Amsterdam UMC
Universitair Medische Centra

Primaire preventie met acetylsalicylzuur bij alle patiënten met chronische nierschade ??

33e Workshop Nierziekten Papendal 2022 14 december 2022

S. Azam Nurmohamed
internist-nefroloog

Disclosure belangen S.A. Nurmohamed

(potentiële) belangenverstrengeling	Geen / Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Geen
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• Novartis. Novartis Transplantation Advisory Board • Chiesi. Sponsoring research fund (PRISMA) • Astellas. Speaker at Transplantatie Symposium 2022

Man, 63 jaar		
Voorgeschiedenis Hypertensie Myocardinfarct	**Roken** ++	**Bloeddruk: 120/75** **Lengte: 1,78 m** **Gewicht: 81 kg**
Laboratorium-onderzoek: Kreatinine: 79 umol/L; eGFR: 96 ml/min/1,73m^2 24 uurs urine: Eiwit < 0,05 g		**Medicatie** o.a. statine en ARB

ASA ☑ JA ☐ NEE

Man, 63 jaar		
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ASA ☐ JA ☑ NEE

Man, 63 jaar		
Voorgeschiedenis Hypertensie ~~Myocardinfarct~~ DM2	**Roken** ++	**Bloeddruk: 120/75** **Lengte: 1,78 m** **Gewicht: 81 kg**
Laboratorium-onderzoek: Kreatinine: 79 umol/L; eGFR: 96 ml/min/1,73m^2 24 uurs urine: Eiwit: 1,5 g		**Medicatie** o.a. statine en ARB Metformine, insuline

ASA ☐ JA ☐ NEE

Man, 63 jaar		
Voorgeschiedenis Hypertensie ~~Myocardinfarct~~ DM2	**Roken** ++	**Bloeddruk: 120/75** **Lengte: 1,78 m** **Gewicht: 81 kg**
Laboratorium-onderzoek: Kreatinine: 279 umol/L; eGFR: 21 ml/min/1,73m^2 24 uurs urine: Eiwit: 1,5 g		**Medicatie** o.a. statine en ARB insuline

ASA ☐ JA ☐ NEE

Acetylsalicylzuur

Acetyl Spirsäure (=salicylzuur) → Aspirin

Singer, H. Ueber Aspirin. *Pflüger, Arch.* **84**, 527–546 (1901).

→Pijnstillend

→Koortswerend

→Ontstekingsremmend

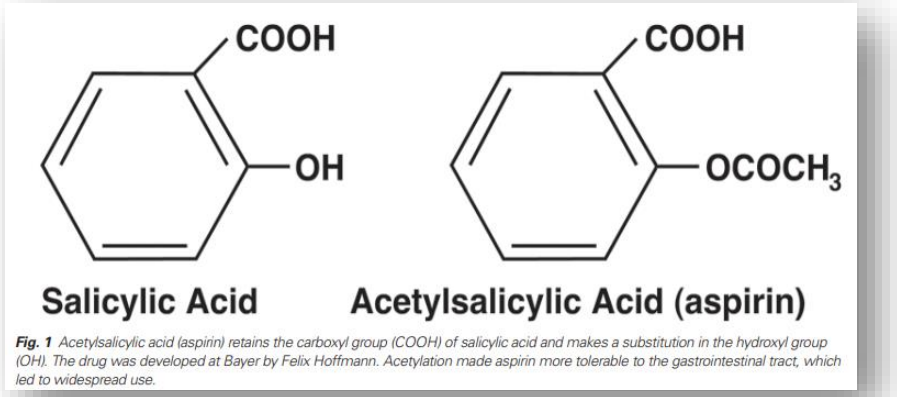


Fig. 1 *Acetylsalicylic acid (aspirin) retains the carboxyl group (COOH) of salicylic acid and makes a substitution in the hydroxyl group (OH). The drug was developed at Bayer by Felix Hoffmann. Acetylation made aspirin more tolerable to the gastrointestinal tract, which led to widespread use.*

Laurence Craven (1883-1957)

1945-1946: nabloedingen bij aspirine kauwgom bij patiënten na tonsillectomie (verlenging prothrombine tijd)

1948-1950: dagelijks aspirine bij 400 patiënten → geen myocardinfarct (Craven LL. Acetylsalicylic acid: possible preventive of coronary thrombosis. Ann West Med Surg 1950;4:)

GRONDLEGGER VAN CONCEPT VAN PRIMAIRE PREVENTIE

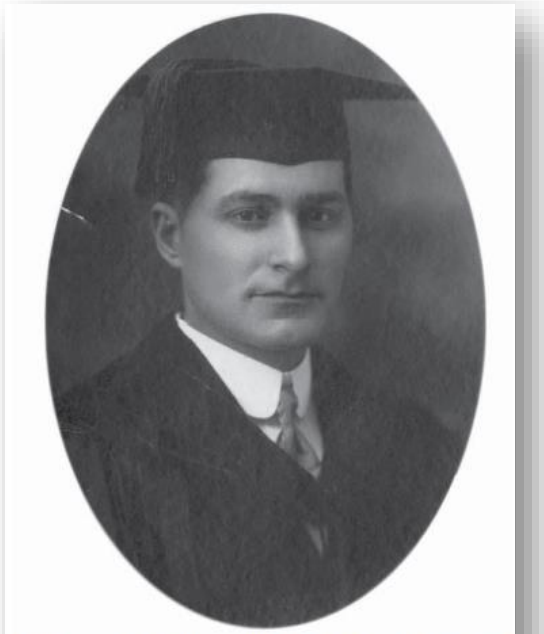


Fig. 2 *Photograph of Dr. Lawrence L. Craven in 1914, at the age of 31, when he graduated from the University of Minnesota College of Medicine and Surgery. Photo courtesy of the University of Minnesota Archives.''*

Tex Heart Inst J 2007;34:179-86

The rise and fall of aspirin in the primary prevention of cardiovascular disease

Raber et al. Lancet 2019

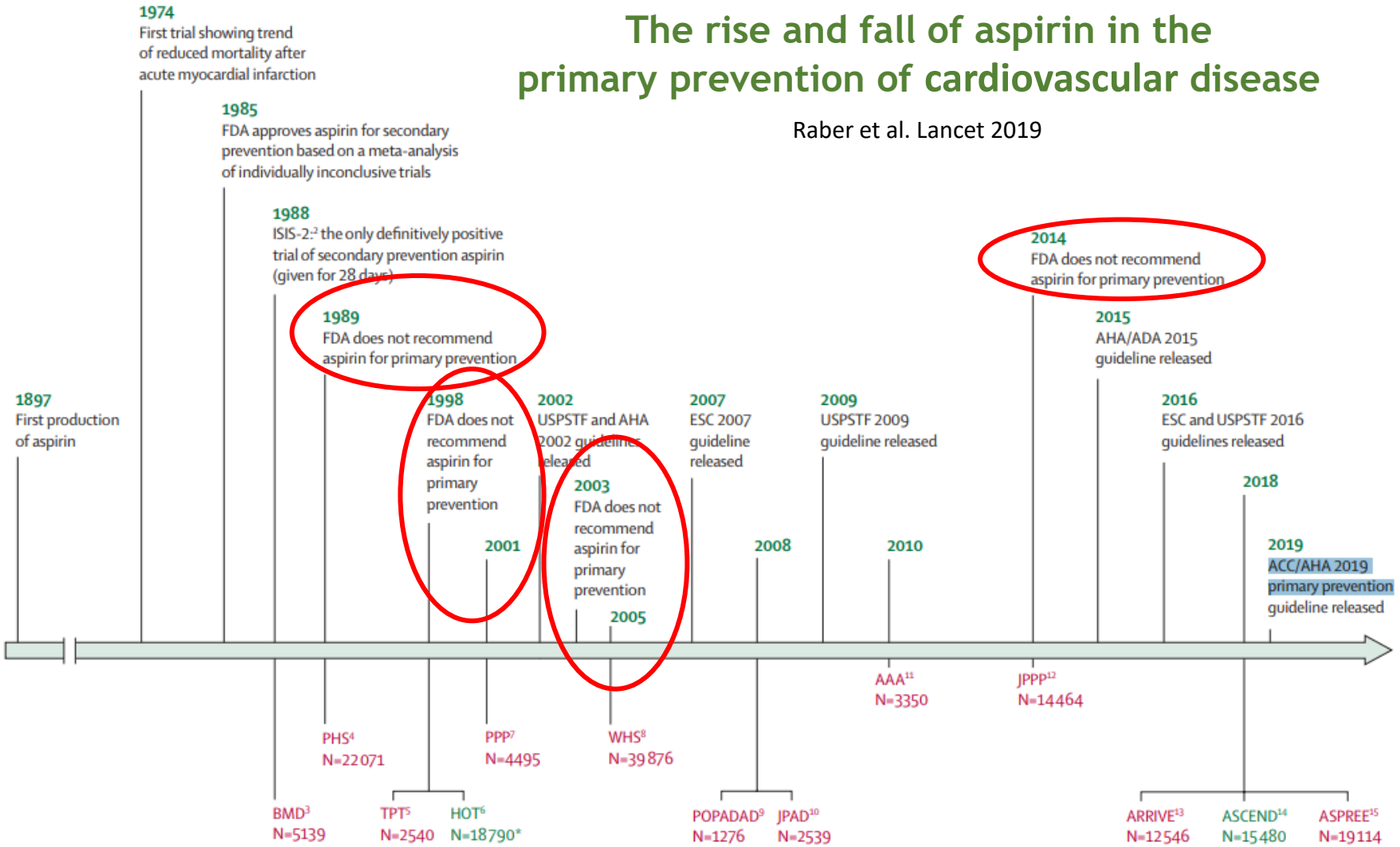


Figure: **History of aspirin for use in the primary prevention of cardiovascular disease**

Includes major completed trials, US FDA reviews, and international practice guidelines. Green indicates trials with significant reduction in the primary endpoint. Red indicates trials without significant reduction in the primary endpoint. AAA=aspirin for asymptomatic atherosclerosis. ADA=American Diabetes Association. AHA=American Heart Association. ARRIVE=aspirin to reduce risk of initial vascular events. ASCEND=a study of cardiovascular events in diabetes. ASPREE=aspirin in reducing events in the elderly. BMD=British male doctors. ESC=European Society of Cardiology. FDA=Food and Drug Administration. HOT=hypertension optimal treatment. ISIS-2=second international study of infarct survival. JPAD=Japanese primary prevention of atherosclerosis with aspirin for diabetes. JPPP=Japanese primary prevention project. PHS=physicians' healthy study. POPADAD=prevention of progression of arterial disease and diabetes. PPP=primary prevention project. TPT=thrombosis prevention trial (excluding warfarin arm). USPSTF=US Preventive Services Task Force. WHS=women's health study. *Ambiguity exists around the primary composite outcome in HOT[6] and the benefit for aspirin was susceptible to changes in the outcome tested.

JAMA | Original Investigation

Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events

A Systematic Review and Meta-analysis

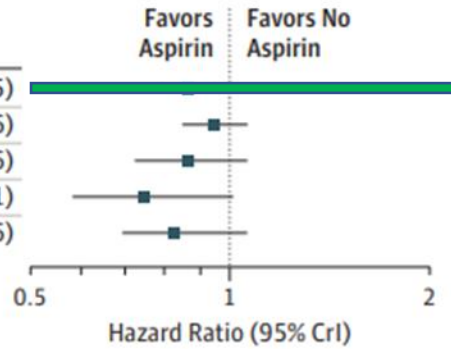
Zheng et al. JAMA 2019

Laag geschat 10-jaars CV risico (<10%)

Figure 2. Cardiovascular and Bleeding Outcomes for Studies With Patients at High and Low Risk for the Primary CV Outcome and With Diabetes

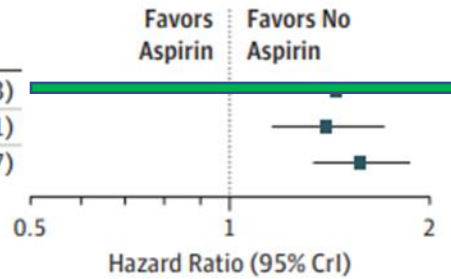
A Participants with low CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome	6	1559	56 212	1753	56 354	0.34 (0.14 to 0.52)	0.87 (0.79-0.95)	
All-cause mortality	6	1903	56 212	1905	56 354	0.01 (-0.27 to 0.27)	0.95 (0.85-1.06)	0
CV mortality	6	405	56 212	448	56 354	0.07 (-0.03 to 0.16)	0.87 (0.72-1.06)	0
Myocardial infarction	6	649	56 212	793	56 354	0.27 (0.00 to 0.49)	0.75 (0.58-1.01)	2
Ischemic stroke	5	508	49 942	593	50 078	0.16 (0.02 to 0.29)	0.83 (0.69-1.06)	8



