Preventing cardiovascular events after pneumonia with aspirin: one step forward, but still many to go

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Cardiovascular (CV) diseases and lower respiratory tract infections dominate human burden of disease across the world. Combined, they cause nearly 20 million or 36% of annual global deaths [1]. Additionally, both are linked together and interact bidirectionally: underlying CV disease is an established risk factor for the development of pneumonia and poor prognosis during pneumonia [2, 3], and *vice versa*, the role of pneumonia as risk factor for CV complications and new-onset CV disease has been demonstrated [4–6].

In particular, the latter association has received growing interest during recent years. In 2012, Corrales-Medina *et al.* [7] described a 30-day overall CV complication rate of 27% in 1343 inpatients and 2% in 944 outpatients with community-acquired pneumonia (CAP). Other studies added to that evidence, with a recent systematic review reporting a pooled 9% risk for heart failure, 7% risk for arrhythmias and 5% risk for acute coronary syndromes in hospitalised patients with CAP [8]. CV complications in CAP were associated with CAP severity, pre-existing CV disease and age, and considerably increased the risk of mortality [8, 9]. Additionally, large trials identified pneumonia as an independent risk factor for long-term new onset CV diseases, with nearly doubled 10-year risks for new onset CV disease and heart failure [5, 6]. Given the burden of approximately 300 000 annual hospitalised CAP cases alone in Germany, the resulting numbers of CV events are of major concern [2]. Moreover, viral respiratory infections have also been associated with CV events, with an up to six-fold elevated rate of myocardial infarctions within 7 days after influenza infection [10], and somewhat lower associations for other respiratory viruses [10, 11]. Very recently, evidence on cardiac involvement expanded to infections with severe acute respiratory syndrome coronavirus 2: based on cardiac magnetic resonance imaging after recovery from coronavirus disease 2019 (COVID-19) in 100 German patients, cardiac involvement was present in 78% and ongoing myocardial inflammation in 60% of patients, suggesting regular CV complication assessments after COVID-19 recovery [12].

Whereas epidemiological data are convincing and justify any efforts to interrupt the detrimental interaction between CV disease and respiratory infections, less is known on the potential mechanisms by which pneumonia causes CV events [4, 13]. Multiple pathways seem to play a role, including sepsis- and hypoxia-associated increased cardiac oxygen demand, inflammation-associated thrombus and/or

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arteriosclerotic plaque formation and direct toxic effects [13]. In patients with pneumonia and high baseline CV risk, markers of platelet activation were associated with acute coronary syndromes, and pneumonia significantly enhanced coronary artery calcium as marker of coronary atherosclerotic disease progression [14, 15]. On the other hand, direct invasion of pneumococci into cardiomyocytes causing necroptosis and scarring was demonstrated in a non-human primate model [16]. Additionally, CV side-effects of commonly prescribed antibiotics like macrolide- or quinolone-associated QT prolongation may add to the risk [17]. However, details and the relevance of any interaction between these mechanisms remain to be elucidated.

Given these pathophysiological uncertainties, it is not surprising, but all the same alarming, that even less is known about possible interventions to reduce CV events after pneumonia. Whereas current CAP guidelines highlight the association between pneumonia and CV events, in the absence of guiding data clinicians are left without recommendations for follow-up procedures and/or preventive interventions. Given the pathophysiological rationale of pro-inflammatory and pro-thrombotic stimuli promoting CV events in the context of pneumonia, aspirin represents a promising candidate for prevention: it has well described anti-platelet and immunomodulatory effects and has an established role in secondary prophylaxis of CV events [18, 19]. However, data on aspirin in pneumonia are sparse. A single centre retrospective trial evaluated 1005 hospitalised CAP patients in Italy and found nonfatal CV events within 30 days in 51/615 (8.3%) aspirin non-users compared to 19/390 (4.9%) aspirin users. Prior aspirin use was associated with a reduced hazard ratio for hospital death of 0.43 (95% CI 0.25–0.75) after Cox regression analysis [20]. Additionally, a small open-label Turkish randomised trial including 185 hospitalised CAP patients with at least two additional CV risk factors reported a reduction of CV events within 1 month from 10/94 (11%) in the control group to 1/91 (1%) with aspirin 300 mg per day [21]. Given the preliminary nature of such evidence, no clear recommendation could be excerpted from these studies so far.

