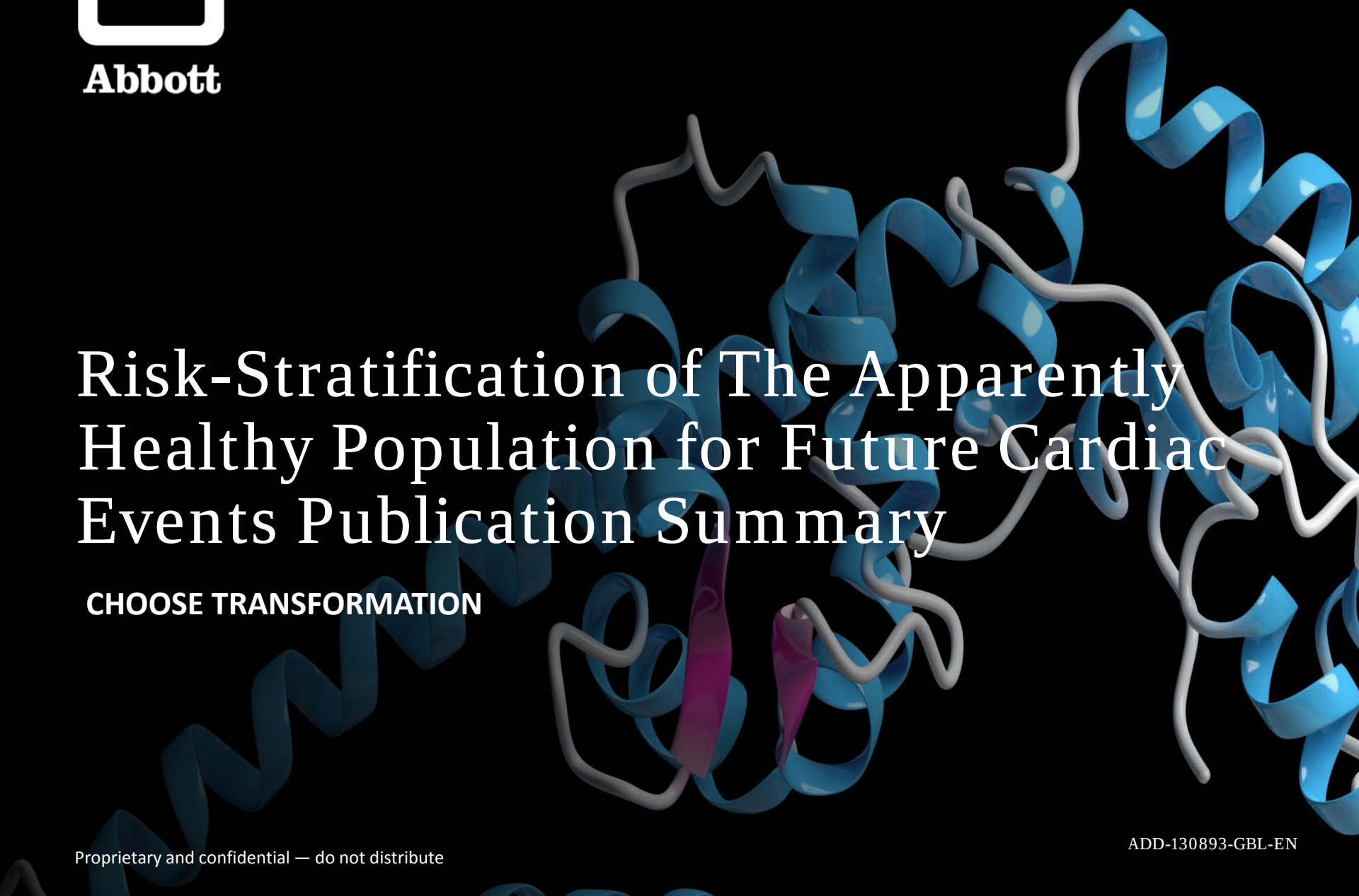
DIAGNOSTICS



Risk-Stratification of The Apparently Healthy Population for Future Cardiac Events Publication Summary

