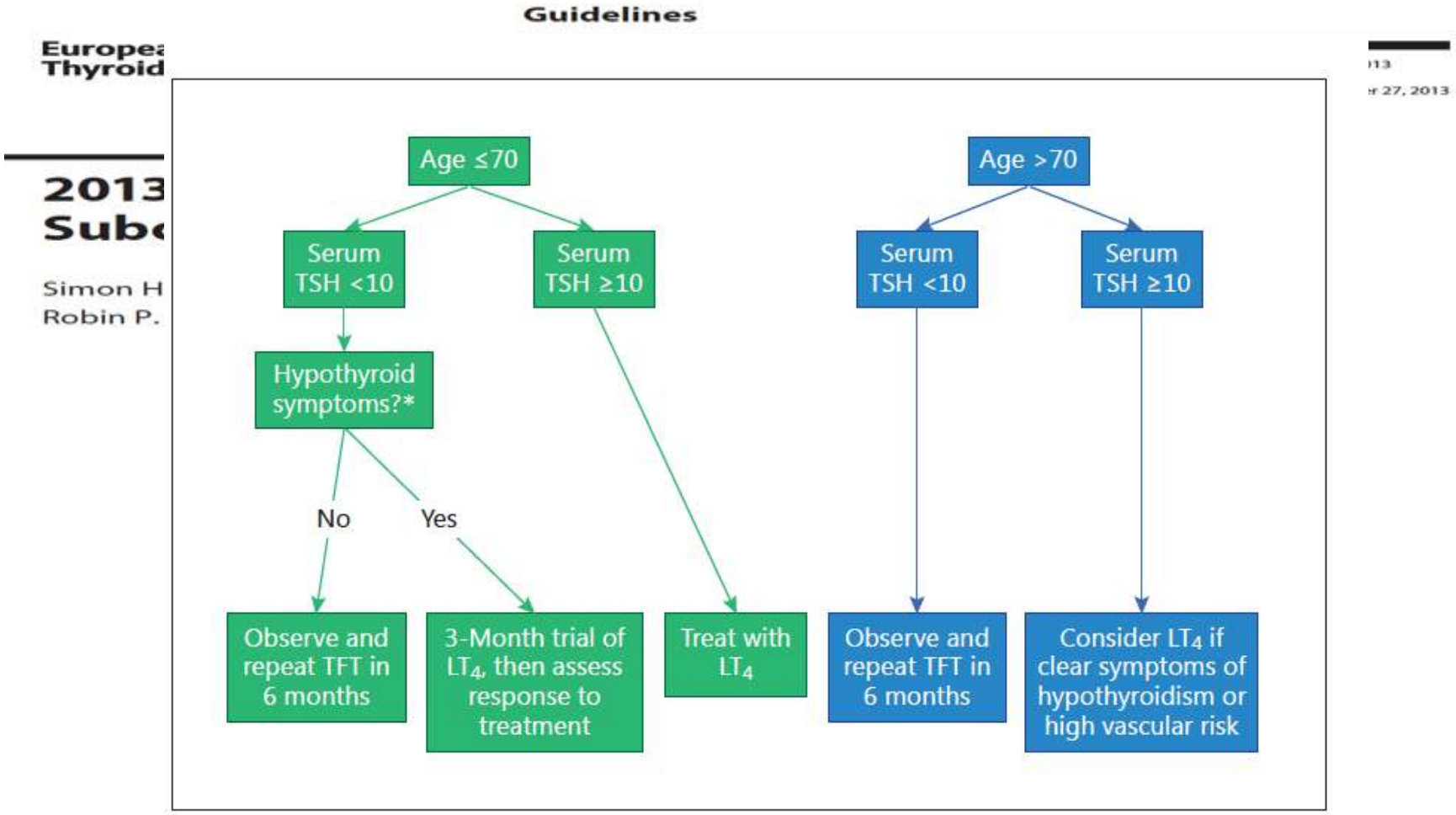
Impact of Thyroid Hormone Therapy on Atherosclerosis in the Elderly With Subclinical Hypothyroidism: A Randomized Trial

