**AS A: When to Prescribe?**

### Introduction/Background

- The benefit of ASA in the 2nd prevention of stroke & MI is well established, however, its use in 1st prevention is controversial. Clinical trials of ASA in patients without CVD have been inconsistent in demonstrating CVD outcome benefit that could outweigh the ↑ bleed risk.
- Three RCTs published in 2018 provided more evidence for ASA in 1st prevention (ASCEND: A Study of Cardiovascular Events in Diabetes; ASPREE: Aspirin in Reducing Events in the Elderly; ARRIVE: Aspirin to Reduce Risk of Initial Vascular Events.)

<table>
<thead>
<tr>
<th>Cardiovascular disease (CVD)</th>
<th>is an umbrella term for several linked pathologies such as coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease (PAD), rheumatic and congenital heart diseases, and venous thromboembolism (VTE).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary (1st) prevention</strong></td>
<td>Prevention of the 1st CVD event (e.g. heart failure, MI, fatal CHD, stroke) in people who have NOT yet developed CVD.</td>
</tr>
<tr>
<td><strong>Secondary (2nd) prevention</strong></td>
<td>Prevention of recurring CVD events in people with established CVD.</td>
</tr>
</tbody>
</table>

### When Should ASA Not Be Recommended?

#### Contraindications to ASA include:

- Patients who have had a bronchospastic reaction, generalized urticaria, angioedema, severe rhinitis, laryngeal edema or shock precipitated by ASA or NSAIDs, active peptic ulcer, severe renal impairment (CrCl<10-30mL/min).
- Disorders where there is already a risk of bleeding such as hemophilia, telangiectasia and von Willebrand’s disease.
- Children, teenagers or young adults with chickenpox, influenza or flu-like illness due to the association with Reye’s syndrome.

### Secondary Prevention: Should ASA Be Recommended?

- **YES.** ASA is indicated for thrombocyte therapy in patients undergoing procedures such as coronary angioplasty, placement of intracoronary stents or coronary artery bypass to prevent thrombosis in patients with AF who are at low risk of stroke or in whom oral antiplatelet agents are contraindicated.*
- In 195 trials of antiplatelet therapy versus control among a total of 135,640 patients at high risk of occlusive arterial disease, antiplatelet therapy showed a significant reduction of MI, stroke/TIA, CAD, high risk of embolism (AF, cardiac valve disease/surgery), PAD ( intermittent claudication, peripheral grafting/angioplasty.), AT 2002 meta-analysis.
- In 16 secondary prevention trials (n=17,000), ASA reduced: ATT 2009 meta-analysis
  - **Coronary events** (4.3% ASA group vs. 5.3% placebo), rate ratio (RR) = 0.80, 95% CI 0.73-0.88, NNT=100 per year
  - **Stroke** (2.08% vs. 2.54% placebo), RR = 0.81, 95% CI 0.71-0.92, NNT=217 per year
  - **Serious vascular events** (6.7% ASA vs. 8.2% placebo), RR = 0.81, 95% CI 0.75-0.87, NNT=67 per year
  - **Total mortality, RR=0.90, 95% CI 0.82-0.99** (data not published to calculate ARR or NNT)
- **Of note:** there have been no RCTs in ACS in the drug-eluting stent era where patients were randomized to ASA versus no ASA. Recent evidence supports 6-12 months of dual antiplatelet therapy (DAPT) in 2nd prevention. See RxFiles DAPT and Triple Therapy Chart.

### Should We Stop ASA in Primary Prevention?

- **May be** – use clinical judgement; consider patient values and bleed risk versus CVD benefits (see below and next page)
- For patients who have been on ASA for primary prevention for many years, it is unknown whether stopping it will cause any benefits or harms. The ASCEND, ASPREE, & ARRIVE trials started ASA 100mg/d mostly in patients who were not taking ASA.

