Acute and Subacute Triggers of Cardiovascular Events

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Inability to predict short-term cardiovascular (CV) events and take immediate preemptive actions has long been the Achilles heel of cardiology. However, certain triggers of these events have come to light. Although these triggers are nonspecific and are part of normal life, studying their temporal relationship with the onset of CV events provides an opportunity to alert high-risk atherosclerotic patients who may be most vulnerable to such triggers, the "vulnerable patient". Herein, we review the literature and shed light on the epidemiology and underlying pathophysiology of different triggers. We describe that certain adrenergic triggers can precipitate a CV event within minutes or hours; whereas triggers that elicit an immune or inflammatory response such as infections may tip an asymptomatic "vulnerable patient" to become symptomatic days and weeks later. In conclusion, healthcare providers should counsel high-risk CV patients (e.g., in secondary prevention clinics or those with coronary artery Calcium > 75th percentile) on the topic, advise them to avoid such triggers, take protective measures once exposed, and seek emergency care immediately after becoming symptomatic after such triggers. Furthermore, clinical trials targeting triggers (prevention or intervention) are needed. **(Am J Cardiol 2018;122:2157−2165)**

Triggers: The Straw that Breaks the Vulnerable Patient's Back

There is consensus in opinion leaders that myocardial infarction (MI) and other forms of acute coronary syndromes are the result of a series of chronic interactions involving the vascular wall, the metabolic system, the immune system, the coagulation/anticoagulation system, and the myocardium. This process takes decades to reach a tipping point and surface clinically however it is not clear what defines the slope of the trajectory to the tipping point and why certain patients with similar risk factor profiles have different trajectories and outcomes.

The Perfect Storm of Vulnerability

There is also a consensus in opinion leaders[1−3] that points to the formation of a perfect storm of vulnerability to cardiovascular (CV) events. The more perfect, the more catastrophic. Generally, the sources of vulnerability in this storm arise from 3 major players: atherosclerotic plaque, blood, and myocardium (Figure 1). Characteristics of these vulnerability players are that the plaque is unstable, the blood is thrombogenic, and the myocardium is arythmogenic (Tables 1−3). The variables involved in such a storm of vulnerability are numerous and their interactions are quite complex. However, one thing is becoming increasingly clear is that the immune system plays a key role in such a transition from asymptomatic status to symptomatic.

Circadian Variation and Waking from Sleep

Transient myocardial ischemia, MI, thrombotic stroke, and sudden cardiac death each occur in a circadian pattern with increased frequency in the morning.[4−6] Likewise, plasma cortisol and epinephrine levels, sympathetic activity, blood pressure, heart rate, coronary blood flow, blood viscosity, and platelet aggregability each peak in the morning whereas core temperature and fibrinolytic activity trough in the morning.[5,7] The parameters described above vary depending on sleep cycles rather than daylight.[8,9] Linking these circadian patterns suggested that acute pathophysiologic processes trigger clinical CV events.

Numerous other acute triggers of CV events have been delineated (Table 4). Acute triggers are common: 48.5% of 849 patients with MI reported at least one possible trigger, including emotional upset (18.4%), moderate physical activity (14.1%), and heavy physical activity (8.7%); and others included lack of sleep and overeating.[10]

Physical Trigger—Physical Exertion

Physical activity increases the risk for MI[11] and the increased risk is directly related to the amount of exertion.[12] In patients with coronary disease, in the hour after heavy physical exertion relative risks of MI of 107, 19.4, 8.6, and 2.4 were observed in patients who usually exercised < 1 time/week, 1 to 2 times/week, 3 to 4 times/week, and > 5 times/week, respectively.[11] Shoveling snow was associated with CV mortality.[13] Sexual activity is associated with MI in sedentary patients.[14] The risk of "love death" (CV death during sexual activity) increases when the partner is outside of marriage.[15]

