Gastrointestinal Events with Clopidogrel: A Nationwide Population-Based Cohort Study

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BACKGROUND: Clopidogrel prevents cardiovascular events, but has been linked with adverse gastrointestinal (GI) complications, particularly bleeding events.

OBJECTIVE: We aimed to investigate the risk of adverse GI events in patients treated with clopidogrel.

DESIGN: A nationwide population-based cohort study based on linkage of three administrative registries in Denmark.

PARTICIPANTS: All individuals who redeemed at least one prescription of clopidogrel from 1996 to 2008 were included as exposed subjects (n=77,503). For each exposed subject, three matched controls were randomly selected from the background population (n=232,510).

ANALYSES: Follow-up began on January 1, 1996, and was censored on December 31, 2007, or if patients emigrated or died. The study endpoint was the occurrence of any gastritis, GI ulcer or bleeding. Analyses were adjusted for comorbidity and medication.

RESULTS: Regardless of dose, adjusted odds ratios associating clopidogrel use with the study endpoint were statistically significant and followed a dose–response pattern. The crude absolute risk of GI events were: never users: 2.2 %; <0.1 defined daily dose (DDD) of clopidogrel per day: 7.1 %; 0.1–0.39 DDD: 6.0 %; 0.4–0.79 DDD: 5.7 %; ≥0.80 DDD: 4.4 %. Adjusted odds ratios were: <0.1 DDD: 1.34, 95 % CI: 1.26–1.42; 0.1–0.39 DDD: 1.58, 95 % CI: 1.48–1.68; 0.4–0.79 DDD: 1.91, 95 % CI: 1.77–2.06; ≥0.80 DDD: 1.77, 95 % CI: 1.66–1.89, all p-values<0.01. Depending on the dose, numbers needed to harm ranged from 58 to 33 patients receiving 12 months of clopidogrel treatment.

CONCLUSIONS: The well-known cardioprotective effect of clopidogrel must be carefully weighed against an increased risk of GI events.

KEY WORDS: clopidogrel; coronary artery disease; gastritis; gastrointestinal hemorrhage; stomach ulcer.

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Abbreviations

ADP	Adenosine diphosphate
ATC	Anatomical Therapeutical Chemical
DDD	Defined daily dose
GI	Gastrointestinal
ICD	International Classification of Diseases

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INTRODUCTION

The benefits of antiplatelet therapy for atherosclerotic cardiovascular disease have been amply documented over the past decades. Thus, antiplatelet drugs are mandatory in the treatment and secondary prevention of coronary artery disease, particularly in the setting of acute coronary syndromes[1,2] and percutaneous coronary interventions.[3] Aspirin (acetylsalicylic acid) significantly reduces clinical events and death in a broad spectrum of cardiovascular patients,[4,5] and additional cardiovascular protection is achieved when combining aspirin with clopidogrel.[6,7] Clopidogrel prevents the binding of adenosine diphosphate (ADP) to purinergic $P2Y_{12}$-receptors on the platelet surface, thus inhibiting platelet aggregation.

Cardiovascular protection by aspirin is obtained at the expense of an increased risk of gastrointestinal (GI) bleeding events.[8,9] GI bleeding can be life-threatening, especially in patients with acute coronary syndromes.[10,11] Although the use of clopidogrel increases the risk of GI bleeding, it is not associated with increased short-term mortality after admission with GI bleeding.[12] Initial data showing that clopidogrel caused fewer GI erosions[13] and bleeding events than aspirin[6] prompted its use as the preferred antiplatelet drug in aspirin-treated patients with GI complications. However, more recent studies have reported a significantly increased risk of GI bleeding during treatment with clopidogrel.[14,15] Importantly, the risk of bleeding increases when combining clopidogrel with aspirin.[16,17]

Currently, the use of proton pump inhibitors is the prevailing strategy for the prevention of GI bleeding during antiplatelet therapy.[18,19] Whether these drugs may reduce the cardiovascular protection by antiplatelet drugs has been discussed,[20] but the randomized COGENT trial showed that in patients treated with aspirin and clopidogrel, proton pump inhibitors reduce GI bleeding complications without increasing cardiovascular event rates.[21]

Although bleeding, including GI bleeding, is the most frequent complication of clopidogrel therapy, safety data on the use of clopidogrel obtained from unselected patients are sparse. Clopidogrel remains the second most prescribed drug worldwide,[22] and investigating clopidogrel-related bleeding is important. We conducted a nationwide population-based cohort study to assess the risk of adverse GI events in an unselected population of real-world patients treated with clopidogrel.

