OPINION

Short-term vascular risk: time to take notice?

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Abstract | Current guidance around the prevention of cardiovascular events is based on long-term risk, typically calculated over 10 years. A growing body of evidence, however, suggests that vascular risk fluctuates greatly over much shorter time periods. We suggest a new paradigm for cardiovascular risk management that is based on targeting interventions during periods of enhanced risk. During such high-risk time windows, prophylactic therapy could have a disproportionately large absolute benefit, altering the risk–benefit balance and cost-effectiveness of available treatments. Major surgery is an example of an exposure known to lead to a transient increase in vascular risk. Emerging evidence supports the usefulness of short-term preventative interventions in the perioperative period. Influenza infection is another exposure known to increase the risk of vascular events, and cardiovascular mortality and morbidity are likely to be major features associated with pandemic influenza. Important questions remain, however, before preventative interventions can be offered as a routine part of influenza management.

Smeeth, L. & Hingorani, A. D. *Nat. Rev. Cardiol.* **7**, 409–412 (2010); published online 4 May 2010; doi:10.1038/nrcardio.2010.64

Considering risk fluctuation is vital

Atherosclerosis is a fairly benign chronic condition; its devastating effects on morbidity and mortality result largely from acute arterial events, such as myocardial infarction (MI) and stroke. Interventions to reduce the risk of such vascular events are currently guided by estimations of long-term cardiovascular risk. For example, both US national guidelines[1] and the guidance by the UK's National Institute for Health and Clinical Excellence[2] recommend the use of statins by people whose absolute risk of a cardiovascular event exceeds 20% over the next 10 years. Emerging evidence, however, indicates that the risk of vascular events is not homogeneous over time, but rises and falls within short time periods in response to a range of common physiological and environmental exposures.

An example of one of these factors is infection. The risk of MI is increased up to fourfold (Figure 1) and that of stroke more than twofold in the period following naturally occurring infections.[3] Such an effect on cardiovascular risk may be particularly marked in the setting of influenza infection.[4,5] In an influenza pandemic, during which a substantial proportion of the adult population may be infected, even a short-lived effect could lead to a high number of vascular events. The high risk of vascular events following major surgery is also well established. In the first 30 days following major elective noncardiac surgery, the absolute risk of nonfatal MI, cardiac arrest or cardiovascular mortality is 6%,[6] a higher absolute risk during a single month than many people experience over 5 years. A link between short-term systemic inflammation and endothelial dysfunction was observed after therapy for severe periodontal disease, an intervention known to lead to a marked inflammatory response,[7] and may also underlie the increased cardiovascular risk associated with other infections or surgery.

Environmental exposures can also increase short-term cardiovascular risk, and while their effects may seem small, the large number of individuals affected could translate into a substantial public health impact. Evidence exists that short-term fluctuations in air pollution affect the risk of MI. The most consistent finding relates to small particulate matter, with estimates for the increased risk of MI ranging from 5% to 17% per 10 mg/m^3 increase in particulate matter of <2.5 μm diameter.[8] Unusually high or low ambient temperatures are also associated with an increased risk of MI.[9] A relative risk of MI of 1.02 per degree temperature may sound small, but because the whole population is exposed, this risk translates into a 2% increase in the total number of MIs for each degree change.

Other factors that affect physiology may also lead to short-term increases in cardiovascular risk. Acute exertion has long been recognized as a trigger for MI[10] and even an apparently benign activity such as watching a soccer match is associated with a doubling in the risk of cardiovascular events.[11]

It is time to take notice of these acute fluctuations. The fluctuation of cardiovascular risk across short time periods has not been taken into account by the current general guidelines for reduction of cardiovascular risk.

Prevention at high-risk times

We suggest a new paradigm for cardiovascular risk management that is based on identifying specific periods of enhanced risk and targeting interventions during these periods. During such high risk periods, the absolute benefits of interventions are far higher than in periods of lesser risk, which provides an opportunity to prevent large numbers of vascular events. This opportunity is currently being largely ignored. The absolute risk of an event over a 30-day period is <0.2% in individuals with a 10-year risk of cardiovascular disease of 20% (currently the recommended threshold for statin treatment). By contrast, the observed 30-day event rate for people older than 50 years of age who undergo elective surgery is 6%. Administration of statins to people at increased risk of vascular disease was shown to reduce the long-term risk of a first or recurrent vascular event by around 20% in primary and secondary prevention studies, respectively.[12,13] Therefore, among the group of people who are at the recommended threshold for preventative statin treatment, around 3,000 people would need to be treated (Box 1) with statins for 1 month to prevent one event.

Competing interests
The authors declare no competing interests.