CHOOSE TRANSFORMATION

ADD-130893-GBL-EN

ARIC 2019

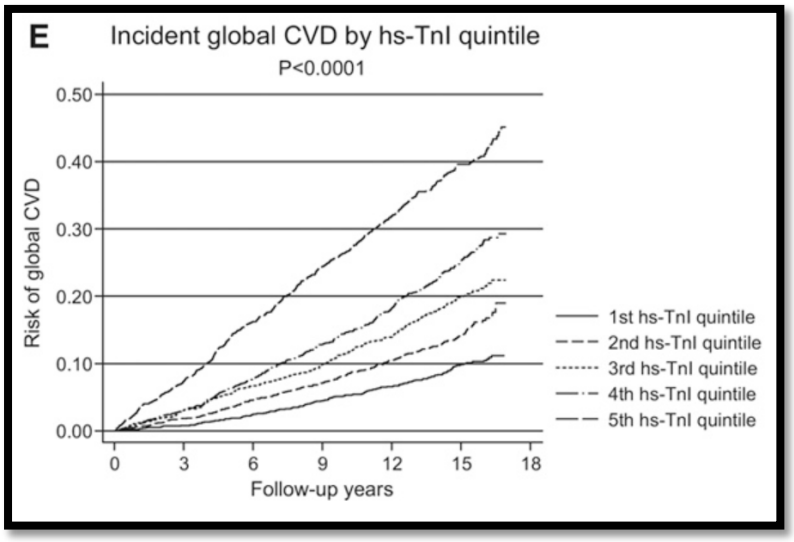
Year: 2019; Circulation

Publication title: High-Sensitivity Troponin I and Incident Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study

Author: Jia X, Sun W, Hoogeveen RC, et al.

Population: 8,121 asymptomatic participants in a median of 15 years follow-up period

Study Objective: To assess whether plasma troponin I measured by Abbott's high-sensitive Troponin-I assay (hsTnI) is associated with incident cardiovascular disease (CVD) and mortality in a community-based sample without prior CVD.



Key takeaways: 1) Elevated hsTnI is strongly associated with increased CVD risk in the general population. Compared to low hsTnI (lowest quintile, hsTnI ≤1.3 ng/L), elevated hsTnI (highest quintile, hsTnI ≥3.8 ng/L) was associated with greater CVD risk (HR, 3.01; 95% CI, 2.50–3.63)

HR (hazard ratio) of 3.01 means subjects in the highest hsTnI quintile were ~3 times more likely than the lowest quintile to develop CVD risk

Association of Incident Events With hsTnI by Quintiles

Incident Events	hs-TnI, ng/L					*P* Trend for Linearity
	Quintile 1 [0–1.3]	Quintile 2 [1.4–1.9]	Quintile 3 [2.0–2.5]	Quintile 4 [2.6–3.7]	Quintile 5 [3.8–2575.4]	
Global CVD						
n/N	164/1726	246/1744	282/1514	359/1541	581/1596	<0.001
Model 1	Reference	1.43 (1.17–1.74)	1.86 (1.53–2.26)	2.19 (1.81–2.65)	3.78 (3.16–4.54)	<0.0001
Model 2	Reference	1.36 (1.11–1.66)	1.67 (1.37–2.03)	1.86 (1.53–2.25)	3.01 (2.50–3.63)	<0.0001

* Model 2 adjusts for age/sex/race and traditional risk factors

2) Supplemental Data from Tables 3 and 4* in ARIC support Abbott's recommended cut-off values in our ARCHITECT STAT hsTnI package insert.

Supplemental Table 3. Hazard ratio and 95% confidence intervals of incident events based on hs-TnI categories in women.

Event		hs-TnI, ng/L			P trend for linearity
		<4	4–10	>10	
Global CVD	n/N (%)	630/4065	149/452	81/168	<0.001
	Model 1	*Ref.*	2.07 (1.72-2.48)	3.49 (2.76-4.41)	<0.0001
	Model 2	*Ref.*	1.69 (1.40-2.04)	2.73 (2.15-3.47)	<0.0001

Supplemental Table 4. Hazard ratio and 95% confidence intervals of incident events based on hs-TnI categories in men.

