



IMMDA ADVISORY STATEMENT

Reducing Risk for Acute Cardiac Events in Susceptible Marathon Runners

This paper and statement were prepared for IMMDA by:

Arthur J. Siegel, MD
Director, Internal Medicine, McLean Hospital, Belmont, MA
Assistant Professor of Medicine, Harvard Medical School, Boston, MA

This statement was unanimously approved at the IMMDA Spring Meeting: March 21, 2009 in Barcelona Spain.

This paper was editorially prepared for publication by an IMMDA committee of Arthur J. Siegel, MD (Chair), Lewis G. Maharam, M.D., FACSM; Pedro Pujol, M.D., FACSM; W. Bruce Adams, MD, Steve Van Camp, M.D., FACSM, Paul Thompson, M.D., FACSM and Timothy D. Noakes, MBChB, MD, DSc

Advisory Statement:

We recommend consideration of regular physician supervised prophylactic aspirin and statin usage for primary prevention of acute cardiac events on a case by case basis in susceptible runners who may otherwise be at low baseline risk. Runners are advised to discuss the risks and benefits of this recommendation with their physicians.

Background:

Marathon running has been shown to confer an increase in the absolute and relative risk for acute cardiac events including sudden death in susceptible individuals. The perceived increase in frequency of such events may be mediated in part by platelet activation and elevated inflammatory biomarkers related to exertional rhabdomyolysis. These findings justify

consideration of prophylactic usage of aspirin and statins (3-methyl-glutaryl-CoA reductase inhibitors) for primary prevention of cardiovascular morbidity and mortality in susceptible marathon runners who may otherwise be at low baseline risk.

WHEREAS marathon running has been shown to

- increase the absolute and relative risk for acute cardiac events including myocardial infarction and sudden death in susceptible individuals.
- induce a hemostatic imbalance with in vivo platelet activation
- elevate inflammatory biomarkers independently predictive of acute cardiac events [interleukin(IL)-6 and C-reactive protein (CRP)]

Rationale:

Marathon running has been shown to confer an increase in absolute and relative risk for acute cardiac events estimated as up to 16 times baseline for previously sedentary persons who are otherwise at low risk.^{1,2,3} An apparent increase in the frequency of such events including multiple cases at recent Marine Corps, Los Angeles and New York City marathons may relate to the greater participation of susceptible individuals, as shown by an increase in entrants aged 40 to 59 from 4,000 in 2004 to 10,000 in 2007 at the Boston marathon.

A post-race hemostatic imbalance with in vivo platelet activation and elevated inflammatory biomarkers (IL-6, CRP) independently predictive of acute cardiac events including sudden death has been demonstrated in asymptomatic middle-aged male marathon runners.^{4,5,6,7}

Atherothrombosis has been shown to mediate acute exertional cardiac events in runners as in high risk individuals such as diabetics, implicating a pathogenic role for these findings.^{8,9,10,11,12}

While no strategies have thus far been shown definitively to reduce exercise-related acute cardiac events,¹ prophylactic usage of aspirin and statins may be justified in otherwise low risk runners for primary prevention of acute exertional cardiac events as applicable in other individuals such as firefighters.¹³ This recommendation should be regarded as pragmatic, being based on a reasonable extrapolation from existing evidence on primary prevention in the absence of prospective studies related to exercise in runners. Runners are advised to discuss the risks and benefits of this recommendation with their physicians.

14,15,16,17,18,19,20

References:

1. Thompson PD, Franklin BA, Balady GJ, Blair SN, et al. Exercise and acute cardiovascular events placing the risks in perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation*. 2007;115(17):2358-68.
2. Albert CM, Mittleman MA, Chae CU, Lee IM, Hennikens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med*. 2000;343(19):1355-61.
3. Tunstall Pedoe DS. Marathon cardiac deaths. The London experience. *Sports Med*. 2007;37(4-5): 448-50.
4. Siegel AJ, Stec JJ, Lipinska I, Van Cott EM, Lewandrowski KB, Ridker PM, Tofler GH. Effect of marathon running on inflammatory and hemostatic markers. *Am J Cardiol* 2001;88:35-7.
5. Kratz A, Wood MJ, Siegel AJ, Hiers JR, VanCott EM. Effects of marathon running on platelet activation markers. Direct evidence for in vivo platelet activation. *Am J Clin Pathol* 2006;125:296-300.
6. Saenz AJ, Lee-Lewandrowsi E, Wood MJ, Neilan TG, Siegel AJ, Januzzi JL, Lewandrowski KB. Measurement of a Plasma Stroke Biomarker Panel and cardiac troponin T in marathon runners before and after the 2005 Boston Marathon. *Am J Clin Pathol* 2006;126 (2):185-9.
7. Siegel AJ, Januzzi J, Sluss P, Lee-Lewandrowski E, Wood M, Shirey T, Lewandrowski KB. Cardiac Biomarkers, Electrolytes and other Anylates in Collapsed Marathon Runners. *Am J Clin Path*. 2008. 129(6):945-51
8. Giri S, Thompson PD, Kierman FJ, et al. Clinical and angiographic characteristics of exertion-related acute myocardial infarction. *JAMA* 1999.282:1731-36.

9. Libby P, Ridker P. Inflammation and atherosclerosis: the role of C-reactive protein in risk assessment. *Am J Med.* 2004; 116 (6A): 9S-16S.
10. Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. *Circulation* 2006;114:1863-72
11. Libby P, Sasiela W. Plaque stabilization: can we turn theory into evidence? *Am J Cardiol.*2006; 98 (11A) 26P-33P.
12. Forrester JS, Libby P. The inflammation hypothesis and its potential relevance to statin therapy. *Am J Cardiol.* 2007; 99(5):732-8.
13. Kales SN, Soteriades ES, Christophi CA, Christiani DC. Emergency duties and deaths from heart disease among firefighters in the United States. *N Eng J Med* 2007;356:1207-11.
14. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. *JAMA*2007: 297:2018-24.
15. Berger JS, Roncaglioni MC, Avanzini F, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA.* 2006;295(3):306-13.
16. Levantesi G, Scarano M, Marfisi RM, Borelli G, Marchioli R. Meta-analysis of the effect of statin treatment on risk of sudden death. *Am J Clin Cardiol.* 2007;100(11):1644-50.
17. Ridker P, Danielson E, Fonseca FAH et al for the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-Reactive protein. *N Engl J Med.*2008;359:2195-207.
18. Jacobson TA, Wertz DA, Hoy T et al. Comparison of cardiovascular event rates in patients without cardiovascular disease in whom atorvastatin or simvastatin was newly initiated. *Mayo Clin Proc.*2008;83(12):1316-25.

19. Tsang JLY, Mendelsohn A, Tan MKK et al. Discordance between physicians' estimation of patient cardiovascular risk and use of evidence based medical therapy. *Am J Cardiol* 2008;102:1142-5.

20. Mills EJ, Rachlis B, Wu P, Devereaux PJ. Primary prevention of cardiovascular mortality and events with Statin Treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol*. 2008; 52(22):1769-81.

21. Shalev V, Chodick G, Silber H et al. Continuation of statin treatment and all-cause Mortality: a population-based cohort study. *Arch Intern Med*. 2009; 169(3):260-8.