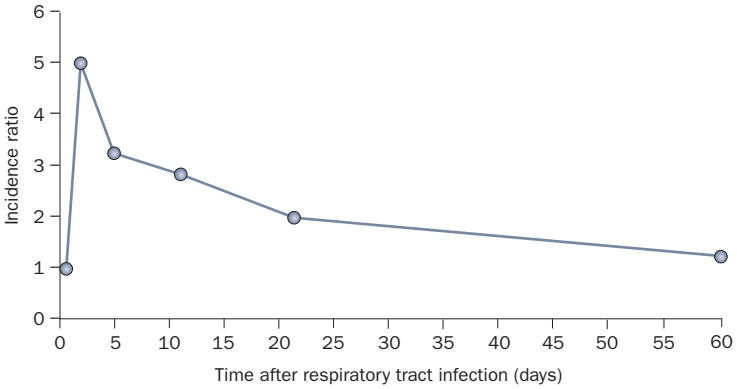

Figure 1 | Incidence ratio of myocardial infarction in days following presentation with a respiratory tract infection. Data from Smeeth *et al. N. Engl. J. Med.* **351**, 2611–2618 (2004).[3]

Box 1 | The number needed to treat

The number needed to treat (NNT) is the number of patients who need to be treated to prevent one additional adverse outcome (such as, in this article's examples, myocardial infarction or stroke). For example, if a drug has an NNT of 5, five people need to be treated with the drug to prevent one additional adverse outcome. The NNT is calculated as 1 divided by the absolute risk reduction, which means that for any given relative risk reduction, the NNT will be lower among people at high risk of experiencing the adverse outcome than among people at low risk.

Assuming the same relative reduction in risk with statin treatment, the number needed to be treated for 1 month postoperatively could be as low as 84. Therefore, targeting statin treatment to high-risk periods would be highly cost-effective.

Prophylactic interventions to prevent cardiovascular disease could be particularly important in those people whose 10-year risk of cardiovascular disease is well below the widely used 20% threshold—and who thus will not be taking a statin or other preventative therapies—but who will experience transient periods of much higher risk. During these high-risk periods, the relative risk reductions achieved by prophylactic therapy will translate into a large absolute benefit, which provides an opportunity to prevent major events. The concept of providing prophylactic pharmacological interventions during high-risk periods is already well established for preventing venous thromboembolism during hospital admission.[14] Such an approach, however, has not been widely considered or evaluated for arterial thromboembolic disease.

Possible short-term therapies

Possible therapies for use over short periods of increased risk are likely to be those shown to be safe and efficacious in long-term settings. The two most widely used long-term prophylactic drug therapies for cardiovascular disease are statins and aspirin. Growing evidence shows that statins exert rapid effects: endothelial function and arterial flow improve within 24 h of initiation of statin administration,[15] and the levels of inflammatory markers such as C-reactive protein are reduced within 3 days.[16] The beneficial effects of statin therapy among people at increased risk of vascular disease are clear; the life-table plot for the occurrence of cardiovascular events of the group of patients receiving statins separates almost immediately from that of patients receiving placebo.[12] Although the number of events that occurred in the first few weeks of these trials were small, which limits the power to analyze this time frame, substantial benefits of statin administration on vascular end points are evident in the first year of treatment.[13] Furthermore, early initiation of statin therapy in acute coronary syndrome reduces the risk of death and nonfatal vascular events.[17] These findings suggest that the benefits of statins would be exhibited during short-term high-risk periods.

The evidence for short-term cardiovascular effects of aspirin and other antiplatelet agents is strong. Although the risk–benefit ratio of aspirin therapy in primary prevention of cardiovascular disease seems likely to be unfavorable in people at low to moderate vascular risk,[18] during high-risk windows its beneficial effects may well outweigh the documented risks of hemorrhage. The benefits of aspirin or clopidogrel or both during acute vascular events are established, and stopping antiplatelet therapy is associated with a rapid increase in risk of recurrent MI and death.[19] Prasugrel[20] and ticagrelor,[21] novel antiplatelet agents with a more rapid onset than clopidogrel, may be of particular value as acute short-term therapies.

Antihypertensive drugs, such as calcium-channel blockers, rapidly reduce blood pressure. In randomized trials, their full effect on blood-pressure reduction is achieved within the first year of treatment.[22] Whether protective effects are seen more rapidly is unclear. Anticoagulation agents are other potential therapies for acute periods of high cardiovascular risk. Among these, the relatively slow onset and the need for dose adjustment and monitoring make warfarin problematic as an acute therapy compared with newer agents. Both rivaroxaban[23] (a factor Xa inhibitor) and dabigatran[24] (a thrombin inhibitor), however, do not have these problems, which makes them good candidates for study as prophylactic agents during short-term high-risk periods.

