# ASA ASPIRIN FOR PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

## BOTTOMLINE

- There is no compelling evidence to use ASA for individuals who do not have a history of cardiovascular or cerebrovascular disease (i.e. primary prevention).
- Recent studies have concluded ASA offered little to no benefit for primary prevention, & increased the risk of major bleeding across all patient populations studied.
- Avoid ASA for primary prevention in individuals who are ≥70 years of age, ASPREE are at low to moderate risk of CV events, ARRIVE or have an elevated risk of CV events but a high risk of bleeding, as these individuals are more likely to bleed than benefit.
- Consider shared decision making with those who have diabetes, ASCEND or have an elevated risk of CV events & low risk of bleeding.
- Implement interventions which can reduce CV risk (e.g. **smoking cessation, exercise, healthy eating, BP and lipid control**).

## REVIEW OF THE RECENT EVIDENCE

- In 2018, 3 large randomized controlled trials comparing ASA to placebo for primary prevention were published. ASA consistently increased the risk of bleeding, and offered a modest benefit only for those with diabetes, as summarized in the following table:

| | ARRIVE [1] | ASPREE [2] | ASCEND [3] |
|---|---|---|---|
| **POPULATION** | Low to Moderate risk of CVD | Community-dwelling older adults ≥70 years of age | Diabetes |
| **NUMBER OF PATIENTS** | 12,546 | 19,114 | 15,480 |
| **AGE** | 63.9 years (mean) | 74 years (median) | 63.3 years (mean) |
| **FOLLOW-UP** | 5 years (median) | 4.7 years (median) | 7.4 years (mean) |
| **CV OUTCOMES** | **CV death, MI, unstable angina, stroke, TIA**<br>4.29% vs 4.48%<br>No difference | **CV disease (fatal CAD, MI, stroke, HF hospitalization)**<br>4.7% vs 4.9%<br>No difference | **Serious vascular event (MI, stroke / TIA, vascular death except intracranial bleeds)**<br>8.5% vs 9.6%<br>RR 0.88 (95% CI 0.79-0.97)<br>ARR 1.1%, NNT 91 |
| **HARM** | **GI Bleed:**<br>0.97% vs 0.46%<br>HR 2.11 (95% CI 1.36-3.28)<br>ARI 0.51%, NNH 196 | **Major Bleeding:**<br>3.79% vs 2.76%<br>HR 1.38 (95% CI 1.18-1.62)<br>ARI 1.03%, NNH 100 | **Major Bleeding:**<br>4.1% vs 3.2%<br>RR 1.29 (95% CI 1.09-1.52)<br>ARI 0.9%, NNH 112 |
| **COMMENTS** | • The CV event rate was lower than expected. The mean Framingham 10-year CVD risk score was 14% (i.e. moderate risk), but the actual event rate was ~4% (i.e. low risk).<br>• The primary endpoint was expanded to include unstable angina & TIA due to lower than expected event rates.<br>• ~30% stopped the study early (29.4% ASA, 29.9% placebo).<br>• Per-protocol analysis showed a modest benefit for MI (0.98% vs 1.84%, HR 0.53 [95% CI 0.36-0.79], ARR 0.86%, NNT 117); the primary endpoint remained non-statistically significant. | • Original primary endpoint was death, dementia, or physical disability.[4] These results are from the publication focusing on CV outcomes.[2]<br>• 42% of bleeds were GI bleeds (25% were on a PPI, 14% on NSAIDs).<br>• ~1/3 stopped their assigned therapy early (38% ASA, 36% placebo).<br>• 11% had previous regular ASA use. | • During the study, the primary endpoint was expanded to include TIA, the sample size was increased, and the follow-up period was extended.<br>• 41% of bleeds were GI bleeds (25% were on a PPI).<br>• Estimated mean adherence in both groups was 70%.<br>• ~35% had prior ASA use.<br>• 2018 Diabetes Canada: ASA should not be used routinely for the primary prevention of CVD events in people with diabetes. [A,1A (5)] This statement was published prior to the release of ASCEND, which further supports the recommendation. |

