Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: a systematic review and meta-analysis

Anne Bellemain-Appaix,[1 3] Mathieu Kerneis,[2 3] Stephen A O'Connor,[2 3] Johanne Silvain,[2 3] Michel Cucherat,[4] Farzin Beygui,[2 3] Olivier Barthélémy,[2 3] Jean-Philippe Collet,[2 3] Laurent Jacq,[1] François Bernasconi,[1] Gilles Montalescot,[2 3] for the ACTION Study Group

EDITORIAL by Rade

[1]Service de Cardiologie-La Fontonne Hospital, Antibes, France
[2]Institut de Cardiologie, INSERM UMRS1166, Pitié-Salpêtrière Hospital (AP-HP), Université Paris 6, France
[3]ACTION Study Group, Paris, France
[4]UMR CNRS 5558, Université Lyon 1 Laennec, Lyon, France
Correspondence to: G Montalescot ACTION Study Group, Institut de Cardiologie, Bureau 2-236, Pitié-Salpêtrière Hospital, 47 Boulevard de l'Hôpital, 75013 Paris, France
gilles.montalescot@psl.aphp.fr

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STUDY QUESTION

Is pretreatment with $P2Y_{12}$ inhibitors (administration before a coronary angiogram) better than no pretreatment in patients with non-ST elevation acute coronary syndrome (ACS), whether managed invasively or not, in modern practice?

SUMMARY ANSWER

No, pretreatment with thienopyridines is associated with no significant reduction of mortality but with a significant excess of major bleeding no matter the management strategy adopted.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Current guidelines that recommend systematic pretreatment are based on old studies, whereas recent trials, although underpowered, tend to show an unfavourable benefit-risk balance in patients with non-ST elevation ACS. This meta-analysis shows that the concept of systematic and immediate pretreatment with $P2Y_{12}$ antagonists in patients admitted with non-ST elevation ACS needs to be reconsidered.

Selection criteria for studies

We searched Medline, Embase, Cochrane Controlled Trials, and BioMed Central databases for randomized placebo-controlled trials and observational studies comparing pretreatment with $P2Y_{12}$ inhibitors versus no pretreatment in patients with non-ST elevation acute coronary syndrome (ACS) from August 2001 to March 2014. Data on sample size, study characteristics, drug dose and delay of administration, and outcomes were independently extracted and analyzed. A random-effect model was applied. The analysis was performed (i) for all included patients with non-ST elevation ACS irrespective of management strategy and (ii) for only those patients managed by percutaneous coronary intervention (PCI).

Primary outcome(s)

All cause mortality (primary efficacy endpoint) and major bleeding (safety endpoint).

Main results and role of chance

Results for all cause mortality, major bleeding, and major adverse cardiovascular events are summarized in the figure for all patients with non-ST elevation ACS and for those managed by PCI. Stent thrombosis, stroke, and urgent revascularization did not differ between groups (pretreatment *v* no pretreatment). The results were consistent for both thienopyridines (clopidogrel and prasugrel) and were confirmed in sensitivity analyses (according to clopidogrel loading dose, in randomised trials only, and after the exclusion of the old CURE study).

Bias, confounding, and other reasons for caution

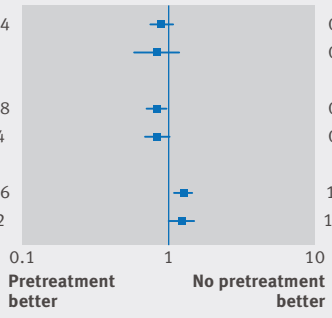
Confidence intervals are wide, and variability must be taken into consideration. Confounding by indication can't be excluded in registries, but the global results using all studies available were confirmed in the more robust subgroup of randomised controlled trials and the pre-specified sensitivity analyses. A higher dose than 300 mg of clopidogrel could have given a different result, but a recent study did not confirm this. Because no data are available for ticagrelor, conclusions cannot be drawn for this drug.

Study funding/potential competing interests

No external source of funding. The study was led by the ACTION-study-group (www.action-coeur.org). GM, J-PC, JS, and AB-A have received consulting fees or grant support from pharmaceutical companies active in antiplatelet therapies.