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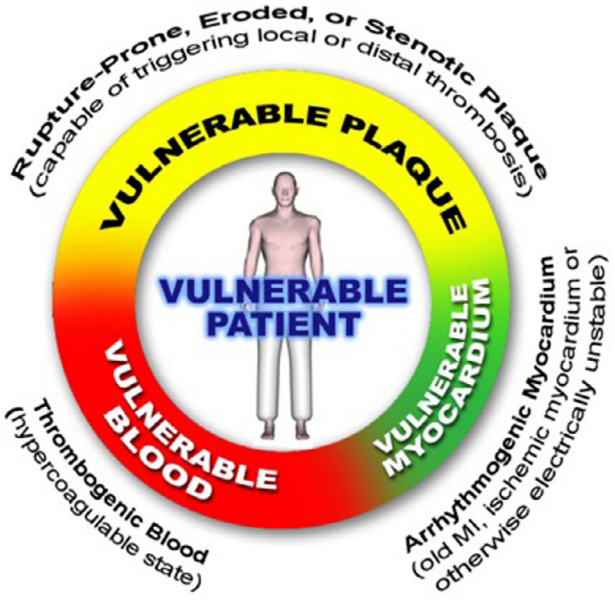

Figure 1. The perfect storm of vulnerability (central illustration).

Table 1
Markers of vulnerable plaque

Morphology/Structure
• Thin cap
• Large lipid core size
• Plaque stenosis (luminal narrowing)
• Expansive remodeling (versus constrictive remodeling)
• Color (yellow, glistening yellow, red, etc)
• Lipid content versus collagen content; mechanical stability (stiffness and elasticity)
• Calcification burden and pattern (nodule versus scattered, superficial versus deep, etc)
• Shear stress (flow pattern throughout the coronary artery)
Activity/Function
• Plaque inflammation (macrophage density, rate of monocyte infiltration and density of activated T cells)
• Endothelial denudation or dysfunction (local nitric oxide production, anti- or pro-coagulation properties of the endothelium)
• Plaque oxidative stress
• Superficial platelet aggregation and fibrin deposition (residual mural thrombus)
• Rate of apoptosis (apoptosis protein markers, coronary microparticles, etc)
• Angiogenesis, leaking vasa vasorum, and intraplaque hemorrhage
• Matrix-digesting enzyme activity in the cap (matrix metalloproteinases 2, 3, 9, etc)
Pan-arterial
• Transcoronary gradient of serum markers of vulnerability
• Total coronary calcium burden
• Total coronary vasoreactivity (endothelial function)
• Total arterial burden of plaque including peripheral (carotid intima medial thickness, etc)

Physical Trigger—Surgery

Cardiac complications are the largest contributor to postoperative mortality. The majority of perioperative MIs are type II events while type I events also occur Surgery increases the risk of type I MIs by increasing catecholamines, cortisol, heart rate, blood pressure, coronary vasoconstriction and shear stress, and promoting a procoagulant state. Surgery and anesthesia can precipitate type II MIs by adversely influencing myocardial oxygen supply and demand via hypotension, anemia, hypoxia, and hypervolemia, which can worsen systolic and diastolic dysfunction.[16]

