

# openheart Prerace aspirin to protect susceptible runners from cardiac arrest during marathons: is opportunity knocking?

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## ABSTRACT

While endurance exercise such as marathon training is cardioprotective, an increasing frequency of race-related cardiac arrests and sudden death has been observed in middle-aged men since the year 2000. An evidence-based strategy for prevention is considered based on identifying atherothrombosis as the underlying cause in this susceptible subgroup. Review of all articles on PubMed related to acute cardiac events during marathons. Male gender and the marathon compared with the half-marathon were identified as significant risk factors for race-related cardiac arrests, which events increased 2.3-fold in the latter half of a 10-year prospective registry beginning in the year 2000. There were 50 cardiac arrests in runners who were 86% male with a mean age of 42 years. The main cause of sudden death was atherosclerotic heart disease in those over the age of 40 including myocardial infarction in 12 of 13 (93%) cases over the age of 45 as assessed retrospectively. Inflammatory biomarkers predicting acute cardiac events and hypercoagulability with in vivo platelet activation were demonstrated in same-aged asymptomatic middle-aged men during marathons. Excess cardiac morbidity and mortality in middle-aged men during marathons is mediated by atherothrombosis which may render non-obstructive coronary atherosclerotic plaques vulnerable to rupture. Prerace low-dose aspirin usage is prudent to protect susceptible runners from a high, if transient, risk for cardiac arrest during races as evidence-based to prevent first myocardial infarctions in same-aged healthy men.

## CARDIAC ARRESTS HAVE INCREASED IN FREQUENCY IN MIDDLE-AGED MEN DURING MARATHONS SINCE THE YEAR 2000 WITH ATHEROSCLEROTIC CORONARY ARTERY DISEASE AS THE MAIN CAUSE OF SUDDEN DEATH

While leisure-time running reduces all-cause and cardiovascular mortality risk,<sup>1</sup> an increased frequency of cardiac arrest and sudden death has been observed in middle-aged men during marathons since the year 2000.<sup>2-3</sup> A 10-year prospective registry of long-distance running races showed that male gender and the

marathon as opposed to the half-marathon were significant risk factors for cardiac arrest.<sup>2</sup> Such events increased 2.3-fold in middle-aged men in the latter half of the study in runners with an average age of 42 years. Cardiac arrest also increased from 1 in 29 000 to 1 in 22 000 in men over the age of 29, comparing decades before and after the year 2000 at two specific marathon venues.<sup>3</sup>

Atherosclerotic heart disease was the main cause of marathon-related sudden cardiac death in participants over the age of 40 in two retrospective studies in contrast to mostly non-preventable causes in younger athletes.<sup>4-7</sup> These studies clearly demonstrate an increasing frequency of race-related cardiac arrests in middle-aged men in contrast to a declining rate of sudden cardiac deaths in the general population.<sup>8</sup>

## BIOMARKERS PREDICTING ACUTE CARDIAC EVENTS IN HEALTHY PERSONS ARE TRANSIENTLY ELEVATED IN ASYMPTOMATIC MIDDLE-AGED MEN DURING MARATHONS

Middle-aged male physician-runners who were attendees at prerace symposia of the American Medical Athletic Association provided prerace and postrace blood samples for analysis at sequential Boston marathons.<sup>9</sup> Postrace elevations in creatine kinase as an index of exertional rhabdomyolysis in these asymptomatic respondents were accompanied by neutrophilia with elevated interleukin 6 and C reactive protein as inflammatory biomarkers predicting cardiovascular events in healthy persons.<sup>10-14</sup> Elevated fibrinogen, von Willebrand factor and D-dimer with in vivo platelet activation indicated a haemostatic imbalance with procoagulant effects.<sup>15-16</sup> A biomarker profile representing a 'perfect storm' for an acute coronary syndrome was present in these asymptomatic runners who also showed concurrent release of cardiac troponin T and N-terminal pro-brain natriuretic peptide.<sup>17</sup>



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Perhaps reprising the index case of Pheidippides in 490 B.C., (figure 1) these findings indicate a high, if transient, risk for atherothrombosis during marathons, which may cause low-profile coronary atherosclerotic plaques to morph into the culprit lesions of acute coronary thrombosis.<sup>18 19</sup> Coronary plaque rupture triggering type 1 acute myocardial infarction was observed in vivo in two runners during post-race coronary angiography after the 2011 Boston marathon.<sup>20 21</sup> The increase in cardiac arrests in susceptible runners during marathons may be seen as a specific clinical example of exertional sudden cardiac death as occurs in on-duty police officers.<sup>22 23</sup> Inflammation-induced atherothrombosis also accounts for the increased cardiac risk of systemic infections such as community-acquired bacteraemia and scrub typhus.<sup>24 25</sup>