Event		hs-TnI, ng/L			P trend for linearity
		<6	6–12	>12	
Global CVD	n/N (%)	592/3002	109/266	71/168	<0.001
	Model 1	*Ref.*	2.16 (1.76-2.66)	2.46 (1.91-3.16)	<0.0001
	Model 2	*Ref.*	1.95 (1.58-2.41)	2.08 (1.61-2.70)	<0.0001

Note: Model 1 was adjusted by age and race; Model 2 was Model 1 plus total cholesterol, HDL-C, systolic blood pressure, use of antihypertensive medication, current smoking, and diabetes status

*The above Tables are adapted from Supplemental Table 3 and Supplemental Table 4 from "High-Sensitivity Troponin I and Incident Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study

3) hsTnI, when added to the traditional risk factors model, resulted in statistically significant improvement in risk prediction for CVD

Comparison of 10-Year Risk Prediction for Incident Events Using PCE Alone and With hsTnI

Incident Events	Models	AUC Primary Mode (95% CI)	AUC Comparison Mode (95% CI)	ΔAUC (95% CI)	NRI (95% CI)	Continuous NRI (95% CI)
Global CVD	PCE + hs-TnI vs PCE	0.719 (0.707 to 0.731)	0.736 (0.724 to 0.750)	0.018 (0.012 to 0.024)	0.055 (0.021 to 0.088)	0.289 (0.210 to 0.365)

*AUC, area under the receiver operating characteristic curve; NRI, net reclassification improvement; PCE, Pooled Cohort Equation; The PCE model includes traditional risk factors, such as age, sex, race, current smoking, SBP, total cholesterol, HDL-C, diabetes mellitus status, and antihypertensive medication use.

As compared to traditional risk factors alone, both AUC and net reclassification improvement demonstrated statistically significant increase in risk prediction for future CVD events in asymptomatic population when hsTnI is added to the primary risk prediction model.

Relevance of publication:

1) The study data suggest that hsTnI could be a pragmatic biomarker to for risk assessment of CVD
2) Adding hsTnI to traditional risk prediction models presents a potentially effective approach for future CVD risk prediction algorithms in asymptomatic population

GSSFHS 2019

Year: 2019; Circulation

Publication title: Cardiac Troponin T and Troponin I in the General Population: Comparing and Contrasting Their Genetic Determinants and Associations With Outcomes

Author: Welsh P, Preiss D, Hayward C, et al.

Population: 19,501 asymptomatic participants in a median of 7.8 years follow-up period in Generation Scotland Scottish Family Health Study (GSSFHS)

Study Objective: To compare and contrast the association of cTnT (Cobas platform, Roche) and cTnI (Architect platform, Abbott) with CVD and non-CVD outcomes in population CVD screening.

Key takeaways: 1) Data suggest that TnT has a low rate of detectable concentrations in healthy population as compared to hsTnI

Detectable concentrations of hsTnI and TnT

Study Population (n=19,501)	hsTnI (n=14,579)	TnT (n=10,395)
Proportion of study population with detectable Troponin concentration	**74.8%**	**53.3%**

2) hsTnI demonstrates a stronger association with the primary CVD outcomes than TnT with consistently higher hazard ratio, suggesting hsTnI is a more consistent predictor of CVD events. In particular, TnT showed no association with MI or CHD after adjusting for traditional risk factors.

Association of Troponin I and Troponin T (per 1 SD Increase on the Log Scale) With Risk of Different Events, Adjusted for ClassicalcRisk Factors, and the Troponins in Separate Models

CVD Events	Troponin I Hazard Ratio (95% CI)	Troponin T Hazard Ratio (95% CI)	Ratio of the Hazard Ratio* (95% CI)
CVD (n=1177)	1.24 (1.17–1.32)	1.11 (1.04–1.19)	1.12 (1.04–1.12)
CVD death (n=266)	1.56 (1.38–1.75)	1.52 (1.31–1.77)	1.02 (0.87–1.20)

3) Judged by using the continuous net reclassification index, adding hsTnI to the primary CVD risk prediction model with traditional risk factors yields a statistically significant improvement of 7.7% (95% CI, 2.8%–11.7%; P=0.004) in asymptomatic population. But TnT does not show the same benefit.

