Underutilization of Aspirin in Secondary Prevention

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Introduction

- Aspirin is an effective and low-cost option for reducing atherosclerotic cardiovascular disease (CVD) events and improving mortality rates among individuals with established CVD. To guide efforts to mitigate the global CVD burden, there is a need to understand current levels of aspirin use for secondary prevention of CVD.

- Worldwide, aspirin is underused in secondary prevention, particularly in low-income countries. National health policies and health systems must develop, implement, and evaluate strategies to promote aspirin therapy.

- We researched the literature with the intention of finding the incidence of utilization of aspirin in various countries and the reason why underdeveloped countries underutilize aspirin. We are also going to make some suggestions as to how to optimize the use of aspirin in these countries.

Aspirin

- Acetylsalicylic acid, or aspirin, was introduced in the late 1890s and has been used to treat a variety of inflammatory conditions; however, the antiplatelet activity of this agent was not recognized until almost 70 years later.

- Recent advances in our understanding of the central role of platelets in the pathophysiology of cardiovascular disease have spurred in-depth investigations into the mechanisms of action of aspirin and the clinical utility of this agent in the treatment of common cardiovascular disorders.

Mechanism of Action of Aspirin

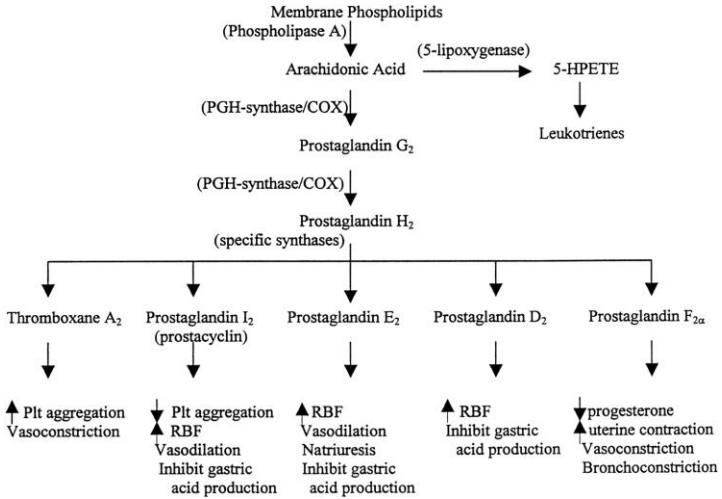

Figure 1: Mechanism of action of Aspirin

Aspirin exerts its effect primarily by interfering with the biosynthesis of cyclic prostanoids, ie, thromboxane A2 (TXA2), prostacyclin, and other prostaglandins. These prostanoids are generated by the enzymatically catalyzed oxidation of arachidonic acid, which is derived from membrane phospholipids. Arachidonic acid is metabolized by the enzyme prostaglandin (PG) H-synthase, which, through its cyclooxygenase (COX) and peroxidase activities, results in the production of PGG2 and PGH2, respectively. PGH2 is then modified by specific synthases, thus producing prostaglandins D2, E2, F2α, I2 (prostacyclin), and TXA2, all of which mediate specific cellular functions.

The Challenge with the Use of Aspirin

- Aspirin decreases mortality and reinfarction when given as short-term therapy for AMI (acute myocardial infarction), when given to patients with unstable angina, and when given as long-term secondary preventive therapy in a wide range of patients with established cardiovascular disease.

- Despite the strength of the data in this regard, studies suggest that aspirin remains underused for both the treatment of acute coronary syndromes and for secondary prevention of recurrent events.

- More than 10% of patients suffering from an AMI do not receive aspirin therapy despite the absence of contraindications, and 20% to 50% of postinfarction patients may not be taking aspirin on an ongoing basis.

- The underutilization of aspirin in the elderly population shows even worse results: almost 30% of Medicare patients hospitalized for unstable angina are not treated with aspirin in the short term, and as many as 80% of nursing home patients with a prior history of MI may not be given aspirin.

Clinical Data

- The dose of aspirin should always be the lowest dose that is known to be effective (i.e. 160 to 325 mg for acute treatment of cardiovascular events and 75 to 160 mg/d for primary and secondary prevention) because higher doses result in higher rates of complications.

- In patients who are at high risk of a future cardiac event owing to the presence of significant risk factors, prophylactic aspirin should be considered but weighed against the risk of potential complications.

- In patients at low risk of cardiac events, the risk/benefit ratio must be considered in that the risk of hemorrhagic complications may outweigh the benefits of therapy, and the current data do not support the use of prophylactic aspirin therapy in this setting.

