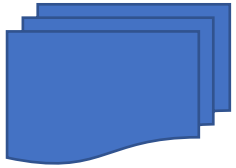

Literatuur

Tine De Backer

Farmacotherapeutisch Bijblijven

woensdag 8 februari 2023

Artikels

1. Colchicine and Cardiovascular Outcomes: a critical appraisal of recent studies

Maciej Banach, Peter E. Penson

Current Atherosclerosis Reports (2021) 23: 32

2. Systematic review and meta-analysis of headto-head trials comparing sulfonylureas and low hypoglycaemic risk antidiabetic drugs

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3. First-trimester exposure to benzodiazepines and risk of congenital malformations in offspring: A population-based cohort study in South Korea

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PLoS Med 2022; 19(3): e1003945. https://doi.org/10.1371/journal. pmed.1003945

4. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

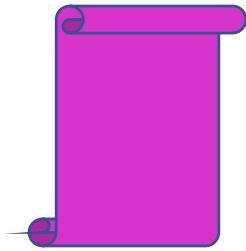
Isla S Mackenzie, Amy Rogers, Neil R Poulter, Bryan Williams, Morris J Brown, David J Webb

The Lancet 2022; October 11, 2022 https://doi.org/10.1016/S0140-6736(22)01786-X

1. Colchicine and Cardiovascular Outcomes: a critical appraisal of recent studies

Maciej Banach, Peter E. Penson

Current Atherosclerosis Reports (2021) 23: 32

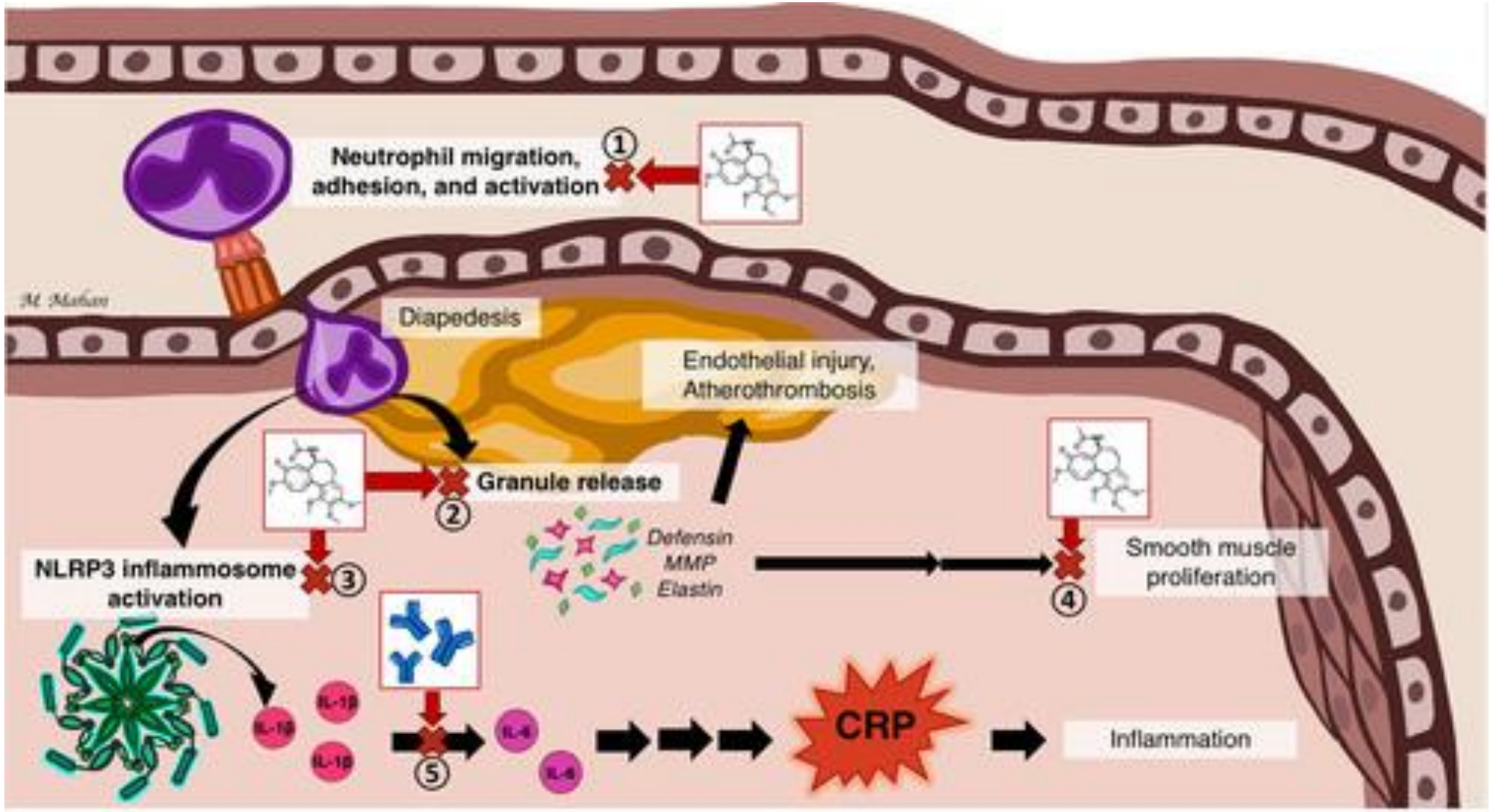


Colchicine vermindert de inflammatie veroorzaakt door de vorming van urinezuurkristallen in de gewrichten; het heeft op zich geen analgetisch effect.

- Colchicine wordt soms ook gebruikt bij recidiverende pericarditis (indicatie niet vermeld in de SKP) en Familiale Middellandse Zeekoorts.

Colchicine Opocalcium 1mg tabl. (deelb.)

BCFi
BELGISCH CENTRUM VOOR FARMACOTHERAPEUTISCHE INFORMATIE



Spyridon G. Deftereos. Circulation. Colchicine in Cardiovascular Disease: In-Depth Review, Volume: 145, Issue: 1, Pages: 61-78, DOI: (10.1161/CIRCULATIONAHA.121.056171)

Colchicine and Cardiovascular Outcomes: a critical appraisal of recent studies

- Background & Aim:

  -Role for inflammation in the pathogenesis of atherosclerotic cardiovascular disease.

  -Colchicine = a widely used and safe anti-inflammatory drug in patients with atherosclerosis.

Rationale for the use of colchicine in this setting and critical appraisal of recent outcome trials.

- Results:

  -2 large randomised-controlled trials: **LoDoCo2** (patients with chronic coronary syndromes) and **COLCOT** (acute coronary syndromes): reductions in atherosclerotic cardiovascular events, but not mortality.

  -A smaller study **COPS** (acute coronary syndromes): no beneficial effect of colchicine (probably underpowered).

- Conclusion:

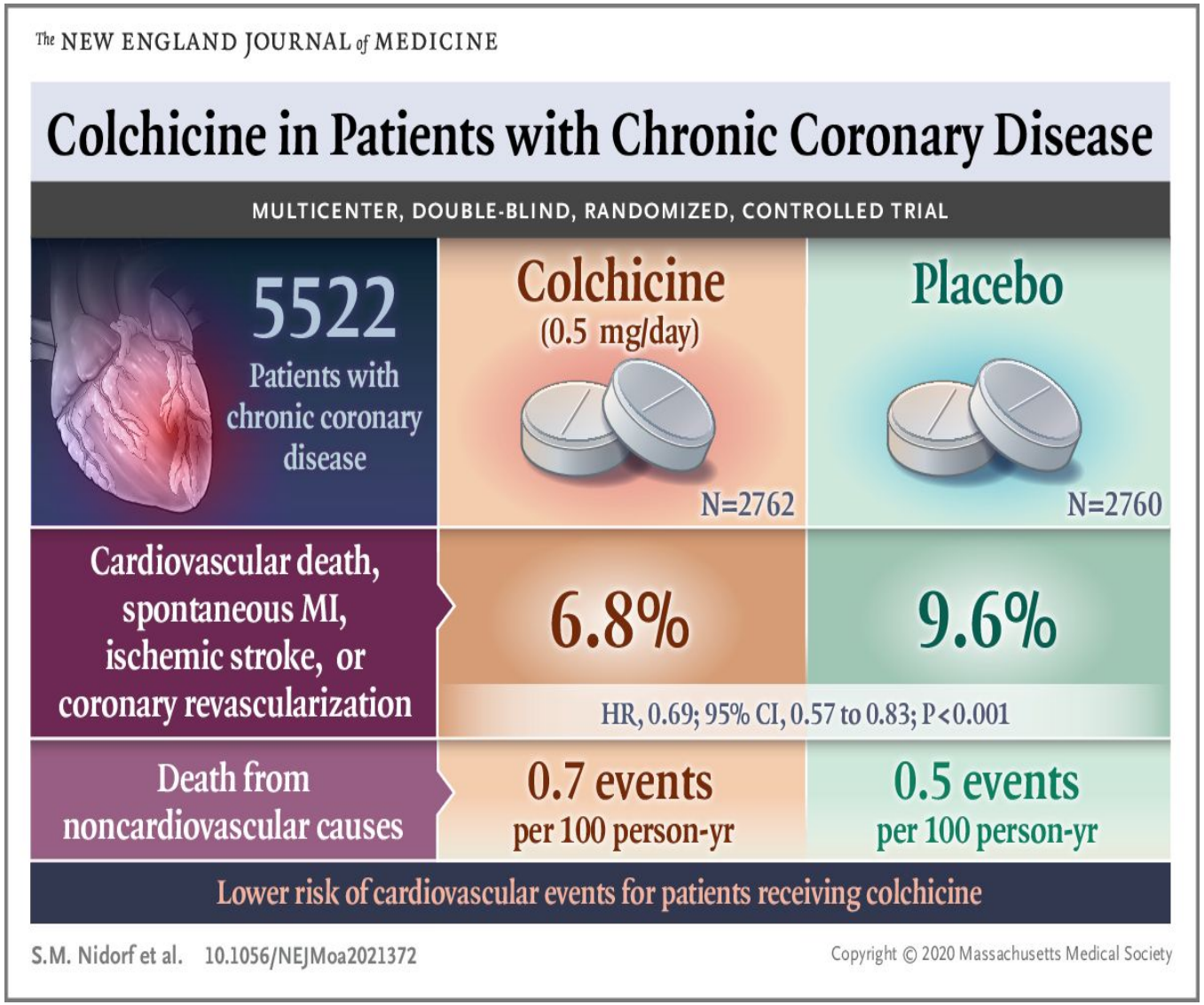
  -Colchicine effective at reducing cardiovascular events in chronic and acute coronary syndromes

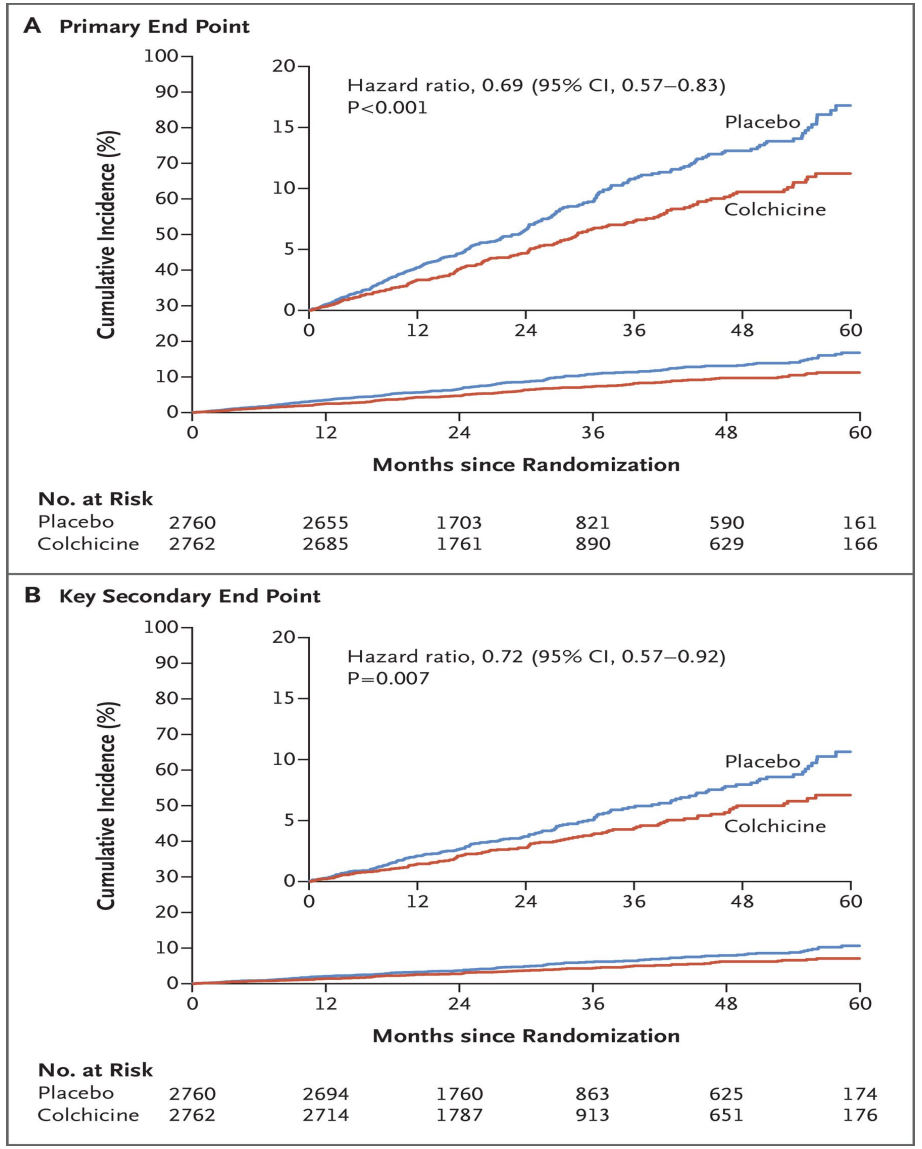
  -No reductions in all-cause mortality during the period of follow-up in trials to date.

