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Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial

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Rationnel

- L'allopurinol est avant tout un hypouricémiant mais aussi un antioxydant qui peut être bénéfique pour les coronaires car:

➢ Il protège l'endothélium vasculaire

➢ Il diminue l'inflammation endothéliale

➢ Il diminue l'athérogénèse et le risque de thrombose.

De plus l'allopurinol pourrait diminuer la MVO_2

Tous ces effets ont été rapportés chez l'animal mais pas chez l'homme.

Méthodes

Methods 65 patients (aged 18–85 years) with angiographically documented coronary artery disease, a positive exercise tolerance test, and stable chronic angina pectoris (for at least 2 months) were recruited into a double-blind, randomised, placebo-controlled, crossover study in a hospital and two infirmaries in the UK. We used computer-generated randomisation to assign patients to allopurinol (600 mg per day) or placebo for 6 weeks before crossover. Our primary endpoint was the time to ST depression, and the secondary endpoints were total exercise time and time to chest pain. We did a completed case analysis. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN 82040078.

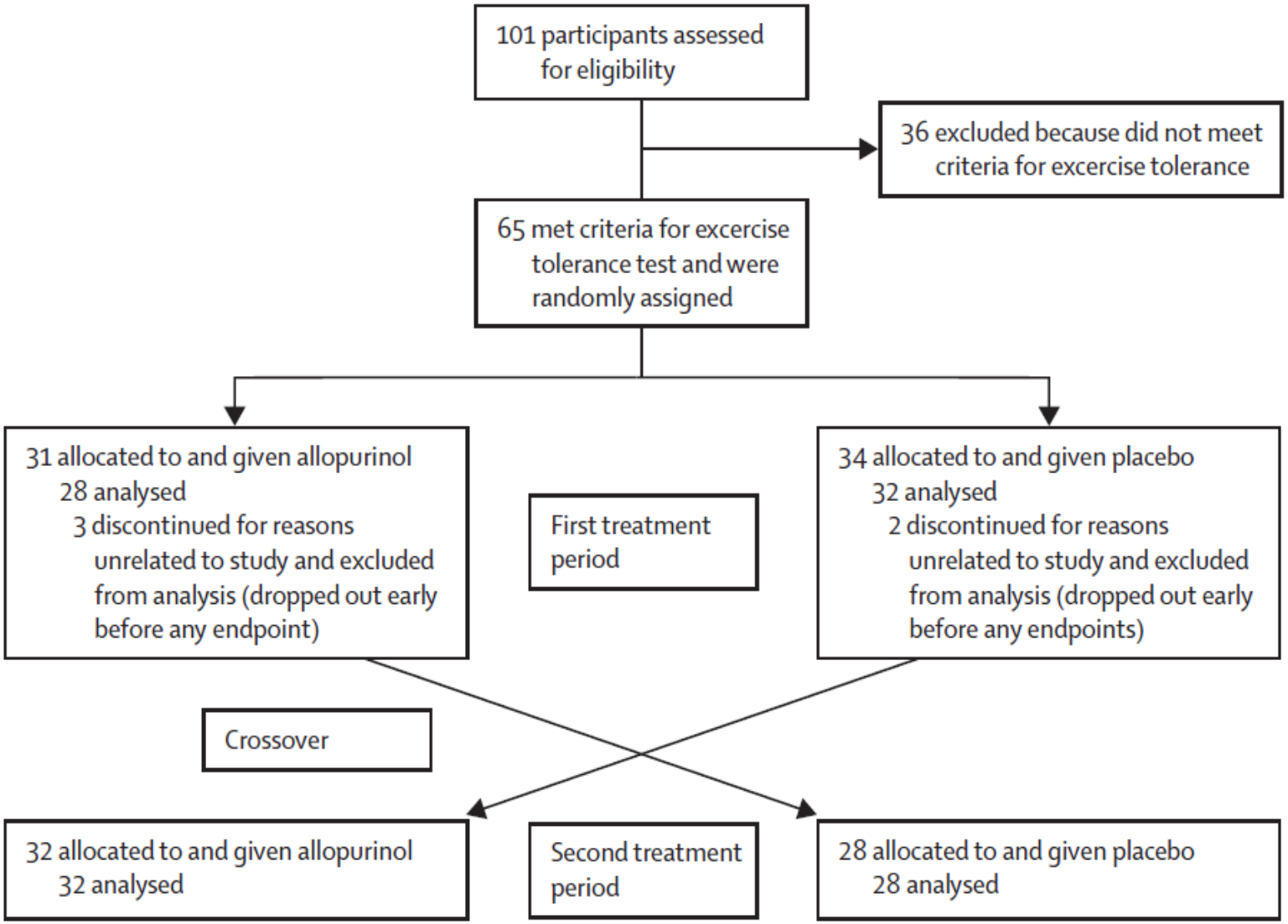


Figure 1: Trial profile

	All (n=60)	Placebo first (n=32)	Allopurinol first (n=28)	Dropouts (n=5)
Age (years; mean, SD)	64·6 (9·3)	64·0 (8·9)	65·2 (9·6)	66·6 (7·7)
Men	50 (83%)	28 (88%)	22 (79%)	3 (60%)
Women	10 (17%)	4 (13%)	6 (21%)	2 (40%)
Angina Canadian Cardiovascular Society stage[16]				
I	9 (15%)	4 (13%)	5 (18%)	0
II	42 (70%)	23 (72%)	19 (68%)	3 (60%)
