The International Journal of Lower Extremity Wounds
2018, Vol. 17(4) 261–267

DOI: 10.1177/1534734618810944
journals.sagepub.com/home/ijl
SAGE

Acute Cardiac Events in Patients With Severe Limb Infection

Mohita Singh, MD[1], Khurrum Khan, MD[2], Evan Fisch, BS[2], Christopher Frey, BS[2], Kristen Mathias, BA[2], Hani Jneid, MD[2,3], Daniel M. Musher, MD[2,3], and Neal R. Barshes, MD, MPH[2,3]

Abstract

Recent studies have shown an association between infections, such as influenza, pneumonia, or bacteremia, and acute cardiac events. We studied the association between foot infection and myocardial infarction, arrhythmia, and/or congestive heart failure. We analyzed the records of 318 consecutive episodes of deep soft tissue infection, gangrene, and/or osteomyelitis in 274 patients referred to a vascular surgery service at a tertiary center. We identified 24 acute cardiac events in 21 of 318 (6.6%) episodes of foot infection or foot gangrene. These 24 events included 11 new myocardial infarctions (3.5%), 8 episodes of new onset or worsening congestive heart failure (2.5%), and 5 new arrhythmias (1.6%). Tachycardia and systemic inflammatory response syndrome were associated with acute cardiac events ($P < .05$ for each). The 1-year survival of patients with acute cardiac events was 50.4%, significantly lower than the 91.7% 1-year survival of patients without acute cardiac events ($P < .0015$). Acute cardiac complications are not uncommon among patients presenting with severe foot infection and are associated with a high 1-year mortality. Primary care physicians, cardiologists, and vascular and orthopedic surgeons must keep a high index of suspicion for the occurrence of an acute cardiac event.

Keywords

acute coronary syndrome, myocardial infarct, arrhythmia, acute heart failure, diabetic foot infection, mortality

The incidence of foot infection in patients with diabetes has been reported to be as high as 36.5 per 1000 persons per year, with underlying osteomyelitis present in 20% to 68% of these patients.[1-10] More than 60% of all nontraumatic lower limb amputations are performed in diabetic individuals, accounting for nearly 82 000 lower limb amputations per year in the United States.[11,12] Recent studies have shown a high degree of association between infections, such as influenza, pneumonia, or bacteremia, and acute cardiac events.[13-20] The principal proposed mechanisms are that inflammatory reactions elsewhere in the body precipitate inflammation and disruption of a vulnerable or at-risk coronary artery plaque or that acute physiologic stress causes cardiac ischemia.[21] We hypothesized that severe foot infections may similarly precipitate acute cardiac events, especially because they tend to occur in patients with cardiac risk factors such as poorly controlled diabetes mellitus or peripheral vascular disease. Accordingly, we designed this study to explore the incidence of acute cardiac events, including myocardial infarction (MI), arrhythmia, and congestive heart failure (CHF) in patients with severe limb infections.

Methods

Study Population

The Vascular Surgery Service of the Michael E. DeBakey Veterans Affairs Medical Center maintains a limb salvage service that provides consultations around the clock for hospitalized patients who have potentially serious infection of the lower extremities. The general approach to management includes the following: empiric parenteral antibiotics; prompt surgical drainage with minor amputations if needed, almost always done under ankle block anesthesia and monitored anesthesia care; and either endovascular intervention or surgical bypass for patients with peripheral artery disease.

[1]UT Southwestern, Dallas, TX, USA
[2]Baylor College of Medicine, Houston, TX, USA
[3]Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA

Corresponding Author:
Mohita Singh, Division of Cardiology, Department of Internal Medicine, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA.
Email: mohita.singh@phhs.org

For the purposes of this study, we used available records to identify all patients seen by the Vascular Surgery Service between January 1, 2011, and October 31, 2017, for a deep soft tissue infection (including abscess and septic arthritis), probable or definite osteomyelitis,[22] and/or gangrene of any part of the foot. More than one episode from a single patient was included only if a subsequent infection appeared in a noncontiguous area. Infections associated with prosthetic orthopedic implants were excluded. This study was approved by the Institutional Review Board of Baylor College of Medicine and the Research Committee of the Michael E. DeBakey Veterans Affairs Medical Center.

