Role of antiplatelet Agents in Diabetic Kidney Disease

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Disclosure of Interests

No relevant disclosures

Outline

- The Antithrombotic Trialists' Collaboration IPD
  - All-comers, subgroup analyses include HD and DM
- Aspirin in CKD and DM for cardiovascular events
  - (not dialysis access)
- All antiplatelet agents in CKD
- ADP receptor antagonists in DM and CKD

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Aspirin: General Population

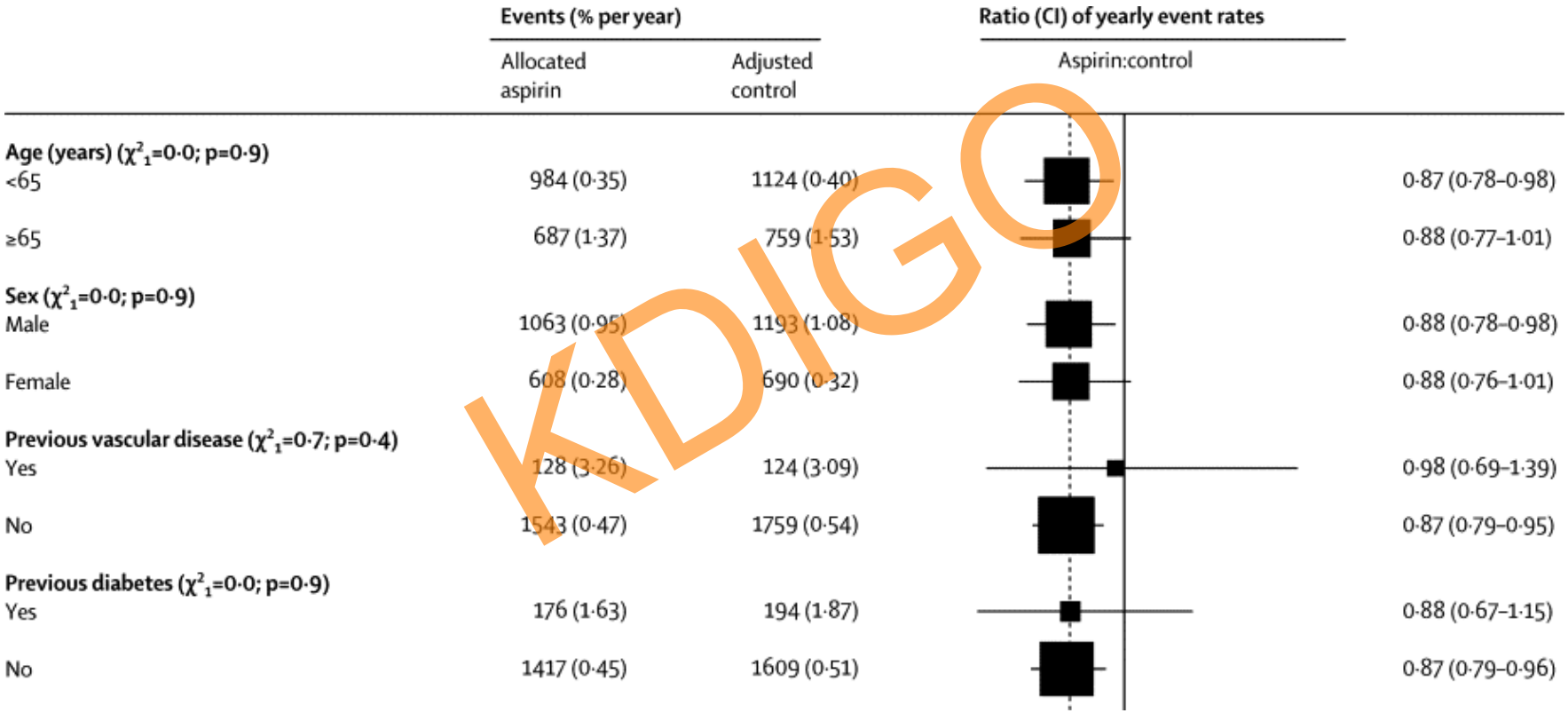
- Primary: 95,000 people, 660,000 person years, 6 trials
- Secondary: 17,000 people, 43,000 person-years, 16 trials

Outcome	Relative rate		Absolute difference Events /yr/1000 patients*	
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention
Major cardiovascular disease	0.88 (0.82-0.94)	0.81 (0.75-0.87)	-0.7	-14.9
Myocardial infarction	0.82 (0.75-0.90)	0.80 (0.73-0.88)	-0.6	-10.00
Stroke	0.95 (0.85-1.06)	0.81 (0.71-0.92)	-0.1	-4.6
Cardiovascular mortality	0.97 (0.87-1.09)	0.91 (0.82-1.00)	-0.1	-2.9
Major extracranial bleeding	1.54 (1.30-1.82)	2.69 (1.25-5.76)	0.3	Incomplete reporting

ATT, *Lancet* 2009; 373: 1849-60

* Negative: events prevented by aspirin
Positive: events caused by aspirin

ATT: aspirin for CV events in DM



* CKD not evaluated

ATT, *Lancet* 2009; 373: 1849-60

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Aspirin in CKD and Hypertension