This striking evidence gap is approached by the study of Hamilton *et al.* [22], now published in the *European Respiratory Journal*, evaluating the association of prior aspirin use with CV events after an episode of pneumonia in a large database. Although this is a retrospective observational trial, it persuades with a high patient number from a large UK primary care database and an elaborated statistic approach. By combining propensity score matching for reduction of group differences between aspirin users and non-users with a prior event rate ratio analysis using the same individual before the pneumonia as control for CV events after the pneumonia, some confounding inherent to observational trials is reduced. Among 48 743 patients aged over 50 years with a pneumonia event coded in primary care, the authors identified 9864 patients on chronic aspirin prescriptions within the 12 months prior to and 6 months after pneumonia, and matched these to a similar number of aspirin non-users by a propensity score. The primary outcome was the combination of stroke and myocardial infarction as coded in the database. Event ratios within 6 months prior and posterior to the pneumonia were compared between aspirin users and non-users. The analysis revealed 1) concurrent with recent literature, an increase of CV events within the 6 months after the pneumonia event (493 *versus* 877 events); and 2) a significant association of prior aspirin use with reduced CV events after pneumonia (HR 0.64, 95% CI 0.52–0.79). Various sensitivity analyses supported this result, including a Cox regression analysis, the absence of associations of aspirin use with the risk of fracture or constipation, and the absence of associations of paracetamol, proton pump inhibitor or levothyroxine use with CV events.

What are clinical consequences and where to go from here?

The present study probably pushes information as far as observational data can go by evaluating a large cohort and employing robust methodology. However, there are still important limitations, including censoring of 10% of patients with intermittent aspirin use, missing linkage with hospital data, implying incompleteness of pneumonia and CV event data, missing information on other important CV risk factors and/or pneumonia severity and aetiology, and relevant residual confounding resulting from incomplete matching by the propensity score. Thus, the evidence is supportive for a role of aspirin in CV prevention after pneumonia, but confirmation by prospective data is needed, and a randomised trial on aspirin as adjunctive drug in CAP is to be claimed before treatment with aspirin, solely based on the presence of the CV risk factor pneumonia, can be recommended.

For such a trial, endpoint and follow-up definitions are relevant. Prior randomised trials on aspirin for prevention of acute respiratory distress syndrome (ARDS) progression in patients at risk of ARDS and for prevention of sepsis in healthy elderly failed [23, 24]. However, informed by the data of Hamilton *et al.* [22], focusing on prevention of CV events after pneumonia might be the most promising target. Such a trial should be tailored to patients at risk for CV events. Hence, more information on risk factors is needed. Promising data indicate that beside age and established CV risk factors, cardiac biomarkers like troponin and brain natriuretic peptide indicate an elevated risk of post-pneumonia CV events [25, 26]. To start with,

treating hospitalised pneumonia patients would provide higher probability of CV events. Additionally, it remains unclear whether *de novo* initiation of aspirin during the pneumonia, which would be the realistic scenario for a trial, would translate into effects similar to those of prior aspirin use. Preliminary data from a small randomised trial evaluating aspirin after human endotoxin challenge suggests, that for the immunomodulatory properties of aspirin, differences exist between treatment onset before or after the infection event [19]. Finally, the role of pneumonia aetiology regarding CV risk and any aspirin effect remains to be elucidated. Trials with aspirin as adjunctive treatment started in patients with COVID-19 [27], but given the specific pathophysiology of this infection, extrapolation to other patients with pneumonia will not be possible.

Until such evidence from prospective trials arises, clinicians are still advised to rigorously monitor and treat CV risk factors and CV complications in patients with pneumonia. Additionally, the risk of harm by an otherwise indicated secondary prophylaxis with aspirin during pneumonia seems limited. Therefore, routine evaluation of pre-existing indications for and continuation of indicated prior aspirin during and after any pneumonia is recommended.

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