  -Mild gastrointestinal symptoms are the most commonly reported adverse effects, although in well-designed randomised controlled trials these are relatively uncommon.

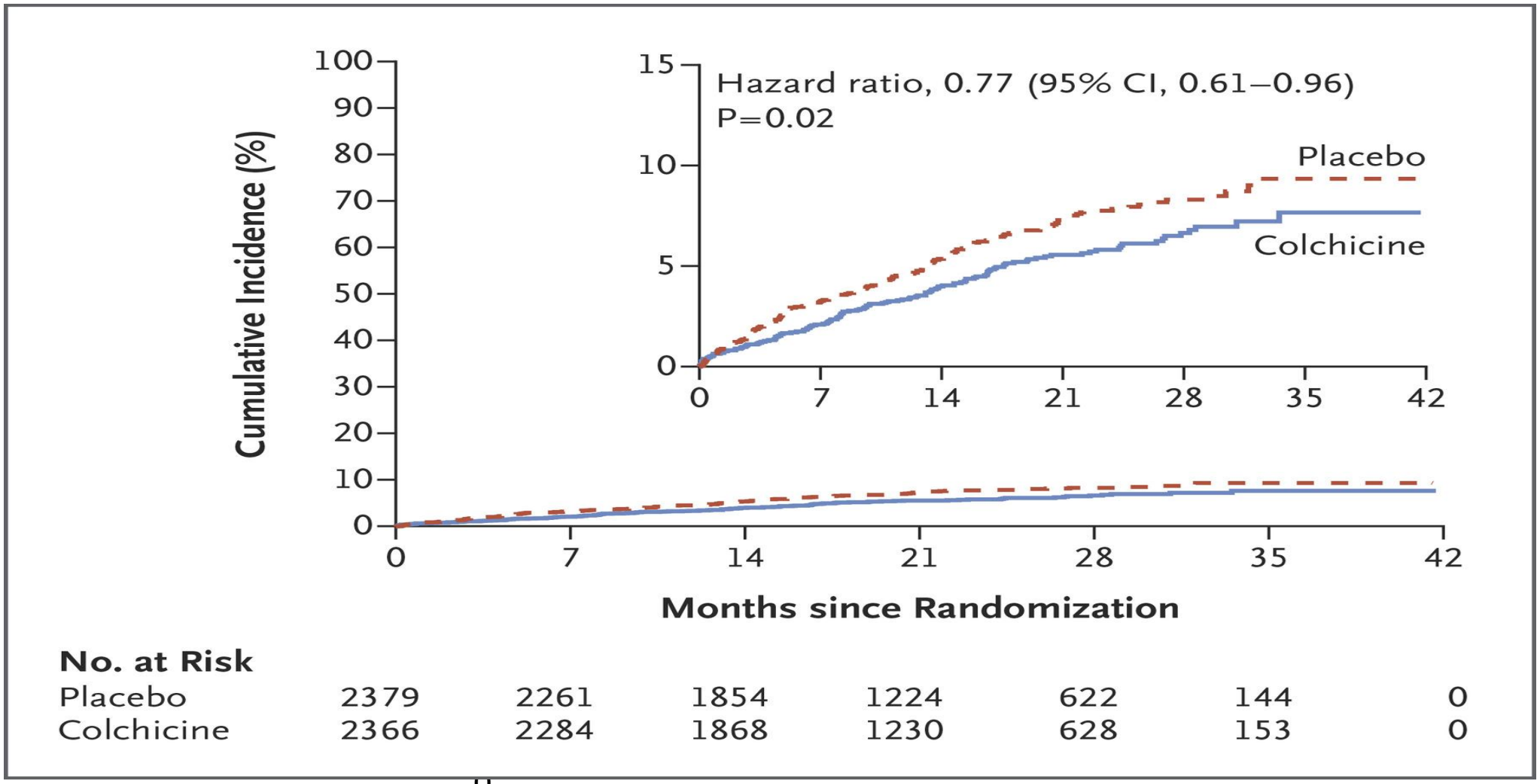
LoDoCo2 Trial Low Dose Colchicin for Secondary Prevention of CVD

Colchicine in Patients with Chronic Coronary Disease





COLCOT(Colchicine Cadiovascular Outcomes trial)trial
Colchicine in Patients with recent MI



N Engl J Med 2019; 381:2497-2505. DOI: 10.1056/NEJMoa1912388

COLCOT(Colchicine Cadiovascular Outcomes trial)trial

Colchicine in Patients with recent MI

COLCOT: Early initiation of low-dose colchicine after myocardial infarction reduces the risk of ischemic CV events by 48% compared with placebo.

From December 2015 to August 2018,
4745 patients recruited in COLCOT

↓

Safety population for TTI analysis,
N=4661

↓

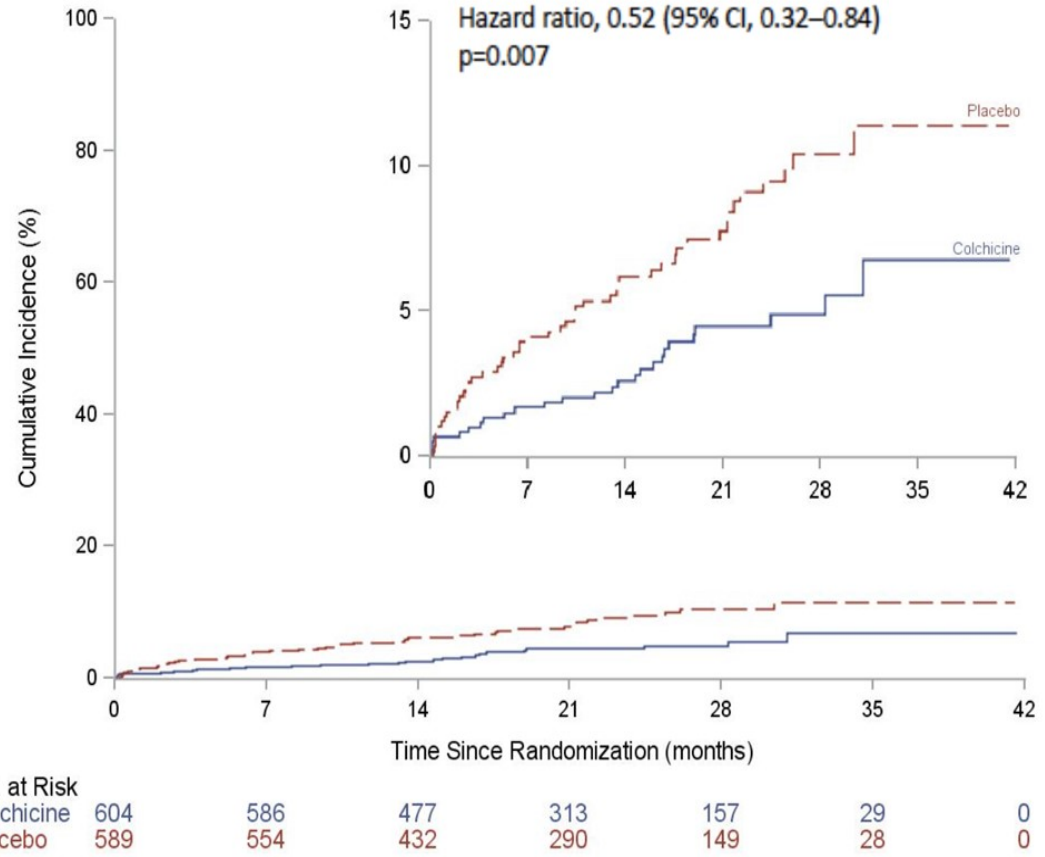
Randomized to Colchicine **(N=2322)**
0.5 mg daily vs. Placebo **(N=2339)**

↓

Median Follow-up **22.7 months**

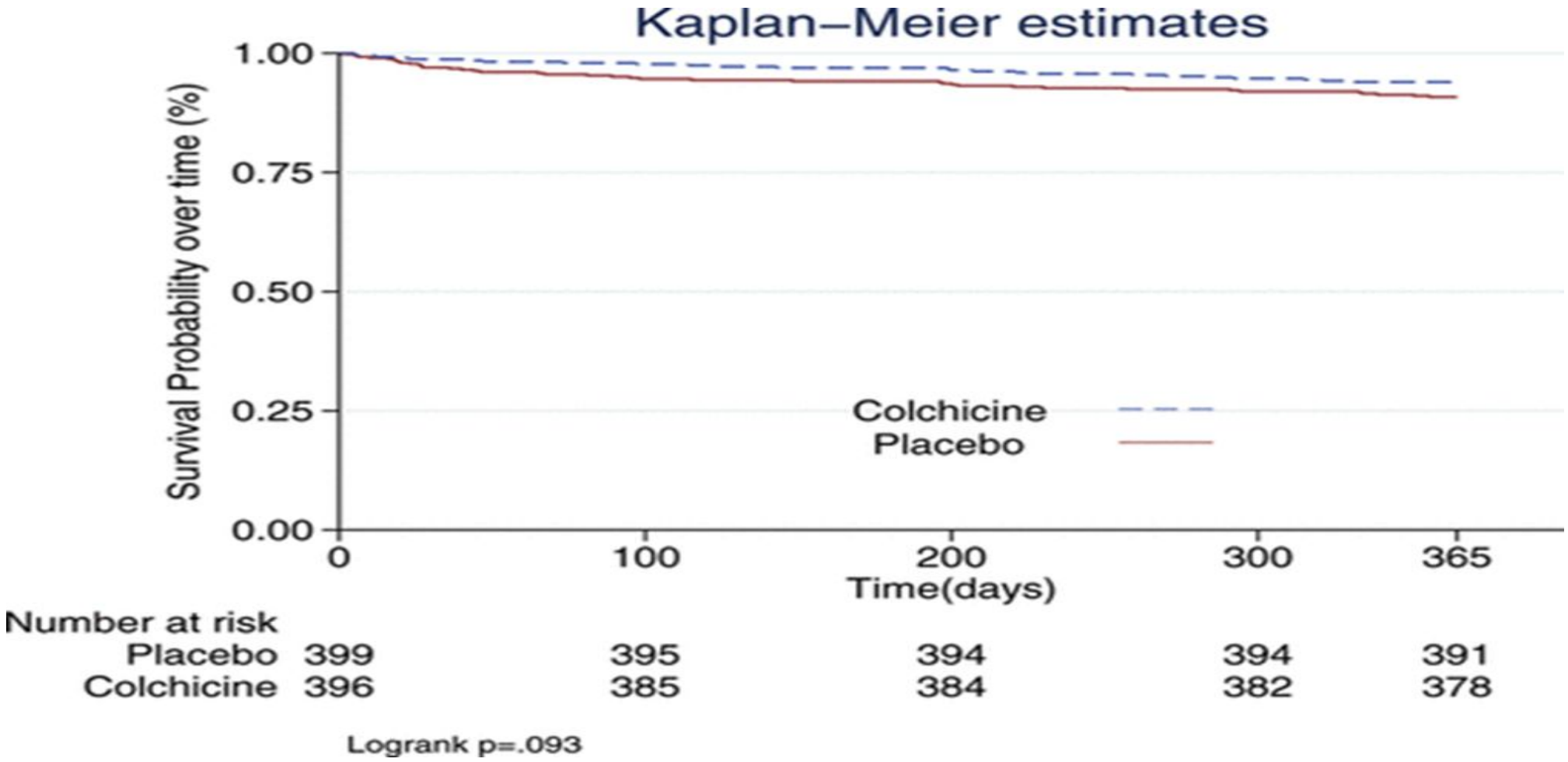
↓

Occurrence of the primary efficacy endpoint when treatment is initiated ≤ day 3 post-MI :
4.3% with colchicine vs. 8.3% with placebo



N Engl J Med 2019; 381:2497-2505. DOI: 10.1056/NEJMoa1912388

COPS Colchicine in Patients With Acute Coronary Syndrome The Australian COPS Randomized Clinical Trial



David C. Tong. Circulation. Colchicine in Patients With Acute Coronary Syndrome, Volume: 142, Issue: 20, Pages: 1890-1900, DOI: (10.1161/CIRCULATIONAHA.120.050771

