Diabetes and Hypertension Project ECHO* Clinic

*ECHO: Extension of Community Healthcare Outcomes

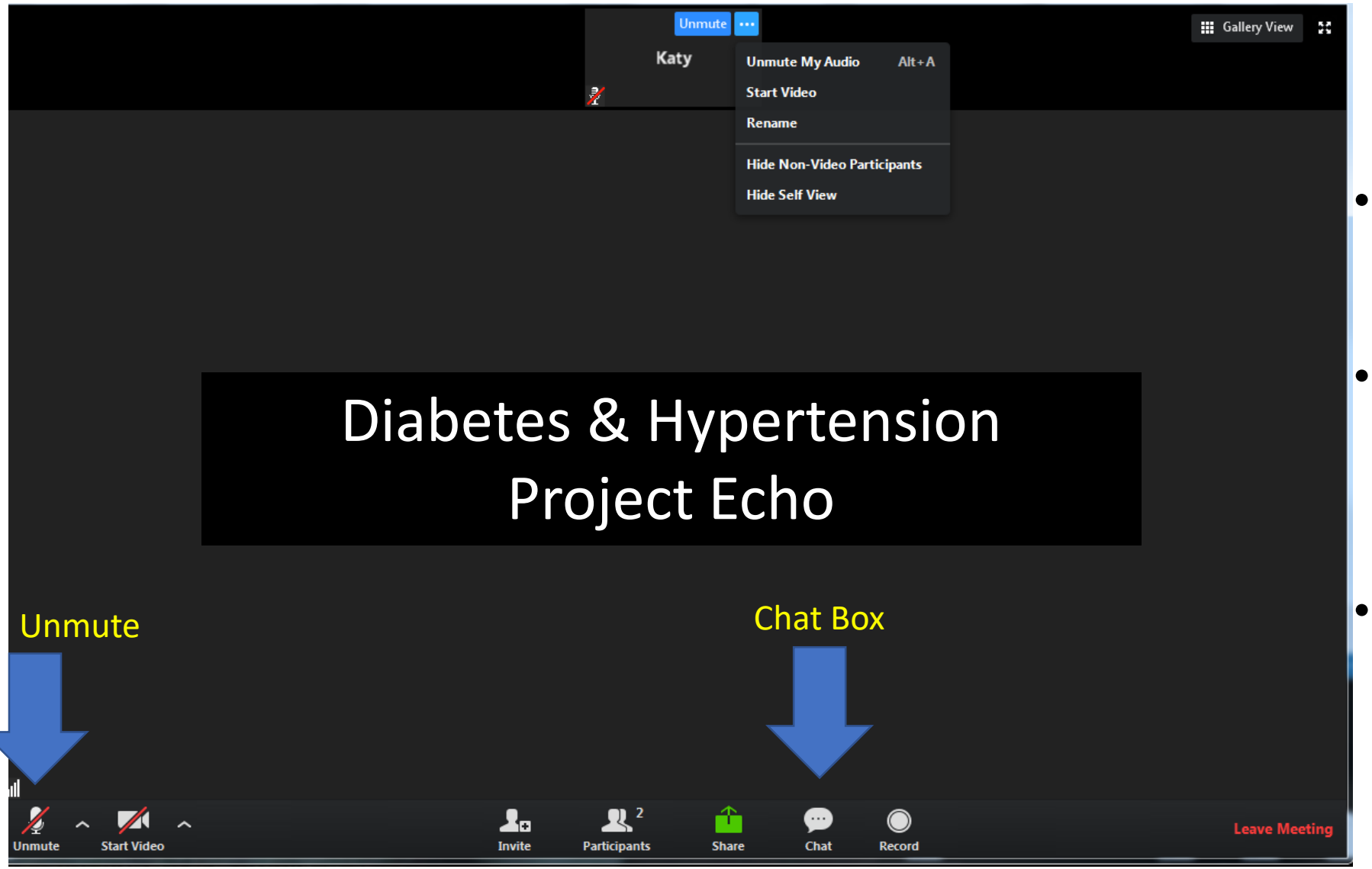
Feb. 10, 2022

Before we begin:

- Rename your Zoom screen with your name and organization
- Claim CE: text 25391-25389 to 804-625-4041
  - Go to **vcuhealth.org/echodmhtn** for instructions on creating your account

The Diabetes and Hypertension ECHO is made possible by funding through CDC Cooperative Agreement NU58DP006620-InnoVAte.

Zoom Reminders



- You are all on mute. Please unmute to talk.
- If joining by telephone audio only, press *6 to mute and unmute.
- Use the chat function to speak with our team or ask questions.

Helpful Reminders

- Please feel free to eat your lunch or step away briefly if needed
- We are recording and can share sessions upon request
  - Each session's slides are available on www.vcuhealth.org/echodmhtn
- Please **do not share any protected health information** in your discussion or the chat box
- Project ECHO operates on the "All Teach, All Learn" model
  - Feel free to ask questions in the chat or unmute to ask questions at designated times
  - We're all here to learn from each other and value each person's input and expertise!

VCU Health Diabetes & Hypertension ECHO Clinics

VCU Hub Team	
Principal Investigator	Dave Dixon, PharmD
Administrative Medical Director ECHO Hub	Vimal Mishra, MD, MMCi
Clinical Experts	Niraj Kothari, MD Trang Le, MD
Project Coordinator/IT Support	Madeleine Wagner

- One-hour ECHO clinics on 2nd Thursdays
- Every ECHO clinic includes a didactic presentation followed by case discussions
- Website: www.vcuhealth.org/echodmhtn
  - Directions for claiming CE can be found here
  - You have up to six days after our session to claim CE by texting **25391-25389** to **804-625-4041**

Disclosures

Trang Le, M.D., has no financial conflicts of interest to disclose.

Niraj Kothari, M.D., has no financial conflicts of interest to disclose.

There is no commercial or in-kind support for this activity.