III	9 (15%)	5 (16%)	4 (14%)	2 (40%)
Number of vessels with coronary artery disease				
1	10 (17%)	4 (13%)	6 (21%)	1 (20%)
2	24 (40%)	14 (44%)	10 (36%)	2 (40%)
3	26 (43%)	14 (44%)	12 (43%)	2 (40%)
Left ventricle systolic function				
Normal	51 (85%)	26 (81%)	25 (89%)	4 (80%)
Mild impairment	9 (15%)	6 (19%)	3 (11%)	1 (20%)
Renal function				
Normal	55 (92%)	28 (88%)	27 (96%)	4 (80%)
Mild impairment	5 (8%)	4 (13%)	1 (4%)	1 (20%)

	All (n=60)	Placebo first (n=32)	Allopurinol first (n=28)	Dropouts (n=5)
Medical history				
Hypertension	27 (45%)	13(41%)	14 (50%)	2 (40%)
Diabetes mellitus	7 (12%)	4 (13%)	3 (11%)	1 (20%)
Hypercholesterolaemia	26 (43%)	15 (47%)	11 (39%)	2 (40%)
Peripheral vascular disease	1 (2%)	1 (3%)	0	0
Cerebral ischaemic attack or transient ischaemic attack	4 (7%)	3 (9%)	1 (4%)	1 (20%)
Myocardial infarction	12 (20%)	7 (22%)	5 (18%)	0
Percutaneous coronary intervention	7 (12%)	3 (9%)	4 (14%)	0
Coronary artery bypass graft	7 (12%)	4 (13%)	3 (11%)	0
Smoking status				
Current smoker	5 (8%)	4 (13%)	1 (4%)	0
Ex-smoker	31 (52%)	14 (44%)	17 (61%)	2 (40%)
Non-smoker	24 (40%)	14 (44%)	10 (36%)	3 (60%)
Drugs				
Aspirin	60 (100%)	32 (100%)	28 (100%)	4 (80%)
β blocker	52 (87%)	27 (84%)	25 (89%)	4 (80%)
Oral nitrate	29 (48%)	16 (50%)	13 (46%)	4 (80%)
Calcium antagonists	13 (22%)	7 (22%)	6 (21%)	0
Nicorandil	13 (22%)	8 (25%)	5 (18%)	1 (20%)
Angiotensin-converting-enzyme inhibitor	28 (47%)	17 (53%)	11 (39%)	2 (40%)
Angiotensin-receptor blocker	6 (10%)	2 (6%)	4 (14%)	1 (20%)
Statin	58 (97%)	31 (97%)	27 (96%)	3 (60%)

Data are number (%), unless otherwise indicated. Percentages might not add up to 100% because of rounding.