- As newer aspirin regimens with improved safety profiles are developed, the risk/benefit ratio may change to support the use of aspirin as primary prevention in a broader range of patients.

Collection of the Data

- Estimates are weighted by each country's 2019 population of individuals aged 40 to 69 years.
- Direct standardization of age to the World Health Organization reference population was used, except in the income group and overall estimates.
- Income group refers to World Bank per capita income categories in the year the survey was conducted.
- Education was unavailable in the survey from Tokelau.
- Urban vs rural residence was unavailable in the surveys from Bermuda, Botswana, Brunei, Ecuador, Eswatini, Kiribati, Kuwait, Lebanon, Myanmar, Nauru, Solomon Islands, Sri Lanka, St Vincent and the Grenadines, Tajikistan, Timor-Leste, Tokelau, Tuvalu, and the US

Design, Setting, and Participants

- Cross-sectional analysis using pooled, individual participant data from nationally representative health surveys conducted between 2013 and 2020 in 51 low-, middle-, and high-income countries. Included surveys contained data on self-reported history of CVD and aspirin use. The sample of participants included nonpregnant adults aged 40 to 69 years.
- The per capita income levels and world region; individuals' socioeconomic demographics were collected.
- Self-reported use of aspirin for secondary prevention of CVD.

- Results:
    - 1. Therapeutic benefit in a variety of cardiovascular diseases has been demonstrated with doses of 30 to 1500 mg/d; higher doses do not appear to be more effective but may increase the risk of GI side effects.

    - 2. Low-dose aspirin or controlled-release preparations may result in somewhat preferential inhibition of platelet COX over endothelial COX.

Acute Myocardial Infarction

- The Second International Study of Infarct Survival (ISIS-2) established the benefit of aspirin.
- In this trial, 17,187 patients presenting within 24 hours of the onset of a suspected acute MI (AMI) were randomized into 4 groups:
    1. Intravenous streptokinase (1.5 MU)
    2. Aspirin 162.5 mg daily for 30 days
    3. Both intravenous streptokinase (1.5 MU) and 162.5 mg of aspirin daily for 30 days
    4. Neither intravenous streptokinase (1.5 MU) nor 162.5 mg of aspirin daily for 30 days
- At the end of 5 weeks, patients receiving aspirin therapy alone (Group 2) had a highly significant 23% reduction in vascular mortality and a nearly 50% reduction in the risk of nonfatal reinfarction and nonfatal stroke.
- This benefit occurred irrespective of whether heparin was given.
- These reductions translate into the avoidance of ≈25 deaths and 10 to 15 nonfatal reinfarctions or strokes by treating 1000 patients with aspirin for 1 month.

Acute Myocardial Infarction (cont.)

- There was no increase in major bleeding complications (including no increase in cerebral hemorrhage or need for transfusion) with aspirin therapy, and the mortality benefit was maintained after 10 years of follow-up, indicating clearly that the risk/benefit ratio weighed heavily towards benefit.
- In ISIS-2, administration of streptokinase alone (Group 1) was associated with a 25% reduction in vascular deaths,
- The addition of aspirin therapy to streptokinase (Group 3) was additive (42% reduction in vascular mortality with combined aspirin and streptokinase therapy).
- A meta-analysis of 32 trials using aspirin as adjunctive therapy to thrombolysis demonstrated significantly decreased reocclusion rates (11% versus 25%) and recurrent ischemic events (25% versus 41%) with aspirin therapy.

Unstable Angina

- Several studies have clearly demonstrated a beneficial role for aspirin in the treatment of unstable angina.
- Despite instituting aspirin therapy at various doses (75 to 1300 mg/d) and differing intervals after a patient's initial presentation (<24 hours to <8 days), these trials have consistently demonstrated a significant decrease in the incidence of death or death and nonfatal MI.

Second Prevention after MI

- These results clearly demonstrate a significant treatment effect of aspirin when given as secondary prevention in patients with MI.

- The results were significant in all groups irrespective of age, gender, or the presence of hypertension or diabetes.

After Revascularization

- Significantly decreased the 30-day combined end point of death, target-vessel revascularization, angiographic thrombosis, or MI (relative risk [RR] 0.15 for combined therapy versus aspirin alone).
    1. Warfarin and aspirin
    2. Aspirin and ticlopidine
    3. Aspirin alone

- This benefit is seen irrespective of whether the stent deployment is felt to be “successful” with a low risk for thrombosis or if high-risk markers for stent thrombosis are present.