Main Colchcine trials and CV outcomes

TRIAL (year)	LoDoCo [43] (2013)	COLIN [65] (2017)	**LoDoCo2[45] (2020)**	COLCHICINE-PCI [68] (2020)	**COPS [64] (2020)**	**COLCOT [46] (2019)**
Patients enrolled	535 (473 male)	44 (35 male)	5522 (4676 male)	400 (374 male)	795 (632 male)	4745 (3836 male)
Median follow-up	3 years	1 month	28.6 months	1 month	12 month	22.6 months
Setting	CCS	ACS	CCS	ACS/CCS	ACS	ACS
Study design and aims	Randomized, prospective, observer-blinded endpoint trial to assess efficacy of continuous low-dose of colchicine treatment in patients with stable CAD in reducing CV events	Randomized, prospective, open-label, controlled trial to assess effect of colchicine plus OMT or OMT alone in STEMI patients	Randomized, controlled, double-blind trial to further assess the effect of colchicine in patients with chronic coronary disease	Randomized, double-blinded, placebo-controlled trial to determine the effects of acute preprocedural oral administration of 1.8 mg of colchicine on PCI-related myocardial injury	Randomized, double-blind, placebo-controlled trial to assess the effect of oral colchicine on CV events in patients presenting with ACS	Randomized, double-blind, placebo-controlled, investigator-initiated trial to assess the effects of colchicine on CV outcomes and its safety profile in patients with recent MI (within 30 days)
Colchicine dosing regimen	0.5 mg QD	1 mg QD for 1 month	0.5 mg QD	Acute preprocedural oral use of 1.8 mg of colchicine	0.5 mg BID for first month followed by 0.5 mg QD for 11 months	0.5 mg QD
Primary endpoint	Composite of ACS, fatal or nonfatal out-of-hospital cardiac arrest, or noncar- dioembolic ischemic stroke	CRP peak during the index hospitalization	Composite of cardiovascular death, spontaneous (non- procedural) MI, ischemic stroke, or ischemia-driven coronary revascularization	PCI-related myocardial injury	Composite of death from any cause, ACS (STEMI/NSTEMI/UA), ischemia-driven urgent revascularization and non-cardioembolic ischemic stroke	Composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization in a time-to-event analysis
Secondary endpoints	Components of the primary outcome and the components of ACS unrelated to stent disease	Troponin peak, tolerance of colchicine, hospitalization duration, MACE at 1-month follow-up; cardiac remodeling	Composite of cardiovascular death, spontaneous MI, or ischemic stroke	MACEs at 30 days; composite of the earliest occurrence of death from any cause, nonfatal MI, or target vessel revascularization; PCI-related MI; change in plasma inflammatory markers concentration between baseline and post-PCI	Components of the primary endpoint and hospitalization for chest pain	Components of the primary efficacy end point; composite of death from CV causes, resuscitated cardiac arrest, MI, or stroke; total mortality in time to-event analyses
Primary endpoint reached	YES 5.3%—colchicine 16.0%—placebo HR 0.33 (95% CI	NO 29.03 mg/L – colchicine 21.86 mg/L – control group	YES 6.8%—colchicine 9.6%—placebo HR 0.69 (95% CI	NO 57.3%—colchicine 64.2%—placebo P = 0.19	NO 24 events – colchicine (24/396) 38 events –	YES 5.5%—colchicine 7.1%—placebo HR 0.77 (95% CI

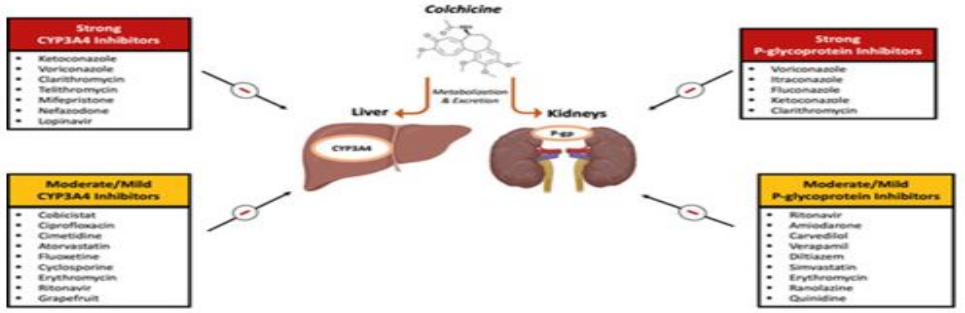
Colchicine adverse effects

- Pharmacological mechanisms of action of colchicine are not fully understood, possible off-target detrimental effects

- Trend towards increased non-CV deaths with colchicine; specific cause of death responsible for this excess of deaths has not been identified yet.

- Side effects of colchicine.
  GI-related adverse effects: diarrhea, nausea, vomiting
  Pneumonia (possibly related to immunosuppressive effects of colchicine)
  Myalgia (mainly when combining with statins), rhabdomyolysis (especially if renal impairment)

- Drug-drug interactions



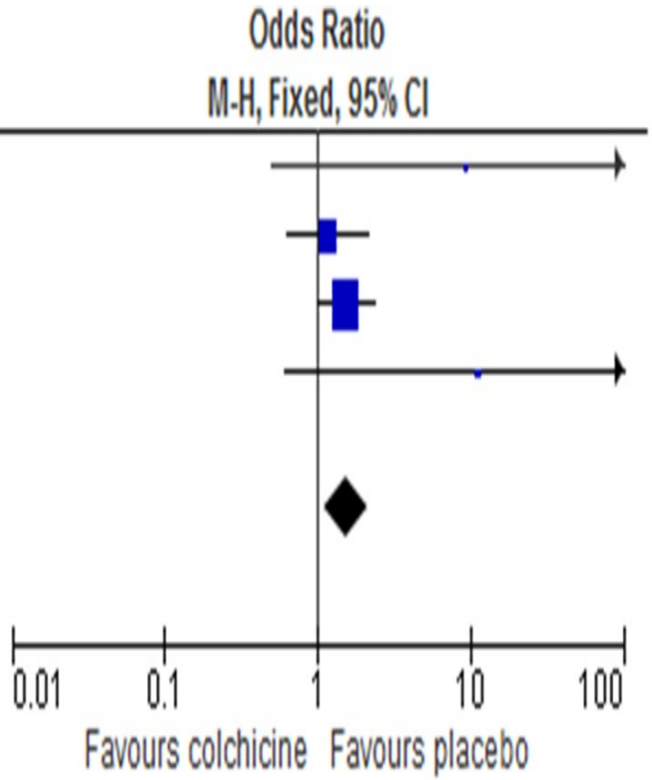
Forest plots regarding **non CV death for colchicine vs optimal medical therapy**.

ESC Working Group Cardiovascular Pharmacotherapy

Study or Subgroup	Colchicine Events	Colchicine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
LoDoCo 1	4	243	0	250	0.9%	9.41 [0.50, 175.78]	2012
COLCOT	23	2366	20	2379	35.9%	1.16 [0.63, 2.11]	2019
LoDoCo 2	53	2762	35	2760	62.4%	1.52 [0.99, 2.34]	2020
COPS	5	396	0	399	0.9%	11.22 [0.62, 203.68]	2020
Total (95% CI)		5767		5788	100.0%	1.55 [1.10, 2.17]	
Total events	85		55				

Heterogeneity: $Chi^2 = 4.16$, $df = 3$ ($P = 0.25$); $I^2 = 28\%$

Test for overall effect: $Z = 2.53$ ($P = 0.01$)

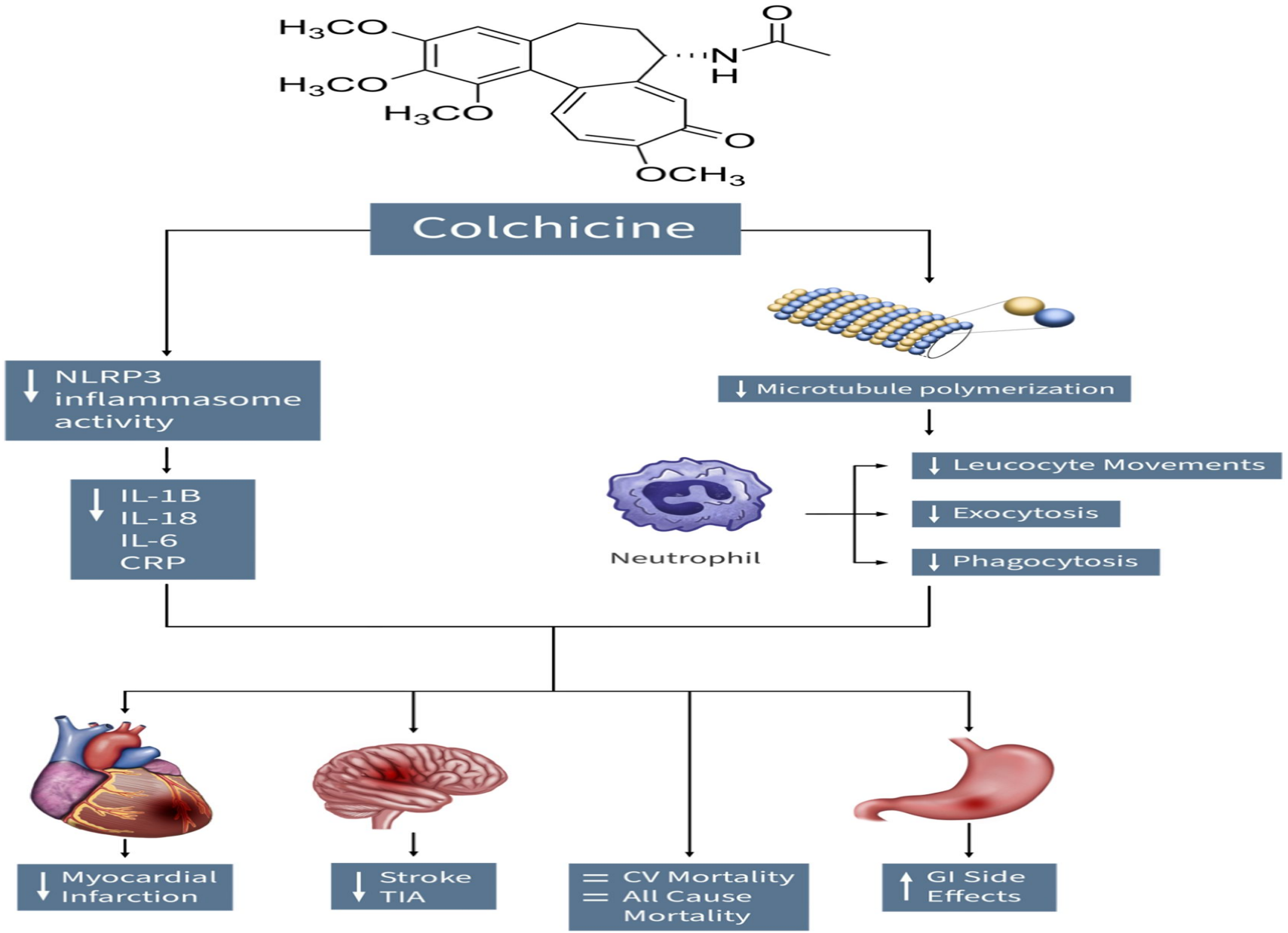


Eur Heart J Cardiovasc Pharmacother, Volume 7, Issue 3, May 2021, Pages e18–e19, https://doi.org/10.1093/ehjcvp/pvaa137

OXFORD UNIVERSITY PRESS

Colchicine Drug-Drug interactions

Drug (or class) interacting	Interaction	Collateral effects
Carvedilol	Increase colchicine serum concentrations due to intestinal, renal and liver P-gp inhibition	Neuromyopathy, rhabdomyolysis, hepato- and nephrotoxicity, cardiotoxicity
Ranolazine		
Spironolactone		
Ticagrelor	Reduced colchicine clearance due to inhibition of CYP450 3A4, by which colchicine is metabolized	Colchicine toxicity (nausea, vomiting, diarrhea, fatigue, myalgia, paresthesia)
Digoxin	Increase concentrations of both drugs due to competitive inhibition of P-gp efflux transporter in the intestine, renal proximal tubule and liver	Rhabdomyolysis, digoxin and colchicine toxicity (arrhythmias, GI symptoms, fatigue, myalgia, paresthesia)
Antiarrhythmic drugs		
Amiodarone	Increase colchicine serum concentrations due to intestinal, renal and liver P-gp inhibition	Neuromyopathy, rhabdomyolysis, hepato- and nephrotoxicity, cardiotoxicity
Quinidine		
Diltiazem	Coadministration with inhibitors of CYP450 3A4 may significantly increase the serum concentrations of colchicine, which is primarily metabolized by the isoenzyme	Myopathy, neuropathy, multiorgan failure, and pancytopenia
Verapamil		
Dronedarone		
Statins	Pharmacodynamic and pharmacokinetic interactions. HMG-CoA reductase inhibitors have in fact individually myotoxic effects (additive to those of colchicine) but are also substrates of the CYP450 3A4 isoenzyme and P-glycoprotein efflux transporter, thus competitive inhibition may occur resulting in increased drug absorption and decreased excretion	Muscle weakness and markedly elevated creatine kinase levels; myopathy up to rhabdomyolysis resulting in myoglobinuric and acute renal failure
Hydroxychloroquine	Additive pharmacodynamic risk of peripheral neuropathy	Peripheral neuropathy
Antibiotics		
Clarithromycin	Inhibition of the CYP450 3A4-mediated metabolism and P-glycoprotein (P-gp)-mediated colchicine transport by clarithromycin resulting in significantly serum colchicine increase	Myopathy, neuropathy, multiorgan failure, pancytopenia
Other Macrolides	Coadministration with inhibitors of CYP450 3A4 may significantly increase the serum concentrations of colchicine, which is primarily metabolized by the isoenzyme	
Ciprofloxacin		
Antiviral		
Darunavir/ Ritonavir		
Boceprevir/Telaprevir		
Antimycotic		
Fluconazole		
Ketoconazole		



Thomas Kofler. Journal of the American Heart Association. Colchicine in Patients With Coronary Artery Disease: A Systematic Review and Meta-Analysis of Randomized Trials, Volume: 10, Issue: 16, DOI: (10.1161/JAHA.121.021198)

Reflections

- Varying results (different populations, different settings,)
- CV benefit highly probable
- No reduction in mortality sure (neutral? Power?)
- Increase in Non-CV death probable (chance of play?)
- Side effects (GI) sure (still exaggerated?)
- Drug Drug interactions sure

2. Systematic review and meta-analysis of head-to-head trials comparing sulfonylureas and low hypoglycaemic risk antidiabetic drugs

Vallo Volke, Urmeli Katus, Annika Johannson, et al.

