

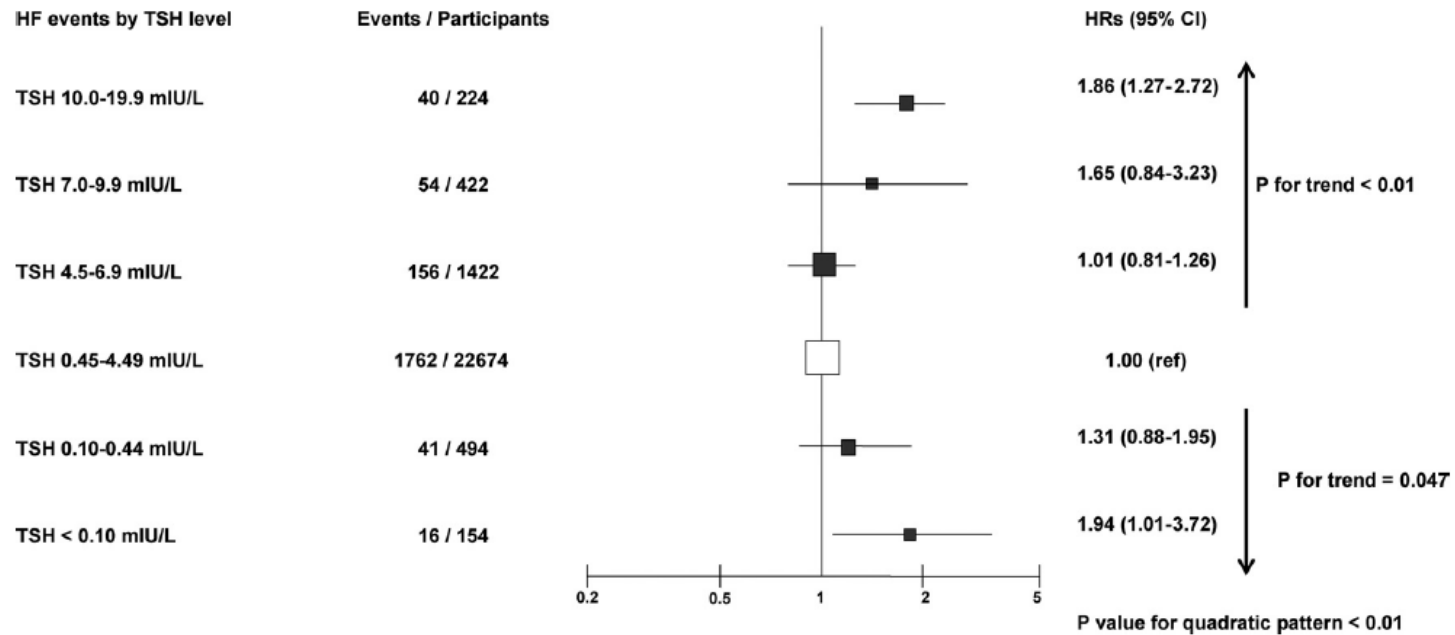


The Effect of Thyroid Function on Clinical Outcome in Patients with Heart Failure

Shmuel Chen, Ayelet Shauer, Donna R. Zwas, Chaim Lotan,
Andre Keren and Israel Gotsman

Introduction

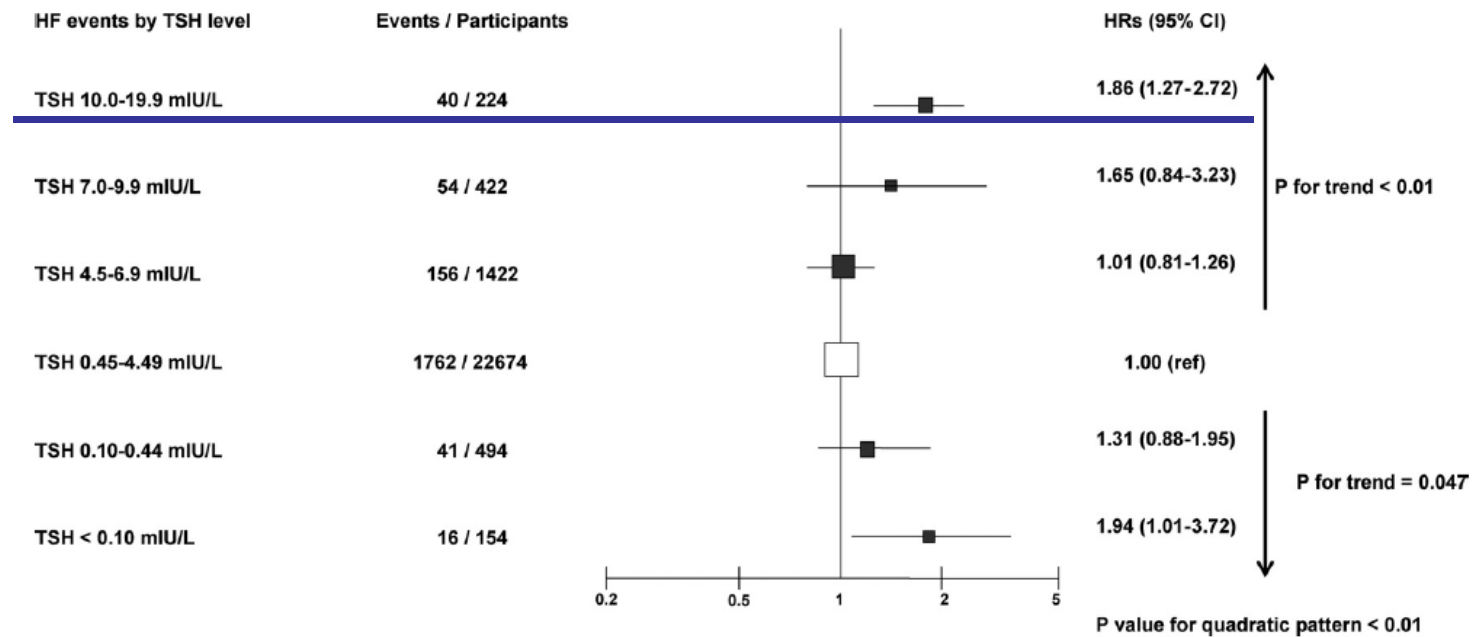
Hypothyroidism is a risk factor for developing heart failure



Subclinical Thyroid Dysfunction and the Risk of Heart Failure Events : An Individual Participant Data Analysis From 6 Prospective Cohorts. Gencer B. et al. Circulation. 2012.