Determination of Baseline Characteristics

The electronic medical record was reviewed to determine baseline characteristics, including patient's demographics and comorbidities, and laboratory values at the time of admission. Findings that might pertain to cardiac complications, such as chest pain, shortness of breath, palpitations, abnormal electrocardiogram, elevated B-natriuretic peptide, troponin, or CPK-MB, were recorded. We calculated a modified systemic inflammatory response syndrome (SIRS) score by substituting a serum bicarbonate level <22 mmol/L on routine serum biochemistries for the $PaCO_2$ levels on arterial blood gases.

Assessment of Cardiac Complications

Medical progress notes were reviewed for evidence of acute MI, cardiac arrhythmia, or newly recognized or worsening CHF at the time of admission or in the ensuing 30 days. In accordance with the American College of Cardiology guidelines, the diagnosis of acute MI was made based on the third universal definition of MI, specifically the presence of a serum troponin that exceeded the 99th percentile upper limit of normal in all cases but one, and an elevated creatine kinase-MB in the remaining case in addition to $\geqslant 1$ of the following: (*a*) symptoms of myocardial ischemia; (*b*) electrocardiogram changes consistent with ischemic changes; (*c*) new loss of viable myocardium or regional wall motion abnormality by imaging; and (*d*) identification of intracoronary thrombus by angiography or autopsy.[13,23] Guidelines distinguish between Type 1 MI as a spontaneous event usually due to a disrupted endothelial plaque in a coronary artery and Type 2 MI, which reflects an ischemic imbalance in cardiac oxygen demand and supply. Arrhythmias were defined as atrial flutter, atrial fibrillation, or ventricular tachycardia; terminal arrhythmias were excluded. We used Framingham study criteria to determine the development of new CHF or acute worsening of chronic CHF by searching the medical records for new symptoms, physical findings, laboratory abnormalities (such as increased B-natriuretic peptide), chest radiograph (for new or increased heart size or pulmonary vascular congestion), and echocardiograms. All cardiac findings in patients who were thought to have acute cardiac events were verified by a senior attending cardiologist. For the purposes of this analysis, only the first cardiac event associated with infection of the foot was included.

Statistical Analysis

Nonparametric analyses were used for all comparisons between groups, including the Mann-Whitney rank-sum test for continuous variables and χ^2 or Fisher's exact test for binary variables. Cox regression was used to estimate hazard ratios for multivariate models using time-to-event data, with final models created through backward selection. A P value $<.05$ was considered significant for all analyses. All statistical analyses were performed using Rstudio version 1.0.143.[24]

Results

Patient Characteristics

During the 6.8-year period, 318 episodes of foot infection or foot gangrene in 274 patients met the inclusion criteria. These included 315 episodes (99.1%) in men, 271 episodes (85.2%) in patients with diabetes, 129 episodes (40.6%) in patients with peripheral arterial disease, and 35 episodes (11.0%) in patients with end-stage renal disease. The median age was 65 years. Forty-two (13.2%) and 44 (13.8%) episodes, respectively, occurred in patients with a prior history of acute coronary syndrome (ACS) or cardiac arrhythmia (Table 1).

Acute Cardiac Events

A total of 24 acute cardiac events occurred within 30 days of admission in 21 of the 318 episodes of foot infection or foot gangrene in 274 patients, resulting in a total incidence of 6.6%. These 24 events included 11 new MI (3.5% incidence), 8 episodes of new-onset CHF or acute decompensation of chronic CHF (2.5%), and 5 new arrhythmias (1.6%). Of the 3 patients who experienced 2 cardiac complications, one had a MI with arrhythmia, one had MI with acute decompensation of heart failure, and one had a new arrhythmia with new-onset CHF (Table 2). Eight of 24 (33.3%) of these events occurred after an operation. In 14 of the 24 (58.3%) episodes, acute cardiac event(s) occurred at the time of, or within 7 days of hospitalization. Interestingly, in 7 patients (33.3%), this event was the first documentation of cardiac disease. No patient had more than one hospitalization for foot infection together with a cardiac complication. Of the 11 patients who had MI, 7 underwent coronary angiograms.