Aspirin Therapy in Diabetes

Objectives:

- Review recommendations for use of aspirin for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD)
- Discus controversies aspirin use for primary prevention in patients with diabetes, hypertension, and chronic kidney disease

10. Cardiovascular Disease and Risk Management: *Standards of Medical Care in Diabetes—2022*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2022;45(Suppl. 1):S144–S174 | https://doi.org/10.2337/dc22-S010

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc22-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc22-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

Secondary Prevention

- Recommendation 10.34: Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and atherosclerotic cardiovascular disease
- Aspirin as been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke and is *strongly recommended*.

Primary Prevention:

- Recommendation 10.39: Aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding.

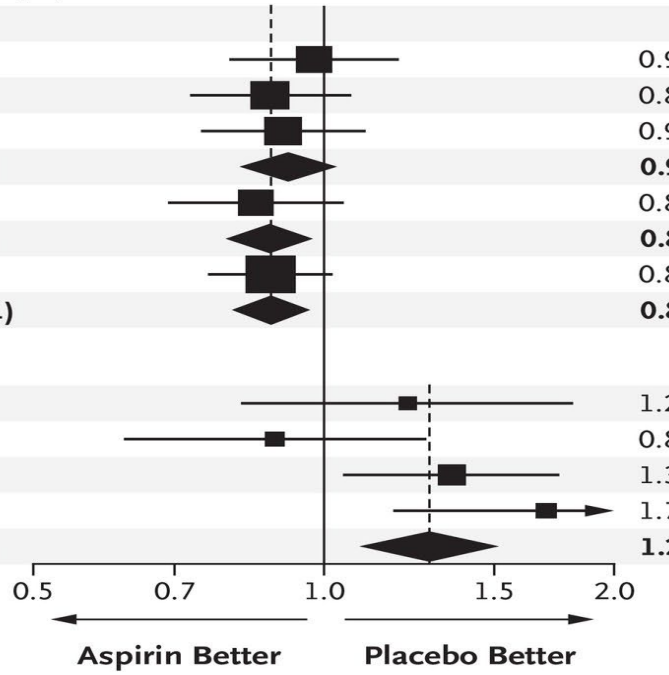
Primary Prevention

- ASCEND (A Study of Cardiovascular Events iN Diabetes) trial randomized 15,480 patients with diabetes but no evident cardiovascular disease to aspirin 100 mg daily or placebo.
- Primary efficacy end point : vascular death, MI, or stroke or transient ischemic attack.
- Primary safety outcome : major bleeding (i.e., intracranial hemorrhage, sight threatening bleeding in the eye, GI bleeding, or other serious bleeding).
- mean follow-up of 7.4 years; 12% *reduction* in the primary efficacy end point (8.5% vs. 9.6%; *P* = 0.01).
- major bleeding *increased* from 3.2% to 4.1% in the aspirin group (rate ratio 1.29; *P*=0.003), with most of the excess being GI bleeding and other extracranial bleeding.

The ASCEND Study Collaborative Group. N Engl J Med 2018;379:1529-1539

Effect of Assignment to Aspirin Group on Components of Serious Vascular Events, the Combined Outcome of Serious Vascular Event or Revascularization, and Major Bleeding and Its Components.

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



The ASCEND Study Collaborative Group. N Engl J Med 2018;379:1529-1539

Other trials of aspirin for primary prevention

- ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events] patients *without* diabetes (n=12,546) 60 months follow-up,
  - primary end point occurred in 4.29% vs. 4.48% of patients in the aspirin versus placebo groups (HR 0.96(95%CI 0.81-1.13], p=0.60
  - GI bleeding events (characterized as mild) occurred in 0.97% of patients in the aspirin group vs. 0.46% in the placebo group (HR 2.11 [95% CI 1.36-32.8), P<0.0007

Lancet 2018;392:1036–1046

Other trials of aspirin for primary prevention

- ASPREE [Aspirin in Reducing Events in the Elderly]) (n=19,114, 11% with diabetes), found no benefit of aspirin on the primary efficacy end point (fatal CHD, MI, stroke, or hospitalization for heart failure) and an increased risk of bleeding, median of 4.7 years of follow-up
  - rates per 1,000 person-years were 10.7 vs. 11.3 events in aspirin vs. placebo groups (HR 0.95 [95% CI 0.83–1.08]).
  - rate of major hemorrhage per 1,000 person-years was 8.6 events vs. 6.2 events, respectively (HR 1.38 [95% CI 1.18–1.62], p<0.001

N Engl J Med 2018;379:1509–1518

Primary Prevention

- Aspirin appears to have a modest effect on ischemic vascular events, with the absolute decrease in events depending on the underlying ASCVD risk
- The main adverse effect is an increased risk of gastrointestinal bleeding.
- However, for adults with ASCVD risk >1% per year, the number of ASCVD events prevented will be similar to the number of episodes of bleeding induced
- These complications do not have equal effects on long-term health

Primary Prevention

Recommendations for using aspirin as primary prevention include both men and women aged ≥50 years with diabetes and at least one additional major risk factor:

- family history of premature ASCVD,
- hypertension,
- dyslipidemia,
- smoking, or
- Chronic kidney disease/albuminuria) who are not at increased risk of bleeding (e.g., older age, anemia, renal disease)

Primary prevention

- Patient age >70 years, with or without diabetes, the balance appears to have greater risk than benefit
- Thus, for primary prevention, the use of aspirin needs to be carefully considered and may generally not be recommended.
- Aspirin may be considered in the context of high cardiovascular risk with low bleeding risk, but generally not in older adults.
- Aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.

