ASCEND: Is it the End of Aspirin for Primary Prevention in Diabetes?

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NYSCHP Annual Assembly
April 13, 2019

Disclosure Statement

No actual or potential conflicts of interest to disclose.

Lecture Objective

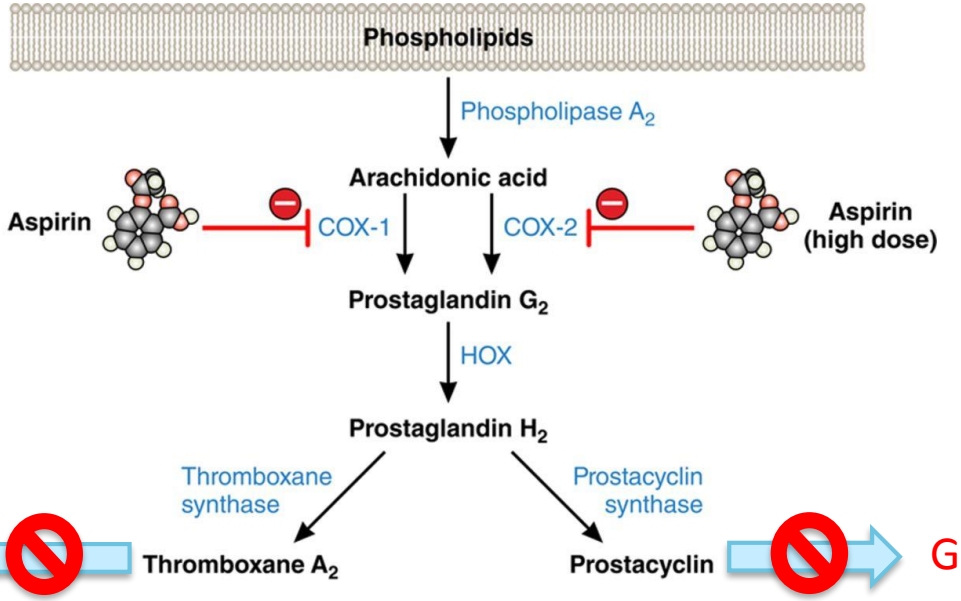
By the end of the presentation, learners will be able to:

- Discuss the recent literature evaluating the use of aspirin in primary prevention of cardiovascular events in patients with diabetes

Aspirin (acetylsalicylic acid)

Irreversibly blocks cyclooxygenase 1 and 2

- Low-dose aspirin (typically 75-162 mg) results in inhibition of TXA_2 and prostacyclin synthesis
  - Inhibits platelet aggregation, vasoconstriction and proliferation of vascular smooth-muscle cells
  - Increased risk of GI bleed with long-term use



TXA2: thromboxane A2; GI: gastrointestinal

Circulation. 2016; 134:1579–1594.

Background

T2DM associated with ↑ CV risk

- Approximately 2 – 4x risk of coronary heart disease, ischemic stroke, and mortality[1]

Aspirin and CV Disease

- Low-dose aspirin use well established and strongly recommended for secondary prevention of CV and cerebrovascular events
- Low-dose aspirin use for primary prevention remains controversial[2-4]
  - Clinical practice guidelines remain inconsistent

1. *Lancet*. 2010 Jun 26; 375(9733):2215-22.
2. *Lancet*. 2009 May 30;373(9678):1849-60.
3. *JAMA*. 2014; 312:2510-2520.
4. *Am J Med*. 2016; 129:e35-e36.

T2DM: type 2 diabetes mellitus; CV: cardiovascular

A Study of Cardiovascular Events iN Diabetes (ASCEND)

Study Objective

To assess the efficacy and safety of aspirin compared to placebo in people who have diabetes without any history of CV disease

Study Design

Multicenter, randomized, two-by-two factorial, double-blind, placebo controlled trial

- Enteric coated aspirin 100 mg vs placebo
- Omega-3 fatty acid 1 g capsule vs placebo*

Enrollment period: June 2005 – July 2011

Setting: United Kingdom

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* Results reported separately

Study Population

Inclusion Criteria

- Men and women ≥ 40 years of age
- Diagnosis of type 1 or 2 diabetes
- Absence of baseline CV disease
  - MI
  - Angina
  - Revascularization procedure
  - Stroke
  - Transient ischemic attack

Exclusion Criteria

- Clear indication for aspirin
- Presence of clinically significant co
  trial regimen for at least 5 years
- Contraindication to aspirin
  - High risk of bleed
  - Active hepatic disease
  - Use of warfarin or other anticoagulants
  - History of aspirin allergy