Anxiety, Emotional Upset, and Acute Mental Stress

Abundant data correlates anxiety and acute mental stress with adverse CV events.[17,18–20] Ischemia induced by the mental stressors public speaking and mental arithmetic was associated with subsequent cardiac events.[21] In patients with ischemic heart disease (IHD) tension, sadness, or frustration more than doubled the likelihood of ischemia on ambulatory electrocardiographic monitoring.[19] Acute MI was associated with an episode of anger,[18] a high-pressure deadline at work,[22] high-job strain (high-psychological demands and low-decision latitude),[17] and bereavement after the death of a loved one.[23] CV events occur least frequently on Sundays (when most people are not working) and occur with 30% to 33% increased RR on Mondays in working people.[24] Patients with an emotional trigger had increased anxiety levels after MI, increased 30-day rehospitalization rates (27.6% vs 19.3%, $p < 0.05$) and a trend towards increased 30-day mortality rates (4.1% vs 2.0%, $p = 0.10$).[25] Regional brain activity (resting amygdalar activity) was linked with risk of CV events. After multivariate adjustment, Amygdalar activity was associated with increased bone-marrow activity ($r = 0.47$; $p < 0.0001$), arterial inflammation ($r = 0.49$; $p < 0.0001$), and risk of CV events (standardised hazard ratio 1.59, 95% confidence interval 1.27 to 1.98; $p < 0.0001$). This study sheds novel mechanistic light on the underlying links between anxiety, inflammation, and CV events. Their findings support the notion that a wave of inflammatory tsunami may be created by emotional stressors that could tip the scale of vulnerability in a high-risk patient toward an event.[26]

Community-Wide Events

Acute mental stress is the common pathway whereby stressful or traumatizing events are associated with

Table 2
Markers of vulnerable (thrombogenic) blood

- Markers of blood hypercoagulability (fibrinogen, D-dimer, and factor V Leiden, etc)
- Increased platelet activation and aggregation (gene polymorphisms of platelet glycoproteins IIb/IIIa, Ia/IIa, Ib/IX, etc)
- Increased coagulation factors (clotting of factors V, VII, and VIII; von Willebrand factor; factor XIII; etc)
- Decreased anticoagulation factors (proteins S and C, thrombomodulin, antithrombin III, etc)
- Decreased endogenous fibrinolysis activity (reduced t-PA, increased PAI-1, certain PAI-1 polymorphisms, etc)
- Prothrombin mutation (G20210A, etc)
- Other thrombogenic factors (anticardiolipin antibodies, thrombocytosis, sickle cell disease, polycythemia, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, etc)
- Increased viscosity
- Nonspecific markers of inflammation (C-reactive protein, CD40L, ICAM-1, VCAM-1, P-selectin, leukocytosis, and other serological merkers related to the immune system, etc; these markers are not specific to atherosclerosis)
- Serum markers of metabolic syndrome (diabetes mellitus, hypertriglyceridemia, etc)
- Specific markers of immune activation (anti-LDL antibody, anti-HSP antibody, etc)
- Markers of lipid peroxidation (ox-LDL, ox-HDL, etc)
- Matrix metalloproteinase-12
- Circulating apoptosis maker(s), (exosomes, Fas/Fas ligand, not specific to plaque)
- Circulating nonesterified fatty acids (NEFA)

HDL = high-density lipoprotein; ICAM = intercellular adhesion molecule; LDL = low-density lipoprotein; PAI-1 = plasminogen activator inhibitor; t-PA = tissue plasminogen activator; VCAM = vascular cell adhesion molecule.

Table 3
Markers of vulnerable (arrhythmogenic) myocardium

With atherosclerosis derived myocardial ischemia as shown by:
Electrocardiography (ECG) abnormalities
- During rest
- During stress test
- Silent ischemia (ST changes on Holter monitoring, etc)

Perfusion and viability disorder
- Positron emission tomography (PET) scan
- Single-photon emission computed tomography (SPECT)

Wall motion abnormalities
- Echocardiography
- Magnetic resonance (MR) imaging
- X-ray ventriculogram
- Multi-slice computer tomography (MSCT)

Without atherosclerosis-derived myocardial ischemia:
Sympathetic hyperactivity
Impaired autonomic reactivity
Left ventricular hypertrophy
Anomalous origination of a coronary artery
Myocarditis
Myocardial bridging

Electrophysiological disorders (Long-QT syndrome, Brugada syndrome, Wolff-Parkinson-White syndrome, Sinus and atrioventricular conduction disturbances, catecholaminergic polymorphic ventricular tachycardia, T-wave alternans, drug-induced Torsades de pointes, Commotion cordis, etc)

increased CV end points across populations on a large scale. Large earthquakes frighten affected communities and were associated with cardiac deaths in Athens, Greece,[27] Northridge, CA,[28–30] and Hanshin-Awaji, Japan.[31]

