UPDATES IN ASPRIN:
PHARMACOTHERAPEUTIC CONSIDERATIONS & GUIDELINE RECOMMENDATIONS

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I, Michael J. Scalese, have no actual or potential conflict of interest in relation to this program.
OBJECTIVES

1. Describe the pharmacology, dosing, and historical role of aspirin

2. Discuss the use of aspirin for the primary prevention of CV disease


4. Apply guideline recommendations and supporting primary literature for aspirin use to patient cases
Pharmacology and Historical Use
Salicylates

- Use of salicylates dates back to the 3rd millennium BC
  - Found naturally in Myrtle and White Willow
  - Anti-inflammatory and antipyretic properties
- Became commercially available in 1874 as salicylic acid
  - ↓ Fever, pain, and inflammation
  - Primary Treatment for Rheumatic Fever

Circulation 2011;123:768-778
ASPIRIN (ACETYLSALICYLIC ACID)

► First synthesized in 1895 by chemist Felix Hoffman
  ► Manufacturing push to find better alternative to salicylic acid
  ► Hoffman sought to make a better option for his father’s arthritis/rheumatism

► The name “Aspirin” was coined by Bayer Corporation
  ► Patented name for brand product not the chemical entity
  ► Trademark lost after confiscation of Bayer’s US assets after WWI
    ► Aspirin became the common name of the chemical compound

► Aspirin name thought to come from St. Aspirinius, the patron saint against headaches

Circulation 2011;123:768-778
ASPIRIN PHARMACOLOGY

Physiological stimuli

- Arachidonic acid
  - COX1
    - Protective Prostaglandins
      - Stomach mucosa
    - Platelet stickiness

Infection, Injury

- COX2
  - Inflammatory Prostaglandins
    - Pain
    - Fever
    - Inflammation

Circulation 2011;123:768-778
ASPIRIN PHARMACOLOGY

Platelet COX-1

After aspirin

- AA access obstructed by acetyl group in aspirin-modified COX
- acetylation of serine 529 by aspirin

Platelet Activation

Circulation. 2011;123:768-778
**PHARMACOLOGY KEY POINTS**

- **Irreversible COX-1 inhibition (Selective when less ≤ 100mg)**
  - Serine (529) acetylation
  - Blocks formation of thromboxane A2

- **Inhibits COX-2 at higher doses (>100mg/day)**
  - Analgesic & antipyretic effects
  - Increased bleeding risk
  - Increased thrombosis risk at high doses
Primary Prevention
Cardiovascular Disease Statistics
2017 Update

- Cardiovascular disease (CVD) accounts for approximately 1 out of 3 deaths
  - 800,000 deaths in the United States annually
  - 1 death every 40 seconds

- Stroke accounts for 1 of 20 deaths in the US
  - 1 death every 40 seconds
  - Leading cause of long-term disability in the US

- Increased rates of obesity: an estimated 37.7% of adults are obese
  - 1 in 3 adults do not meet current recommendations for physical activity

- An estimated 85.7 million Americans (34% of the population) have high blood pressure
  - An estimated 45% of Americans with hypertension do not have controlled blood pressure.
Heart Disease Death Rates, 2008-2010
Adults, Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics

https://nccd.cdc.gov/DHDSPAtlas/
CV Deaths in Alabama

- Alabama CVD deaths
  - 294 deaths/100k people
  - 2nd highest in the US (rank 51/52)

- Alabama Stroke related deaths
  - 48.6 deaths/100k people
  - Highest in the US (rank 52/52)

- Impacts men more than women

Circulation. 2017;135:00-00
https://nccd.cdc.gov/DHDSAtlas/
TRENDS IN CARDIOVASCULAR DEATH

Circulation. 2017;135:00–00.
PRIMARY PREVENTION

- Recognize CVD risk status
  - Known risk factors: older age, males, dyslipidemia, hypertension, diabetes, smoking, physical inactivity

- Primary goal is risk factor reduction
  - Secondary goal is identifying other therapies that are safe and effective