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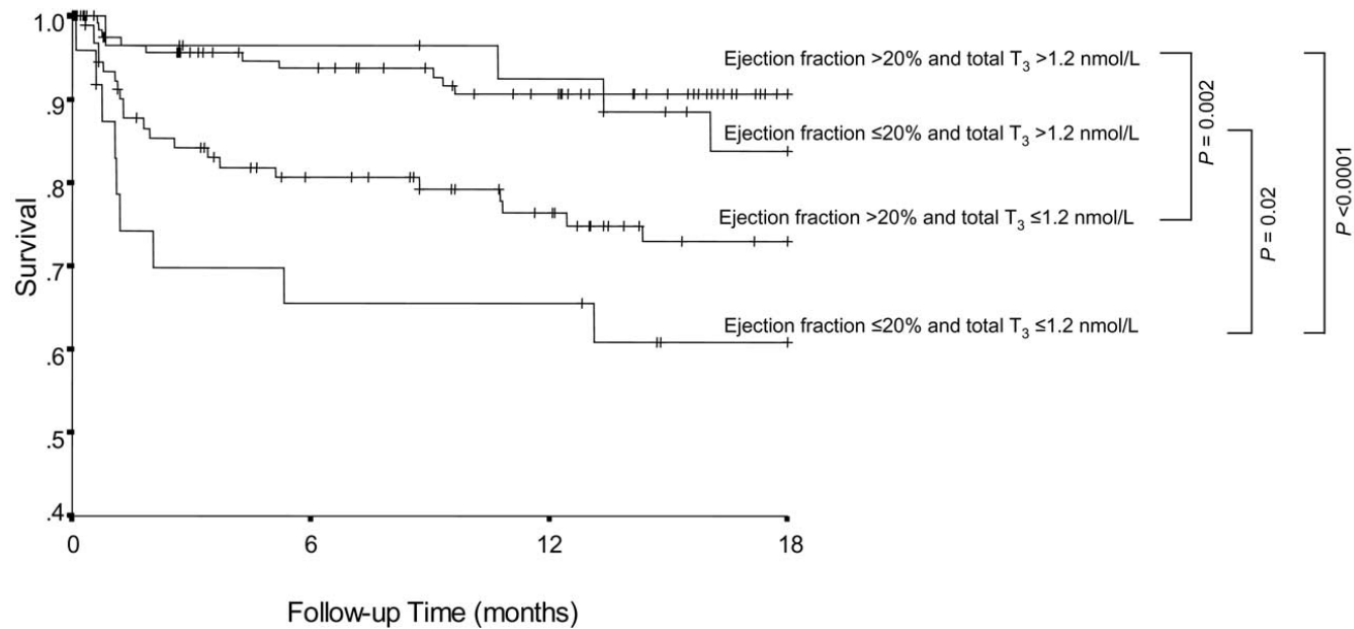
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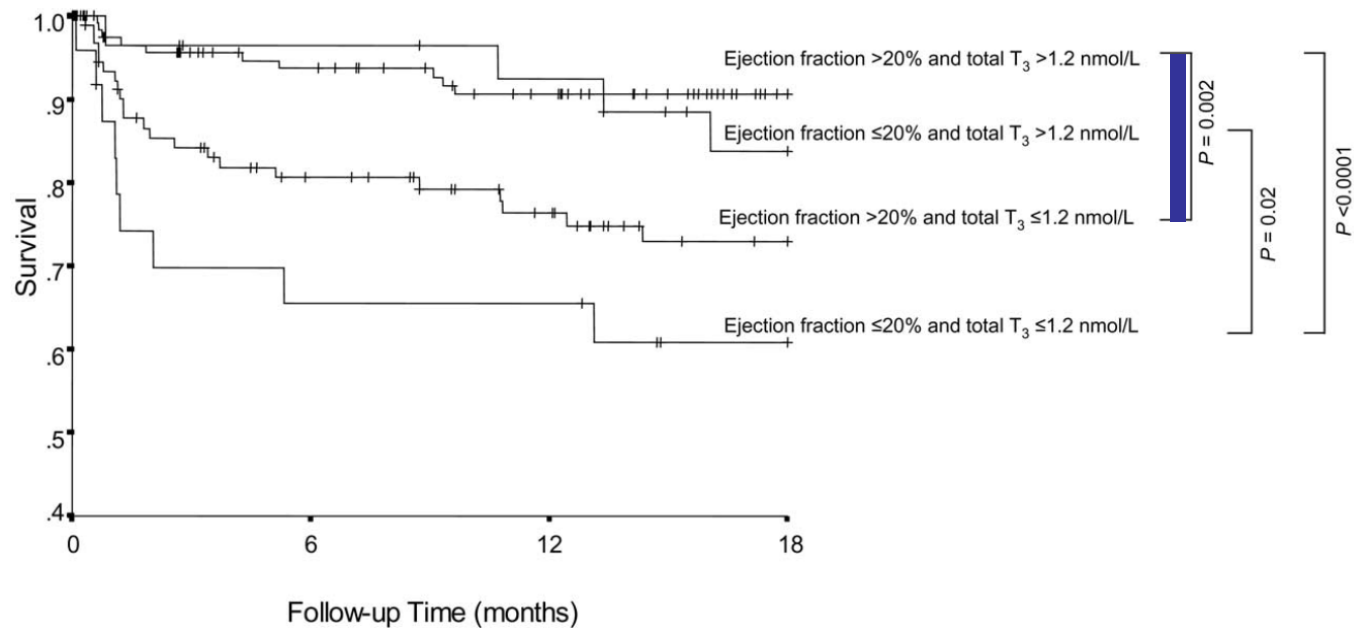
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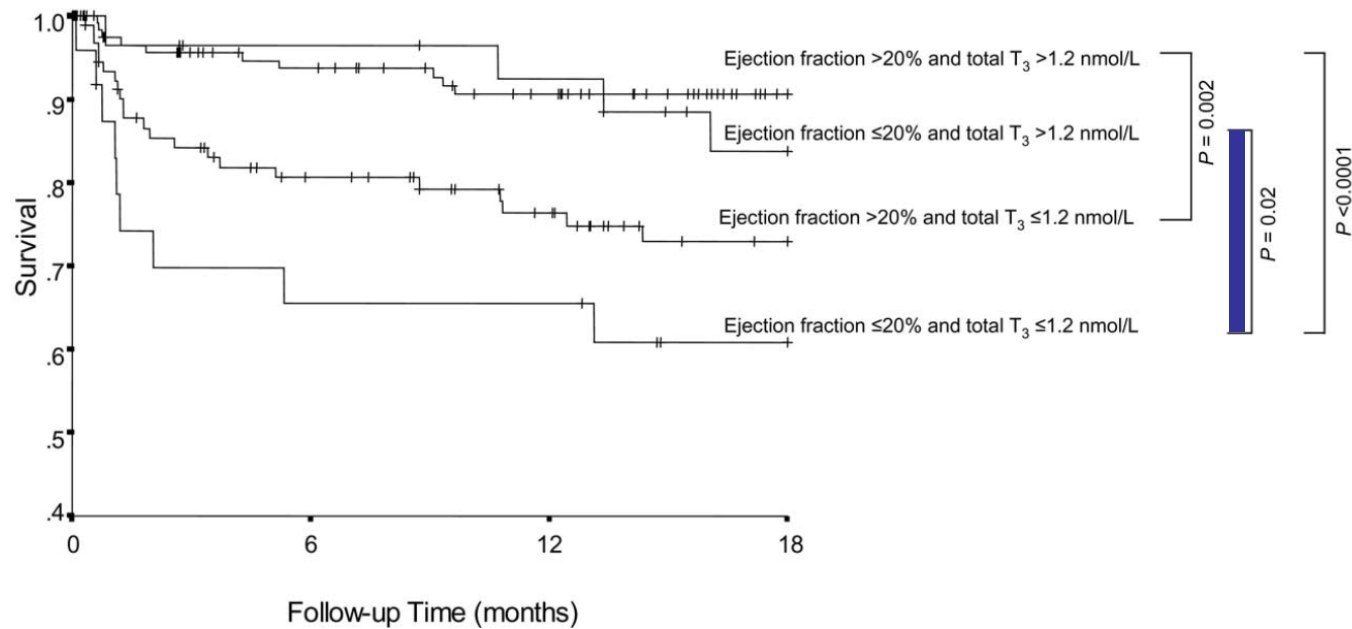
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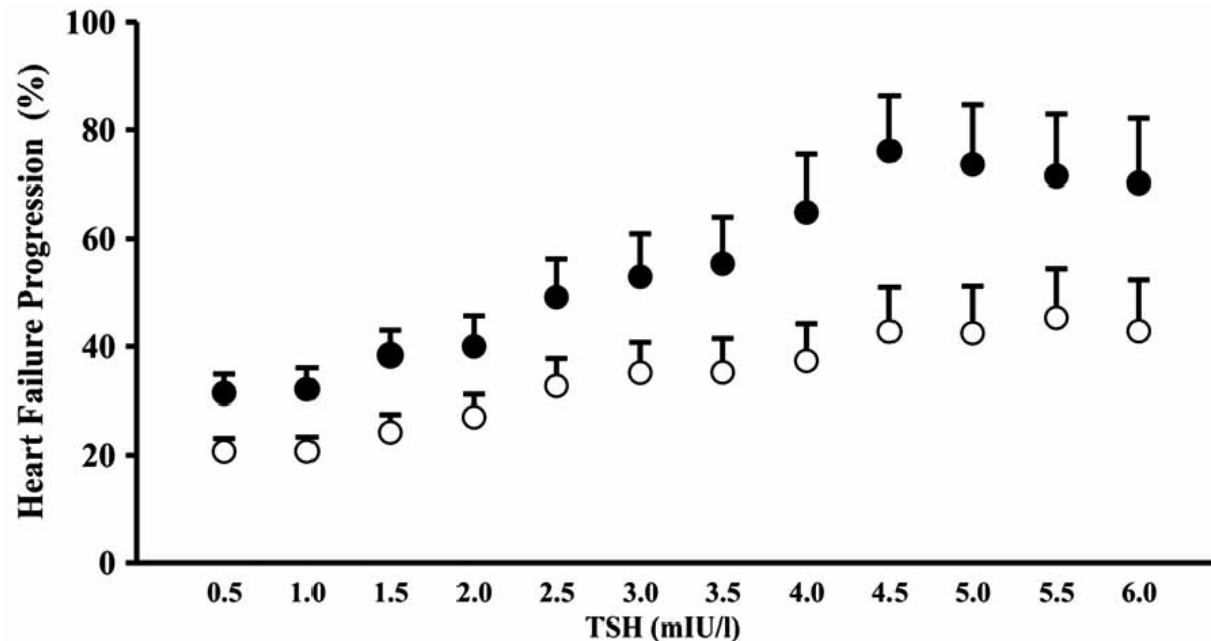
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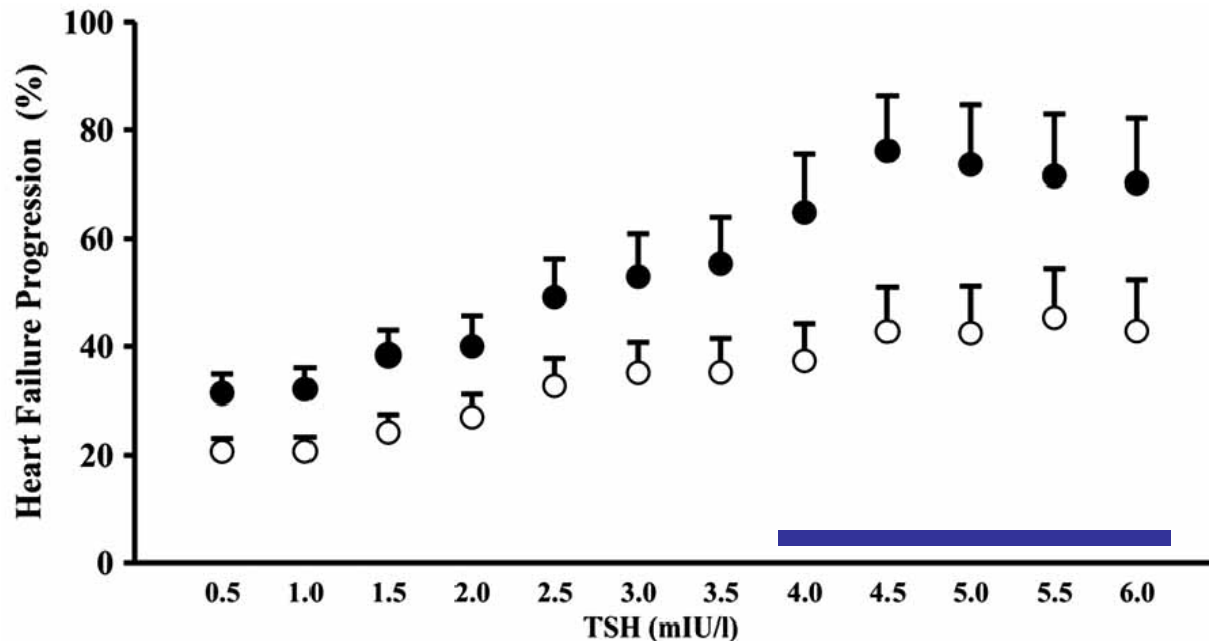
Subclinical hypothyroidism has been shown to impact heart failure progression in patients with heart failure