NNT: 294

Bleeding Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	5	665	49 942	465	50 078	0.40 (0.25 to 0.57)	1.45 (1.28-1.63)	
Intracranial bleeding	6	245	56 212	175	56 354	0.13 (0.05 to 0.22)	1.41 (1.16-1.71)	0
Major GI bleeding	5	359	48 992	228	49 110	0.27 (0.15 to 0.40)	1.58 (1.34-1.87)	9



NNH: 249

JAMA | Original Investigation

Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events

A Systematic Review and Meta-analysis

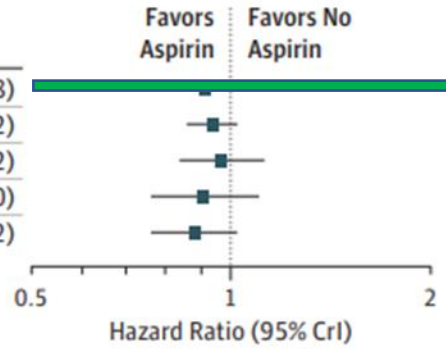
Zheng et al. JAMA 2019

Hoog geschat 10-jaars CV risico (>10%)

Figure 2. Cardiovascular and Bleeding Outcomes for Studies With Patients at High and Low Risk for the Primary CV Outcome and With Diabetes

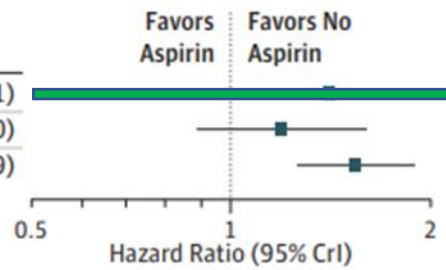
B Participants with high CV risk

Cardiovascular Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
Composite CV outcome[a]	8	1645	25 411	1649	23 703	0.63 (0.18 to 1.04)	0.91 (0.84-0.98)	
All-cause mortality	7	1719	25 411	1683	23 703	0.43 (-0.02 to 0.84)	0.94 (0.86-1.02)	0
CV mortality	7	590	25 411	549	23 703	0.04 (-0.27 to 0.32)	0.97 (0.84-1.12)	14
Myocardial infarction[a]	8	820	25 411	806	23 703	0.32 (-0.16 to 0.74)	0.91 (0.76-1.10)	3
Ischemic stroke[a]	6	323	15 374	350	13 674	0.28 (-0.12 to 0.63)	0.88 (0.76-1.02)	8



NNT: 160

Bleeding Outcomes	No. of Studies	Aspirin: No. of Events	Aspirin: No. of Participants	No Aspirin: No. of Events	No Aspirin: No. of Participants	Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
Major bleeding	6	530	24 773	369	23 065	0.64 (0.35 to 0.97)	1.41 (1.23-1.61)	
Intracranial bleeding	6	104	24 773	82	23 065	0.07 (-0.04 to 0.21)	1.19 (0.89-1.60)	0
Major GI bleeding	5	34	19 452	30	19 444	0.39 (0.16 to 0.69)	1.54 (1.26-1.89)	15



NNH: 152

JAMA | Original Investigation

Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events

A Systematic Review and Meta-analysis

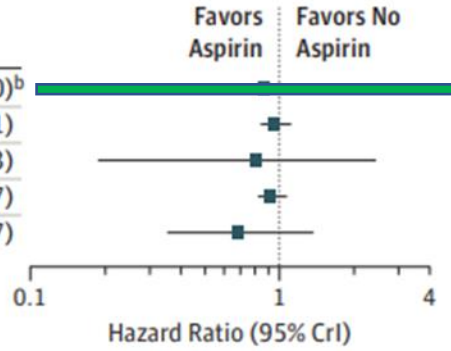
Zheng et al. JAMA 2019

Hoog geschat 10-jaars CV risico (diabetes!)

Figure 2. Cardiovascular and Bleeding Outcomes for Studies With Patients at High and Low Risk for the Primary CV Outcome and With Diabetes

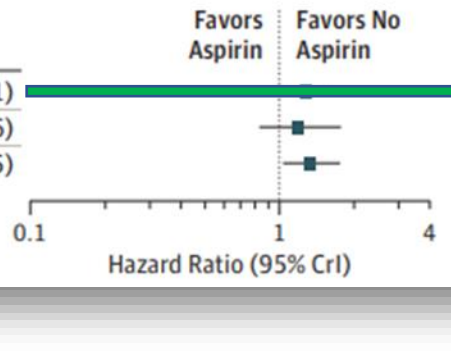
C Participants with diabetes

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Composite CV outcome	8	977	14916	1072	14898	0.65 (0.09 to 1.17)	0.90 (0.82-1.00)[b]	
All-cause mortality	5	1028	11938	1055	11946	0.24 (-0.49 to 0.91)	0.97 (0.85-1.11)	0
CV mortality	4	264	10159	279	10167	0.05 (-1.27 to 0.94)	0.82 (0.19-2.43)	35
Myocardial infarction	8	472	11788	490	11700	0.26 (-0.47 to 0.88)	0.94 (0.83-1.07)	14
Ischemic stroke	3	275	9535	317	9511	0.83 (-0.50 to 1.70)	0.70 (0.36-1.37)	23



NNT: 153

Bleeding Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Increase, % (95% CI)	HR (95% CrI)	I^2
		No. of Events	No. of Participants	No. of Events	No. of Participants			
Major bleeding	3	370	10029	287	10047	0.80 (0.29 to 1.39)	1.29 (1.11-1.51)	
Intracranial bleeding	2	63	9002	52	9017	0.12 (-0.09 to 0.43)	1.21 (0.84-1.76)	1
Major GI bleeding	2	142	9002	105	9017	0.41 (0.06 to 0.86)	1.35 (1.05-1.75)	1



NNH: 121

Overwegingen bij alle studies

- Fatale bloedingen komen niet vaak voor
- De kans op gastro-intestinale bloedingen kan wellicht worden verkleind
- Twijfelachtige risico-reductie in all-cause mortaliteit

ACC/AHA CLINICAL PRACTICE GUIDELINE

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

CLASS (STRENGTH) OF RECOMMENDATION

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

Recommendations for Aspirin Use

Referenced studies that support recommendations are summarized in Online Data Supplements 17 and 18.

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.[S4.6-1–S4.6-8]
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.[S4.6-9]
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.[S4.6-10]

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R — **(Randomized)**
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL C-LD — **(Limited Data)**
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

Cardiovasculair risicomanagement (CVRM) 2019

Federatie Medisch Specialisten

Antitrombotica bij CVRM

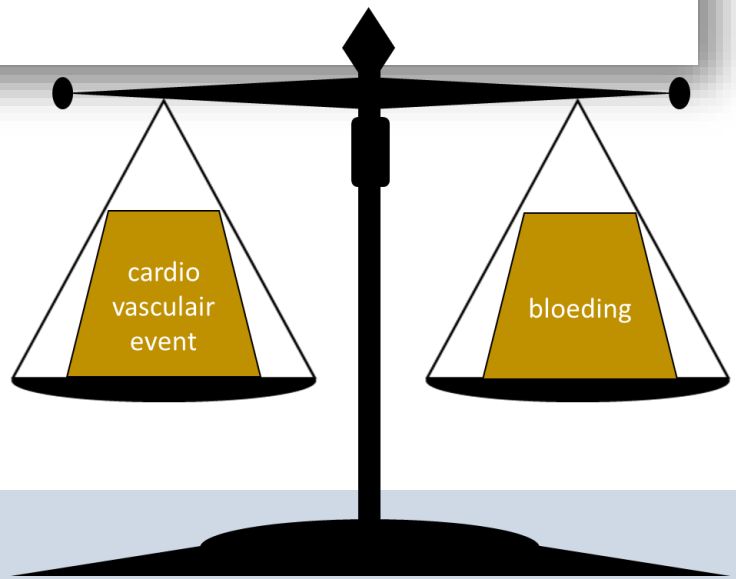
Uitgangsvraag

Wat is de effectiviteit van antitrombotische behandeling bij personen zonder hart- en vaatziekten?

Aanbeveling

Geef geen antitrombotische therapie bij personen zonder hart – en vaatziekten met als doel het voorkomen van hart- en vaatziekten.

Er is GEEN indicatie voor primaire preventie!



Man, 63 jaar		
Voorgeschiedenis Hypertensie ~~Myocardinfarct~~ DM2	**Roken** ++	**Bloeddruk: 120/75** **Lengte: 1,78 m** **Gewicht: 81 kg**
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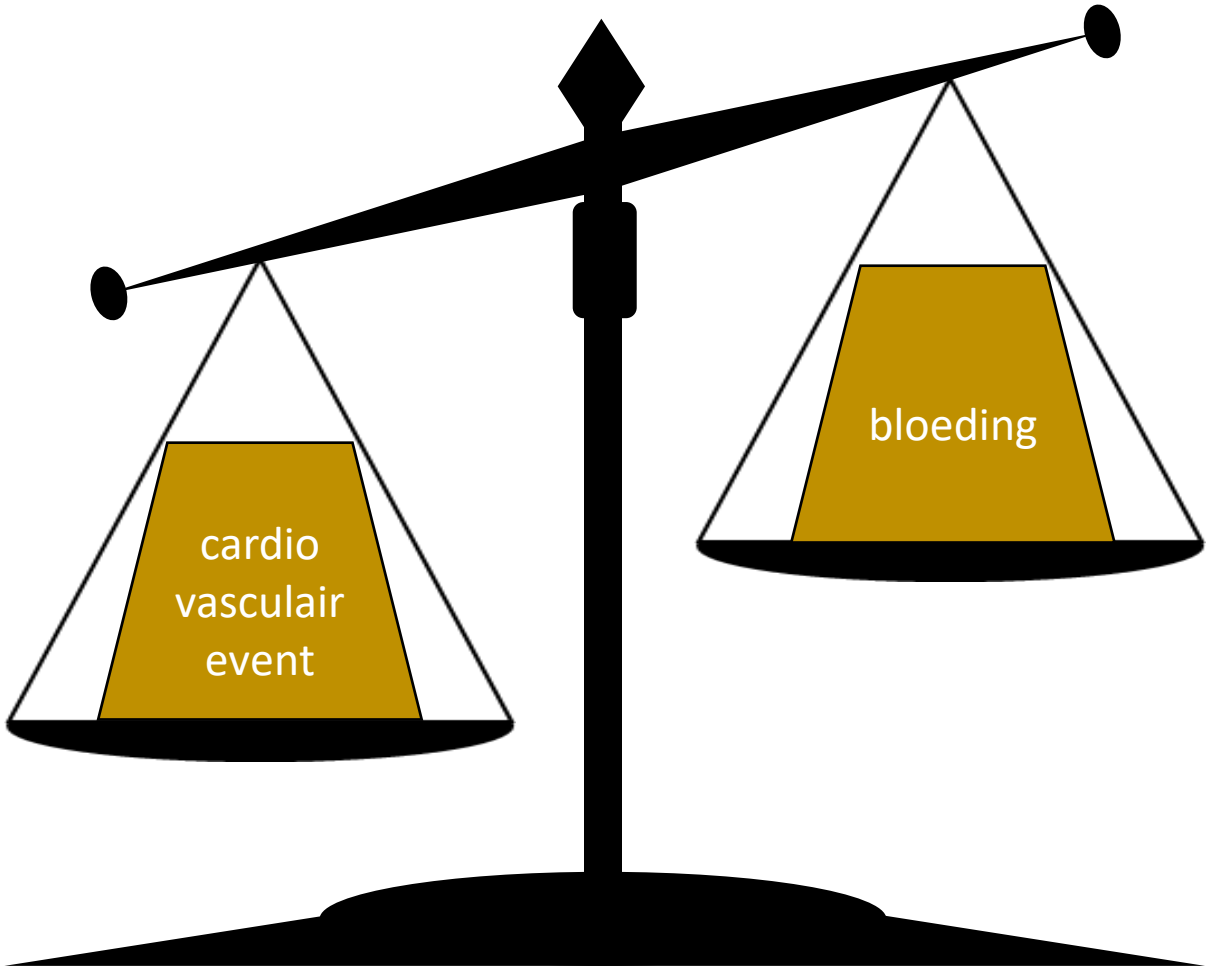
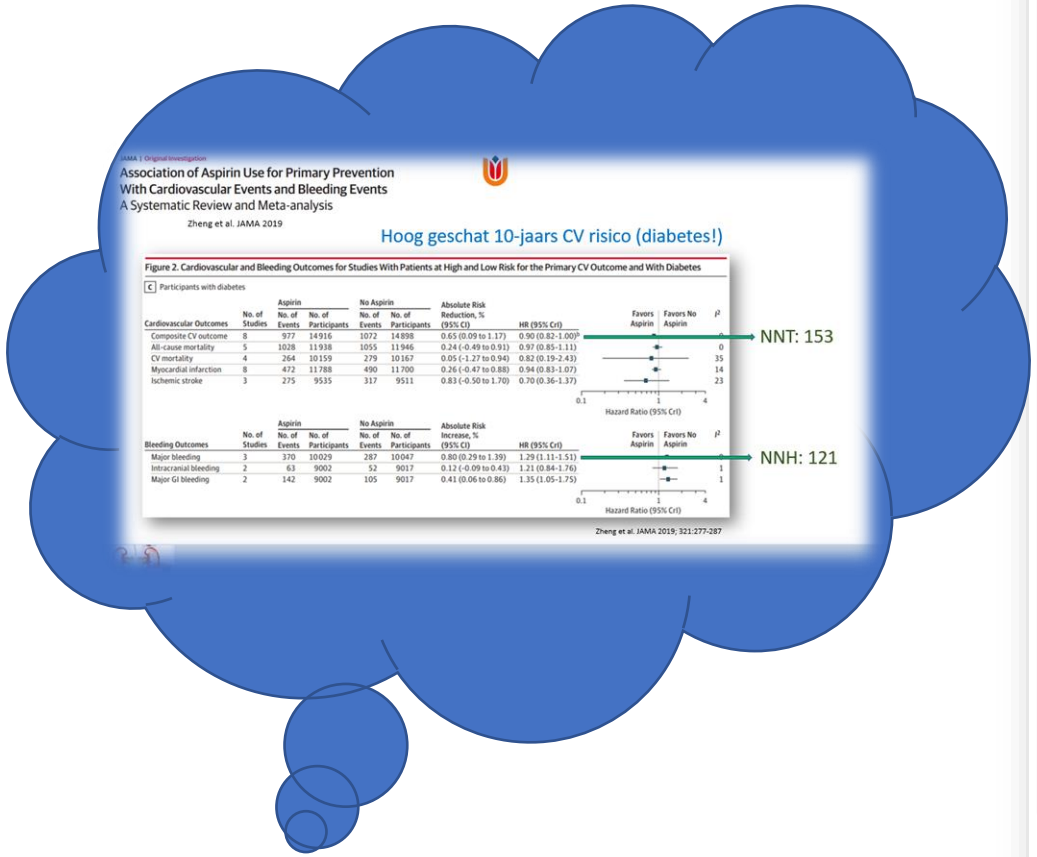
ASA ☐ JA ☐ NEE

