Reconsidering low-dose aspirin Therapy

For Primary Cardiovascular Disease Prevention

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Defining Primary and Secondary Prevention

- Primary prevention is an action performed to preclude the development of a disease.
- Secondary prevention is an action performed to take care of early symptoms of a disease and preclude the development of possible irreparable medical conditions.

-online Med Dictionary

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Practice Guidelines in Question

- One DARTNet group recently decided to turn off the recommendation for low-dose aspirin therapy for primary prevention

- The data behind aspirin for primary prevention in high risk patients (e.g. diabetes, CKD, PAD) is in question.

- Aspirin is still **unquestionably indicated** for secondary prevention in patients with a history of **known CAD or thrombotic CVA/TIA** and during acute attacks.

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ADA
2010 Clinical Practice Guidelines

- The section "Antiplatelet agents" has been revised to:

"*consider* **aspirin therapy as a primary prevention strategy in those with diabetes at increased cardiovascular risk (10-year risk >10%). This includes men >50 years of age or women >60 years of age with *at least one additional major risk factor*.**"

USPSTF vs. FDA

- Low-dose aspirin has been recommended for primary prevention of CV events for many years by the USPSTF, but guidelines remain ambiguous.
- **USPSTF A recommendation** in men and women: Encourage aspirin use when potential CVD benefit outweighs potential risk of bleeding

BUT

They also state that "calculations for benefits and harms rely on assumptions" and are "imprecise."

USPSTF vs. FDA

- Aspirin has **not** been approved by the FDA for primary prevention of CV events.
- Low-dose aspirin has been denied **twice** for primary prevention labeling, once in 1998 and again in 2003, due to lack of evidence supporting its efficacy.
- "It's a very slippery slope when you try to interpret data from trials negative on their primary endpoint, picking out some things that looked pretty good and choosing to emphasize the benefits from those secondary analyses."

-Steve Nissen, MD, FDA Voting Member

Why the controversy?

"In our therapeutic greed to try to reduce risk further, we have been extrapolating [secondary prevention] aspirin data to primary prevention, and actually the data from primary prevention [trials] are weak."

–Jill Belch, MD, POPADAD study Investigator

CAD Risk Equivalents and Hypertension

Study Name	Subjects	Primary Endpoints	Outcomes
POPADAD Prevention of Progression of Arterial Disease and Diabetes *BMJ* (2008)	1,276 patients with **DM and PAD**	CV events CV mortality	NEGATIVE[Δ] NEGATIVE[Δ]
PPP Primary Prevention Project *Diabetes Care* (2003)	1,031 patients >50 years old with **DM2**	CVA MI CV mortality	NEGATIVE NEGATIVE NEGATIVE
JPAD Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes *JAMA* (2008)	2,539 patients with **DM2**	CVA MI PAD	NEGATIVE NEGATIVE NEGATIVE
DOPPS Dialysis Outcomes and Practice Patterns Study *Am J Kid Dis* (2007)	28,320 patients with **CKD**	MI CV events CVA	NEGATIVE[‡] NEGATIVE[‡] POSITIVE*
HOT Hypertension Optimal Treatment *Lancet* (1998)	18,790 patients with **HTN**	MI CVA CV mortality	NEGATIVE NEGATIVE NEGATIVE

[Δ] Planned subanalyses by age, gender, and ABI were also negative for this endpoint.

[‡] Low-dose aspirin resulted in increases in MI and CV events in this study.

*Patients with cerebrovascular disease were included in this count.

The BIG Picture

- **13 of 14 primary endpoints in 4 studies were negative for patients with DM, PAD, and CKD (CAD risk equivalents).**
  - **The one positive endpoint in patients with CKD included confounders.**
- **The primary endpoints were negative in patients with HTN (high risk).**