- Benefits of aspirin use in patient with known CVD is well established

- Weigh risks/benefits of primary prevention
  - CVD reduction & increased bleed risk
  - Used evidence based recommendations
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<td>Use aspirin for adults aged 50-59 years</td>
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<tr>
<td>- 10-year ASCVD risk &gt;10%</td>
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<td>- Life expectancy &gt;10 years</td>
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<td>- Willing to take ASA &gt;10 years</td>
<td>Use aspirin for adults &gt;50 years</td>
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<td>- Diabetes</td>
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<td>- No ↑ risk of bleeding</td>
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<tr>
<td>- 10-year ASCVD risk &gt;10% (includes most men and women ≥50 y with diabetes and ≥1 other ASCVD risk factors)</td>
<td>Suggest aspirin use for primary prevention</td>
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<tr>
<td>- Individualize the decision for adults aged 60-69</td>
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<tr>
<td>- 10-year ASCVD risk &gt;10%</td>
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<td>- No ↑ risk of bleeding</td>
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<td>- Life expectancy &gt;10 years</td>
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<tr>
<td>- Willing to take ASA &gt;10 years</td>
<td>Aspirin use for primary prevention not recommended</td>
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<tr>
<td>- Diabetes, &lt;50 years old</td>
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<td>- 10-year ASCVD risk 5%-10%</td>
<td>Can be useful in women &gt;65 years if</td>
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<td>- Individualize</td>
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<td>- Diabetes</td>
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<tr>
<td>- 10-year ASCVD risk &lt;5%</td>
<td>- blood pressure is controlled</td>
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<td>- Not recommended</td>
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<td>- Diabetes</td>
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<tr>
<td>- 10-year ASCVD risk &lt;5%</td>
<td>- benefit outweighs risk</td>
<td></td>
<td></td>
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<tr>
<td>- Not recommended for adults &lt;50 or &gt;70</td>
<td>May be reasonable in women &lt;65 years</td>
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<tr>
<td>- For prevention of ischemic stroke</td>
<td>Not recommended for women &lt;65 years</td>
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<tr>
<td>- For prevention of myocardial infarction</td>
<td>Not recommended for routine use</td>
<td></td>
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<tr>
<td>- Men: Aged 45-59 with 10-y CHD risk ≥4%</td>
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<tr>
<td>- Aged 60-69 with 10-y CHD risk ≥9%</td>
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<tr>
<td>- Aged 70-79 with 10-y CHD risk ≥12%</td>
<td>Consider only in special circumstances</td>
<td></td>
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<tr>
<td>- ↑ CHD risk</td>
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<tr>
<td>- ↓ bleeding risk</td>
<td>Not recommended for women &lt;65 years</td>
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<tr>
<td>- Men &lt;45 &amp; &gt;80</td>
<td>Not recommended for men &lt;45 &amp; &gt;80</td>
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<tr>
<td>- Women: Aged 55-59 with 10-y stroke risk ≥3%</td>
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<tr>
<td>- Aged 60-69 with 10-y stroke risk ≥8%</td>
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<tr>
<td>- Aged 70-79 with 10-y stroke risk ≥11%</td>
<td>Not recommended for women &lt;55 &amp; &gt;80</td>
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</tbody>
</table>
USPSTF 2016

- Updated 2009 recommendations
  - Included 3 new systematic reviews
  - Used CVD microsimulation model
  - Recommendations made with “moderate certainty”
- Apply to patients ≥ 40 years
  - No known CVD
  - No ↑ risk of bleeding
    - GI ulcer
    - Recent bleeding
    - Medications with ↑ risk of bleeding

- Goal is to balance benefit and harm
  - ↓ MI, Stroke, CV death
  - ↓ GI bleeding, Hemorrhagic stroke

- Magnitude of risk reduction based on baseline CVD risk
  - Incorporated the ACC/AHA ASCVD risk calculator
  - 10-year risk for ASCVD event