Investigations of other large-scale events reported mixed results. A community near Tel Aviv, Israel did not suffer directly from missle attacks but could hear missile explosions in neighboring communities. This anxiety was associated with marked increases in MI and sudden death during the first days of the Gulf War.[32] Ventricular arrhythmias[33] and MI[34] rates increased after September 11, 2001 within and remotely from New York City. However, in larger sample sizes and when seasonal variation was accounted for no association was found between the September 11 terrorist attacks and CV-related hospital admissions and death rates in New York City.[35,36] The Los Angeles riots in 1992 increased total deaths and deaths from violence or trauma but there was no association with atherosclerotic CV disease deaths in Los Angeles in the days after the riots.[37] Beyond seasonal variation, cardiac deaths increase by 4.65% during the Christmas and New Year's holidays, which may relate to the mental stress of holiday preparation, shopping, financial pressure, and family gatherings.[38,39]

All considered, it appears that an event must cause marked acute mental stress across the entire study population for community-wide CV event rates to be affected, as with earthquakes and audible missile strikes.

Sporting Events

Reviewed elsewhere, sporting events have been associated with increased CV events when games elicit strong negative emotions in many passionate fans.[40–43] "Risky" games share many of the following features: high importance, high intensity or drama, widespread and avid community support, and a loss (especially an unexpected loss). Interestingly, victories have been associated with decreased CV events in highly supportive communities.

Throughout a competitive game the spectating experience is similar for passionate fans on both sides who experience anxiety which may manifest as palpitations and diaphoresis. Fans from both sides typically engage in similar behaviors including social gatherings, eating fatty foods, alcoholic beverages, smoking, and gambling. The observation, however, that the game's outcome matters that high-stakes losses often correlate with increased CV events and monumental victories have been associated with decreased CV events, suggests that high-risk behaviors are not the sole underlying pathophysiology. Emotions, both positive and negative, influence CV events.

Pathophysiology Linking Acute Mental Stress to CV Events

Mental stress triggers the body's fight or flight response which augments humans' ability to cope with danger by impairing vagal tone and upregulating the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenal-medullary system.[44–46] These same physiologic responses, however, also have the potential to cause endothelial

Table 4
Clinical triggers of cardiovascular events

Physical	Emotional/mental	Community-wide event	Toxin
Physical exertion:	Anger, frustration	Monday (working population)	Cigarettes
Snow shoveling:	Anxiety, tension	Christmas holiday	Marijuana
Sexual activity:	Job strain (deadlines)	New Year's holiday	Cocaine
Surgery	Bereavement, grief	Earthquakes	
Waking from sleep	Sexual excitement and engagement	Threat of violence (missile attacks)	Air pollution
Respiratory infections (Influenza)		Dramatic sporting events	
Cold temperature			
Extreme heat			
Low barometric pressure			

dysfunction, myocardial ischemia, plaque rupture, platelet aggregation, and arrhythmias (Figure 2). The sympathetic-adrenal-medullary system increases heart rate, blood pressure, ventricular contractility, cardiac work index, systemic vascular resistance, coronary resistance, coronary shear stress, thrombus formation, and the risk of arrhythmias.[46] The hypothalamic-pituitary-adrenocortical axis increases plasma cortisol and corticotrophin-releasing hormone. Cortisol increases blood pressure and plasma glucose levels and alters the inflammatory response and platelet function.[47] Corticotrophin-releasing hormone increases the inflammatory response, monocyte-endothelium cell adhesion, macrophage activation, and endothelin-1 release.[48,49]

