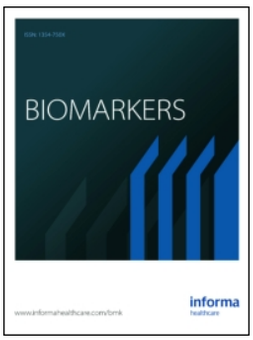

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ORIGINAL ARTICLE

Comparison of temporal changes in established cardiovascular biomarkers after acute coronary syndrome between Caucasian and Chinese patients with diabetes mellitus

Nermina Buljubasic[a*#], Wei Zhao[b,c,d,e*#], Jin Cheng[a], Huijuan Li[f], Rohit Oemrawsingh[a,g], Martijn Akkerhuis[a], Haiyi Yu[b,c,d,e], Lequn Zhou[b,c,d,e], Yangfeng Wu[f], Eric Boersma[a†#] and Wei Gao[b,c,d,e†]

[a]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; [b]Department of Cardiology and Institute of Vascular Medicine, Peking University Third Hospital, Beijing, China; [c]Key Laboratory of Cardiovascular Molecular Biology and Regulatory Peptides, Ministry of Health, Beijing, China; [d]Ministry of Education, Key Laboratory of Molecular Cardiovascular Science, Beijing, China; [e]Beijing Key Laboratory of Cardiovascular Receptors Research, Beijing, China; [f]Peking University Clinical Research Institute, Beijing, China; [g]Department of Cardiology, Albert Schweitzer Hospital, Dordrecht, The Netherlands

ABSTRACT

Background: Population means of conventional cardiovascular biomarkers are known to differ between ethnic groups. In this study we performed detailed comparisons in the temporal pattern of these biomarkers between Caucasian and Chinese diabetic patients with acute coronary syndrome (ACS).

Methods: We studied differences in temporal changes of established cardiovascular biomarkers, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, cardiac Troponin T (TnT), NT-proBNP and C-reactive protein (CRP), in 48 Chinese and 48 clinically matched Caucasian patients with type 2 diabetes mellitus who were admitted for ACS. Blood samples were collected at regular time intervals during 30 days to 1 year after the index ACS.

Results: In the >30 day post ACS period, mean serum levels of LDL (2.16 vs. 1.47 mmol/L; *p*-value <0.001), total cholesterol (4.08 vs. 3.11 mmol/L; *p*-value <0.001), TnT (11.0 vs. 7.76 ng/L; *p*-value 0.010) and CRP (2.0 vs. 0.78 mg/L; *p*-value <0.001) were systematically higher in Caucasian than in Chinese patients. HDL and NT-proBNP levels were similar.

Conclusions: Our study showed clinically relevant differences in levels of established cardiovascular biomarkers between Caucasian and Chinese post ACS patients. Further cross-ethnic studies are warranted to determine secondary prevention treatment biomarker targets in specific populations.

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KEYWORDS
Acute coronary syndrome; biomarkers; cardiovascular disease; coronary artery disease; ethnicity; linear mixed effect models

Introduction

For decades coronary artery disease (CAD) has been the leading cause of mortality and morbidity worldwide (Shepard *et al.* 2015, Roth *et al.* 2017). Global analyses have demonstrated a favourable trend in economically developed (Western) countries with declining (age-standardized) CAD mortality rates over the past decennia, whereas its incidence is increasing in non-Western regions (Roth *et al.* 2015, Joseph *et al.* 2017, Roth *et al.* 2017). Various factors are attributable for this epidemiological shift, but fact is that CAD has become a major burden to non-Western societies (Reddy, 2004).

Recognition of CAD onset in the asymptomatic phase is the cornerstone of successful primary prevention. Also, in patients with established disease, the success of secondary prevention depends on early recognition of individuals with high risk of cardiovascular (CV) events. Blood biomarkers, reflecting underlying pathophysiological processes, can be instrumental in this respect (Wang *et al.* 2017). For example, inflammatory markers, such as C-reactive protein (CRP) and interleukin-18, have been extensively studied and shown to be a valuable predictor for adverse outcomes in patients with CAD (He *et al.* 2010, Cheng *et al.* 2015). Thus far, most CV biomarkers have been merely validated in Caucasians, and little is known about their generalizability to other ethnic groups. Furthermore, existing inter-ethnic CV biomarker studies have focussed on general populations (Gijsberts *et al.* 2015), and biomarker data in CAD populations from different ethnic groups are scarce. Finally, inter-ethnic biomarker

