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RESEARCH ARTICLE

Rationale for Pre-Race Aspirin to Attenuate Risk for Marathon-Related Cardiac Arrest: Confounding the Legacy of Pheidippides

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ABSTRACT:

While increasing levels of recreational sports participation are incrementally cardioprotective, strenuous physical exertion transiently increases the risk for acute cardiac events including sudden death. The frequency of marathon-related cardiac arrests has been increasing since the year 2000 mainly in middle-aged men due to atherosclerotic coronary artery disease. Coronary artery calcium scores and post-race cardiac biomarkers are recommended to identify runners who might benefit the most from pre-race aspirin for enhanced primary prevention.

Keywords: marathon, cardiac arrest, aspirin, primary cardiovascular prevention

The scope of the problem:

Although increasing levels of physical exercise confer incrementally greater lifetime cardioprotective benefits^{1,2}, vigorous physical exertion transiently increases the risk for acute cardiac events including sudden death in elite and recreational athletes³⁻⁸. Marathon training reduces a runner's overall lifetime risk of sudden cardiac death except for transiently increasing this risk during the race. This paradox has been described by some as representing a U-shaped curve^{9,10}.

A retrospective study of mortality during United States marathons since 2000 showed that atherosclerotic coronary heart disease in middle-aged men was the main cause of death¹¹. A 10-year prospective registry of United States road races beginning in 2000 showed male gender and the marathon to be independent and significant risk factors for cardiac arrest, which events increased significantly in frequency during the second half of the study¹². Marathon-related cardiac arrests also increased in this same demographic in other countries and during other endurance sports^{13,14}.

Pre-race aspirin use as an evidence-based intervention:

Pre-race low-dose aspirin use has been proposed to mitigate this conundrum based on a 44% reduction in first heart attacks in healthy middle-aged men in the final report on aspirin in the Physicians Health Study, a randomized controlled prospective primary prevention trial¹⁵⁻²¹. A 31% reduction in major acute cardiac events was also demonstrated in persons at moderate baseline cardiovascular risk in the aspirin arm of the prospective randomized International Polycap-3 Study²²⁼²³.

Coronary artery calcium scores and post-race cardiac biomarkers have been recommended as ancillary measures for risk stratification to identify athletes most likely to benefit from enhanced primary prevention with pre-race aspirin (Table 1)²⁴⁻²⁷. Such findings reflect dynamic changes in risk factors for runners in contrast to polygenic risk scores as predictive for coronary atherosclerosis in middle-aged patients²⁸. Using these exercise-dependent measure to guide enhanced preventive measures such as aspirin is similar to a proposal advanced for patients with high-risk lipoprotein(a) genotypes²⁹.

Approach to risk stratification for runners:

Coronary artery calcium scores are especially relevant in experienced runners, as the intensity of marathon racing promotes progression of coronary atherosclerosis in middle-aged and older men to a

greater degree than the volume of training²⁹. As an index of coronary atherosclerotic burden, such scores stratify risk for sudden cardiac death^{30,31}. In contrast, post-race cardiac biomarkers are useful for risk stratification especially among novices, as greater elevations are more likely to occur in those who have had lesser degrees of training³².

As in patients with diabetes or acute cardiac conditions, elevated cardiac biomarkers in asymptomatic athletes confer prognostic significance for major acute cardiac events as in high-risk patients with diabetes³³⁻³⁹. Patients with elevated troponin levels associated with COVID-19 infection demonstrated microinfarctions by cardiac magnetic resonance imaging attributed to inflammation-induced hypercoagulability⁴⁰. A similar pathogenic scenario has been shown to occur in Boston marathon runners, who demonstrated a post-race hemostatic imbalance with prothrombotic effects including *in vivo* activation of platelets and elevated D-dimer levels concurrent with biomarker elevations^{41,42}.

While there is no 'sweet spot' where the acute cardiac risk of the marathon is zero⁴⁵, aspirin use allows runners to maximize the cardiovascular benefit of training while minimizing the risk of the race. This strategy pertains to Boston marathon legends like five-time winner Clarence DeMar ("Mr. Marathon"), who showed advanced coronary atherosclerosis on post-mortem examination as reported by Paul Dudley White, M.D.⁴⁶. David McGillivray, the Boston marathon's race director is a contemporary example, having completed that race more than 50 times including twice after three-vessel coronary artery bypass surgery in 2018⁴⁷. Aspirin use is clearly the evidence-based intervention of choice to attenuate the risk for a major cardiovascular event during races especially in such Masters athletes who are middle-aged and beyond⁴⁸.

Pre-race aspirin use is appropriate for shared decision making with marathon runners, especially those undertaking the sport to maximize heart health but lacking awareness of the associated risks. Pre-race aspirin provides such runners with the benefit of having an agent on board with a class 1A recommendation for pre-hospital administration in acute coronary syndromes should chest pain occur during or after a race.

The anti-inflammatory and anti-thrombotic properties of aspirin present an opportunity for the marathon medical community to reduce race-related cardiac arrests in middle-aged men, as was successfully accomplished with alternative evidence-based interventions in curtailing race-related fatalities mainly in young women due to

exercise-associated hyponatremia⁴⁹. As inflammation consequent to exertional rhabdomyolysis is the shared root cause of both life-threatening conditions, the hypothesis that muscle injury causes adverse effects on the heart is validated, as advanced in the first medical study on Boston marathon runners in 1899⁵⁰.

As an agent known to Hippocrates in the time of Pheidippides, aspirin is positioned to mitigate the marathon-related risk of cardiac arrest, reverberating in this sport in the modern era since the latter's index case in 460 BC. The importance of determining the cause of death in such cases is essential for progress in addressing this complex clinical problem, as illustrated in the recent case of a cardiac arrest in a 26 year old experienced marathon runner seconds after crossing the finish line with a personal best time at the Mesa Marathon in Arizona, USA, on February 4, 2023, (Figure 1)^{51,52}. To quote Amby Burfoot, Runners World editor-in-chief emeritus and 1968 Boston marathon champion, "Just because the incidence of cardiac arrest during marathons is low doesn't mean it can't be lower" (personal communication).

Conclusion:

Pre-race low-dose aspirin is evidence-based to attenuate the increasing frequency of cardiac arrest during marathons in middle-aged men due to atherosclerotic coronary heart disease. Coronary artery calcium scores and post-race cardiac biomarkers are recommended to identify those runners who might benefit the most from this measure to enhance primary prevention.

Take-aways:

- Marathon-related cardiac arrests have increased in frequency since the year 2000 mainly in middle-aged men due to atherosclerotic coronary artery disease.
- Aspirin reduces first heart attacks in healthy middle-aged men and decreases major acute cardiovascular events in those with mild to moderate baseline cardiovascular risk as shown in prospective randomized controlled prevention trials.
- Coronary artery calcium scores and post-race cardiac biomarkers reliably stratify risk to identify those who might benefit the most from aspirin for 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				
If CAC score = 0	Aspirin not recommended	Consider aspirin	Recommend aspirin	Recommend aspirin
If CAC score >0	Consider aspirin	Consider aspirin	Recommend aspirin	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 26-year-old experienced non-elite runner experienced cardiac arrest moments after this picture showed him crossing the finish line of the Mesa Marathon, Mesa, Arizona, USA, on February 4, 2023⁴⁵.



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