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Optimization of secondary prevention and risk stratification in patients with coronary heart disease

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Chapter 6.

A rapid (differential) effect of rosuvastatin and atorvastatin on high-sensitivity cardiac Troponin-I in subjects with stable cardiovascular disease

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Abstract

Serum troponin within the normal range is an emerging predictor of cardiovascular mortality. We aimed to determine how rapidly high-sensitivity troponin -I (hs-cTnI) levels are lowered by statin therapy in patients with stable cardiovascular disease. In the RADAR substudy, patients were randomized, to atorvastatin 20 mg/day (n = 39) or rosuvastatin 10 mg/day (n = 39) and up-titrated in 6 week intervals to 80 mg of atorvastatin or 40 mg of rosuvastatin. Hs-cTnI concentrations were measured at baseline and at 6 and 18 weeks of follow-up. Statin treatment resulted in a mean change of serum hs-cTnI of -8.2% (p=0.010) after 6 weeks and - 12.3% (p=0.001) after 18 weeks. After 18 weeks, hs-cTnI levels were lowered by 21.8% with atorvastatin and by 4.1% with rosuvastatin (p=0.001 and p=0.133, respectively). During statin therapy serum hs-cTnI levels decreased rapidly within weeks of treatment, suggesting an effect beyond long-term atherosclerosis regression. Mechanisms that mediate this effect require further study.

Introduction

Serum cardiac troponin is a specific marker of myocardial injury and is the cornerstone in the diagnosis and acute management of myocardial infarction.(1) The introduction of high sensitivity assays (hs-cTn), which are up to 100 times more sensitive compared with the first-generation assays, permits the accurate determination of very low levels of circulating cardiac troponin.(2) Minor increases in troponin level might be due to myocardiocyte necrosis or apoptosis which in turn might be caused by subclinical coronary artery disease resulting in transient ischaemia, inflammation, myocardial strain or volume or pressure overload.(3) Interestingly, several studies show that elevated serum hs-cTn levels, even those within the normal range, are an emerging independent predictor of cardiovascular (CV) mortality in patients with and without cardiovascular disease (CVD).(4-8) With the development of these high sensitivity assays, cardiac troponin assessment may potentially be added to other traditional risk factors to predict cardiovascular risk.

Like hs-cTn, elevated brain-type natriuretic peptide (BNP), to levels still normal, is associated with higher risk of heart failure, and interventions in response to these minor increases, improve outcome.(9)

Recently, Ford et al. explored in the West of Scotland Coronary Prevention Study (WOSCOPS) cohort whether hs-cTnI could be modified by statins.(4) They showed that circulating cTnI was lowered by 13% at 1 year in the pravastatin group as compared with placebo ($p < 0.001$). Furthermore, the group with the biggest decline of cTnI levels at 1 year was associated with a 5-fold greater reduction of future coronary risk compared with the group with the biggest decline, independent of cholesterol lowering. The authors concluded that serial hs-cTnI measurements have major potential to monitor cardiovascular future coronary risk and may predict future coronary heart disease risk reduction following therapeutic interventions.

However, the earliest onset of this effect and specificity as to the statin used are unknown. The present analysis from a randomized study sought to characterize the effect (magnitude and time of onset) of atorvastatin (ATOR) or rosuvastatin (ROSU) on hs-cTnI levels within the normal range in patients with stable CVD.

Materials and Methods

Study design

The RADAR (Rosuvastatin and Atorvastatin in different Dosages And Reverse cholesterol transport) study was a randomised, open label trial, conducted in 29 centres in The Netherlands.(22) Three pre-selected hospital centres were designated to store biobank samples and to perform extended lab sampling and

storage for their patients to obtain the metabolite profiles. By protocol, a total of 80 patients were included in this present official and prospective sub study of the RADAR study to assess serum hs-cTnI. So it was a prospectively defined subset of patients from those 3 pre-selected hospitals that were included in this sub study. Several RADAR sub studies have been published earlier with the same patient population as was currently used. (23-25)

The RADAR study design has been described in detail elsewhere and is presented in Figure 1.(22) In short, patients with stable CVD entered a 6-week dietary run-in phase. Subsequently, they were, if eligible, randomised to receive either ATOR 20mg or ROSU 10mg. On the following visits, at 6 and 12 weeks the doses were, by protocol, forced up-titrated to 40 mg ATOR or 20mg ROSU (at 6 weeks) and 80 mg ATOR or 40 mg ROSU (at 12 weeks). The study was designed and conducted in accordance with the Declaration of Helsinki and in compliance with the ethical principles of Good Clinical Practice. Appropriate ethics committees or institutional review boards approved the study, and all patients gave written, informed consent.

