Aspirin and the Prevention of Cardiovascular Disease in Chronic Kidney Disease

Time to Move Forward?*

Ravinder K. Wali, MD
Fairfax, Virginia

Chronic kidney disease (CKD) is a common global public health problem. More than 500 million people worldwide—about 1 in 10 adults—have some form of kidney damage (1). In the U.S., an estimated 20 million people have CKD, and this number is believed to be increasing exponentially within an aging population (2).

Numerous epidemiological studies have consistently demonstrated that persons with CKD are at risk of developing cardiovascular disease (CVD) events (3–6). Persons with CKD who have an acute coronary event fare worse than persons who do not have CKD, despite optimal treatment (7,8). Persons with CKD oftentimes die of CVD-related events long before there is significant progression in their CKD and the need for either dialysis or kidney transplantation arises.

The spectrum of CVD in persons with CKD is perhaps more complex than CVD in the general population because CKD patients have specific comorbidities that develop and progress due to the metabolic complexity of CKD (9). One critical component of CVD in the CKD population is the development of accelerated atherosclerosis (10,11). As in the general population, atherosclerotic disease can remain asymptomatic for a variable period of time (12) in patients with CKD, and then—for as yet poorly understood reasons—it can suddenly change course with the development of thrombosis. This change toward atherothrombosis (13) is the harbinger for the development of acute vascular events, including sudden death (12–14). Platelet adhesion, aggregation, and activation play a critical role in the development and progression of atheromatous plaques (12,14). Therefore, antiplatelet therapy with aspirin or other antiplatelet agents is crucial in the prevention of thrombus formation as well as thrombus progression.

A meta-analysis of randomized clinical trials (15) and observational studies in high-risk patients (with established CVD) have demonstrated that long-term treatment with a single daily dose of aspirin typically prevents at least 10 to 20 fatal and nonfatal vascular events for every 1,000 patients during a 1-year treatment period. Conversely, the risk of major bleeding complications with low-dose aspirin therapy was 1 to 2 per 1,000 patients for 1 year, and with the absolute number of hemorrhagic strokes being 1 to 2 per 10,000 patients. Hence, on balance, the benefits outweigh the risks (15).

The studies of single-dose aspirin therapy for the primary prevention of CVD events in low- and intermediate-risk populations over the past 3 decades have generated divergent results. The current recommendations for the use of low-dose aspirin in the primary prevention of CVD events in persons without underlying CVD or at low risk for the development of these events is fraught with inconsistencies (15–18). However, a recent meta-analysis that evaluated and analyzed individual patient data, compared with earlier meta-analyses that only included aggregate data (15), concluded that the use of aspirin was associated with only a 20% reduction in nonfatal myocardial infarction and without any benefit with regard to fatal infarcts, different types of strokes, and vascular deaths, while there was a statistically significant increase in the risk for major gastrointestinal and extracranial bleeds (absolute increased risk of 0.03% per year) (17).

In this issue, Jardine et al. (19) explored the interesting and challenging clinical dilemma of whether low-dose aspirin therapy can prevent cardiovascular disease events in patients with different stages of CKD. They stratified enrollees of the HOT (Hypertension Optimal Treatment) trial by estimated glomerular filtration rate (eGFR) calculated from their baseline creatinine levels obtained at different centers at the time of randomization. They then examined the effects of aspirin therapy (75 mg/day) versus placebo on the risk of cardiovascular events in 3,619 hypertensive persons who also had CKD (eGFR <60 ml/min/1.73 m²) at the time of enrollment. Overall, use of low-dose aspirin compared with placebo over a mean follow-up period of nearly 4 years resulted in an absolute risk reduction of major CVD events by 0.28%, 0.74%, and >7% in the different eGFR groups (≥60, 45 to 59, and <45 ml/min/1.73 m²), respectively. As is evident, the most notable impact was in the group with advanced CKD (eGFR <45 ml/min/1.73 m²). Contrary to the results of meta-analyses of other primary prevention trials (17), Jardine et al. (19), in fact, showed that all-cause mortality, cardiovascular mortality, and strokes were prevented by low-dose aspirin therapy in subjects with an eGFR <45 ml/min/1.73 m². The use of low-dose aspirin therapy did
increase the risk of major bleeding; however, and perhaps surprisingly, this complication was not any higher in the lowest eGFR group, as one may have expected. Use of low-dose aspirin for CKD was associated with major bleeding in 27 per 1,000 persons and minor bleeding in 12 per 1,000 persons in the low eGFR group. Unfortunately, since the HOT study did not categorize the types of stroke, we do not know if any of the major bleeding events included hemorrhagic stroke, and this is a cause for concern in the CKD population with their increased risk for bleeding (20,21). The risk of major and minor bleeding in CKD subgroups as reported by Jardine et al. (19) was nearly 10 times higher than what has been reported for the general population (15).