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Introduction

Data regarding the clinical significance of TSH levels alone as a predictor of outcome is sparse.

Particularly, the significance of mildly elevated TSH (<10) and the significance of subclinical hypothyroidism in these patients are not well defined.

Purpose

To evaluate the significance of TSH on clinical outcome (mortality and morbidity) in patients with chronic HF.

- Mildly elevated TSH (<10) / subclinical hypothyroidism

Methods

All patients with a diagnosis of heart failure at a Health Maintenance Organization - Clalit Health Services in Jerusalem

N=5,599

Followed for cardiac-related hospitalizations and death

Median follow-up time was 434 days

Patients were divided into quartiles based on TSH levels

Demographics and Clinical characteristics

	TSH (mIU/L)					P Value
	≤ 1.3 (N=1312)	1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≥ 3.6 (N=1389)	Total (N=5599)	
Age	75±13	74±13	75±13	76±14	75±13	0.006
Gender (Male)	683 (52)	830 (54)	634 (47)	584 (42)	2731 (49)	<0.001
Diabetes Mellitus	612 (47)	740 (48)	671 (50)	656 (47)	2679 (48)	0.42
Hyperlipidemia	1107 (84)	1294 (84)	1134 (84)	1131 (81)	4666 (83)	0.16
Hypertension	1079 (82)	1264 (82)	1142 (85)	1164 (84)	4649 (83)	0.13
Ischemic Heart Disease	990 (75)	1147 (74)	993 (74)	999 (72)	4129 (74)	0.21
Atrial Fibrillation	274 (21)	353 (23)	380 (28)	499 (36)	1506 (27)	<0.001
S/P Coronary bypass surgery	210 (16)	267 (17)	237 (18)	264 (19)	978 (17)	0.23
COPD	138 (11)	167 (11)	131 (10)	126 (9)	562 (10)	0.41
Peripheral vascular disease	222 (17)	281 (18)	229 (17)	246 (18)	978 (17)	0.78
S/P TIA or CVA	298 (23)	343 (22)	306 (23)	330 (24)	1277 (23)	0.78

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eGFR (mL/min per 1.73m2)*	66±30	67±42	65±37	60±42	65±38	<0.001
Hemoglobin (g/dL)	13±2	13±2	13±2	12±2	13±2	<0.001
Sodium (mEq/L)	140±3	140±3	140±3	139±3	140±3	0.003
Glucose (mg/dL)	120±58	116±47	120±53	116±53	118±53	0.12
Calcium (mg/dL)	9.2±0.5	9.2±0.5	9.1±0.5	9.1±0.6	9.2±0.5	0.001
LDL (mg/dL)	95±33	94±31	95±32	96±32	95±32	0.36
HDL (mg/dL)	44±13	44±13	44±13	46±13	45±13	0.03
Triglycerides (mg/dL)	146±110	151±200	144±83	144±83	146±131	0.37
Albumin (g/dL)	3.9±0.4	4.0±0.4	3.9±0.4	3.9±0.4	3.9±0.4	0.008
Iron (µg/dL)	64±29	65±29	64±31	62±28	64±29	0.08

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QRS interval (ms)	100±27	101±27	100±26	105±31	102±28	<0.001
QTc interval (ms)	448±41	448±41	448±40	457±46	450±42	<0.001
Left bundle branch block	49 (5)	50 (4)	54 (5)	80 (8)	233 (6)	0.006
Atrial fibrillation rhythm	93 (10)	111 (10)	118 (12)	143 (14)	465 (11)	0.008
Pacemaker	55 (6)	72 (6)	68 (7)	89 (9)	284 (7)	0.07
Reduced LV function	175 (57)	227 (57)	183 (53)	190 (51)	775 (54)	0.24
E/A ratio	1.3±0.8	1.3±0.7	1.3±0.7	1.5±0.9	1.3±0.8	0.06
Severe Mitral Regurgitation	59 (22)	79 (22)	64 (21)	79 (23)	281 (22)	0.84
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ACE-inhibitor / ARB	990 (75)	1197 (77)	1043 (77)	1027 (74)	4257 (76)	0.11
Beta blockers	902 (69)	1097 (71)	941 (70)	908 (65)	3848 (69)	0.01
Spirolactone	399 (30)	457 (30)	462 (34)	497 (36)	1815 (32)	<0.001
Furosemide	845 (64)	999 (65)	958 (71)	992 (71)	3794 (68)	<0.001
Thiazide	280 (21)	399 (26)	354 (26)	338 (24)	1371 (24)	0.01
Digoxin	111 (8)	159 (10)	166 (12)	182 (13)	618 (11)	<0.001
Amiodarone	164 (13)	199 (13)	214 (16)	400 (29)	977 (17)	<0.001
Aspirin	900 (69)	1068 (69)	897 (66)	857 (62)	3722 (66)	<0.001
Corticoidsteroids	198 (15)	221 (14)	175 (13)	167 (12)	761 (14)	0.09
Eltroxin	162 (12)	158 (10)	227 (17)	704 (51)	1251 (22)	<0.001
Anti-thyroid	28 (2)	12 (1)	5 (0)	14 (1)	59 (1)	<0.001

Demographics and Clinical characteristics

	TSH (mIU/L)					P Value
	≤ 1.3 (N=1312)	1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≥ 3.6 (N=1389)	Total (N=5599)	
ACE-inhibitor / ARB	990 (75)	1197 (77)	1043 (77)	1027 (74)	4257 (76)	0.11
Beta blockers	902 (69)	1097 (71)	941 (70)	908 (65)	3848 (69)	0.01
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Anti-thyroid	28 (2)	12 (1)	5 (0)	14 (1)	59 (1)	<0.001

Demographics and Clinical characteristics

	TSH (mIU/L)					P Value
	≤ 1.3 (N=1312)	1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≥ 3.6 (N=1389)	Total (N=5599)	
ACE-inhibitor / ARB	990 (75)	1197 (77)	1043 (77)	1027 (74)	4257 (76)	0.11
Beta blockers	902 (69)	1097 (71)	941 (70)	908 (65)	3848 (69)	0.01
Spirolactone	399 (30)	457 (30)	462 (34)	497 (36)	1815 (32)	<0.001
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Eltroxin	162 (12)	158 (10)	227 (17)	704 (51)	1251 (22)	<0.001
Anti-thyroid	28 (2)	12 (1)	5 (0)	14 (1)	59 (1)	<0.001

Demographics and Clinical characteristics

	TSH (mIU/L)					P Value
	≤ 1.3 (N=1312)	1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≥ 3.6 (N=1389)	Total (N=5599)	
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Beta blockers	902 (69)	1097 (71)	941 (70)	908 (65)	3848 (69)	0.01
Spirolactone	399 (30)	457 (30)	462 (34)	497 (36)	1815 (32)	<0.001
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Eltroxin	162 (12)	158 (10)	227 (17)	704 (51)	1251 (22)	<0.001
Anti-thyroid	28 (2)	12 (1)	5 (0)	14 (1)	59 (1)	<0.001

