HOSPITAL CHRONICLES 2010, SUPPLEMENT: 92–97

ATHENS CARDIOLOGY UPDATE 2010

Coronary Artery Disease, Nicotine Addiction, and Depression: The Tragic Triad

Andreas Asimakos, MD and Paraskevi Katsaounou, MD

Intensive Care Medicine, Evagelismos Hospital, Athens, Greece

KEY WORDS: *smoking; cardiovascular disease depression*

Correspondence to:
Paraskevi Katsaounou, MD,
E-mail: paraskevi@katsaounou.gr

A great number of diseases are directly related to active smoking. In the resent years more and more malignant neoplasms were causally related to active smoking.[1] Lung cancer is the "leader" of smoking related neoplasm's and the 3rd cause of death in high income countries,[2] followed by cancer of the oral cavity/pharynx, laryngeal, esophageal, stomach, pancreatic, kidney, bladder, cervical cancer, leukemia and other malignant neoplasm's. Among other diseases, cardiovascular (coronary heart disease, peripheral vascular disease cerebrovascular disease and abdominal aortic aneurysm) and respiratory diseases (chronic obstructive pulmonary disease-COPD, pneumonia) are also causally related to cigarette smoking. According to World Health Organization (WHO) 5 out of 6 leading causes of death world wide (*Ischemic heart disease, cerebrovascular disease*, HIV/AIDS, *COPD*, *lower respiratory infections trachea, bronchus, lung cancers*) are smoke related. WHO claims that under the baseline scenario, total tobacco-attributable deaths will rise from 5.4 million in 2005 to 6.4 million in 2015 and 8.3 million in 2030. Projected deaths for 2030 range from 7.4 million in the optimistic scenario to 9.7 million in the pessimistic scenario. According to their baseline projection, smoking will kill 50% more people in 2015 than HIV/AIDS, and will be responsible for 10% of all deaths globally[2].

SMOKING AND CARDIOVASCULAR DISEASE

Cardiovascular diseases are the first cause of death independently of income state and existing evidence is more than sufficient to establish a causal relationship between each of them and cigarette smoking[1].

SMOKING AND CORONARY ARTERY DISEASE (CAD)

The role of smoking in ischemic heart disease includes endothelial dysfunction, increased hematologic thrombogenicity, enhanced inflammatory response and oxidative modification.[3] Tissue factor (TF) is highly expressed in atherosclerotic plaques and may play a role in thrombosis. Current smokers have significantly higher levels of circulating TF activity than nonsmokers[4]. Smoking impairs endothelial vasodilator function since flow-dependent dilation is significantly blunted in current smokers compared with nonsmokers and long-term cigarette smoking is associated with impaired endothelium-dependent coronary vasodilatation regardless of the presence or absence of coronary atherosclerotic lesions.[5]

Young smokers are characterized by epicardial coronary endothelial dysfunction, elevated white blood cell (WBC) counts and increased levels of inflammatory biomark-

ers and oxidative stress[6]. Elevated WBC counts are associated with greater coronary heart disease mortality[7]. Smoking leads to increased oxidative modification of important biologic molecules in vivo[8] and reduces nitric oxide (NO) biosynthesis[9]. It's no wonder that smoking increases CAD mortality[10] and rate of progression[11], multiplies risk factor for CAD along with hypertension and hypercholesterolemia[12], increases the risk of angina[13], of sudden cardiac death[14], of acute nonfatal myocardial infraction (MI)[15] and of Q-wave MI after percutaneous coronary revascularization[16].

In summary:

- Smoking plays a role in the development of CAD via:
  - Endothelial dysfunction
  - Increased thrombogenicity
  - Elevated WBC counts
  - Increased oxidative stress
  - Reduced NO biosynthesis
- Smoking acts as a multiplicative risk factor for development of CAD
- Smoking is associated with an increased
  - Rate of progression of CAD
  - Risk of angina
  - Risk of acute myocardial infarction
  - Risk of sudden cardiac death
  - Risk of Q-wave myocardial infarction after percutaneous coronary revascularization.