METHODS

Study Design

An observational design employing nationwide registries was used. All subjects who redeemed at least one prescription of clopidogrel within the study period from 1996 to 2008 in Denmark were included as exposed subjects (n=77,503). For each exposed subject, three controls were randomly selected from the background population using the Danish Civil Registration System (n=232,510). Controls were matched with exposed subjects for age (same birth year) and gender using an intensity sampling technique,[23] i.e., controls had to be alive and at risk of a GI diagnosis at the time the corresponding exposed subject redeemed a prescription of clopidogrel. Each control was assigned a dummy index date identical to that of the corresponding exposed subject.

Setting

The study cohort was the entire Danish population totalling approximately 5.5 million inhabitants, and the study period was January 1, 1996, to December 31, 2007. Danish citizens and permanent residents qualify for unfettered access to general practitioners and hospitals provided by the Danish National Health Service. The healthcare system also provides partial reimbursement for prescribed medications, including clopidogrel.

A total of three nationwide administrative registers were used in the study and linked at an individual level: 1) The Danish National Registry of Patients holds data on all nonpsychiatric admissions to Danish hospitals since 1977, including all outpatient contacts from 1996 an onwards, with diagnoses encoded according to the International Classification of Diseases ([ICD], 8th revision until the end of 1993, and 10th revision thereafter).[24] Upon discharge, patients are assigned an ICD code corresponding to the reason for admission. ICD codes are used at the discretion of the discharging physician who can use one or several codes per visit. The register has a nationwide coverage and an almost complete capture of contacts;[24] 2) The Register of Medicinal Product Statistics was used to identify all prescriptions of clopidogrel redeemed from 1996 through 2007. This register, which is governed by the Danish Medicines Agency, covers all drugs dispensed at pharmacies in Denmark from 1995 and forward, with each drug being classified according to the international Anatomical Therapeutical Chemical (ATC) system. Among other things, each prescription record holds information on drug dosage and date of dispensation. All sales are referable to the individual who redeemed the prescription, and the capture and validity is high;[25] 3) Unambiguous, individual-level linkage between the aforementioned registers was enabled by the Danish Civil Registration System. According to this system, a permanent and unique 10-digit identification number is assigned to every Danish inhabitant at birth and to residents on immigration.[26]

The project was approved and controlled by the National Board of Health, the Danish Data Protection Agency and the Danish Medicines Agency.

Patients with Adverse GI Events

The study endpoint was the occurrence of any gastritis, GI ulcer or bleeding between January 1, 1996, and December 31, 2007. The following diagnoses were included: acute haemorrhagic gastritis (K29.0), bleeding and non-bleeding ulcers in the stomach (K25.0–25.7, 25.9), bleeding and non-bleeding duodenal ulcers (K26.0–26.7, 26.9), bleeding and non-bleeding gastro-duodenal ulcers (K27.0–27.7, 27.9), bleeding and non-bleeding gastrojejunal ulcers (K28.0–28.7, 28.9), haematemesis (K92.0), melaena (K92.1), and GI haemorrhage without specification (K92.2).

Clopidogrel Use and Concomitant Medical Therapy

The primary exposure was the use of clopidogrel (ATC B01AC04). In Denmark, clopidogrel is available only by prescription. Patterns of drug use were analysed for the period from January 1, 1996, to the date of GI complication or the corresponding dummy index date among controls. Since clopidogrel was not commercially

available prior to 1998, our population was treatment-naive. Information on whether the drugs were used systematically or temporarily was included in the analyses of drug use via the defined daily dose (DDD) and dates of prescription. The DDD concept was used according to the World Health Organization definition; the assumed average maintenance dose per day for a drug used for its main indication in adults.[27] The DDD of clopidogrel is 75 mg, which is equivalent to the daily dose recommended in current clinical guidelines.