### Table 3. Lifetime Events in 10,000 Women Taking Aspirin*

<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Nonfatal MIs prevented</th>
<th>Nonfatal ischemic strokes prevented</th>
<th>CRC cases prevented</th>
<th>Serious GI bleeding events caused</th>
<th>Hemorrhagic strokes caused</th>
<th>Net life-years gained</th>
<th>QALYs gained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aged 50 to 59 years</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10%</td>
<td>148</td>
<td>137</td>
<td>139</td>
<td>209</td>
<td>35</td>
<td>219</td>
<td>621</td>
</tr>
<tr>
<td>15%</td>
<td>150</td>
<td>143</td>
<td>135</td>
<td>200</td>
<td>34</td>
<td>334</td>
<td>716</td>
</tr>
<tr>
<td>20%</td>
<td>152</td>
<td>144</td>
<td>132</td>
<td>184</td>
<td>29</td>
<td>463</td>
<td>833</td>
</tr>
<tr>
<td><strong>Aged 60 to 69 years</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>101</td>
<td>116</td>
<td>105</td>
<td>230</td>
<td>32</td>
<td>-12</td>
<td>284</td>
</tr>
<tr>
<td>15%</td>
<td>110</td>
<td>129</td>
<td>93</td>
<td>216</td>
<td>34</td>
<td>17</td>
<td>324</td>
</tr>
<tr>
<td>20%</td>
<td>111</td>
<td>130</td>
<td>97</td>
<td>217</td>
<td>33</td>
<td>48</td>
<td>360</td>
</tr>
</tbody>
</table>

### Table 2. Lifetime Events in 10,000 Men Taking Aspirin*

<table>
<thead>
<tr>
<th>CVD risk</th>
<th>Nonfatal MIs prevented</th>
<th>Nonfatal ischemic strokes prevented</th>
<th>CRC cases prevented</th>
<th>Serious GI bleeding events caused</th>
<th>Hemorrhagic strokes caused</th>
<th>Net life-years gained</th>
<th>QALYs gained</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aged 50 to 59 years</strong></td>
<td></td>
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<tr>
<td>10%</td>
<td>225</td>
<td>84</td>
<td>139</td>
<td>284</td>
<td>23</td>
<td>333</td>
<td>588</td>
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<tr>
<td>15%</td>
<td>267</td>
<td>86</td>
<td>121</td>
<td>260</td>
<td>28</td>
<td>395</td>
<td>644</td>
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<tr>
<td>20%</td>
<td>286</td>
<td>92</td>
<td>122</td>
<td>248</td>
<td>21</td>
<td>605</td>
<td>834</td>
</tr>
<tr>
<td><strong>Aged 60 to 69 years</strong></td>
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<td></td>
</tr>
<tr>
<td>10%</td>
<td>159</td>
<td>66</td>
<td>112</td>
<td>314</td>
<td>31</td>
<td>-20</td>
<td>180</td>
</tr>
<tr>
<td>15%</td>
<td>186</td>
<td>80</td>
<td>104</td>
<td>298</td>
<td>24</td>
<td>96</td>
<td>309</td>
</tr>
<tr>
<td>20%</td>
<td>201</td>
<td>84</td>
<td>91</td>
<td>267</td>
<td>27</td>
<td>116</td>
<td>318</td>
</tr>
</tbody>
</table>
USPSTF 2016

- Aspirin reduced stroke and MI risk in adults aged 50-69
  - ↑ benefit with ↑ ASCVD risk

- Small to moderate risk of harm in adults aged 60-69

- Small risk of harm in adults aged 59 or younger

- Limited evidence in patients less than 50 or older than 69

- Use aspirin for adults aged 50-59
  - 10-year ASCVD risk > 10%
  - No ↑ risk of bleeding
  - Life expectancy > 10 years
  - Willing to take ASA > 10 years

- Individualized use for adults aged 60-69
  - 10-year ASCVD risk > 10%
  - No ↑ risk of bleeding
  - Life expectancy > 10 years
  - Willing to take ASA > 10 years

- No rec’s for adults < 50 years or ≥ 70 years

References:

2016 Meta-analysis

- Included data from 11 RCTs
  - 4 published since 2009 review
  - 2 good quality studies
  - 9 fair quality studies

- Total of 111,445 patients evaluated

- Aspirin vs placebo for primary prevention

- Heterogeneity was a limitation
  - Few credible subgroups

- All Aspirin doses (50-500mg)
  - No CVD mortality or stroke benefit
  - Small reduction in all-cause mortality
    - RR 0.94 (95% CI 0.89-0.99)
  - Reduced non-fatal MI
    - RR 0.78 (95% CI 0.71-0.87)