SMOKING AND PERIPHERAL VASCULAR DISEASE (PVD):

PVD affects approximately 20% of adults older than age 55[17]. Approximately half of patients with PVD are asymptomatic[18] and 5% to 10% of them will progress to symptomatic PVD over 5 years[19]. Patients with symptomatic PVD are at higher risk for other cardiovascular disease and mortality[20]. Current smokers develop asymptomatic PVD 2,8 times more often than nonsmokers and ex-smokers 1,6 times respectively.[20] The rate of development of intermittent claudication (IC) is approximately 4 times as great in current smokers as in nonsmokers (OR 4.1[2.3-7.9]) and risk tends to increase with the intensity of smoking. The 5-year mortality for patients with IC who continue to smoke is 40% to 50%[20,21]. For smokers, the risk of PVD is greater than the risk of CAD.[22] Smoking is the most important risk factor for the progression PVD and symptoms occur approximately a decade earlier in smokers than nonsmokers while smokers with PVD have twice the amputation rate of nonsmokers[23]. Continued smoking after lower limb bypass surgery results in a threefold increased risk of graft failure. Smoking cessation, even if instigated after the operation, restores graft patency towards the patency of never smokers.[24] Smoking is also associated with increased mortality after vascular surgery.[25]

In summary:

- Smoking is associated with an increased risk of
  - Asymptomatic PVD
  - Intermittent claudication
  - Progression of PVD
  - Amputation due to complications of PVD
  - Femoral-popliteal bypass graft failure
  - Mortality after vascular surgery
- Symptoms of PVD occur approximately a decade earlier in smokers than in nonsmokers
- Current smokers are at greater risk for developing PVD than coronary artery disease.

SMOKING AND ABDOMINAL AORTIC ANEURYSM (AAA)

The association between smoking and aortic aneurysm is substantially stronger than the association between smoking and coronary or cerebrovascular disease. Current smokers develop AAA 3 times more often than CAD and 4,7 times than cerebrovascular disease[26]. Smoking is an independent and remains the most important avoidable risk factor for AAA, with level of exposure (cigarettes/day) being more significant than duration[27]. In fact the progression of aortic atherosclerosis is directly associated to the number of cigarettes smoked per day[28]. Smoking also accelerates AAA expansion while other factors including lipids and blood pressure are not associated with AAA growth[29].

In conclusion:

- Current smokers have a higher risk of developing an AAA than either coronary artery disease or cerebrovascular disease
- Smoking is associated with an increased risk of
  - Formation of AAA
  - Progression of aortic atherosclerosis
  - Expansion of AAA

SMOKING AND STROKE:

Smoking contributes to 12% to 14% of all stroke deaths. Smoking also potentiates the effects of other stroke risk factors and increases stroke risk acutely, effecting the thrombus formation and chronically, increasing the burden of atherosclerotic disease[30]. Both active smoking and environmental tobacco smoke exposure are associated with increased progression of carotid atherosclerosis[31]. The number of cigarettes smoked per day is associated positively with the risk of stroke in women. Compared with the women who had never smoked, those who smoked 1 to 14 cigarettes per day had an age-adjusted relative risk of 2.2 (95 percent confidence interval, 1.5 to 3.3), whereas those who smoked 25 or more cigarettes per day had a relative risk of 3.7 (95 percent confidence interval, 2.7 to 5.1). For women in this latter group, the relative risk of subarachnoid haemorrhage was 9.8 (95 percent confidence

interval, 5.3 to 17.9), as compared with those who had never smoked[32]. Cigarette smoking increases the risk of total hemorrhagic stroke in women (both intracerebral and subarachnoid) and this is also positively associated with the amount of cigarettes smoked per day[33]. Smoking also increases the mortality rate from stroke in men[34].

In conclusion:

- Smoking contributes to 12% to 14% of all stroke deaths
- Increases the risk of
  - Progression of carotid atherosclerosis
  - Ischemic stroke
  - Hemorrhagic stroke
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- Increases stroke-related mortality.

CARDIOVASCULAR DISEASE AND ENVIRONMENTAL TOBACCO SMOKE

Environmental tobacco smoke effects cardiovascular system in several ways. Environmental tobacco smoke increases the risk of heart disease among non smokers by 30%[35], increases arterial stiffness, oxidative stress, inflammation, atherosclerosis and infract size while changing platelet and endothelial function, heart rate variability and energy metabolism[36]. Passive smoking may activate thromboxane A_2 release from the platelets, contributing to the development of hemostatic imbalance[37], and significantly reduces mean coronary flow velocity reserve in nonsmokers thus causing endothelial dysfunction of the coronary circulation[38]. Exposure to environmental tobacco smoke increases the risk of non-fatal acute myocardial infraction in a graded manner[15]. A public ordinance reducing exposure to second hand smoke in Pueblo city, Colorado, was associated with a decrease in acute myocardial infraction hospitalizations[39].

In conclusion:

- Exposure to environmental tobacco smoke increases risk of
  - Heart disease, by 30%
  - Acute myocardial infarction (MI)
- Environmental tobacco smoke affects multiple factors associated with the development of coronary artery disease, including
  - Platelet activation
  - Vascular endothelial dysfunction.