a) Mean CIMT	Levothyroxin n	Levothyroxin mean ± SD	Placebo n	Placebo mean ± SD	Between-group Difference (mm, 95% CI) [a]	P value	P for interaction
Mean carotid IMT (mm)	96	0.85 ± 0.14	89	0.82 ± 0.13	0.02 (-0.01 - 0.06)	0.30	
Stratified by sex							
Male (mm)	52	0.86 ± 0.16	46	0.83 ± 0.14	0.04 (-0.02 - 0.09)	0.17	0.38
Female (mm)	44	0.83 ± 0.11	43	0.81 ± 0.11	0.00 (-0.05 - 0.06)	0.95	
Stratified by baseline TSH							
4.6 - 6.9 mIU/L (mm)	75	0.84 ± 0.15	67	0.84 ± 0.12	0.01 (-0.03 - 0.05)	0.66	
7.0 - 9.9 mIU/L (mm)	17	0.87 ± 0.10	17	0.77 ± 0.15	0.08 (-0.01 - 0.17)	0.07	0.24
≥ 10 mIU/L (mm)	4	0.80 ± 0.09	5	0.82 ± 0.08	-0.06 (-0.23 - 0.12)	0.52	
Stratified by prior CVD [b]							
Yes (mm)	22	0.89 ± 0.16	19	0.85 ± 0.15	0.03 (-0.04 - 0.12)	0.38	0.70
No (mm)	74	0.83 ± 0.13	70	0.82 ± 0.12	0.02 (-0.03 - 0.06)	0.45	
Stratified by use of lipid-lowering medication [c]							
Yes (mm)	43	0.83 ± 0.12	32	0.84 ± 0.12	-0.01 (-0.07 - 0.05)	0.70	0.19
No (mm)	48	0.86 ± 0.15	52	0.81 ± 0.13	0.04 (-0.01 - 0.09)	0.09	