Statistical Analysis

Categorical variables are presented as absolute counts (percentages). Continuous data are presented as means (standard deviation). The χ^2-test and Mann–Whitney test were used to compare categorical and continuous variables as appropriate. Follow-up began on January 1, 1996, and was censored on December 31, 2007, or if the patient emigrated or died. Crude and adjusted odds ratios were calculated and are given with 95 % confidence intervals. Cox proportional hazard regression models were used to analyse the risk of GI events in clopidogrel users vs. nonusers. The proportional hazard assumption was checked by inspection of survival plots. Analyses were performed using STATA 9.0 (STATA Corp., College Station, TX, USA) and IBM SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Figure 1 was prepared using GraphPad Prism® version 5.0 (GraphPad Software, San Diego, CA, USA).

Due to imbalances in confounders typical for observational studies, extensive confounder control was performed, including all unevenly distributed variables considered as potential confounders. Thus, all variables in Table 2 were included in the statistical analysis and analyses for interaction were performed.

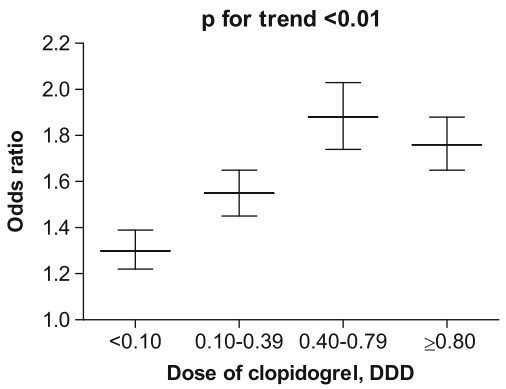

Figure 1. Risk of adverse gastrointestinal events (gastritis, gastrointestinal ulcer or bleeding) in patients treated with clopidogrel. Error bars depict standard deviation. DDD, defined daily dose.

RESULTS

Baseline Characteristics

Descriptive data and baseline characteristics are presented in Table 1. The study population included 77,503 exposed subjects and 232,510 controls. The mean age was 66 years, and 65 % were male. Prior gastroduodenal ulcer or gastritis were more common among clopidogrel users than nonusers

Table 1. Baseline Characteristics of Clopidogrel Users and Nonusers

Variable	Clopidogrel users (n=77,503)	Nonusers (n=232,510)
Demographics		
Age, years, mean (SD)	65.7 (12.7)	65.7 (12.7)
Men	50,118 (64.7)	150,354 (64.7)
Women	27,385 (35.3)	82,156 (35.3)
Medication		
Clopidogrel	77,503 (100)	0 (0)
Aspirin	44,015 (56.8)	54,610 (23.5)
Dipyridamole	8,123 (10.5)	7,331 (3.2)
Oral anticoagulants	1,287 (1.7)	2,429 (1.0)
NSAID	59,600 (76.9)	162,795 (70.0)
Statins	30,345 (39.2)	26,735 (11.5)
Thiazide diuretics	24,895 (32.1)	53,675 (23.1)
Loop diuretics	18,105 (23.4)	31,725 (13.6)
Spironolactone	11,292 (14.6)	11,889 (5.1)
Other diuretics	8,737 (11.3)	16,926 (7.3)
Beta-blockers	36,288 (46.8)	43,114 (18.5)
ACE/AT-II inhibitors	38,658 (49.9)	46,380 (19.9)
ACE/AT-II inhibitors plus diuretics	6,529 (8.4)	13,129 (5.6)
Calcium channel blockers	27,953 (36.1)	41,744 (18.0)
Proton pump inhibitors	38,914 (50.2)	67,224 (28.9)
Histamine H2 antagonists	15,594 (20.1)	30,738 (13.2)
Other antacid drugs	12,901 (16.6)	25,458 (10.9)
Any antacid drugs	44,714 (57.7)	85,460 (36.8)
Systemic corticosteroids	20,050 (25.9)	47,067 (20.2)
Bronchodilator drugs	23,900 (30.8)	54,703 (23.5)
Smoking cessation drugs	1,969 (2.5)	2,240 (1.0)
Medical history		
Diabetes	10,863 (14.0)	11,894 (5.1)
Atrial fibrillation	8,036 (10.4)	12,080 (5.2)
Angina pectoris	53,523 (69.1)	21,428 (9.2)
Acute myocardial infarction	45,365 (58.5)	10,709 (4.6)
Heart failure	11,243 (14.5)	8,129 (3.5)
Peripheral atherosclerosis	7,356 (9.5)	7,193 (3.1)
Ischaemic stroke	7,003 (9.0)	5,772 (2.5)
Cerebral atherosclerosis	2,784 (3.6)	2,900 (1.2)
Gastroduodenal ulcers or gastritis	10,408 (13.4)	16,865 (7.3)
Liver disease	1,182 (1.5)	3,008 (1.3)
Renal disease	3,603 (4.6)	6,698 (2.9)
COPD	7,011 (9.0)	11,549 (5.0)
Cancer	7,130 (9.2)	21,430 (9.2)
Any fracture	16,730 (21.6)	47,795 (20.6)
Charlson Comorbidity Index, mean (SD)	2.1 (1.9)	0.8 (1.5)
Social status		
Income during index year, Danish kroner, mean (SD)	209,223 (315,460)	224,149 (227,691)
Diagnosis of alcoholism	2,469 (3.2)	6,562 (2.8)
Cohabitation: living with someone	29,030 (37.5)	88,901 (38.2)