CARDIOVASCULAR BENEFITS OF SMOKING CESSATION

The benefits of non-smoking and smoking cessation in healthy individuals and cardiac patients are beyond controversy[40]. Abstention from smoking for a period of only 2 weeks induces a significant decrease in the rate of fibrinogen synthesis by the liver, with a concomitant reduction in the plasma fibrinogen concentration[41], while 8 weeks of smoking reduction results in clinically significant improvements in established cardiovascular risk factors (including fibrinogen, white blood cell count and the high-density/low-density lipoprotein-HDL/LDL ratio). These improvements are even greater after an additional period of abstinence from smoking[42]. Smoking cessation also improves arterial stiffness as assessed by the augmentation index, owing mainly to increasing the small artery compliance, which is known to be an early index of endothelial damage[43]. Quitting smoke leads to a decreased platelet volume and increased susceptibility of platelets to antiaggregatory prostaglandin E1[44], while only two weeks of smoking cessation can ameliorate the enhanced platelet aggregability and intraplatelet redox imbalance in long-term smokers, possibly by decreasing oxidative stress[45]. Cessation of cigarette smoking is associated with a reduction in arrhythmic death for patients with post-myocardial infarction and left ventricular dysfunction[46] and a reduced risk of acute myocardial infraction[15], while the risk for recurrent cardiac arrest is lower among those who quit smoking than among continuing smokers[47]. Patients who continue to smoke after a successful percutaneous coronary revascularization are at greater risk for Q-wave infarction and death than smoke quitters, so the cessation of smoking either before or after percutaneous revascularization is beneficial[16]. Patients who continue to smoke after coronary artery bypass graft surgery have a greater risk of death than those who stop smoking and also they undergo repeat revascularization procedures more frequently[48]. Smoke cessation also lowers the risk of PVD[49] and stroke[50].

In conclusion the cardiovascular benefits of smoking cessation can be divided into:

LONG-TERM BENEFITS

- Reduced risk of
  - Stroke
  - Repeat CABG
  - Recurrent coronary events after MI
  - Arrhythmic death after MI
  - Secondary CVD events
  - Revascularization procedure after CABG
- Reduced
  - Mortality after CABG
  - Mortality after PTCA
  - Levels of inflammatory markers associated with progression of CVD (C-reactive protein, WBC, and fibrinogen)

SHORT-TERM BENEFITS

- ↓ fibrinogen concentration
- ↓ rate of fibrinogen synthesis

- ↓ WBCs
- Improved HDL/LDL ratio
- ↓ risk of stroke
- ↑ HDL; decreased LDL
- ↓ arterial pressure
- ↓ HR
- Improved arterial compliance
- ↓ risk of arrhythmic death after MI
- ↓ platelet volume
- Enhanced platelet cAMP response to stimulation of ADP with prostaglandin E1
- ↓ smoking-induced platelet aggregability.

DEPRESSION, SMOKING AND CARDIOVASCULAR DISEASE

Smokers with psychiatric disorders consume more cigarettes. Namely the Odds Ratio for smokers and major depression is 3.2. Also psychiatric patients who smoke have:

- Higher incidence of illicit drug use.
- Poorer treatment compliance
- Lower Global Assessment Functioning (GAF) score

The relationship between cardiovascular disease and depression poses a lot of interesting questions. Preliminary studies have shown the following:

- Depression increases the risk of coronary artery disease by 1.5 – 2 times in otherwise physically healthy individuals.[51]
- Patients with early-onset depression are at a significantly increased risk for developing cardiovascular disease (CVD) after correcting for cardiovascular risk factors. This effect occurs even in the absence of a diagnosis of major depression.[52]
- Patients with treatment-resistant depression (failure to respond to a single trial of antidepressant) after an acute coronary syndrome are at even greater cardiovascular risk.[53]
- Patients with CVD such as myocardial infarction, stroke, heart failure, and atrial fibrillation are at increased risk of developing depression and, when depression develops, cardiovascular risk is exacerbated further.[51,54]

As for the use of drugs research has shown that:

- The use of antidepressants does not appear to mitigate cardiovascular risk associated with depression, despite altering one or more of the physiological abnormalities linking CVD to depression such as increased inflammatory cytokines, a decreased circulation of endothelial progenitor cells,
- and a deficiency in nitric oxide availability.[55-57]
- The combination of an SSRI and n-3 fatty acids reduce mood-associated cardiovascular risk.[58]
- In patients surviving their first hospitalization for heart failure the use of both TCAs and SSRIs is associated with an increased risk of total and cardiovascular-related mortality.[59]
- Co-administration of an SSRI and a beta-adrenergic blocking agent is associated with an increased risk of total and cardiovascular-related mortality.