HOT study

>18,500 people with high blood pressure randomised to aspirin or placebo for ~5 years

Aged 50-80 years

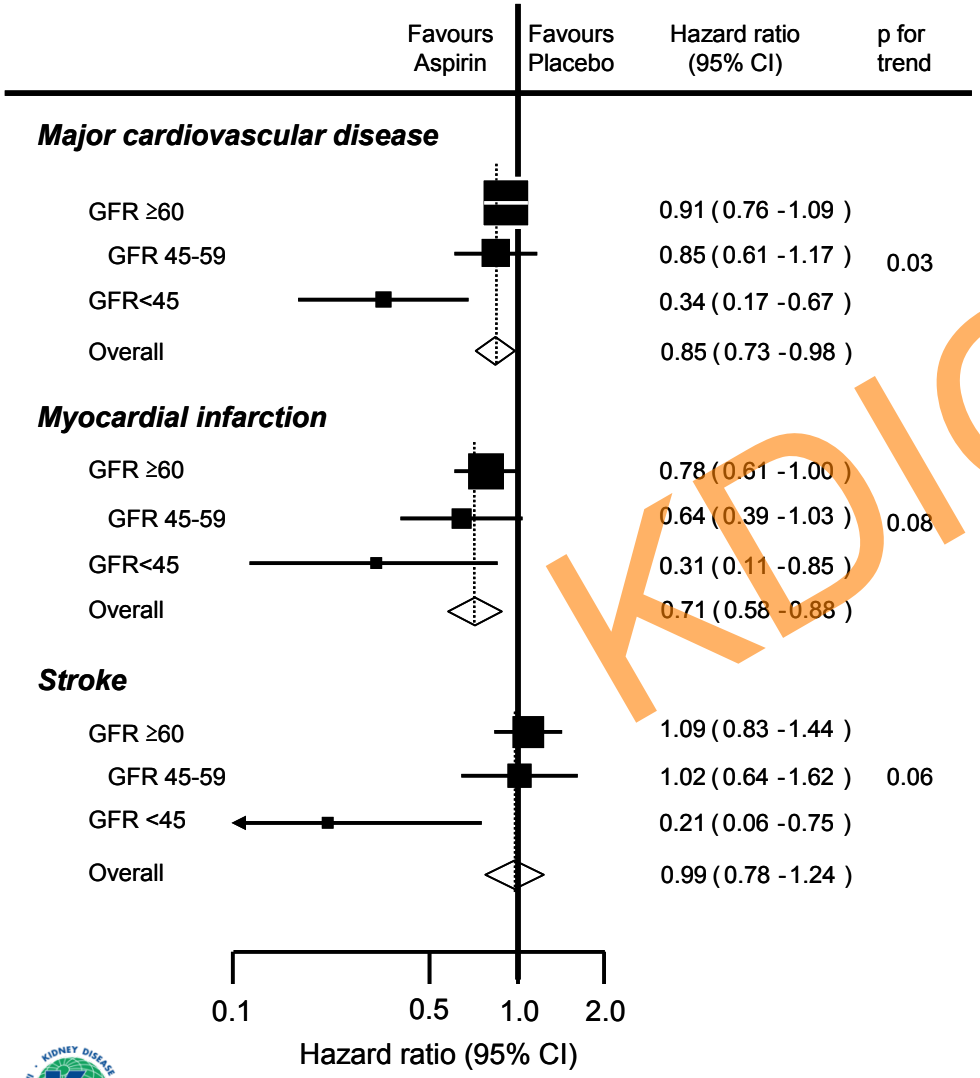
Diastolic blood pressure 100 – 115 mmHg

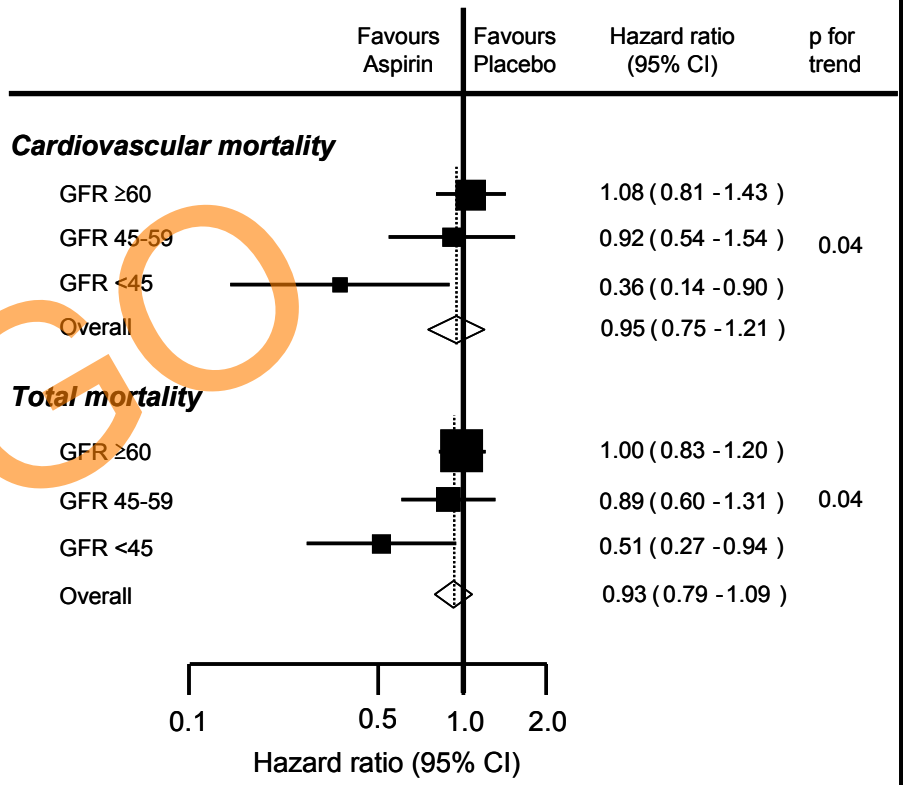
8% had DM

	Glomerular filtration ratio (ml/min/1.73 m^2)					
	≥ 60		45-59		<45	
OVERALL	Aspirin (n=7517)	Placebo (n=7461)	Aspirin (n=1527)	Placebo (n=1556)	Aspirin (n=264)	Placebo (n=272)
eGFR (ml/min/1.73 m^2), median (IQR)	77 (69-88)	77 (69-89)	55 (52-58)	55 (52-58)	40 (34-43)	39 (32-43)
Cr (µmol/L), median (IQR)	81 (71-93)	81 (71-93)	99 (92-115)	100 (93-115)	142 (121-174)	150 (121-177)
Diabetes (%)	8	8	9	7	12	11

