Does aspirin use prevent acute coronary syndrome in patients with pneumonia: multicenter prospective randomized trial

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Objectives **The aim of this study was to test the hypothesis that aspirin would reduce the risk for acute coronary syndromes (ACSs) in patients with pneumonia.**

Backgrounds **Pooled data suggest that pneumonia may trigger an ACS as a result of inflammatory reactions and the prothrombotic changes in patients with pneumonia. Hypothetically considering its antiaggregating and anti-inflammatory effects, aspirin might also be beneficial for the primary prevention of ACS in patients with pneumonia.**

Methods **One hundred and eighty-five patients with pneumonia who had more than one risk factor for cardiovascular disease were randomized to an aspirin group ($n=91$) or a control group ($n=94$). The patients in the aspirin group received 300 mg of aspirin daily for 1 month. ECGs were recorded on admission and 48 h and 30 days after admission to assess silent ischemia. The level of high-sensitivity cardiac troponin T was measured on admission and 48 h after admission. The primary endpoint was the development of ACS within 1 month. The secondary endpoints included cardiovascular death and death from any cause within 1 month.**

Results **The χ^2-test showed that the rates of ACS at 1 month were 1.1% ($n=1$) in the aspirin group and 10.6% ($n=10$) in the control group (relative risk, 0.103; 95% confidence interval 0.005–0.746; $P=0.015$). Aspirin therapy was associated with a 9% absolute reduction in the risk for ACS. There was no significant decrease in the risk of death from any cause ($P=0.151$), but the aspirin group had a decreased risk of cardiovascular death (risk reduction: 0.04, $P=0.044$).**

Conclusion **This randomized open-label study shows that acetyl salicylic acid is beneficial in the reduction of ACS and cardiovascular mortality among patients with pneumonia.** ***Coron Artery Dis*** **24:231–237** © **2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Acute coronary syndrome (ACS) is the leading cause of mortality and morbidity worldwide and refers to a spectrum of clinical presentations ranging from ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) to unstable angina pectoris (UAP) [1,2]. The early recognition and treatment of any condition potentially triggering ACS is therefore of high clinical relevance. In terms of pathophysiology, ACS is often associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery [3,4]. Several retrospective observational studies have shown that acute respiratory infection (ARI) is associated with the development of ACS [5–7]. In a recent prospective study, 7% of patients with pneumococcal pneumonia developed acute myocardial infarction (MI) [8]. ARI may lead to ACS by triggering severe, abrupt, inflammatory changes in coronary plaques over a few days to 2 months [9,10]. ARI can also be associated with coronary vasoconstriction and stimulate shear-induced platelet activity, which also increases the risk for thrombosis [11–13]. Further insight into the potential role of pneumonia in the pathophysiology of ACS may give rise to new strategies such as statin and aspirin use for the prevention of ACS in patients at an increased cardiovascular risk.

Although acetyl salicylic acid (ASA) has been a cornerstone in the treatment of ACS and secondary prevention strategies, its use in primary prevention remains controversial [14,15]. Hypothetically considering its antiaggregating and anti-inflammatory effects, aspirin might also be beneficial for the primary prevention of ACS

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during pneumonia. A retrospective observational study of patients with pneumonia showed that previous use of aspirin was associated with a nonsignificant reduction in mortality (37% risk reduction, $P = 0.45$) [16].

However, there are no prospective randomized clinical trials evaluating the efficacy of aspirin in preventing ACS in patients with pneumonia. To test this hypothesis, we evaluated the preventive effect of ASA administered to patients with pneumonia who had a moderate to high risk for cardiovascular disease (CVD).

Methods

The authors carried out a multicenter, prospective randomized study on patients admitted with community-acquired pneumonia (CAP) with radiological evidence and who had two or more risk factors for CVD. The centers that participated in this study were the Istanbul School of Medicine, Yedikule Chest Disease Training and Research Hospital, Istanbul Sureyyapasa Training and Research Hospital, Diyarbakır School of Medicine, Erciyes School of Medicine, and Afyon Kocatepe School of Medicine. The study was carried out between September 2011 and June 2012 and was approved by the local ethics committees. All patients provided informed consent.

Patients were included if there was a diagnosis of CAP at admission with radiological evidence from chest radiographs or computed tomography and at least two risk factors for CVD. The exclusion criteria were immune suppression, a glomerular filtration rate of less than 60 ml/min according to the CockCroft-Gault formula, presence of congestive heart failure or a history of coronary artery disease, any contraindication to aspirin use, and active malignancy.