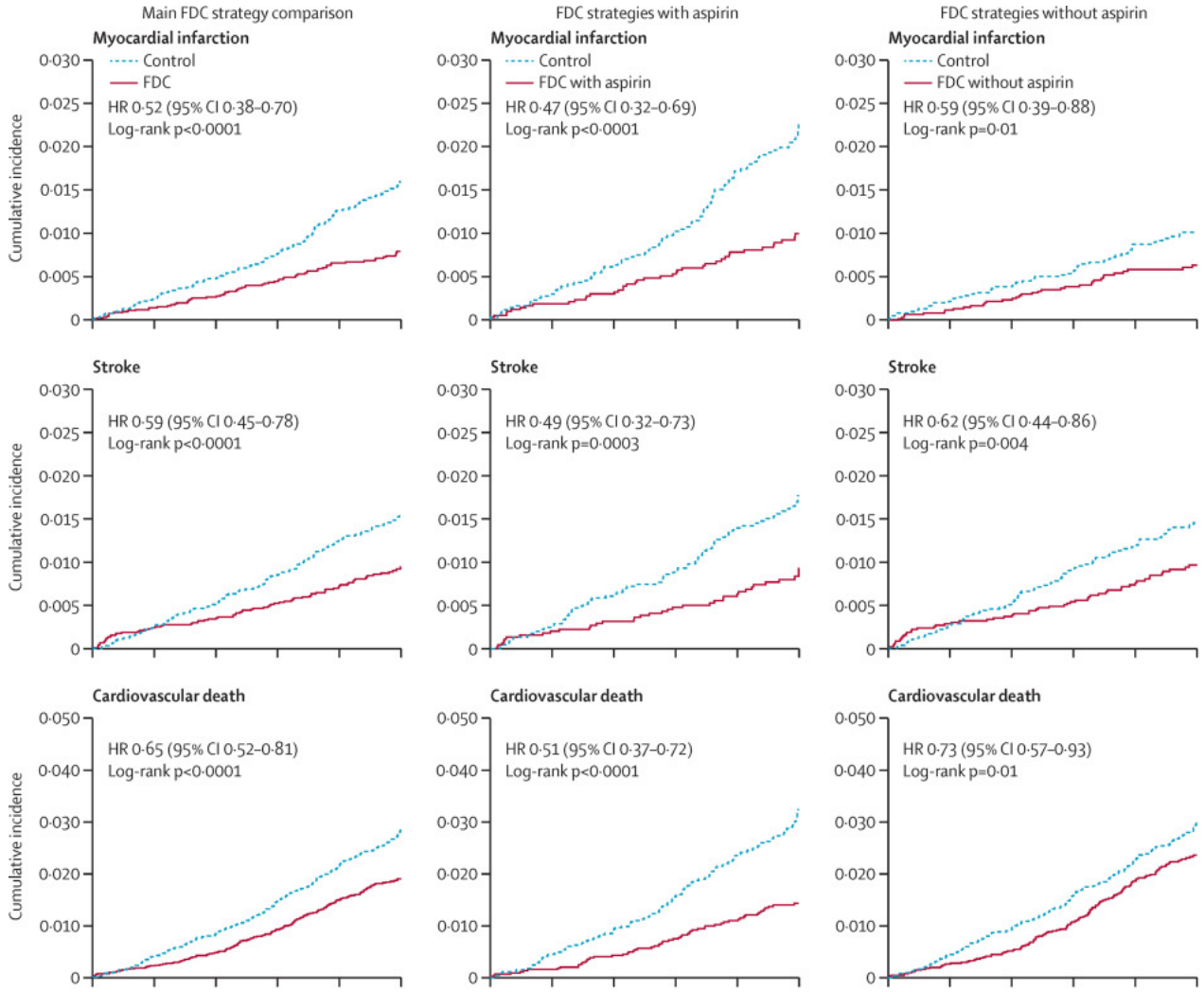
Aspirin Use in People <50 Years of Age

- Aspirin is not recommended for those at low risk of ASCVD (such as men and women aged <50 years with diabetes with no other major ASCVD risk factors) as the low benefit is likely to be outweighed by the risks of bleeding.
- Clinical judgment should be used for those at intermediate risk (younger patients with one or more risk factors or older patients with no risk factors) until further research is available.
- Patients' willingness to undergo long-term aspirin therapy should also be considered

Other factors to consider

- A 2019 joint guidelines by the European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) recommend that 75-100 mg/day of aspirin "may be considered" for primary prevention in the absence of clear contraindications in people with type 2 diabetes at high or very high cardiovascular risk, but not in those at moderate risk.
- ESC/EASD advises that when low-dose aspirin is used, proton pump inhibitors (PPIs) be considered to prevent GI bleeding

Fixed-dose combination therapies with and without aspirin for primary prevention of cardiovascular disease



- individual patient data meta-analysis (n= 18,162, 40% with diabetes)
- randomized to fixed-dose combinations of a statin + 2 or more antihypertensive drugs vs controls (placebo or usual care) +/- aspirin
- aspirin added significant benefit compared to the fixed-dose combination alone, with a risk reduction of 47% for theprimary endpoint (time to first occurrence of a composite of cardiovascular death, MI, stroke, or arterial revascularization)
- no significant increased major bleeding risk with aspirin
- slight increase in GI bleeding, from 0.2% to 0.4%

Lancet 2021 Sep 25;398(10306):1133-1146.

Aspirin Dosing

- Average daily dosages used in most clinical trials involving patients with diabetes ranged from 50 mg to 650 mg but were mostly in the range of 100–325 mg/day.
- Little evidence to support any specific dose, but using the lowest possible dose may help to reduce side effects

Pregnancy

- Recommendation 15.19 Women with type 1 or type 2 diabetes should be prescribed low-dose aspirin 100–150 mg/day starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia.
- A dosage of 162 mg/day may be acceptable
- currently, in the U.S., low-dose aspirin is available in 81-mg tablets.

Pregnancy

- Diabetes in pregnancy is associated with an increased risk of preeclampsia
- The U.S. Preventive Services Task Force recommends the use of low-dose aspirin (81 mg/day) as a preventive medication at 12 weeks of gestation in women at high risk for preeclampsia
- However, low-dose aspirin <100 mg may not be effective in reducing preeclampsia
- Low-dose aspirin >100 mg is required
- insufficient data regarding the benefits of aspirin in women with preexisting diabetes
- ? long-term effects of prenatal aspirin exposure on offspring