Mental stress induced paradoxical vasoconstriction (endothelial dysfunction) occurs especially at locations of coronary artery stenosis and the degree of vasoconstriction correlates with the extent of atherosclerosis.[50] Mental stress increases systemic vascular resistance, the degree of which correlates with the degree of endothelial dysfunction and with decreases in ejection fraction and myocardial ischemia.[51,52] In patients with stable angina mental stress testing increases the rate-pressure product, plasma epinephrine and norepinephrine levels and autonomic arousal.[51] In patients with previous MI, mental stress testing (public speaking) increased blood pressure and cardiac index. However, compared with patients without an emotional trigger, patient with a previous emotionally-triggerred MI featured delayed recovery of blood pressure, delayed recovery of cardiac index and significant increases in leucocyte-, monocyte-, and neutrophil-platelet aggregates.[53]

In patients with endothelial dysfunction the ability to increase tissue-type plasminogen activator activity is impaired whereas the mental stress-induced increase in fibrinogen and von Willebrand factor level is preserved resulting in a stress-induced procoagulant state.[54] Compared with baseline levels, patients with previously scheduled, routine appointments for hypertension demonstrated increases in blood pressure, hematocrit, and levels of fibrinogen, D-dimer, von Willebrand factor, and tissue-type plasminogen activator antigen after the Hanshin-Awaji Earthquake.[31,55] Patients with stress-associated MI related to World Cup soccer matches had increased levels of inflammatory and vasoconstrictive mediators including endothelin-1 compared with healthy controls and with patients with acute MI without an emotional trigger.[56] Holter-monitor data demonstrated increased sympathetic activity (heart rate) and withdrawal of parasympathetic activity (heart-rate variability) beginning at the time of a large earthquake in Taiwan and lasting approximately 40 minutes.[56] Patients with significant ST segment depression (27% of patients) had larger surges of sympathetic over parasympathetic activity.[57]

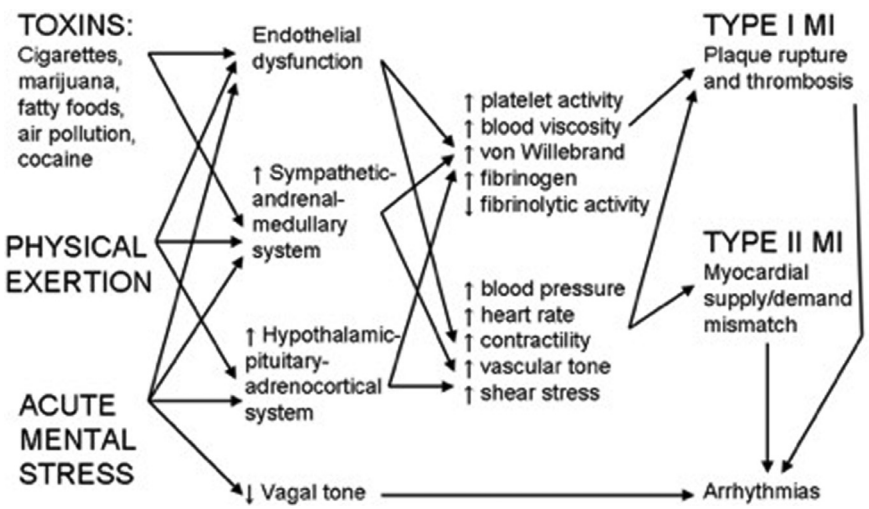

Figure 2. Pathways whereby acute triggers influence physiologic processes which increase the risk of cardiovascular events. ↑ = increase, ↓ = decrease, MI = myocardial infarction.

The processes described above enhance a healthy person's ability to respond to danger. However, in a patient with preexisting endothelial dysfunction and coronary stenosis these same processes adversely alter the myocardial supply-demand ratio and can even trigger acute CV events.