Relevance of publication:

1) The study data suggest that cardiac troponin I appears to be a more specific biomarker of risk of composite cardiovascular disease and coronary heart disease.
2) The findings help inform the selection of an optimal troponin assay for future CVD risk screening in the general population.
3) As stated in the publication: “It is most surprising, however, that cTnT showed no association with MI or CHD after adjusting for classical risk factors; cTnI did.”

HUNT 2018

Year: 2018; The American Journal of Cardiology

Publication title: Relative Prognostic Value of Cardiac Troponin I and C-reactive Protein in the General Population (from the Nord-Trondelag Health [HUNT] Study)

Author: Fjola D. Sigurdardottir, Magnus N. Lyngbakken, Oddgeir L. Holmen

Population: 9005 participants

Study Objective: 1) To assess the CVD risk associated with increased concentrations of hs-CRP and hsTnI

2) To compare the prognostic accuracy of hs-CRP with that of hsTnI

3) To compare the incremental prognostic information provided by hs-CRP and hsTnI with 2 Framingham risk score models and their components

Category		Model 1 (events = 733)
hs-TnI (ng/L)	<4 (♀); <6 (♂)	REF
	4–10 (♀); 6–12 (♂)	4.33 (3.69–5.08)*
	>10 (♀); >12 (♂)	9.76 (7.97–11.95)*
hs-CRP (ng/L)	<1	REF
	1–3	2.20 (1.84–2.62)*
	>3	2.81 (2.32–3.39)*

Key takeaways: 1) Subjects in the highest hs-TnI category (>10 ng/L for women and >12 ng/L for men) had a hazard ratio (HR) of 9.76 compared with the lowest category (<4 ng/L for women and <6 ng/L for men).

HR of 9.76 means subjects in the highest category were ~9 times more likely than the lowest category to reach the composite end point of hospitalization for acute myocardial infarction or heart failure, or cardiovascular death

2) Addition of hs-TnI and hs-CRP to Framingham risk score showed an improvement in net reclassification

- hs-TnI (0.3456), which means a combined net improvement of ~34.5% over Framingham, and hs-CRP (0.2059), which means a combined net improvement of ~21% over Framingham

- Hence, based upon Net Reclassification Improvement for cardiovascular disease, hs-TnI (NRI- 0.3456) reclassified subjects **~68% more accurately** than hs-CRP (0.2059)

Relevance of publication:

1) The male/female risk categories used in this paper are those that are in the Abbott ARCHITECT STAT high-sensitive Troponin I package insert

2) The publication's data suggest that compared to Framingham, hs-TnI results in a significant reclassification of subjects to their correct risk category

3) Higher concentrations of hs-TnI in apparently healthy subjects are strongly associated with increased risk of CVD, and hs-TnI may therefore be better suited for CVD screening in an asymptomatic general population than hs-CRP

WOSCOPS 2016

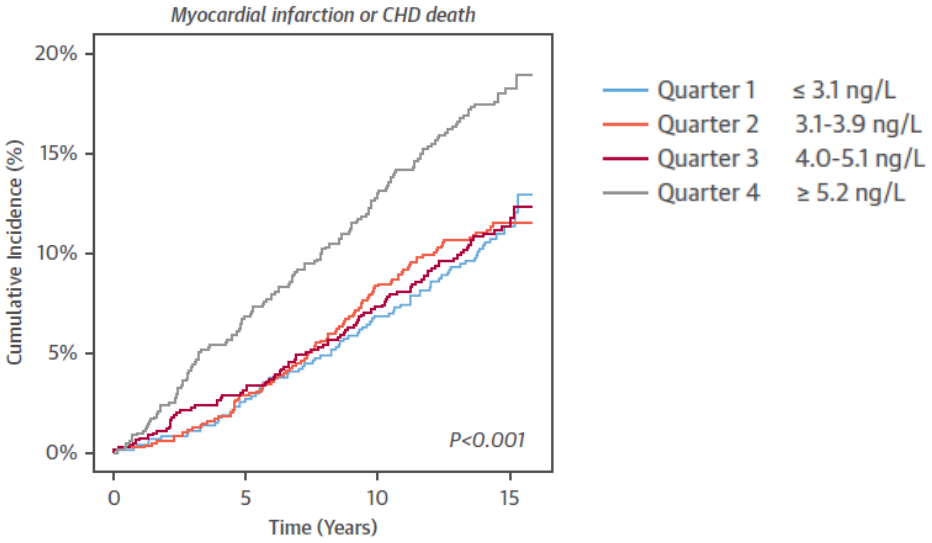
Year: 2016; Journal of the American College of Cardiology