- Aspirin doses ≤ 100mg
  - No reduction in All-cause or CVD mortality
  - Reduction in non-fatal stroke
    - RR 0.86 (95% CI 0.76-0.98)
  - Reduction in nonfatal MI
    - RR 0.83 (95% CI 0.74-0.94)

APPROACH TO PRACTICE

Patient Age
(50-69 years)

ASCVD Risk Assessment
(10 year risk >10%)

Evaluate GI Bleed risk
(Minimal bleeding risk)

Willingness to Take Aspirin >10 years
(Discuss with patient)
**Approach to Practice**

- Use 75-162 mg on non-enteric coated ASA
  - Low dose appears to be equally efficacious & lower bleed risk
  - No evidence for GI protection with enteric coating
    - Bleeding secondary to systemic prostaglandins not local effects
    - May ↑ ASA resistance

- Consider GI Prophylaxis
  - PPI appear to be more beneficial than H2RA’s

- New Aspirin-Guide APP available
  - Assesses ASCVD risk VS GI bleed risk
Colorectal Cancer (CRC)
CRC PRIMARY PREVENTION

- 6% of Americans will develop CRC in their lifetime
- Patients with ↑ CVD risk also have ↑ CRC risk
  - Overlapping risk factors
- Aspirin
  - ↓ intestinal carcinogenesis
  - ↓ prostaglandin associated with tumor angiogenesis
  - ↑ rate of apoptosis

Aspirin had no effect on CRC incidence in short term
- Initial period of 0-12 years
- RR 0.99 (95% CI 0.85-1.15)

Aspirin associated with decrease in colorectal cancer over longer period
- 20 year follow up
- RR 0.60 (95% CI 0.47-0.76)

**USPSTF 2016**
- Use aspirin for adults aged 50-59
  - No ↑ risk of bleeding
  - Life expectancy >10 years
  - Willing to take ASA >10 years

- Individualized use for adults aged 60-69
  - No ↑ risk of bleeding
  - Life expectancy >10 years
  - Willing to take ASA >10 years
Preeclampsia
PREECLAMPSIA

- New onset hypertension + proteinuria or end-organ damage
  - After 20 weeks gestation
  - Previously normotensive

- Associated with maternal and fetal morbidity and mortality

- Pathogenesis not well understood
  - ↑ inflammation
  - ↑ platelet turnover
  - ↑ platelet-derived thromboxane levels

- Low dose aspirin
  - ↓ platelet thromboxane synthesis while
  - Maintains vascular wall prostacyclin synthesis

NEJM. 2017; DOI: 10.1056/NEJMoa1704559
### ASPRE Trial (2017)

- 1776 singleton pregnancies
  - 11-14 weeks gestation
- High-risk for preterm preeclampsia
- Aspirin 150mg vs placebo
- Followed through 36 weeks gestation
- ~10% were multiparous with previous preeclampsia

![Outcome ASA group N=798 [N (%)] Placebo group N=822 [N (%)] Odds ratio (95% CI)]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ASA group N=798 [N (%)]</th>
<th>Placebo group N=822 [N (%)]</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm preeclampsia (&lt;37 weeks)</td>
<td>13 (1.6)</td>
<td>35 (4.3)</td>
<td>0.38 (0.20-0.74)</td>
</tr>
<tr>
<td>Adverse outcomes (&lt;37 weeks)</td>
<td>79 (9.9)</td>
<td>116 (14.1)</td>
<td>0.69 (0.46-1.03)</td>
</tr>
<tr>
<td>Adverse outcomes (&gt;37 weeks)</td>
<td>178 (22.3)</td>
<td>171 (20.8)</td>
<td>1.12 (0.82-1.54)</td>
</tr>
</tbody>
</table>

NEJM. 2017; DOI: 10.1056/NEJMoa1704559
Consider low-dose ASA (81-150 mg) in high risk pregnancies

High risk criteria is variable (USPSTF, AHA, ACC, WHO, ACOG, etc)
- Previous pregnancy with preeclampsia (especially early onset)
- Multifetal gestation
- Chronic hypertension
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease
- Autoimmune disease (antiphospholipid syndrome, systemic lupus erythematosus)