Table 1: **Baseline characteristics of participants**

	Baseline	Placebo	Allopurinol
Haemoglobin (g/L)	13·8 (1·3)	13·6 (1·1)	13·5 (1·4)
White blood cells ($\times 10^9$ per L)	6·7 (1·6)	6·8 (1·6)	6·6 (1·4)
Platelets ($\times 10^9$ per L)	224·4 (60·3)	219·6 (58·6)	218·4 (73·1)
Sodium (mmol/L)	140·5 (2·7)	140·4 (2·6)	140·4 (2·6)
Potassium (mmol/L)	4·3 (0·3)	4·3 (0·3)	4·3 (0·3)
Urea (mmol/L)	6·4 (1·5)	6·9 (1·8)	6·5 (1·7)
Creatinine (∝mol/L)	84·9 (16·1)	85·0 (17·3)	82·9 (15·9)
Estimated glomerular filtration rate (mL per min)	59·6 (1·7)	59·1 (3·2)	59·4 (2·4)

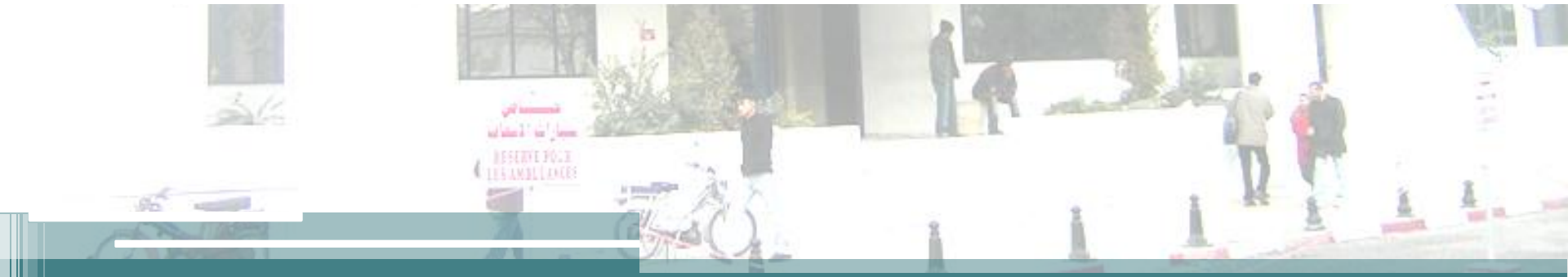
Data are mean (SD).

Table 2: Haematology and biochemistry results

	Baseline	Placebo	Allopurinol	Point estimate* (95% CI)	Mann-Whitney p value*
Total exercise time (s)	301 (251–447)	307 (232–430)	393 (280–519)	58 (45–77)	0·0003
Time to ST depression (s)	232 (182–380)	249 (200–375)	298 (211–408)	43 (31–58)	0·0002
Time to symptoms (s)	234 (189–382)	272 (200–380)	304 (222–421)	38 (17–55)	0·001

Data are median (IQR), unless otherwise indicated. *For difference between allopurinol and placebo.

Table 3: **Effect of allopurinol on total exercise time, time to ST depression, and time to symptoms**