Publication title: High-Sensitivity Cardiac Troponin, Statin Therapy, and Risk of Coronary Heart Disease

Author: Ian Ford, Anoop S.V. Shah, Ruiqi Zhang

Population: 3,318 participants

Study Objective: This study sought to determine whether troponin concentration could predict coronary events, be modified by statins, and reflect response to therapy in a primary prevention population

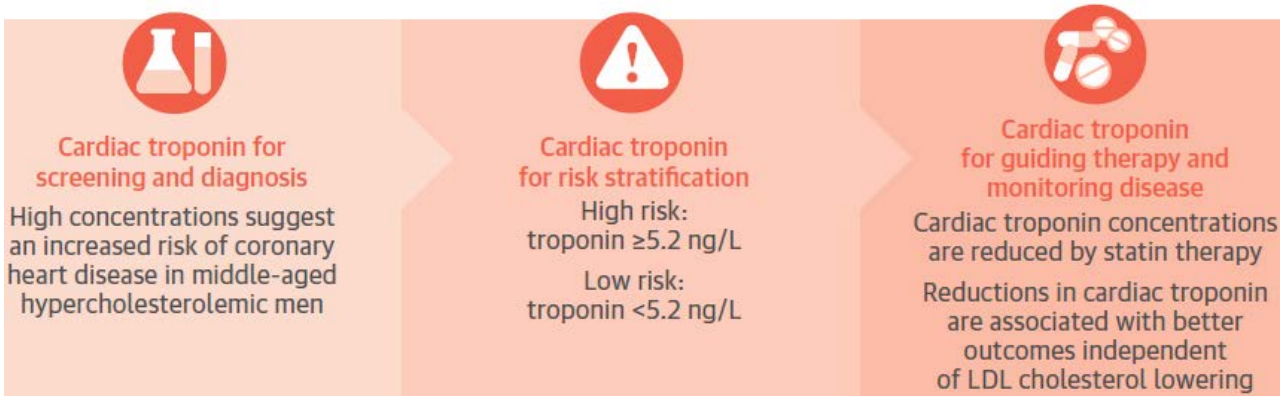


Key takeaways: 1) Compared to the lowest quarter (≤3.1 ng/l), patients in the highest quarter (≥5.2 ng/l) were at the highest risk for nonfatal myocardial infarction or death from coronary heart disease at 5 and 15 years (HR: 2.27)

2) There was a 5-fold greater reduction in coronary events when troponin concentrations decreased by more than a quarter, rather than increased by more than a quarter, for both placebo and pravastatin

3) Pravastatin reduced troponin concentration and doubled the number of men whose troponin fell more than a quarter, which identified them as having the lowest risk for future coronary events (1.4% over 5 years)

Relevance of the publication:



Novel Applications of Cardiac Troponins: Stratifying Risk and Guiding Therapy for Prevention of Cardiovascular Disease

1) High sensitivity cardiac troponin assays can be used to predict future risk of coronary heart disease and to assess response to statin therapy

2) Troponin concentrations are reduced by statin therapy

3) Reductions in troponin concentrations are associated with better outcomes **independent** of LDL cholesterol lowering

These findings suggest that high-sensitivity cardiac troponin has major potential to identify those at greatest risk and to assess their response (change at 1 year associated with future coronary risk) to interventions for the prevention of CAD