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Studies in Men and Women

Study Name	Subjects	Primary Endpoint(s)	Outcomes	Secondary Endpoints	Outcomes
BDT British Doctor's Trial *BMJ* (1988)	5,139 healthy male physicians	MI CVA CV mortality	NEGATIVE NEGATIVE NEGATIVE		
PHS Physician's Health Study *NEJM* (1989)	22,071 healthy male physicians	CV mortality	NEGATIVE	CVA Fatal MI Non-fatal MI	NEGATIVE POSITIVE POSITIVE
TPT Thrombosis Prevention Trial *Lancet* (1998)	5,085 men; 1,268 received ASA and placebo warfarin, 1,272 received double placebo	IHD	NEGATIVE	CVA Fatal MI Total mortality Non-fatal MI	NEGATIVE NEGATIVE NEGATIVE POSITIVE
WHS Women's Health Study *NEJM* (2005)	39,876 women	First major CV event	NEGATIVE	MI Fatal CVA CV mortality Non-fatal CVA	NEGATIVE NEGATIVE NEGATIVE POSITIVE

The BIG Picture

- Primary endpoints were negative in ALL studies in men and women.
- Although some studies had positive secondary endpoints, the validity of these endpoints is somewhat controversial when the primary endpoint is negative.

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Meta-analyses

Study	Studies Evaluated	Endpoints	Outcomes
BMJ (2002) Antithrombotic Trialists' Collaboration	287 primary & secondary prevention studies*	Non-fatal MI Non-fatal CVA CV mortality	POSITIVE POSITIVE POSITIVE

*Overall totals of these patients were disproportionate, with less than 12,000 (9%) of the 135,000 total patients evaluated having no previous CVD history or acute attacks.

The results of this study are difficult to assess because of the heterogeneity of the patient population and the well demonstrated significant benefit of aspirin therapy in treatment of known CAD and acute events.

Meta-analyses
BDT, PHS, TPT, HOT, WHS, PPP

Study	Endpoints	Outcomes	Adverse Bleeding Events	Study Facts
Am J Cardiol (2006) Bartolucci & Howard	CVA CV mortality CV events MI (Non-fatal)	NEGATIVE NEGATIVE POSITIVE POSITIVE	Not evaluated	Bayer funded
JAMA (2006) Berger, et. al	CV mortality CVA MI	NEGATIVE NEG/POS* NEG/POS*	Significantly increased	Sex-specific
Lancet (2009) Antithrombotic Trialists' Collaboration	CVA CV mortality CV events MI (Non-fatal)	NEGATIVE NEGATIVE POSITIVE POSITIVE	Highly significantly increased	Reduction in major coronary events and CVA did not differ between men and women. ‡

*Reduction in CVA was significant in women only, and reduction in MI was significant in men only.
‡Current speculation is that aspirin is more effective for MI prevention in men and ischemic CVA prevention in women.