### Primary Prevention + Diabetes: Should ASA Be Recommended?

- **Maybe, maybe not...** depends on patient values.
- **ASA 75–162mg/d may be considered for 1st prevention and at ↑ risk of CVD after a discussion on the benefits vs ↑ risk of bleeding.**

#### ASCEND trial summary

<table>
<thead>
<tr>
<th>INCLUSION</th>
<th>DM, age ≥ 40 yrs and no known CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>POPULATION</td>
<td>n=15,480, 94% T2DM, 56% &lt; 9yr duration of DM, mean age = 63, 63% female, 96% Caucasian, mean BMI~31kg/m², 8.3% current smoker, ~62% HTN, mean SBP=136mmHg, 35% previous ASA use, vascular risk (40 low, 43% moderate, 17% high)</td>
</tr>
<tr>
<td>Baseline meds</td>
<td>75% statins, 58% ACEI/ARB, 13% beta-blocker, 25% CCB, 19% thiazide or related diuretic, 25% insulin, 65% metformin, 27% sulfonylurea, 12% thiazolidinedione, 14% PPI, 9% NSAID</td>
</tr>
<tr>
<td>RESULTS</td>
<td>EC ASA 100mg/d vs placebo in 7.4 years resulted in:</td>
</tr>
<tr>
<td>- 91 pts need to be treated to avoid a serious vascular event (nonfatal MI, nonfatal stroke, TIA or death from any vascular event) (8.5% ASA vs 9.6% placebo) in 7.4 yrs,</td>
<td></td>
</tr>
<tr>
<td>- 112 pts need to be treated to cause 1 extra major bleed (intracranial hemorrhage, eye bleed, GI bleed) (4.1% ASA vs 3.2% placebo) in 7.4 yrs,</td>
<td></td>
</tr>
<tr>
<td>- 215 pts need to be treated to cause 1 extra serious GI bleed (1.8% ASA vs 1.3% placebo) in 7.4 yrs</td>
<td></td>
</tr>
<tr>
<td>- No significant difference in all-cause mortality or death from vascular cause (excluding intracranial hemorrhage), any hemorrhagic stroke, any intracranial bleed or any major bleed</td>
<td></td>
</tr>
</tbody>
</table>

- Data from 10 studies (n=30,448) in participants with diabetes, aspirin was associated with reduction (of borderline significance) in composite CV outcome (HR=0.89, 95% CI 0.80-1.00, ARR=0.65%, NNT=153/5 yrs), an ↑ in major bleeding (HR=1.29, 95% CI 1.11-1.51, ARI=0.80%, NNH=121/5 yrs) and major GI bleeding (HR=1.35, 95% CI 1.05-1.75, ARI=0.41%, NNH=243/5 yrs). Zheng, 2019

**Bottom line:** CV benefits similar to harms (major bleed, GI bleed).
**What are the significant reduction of cancer events reported in the ASPREE trial?**

In an updated (2019) meta-analysis of 16 RCTs (n=104,018, age\(\text{mean}=60.5\) yrs, follow-up=5.5 yrs, 39% female), there was an associated risk of mortality due to any cancer in the ASPREE group (3.1%) vs. placebo group (2.3%). In subgroup analysis, ASA 100 mg/d vs placebo showed no benefit for cancer prevention or mortality risk (HR=0.87, 95% CI 0.79-0.95, ARR=0.34%, NNT=297/5 yrs), but not at \(1\)% level of significance because of the higher relative risk of major bleeding (HR=1.45, 95% CI 1.28-1.63, ARR=0.40%, NNNH=249/5 yrs) vs intracranial bleeding (HR=1.41, 95% CI 1.16-1.71, ARR=0.13%, NNNH=796/5 yrs).