ACE angiotensin-converting enzyme; AT-II angiotensin-II, COPD chronic obstructive pulmonary disease; NSAID non-steroidal anti-inflammatory drugs. All values are given as numbers and percentages unless otherwise indicated

(13.4 % vs. 7.3 %). Likewise, comorbidity and concomitant medical treatment, including proton pump inhibitors, other antacid drugs and antiplatelet treatment, were more common among clopidogrel users (Table 1).

Clopidogrel and the Risk of Adverse GI Events

Among controls, a total of 5,143 GI events were observed, including 1,339 ulcers with bleeding, 1,965 ulcers without bleeding, and 1,839 cases of gastritis. Among individuals exposed to clopidogrel, the corresponding figures were 4,406 GI events, distributed with 1,180 ulcers with bleeding, 1,433 ulcers without bleeding, and 1,793 events of gastritis. Among non-clopidogrel, non-aspirin exposed, the crude risk of GI events was 1.6 %, and among non-clopidogrel, aspirin exposed the risk was 4.1 %. Among clopidogrel, non-aspirin exposed the risk of GI events was 6.1 %, and among patients on dual antiplatelet treatment with aspirin and clopidogrel, the risk was 6.6 %.

The sex and age matched odds ratios associating clopidogrel use with the risk of gastritis, GI ulcer or bleeding were significant and followed a dose–response pattern. Accordingly, increasing doses of clopidogrel yielded increasing odds ratios of suffering GI events (Table 2 and Figure 1, trend in strata: $p<0.01$). The dose–response relationship is also clearly seen in Figure 2, which shows the cumulated hazard of the study endpoint after start of clopidogrel by years after first use. In patients receiving <0.10, 0.10–0.39, 0.40–0.79 or ≥0.80 of the DDD of clopidogrel, the risk of adverse GI events (gastritis, GI ulcer or bleeding) was calculated as numbers needed to harm based on 12 months of treatment. In these strata, the numbers needed to harm were 58, 42, 43 and 33, respectively. As shown in Table 2, prior use of proton pump inhibitors was strongly associated with the risk of adverse GI events (odds ratio 20.0 [95 % confidence interval 18.5 to 21.6]).

Table 2. Risk of Adverse Gastrointestinal Events (Gastritis, Gastrointestinal Ulcer or Bleeding) After Initiation of Clopidogrel Treatment

Variable	Odds ratio (95 % confidence interval)	P-values
Dose of clopidogrel		
<0.10 DDD	1.34 (1.26 to 1.42)	<0.01
0.10–0.39 DDD	1.58 (1.48 to 1.68)	<0.01
0.40–0.79 DDD	1.91 (1.77 to 2.06)	<0.01
≥0.80 DDD	1.77 (1.66 to 1.89)	<0.01
Aspirin	1.05 (1.01 to 1.10)	0.03
Dipyridamole	1.36 (1.26 to 1.47)	<0.01
Oral anticoagulants	1.36 (1.18 to 1.56)	<0.01
NSAIDs	1.00 (0.95 to 1.06)	1.00
Proton pump inhibitors	20.1 (18.6 to 21.7)	<0.01
Histamine H2 antagonists	0.96 (0.92 to 1.00)	0.05
Other antacid drugs	1.23 (1.17 to 1.29)	<0.01
Systemic corticosteroids	1.06 (1.01 to 1.11)	0.02
Gastroduodenal ulcers or gastritis	1.37 (1.30 to 1.44)	<0.01
Diagnosis of alcoholism	1.50 (1.38 to 1.64)	<0.01