Table 1. Characteristics of Patients Presenting With Foot Infection or Foot Gangrene.

Variable	All Episodes (N = 318)	Episodes With Acute Cardiac Event(s) (n = 21)	Episodes Without Acute Cardiac Event (n = 297)	*P*
Age, years	65 (59-70)	68 (64-71)	65 (59-70)	.19
Male	315 (99.1)	21 (100)	294 (98.9)	.64
Diabetes	271 (85.2)	19 (90.4)	252 (84.8)	.48
Insulin use	185 (58.2)	13 (61.9)	172 (57.9)	.72
Hemoglobin A1c, %	7.7	7.1 (6.7-8.8)	7.8 (6.5-9.7)	
Peripheral artery diseases	129 (40.6)	11 (52.4)	118 (39.7)	.25
Prior history of acute coronary syndrome	42 (13.2)	3 (14.3)	39 (13.1)	.95
Prior history of cardiac arrhythmia	44 (13.8)	5 (23.8)	39 (13.1)	.21
End-stage renal disease	35 (11.0)	3 (14.3)	32 (10.8)	.62
Temperature >100.4°F	22 (6.9)	3 (14.3)	19 (6.3)	.17
Heart rate >90 beats/min	115 (36.2)	12 (57.1)	103 (34.7)	.04*
Respiratory rate >20 breaths/min	7 (2.2)	2 (9.5)	5 (1.7)	.14
Hypotension	12 (3.8)	1 (4.8)	11 (3.5)	.81
White blood cell count >12 000/mm^3	112 (35.2)	9 (42.9)	103 (34.7)	.48
Serum bicarbonate <22	19 (6.0)	1 (4.8)	18 (6.1)	.70
Glucose	188 (126-257)	217 (144-239)	185 (125-257)	.43
⩾2 modified SIRS criteria	27 (8.5)	5 (23.8)	22 (7.4)	.03*

Abbreviation: SIRS, systemic inflammatory response syndrome. *P < 0.05.

Table 2. Incidence and Type of Cardiac Event(s) in 309 Patients With Foot Infection.

Event	Number of Events (% of Cases With Event)
Myocardial infarction	11 (3.5)
Arrhythmia	1
New or worsening CHF	1
New arrhythmia	5 (1.6)
New or worsening CHF	1
New or worsening CHF	8 (2.5)
New CHF	2
Acute on chronic	6
Total patients with cardiac event(s)	21 (6.6)
Total cardiac events	24 (7.5)

Abbreviation: CHF, congestive heart failure.

All 7 patients had evidence of underlying coronary artery disease, and intervention was attempted in 6 patients. Four of these were classified as Type 1 MI (Table 3). All 11 patients were discharged on high-dose statin therapy.

Patient Survival

The 1-year survival of patients with acute cardiac events was 50.4%, significantly lower than the 91.7% 1-year survival of patients without acute cardiac events ($P < .0015$; see Figure 1). All deaths among patients with acute cardiac events occurred more than a month after presentation, and 30-day survival for patients with and without cardiac events was 100% and 99.7%, respectively. New-onset CHF and arrhythmias had particularly poor prognoses, being associated with 95% and 78% one-year mortality, respectively. In contrast, the 1-year mortality for patients with MI was 28%.

Factors Associated With Acute Cardiac Events

Bivariate logistic regression models were used to identify factors associated with the occurrence of acute cardiac events. Heart rate (as a continuous variable), tachycardia (heart rate >90 beats per minute), and the number of criteria for the SIRS were all significantly associated with acute cardiac events ($P = .04$, .04, and .01, respectively), but were weakly explanatory (model R^2 values of ~2%). The presence of an acute cardiac event was not significantly associated with maximum temperature at the time of presentation, hypotension, age, hemoglobin A1c, history of diabetes, peripheral artery disease, CHF, or prior ACS.