Primary Prevention

- There have been 2 large, randomized trials of aspirin for the primary prevention of cardiovascular events that enrolled male physicians without prior MI and with a low incidence of prior cardiovascular disease (eg, TIA or angina). The Physicians' Health Study randomized 22,071 subjects between the ages of 40 and 84 years to treatment with aspirin (325 mg every other day) or placebo. The study was stopped prematurely after an average follow-up of 5 years owing to a highly significant 44% reduction in the risk of MI in the aspirin-treated group (0.26% per year versus 0.44% per year), an effect that was limited to participants over the age of 50 years.

- After >6 years of follow-up, there was a 20% reduction in ischemic heart disease events (cardiac death, fatal or nonfatal MI) in the aspirin-treated groups. This difference was almost entirely accounted for by a 32% reduction in nonfatal events, without a significant effect on mortality. In contrast, warfarin therapy resulted in a 21% reduction in ischemic events, mostly as a result of a 39% reduction in fatal events. Neither of these therapies alone resulted in an increase in the total number of strokes. The combination of aspirin and warfarin produced the greatest reduction in ischemic events (34%) but was also associated with an increase in hemorrhagic and fatal strokes.

Primary prevention, contd.

- Patients with chronic stable angina have a significant risk of developing subsequent cardiovascular events, and several studies have demonstrated a beneficial effect of aspirin in this group of patients. In the Physicians Health Study, patients who had chronic stable angina and received aspirin had an 87% reduction in the risk of MI compared with their counterparts who received placebo. Similarly, in the Swedish Angina Pectoris Aspirin Trial, 2035 patients with chronic stable angina but without prior MI who received aspirin (75 mg/d) had a 34% decrease in the combined risk of MI and sudden death.

- In summary, the primary prevention trials demonstrate that aspirin therapy does not decrease cardiovascular mortality but significantly decreases the risk of nonfatal MI.

Aspirin in Cerebrovascular Disease: Acute Therapy

- Estimates are weighted by each country's 2019 population of individuals aged 40 to 69 years.
- Direct standardization of age to the World Health Organization reference population was used, except in the income group and overall estimates.
- Income group refers to World Bank per capita income categories in the year the survey was conducted.
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Secondary and Primary Prevention

- Overall, there was a highly significant 17% reduction in the risk of nonfatal stroke and of all vascular events (nonfatal stroke or MI or vascular death) in patients treated for a mean of 33 months. This effect was similar whether the patient presented with a TIA or a completed stroke and resulted in a reduction of 37 vascular events per 1000 patients treated.
- A low-dose aspirin regimen appears appropriate for secondary prevention of cerebrovascular disease.

What is the Issue?

- Aspirin is an effective and low-cost option for reducing atherosclerotic cardiovascular disease (CVD) events and improving mortality rates among individuals with established CVD. To guide efforts to mitigate the global CVD burden, there is a need to understand current levels of aspirin use for secondary prevention of CVD. Worldwide, aspirin is underused in secondary prevention, particularly in low-income countries. National health policies and health systems must develop, implement, and evaluate strategies to promote aspirin therapy.

- The pooled data set included nationally representative health surveys conducted from 2013 to 2020 in 51 countries.

- By World Bank income group, 7 surveys were conducted in low-income countries, 23 in lower-middle-income countries, 14 in upper-middle-income countries, and 7 in high-income countries. The median response rate was 85% in the 50 surveys, the response rates were lower in high-income countries (median, 57%) than in other income groups (median, 98%, 86%, and 82% in low-income, lower-middle-income, and upper-middle-income countries, respectively).