NSAIDs Non-steroidal anti-inflammatory drugs. The table is stratified according to potential risk factors for adverse gastrointestinal events. The risk of gastrointestinal events associated with each variable is adjusted for the effect of all other variables in the table

DISCUSSION

To the best of our knowledge, this is the largest study investigating the risk of adverse GI events in patients treated with clopidogrel. While other studies have evaluated clopidogrel use specifically in patients diagnosed with GI bleeding,[15–17] this is the first large study to investigate clopidogrel use in a broader spectrum of patients and determine its association with GI events. In a nationwide population, the risk of adverse GI events was significantly increased in all patients treated with clopidogrel, regardless of dose and with numbers needed to harm ranging from 58 to 33 patients receiving 12 months of clopidogrel treatment.

The risk of GI bleeding in patients treated with antiplatelet drugs is well known. GI complications of low-dose aspirin are caused by a combination of topical mucosal injury and systemic effects by inhibition of protective gastric prostaglandin synthesis, which would normally increase mucosal blood flow and secretion of mucus and bicarbonate, as well as promote epithelial proliferation.[28] Importantly, the antithrombotic properties of clopidogrel are different from those of aspirin, and the mechanism by which clopidogrel causes GI damage is controversial.[18] Platelet inhibition *per se* likely contributes to an impaired ulcer healing by reducing release of platelet-derived growth factors that promote angiogenesis, which plays a critical role in the repair of mucosal disruptions. Moreover, the suppression of platelet-derived growth factor release may be related to GI ulceration during clopidogrel treatment.[18,29]

Figure 2 shows a dose–response relationship between clopidogrel use and the risk of the study endpoint. Previous studies have consistently reported that no dose–response relationship exists for aspirin-related risk of GI ulcer or bleeding.[8,15,30] In clinical practice, all patients treated with clopidogrel receive 75 mg daily, and the figure thus also reflects the importance of treatment duration. Moreover, the groups continue to separate, thus supporting the importance of ischaemic heart disease as a risk factor for adverse GI events.[10] This fact is further supported by the clear separation of even the lowest dose stratum from never users of clopidogrel.

We found that prior use of proton pump inhibitors was strongly associated with the study endpoint. This is plausible, given that most patients experiencing GI ulcer or bleeding are treated with a proton pump inhibitor (confounding by indication), and that prior GI ulcer or bleeding dramatically increases the risk of recurrent ulcer or

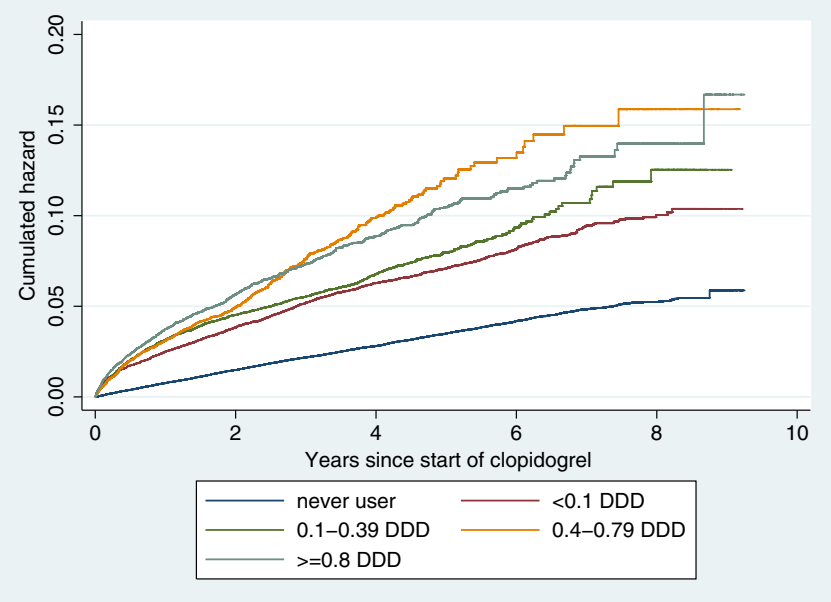

Figure 2. Cumulated hazard of adverse gastrointestinal events (gastritis, gastrointestinal ulcer or bleeding) after start of clopidogrel by years after first use. DDD, defined daily dose.