Seasonal Variation, Cold Temperatures, Influenza, and Weather

In addition to daily circadian variation CV events also occur with seasonal variation with increased rates in the winter,[24] including in winter in the southern hemisphere in Australia.[58] Multivariate analysis indicates that cold temperatures and respiratory infection are the most important factors contributing to increased all-cause and CV deaths in the winter (dew point temperature, precipitation, barometric pressure, air pollution, hours of daylight, and day of week were also considered).[24] All-cause death rate increased by 0.49% for every 1˚C decrease.[24] Cold temperatures enhance sympathetic stimulation and increase blood pressure, vascular resistance, fibrinogen level, platelet count, blood viscosity, and some clotting factors.[59–61] Further, cholesterol crystallization is enhanced with small changes in core temperature which increases the risk of plaque rupture.[62]

The multivariate analysis described above found all-cause, circulatory and coronary heart disease deaths to be strongly associated with the 14-day lag of influenza levels.[24] Acute MI was associated with acute respiratory tract infection within 1 to 5 days (odds ratio 3.6), within 6 to 10 days (odds ratio 2.3), and within 11 to 15 days (odds ratio 1.8).[63] Ischemic stroke was associated with febrile illness during the previous month, 80% of which were respiratory infections.[64] Moreover, influenza vaccination has proved efficacy in reducing the risk of MI in patients with coronary heart disease.[65] By multivariate analysis vaccination in the current year remained strongly associated with freedom from MI with an odds ratio of 0.33. Accordingly, influenza vaccination is recommended by all major public health advisories for all persons with CV disease, diabetes or at least 50 years of age.

Toxins

Air pollution has a small acute and subacute association with all-cause and cardiac deaths.[24,66] Cigarette smoking acutely impairs endothelial function.[67] Ischemia on ambulatory electrocardiographic monitoring was >5 times more likely while smoking cigarettes compared with while not smoking.[12] The relative risk of MI increases 4.8-fold within 1 hour of smoking marijuana[68] and increases 23.7-fold after using cocaine.[69] Cocaine commonly leads users to seek emergency attention for chest pain and approximately 6% of patients with cocaine-associated chest pain have acute MI through a variety of mechanisms.[70]

Takotsubo (Stress) Cardiomyopathy

Of 1,750 patients with takotsubo cardiomyopathy from The International Takotsubo Registry[71,72] 71.5% had an identifiable trigger, including physical triggers (36.0%), emotional triggers (27.7%), and both physical and emotional triggers (7.8%). Physical triggers included acute respiratory failure, surgery, fracture, central nervous system conditions, infection, and malignancy. Emotional triggers included grief/loss, panic/fear/anxiety, interpersonal conflict, anger/frustration, and financial/employment problems.[71,72] The pathophysiology of takotsubo cardiomyopathy is believed to involve myocardial stunning from microvascular dysfunction, which may result from catecholamine excess and/or from direct innervation originating in the brain stem.[73]

Spontaneous Coronary Artery Dissection

Spontaneous coronary artery dissection is increasingly recognized as a cause of MI. Emotional (48.3%) and physical (28.1%) stressors were common precipitants of spontaneous dissection and patients often also had systemic inflammatory disease (11.9%) and fibromuscular dysplasia (62.7%).[74]

Acute Versus Subacute Triggers

Considering the time interval between the exposure to various triggers discussed in this manuscript and CV events, one can classify them into 2 main categories, acute versus subacute. Triggers such as shocking news, shoveling snow, or vigorous physical activity are in nature an acute trigger and may result in an event in a very short term (minutes or hours), whereas triggers like influenza infection or relapse of an autoimmune disease, or a depressive mood that spikes inflammatory response would fall under subacute category resulting in a more distant event (days, weeks, or even months).