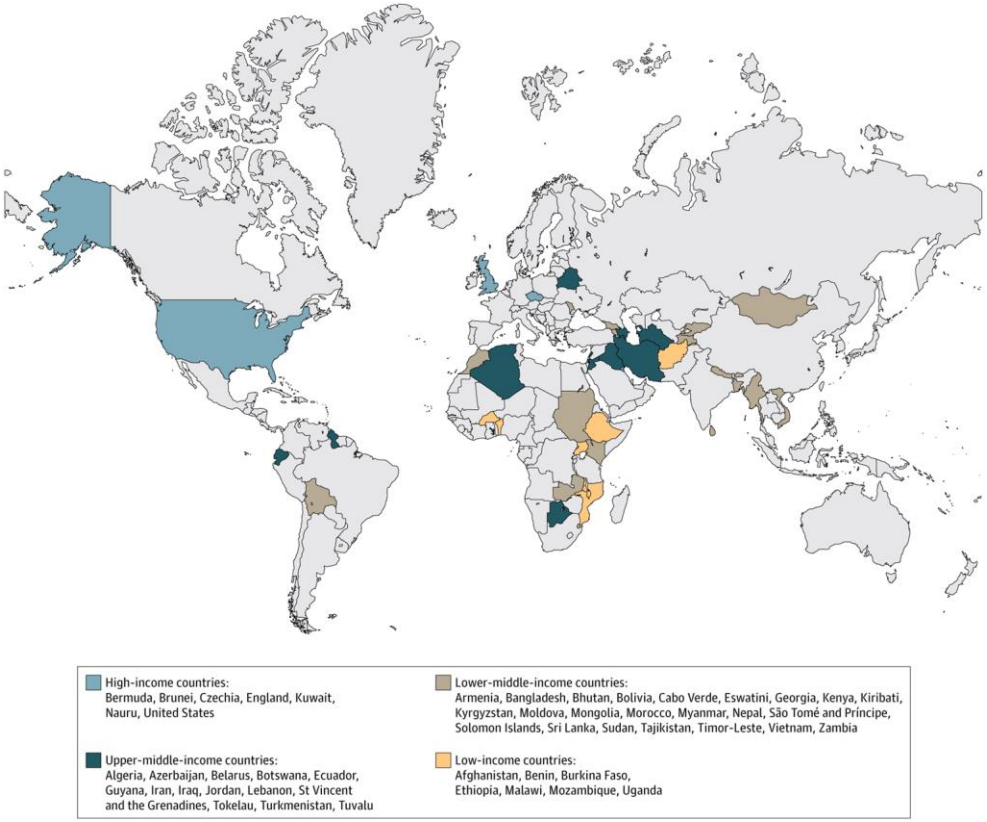

Figure 2: Geographical map showing countries with different income strata

Aspirin Use for Secondary Prevention of CVD Across the Pooled Sample and by Income Group

- Among individuals with a self-reported history of CVD, aspirin use for secondary prevention in the overall pooled sample was 40.3% (95% CI, 37.6%-43.0%).
- By income group, estimates were 16.6% (95% CI, 12.4%-21.9%) in low-income countries, 24.5% (95% CI, 20.8%-28.6%) in lower-middle-income countries, 51.1% (95% CI, 48.2%-54.0%) in upper-middle-income countries, and 65.0% (95% CI, 59.1%-70.4%) in high-income countries.

Aspirin Use for Secondary Prevention of CVD Across Countries

- At the country level, 41% of the variation in aspirin use for secondary prevention was accounted for by per capita income.
- Countries meeting the WHO target that at least 50% of eligible people receive aspirin for secondary CVD prevention included Belarus, Czechia, England, Iran, Iraq, Jordan, Kuwait, Lebanon, Turkmenistan, and the US.