Study population

Patients aged between 40-80 years were eligible for study participation if they had established CVD, fasting high-density lipoprotein cholesterol (HDL-c) <1.0 mmol/L and fasting triglycerides \leq 4.5 mmol/L at visits 1 and 2. Exclusion criteria were the use of other lipid-lowering drugs after enrolment, pregnancy or lactation, active arterial disease described as within 2 months of entry into the dietary lead-in phase or likely intervention within 6 months of randomisation, cases of familial hypercholesterolemia, severe concomitant morbidity or indices of impaired renal or liver function.

Measurements and statistical analysis

Hs-cTnI was measured at week 0 (baseline) and after 6 and 18 weeks of treatment. Patients were required to fast for at least 12h before blood collection and abstained from alcohol for the same period prior to blood sampling. Plasma samples were isolated after centrifugation at 4°C, 3000 rpm for 15 min and stored in -80°C freezers until analysis.

Hs-cTnI concentrations were measured using an automated clinically validated assay (i1000SR ARCHITECT, Abbott, UK). The assay has a limit of detection of 1.3 ng/L with a 99th percentile in the general population of 34.2 ng/L for men and 15.6 ng/L for women.(2) Two-level quality controls from the manufacturer ran with coefficients of variation <6%. Pre-specified, by protocol and according to current literature all patients with hs-cTnI levels above the 99th percentile were excluded from further analysis.(4-8)

Comparisons of baseline characteristics between groups were made using chi-square test for categorical variables and independent T-test or Mann-Whitney

U test for continuous variables. First, median changes in hs-cTnI levels between 2 time points were determined using a Wilcoxon-signed rank test. Next, hs-cTnI was log-transformed since it was non-normally distributed. Mean log changes in hs-cTnI and mean low-density-lipoprotein cholesterol (LDL-c) levels between 2 time points were determined using a paired sample T-test. To compare the differences in hs-cTnI levels between treatment groups an independent T-test was performed. A multivariate regression analysis was used to compare the change between baseline and week 18 between the treatment groups which was adjusted for baseline log hs-cTnI concentrations and prior aspirin use. A Pearson correlation coefficient was used for the total group, for the ATOR group as for the ROSU group to assess the association between changes in LDL-c and changes in log hs-cTnI. Analyses were conducted with SPSS 23.0 statistical analysis software (IBM, Armonk, NY, USA).

Results

In all 80 randomized patients sufficient sample material to measure hs-cTnI was available. In 2 patients hs-TnI concentrations were at or above the sex-specific 99th percentile and they were excluded for further study.

Of the 78 remaining study participants mean age was 65 years and 73 (94%) were male. As expected, the baseline characteristics, concomitant medication use and prior cardiovascular disease were similar in the two treatment groups (Table 1). Patients in the ATOR group used significantly more often aspirin than patients in the ROSU group. The lipid profiles at baseline did not differ between the two groups. There was a clear decrease of all the measured lipid levels during follow-up. In short, LDL-c decreased from 3.78 mmol/L to 1.70 mmol/L after 18 weeks in the ROSU group, and from 3.63 mmol/L to 1.77 mmol/L in the ATOR group. The decline of LDL-c did not differ significantly between the two treatment groups.

Effects of increasing doses of statin therapy on hs-cTnI are summarized in table 2. Median baseline hs-cTnI in the combined statin group was 4.50 ng/L (IQR: 3.35-6.67). Divided by treatment group, the median baseline was 3.90 ng/L (IQR: 3.10-5.65) for ATOR and 4.90 ng/L (IQR: 4.20-7.10) for ROSU. The median change from baseline in the combined statin group was -0.7 ng/L (IQR: -2.0 to 0.3), (p-value = 0.005) after 6 weeks and -0.8 ng/L (IQR: -2.1 to 0.4), (p-value <0.001) after 18 weeks. In the ATOR group, median hs-cTnI changes were -0.7 ng/L (IQR: -1.8 to 0.6), (p-value = 0.032) after 6 weeks and -1.1 ng/L (IQR: -1.9 to 0.0), (p-value <0.001) after 18 weeks. In the ROSU group no significant differences were observed. The median changes from baseline were -0.7 ng/L (IQR: -2.0 to 0.2), (p-value = 0.069) after 6 weeks and -0.6 ng/L (IQR: -2.1 to 1.1), (p-value = 0.124) after 18 weeks.