Further clinical study needs to be done in order to determine the optimum antidepressant strategy in patients with heart failure.

REFERENCES

1. 2004 Surgeon General's Report – The Health Consequences of Smoking. Executive summery.
2. Mathers C, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, 2006, e442.
3. Lavi S, Prasad A, Yang EH, et al. Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. *Circulation* 2007;115:2621-2627.
4. Sambola A, Osende J, Hathcock J, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. *Circulation* 2003;107:973-7.
5. Zeiher AM, Schδchinger V, Minners J. Long-term cigarette smoking impairs endothelium-dependent coronary arterial vasodilator function. *Circulation* 1995;92:1094-100.
6. Lavi S, Prasad A, Yang EH, et al. Smoking is associated with epicardial coronary endothelial dysfunction and elevated white blood cell count in patients with chest pain and early coronary artery disease. *Circulation* 2007;115:2621-7.
7. Stewart RA, White HD, Kirby AC, et al. White blood cell count predicts reduction in coronary heart disease mortality with pravastatin. *Circulation* 2005 Apr 12;111(14):1756-62.
8. Morrow JD, Frei B, Longmire AW, et al. Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. *N Engl J Med* 1995;332:1198-203.
9. Barua RS, Ambrose JA, Eales-Reynolds LJ, et al. Dysfunctional endothelial nitric oxide biosynthesis in healthy smokers with impaired endothelium-dependent vasodilatation. *Circulation* 2001;104:1905-10.
10. Willett WC, Green A, Stampfer MJ, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987;317:1303-9.
11. Waters D, Lesperance J, Gladstone P, et al. Effects of cigarette smoking on the angiographic evolution of coronary atherosclerosis. A Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) Substudy. CCAIT Study Group. *Circulation* 1996;94:614-21.
12. Burns DM. Epidemiology of smoking-induced cardiovascular disease. *Prog Cardiovasc Dis* 2003;46:11-29.
13. Willett WC, Green A, Stampfer MJ, et al. Relative and absolute excess risks of coronary heart disease among women who smoke