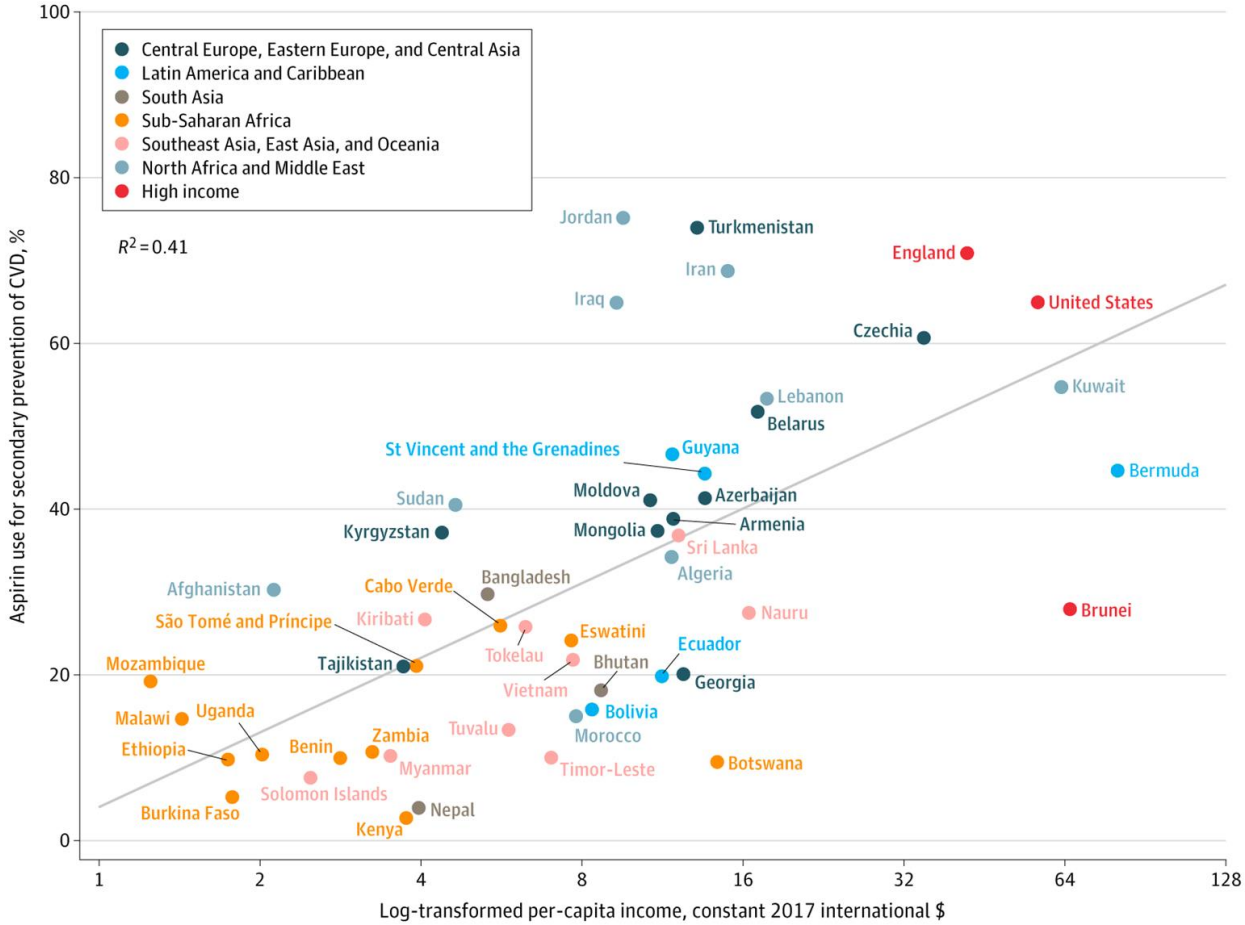

Figure 3: A plot of Aspirin use versus per capita income in various countries

Aspirin Use for Secondary Prevention of CVD Across Individual Characteristics

- In the overall pooled sample, among those with a history of CVD, greater aspirin use was observed among individuals who were older, were male, had higher levels of education, and lived in urban as opposed to rural areas.
- There were consistent gradients of greater aspirin use in countries with more income within a given individual characteristic.
- In high-income vs low-income countries, the absolute difference in aspirin use for secondary prevention was 2- to 5-fold greater relative use and between 20% to 60% greater absolute use by age, sex, education, or urban vs rural residence.