**ASAPRRE trial summary**

- **INCLUSION**: Community-dwelling adults ≥ 70 yrs in Australia & US (or ≥ 65 yrs if Hispanic or Black in US) & did not have CVD or cerebrovascular disease, dementia or physical disability
- **POPULATION**: n=19,114, median age=74 yr, 50% ≥ 74 yr, 56% female, 85% White Australia, 5.7% White US, BMI=28 kg/m\(^2\), 33% living alone, ~4% smokers, ~11% DM, 74% HTN, 65% dyslipidemia, 19% personal hx of cancer, frailty score 59% not frail, 39% pre-frail, 2% frail, and adhered at least 50% to taking medications during 4-week run-in phase
- **RESULTS**: EC ASA 100mg/d vs placebo in 4.7 years resulted in:
  - No significant difference in primary outcome<sup>composite</sup> death from any cause, dementia & persistent physical disability, HR=1.01, 95% CI 0.92-1.11
  - In the subgroup analysis, the "Not frail" group (n=11,246) favours placebo for the primary outcome, HR=1.17, 95% CI 1.01-1.36, 14.5% ASA group vs 12.3% placebo group, ARR=2.2, NNNH=45/4.7 yrs
  - No significant difference in MACE, CVD, fatal CVD, hospitalization for HF, fatal/non-fatal MI, fatal/non-fatal ischemic stroke.

**Bottomline**: No benefit and increased likelihood of harm.

---

**Primary prevention + Risk of cardiovascular disease (CVD): Should ASA be recommended?**

- **Not probable.** May also depend on patient values and preferences.
- **European guidelines do not recommend antiplatelet therapy in individuals without CVD because of the ↑ risk of major bleeding.<sup>11</sup>**
- **Bottomline**: For low, moderate and high risk of CVD, harms (e.g. major bleed, GI bleed) may outweigh CV benefits (see details below).

**Low risk CVD (estimated 10-year risk of cardiovascular composite < 10%)**

- In 6 studies (n=112,566) with LOW baseline CV risk (median=6.8% range 2.6%-8.1%), ASA was associated with ↓ in CV composite outcome<sup>CV</sup> mortality, MI & non-fatal stroke (HR=0.87, 95% CI 0.79-0.95, ARR=0.34%, NNT=297/5 yrs), ↑ risk of major bleeding (HR=1.45, 95% CI 1.28-1.63, ARR=0.40%, NNNH=249/5 yrs) & intracranial bleeding (HR=1.41, 95% CI 1.16-1.71, ARR=0.13%, NNNH=796/5 yrs).<sup>2</sup> Zheng, 2019

**Moderate-risk high-risk CVD (without diabetes, estimated 10-year risk CV composite ≥ 10%)**

- In subgroup analysis, CVD risk score ≤ 10.5% group favours ASA, HR=0.58, 95% CI 0.35-0.97 (CVD risk score calculated by combining The Prospective Cardiovascular Muenter Study Project (PROCAM), Framingham & Systematic Coronary Risk Evaluation (SCORE) risk calculators).

**Arrive trial summary**

- **INCLUSION**: ≥ 65 yrs with 2-4 risk factors (RFs) or ≥ 60 yrs with ≥ 3 RFs. RFs= (TC >5.18 mmol/L or LDL > 3.37 mmol/L, TC >6.13 mmol/L or LDL >4.14 mmol/L), HDL < 1.03 mmol/L, current smoking, high BP (≥140/90 mmHg), receiving antihypertensives, and/or a positive family history of CVD.
- **EXCLUSION**: Hx of a vascular event (e.g. stroke, MI, coronary angioplasty/stenting, CABG, relevant arrhythmias, HF, vascular intervention), DM, required antiplatelet/anticoagulants/NSAIDs & high risk of GI/other bleeding e.g. gastric/duodenal ulcers
- **POPULATION**: n=12,546 in 7 countries (24% Germany, 3% Italy, 1% Ireland, 25% Poland, 3% Spain, 40% UK, 4% US), age\(\text{mean}=64\) yr, 70% male, 29% current smoker, BMI=28 kg/m\(^2\), 58% high TC, 45% high LDL, 14% low HDL, 63% high SBP, SBP\(\text{mean}=145\) mmHg, 65% taking antihypertensive, Mean Framingham-10 yr CHD risk score 14%, Mean ACC/AHA 10 yr ASCVD risk score 17%.
- **RESULTS**: EC ASA 100 mg/d vs placebo in 5 years resulted in:
  - No significant difference in primary outcome of composite MI, stroke, cardiovascular death, unstable angina, or TIA
  - In subgroup analysis, CVD risk score ≤ 10.5% group favours ASA, HR=0.58, 95% CI 0.35-0.97 (CVD risk score calculated by combining The Prospective Cardiovascular Muenter Study Project (PROCAM), Framingham & Systematic Coronary Risk Evaluation (SCORE) risk calculators).