BIOMARCARE 2016- 74,738 PARTICIPANTS

Year: 2016; European Heart Journal

Publication title: Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium

Author: Stefan Blankenberg, Veikko Salomaa

Population: 74,738 participants

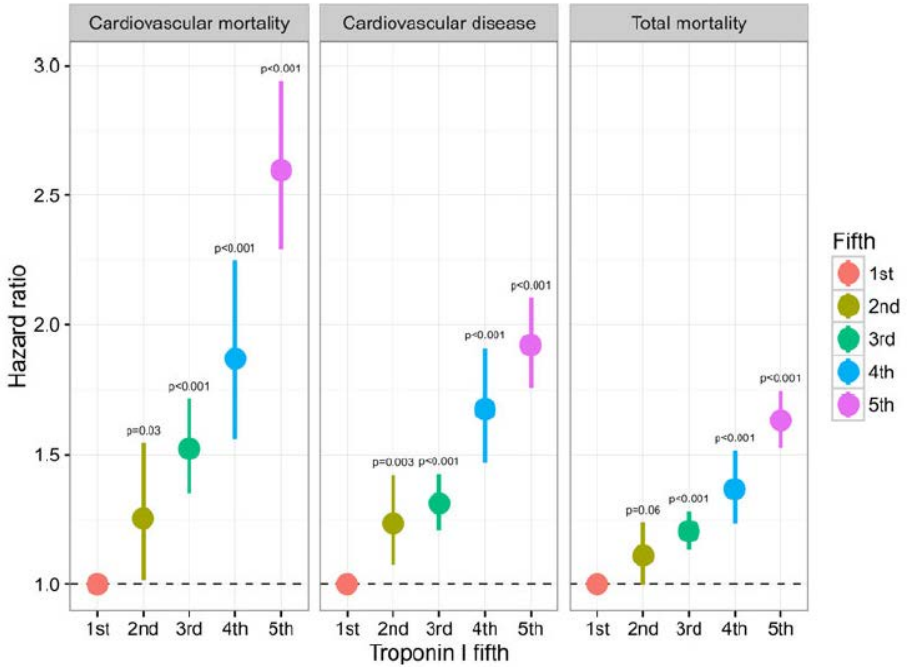
Study Objective: 1) To evaluate the distribution of troponin I concentrations in population cohorts across Europe

2) To characterize the association with cardiovascular outcomes

3) To determine the predictive value beyond the variables used in the ESC SCORE

4) To test a potentially clinically relevant cut-off value

5) To evaluate the improved eligibility for statin therapy based on elevated troponin I concentrations retrospectively



Troponin I quintiles: 2.5, 2.8, 5.4, 5.9 ng/L

Key takeaways: 1) Individuals in the top fifths of the troponin I distribution compared with the bottom fifth had a 160% increase in mortality from cardiovascular causes, 92% increase in risk for a first cardiovascular event, and a 63% increase in the risk of overall mortality

Relevance of the publication: Based upon this publication, INVOLVING ALMOST **75,000** PEOPLE**,** Abbott high sensitivity troponin I assay easily and reliably detects very low levels of troponin I and thus opens the possibility of stratifying risk by use of a cardiac-specific biomarker

ADD-130893-GBL-EN

JUPITER 2015

Year: 2015; Circulation

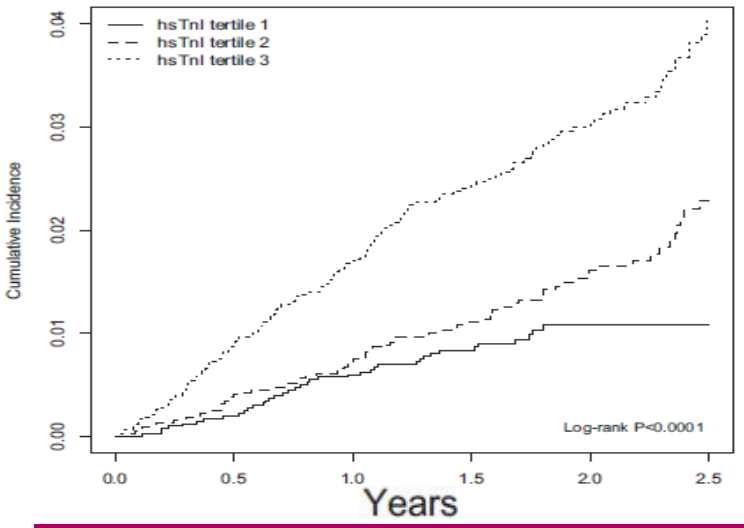
Publication title: High-Sensitivity Cardiac Troponin I and B-Type Natriuretic Peptide as Predictors of Vascular Events in Primary Prevention. Impact of Statin Therapy

