Commentary

Aspirin for CV Risk Reduction To Be or Not To Be? That is the Question

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Recent United States Preventive Services Task Force (USPSTF) recommendations [JAMA.2022;327(16):1577-1584.doi:10.1001/jama.2022.4983]for cardiovascular disease (CVD) prevention can be summarized as follows with their rationale:

Adults aged 40 to 59 years with a 10% or greater 10-year cardio-vascular diseases (CVD) risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD in adults aged 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.
Adults 60 years or older	The USPSTF recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults 60 years or older.

Rational	Assessment
Benefits of aspirin use	Adequate evidence that low-dose aspirin has a small benefit to reduce risk for cardiovascular events (nonfatal mycocardial infarction and stroke) in adults 40 years or older who have no history of EVD but are at increased EVD risk. Evidence shows that the absolute magnitude of benefit increases with increasing 10 year EVD risk and that the magnitude of the lifetime benefits is greater when aspirin is initiated at a younger age.
Harms of aspirin use	Adequate evidence that aspirin use in adults increases the risk for gastrointestinal bleeding, intracranial bleeding, and hemorrhagic stroke. The USPSTF determined that the magnitude of the harms is small overall but increases in older age groups, particularly in adults older than 60 years.
USPSTF assessment	The USPSTF concludes with moderate certainty that aspirin use for the primary prevention of EVD events in adults aged 40 to 59 years who have a 10% or greater 10-year EVD risk has a small net benefit. The USPSTF concludes with moderate certainty that initiating aspirin use for the primary prevention of EVD events in adults 60 years or older has not net benefit.

Source: USPSTF recommendations and rationale [JAMA.2022;327(16):1577-1584. doi:10.1001/jama.2022.4983]

The holy grail of preventive medicine is that benefit must outweigh the harm. If one subscribes to that commandment, then it makes sense to, not administer a medicine when the subject is healthy or is at a high risk of a harm for any reason (inclusive of their inherent genetics or concurrent ailments). The second statement also stands true to the statuary Hippocratic Oath or the fiduciary responsi-bility of the health care practitioner.

The conundrum is to tease the evidence and make an informed decision on who could benefit. Whilst the best way in the development of evidence is by a randomized control trial, in today's world it would be not possible to conduct a population based randomized controlled placebo control trial with aspirin (only). The reasons are large sample size, high cost, diverse global management/treatment practices or guidelines, high variability of background/ epidemiological natural history of the diseases, confounding illnesses, life style choices of non-pharmacological management of health, and a list of variables that could introduce the biases in such a trial or make the understanding of results complex/ complicated.

Given this, the experts have two choices. (1) one is to synthesize the evidence with statistical modeling/ metanalysis/systematic reviews/pooled analyses from existing results (despite the complexities and controversies of these methodologies) or (2) conduct a multicenter global

trial with a modest sample population whilst addressing the pharmacological and non-pharmacological preventative treatment strategies and piggyback a research question with a placebo control trial (preferably double blinded).

The USPSTF systematic review on aspirin effectiveness in reduction of CVD events (myocardial infarctions and strokes), CV mortality, and all-cause mortality in subjects with no history of CVD utilizes the first approach. This systematic analysis also included a microsimulation modeling study (for primary prevention only) to assess the net benefit and harm from aspirin; stratified for age, gender, and CVD risk level.

In the background, the Million Heart Attack and Stroke study (https://millio-hearts.hhs.gov/) suggested that improvement through key CV risk factors would need to increase (Table) (data from 2013-2016) if 1 million heart attack and strokes were to be prevented by 2022.

In secondary prevention, the absolute benefits on occlusive events are far greater than the absolute risks of major bleeding. In primary prevention, however, among apparently healthy people, the benefit-to-harm ratio is less clear.

Given all of this, the magnitude of change projected (in Million Heart Study) from the pharmacological treatment for primary prevention could exponentially increase the healthcare expenditure budget. Hence, it makes sense to follow the results/recommendations of USPSTF.

In contrast to the first approach (systematic review/ statistical modeling); to unravel the conundrum; investigators reported a randomized placebo control trial; at 86 centers in 9 countries in 5713 subjects with intermediate CV risk (elevated INTERHEART RISK SCORE) [JAMA. 2021;325(12) 1135.do1:10.1001/ jama. 2021. 3576 and NEJM2021;384:216-28 doi: 10.1056/ nejmoa 2028220].

The randomization consisted of daily consumption of Polypill (containing 40-mg Simvastatin, 100-mg Atenolol, 25-mg Hydrochlorothiazide, and 10-mg Ramipril) with or without 75-mg aspirin or placebo.

The primary outcome (death from CV caused, myocardial infarction or stroke, resuscitated cardiac arrest, heart failure or revascularization) in this 2-by-2 factorial design study. The outcomes demonstrated in this trial can be summarized as below.

