The last 2 decades have seen major advances in understanding of the mechanism of onset and treatment of acute coronary syndromes. It has become accepted that acute myocardial infarction (MI), sudden cardiac death, and stroke can be triggered by stressors such as heavy physical exertion and severe emotional stress; the clinical implications that can be derived from the findings of triggering remain uncertain, however.

The triggering studies were stimulated by observations of a circadian variation and morning peak in MI, sudden cardiac death, and stroke that indicated that events did not occur randomly. In a 1989 review in Circulation, we stated that although the primary value of recognizing the circadian variation of acute coronary events was the emphasis that could be placed on pharmacological protection during the morning hours, the main significance was the support it provided for the broader concept that the onset of coronary thrombosis at any time of the day is frequently triggered by activities of the patient.

The aim of the present review is to update current knowledge about triggering of acute cardiovascular disease (CVD), place it in the context of advances in understanding of the mechanisms of onset, and suggest a 5-faceted strategy to protect against the pathophysiological effects of triggering. The rationale for such a strategy is discussed, with areas for further research highlighted.

Long-Term Risk Factor Management

The treatment of hyperlipidemia and hypertension illustrates long-term risk factor management, in which an individual may take a daily lipid-lowering or antihypertensive agent for several years to reduce the risk of MI. Although the relative risk reduction with treatment may be 30%, the absolute risk reduction varies considerably, depending on the overall risk profile of a particular individual. For instance, in a moderately high-risk person with a 10% to 15% 5-year CVD event rate, a 30% risk reduction from 5 years of daily antihypertensive or lipid-lowering therapy translates into 4 CVD events prevented per 100 such subjects treated. The chance that a CVD event will be prevented in such an individual over a single day is ~1 in 45 000. Thus, the absolute benefit from the preventive therapy on a specific day is very low, yet daily therapy is the standard of care.

Long-term daily therapy is used in part because atherosclerosis has been regarded as slowly progressive. Because it is not possible to predict when an MI will occur, it is logical to provide daily prevention therapy over long periods of time. Furthermore, the major randomized studies have been conducted with long-term daily therapy, and the discipline of taking daily therapy is considered to improve patient compliance. As opposed to a gradual progression of stenoses, however, CVD events frequently occur abruptly after plaque rupture and thrombosis. In addition, plaque injury and nonocclusive thrombosis may lead to healing and a stepwise increase in stenosis.

Concurrent with progress in understanding the determinants of plaque vulnerability to rupture, triggering activities have been identified, such as heavy physical exertion, severe emotional stress, and respiratory infection, that can precipitate MI, sudden death, stroke, and acute left ventricular dysfunction.

The triggering data raise the possibility that a strategy directed against the short-term risk posed by triggering activities could complement a long-term risk factor reduction approach. Prevention of CVD at times of increased risk due to a trigger can be designated as triggered acute risk prevention (TARP) and can be considered analogous to the way a protective tarpaulin (often abbreviated as tarp) can be placed when rain is imminent.

Terminology

The following terms are important to an understanding of short-term risk:

1. Trigger: An activity that produces short-term physiological changes that may lead directly to onset of acute CVD.
2. Acute risk factor: A short-term physiological change, such as a surge in arterial pressure or heart rate, an increase in coagulability, or vasoconstriction, that follows a trigger and may result in disease onset.
3. Hazard period: The time interval after trigger initiation associated with an increased risk of disease onset because of the trigger. The onset and offset times of the hazard period, which could also be designated a "vulnerable
period," may be sharply defined, as in heavy exertion, or less well defined, as with respiratory infection. The duration of the hazard period may also vary, e.g., from <1 hour during heavy physical exertion to weeks or months with bereavement.

(4) Triggered acute risk prevention (TARP): Cardiovascular risk reduction that focuses on the short-term increase in risk associated with a trigger.

Evidence for Triggering of Acute CVD

Evidence for triggering has been summarized previously and is based on the following points. First, MI results from plaque rupture or erosion and thrombosis. Second, thrombotic occlusion frequently occurs at coronary artery sites that do not have severe stenosis before the acute plaque rupture. Third, there is a morning peak in frequency of MI, sudden cardiac death, and stroke that coincides with heightened blood pressure, heart rate, vasoconstriction, and prothrombotic changes. Fourth, physical and emotional stressors cause similar acute physiological changes to those seen in the morning period. These physiological changes can transiently increase the risk of plaque rupture and thrombosis and decrease the threshold for ventricular fibrillation. Fifth, epidemiological studies, stimulated by the development of the case-crossover study design, have confirmed and characterized several acute triggers of MI and sudden cardiac death.