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MI: myocardial infarction; TIA: Transient ischemic attack

Outcomes

Primary Efficacy Outcome

First SVE, defined as composite of nonfatal MI, stroke, TIA, or vascular death

Primary Safety Outcome

First major bleed, defined as composite of intracranial hemorrhage, sight-threatening bleed in eye, GI bleed, or any other bleed

Secondary Outcome

GI related cancers

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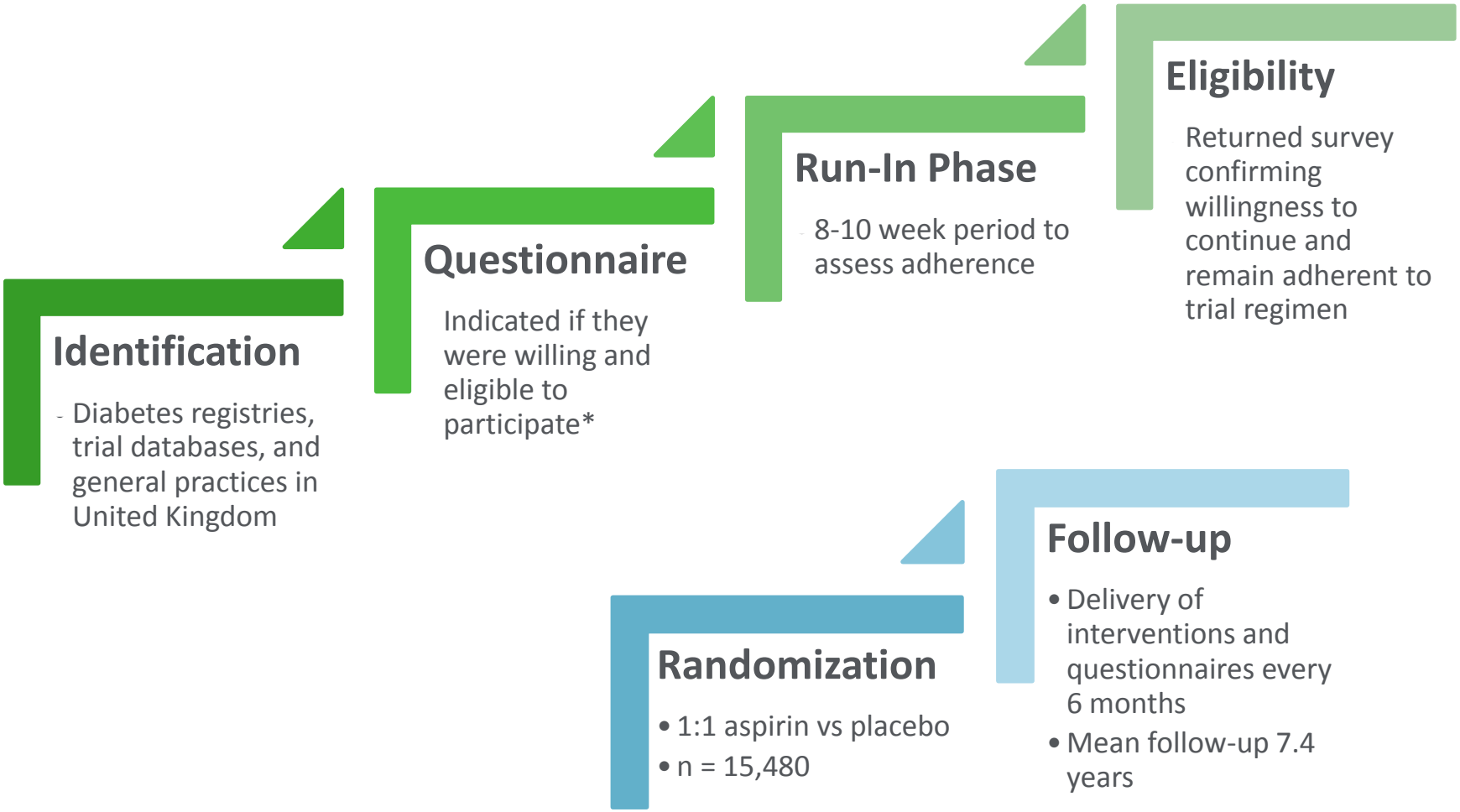
SVE: serious vascular event