Discontinue aspirin 7-10 days before expected delivery
- ↓ delivery related bleeding

NEJM. 2017; DOI: 10.1056/NEJMo1704559
Secondary Prevention
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Starting Year</th>
<th>Publication Year</th>
<th>Aspirin Daily Dose, mg</th>
<th>No. of Patients</th>
<th>Study Duration</th>
<th>Age, %</th>
<th>Htn, %</th>
<th>Diabetes Mellitus, %</th>
<th>β-Blocker, %</th>
<th>Time From MI to Enrollment</th>
<th>Rese:vasculation (PCI/CABG), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>1971</td>
<td>1974</td>
<td>300</td>
<td>1230</td>
<td>13 mo</td>
<td>55</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>10 wk</td>
<td>0</td>
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<tr>
<td>Cardiff II</td>
<td>NA</td>
<td>1979</td>
<td>500</td>
<td>1725</td>
<td>12 mo</td>
<td>56</td>
<td>85</td>
<td>NA</td>
<td>0.5</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>PARIS I</td>
<td>1975</td>
<td>1980</td>
<td>672</td>
<td>1216</td>
<td>41 mo</td>
<td>56</td>
<td>87</td>
<td>NA</td>
<td>10.4</td>
<td>8 wk to 60 mo</td>
<td>0</td>
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<tr>
<td>AMS</td>
<td>1975</td>
<td>1980</td>
<td>1000</td>
<td>4524</td>
<td>38 mo</td>
<td>55</td>
<td>89</td>
<td>NA</td>
<td>11</td>
<td>8 wk to 60 mo</td>
<td>0</td>
</tr>
<tr>
<td>CDP-A</td>
<td>1972</td>
<td>1975</td>
<td>750</td>
<td>1725</td>
<td>22 mo</td>
<td>56</td>
<td>100</td>
<td>NA</td>
<td>14</td>
<td>75% &gt;60 mo</td>
<td>0</td>
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<tr>
<td>GAMIS</td>
<td>1970</td>
<td>1980</td>
<td>1500</td>
<td>626</td>
<td>24 mo</td>
<td>59</td>
<td>78</td>
<td>19</td>
<td>20</td>
<td>30-42 days</td>
<td>0</td>
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<tr>
<td>Microstat</td>
<td>NA</td>
<td>1979</td>
<td>1500</td>
<td>1340</td>
<td>24 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
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<tr>
<td>Acute MI</td>
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<tr>
<td>ISIS-I</td>
<td>1985</td>
<td>1987</td>
<td>162.5</td>
<td>619</td>
<td>1 mo</td>
<td>60</td>
<td>80</td>
<td>22</td>
<td>5</td>
<td>&lt;24 h</td>
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<tr>
<td>ISIS-II</td>
<td>1988</td>
<td>1987</td>
<td>162.5</td>
<td>17187</td>
<td>35 days</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;24 h</td>
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<tr>
<td>Dutch-aspirin</td>
<td>NA</td>
<td>1990</td>
<td>100</td>
<td>3</td>
<td>62.5</td>
<td>74</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>&lt;12 h</td>
<td>Rare, none within 1 wk</td>
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<tr>
<td>Huddinge</td>
<td>NA</td>
<td>1988</td>
<td>167 (500 every 3 days)</td>
<td>20</td>
<td>1 mo (12 mo)</td>
<td>63</td>
<td>80</td>
<td>NA</td>
<td>NA</td>
<td>&lt;24 h</td>
<td>10</td>
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<tr>
<td>Frankfurt</td>
<td>NA</td>
<td>1976</td>
<td>1320</td>
<td>39</td>
<td>14 days</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>APRICO</td>
<td>NA</td>
<td>1993</td>
<td>325</td>
<td>182</td>
<td>3 mo</td>
<td>57</td>
<td>86</td>
<td>NA</td>
<td>43</td>
<td>10.4</td>
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<tr>
<td>Unstable angina</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>WA-pilot</td>
<td>1974</td>
<td>1986</td>
<td>324</td>
<td>50</td>
<td>3 mo</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3.5</td>
</tr>
<tr>
<td>WA-main</td>
<td>1974</td>
<td>1983</td>
<td>324</td>
<td>3000</td>
<td>3 mo</td>
<td>56</td>
<td>100</td>
<td>41</td>
<td>17</td>
<td>48 h</td>
<td></td>
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<tr>
<td>RISC</td>
<td>1985</td>
<td>1990</td>
<td>75</td>
<td>796</td>
<td>12 mo</td>
<td>58</td>
<td>100</td>
<td>38</td>
<td>8</td>
<td>88</td>
<td>3.9</td>
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<tr>
<td>ALDUSA-pilot</td>
<td>NA</td>
<td>1987</td>
<td>324-340</td>
<td>84</td>
<td>12 mo</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Théroux**</td>
<td>1985</td>
<td>1988</td>
<td>560</td>
<td>479</td>
<td>6 days (2 mo)</td>
<td>58</td>
<td>71</td>
<td>38</td>
<td>13</td>
<td>&lt;24 h</td>
<td>48</td>
</tr>
<tr>
<td>ATRACS-pilot†</td>
<td>1987</td>
<td>1993</td>
<td>325-380</td>
<td>93</td>
<td>3 mo</td>
<td>62</td>
<td>60</td>
<td>49</td>
<td>37</td>
<td>&lt;48 h</td>
<td>50</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
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<td></td>
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</tr>
<tr>
<td>Perth†</td>
<td>1985</td>
<td>1991</td>
<td>100</td>
<td>212</td>
<td>5 mo</td>
<td>55</td>
<td>84</td>
<td>34</td>
<td>4</td>
<td>–</td>
<td>100% PCI for stable CAD</td>
</tr>
<tr>
<td>M-HEART III</td>
<td>NA</td>
<td>1995</td>
<td>325</td>
<td>503</td>
<td>6 mo</td>
<td>58</td>
<td>83</td>
<td>50</td>
<td>18</td>
<td>–</td>
<td>100% PCI for stable CAD</td>
</tr>
<tr>
<td>Stable CAD</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SAPAT†</td>
<td>1985</td>
<td>1992</td>
<td>75</td>
<td>2035</td>
<td>50</td>
<td>67</td>
<td>52</td>
<td>41</td>
<td>7</td>
<td>–</td>
<td>100% enrolled after CABG</td>
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<tr>
<td>WA bypass N-89#</td>
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</table>
**Aspirin in ACS**

