



Preventing Acute Cardiac Events during Marathons with Pre-Race Aspirin

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Abstract

Objectives: Reducing sudden cardiac death during sport is the highest clinical priority in preventive sports cardiology. While the overall cardiovascular risk of long distance running is low, the frequency of cardiac arrest and sudden death in middle-aged males during marathons has increased since the year 2000. An evidence-based strategy for reducing race-related acute cardiac events in this vulnerable subgroup is considered based on identification of the underlying cause.

Method: Review of articles in PubMed on adverse cardiac events during marathons.

Findings: Recent epidemiological studies identified atherosclerotic heart disease as the underlying cause of cardiac arrest and sudden death in middle-aged males during marathons since the year 2000. Same-aged asymptomatic middle-aged male runners showed a post-race polymorphonuclear leukocytosis with sequential increases in interleukin-6 and C-reactive protein likely due to rhabdomyolysis after 'hitting the wall'. Elevated fibrinogen, von Willebrand factor and D-dimer with in vivo platelet activation indicated concurrent hyper-coagulability. Cardiac troponins I and T and NT-pro-B-type natriuretic peptide were transiently elevated after races in these same asymptomatic subjects.

Conclusions: Asymptomatic middle-aged male runners are at transient high risk for acute cardiac events during marathons as demonstrated by stratification of validated biomarkers. Pre-race aspirin usage is prudent to address the increasing frequency of race-related acute cardiac events in this vulnerable subgroup based on conclusive evidence for its ability to protect same-aged healthy males from first acute myocardial infarctions in a randomized prospective primary prevention trial. Prospective studies are needed to assess the efficacy of this strategy.

Keywords

Marathon running, Sudden cardiac death, Atherothrombosis, Aspirin usage pre-race

The marathon is regarded by many as the road map to optimal cardiovascular health in middle age and beyond embodied in 'Life's Simple 7' by the American Heart Association (AHA) in spite of the index case of Pheidippides in 490 B.C. (Figure 1) [1,2]. Epidemiological studies addressing ongoing concerns over such marathon-related events provide robust evidence upon which to evaluate this risk.



After running across the Plain of Marathon, Pheidippides delivered his message and died.
Figure 1: Pheidippides' sudden cardiac death in the Atheneum in 490 B.C. after declaring victory over the invading Persian army on the Plains of Marathon (by anonymous).

Unforseeing one! Yes, he fought on Marathon day: So, when Persia was dust, all cried "To Akropolis! Run, Pheidippides, one race more. Till in Athens he broke, "Rejoice, we conquer!" Joy in his blood bursting his heart, he died --- the bliss! 'Pheidippides' by Robert Browning, 1879

While the cardiovascular risk of long distance running is acknowledged as low, A 10-year prospective registry of long distance road races in the United States beginning in the year 2000 characterized the low overall incidence of 1 cardiac arrest in every 184,000 participants as good news for runners [3,4]. Male gender and the full marathon compared to the half-marathon were significant risk factors for cardiac arrest, however, which events increased 2.3-fold in middle-aged males beginning in 2005. While the overall rate of cardiac arrest was reported as 1 in 57,000 runners in United States marathons from 1982 to 2009, such events increased to 1 in 22,000 from 1 in 29,000 in males over age 29 since the year 2000 [5,6]. Atherosclerotic heart disease was the main cause of marathon-related sudden cardiac death in males over age 40 including acute myocardial infarction in 17 of 18 cases in a retrospective study [7].

The increasing frequency of race-related cardiac arrests in runners with low baseline metrics for cardiovascular disease is unexpected

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especially occurring concurrently with a 38% decline in cardiac mortality in the general population [8,9]. An explanation for these findings may emerge from observations on asymptomatic middle-aged male physician-runners providing pre- and post-race blood samples as attendees of pre-race scientific symposia of the American Medical Athletic Association. Post-race elevations of creatine kinase as an index of skeletal muscle injury after glycogen depletion or 'hitting the wall' were accompanied by a polymorphonuclear leukocytosis with increased interleukin (IL)-6 and C-reactive protein [10-12]. Predictive of acute cardiac events in healthy persons, elevated inflammatory biomarkers occurred concurrently with increased fibrinogen, von Willebrand factor, D-dimer and *in vivo* platelet activation indicating transient hypercoagulability [13,14]. Cardiac troponins I and T and NT-pro-B-type natriuretic peptide were also transiently elevated post-race in these same asymptomatic runners [15-17].

Post-race changes in validated biomarkers in asymptomatic runners similar to those in patients with acute coronary syndromes demonstrate transient high risk for acute cardiac events. Atherothrombosis is the shared clinical paradigm with IL-6 implicated in promoting rupture of non-obstructive coronary plaques [18-21]. Leakage of high-sensitivity cardiac troponins has also been shown to stratify risk for cardiovascular events in healthy persons in primary prevention studies and in patients with ischemic heart disease [22,23]. The report of acute myocardial infarctions due to coronary plaque rupture in runners immediately after the 2011 Boston marathon provides closure regarding the pathophysiological relevance of biomarker findings in asymptomatic runners [24]. Acute cardiac events in susceptible runners during races are due to type 1 myocardial infarctions similar to the cause of exertional fatalities in first responders such as on-duty firemen and police officers [25-27].