Patient Enrollment and Follow-up



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* Family doctor informed of potential participation. Reqested to submit blood/urine samples and vitals

Baseline Characteristics (n= 15,480)

	Aspirin (n=7740)	Placebo (n=7740)
Age, years	63.2±9.2	63.3±9.2
Male sex (%)	62.6%	62.5%
White race (%)	96.5%	96.5%
BMI, kg/m^2	30.8±6.2	30.6±6
Type 2 diabetes (%)	94.1%	94.1%
Duration of diabetes (yea median [IQR]		3-13]
Hypertension (%)		.6%
Statin Use (%)		.9%
High Vascular Risk* (%)		.4%
Reported as mean ± SD unless c * Calculated ≥ 10% 5 year risk o		

Run-in phase data	
A1c (%) n = 9813	
• <7.5%	• 6824 (69%)
eGFR (ml/min/1.73m^2) n = 9815	
• ≥90	• 4523 (46%)
UACR (mg/mmol) n = 9774	
• ≥ 30	• 160 (2%)

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eGFR: estimated glomerular filtration rate; UACR: urinary albumin/creatinine ratio

Outcomes

Primary Efficacy Outcome

	Aspirin (n=7740)	Placebo (n=7740)	HR (95% CI)	p-value
First SVE	658 (8.5%)	743 (9.6%)	0.88 (0.79-0.97)	p = 0.01

Primary Safety Outcome

	Aspirin (n=7740)	Placebo (n=7740)	RR (95% CI)	p-value
First major bleed	314 (4.1%)	245 (3.2%)	1.29 (1.09-1.52)	p = 0.003
Intracranial	55 (0.7%)	45 (0.6%)	1.22 (0.82-1.81)	
Ocular	57 (0.7%)	64 (0.8%)	0.89 (0.62-1.27)	
GI	137 (1.8%)	101 (1.3%)	1.36 (1.05-1.75)	

Secondary Outcome

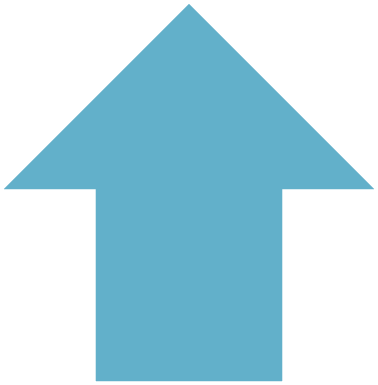
	Aspirin (n=7740)	Placebo (n=7740)	RR (95% CI)	p-value
Gastrointestinal tract cancer	157 (2.0)	158 (2.0)	0.99 (0.80-1.24)	p = 0.88
Hepatobiliary and pancreatic cancers	87 (1.1)	82 (1.1)	1.06 (0.78-1.43)	

Authors' Conclusion

- Aspirin significantly reduced risk of SVE and also significantly increased the risk of major bleeding
  - 91 NNT vs 112 NNH
- No group in which the benefits clearly outweighed risks
- Aspirin did not reduce the risk of GI related cancers
  - Longer follow-up warranted

NNT: number needed to treat; NNH: number needed to harm

Study Critique



Strengths

- Long follow-up
- Large trial
- Randomized, blinded design
- Improved assessment of aspirin

Limitations

- Intention-to-treat analysis underestimation
- 100 mg dosing
- Relationship between PPI use and GI bleed
- Lack of statistical power to assess cancer risk
- Generalizability of study participants

Recommendations for Clinical Practice

2018 American Diabetes Association Guideline	2019 American Diabetes Association Guideline	2019 ACC/AHA Guideline on Primary Prevention Of CV Disease
Consider low-dose aspirin if no ↑ risk of bleed in patients with type 1 or type 2 diabetes aged ≥ 50 years with at least **1 additional risk factor**: • Hypertension • Hyperlipidemia • Smoking • Albuminuria • Family history of premature CV events (LOE C)	Aspirin (75–162 mg/day) **may be considered** primary prevention in those with diabetes at increased CV risk, **after a discussion with patient on benefits vs increased bleeding risk**." (LOE C)	Aspirin (75-100 mg/day) **might be considered** for primary prevention of ASCVD among **select adults 40-70 years of age** at **higher ASCVD risk** but **not at increased bleeding risk**. (COR IIb; LOE A)

COR: class of recommendation; LOE: level of evidence

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J Am Coll Cardiol. 2019;CIR0000000000000678.
Diabetes Care. 2019; 42(Supplement 1):S103-S123.

Questions?

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