Triggers That Have Been Identified

In the Multicenter Investigation of Limitation of Infarct Size (MILIS), almost half (48%) of the patients reported a possible trigger, of whom 13% reported a combination of 2 or more possible triggers (Figure 3). The activities most commonly reported were emotional upset (18%), moderate physical activity (14%), heavy physical activity (9%), lack of sleep (8%), and overeating (7%). This and other similar analyses are limited by a lack of control data, because exposure to potential triggers is common, yet MI occurs rarely. To address this and other limitations in the study of triggering, Maclure and Mittleman developed the case-crossover study design, initially for the National Institutes of Health–sponsored Determinants of Onset of Myocardial Infarction Study (ONSET study). A feature of the case-crossover design is

![Figure 1. Potential mechanisms by which a trigger may increase the risk of MI or sudden cardiac death. The relative contribution of each physiological change may vary depending on the specific trigger and differences in pathophysiology between infarction and sudden cardiac death. VT/VF indicates ventricular tachycardia/ventricular fibrillation.](image)

![Figure 2. Relative risk of MI during vigorous exertion. For the 640 subjects with acute MI who received primary angiographic assessment, the relative risk was 10.1 (95% CI 1.6 to 65.6) greater during vigorous exertion than at other times. Elevated relative risk was seen among individuals with very low activity (30.5, 95% CI 4.4 to 209.9) or low activity (20.9, 95% CI 3.1 to 142.1), but not among those who were moderately active (2.9, 95% CI 0.5 to 15.9) or highly active (1.2, 95% CI 0.3 to 5.2). Adapted with permission from Giri et al.](image)
that each person is matched against themselves, with a hazard and control period, to determine the relative risk of a potential trigger leading to MI (Figure 4).

**Heavy Physical Exertion**

In the ONSET study, heavy physical exertion (≥6 metabolic equivalents [METs]) in the hour before onset of MI symptoms was reported by 4.4% of patients and was associated with a relative risk of 5.9. In this population, heavy exertion can be considered to be the final component cause in 3.8% of cases, ie, ≈80% of the cases that occurred within 1 hour of exertion were triggered by it. Triggering of MI by heavy exertion has been observed in other studies, including the Stockholm Heart Epidemiology Program (SHEEP), in which the relative risk for heavy exertion was 6.1, and the Triggers and Mechanisms of Myocardial Infarction (TRIMM) study, in which the relative risk was 2.1. Although these studies included patients with both non-ST-elevation and ST-elevation MI, a 10-fold increase in relative risk for heavy exertion triggering MI was reported among a cohort with ST-elevation MI (Figure 2). In the ST-elevation cohort, heavy exertion was reported by 10% of individuals in the hour before MI and comprised aerobic activity, such as running or jogging (40%), isometric or heavy lifting (19%), or a mixture of the 2 (41%). A similar breakdown of aerobic (30%) isometric (18%), and mixed (50%) activities was seen in ONSET. In all studies, including that by Giri et al, the frequency of regular exertion modified the relative risk of MI. For instance, in ONSET, sedentary individuals had a 107-fold relative risk for heavy exertion triggering MI triggered by exertion, whereas the risk was only doubled among those reporting physical activity at least 5 times per week.