Blum M et al, JCEM 2018

ETA guidelines



Pearce SH et al, Eur Thy J 2013

Thyroid function in Cardiac Disease

TFT during AMI

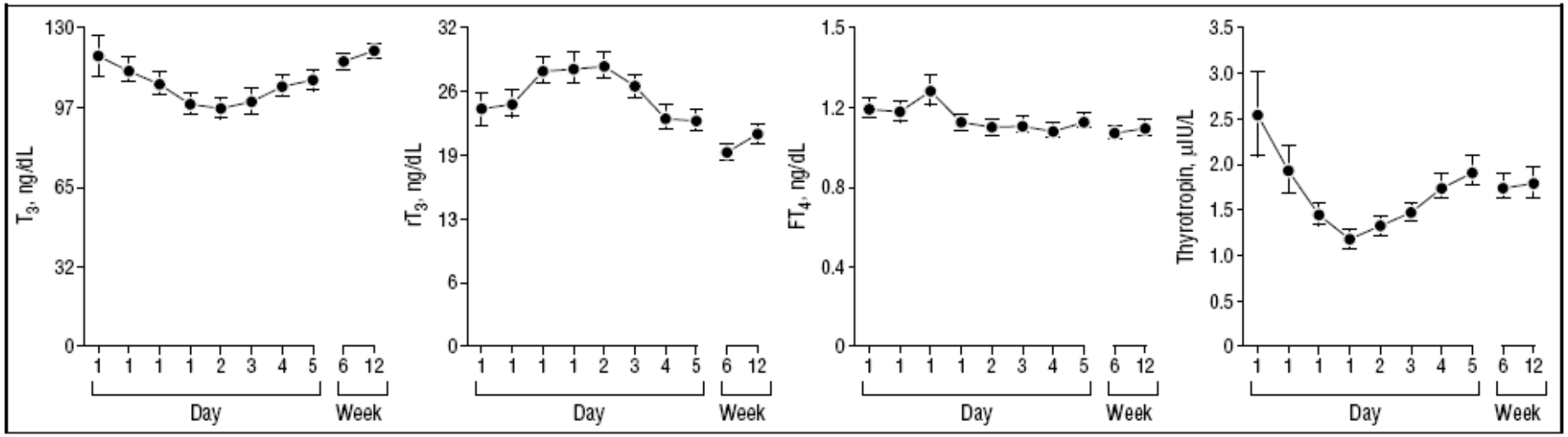
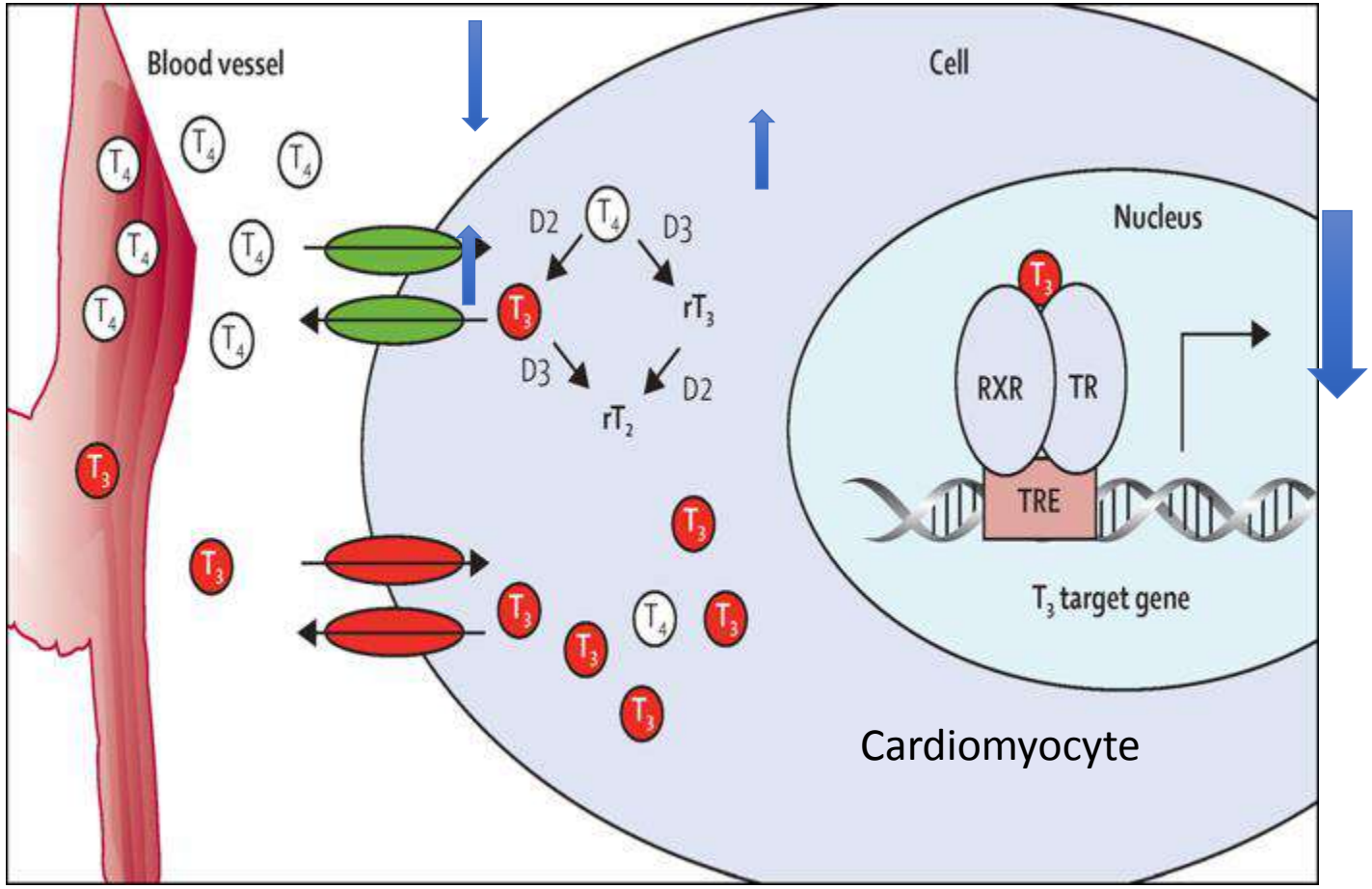


Figure 1. Serum profile of total triiodothyronine (T_3), reverse T_3 (rT_3), free thyroxine (FT_4), and thyrotropin in 47 patients with acute myocardial infarction during the first 5 days and 6 and 12 weeks later. Note that the time scale is not linear. Values are expressed as mean±SEM. To convert nanograms per deciliter to nanomoles per liter (T_3 and rT_3), multiply by 0.0154. To convert nanograms per deciliter to picomoles per liter (FT_4), multiply by 12.87.