CONTACT Eric Boersma h.boersma@erasmusmc.nl Department of Cardiology, Erasmus Medical Center, Room Na-317, P.O. Box 2040, Rotterdam, 3000 CA, The Netherlands
*These authors shared first authorship.
†These authors shared last authorship.
#Nermina Buljubasic and Eric Boersma are responsible for statistical design and analysis. n.buljubasic@erasmusmc.nl (N. Buljubasic), h.boersma@erasmusmc.nl (E. Boersma)

Supplemental data for this article can be accessed here.

studies are typically characterized by cross-sectional designs, with single measurements at a certain baseline moment. Hence, the observed results might easily be affected by accidental factors. Insight into longitudinal biomarker patterns by means of repeated blood sampling may nullify these random variations, and thus reveal true differences in biomarker levels between populations.

The need for biomarker validation in order to optimize secondary prevention strategies is especially warranted in Asia, where CAD now is an upcoming epidemic (Reddy, 2004). Concerns especially exist in the (rural) Chinese population, where an increasing number of patients with coronary heart disease is leading to rapidly increasing mortality rates (Li and Ge 2015). Similar to this worrisome trend are the rising numbers in prevalence of diabetes mellitus type 2 (DM2), which has become a serious health concern, leading to the world's largest epidemic in China (Chan *et al.* 2009, Wang *et al.* 2017). The joint effect of established coronary heart disease and prevalent diabetes markedly increase the risk of coronary mortality (Hu *et al.* 2005). Biomarkers should especially be further investigated in these high-risk groups, since they are particularly prone to recurrent events and might benefit most from secondary prevention strategies. Nevertheless, biomarker studies in Asian populations have been mainly focussed on South Asians (Gijsberts *et al.* 2015). But, within Asia, there is broad geographical variation in patient risk profiles, which makes it unlikely that findings from South Asians can easily be extrapolated to Chinese individuals. In fact, far less biomarkers have been investigated in Chinese cohorts, residing in their country of origin.

Against this background, we evaluated differences in levels of serum high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, cardiac Troponin T (TnT), N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) and CRP – which we consider the most relevant CV biomarkers – between Dutch-Caucasian and Chinese DM2 patients presenting with acute coronary syndrome (ACS). In particular, we aimed to reveal inter-ethnic differences in the temporal evolution of these CV biomarkers during 1 year following the index ACS event.

Clinical significance

- Most cardiovascular biomarkers have been merely validated in Caucasians.
- Chinese populations are underreported in cardiovascular biomarker research.
- LDL and total cholesterol are higher in Caucasians than in Chinese.
- Troponin T and CRP are systematically higher in Caucasians than in Chinese.
- Biomarkers studied in Caucasians may not be directly extrapolated to Chinese.

Methods

Study design and patients

Figure 1 describes a patient flow diagram to illustrate the flow of participants through the study. We selected 48 Chinese ACS patients with established DM2 from the 'Peking and Rotterdam on Mission to Reduce Coronary Artery Disease' (PRoMISS) study. PRoMISS is a prospective, observational study, conducted in 12 hospitals in the larger area of Beijing (China), and enrolled patients during 2013–2014 admitted for an ACS and with a clinical diagnosis of DM2 prior to this index event. The definition of ACS covered unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). Blood samples (non-fasting) were taken from