Because there is no existing study on this subject, we could not carry out power analysis before this study was conducted. However, post-hoc analysis showed that with this sample size ($n = 91$ vs. 94) the power of this study was 0.72 for a difference of 10% in the incidence of ACS between the groups.

Study protocol

Eligible patients were assigned to the aspirin or the control group according to a computer-generated random sequence. Both groups were administered standard antibiotic therapy. The aspirin group was administered a loading dose of 300 mg oral ASA, followed by a maintenance dose of 300 mg oral ASA once-daily for 1 month.

Standard blood tests were obtained for each patient (complete blood count, urea, creatinine, electrolytes, and high-sensitivity C-reactive protein). Blood was collected for the measurement of high-sensitivity cardiac troponin T (hs-cTnT) on admission and 48 h after admission. hs-cTnT measurement was performed at the end of the study. ECGs were recorded on admission and 48 h and 30 days after admission to assess silent ischemia.

Demographic information (age, sex) was obtained for each patient. The presence of diabetes mellitus, hypertension, and/or dyslipidemia; use of tobacco; and a family history of coronary heart disease were ascertained. Administration of cardioprotective drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, β-blockers, and calcium channel blockers at admission was recorded. The British Thoracic Society CURB-65 score was obtained on admission.

Outcomes

The primary endpoint was the occurrence of an ACS within 1 month of admission for CAP. The secondary endpoints included cardiovascular death and death from any cause within 1 month. Previous studies have shown that patients with CAP have an almost eight-fold increase in the risk for ACSs within 15 days after admission, and the majority of studies have shown that the increased risk for MI after CAP was transient [17,18]. Therefore, the use of an early 30-day endpoint of ACS or mortality minimizes the influence of other comorbid conditions.

Acute coronary syndrome

In accordance with the American Heart Association and European Society of Cardiology guidelines, a patient was diagnosed with ACS if at least two of the following criteria were fulfilled: (a) chest pain characteristic of angina (new-onset angina pectoris or a recent increase in the severity of angina pectoris); (b) characteristic changes in the ECG; and (c) a serial increase in the concentration of cardiac enzymes. In addition, angiography documenting recent coronary occlusion was considered to be an ACS event. An elevated level of cardiac enzyme in the absence of compatible clinical history was not diagnosed as ACS.

Statistical analysis

Statistical analysis was carried out using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous data are expressed as mean ± SD and categorical data are expressed as percentages. The χ^2-test was used to assess differences between categorical variables among the groups. The relationships among parameters were assessed using the Pearson correlation analysis. Student's t-test was used to compare unpaired samples. Multivariable logistic regression analysis was used to evaluate the impact of variables on the primary endpoint. The results are presented as relative risks with the 95% confidence interval (CI). A P-value less than 0.05 was considered statistically significant.