Discussion

Our study found a 6.6% incidence of acute cardiac events within 30 days of hospitalization for severe limb infection, including a new MI in 3.5%, new onset or worsening CHF in 2.5%, and/or a new major arrhythmia in 1.6%. Of the patients with MI, 7 of 11 (64%) had a Type 2 MI. Patients with a cardiac event during their hospital stay had significantly decreased survival (50.4% vs 91.7%, $P < .015$) at 1 year compared with their counterparts without cardiac events. In one third of those patients, this event was their

Table 3. Summary of Patients With Cardiac Events.

Age (Years)	Infection	No. SIRS Criteria	Postoperative Event?	HgbA1c	Prior CV Disease	MI	Arrhythmia	Heart Failure	Outcome
72	L first toe; wet gangrene	3	No	10.5	CAD, CHF	—	—	Acute on chronic	Survived
53	L first toe; edema, erythema to mid-calf	4	No	8.6	—	NSTEMI	—	—	Survived; PCI to LAD
73	R first toe; ulceration, exposed bone, necrotic tissue	1/0/0	No	6.6	CHF	NSTEMI	—	Acute on chronic	Survived, PCI to RCA
59	L third to fifth toes; dry gangrene. L first to second toes; erythema	4/1/0	Yes	11.9	—	Cardiac arrest	AF with RVR		Died (day 34)
68	R first toe; ulcer with serous drainage	1/0/0	No	6.2	CAD, CHF	NSTEMI	—	—	Survived
71	R first toe; ulcer with purulent drainage	1/0/0	Yes	7.1	—	—	—	New CHF	Survived
71	L first toe; erythema and edema	1/0/0	Yes	5.6	CAD	—	AF with RVR	—	Died (day 47)
47	R second to fourth toe; wet gangrene	3/1/0	Yes	12.8	CAD	—	—	Acute on chronic	Survived
64	L first toe; erythema and purulent drainage	1/0/0	Yes	8.8	CHF	—	Polymorphic VT	—	Survived
67	LLE; erythema	3/1/0	No	6.9	CAD, CHF	—	—	Acute on chronic	Survived
83	R first toe; erythema, purulence and drainage	1/0/0	No	7.5	CHF	—	—	Acute on chronic	Survived
66	R third toe; cyanotic changes, no purulence or drainage	3/1/0	No	7.1	CAD	NSTEMI	Atrial flutter	—	Survived
68	R fourth to fifth toes; ulcers	2/1/0	No	6.7	—	NSTEMI	—		Survived; unsuccessful PCI to calcified LCx
71	L first to fifth toes; cyanotic changes	4/1/0	No	6.3	—	—	AF with RVR	New CHF	Survived
64	R fifth toe; gangrene	2/1/0	No	6.9	—	NSTEMI	—	—	Survived; FFR of LCx
69	R third to fourth toes; gangrene	3/1/0	No	9.7	—	NSTEMI	—	—	Survived
68	R first to third toes; wet gangrene	4/1/1	Yes	5.6	CAD	NSTEMI	—	—	Survived; PCI to LCx and RAM intermedius
94	L first to second toes; exposed bone	1/0/0	Yes	6.7	CAD, CHF	—	—	Acute on chronic	Survived
63	R first toe; erythema, edema, and purulent exudate from wound	2/1/0	No	8.4	CAD	NSTEMI	—	—	Survived; 3v CAD, no intervention
56	R second toe; purulent drainage, foot with swelling and erythema	2/1/0	Yes	8.5	CAD	NSTEMI	—	—	Survived; PCI to RCA
66	L second toe with erythema, edema, purulence		No	10.6		NSTEMI	—	—	Survived

Abbreviations: SIRS, systemic inflammatory response syndrome; HgBAc1, hemoglobin Ac1; CV, cardiovascular; MI, myocardial infarction; L, left; CAD, coronary artery disease; CHF, congestive heart failure; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; R, right; RCA, right coronary artery; AF, atrial fibrillation; RVR, rapid ventricular rate; VT, ventricular tachycardia; LLE, left lower extremity; LCx, left circumflex; FFR, fractional flow reserve; RAM, Ramus.