Jardine, *JACC* 2010

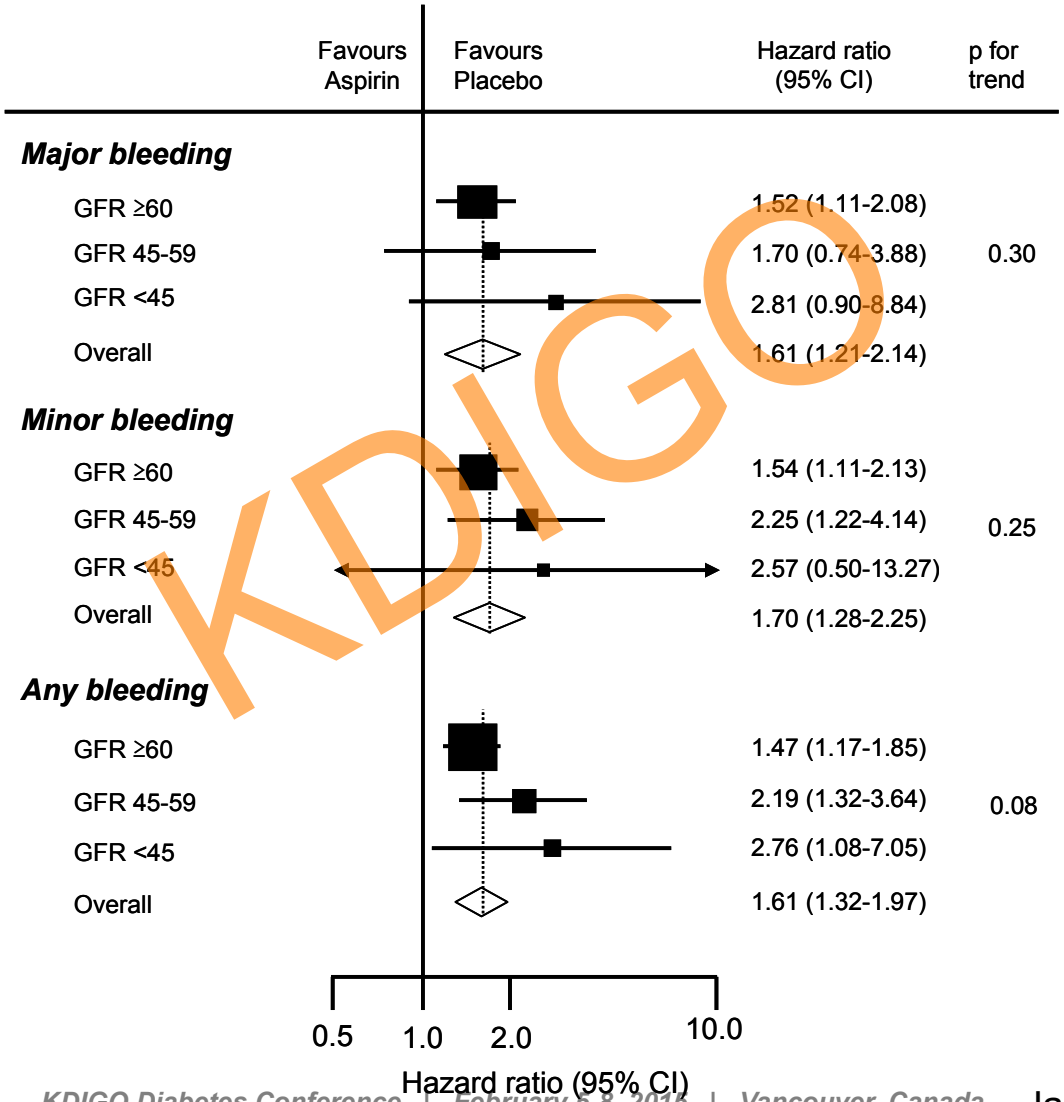
1ary prevention with aspirin in CKD





Jardine, *JACC* 2010

Aspirin-induced Bleeding In CKD



Jardine, *JACC* 2010

1ary prevention with aspirin in DM

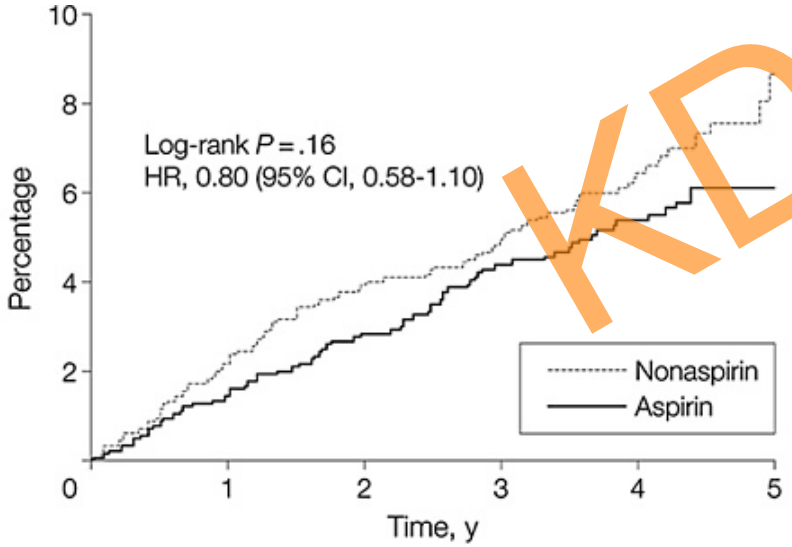
JPAD

DM2, n=2539

13% nephropathy

~18% proteinuria >15mg/dl

Composite: Fatal/non-fatal MI & stroke, & PAD



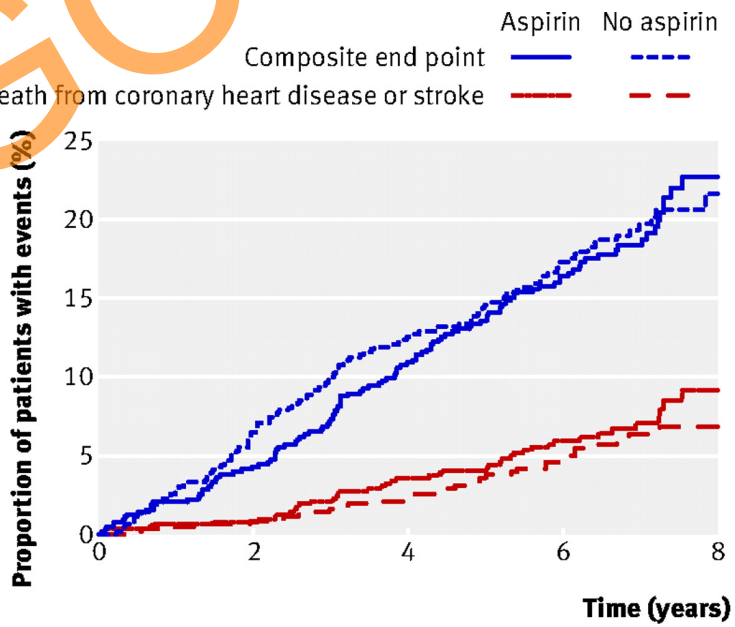
Ogawa H *JAMA*. 300(18):2134-41

POPADAD

DM1/2 + asymptomatic PVD, n=1276

No albuminuria information

Composite: Fatal/non-fatal MI & stroke, amputation



Belch J *BMJ* 2008;337:a1840

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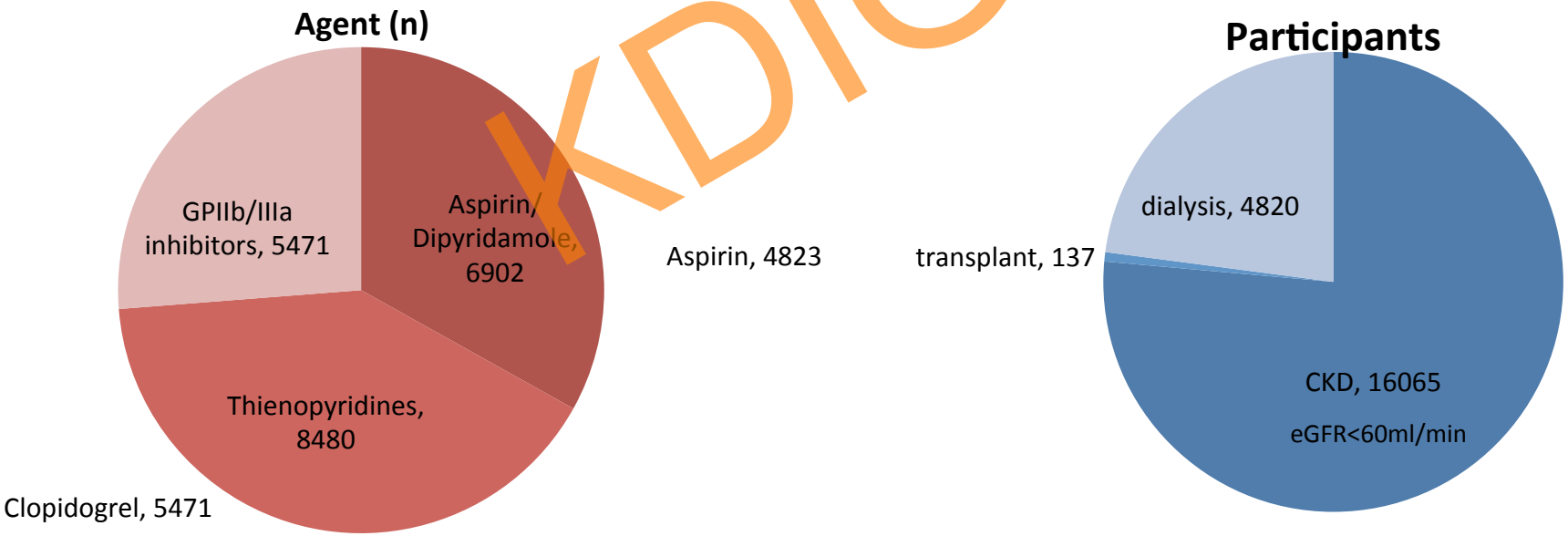
Antiplatelets in Kidney Disease: SR

- Combined primary and secondary prevention
- 50 studies (n=27,139)
  - 44 (n=21,460) compared antiplatelet with placebo
- Studies
  - Median 100 participants (range 16-4,087)
