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EDITORIAL COMMENT

Exercise *Is* Medicine

Proof . . . and Possibilities?*

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"A vigorous five-mile walk will do more good . . . than all the medicine . . . in the world"
—Paul Dudley White (1)

Although shared more than one-half century ago, these words of clinical wisdom from Paul Dudley White still reinforce a central tenet of preventive cardiology. The health benefits of regular physical activity (PA) and exercise on mortality, both all-cause and cardiovascular, are well established (2). Likewise, physical inactivity portends increased risk of mortality and significant cardiovascular-related morbidity, such as diabetes and atherosclerotic cardiovascular disease (3). It has become evident that incorporation of an individualized "exercise prescription" should be an essential element of comprehensive cardiovascular care, requiring more attention than just simple words of encouragement at the end of an office encounter. Indeed, important "Exercise is Medicine" initiatives (2), sponsored by the American College of Sports Medicine and American Medical Association, have raised notice for the documentation of PA as a recorded vital sign in clinical practice. From an epidemiologic standpoint, the inclusion of PA within risk stratification approaches may be of significant benefit, although this is currently not commonly used in clinical practice.

In this issue of *iJACC*, Arnson et al. (4) address the potential of adding a simple measure of PA as a "vital sign" by examining the relationship between PA, coronary artery calcium (CAC) burden, and all-cause mortality. Specifically, the investigators addressed the question of whether the combination of CAC scores and self-reported exercise provides additive prediction of mortality in asymptomatic patients. In this study, 10,690 patients, who underwent CAC scanning by either electron beam or multislice computed tomography, were followed for the primary outcome of all-cause mortality over a mean period of approximately 9 years. CAC was quantified by the Agatston method to provide a summed total CAC score and patients were categorized to 1 of 4 groups (no exercise, low exercise, moderately active, and highly active) based on a single-item questionnaire assessing subjective exercise habits. The investigators found that, compared with the more active groups, the no-exercise (i.e., sedentary) group had increased prevalence of cardiovascular risk factors, were more likely to be on a statin, and had higher mean CAC scores. The primary finding from the analysis was that compared with highly active patients with a CAC score of 0, there was a progressive increase in all-cause mortality for each reported decrement in exercise that was more pronounced in those with increased CAC scores (2.48-fold for CAC 1 to 399 and 3.1-fold for CAC >400). Among patients with a CAC score of 0, the level of exercise did not have a significant impact on mortality (5).

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The investigators should be commended for this important work, which sets the stage for future investigation focused on validating the benefit of routinely assessing PA as a vital sign. One of the strengths of this analysis is the long-term and prospective follow-up of mortality in a robust cohort of patients stratified by CAC scores. Consistent with the "Exercise is Medicine" philosophy, these data affirm that poorer outcomes are more likely in patients with and without underlying subclinical atherosclerosis lacking regular exercise and PA. Perhaps more importantly, this study demonstrates that within

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this population the inclusion of a self-reported PA measure may provide additive long-term prognostic information. Additional, compelling results from the analysis suggest that PA may be protective in patients with increasing CAC scores. Potential benefits of PA include anti-inflammatory, antithrombotic, anti-atherogenic, anti-ischemic, antiarrhythmic effects, and improvements in traditional cardiovascular disease risk factors (e.g., blood pressure, lipids) (2,6). As the investigators note, this suggestion raises the possibility that expanding cardiac rehabilitation into a comprehensive risk reduction strategy in higher risk primary prevention patients may be an approach worthy of further consideration (6). From a translational research perspective, mechanisms underlying potential "plaque stabilization" in the habitual exercising population are unknown and represent important future directives.

One intriguing population in this dataset was the group of high-level (high-frequency) exercisers. Recent data suggest that long-term exposure to endurance exercise is associated with a paradoxical increase in CAC (7,8). Although the clinical significance remains uncertain (3), it has been hypothesized that increased CAC represents a maladaptive response to high-level endurance training. In this analysis, higher overall mean CAC scores (153.7 ± 459.0) and percentage of patients with CAC scores >400 (10.5%) were present in the highly active group compared with the low (132.1 ± 404.0, 9.3%) and moderately active groups (134.3 ± 404.0, 8.8%). The lowest percentage of patients with CAC scores of 0 was also present in the highly active group. Despite these trends, patients in the highly active group maintained the lowest cumulative mortality. The associations among long-term endurance exercise, CAC, and clinical outcomes remains an active arena of discovery. Results from Arnson et al. (4) provide new insight and suggest that whereas paradoxical increases in CAC seen in high-level exercisers may be, in fact, present, adaptive rather than pathophysiologic mechanisms may be involved. Further carefully designed epidemiologic and mechanistic studies are needed as significant knowledge gaps remain for this growing, highly active population.

There are important limitations of this analysis. First and most significant is the inability to conclude causation regarding the impact of PA on all-cause mortality in patients with CAC. Second, there was no longitudinal follow-up of baseline measures in the study population and no adjustment for active medical therapy or potentially unmeasured covariables such as dietary pattern that could have affected the measured outcome. Finally, although the use of a single-item questionnaire assessing PA has a definite time efficiency advantage in clinical practice, correlation between objective measures of PA and self-reported exercise have been weak (9). The lack of objective measures of fitness (e.g., oxygen consumption) as well as reported intensity, duration, and type of activity or exercise are also substantial limitations of this study.

For generations, participation in regular PA as a part of a healthy lifestyle has been an emphasized area of patient counseling in clinical practice. As advancements in imaging improve risk stratification models, Arnson et al. (4) suggest adding potentially valuable data, the vital sign of PA. Increases in regular PA not only reduce mortality for those who were previously sedentary, but also may have protective effects for patients with subclinical atherosclerosis. These findings support the mandate that regular assessment of and recommendation for at least moderate regular PA should be a routine part of cardiology practice. Standardizing PA as a vital sign may lead to improved clinical cardiovascular outcomes and efficacy in the implementation of comprehensive cardiovascular risk reduction. Intriguingly, results from the current study suggest that simple questions assessing PA habits may be adequate. For patients engaged in high-level endurance exercise, this provocative publication suggests that dense CAC found in asymptomatic high-level exercisers may not adversely affect outcome.

Paul Dudley White once said, "if bicycling can be restored to the daily life of Americans, it can be a vital step toward rebuilding health and vigor in all of us" (1). The health benefits of exercise are well established, and for the first time, Arnson et al. (4) demonstrate a potential association of exercise and mortality in an asymptomatic population with CAC. These findings support the concept of exercise as medicine and, though not proof, raise many possibilities.

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