<table>
<thead>
<tr>
<th>Indication: Secondary Prevention</th>
<th>ASA Dose/Duration (Initially)*</th>
<th>ASA Dose (Indefinitely)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemia-guided Strategy</strong> (Medical Management)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI/UA</td>
<td>162-325 mg Promptly on presentation Chew/swallow</td>
<td>81-162 mg daily*</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI/UA</td>
<td>162-325 mg Prior to procedure</td>
<td>81-162 mg daily*</td>
</tr>
<tr>
<td>STEMI</td>
<td>81-325 mg daily*</td>
<td><em>81 mg is preferred dose</em></td>
</tr>
</tbody>
</table>

*81 mg is preferred dose*

J Am Coll Cardiol. 2014;64(24):e139-228
Circulation 2013;127(4):e362-425
## ASA Dose Comparison (CURRENT-OASIS 7)

<table>
<thead>
<tr>
<th></th>
<th>ASA 75-100 mg</th>
<th>ASA 300-325 mg</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death/MI/Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI (2N=17,232)</td>
<td>4.2</td>
<td>4.1</td>
<td>0.98</td>
<td>0.84-1.13</td>
<td>0.76</td>
</tr>
<tr>
<td>No PCI (2N=7855)</td>
<td>4.7</td>
<td>4.4</td>
<td>0.92</td>
<td>0.75-1.14</td>
<td>0.44</td>
</tr>
<tr>
<td>Overall (2N=25,087)</td>
<td>4.4</td>
<td>4.2</td>
<td>0.96</td>
<td>0.85-1.08</td>
<td>0.47</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>2.1</td>
<td>1.9</td>
<td>0.91</td>
<td>0.73-1.12</td>
<td>0.37</td>
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<tr>
<td>TIMI Major Bleed</td>
<td>1.03</td>
<td>0.97</td>
<td>0.94</td>
<td>0.73-1.21</td>
<td>0.71</td>
</tr>
<tr>
<td>CURRENT Major Bleed</td>
<td>2.3</td>
<td>2.3</td>
<td>0.99</td>
<td>0.84-1.17</td>
<td>0.90</td>
</tr>
<tr>
<td>CURRENT Severe Bleed</td>
<td>1.7</td>
<td>1.7</td>
<td>1.00</td>
<td>0.83-1.21</td>
<td>1.00</td>
</tr>
</tbody>
</table>