### ASPIRIN USAGE IS CARDIOPROTECTIVE DURING SHORT-TERM HIGH RISK DUE TO SYSTEMIC INFLAMMATION

Aspirin usage has been shown to decrease 30-day cardiac mortality in critically ill patients with sepsis and to reduce the morbidity and mortality of pre-eclampsia by 30% in an evidence-based review for the US Preventive Service Task Force.<sup>26 27</sup> These systematic reviews provide a rationale for recommending pre-race aspirin usage to offset

high short-term cardiac risk in susceptible middle-aged men during marathons as has recently been proposed for serious systemic infections.<sup>28–31</sup> This strategy qualifies as concordant with primary aspirin prophylaxis endorsed for high-risk subgroups based on appropriate risk stratification by the American Heart Association (AHA) and the Working Group on Thrombosis of the European Society of Cardiology.<sup>32 33</sup> These recommendations rightfully apply to the high risk for major cardiovascular events due to inflammation-induced atherothrombosis in both short-term and chronic clinical conditions as recently demonstrated in patients with rheumatological disorders in a population-based cohort study.<sup>34</sup>

### SHOULD SUSCEPTIBLE RUNNERS TAKE PRERACE ASPIRIN TO PREVENT CARDIAC ARREST DURING MARATHONS?

The rationale for recommending pre-race aspirin usage to protect susceptible middle-aged men from short-term high risk for exertional myocardial infarctions rests on conclusive evidence for prevention of first acute myocardial infarctions in same-aged healthy men in the prospective randomised controlled Physicians Health Study (PHS).<sup>35</sup> This strategy also confers a class I recommendation for prehospital treatment in case an acute coronary syndrome arises especially near the finish line where most cardiac arrests take place.<sup>36 37</sup> A single low-dose



*After running across the Plain of Marathon, Phidippides delivered his message and died.*

**Figure 1** Pheidippides' sudden cardiac death in the Athenaeum in 490 B.C. after declaring victory over the invading Persian army on the Plains of Marathon (by anonymous).



- If cardiac arrests during marathons are due to atherosclerotic heart disease in some middle-aged men
- And same-aged asymptomatic marathoners show biomarkers of inflammation during races which predict cardiovascular events in healthy persons
- And aspirin has been conclusively shown to prevent first myocardial infarctions in healthy men
- Pre-race aspirin usage may protect susceptible runners from cardiac arrest.

**Figure 2** Rationale for prerace aspirin usage to protect susceptible runners from cardiac arrest during marathons

aspirin would provide antithrombotic benefit during and for the 24 h of highest postrace cardiac risk even if taken at the starting line so long as it is not enteric coated.<sup>38</sup>

Low-dose aspirin confers antithrombotic benefit by irreversibly inhibiting platelet cyclo-oxygenase with minimal exposure to adverse effects such as gastrointestinal bleeding or renal injury during dehydration.<sup>39</sup>

Analogous to the urgent advisory by the US Food and Drug Administration on excess sudden cardiac death associated with short-course azithromycin,<sup>40–41</sup> what message should be conveyed to susceptible males regarding this same risk during marathon running? The recommendation for middle-aged men to take prerace aspirin on approval by their physicians was provided in the programme of the 2014 Rio de Janeiro marathon by its medical director, Paulo Afonso Lourega de Menezes.<sup>42</sup> As with excess sudden cardiac death with azithromycin, disclosure allows susceptible males to participate cognisant of transiently high short-term cardiac risk and with the benefit of cardioprotective measures (figure 2).<sup>43</sup>

Endorsed by a group of international marathon medical directors based on clinical urgency,<sup>44–45</sup> this measure presents an opportunity to decrease cardiac morbidity and mortality in susceptible males at high risk by appropriate risk stratification as has been achieved through a consensus process in the marathon medical community for exercise-associated hyponatremia.<sup>46–47</sup>

## Overview

The rationale for prerace aspirin usage in middle-aged men before marathons links recent evidence demonstrating an increased risk for cardiac arrest and sudden death in this subgroup to elevated biomarkers predicting cardiac events in same-aged asymptomatic males during races. Prerace aspirin usage for high short-term cardiac risk is concordant with evidence for reduced short-term cardiac risk during inflammation and is concordant with subspecialty guidelines endorsing aspirin for primary prevention in subgroups at high risk by appropriate risk stratification. Pending results of a prospective randomised trial specifically in runners, a prudent strategy for

susceptible runners would be to take a prerace low-dose aspirin on approval by their physicians.

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