Community-acquired pneumonia: Pathogenesis of acute cardiac events and potential adjunctive therapies

Charles Feldman\textsuperscript{1} MB BCh, DSc, Ronald Anderson\textsuperscript{2} PhD

\textsuperscript{1}Division of Pulmonology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

\textsuperscript{2}Institute of Cellular and Molecular medicine, Department of Immunology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

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Corresponding author: Charles Feldman
Department of Internal Medicine
University of the Witwatersrand Medical School
7 York Road, Parktown, 2193
Johannesburg
South Africa
Email: charles.feldman@wits.ac.za

ABSTRACT

Despite advances in antimicrobial chemotherapy and access to sophisticated intensive care facilities, bacterial community-acquired pneumonia (CAP) continues to carry an unacceptably high mortality rate of 10-15\% in hospitalized cases. CAP, considered by many to be the most under-estimated disease worldwide, poses a particular threat to the elderly whose numbers are steadily increasing in developed countries. Indeed elderly patients with severe CAP, as well as those with other risk
factors, are at significant risk for development of inflammation-mediated acute cardiac events which may undermine the success of antimicrobial therapy. Adjunctive anti-inflammatory strategies are therefore of considerable potential benefit in this setting. Currently, the most promising of these are the macrolides, corticosteroids, and, more recently, statins, all of which target immune/inflammatory cells. In addition, recent insights into the immunopathogenesis of acute coronary events in patients with CAP have revealed a probable pivotal role of platelet activation, potentially modifiable by agents which possess anti-inflammatory and/or platelet-targeted activities. Statins, which not only possess anti-inflammatory activity, but which also appear to target several pathways involved in platelet activation, seem particularly well-suited as adjuncts to antibiotic therapy in bacterial CAP. Following a brief consideration of the immunopathogenesis of bacterial CAP, this review is focused on mechanisms of platelet activation by CAP pathogens, as well as the pharmacological control thereof, with emphasis on statins.

INTRODUCTION

Despite years of intensive investigation into various aspects of the infection, as well as substantial advances in medical and nursing care, including the development of potent antimicrobial chemotherapy, and the establishment of intensive care unit facilities, community-acquired pneumonia (CAP) continues to cause considerable morbidity and mortality worldwide.\textsuperscript{1,2} The use of adjunctive therapy, with agents that target diverse or specific components of disease pathogenesis represents a potential strategy to improve the poor outcome.\textsuperscript{1-4} To this end, various adjunctive therapies have been investigated, many of them proving rather disappointing. One area of re-emerging research interest in patients with CAP, first described in 1993,\textsuperscript{5} is the occurrence of cardiac complications, which may be the primary cause of treatment failure and are recognized to be associated with a worse prognosis.\textsuperscript{6,7} This review will describe pathogenic mechanisms in CAP, highlighting aspects that relate to cardiac complications and their mechanisms, as well as identifying potential adjunctive therapies targeting them.
PATHOGENESIS OF CAP

The three most common causes of bacterial CAP are *Streptococcus pneumoniae* (the pneumococcus), *Haemophilus influenzae* and *Moraxella catarrhalis*. Collectively, these organisms account for >80% of cases of CAP, the pneumococcus being the predominant cause (>60% of cases). Colonization of the upper airways by these organisms is mediated via the interaction of bacterial surface adhesins with respiratory epithelium which is a prerequisite for development of invasive disease. During this phase, the organisms co-exist with the host, kept in check by host defenses and/or concealment in biofilm.¹

The transition of these airway colonists to menacing pathogens can be triggered by various events including:

- genotypic modifications leading to a more virulent phenotype
- transmission to a suitably vulnerable, immunocompromised host
- development by the host of an acute or chronic immunosuppressive viral infection.