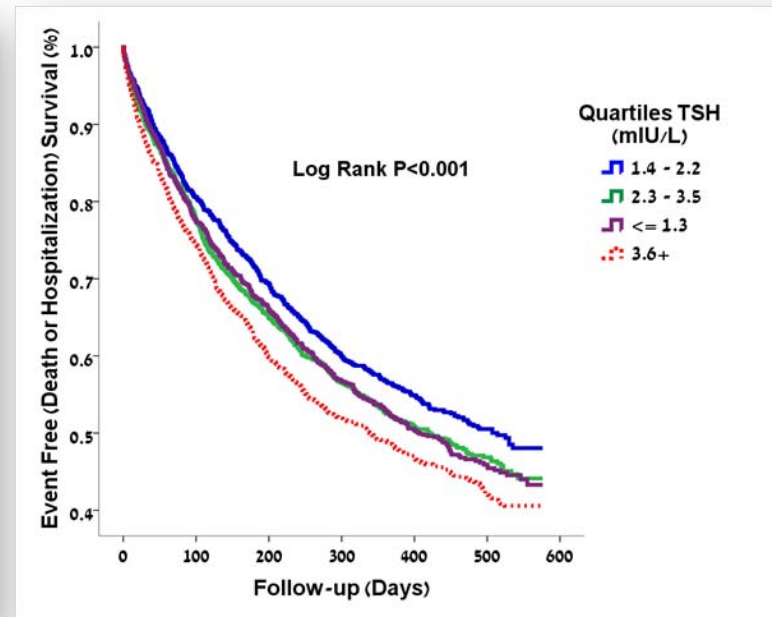
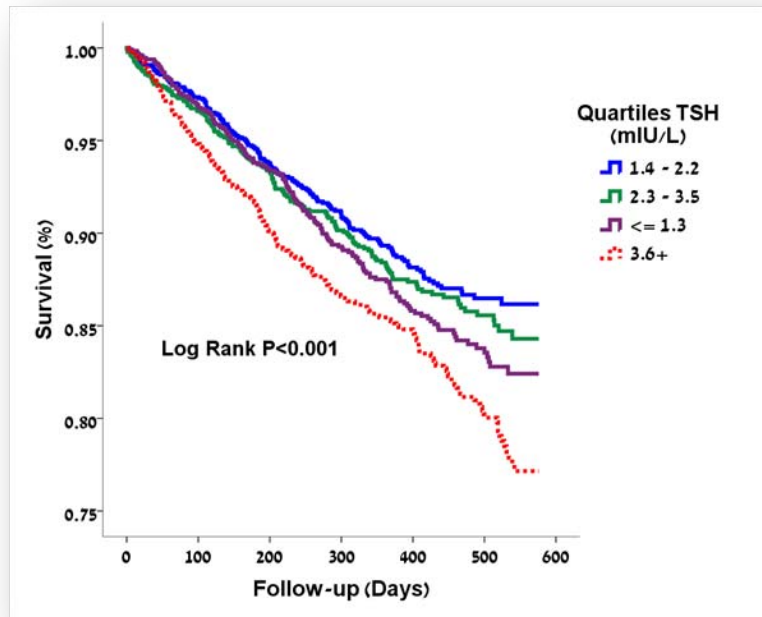
Demographics and Clinical characteristics

	TSH (mIU/L)					P Value
	≤ 1.3 (N=1312)	1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≥ 3.6 (N=1389)	Total (N=5599)	
ACE-inhibitor / ARB	990 (75)	1197 (77)	1043 (77)	1027 (74)	4257 (76)	0.11
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Corticoidsteroids	198 (15)	221 (14)	175 (13)	167 (12)	761 (14)	0.09
Eltroxin	162 (12)	158 (10)	227 (17)	704 (51)	1251 (22)	<0.001
Anti-thyroid	28 (2)	12 (1)	5 (0)	14 (1)	59 (1)	<0.001

Demographics and Clinical characteristics

	TSH (mIU/L)					P Value
	≤ 1.3 (N=1312)	1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≥ 3.6 (N=1389)	Total (N=5599)	
ACE-inhibitor / ARB	990 (75)	1197 (77)	1043 (77)	1027 (74)	4257 (76)	0.11
Beta blockers	902 (69)	1097 (71)	941 (70)	908 (65)	3848 (69)	0.01
Spirolactone	399 (30)	457 (30)	462 (34)	497 (36)	1815 (32)	<0.001
Furosemide	845 (64)	999 (65)	958 (71)	992 (71)	3794 (68)	<0.001
Thiazide	280 (21)	399 (26)	354 (26)	338 (24)	1371 (24)	0.01
Digoxin	111 (8)	159 (10)	166 (12)	182 (13)	618 (11)	<0.001
Amiodarone	164 (13)	199 (13)	214 (16)	400 (29)	977 (17)	<0.001
Aspirin	900 (69)	1068 (69)	897 (66)	857 (62)	3722 (66)	<0.001
Corticoidsteroids	198 (15)	221 (14)	175 (13)	167 (12)	761 (14)	0.09
Eltroxin	162 (12)	158 (10)	227 (17)	704 (51)	1251 (22)	<0.001
Anti-thyroid	28 (2)	12 (1)	5 (0)	14 (1)	59 (1)	<0.001

Survival and event free survival according to TSH levels



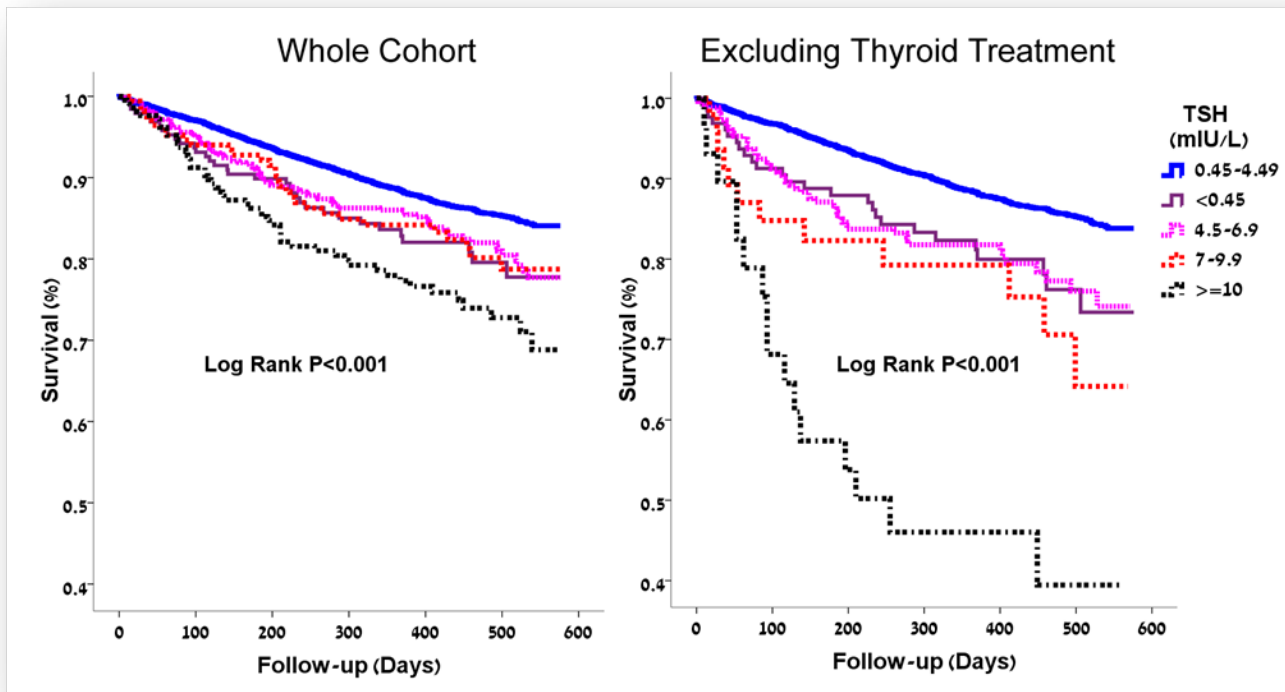
Mortality according to TSH levels

		TSH (mIU/L)				P value
		1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≤ 1.3 (N=1312)	≥3.6 (N=1389)	
Mortality	Univariable	1.0 (Reference)	1.10 (0.89-1.37) 0.38	1.22 (0.99-1.51) 0.07	1.53 (1.26-1.87) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.03 (0.80-1.32) 0.82	1.16 (0.91-1.48) 0.24	1.36 (1.08-1.71) 0.01	0.002
	Multivariable and drugs	1.0 (Reference)	1.04 (0.81-1.34) 0.75	1.13 (0.89-1.45) 0.32	1.40 (1.09-1.78) 0.008	0.03
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.13 (1.02-1.27) 0.02	1.13 (1.02-1.27) 0.03	1.30 (1.17-1.44) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.09 (0.97-1.22) 0.13	1.14 (1.02-1.28) 0.02	1.20 (1.08-1.34) <0.001	0.008
	Multivariable and drugs	1.0 (Reference)	1.06 (0.95-1.18) 0.34	1.13 (1.01-1.26) 0.03	1.18 (1.05-1.33) 0.005	0.02
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.15 (1.03-1.29) 0.01	1.13 (1.01-1.27) 0.03	1.27 (1.14-1.42) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.10 (0.99-1.24) 0.08	1.14 (1.02-1.28) 0.02	1.18 (1.05-1.32) 0.004	0.03
	Multivariable and drugs	1.0 (Reference)	1.07 (0.95-1.20) 0.26	1.13 (1.01-1.27) 0.04	1.15 (1.02-1.29) 0.03	0.09