**Treatment-related adverse events reported include:**

- Any GI bleeding: HR=2.11, 95% CI 1.36-3.28, ARR=0.51%, NNNH=196/5 yrs.
- Predominantly mild GI bleeding events: 0.67% ASA group vs 0.35%, ARR=0.32%, NNNH=313/5 yrs.
- Dyspepsia: 3.60% ASA group vs 3.14% placebo, ARR=0.47%, NNNH=215/5 yrs.
- Epistaxis: 1.85% ASA group vs 0.89% placebo, ARR=0.96%, NNNH=104/5 yrs.
- GERD: 1.12% ASA group vs 0.96% placebo, ARR=0.16%, NNNH=623/5 yrs.
- Upper abdominal pain: 1.08% vs 0.92% placebo, ARR=0.16%, NNNH=624/5 yrs.

**What are the overall bleeding risks of ASA in general population? Major bleeding rates vary, but 1-4% have been reported.**

- In 12 studies (160,404 participants), ASA was associated with ↑ risk of major bleeding (HR=1.43, 95% CI 1.30-1.56, ARR=0.47%, NNNH=210/5 yrs), intracranial hemorrhage (HR=1.34, 95% CI 1.14-1.57, ARR=0.11%, NNNH=927/5 yrs), major GI bleed (HR=1.56, 95% CI 1.38-1.78, ARR=0.30%, NNNH=334/5 yrs) compared to no ASA.<sup>9</sup><sup>2</sup> Zheng, 2019

- ASA 75-100 mg daily should not be administered for the primary prevention of ASCVD among adults at ↑ risk of bleeding (e.g. age ≥ 75 yrs, active ulcerative GI disease, drugs e.g. NSAIDs, steroids, anticoagulants), alcohol, renal impairment (CrCl < 50 mL/min)<sup>14</sup> ACC/AHA

**Does ASA help prevent cancer?**

- Uncertain if ASA offers cancer protection or mortality risk
- In 2007, the U.S. Preventive Services Task Force (USPSTF) recommended ASA for the prevention of colorectal cancer.
- In a 2015 meta-analysis, ASA 75-500 mg/day  for at least 4 years showed a reduction in cancer incidence (RR=0.86, 95% CI 0.74-0.99) in 1’ & 2’ CVD prevention trials vs no ASA. In 6 CVD 1’ prevention trials (n=72,926), cancer incidence was similar between ASA & no ASA groups. 12
- In the 2018 ASPREE trial, there was an associated risk of mortality due to any cancer in the ASA group (3.1%) vs. placebo group (2.3%), ARR=0.8%, HR=1.31, 95% CI 1.10-1.56, NNNH=137/4.7 yrs. A higher rate of death from GI/cerebrovascular cancer in the ASA group than in the placebo group, HR=1.77, 95% CI 1.02-3.06, ARR=0.15%, NNNH=639/4.7 yrs.
- In an updated (2019) meta-analysis of 16 RCTs (n=104,018, age\(\text{mean}=60.5\) yrs, follow-up=5.5 yrs, 39% female), ASA was not associated with significant reduction of cancer-related mortality compared to placebo.<sup>3</sup>
Summary table