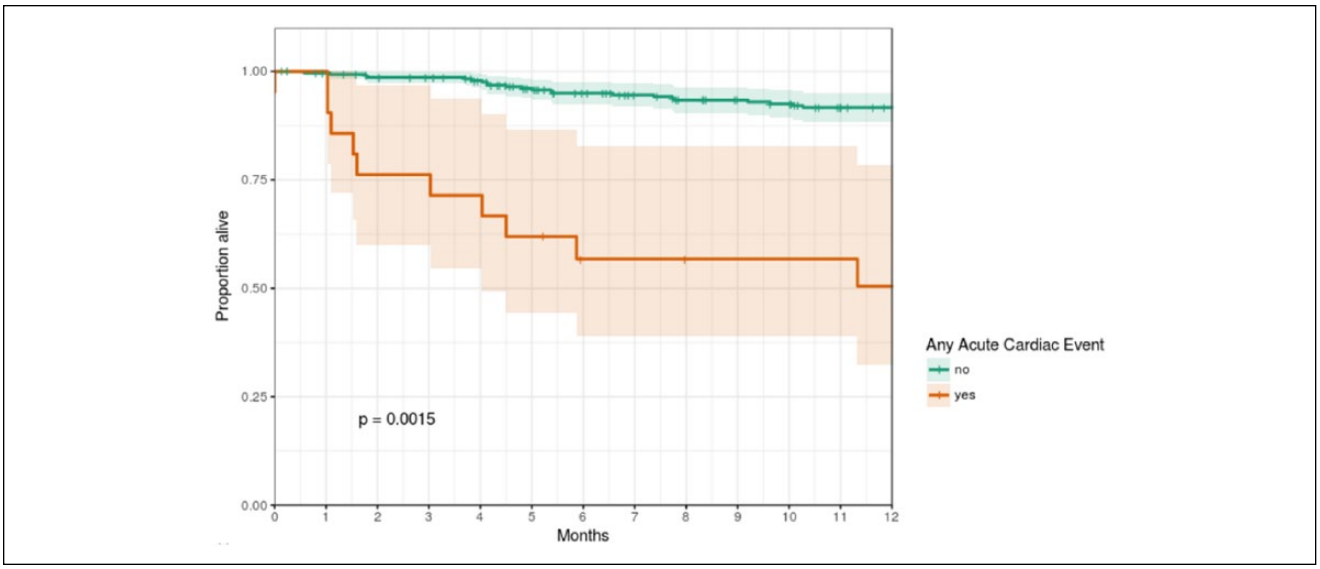

Figure 1. Kaplan-Meier plot demonstrating survival during the first year after onset of a foot infection or foot gangrene among patients with and without acute cardiac events (shadowing around each line indicates the upper and lower 95% confidence limits).

first diagnosis of cardiac disease. The presence of SIRS criteria at admission was associated with increased risk of acute cardiac events, suggesting a link between the severity of infection and the likelihood of an acute cardiac event. To our knowledge, the present study was the first to examine cardiac events, which are not only limited to MI but also included arrhythmia and worsening of CHF, and their impact on long-term survival in diabetic patients with foot infection.

Previous studies have demonstrated a strong correlation between acute infection and development of arrhythmias, MI, and other cardiac complications.[13-19,25] Two prior retrospective case series analyses have explored the relationship between cellulitis and cardiac complications. The studies reported cardiac complications in roughly 2% of their study population.[26,27] Both of these studies excluded patients with diabetic foot ulcers. A retrospective trial in Taiwan studied 1130 patients with diabetic foot ulcers in an attempt to identify major causes of associated in-hospital complications. This study reported a 1.9% rate of major acute cardiac events, defined as cardiac death, nonfatal MI, sudden onset of pulmonary edema, and sudden cardiac arrest.[25] The authors did not report the incidence of new onset arrhythmias, heart failure exacerbations, or effects on mortality at 1 year.