  - Median followup: 9 mths (1-61)



Palmer, Cochrane Database, 2013

Antiplatelets in Kidney Disease: SR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatal or nonfatal myocardial infarction	17	14451	Risk Ratio (IV, Random, 95% CI)	0.87 [0.76, 0.99]
2 Fatal or nonfatal stroke	11	9544	Risk Ratio (IV, Random, 95% CI)	1.00 [0.58, 1.72]
3 Haemorrhagic stroke	6	6044	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.69, 2.17]
4 All-cause mortality	29	16152	Risk Ratio (IV, Random, 95% CI)	0.95 [0.83, 1.07]
5 Cardiovascular mortality	18	9337	Risk Ratio (IV, Random, 95% CI)	0.87 [0.65, 1.15]
6 Fatal bleeding	16	7037	Risk Ratio (IV, Random, 95% CI)	5.11 [0.25, 106.00]
7 Major bleeding	26	15992	Risk Ratio (IV, Random, 95% CI)	1.35 [1.10, 1.65]
8 Minor bleeding	18	13106	Risk Ratio (IV, Random, 95% CI)	1.54 [1.26, 1.90]
9 End-stage kidney disease	8	825	Risk Ratio (IV, Random, 95% CI)	0.96 [0.67, 1.37]
10 Doubling of serum creatinine	2	126	Risk Ratio (IV, Random, 95% CI)	0.43 [0.12, 1.47]
11 Kidney transplant graft loss	2	91	Risk Ratio (IV, Random, 95% CI)	1.08 [0.58, 2.01]
12 Transplant rejection	2	97	Risk Ratio (IV, Random, 95% CI)	0.95 [0.77, 1.19]

Palmer, Cochrane Database, 2013

Medication Type

Outcome	Aspirin: RR (95% CI)	Thienopyridines: RR (95% CI)	Glycoprotein IIb/IIIa inhibitors: RR (95% CI)	All medications: RR (95% CI)*
Fatal or nonfatal myocardial infarction	0.68 (0.46 to 0.99)	0.83 (0.57 to 1.21)	0.93 (0.81 to 1.07)	0.87 (0.76 to 0.99)
All-cause death	0.88 (0.61 to 1.27)	1.10 (0.80 to 1.51)	0.83 (0.60 to 1.16)	0.95 (0.83 to 1.07)
Major bleeding	1.37 (0.71 to 2.55)	1.27 (0.85 to 1.91)	1.45 (1.04 to 2.04)	1.35 (1.10 to 1.65)

*There were no significant differences among antiplatelet types in any of the reported outcomes listed.