The CAP pathogens utilize a range of predominantly protein virulence factors, to subvert innate and adaptive pulmonary host defenses, promoting invasion of the lower airways, as well as persistence and extra-pulmonary dissemination in severe disease.¹

Containment of the infection until implementation of effective antimicrobial therapy is dependent on the efficacy of innate pulmonary host defenses. Notwithstanding non-specific airway and infiltrating opsonins, these include various families of pattern recognition receptors (PRRs) present in/on airway cells of the innate immune system (macrophages, dendritic cells, natural killer cells, mast cells), as well as epithelial cells. Well-characterized PRR families which recognize molecular structures common to
Figure 1: The pathogenesis of bacterial CAP. The transition of CAP pathogens (purple circles in nasal passage and lungs) from quiescent colonists to an aggressive phenotype enables invasion of the lower airways. Interaction of bacterial cell-wall and intracellular components (lipoteichoic acid, peptidoglycan, nucleic acids, pneumolysin and other pore-forming toxins) with pattern recognition receptors (T) in/on resident cells of the pulmonary innate immune system (in this case macrophages, indicated by Mφ) leads to activation of latent cytosolic transcription factors including, but not limited to, nuclear factor kappa B (NFκB). Nuclear translocation of the activated transcription factors results in the induction of genes encoding various pro-inflammatory cytokines/chemokines (IL-1β, IL-6, IL-8, IL-17, IL-18, TNF). These, in turn, promote localized activation of vascular endothelium and presentation of chemoattractants enabling the transendothelial migration (TEM) of monocytes (M) and neutrophils (N), as well as exudation of pro-inflammatory complement proteins and acute phase reactants. Recruitment of these mobilizable, systemic elements of the innate immune system reinforces pulmonary host defenses. However, prolonged and misdirected inflammatory responses may intensify pulmonary damage via the excessive release of indiscriminate phagocyte-derived reactive oxygen species and proteases acting in tandem with microbial cytotoxins; these mechanisms may also favor the extrapulmonary dissemination of CAP pathogens and pro-inflammatory cytokines/chemokines resulting in a systemic inflammatory response with accompanying endothelial dysfunction and resultant exposure/release of factor VII, tissue factor, Von Willebrand factor, and sub-endothelial collagen, creating a pro-coagulant state.
microbial and viral pathogens, include: i) the Toll-like receptors (TLRs) and nucleotide
oligomerization domain-like receptors (NLRs) of which there are at least 11 and 22
members respectively; ii) the inflammasomes, such as NLPR3, a subset of NLRs; and
iii) the abundant cytosolic microbial and viral nucleic acid sensors.\textsuperscript{8,9}

However, should these mechanisms be overcome by CAP organisms, the
resultant sustained and ineffective pulmonary inflammatory response, in concert with
bacterial toxins, predisposes to acute respiratory distress syndrome/acute lung injury.
These events in turn also promote extrapulmonary dissemination of the pathogens and
their pro-inflammatory products leading to a systemic inflammatory response with
accompanying endothelial dysfunction and a pro-coagulant state. The consequences
include the potential for the development of acute coronary events, as discussed more
fully below, as well as septic shock and multiorgan dysfunction syndrome.\textsuperscript{1} A generic
scheme summarizing these mechanisms is shown in Figure 1.

**CAP, ACUTE CARDIAC EVENTS AND PLATELET ACTIVATION**

With respect to CAP-associated cardiovascular disorders, the increased risk for
cardiac events in hospitalized patients may be as high as 8-fold in the 15 day period
following admission, and greatest (100-fold increased risk) within the first 2 – 3 days.\textsuperscript{6}
Incident cardiac complications associated with increased morbidity and mortality include
myocardial infarction (MI, predominantly silent) and new or worsening heart failure or
arrhythmias, with the major risk factors being older age, nursing home residence, pre-
existing chronic respiratory or cardiovascular conditions, severity of CAP, and
smoking.\textsuperscript{6,7}

In addition to the mechanisms described above, a recent study by Cangemi et al.
has implicated direct effects of CAP pathogens on platelet activation in the
pathogenesis of myocardial infarction, providing insights into potential adjunctive anti-
thrombotic strategies.\textsuperscript{10} Although the underlying mechanisms of platelet activation in
CAP and a causative link with CVD and cerebrovascular disease remain to be conclusively established, several possibilities exist, specifically in relation to bacterial CAP. These include:

- **direct interaction of bacteria with TLRs expressed in/on platelets, specifically TLR2 and TLR4 which recognize Gram-positive cell-wall lipoteichoic acid/peptidoglycan** and Gram-negative endotoxin respectively. The consequence is activation of the fibrinogen-binding integrin, GPIIb/IIIa (αIIbβ3), mobilization of α- and dense granules, and release of adenosine diphosphate (ADP) and production of thromboxane A₂ (TxA₂), both potent autocrine and paracrine activators of platelets via their interaction with P2Y12 purinergic and TxA₂ (TP) receptors respectively, both types being G-protein-coupled receptors (GPCR). The consequence is platelet aggregation and vasoconstriction.