The beneficial effects of β-blocker use following MI suggest that these agents may have a useful role also in other high-risk periods. Considerable interest has been raised about their role in the postoperative period, particularly in preventing MI, as discussed in the next section of this article.

Measures that are not based on drug treatment may also have a role in reducing short-term cardiovascular risk. Ischemic preconditioning involves deliberately exposing tissues to brief, repeated periods of vascular occlusion to render them resistant to the adverse effects of severe ischemia.[25] Inducing episodes of myocardial ischemia is not a practical intervention for widespread use. However, in a study of remote conditioning, arm ischemia induced in three 5 min cycles by means of an inflatable cuff protected the myocardium perioperatively.[26] Such remote ischemic preconditioning could be a simple and cheap method of providing vascular protection during short-term periods of increased risk. Preconditioning would be expected to reduce the severity of an ischemic event rather than prevent occurrence altogether, which suggests that this approach might be most useful as adjunctive therapy.

Balancing benefits and harms

Before short-term interventions to prevent arterial vascular events during high-risk periods can be advocated, we need clearer evidence on their effectiveness. The overarching question that needs to be

Box 2 | Rationale for short-term interventions to prevent cardiovascular risk

- Atherosclerosis is relatively benign until acute arterial events occur
- The prevention of cardiovascular events is currently based on long-term risk assessment
- Several factors have been identified that markedly increase the risk of cardiovascular events in the short term, for example infection and major surgery
- During short-term high-risk periods interventions may have a disproportionately large beneficial effect, dramatically altering the risk–benefit or cost–benefit ratio
- Interventions—such as therapy with statins, or perhaps with aspirin or other antiplatelet agents—could be utilized for short periods during transient times of very high risk
- Key unanswered questions include which patients to treat, how to identify them, which interventions to use, and what the appropriate dose and length of therapy should be, as well as what the balance between benefits and harms of any chosen intervention is

addressed is to establish the overall risk or cost versus the benefit of these approaches. Currently, decisions about who should receive statin therapy are largely driven by cost-effectiveness, whereas for aspirin the main deciding factor is the balance between clinical risk and benefit. During transient periods of high vascular risk, both cost-effectiveness and the risk–benefit balance change radically. The low numbers needed to treat to prevent events during such high-risk periods mean that statin therapy may become highly cost-effective. The bleeding hazards associated with aspirin therapy may be outweighed by its raised potential for benefit during these periods.

Evidence to date

Evidence for the risks of aspirin when used for primary prevention emphasizes the need to be able to identify those people who will benefit the most from intervention during periods of short-term enhanced risk. One study has demonstrated the feasibility of identifying high-risk periods and initiating transient treatment with aspirin and β-blockers.[27] However, while this approach was shown to be feasible, its effectiveness has not yet been clearly demonstrated. The largest body of research into the effectiveness of prophylactic therapy in periods of high cardiovascular risk comes from studies in the perioperative period, but even in this setting the findings are inconclusive. A systematic review that included two small trials and several large observational studies of perioperative statin therapy concluded that the data are insufficient to reliably guide therapy.[28] A subsequent trial among patients undergoing noncardiovascular surgery did not find a significant beneficial effect of perioperative statin therapy.[29] However, among patients undergoing vascular surgery, a marked protective effect of fluvastatin given perioperatively against cardiovascular death or MI was observed (hazard ratio 0.47, 95% CI 0.24–0.94).[30] For perioperative β-blockers, the largest trial to date found a reduction in the primary cardiovascular end point (a composite of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest), but a higher risk of stroke and total deaths among patients who received β-blockers perioperatively than among patients who did not receive this treatment.[31] An updated meta-analysis concluded that the "evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having noncardiac surgery".[32]

Future perspectives

The inconclusive research results obtained to date highlight the importance of large randomized trials to guide therapy. An example currently applicable would be offering people with influenza-like illness randomization to short-term vascular prophylactic therapies or placebo or no prophylactic treatment. A discussion of the rationale for use of these approaches in the prevention of cardiovascular risk is needed (Box 2). Key research questions on these potential therapeutic strategies include which patients warrant treatment and how can they be identified, which interventions to use, drug dosage, length of treatment, and safety.

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Acknowledgments

Patrick Vallance contributed to discussions and Raymond Macallister provided useful comments on an earlier draft of the article. L. Smeeth is supported by a senior clinical fellowship from the Wellcome Trust (082178) and A. D. Hingorani is supported by a senior fellowship from the British Heart Foundation. The funders played no role in the preparation and content of the article.