Palmer, Cochrane Database, 2013

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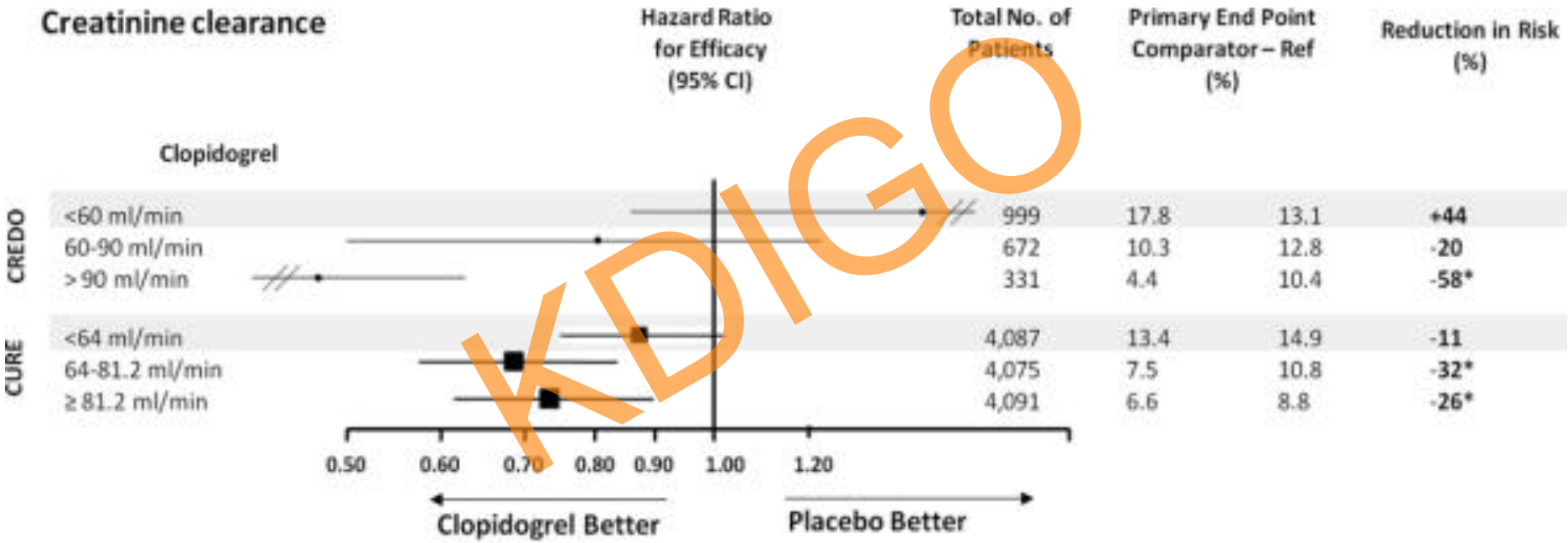
Clopidogrel in CKD



CURE
N=12253, non-ST elevation acute coronary syndrome
Placebo controlled clopidogrel for 12 months

CREDO
n=2116, Elective PCI
Placebo controlled clopidogrel 75mg for 12 months

Montalescot *Circulation*. 122(11):1049-1052, 2010.

Clopidogrel in Diabetic Kidney Disease

CHARISMA RCT
n=2009
Multiple vascular risk factors

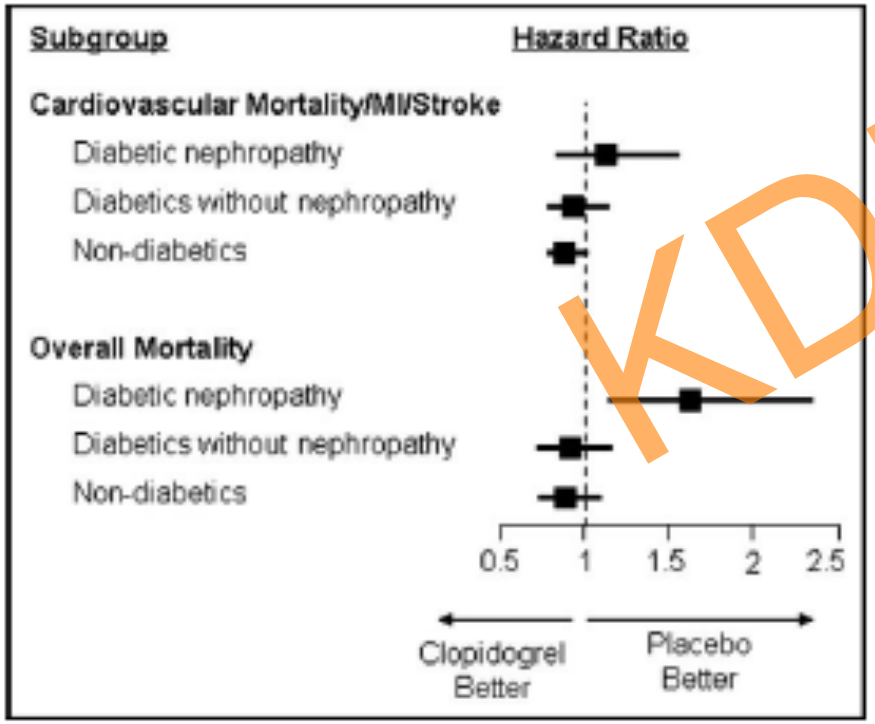


Figure 3. Forest plot of the effect of drug assignment and diabetic nephropathy status on the primary end point and overall mortality.