Our study adds to the growing body of literature that recognizes that inflammation elsewhere may also cause inflammation in coronary arteries and make preexisting atherosclerotic lesions more vulnerable to rupture.[19,28] Four of our patients had a Type 1 MI where the event was secondary to rupture of a vulnerable plaque. The idea that inflammation can cause plaque rupture is now generally accepted.[19,21,29-31] Biomarkers of inflammation, including C-reactive protein and interleukin-6 are elevated in patients with ACSs, and C-reactive protein levels are independent risk factors and future predictors of coronary events in patients with coronary disease.[24] However, most of our patients suffered from a Type 2 MI, highlighting the fact that the decreased survival at 1 year is not explained solely by patients who are at risk for acute cardiac events secondary to plaque rupture. Rather, inflammation creates an environment, possibly driven by a combination of hypotension and a pro-coagulable state that places patients at risk for acute cardiac events with consequent negative outcomes. Clearly, SIRS increase physiologic stress, thereby creating potential for an imbalance between blood supply and oxygen demand in the myocardium. SIRS has also been associated with increased risk of arterial and venous thrombosis.[32,33] Therefore, our data support the proposal of Naghavi et al[30,31] that there be increased vigilance for vulnerable patients rather than patients with vulnerable plaques.

It is important to recognize these events because of their implications for mortality as shown by the significantly decreased survival of patients with acute cardiac events at 1 year. Vascular and orthopedic surgeons as well as all other physicians who provide care for such patients must keep a high index of suspicion for the occurrence of an acute cardiac event. Moreover, given the finding of decreased survival at 1 year, patients with foot infections and concurrent cardiac events represent a population that can likely benefit from closer follow-up even after recovery and hospital discharge.

Our study has several limitations including a retrospective cohort analysis design, where we were unable to directly compare cases with controls. But the fact that we included consecutive patients seen by the vascular surgery service,

and the fact that all patients included in the study obtain their care at the same medical center decreased the likelihood of inherent bias. Furthermore, rather than relying on discharge diagnosis codes, patients were only included after a careful review of their medical records by participating physicians and each acute cardiac event identified was personally reviewed by a senior attending cardiologist. The principal advantage of this approach is the preciseness of the data that we analyzed; a disadvantage is that the limited number of cases did not allow us to construct more inclusive multivariate models in our analysis. Therefore, future larger analysis with control groups are required to extend our findings.