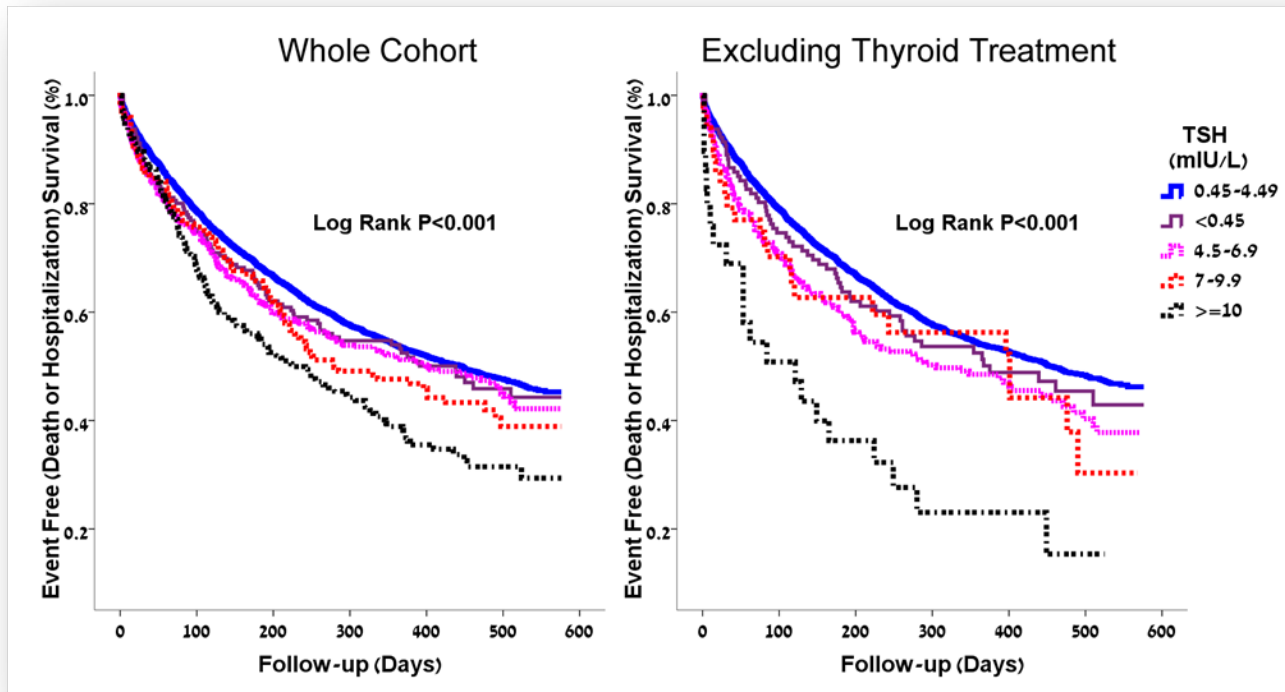
Mortality according to TSH levels

		TSH (mIU/L)				P value
		1.4 - 2.2 (N=1548)	2.3 - 3.5 (N=1350)	≤ 1.3 (N=1312)	≥3.6 (N=1389)	
Mortality	Univariable	1.0 (Reference)	1.10 (0.89-1.37) 0.38	1.22 (0.99-1.51) 0.07	1.53 (1.26-1.87) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.03 (0.80-1.32) 0.82	1.16 (0.91-1.48) 0.24	1.36 (1.08-1.71) 0.01	0.002
	Multivariable and drugs	1.0 (Reference)	1.04 (0.81-1.34) 0.75	1.13 (0.89-1.45) 0.32	1.40 (1.09-1.78) 0.008	0.03
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.13 (1.02-1.27) 0.02	1.13 (1.02-1.27) 0.03	1.30 (1.17-1.44) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.09 (0.97-1.22) 0.13	1.14 (1.02-1.28) 0.02	1.20 (1.08-1.34) <0.001	0.008
	Multivariable and drugs	1.0 (Reference)	1.06 (0.95-1.18) 0.34	1.13 (1.01-1.26) 0.03	1.18 (1.05-1.33) 0.005	0.02
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.15 (1.03-1.29) 0.01	1.13 (1.01-1.27) 0.03	1.27 (1.14-1.42) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.10 (0.99-1.24) 0.08	1.14 (1.02-1.28) 0.02	1.18 (1.05-1.32) 0.004	0.03
	Multivariable and drugs	1.0 (Reference)	1.07 (0.95-1.20) 0.26	1.13 (1.01-1.27) 0.04	1.15 (1.02-1.29) 0.03	0.09

Survival according to TSH levels



Event free survival according to TSH levels



Mortality according to TSH levels

		TSH (mIU/L)				P Value
		0.45-4.4 (N=4490)	0.45< (N=193)	4.5-9.9 (N=703)	≥10 (N=213)	
Mortality	Univariable	1.0 (Reference)	1.51 (1.07-2.14) 0.02	1.40 (1.14-1.70) 0.001	2.12 (1.59-2.82) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.30 (0.86-1.97) 0.21	1.23 (0.97-1.56) 0.09	1.90 (1.39-2.60) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.26 (0.83-1.90) 0.28	1.40 (1.09-1.80) 0.009	2.15 (1.51-3.06) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.08 (0.88-1.33) 0.46	1.15 (1.03-1.29) 0.01	1.54 (1.29-1.84) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.05 (0.83-1.33) 0.71	1.10 (0.97-1.25) 0.15	1.35 (1.10-1.65) 0.003	0.02
	Multivariable and drugs	1.0 (Reference)	0.99 (0.78-1.26) 0.96	1.10 (0.96-1.27) 0.17	1.32 (1.07-1.64) 0.01	0.06
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.03 (0.83-1.28) 0.77	1.14 (1.02-1.28) 0.03	1.44 (1.20-1.74) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.00 (0.78-1.28) 1	1.10 (0.96-1.26) 0.17	1.27 (1.02-1.56) 0.03	0.11
	Multivariable and drugs	1.0 (Reference)	0.94 (0.74-1.21) 0.65	1.08 (0.94-1.25) 0.27	1.22 (0.97-1.53) 0.09	0.28

Mortality according to TSH levels

		TSH (mIU/L)				P Value
		0.45-4.4 (N=4490)	0.45< (N=193)	4.5-9.9 (N=703)	≥10 (N=213)	
Mortality	Univariable	1.0 (Reference)	1.51 (1.07-2.14) 0.02	1.40 (1.14-1.70) 0.001	2.12 (1.59-2.82) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.30 (0.86-1.97) 0.21	1.23 (0.97-1.56) 0.09	1.90 (1.39-2.60) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.26 (0.83-1.90) 0.28	1.40 (1.09-1.80) 0.009	2.15 (1.51-3.06) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.08 (0.88-1.33) 0.46	1.15 (1.03-1.29) 0.01	1.54 (1.29-1.84) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.05 (0.83-1.33) 0.71	1.10 (0.97-1.25) 0.15	1.35 (1.10-1.65) 0.003	0.02
	Multivariable and drugs	1.0 (Reference)	0.99 (0.78-1.26) 0.96	1.10 (0.96-1.27) 0.17	1.32 (1.07-1.64) 0.01	0.06
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.03 (0.83-1.28) 0.77	1.14 (1.02-1.28) 0.03	1.44 (1.20-1.74) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.00 (0.78-1.28) 1	1.10 (0.96-1.26) 0.17	1.27 (1.02-1.56) 0.03	0.11
	Multivariable and drugs	1.0 (Reference)	0.94 (0.74-1.21) 0.65	1.08 (0.94-1.25) 0.27	1.22 (0.97-1.53) 0.09	0.28

Mortality according to TSH levels

		TSH (mIU/L)				P Value
		0.45-4.4 (N=4490)	0.45< (N=193)	4.5-9.9 (N=703)	≥10 (N=213)	
Mortality	Univariable	1.0 (Reference)	1.51 (1.07-2.14) 0.02	1.40 (1.14-1.70) 0.001	2.12 (1.59-2.82) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.30 (0.86-1.97) 0.21	1.23 (0.97-1.56) 0.09	1.90 (1.39-2.60) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.26 (0.83-1.90) 0.28	1.40 (1.09-1.80) 0.009	2.15 (1.51-3.06) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.08 (0.88-1.33) 0.46	1.15 (1.03-1.29) 0.01	1.54 (1.29-1.84) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.05 (0.83-1.33) 0.71	1.10 (0.97-1.25) 0.15	1.35 (1.10-1.65) 0.003	0.02
	Multivariable and drugs	1.0 (Reference)	0.99 (0.78-1.26) 0.96	1.10 (0.96-1.27) 0.17	1.32 (1.07-1.64) 0.01	0.06
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.03 (0.83-1.28) 0.77	1.14 (1.02-1.28) 0.03	1.44 (1.20-1.74) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.00 (0.78-1.28) 1	1.10 (0.96-1.26) 0.17	1.27 (1.02-1.56) 0.03	0.11
	Multivariable and drugs	1.0 (Reference)	0.94 (0.74-1.21) 0.65	1.08 (0.94-1.25) 0.27	1.22 (0.97-1.53) 0.09	0.28