Latest Meta-Analysis T2DM Pts

- 6 studies culled from 157 (10,117 pts.)
- No reduction in:
  - Major CV events
  - CV mortality
  - All cause mortality
- Reduction in MI in men but not women
- NNT – 500-1000 pt-yrs (To prevent 1 CV event)
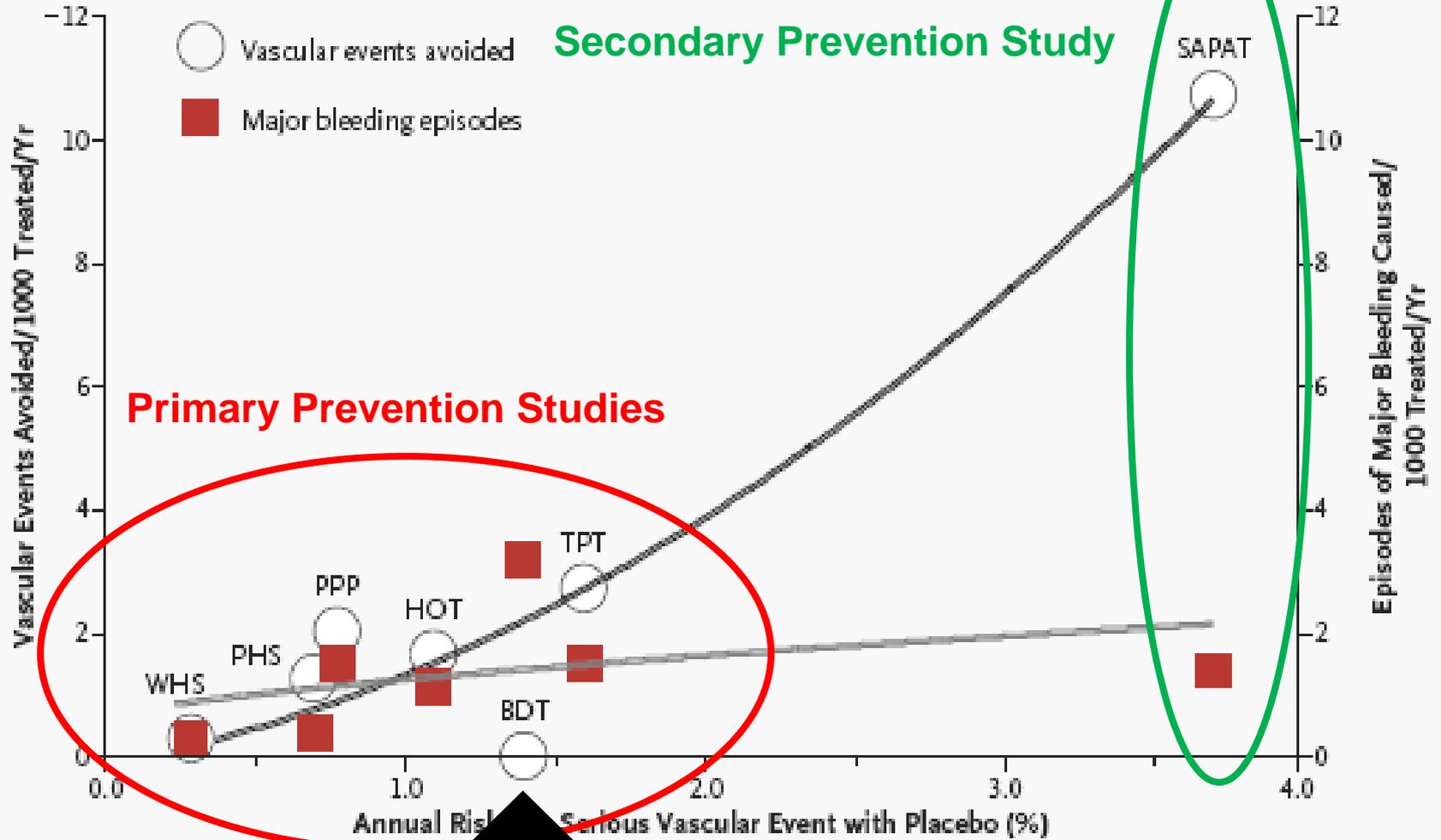- Harm – 1events per 500-1000 pt-yrs

De Barardis BMJ 2009;339:b4531

Consensus? No.

- **There are inconsistent and conflicting results across 3 meta-analyses of the same 6 studies.**
- **However, all demonstrated no reduction in CV mortality and significant increases in bleeds when evaluated.**
- **New Meta-analysis of DM only showed little benefit**

Adverse Events by Study

- HOT and PPP
  - Significant increases in non-fatal bleeds
- WHS
  - Significant increase in GI bleeds requiring transfusion, PUD, hematuria, easy bruising, and epistaxis
- PHS
  - Significant increase in hemorrhagic ulcers, increased frequency of necessary transfusions, bruising, GI bleeds, and epistaxis
- BDT
  - Significant increase in PUD and a trend toward increasing disabling and fatal hemorrhagic CVA
- TPT
  - Significant increases in hemorrhagic CVA
- The 2009 ATT meta-analysis noted that the main risk factors for CVD were also risk factors for bleeding.

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Many studies suggest that the benefits of low-dose aspirin for primary prevention may not appropriately outweigh the harms, even in high risk groups.

Petromo, et. al, *NEJM* (2005) 353 : 2373-2383

Conclusions

- Current studies do not *clearly* or *consistently* demonstrate a beneficial effect of low-dose aspirin for the primary prevention of CV events.
  - Primary endpoints have been negative in all individual studies of patients without known CVD, including persons with CAD risk equivalents.
  - Reduction in CV mortality has not been shown in any individual study or meta-analysis.
- Aspirin has been shown to increase the risk of serious adverse bleeding events such as hemorrhagic stroke, GI bleeds, and necessary transfusions.

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Discussion

- Questions?

- Comments?

- Concerns?