Author: Brendan M. Everett, Tanja Zeller, Robert J. Glynn

Population: 12,956 participants

Study Objective: To determine whether the marker of myocardial injury (hsTnI) was associated with adverse outcomes in JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and whether the effectiveness of statin therapy was modified by circulating hsTnI or BNP concentrations

First MACE



The sex-specific tertile cut points for hsTnI were 3.0 and 4.6 ng/L in men and 2.6 and 3.9 ng/L in women

Key takeaways: 1) The incidence of the composite primary end point i.e., the occurrence of a first major cardiovascular event depended upon the hsTnI category

Incidence Rate per 100 person-years

Primary Endpoint	Tertile 1	Tertile 3
Cardiovascular Death	0.07	**0.30**
Myocardial Infarction	0.12	**0.49**

2) Participants with hsTnI values in the top tertile were at increased risk of cardiovascular mortality and nonfatal MI

Relevance of the publication: 1) Rosuvastatin was equally effective in reducing the relative risk of major vascular events across categories of hsTnI

2) In the highest category of baseline hsTnI, rosuvastatin therapy was associated with the most substantial reduction in the absolute risk of cardiovascular events

ADD-130893-GBL-EN

HUNT 2015

Year: 2015; Clinical Chemistry

Publication title: Impact of Sex on the Prognostic Value of High-Sensitivity Cardiac Troponin I in the General Population: The HUNT Study

Author: Torbjorn Omland, James A. de Lemos, Oddgeir L. Holmen

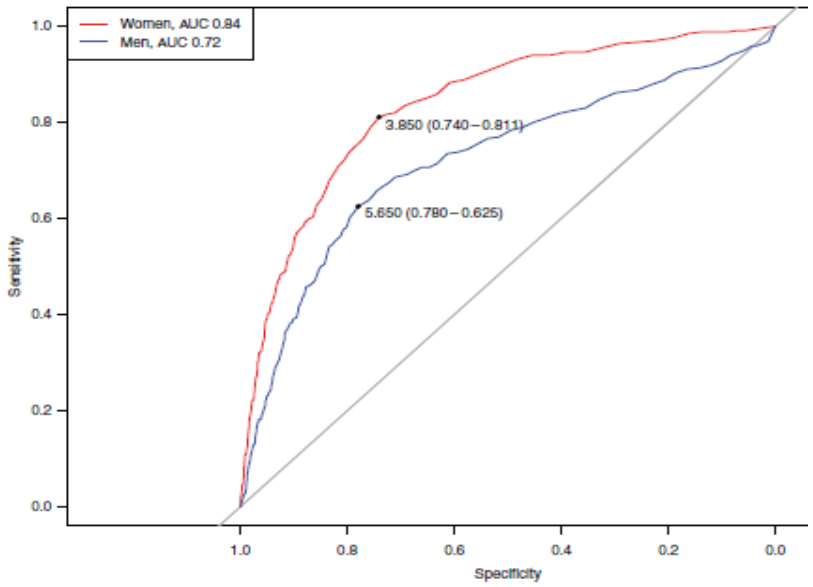
Population: 9712 participants

Study Objective: 1) The objectives of the current study were

1) To assess the distribution of hs-cTnI concentrations across sexes in a large population based epidemiological study in Norway

2) To investigate whether the association of hs-cTnI and risk of cardiovascular death differs between women and men

3) To assess whether sex-dependent differences in cardiovascular risk are modified by hs-cTnI concentrations



AUC (Area Under the Curve): Men 0.72, Women 0.84

The cutoffs providing optimal discriminatory power concerning the incidence of cardiovascular death were 3.85 ng/L in women and 5.65 ng/L in men

Key takeaways: 1) In the overall study cohort, there was a strong and graded association between concentrations of hs-cTnI and the incidence of cardiovascular death

Relevance of publication: 1) For concentrations in the upper part of the reference interval, it was observed that for a given hs-cTnI value, the risk of cardiovascular death was higher in **women** than in men

2) Higher risk in the higher concentration range for women was observed when participants were divided in 4 categories according to the cutoffs which justifies the use of separate male and female cut-offs

Abbott

ADD-130893-GBL-EN