Table 1. Patient demographics and baseline characteristics

	ROSU + ATOR (n=78)	Rosuvastatin (n=39)	Atorvastatin (n=39)	p-value
<i>Patiënt characteristics</i>				
Gender, male (%)	73 (93.6)	37 (95)	36 (92.3)	0.644
Age, years	64.9 (8.9)	65.8 (7.7)	64.1 (9.8)	0.403
Body mass index (kg/m ²)	28.5 (3.8)	29.0 (4.0)	28.1 (3.5)	0.279
Systolic blood pressure (mmHg)	139.3 (17.5)	140.1 (17.6)	138.5 (17.6)	0.695
Diastolic blood pressure (mmHg)	81.3 (8.0)	81.7 (7.9)	80.9 (8.1)	0.642
Diabetes mellitus	13 (16.7)	5 (12.8)	8 (20.5)	0.362
<i>Concomitant medication</i>				
Beta blockers	62 (79.5)	28 (71.8)	34 (87.2)	0.092
Antihypertensive medication	49 (59.0)	24 (61.5)	22 (56.4)	0.645
Platelet inhibitors	8 (10.3)	4 (10.3)	4 (10.3)	1.000
Ascal	63 (80.8)	28 (71.8)	35 (89.7)	0.044
Vitamin K antagonist	11 (14.1)	8 (20.5)	3 (7.7)	0.104
<i>Laboratory measurements</i>				
Creatinine, µmol/L	103.8 (16.4)	103.6 (16.5)	104.1 (16.5)	0.886
Total-c, mmol/L	5.78 (1.20)	5.85 (1.25)	5.70 (1.16)	0.569
HDL-c, mmol/L	0.64 (0.10)	0.66 (0.09)	0.62 (0.11)	0.090
LDL-c, mmol/L	3.70 (0.94)	3.78 (0.86)	3.63 (1.01)	0.506
Triglycerides, mmol/L	3.01 (1.54)	2.84 (1.54)	3.17 (1.55)	0.349
<i>Prior cardiovascular disease</i>				
Transient ischaemic attack	5 (6.4)	2 (5.1)	3 (7.7)	0.644
Ischaemic stroke	4 (5.1)	3 (7.7)	1 (2.6)	0.305
Carotid artery disease	0 (-)	0 (-)	0 (-)	-
Angina pectoris	61 (78.2)	31 (79.5)	30 (76.9)	0.784
Myocardial infarction	53(67.9)	29 (74.4)	24 (61.5)	0.225
PTCA	30 (38.5)	15 (38.5)	15 (38.5)	1.000
Peripheral arterial disease	6 (7.7)	2 (5.1)	4 (10.3)	0.395

Categorical variables expressed by number (%)

Numerical variables expressed by mean (SD) or median (IQR)

Comparisons between groups were made using chi-square test for categorical variables and independent T-test or Mann-Whitney U test for continuous variables

Figure 2 illustrates the time course of mean log hs-cTnI during statin therapy. The mean log hscTn-I value at baseline in the combined statin group was 0.70 (SEM: 0.03). After 6 weeks the mean log hs-cTnI was 0.64 (SEM: 0.03) and after 18 week 0.61 (SEM: 0.03). The mean changes of log hs-cTnI were -8.2% (p-value= 0.010) after 6 weeks and -12.3% (p-value < 0.001) after 18 weeks of treatment. The difference between 6 and 18 weeks was -4.5% (p-value = 0.202).

A repeated measure ANOVA determined that mean log hs-cTnI concentrations differed statistically significantly between time points (p-value < 0.001).