Effect of thienopyridine pretreatment on main ischaemic and haemorrhagic endpoints* for (i) all patients with non-ST elevation acute coronary syndrome and (ii) only patients who underwent percutaneous coronary intervention (PCI)

Analysis	No of events/patients: Pretreatment	No of events/patients: No pretreatment	Odds ratio (95% CI)	Odds ratio (95% CI) (P value)	I^2 value (%) (P value)
All deaths					
All patients	594/20 128	477/11 954		0·90 (0·75 to 1·07) (P=0.24)	10 (P=0.35)
PCI treated patients only	146/12 300	79/6 121		0·83 (0·59 to 1·17) (P=0.29)	6 (P=0.38)
Major adverse cardiovascular events					
All patients	1294/20 128	968/13 488		0·84 (0·72 to 0·98) (P=0.02)	52 (P=0.05)
PCI treated patients only	937/12 300	556/6 134		0·83 (0·69 to 1·01) (P=0.06)	55 (P=0.04)
Major bleeding					
All patients	551/20 281	305/13 636		1·27 (1·10 to 1·47) (P<0.001)	0 (P=0.52)
PCI treated patients only	344/12 453	151/6 282		1·23 (1·00 to 1·50) (P=0.048)	0 (P=0.58)



*All endpoints were considered at shortest follow up available in each study, which was 7 or 30 days

Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study

Michael Fralick,[1] Erin M Macdonald,[2] Tara Gomes,[2 3 4] Tony Antoniou,[2 3 4 5] Simon Hollands,[2] Muhammad M Mamdani,[2 3 4 6 7] David N Juurlink,[2 3 8 4] for the Canadian Drug Safety and Effectiveness Research Network (CDSERN)

EDITORIAL by Etminan and Brophy

[1]Department of Internal Medicine, University of Toronto, Toronto, ON, Canada, M5G 2C4
[2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada, M5N 4M5
[3]Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada, M5B 1W8
[4]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, M5T 3M7
[5]Department of Family and Community Medicine, St Michael's Hospital, Toronto
[6]Applied Health Research Centre, St Michael's Hospital, Toronto
[7]King Saud University, Riyadh, Saudi Arabia
[8]Sunnybrook Research Institute, Toronto, ON, Canada, M4N 3M5
Correspondence to: D N Juurlink, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue G106, Toronto, ON, Canada, M4N 3M5 dnj@ices.on.ca

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STUDY QUESTION

Is co-trimoxazole treatment associated with a higher risk of sudden death than other antibiotics used for urinary tract infections in patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers?

SUMMARY ANSWER

In older patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers, co-trimoxazole was associated with an increased risk of sudden death.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The prescribing of co-trimoxazole with angiotensin converting enzyme inhibitors or angiotensin receptor blockers results in a sevenfold increase in the risk of hospital admission with hyperkalemia relative to amoxicillin. This combination is also associated with an increased risk of sudden death in older patients; when clinically appropriate, clinicians should either choose alternative antibiotics or limit the dose and duration of co-trimoxazole treatment in this situation.

Participants and setting

We included Ontario residents aged 66 years or older receiving an angiotensin converting enzyme inhibitor or angiotensin receptor blocker who died suddenly shortly after receiving an outpatient prescription for one of co-trimoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin. We matched each case of sudden death with up to four controls on age, sex, chronic kidney disease, and diabetes.