In addition to nonfatal MI, heavy exertion transiently increases the risk of sudden cardiac death. Among 21,481 US male physicians initially free of self-reported CVD, the relative risk of sudden death during and up to 30 minutes after vigorous exertion (≥6 METs) was 16.9 (95% confidence interval [CI] 10.5 to 25.0). The absolute risk of sudden death during any individual episode of heavy exertion, however, was very low (1 sudden death per 1.51 million episodes of exertion). The absolute risk of sudden death with moderate to vigorous exertion (≥5 METS) was even lower among female participants in the Nurses Health Study, at 1 per 36.5 million hours of exertion. Among the nurses, 3% of the 288 sudden deaths occurred during moderate to vigorous activity. This was associated with only a doubling in relative risk during exercise (2.38 [95% CI 1.23 to 4.60]), which was no longer significant in those who exercised 2 or more hours per week. In a study of men, regular activity also modified the risk of cardiac arrest during exercise; relative risk was 56 (95% CI 23 to 131) among sedentary individuals but only 5-fold among those who exercised regularly. Among the habitually vigorous men, the overall risk of cardiac arrest (during and not during vigorous activity) was only 40% that of the sedentary men (95% CI 0.23 to 0.67). These data indicate that although vigorous exertion can trigger MI and sudden death, the absolute risk of any individual episode is very low. Moreover, regular exercise is protective in reducing the risk of an exercise-triggered event, in addition to its benefits on overall risk.

**Sexual Activity**

In ONSET, 48% of the subjects reported being sexually active in the year preceding the MI. The usual frequency of sexual activity among the 858 sexually active patients was 1 to 11 times per year (25%), 1 to 3 times per month (30%), 1 to 2 times per week (23%), and ≥2 times per week (22%). Among these individuals, 3% reported sexual activity in the 2 hours before onset of symptoms, with a relative risk of 2.5 (95% CI 1.7 to 3.7) for MI. Similar results were found in the SHEEP study. In ONSET, the relative risk for sexual activity triggering MI was similar for individuals with prior MI (2.9, 95% CI 1.3 to 6.5) or without known prior coronary disease (2.5, 95% CI 1.7 to 3.7).

These data provide helpful information for counseling the many patients who survive MI each year or who have existing cardiac disease. Counseling has been based in part on the presumed physiological equivalence of sexual activity and a...
measure of physical activity, although this equivalence does not take into account the variable emotional and physical interplay.\textsuperscript{37} For sexual activity, as for other triggers, the most important information for counseling is not the relative risk of a potential trigger but the absolute difference in risk the activity produces. To estimate absolute risk, data on relative risk can be combined with baseline risk from populations similar to that from which the study patients originated. For instance, Framingham Heart Study data indicate that the risk that a 50-year-old nonsmoking, nondiabetic man will experience an MI is $\approx 1\%$ per year, or 1 chance in 1 million per hour.\textsuperscript{35,38} Because the relative risk of MI is doubled by sexual activity, by engaging in sexual activity, such an individual would only increase his hourly risk to 2 in 1 million, and only for a 2-hour period. Weekly sexual activity would only increase his annual risk of MI from 1\% to 1.01\%, a negligible effect because the absolute risk difference is small, the risk is transient, and the activity is relatively infrequent. Even if the baseline yearly risk of reinfarction or death for an individual with a prior MI is increased to 10\%,\textsuperscript{39} the absolute increase in risk with sexual activity would be very low. Moreover, in ONSET, the relative risk of MI after sexual activity decreased from 3.0 in sedentary individuals to 1.2 for patients who engaged in physical exertion of 6 METS $\pm$ 3 times per week. Although sudden death is not considered in the analysis, and bias may be introduced by reliance on self-reporting, this evidence provides reassurance that although there is a modest transient increase in risk, the absolute risk of MI with sexual activity is very low, even in individuals with known cardiac disease. In addition, they indicate that regular physical activity further lowers the risk. In those with prior MI, return to physical activity is helped by a cardiac rehabilitation program.

Psychosocial Triggers

Anger

In ONSET, 2.4\% of patients reported anger that scored $\geqslant 5$ on a 7-point anger scale in the 2-hour period before MI. This level of anger, which corresponded with “very angry, body tense, clenching fists or teeth” up to “furious or enraged,” was associated with a transient 2-hour risk increase of 2.3 (95\% CI 1.2 to 3.2) above baseline when the control was usual annual frequency.\textsuperscript{7} When the control period was the same 2-hour period the day before MI, the relative risk was 4.0 (95\% CI 1.9 to 9.4). The most frequent reported contributors to anger were arguments with family members (25\%), conflicts at work (22\%), and legal problems (8\%). In the SHEEP study, the relative risk was 9-fold for anger as a trigger.\textsuperscript{40} Koton et al\textsuperscript{41} showed an odds ratio of 14 (95\% CI 3 to 253) for anger triggering stroke in the subsequent 2 hours. A schema of possible pathophysiological mechanisms by which anger and other triggers may lead to MI and sudden cardiac death is described in Figure 1.