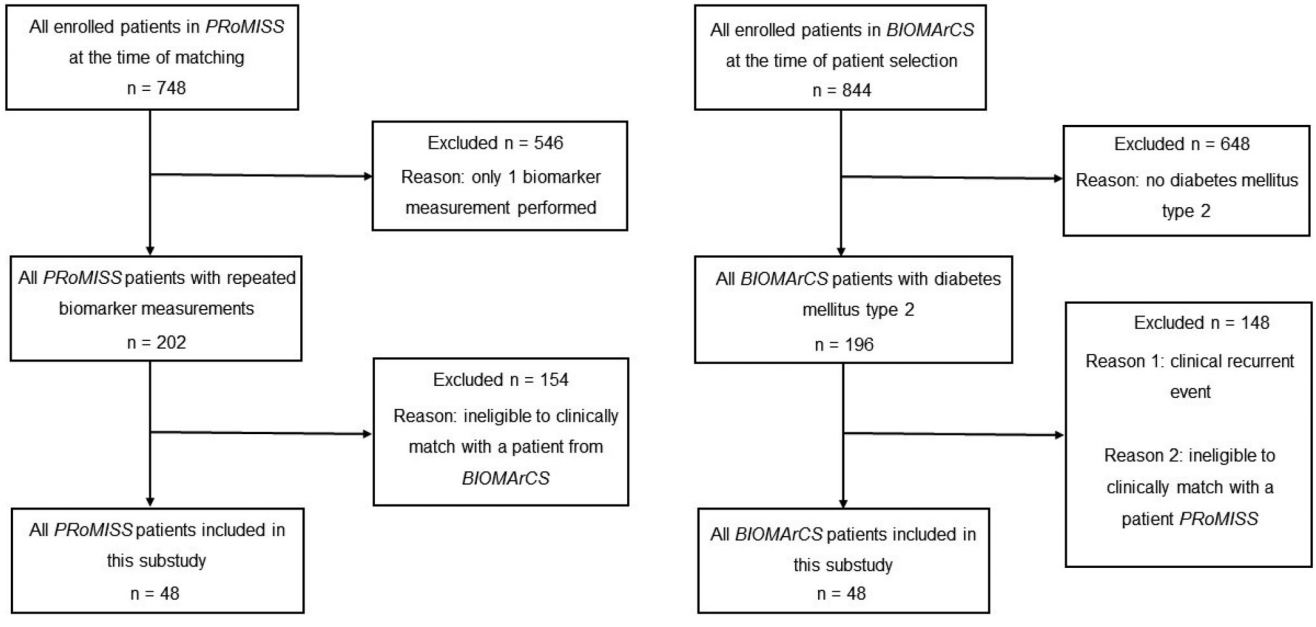

Figure 1. Study flow chart. A patient flow diagram according to the international STARD guidelines to report flow of participants through the study.

PRoMISS patients at the day of hospital admission, at the day of hospital discharge, followed by monthly blood sample collection until 1 year follow-up. Altogether a median of 9 repeated samples per patient were available in the Chinese cohort.

Subsequently, we selected 48 DM2-ACS patients with Caucasian ethnicity from the Dutch prospective, observational 'BIOMarker study to identify the Acute risk of a Coronary Syndrome' (BIOMArCS) (Oemrawsingh *et al.* 2016). BIOMArCS enrolled 844 ACS patients with and without diabetes mellitus in 18 participating hospitals in The Netherlands during 2008–2015. A subgroup of 23% ($n = 196$) in this cohort was diagnosed with DM2. Patients underwent blood sampling at admission, at the day of hospital discharge and subsequently every fortnight during the first 6 months after discharge, followed by monthly blood sample collection until 1 year. A median of 16 repeated samples per patient was available in BIOMArCS. Chinese-PRoMISS and Caucasian-BIOMArCS patients were 1:1 matched on age (±5 year range), sex, admission diagnosis, history of CAD, and risk factor profile, including diabetes mellitus, hypercholesterolaemia, hypertension, peripheral vascular disease and smoking. At the time of matching, from the completed BIOMArCS study 48 diabetic patients could be optimally paired according to the matching criteria with 48 patients from the ongoing PRoMISS study. None of the patients experienced a recurrent ACS event throughout follow-up.

The PRoMISS and BIOMArCS studies were approved by the medical ethics committees of the participating hospitals. All participating patients from both studies provided written informed consent. Information on baseline characteristics and medication use was directly derived from patients' medical records and prospectively entered into a dedicated database.

Biomarker analysis

In PRoMISS and BIOMArCS, after preparation, aliquots were frozen at −80 degrees Celsius within two hours after withdrawal. Blood samples were initially handled and securely stored on-site, and then transported to the central laboratory of the Peking University Third Hospital, Beijing, China (PRoMISS) or the Erasmus MC, Rotterdam, the Netherlands (BIOMArCS) for long-term storage. After completion of data collection, blood samples were analysed batch-wise on the Roche Cobas® 8000 analysis platform (e601 immunoassay analyzer), using the fifth generation high sensitivity assay, with the following reagents (Roche Diagnostics Mat.-No./ Genisys-No): HDL: 04399803190; LDL: 03038866322; total cholesterol: 03039773190; TnT: 05092728190; NT-proBNP: 05390109190; CRP: 04628918190. PRoMISS and BIOMArCS samples were analysed in two different central laboratories (in China and the Netherlands), but the reagents, including calibration and control materials, had the same production lot number, and analysis protocols were identical had the same production lot number and analysis protocols were identical.

Statistical analysis

Categorical data are presented as numbers and percentages. Continuous variables are presented as mean ± standard deviation (SD) in case of a normal distribution, or as median and interquartile range (IQR) in case of a skewed distribution. Normality of the distributions of continuous variables was examined by visual inspection of the histogram and by normal Q–Q plots. The measured biomarkers showed a skewed distribution and were therefore log2-transformed for analysis. Missing values on baseline characteristics and medication use were minimal (7% missing information on gender and 3% missings on type of medication used) and addressed by complete case analysis. There were no missing values on biomarker levels.