Aspirin has been demonstrated to mitigate excess short-term acute cardiac risk during systemic inflammation in clinical

conditions including septicemia, influenza and preeclampsia [28-30]. As proposed for cardio-protection in patients with life-threatening infections [31], aspirin pre-race usage has been proposed as prudent for middle-aged males based in part on conclusive evidence for protection of same-aged healthy male physicians from first acute myocardial infarctions in the randomized prospective Physicians Health Study [32-35].

Middle-aged males who do not qualify for continuous aspirin at baseline meet criteria for such usage during marathons as a high-risk subgroup in guidelines of the AHA, American College of Cardiology (ACC) and the European Society of Cardiology [36,37]. A single pre-race low-dose aspirin would provide susceptible runners with the only medication given a grade 1A recommendation for pre-hospital treatment for an acute coronary syndrome while minimizing the risk for adverse events such as gastrointestinal bleeding during continuous usage.

Responsibility for disclosure of the increased cardiac risk for middle-aged males during marathons rightly falls upon the medical community similar to the United States Food and Drug Administration's warning on excess sudden cardiac deaths during short-course treatment with azithromycin [38,39]. The 2014 Rio de Janeiro marathon was first to recommend pre-race aspirin usage for males over age 40 upon approval by their physicians based upon an advisory from the International Marathon Medical Directors Association (IMMDA) [40,41]. Successful resuscitation following cardiac arrest occurred at the finish line in the 2014 and 2015 races with a full recovery after coronary stent placements in the latter case (personal communication, Paulo Afonso Lourega de Menezes, M.D., medical director). (Figure 2).

Measurement of coronary artery calcium density may be especially useful for stratifying risk for pre-race aspirin usage in experienced runners among whom such scores are paradoxically higher than in matched non-running controls and correlate inversely with short-term event free survival [42-45]. Disclosure of his personal diagnosis of coronary heart disease by Dave McGillivray, race director of the Boston marathon since 1988, put runners on notice about the potential for development of symptomatic coronary heart disease including the 50% of runners above the most common age of 46 among the 35,384 entrants to the 2014 Boston race [46,47].

Middle-aged males morph into transiently increased risk for acute coronary events during marathons in contrast to beneficial effects of recreational marathon training on the myocardium [48]. Testing the efficacy of pre-race aspirin usage to reduce preventable acute cardiac events in middle-aged males as advocated by IMMDA would require staunch collaboration across the sports medicine community [49]. Aspirin usage to reduce sports-related acute cardiac risk is not yet on the radar screen in subspecialty articles by preventive cardiologists, which focus on mostly non-preventable causes of sudden cardiac death in athletes below the age of 30 [50-53].

Beyond standing up for better heart health and evidence that moderate-to-vigorous physical activity at a lower than currently recommended dose is associated by meta-analysis with lower 10-year all-cause mortality in older adults [54,55], the jury may now be in regarding excess cardiovascular morbidity and mortality associated



Figure 2: Paulo Afonso Lourega de Menezes, M.D., medical director of the Rio de Janeiro marathon, with his team at the finish line medical tent. Runners in cardiac arrest were successfully resuscitated in 2014 and 2015 in spite of their recommendation that males over age 40 take pre-race aspirin upon approval by their physicians.

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| <ul style="list-style-type: none"> • If marathon-related cardiac arrests and sudden deaths are increasing in males over age 40 due mainly to atherosclerotic heart disease |
| <ul style="list-style-type: none"> • And stratification with validated biomarkers indicates high short-term cardiac risk in same-aged asymptomatic males during races |
| <ul style="list-style-type: none"> • And aspirin has been conclusively shown to prevent first myocardial infarctions in same-aged healthy males in a randomized prospective primary prevention trial |
| <ul style="list-style-type: none"> • Pre-race aspirin usage is prudent to protect susceptible runners from excess race-related cardiac morbidity and mortality. |

Figure 3: Rationale for pre-race aspirin usage to protect susceptible runners from marathon-related acute cardiac events

with running marathon in middle-aged apparently healthy males [56,57]. As if crossing the Rubicon, running marathons for this vulnerable subgroup may enter the realm of 'you can have too much of a good thing' from the usual and customary terrain of 'if some is good, more is better'.

Mitigation of the increasing frequency of acute cardiac events in middle-aged males during marathons with pre-race aspirin may be achievable as was accomplished in reducing fatal cerebral edema in young females through a robust consensus process (Figure 3) [58-60]. In contrast to the United States Preventive Services Task Force's recent recommendation for aspirin usage begin at age 50, [61] male runners over age 30 may benefit based on recent findings. While avid bystander cardiopulmonary resuscitation during races has improved survival, prevention trumps treatment in this domain [62,63]. The efficacy of pre-race aspirin usage can be assessed prospectively to determine if this remedy known to Hippocrates in the time of Pheidippides can prevent non-obstructive coronary artery plaques from becoming vulnerable to rupture during transient race-related inflammatory stress.

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