Antibiotic use and risk of sudden death within seven and 14 days

Antibiotic use	No (%) cases	No (%) controls	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Seven days				
Amoxicillin (reference)	226 (22.0)	1098 (29.4)	1.0 (reference)	1.0 (reference)
Co-trimoxazole	288 (28.0)	734 (19.7)	1.83 (1.50 to 2.24)	1.38 (1.09 to 1.76)
Ciprofloxacin	340 (33.1)	964 (25.8)	1.66 (1.37 to 2.00)	1.29 (1.03 to 1.62)
Norfloxacin	79 (7.7)	455 (12.2)	0.81 (0.61 to 1.08)	0.74 (0.53 to 1.02)
Nitrofurantoin	94 (9.2)	482 (12.9)	0.87 (0.66 to 1.15)	0.64 (0.46 to 0.88)
14 days				
Amoxicillin (reference)	418 (22.9)	2021 (29.8)	1.0 (reference)	1.0 (reference)
Co-trimoxazole	474 (25.9)	1262 (18.6)	1.80 (1.54 to 2.09)	1.54 (1.29 to 1.84)
Ciprofloxacin	603 (33.0)	1888 (27.9)	1.50 (1.30 to 1.72)	1.18 (1.00 to 1.39)
Norfloxacin	158 (8.6)	832 (12.3)	0.89 (0.73 to 1.09)	0.83 (0.65 to 1.05)
Nitrofurantoin	174 (9.5)	768 (11.3)	1.08 (0.88 to 1.32)	1.03 (0.81 to 1.30)

*Analysis adjusted for disease risk index.

Design, size, and duration

Our population based nested case-control study included 1027 cases of sudden death and 3733 matched controls over the 17 year study period.

Primary outcome(s), risks, exposures

The primary outcome was sudden death within seven days of an outpatient prescription of one of co-trimoxazole, amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin. The secondary outcome was sudden death within 14 days of receiving one of the study antibiotics. Odds ratios for the association between sudden death and exposure to each antibiotic (relative to amoxicillin) were adjusted for predictors of sudden death according to a disease risk index.

Main results and the role of chance

Co-trimoxazole was associated with a significantly increased risk of sudden death within seven days relative to amoxicillin (adjusted odds ratio 1.38, 95% confidence interval 1.09 to 1.76). The risk was marginally higher at 14 days (adjusted odds ratio 1.54, 1.29 to 1.84). The absolute risk can be approximated at three sudden deaths within two weeks for every 1000 prescriptions for co-trimoxazole, compared with one sudden death per 1000 amoxicillin prescriptions. Ciprofloxacin was also associated with an increased risk of sudden death within seven days (adjusted odds ratio 1.29, 1.03 to 1.62) but not within 14 days (1.18, 1.00 to 1.39). An increased risk of sudden death was not observed with nitrofurantoin or norfloxacin.

Bias, confounding, and other reasons for caution

We did not have access to data on serum potassium or creatinine concentrations, adherence to treatment, non-prescription drug use, and other risk factors for sudden death.

Generalisability to other populations

Our findings derive from patients aged 66 years and older, and the generalisability to younger patients is unknown.

Study funding/potential competing interests

This study was supported in part by a grant from the Canadian Drug Safety and Effectiveness Research Network and by the Institute for Clinical Evaluative Sciences. TA is supported by a new investigator award from the Canadian Institute for Health Research and Ontario HIV Treatment Network. MMM has served on advisory boards and/or received honorariums from Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Hoffman La Roche, Novartis, Novo Nordisk, and Pfizer.

Milk intake and risk of mortality and fractures in women and men: cohort studies

Karl Michaëlsson,[1] Alicja Wolk,[2] Sophie Langenskiöld,[3] Samar Basu,[3] Eva Warensjö Lemming,[1 4] Håkan Melhus,[5] Liisa Byberg[1]

EDITORIAL by Schooling

[1]Department of Surgical Sciences, Uppsala University, SE-751 85 Uppsala, Sweden
[2]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[3]Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden
[4]Swedish National Food Agency, Uppsala, Sweden
[5]Department of Medical Sciences, Uppsala University, Uppsala, Sweden
Correspondence to: K Michaëlsson
karl.michaelsson@surgsci.uu.se

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STUDY QUESTION

Is a high consumption of milk associated with mortality and fractures in women and men?

SUMMARY ANSWER

High milk intake was associated with higher mortality in both a cohort of women and a cohort of men, and with a higher incidence of fracture in women.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

A high milk intake is recommended for the prevention of osteoporotic fractures, but milk is also the major dietary source of galactose intake. The addition of galactose by injections or in the diet is an established animal model of aging by induction of oxidative stress and inflammation. A high milk intake in both cohorts was associated with higher rates of mortality and fracture and with higher levels of oxidative stress and inflammatory biomarkers, a pattern not observed with high intake of fermented milk products such as yogurt.

