

**Quality Assurance Conference
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**ASPIRIN DOSE FOR THE SECONDARY PREVENTION OF
CVD**

CVD

- * Leading cause of death in the US
 - * >1,000,000 deaths annually
 - * Even pts who were free from disease at age 70 had a lifetime risk of 35% and 24% in men and women, respectively.
- (FRAMINGHAM HEART STUDY)

2004 Age-Adjusted Death Rates for CVD by State

State	Rank
Minnesota	#1
North Dakota	#11

Role of ASA on Secondary Prevention of CVD

- * Risk Factor Reduction:
 - * Lipid Modification
 - * HTN Control
 - * Therapeutic Lifestyle Changes (TLC)
 - * Glycemic Control (DM)
 - * Other Therapy
 - Aspirin
 - B-blockers, ACE-Is/ARBs, Clopidogrel
- * >50 million US adults (36% of Population)
- * Either 81mg/d or 325mg/d
- * CVD Pts
- * 80% more
- * 10-20 Billion ASA tablets consumed annually for CVD prevention alone.

Aspirin

Felix Hoffman (1897) of Bayer Co.

- Synthesized the acetylated form of Salicylic acid - "aspirin"

Sir John Vane (1971)

- demonstrated MOA of ASA as the inhibition of prostaglandin synthesis.

ASPIRIN PATHWAY

Antithrombotic Trialists Collaboration overview

* 195 randomized trials of antiplatelet therapy, principally with aspirin,

* >135,000 Pts w/ prior CVD

Major Conclusions:

- 22% risk reduction of subsequent vascular events

- no difference in efficacy between doses of 75 to 150 mg/day (low-dose) and 160 to 325mg/day (medium-dose) ASA.

WHAT IS THE OPTIMAL DOSE OF ASA FOR SECONDARY PREVENTION OF CVD?

Origin of the 2 most common doses.

* 1st tablet preparation (1900) sold as a 5-grain (approx. 325mg tab) pill.

* The childrens dosage, 81mg (1922) $\frac{1}{4}$ the adult dose, arbitrarily determined

Pharmaceutical market research

* 60% choosing 81 mg/d

* 35% prescribing 325 mg/d

* dosage used does not appear to be affected by physician specialty

* Although cardiologists tend to use 325 mg/d slightly more frequently

Long Term Therapy

- * Irreversible inhibition of platelet COX-1
- * Minimal de novo COX-1 synthesis (no nucleus)
- * New platelets approx 10% of tot. platelet count, (platelet lifespan 8-10 days)
- * Once complete inhibition is achieved as low as 30mg/d is effective
 - * long-term aspirin Tx: as low as 30 mg/d are adequate to fully inhibit platelet thromboxane production
- dosages as high as 1300 mg/d are also approved for use.
- * chronic stable angina 50 mg/d
- * 100mg every other day also effective

* The available evidence, predominantly from secondary-prevention observational studies, supports that, whereas dosages greater than 75 to 81 mg/d do not enhance efficacy, whereas larger dosages are associated with an increased incidence of bleeding events, primarily related to gastrointestinal tract toxicity.

* (Campbell, JAMA, 2007, 297(18):2018-2024.)

CLINICAL EFFICACY DUTCH TIA STUDY GROUP, 1991

prospective study, followed for 2.6 yrs.

- n=3131 (s/p stroke or TIA)
- 33mg/d vs 283mg/d
- end pt. (vasc. Death, MI, stroke)
- similar in the 2 groups
(14.7% for 30 mg/d vs 15.2% for 283 mg/d)

META-ANALYSES

1.) Metaregression Analysis of the Dose-Response Effect of Aspirin on Stroke Eric S. Johnson, MPH; Stephan F. Lanes, PhD; Charles E. Wentworth III, MS; Margaret H. Satterfield, MSN; Bethlehem L. Abebe, BA; Linda W. Dicker, PhD, Arch Intern Med. 1999;159:1248-1253.

- analyses of 11 clinical trials, 5228 pts,
- ASA vs placebo in post-stroke/TIA pts
- Similar efficacy of ASA dosages ranging from 50-1500mg/d

2.) Antithrombotic Trialists' Collaboration. BMJ 2002;324:71-86
no relationship between dose and efficacy.

- the greatest risk rxn trials using a 75- to 150-mg dose of ASA.

3.) Seeking the optimal aspirin dose in acute coronary syndromes .
The American Journal of Cardiology , Volume 90 , Issue 6 , Pages
622 - 625 D . Kong

- ASA vs placebo

- lower dosages of aspirin were associated with improved outcomes.

RETROSPECTIVE ANALYSES

1.) BRAVO trial (Blockade of the Glycoprotein IIb/IIIa Receptor to
Avoid Vascular Occlusion) (n= 9190)

1 of 2 doses Itrafiban or placebo in addition to ASA 75mg to 325
mg (at MDs discretion)

- The combined end point of all-cause mortality, MI, or stroke
outcomes occurred equally between these 2 cohorts

2.) GUSTO IIb (Global Use of Strategies to Open Occluded
Coronary Arteries) and the PURSUIT (Platelet Glycoprotein IIb/IIIa
in Unstable Angina: Receptor Antagonism Using Integrilin
Therapy) trials (n = 20 521)

- ASA doses <150mg, dec. incidence of 1st endpoint of death, MI,
stroke in 6 months

3.) CURE (Clopidogrel in Unstable Angina to Prevent Recurrent
Events)

(n=12,562) Non-ST-elevation ACS

- Randomized to clopidogrel or placebo in addition to long-term
ASA 75mg to 325mg (at MDs discretion)

- the lowest event rates were in patients treated with 100 mg/d or
less of aspirin

The one nearly constant finding among all of these studies has been
the lack of a relationship between increasing aspirin dosage and
improved efficacy. In fact, the trend in benefit has almost uniformly
favored lower dosages.