BMC Endocrine Disorders (2022) 22:251 ***https://doi.org/10.1186/s12902-022-01158-5***

De hypoglykemiërende sulfamiden verlagen de glykemie door stimulatie van de endogene insulinesecretie.

Langerwerkende middelen (**glibenclamide, gliclazide** met gereguleerde afgifte, **glimepiride**) en Korterwerkende middelen (**gliquidon**).

Glipizide (Minidiab) is uit de markt genomen in november 2020.

De hypoglykemiërende sulfamiden zijn een behandelingsoptie bij onvoldoende doeltreffendheid van metformine of bij contra-indicatie voor metformine. De voorkeur gaat uit naar kortwerkende middelen wegens een minder groot risico van hypoglykemie.

De hypoglykemiërende sulfamiden verminderen de microvasculaire complicaties van type 2-diabetes, maar niet de macrovasculaire complicaties.

Systematic review and meta-analysis of head-to-head trials comparing sulfonylureas and low hypoglycaemic risk antidiabetic drugs

- *Background*

Safety of sulfonylurea drugs in the treatment of Type 2 Diabetes is still under debate.

- *Aim*

To compare the all-cause mortality and cardiovascular adverse events of sulfonylureas and drugs with a low risk for hypoglycaemia in adults with type 2 diabetes.

- *Methods*

Systematic review and meta-analysis of randomised controlled trials.

Randomised controlled head-to-head trials that compared sulfonylureas with active control with low hypoglycaemic potential in adults (≥18 years old) with type 2 diabetes.

Metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists.

- *Outcomes*

Primary endpoint: all-cause mortality. Secondary endpoints: MACE, cardiovascular events and severe hypoglycaemia.

Systematic review and meta-analysis of head-to-head trials comparing sulfonylureas and low hypoglycaemic risk antidiabetic drugs

- *Results*

31 studies (26,204 patients, 11,711 patients given sulfonylureas and 14,493 given comparator drugs).

In comparison to drugs with low hypoglycaemic potential, sulfonylureas had higher odds for all-cause mortality (**OR 1.32**, 95% CI 1.00-1.75), MACE (**OR 1.32**, 95% CI 1.07–1.61), myocardial infarction (fatal and non-fatal) (OR **1.67**, 95% CI 1.17–2.38) and hypoglycaemia (OR **5.24**, 95% CI 4.20–6.55).

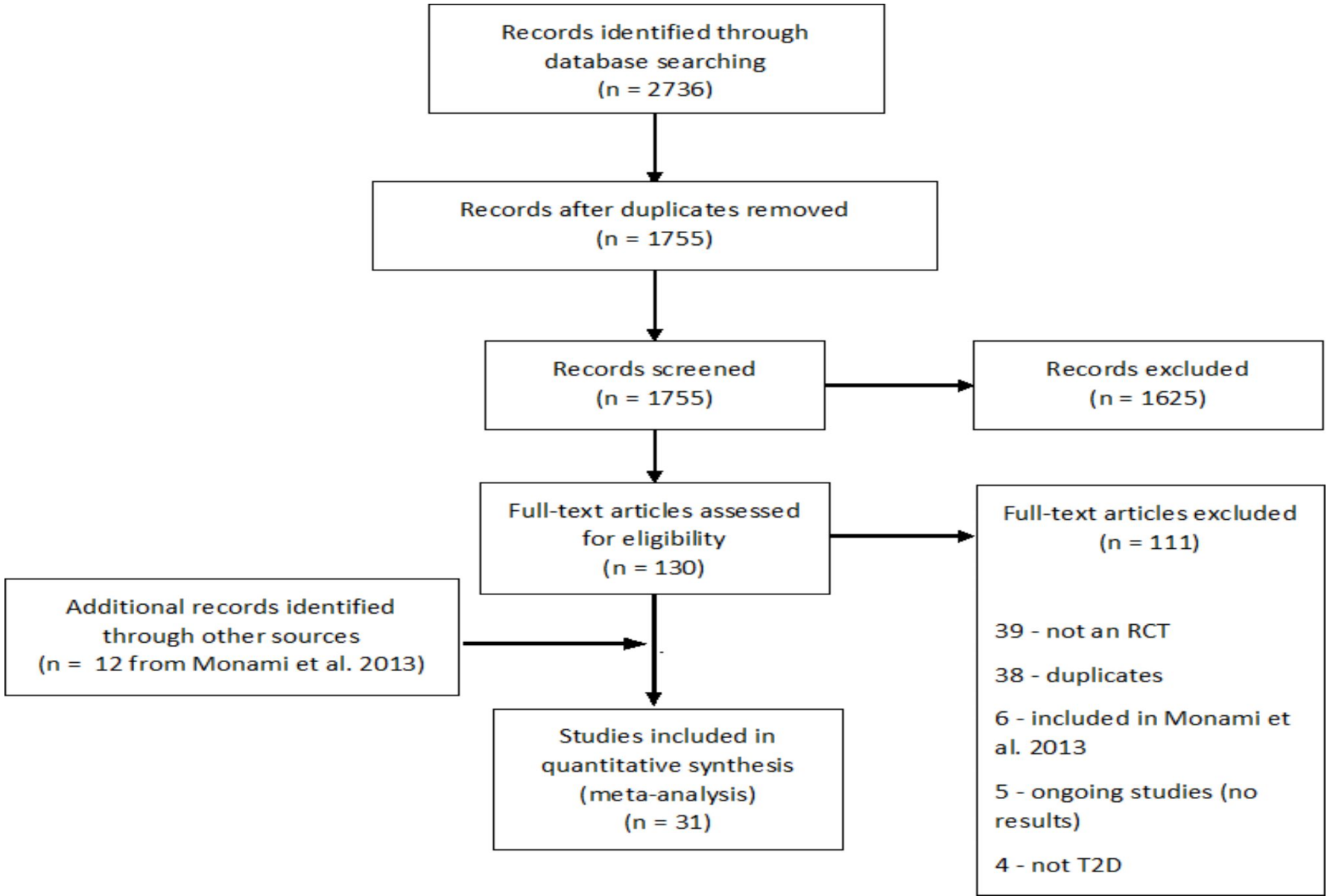
Sensitivity analysis revealed differences in the effect of sulfonylureas, with an increased risk of all-cause mortality with **glipizide** but not the other molecules.

- *Conclusion*

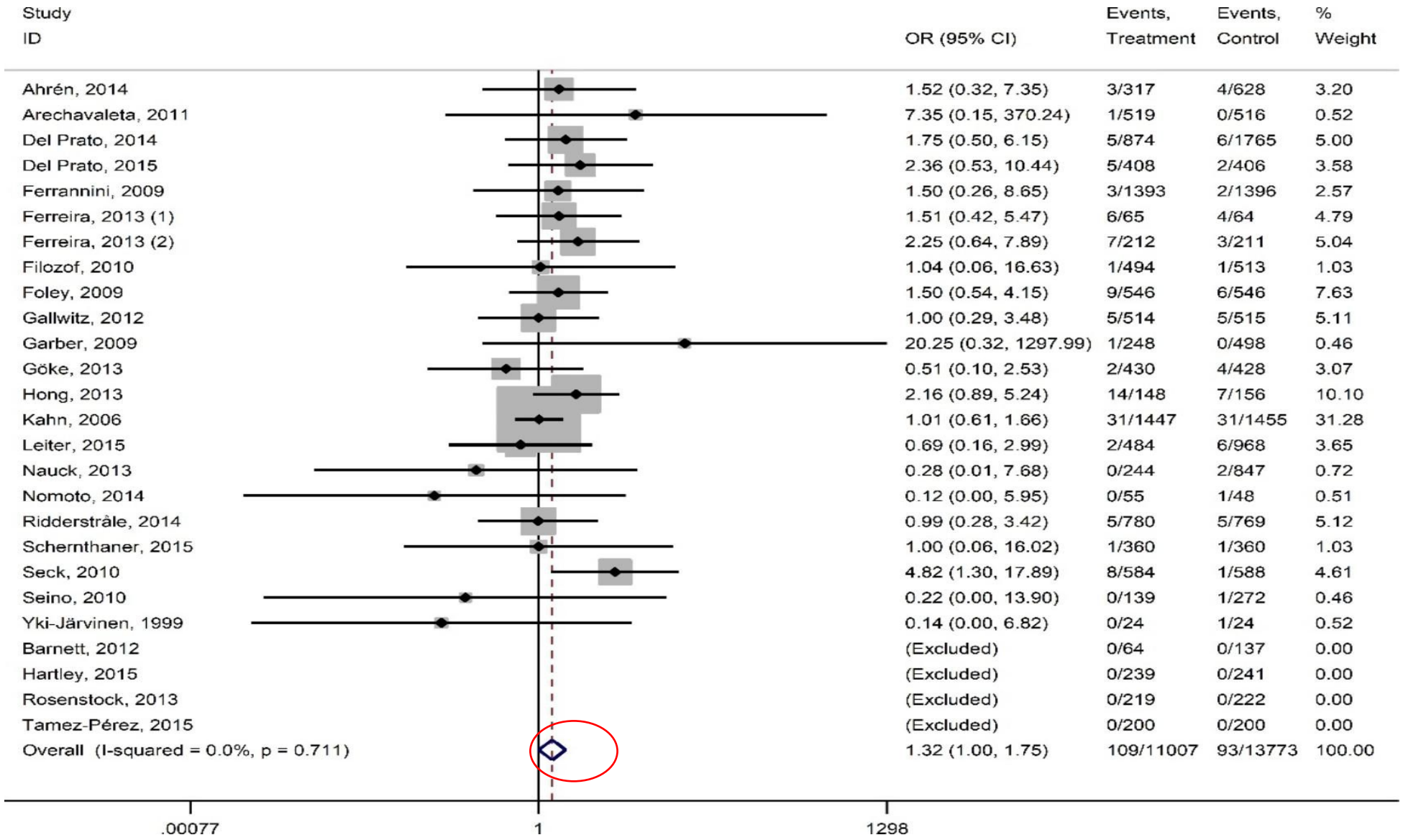
Concern about the safety of SUs compared to alternative drugs.

Important differences may exist within the drug class, glimepiride seems to have best safety

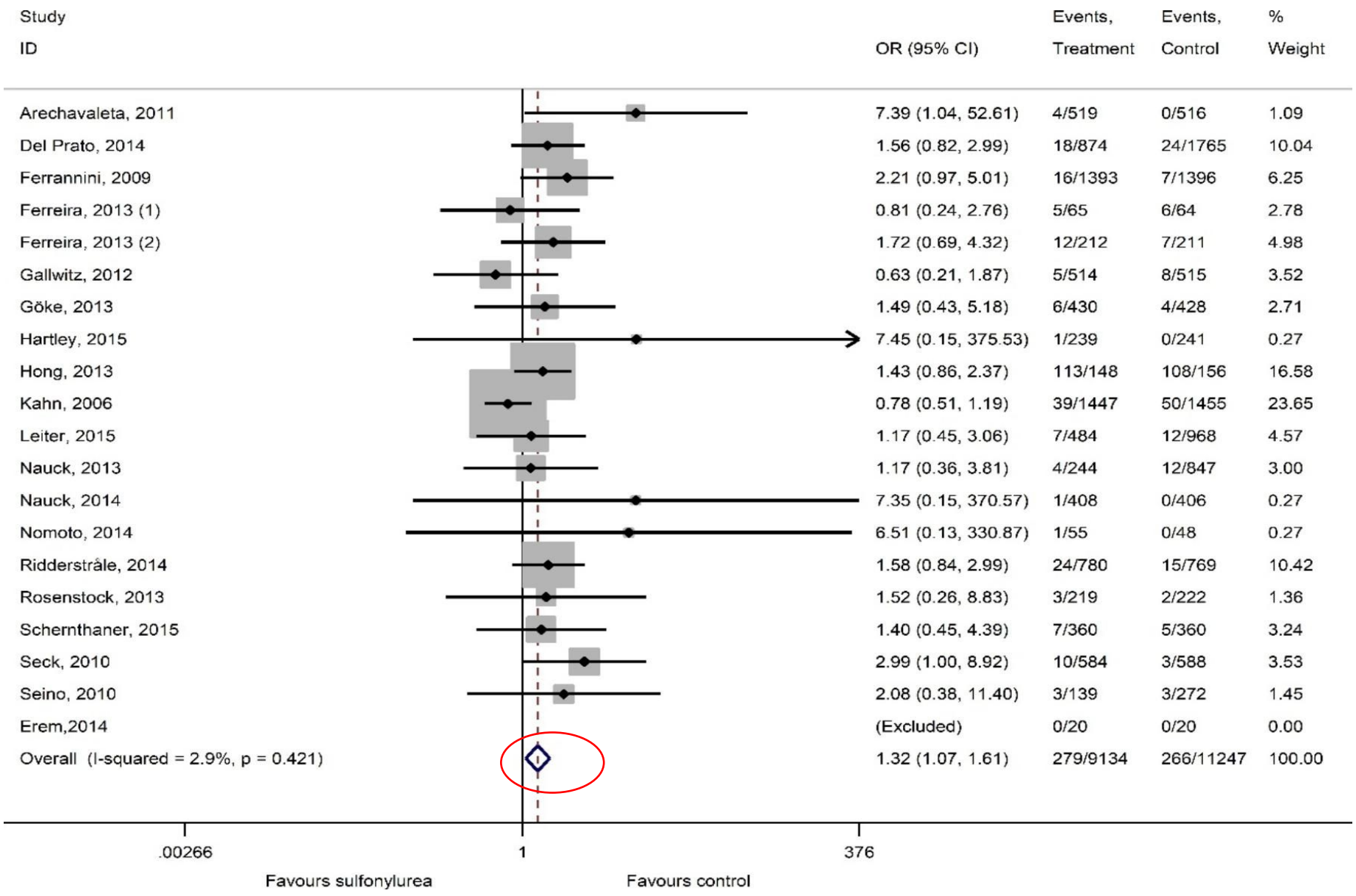
Flow diagram of study identification, inclusion and exclusion