chronische nierschade?



Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study

Tonelli et al. Lancet 2012



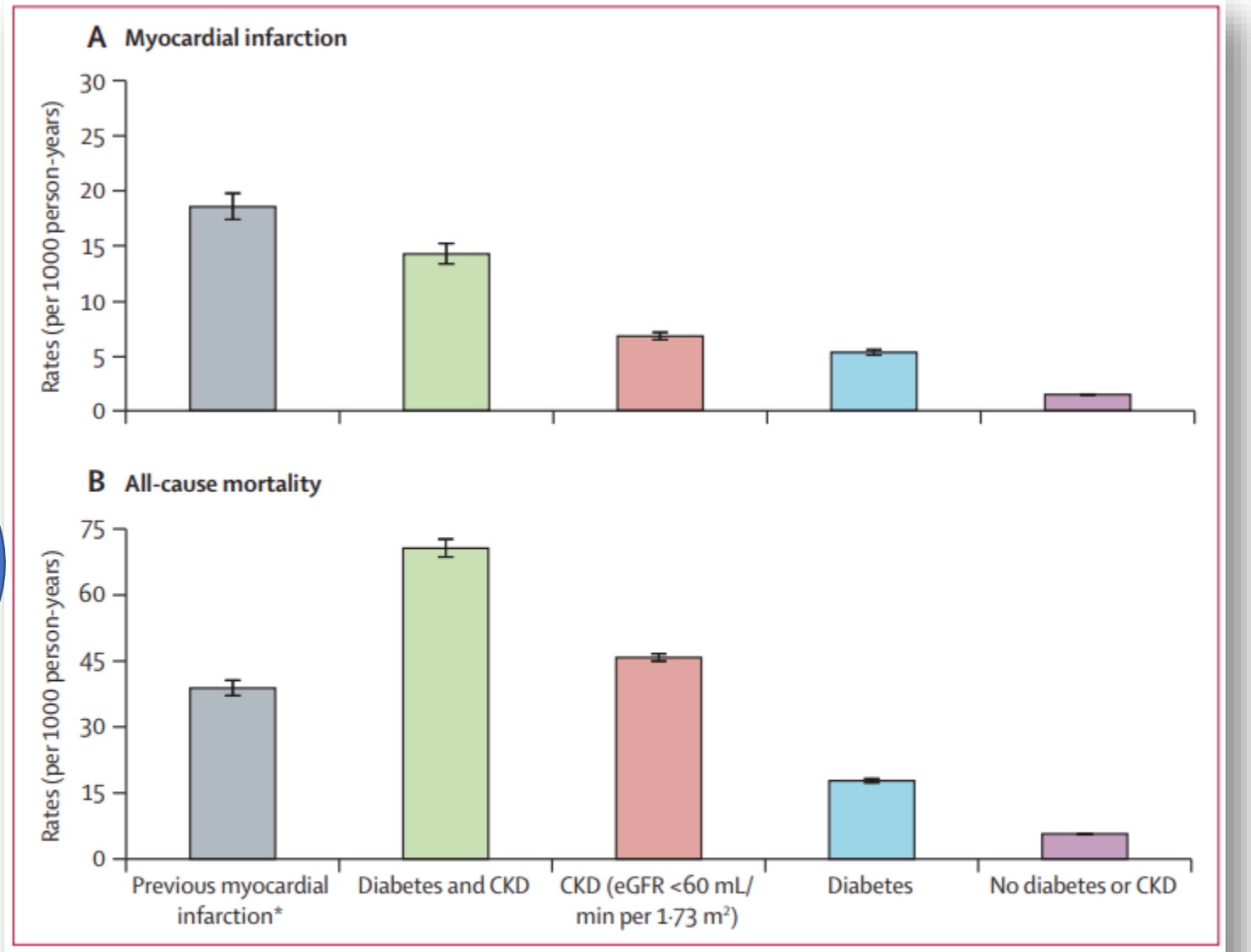


***Figure 1:* Unadjusted rates of clinical outcomes in each risk group**

Unadjusted rates and 95% CIs of myocardial infarction (A) and all-cause mortality (B) per 1000 person-years. Chronic kidney disease is defined as estimated glomerular filtration rate lower than 60 mL/min per 1·73 m² with or without proteinuria. CKD=chronic kidney disease. *Includes participants with or without diabetes and chronic kidney disease.

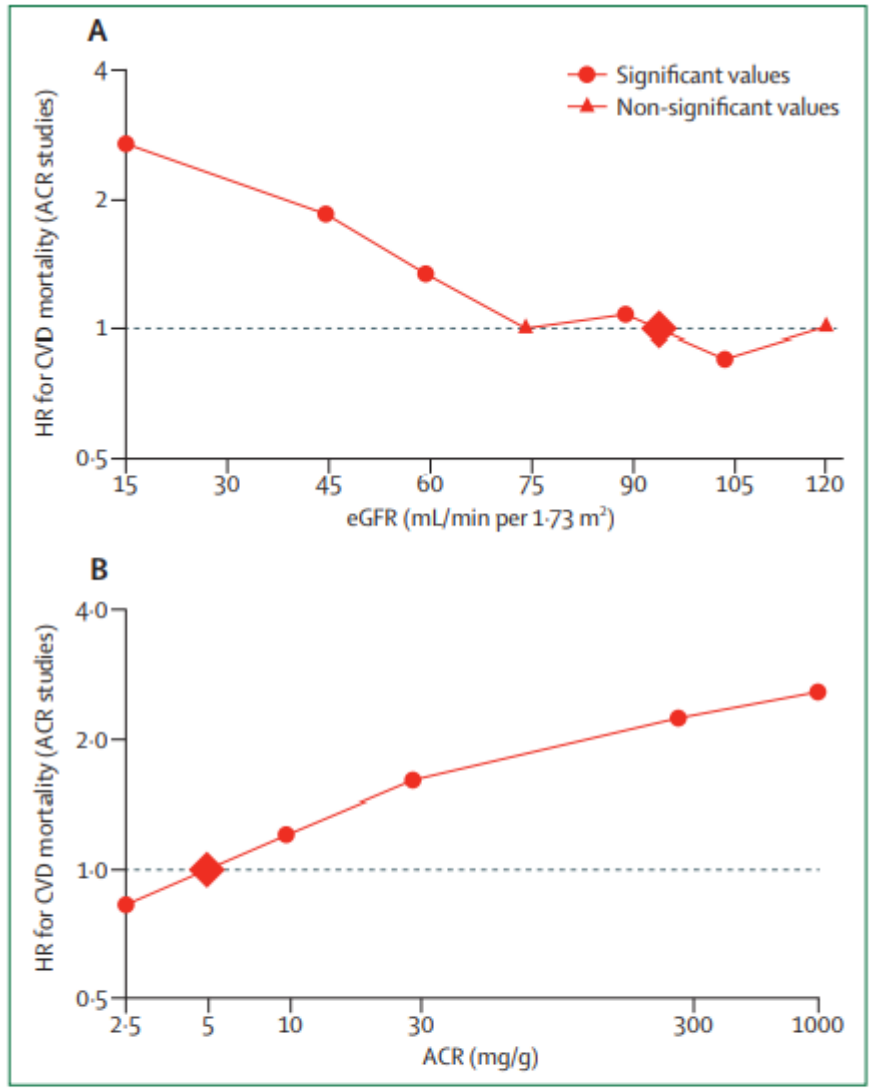


Figure 1: **Independent associations of kidney function and proteinuria with cardiovascular mortality**
(A) Kidney function (eGFR); reference value of 95 mL/min per 1·73 m² is shown with a diamond. (B) Albuminuria (ACR); the reference value of 5 mg/g is shown with a diamond. Hazard ratios are adjusted for each other (eGFR or ACR), age, sex, ethnic origin, and traditional cardiovascular risk factors. HR=hazard ratio. CVD=cardiovascular disease. ACR=albumin-to-creatinine ratio. eGFR=estimated glomerular filtration rate. Based on data in reference 5.

