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RESEARCH ARTICLE

Rationale for Expanding the Use of Low-Dose Aspirin for Primary Cardiovascular Prevention during the COVID-19 Pandemic

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ABSTRACT

The COVID-19 pandemic has decreased life-expectancy in the United States in 2021, causing over one million deaths especially in elderly persons with medical co-morbidities. While now waning, this epidemic continues to cause more than 500 fatalities per week mostly in individuals over70 years of age who are unvaccinated. Since viral epidemics have been shown to increase mortality due to atherosclerotic coronary heart disease and low-dose aspirin has been shown to reduce first myocardial infarctions by 44%, we recommend consideration of expanding the use of aspirin for primary cardiovascular prevention to reduce the cardiac morbidity and excess mortality associated with COVID-19 infections. Such aspirin use may be seen as especially appropriate for vulnerable elderly persons who qualify for treatment with Paxlovid (ritonavir-boosted nirmatrelvir) but are currently excluded for such in primary prevention guidelines of subspecialty societies. The rationale for this approach is further supported by recent proof of concept that vaccination, an alternative intervention for primary cardiovascular prevention, reduces the excess mortality associated with COVID-19 infection.

Can greater use of aspirin for primary cardiovascular prevention mitigate the excess cardiac mortality associated with COVID-19 as shown with prior viral epidemics [1-3]? Recommendations from the 2019 ACC/AHA and 2021 ESC guidelines currently advise limited aspirin use for primary prevention except in persons aged 40 to 59 years with elevated ASCVD risk scores (10-year risk ≥10%) and for those aged 60 to 69 years only with risk ≥20% in the context of no excess risk of bleeding (Figure 1) [4,5]. These guidelines have been endorsed by the United States Preventive Services Task Force, which acknowledge that low-dose aspirin in the primary prevention setting reduces the risk of major atherosclerotic cardiovascular events including myocardial infarction and ischemic stroke offset by an increased risk of gastrointestinal bleeding [7,8]. Currently endorsed guidelines specifically recommend against aspirin use in individuals at age 70 and beyond.

Keywords: aspirin, COVID-19 pandemic, primary cardiovascular prevention

Introduction

Based on conclusive evidence that low-dose aspirin reduces the risk for first acute myocardial infarctions by 44% in middle-aged men in a randomized controlled primary prevention trial and the proof of concept that inhibition of inflammation can reduce cardiovascular events [9,10], low-dose aspirin has been recommended to reduce the risk for cardiac morbidity and mortality in the vulnerable elderly[11,12]. This strategy may seem as paradoxical as prior proposals to use low-dose aspirin to decrease the relative risk for exertional cardiac arrest and sudden death in endurance athletes such as marathon runners during races[13,14]. Coronary artery calcium scores and inflammatory markers such as C-reactive protein levels are reliable and validated indices by which to stratify risk in individual persons to assess benefit versus bleeding risk on a case-by-case basis[15-17]. The benefit increases with age and medical vulnerability just as this measure counterintuitively reduces risk for sudden cardiac death in the most experienced endurance athletes who would be excluded for such use by consideration of traditional risk factors only.

This intervention is supported by evidence that early aspirin use reduces in-hospital morbidity and mortality in patients with moderate to severe COVID-19 infection[18-21]. While additional studies are needed to determine the benefit of low-dose aspirin use for primary cardiovascular prevention, this intervention is currently the standard of care for reducing preeclampsia in high-risk women with daily low-dose aspirin from week sixteen through delivery[22]. Aspirin's ability to reduce the excess cardiovascular morbidity and mortality associated with prior viral epidemics suggests a potentially selective benefit for vulnerable elderly persons especially with co-morbid risk factors, who are specifically excluded from such aspirin use in current subspecialty guidelines.

Recent evidence provides proof of concept that the excess mortality attributable to COVID-19 infection can be reduced by vaccination, which is an alternative modality for primary cardiovascular prevention[23]. Analogous to the apparently paradoxical or counter-intuitive recommendation for prophylactic low-dose aspirin use in athletes who qualify by stratification of independent risk factors such as high coronary calcium scores and elevated inflammatory biomarkers, clinicians are advised to consider such usage in individuals of any age, especially the elderly, with medical co-morbidities such as diabetes mellitus, obesity, hypertension and the like, which exacerbate the risk for hospitalization and death due to Covid-19 infection.

Emerging evidence that early aspirin use reduces hospitalizations and in-hospital mortality associated with moderate and severe COVID-19infection, respectively, justifies such expanded usage for primary cardiovascular prevention. Individuals who qualify for early treatment with Paxlovid (ritonavir-boosted nirmatrelvir) during COVID-19 infection are most likely to benefit from such aspirin prophylaxis regardless of vaccination status 24,25. While a randomized prospective primary prevention trial of low-dose aspirin regarding COVID-19 would be ideal as was accomplished in the Physicians Health Study, such a trial lacks feasibility. This strategy may also confer two unintended but impactful consequences. Reductions in morbidity would serve to conserve limited and vital medical resources such as the capacity for treatment in intensive care units. There is additionally a potential benefit in the realm of population medicine by enhancing equity with regard to access to beneficial treatments and reducing disparities in our current health care system.

Access to low-dose aspirin for primary prevention would extend this cardiovascular protection to those who are marginalized in our current health care system, likely lacking access to benefit of innovations such as vaccination. This measure would thereby compensate to some degree by providing some degree of cardiovascular protection to those marginalized in society and relegated to adverse clinical outcomes by disparities in access to limited resources.

Primary care clinicians are well advised to consider prescribing low-dose aspirin for primary cardiovascular prevention, taking medical co-morbidities as well as age into account when assessing the risk-benefit ratio of this measure in specific cases26. What could be more advantageous than aspirin, which is inexpensive, readily available world-wide and safe in the absence of high risk for gastrointestinal or other causes of bleeding as recently demonstrated using aspirin in the polypill with to improve and promote cardiovascular health27. Given the importance of urgent and simple solutions to restraining the pandemic impact of COVID-19, the polypill strategy should be considered by physicians and public health systems as a readily available and innovative option to protect cardiovascular health.

New 2019 ACC/AHA Guideline

Prevention of CVD

Recommendations for Aspirin Use

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (S4.6-1-S4.6-8).
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults > 70 years of age (S4.6-9).
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk for bleeding (S4.6-10).

Arnett DK, et al. *J Am Coll Cardiol*. 2019. [Epub ahead of print]

Figure 1: Indications for administration of low-dose aspirin (75-100 mg orally daily) for primary prevention of ASCVD for adults over age 40 in the absence of an increased risk for bleeding risk (S4.6-10).

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