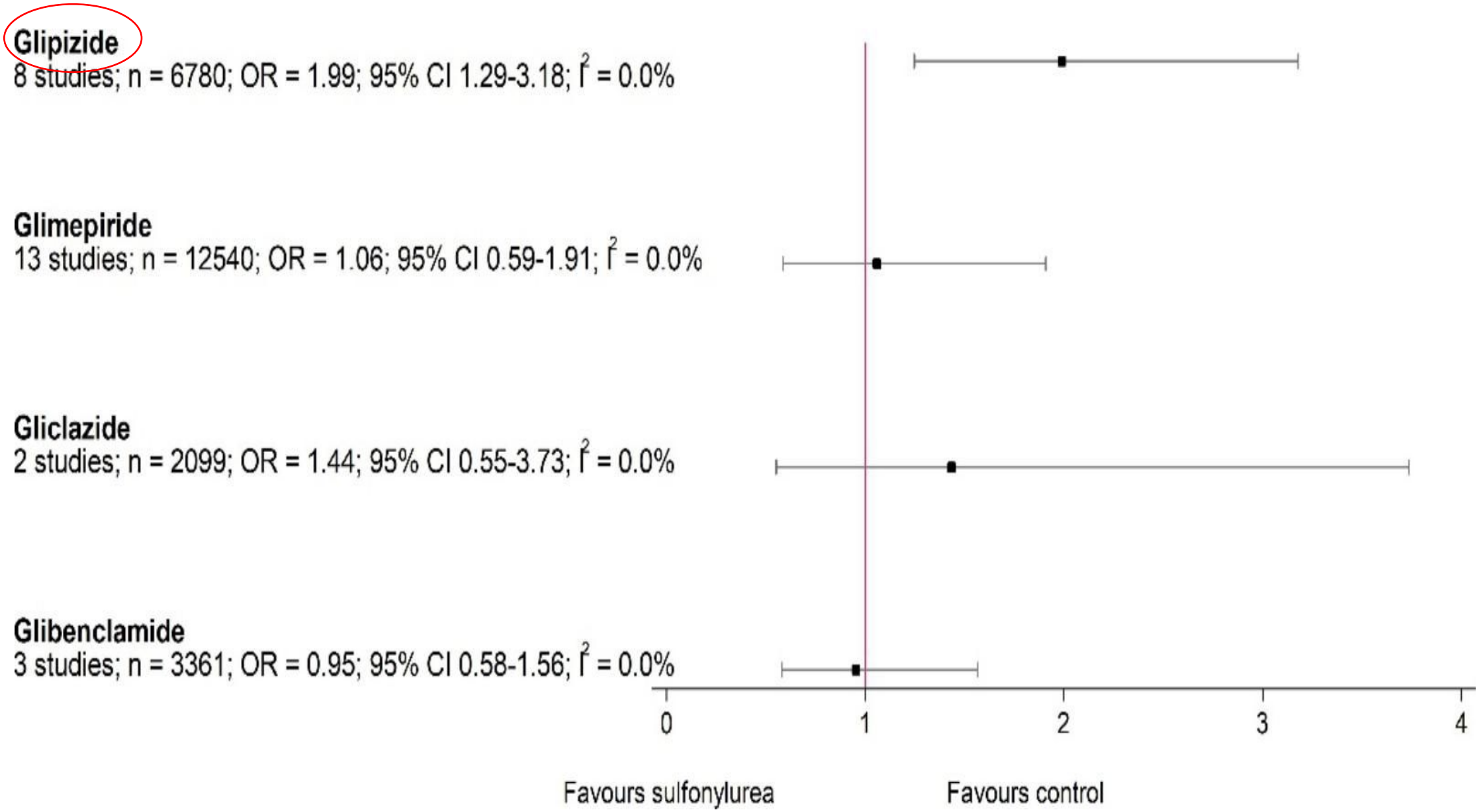
All-cause mortality of sulfonylureas versus active control.



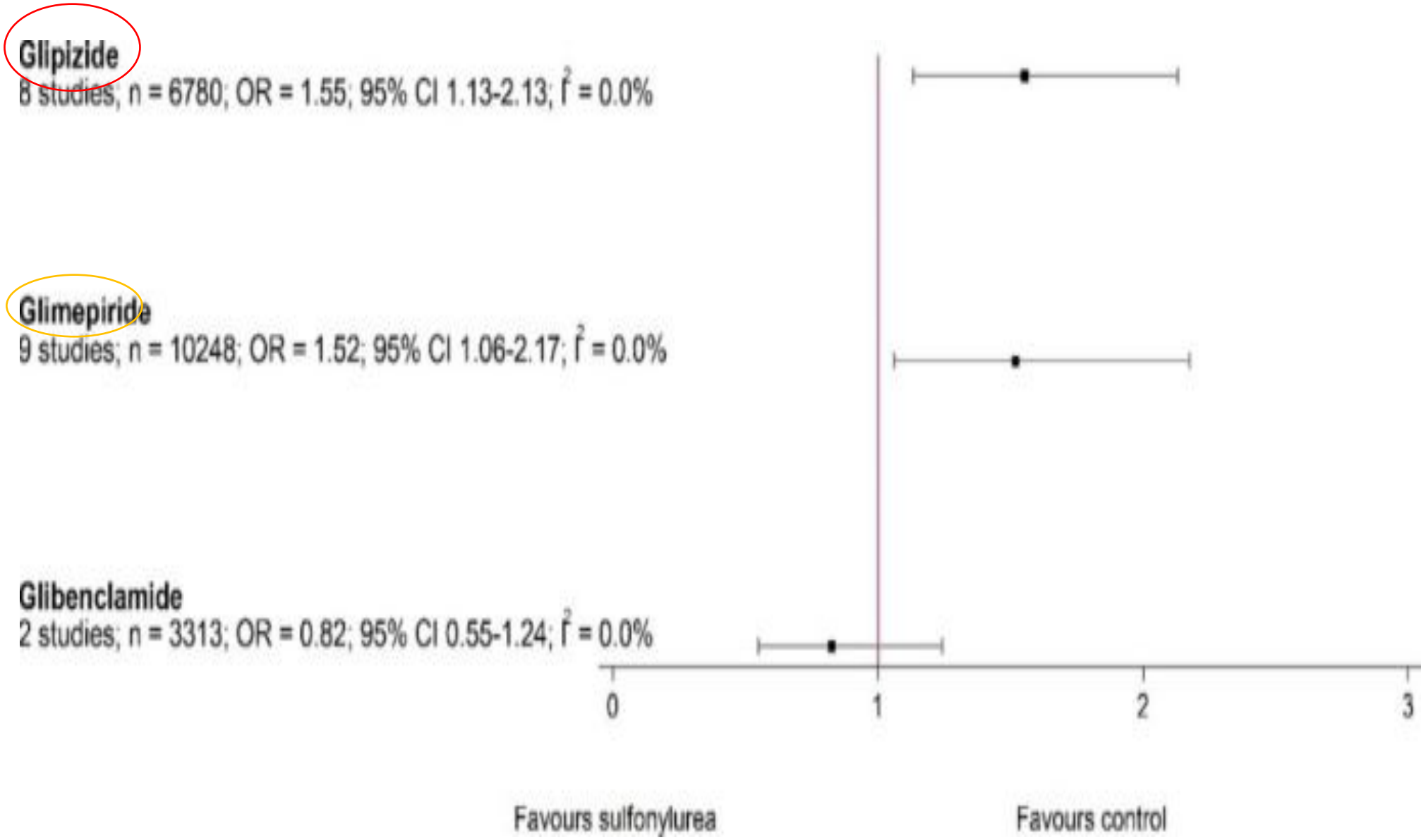
MACE, sulfonylureas versus active control.



All-cause mortality of different sulfonylureas versus active control



MACE, different sulfonylureas versus active control



Components of MACE and severe hypoglycaemia: sulfonylureas versus active control

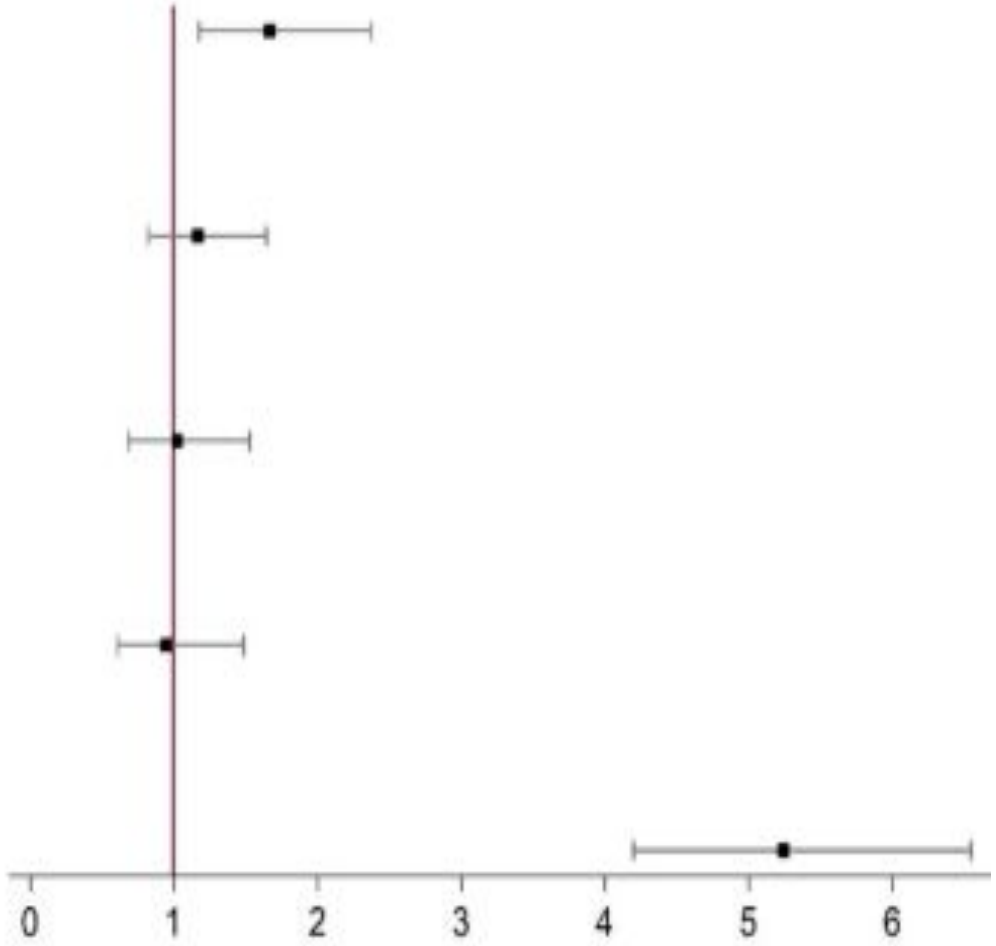
MI (fatal and non-fatal)
16 studies; n = 15974; OR = 1.67; 95% CI 1.17-2.38; I^2 = 29.1%

Stroke (fatal and non-fatal)
16 studies; n = 17875; OR = 1.17; 95% CI 0.82-1.65; I^2 = 0.0%

Acute coronary syndrome
9 studies; n = 12311; OR = 1.02; 95% CI 0.45-4.35; I^2 = 0.0%

Cardiac failure
16 studies; n = 18018 ; OR = 0.95; 95% CI 0.61-1.49; I^2 = 0.0%

Severe hypoglycaemia
26 studies; n = 22678; OR = 5.24 ; 95% CI 4.20-6.55; I^2 = 0.0%



Conclusion

- In comparison to drugs with low hypoglycaemic potential, sulfonylureas had higher odds for all-cause mortality, MACE, myocardial infarction (fatal and non-fatal) and hypoglycaemia.
- Concerns about the possible harm related to SU therapy compared to drugs with low hypoglycaemic propensity
- Further studies are necessary.
- Important differences may exist within the class, and glimepiride seems to be the safest option according to collective evidence.

Reflections

- Glipizide (Minidiab®) is uit de markt genomen. Er zijn andere hypoglykemiërende sulfamiden beschikbaar voor de behandeling van diabetes type 2, onder meer gliquidon, dat ook een korte halfwaardetijd heeft en via de lever wordt gemetaboliseerd.

- Risk of bias from low to high. Studies RoB low: higher OR

- Why Glipizide? (alle studies used long-acting formulation, so no PK issue)

- SU higher mortality compared with DPP-4 inhibitors only (not with others?)

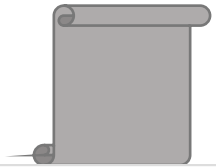
- Literature search till 2015, Settings, stage of disorder, country of origin?, small number of events, dose –response? Other covariates? (age, BMI, ..), time on-treatment?

- Authors: duscussion: sometimes confusing: Glimiperide best? Glibenclamide? (even better (however lower number of studies) Gliclaizde as SU in vast majority? (? 2)

3. First-trimester exposure to benzodiazepines and risk of congenital malformations in offspring: A population-based cohort study in South Korea

Yunha Noh, Hyesung Lee, Ahhyung Choi, et al.