Differences in baseline clinical characteristics between the Chinese-PRoMISS and Caucasian-BIOMArCS patients were evaluated by the paired samples *t*-test (for continuous variables), McNemar test (for categorical variables) or Marginal Homogeneity (for categorical variables with more than two categories) to account for the 1:1 matching.

Linear mixed effect (LME) models were applied with nested random effects (to account for the paired data). A grouping variable (PRoMISS or BIOMArCS) and time were entered as fixed effects, and paired individuals were entered as random effects, to determine mean biomarker levels in both cohorts. Interaction terms (grouping variable x time) were added (as fixed effects) to determine differences in biomarker evolution over time between the PRoMISS-Chinese and BIOMArCS-Caucasian patients. LME analyses were conducted with biomarker values on the log2 scale, but the main results are presented on the linear scale for ease of interpretation.

A substantial difference in medication use was observed between the PRoMISS-Chinese and BIOMArCS-Caucasian patients, which could have influenced biomarker levels. Therefore, adjusted LME models were constructed, including medication use (aspirin, statins, beta-blockers, ACE-inhibitors or angiotensin-II receptor blockers, nitrates and antidiabetics) as potential confounding factors. Thereby a certain amount of potential bias was addressed.

Data analyses were performed with SPSS version 21 and RStudio software version 1.0.136. All statistical tests were two-tailed and *p*-values <0.050 were considered statistically significant.

Results

Patient characteristics

Baseline clinical characteristics of the two successfully matched patient study cohorts are presented in Table 1. The BIOMArCS-Caucasian and PRoMISS-Chinese patients had a mean age of 60.2 ± 8.0 years and 60.0 ± 8.1, respectively. Most patients were men (BIOMArCS 87.5%, PRoMISS 85.4%), presenting with a STEMI (64.4% in both cohorts). As expected after matching, baseline clinical characteristics and cardiovascular risk factors were similarly distributed in the two study cohorts. Overall, commonly prescribed cardiovascular drugs

Table 1. Baseline clinical characteristics of the (matched) study patients.

	BIOMArCS-Caucasian (n = 48)	PRoMISS-Chinese (n = 48)	*p* Value
Patient characteristics			
Age, years	60.2 ± 8.0	60.0 ± 8.1	0.89
Male gender, n (%)	42 (87.5)	41 (85.4)	0.25
Admission diagnosis, n (%)			1.00
STEMI	31 (64.6)	31 (64.6)	
NSTEMI	10 (20.8)	10 (20.8)	
UAP	7 (14.6)	7 (14.6)	
Cardiovascular risk factors, n (%)			
Smoking			0.56
Current	20 (41.7)	16 (33.3)	
Former	11 (22.9)	14 (29.2)	
Never	17 (35.4)	18 (37.5)	
Diabetes Mellitus	48 (100.0)	48 (100.0)	1.00
Hypertension	31 (64.6)	33 (68.8)	0.80
Hypercholesterolaemia	27 (56.2)	25 (52.1)	0.79
Medical history, n (%)			
Previous myocardial infarction	10 (20.8)	7 (14.6)	0.55
Previous PCI	10 (20.8)	7 (14.6)	0.51
Previous CABG	5 (10.4)	0 (0.0)	0.06
Previous stroke	2 (4.2)	2 (4.2)	1.00
History of peripheral vascular disease	2 (4.2)	0 (0.0)	0.50
Medication use at first blood sample moment >30 days after admission, n (%)			
Aspirin	46 (95.8)	42 (87.5)	0.29
Statin	45 (93.8)	37 (77.1)	0.06
Beta-blocker	44 (91.7)	33 (68.8)	0.007
ACE-inhibitor or ARB	38 (79.2)	29 (60.4)	0.06
Nitrates	12 (25.0)	0 (0.0)	<0.001
Anti-diabetics	43 (89.6)	33 (68.8)	0.021

Values are expressed as mean ± standard deviation or proportion, n (%). *p*-values were obtained by paired samples *t*-test (for the continuous variable), McNemar test (for categorical variables) or Marginal Homogeneity (for categorical variables with more than two categories), whichever was appropriate.
ARB: angiotensin II receptor blocker; CABG: coronary artery bypass graft surgery; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UAP: unstable angina pectoris.

after an ACS were more frequently used in the BIOMArCS-Caucasian patients than in the PRoMISS-Chinese patients, in particular beta-blockers (BIOMArCS 91.7%, PRoMISS 68.8%, $p = 0.007$), nitrates (BIOMArCS 25.0%, PRoMISS 0%, $p < 0.001$) and anti-diabetics (BIOMArCS 89.6%, PRoMISS 68.8% $p = 0.021$).