cigarettes. *N Engl J Med* 1987;317:1303-9.
14. Wannamethee G, Shaper AG, Macfarlane PW,et al. Risk factors for sudden cardiac death in middle-aged British men. *Circulation* 1995;91:1749-56.
15. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006;368:647-58.
16. Hasdai D, Garratt KN, Grill DE, et al. Effect of smoking status on the long-term outcome after successful percutaneous coronary revascularization. *N Engl J Med* 1997;336:755-61.
17. Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of peripheral arterial disease. *JAMA* 2006;295:547-53.
18. Hooi JD, Kester AD, Stoffers HE, et al. Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *Am J Epidemiol* 2001;153:666-72.
19. Hooi JD, Stoffers HE, Knottnerus JA, et al. The prognosis of non-critical limb ischaemia: a systematic review of population-based evidence. *Br J Gen Pract* 1999;49:49-55.
20. Hooi JD, Stoffers HE, Kester AD, et al. Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. Peripheral Arterial Occlusive Disease. *Scand J Prim Health Care* 1998;16:177-82.
21. Kannel WB, Shurtleff D. The Framingham Study. Cigarettes and the development of intermittent claudication. *Geriatrics* 1973;28:61-8.
22. Price JF, Mowbray PI, Lee AJ, et al. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J* 1999;20:344-53.
23. Bendermacher BL, Willigendael EM, Teijink JA, et al. Medical management of peripheral arterial disease. *J Thromb Haemost* 2005;3:1628-37.
24. Willigendael EM, Teijink JA, Bartelink ML, et al. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. *J Vasc Surg* 2005;42:67-74.
25. Kazmers A, Kohler TR. Very late survival after vascular surgery. *J Surg Res* 2002;105:109-14.
26. Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. *J Vasc Surg* 2003;38:329-34.
27. Vardulaki KA, Walker NM, Day NE, et al. Quantifying the risks of hypertension, age, sex and smoking in patients with abdominal aortic aneurysm. *Br J Surg* 2000;87:195-200.
28. Witteman JC, Grobbee DE, Valkenburg HA, et al. Cigarette smoking and the development and progression of aortic atherosclerosis. A 9-year population-based follow-up study in women. *Circulation* 1993;88:2156-62.
29. Brady AR, Thompson SG, Fowkes FG, et al. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. *Circulation* 2004;110:16-21.
30. Goldstein LB, Adams R, Alberts MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:1583-633.
31. Howard G, Wagenknecht LE, Burke GL, et al. Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *JAMA* 1998;279:119-24.
32. Colditz GA, Bonita R, Stampfer MJ, et al. Cigarette smoking and risk of stroke in middle-aged women. *N Engl J Med* 1988;318:937-41.
33. Kurth T, Kase CS, Berger K, et al. Smoking and risk of hemorrhagic stroke in women. *Stroke* 2003;34:2792-5.
34. Hart CL, Hole DJ, Smith GD. Risk factors and 20-year stroke mortality in men and women in the Renfrew/Paisley study in Scotland. *Stroke* 1999;30:1999-2007.
35. Whincup PH, Gilg JA, Emberson JR, et al. Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ* 2004;329:200-5.
36. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. *Circulation* 2005;111:2684-98.
37. Schmid P, Karanikas G, Kritz H, et al. Passive smoking and platelet thromboxane. *Thromb Res* 1996;81:451-60.
38. Otsuka R, Watanabe H, Hirata K, et al. Acute effects of passive smoking on the coronary circulation in healthy young adults. *JAMA* 2001;286:436-41.
39. Bartecchi C, Alsever RN, Nevin-Woods C, et al. Reduction in the incidence of acute myocardial infarction associated with a citywide smoking ordinance. *Circulation* 2006;114:1490-6.
40. Twardella D, Kópper-Nybelen J, Rothenbacher D, et al. Short-term benefit of smoking cessation in patients with coronary heart disease: estimates based on self-reported smoking data and serum cotinine measurements. *Eur Heart J* 2004;25:2101-8.
41. Hunter KA, Garlick PJ, Broom I, et al. Effects of smoking and abstention from smoking on fibrinogen synthesis in humans. *Clin Sci (Lond)* 2001;100:459-65.
42. Eliasson B, Hjalmarson A, Kruse E, et al. Effect of smoking reduction and cessation on cardiovascular risk factors. *Nicotine Tob Res* 2001;3:249-55.
43. Oren S, Isakov I, Golzman B, et al. The influence of smoking cessation on hemodynamics and arterial compliance. *Angiology* 2006;57:564-8.
44. Terres W, Becker P, Rosenberg A. Changes in cardiovascular risk profile during the cessation of smoking. *AAm J Med* 1994;97:242-9.
45. Morita H, Ikeda H, Haramaki N, et al. Only two-week smoking cessation improves platelet aggregability and intraplatelet redox imbalance of long-term smokers. *J Am Coll Cardiol* 2005;45:589-94.
46. Peters RW, Brooks MM, Todd L, et al. Smoking cessation and arrhythmic death: the CAST experience. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *J Am Coll Cardiol* 1995;26:1287-92.

47. Hallstrom AP, Cobb LA, Ray R. Smoking as a risk factor for recurrence of sudden cardiac arrest. *N Engl J Med* 1986;314:271-5.
48. Van Domburg RT, Meeter K, van Berkel DF, et al. Smoking cessation reduces mortality after coronary artery bypass surgery: a 20-year follow-up study. *J Am Coll Cardiol* 2000;36:878-83.
49. Jonason T, Bergström R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. *Acta Med Scand* 1987;221:253-60.
50. Robbins AS, Manson JE, Lee IM, et al. Cigarette smoking and stroke in a cohort of U.S. male physicians. *Ann Intern Med* 1994;120:458-62.
51. Lett H, Blumenthal J, Babyak M, et al. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med* 2004;66:305–315.
52. Rugulies R. Depression as a predictor for coronary heart disease. A review and meta-analysis. *Am J Prev Med* 2002;23:51–61.
53. Frasure-Smith N, Lespérance F, Habra M, et al. Atrial Fibrillation and Congestive Heart Failure Investigators. Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibril- lation and heart failure. *Circulation* 2009;120:134–340.
54. Carney R, Freedland K. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry* 2009;166:410 – 417.
55. Follath F. Depression, stress and coronary heart disease – epidemiology, progno- sis and therapeutic sequelae. *Rev Med Suisse* 2009;5:515–516, 518–519.
56. Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *Am J Cardiol* 2001;88:196–198.
57. Dome P, Teleki Z, Rihmer Z, et al. Circulating endothelial progenitor cells and depression: a possible novel link between heart and soul. *Mol Psychiatry* 2009; 14:523–531.
58. Carney RM, Freedland KE, Rubin EH, Rich MW, Steinmeyer BC, Harris WS. Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. *JAMA* 2009;302:1651.
59. Fosbøl E, Gislason G, Poulsen H, et al. Prognosis in heart failure and the value of *b*-blockers are altered by the use of antidepressants and depend on the type of antidepressants used. *Circulation* 2009;2:582–590.