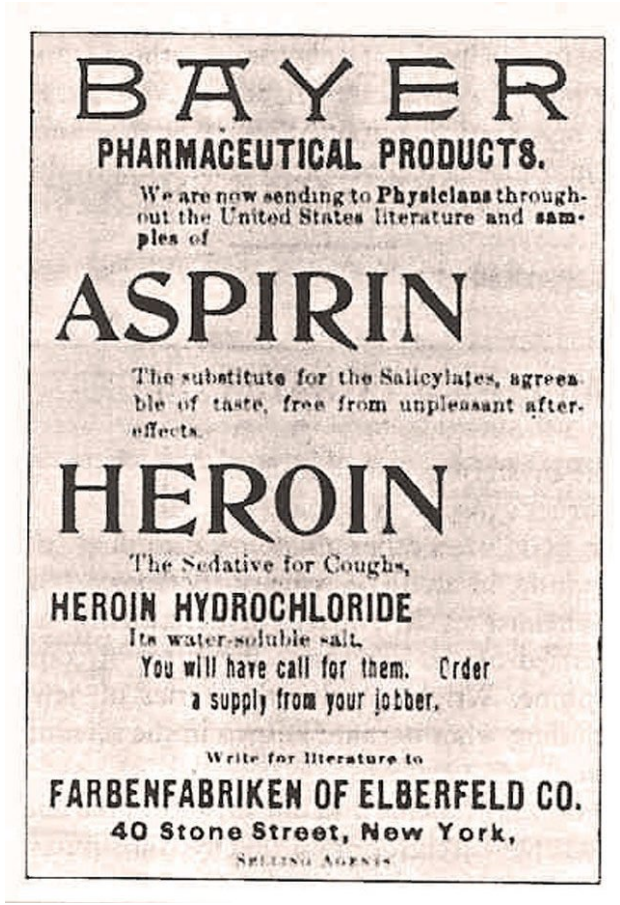
AmJ Obstet Gynecol 2018;218:287–293.e1110.
N Engl J Med 2017;377:613–622
Lancet 2020;395:285–293

Summary:

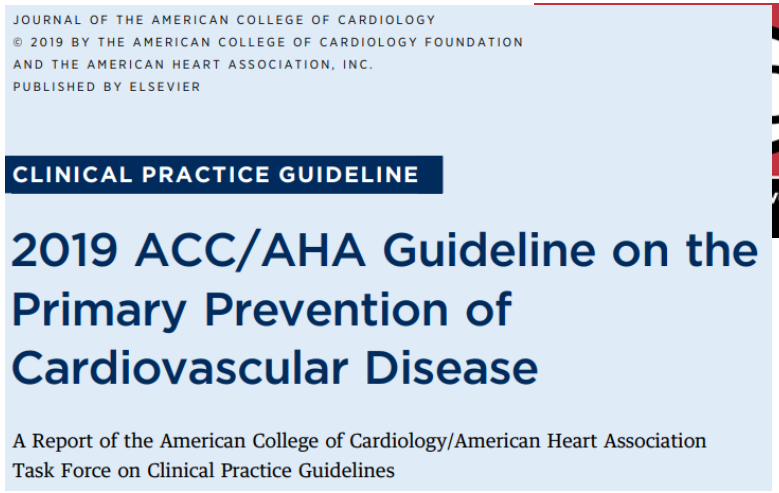
- Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention) and is strongly recommended.
- In primary prevention, however, among patients with no previous cardiovascular events, its net benefit is more controversial – consider age and comorbidities
- Pregnancy

Should we prescribe aspirin for HTN/CKD patients?

- Conventional wisdom was that nearly every patient could benefit from aspirin therapy
- More recent data have presented more controversy



Aspirin use in HTN patients



- Particularly beneficial for secondary prevention
- ASA role in primary prevention is still less clear, as mentioned previously
- Primary adverse event: bleeding
- Would assess overall cardiovascular risk—low risk patients unlikely to benefit from ASA; patients over 70 unlikely to benefit
- Intermediate and high CV risk patients may benefit from low dose ASA after assessment of bleeding risk

Don’t NSAIDs affect BP control?

- ASA is not associated with impaired BP control, in contrast to other NSAIDs
- NSAID-induced HTN is likely caused by COX-2 inhibition-–ASA (especially low dose) does not inhibit COX-2

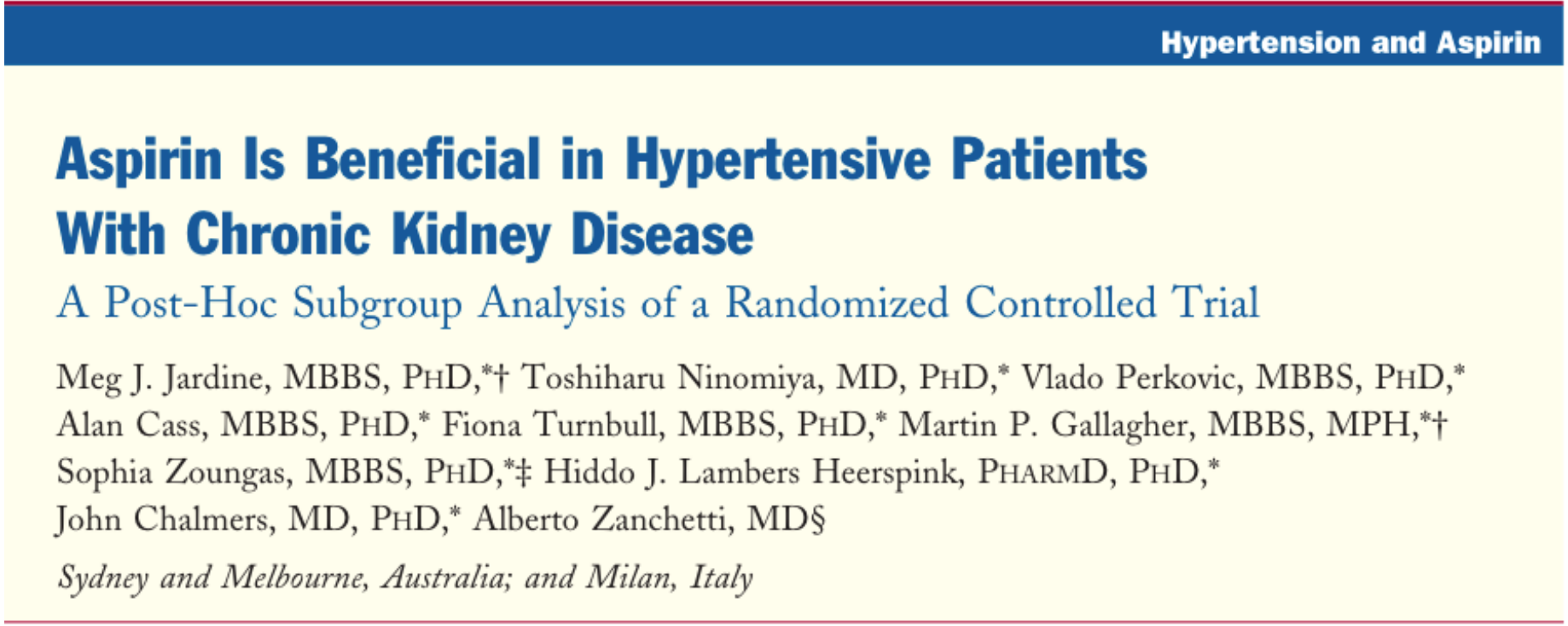
Low-dose aspirin does not interfere with the blood pressure-lowering effects of antihypertensive therapy.