Biomarker trajectories

BIOMArCS-Caucasian patients had statistically significant higher mean longitudinal levels for most lipid biomarkers than their PRoMISS-Chinese counterparts. Especially, clinically relevant higher mean LDL (2.16 vs. 1.47 mmol/L; *p*-value <0.001) and total cholesterol (4.08 vs. 3.11 mmol/L; *p*-value <0.001) levels were found (Figure 2, Table 2). These differences persisted and remained significant in a subanalysis of statin users only (results not shown). The estimated mean lipid biomarker levels did not change during the study period in BIOMArCS-Caucasian patients (Figure 2, Supplementary Table 1). In PRoMISS-Chinese patients, however, these biomarkers had a slight, but statistically significant, tendency to increase over time. Since the monthly increase was only 0.5% (cholesterol) to 4.3% (HDL) of the longitudinal mean level, the differences between BIOMArCS and PRoMISS remained fairly constant during the >30 days post ACS study period.

With respect to the established non-lipid cardiovascular biomarkers that we studied: BIOMArCS-Caucasians had higher mean longitudinal levels of TnT (11.0 vs. 7.76 ng/L; *p*-value 0.010) and CRP (2.07 vs. 0.78 mg/L; *p*-value <0.001) than PRoMISS-Chinese patients (Figure 3, Table 2). NT-proBNP levels were similar. In both cohorts, TnT, NT-proBNP and CRP slightly decreased over time (Figure 3, Supplementary Table 1), with a somewhat steeper decline in NT-proBNP in PRoMISS. Again, however, the monthly changes were far smaller than the longitudinal mean levels, so that the BIOMArCS-PRoMISS differences in mean levels were factually time-independent.

Discussion

This study investigated temporal cardiovascular biomarker profile differences between Caucasian and Chinese DM2 patients by high-frequency blood sampling during 1 year after their ACS index event. Overall, we found persistently higher levels of LDL, total cholesterol, TnT and CRP in Caucasian patients as compared to Chinese patients. We did not observe significant differences in HDL and NT-proBNP values between the two cohorts.

In general, studies investigating inter-ethnic cardiovascular biomarker differences between Caucasian and Chinese patients in a CAD population have barely been performed. So far, only one systematic review has reported differences in ten conventional cardiovascular biomarkers between diverse ethnic Asian groups and Caucasians in the general population (Gijsberts *et al.* 2015). It is important to note that only 5 out of the 33 studied cohorts were from Chinese origin, of which only 1 resided in the country of origin. The vast majority of biomarker levels was described in South