Anxiety

An elevated relative risk of 1.6 (95\% CI 1.1 to 2.2) was associated with episodes of marked anxiety above the 75th percentile on an anxiety scale within the 2 hours before MI.\textsuperscript{7}

Bereavement

Increased cardiac mortality in bereaved individuals is well described and has been portrayed as “the broken heart.”\textsuperscript{42–46} In a cohort of middle-aged widowers, a 40\% increase in the mortality rate was observed in the first 6 months after bereavement.\textsuperscript{44}

Work-Related Stress

A high-pressure work deadline in the prior 24 hours was associated with a 6-fold increase in relative risk of MI in the SHEEP study,\textsuperscript{9} whereas in ONSET, the relative risk over a 7-day hazard period was 2.3 (95\% CI 1.4 to 4.0) for a high-pressure deadline and 2.2 (95\% CI 1.0 to 5.0) for firing somebody.\textsuperscript{7} The emotional significance of a job stress influenced its contribution to relative risk of MI. Thus, when increased work responsibilities affected men in a very or fairly negative way in the SHEEP study, the relative risk, adjusted for other risk factors, was 6.3 (95\% CI 2.7 to 14.7), whereas the relative risk was only 1.5 (95\% CI 0.9 to 2.3) when the increased work responsibilities did not mean very much and 0.7 (95\% CI 0.5 to 0.9) when they had a positive effect. Corresponding relative risks among women were 3.8 (95\% CI 1.3 to 11.0), 0.8 (95\% CI 0.3 to 2.5), and 1.0 (95\% CI 0.6 to 1.8).\textsuperscript{9}

Population Stressors

Earthquakes\textsuperscript{47,48} and wartime missile attack\textsuperscript{49} have been associated with acute increases in cardiovascular risk. In the week after the Los Angeles, Calif, earthquake of 1994, which occurred at 4:31 AM, there was a 35\% increase in nonfatal MI compared with the week before and a 4-fold increase in sudden cardiac death on the day of the earthquake\textsuperscript{48,50} (Figure 5). For the 6 days after this spike, however, the number of sudden deaths fell below the baseline, which suggests that some of the initial deaths may have been moved forward by several days in individuals who were predisposed, rather than being excess deaths.\textsuperscript{50} In contrast to the Los Angeles earthquake, the 1989 Loma Prieta, San Francisco Bay (Calif) earthquake, which occurred at 5:04 PM, was not associated with increased MI, which led Brown\textsuperscript{51} to suggest that the added stress of abrupt awakening in the 4:31 AM Los Angeles earthquake contributed to the triggered events.

During the first week of Iraqi missile attacks on Israel in 1991, Meisel and colleagues\textsuperscript{49} found a doubling of nonfatal MI compared with a control period 1 year previously. This was mirrored by a near doubling of sudden out-of-hospital deaths for the corresponding 1-month period.\textsuperscript{49} More recently, Allegra et al\textsuperscript{52} reported a 49\% increase in patients admitted with MI through 16 emergency departments within a 50-mile radius of the World Trade Center in the 60 days after September 11, 2001, compared with the 60 days beforehand (118 MIs after versus 79 before, \textit{P}=0.01). Galea, in an accompanying introduction,\textsuperscript{53} highlighted the need for further study of population responses to disasters.

Sporting events provide another example of population stress. On the day of the 1996 European football final that Holland narrowly lost to France after penalties, Dutch men had an increased relative risk of MI or stroke of 1.5 (95\% CI 1.1 to 2.1), whereas there was no increased risk among Dutch women, French men, or French women.\textsuperscript{54,55}
Respiratory Infection
Using a case-control study design, Spodick et al\(^5\) reported a
doubling of risk of MI with respiratory infection. More
recently, Smeeth and colleagues\(^1\) confirmed an increased
risk of MI and stroke after a respiratory tract infection, which
was highest during the first 3 days (relative risk for MI 4.9
[95% CI 4.4 to 5.5] and for stroke 3.2 [95% CI 2.8 to 3.6];
Figure 6). The risks were also raised with a urinary tract
infection (relative risk for MI 1.7 [95% CI 1.3 to 2.0] and for
stroke 2.7 [95% CI 2.3 to 3.2]).