ADVERSE EFFECTS

1.) UK-TIA trial J Slattery, C P Warlow, C J Shorrocks, M J Langman

- almost double the risk of gastrointestinal bleeding among patients randomized to 1200 mg/d of aspirin compared with 300 mg/d (odds ratio, 6.4 [95% CI, 2.5-16.5] vs 3.3 [95% CI, 1.2-9.0]).⁵¹

2.) Dutch-TIA trial

- less bleeding was noted in the 30-mg group (2.6%) than the 283-mg group (3.2%)

3.) BRAVO and CURE trials

4.) Analysis of Risk of Bleeding Complications After Different Doses of in 192,036 Patients Enrolled in 31 Randomized Controlled Trials . The American Journal of Cardiology , Volume 95 , Issue 10 , Pages 1218 - 1222 V . Serebruany , S

PREVAILING RECOMMENDATIONS

AHA/ACC Guidelines 2006

- 75 to 162 mg/d

American Diabetes Association

- 81 to 325 mg/d

USFDA

- 75 to 325 mg/d

American College of Chest Physicians (2008) Evidence-Based Clinical Practice Guidelines (8th Edition)

- 75 to 100 mg/d

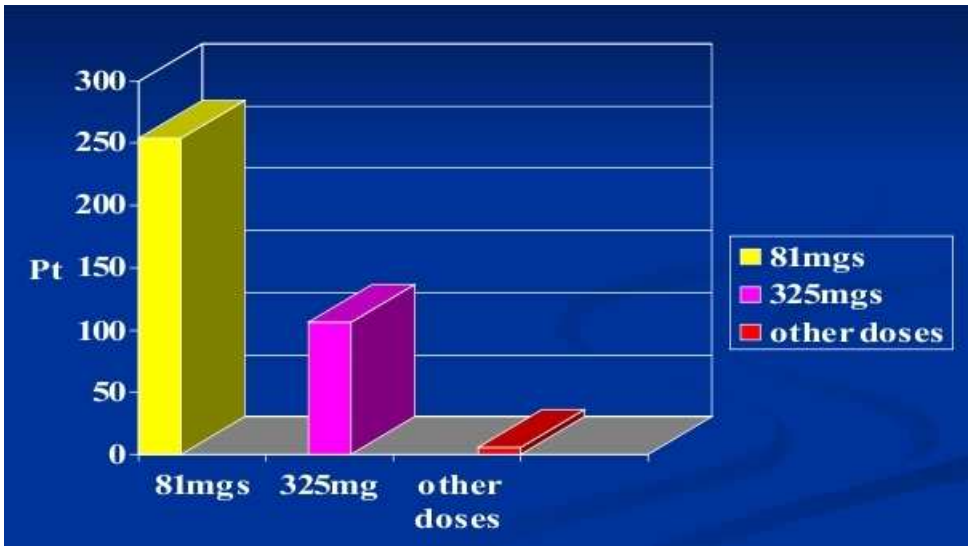
CHART REVIEW

* 510 charts from FMR

* 50 y/o and older

* Seen at the clinic from June 2007 to June 2008

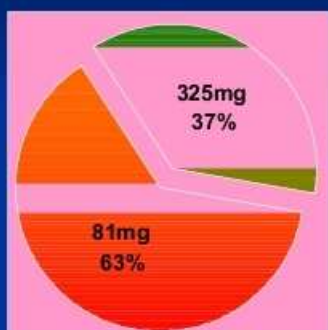
* M: 272 F: 238



Secondary Prevention

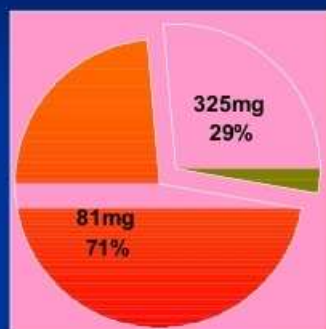
<i>Dx</i>	<i>81mgs</i>	<i>%</i>	<i>325mgs</i>	<i>%</i>
CAD w/ Stent	7	5%	15	10%
CAD	30	20%	12	8%
CVA	9	6%	10	7%
MI	0	0	10	7%
IHD	6	4%	9	6%
CHF	10	10%	4	3%
AF	10	7%	4	3%
CHD	7	4%	0	0%
Aortic stenosis	2	1%	0	0%
	81	56%	64	44%

US



81mg
325mg

CLINIC



81mg
325mg

Conclusion

- * +ve association between ASA dose and adverse effect.
- * no dose relationship with efficacy.
- * clinical data are most supportive of a 75 or 81mg daily dose.

Recommendation

Based on the collective results of the different studies reviewed, I recommend that Pts on long-term ASA therapy for secondary prevention of CVD should be on a daily dose no higher than 81mg.