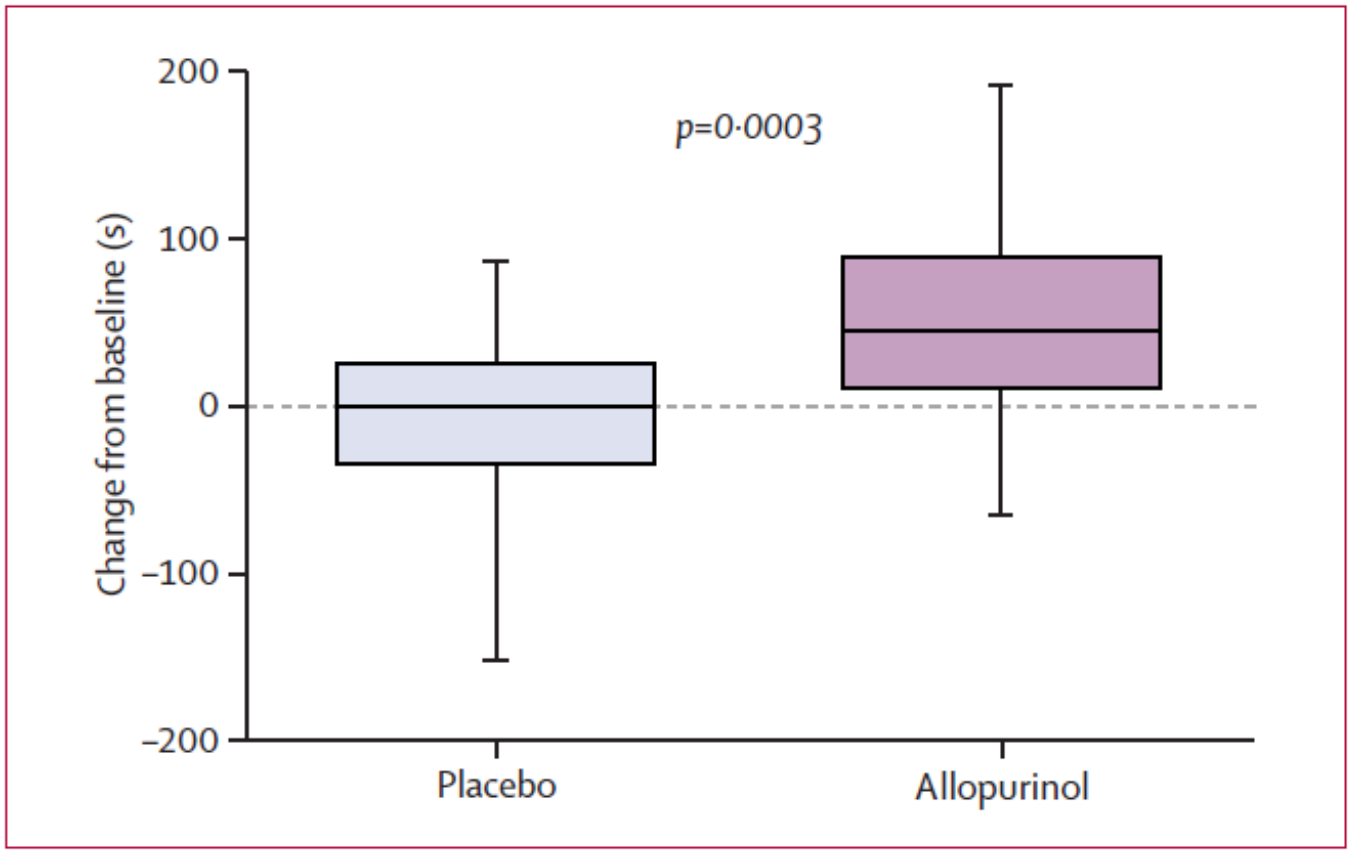


Figure 2: **Change in total exercise time from baseline**
Data are median (IQR).