Alberto Zanchetti[a], Lennart Hansson[b], Gastone Leonetti[a], Karl-Heinz Rahn[c], Luis Ruilope[d], Ingrid Warnold[e] and Hans Wedel[f]

- Review of data from the Hypertension Optimal Treatment (HOT) study demonstrated no difference in achievable SBP/DBP with ASA 75mg daily

More controversy: ASA use in CKD patients

- CV risk calculators usually do not take CKD into account
- Pathophysiologic differences may explain decreased/lack of benefit for ASA as primary prevention in CKD patients
- Huge problem--cardiovascular disease is the leading cause of death in CKD patients (~50%)
  - 4.6% of worldwide deaths in 2017
- Disordered platelet function, prolonged bleeding time



Aspirin Is Beneficial in Hypertensive Patients With Chronic Kidney Disease

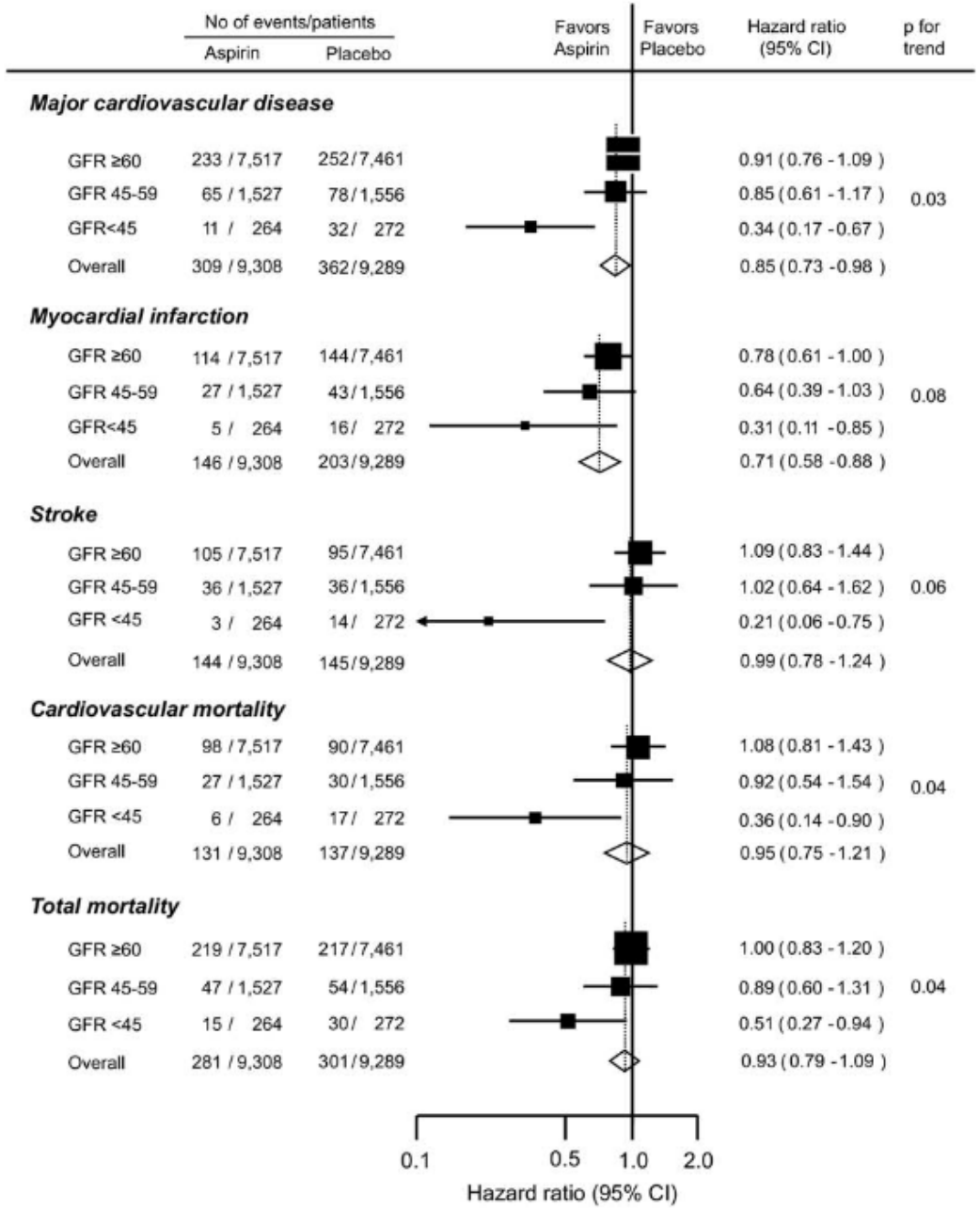
A Post-Hoc Subgroup Analysis of a Randomized Controlled Trial

