Table 1. Median Plasma Levels of Thrombin-Antithrombin Complex and of Prothrombin Fragment 1+2 in the Aspirin Plus Clopidogrel and Aspirin-Alone Groups

Hours After Stopping Enoxaparin	TAT (μg/l)							F_{1+2} (nmol/l)						
	−12	0	3	6	12	24	48	−12	0	3	6	12	24	48
Aspirin alone	4.6	4.1	6.8	6.7*	16.3†	17.0*	10.4	0.94	0.80	0.88*	0.97†	1.08†	1.14†	0.89
Aspirin plus clopidogrel	3.9	6.9	4.7	6.4	6.3	8.8	3.5	0.76	0.86	0.92*	0.98*	1.00*	1.34†	0.85

The p values are calculated in comparison to baseline (time 0) levels. Hour 0: 12 h after last enoxaparin dose. *$p < 0.05$. †$p < 0.01$.
F_{1+2} = prothrombin fragment 1+2; TAT = thrombin-antithrombin complex.

In the current study, the thrombin generation marker F1+2 in the clopidogrel group increased up to 24 h, whereas TAT, a marker of thrombin activity, remained stable. An explanation might be that clopidogrel could affect proteins that bind thrombin, such as thrombomodulin or protease-activated receptors, thus influencing the levels of circulating TAT.

In conclusion, rebound coagulation activity as reflected by increasing thrombin generation occurs within hours after discontinuation of low-molecular-weight heparin treatment. Clopidogrel reduces this reactivation, and this might partially account for the overall clinical benefits observed when adding clopidogrel to aspirin treatment in ACS patients.

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Letters to the Editor

Pregnancy-Associated Plasma Protein-A and Acute Coronary Syndromes: Cause or Consequence?

Heeschen et al. (1) report an approximately two-fold risk of death and myocardial infarction (MI) at 1 and 6 months linked with pregnancy-associated plasma protein-A (PAPP-A) >12.6 mIU/l among patients admitted for acute coronary syndromes (ACS), even with normal troponin levels. The investigators hypothesize plaque proteolysis by PAPP-A and harmful activation of insulin-like growth factor-1 (IGF-1) through PAPP-A's lysis of IGF-binding proteins. We propose an alternative view.

Extracellular matrix degradation by PAPP-A, to our knowledge, has never been documented. Moreover, IGF-1 exerts broad cardiovascular protection, through insulin-sensitizing, nitric oxide–mediated, antiapoptotic, regenerative, preconditioning, and anti-inflammatory effects (2). How, then, can two apparently divergent properties (predictor of risk for PAPP-A and vasculoprotective for IGF-1) be reconciled?

Hypoxic/oxidative/inflammatory stress enhances PAPP-A's bioactivity (2–4). Circulating PAPP-A levels are increased in ACS patients (1,4) and correlate (although not in all studies) with indices of inflammation and myocardial damage (1,2,4). Experimental damage raises local PAPP-A expression and IGF-1 bioactivity (2,4) with immunomodulatory and anti-inflammatory actions (4,5). During pregnancy, plasma PAPP-A is increased over 150-fold, with no parallel increase in ischemic risk; rather, reduced PAPP-A predicts adverse outcomes (6). These data suggest that PAPP-A is involved in physiological repair and replicative programs through its product, namely free IGF-1 (2–4).

Another circulating biomarker, B-type natriuretic peptide (BNP), is cardioprotective and secreted in proportion to the extent

of ischemia. Elevated levels powerfully predict adverse events in patients with coronary syndromes (7). Intravenous BNP (nesiritide) is of proven benefit in managing cardiac patients.

Raised PAPP-A and BNP levels may be part of endogenous compensatory pathways aimed at tissue salvage and repair. We believe they strongly predict adverse outcomes because they are sensitive signals of damage, without necessarily causing it.

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REPLY

We thank Dr. Conti and colleagues for their interesting contribution regarding our recent study on the predictive value of pregnancy-associated plasma protein-A (PAPP-A) in patients with acute coronary syndromes (ACS) (1). As stated in the discussion section of our report, the exact role of PAPP-A in the pathophysiology in ACS still remains illusive. In this context, we could only speculate about the putative role of the metalloproteinase (MMP) PAPP-A in the setting of atherosclerotic plaque destabilization, which may lead to clinical manifestation as an ACS. We completely agree with Dr. Conti and colleagues that no data are currently available directly demonstrating that PAPP-A per se leads to degradation of extracellular matrix. However, because matrix degradation has been shown for other MMPs, it is quite reasonable to assume that PAPP-A may also act at least in part through a similar mechanism.

Of note, release and subsequent activation of insulin-like growth factor-1 (IGF-1), a potential protective factor in the cardiovascular system, through PAPP-A activation may indeed represent an alternative mechanism as suggested by Conti et al. (2). Although this potential mechanism proposed by Dr. Conti and co-workers is similarly reasonable and appealing, there is also no definitive evidence that this is the most relevant mechanism of action of PAPP-A in the setting of an ACS. Unfortunately, we can neither support nor disprove the researchers' hypothesis as we did not have a chance to measure IGF-1 levels in our study populations. Actually, it would not seem to be appropriate to draw mechanistic conclusions from this kind of clinical study. Circulating levels of biomarkers such as PAPP-A only represent the integral of PAPP-A generation as well as degradation in patients with ACS, but these studies alone cannot provide any hint on the source and the mode of action of PAPP-A in unstable atherosclerotic plaques, respectively. Thus, one should be very cautious in drawing any definite mechanistic conclusions from the levels of circulating biomarkers in any disease. Apparently, further experimental studies are truly needed to prove the exact role and mechanism of PAPP-A in atherosclerosis and its complications.

In summary, we aimed in our study to place the biomarker PAPP-A into the context of inflammation and matrix degradation as this view is supported by the current literature (3–5). Independent of the actual mechanism by which PAPP-A may contribute to plaque destabilization and/or plaque healing, however, PAPP-A remains an independent and powerful predictor for adverse events in patients with ACS and, thus, deserves further investigation regarding its clinical utility as a diagnostic biomarker.

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