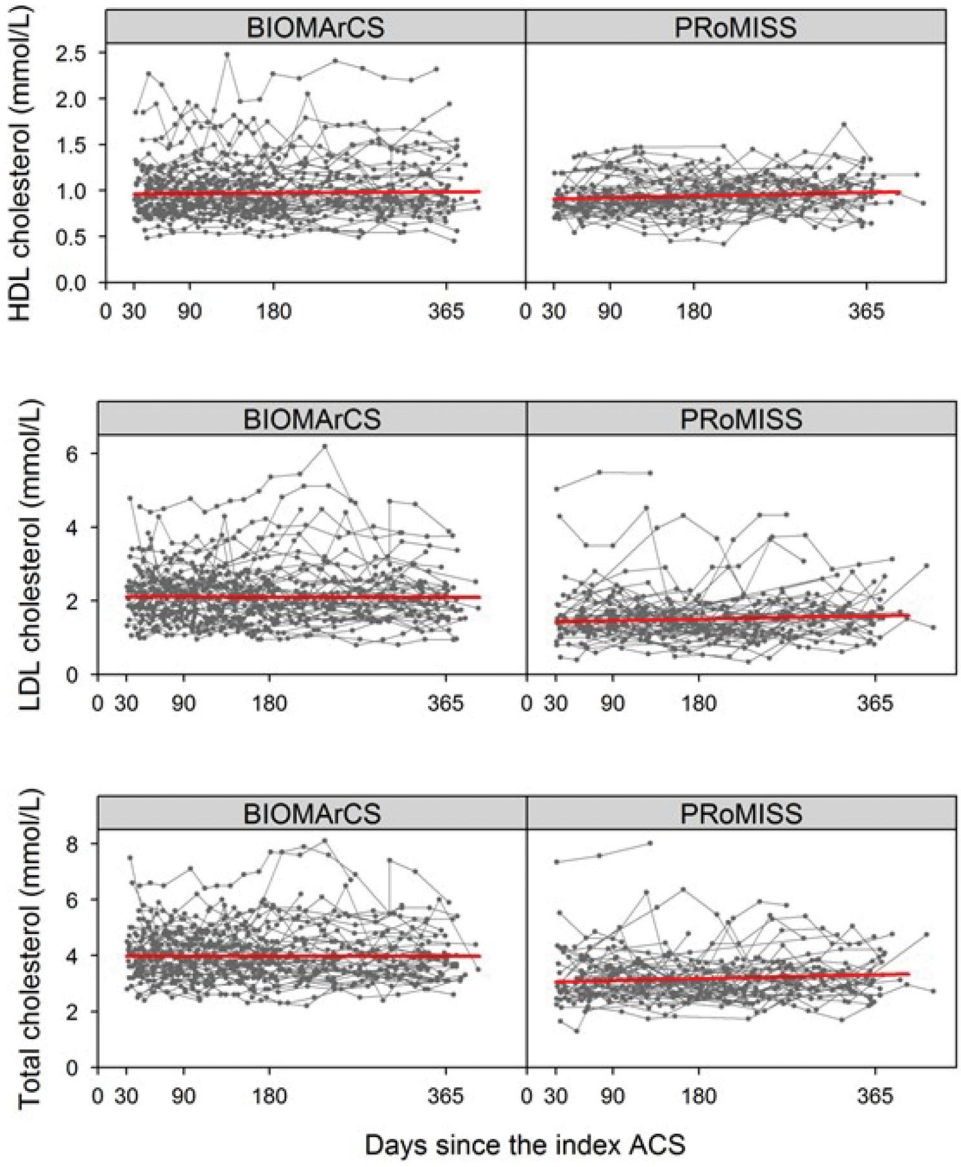

Figure 2. Serial measurements and temporal evolvement of lipid biomarkers in the BIOMArCS-Caucasian and PRoMISS-Chinese patients. The graphs show evolvement of HDL, LDL and total cholesterol >30 days since the index ACS event until 1-year in Caucasian (left) and Chinese (right) patients, who have not experienced a recurrent event during follow-up. The points represent measurements in individual patients. The bold line in each graph represents the average value, using linear mixed models with nested random effects. HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 2. Mean biomarker levels in the study patients 30 days to 1 year after the index ACS admission.

	BIOMArCS-Caucasian (n = 48)	PRoMISS-Chinese (n = 48)	Mean difference (95% CI)	*p* Value
HDL, mmol/L	0.97 (0.81–1.15)	0.94 (0.81–1.10)	0.03 (−0.06–0.13)	0.491
LDL, mmol/L	2.16 (1.60–2.94)	1.47 (1.11–1.89)	0.69 (0.40–1.04)	<0.001
Cholesterol, mmol/L	4.08 (3.34–4.92)	3.11 (2.66–3.64)	0.97 (0.62–1.37)	<0.001
Troponin T, ng/L	11.04 (6.40–18.10)	7.76 (5.07–12.27)	3.28 (0.71–6.62)	0.010
NT-proBNP, pmol/L	13.47 (5.85–31.58)	15.97 (7.73–31.79)	−2.50 (−7.42–5.28)	0.457
CRP, mg/L	2.07 (0.88–4.80)	0.78 (0.38–1.68)	1.28 (0.69–2.12)	<0.001

Data represent mean (95% confidence interval) biomarker values that were derived from nested linear mixed effects models, with adjustment for the use of cardiovascular medication, including aspirin, statins, beta-blockers, ACE-inhibitors or angiotension-II receptor blockers, nitrates and anti-diabetics.
CRP: C-reactive Protein; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; NT-proBNP: N-terminal pro B-type Natriuretic Peptide.

Asians, who are known to carry a more unfavourable cardiovascular risk and biomarker profile. Thus, sufficient evidence on inter-ethnic biomarker differences with data from Chinese CAD individuals is currently lacking. This underscores the need for ethnicity-driven biomarker research with a specific focus on Chinese individuals with CAD. Furthermore, the observed blood biomarker differences are based on only one blood sample, which reflects a snapshot and not a state during a longer period.