Global Kidney Disease 5

Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention

Gansevoort et al. Lancet 2013

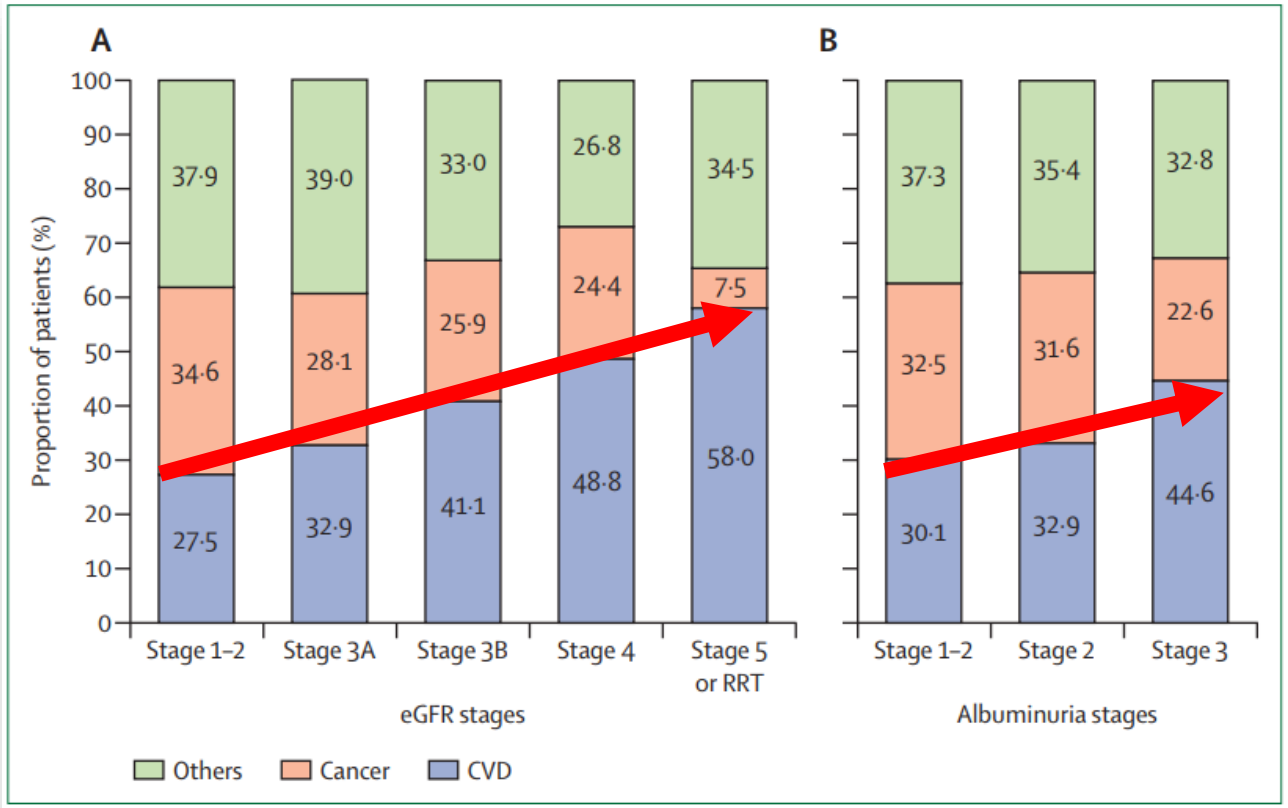


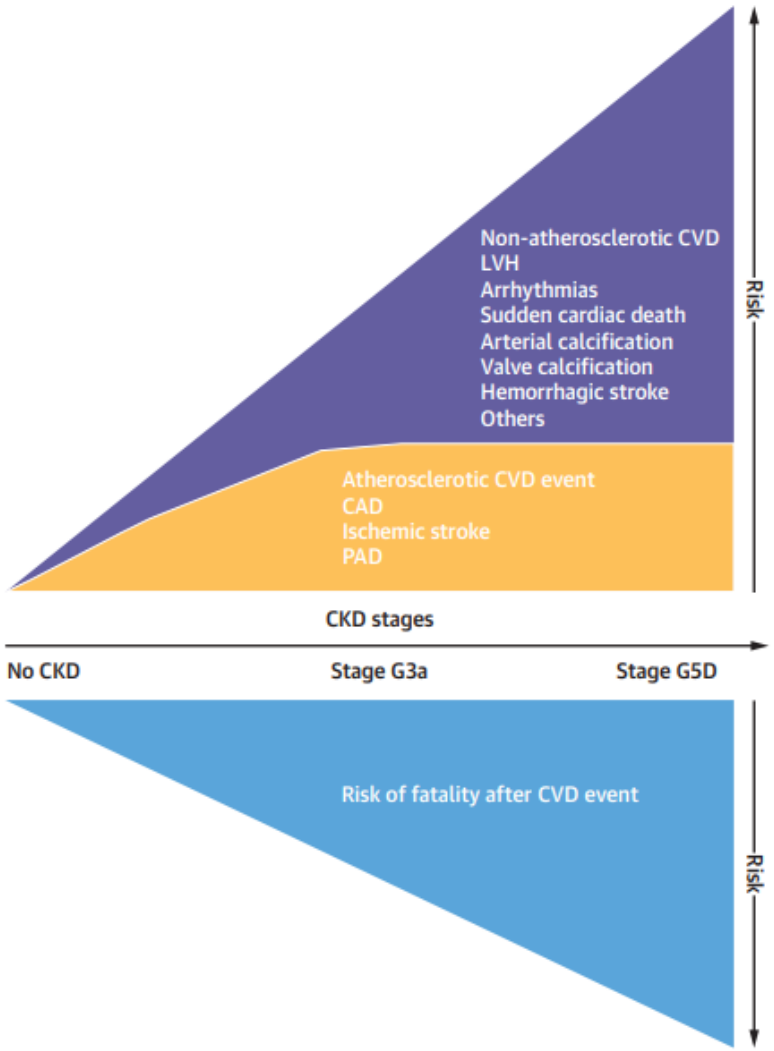
Figure 3: **Causes of death per chronic kidney disease stage (Canadian data)**
(A) eGFR stages and (B) albuminuria stages. Data are adjusted per eGFR and albuminuria stage for age and sex to the WHO world averages in 2000–05. RRT=renal replacement therapy. Based on data in references 24 and 25 (appendix pp 1–2).

Chronic Kidney Disease and Coronary Artery Disease

JACC State-of-the-Art Review

Sarnak et al. J Am Coll Cardiol 2019

CENTRAL ILLUSTRATION Changes in Cardiovascular Disease Risk During Chronic Kidney Disease Progression



Sarnak, M.J. et al. J Am Coll Cardiol. 2019;74(14):1823-38.

Cardiovascular disease (CVD) event **(upper triangle)**; contributions of atherosclerotic CVD **(yellow)**; nonatherosclerotic CVD **(purple)**, and risk of fatality after CVD event **(blue)**. Reproduced with permission from Wanner et al. (10). CAD = coronary artery disease; LVH = left ventricular hypertrophy.

Aspirin Is Beneficial in Hypertensive Patients With Chronic Kidney Disease

A Post-Hoc Subgroup Analysis of a Randomized Controlled Trial

Hypertension Optimal Treatment (HOT)

Jardin. J Am Coll Cardiol 2010

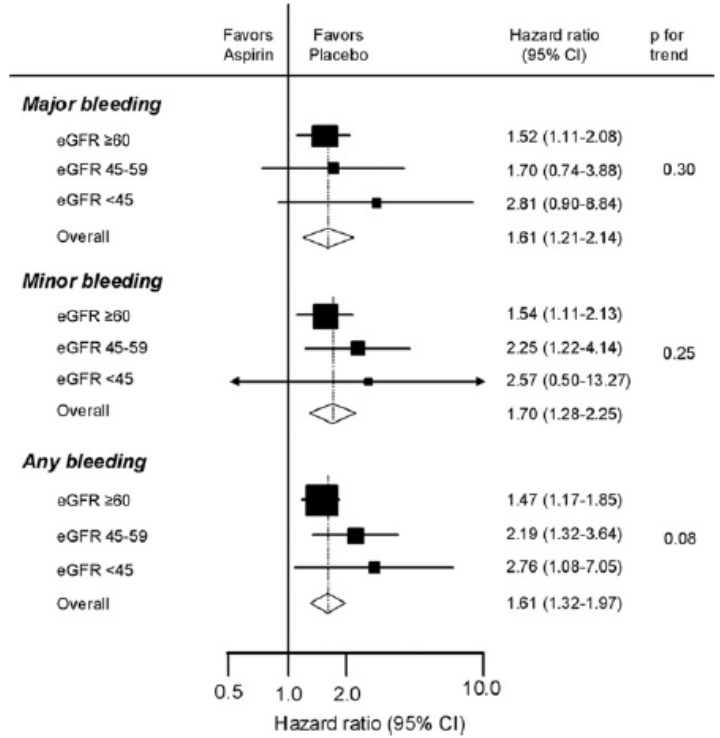


Figure 4 Effect of Aspirin on Bleeding Rates

Effect of randomization to aspirin on bleeding rates according to estimated glomerular filtration rate (eGFR) category. CI = confidence interval.

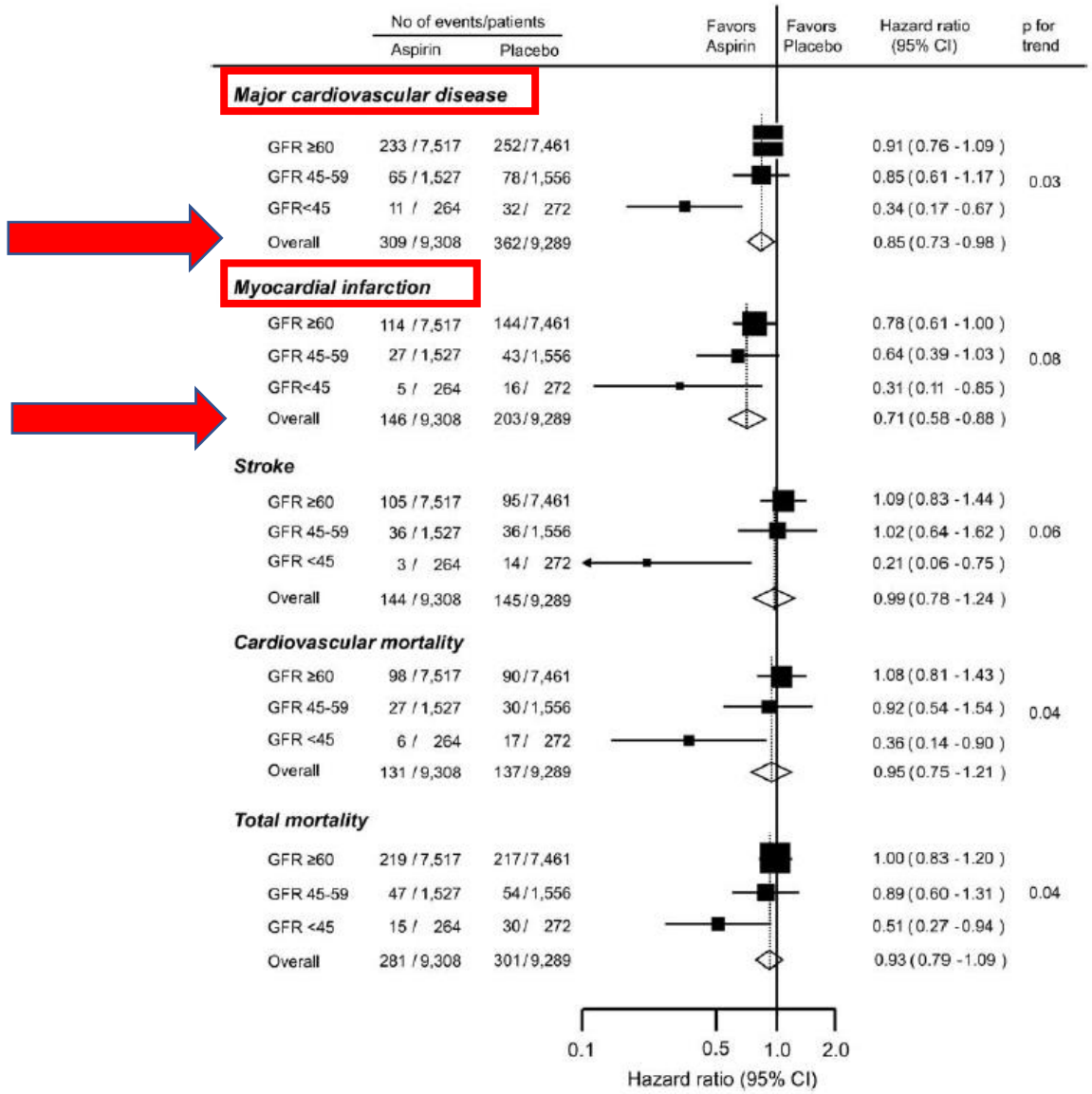


Figure 2 Effect of Aspirin According to eGFR Category

Effect of randomized aspirin on outcomes according to estimated glomerular filtration rate (eGFR) category. CI = confidence interval.

Aspirin Is Beneficial in Hypertensive Patients With Chronic Kidney Disease

A Post-Hoc Subgroup Analysis of a Randomized Controlled Trial

Hypertension Optimal Treatment (HOT)

Jardin. J Am Coll Cardiol 2010

Table 2 Events Prevented and Caused by Aspirin Therapy for Every 1,000 Patients Treated According to eGFR Category

	eGFR, ml/min/1.73 m²			
	≥60	45–59	<45	Overall
Events prevented by aspirin therapy				
Major cardiovascular events	3 (−3 to 8)	8 (−7 to 22)	76 (31 to 121)	6 (0 to 11)
Myocardial infarctions	4 (0 to 8)	10 (−1 to 20)	40 (7 to 72)	6 (2 to 10)
Stroke	−1 (−5 to 2)	0 (−11 to 10)	40 (11 to 69)	0 (−3 to 4)
Cardiovascular mortality	−1 (−5 to 3)	2 (−8 to 11)	40 (6 to 74)	1 (−3 to 4)
Total mortality	0 (−5 to 5)	4 (−9 to 17)	54 (7 to 100)	2 (−3 to 7)
Events caused by aspirin therapy				
Major bleeding	4 (1 to 8)	4 (−2 to 10)	27 (−1 to 55)	6 (3 to 8)
Minor bleeding	4 (1 to 8)	12 (3 to 21)	12 (−8 to 31)	6 (2 to 9)
Any bleeding	8 (3 to 12)	16 (5 to 27)	39 (5 to 72)	10 (6 to 14)

Values are absolute risk change (95% confidence interval) per 1,000 patients treated for an average of 3.8 years.
eGFR = estimated glomerular filtration rate.