Heavy Meal
In the MILIS study, 7% of individuals identified overeating
as a potential trigger of their MI.\(^2\) In several circadian
analyses, a secondary evening peak of MI occurs at \(\approx 8\) PM,\(^3\) which could be due in part to the evening meal. In an analysis
from Lipovetsky et al,\(^4\) there was a 4-fold increase in relative
risk of MI over baseline during the first hour after a heavy
meal. Heavy fatty meals may produce a prothrombotic response,\(^5\) an inhibition of vascular reactivity,\(^6\) and an
increase in heart rate and catecholamines, the latter more so
after a high-carbohydrate meal.\(^7\)

Drugs and Recreational Habits
Cocaine has been recognized to precipitate MI.\(^8,9\) In ONSET,
a 23.7-fold increase in relative risk of MI over baseline
occurred in the 1 hour after cocaine use.\(^10\) Marijuana led to a
4.8-fold increased risk over baseline in the 1 hour after use.\(^11\)
The elevated risk fell rapidly thereafter.

Environmental Stress
Blizzards have been linked to increased MI, with snow
shoveling receiving particular attention as a trigger.\(^12,13\) Air
pollution has also been identified as an acute trigger of MI
and stroke.\(^14,15\) Inflammatory and prothrombotic factors are
potential mediators,\(^16\) although a reduction in heart rate
variability may also contribute to the link between pollution
and sudden cardiac death.\(^17\) Although the risk for ischemic
stroke in 1 study was only 1% higher on days with relatively
high levels of air pollution compared with low pollution days,
the total number of increased strokes could be significant
from a public health perspective given the large number of
at-risk people exposed to the pollution.\(^18\) Exposure to traffic
and associated pollution and emotional stress has been
associated with an increased relative risk of MI of 2.7 (95%
CI 2.1 to 3.6).\(^19\)

Seasonal and Other Variations
A seasonal variation in the incidence of MI, cardiac death,
and stroke is consistently described, with a winter peak up to
60% greater than the summer nadir.\(^20,21\) The mechanisms
underlying this variation, which holds true in both cold and
warmer climates, are not fully understood.\(^22,23\) Besides cold
ambient temperature, hypotheses advanced include respira-
tory infections, hypercoagulable state, and increases in blood
pressure, serum lipids, and glucose.\(^24,25\) A daily variation in
CVD and stroke has also been described, with a peak
incidence on Mondays.\(^26,27\) Holidays such as Christmas
and New Year’s day have also been associated with increased
cardiac mortality.\(^28\) Timing within the menstrual cycle may
also influence risk, possibly due to cyclical changes in
estradiol levels.\(^29\) Among premenopausal women in ONSET,
the early follicular phase was associated with a relative risk of
MI of 3.3 (95% CI 1.4 to 7.7) compared with the other 3
phases of the menstrual cycle.\(^30\)

Strategy for TARP
Five broad approaches can be considered for triggered acute
risk prevention (Table). Because of the limited evidence thus
far, these approaches provide a framework for future research
rather than a concrete guide for clinical management.

First, one can adopt a long-term behavioral and pharma-
cutical approach that focuses on absolute risk reduction.
This corresponds to traditional risk factor modification,
which emphasizes optimal blood pressure and lipid levels, not smoking, being physically active, and maintaining optimal weight. By reducing the atherosclerotic burden and the number of vulnerable plaques, such a long-term strategy would reduce the risk that a trigger would produce an acute CVD event.

Second, a long-term preventive approach can be directed against a specific trigger. For instance, regular physical activity reduces the likelihood that MI will be triggered by heavy exertion. Stress reduction training can be used to limit the responses of anger and anxiety. At a public health level, provision of defibrillators and rapid cardiac resuscitation capability in sporting arenas, aircraft terminals, and as part of response preparedness for natural and man-made disasters may reduce cardiac death where large numbers of people congregate and are exposed to increased stress levels. Vaccinations can protect against the increased CVD risk posed by influenza and pneumonia. Although more prospective studies are needed and potential selection bias must be considered, influenza vaccination has been associated with a halving in the rate of primary cardiac arrest, MI, and stroke.