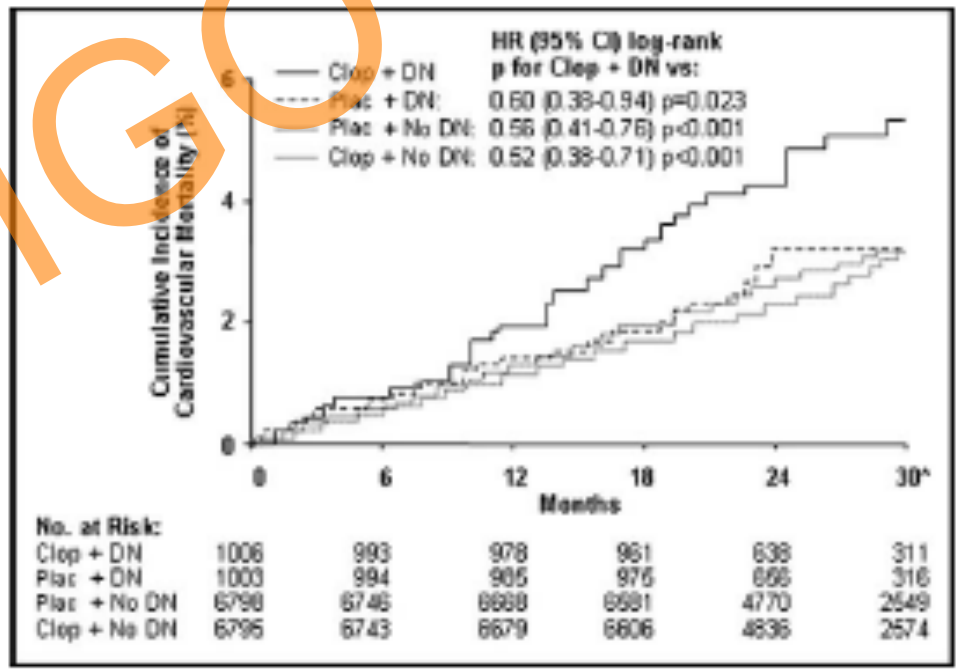


Figure 2. Kaplan-Meier estimates of cumulative incidence of CV mortality. *Kaplan-Meier curves truncated to 30 months. Clop – clopidogrel; DN – diabetic nephropathy; Plac – placebo.

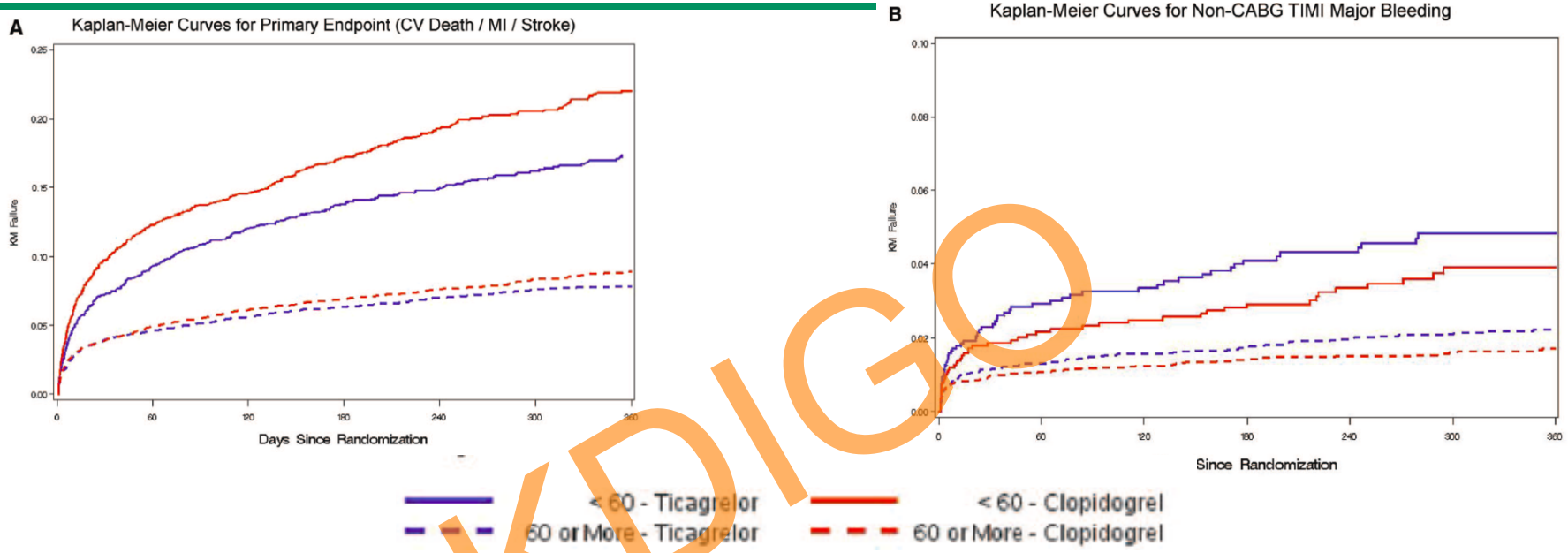
ADP R antagonists: agent or class?