The importance of investigating this matter is endorsed by evidence that some biomarkers (e.g. CRP, IL-6, fibrinogen) were not able to predict incident CAD events risk

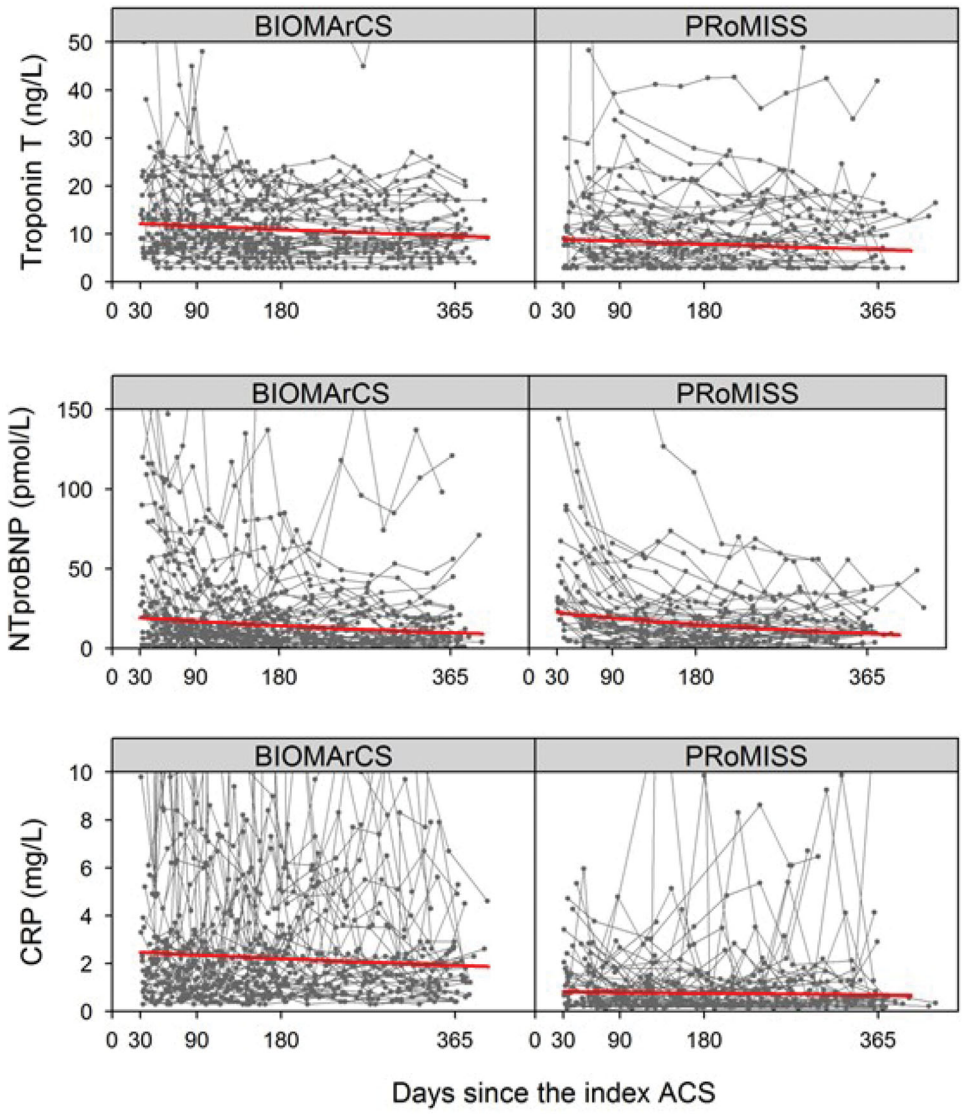

Figure 3. Serial measurements and temporal evolvement of acute-phase biomarkers in the BIOMArCS-Caucasian and PRoMISS-Chinese patients. The graphs show evolvement of Troponin T, NT-proBNP and CRP >30 days since the index ACS event until 1-year in Caucasian (left) and Chinese (right) patients, who have not experienced a recurrent event during follow-up. The points represent measurements in individual patients. The bold line in each graph represents the average value, using linear mixed models with nested random effects. CRP: C-reactive Protein; NT-proBNP: N-Terminal fragment of Pro-Brain Natriuretic Peptide.

among asymptomatic Chinese people in contrast to positive associations found in Caucasians (Veeranna *et al.* 2013). Therefore, it seems inevitable to create ethnic-specific cut-off points in order to detect high-risk individuals for risk stratification. Although it has been demonstrated that these biomarkers retain their predictive value in Chinese cohorts despite their lower values, clear cut-off points are not known and should be further investigated. Also it is a matter of debate whether patients with lower values (e.g. LDL, CRP) would still benefit from treatment with anti-inflammatory agents or statins. For example, it seems that Asian patients are likely to benefit from lowering LDL by statins despite their lower values (Sakamoto and Ogawa 2010). However, the threshold for treatment initiation and targets for treatment follow-up are possibly lower than for Caucasians. These thresholds and targets need to be determined in future studies as well.