Mortality according to TSH levels

		TSH (mIU/L)				P Value
		0.45-4.4 (N=4490)	0.45< (N=193)	4.5-9.9 (N=703)	≥10 (N=213)	
Mortality	Univariable	1.0 (Reference)	1.51 (1.07-2.14) 0.02	1.40 (1.14-1.70) 0.001	2.12 (1.59-2.82) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.30 (0.86-1.97) 0.21	1.23 (0.97-1.56) 0.09	1.90 (1.39-2.60) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.26 (0.83-1.90) 0.28	1.40 (1.09-1.80) 0.009	2.15 (1.51-3.06) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.08 (0.88-1.33) 0.46	1.15 (1.03-1.29) 0.01	1.54 (1.29-1.84) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.05 (0.83-1.33) 0.71	1.10 (0.97-1.25) 0.15	1.35 (1.10-1.65) 0.003	0.02
	Multivariable and drugs	1.0 (Reference)	0.99 (0.78-1.26) 0.96	1.10 (0.96-1.27) 0.17	1.32 (1.07-1.64) 0.01	0.06
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.03 (0.83-1.28) 0.77	1.14 (1.02-1.28) 0.03	1.44 (1.20-1.74) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.00 (0.78-1.28) 1	1.10 (0.96-1.26) 0.17	1.27 (1.02-1.56) 0.03	0.11
	Multivariable and drugs	1.0 (Reference)	0.94 (0.74-1.21) 0.65	1.08 (0.94-1.25) 0.27	1.22 (0.97-1.53) 0.09	0.28

Mortality according to TSH levels

		TSH (mIU/L)				P Value
		0.45-4.4 (N=4490)	0.45< (N=193)	4.5-9.9 (N=703)	≥10 (N=213)	
Mortality	Univariable	1.0 (Reference)	1.51 (1.07-2.14) 0.02	1.40 (1.14-1.70) 0.001	2.12 (1.59-2.82) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.30 (0.86-1.97) 0.21	1.23 (0.97-1.56) 0.09	1.90 (1.39-2.60) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.26 (0.83-1.90) 0.28	1.40 (1.09-1.80) 0.009	2.15 (1.51-3.06) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.08 (0.88-1.33) 0.46	1.15 (1.03-1.29) 0.01	1.54 (1.29-1.84) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.05 (0.83-1.33) 0.71	1.10 (0.97-1.25) 0.15	1.35 (1.10-1.65) 0.003	0.02
	Multivariable and drugs	1.0 (Reference)	0.99 (0.78-1.26) 0.96	1.10 (0.96-1.27) 0.17	1.32 (1.07-1.64) 0.01	0.06
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.03 (0.83-1.28) 0.77	1.14 (1.02-1.28) 0.03	1.44 (1.20-1.74) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.00 (0.78-1.28) 1	1.10 (0.96-1.26) 0.17	1.27 (1.02-1.56) 0.03	0.11
	Multivariable and drugs	1.0 (Reference)	0.94 (0.74-1.21) 0.65	1.08 (0.94-1.25) 0.27	1.22 (0.97-1.53) 0.09	0.28

Mortality according to TSH levels

		TSH (mIU/L)				P Value
		0.45-4.4 (N=4490)	0.45< (N=193)	4.5-9.9 (N=703)	≥10 (N=213)	
Mortality	Univariable	1.0 (Reference)	1.51 (1.07-2.14) 0.02	1.40 (1.14-1.70) 0.001	2.12 (1.59-2.82) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.30 (0.86-1.97) 0.21	1.23 (0.97-1.56) 0.09	1.90 (1.39-2.60) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.26 (0.83-1.90) 0.28	1.40 (1.09-1.80) 0.009	2.15 (1.51-3.06) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.08 (0.88-1.33) 0.46	1.15 (1.03-1.29) 0.01	1.54 (1.29-1.84) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.05 (0.83-1.33) 0.71	1.10 (0.97-1.25) 0.15	1.35 (1.10-1.65) 0.003	0.02
	Multivariable and drugs	1.0 (Reference)	0.99 (0.78-1.26) 0.96	1.10 (0.96-1.27) 0.17	1.32 (1.07-1.64) 0.01	0.06
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.03 (0.83-1.28) 0.77	1.14 (1.02-1.28) 0.03	1.44 (1.20-1.74) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.00 (0.78-1.28) 1	1.10 (0.96-1.26) 0.17	1.27 (1.02-1.56) 0.03	0.11
	Multivariable and drugs	1.0 (Reference)	0.94 (0.74-1.21) 0.65	1.08 (0.94-1.25) 0.27	1.22 (0.97-1.53) 0.09	0.28

Mortality according to TSH levels (exclusion of patients with eltroxin treatment)

		TSH (mIU/L)				P Value
		0.45-4.4 (N=3828)	0.45< (N=129)	4.5-9.9 (N=309)	≥10 (N=29)	
Mortality	Univariable	1.0 (Reference)	1.77 (1.19-2.63) 0.005	1.89 (1.45-2.46) <0.001	6.75 (4.10-11.1) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.37 (0.84-2.24) 0.21	1.45 (1.05-2.00) 0.02	7.00 (4.12-11.9) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.27 (0.78-2.07) 0.34	1.44 (1.05-2.00) 0.03	6.47 (3.77-11.1) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.12 (0.87-1.44) 0.38	1.31 (1.11-1.53) 0.001	2.67 (1.75-4.07) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.04 (0.77-1.39) 0.81	1.26 (1.05-1.52) 0.01	2.29 (1.46-3.57) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	0.98 (0.73-1.32) 0.88	1.22 (1.01-1.47) 0.04	2.42 (1.55-3.80) <0.001	<0.001
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.05 (0.81-1.37) 0.7	1.27 (1.07-1.50) 0.006	2.06 (1.26-3.37) 0.004	0.001
	Multivariable	1.0 (Reference)	0.98 (0.72-1.34) 0.9	1.27 (1.05-1.54) 0.01	1.68 (0.99-2.86) 0.06	0.02
	Multivariable and drugs	1.0 (Reference)	0.92 (0.67-1.26) 0.61	1.22 (1.01-1.48) 0.04	1.82 (1.07-3.11) 0.03	0.03

Mortality according to TSH levels (exclusion of patients with eltroxin treatment)

		TSH (mIU/L)				P Value
		0.45-4.4 (N=3828)	0.45< (N=129)	4.5-9.9 (N=309)	≥10 (N=29)	
Mortality	Univariable	1.0 (Reference)	1.77 (1.19-2.63) 0.005	1.89 (1.45-2.46) <0.001	6.75 (4.10-11.1) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.37 (0.84-2.24) 0.21	1.45 (1.05-2.00) 0.02	7.00 (4.12-11.9) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.27 (0.78-2.07) 0.34	1.44 (1.05-2.00) 0.03	6.47 (3.77-11.1) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.12 (0.87-1.44) 0.38	1.31 (1.11-1.53) 0.001	2.67 (1.75-4.07) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.04 (0.77-1.39) 0.81	1.26 (1.05-1.52) 0.01	2.29 (1.46-3.57) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	0.98 (0.73-1.32) 0.88	1.22 (1.01-1.47) 0.04	2.42 (1.55-3.80) <0.001	<0.001
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.05 (0.81-1.37) 0.7	1.27 (1.07-1.50) 0.006	2.06 (1.26-3.37) 0.004	0.001
	Multivariable	1.0 (Reference)	0.98 (0.72-1.34) 0.9	1.27 (1.05-1.54) 0.01	1.68 (0.99-2.86) 0.06	0.02
	Multivariable and drugs	1.0 (Reference)	0.92 (0.67-1.26) 0.61	1.22 (1.01-1.48) 0.04	1.82 (1.07-3.11) 0.03	0.03

Mortality according to TSH levels (exclusion of patients with eltroxin treatment)