- PLATO
  - N=18624, acute coronary syndrome
  - Ticagrelor (90mg bd) v clopidogrel (75mg) daily)
  - Median 9mo FU

  - CG defined subgroup analysis
- CG GFR<60ml/min
  - n=3237
  - DM = 33%
- CG GFR≥60ml/min
  - n=11965
  - DM = 23%

James, S *Circulation*. 2010; 122:1056-1067

ADP R antagonist: head to head

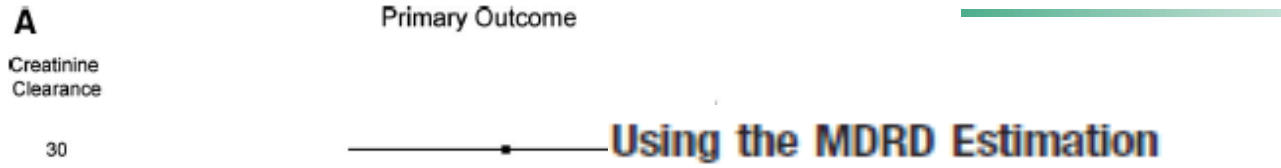


CV composite	RR (95%CI)
Overall	0.84 (0.76, 0.93)
<60	0.77 (0.65, 0.90)
≥60	0.90 (0.79, 1.02)
p heterogeneity	0.13

Major bleeding	RR (95%CI)
Overall	1.07 (0.97, 1.19)
<60	1.07 (0.88, 1.30)
≥60	1.08 (0.96, 1.22)
p heterogeneity	0.92

James, S *Circulation*. 2010; 122:1056-1067

ADP R antagonist: head to head



CrCl, mL/min	HR (95% CI)	*P* for Interaction
Primary outcome: cardiovascular death/ myocardial infarction/stroke		
Overall	0.84 (0.76–0.93)	
<60	0.71 (0.59–0.86)	0.03
≥60	0.90 (0.80–1.02)	
All-cause death		
Overall	0.79 (0.68–0.92)	
<60	0.64 (0.50–0.81)	0.02
≥60	0.91 (0.75–1.09)	
Major bleeding, PLATO defined		
Overall	1.07 (0.97–1.19)	
<60	1.08 (0.87–1.34)	0.98
≥60	1.08 (0.96–1.20)	

Ticagrelor Better

Clopidogrel Better

Prasugrel/ticagrelor v clopidogrel

	Ticagrelor v clopidogrel	Prasugrel v clopidogrel
Trial	PLATO, 2010	TRITON-TIMI, 2007
Source	James Circulation. Palmer, Cochrane SR	Unpublished data. (Palmer, Cochrane SR)
CKD (n)	3237 Incl. 33% with DM	1490 Incl. 30% with DM
MI		0.78 (0.58,1.05)
Stroke	1.79 (0.43, 7.51)	
All-cause mortality	0.72 (0.58, 0.89)	0.81 (0.56, 1.18)
CV mortality		1.35 (0.87, 2.10)
Fatal bleeding	0.48 (0.15, 1.54)	
Major bleeding	1.12 (0.90, 1.39)	

ADP R antagonists in DM2

Adenosine-diphosphate (ADP) receptor antagonists (clopidogrel, ticlopidine, prasugrel, ticagrelor) for the prevention of cardiovascular disease in type 2 diabetes mellitus

Patient or population: patients with type 2 diabetes mellitus
Settings: out-patients
Intervention: ADP receptor antagonists
Comparison: Aspirin (/dipyramidole)/placebo

Inclusion: at least 12 months
8 studies, n=21739

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ADP receptor antagonist				
All-cause mortality (ticlopidine vs placebo)	14.1%	17.4%	RR 1.29 (0.71 to 2.32)	335 (1)	moderate quality	See[a]
Vascular mortality (ticlopidine vs placebo)	11%	10.5%	RR 0.94 (0.47 to 1.88)	335 (1)	moderate quality	See[a]
Myocardial infarction (fatal and non-fatal) (ticlopidine vs placebo)	11.7%	9.3%	RR 0.78 (0.39 to 1.57)	335 (1)	moderate quality	See[a]
Stroke (fatal and non-fatal) (a. ticlopidine vs aspirin) (b. clopidogrel vs aspirin & dipyramidole)	a. 0.14% b. 0.11%	a. 0.9% b. 0.12%	a. RR 0.56 (0.37 to 0.94) b. RR 1.12 (0.95 - 1.32)	a. 597 (1) b. 5770 (1)	a. moderate quality b. moderate quality	a. See[a] b. See[b]

Valentine et al, Cochrane Database of SRs, 2012

Uncertainties

- Aspirin for primary prevention may be beneficial in CKD
  - Some evidence for early CKD
  - Very little for advanced CKD
  - Impact on bleeding poorly defined
- Benefits and harms of ADP receptor antagonists poorly understood
  - Some suggestions impact may be different from general population for CKD and for diabetic nephropathy
  - Little known on effects and harms in diabetic population
- Comparative studies are needed
  - Possible there is not a uniform class effect for ADP receptor antagonists in CKD

Aspirin-induced Bleeding

- Primary prevention trials
  - 0·10% *vs* 0·07% per year; RR 1·54 [1·30–1·82], p<0·0001
- Secondary prevention trials
  - Reporting too incomplete
  - Stroke subtype rarely reported

ATT, *Lancet* 2009; 373: 1849-60