Low-Dose Aspirin Therapy in Patients With Type 2 Diabetes and Reduced Glomerular Filtration Rate

Subanalysis from the JPAD trial

The Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial

Saito et al. Diabetes Care 2011

>90 ml/min/1,73m^2 >60-89 ml/min/1,73m^2 <60 ml/min/1,73m^2

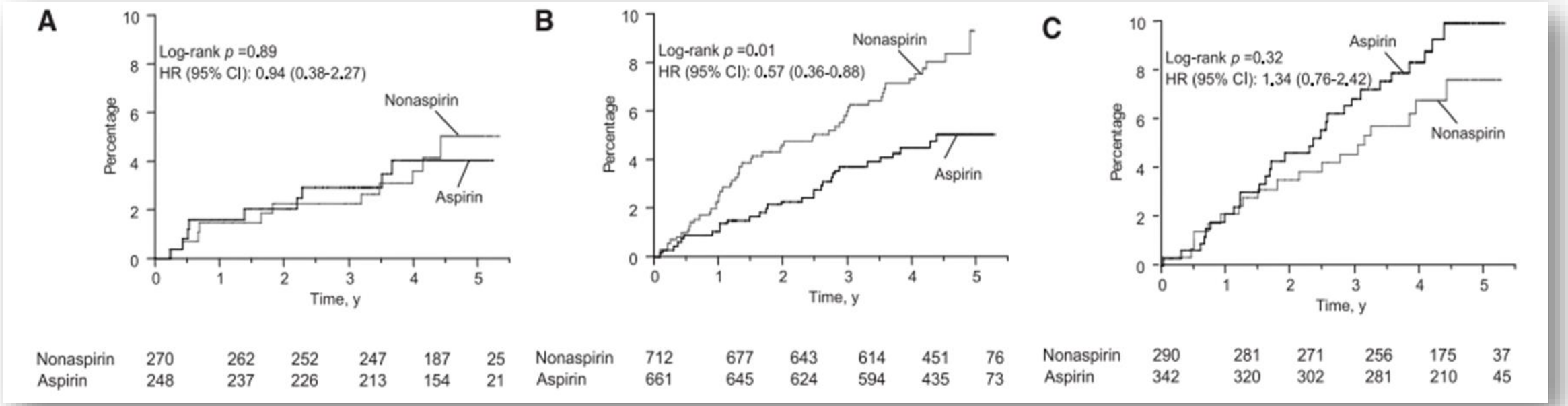


Figure 1—*Percentage of primary end points by category of patients with eGFR of at least 90 mL/min/1.73 m^2 (A), 60–89 mL/min/1.73 m^2 (B), or <60 mL/min/1.73 m^2 (C).*

Aspirin and cardiovascular primary prevention in non-endstage chronic kidney disease: A meta-analysis

Major et al. Atherosclerosis 2016

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
HARP-I	0	108	0	110		Not estimable
HOT	76	1791	110	1828	59.4%	0.71 [0.53, 0.94]
JPAD	24	342	15	290	40.6%	1.36 [0.73, 2.54]
Total (95% CI)		**2241**		**2228**	**100.0%**	**0.92 [0.49, 1.73]**
Total events	100		125			

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 3.48$, df = 1 (P = 0.06); $I^2 = 71\%$

Test for overall effect: Z = 0.26 (P = 0.79)

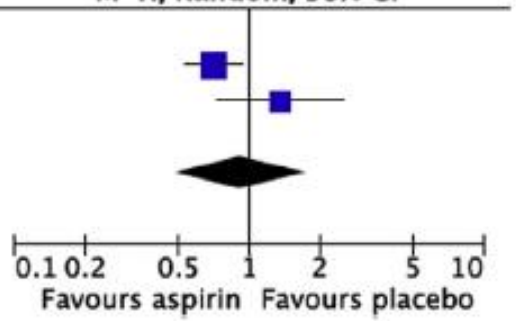


Fig. 2. Forest plot of risk ratios for CVD events using a random effects model and M-H method.

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
HARP-I	2	108	1	110	5.9%	2.04 [0.19, 22.14]
HOT	26	1791	13	1828	76.4%	2.04 [1.05, 3.96]
JPAD	6	342	3	290	17.7%	1.70 [0.43, 6.72]
Total (95% CI)		**2241**		**2228**	**100.0%**	**1.98 [1.11, 3.52]**
Total events	34		17			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 2 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 2.30 (P = 0.02)

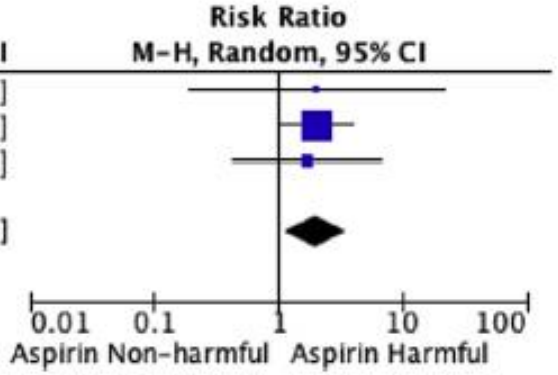
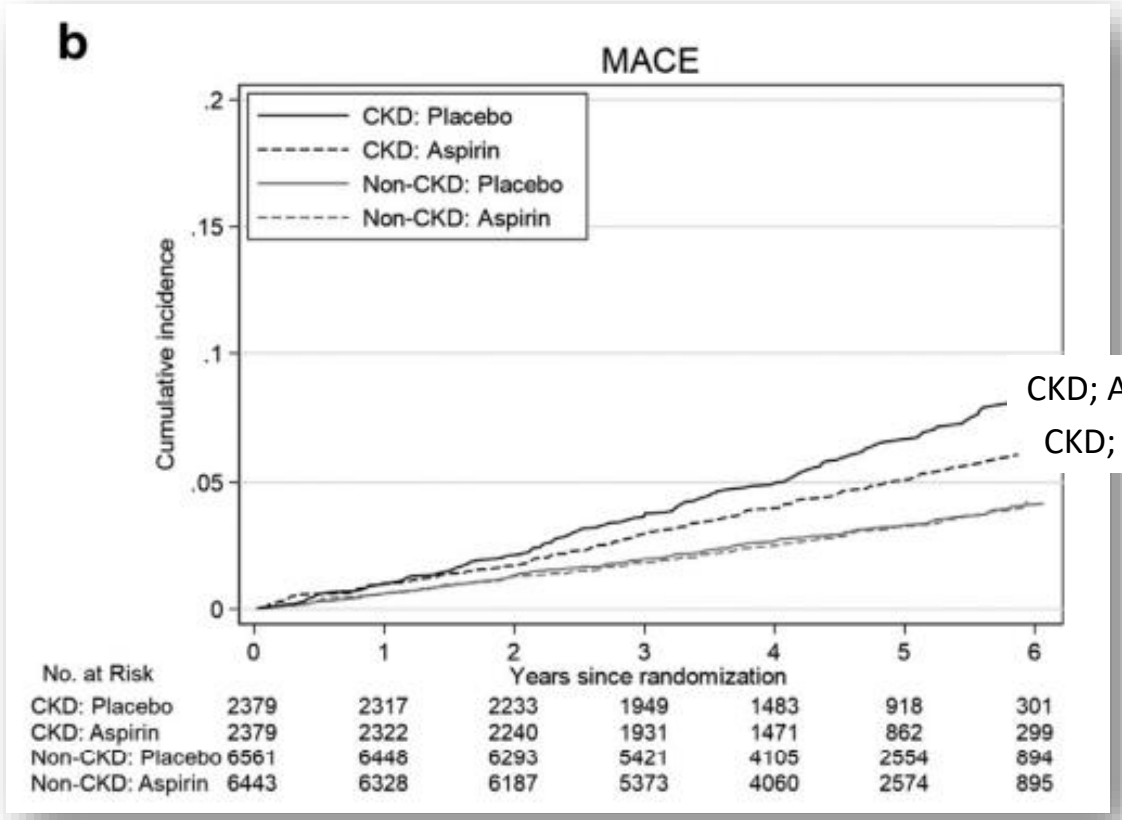


Fig. 3. Forest plot of risk ratios for major bleeding events using a random effects model and M-H method.

Subgroup analysis of the ASPirin in Reducing Events in the Elderly randomized clinical trial suggests aspirin did not improve outcomes in older adults with chronic kidney disease

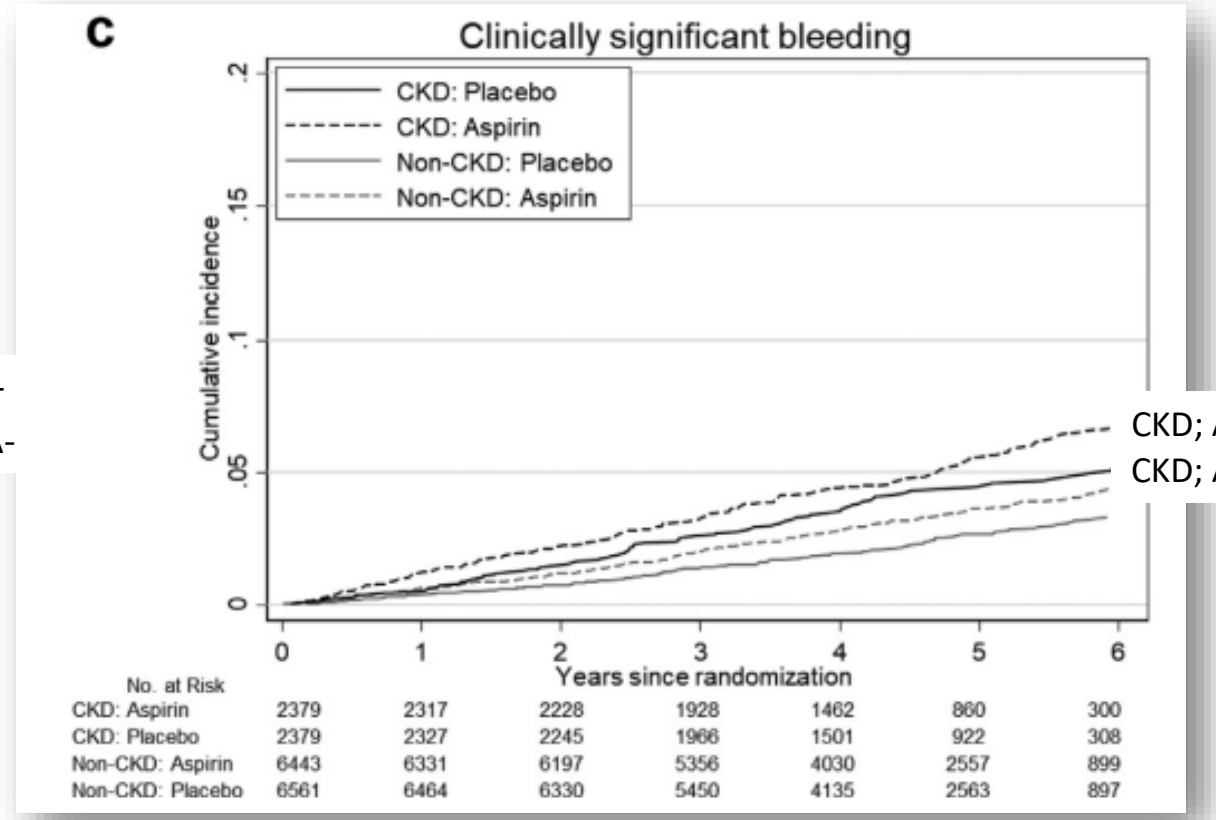
see commentary on page 308

Wolfe. Kidney International 2021



CKD; ASA+

CKD; ASA-



CKD; ASA-

CKD; ASA+

Figure 2 | Cumulative incidence in the aspirin and placebo groups of (a) dementia, persistent physical disability or death; (b) major adverse cardiovascular events (MACE: coronary heart disease death, nonfatal myocardial infarction, or nonfatal ischemic stroke), and (c) clinically significant bleeding. CKD, chronic kidney disease.

Subgroup analysis of the ASPirin in Reducing Events in the Elderly randomized clinical trial suggests aspirin did not improve outcomes in older adults with chronic kidney disease