		TSH (mIU/L)				P Value
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Mortality	Univariable	1.0 (Reference)	1.77 (1.19-2.63) 0.005	1.89 (1.45-2.46) <0.001	6.75 (4.10-11.1) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.37 (0.84-2.24) 0.21	1.45 (1.05-2.00) 0.02	7.00 (4.12-11.9) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	1.27 (0.78-2.07) 0.34	1.44 (1.05-2.00) 0.03	6.47 (3.77-11.1) <0.001	<0.001
Mortality and Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.12 (0.87-1.44) 0.38	1.31 (1.11-1.53) 0.001	2.67 (1.75-4.07) <0.001	<0.001
	Multivariable	1.0 (Reference)	1.04 (0.77-1.39) 0.81	1.26 (1.05-1.52) 0.01	2.29 (1.46-3.57) <0.001	<0.001
	Multivariable and drugs	1.0 (Reference)	0.98 (0.73-1.32) 0.88	1.22 (1.01-1.47) 0.04	2.42 (1.55-3.80) <0.001	<0.001
Cardiac-related hospitali-zation	Univariable	1.0 (Reference)	1.05 (0.81-1.37) 0.7	1.27 (1.07-1.50) 0.006	2.06 (1.26-3.37) 0.004	0.001
	Multivariable	1.0 (Reference)	0.98 (0.72-1.34) 0.9	1.27 (1.05-1.54) 0.01	1.68 (0.99-2.86) 0.06	0.02
	Multivariable and drugs	1.0 (Reference)	0.92 (0.67-1.26) 0.61	1.22 (1.01-1.48) 0.04	1.82 (1.07-3.11) 0.03	0.03

Mortality according to TSH levels

3675 patients (66% of cohort) had follow up TSH value available at a median of 313 days (IQR 196-420 days)

Beginning of follow up period		End of follow up period	
Normal	>	Normal	
Abnormal	>	Normal	
Normal	>	Abnormal	
Abnormal	>	Abnormal	

Mortality according to TSH levels

3675 patients (66% of cohort) had follow up TSH value available at a median of 313 days (IQR 196-420 days)

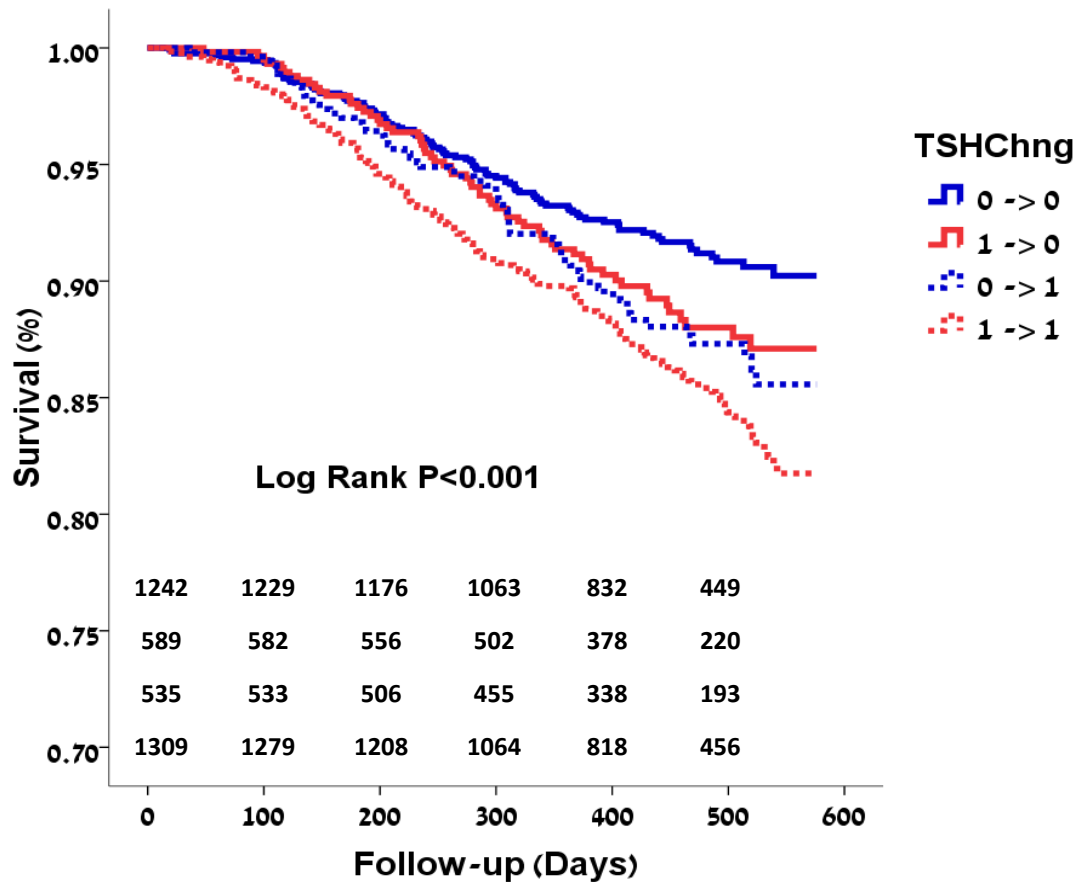
Beginning of follow up period		End of follow up period	
Normal	>	Normal	
Abnormal	>	Normal	
Normal	>	Abnormal	
Abnormal	>	Abnormal	

Mortality according to TSH levels

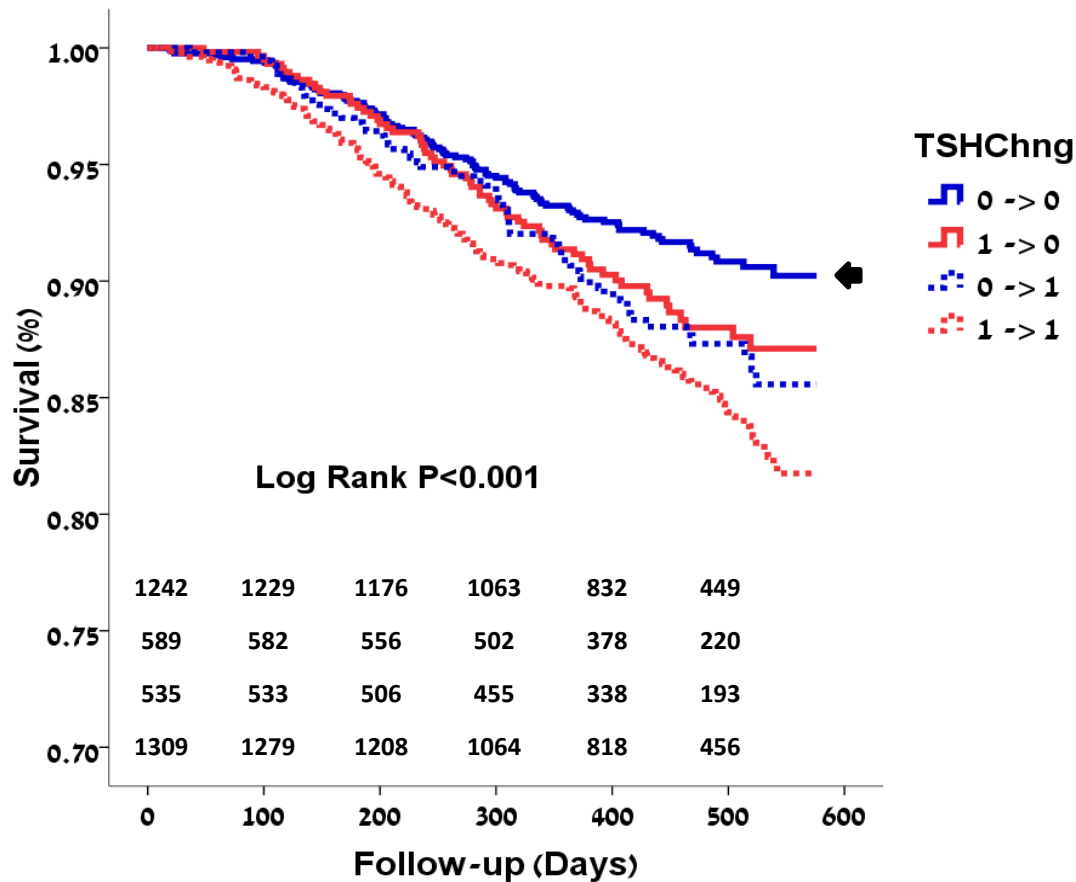
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Normal	>	Normal	
Abnormal	>	Normal	
Normal	>	Abnormal	
Abnormal	>	Abnormal	