Results

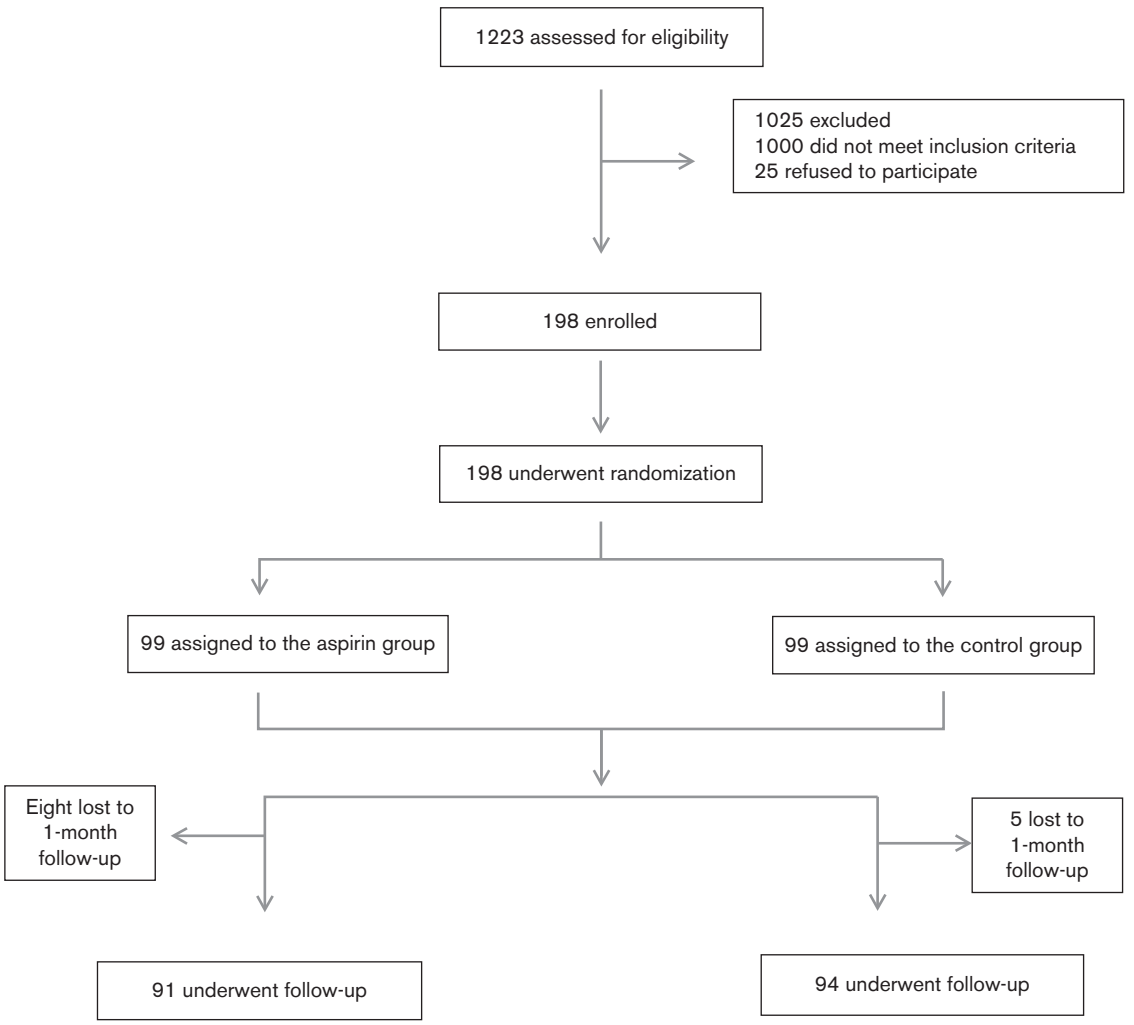
We assessed 1223 patients for eligibility. One thousand patients did not fulfill the inclusion criteria and 25 of them refused to participate. In total, 198 patients underwent randomization to two groups. Eight patients in the aspirin group and five patients in the control group were lost to 1-month follow-up. Finally, 91 patients in the aspirin group and 95 patients in the control group underwent 1-month follow-up in the present study (Fig. 1).

The data on age, sex, and cardiovascular risk factors are summarized in Table 1. The aspirin and control groups were similar with respect to the baseline characteristics, except hypertension, which was more common in the aspirin group. As shown in Table 1, there was no significant difference between the groups in cardiovascular therapies. The admission biomarker profiles were similar in the aspirin and the control group, including creatinine, white blood cells, hemoglobin, high-sensitivity CRP, and hs-cTnT (Table 1).

Patients were assigned to low-risk, intermediate-risk, and high-risk classes according to the CURB-65 score (five variables): low risk, classes 0–1; intermediate risk, class 2; and high risk, classes 3–5. Eleven of the 91 patients in the aspirin group and 16 of the 95 patients in the control group had intermediate to high risk ($P = 0.36$).

At 48 h after randomization, the proportion of patients with an elevated hs-cTnT level from baseline was significantly higher in the control group (35.2% in the aspirin group, 55.3% in the control group; $P = 0.006$). In addition, the proportion of patients who had a two-fold increase in the hs-cTnT levels when compared with the baseline was significantly higher in the control group

Fig. 1



Study profile.

Table 1 Baseline characteristics of the study patients

	Aspirin ($n=91$)	Control ($n=94$)	*P*-value
Age (years)	68.17±10.16	66.2±11.88	0.893
Male [*n* (%)]	56 (61.5)	67 (71.3)	0.113
Diabetes mellitus [*n* (%)]	38 (41.8)	26 (27.7)	0.062
Hypertension [*n* (%)]	70 (76.9)	56 (59.6)	0.018
Hyperlipidemia [*n* (%)]	32 (35.2)	23 (24.5)	0.153
Smoking [*n* (%)]	57 (62.6)	59 (62.8)	0.986
Family history [*n* (%)]	36 (39.6)	28 (29.8)	0.278
Framingham risk score 5–10% [*n* (%)]	33 (36)	35 (37)	0.962
Framingham risk score 10–20% [*n* (%)]	34 (37)	36 (38)	0.891
Framingham risk score>20% [*n* (%)]	24 (26)	23 (24)	0.765
Biochemical parameters			
Creatinine (mg/dl)	1.03±0.37	1.043±0.39	0.945
White blood cell (μl)	13156±7600	13107±7680	0.966
Hemoglobin (g/l)	12.27±1.87	12.24±2.37	0.912
hsCRP (mg/l)	104.76±103	127.18±118	0.171
hs-cTnT on admission (ng/ml)	31±64	40±102	0.499
hs-cTnT 48 h after admission (ng/ml)	30±60	49±119	0.163
Two-fold increased hs-cTnT after 48 h (%)	5.5	14.9	0.036
Increased hs-cTnT after 48 h (%)	35.2	55.3	0.006
Drug usage			
RAAS blocker [*n* (%)]	34 (37)	31 (32)	0.532
β-Blocker [*n* (%)]	21 (23)	18 (19)	0.514
Calcium channel blocker [*n* (%)]	23 (25)	19 (20)	0.595
Statins [*n* (%)]	20 (21)	24 (25)	0.591

hsCRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; RAAS, renin–angiotensin–aldesterone system.

(5.5% in the aspirin group vs. 14.9% in the control group; $P = 0.036$).

In our study, an ACS occurred in 1.1% ($n = 1$) of patients in the aspirin group and in 10.6% ($n = 10$) in the control group, with a significant absolute risk reduction of 9.5% (relative risk, 0.103; 95% CI 0.005–0.746; $P = 0.015$; Table 2). The following ACS subtypes were observed: STEMI, two; NSTEMI, five (ECG changes were documented in all cases and all patients had elevated hs-cTnT levels); UAP, two; two patients were referred for coronary angiography; and the other two patients refused coronary angiography and underwent noninvasive stress testing, which indicated reversible ischemia. After 1 month of follow-up, three patients in the aspirin group and eight patients in the control group had died ($P = 0.151$; Fig. 2). Four patients who had ACS died from cardiovascular causes, such as shock and malignant ventricular arrhythmias. Aspirin therapy was associated with a significant reduction in the risk of cardiovascular death (risk reduction: 0.04, $P = 0.044$; Fig. 2).

A multivariable logistic regression model of CAP-related ACSs was constructed in which a two-fold increase in the hs-cTnT levels in comparison with the baseline was the outcome variable. Randomization to the control group (i.e. absence of aspirin use) was associated with a significant increase in the 30-day ACS rate.

In subgroup analyses, the benefit of aspirin was consistent across all subgroups analyzed. The most consistent benefit of aspirin was observed in the subgroups of diabetic patients and patients with a Framingham risk score of greater than 20. There were no reported side effects of aspirin including clinically relevant gastrointestinal bleeding in the aspirin group.

Discussion

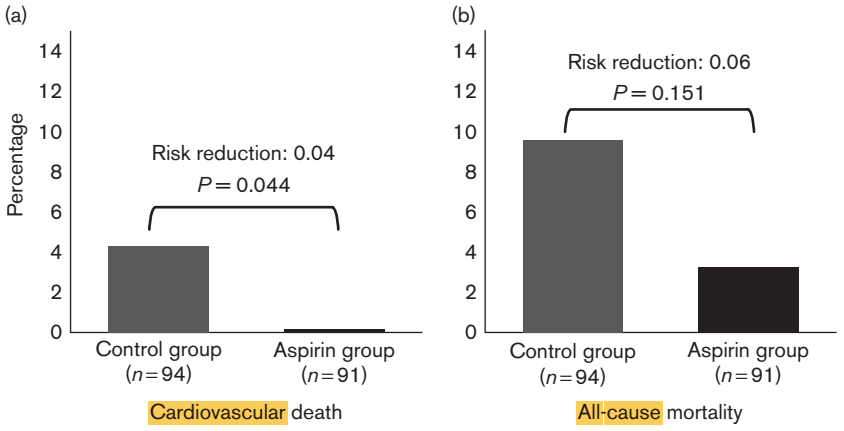
This randomized, controlled, prospective primary prevention trial of ASA in the treatment of patients with pneumonia shows that the administration of ASA reduces the risk for ACS after CAP. Pneumonia is a leading cause of morbidity and mortality worldwide and more than one-quarter of deaths within 30 days are related to comorbidities such as ACS [19]. Despite medical advances, such as antibiotic therapy, mortality rates for pneumonia remain unchanged [20]. The aim of our study was to assess whether ASA treatment is associated with a reduction in recurrent ACS after CAP.