bleeding.[31–33] Therefore, in a non-randomized study like the present, the use of proton pump inhibitors may be considered a risk marker of GI events.

In our study, an unexpected finding was that non-steroidal anti-inflammatory drugs did not increase the risk of GI events (Table 2). Of importance, low-dose non-steroidal anti-inflammatory drugs (ibuprofen 200 mg) were available over the counter in Denmark during the study period, and this may have reduced our risk estimates.

The use of aspirin only increased the risk of GI events marginally (Table 2). However, dual antiplatelet treatment (low-dose aspirin + clopidogrel) does not necessarily increase bleeding risk compared to clopidogrel alone, as shown in a recent large registry study.[34] The study also showed that vitamin K antagonist monotherapy does not significantly increase bleeding compared with aspirin monotherapy,[34] and this may at least partly explain the relatively low GI event risk conferred by oral anticoagulants in our data set (Table 2).

A previous randomised study showed that clopidogrel may be safer than aspirin in patients at average risk of GI bleeding, although the study was not designed for this purpose.[6] However, our study shows a strong association between clopidogrel use and adverse GI events across a very broad spectrum of "real-world" patients, who did not participate in any controlled trial. Current guidelines recommend the use of proton pump inhibitors to prevent adverse GI complications of antiplatelet treatment.[18,19]

The emergence of new ADP-receptor antagonists, such as prasugrel and ticagrelor, has challenged the position of clopidogrel.[35,36] However, given the vast experience with clopidogrel and the fact that it is now widely available in its generic form at reduced cost, the use of clopidogrel will prevail for many years. Therefore, evaluating adverse GI events in patients treated with clopidogrel is highly relevant.[18] The association between clopidogrel use and GI events is particularly important, because GI complications likely reduce compliance with antiplatelet therapy.[10,37] Given the cluster of cardiovascular events observed within the very first days of clopidogrel cessation,[38] even a transitory discontinuation of clopidogrel therapy may increase the risk of thrombotic events.

Limitations

Observational studies do not allow for the inference of cause-effect relationships, as selection bias and residual confounding cannot be entirely excluded. However, the Danish National Registry of Patients includes all hospital admissions in Denmark and is therefore unlikely to be affected by selection bias introduced by the selective inclusion of specific hospitals, health insurance systems, or age groups. The agreement between drug dispensing and drug use is likely to be high, since only partial reimbursement of drug expenses is offered, and most drugs, including clopidogrel, were not available over the counter in Denmark during the study period. Important exceptions are aspirin and low-dose ibuprofen (200 mg). Patients on chronic aspirin treatment, however, usually receive aspirin on prescription to obtain partial reimbursement. Although we had to use prescription data as a proxy for actual clopidogrel use, we did not base clopidogrel exposure on written prescriptions, but on actual dispensing at pharmacies. The use of ICD codes likely underestimates the true

number of GI events and some ICD codes (e.g., gastritis) may be used ambiguously. Any such misclassification is most likely to have been non-differential between clopidogrel users and non-users. ICD codes are used at the discretion of the discharging physician. We did not have data on lifestyle indices such as smoking habits and bodyweight, but we partly adjusted for these by the inclusion of lifestyle-related diseases such as coronary artery disease, cancer, diabetes, and chronic obstructive lung disease in our regression model.

Conclusion

Clopidogrel use is associated with an increased risk of adverse GI events such as gastritis, ulcer and bleeding, yet the risk is only modest with an odds ratio of less than 2.0. The well-known benefits of clopidogrel in patients at increased cardiovascular risk thus must be weighed against an increased GI risk. The decision to treat a patient with clopidogrel ultimately relies on the balancing of benefits and risks.

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Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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