Infection; a Subacute Trigger

The notion that infection of atherosclerotic plaques with certain pathogens (e.g., Chlamydia) causes acute coronary events, and therefore antibiotic treatment could be a therapeutic option has long lost steam. Several clinical trials dramatically failed to prove that targeted antimicrobial treatments improve outcomes. However, this dramatic failure did not shut the door to countless research and publications showing a strong link between infection and CV events. Influenza infection exerts prominent inflammatory and thrombotic effects on atherosclerotic plaques of apolipoprotein E-deficient mice by increasing the homing of macrophages and other inflammatory cells into the arterial wall.[75] Influenza virus can directly infect and reside in atherosclerotic arteries and infection was associated with systemic and arterial-level proinflammatory changes.[76] Exaggerated inflammation in atherosclerotic plaques may tip a stable plaque to unstable and result in plaque rupture or other atherothrombotic events. Infection is most likely not an acute trigger as these changes at plaque levels may take days or weeks. However, it is now clear that infection, particularly influenza can enhance the dynamics of instability both inside an unstable plaque and in the circulating blood.[77–80]

Clopidogrel versus aspirin in patients at risk of ischemic events trial[81] showed that short-term changes in leukocyte counts result in an increased period of stroke risk. High leukocyte count in 34.2% of stroke patients versus 18% of control group suggests a strong association of leukocytosis and coagulation disorder, resulting in increased stroke prevalence.[82] Platelets play a major role in atherothrombosis and infections such as pneumonia with pneumococcus can cause platelet activation and aggregation.[83] Persistent enterovirus infection has shown a significant role for the development of acute stroke.[84] The RR for MI occurring within 1 to 7 days after respiratory infection symptoms was 17.0 (95% confidence interval 13.2 to 21.8), and declined with subsequent time periods.[85] Two pathways are hypothesized to link cold exposure and ischemic heart disease (IHD): a direct pathway and an indirect pathway through influenza infection. IHD incidence through the direct pathway occurred mostly within 10 days, while IHD through influenza infection peaked at 4 to 6 days, followed by delayed incidences of up to 20 to 30 days. Influenza can therefore be a plausible explanation for the delayed association between cold exposure and CV mortality.[86]

The CANTOS trial[87] recently provided compelling evidence in support of the inflammatory hypothesis by testing canakinumab, a monoclonal antibody targeting interleukin-1β in a randomized trial of 10,061 patients with previous myocardial infarction and elevated C-reactive protein levels. Compared with placebo, patients in the 150 mg canakinumab group had a 15% lower risk of the combined end point nonfatal myocardial infarction, nonfatal stroke, or CV death.

Acute Triggers—Implications for Therapy

Now that the link between CV events and acute triggers has been established it stands to reason that CV events might be reduce if high-risk patients could either avoid such triggers or be educated to prepare and counter their potential detrimental effects, previous or after the exposure. High-risk patients include those with established CV disease but also those with high-coronary calcium scores particularly those in the top 90th percentile. Such high-risk persons should avoid acute triggers including snow shoveling, smoking marijuana, cocaine, large fatty meals, vigorous physical activity without conditioning, and air pollution. If snow shoveling cannot be avoided then it should be done with warm clothing and in small-to-moderate increments rather than all at once. Exercise regimens should be light and modest at first and increase gradually over time (overexertion should be definitely avoided). Thanks to previous trigger studies,[65] taking flu vaccine is already in the national guidelines for secondary prevention but has yet to be incorporated for primary prevention of ASCVD in the high-risk asymptomatic (vulnerable) patients. Similarly, recommending prophylactic therapies to keep blood pressure and heart rate in check before, during, and after major sport events for die-heart fans is reasonable but yet to be tested in clinical trials. Unfortunately, such epidemiological trials currently do not seem to be a priority of the NIH. We hope with the growing awareness of triggers management similar to risk factor management, the NIH decision makers will realize the potential population-based life-saving effects of triggers management in high-risk patients and support such trials.