Third, one can determine that the absolute risk of the trigger is very low and does not require intervention. For instance, the data on sexual activity and triggering are reassuring. In an individual considered to be at low risk of having atherosclerotic disease or vulnerable plaques, even a maximal stress such as skydiving, mountain climbing, or major emotional stress should pose little absolute risk. Nonetheless, even in young individuals without significant atherosclerosis, a major extraneous, sympathetic surge that results from cocaine usage can trigger MI and sudden death or be a mechanism for subclinical plaque disruption and progression of atherosclerosis.

Fourth, individuals at increased absolute risk could modify or avoid the specific triggering activity. Although data are limited, common-sense strategies include using a snow blower service instead of shoveling snow; avoiding an angry confrontation with a neighbor or incorporating relaxation strategies at the time of a severe emotional stress; providing social support and sensitivity at the time of bereavement; limiting hand contact with those with respiratory infection; having smaller, less lipid-rich meals accompanied by foods containing antioxidants, such as fruit and vegetables; and ensuring adequate air conditioning and limiting time outdoors during days of extreme temperatures or high pollution. Although these measures may seem obvious, they are practical, nonpharmacological, and often not followed. From a public health perspective, the recognition that pollution can acutely trigger CVD provides further impetus for tighter pollution control.

Finally, medication could be taken in an effort to sever the link between the stressor and the potential pathophysiological consequences. Although unproven, protection against triggered events may be a contributing mechanism of action for therapies that are effective in prevention, such as aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors.

### Areas for Future Research

**Characterization of Triggers**

Although there has been much progress in defining the triggers of acute CVD, there remains a need to better characterize the frequency of specific triggers and their relative, absolute, and attributable risks, as well as to better understand the modifiers of risk, including individual differences in response to the same trigger. The incorporation of triggering questions into prospective trials of medication and devices, including implantable defibrillators, would be useful. Further study is needed to differentiate excess CVD events from events that would have occurred several hours or days later if the patient had not been exposed to the earlier trigger. The mechanisms by which stressors trigger MI, sudden cardiac death, and stroke and the potential protective role of routine and novel therapies need to be better characterized in both human and animal models. For instance, a better understanding of the role of tachycardia and acute inflammation in plaque rupture may lead to evaluation of heart rate–lowering drugs or agents such as matrix metalloproteinase inhibitors and statins against triggered events.

**Multiple Triggers**

One fourth of MILIS study subjects who reported a possible trigger identified ≥2 possible triggers. Further study is required on the effect on risk of multiple concurrent triggers, such as heavy exertion during a respiratory infection, or at the time of emotional stress, such as rushing to catch a plane while carrying a suitcase.

**Progression of Atherosclerosis**

The contribution of triggers such as severe emotional stress to the progression of vascular disease, mediated by catecholamine-induced uptake of low-density lipoprotein into vessel walls, endothelial dysfunction, and asymptomatic plaque rupture, requires further study. It may be difficult to separate patients for whom MI is the first clinical event from those with premonitory symptoms that may have been triggered by a stressor or those in whom culprit plaque rupture occurred unrecognized 1 to 2 weeks before the MI. In the SHEEP study, the relative risk of exertion triggering MI, which was 3.3 overall, increased to 6.1 among those without premonitory symptoms.

**Relationship Between Triggering and Plaque Vulnerability**

An inverse relation probably exists between the degree of plaque vulnerability and the intensity of the trigger required to produce rupture and thrombosis. Thus, an individual with an extremely vulnerable plaque or severe stenosis may develop occlusion without a demonstrable trigger, whereas...
someone with no vulnerable lesions or stenosis may require a major identifiable stressor to trigger plaque rupture and thrombosis. Plaque disruption is often present at >1 location in the same individual. For instance, Takano et al.\textsuperscript{100} reported an average of 1.67 ruptured plaques per person in nonculprit vessels of patients with acute coronary syndromes. This may reflect a general increase in vascular inflammatory activity associated with higher CRP levels.\textsuperscript{101} These considerations suggest that transient increases in plaque vulnerability may occur over weeks and months in association with bereavement or other longer-term stressors.\textsuperscript{102} A preventive approach, which would require validation in randomized trials, would be to initiate or increase the dose of an agent that may reduce inflammation and plaque vulnerability over these hazard intervals. Such a therapeutic approach would be aided by a means to assess plaque vulnerability.\textsuperscript{5} Although most plaque vulnerability detectors under investigation require an invasive approach, in the future there may be plasma markers or noninvasive tests to assess vulnerability as a guide to preventive therapy.