Table 2. Troponin concentrations (in ng/L)

	Baseline	Week 6	W6-Baseline	p-value	Week 18	W18-Baseline	p-value
ROSU+	4.50	4.25	-0.7	0.005	4.20	-0.8	<0.001
ATOR	(3.35-6.75)	(2.80-6.00)	(-2.0 to 0.3)		(2.68-6.43)	(-2.1 to 0.4)	
ROSU	4.90	4.90	-0.7	0.069	4.90	-0.6	0.124
	(4.20-7.10)	(3.25-6.63)	(-2.0 to 0.2)		(3.35-8.00)	(-2.1 to 1.1)	
ATOR	3.90	4.00	-0.7	0.032	3.50	-1.1	<0.001
	(3.10-5.65)	(2.45-5.50)	(-1.8 to 0.6)		(2.05-5.10)	(-1.9 to 0.0)	

Values are presented as median with interquartile range.

The W6-Baseline and W18-Baseline time points are given in absolute values' differences from baseline.

W6 = Week 6, W18 = Week 18

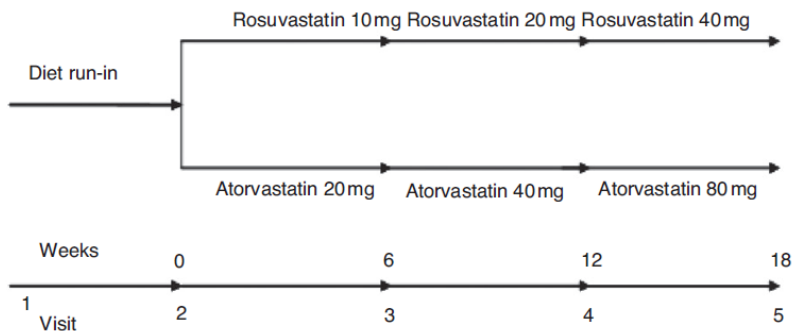


Figure 1. RADAR study design.

Figure 3 presents the time-courses of log hs-cTnI in the separate statin regimens. At baseline the mean log hs-cTnI level was 0.64 (SEM 0.04) in the ATOR group and 0.75 (SEM 0.04) in the ROSU group. Baseline log hs-cTnI levels between the two statin groups tended to differ significant (p-value = 0.053). After 6 weeks mean log hs-cTnI level in the ATOR group was 0.58 (SEM: 0.04) and 0.70 (SEM: 0.05) in the ROSU group (p-value = 0.071), and after 18 weeks 0.50 (SEM: 0.04) in the ATOR group and 0.72 (SEM: 0.05) for the ROSU group. ATOR reduced log hs-cTnI by 9.1% (p-value = 0.074) after 6 weeks and by 21.8% (p<0.001) after 18 weeks. In the ATOR group the difference of log hs-cTnI between 6 and 18 weeks was 14% (p-value = 0.023). The reduction of log hs-cTnI in the ROSU group was 7.2% (p-value = 0.071) after 6 weeks and 4.1% (p-value = 0.133) after 18 weeks. When adjusted for baseline log hs-cTnI levels and prior aspirin use, ATOR reduced hs-cTnI levels between baseline and 18 weeks more distinctly than ROSU (mean

log difference 0.09; $p=0.022$). Mean changes of hs-cTnI between baseline and 18 weeks of treatment were not correlated using a Pearson correlation with mean changes of LDL-c in the combined group, ATOR or ROSU group ($R = 0.011$, $p\text{-value} = 0.928$; $R = 0.17$, $p\text{-value} = 0.334$; and $R = -0.072$, $p\text{-value} = 0.698$, respectively). (Results are not shown)

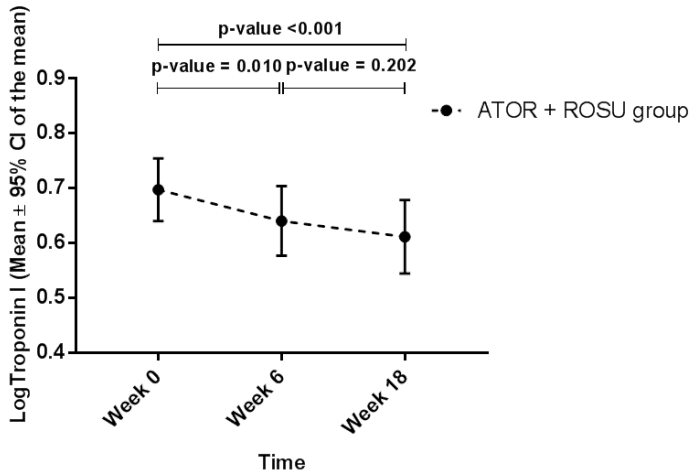


Figure 2. The figures illustrate the effect of statin therapy on the total group. Hs-cTnI was log-transformed since it was non-normally distributed. Hs-cTnI is expressed as mean \pm 95% confidence interval of the mean.