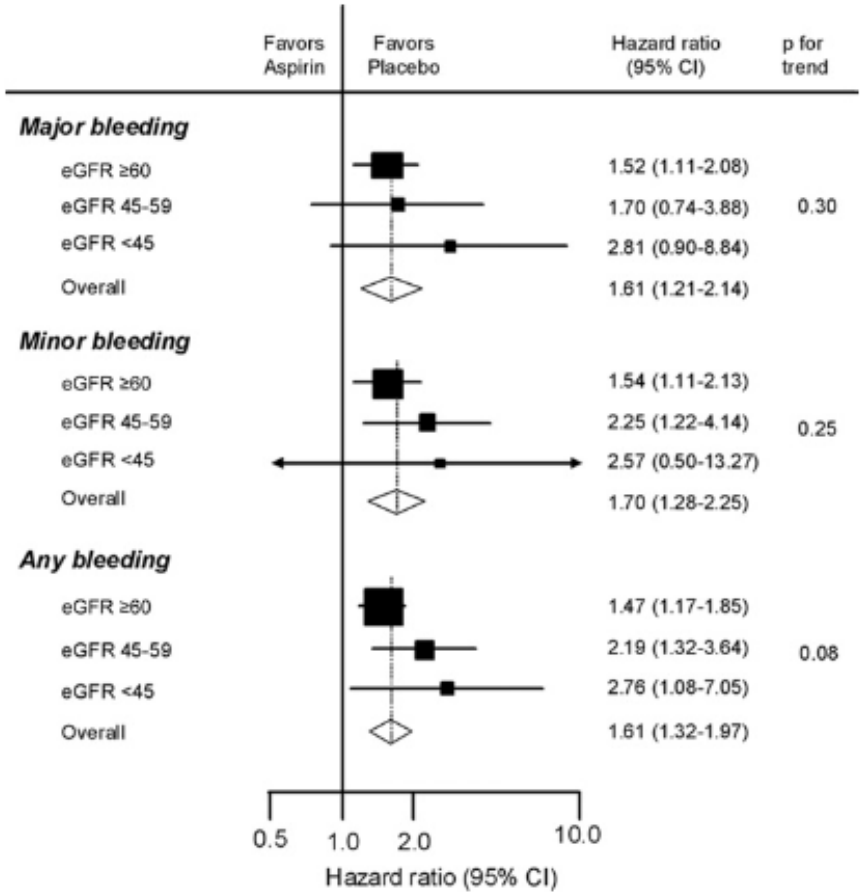
Meg J. Jardine, MBBS, PHD,*† Toshiharu Ninomiya, MD, PHD,* Vlado Perkovic, MBBS, PHD,* Alan Cass, MBBS, PHD,* Fiona Turnbull, MBBS, PHD,* Martin P. Gallagher, MBBS, MPH,*† Sophia Zoungas, MBBS, PHD,*‡ Hiddo J. Lambers Heerspink, PHARMD, PHD,* John Chalmers, MD, PHD,* Alberto Zanchetti, MD§

Sydney and Melbourne, Australia; and Milan, Italy

- Compared ~18000 patients with CKD between ASA 75mg and placebo
- Primary endpoint: major cardiovascular events
- Secondary endpoints: MI, stroke, CV mortality, total mortality, death due to kidney failure, change in eGFR

Results


No of events/patients
Aspirin
Placebo
Favors Aspirin
Favors Placebo
Hazard ratio (95% CI)
p for trend
Major cardiovascular disease
GFR ≥60 233 / 7,517 252 / 7,461 0.91 (0.76 - 1.09)
GFR 45-59 65 / 1,527 78 / 1,556 0.85 (0.61 - 1.17) 0.03
GFR<45 11 / 264 32 / 272 0.34 (0.17 - 0.67)
Overall 309 / 9,308 362 / 9,289 0.85 (0.73 - 0.98)
Myocardial infarction
GFR ≥60 114 / 7,517 144 / 7,461 0.78 (0.61 - 1.00)
GFR 45-59 27 / 1,527 43 / 1,556 0.64 (0.39 - 1.03) 0.08
GFR<45 5 / 264 16 / 272 0.31 (0.11 - 0.85)
Overall 146 / 9,308 203 / 9,289 0.71 (0.58 - 0.88)
Stroke
GFR ≥60 105 / 7,517 95 / 7,461 1.09 (0.83 - 1.44)
GFR 45-59 36 / 1,527 36 / 1,556 1.02 (0.64 - 1.62) 0.06
GFR <45 3 / 264 14 / 272 0.21 (0.06 - 0.75)
Overall 144 / 9,308 145 / 9,289 0.99 (0.78 - 1.24)
Cardiovascular mortality
GFR ≥60 98 / 7,517 90 / 7,461 1.08 (0.81 - 1.43)
GFR 45-59 27 / 1,527 30 / 1,556 0.92 (0.54 - 1.54) 0.04
GFR <45 6 / 264 17 / 272 0.36 (0.14 - 0.90)
Overall 131 / 9,308 137 / 9,289 0.95 (0.75 - 1.21)
Total mortality
GFR ≥60 219 / 7,517 217 / 7,461 1.00 (0.83 - 1.20)
GFR 45-59 47 / 1,527 54 / 1,556 0.89 (0.60 - 1.31) 0.04
GFR <45 15 / 264 30 / 272 0.51 (0.27 - 0.94)
Overall 281 / 9,308 301 / 9,289 0.93 (0.79 - 1.09)
0.1
0.5
1.0
2.0
Hazard ratio (95% CI)


Favors Aspirin
Favors Placebo
Hazard ratio (95% CI)
p for trend
Major bleeding
eGFR ≥60 1.52 (1.11-2.08)
eGFR 45-59 1.70 (0.74-3.88) 0.30
eGFR <45 2.81 (0.90-8.84)
Overall 1.61 (1.21-2.14)
Minor bleeding
eGFR ≥60 1.54 (1.11-2.13)
eGFR 45-59 2.25 (1.22-4.14) 0.25
eGFR <45 2.57 (0.50-13.27)
Overall 1.70 (1.28-2.25)
Any bleeding
eGFR ≥60 1.47 (1.17-1.85)
eGFR 45-59 2.19 (1.32-3.64) 0.08
eGFR <45 2.76 (1.08-7.05)
Overall 1.61 (1.32-1.97)
0.5
1.0
2.0
10.0
Hazard ratio (95% CI)