**Therapeutic Approach**

Many individuals at moderate to high risk of CVD are already taking daily medication that, as part of their mechanism of action, may be protective against triggered events. Indeed, protection against triggers, some of which cannot be anticipated, provides a further rationale for daily evidence-based therapy that is active over a 24-hour period. Trigger-related considerations do not in any way detract from the recommendation for long-term daily use of medication established to be effective in primary and secondary prevention.

For those taking daily evidence-based therapy or for whom regular therapy is not indicated, it remains unknown whether incremental therapy during a hazard period of increased risk is useful. Large numbers of randomized individuals would be required to test whether short-term strategies directed at specific triggers would be feasible or would lower the occurrence of CVD events beyond current preventive approaches. However, the recognition that bereavement and other prolonged periods of severe stress are associated with increased CVD risk should provide an impetus for physicians to review such individuals more closely for symptoms or changes in blood pressure, lipids, and other risk factors. Although the physician is best placed to initiate and monitor therapy, the active involvement of patients in their care is consistent with moves toward greater patient awareness and may improve compliance and stimulate individuals to lower their overall cardiac risk.\textsuperscript{103} Underutilization of evidence-based therapies, such as \(\beta\)-blockers, is well recognized among patients before MI, despite known CVD or risk factors,\textsuperscript{104} and long-term adherence in secondary prevention remains suboptimal.\textsuperscript{105} The demonstration that \(\beta\)-blockers reduce somatic symptoms associated with anxiety has led to an informal use for performance anxiety.\textsuperscript{106} Patients accept the prophylactic use of sublingual nitroglycerin for exercise-induced angina and “pill in the pocket” strategies for supraventricular tachycardia. Although the focus has been on prevention, a potential benefit that needs to be evaluated of having medication such as aspirin in the wallet or handbag is that it is immediately available if symptoms of MI develop.

**Absolute Risk Versus Relative Risk**

Triggering findings, such as the observation that up to 10% of ST-elevation MIs may be triggered by heavy physical exertion, provide insight into the mechanism of the onset of CVD and its prevention. These data, however, together with those of relative risk, must be balanced by the recognition that the absolute risk for any potential triggering activity to cause MI is the most important clinical measure. If the absolute risk is extremely small, then even a substantial increase in that risk may not be clinically meaningful nor warrant a specific therapy. It would be cause for significant concern if a focus on small risks associated with stressors of daily living led to excessive caution and reduced enjoyment of life, because many pleasures of life are associated with adrenergic activation. Hopefully, recognition of the low absolute risk for stressors such as heavy physical activity, and the ability of regular moderate activity to attenuate the immediate risk, would alleviate anxiety and provide reassurance and support for current recommendations regarding regular activity. Public health measures such as curbs on pollution, vaccinations for influenza, wider provision of public-access defibrillators, and optimal acute response to disasters\textsuperscript{31} may have a significant impact on numbers of triggered MIs and sudden cardiac deaths, even though the risk reduction for any individual is low.

**Conclusion**

It has now been established that nonfatal MI, stroke, and sudden cardiac death can be precipitated by triggers; however, the clinical utility of these findings remains unclear. We have presented a hypothetical framework for acute risk reduction that complements long-term preventive strategies and emphasizes short-term changes in risk of plaque rupture and thrombosis due to triggering. Greater understanding of triggering, from the basic science to the epidemiological level, should facilitate progress. The means of prevention would not be to eliminate all potential triggering activities (an undesirable and unattainable goal) but to design strategies that can be evaluated in randomized studies for their ability to sever the linkage between a trigger and its potentially adverse consequence. A preventive approach to short-term risk could have made a significant difference to John Hunter (1728–1793), surgeon and medical educator at St George’s Hospital, London, United Kingdom, who presciently stated, “My life is at the mercy of any rogue who chooses to provoke me” and indeed died shortly after an acrimonious meeting with hospital administrators.

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