<table>
<thead>
<tr>
<th>Trials</th>
<th>Primary Outcome</th>
<th>CV composite</th>
<th>Major bleed</th>
<th>Intracranial hemorrhage</th>
<th>Major GI bleed</th>
<th>GI/ Colorectal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes 2019</td>
<td>n=15,480, 94% T2DM, age mean = 63.3 yr, follow-up = 7.4 yr</td>
<td>Nonfatal MI, nonfatal stroke, TIA or death from any vascular event [8.5% ASA vs 9.6% placebo, RR=0.88, 95% CI 0.79-0.97, NNT=91]</td>
<td>Any major bleed intracranial hemorrhage, 4.1% ASA vs. 3.2% placebo, RR=1.29, 95% CI 1.09-1.57, NNT=112</td>
<td>NS</td>
<td>1.8% ASA vs. 1.3% placebo, RR=1.36, 95% CI 1.05-1.75, NNT=215</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes 2019</td>
<td>n=10, 304,448 patients, follow-up = 5 yrs (7.6-7.7)</td>
<td>CV mortality, MI &amp; nonfatal stroke (HR=0.89, 95% CI 0.80-1.00, ARR=0.65%, NNT=153)</td>
<td>HR=1.29, 95% CI 1.11-1.51, ARR=0.80%, NNT=124</td>
<td>NS</td>
<td>HR=1.35, 95% CI 1.05-1.75, ARR=0.41%, NNT=243</td>
<td>NS</td>
</tr>
<tr>
<td>Elderly</td>
<td>n=19,114 healthy elderly, age avg=74 yr, follow-up = 4.7 yrs</td>
<td>Composite death from any cause, dementia &amp; persistent physical disability; NS</td>
<td>Fatal CHD, nonfatal MI, nonfatal or fatal stroke, HF hospitalization: NS</td>
<td>Major hemorrhagic event: HR=1.38, 95% CI 1.18-1.62, ARR=1.03%, NNT=97</td>
<td>Upper GI bleed: HR=1.87, 95% CI 1.32-2.66, ARR=0.43%, NNT=230</td>
<td>Death from GI/ colorectal cancer, HR=1.77, 95% CI 1.02-3.06, ARR=0.15%, NNT=639</td>
</tr>
<tr>
<td>Low CV risk 2019</td>
<td>6 studies, n=112,566, CV risk = 6.8%, range 2.6%-8.1%</td>
<td>CV mortality, MI &amp; nonfatal stroke (HR=0.87, 95% CI 0.79-0.95, ARR=0.34%, NNT=297)</td>
<td>HR=1.45, 95% CI 1.28-1.63, ARR=0.40%, NNT=249</td>
<td>HR=1.41, 95% CI 1.16-1.71, ARR=0.37%, NNT=268</td>
<td>Upper GI bleed: HR=1.58, 95% CI 1.34-1.87, ARR=0.27%, NNT=320</td>
<td>NS</td>
</tr>
<tr>
<td>Moderate-High CV risk 2019</td>
<td>n=12,546 with moderate CV risk, mean age = 63.9 yr, follow-up = 5 yr</td>
<td>MI, stroke, cardiovascular death, unstable angina, or TIA – NS</td>
<td>NS</td>
<td>HR=1.50, 95% CI 1.12-2.02, ARR=0.13%, NNT=796</td>
<td>Upper GI bleed: NS</td>
<td>Incidence of colon cancer higher in ASA group – 0.22% ASA group vs 0.10% placebo</td>
</tr>
<tr>
<td>High CV risk 2019</td>
<td>7 studies, n=50,383, CV risk =12.7%, range 10.2%-15.9%</td>
<td>CV mortality, MI &amp; nonfatal stroke (HR=0.92, 95% CI 0.84-1.00, ARR=0.51%, NNT=196)</td>
<td>AR=0.64, HR=1.41, 95% CI 1.23-1.61, NNT=152</td>
<td>NS</td>
<td>AR=0.39, HR=1.54, 95% CI 1.26-1.89, NNT=255</td>
<td>NS for overall cancer mortality</td>
</tr>
</tbody>
</table>

For above trials and meta-analysis, ASA showed no significant differences in individual components of all-cause mortality, CV mortality, MI, ischemic stroke, or total stroke compared to placebo

Examples:

Would you prescribe EC ASA 81mg/d in these situations?

A. 55 yr old women newly diagnosed with type 2 diabetes, smokes 1 pisp x 40 years, BMI=40kg/m2, no family hx of heart disease.
B. 68 yr old male diagnosed with Type 2 diabetes, family hx of heart disease (brother had a heart attack at age 60), non-smoker.
C. 75 yr old male who has transient ischemic attacks (TIAs).
D. 60 yr old female with AF, no CAD or arterial vascular disease, CHADS2=0, CHA2DS2-VASc=1, HASBLED=0, likes to drink 1-2 glasses of wine with supper daily.