see commentary on page 308

Wolfe. Kidney International 2021

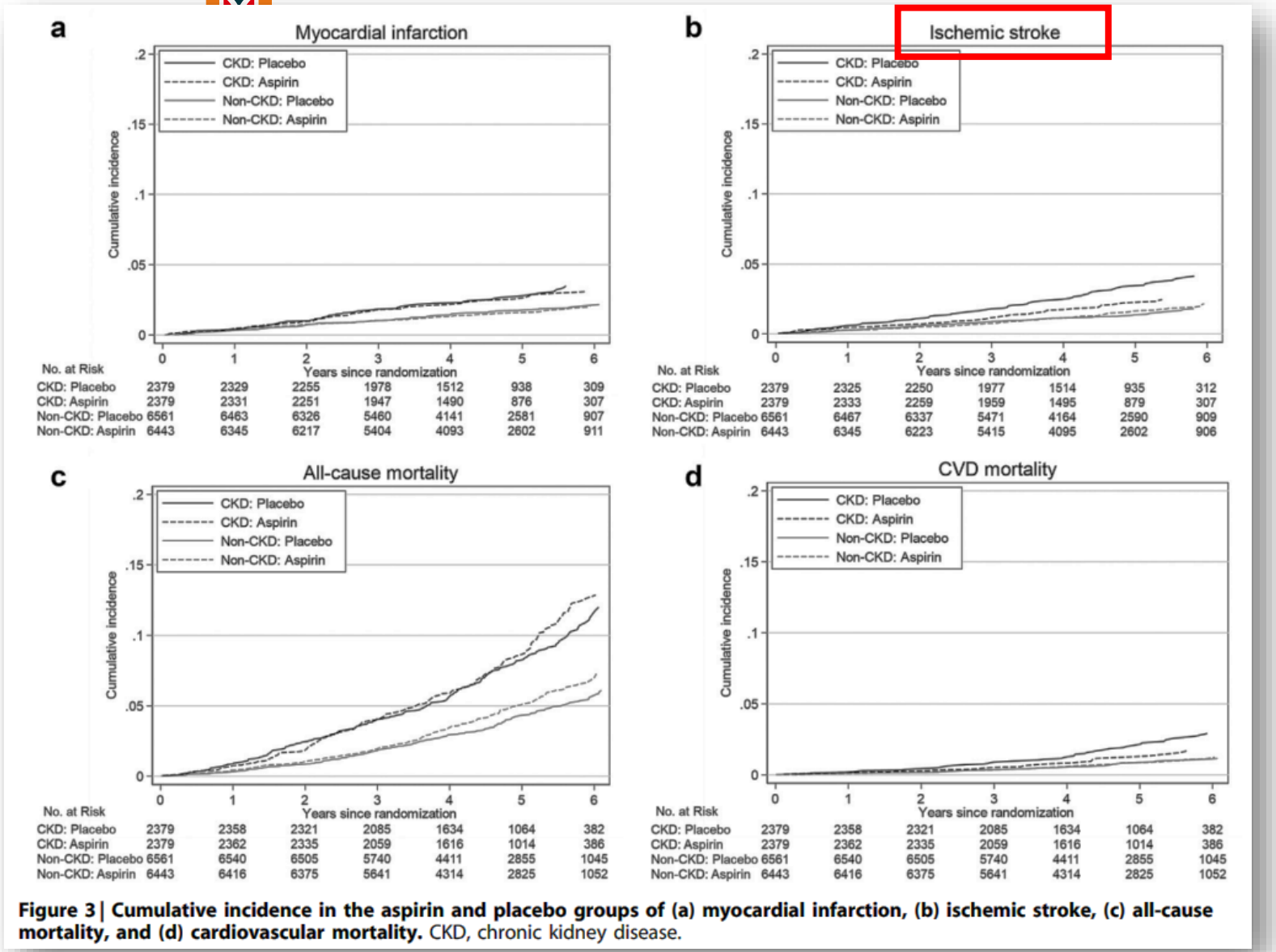


Figure 3 | Cumulative incidence in the aspirin and placebo groups of (a) myocardial infarction, (b) ischemic stroke, (c) all-cause mortality, and (d) cardiovascular mortality. CKD, chronic kidney disease.

Cochrane Library

Antiplatelet agents for chronic kidney disease (Review)

Cochrane Database of Systematic Reviews

2022 Natale P, Palmer SC, Saglimbene VM, Ruospo M, Razavian M, Craig JC, Jardine MJ, Webster AC, Strippoli GFM

Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)
	Risk with control	Risk with antiplatelet agents			
Fatal or nonfatal myocardial infarction Follow-up: 3 to 61.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 0.88 (0.79 to 0.99)	15,289 (18)	**moderate** [1] ⊕⊕⊕⊙
	70 per 1,000	8 fewer per 1,000 (1 to 15 fewer)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 0.85 (0.74 to 0.99)	11,912 (11)	**moderate** [1] ⊕⊕⊕⊙
	85 per 1,000	13 fewer per 1,000 (1 to 22 fewer)			
	HD patients		RR 0.83 (0.49 to 1.41)	2929 (6)	**moderate** [1] ⊕⊕⊕⊙
	20 per 1,000	3 fewer per 1,000 (10 fewer to 8 more)			
Fatal or nonfatal stroke Follow-up: 3 to 61.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 1.01 (0.64 to 1.59)	10,382 (12)	**very low** [1,2,3] ⊕⊙⊙⊙
	20 per 1,000	0 per 1,000 (7 fewer to 12 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 1.06 (0.64 to 1.74)	7062 (5)	**very low** [1,2,3] ⊕⊙⊙⊙
	25 per 1,000	2 more per 1,000 (9 fewer to 19 more)			
	HD patients		RR 0.62 (0.15 to 2.60)	2872 (6)	**very low** [1,2,3] ⊕⊙⊙⊙
	10 per 1,000	4 fewer per 1,000 (8 fewer to 16 more)			

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Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)
	Risk with control	Risk with antiplatelet agents			
Death (any cause) Follow-up: 0.9 to 88.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 0.94 (0.84 to 1.06)	18,241 (35)	**low** [1,2] ⊕⊕⊖⊖
	74 per 1,000	4 fewer per 1,000 (12 fewer to 4 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m²)		RR 0.97 (0.81 to 1.16)	13,234 (19)	**low** [1,2] ⊕⊕⊖⊖
	72 per 1,000	2 fewer per 1,000 (14 fewer to 12 more)			
	HD patients		RR 0.86 (0.72 to 1.03)	4523 (14)	**low** [1,2] ⊕⊕⊖⊖
	87 per 1,000	12 fewer per 1,000 (24 fewer to 3 more)			
Cardiovascular death Follow-up: 0.9 to 88.2 months (median 12 months)	All patients (predialysis, dialysis, transplant recipients)		RR 0.87 (0.65 to 1.15)	9606 (21)	**very low** [1,2,3] ⊕⊖⊖⊖
	36 per 1,000	5 fewer per 1,000 (13 fewer to 5 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m²)		RR 0.98 (0.60 to 1.59)	6525 (10)	**very low** [1,2,3] ⊕⊖⊖⊖
	37 per 1,000	1 fewer per 1,000 (15 fewer to 22 more)			
	HD patients		RR 0.71 (0.47 to 1.09)	2597 (9)	**very low** [1,2,3] ⊕⊖⊖⊖
	38 per 1,000	11 fewer per 1,000 (20 fewer to 3 more)			

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Natale P, Palmer SC, Saglimbene VM, Ruospo M, Razavian M, Craig JC, Jardine MJ, Webster AC, Strippoli GFM

Comparison: placebo or no treatment

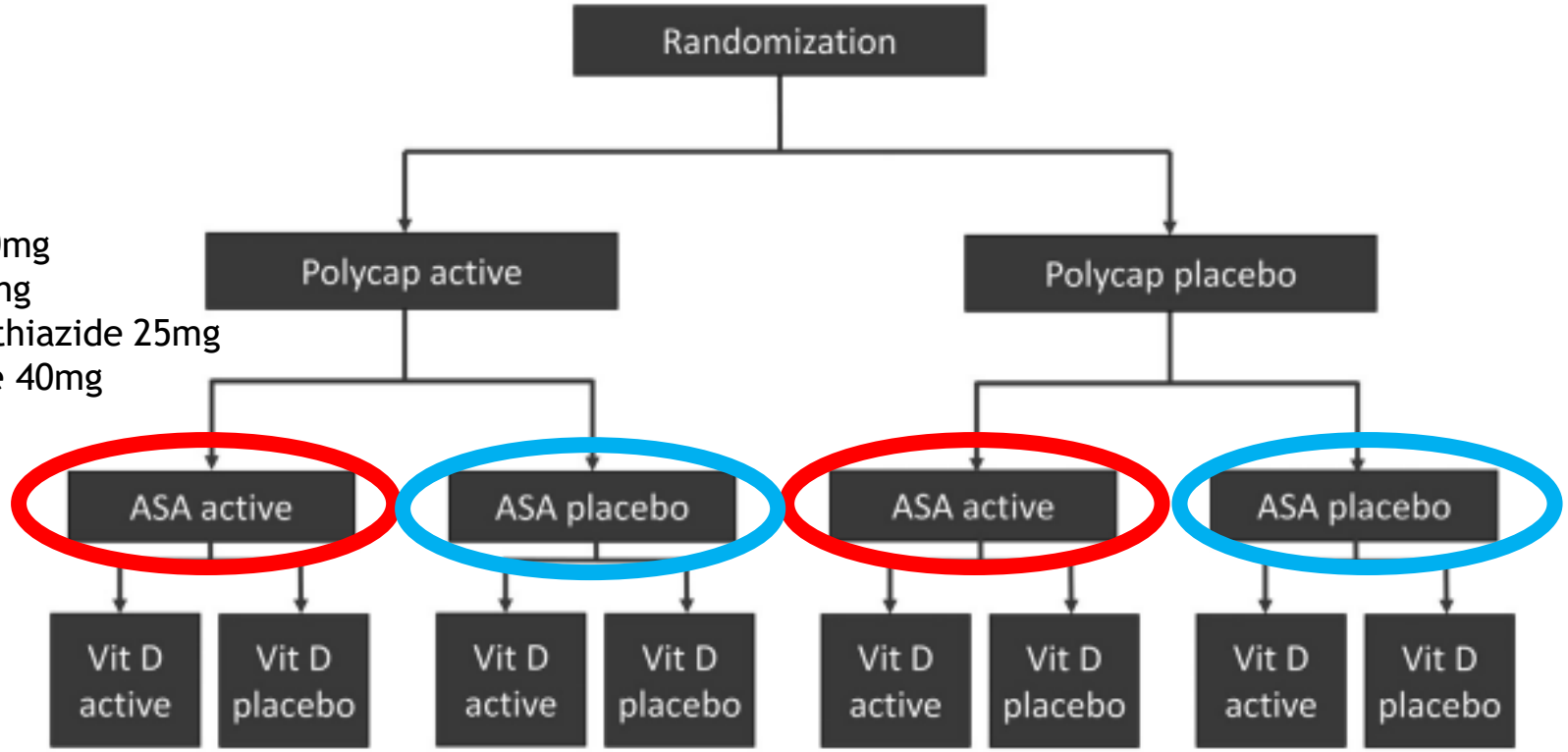
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of partici-pants (RCTs)	Certainty of the evidence (GRADE)
	Risk with control	Risk with antiplatelet agents			
Major bleeding Follow-up: 0.7 to 61.2 months (median 6 months)	All patients (predialysis, dialysis, transplant recipients)		RR 1.35 (1.10 to 1.65)	16,194 (29)	**moderate** [1] ⊕⊕⊕⊙
	29 per 1,000	10 more per 1,000 (3 to 19 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 1.51 (1.15 to 1.98)	11591 (12)	**moderate** [1] ⊕⊕⊕⊙
	35 per 1,000	18 more per 1,000 (5 to 34 more)			
	HD patients		RR 0.90 (0.53 to 1.55)	4119 (15)	**moderate** [1] ⊕⊕⊕⊙
	13 per 1,000	1 fewer per 1,000 (6 fewer to 7 more)			
Minor bleeding Follow-up: 0.5 to 84 months (median 6 months)	All patients (predialysis, dialysis, transplant recipients)		RR 1.55 (1.27 to 1.90)	13,218 (21)	**low** [1,3] ⊕⊕⊙⊙
	92 per 1,000	51 more per 1,000 (25 to 83 more)			
	CKD patients (GFR 15 to 60 mL/min/1.73 m^2)		RR 1.48 (1.20 to 1.83)	11,530 (12)	**low** [1,3] ⊕⊕⊙⊙
	103 per 1,000	50 more per 1,000 (21 to 86 more)			
	HD patients		RR 1.87 (0.65 to 5.40)	1240 (8)	**low** [1,3] ⊕⊕⊙⊙
	8 per 1,000	7 per 1,000 (3 fewer to 35 more)			

The International Polycap Study-3 (TIPS-3): Design, baseline characteristics and challenges in conduct

Joseph et al. Am Heart J 2018

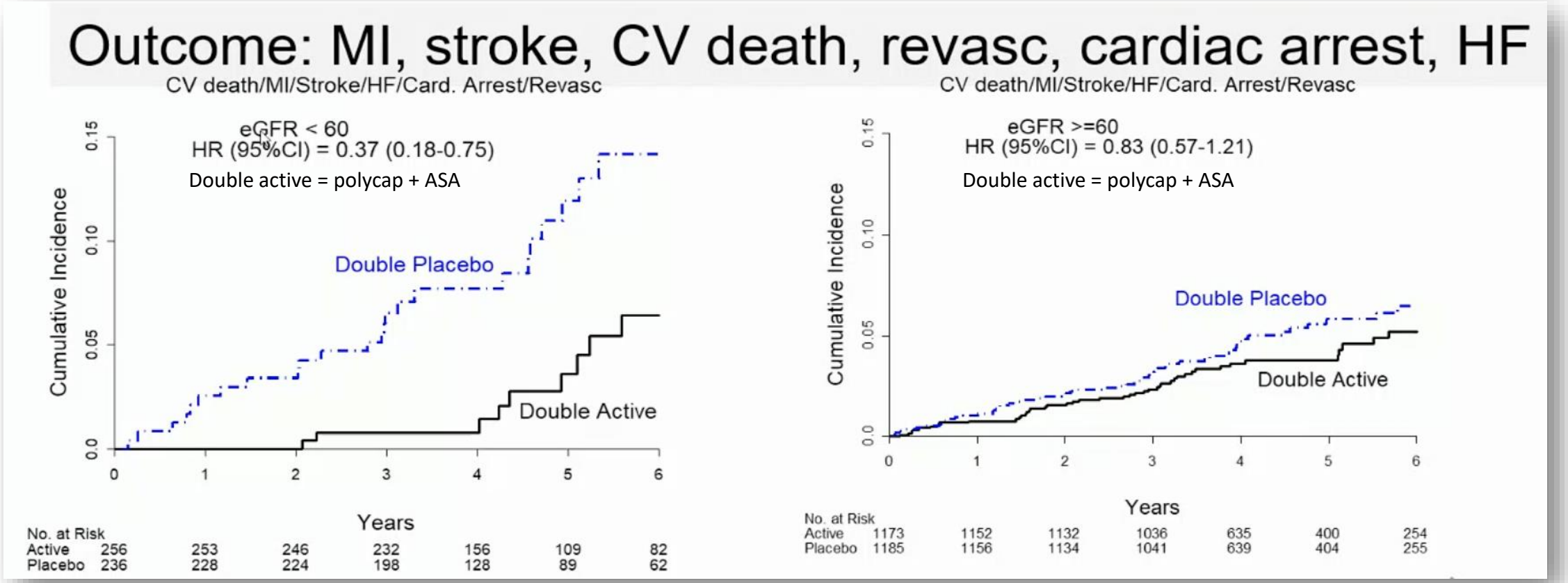
Figure 1

Polycap:
Atenolol 100mg
Ramipril 10mg
hydrochloorthiazide 25mg
Simvastatine 40mg



2x2x2 factorial study design of TIPS-3. Vit D = vitamin D.

