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# Pre-race aspirin to enhance primary prevention of marathon-related cardiac arrests: confronting Pheidippides' legacy

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Although increasing levels of physical exercise confer incrementally greater lifetime cardioprotective benefits (marathon training)[1], episodes of vigorous physical exertion (the race) transiently increase the risk for acute cardiac events including sudden death [2]. Undoubtedly the ultimate overuse sports injury, sudden cardiac death during sport occurs in both elite and recreational athletes[3-7]. The paradox that vigorous exercise decreases one's lifetime risk for major acute cardiac events, but may also trigger sudden death, may represent a U-shaped benefit-risk curve[8].

A retrospective study of mortality during United States marathons beginning in 2000 determined that atherosclerotic coronary heart disease in middle-aged men was the main cause of death [9]. A 10-year prospective registry of United States road races from 2000 identified male gender and the marathon as the only significant and independent risk factors for cardiac arrest[10]. Similar observations have been reported during marathons in this same demographic in other countries and during other endurance sports[11-13].

Pre-race low-dose aspirin use has been proposed to mitigate this dilemma based on a 44% reduction in first heart attacks in middle-aged men in the final report on this agent in the Physicians Health Study, a randomized controlled prospective primary prevention trial[14-19]. Coronary artery calcium scores and cardiac biomarkers have also been recommended to identify runners most likely to benefit from this intervention[20,21]. The impact of including such assessments in decision-making may qualify runners for aspirin use who fall below the threshold in sub-specialty guidelines (Figure 1)[22].

This enhanced risk stratification is appropriate for diverse participants including novices, as runners who are less trained are more likely to have elevated post-race cardiac biomarkers[23]. High coronary artery calcium scores occur more commonly in habitual marathon runners, as exercise volume and especially intensity promote progression of coronary atherosclerosis[24,25]. Such scores also reliably stratify risk for sudden cardiac death[26]. While the clinical significance of exercise-related elevations in inflammatory and cardiac biomarkers in asymptomatic athletes is uncertain[27,28], recent studies suggest that such findings may have prognostic significance for major acute cardiovascular events as in patients with acute cardiac conditions [29-35].

Health care providers are advised to consider expanded risk stratification for pre-race aspirin use with patients who choose to run marathons, especially those who undertake training to maximize cardiovascular health but may be unaware of the risk associated with races. Using aspirin in those identified at high risk by these ancillary screening measures is analogous to advising such use based on lipoprotein subtypes[36].

Post-race activation of atherothrombosis is a likely proximate cause of cardiac arrest in middle-aged male runners with atherosclerotic coronary heart disease, which has been demonstrated by a concurrent post-race hemostatic imbalance with prothrombotic effects including *in vivo* activation of platelets in asymptomatic Boston marathon runners[37,38]. The anti-inflammatory and anti-thrombotic effects of aspirin also provide at-risk runners with the advantage of having an agent on board with a class 1A recommendation for pre-hospital administration should chest pain develop during or after races.

The efficacy of pre-race aspirin for reducing marathon-related fatalities can be assessed by a follow-up registry, as a prospective study like the aspirin arm of the Physicians Health Study lacks feasibility due to the infrequency of index events. The marathon medical community may hopefully undertake this measure to address the increasing frequency of race-related cardiac arrests in middle-aged men, as was successfully accomplished in curtailing fatalities due to exercise-associated hyponatremia mainly in novice and younger women [39]. As inflammation due to exertional rhabdomyolysis is the root cause of these life-threatening conditions, the hypothesis that muscle injury may cause adverse effects on the heart is validated, as advanced in the first medical study on Boston marathon runners in 1899 [40].

Aspirin is a prime candidate to attenuate the incongruous cardiovascular conundrum presented by marathon training and racing. This agent is readily available worldwide, inexpensive and safe as determined in the polypill trials, which also showed a 31% reduction in acute cardiac events in individuals at moderate baseline cardiovascular risk[41,42]. To quote Amby Burfoot, Runners World editor-emeritus and 1968 Boston marathon champion: “Just because the incidence of cardiac arrest is low doesn’t mean it can’t be lower” (personal communication).

In summary, pre-race low-dose aspirin use qualifies as evidence-based to mitigate the increasing frequency of marathon-related cardiac arrests in middle-aged men due to atherosclerotic coronary heart disease. Assessment of coronary artery calcium scores and post-race cardiac biomarkers can stratify risk to identify runners who might benefit the most from such enhanced primary prevention.

Table 1: The impact on therapeutic decision-making for pre-race aspirin use by including coronary artery calcium scores and inflammatory/cardiac biomarkers in risk calculations (RED=No, Yellow=consider, GREEN=YES).

| Proposed Guideline Using 10-year ASCVD Risk Estimate, Coronary Artery Calcium (CAC) Score, and hs-CRP to Guide Aspirin Therapy | | | | |
|---|---|---|---|---|
| Patient's 10-year atherosclerotic disease (ASCVD) risk estimate: | < 5% | 5-7.5% | >7.5-20% | >20% |
| Consulting ASCVD risk estimate alone: | Aspirin not recommended | Consider aspirin | Recommend aspirin | Recommend aspirin |
| Consulting ASCVD risk estimate + CAC<br>If CAC score = 0<br>If CAC score >0 | Aspirin not recommended<br>Consider aspirin | Consider aspirin<br>Consider aspirin | Recommend aspirin<br>Recommend aspirin | Recommend aspirin<br>Recommend aspirin |
| If elevated hs-CRP: | Recommend aspirin | Recommend aspirin | Recommend aspirin | Recommend aspirin |
| Does hs-CRP modify treatment plan? | Yes | Yes | No | No |

Adapted from Greenland, P. et al. J Am Coll Cardiol. 2018;72(4):434-47.

Figure 1: This figure illustrates use of hs-CRP elevation as a marker for inflammation in addition to ASCVD risk estimate and coronary artery calcium score to reclassify a patient's risk when considering recommendation for aspirin therapy.

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