aggregates (MPA) assessed by flow cytometry. MPA have been proven a robust and reproducible in vivo marker of platelet activation (5), even in the clinical setting (5), and could have been used in order to assess more accurately the extend of platelet reactivity and to understand the role of platelet function, and more than that, the role of antiplatelet therapy.

In conclusion, a number of factors should be taken into consideration before establishing a connection between CAP, platelet activation, and MI. Platelets' pathophysiological interplay between inflammation and thrombosis suggested by in vitro studies needs to be further investigated in well-designed clinical studies with robust platelet activation markers.

Eleni Gavrilaki, MD, MSc
*Eugenia Gkaliagkousi, MD, PhD
Stella Douma, MD
*Hippokration General Hospital
54643 Thessaloniki
Greece
E-mail: eugalant@yahoo.com
http://dx.doi.org/10.1016/j.jacc.2014.11.073

REFERENCES


Platelet Activation and Myocardial Infarction in Patients With Pneumonia

Are Statins the Answer?

In this population-based cohort study, Cangemi et al. (1) found that increased platelet activation and thromboxane overproduction was associated with myocardial infarction in patients with pneumonia. Moreover, they also suggested that aspirin alone was insufficient to inhibit thromboxane production. Although, the study is observational in nature, it adds to already accumulated evidence that suggests increased cardiovascular events with infection and sepsis (2). Statins with their anti-inflammatory and antithrombotic effects may play a role in the treatment of pneumonia and prevent associated cardiovascular complications. Statins have been shown, not only to inhibit thromboxane synthesis (3), but to also do so in case of incomplete inhibition by aspirin (4). Statins also decrease P-selectin and soluble CD40 ligand, both of which play a role in atherosclerosis and consequent cardiovascular events. Epidemiological evidence has shown a beneficial effect in the treatment of pneumonia (5). However, the available evidence is weak because it is based on observational design. Given the biological plausibility of the association, randomized controlled trials are needed to define the role of statins in the treatment of pneumonia and its associated cardiovascular complications.

*Abdur Rahman Khan, MD
Aref A. Bin Abdulhak, MD
Faraz Khan Luni, MD
Ragheb Assaly, MD
*Department of Internal Medicine
University of Toledo
Health Sciences Campus
3000 Arlington Avenue
Toledo, Ohio 43614
E-mail: abdur.khan@utoledo.edu
http://dx.doi.org/10.1016/j.jacc.2014.11.074

REFERENCES


REPLY: Platelets Interplay Between Pneumonia and Cardiovascular Events
Establishing a Link?
Platelet Activation and Myocardial Infarction in Patients With Pneumonia
Are Statins the Answer?

We thank Dr. Gavrillaki and colleagues for the comments related to our recent paper (1) demonstrating a significant association between in vivo platelet activation and myocardial infarction (MI) in 278 patients affected by community-acquired pneumonia (CAP) and suggesting a potential role for platelets in precipitating coronary ischemia.

Dr. Gavrillaki and colleagues raise some issues that need to be addressed. The authors question the putative interplay between infections and MI overall because interventional trials with antibiotics failed to show a reduction of MI. However, trials with antibiotics have serious clinical and methodological limitations regarding dosages of the antibiotics, wide variation in sample size and follow-up, and limited use of antibiotics (essentially macrolides and fluoroquinolone) (2). Furthermore, interventional trials with antibiotics have been performed in patients with stable or acute coronary heart disease on the assumption that microorganisms, in particular Chlamydia pneumoniae, are implicated in atherosclerosis initiation and progression (2).

Hence, it is methodologically inappropriate to extrapolate from these findings that infections cannot precipitate MI because these clinical settings are different in terms of clinical course, concomitant treatment, and very likely, mechanism of disease from CAP-related MI. In this context, it is clinically relevant that pneumonia severity score was a strong predictor of MI, indicating that the severity of infection and/or inflammation plays a key role in favoring myocardial ischemia. Platelet activation may be one mechanism through which CAP precipitates MI via a process of coronary thrombosis and/or vasoconstriction. We don’t have conclusive data on this issue, but it is interesting to underscore that most patients with CAP disclosed non-ST-segment elevation MI, indicating that type II MI and, therefore, coronary vasoconstriction might have an important role in favoring myocardial ischemia. We agree with the authors that the concomitant presence of cardiovascular disease or atherosclerotic risk factors could account for platelet activation detected at admission, but its significant reduction, observed at discharge, points to a role of CAP in favoring platelet activation. The mechanism(s) accounting for CAP-related platelet activation were not investigated in the study and consequently may be only a matter of speculation. Analysis of more sophisticated markers of platelet activation will certainly help to provide more insight into the role of platelets as a determinant of myocardial ischemia in pneumonia. However, we believe that at this moment, it is more crucial to know whether platelet activation represents a mere epiphenomenon of CAP or has a role in triggering coronary thrombosis and/or vasoconstriction. Thus, interventional trials with aspirin or other antiplatelet drugs could be of interest to investigate whether platelets actually have a role in precipitating MI in patients with pneumonia.

Interestingly, Dr. Khan and colleagues, in their letter, suggest that statins may be an intriguing alternative because they possess antiplatelet activity, and a recent meta-analysis demonstrated a potential role of statins in reducing CAP-related mortality (3). We agree with this hypothesis because statins disclose an early and late antiplatelet effect, which is mediated by down-regulation of Nox2-derived oxidative stress and lipid-lowering activity, respectively (4). Nox2 down-regulation may be of interest because in patients with CAP Nox2, the most important cellular producer of oxygen free radicals, is up-regulated and associated with myocardial damage and ischemia (5). Furthermore, statins amplify the platelet response to aspirin by reducing platelet eicosanoid formation, namely isoprostanes and thromboxane A2, and could, in turn, be useful in case of incomplete COX1 inhibition by aspirin (4). Hence, statins may be tested as an alternative to aspirin or on top of aspirin to assess whether they are able to reduce cardiac complications in patients with CAP.

*Francesco Violi, MD
Camilla Calvieri, MD
Marco Falcone, MD
Gloria Taliani, MD
Roberto Cangemi, MD
on behalf of the SIXTUS Study Group