In summary, infections of the foot, including soft tissue infection, gangrene, and osteomyelitis, that are serious enough to warrant referral to a vascular surgery service are associated with increased risk of acute cardiac events including MI, arrhythmia, and new or worsening CHF. In one third of our cases, the event associated with infection of the foot was the first documentation of the presence of heart disease. The occurrence of acute cardiac events in these patients portends a poor prognosis, specifically a substantial decrease in the 1-year survival and, therefore, warrants particular care in managing such patients, including close follow-up during hospitalization and after discharge as well as special efforts at communication with patients and their families.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Tennvall GR, Apelqvist J, Eneroth M. Costs of deep foot infections in patients with diabetes mellitus. *Pharmacoeconomics*. 2000;18:225-238.
2. Fleischer AE, Didyk AA, Woods JB, Burns SE, Wrobel JS, Armstrong DG. Combined clinical and laboratory testing improves diagnostic accuracy for osteomyelitis in the diabetic foot. *J Foot Ankle Surg*. 2009;48:39-46.
3. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg*. 2006;45(5 suppl):S1-S66.
4. Lavery LA, Peters EJ, Armstrong DG, Wendel CS, Murdoch DP, Lipsky BA. Risk factors for developing osteomyelitis in patients with diabetic foot wounds. *Diabetes Res Clin Pract*. 2009;83:347-352.
5. Lindbloom BJ, James ER, McGarvey WC. Osteomyelitis of the foot and ankle: diagnosis, epidemiology, and treatment. *Foot Ankle Clin*. 2014;19:569-588.
6. Shank CF, Feibel JB. Osteomyelitis in the diabetic foot: diagnosis and management. *Foot Ankle Clin*. 2006;11:775-789.
7. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. *JAMA*. 1995; 273:721-723.
8. Newman LG, Waller J, Palestro CJ, et al. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. *JAMA*. 1991;266:1246-1251.
9. Balsells M, Viadé J, Millán M, et al. Prevalence of osteomyelitis in non-healing diabetic foot ulcers: usefulness of radiologic and scintigraphic findings. *Diabetes Res Clin Pract*. 1997;38:123-127.
10. Hartemann-Heurtier A, Senneville E. Diabetic foot osteomyelitis. *Diabetes Metab*. 2008;34:87-95.
11. Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. *J Vasc Surg*. 2010;52(3 suppl):17S-22S.
12. American Diabetes Association. Economic costs of diabetes in the US in 2012. *Diabetes Care*. 2013;36:1033-1046.
13. Kloner RA. Natural and unnatural triggers of myocardial infarction. *Prog Cardiovasc Dis*. 2006;48:285-300.
14. Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol*. 1994;23:809-813.
15. Baylin A, Hernandez-Diaz S, Siles X, Kabagambe EK, Campos H. Triggers of nonfatal myocardial infarction in Costa Rica: heavy physical exertion, sexual activity, and infection. *Ann Epidemiol*. 2007;17:112-118.
16. Sims JB, de Lemos JA, Maewal P, Warner JJ, Peterson GE, McGuire DK. Urinary tract infection in patients with acute coronary syndrome: a potential systemic inflammatory connection. *Am Heart J*. 2005;149:1062-1065.
17. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351:2611-2618.
18. Spodick DH, Flessas AP, Johnson MM. Association of acute respiratory symptoms with onset of acute myocardial infarction: prospective investigation of 150 consecutive patients and matched control patients. *Am J Cardiol*. 1984;53: 481-482.
19. Corrales-Medina VF, Serpa J, Rueda AM, et al. Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes. *Medicine (Baltimore)*. 2009;88:154-159.
20. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med*. 2018;378:345-353.
21. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol*. 2005;46:937-954.
22. Berendt AR, Peters EJ, Bakker K, et al. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. *Diabetes Metab Res Rev*. 2008;24(suppl 1):S145-S161.
23. Jneid H, Alam M, Virani SS, Bozkurt B. Redefining myocardial infarction: what is new in the ESC/ACCF/AHA/ WHF Third Universal Definition of myocardial infarction? *Methodist Debakey Cardiovasc J*. 2013;9:169-172.

24. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. *Am Heart J*. 2004;148(1 suppl):S19-S26.
25. Hung SY, Huang YY, Hsu LA, et al. Treatment for diabetic foot ulcers complicated by major cardiac events. *Can J Diabetes*. 2015;39:183-187. doi:10.1016/j.jcjd.2014.11.002
26. Figtree M, Konecny P, Jennings Z, Goh C, Krilis SA, Miyakis S. Risk stratification and outcome of cellulitis admitted to hospital. *J Infect*. 2010;60:431-439.
27. Carratalà J, Rosón B, Fernández-Sabé N, et al. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. *Eur J Clin Microbiol Infect Dis*. 2003;22:151-157.
28. Ramirez J, Aliberti S, Mirsaeidi M, et al. Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. *Clin Infect Dis*. 2008;47:182-187. doi:10.1086/589246
29. Biasucci LM, Leo M, De Maria GL. Local and systemic mechanisms of plaque rupture. *Angiology*. 2008;59(2 suppl):73S-76S. doi:10.1177/0003319708319747
30. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part II. *Circulation*. 2003;108:1773-1778.
31. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. *Circulation*. 2003;108:1664-1672.
32. Fitzgerald JR, Foster TJ, Cox D. The interaction of bacterial pathogens with platelets. *Nat Rev Microbiol*. 2006;4:445-457.
33. Donzé JD, Ridker PM, Finlayson SR, Bates DW. Impact of sepsis on risk of postoperative arterial and venous thromboses: large prospective cohort study. *BMJ*. 2014;349:g5334.