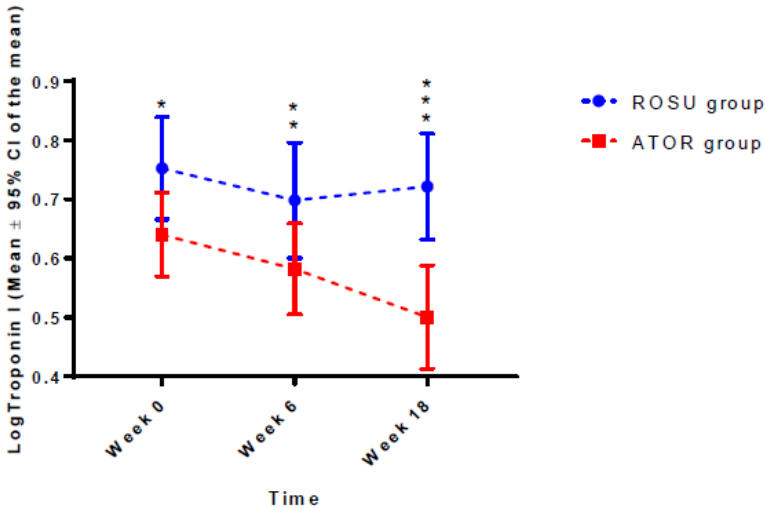


Figure 3. For each time point mean value and 95% confidence interval of the mean are presented. *P* values refer to differences between the two treatment groups for each time point ($P=0.053^*$, $P=0.071^{**}$, $P=0.001^{***}$).

Discussion

In this substudy of the RADAR trial, the effect of ATOR and ROSU on serum hs-cTnI was explored. Hs-cTnI levels of patients with stable CVD decreased significantly within weeks of statin treatment. Furthermore, a reduction of hs-cTnI levels occurred with a low dose of statins and in addition, there was evidence that this effect was more pronounced in the ATOR treatment regimen than in the ROSU treatment regimen.

These novel findings suggest a rapid benefit of statin treatment on ongoing subclinical myocardial damage. With the hs-cTn assays, cTn concentrations are emerging as promising biomarkers for the prediction of cardiovascular events and mortality. Several studies demonstrated that increases of cTnI within the normal range are associated with increased cardiovascular risk.(4-7, 10-14) In this relatively uncharted field serial cTn measurements have a major potential to monitor risk and to assess the influence of therapeutic interventions on cardiovascular risk.(4) Our results emphasise this, showing that initiation of lipid lowering treatment provides a rapid, as opposed to long-term, effect on cTn.

Only, limited information is available about the time frame in which statin therapy can reduce serum cTn levels. We show that after 6 weeks of treatment with ATOR 20mg or ROSU 10mg once daily the average decrease of hs-cTnI is 8%. No earlier studies studied the effect of statin therapy in this time frame. Furthermore, it was unknown whether this decline advances with such a low level and whether this decrease associates with a better patient outcome. After 18 weeks serum hs-cTnI levels were on average 12% lower than at baseline in the combined statin group, 22% in the ATOR group and 4% in the ROSU group. Earlier Graving et al.(15) reported in elderly patients with chronic heart failure that hs-cTnI levels at 3 months of therapy with 10 mg ROSU did not differ from the hs-cTnI levels at 3 months of placebo therapy. This study, however, differs in several aspects from the current study. First of all, an hs-cTnT assay was used instead of an hs-cTnI assay in the present study. Secondly, their study population consisted of elderly patients with heart failure which might have influenced the change of cTn levels and thirdly, in the study of Graving et al.(15) patients received ROSU 10mg daily for 3 months whereas in the present study the doses were up-titrated every 6 week, to ROSU 40mg after 12 weeks.

Ford et al.(4) showed that after 1 year therapy with pravastatin hs-cTnI levels were reduced by 19% (compared to 6% in the placebo group). In twice as many participants in the statin group compared with the placebo group, hs-cTnI levels decreased by >25%. This group was at the lowest risk for future events. White et al.(6) also assessed the effect of 1-year statin therapy on cTnI concentration. These authors found that compared with placebo, pravastatin 40 mg once daily reduced cTnI levels by a median of 3 ng/L. In the placebo group TnI levels did not change in 1 year. However, this treatment effect did not result in important differences in future cardiac events.