Participants and setting

Two cohorts, one comprising women and one comprising men, in three counties in central Sweden.

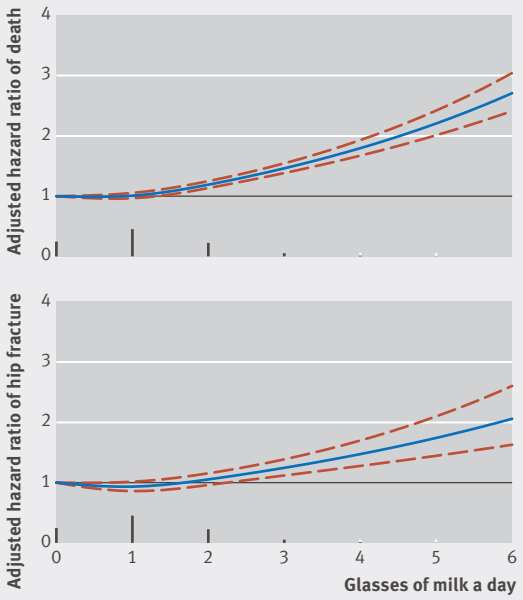
Design, size, and duration

Two large Swedish cohorts, one with 61 433 women (39-74 years at baseline, 1987-90) and one with 45 339 men (45-79 years at baseline, 1997), were administered food frequency questionnaires. The women responded to a second food frequency questionnaire in 1997. We applied multivariable survival models to determine the association between milk consumption and time to mortality or fracture. In subsamples of two additional cohorts, one in men and one in women, we assessed the relation between milk intake and urine 8-iso-PGF2α (a biomarker of oxidative stress) and serum interleukin 6 (a main biomarker of inflammation).

Main results and the role of chance

During a mean follow-up of 20.1 years, 15 541 women died and 17 252 had a fracture, with 4259 cases of hip fracture. In the male cohort with a mean follow-up of 11.2 years, 10 112 men died and 5066 had a fracture, with 1166 cases of hip fracture. In women, we observed a positive association between milk intake and total mortality as well as hip fracture, as illustrated by the adjusted spline curves in the figure. The adjusted mortality hazard ratio for three or more glasses of milk a day (one glass equates to 200 g/d) compared with less than one glass a day was 1.93 (95% confidence interval 1.80 to 2.06). For every glass of milk, the hazard ratio of all cause mortality was 1.15 (1.13 to 1.17) in women and 1.03 (1.01 to 1.04) in men. For every glass of milk in women no reduction was observed in fracture risk with higher milk consumption for any fracture (1.02, 1.00 to 1.04) or for hip fracture (1.09, 1.05 to 1.13). The corresponding hazard ratios in men were 1.01 (0.99 to 1.03) and 1.03 (0.99 to 1.07). Positive associations were seen between milk intake and both urine 8-iso-PGF2α and serum interleukin 6 levels. In a sensitivity analysis, the risk estimates of the outcomes associated with consumption of cheese or fermented milk products were in the opposite direction of estimates associated with milk consumption.

Multivariable adjusted spline curves showing relation between milk intake with time to death from all causes and hip fracture in women in Swedish Mammography Cohort



Covariates were age, total energy intake, body mass index, height, educational level, living alone, calcium and vitamin D supplement use, healthy dietary pattern, physical activity, smoking status, cortisone use, and Charlson's comorbidity index. Spike plot represents distribution of milk intake. One glass of milk corresponds to 200 g

Bias, confounding, and other reasons for caution

Given the observational study designs with the inherent possibility of residual confounding and reverse causation phenomena, we recommend that the results should be interpreted with caution.

Generalisability to other populations

Our results might not apply to people of other ethnic origins, such as those with a high prevalence of lactose intolerance, or to children and adolescents.

Study funding/potential competing interests

This study was supported by grants from the Swedish Research Council.