Developing the utility of blood biomarker associations beyond population sample linkage to events in cardiovascular patients

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This editorial refers to ‘The value of N-terminal fragment of brain natriuretic peptide and tissue inhibitor of metalloproteinase-1 levels as predictors of cardiovascular outcome in the LIPID study’ by M.J. West et al., on page 923

West et al. report a small, well designed post hoc nested case–control sample from the LIPID trial of pravastatin. This was completed in low risk subjects with documented coronary disease in the form of a previous confirmed acute coronary syndrome (ACS). This additional report examines biomarker linkage over a relatively short time frame of 2–3 years and highlights two measurements perhaps not intuitively linked to the biology of coronary disease progression. The conditional logistic regression analysis shows a significant linkage association following point analysis for N-terminal brain natriuretic peptide (NT-BNP) and tissue metalloproteinase-1 (TIMP-1). TIMP-1 has been linked to cardiovascular events in low risk patients previously, in patients with less well confirmed coronary disease. Its re-affirmation here as a population predictor of events in this group of patients is of value. Similarly for NT-BNP, which is frequently presumed to be linked to cardiac events largely via the presence of association with ventricular dilatation, remodelling, or ventricular ‘dysfunction’ (not factors intuitively present even in patients with a confirmed yet uncomplicated ACS), this is not the first report to link it to coronary outcomes even in the absence of overt ventricular impairment. More interestingly, in this report there was a significant linkage expressed by both markers to subsequent emergent stroke disease. Both NT-BNP (indirectly) and TIMP-1 (directly) can be linked, at least theoretically, to structural change within the heart, be it myocytic, functional (i.e. linked to dynamic contractile changes), geometric (fixed changes in cardiac shape or wall thickness), or within the connective tissue support structure. Both are of course linked in the biology of hypertension and/or hypertensive heart disease and vascular atherosclerosis, but this and other conventional risk factors were clearly accounted for in the analysis of West et al. These authors were concerned to address the apparent lack of statistical association seen with high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) in this study. These are well described and useful biomarkers, but may simply not be sensitive or specific enough to stand out using this form of analysis (the number, frequency, or timing of sampling in a multicentre trial) or in this sample (in this number of patients, with this level of disease risk, and at this stage in the evolution of atherosclerosis).

As here for the LIPID study, most large-scale clinical trials collect large numbers of blood samples taken as a protocol routine. The subsequent analyses conducted are published as valid secondary end-points that give a degree of useful, if limited, information. However, in the setting of multicentre trials, the analyte selected for the population sample studied is not directed at new underlying biology. This is understandable as the blood biomarker is often not the primary goal of the study. In many instances, despite large numbers of repeated visits, the biomarker data reported are often a single measure in a subset of the trial population.

The association of both NT-BNP and TIMP-1 with the pathology of atherosclerosis is not in doubt. As in the report of West et al., the statistically significant population associations of biomarkers that are demonstrable will vary dependent on the clinical patient sample and the point of analysis. This is because the evolution of disease and its controlling or mediating factors (which many biomarkers represent) are not likely to be either linear or a static hierarchy (with different factors dominating disease progression at different times in individual patients). In turn the selected biomarker (or physical biometry for that matter) will indicate predominantly one aspect of the biology of disease progression (e.g. for TIMP-1 the connective tissue composition and turnover of blood vessels or myocardium). In addition, the accuracy of...
blood biomarker estimates is dependent on variance attributable to both the biology and the analytical technique, sampling density, storage, and the stage of the disease at the time of sampling.11 The accuracy of a physical biomeasurement will be operator and technique dependent.

Currently routine management of acute and chronic disease is traditionally defined by symptomatic assessment, physical examination, and, for some cardiovascular states, intermittent physical measurements. These processes are clearly operator dependent, relying on an accurately obtained and truthful symptomatic enquiry, and skill in physical examination and/or technical biomeasurement and their interpretation in individual circumstances (such as blood pressure, echocardiography; electrocardiography; angiographic or other imaging technologies, etc.). Currently the most obvious area where blood biomarker measurement has revolutionized standards of definition of disease and fundamentally altered patterns of cardiovascular care would be in the clarification and redefinition of treatment in ACS.13 Previously defined by relatively insensitive and non-specific symptomatic scoring, cardiac troponin measurements have revolutionized the recognition of and provided targeting for the accelerated management of coronary disease. However, the interpretation and application of biomarker and/or physical biomeasurements by repeat measures within an individual are now needed to move this technology beyond linkage analysis and implication in the general processes of pathobiology.