PLoS Med 2022; 19(3): e1003945. https://doi.org/10.1371/journal. pmed.1003945



Stofnaam	Werkingsduur	Voorbeelddosis	Equivalente dosis diazepam	Omrekenfactor
alprazolam	ML	0,5 mg	5 mg	x 10
bromazepam	ML	3 mg	3 mg	x 1
brotizolam	UK	0,25 mg	10 mg	x 40
clobazam	L	10 mg	5 mg	x 0,5
clorazepaat	L	10 mg	7,5 mg	x 0,75
clotiazepam	ML	5 mg	10 mg	x 2
diazepam	L	10 mg	10 mg	x 1
ethylloflazepaat	L	2 mg	10 mg	x 5
flunitrazepam	K	1 mg	10 mg	x 10
flurazepam	L	27 mg	9 mg	x 0,33
loprazolam	K	1 mg	10 mg	x 10
lorazepam	ML	1 mg	5 mg	x 5
lormetazepam	K	1 mg	10 mg	x 10
nitrazepam	L	5 mg	5 mg	x 1
nordazepam	L	5 mg	5 mg	x 1
oxazepam	K	15 mg	4,5 mg	x 0,3
prazepam	L	10 mg	5 mg	x 0,5
triazolam	UK	0,125 mg	10 mg	x 80

Benzodiazepines

- Er bestaan tussen de verschillende benzodiazepines geen klinisch relevante verschillen voor wat betreft hun hypnotische, sedatieve, anxiolytische of spierrelaxerende eigenschappen; dit is alleen een kwestie van dosis en farmacokinetische eigenschappen.
- Farmacokinetische eigenschappen zoals de halfwaardetijd en het al of niet vormen van actieve metabolieten kunnen de duur van de effecten beïnvloeden. Klassiek onderscheidt men **kortwerkende** (halfwaardetijd, T1/2, minder dan 10 uur), **middellangwerkende** (T1/2 10-20 uur) en **langwerkende** benzodiazepines (T1/2 > 20 uur). In verschillende bronnen wordt eenzelfde product soms in een verschillende categorie geplaatst en een andere T1/2 gemeld.
- Het is aanbevolen voor gebruik als hypnoticum een middellangwerkend of kortwerkend benzodiazepine (maar niet flunitrazepam) te kiezen, en voor gebruik bij angst een middel met middellange of lange werkingsduur.
- Benzodiazepines hebben een plaats bij acute alcoholontwenning
- Bepaalde benzodiazepines worden gebruikt bij epilepsie.
- Midazolam wordt ook gebruikt in de anesthesie en voor palliatieve sedatie (indicatie niet vermeld in de SKP).
- Flunitrazepam is een "geneesmiddel gelijkgesteld aan de verdovende middelen" . Het wordt door bepaalde toxicomanen misbruikt, en waakzaamheid en voorzichtigheid bij het voorschrijven en afleveren ervan is geboden. Het wordt soms ook gebruikt voor criminele doeleinden (“*date rape drug*”).
- Bij acute verwardheid met agitatie buiten de context van dementie waarbij een sederende behandeling noodzakelijk is, gaat de voorkeur vaak uit naar een middellangwerkend benzodiazepine zoals lorazepam, ook al zijn hierover zeer weinig studies.

Benzodiazepines

- **Zwangerschap**
  - Benzodiazepines en verwante middelen (Z-drugs) **zijn af te raden** tijdens de zwangerschap.
  - **Abrupt onderbreken** van een benzodiazepine of Z-drug omwille van zwangerschap is formeel **af te raden**.
  - **Eerste trimester van de zwangerschap: er zijn geen eenduidige aanwijzingen van een verhoogd risico van aangeboren afwijkingen.**
  - **Perinatale periode: respiratoire depressie, floppy-infantsyndroom (o.a. hypotonie, hyporeflexie, hypothermie, slecht drinken) en ontwenningsverschijnselen bij de pasgeborene (o.a. prikkelbaarheid, hypertonie, tremoren, onregelmatige ademhaling, braken, diarree, convulsies, hard huilen).**
  - Het niet behandelen van ernstige angststoornissen, agitatie of slapeloosheid kan nadelige gevolgen hebben voor moeder en kind. Indien tijdens de zwangerschap toch een hypnoticum of anxiolyticum wordt gegeven, gaat de voorkeur naar **producten met korte werkingsduur** waarmee ruime ervaring is opgedaan (bv oxazepam bij angst, een Z-drug bij slapeloosheid), aan een zo laag mogelijke dosis en voor een zo beperkt mogelijke periode. Onze bronnen raden oxazepam aan bij angst en een Z-drug bij slapeloosheid.
- **Borstvoeding**: chronisch gebruik van hypnotica, sedativa en anxiolytica is af te raden. Incidenteel gebruik van kort/middellangwerkende benzodiazepines is aanvaardbaar; hierbij dient men alert te zijn voor ongewenste effecten bij het kind (o.a. sedatie, moeilijkheden bij het drinken).

First-trimester exposure to benzodiazepines and risk of congenital malformations in offspring: A population-based cohort study in South Korea

- *Background*

Benzodiazepines are frequently prescribed during pregnancy;

however, evidence about possible teratogenicity is equivocal.

- *Aim*

To evaluate the association between first-trimester benzodiazepine use and the risk of major congenital malformations.

- *Methods and findings*

Korea's nationwide healthcare database, a population-based cohort study of women who gave birth during 2011 to 2018 and their live-born infants.

Exposure was defined as one or more benzodiazepine prescriptions during the first trimester. Relative risks (RRs) and confidence intervals (CIs) of overall congenital malformations and 12 types of organ-specific malformations. Infants were followed from birth to death or 31 December 2019, whichever came first (up to 8 years of age).

First-trimester exposure to benzodiazepines and risk of congenital malformations in offspring: A population-based cohort study in South Korea

- *Results*

Among a total of 3,094,227 pregnancies, 40,846 (1.3%) were exposed to benzodiazepines during the first trimester (mean [SD] age, 32.4 [4.1] years).

The absolute risk of overall malformations was 65.3 per 1,000 pregnancies exposed to benzodiazepines versus 51.4 per 1,000 unexposed pregnancies.

The adjusted **RR was 1.09** (95% CI 1.05 to 1.13, $p < 0.001$) for overall malformations and **1.15** (1.10 to 1.21, $p < 0.001$) for heart defects.

Based on mean daily lorazepam-equivalent doses, adjusted RRs for overall malformations and heart defects 1.05 (0.99 to 1.12, $p = 0.077$) and 1.12 (1.04 to 1.21, $p = 0.004$) for <1 mg/day and **1.26** (1.17 to 1.36, $p < 0.001$) and **1.31** (1.19 to 1.45, $p < 0.001$) for **>2.5 mg/day** doses, respectively, suggesting a **dose–response relationship.**

A small but significant increase in risk for overall and heart defects was detected with several specific agents (range of adjusted RRs: 1.08 to 2.43).

First-trimester exposure to benzodiazepines and risk of congenital malformations in offspring: A population-based cohort study in South Korea

- *Conclusion*

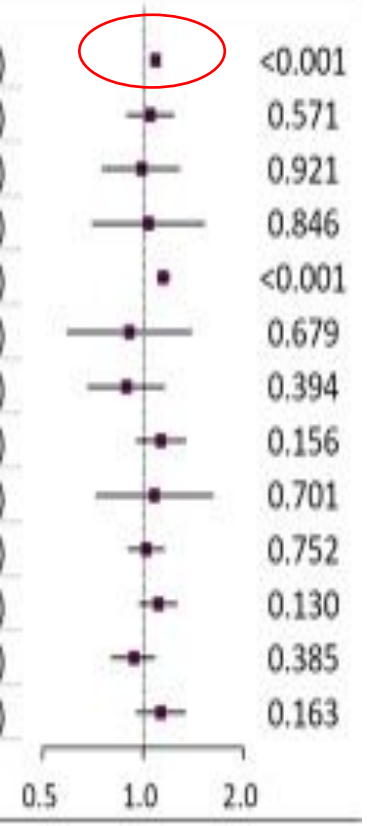
In this large nationwide cohort study, first-trimester benzodiazepine exposure was associated with a small increased risk of overall malformations and heart defects, particularly at the higher daily dose.

The absolute risks and population attributable fractions were modest.

The benefits of benzodiazepines for their major indications must be considered despite the potential risks; if their use is necessary, the lowest effective dosage should be prescribed to minimize the risk.

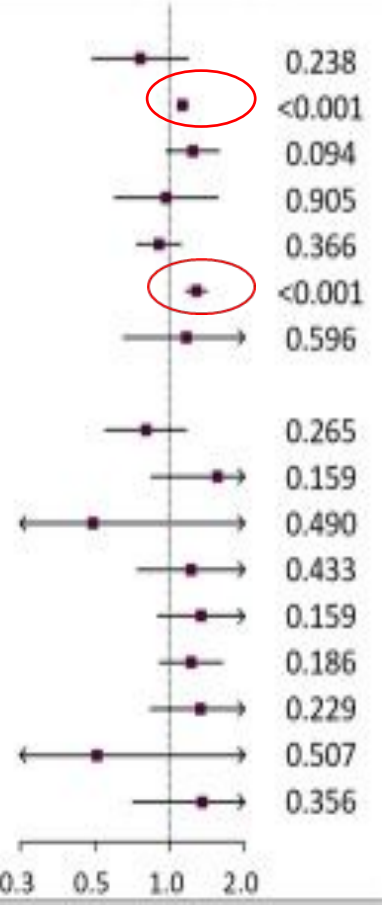
Absolute and relative risks of congenital malformations in infants following maternal exposure to benzodiazepines during the first trimester.

Outcomes	Benzodiazepines (n = 40,846) No. of Events	Benzodiazepines (n = 40,846) Risk/1,000 Births	Unexposed (n = 3,053,381) No. of Events	Unexposed (n = 3,053,381) Risk/1,000 Births	RD_{1000}*	PAF	Relative risk (95% CI) Unadjusted	Relative risk (95% CI) PS-adjusted	PS-adjusted relative risk (95% CI)	*p*-value
Overall congenital malformations	2,667	65.3	156,896	51.4	13.9	0.36%	1.27 (1.22–1.32)	1.09 (1.05–1.13)		<0.001
Nervous system	155	3.8	10,032	3.3	0.5	0.20%	1.15 (0.99–1.35)	1.05 (0.89–1.24)		0.571
Eye	57	1.4	4,044	1.3	0.1	0.07%	1.05 (0.81–1.37)	0.99 (0.75–1.29)		0.921
Ear, face, and neck	27	0.7	1,835	0.6	0.1	0.13%	1.10 (0.75–1.61)	1.04 (0.70–1.53)		0.846
Heart	1,588	38.9	83,584	27.4	11.5	0.55%	1.42 (1.35–1.49)	1.15 (1.10–1.21)		<0.001
Respiratory system	23	0.6	1,658	0.5	0.0	0.05%	1.04 (0.69–1.56)	0.91 (0.59–1.40)		0.679
Oral clefts	60	1.5	4,252	1.4	0.1	0.07%	1.05 (0.82–1.36)	0.89 (0.68–1.16)		0.394
Digestive system	142	3.5	8,697	2.8	0.6	0.29%	1.22 (1.03–1.44)	1.13 (0.95–1.35)		0.156
Abdominal wall	27	0.7	1,284	0.4	0.2	0.75%	1.57 (1.07–2.30)	1.08 (0.72–1.63)		0.701
Urinary system	258	6.3	16,876	5.5	0.8	0.19%	1.14 (1.01–1.29)	1.02 (0.90–1.16)		0.752
Genital organs	227	5.6	13,514	4.4	1.1	0.34%	1.26 (1.10–1.43)	1.11 (0.97–1.27)		0.130
Limb	184	4.5	12,956	4.2	0.3	0.08%	1.06 (0.92–1.23)	0.94 (0.80–1.09)		0.385
Others	149	3.6	8,927	2.9	0.7	0.33%	1.25 (1.06–1.47)	1.13 (0.95–1.34)		0.163