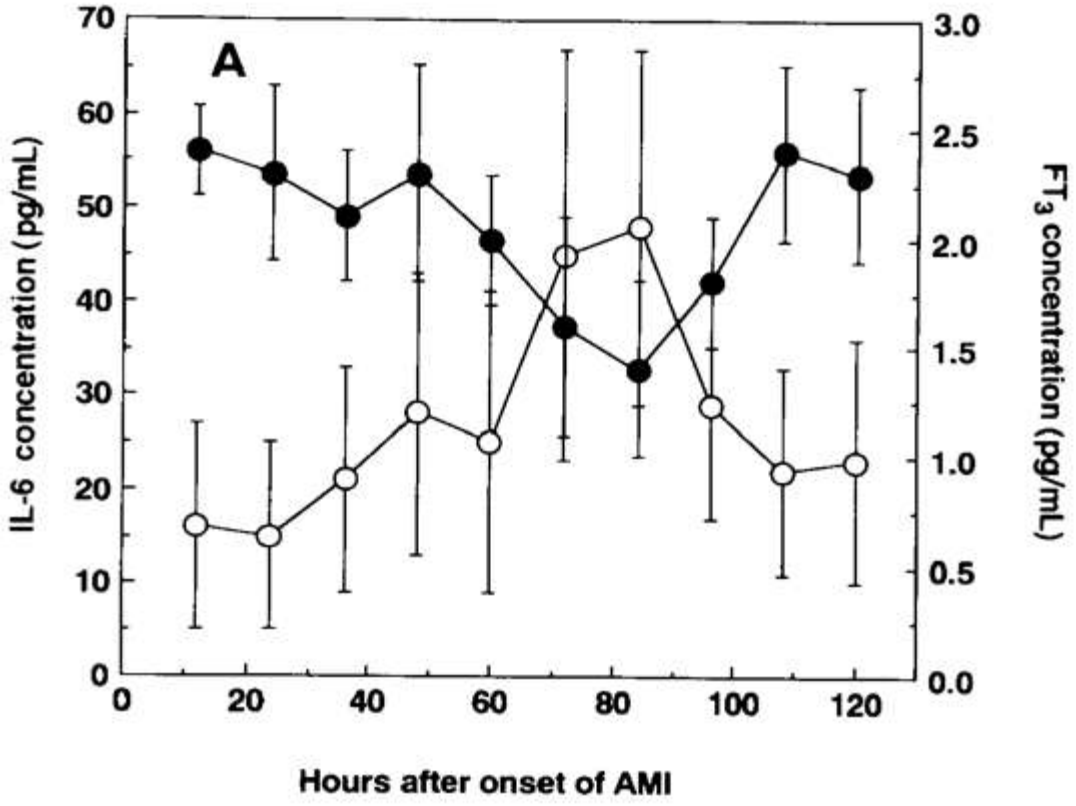
Friberg et al, 2002

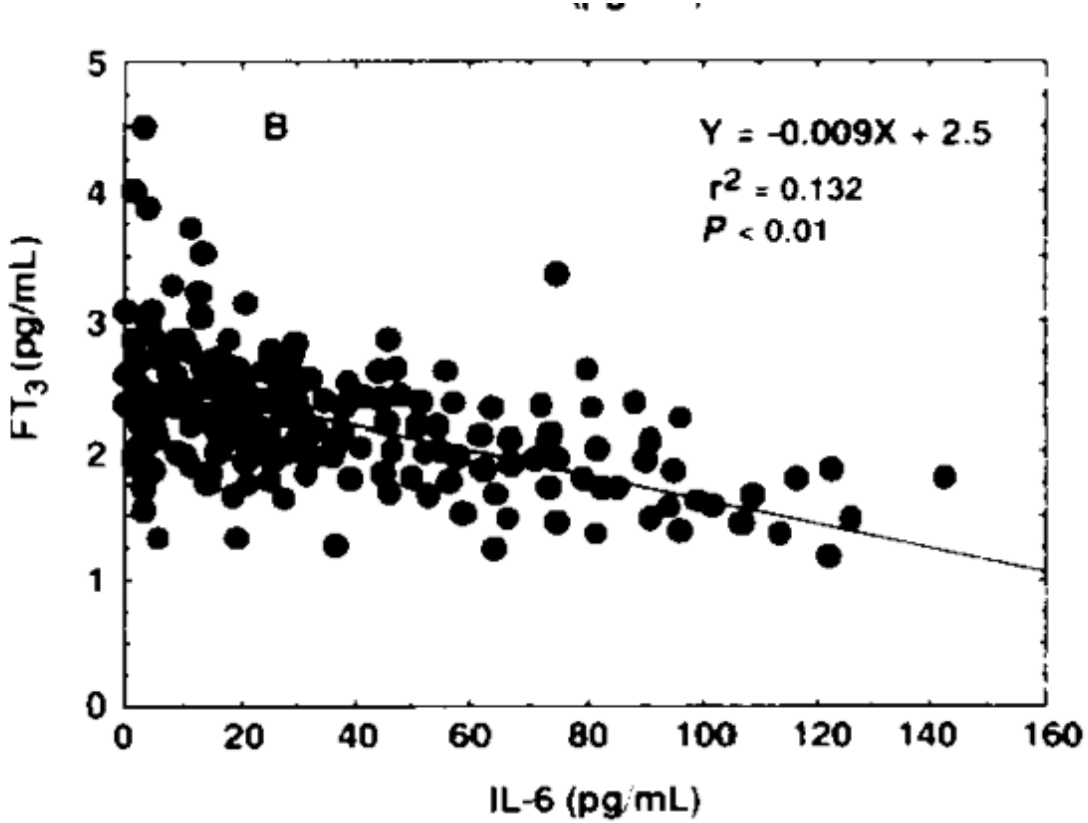
Mechanism of TFT change in AMI



Adapted from Boelen et al, Lancet Diab Endocrinol 2015

Role of inflammation





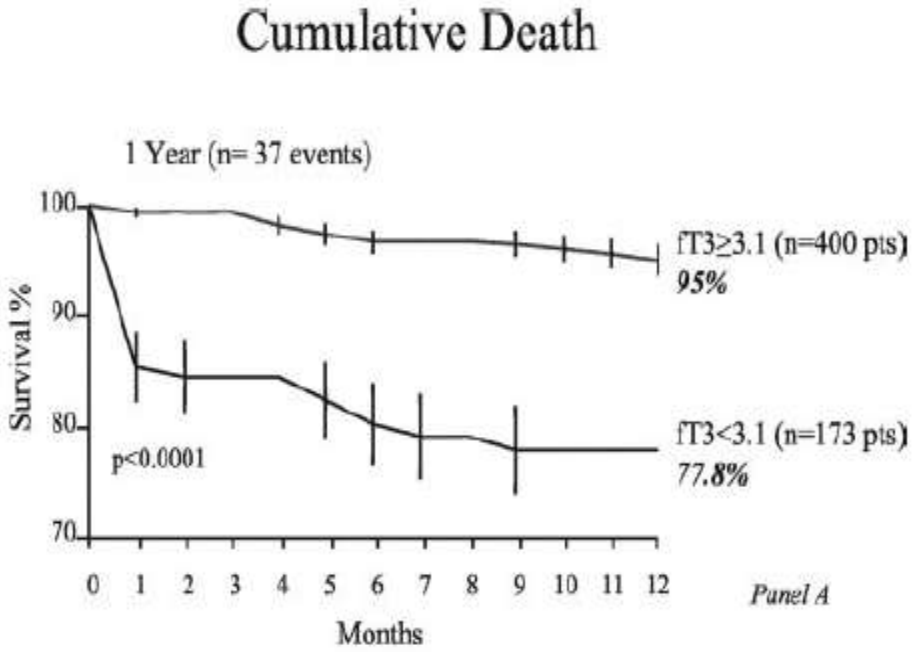
Kimura T et al, EJE 2000

TFT in cardiac patients

TABLE 3. Multivariate Analysis of Predictors of 1-Year Mortality

Variables	Hazard Ratio	Standard Error	95% CI	*P*
Cumulative death				
fT3	3.582	0.2784	2.0755 to 6.1815	0.0001
Age	1.051	0.0173	1.0154 to 1.0866	0.005
LVEF	1.037	0.0119	1.0132 to 1.0616	0.006
Dyslipidemia*	2.955	0.4460	1.2331 to 7.0841	0.023
Cardiac death				
FT3	2.359	0.3742	1.1329 to 4.9122	0.016
Age	1.047	0.0243	0.9984 to 1.0982	0.040
LVEF	1.069	0.0178	1.0329 to 1.1075	0.0001
Dyslipidemia*	4.236	0.5922	1.3272 to 13.5246	0.04

*Dichotomized variable.