- The primary outcome for the polypill comparison occurred in 126 participants (4.4%) in the polypill group and in 157 (5.5%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.63 to 1.00).
- The primary outcome for the aspirin comparison occurred in 116 participants (4.1%) in the aspirin group and in 134 (4.7%) in the placebo group (hazard ratio, 0.86; 95% CI, 0.67 to 1.10).
- The primary outcome for the polypill-plus-aspirin comparison occurred in 59 participants (4.1%) in the combined-treatment group and in 83 (5.8%) in the double-placebo group (hazard ratio, 0.69; 95% CI, 0.50 to 0.97).

Lessons learned:

The evidence from both approaches is self-explanatory. As physicians, the responsibility of generating evidence has been very high for regulatory approvals and policy making guidelines. However, in current and future times the focus for precision medicine and targeted approached for evidence informed practice (which considers the patient's agreement in treatment/management); a deeper understanding of statistical methods and modeling is expected. Thus Physician-Scientist (academic or industry) may need to also be experts in benefit-risk and health economic paradigms as well as trial design specifics and statistics. In summary,

1. The USPSTF systematic review and Million Heart Study data is US/region centric. However, (a) The epidemiology of heart disease morbidity and mortality has regional/population variability. (b) Thus, evidence generation and implementation must consider the ethnic and population/genetic and migratory secular

Table : Prevention in heart attacks and strokes

Management/Treatment	Current use	Proposed target use
Aspirin as appropriate	61%	>80%
Blood pressure control	49%	>80%
Cholesterol management	55%	>80%
Smoking cessation (prevalence reduction)	22%	20% (<18%)
Sodium intake reduction	3.5 g/day	20% reduction (<2.8 g/day)
Physical inactivity reduction	29% (inactive)	20% reduction (<23%)

Source: Adapted from Million Hearts 2022 (https://millionhearts.hhs.gov/files/MH-Snapshots-of-Progress-2022-508.pdf)

trends of the disease and disease management practices.

2. The USPSTF systematic review addresses the balance of benefit and harm and could benefit with some estimations and projections of the costs (effectiveness, utility vis-à-vis benefit and harm) especially in secondary prevention but is not conclusively same for primary prevention.
3. "Polypill Study" had more regional representation overcoming limitation of population bias and utilized a risk stratification (validated from a large population study). However, it is not uniformly accepted and hence has its own limitation for practical implementations.
4. The evidence from the Polypill study though remarkable shows the difficulty in study designs, global implementation. For example (a) lf assumed a CV event rate is 1.2% per year in the placebo group then with enrollment of 5000 sample population in period of 2 years and mean follow-up of 5 years could detect a 35% lower relative risk with polypill vs placebo (80% power); (b) The Hazard Ratios presented do suggest 37%, 33% and 31% risk reduction; but the width of the confidence interval (which was not adjusted for multiplicity. The analysis conducted with use of proportional-means model) did cross the line of unity (beyond 1 - except with compared polypill with double placebo) and no statistical significance was reported.

In my opinion:

A. Common sense and evidence collected on experience, research designs, statistics, statistical modeling, and health economics must become more entrenched and enshrined to ensure that the results have high internal and external (dual) validity.

B. Astute (expert) understanding of epidemiological variations, statistical approaches must for clinicians, medicine developers, policy makers, and health economists alike.

C. Genetics, patient centered research (study designs) and real-world evidence generation is expected to influence future implementation at population level.

Recent publications of interest

1. Wang M, Yu H, Li Z, Gong D, Liu X. Benefits and Risks Associated with Low-Dose Aspirin Use for the Primary Prevention of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Randomized Control Trials and Trial Sequential Analysis. *Am J Cardiovasc Drugs. 2022 May 16*. doi: 10.1007/s40256-022-00537-6.
2. Li J, Chen Y, Ou Z, Ouyang F, Liang J, Jiang Z, Chen C, Li P, Chen J, Wei J, Zeng J. Aspirin Therapy in Cardiovascular Disease with Glucose-6-Phosphate Dehydrogenase Deficiency, Safe or Not? *Am J Cardiovasc Drugs. 2021 Jul;21(4):377-382*. doi: 10.1007/s40256-020-00460-8.
3. Fras Z, Sahebkar A, Banach M. The Use of Aspirin in Contemporary Primary Prevention of Atherosclerotic Cardiovascular Diseases Revisited: The Increasing Need and Call for a Personalized Therapeutic Approach. *Am J Cardiovasc Drugs. 2021 Mar;21(2):139-151*. doi: 10.1007/s40256-020-00424-y.
4. Mainoli B, Duarte GS, Costa J, Ferreira J, Caldeira D. Once-versus Twice-Daily Aspirin in Patients at High Risk of Thrombotic Events: Systematic Review and Meta-Analysis. *Am J Cardiovasc Drugs. 2021 Jan;21(1):63-71*. doi: 10.1007/s40256-020-00409-x

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