In the present study statin therapy led to a decline of hs-cTnI independently of LDL-c reductions. Statins are the most widely prescribed agents in treating CVD and are well-known for their pleiotropic lipid-lowering independent effect. Statins positively interfere with critical components of the atherosclerotic process, and have beneficial anti-inflammatory effects on the vascular wall, improve nitric oxide bioavailability and improve endothelial function.(16) These processes can lead to cardiomyocyte necrosis, apoptosis or reversible injury with increased cardiomyocyte membrane permeability, which in turn can result in cardiac troponin release.(17) Differences between LDL-c lowering effects between statins are well known (18) but variances in pleiotropic effects are less clear. However, there are differences in pharmacokinetics and pharmacodynamics between statins(19) which might explain differences observed between ATOR and ROSU. For example, ATOR is a relatively lipophilic compound while ROSU is relatively hydrophilic.(20) However, whether this physico-chemical difference underlies different hs-cTnI release patterns is unknown as yet.

Some limitations need to be addressed. First of all, our substudy had no placebo controlled group, which makes it difficult to relate statin therapy to the decline of cTnI concentrations observed. However, earlier studies showed that statin therapy compared to placebo reduces hs-cTnI concentrations more effectively after one year.(4) In the present study recruitment in the phase with lifestyle and diet modification might have led to change in hscTnI concentration. However, the first blood withdrawal was after a 6 week diet run-in period and therefore any further changes of hscTnI levels are not likely to depend on dietary or lifestyle changes. Secondly, this study contains patients with known CVD only which makes it difficult to generalize our findings in broader populations. Thirdly, there was no long-term follow up data available to assess the role of our findings on patients' outcome. Fourth, some biological intra-individual variation of hs-cTnI exists, which might have influenced the results. However, the biological intra-individual variation is about 3% for hs-cTnI concentrations.(21) In the present study the average statin-induced decrease of hs-cTnI was 12%, so if any, the biological intra-individual variation can only partly contribute to the decrease of hs-cTnI. Furthermore, only patients who were stable for at least 2 months prior to inclusion were included and none of the patients had a cardiac event during the follow-up which could have affected their serum hs-cTnI concentrations. Lastly, though the difference in the log of the troponin I over time decreased during statin therapy the data on rosuvastatin to atorvastatin only showed no overlap at 18 weeks, while before that time it did. Whether troponin levels are or are not different in ATOR versus ROSU treatment should be handled with caution. Nevertheless, there was an overall decline of troponin levels after statin treatment was initiated.

Conclusion

In patients with stable CVD hs-cTnI decreased significantly during statin therapy, which was independent of decreases of LDL-c concentrations. Statin-induced effect on hs-cTnI was evident as early as after 6 weeks. This effect was more pronounced with atorvastatin than with rosuvastatin. This novel finding suggests a rapid benefit of statin treatment on ongoing subclinical myocardial damage. Whether the short-term effects of statin therapy on hs-cTnI are directly related to improved patient outcome is still unknown, but our findings suggest an urgent need to test this potential.

Study highlights

What is the current knowledge on the topic?

Serum troponin within the normal range is an emerging predictor of cardiovascular mortality.

Recently, a randomized trial showed that circulating troponin I was lowered by 13% at 1 year in the pravastatin group as compared with placebo.

What question did this study address?

The aim of this study was to determine how rapidly high-sensitivity troponin -I (hs-cTnI) levels are lowered by statin therapy in patients with stable cardiovascular disease.

What does this study add to our knowledge?

Hs-cTnI decreased significantly during statin therapy, which was independent of decreases of LDL-c concentrations. Statin-induced effect on hs-cTnI was evident as early as after 6 weeks. This novel finding suggests a rapid benefit of statin treatment on ongoing subclinical myocardial damage.

How might this change clinical pharmacology or translational science?

Whether the short-term effects of statins on hs-cTnI are directly related to improved patient outcome is unknown, but our findings suggest an urgent need to test this potential. Serial troponin measurements could have major potential to assess cardiovascular risk and monitor the impact of therapeutic interventions.

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