FT3 was the most potent independent predictor of survival; more than age and LVEF

Iervasi et al, 2003

T3 treatment of low T3 syndrome in chronic Heart Failure

Parameters	Patients treated with L-T_3		
	Before L-T_3	After L-T_3	*P* value before L-T_3 *vs.* after L-T_3
LV EDV (ml/m^2 bs)	133 (114–158)	142 (132–161)	0.02
LV ESV (ml/m^2 bs)	103 (84–127)	108 (89–124)	ns
LV SV (ml/m^2 bs)	35 (28–39)	40 (34–44)	0.01
CO (liter/min)	4.1 (3.3–5.4)	4.8 (3.4–5.4)	ns
CI (liter/m^2 bs × min)	2.2 (1.7–2.8)	2.5 (1.9–2.7)	ns
LV EF (%)	25 (18–32)	28 (22–32)	ns
SVR (dyne/sec × cm)	2.07 (1.92–3.13)	2.10 (1.87–2.48)	ns
Elastance	1.36 (0.93–1.63)	1.27 (0.91–1.36)	ns
External cardiac work (ml × mm Hg × bpm)	201,226 (161,084–3,002,307)	226,519 (169,276–266,388)	ns
Internal cardiac work (ml × bpm × mm Hg/2)	401,849 (348,910–534,505)	396,885 (343,080–473,613)	ns
Total cardiac work	626,859 (492,291–787,522)	592,085 (540,060–756,684)	ns

Pingitore A et al, JCEM 2008

T3 treatment of low T3 syndrome in AMI

Cardiac magnetic resonance parameters at discharge	Entire population (n = 37)	T3-treated		p value
		YES (n = 19)	NO (n = 18)	
Left ventricular end-diastolic volume (ml/m^2)	88.84 ± 14.71	89.56 ± 18.78	88.07 ± 9.14	0.76
Left ventricular end-systolic volume (ml/m^2)	39.91 ± 12.70	40.67 ± 14.08	39.10 ± 11.42	0.71
Left ventricular ejection fraction (%)	53.43 ± 10.04	52.89 ± 9.72	54 ± 10.63	0.74
Stroke volume (ml/kg)	47.97 ± 8.43	47.67 ± 6.16	48.29 ± 10.49	0.83
Late gadolinium enhancement extent (% of mass)	17 ± 9.87	19 ± 10.80	14.89 ± 8.58	0.21
Cardiac magnetic resonance parameters at sixth month				
Left ventricular end-diastolic volume (ml/m^2)	90.06 ± 14.96	91.52 ± 17.60	88.52 ± 11.87	0.55
Left ventricular end-systolic volume (ml/m^2)	39.51 ± 15.20	38.91 ± 16.60	40.14 ± 14.02	0.81
Left ventricular ejection fraction (%)	55.35 ± 8.80	56 ± 8.70	54.67 ± 9.11	0.65
Stroke volume (ml/kg)	49.66 ± 7.13	51.09 ± 7.052	48.14 ± 7.09	0.21
Late gadolinium enhancement extent (% of mass)	13.30 ± 8.28	14.37 ± 8.68	12.17 ± 7.93	0.43

Pingitore A et al, Am J Cardiol 2019

Conclusions

1. Mild hypothyroidism is associated with increased cardiovascular risk particularly in younger patients
2. Treatment reduces some CV risk factors in younger patients but not in older individuals
3. Older individuals with mildly raised TSH levels should be monitored and treatment considered only of serum levels rise above 10mU/L
4. More data is required before T3 therapy can be considered safe and effective in Heart Failure and AMI patients


Newcastle
University
Thank you for your attention.