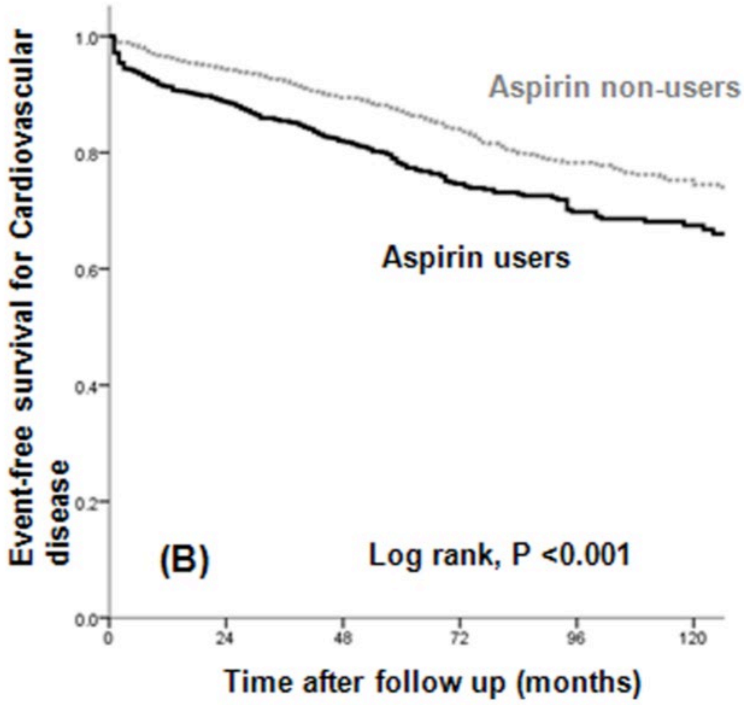
Low-Dose Aspirin for Prevention of Cardiovascular Disease in Patients with Chronic Kidney Disease

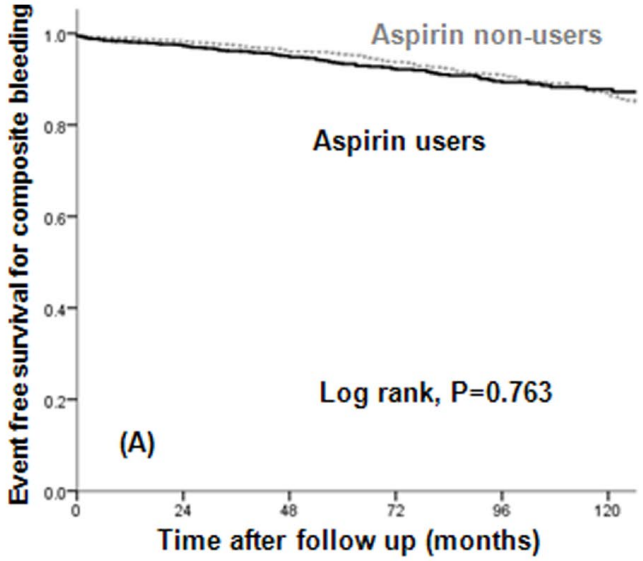
Ae Jin Kim[1], Hye Jin Lim[1], Han Ro[1,2], Kwang-Pil Ko[3], Song Yi Han[1], Jae Hyun Chang[1,2], Hyun Hee Lee[1,2], Wookyung Chung[1,2], Ji Yong Jung[1,2]*

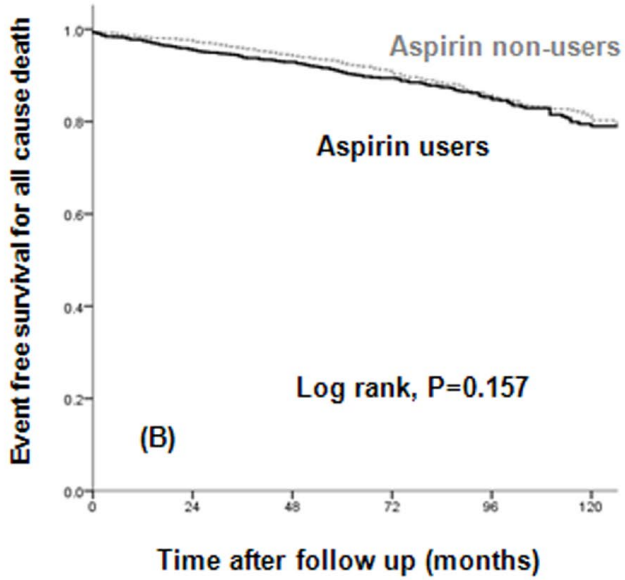
1 Division of Nephrology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea, **2** Gachon University School of Medicine, Incheon, Korea, **3** Department of Preventive Medicine, Gachon University School of Medicine, Incheon, Korea

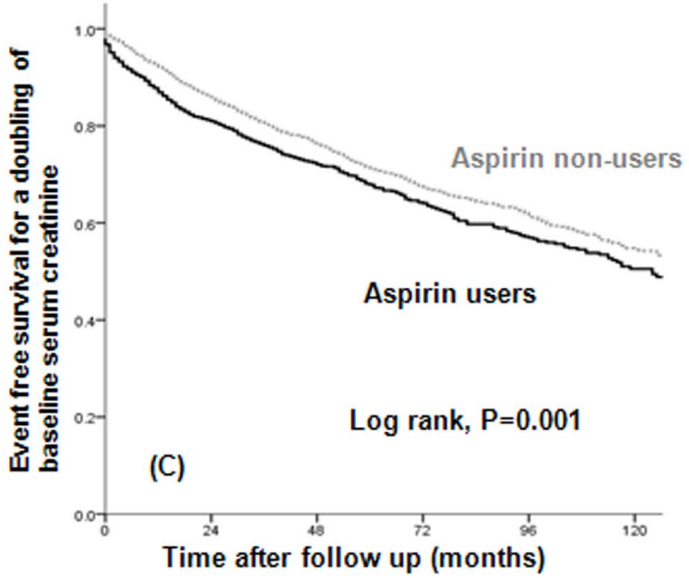
- Compared ~3600 patients with CKD, half receiving 100mg/day ASA and half without ASA
- Primary endpoint: development of atherosclerotic CVD
- Secondary endpoints: death from any cause, bleeding event, doubling of serum Cr, renal death