Pooled analyses of clinical trials have shown an increased incidence of ACS after pneumonia. Correlas-Medina *et al.* [18] observed that the risk for MI in the first 15 days of onset of pneumonia increased 47-fold as compared with that during the 24-month period surrounding the infection. The pathophysiologic mechanism by which pneumonia serves as a trigger for ACS may be multifactorial. Pneumonia increases systemic markers of inflammation, worsens endothelial dysfunction, and activates coagulation pathways that may mediate, at least in part, the transformation of a stable atherosclerotic plaque into an unstable one [21–23]. Therefore, anti-inflammatory therapy and strategies to inhibit platelet activation and aggregation may be beneficial in reducing the incidence of ACS in patients with pneumonia and high cardiovascular risk. In addition, UAP could occur secondary to impaired myocardial oxygen delivery as a

Table 2 **Clinical outcomes in the study population**

	Aspirin ($n=91$)	Control ($n=94$)	Relative risk	*P*-value
Acute coronary syndrome [*n* (%)]	1 (1.1)	10 (10.6)	0.103 (0.005–0.746), risk reduction: 0.095	0.015
Cardiovascular death [*n* (%)]	0 (0)	4 (4.3)	Risk reduction: 0.04	0.044
All-cause mortality [*n* (%)]	3 (3.3)	9 (9.6)	0.34 (0.075–1.33), risk reduction: 0.06	0.151

Fig. 2



Percentage of cardiovascular death (a) and all-cause mortality (b) in the study population.

result of hypoxemia and increased myocardial oxygen demand because of tachycardia and fever in the setting of pneumonia.

ASA is an inexpensive and readily available therapy for CVD prevention. Recent trials and meta-analyses have shown that ASA use for the primary prevention of ACS is beneficial among patients with high cardiovascular risk [24–26]. Observation studies show, however, that only 16–57% of ideal candidates in the USA, 8.5% of Swiss patients, and 11% of Italian patients with high or intermediate cardiovascular risk are administered ASA for primary prevention [27–31].

As a result of its antiplatelet activity, early initiation of ASA is recommended in the setting of MI, and given the pathophysiology of pneumonia, it could similarly be hypothesized that ASA could reduce the risk for ACS in the setting of pneumonia [32,33]. In addition to its antiplatelet activity, there is considerable evidence for other beneficial effects of aspirin such as reducing inflammation. Low-dose aspirin (30–81 mg/day) not only inhibits platelet activation but is also associated with anti-inflammatory effects such as reducing the expression of proinflammatory mediators [34]. Similarly, ASA improves endothelial cell function after vaccination with *Salmonella typhii* [35,36].

Data on the potential benefit of ASA among CAP patients are limited. In a retrospective study, Chalmers and colleagues observed that previous ASA use tended to be associated with lower mortality rate among patients with pneumonia (37% reduction in mortality, $P = 0.11$). Similarly, Winning *et al.* [37] observed that previous ASA use was associated with significantly reduced intensive care unit treatment and shorter hospital stay. An older, small prospective study from 1957 that included relatively young pneumonia patients did not report a benefit of ASA [38]. To our knowledge, there is no other randomized study on low-dose ASA in patients with CAP. In the present study, among the 185 men and women at intermediate to high risk for CVD, ASA therapy reduced the risk for ACS (10.6% in the control group vs. 1.1% in the aspirin group; relative risk: 0.103; 95% CI 0.005–0.746; $P = 0.015$). In this study, ASA use significantly reduced cardiovascular mortality ($P = 0.044$). In addition, aspirin use tended to decrease the all-cause mortality (risk reduction: 0.06, $P = 0.151$). The tendency for improvement in the survival rate with ASA use may be because of a decrease in the risk of thrombotic events in patients with pneumonia. The beneficial effect of ASA was achieved without a significant increase in bleeding.

In the present study, increased hs-cTnT levels alone were not considered to be diagnostic of ACS despite the fact that increased hs-cTnT levels may indicate myocardial damage. A recent retrospective study suggests that pneumonia may be associated with acute myocardial damage and that cardiac troponin I levels may be useful

for risk stratification of patients with CAP [39]. The increased circulating hs-cTnT levels in patients with pneumonia might be because of recurrent silent ischemia (because of ischemia in the face of increased metabolic demands associated with CAP) or a loss of the cellular integrity of the cardiac myocyte. Two-fold and greater elevations in hs-cTnT levels compared with the baseline were associated with an increased risk for clinical ACS in the present study and were common and more pronounced among controls.

Limitations

Limitations of the present study include its open-label design and the relatively small sample size. Symptoms associated with MI such as chest pain may be misdiagnosed as pneumonia, but the ACS events were adjudicated.

Conclusion

This randomized open-label study shows that ASA is beneficial in the reduction of ACS and cardiovascular mortality among patients with pneumonia. Larger prospective placebo-controlled studies are warranted to confirm the reduction of ACS associated with the administration of ASA in the setting of CAP.

Acknowledgements

Conflict of interest

There are no conflicts of interest.

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