Combinatie aspirine en polypil duidelijk effectiever bij CNS



Mann JF et al. LBCT sessie ERA22

Effects of aspirin on cardiovascular outcomes in patients with chronic kidney disease

Johannes F.E. Mann[1,2], Philip Joseph[1], Peggy Gao[1], Prem Pais[3], Jessica Tyrwhitt[1], Denis Xavier[4], Tony Dans[1], Patricio Lopez Jaramillo[5], Habib Gamra[6] and Salim Yusuf[1]; on behalf of the TIPS-3 investigators[7]

Kidney International (2022)

Table 1 | Clinical characteristics of participants with eGFR < and ≥60 ml/min per 1.73 m^2, randomized to aspirin or placebo

	eGFR <60 ml/min per 1.73 m^2		eGFR ≥60 ml/min per 1.73 m^2	
Characteristic	Placebo	Aspirin	Placebo	Aspirin
Randomized	(*n* = 481)	(*n* = 502)	(*n* = 2372)	(*n* = 2357)
Age, yr, mean ± SD	67.4 ± 6.6	66.8 ± 6.9	63.4 ± 6.4	63.1 ± 6.4
Median (Q1–Q3)	67.0 (62.0–72.0)	66.0 (62.0–71.0)	62.0 (59.0–67.0)	62.0 (59.0–67.0)
Female, *n* (%)	320 (66.5)	304 (60.6)	1214 (51.2)	1187 (50.4)
Regions, *n* (%)				
South Asia	254 (52.8)	290 (57.8)	1261 (53.2)	1228 (52.1)
East Asia	208 (43.2)	196 (39.0)	749 (31.6)	760 (32.2)
Other regions	19 (4.0)	16 (3.2)	362 (15.3)	369 (15.7)
Cardiovascular risk factors, *n* (%)				
Hypertension or SBP >140 mm Hg	437 (90.9)	445 (88.6)	1941 (81.8)	1966 (83.4)
Diabetes or FPG level >126 mg/dl	206 (42.8)	209 (41.6)	864 (36.4)	815 (34.6)
Impaired FPG level 110–126 mg/dl	32 (6.7)	40 (8.0)	174 (7.3)	159 (6.7)
Current smoking, *n* (%)	30 (6.2)	25 (5.0)	208 (8.8)	249 (10.6)
INTERHEART risk score, mean ± SD	19.1 ± 5.2	18.7 ± 4.6	17.7 ± 4.7	17.7 ± 4.7
Median (Q1–Q3)	18.0 (15.0–22.0)	18.0 (15.0–21.0)	17.0 (14.0–21.0)	17.0 (14.0–21.0)

Resultaten TIPS3-CKD

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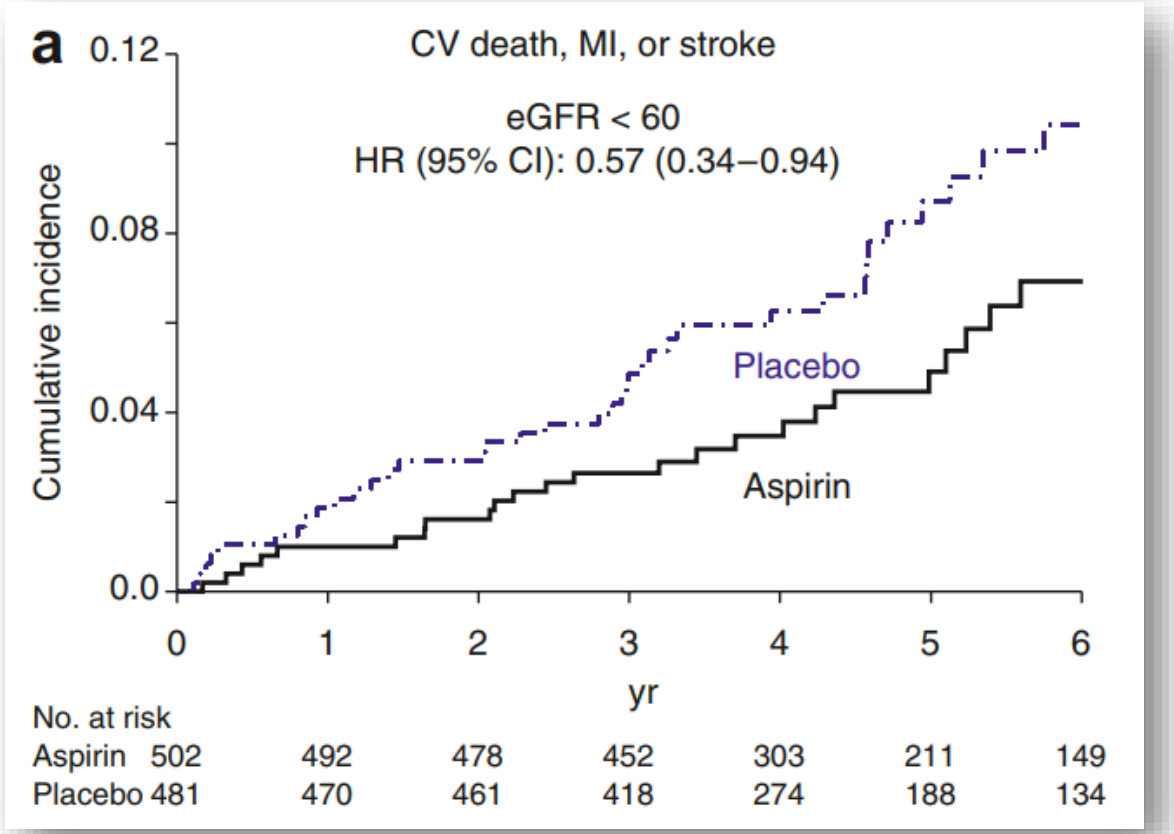

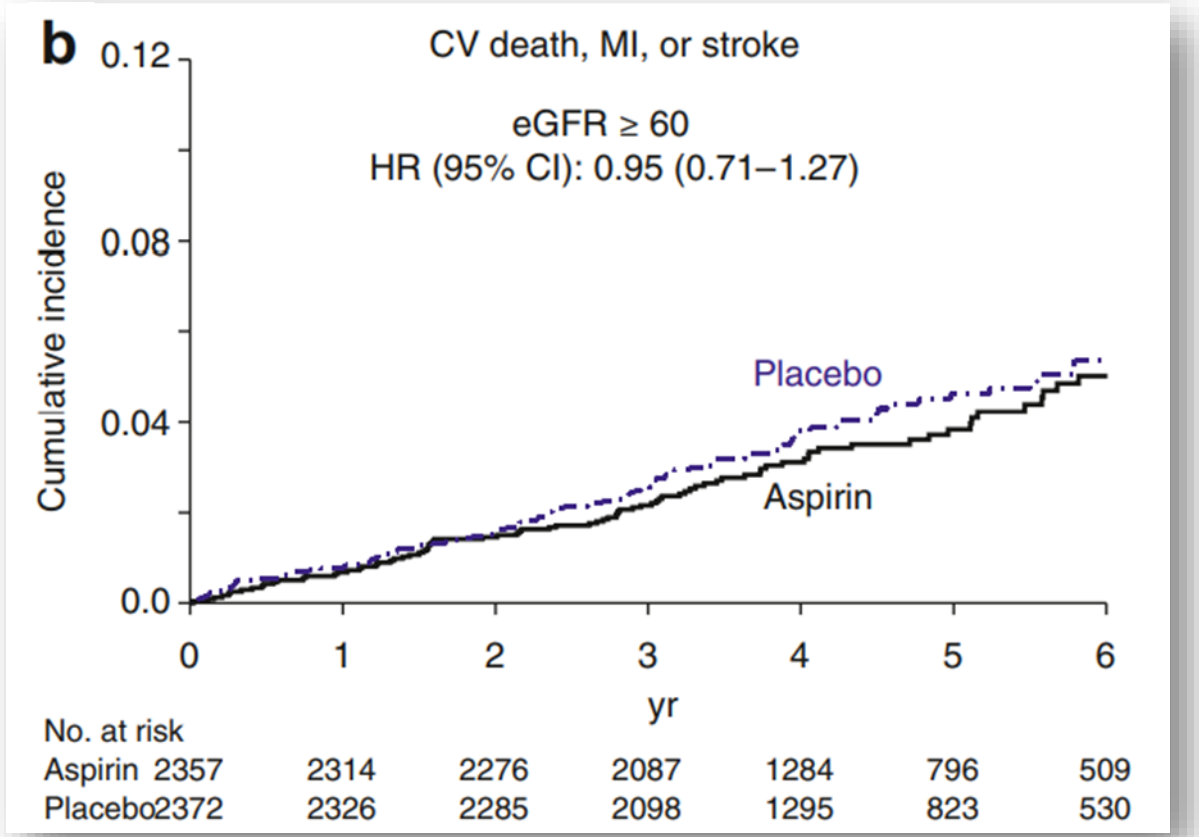

Figure 1 | Primary composite major adverse CV events (myocardial infraction, stroke, or cardiovascular death) in participants with estimated glomerular fraction rate (eGFR) < and ≥60 ml/min per 1.73 m2 , randomized to aspirin (black line) or placebo (blue line). (a) Participants with an eGFR < 60 ml/min per 1,73m^2. (b) Participants with an eGFR ≥ 60 ml/min per 1,73m^2. Unadjusted analysis

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Kidney International (2022)

Aspirine reduceert cardiovasculaire events bij eGFR < 60ml/min/1,73m^2

Niet-significant interactie-effect voor eGFR < of > 60ml/min/1,73m^2 en behandeleffect van aspirine versus placebo (P=0.14)