Regarding perioperative MI, there is little to no evidence supporting the use of aspirin, calcium-channel blockers and alpha2 agonists. Retrospective studies indicate reduced perioperative MI with use of statins and statins should be continued throughout the perioperative period. Prophylactic β blockade is strongly debated but consensus agrees that long-term β blockade should be continued throughout the perioperative period. Perioperatively intravenous β blockers are recommended in managing even modest increases in heart rate. Prophylactic coronary revascularization is rarely recommended, but may be considered especially in patients who underwent major vascular surgery.[16]

Common medications used for prevention of cardiovascular disease may derive efficacy by tempering the impact of triggering events. Beta-blockers reduce ischemic episodes and CV events in patients with CV disease and suppress the morning increase in blood pressure, heart rate, and ischemic episodes, suppress the circadian pattern in CV events, and decrease the incidence of triggered MIs.[88,10] Aspirin likewise has greater effect in the morning hours and decreases the circadian pattern of acute MI.[87] Angiotensin-converting enzyme inhibitors and statins improve endothelial function and reduce mortality and CV end points in a variety of patient populations. Angiotensin-converting enzyme inhibitors may reduce the incidence of triggered acute MI.[25] Statins reduce the lipid and macrophage content of atherosclerotic plaques and reduce progression of mild and moderate plaques to vulnerable plaques.[89] Medication compliance before foreseeable triggering events may be especially important including before physical exertion, high-stakes sporting events, Christmas and New Year's holidays. Taking long-acting medications before bedtime may ensure adequate plasma concentrations upon waking in the morning and may minimize the typical morning increase in CV events. Dietary modifications with Mediterranean and/or plant-based diets should be considered as a nonpharmacologic approach to reducing inflammation. In this light, counseling patients to fully comply with AHA/ACC guidelines for lifestyle modifications is needed.[90,91]

Some patients with high anxiety may benefit from psychiatric counseling or antianxiety medications, though the effects of antianxiety medications on cardiovascular end points are unknown.[92,93] In patients with coronary disease and documented ischemia a stress management program reduced cardiac events compared with an exercise program and reduced cardiac events while also improving treadmill time, lipid profile, and weight loss compared with usual medical care alone.[19] Meta-analyses indicate that compared with other relaxation techniques transcendental meditation best reduces stress and anxiety and improves psychologic health.[94] Transcendental meditation reduces the sympathetic response to mental stress,[95] carotid artery intima-media thickness and left ventricular hypertrophy, decreases blood pressure and cholesterol, and improves exercise tolerance.[94,96] Combined data from 2 randomized trials with a mean follow-up of 7.6 $\pm$ 3.5 years show that transcendental meditation reduces all-cause mortality (relative risk 0.77;

p = 0.039) and cardiovascular mortality (relative risk 0.70; p = 0.045) compared with control groups.[94,96] Transcendental meditation is practiced for 20 minutes twice a day and reduces mental and physical activity by inducing a state of "transcendental consciousness."

Last not least, cardiology lacks clinical trials on triggers. Such trials can evaluate certain preemptive measures including pharmaceutical interventions before expected triggers such as sports events, or after unpredicted triggers such as emotional stressors or natural events such as earthquake. Even if such trials show a small effect, given the large exposure and target population, the outcome benefits may amount to levels seen with breakthrough drugs.

Conclusion

Acute and subacute triggers commonly precipitate CV events. Types of acute triggers span a wide spectrum from physical exertion to cocaine to job stress to spectating sporting events. Most triggers affect more than 1 element of the vulnerable patient (plaque, blood, myocardium). In many cases they increase the risk of both type I (plaque rupture) and type II (myocardial oxygen supply-demand mismatch) acute MIs. The concept of acute triggers of CV events has expanded our understanding of CV disease and has implications for therapies. Physicians should counsel their patients, particularly high-risk patients (e.g., in secondary prevention clinics and those in primary prevention clinics with Coronary Artery Calcium > 75th percentile) about triggers, advise them to avoid such triggers, take protective measures once exposed to triggers, and seek emergency care as soon as they become symptomatic after such triggers. Last not least, cardiology lacks and needs clinical trials on triggers.

Disclosures

The authors have no conflicts of interest to disclose.

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