To put the findings of Jardine et al. (19) into context, it is interesting to examine how the results of this study compare with other studies of low-dose aspirin therapy in a high-risk population other than the CKD population.

It is well known that the presence of diabetes mellitus (types 1 and 2) is considered to be a “CAD equivalent.” At present, the American Diabetic Association and the American Heart Association recommend aspirin therapy for all diabetic patients older than 40 years of age. Ogawa et al. (22), in the JPAD (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetics) study, randomized type 2 diabetic patients without a history of atherosclerotic disease to low-dose aspirin therapy (80 to 100 mg/day) versus placebo. During a median follow-up of >4 years, aspirin therapy did not confer benefit for any CVD events or for total mortality. Only the subgroup analysis of patients 65 years of age or older showed a trend toward a benefit with low-dose aspirin therapy for the primary end point (hazard ratio: 0.68; 95% confidence interval: 0.46 to 0.99) compared with the control group of a similar age. An important and notable finding of this study was that aspirin therapy was associated with an increased risk of gastrointestinal and retinal bleeding as well as the need for blood transfusions (22). One important caveat of this trial was that the study may have been underpowered. However, another study, the POPADAD (Prevention of Progression of Arterial Disease and Diabetes) trial comparing low-dose aspirin with placebo for type 2 diabetic patients with asymptomatic peripheral vascular disease (23) again demonstrated no benefit associated with low-dose aspirin.

Peripheral vascular disease, even without underlying diabetes, is considered a risk factor for cardiac events and strokes. A meta-analysis of 18 randomized controlled clinical trials assessing the effect of aspirin therapy, either alone or with dipyridamole, in 5,269 patients with peripheral vascular disease did not show any benefit in the primary outcome measure of cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death), but did show a statistically significant reduction in nonfatal strokes (24). Fowkes et al. (25) similarly reported lack of benefit in the prevention of vascular events in a randomized control study of asymptomatic atherosclerosis that randomly allocated 3,350 men and women with screening ankle-brachial index ≤0.95 to aspirin versus placebo.

When it comes to patients with CKD, the effect of aspirin in the primary prevention of cardiovascular disease in this population has remained completely unexplored and unproven. Jardine et al. (19) should be commended for demonstrating that persons with CKD might be more amenable to prevention of CVD events with aspirin therapy than is the population at large, and perhaps even more so to such therapy than other high-risk groups, such as those with diabetes mellitus (22,23) or peripheral vascular disease (24,25)—albeit, with an increased risk of bleeding complications. It is noteworthy that the presented post-hoc analysis is of enrollees in the HOT study who mostly (>95%) did not have baseline CVD, and <10% had diabetes mellitus. On the basis of these demographics, the study by Jardine et al. (19) essentially serves as a surrogate for a primary CVD prevention trial in persons with CKD.

Nevertheless, results of subgroup analysis should always be interpreted with caution, and several factors must be considered when interpreting the results of Jardine et al. (19). 1) The present post-hoc analysis should not be taken as robust evidence in favor of aspirin therapy for persons with CKD. 2) The results of this study should be used to generate a hypothesis for a well-designed and appropriately powered study including patients with all stages of CKD. 3) Post-hoc and subgroup analyses are limited with regard to obtaining reliable estimates of risks for common as well as rare adverse events. However, the results of this study can be used to estimate the sample size needed to evaluate whether low-dose aspirin or the use of other antiplatelet agents is safe in this population. The risk of major bleeding as well as paradoxical thrombosis is a genuine concern when using aspirin therapy for patients with CKD (21).

An effective and safe preventive therapy that may abrogate CVD events in patients with CKD could decrease the burden of health care costs, not only by preventing the event per se, but also by avoiding complications associated with the event or due to interventions needed to treat the event (26). Although CVD is highly prevalent among persons with different stages of CKD, clinical trial data of patients with CVD in the general population but without other comorbidities are not necessarily generalizable to the CKD population, as has been recently demonstrated in other studies involving other high-risk patients (22,23). The increased burden of concomitant metabolic and biological characteristics that clearly distinguish persons with CKD (9) could surely influence their response to preventive therapies as well as to other interventions (26).

Now it is time to move forward. For the reasons discussed, the results presented by Jardine et al. (19) should encourage prospective high-quality clinical trials to allow us to develop evidence-based guidelines for the prevention of premature CVD in persons with different stages of chronic kidney disease.
REFERENCES


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