Editorials

Beyond COVID-19:

respiratory infection and cardiovascular events

INFECTIONS TRIGGER CARDIOVASCULAR DISEASE

When someone has an infection their risk of having a heart attack or stroke rises abruptly before returning to pre-infection levels over the next few weeks.[1] The increase in risk is particularly high for respiratory infections like influenza and pneumonia. There are biologically plausible mechanisms by which infections could cause cardiovascular disease (CVD). Respiratory infections could trigger CVD by functional changes, like tachycardia, blood pressure instability, and hypercoagulable states. Increased cardiac demand can be enough to cause myocardial ischaemia downstream of stenosed vessels, even if the obstruction is stable.[2] Infection might worsen or trigger existing CVD. Atheroma is thought to result from inappropriate inflammation. Infection could accelerate this inflammatory process, and destabilise plaques, much as chronic inflammatory conditions worsen coronary disease. Infections are also triggers for arrhythmias, which can in turn cause myocardial infarction and stroke. But even if the association between infections and CVD is only a marker of risk and not causative, it could still be useful clinically. There are precedents for short-term interventions: for example, temporary dual antiplatelet therapy after transient ischaemic attacks (TIAs). The benefit of prevention is proportional to the risk of CVD events, so treatments can be beneficial during periods of higher risk, when the balance of risks to benefits favours intervention.

A typical question GPs ask is: 'Why has this person got this disease at this time?' Often we focus on the diagnosis and cause but forget the temporal element, or at least don't take it into account in our practice. At one time, even death was assumed to strike people at random. During the plague, London haberdasher John Graunt started tallying up parish bills of mortality and found the very young and the very old were more likely to die than those lucky enough to be middle aged.[3] So much in our practice flows from this simple fact. That old people die seems obvious now; it is so ingrained as to be hard to imagine not knowing. But how much more sophisticated is our understanding of other seemingly random events? Tallying the deaths from our 21st century plague shows COVID-19 conforms to the pattern of older people being more likely to die.[4] It also highlights the risks of combining infections with cardiovascular disease, with over 31 000 cardiovascular deaths attributed to COVID-19 in 2020.[5] So, can we move on from treating them like they are unrelated? This isn't a small problem: epidemiology from before the COVID-19 pandemic estimates some 10 000 CVD deaths per year may be related to infections.[6] Therefore, that few weeks of increased risk could represent a huge burden of coordinated disease.

CLINICAL PRACTICE

'... the race is not to the swift, nor the battle to the strong, nor bread to the wise, nor yet favour to men of skill, but time and chance happen to them all'.[7]

Does this describe our approach to CVD events in primary care? Not quite; we are not in the pre-Graunt era. We accept patients have different levels of risk attributable to their risk factors. We treat people accordingly — if their 10-year CVD risk meets a threshold, we offer statins: this drug is cost-effective and safe in the long term, go forth and take them forever. We know this approach saves lives, it is good and necessary, but can we do more? COVID-19 demonstrated the seasonal nature of infections, and the power of epidemiology. This isn't new information; Graunt noticed diseases have seasonal patterns in the 17th century.[3] And it's not just infections; those of us working in the NHS refer to seasonal deterioration in chronic diseases as 'winter pressures'.[6] Primary care adapted in response to epidemiology in the last 18 months, so maybe we can continue to adapt to data on seasonal infections. Infection control drove most of the recent changes in practice. We could continue this focus after the pandemic, doing our best to protect patients with chronic diseases from infections. Remote consulting, separate pathways for infectious patients, and vaccination have a lot to offer. To offer the safest care we have to think about the risks from infections, which includes CVD.

CVD isn't entirely random; most winters there is a spike in CVD and respiratory infections.[6] We have known for years that respiratory infections are followed by a few weeks of higher CVD risk.[1,8] This association was identified in general practice data, but we don't use it in general practice; we don't mention it to people with high 10-year CVD risk, nor when treating patients for respiratory infections. The only concession is offering people influenza and pneumococcal vaccines for secondary CVD prevention. And how often do we represent this to our patients as preventing bad infections, rather than preventing CVD? Even the official NHS website suggests to patients: *'If you have a heart condition you have a greater risk of becoming more seriously ill from flu than the general population'*.[9] Shouldn't we mention that influenza vaccines reduce secondary CVD events, and by an impressive margin?[10] The effect of influenza vaccines is greater than is seen for other secondary prevention measures.[11,12] Perhaps the COVID-related expansion of influenza vaccine coverage will help with primary CVD prevention too. We should certainly tally up the primary care data to find out.

"CVD [cardiovascular disease] *isn't entirely random; most winters there is a spike in CVD and respiratory infections. We have known for years that respiratory infections are followed by a few weeks of higher CVD risk."*

RISK PREDICTION AND INTERVENTIONS

We should also think about how to perform short-term CVD risk assessment and intervention when people are unwell with respiratory infections. One of the lessons of COVID-19 is the need for accurate risk prediction to guide vaccination and shielding.[13] Patients want to know their CVD risk and how to manage it[14] but at the moment we don't know if the risk

"To offer the safest care we have to think about the risks from infections, which includes CVD [cardiovascular disease]."

following infections is simply proportional to 10-year CVD risk, or if we need different tools that take into account risk factors for frequent or severe infections. If we can recognise and predict the risk, we could use infection as a prompt to personalise CVD risk assessments, and perhaps intervene.

Short-term risk assessments are beginning to be brought to bear on CVD; we are starting to intervene at high-risk moments. TIAs mark a peak in stroke risk that lasts for a few weeks. Intervening with short-term dual antiplatelet therapy at this crucial time reduces strokes.[15] And similarly, short courses of dual antiplatelets are used for acute coronary syndrome. Because the treatment is short, the risk of bleeding is likely to be low. This is in contrast to long-term aspirin for primary CVD prevention — which does reduce events, but the risk of bleeding outweighs the benefit.[12] Could we apply similar thinking to the high-risk period following the onset of infections, identify people at risk of infection-related CVD, and intervene with a short course of antiplatelets?

Risk stratification is key — we know aspirin causes bleeds and reduces CVD events by about the same amount in primary prevention.[12] The RECOVERY trial also demonstrated this in patients hospitalised with COVID-19.[16] Aspirin reduced thromboembolic events and increased bleeds, but had no effect on all-cause mortality. Seasonal and infection-related CVD predates the pandemic, and we should explore predicting and preventing CVD related to other respiratory infections as well. We already know infections are associated with CVD events, so let's make use of this fact. As we tally up the bills of mortality from COVID-19, let's think about how infections can trigger us to prevent CVD, rather than allowing infections to trigger CVD events.

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