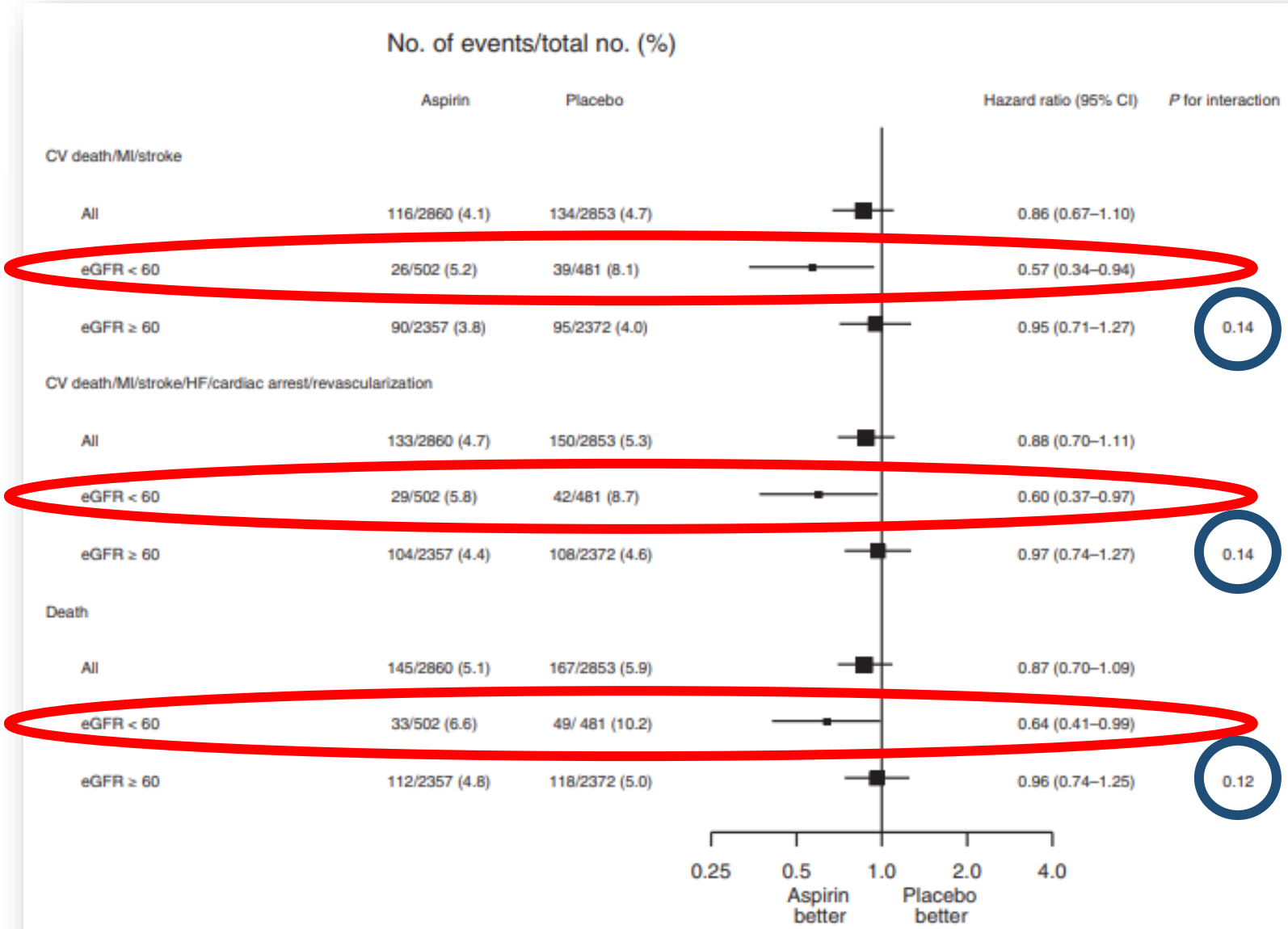

Figure 2 | Outcomes with aspirin versus placebo in all participants and in those with an estimated glomerular fraction rate (eGFR) > or <60 ml/min per 1.73 m^2. Outcomes displayed are the primary composite major adverse CV events (MACEs) of myocardial infraction (MI), stroke, or cardiovascular (CV) death; the expanded MACEs with MI, stroke, CV death, cardiac arrest, revascularization, or heart failure; and all-cause death. Unadjusted analysis; for adjusted analysis, see supplementary tables. CI, confidence interval.

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Kidney International (2022)

Aspirine reduceert cardiovasculaire events bij gestoorde nierfunctie

→ Groter behandeleffect bij slechtere nierfunctie (significante trend (p=0.02))

Risico op bloeding <1% in alle drie eGFR tertielen

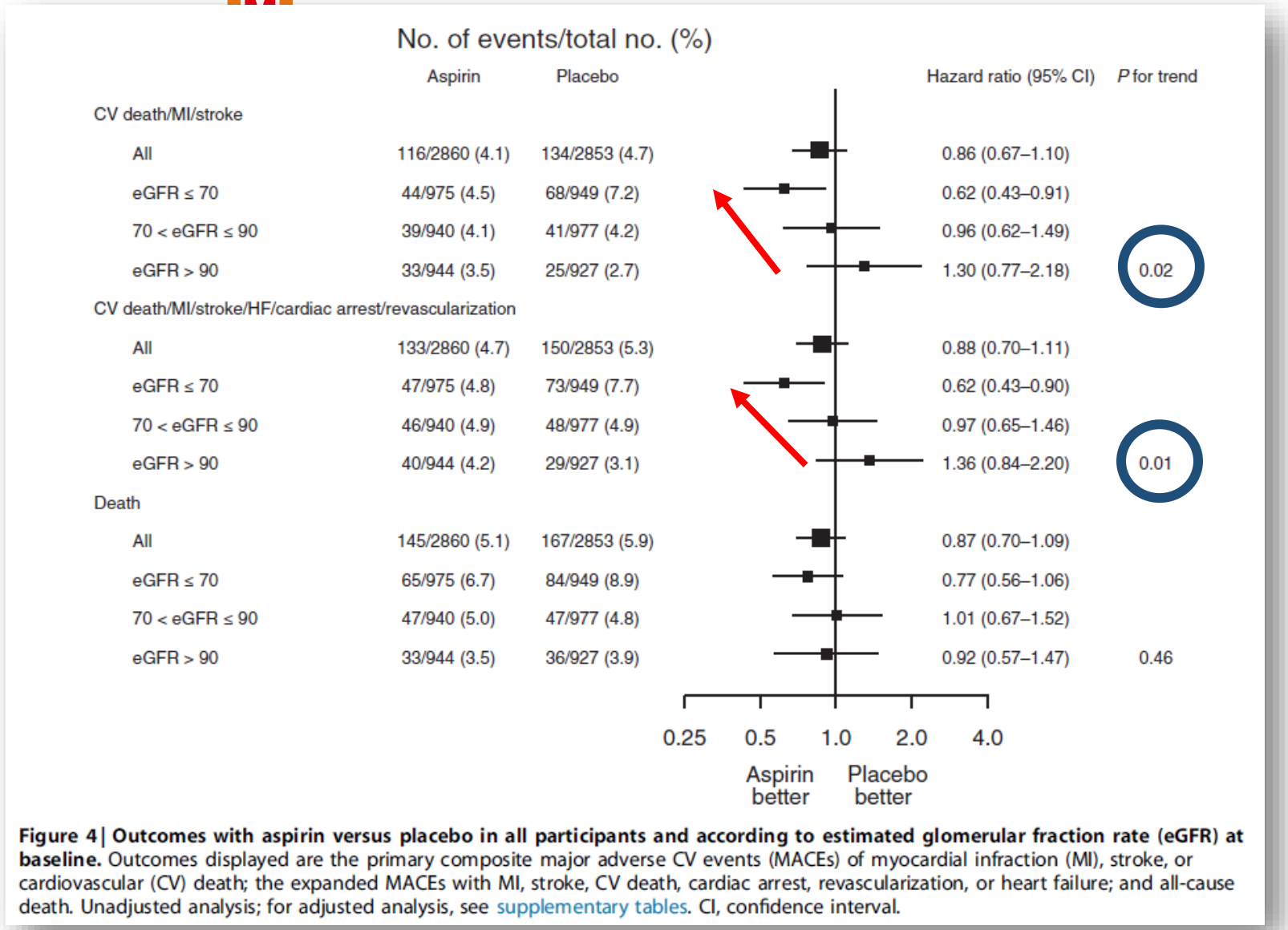

Figure 4| Outcomes with aspirin versus placebo in all participants and according to estimated glomerular fraction rate (eGFR) at baseline. Outcomes displayed are the primary composite major adverse CV events (MACEs) of myocardial infraction (MI), stroke, or cardiovascular (CV) death; the expanded MACEs with MI, stroke, CV death, cardiac arrest, revascularization, or heart failure; and all-cause death. Unadjusted analysis; for adjusted analysis, see supplementary tables. CI, confidence interval.

Aspirine als primaire preventie bij chronische nierschade

	Cardiovasculaire events	bloedingen
Subgroep analyse HOT (RCT)	↓↓	↑↑
Subgroep analyse JPAD (RCT)	eGFR 60-89 ml/min/1,73m^2↓↓	==
Meta-analyse (incl. HOT en JPAD)	==	↑
Subgroep analyse ASPREE (RCT)	AMI: =; iCVA: ↓	↑
Cochrane review (all RCT's)	**↓**	**↑**
Subgroep analyse TIP3 (RCT)	↓↓ (p voor interactie=0.14)	==

- ASA bewezen effectief als secundaire preventie
- ASA mogelijk effectief als primaire preventie (AMI) bij chronische nierschade; geen effect op mortaliteit
- ASA geeft vaker grote bloedingen bij chronische nierschade
- Grote RCT's zijn nodig

Man, 63 jaar		
Voorgeschiedenis Hypertensie ~~Myocardinfarct~~ DM2	**Roken** ++	**Bloeddruk: 120/75** **Lengte: 1,78 m** **Gewicht: 81 kg**
Laboratorium-onderzoek: Kreatinine: 279 umol/L; eGFR: 21 ml/min/1,73m^2 24 uurs urine: Eiwit: 1,5 g		**Medicatie** o.a. statine en ARB insuline

ASA ☐ JA ☐ NEE

Gallagher *et al. Trials* (2022) 23:331
https://doi.org/10.1186/s13063-022-06132-z

Trials

STUDY PROTOCOL Open Access

Aspirin to target arterial events in chronic kidney disease (ATTACK): study protocol for a multicentre, prospective, randomised, open-label, blinded endpoint, parallel group trial of low-dose aspirin vs. standard care for the primary prevention of cardiovascular disease in people with chronic kidney disease

Hugh Gallagher[1*], Jennifer Dumbleton[2], Tom Maishman[3], Amy Whitehead[3], Michael V. Moore[4], Ahmet Fuat[5,6], David Fitzmaurice[7], Robert A. Henderson[8], Joanne Lord[9], Kathryn E. Griffith[10], Paul Stevens[11], Maarten W. Taal[12,13], Diane Stevenson[2], Simon D. Fraser[4], Mark Lown[4], Christopher J. Hawkey[2] and Paul J. Roderick[4]

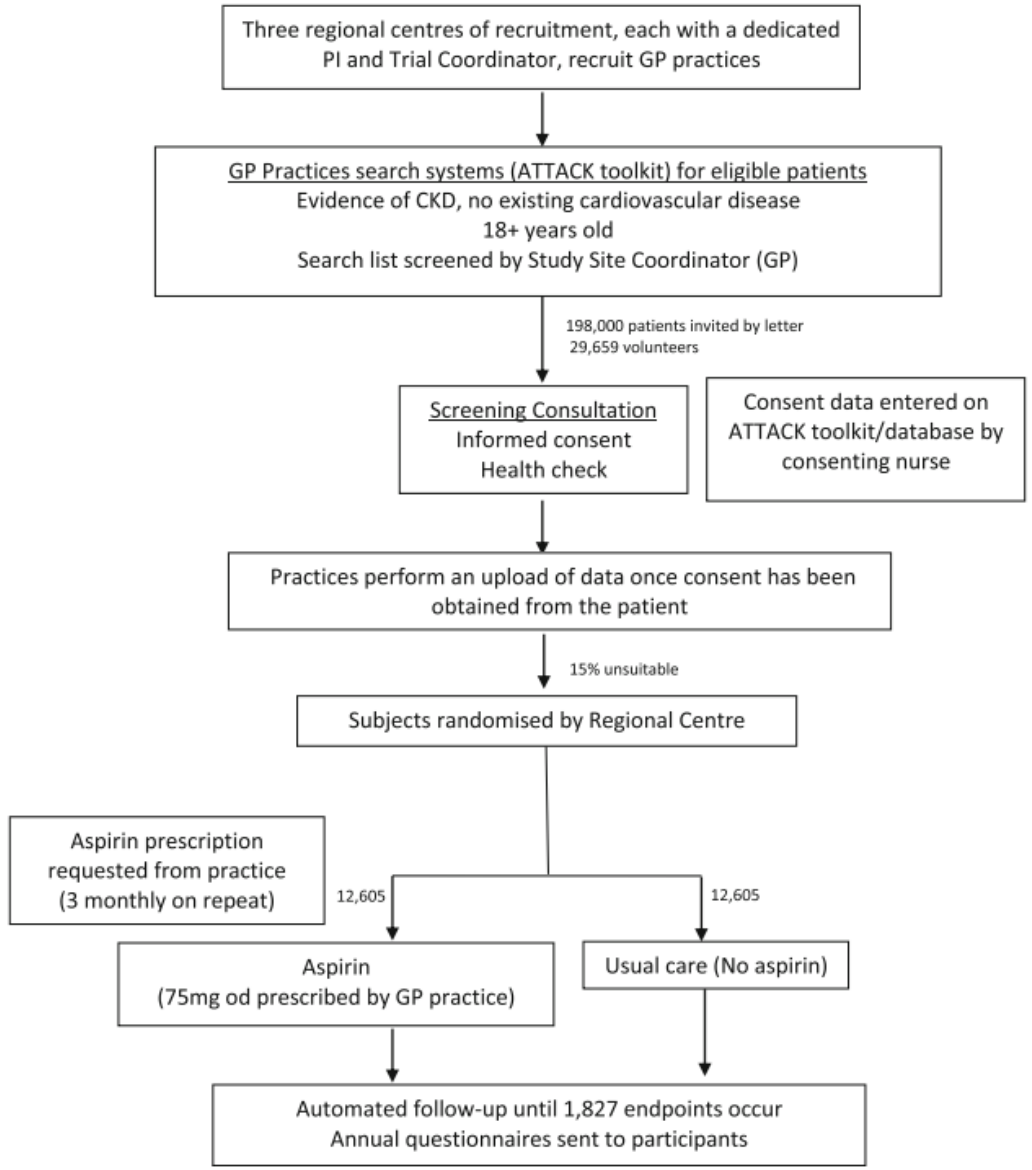

Fig. 1 Trial flow diagram. In total 25,210 patients with CKD will be randomised to receive aspirin in addition to their usual medication or no additional treatment (and avoidance of aspirin), and followed up until 1827 adjudicated major cardiovascular events (primary outcome) have occurred. It is anticipated that 3.5 years of recruitment and 2.5 years of follow-up will be required to complete the trial