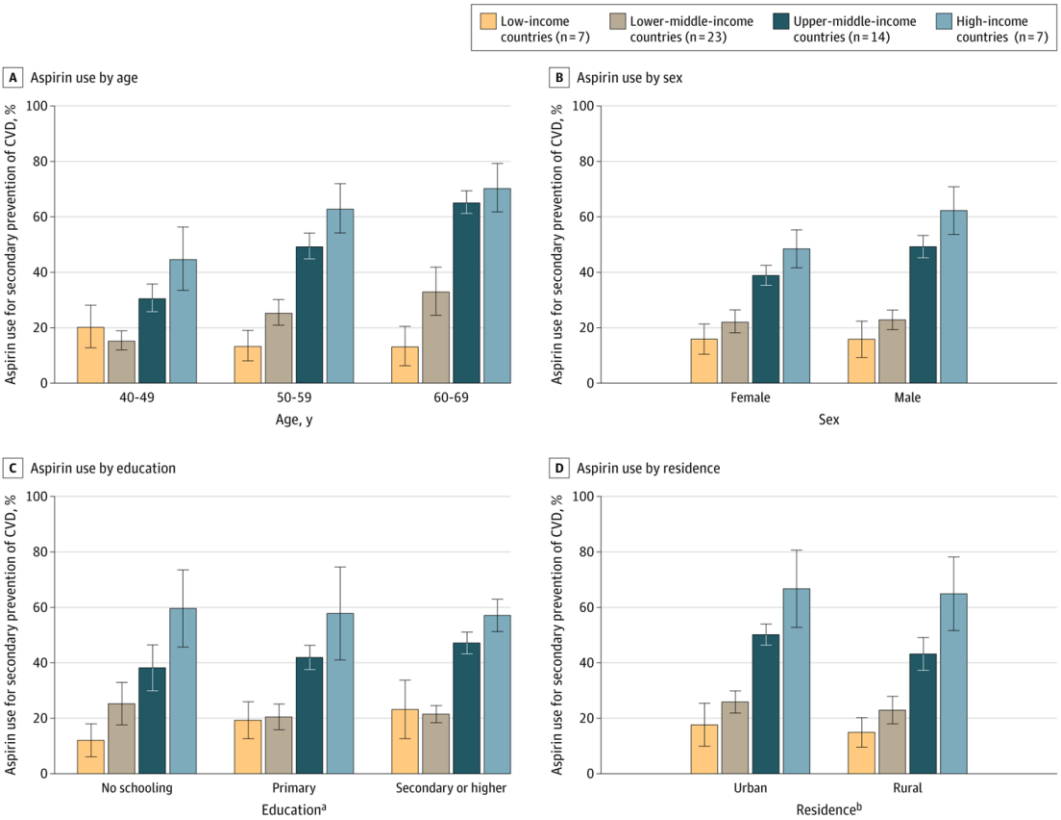

Figure 4A: Shows high use of aspirin in high-income countries in all three age groups.
Figure 4B: Shows comparison of use of aspirin in males and females, indicating that irrespective of males and females, aspirin is still used highly in high-income countries.
Figure 4C: Shows high use of aspirin in high-income countries, irrespective of education level.
Figure 4D: Shows high use of aspirin in high income countries, irrespective of urban or

The research findings revealed marked inequities worldwide, as illustrated by 4-fold greater aspirin use for secondary CVD prevention in high-income countries compared with low-income countries. None of the 30 low-income or lower-middle-income countries in our sample achieved the WHO target that at least 50% of eligible individuals with a history of CVD take aspirin. Only about half of upper-middle-income and high-income countries included in our analysis achieved this target.

Recommendations

- Countries with a high burden of prevalent CVD may benefit from more aggressive policies to improve evidence-based aspirin use.
- Many patients may not understand the role of aspirin in CVD prevention or have variable access to aspirin, whether through prescriptions or over the counter.
- As highlighted in the current study, an individual country with greater economic resources may find it more feasible to scale up, sustain, and codify system-level CVD care.
- In lower income countries, such as Ethiopia and Afghanistan, only 1 in 6 people (16.6 percent) took daily aspirin for secondary prevention compared with nearly 2 in 3 (65 percent) in higher income countries like the United States and the United Kingdom.
- In lower-middle-income countries this number was 24.5 percent and 51.1 percent for upper-middle-income countries.

Recommendations (contd.)

A few innovations and programs may offer generalizable lessons across countries to address the underuse of aspirin for secondary prevention and, consequently, CVD-related mortality.

1. Use of fixed-dose combination therapies (“polypills”), which may include aspirin in addition to antihypertensive and statin therapies. Polypills improve patient adherence and are effective in secondary prevention of CVD even in high-income countries with high rates of drug therapy.
2. WHO’s HEARTS program, launched in 2016, recommends an integrated, multicomponent approach to population-level CVD care, including appropriate use of aspirin. HEARTS has shown excellent results in improving blood pressure control in more than a dozen countries, and future work could assess whether the HEARTS platform can be leveraged to maximize aspirin use for secondary prevention of CVD.
3. Community education, use of community health workers and other trained and trusted lay individuals for outreach to and engagement of patients who may not have ready access to healthcare or be able to get to clinics has great potential to reach the hard-to-reach communities where barriers to care and associated disparities in care exist.

Conclusions

- Worldwide, under-utilization of aspirin for secondary prevention, particularly in low-income countries is a worrisome finding.
- Since aspirin is such an effective and low-cost drug, national health policies, strategies, and health systems must be developed, evaluated, and implemented to promote aspirin therapy.
- A few suggestions for implementing this are the use of fixed-dose combination pills (polypills). including aspirin in addition to antihypertensive and statin therapies, the WHO's HEARTS program, with an integrated, multicomponent approach to population-level CVD care, and community education, use of community health workers and other trained and trusted lay individuals for outreach to and engagement of patients should be implemented.
- After all, helping nations with lower income and inadequate levels of education is something not to be ignored by the rest of the World.

Acknowledgements

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