- **amplification of platelet activation by several strains of bacteria belonging to the Staphylococcus and Streptococcus genera** may also result from their interaction with the platelet α-granule protein, platelet factor-4 (PF4, CXCL4), a pro-thrombotic, CXC chemokine which also possesses antibacterial activity. Pathogen-bound PF4 is recognized by circulating immunoglobulin G, forming a complex which binds to the platelet FcγRIIA receptor, potentiating GPIIb/IIIa activation by mechanisms which remain to be fully characterized, but appear to involve Src and Syk tyrosine kinases.

- **In rodent and murine models of experimental infection**, sustained infection with the pneumococcus has been found to trigger atherogenesis and worsen cerebral ischemia via an interleukin (IL)-1/glycoprotein (GP)Ibα-dependent mechanism, probably due to inflammasome activation, resulting in platelet activation and microvascular coagulation.

Additional mechanisms which may contribute to CAP-associated myocardial infarction include the heterotypic interactions of platelets with neutrophils and vascular
Figure 2: Proposed mechanisms of platelet activation in bacterial CAP. The interaction of bacterial pathogens (purple circles) or their liberated cell-wall components with Toll-like receptors (TLRs) 2 and 4 (represented by symbol T) on platelets (P) results in platelet activation. This, in turn, is characterized by generation of thromboxane A2 (TxA2) and mobilization of platelet intracellular granules resulting in release of stored adenosine diphosphate (ADP). TxA2 and ADP intensify platelet activation via their respective interactions with thromboxane TP and purinergic P2Y12 receptors. Platelet factor-4 (PF4), released via mobilization of intracellular granules, also contributes to platelet activation. This involves interaction of PF4 with CAP pathogens followed by binding of IgG to form a complex, which binds to the platelet FcyRIIA receptor, resulting in activation of the platelet integrin, GPIIb/IIIa (alpha IIb beta 3). In addition to activation of GPIIb/IIIa, these various mechanisms of platelet activation also result in upregulated expression/activation of various other platelet adhesion molecules (GPIba, P selectin, CD40L, ICAM-2) which promote homotypic and/or heterotypic platelet aggregation. In the case of the former, homotypic aggregation results in platelet plug formation. With respect to heterotypic aggregation, the binding of platelets to neutrophils intensifies neutrophil activation, causing binding to and damage of vascular endothelium, thereby potentiating platelet activation and thrombus formation via exposure of, and contact with sub-endothelial connective tissue. The inhibitory actions of statins on these processes are denoted by the intersecting double lines (\(=\)).
endothelium. Activated platelets form stable clusters around neutrophils, a phenomenon known as “satallitism,” involving multiple pro-adhesive mechanisms. These include interactions of P-selectin, CD40L, intercellular adhesion molecule-2 (ICAM-2) and GPIbα on platelets with their respective ligands on neutrophils (P-selectin GP ligand-1, CD40, and the β2-integrins CD11a/CD18 and CD11b/CD18). These interactions not only promote adhesion of neutrophils to activated vascular endothelium and trans-endothelial migration, but also sensitize the pro-oxidative and pro-inflammatory activities of these cells, predisposing to endothelial damage and dysfunction, potentially exacerbating microvascular coagulation. In addition, the presentation by activated platelets of the DNA-binding cytokine, high mobility group box 1 protein (HMGB1) to neutrophils has been reported to promote the formation of neutrophil extracellular traps, leading to further endothelial dysfunction due to histone-mediated damage and thrombin generation. These mechanisms of pathogen-associated platelet activation are shown in Figure 2.

ALTERNATIVE MECHANISMS OF CAP-ASSOCIATED CARDIAC EVENTS

Experimental studies in mice and macaques have revealed that invasive pneumococcal disease leads to translocation of the pneumococcus into the myocardium resulting in the formation of “unique microlesions that disrupt cardiac function.” Bacterial translocation into the heart and formation of microlesions were found to be dependent on the pneumococcal adhesin, choline-binding protein A (CbpA) and the cholesterol-binding, pore-forming cytotoxin, pneumolysin, respectively. In this context it is noteworthy that statin therapy of severe pneumococcal infection in a murine model of sickle cell disease was found to confer protection against the cytolytic actions of pneumolysin by apparent interference with toxin/membrane cholesterol interactions.