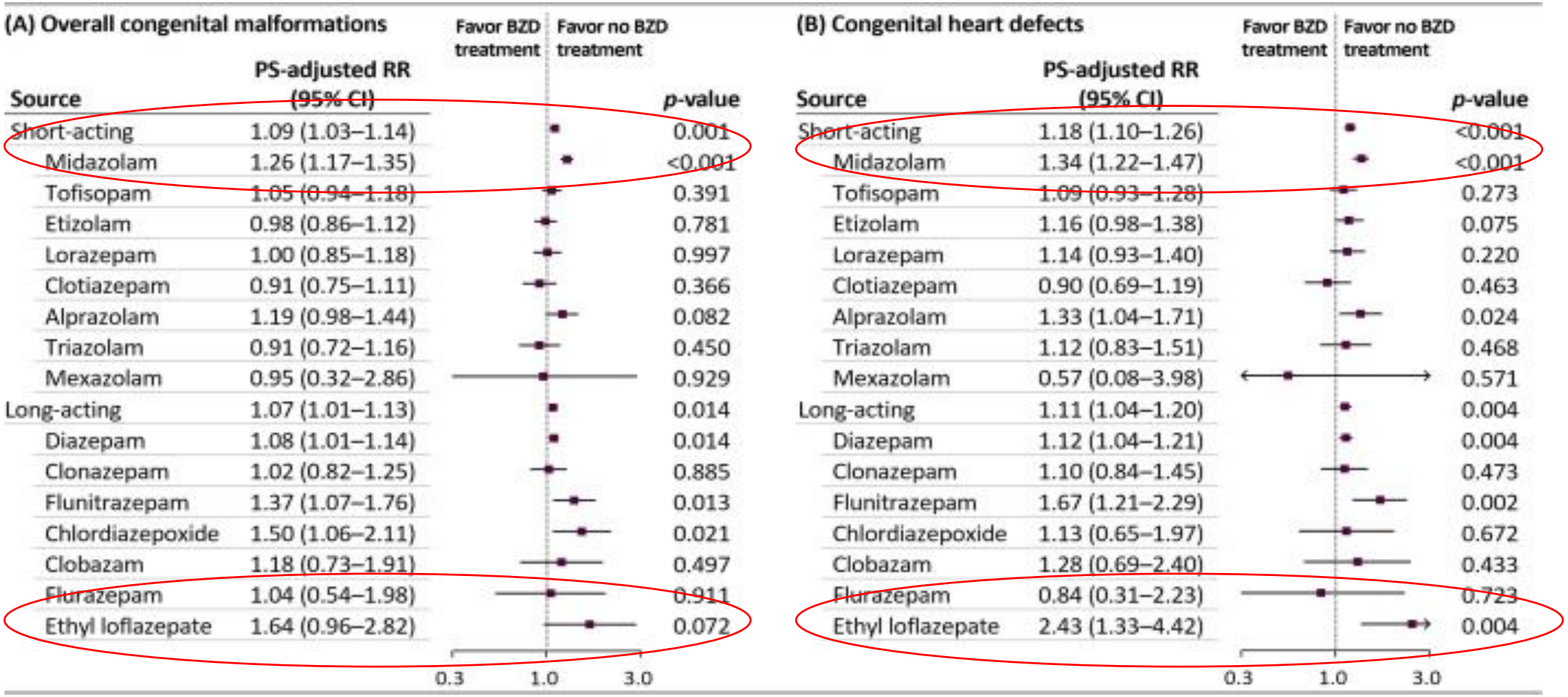


Risks of individual categories of heart and digestive system defects in infants following maternal exposure to benzodiazepines during the first trimester.

Outcomes	Benzodiazepines (n = 40,846) No. of Events	Benzodiazepines (n = 40,846) Risk /1,000 Births	Unexposed (n = 3,053,381) No. of Events	Unexposed (n = 3,053,381) Risk /1,000 Births	RD_{1000}*	PAF	Relative risk (95% CI) Unadjusted	Relative risk (95% CI) PS-adjusted	PS-adjusted relative risk (95% CI)	*p*-value
Subgroups of congenital heart defects										
Cardiac chambers and connections	21	0.5	1,638	0.5	0.0	-0.05%	0.96 (0.62–1.47)	0.76 (0.49–1.20)		0.238
Cardiac septum	1,244	30.5	66,967	21.9	8.5	0.51%	1.39 (1.31–1.47)	1.13 (1.07–1.20)		<0.001
Pulmonary and tricuspid valve	67	1.6	3,459	1.1	0.5	0.59%	1.45 (1.14–1.84)	1.24 (0.96–1.60)		0.094
Aortic and mitral valve	18	0.4	1,109	0.4	0.1	0.28%	1.21 (0.76–1.93)	0.97 (0.60–1.58)		0.905
Other heart defects	96	2.4	6,509	2.1	0.2	0.14%	1.10 (0.90–1.35)	0.91 (0.74–1.12)		0.366
Great arteries	411	10.1	18,704	6.1	3.9	0.84%	1.64 (1.49–1.81)	1.28 (1.16–1.42)		<0.001
Great veins	12	0.3	677	0.2	0.1	0.43%	1.33 (0.75–2.34)	1.17 (0.65–2.13)		0.596
Subgroups of digestive system defects										
Tongue, mouth, and pharynx	28	0.7	2,579	0.8	-0.2	-0.25%	0.81 (0.56–1.18)	0.80 (0.55–1.18)		0.265
Oesophagus	11	0.3	488	0.2	0.1	0.90%	1.69 (0.93–3.06)	1.56 (0.84–2.89)		0.159
Upper alimentary tract	1	0.0	135	0.0	0.0	-0.59%	0.55 (0.08–3.96)	0.49 (0.07–3.67)		0.490
Small intestine	17	0.4	847	0.3	0.1	0.66%	1.50 (0.93–2.42)	1.22 (0.74–2.03)		0.433
Large intestine	26	0.6	1,313	0.4	0.2	0.63%	1.48 (1.00–2.18)	1.34 (0.89–2.03)		0.159
Other defects of intestine	48	1.2	2,625	0.9	0.3	0.48%	1.37 (1.03–1.82)	1.22 (0.91–1.65)		0.186
Gallbladder, bile ducts and liver	19	0.5	1,009	0.3	0.1	0.54%	1.41 (0.89–2.22)	1.33 (0.83–2.13)		0.229
Other defects of digestive system	1	0.0	149	0.0	0.0	-0.66%	0.50 (0.07–3.59)	0.51 (0.07–3.70)		0.507
Diaphragmatic hernia	10	0.2	504	0.2	0.1	0.63%	1.48 (0.79–2.77)	1.36 (0.71–2.60)		0.356



Risks of congenital malformations in infants according to individual benzodiazepine exposure during the first trimester.



Risks of congenital malformations in infants following maternal exposure to benzodiazepines in the first trimester: subgroup analyses.

Subgroups	Benzodiazepine No. of Events	Benzodiazepine No. of Births	Unexposed No. of Events	Unexposed No. of Births	Relative risk (95% CI) Unadjusted	Relative risk (95% CI) PS-adjusted	PS-adjusted relative risk (95% CI)	*p*-value
Overall congenital malformations								
Total	2,667	40,846	156,896	3,053,381	1.27 (1.22–1.32)	1.09 (1.05–1.13)		<0.001
Dose analysis*								
<1 mg/day	1,154	19,668	156,896	3,053,381	1.14 (1.08–1.21)	1.05 (0.99–1.12)		0.077
1–2.5 mg/day	856	13,079	156,896	3,053,381	1.27 (1.19–1.36)	1.04 (0.98–1.12)		0.215
>2.5 mg/day	657	8,099	156,896	3,053,381	1.58 (1.47–1.70)	1.26 (1.17–1.36)		<0.001
Maternal age								
≤35 years	1,856	30,639	122,854	2,470,020	1.22 (1.16–1.27)	1.07 (1.02–1.12)		0.003
>35 years	811	10,207	34,042	583,361	1.36 (1.27–1.46)	1.13 (1.05–1.22)		0.001
Multifetal pregnancy								
No	2,354	39,408	148,354	3,000,478	1.21 (1.16–1.26)	1.08 (1.04–1.13)		<0.001
Yes	313	1,438	8,542	52,903	1.35 (1.22–1.49)	1.18 (1.05–1.31)		0.004
Epilepsy								
No	2,626	40,341	156,536	3,048,871	1.27 (1.22–1.32)	1.09 (1.05–1.13)		<0.001
Yes	41	505	360	4,510	1.02 (0.75–1.39)	1.01 (0.70–1.46)		0.968
Combination of antidepressants								
No	2,322	35,385	156,896	3,053,381	1.28 (1.23–1.33)	1.11 (1.06–1.15)		<0.001
Yes	345	5,461	156,896	3,053,381	1.23 (1.11–1.36)	1.04 (0.93–1.18)		0.490
Congenital heart defects								
Total	1,588	40,846	83,584	3,053,381	1.42 (1.35–1.49)	1.15 (1.10–1.21)		<0.001
Dose analysis*								
<1 mg/day	668	19,668	156,896	3,053,381	1.24 (1.15–1.34)	1.12 (1.04–1.21)		0.004
1–2.5 mg/day	526	13,079	156,896	3,053,381	1.47 (1.35–1.60)	1.13 (1.03–1.23)		0.008
>2.5 mg/day	394	8,099	156,896	3,053,381	1.78 (1.61–1.96)	1.31 (1.19–1.45)		<0.001
Maternal age								
≤35 years	1,073	30,639	64,383	2,470,020	1.34 (1.27–1.43)	1.14 (1.07–1.21)		<0.001
>35 years	515	10,207	19,201	583,361	1.53 (1.41–1.67)	1.20 (1.10–1.32)		<0.001
Multifetal pregnancy								
No	1339	39,408	77,747	3,000,478	1.31 (1.24–1.38)	1.14 (1.07–1.20)		<0.001
Yes	249	1,438	5,837	52,903	1.57 (1.40–1.76)	1.31 (1.15–1.49)		<0.001
Epilepsy								
No	1,562	40,341	83,378	3,048,871	1.42 (1.35–1.49)	1.16 (1.10–1.22)		<0.001
Yes	26	505	206	4,501	1.13 (0.76–1.68)	1.02 (0.62–1.67)		0.945
Combination of antidepressants								
No	1,358	35,385	83,584	3,053,381	1.40 (1.33–1.48)	1.16 (1.10–1.23)		<0.001
Yes	230	5,461	83,584	3,053,381	1.54 (1.36–1.75)	1.26 (1.08–1.46)		0.003

Conclusion

- In this nationwide cohort study, benzodiazepine use during the first trimester was associated with a **small increased risk of overall malformations and heart defects, particularly in the high daily dose group** (at doses higher than the usual daily dose).
- The absolute risks and population attributable fractions were **modest.**
- Findings suggest that the benefits of benzodiazepines for their major indications must be considered despite the potential risks.
- Nonetheless, to minimize the potential risk, **alternative nonpharmacological** strategies could be considered for managing anxiety and insomnia during pregnancy; if benzodiazepines are necessary, the **lowest effective dosage** should be prescribed during early pregnancy.

Reflections

- Study limitations:

Possible exposure misclassification

Residual confounding

Restriction to live births

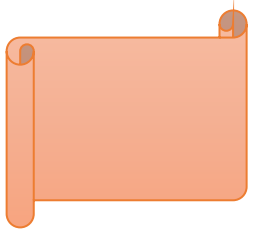
Korean population

Duration of intake?

4. Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

Isla S Mackenzie, Amy Rogers, Neil R Poulter, Bryan Williams, Morris J Brown, David J Webb

The Lancet 2022; October 11, 2022 https://doi.org/10.1016/S0140-6736(22)01786-X



De keuze voor een antihypertensivum met lange werkingsduur maakt eenmaal daagse toediening mogelijk. Bij eenmaal daagse toediening van antihypertensiva moet men nagaan of over 24 uur voldoende bloeddrukdaling wordt bekomen: bloeddruk juist vóór de volgende geneesmiddeleninname meten.

Bij twijfel kan ambulante 24 uurs-bloeddrukmeting nuttig zijn.

Inname van antihypertensiva voor het slapengaan in plaats van ‘s ochtends leidt mogelijk tot een vermindering van de incidentie van cardiovasculaire events. Dit vraagt nog bevestiging en het is onduidelijk of dit geldt voor alle patiënten en voor alle klassen van antihypertensiva; de meeste aanwijzingen voor dit gunstig effect zijn er voor de middelen die inwerken op het renine-angiotensinesysteem [zie Folia april 2020].

BCFi
BELGISCH CENTRUM VOOR FARMACOTHERAPEUTISCHE INFORMATIE

Antihypertensiva

- **diuretica (**zie 1.4. Diuretica)
- **β-blokkers** (zie 1.5. Bèta-blokkers)
- **calciumantagonisten** (zie 1.6. Calciumantagonisten)
- **ACE-inhibitoren** (angiotensineconversie-enzyminhibitoren, zie 1.7.1. ACE-inhibitoren)
- **sartanen** (angiotensine-II-receptorantagonisten, zie 1.7.2. Sartanen)
- combinatiepreparaten van deze middelen (zie 1.1.4. Combinatiepreparaten).

- Er is een beperkte plaats voor:
- α-blokkers (zie 1.1.1. Alfa-blokkers)
- centraal werkende antihypertensiva (zie 1.1.2. Centraal werkende antihypertensiva)
- vasodilatoren (zie 1.1.3. Vasodilatoren).

BCFi
BELGISCH CENTRUM VOOR FARMACOTHERAPEUTISCHE INFORMATIE

Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

- *Background*

Studies have suggested that evening dosing with antihypertensive therapy might have better outcomes than morning dosing.

- *Aim*

The Treatment in Morning versus Evening (TIME) study aimed to investigate whether evening dosing of usual antihypertensive medication improves major cardiovascular outcomes compared with morning dosing in patients with hypertension.

- *Methods*

The TIME study is a prospective, pragmatic, decentralised, parallel-group study in the UK, that recruited adults (aged ≥18 years) with hypertension and taking at least one antihypertensive medication.

Eligible participants randomly assigned (1:1)to take all of their usual antihypertensive medications in either the morning (0600–1000 h) or in the evening (2000–0000 h).

Composite primary endpoint: vascular death or hospitalisation for non-fatal myocardial infarction or non-fatal stroke. Endpoints were identified by participant report or record linkage to National Health Service datasets and were adjudicated by a committee masked to treatment allocation. The primary endpoint was assessed as the time to first occurrence of an event in the intention-to-treat population.

Safety was assessed in all participants who submitted at least one follow-up questionnaire.

Cardiovascular outcomes in adults with hypertension with evening versus morning dosing of usual antihypertensives in the UK (TIME study): a prospective, randomised, open-label, blinded-endpoint clinical trial

- *Results*

Between Dec 17, 2011, and June 5, 2018, 24 610 individuals were screened and 21 104 were randomly assigned to evening (n=10 503) or morning (n=10 601) dosing groups.