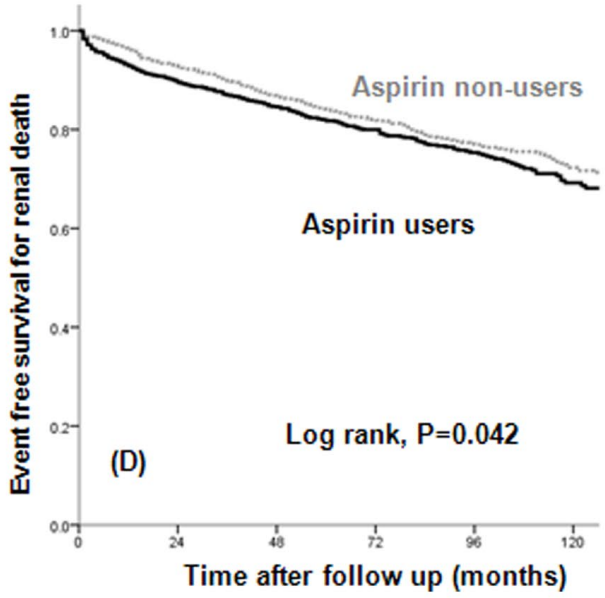
Results


Event-free survival for Cardiovascular disease
Aspirin non-users
Aspirin users
(B)
Log rank, P <0.001
Time after follow up (months)


Event free survival for composite bleeding
Aspirin non-users
Aspirin users
Log rank, P=0.763
(A)
Time after follow up (months)


Event free survival for all cause death
Aspirin non-users
Aspirin users
Log rank, P=0.157
(B)
Time after follow up (months)


Event free survival for a doubling of baseline serum creatinine
Aspirin non-users
Aspirin users
Log rank, P=0.001
(C)
Time after follow up (months)


Event free survival for renal death
Aspirin non-users
Aspirin users
Log rank, P=0.042
(D)
Time after follow up (months)

Aspirin for Primary Prevention of Cardiovascular Disease and Renal Disease Progression in Chronic Kidney Disease Patients: a Multicenter Randomized Clinical Trial (AASER Study)

Marian Goicoechea[1,2] · Soledad García de Vinuesa[1,2] · Borja Quiroga[3] · Eduardo Verde[1,2] · Carmen Bernis[3] · Enrique Morales[2,4] · Gema Fernández-Juárez[2,5] · Patricia de Sequera[6] · Ursula Verdalles[1,2] · Ramón Delgado[7] · Alberto Torres[8] · David Arroyo[9] · Soraya Abad[1,2] · Alberto Ortiz[2,10] · José Luño[1,2]

- Small RCT comparing ASA vs usual therapy in ~100 patients with CKD
- No significant differences in the primary endpoint (CV events + HF or PAD) but did reduce risk of coronary events and renal events

Where do we go from here?

- ASA is not strongly recommended in CKD patients, but low dose ASA could be considered in a robust patient with substantial CKD and low bleeding risk
- Aspirin to Target Arterial Events in Chronic Kidney Disease (ATTACK) trial is recruiting participants
  - ASA as primary prevention of CV events
  - Plans to enroll ~25,000 patients and finish by 2025

Case Study #1

- **48yo M with CKD presents for initial evaluation**
- **Feels fine, just notes dark stools**
- **Meds: amlodipine 10mg daily, aspirin 81mg, naproxen 200mg BID**
- **BP 165/90**
- **Na 140 K 4.0 Cl 110 CO2 24 BUN 38 Cr 2.4**

Any clarifying questions?

Case Study #2

43 year old lady with T2DM diagnosed 2013, hyperlipidemia, HTN, Class II obesity, sarcoidosis, lost to follow up > 2 years, presents to re-establish care

- POCT A1c 12.0%, previously 10% then 7% (preparing for elective hysterectomy)
- current diabetes regimen
  - Trulicity: 1.5mg weekly on Sundays - tolerating well
  - Stopped metformin due to intolerable GI upset, does not wish to reattempt
  - Lantus 30 units in AM, misses 2-3 days per week
- Intermittently on prednisone 10 or 20mg for sarcoidosis, skips some days if she is feeling well
- Review of BGs: none for review, patient reports no hypoglycemia, many values in the 200s, as high as 300s when on higher doses of prednisone for sarcoid

Any clarifying questions?

Case Studies

- Anyone can submit cases: www.vcuhealth.org/echodmhtn
- Receive feedback from participants and content experts
- Earn **$150** for submitting and presenting

Provide Feedback

www.vcuhealth.org/echodmhtn

- Feedback
  - Overall feedback related to session content and flow?
  - Ideas for guest speakers?

Access Your Evaluation

vcuhealth.org/services/telehealth/for-providers/education/diabetes-and-hypertension-project-echo

For Providers

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  - VCU Health Palliative Care ECHO
  - Virginia Opioid Addiction ECHO
  - Virginia Sickle Cell Disease ECHO

Diabetes and Hypertension Project ECHO

Welcome to the Diabetes and Hypertension Extension for Community Health Outcomes or ECHO, a virtual network of multidisciplinary diabetes and hypertension experts. An ECHO model connects professionals with each other in real-time collaborative virtual sessions on Zoom. Participants present de-identified cases to one another, share resources, connect to each other, and grow in their expertise. This ECHO will address practice level issues and solutions related to managing complex patients with difficult to control diabetes and hypertension. Register now for an ECHO Session!

Network, Participate and Present

- Engage in a collaborative community with your peers.
- Listen, learn and discuss informational and case presentations in real-time.
- Take the opportunity to submit your de-identified case study for feedback from a team of specialists for diabetes and hypertension.
- Provide valuable feedback.
- Claim CE credit by texting in attendance.

Benefits

VCU Diabetes & Hypertension Project ECHO Clinics

2nd Thursdays — 12 p.m. to 1 p.m.

Mark Your Calendars — Upcoming Sessions

March 10: Diabetes in Older Adults

April 14: Kidney Nutrition

Please register at www.vcuhealth.org/echodmhtn

Thank you for coming!

Text **25391-25389** to **804-625-4041** for CE credit

Reminder: Mute and Unmute to talk
Press *6 for phone audio
Use chat function for questions