- A few notes on the above trials:
  - Only ~60-70% of patients were on ASA at the end of the studies.
  - Cardiovascular event rates were lower than expected.
  - GI bleeds were the most common type of major bleeding.
  - Follow-up ranged from 4.7 to 7.4 years. Are longer studies needed to assess mortality?
- Several meta-analyses, which included the above trials, have come to similar conclusions (i.e. little to no benefit, with an increased risk of major bleeding). [6,7,8]

- Prior guidelines gave conflicting messages on the role of ASA for primary prevention. Two guideline committees have updated their statements based on the new studies:
  - **2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease**:[9]
    - ASA 75-100mg 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 risk of bleeding. IIb, A
    - ASA 75-100mg daily should not be administered on a routine basis for the primary prevention of ASCVD among adults ≥70 years of age. III (harm), B-R
    - ASA 75-100mg daily should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding. III (harm), C-LD
  - **2019 BEERS Criteria for Potentially Inappropriate Medications in the Older Adult**:[10]
    - ASA for primary prevention of cardiovascular disease should be used with caution in adults ≥70 years. Moderate, Strong

## TRANSLATING THE EVIDENCE FOR PATIENT DISCUSSIONS

- Guidelines and several review articles encourage shared decision making for this topic. Using the **ASCEND** trial results, here are a few examples of communicating the evidence to patients (serious vascular event [MI, stroke / TIA, vascular death except intracranial bleeds]: 8.5% vs 9.6%, RR 0.88 [95% CI 0.79-0.97], ARR 1.1%, NNT 91; major bleeding: 4.1% vs 3.2%, RR 1.29 [95% CI 1.09-1.52], ARI 0.9%, NNH 112):
  - **Using the relative risk reduction / increase** → Taking low-dose ASA for 7.4 years can lower the risk of MI, stroke, TIA or vascular death by 12% (RRR), but increases the risk of major bleeding by 29% (RRI)
  - **Using the absolute risk reduction / increase** → The difference between ASA & placebo was approximately 1% for both the benefit and harm (ARR 1.1%, ARI 0.9%).
  - **Using NNT & NNH:** 91 people would need to be treated with low-dose ASA for 7.4 years in order to prevent one additional MI, stroke / TIA or vascular death (NNT), and 112 would need to be treated to cause one additional major bleed (NNH).

## WHAT'S CHANGED OVER THE DECADES

- There has been a lot of discussion on why recent studies have failed to show a clear benefit for ASA in primary prevention.
- Meta-analyses have included several subgroup analyses, including a comparison of trials published before and after the year 2000. Authors found a difference in the reduction of MI based on publication year, with no statistically significant reduction in the trials published in 2000 on onward.
- When comparing historical to modern day practice, a few things to note are:
  - The definition & diagnosis of MI has changed over the decades. Early studies defined MI solely based on symptoms. Today, studies implement universal definitions for MI and the use of cardiac biomarkers.
  - Today there is better management of CVD risk factors (e.g. improved blood pressure and cholesterol control).
- Since 1988, there have been 13 studies assessing the role of ASA for primary prevention. Only two of these trials showed a statistically significant difference for the primary CV endpoint; however, there are some caveats to consider:
  - Hypertension Optimal Treatment trial (**HOT**, 1998): originally showed a 15% RR with ASA in the primary endpoint (major CV events), which was no longer statistically significant when silent MI was added to the analysis.[11]
  - A Study of Cardiovascular Events in Diabetes (**ASCEND**, 2018): as summarized above, the primary endpoint favoured ASA use but this was after the primary endpoint was expanded, the sample size increased, and the duration of follow-up extended.
- As such, one could argue there has never been compelling evidence to use ASA for primary prevention.
- The evidence regarding ASA in primary prevention is now pretty clear. Harm, though small, generally outweighs any benefit. There is no compelling evidence to use ASA for primary prevention.

**ARI**=absolute risk increase **ARR**=absolute risk reduction **ASA**=acetylsalicylic acid **ASCVD**=atherosclerotic cardiovascular disease **BP**=blood pressure **CAD**=coronary artery disease **CV**=cardiovascular **CVD**=cardiovascular disease **GI**=gastrointestinal **HF**=heart failure **HR**=hazard ratio **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **NSAID**=non-steroidal anti-inflammatory drug **PPI**=proton pump inhibitor **RR**=risk reduction **TIA**=transient ischemic attack

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