Mean age 65·1 years (SD 9·3); 12 136 (57·5%) men; 8968 (42·5%)women;

19 101 (90·5%) White; 98 (0·5%) Black, African, Caribbean, or Black British(ethnicity not reported by 1637 [7·8%]); 2725 (13·0%) had previous cardiovascular disease. Median follow-up was 5·2 years (IQR 4·9–5·7)

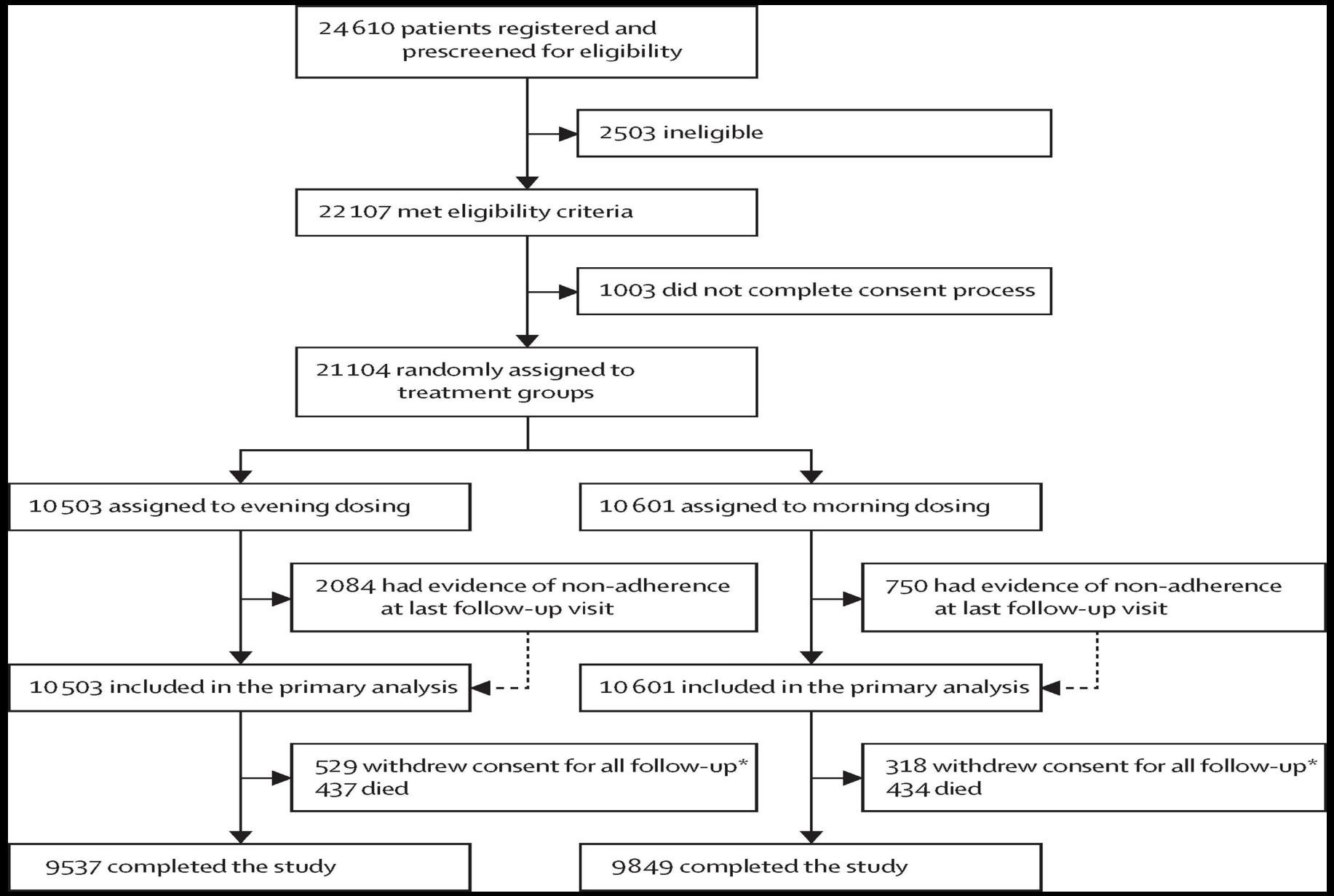
Primary endpoint event occurred in 362 (3·4%) participants assigned to evening treatment (0·69 events [95% CI 0·62–0·76] per 100 patient-years) and 390 (3·7%) assigned to morning treatment (0·72 events [95% CI 0·65–0·79] per 100 patient-years; unadjusted **hazard ratio 0·95** [95% CI 0·83–1·10]; p=0·53). No safety concerns were identified.

- *Interpretation*

Evening dosing of usual antihypertensive medication was not different from morning dosing in terms of major cardiovascular outcomes.

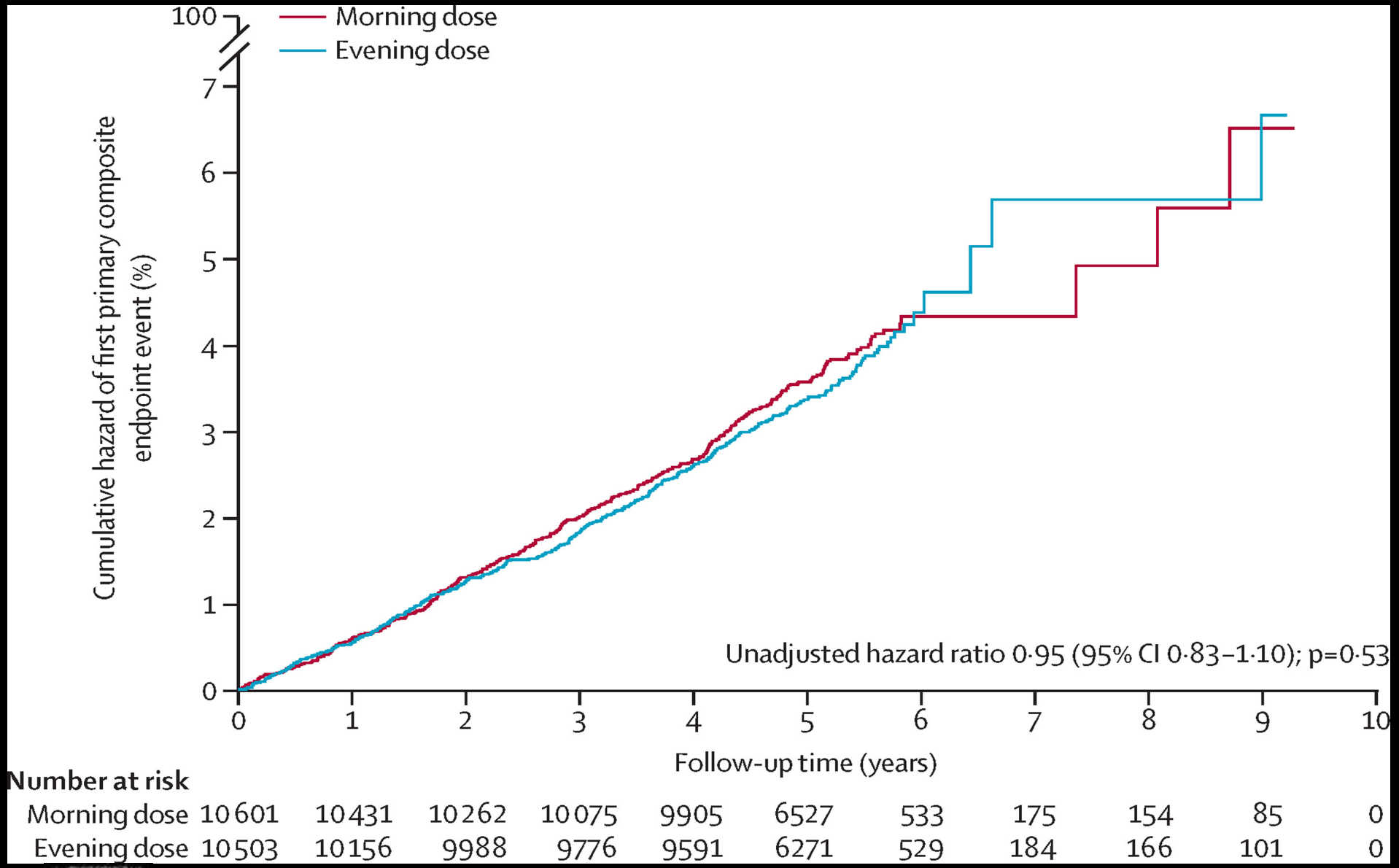
Patients can be advised that they can take their regular antihypertensive medications at a convenient time that minimises any undesirable effects.

Figure 1



The Lancet 2022 4001417-1425DOI: (10.1016/S0140-6736(22)01786-X)

Figure 2



The Lancet 2022 4001417-1425DOI: (10.1016/S0140-6736(22)01786-X)

Primary composite outcome and secondary cardiovascular and mortality outcomes (intention-to-treat population; n=21 104)

	Evening dosing group (n=10 503)		Morning dosing group (n=10 601)		Hazard ratio (95% CI)	p value
	Participants, n (%)	Rate per 100 patient-years (95% CI)	Participants, n (%)	Rate per 100 patient-years (95% CI)		
Primary composite endpoint	362 (3·4%)	0·69 (0·62–0·76)	390 (3·7%)	0·72 (0·65–0·79)	0·95 (0·83–1·10)	0·53
Secondary cardiovascular and mortality endpoints						
Hospitalisation for non-fatal myocardial infarction	134 (1·3%)	0·25 (0·21–0·30)	150 (1·4%)	0·27 (0·23–0·32)	0·92 (0·73–1·16)	0·48
Hospitalisation for non-fatal stroke	129 (1·2%)	0·24 (0·20–0·29)	143 (1·3%)	0·26 (0·22–0·31)	0·93 (0·73–1·18)	0·54
Vascular death	115 (1·1%)	0·22 (0·18–0·26)	108 (1·0%)	0·20 (0·16–0·24)	1·10 (0·84–1·43)	0·49
All-cause death	437 (4·2%)	0·82 (0·74–0·90)	434 (4·1%)	0·79 (0·72–0·87)	1·04 (0·91–1·18)	0·59
Hospitalisation or death from congestive heart failure	76 (0·7%)	0·14 (0·11–0·18)	99 (0·9%)	0·18 (0·15–0·22)	0·79 (0·59–1·07)	0·12

Prespecified adverse events (symptoms) in safety analysis population (n=19 628)

Numbers reported are the number of participants who indicated that they had experienced each prespecified symptom.
* Number of participants who submitted at least one completed study follow-up form.
† Difference in percentage: evening dosing group minus morning dosing group.

	Evening dosing group (n=9574)*	Morning dosing group (n=10 054)*	Between-group difference (95% CI)†
Dizziness or light-headedness	3511 (36·7%)	4007 (39·9%)	−3·2% (−4·6 to −1·8)
Excessive visits to the toilet during the day or night	3825 (40·0%)	3660 (36·4%)	3·6% (2·2 to 4·9)
Sleep problems	4017 (42·0%)	4125 (41·0%)	0·9% (−0·5 to 2·3)
Upset stomach or indigestion	2639 (27·6%)	3050 (30·3%)	−2·8% (−4·1 to −1·5)
Diarrhoea	1803 (18·8%)	2170 (21·6%)	−2·8% (−3·9 to −1·6)
Feeling generally less well	3079 (32·2%)	3311 (32·9%)	−0·8% (−2·1 to 0·6)
Muscle aches	3724 (38·9%)	4352 (43·3%)	−4·4% (−5·8 to −3·0)
Other (not specified)	2970 (31·0%)	2686 (26·7%)	4·3% (3·0 to 5·6)

Added value of the TIME study

The Treatment in Morning versus Evening (TIME) study was a large, pragmatic, decentralised, prospective, randomised, open-label, blinded-endpoint, superiority trial conducted in the UK, comparing cardiovascular outcomes in adults with hypertension randomly assigned to evening versus morning dosing of their usual antihypertensive medications.

No difference between the evening and morning dosing groups for the primary composite outcome of vascular death or hospitalisation for non-fatal myocardial infarction or non-fatal stroke over a median follow-up time of 5·2 years (IQR 4·9–5·7).

No difference in all-cause mortality between the evening and morning dosing groups.

Implications of all the available evidence

These findings are an important addition to the hitherto limited and controversial randomised clinical trial evidence available comparing the effects of dosing times of antihypertensive medication with regard to cardiovascular outcomes.

Given the continued controversy around MAPEC and the Hygia Chronotherapy trial, the evidence from the TIME trial suggests that **dosing time should not be a significant consideration when advising most patients on managing their blood pressure. Instead, clinicians should focus on selecting appropriate medications and supporting adherence to agreed treatment plans.**

Conclusion

- In this pragmatic study, reflecting usual care, allocation to evening dosing of usual antihypertensive medication did not improve the primary composite endpoint of vascular death or hospitalisation for non-fatal myocardial infarction or non-fatal stroke compared with morning dosing.
- Taking medication in the evening was not harmful but provided no additional benefit versus morning dosing.
- Patients should be advised that they need not change their antihypertensive medication dosing time but might choose to take their medication at a time that suits them best, because the timing makes no difference to cardiovascular outcomes.

Reflections

- Positive Health behavior of participants
- Discussion starts with nocturnal HT, however they did not actually study nocturnal HT and effects of timing of medication intake in pts with nocturnal HT; while at th end “TIME study is not a study of nocturnal hypertension..”
- Participant reported AE(questionnaire fu): recall bias, reporting bias
- Smokers and higher BMI provided less BP measurements
- Adherence and non-adherence (to dosing time)?

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Dank U voor uw aandacht

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