Would you stop EC ASA 81mg/d in these situations? (Note: the trials mentioned are in situations in which ASA is prescribed, not stopped)

E. 85 yr old male with T2DM (stable), taking EC ASA 81mg/d for over 20 years, feeling appetite has decline in the last 3 months, eGFR=47mL/min, CrCl=47mL/min, Hemoglobin declined from 150 g/L to 135 g/L in the last 6 months.
F. 80 yr old female with EC ASA 81mg/d and renal function is declining, eGFR=20mL/min, CrCl=25mL/min.
G. 83 yr old male, T2DM with coronary stent on EC ASA 81mg/d and ticagrelor 90mg BID without PPI (no hx of GI bleed or stomach issues). Three months later, develops a GI bleed, treated in hospital and started on pantoprazole 40mg PO bid on discharge.
H. 70 yr old female with hx of cardioembolic stroke taking EC ASA 81mg/d & clopidogrel 75mg/d x 1 yr, complaining about nosebleeds in the winter. No nose bleeds in the summer. She cannot tolerate other oral anticoagulants (eg. warfarin, apixaban, etc).

Answers:

A. Discuss CV benefits/harms of EC ASA 81mg/d (similar benefits and harms)
B. Discuss CV benefits/harms of EC ASA 81mg/d (similar benefits and harms), pt may value CV protection since positive family history.
C. Start EC ASA 81mg/d for secondary prevention of T1As.
D. EC ASA 81mg/d is not recommended when patient does not have CAD or arterial vascular disease as per CCS recommendations.
E. Stop EC ASA 81mg/d and further investigation may be required since Hb is decreasing.
F. Stop EC ASA 81mg/d because of poor renal function, contraindicated when CrCl=30mL/min.
G. Once GI bleed is healed and treated with PPI, restart EC ASA 81mg/d and ticagrelor 90mg BID for continuing secondary prevention of CVD.
H. If nosebleeds are manageable, then consider continuing EC ASA 81mg/d. However, if nosebleeds are uncontrollable, may need to stop EC ASA 81mg/d.

Abbreviations

ns: non-formulary in SK, □: not covered by NIH, ◆: Exceptional Drug Status in SK,♀: female, ♂: male 1°: primary 2°: secondary ACC/AHA=American College of Cardiology/American Heart Association AR=absolute risk increase ARR=absolute risk reduction ASA=Aspirin AECG=Atrial fibrillation ACSVD=atherosclerotic cardiovascular disease AT=antithrombotic trials BP=blood pressure BMI=body mass index CAD=coronary artery disease (CVD) CVD=cerebrovascular disease DM=diabetes mellitus eGFR=estimated glomerular filtration rate EG=gastrointestinal HDL=high density lipoprotein HF=heart failure HTN=hypertension HR=hazard ratio hx=history LDL=low density lipoprotein MACE=major cardiovascular events MI=myocardial infarction N/A=number needed to treat (NNT) NS=not significant NTG=treatment group NT=number of patients randomized and assigned to each group (n) NS=non-significant OR=odds ratio P=probability pt=patient RCT=randomized controlled trial(s) SBP=systolic blood pressure SVD=type 2 diabetes TCA=total cholesterol TIA=transient ischaemic attack UA=unstable angina UK=United Kingdom US=United States yr=year(s)

DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the University of Saskatchewan. Neither the authors nor the University of Saskatchewan nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such information. Any use of the newsletter will imply acknowledgment of the disclaimer and release any responsibility of the University of Saskatchewan, its employees, agents or agents. Readers are encouraged to confirm the information contained herein with other sources. Additional information and resources online at www.RxFiles.ca

Copyright 2018 – RxFiles, University of Saskatchewan, www.RxFiles.ca
References

10 RxTx. Aspirin monograph, accessed July 1, 2019.