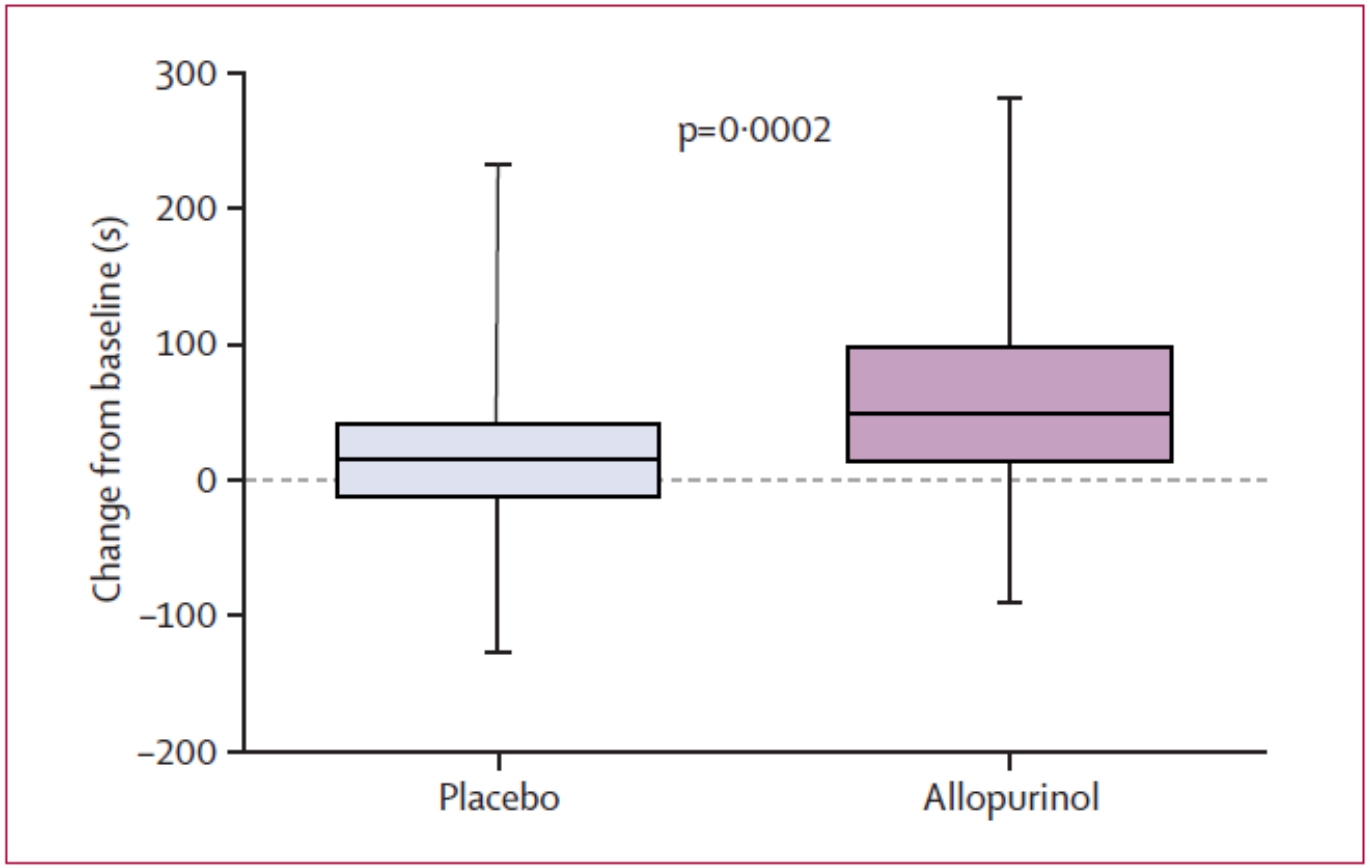


Figure 3: **Change in time to ST depression from baseline**
Data are median (IQR).