With regard to our findings in the lipid profile, marked differences were found between Chinese and Caucasians during follow-up. Overall, except for HDL, average mean levels of LDL and total cholesterol were significantly lower in Chinese than Caucasian patients. Differences in lipid profile among ethnic groups have been described by previous studies before and are in accordance with our results (Goff *et al.* 2006, Frank *et al.* 2014). Especially Chinese have been pointed out to possess a favourable lipid profile (Anand *et al.* 2000). An analysis from the INTERHEART study obtained one non-fasting blood sample from 5731 myocardial infarction patients and 6469 non-cardiac patients to investigate lipid abnormalities among Asian subgroups (Karthikeyan *et al.* 2009). In particular, among the various Asian subgroups, Chinese patients tended to have the lowest LDL levels, but not HDL.

Further, our study showed that on the long run TnT and NT-proBNP levels varied in a similar range in the two cohorts and were not different from each other. This is in contrast to recent findings from the Multi-Ethnic Study of Atherosclerosis, where it has been demonstrated that

Chinese individuals possessed the lowest NT-proBNP levels based upon genetics (Gupta *et al.* 2017). However, this study included asymptomatic individuals without prevalent cardiovascular disease and only a small proportion consisted of Chinese individuals (13%), in whom NT-proBNP levels were measured once at baseline. Further, ethnicity was self-reported, which may have resulted in misclassification. Altogether, the discrepancy with our findings could have been due to a different study population and design.

Lastly, remarkable differences regarding CRP in our study were present. The fact that Chinese patients had sustainably lower levels of CRP than Caucasians in our study is in accordance with existing evidence on CRP in various ethnic groups (Lakoski *et al.* 2006, Saito *et al.* 2007, Kelley-Hedgepeth *et al.* 2008, Saito *et al.* 2014, Sung *et al.* 2014). The underlying pathophysiological mechanism for lower CRP levels in Chinese individuals is unknown, but is speculated to be based upon differences in body mass index and genetics (Kelley-Hedgepeth *et al.* 2008, Saito *et al.* 2014). Nevertheless, despite lower CRP levels, they still independently predict cardiovascular as well as all-cause mortality in Asian populations (Saito *et al.* 2014, Sung *et al.* 2014).

Our study has several limitations. Firstly, due to border law regulations, blood samples could not be shipped from China and therefore needed to be analysed in two separate laboratories. Thus, some amount of analytical variation differences was unavoidable and might have influenced our results. Secondly, with regard to our findings in the lipid profile, we accounted for differences in prevalence of statin use between BIOMArCS-Caucasians and PRoMISS-Chinese in the analysis, but we had no data on the (dynamic changes in) statin dosage. Nevertheless, from empiric data it is most likely that Caucasian patients were prescribed more often high-intensity statin therapy than Chinese patients, which emphasizes the importance of the observed differences in lipid values even more. Furthermore, we do not have specific information on the 'clinical phenotype' of our studied patients, such as left ventricular ejection fraction, infarct size and severity of vessel disease, which might be confounders of the observed biomarker differences between the cohorts. However, by matching on clinical characteristics and admission diagnosis, we tried to limit this type of confounding. Another important limitation is the lack of information on genetic and environmental factors, since the observed differences could partly be due to divergent genetic makeup and different lifestyle (e.g. dietary factors, physical activity). Lastly, blood samples were not fasting samples. Nevertheless, HDL, LDL and total cholesterol are recognized as being relatively unaffected by the non-fasting state. Also, a non-fasting state reflects a state in which patients often present in the hospital and thus mimics clinical practice.

Conclusion

Frequent blood sampling during 1 year post ACS enabled us to reveal that most conventional biomarkers were remarkably lower in diabetic CAD participants from Chinese than Caucasian origin. This could give more insight into blood biomarker related differences among ethnic groups and might serve as a reference pilot study for larger future CAD studies. Our findings underscore the fact that it may not be convenient to apply findings from most Western cohorts to Chinese individuals. In order to provide accurate risk stratification for prediction and treatment benefit, further research should focus on defining clear cut-off values in primary and secondary prevention for each specific ethnic group.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Martijn Akkerhuis http://orcid.org/0000-0003-4833-3130
Eric Boersma http://orcid.org/0000-0002-2559-7128

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