Many valid studies similar to that of West et al.5 reaffirm previously documented biomarker associations but they do not develop new ideas or test new hypotheses. The ability to take these data forward in a practical clinical setting is dependent on the application of repeated measures within individuals, which could potentially define clinical stability and/or allow anticipation of specific clinical events.13 As above, the biomarker (or biomarkers) selected, their sampling frame (both patient and disease state), the technology of measurement, and the pathobiology of disease progression would determine the events predicted. Biomarker selection should be based on a specific target, either an aetiological feature or a prognostic feature. Thus, for example in left ventricular systolic dysfunction (LVSD), one biomarker might express appropriate sensitivity and specificity for the presence and/or progression of ischaemia, whereas a completely different biomarker might illustrate myocyte remodelling, and another might illustrate fluid or volume loading of the heart. It is of interest that traditional mediators of events in LVSD such as norepinephrine, angiotensin II, aldosterone, or renin have rarely been linked to individual circumstances and even more rarely measured serially within individual patients. In the same way, if we integrate these data forward in a practical clinical setting is dependent on the correct interpretation of the change in levels that it might indicate (whether this is a relative increase, relative decrease, or altered intra-subject variance). The change of course is within the individual subject. Finally, we must ensure and test that such systems perform better than the conventional standard using realistic operators (neither individuals with unmatched skill, nor practitioners who pay scant attention to clinical presentation and examination). This is a new and exciting challenge stemming from population research findings such as those summarized by West et al., but importantly extends their impact to the management of individual patients. This holds greater potential for rewards for the considerable research effort by many multicentre trial groups. Finally this application of relevant biomarker technology can be used in many aspects of medical care and not simply cardiovascular disease, far less coronary disease alone.

Conflict of interest: none declared.

References


6. Orn S, Manhenke C, Squire IB, Ng L, Anand I, Dickstein K. Plasma MMP-2, MMP-9 and N-BNP in long-term survivors following
A dangerous bridge: myocardial infarction due to myocardial bridging in left ventricular hypertrophy

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A 63-year-old woman with a history of hypertension presented to the coronary care unit with a subacute anterior wall myocardial infarction (PM). She reported initial left-sided chest pain, dyspnoea, and weakness 18 h before hospital admission, during a long-distance ride in a rental car, without prior exercise. The initial electrocardiogram (Panel C) revealed normal sinus rhythm, left axis deviation, left anterior hemiblock, inversion of the terminal T-waves in the anteroseptal leads, ST-segment-depression in I, aVL, V5–V6, ST-segment-elevation in III and aVR, and obvious signs of marked left ventricular hypertrophy. Serum chemistry revealed elevated levels of cardiac troponin T (1.02 μg/L), creatine kinase (938 IU/L), and lactate dehydrogenase (348 IU/L), also suggestive for a subacute MI. In view of these diagnostic findings, the patient was referred for emergency cardiac catheterization, after receiving aspirin, heparin, a loading-dose of clopidogrel, and a beta-blocker.

Left ventricular angiography demonstrated a moderately depressed left ventricular systolic function with akinesis of the anterolateral and apical anterior wall (Panels A and B). The left ventricular end-diastolic pressure was mildly increased (18–20 mmHg). Coronary angiography exhibited ‘corkscrew appearance’ of all coronary arteries without significant atherosclerosis. Furthermore, myocardial bridging in the distal segment of the left anterior descending (LAD) artery (Panel D) with total systolic compression and almost complete resolution in the diastole was present. The left ventricular end-diastolic pressure was mildly increased (18–20 mmHg). Coronary angiography exhibited ‘corkscrew appearance’ of all coronary arteries without significant atherosclerosis. Furthermore, myocardial bridging in the distal segment of the left anterior descending (LAD) artery (Panel D) with total systolic compression and almost complete resolution in the diastole was present. There was normal antegrade flow (TIMI III) in the LAD distal to the bridging segment without evidence of thrombus. Because of the primarily benign prognosis of myocardial bridging, we decided upon a conservative treatment. The patient was discharged after an uncomplicated hospital course with a medication comprising a beta-blocker, a calcium antagonist, an ACE-inhibitor, and aspirin.

The present case illustrates that MI may be a specific complication of myocardial bridging. Particularly, the presence of left ventricular hypertrophy, additional catecholaminergic triggers, and/or increased thrombocyte activation, may contribute to the genesis of ischaemia in this predominantly angiographic diagnosis of a congenital coronary abnormality.

Panel A. End-diastolic left ventricular angiogram and angiogram of the left coronary artery in RAO 45° and LAO 90°.
Panel B. End-systolic left ventricular angiogram and angiogram of the left coronary artery in RAO 45° and LAO 90°. Compression of the distal LAD with total disappearance (arrows) in the systole.
Panel C. 12-channel-surface-ECG on admission, exhibiting a suscuate anterior MI in the presence of left ventricular hypertrophy.