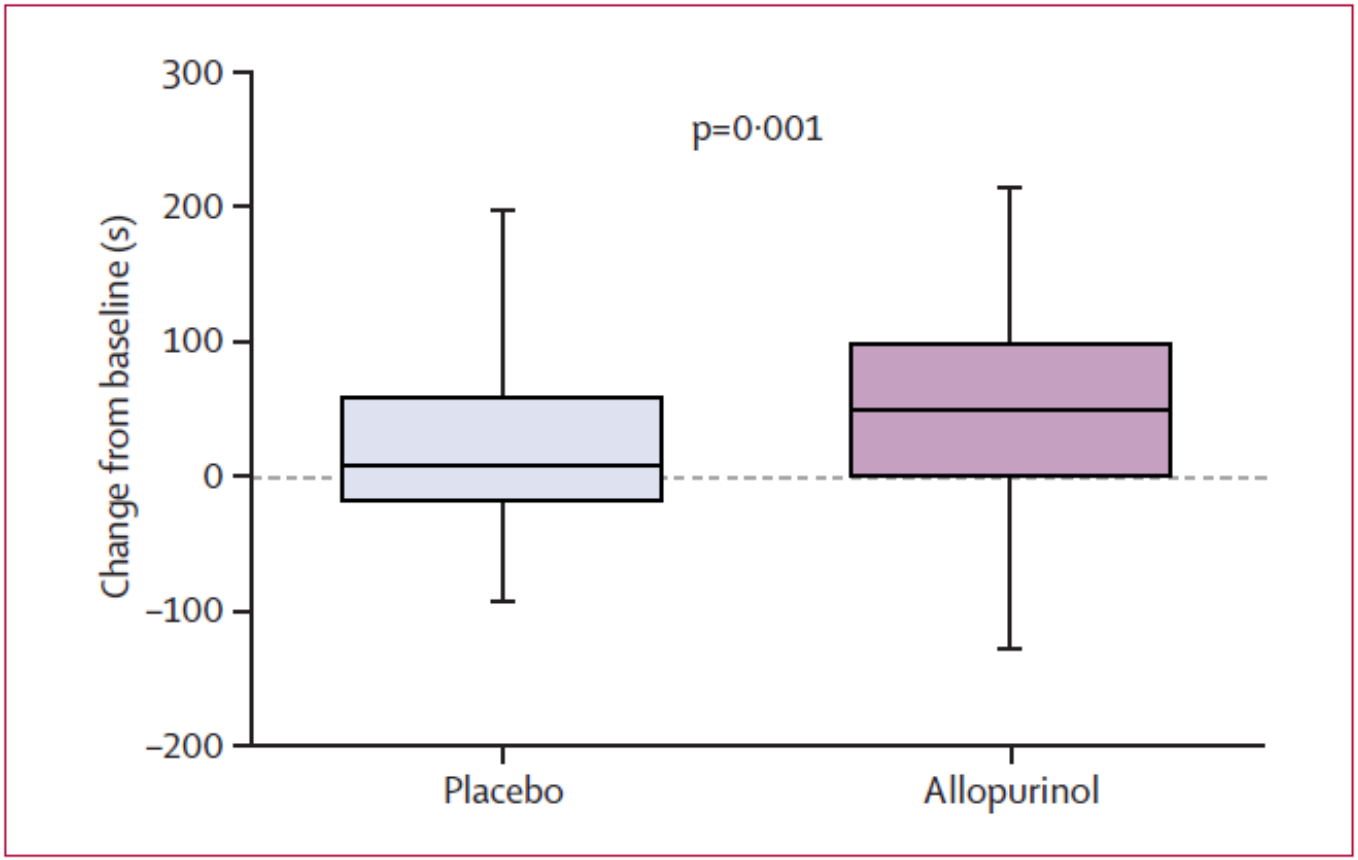


Figure 4: **Change in time to chest pain symptoms from baseline**
Data are median (IQR).

	Baseline	Placebo	Allopurinol	p value*
Heart rate (beats per min)				
Baseline	62·3 (10·3)	61·3 (9·2)	63·8 (8·6)	0·025
Stage 1	95·2 (13·7)	94·3 (13·3)	95·6 (13·5)	0·154
Peak exercise	113·6 (15·3)	112·4 (15·6)	118·5 (15·2)	0·0006
Systolic blood pressure (mm Hg)				
Baseline	126·8 (16·6)	124·3 (13·7)	123·7 (16·2)	0·755
Stage 1	141·6 (21·0)	140·0 (16·1)	135·5 (19·3)	0·042
Peak exercise	159·3 (22·6)	155·1 (18·4)	158·7 (22·4)	0·116
Diastolic blood pressure (mm Hg)				
Baseline	72·8 (8·6)	72·9 (7·7)	72·2 (9·9)	0·577
Stage 1	72·9 (10·6)	74·8 (8·6)	71·7 (10·1)	0·008
Peak exercise	76·1 (12·7)	78·5 (10·2)	75·4 (11·9)	0·015
Rate pressure product (beats per min×mm Hg)				
Baseline	7897 (1709)	7607 (1471)	7910 (1577)	0·123
Stage 1	13 349 (2997)	13 114 (2617)	12 756 (2798)	0·174
Peak exercise	18 210 (4104)	17 484 (3655)	18 842 (3791)	0·001

Data are mean (SD). *For difference between allopurinol and placebo.

Table 4: Haemodynamic responses during exercise testing

	Placebo	Allopurinol	p value*
All responders (n=43)			
Angina episodes per week	1·0 (0–2·5)	0·5 (0–1·5)	0·153
Glyceryl trinitrate (tablets per week)	0·2 (0–2·0)	0·2 (0–1·2)	0·157
Responders with one or more angina per week (n=26)			
Angina episodes per week	2·3 (1·5–4·4)	1·3(0·5–2·3)	0·053
Glyceryl trinitrate use (tablets per week)	1·9 (0·9–3·4)	0·5 (0–2·0)	0·064

Data are median (IQR). *For difference between allopurinol and placebo.

Table 5: Angina episodes

COMMENTAIRES

- L'allopurinol semble efficace dans le traitement de fond de linsuffisance coronarienne.

- Reste à voir si ça se confirme sur un essai contrôlé.