THERAPEUTIC IMPLICATIONS

Among the myriad of adjunctive therapies that have been studied, the three major options are the macrolides, corticosteroids and statins, all of which have been
documented to possess anti-inflammatory activities, targeting various cell types and their mediators, and, to a greater or lesser extent, to have antiplatelet effects.

**Macrolides**

The majority of the publications describing patient outcome with the use of macrolide-based antibiotic regimens have documented clinical benefit in patients with CAP, particularly in the more severely ill cases.\(^{24,25}\) Macrolides have been documented not only to possess adjunctive anti-inflammatory, immunomodulatory activity *in vitro*, but also to inhibit platelet-activating factor (PAF)-mediated platelet aggregation.\(^{26}\) Although these activities may underpin the benefits of these agents in the management of CAP, differentiating them from antimicrobial activity in the clinical setting is very difficult.\(^{7}\)

**Corticosteroids**

The evidence for corticosteroid adjunctive therapy has been less clear-cut, although recent meta-analyses and studies have shown benefit, particularly in the severe CAP subgroup, and especially in the presence of septic shock or with prolonged use of these agents.\(^{27-30}\) Two randomized placebo-controlled studies have recently been reported.\(^{31,32}\) The former study among hospitalized adults with CAP documented a shorter time to clinical stability in patients receiving adjunctive prednisone for 7 days.\(^{31}\) The latter study among patients with severe CAP and high initial inflammatory response (C-reactive protein > 150mg/l) documented less treatment failure with the use of adjunctive methylprednisolone therapy for 5 days.\(^{32}\) Another recent study, confirming several earlier reports of the use of prednisolone or methylprednisolone in children with complicated *Mycoplasma pneumoniae* pneumonia, documented rapid defervescence of infection in most children (86/90 cases) receiving one of these agents as adjunctive therapy.\(^{33}\) Interestingly, prednisolone, which appears to be the most effective corticosteroid in the adjunctive therapy of CAP, has been reported to inhibit platelet
activation in vitro by a non-genomic mechanism not shared with other types of corticosteroid.\textsuperscript{34}

Notwithstanding the fact that some patients who develop CAP may be taking long-term corticosteroids (e.g. inhaled corticosteroids) or macrolides, the studies evaluating the use of these agents as adjunctive therapy in CAP, have been done with the use of these agents as acute therapies.

**Statins**

The statins are lipid-lowering drugs used primarily for the prevention and treatment of cardiac conditions.\textsuperscript{35} They have a variety of well-characterized pleiotropic effects, including anti-inflammatory and immunomodulatory activities that may contribute to their effectiveness against cardiac disease.\textsuperscript{35,36} Many of these target various components of the pathways involved in the pathogenesis of CAP, including the cardiac complications.\textsuperscript{36,37}

These pleiotropic effects of statins occur primarily as a consequence of inhibition of activity of the enzyme, 3-hydroxy-3-methyl-glutaryl (HMG) CoA reductase, not only decreasing the synthesis of mevalonic acid and cholesterol, but also of isoprenoids. This latter activity, attenuates intracellular signaling mediated via the G\textsubscript{βγ} subunit of GPCRs via interference with isoprenylation of the Rac/Rho/Ras family of small GTP-binding proteins. Anti-inflammatory activities of statins mediated via interference with isoprenylation include inhibition of the pro-inflammatory transcription factor, nuclear factor kappa B (NFκB).\textsuperscript{38} and induction of transcription of the gene encoding the anti-oxidative enzyme, heme-oxygenase-1.\textsuperscript{39}

In addition, statins, via their cholesterol-lowering activity, have been reported to disrupt cholesterol-rich membrane lipid rafts with resultant impairment of intracellular signaling by other types of GPCR such as G\textsubscript{αi},\textsuperscript{40} as well as the lectin-like oxidized low-density lipoprotein-1-receptor, LOX-1,\textsuperscript{41} which are dependent on intact lipid rafts.
Statins, in addition to inhibitory effects on immune and inflammatory cells, have also been reported to suppress platelet activation by various mechanisms, which also appear to be largely attributable to inhibition of HMB-CoA reductase. The most well characterized of these include:

- decreasing the concentrations of proatherogenic oxLDL-C\textsuperscript{42} an inflammatory mediator which promotes platelet activation via interactions with the scavenger receptors LOX-1 and CD36, both of which are expressed on platelets,\textsuperscript{43,44} and possibly by decreasing scavenger receptor function (LOX-1) and expression (CD36)

- several mechanisms which suppress platelet activation / aggregation independently of cholesterol-lowering activity, specifically: i) increased production of the enzyme endothelial nitric oxide synthase (eNOS) by platelets; ii) inhibition of synthesis of TxA\textsubscript{2} secondary to decreased activity of phospholipase A\textsubscript{2}; and iii) decreased expression of pro-adhesive CD40L.\textsuperscript{42}

Table 1 summarizes the documented antiplatelet activities of statins, together with those of macrolides, corticosteroids and selective platelet-targeted agents, few of which have been evaluated in CAP.\textsuperscript{26,33,42,45-50} We are unaware of any clinically available selective PAF receptor antagonists. Although the activation of proteinase-activated receptor 1 (PAR1, thrombin activated), TxA\textsubscript{2} receptors (TP) and the purinergic receptor, P2Y\textsubscript{12} (ADP activated) is largely independent of isoprenylation, the requirement for cholesterol-rich membrane lipid rafts for optimal activity\textsuperscript{41} is consistent with possible modulation of these receptors by statins

\textbf{Clinical studies of statin use in patients with CAP}

With respect to clinical relevance, a recent systematic review evaluated the immunomodulatory effects seen with statin use in patients with CAP. Overall, 17 experimental studies and 17 clinical studies were included in the analysis.\textsuperscript{35} In the
**Table 1:** Pharmacological agents which suppress platelet activation most of which have not been evaluated in the clinical setting of CAP

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<th>Agent</th>
<th>Cellular target</th>
<th>Status</th>
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| Statins | - LOX-1/CD36 antagonism  
- Decreased expression of CD40L  
- NFκB inhibition  
- PLA₂ inhibition  
- eNOS enhancement  
- heme-oxygenase induction | Available clinically | 38-44 |
| Aspirin | Cyclooxygenase-1 inhibition  
NFκB inhibition | Available clinically | 45,46,48 |
| Vorapaxar | PAR-1 antagonism | Available clinically | 47 |
| Clopidogrel, prasugrel, ticagrelor | P2Y12 receptor antagonism | Available clinically | 48,49 |
| Eptifibatide, tirofiban | GPIIb/IIIa antagonism | Available clinically | 48 |
| Ozagrel | Thromboxane synthase (TS) inhibition | Limited availability; registered in Japan for asthma and stroke, as well as in China and South Korea | 45 |
| Ramatroban, Seretrodast | TP receptor antagonism | Limited availability; registered in Japan for asthma and rhinitis, as well as in China | 45 |
| Picotamide / EV-077 | Dual TS/TP receptor inhibition/antagonism | Picotamide is registered in Italy for peripheral vascular disease; EV-077 is in the advanced clinical trial stages of development for the treatment of vascular inflammation in diabetes mellitus and coronary artery disease | 45 |
| Prednisolone | Unknown, but believed to be non-genomic | Pre-clinical studies | 34 |
| Azithromycin, clarithromycin | PAF antagonism? | Pre-clinical studies | 26 |
| Fucosylated chondroitin sulfates | Adhesion molecule (L/P-selectin) antagonism | Pre-clinical studies | 50 |
experimental setting the findings were as follows: i) a reduction in release of pro-inflammatory chemokines and cytokines in patients with CAP, in both the pulmonary and systemic compartments; ii) a reduction in activation and recruitment of neutrophils to the lungs after injury to the lungs; and iii) protection of the host from lung injury associated with the lower respiratory tract infection by attenuation of disruption of the pulmonary vasculature. Evaluation of the clinical studies indicated the following: i) a decreased risk of pneumonia in individuals on statins was documented in most studies; and ii) current statin use was mostly associated with improved survival of pneumonia.