GI Bleeds: 30 (0.24%) v 47 (0.38%), P=0.051

No other significant differences between ASA dose groups

Stroke
ASPIRIN IN STROKE

- 2012 Chest Guidelines
  - Aspirin monotherapy 75-100mg (Class I, LOE: A)
  - Clopidogrel + Aspirin (Class I, LOE: B)
  - Recommends clopidogrel or Aspirin 25mg + ER dipyridamole 200mg BID over aspirin monotherapy (Class II, LOE: B)

- 2014 ASA/AHA Secondary prevention guidelines
  - Aspirin monotherapy 50-325mg (Class I, LOE: A)
  - Aspirin 25mg + ER dipyridamole 200mg BID (Class I, LOE: B)
  - Aspirin + clopidogrel x 21 days
    - If started within 24 hours of onset of minor stroke (Class IIb, LOE: B)
    - Not recommended when started days to years after minor stroke or TIA (Class III, LOE:A)
Aspirin Monotherapy

  - Meta-analysis of 195 RCT's
  - ARR of 36/1000 stroke patients over 21 months
  - Doses range 20mg-1300mg

- Antithrombotic Trialists Collaboration (2009)
  - Meta-analysis of 16 secondary prevention trials
  - RRR of 22% for ischemic stroke

- 2016 time-course analysis
  - Pooled analysis of data from over 15,000 subjects in 12 trials
  - Aspirin reduced the relative risk of recurrent ischemic stroke within the first six weeks (1.0 vs 2.4%)
    - RRR of 58%
    - ARR of 1.4 (HR 0.42, 95% CI 0.32-0.55)

- Bottom Line: Low dose aspirin (75mg-100mg) is preferred as monotherapy

BMJ. 2002;324(7329):71
Lancet. 2009;373(9678):1849
Lancet. 2016;388(10042):365
**ASPIRIN/DIPYRIDAMOLE**

- **Dipyridamole**
  - Inhibits PDE → ↑ cAMP
  - ↑ cAMP → ↓ Ca & platelet activation
  - ↓ platelet uptake of adenosine

- **Synergism with aspirin combination**

- **25 mg ASA + 200mg ER dipyridamole BID**

**ESPIRIT**

- ASA 30-325/dipyridamole 200 BID (not fixed combination vs ASA alone)
- Reduced composite outcome (included ischemic events & major bleeding) with combo [HR 0.80 (95% CI 0.66-0.98)]

**Profess**

- ASA/dipyridamole 25/200 mg BID vs clopidogrel 75 mg daily
  - Clopidogrel arm initially combo ASA/clopidogrel
  - Non-significant difference in ischemic outcomes

References:
ASPIRIN + CLOPIDOGREL

**MATCH**
- ASA 75mg + clopidogrel 75mg VS clopidogrel 75mg x 18 months
- Majority of patients had lacunar infarcts
- 80% on ASA prior to indexing stroke
- No difference in MI, stroke, or CV death
- ↑ minor, major, and life threatening bleeding

**CHANCE**
- ASA 75mg daily VS TX group
  - ASA 75mg + clopidogrel 75 mg days 1-21
  - Then clopidogrel 75mg days 22-90
- NIHSS score ≤ 3
- Chinese only population
- Trial lasted 90 days
- ↓ Stroke 11.7% vs 8.2% (HR 0.68 95% CI 0.58-0.82)
- No difference in bleeding

Lancet 2004; 364: 331–37
UPDATES IN ASPIRIN: PHARMACOTHERAPY & GUIDELINE RECOMMENDATIONS

Michael J. Scalese, PharmD, BCPS, CACP
Assistant Clinical Professor
Auburn University Harrison School of Pharmacy
July 22, 2017