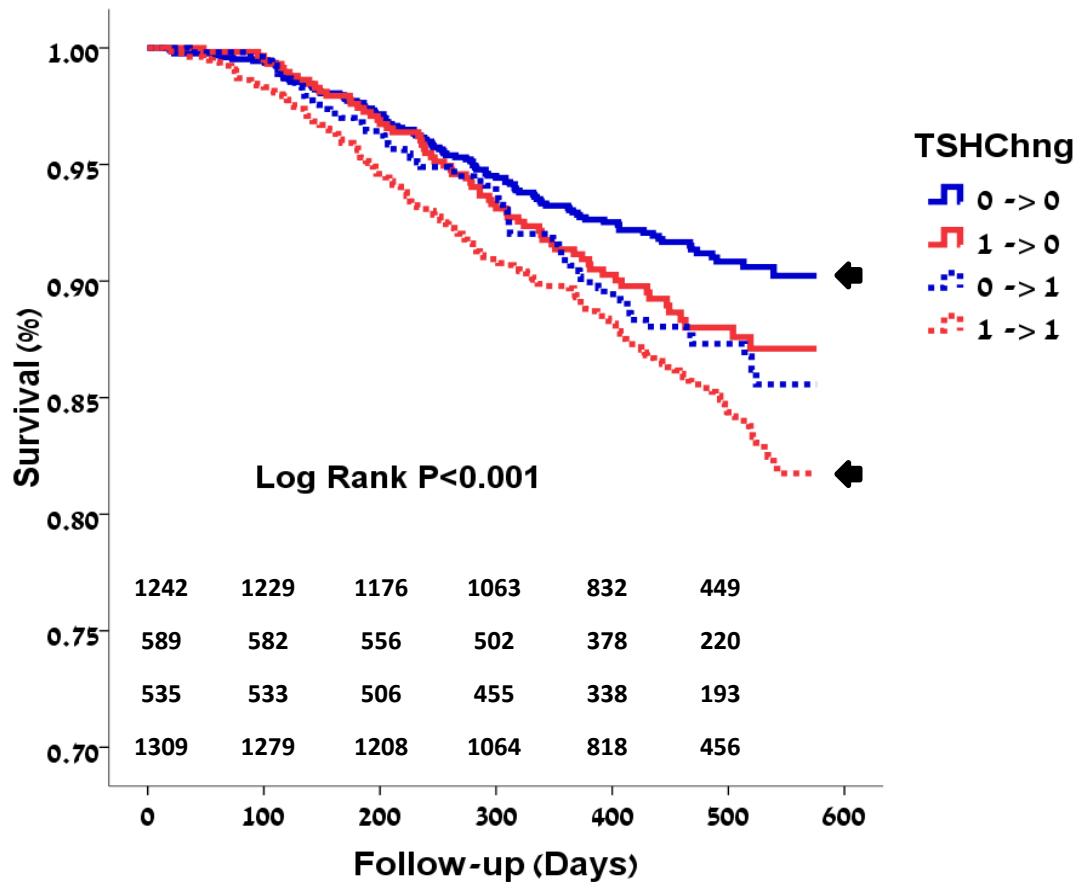
Normalization of TSH values improves outcome



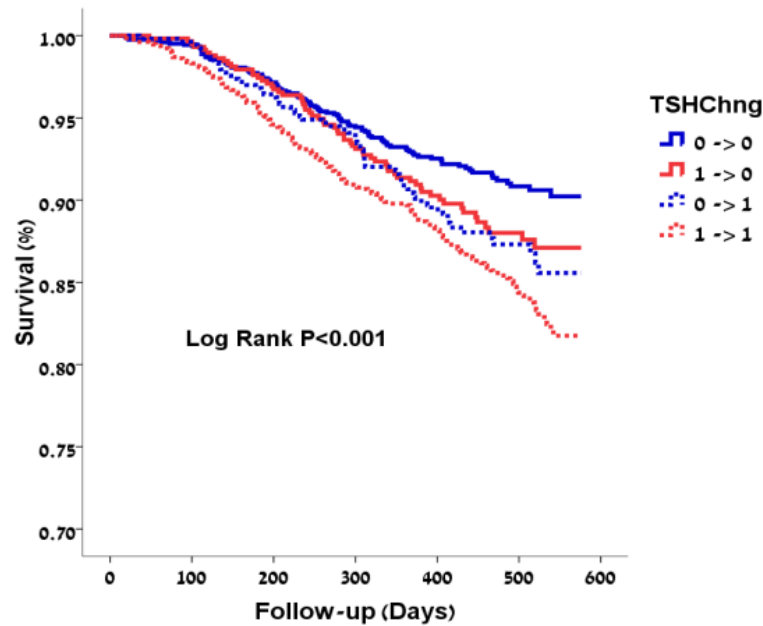
Normalization of TSH values improves outcome



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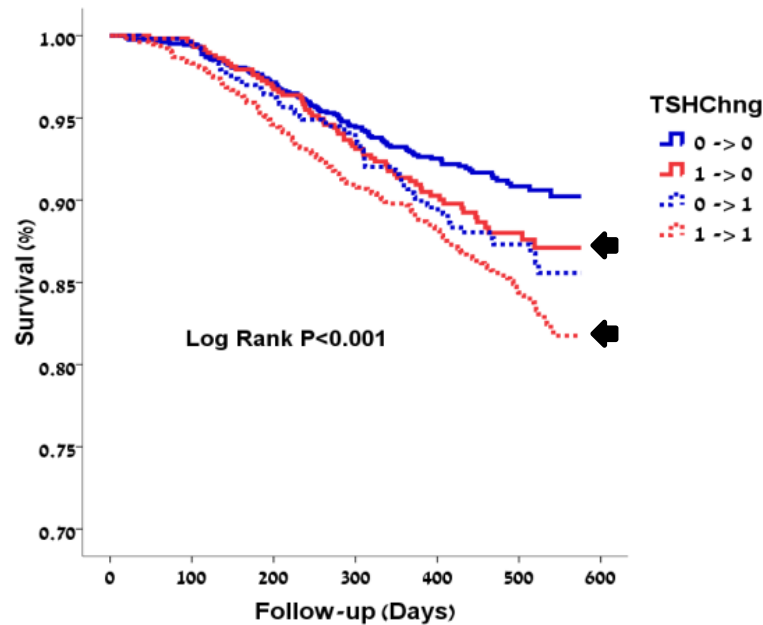


Normalization of TSH values improves outcome



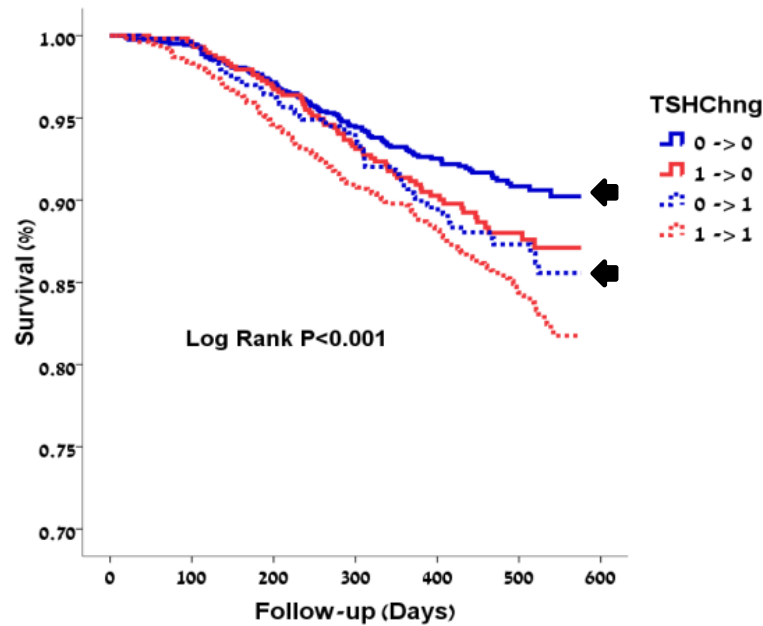
	0 > 0		1 > 0		0 > 1		1 > 1	
	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
0 > 0			3.099	.078	5.231	.022	21.980	.000
1 > 0	3.099	.078			.235	.628	4.093	.043
0 > 1	5.231	.022	.235	.628			2.008	.157
1 > 1	21.980	.000	4.093	.043	2.008	.157		

Normalization of TSH values improves outcome



	0 > 0		1 > 0		0 > 1		1 > 1	
	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
0 > 0			3.099	.078	5.231	.022	21.980	.000
1 > 0	3.099	.078			.235	.628	4.093	.043
0 > 1	5.231	.022	.235	.628			2.008	.157
1 > 1	21.980	.000	4.093	.043	2.008	.157		

Normalization of TSH values improves outcome



	0 > 0		1 > 0		0 > 1		1 > 1	
	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
0 > 0			3.099	.078	5.231	.022	21.980	.000
1 > 0	3.099	.078			.235	.628	4.093	.043
0 > 1	5.231	.022	.235	.628			2.008	.157
1 > 1	21.980	.000	4.093	.043	2.008	.157		

Clinical parameters and TSH

Patients in the highest quartile (≥ 3.6 mIU/L) had more comorbidities (atrial fibrillation, higher BMI, impaired kidney function etc.).

These comorbidities may imply that TSH levels may simply be an indicator of a sicker patient.

Clinical parameters and TSH

Patients in the highest quartile (≥ 3.6 mIU/L) had more comorbidities (atrial fibrillation, higher BMI, impaired kidney function etc.).

These comorbidities may imply that TSH levels may simply be an indicator of a sicker patient.

- Adjustment for these parameters demonstrated that TSH is an independent predictor.
- The correction of TSH levels during follow up resulted in a reduction in mortality and morbidity rates.

Effect of TSH on cardiac function

Via thyroid function

Extra-thyroidal effects

- TSH is able to induce IL-6 and TNF α secretion in vitro.
- TSH may be involved in the modulation of vascular function by increasing NO metabolites.
- TSH levels were correlated in a positive manner with the total cholesterol, non-HDL-C and triglycerides levels.

Summary

An abnormally high TSH was found in 15% percent of the present cohort

TSH is a powerful predictor of clinical outcome including death and cardiac hospitalizations