It is important to note, however, that most clinical studies with statins were done in the situation in which patients were currently taking these agents for their lipid-lowering and cardiovascular effects and their risk of acquiring CAP, and the effects of statin use on outcome, once CAP occurred, were compared to matched patients not taking statins. One exception appears to be a study in which the impact of statin administration on day 1 and 2 of hospital admission to patients with pneumonia resulted in a modest benefit on mortality in cases not admitted to the intensive care unit. These findings are consistent with a rapid onset of cardioprotective and anti-inflammatory action of statins, as reviewed previously. However, a second randomized, placebo-controlled study of statin administration to hospitalized patients with CAP failed to document either a clinical benefit, or a reduction in inflammatory cytokines at 48 hours.

With respect to case control and cohort studies, these have documented that current statin use was associated with a decreased risk of hospitalization for pneumonia and lower 30 day mortality, as well as lower mortality during the 6 month period following pneumonia. A retrospective cohort study documented that statin use was associated with decreased mortality in patients with pneumococcal pneumonia on days 7, 14, 20 and 30. Interestingly, in the latter study, mortality was not decreased in patients given a macrolide for therapy, nor in those on a macrolide as well as a statin compared with those not on a macrolide. One retrospective observational cohort study documented that patients who received a statin on day 1 or day 2 of hospital admission
for pneumonia had a moderate reduction in mortality among cases not admitted to the intensive care unit. 57

Three additional systematic reviews and meta-analyses have been published recently interrogating the potential benefit of statins in the prevention and/or mortality of CAP. 58-60 While all showed benefit in one or more of the endpoints, all three indicated the need for caution in the interpretation of the data due to a number of reasons, including low quality of evidence (observational study designs, heterogeneity, publication bias), weakening of the association in important subgroups accounting for patient differences (e.g. severity of illness, smoking and vaccination status) and in studies with greater methodological rigor, and substantial statistical and clinical heterogeneity. 58-60 Another consideration is the potential confounding that may be associated with the so-called “healthy user effect”, which suggests that statin users may be more health conscious than non-users and the clinical benefits seen may relate to a healthier lifestyle and greater compliance with both statin use and other preventative health measures rather than to the use of statins per se. 35

**Anti-platelet agents**

There is a paucity of definitive studies documenting the potential benefits of anti-platelet agents on CAP outcomes. 61 In the recent study by Cangemi et al. mentioned above, administration of aspirin at a dose of 100mg per day had no effect on either platelet activation or the occurrence of cardiovascular events in patients with pneumonia. 10 These authors suggest that the dose of aspirin they used may have been inadequate and propose that additional dose-ranging studies be undertaken. A single study of patients on prior clopidogrel therapy showed trends towards both an increased incidence of CAP, as well as a decrease in its severity, without controlling for aspirin use. 62

An integrated scheme of the likely sites of the therapeutic activities of statins and the other adjunctive therapies, as well as those of the selective antiplatelet agents listed in Table 1, is shown in Figure 3.
Figure 3: Integrated scheme showing the probable sites of the therapeutic activities of statins, macrolides, corticosteroids, and selective antiplatelet agents. This scheme shows the interactions between inflammation, platelet activation, and coagulation during severe CAP, indicating the proposed sites of action of the various adjunctive agents. See Figure 1 legend for expansion of abbreviation.
CONCLUSIONS

Despite all advances in medical care, patients with CAP still have considerable morbidity and mortality. It has been suggested that adjunctive therapy, with the addition of agents that target aspects of disease pathogenesis may be helpful in improving outcome and to this end a number of agents have been considered. Recent research indicating the relatively frequent occurrence of cardiac events in patients with CAP, that has been documented to be associated with a poorer prognosis, has heightened interest in the use of adjunctive therapies targeting this aspect of the disease pathogenesis. Notwithstanding the potential role of macrolides and corticosteroids, the most promising agents targeting these cardiac events are statins and selective inhibitors of platelet activation. Most of the studies with statins are, however, confounded by multiple methodological and statistical flaws, compounded by the possibility of a “healthy user effect”. Other aspects of statin use, as potential adjunctive therapy in CAP, that need clarification include identification of those statins with the best therapeutic efficacy, their role as an acute intervention in the setting of CAP, the optimal dose that is required, and the optimal duration of treatment to achieve these effects. While similar considerations also apply to all of the other adjunctive therapies described, there is a particular dearth of information regarding the selective anti-platelet agents with regard to their cardioprotective potential in the setting of CAP. Furthermore, future studies should also focus on combinations of the various adjunctive agents. All these questions are best answered by well-designed randomized controlled trials.

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