The impact of treatment with omeprazole on the effectiveness of clopidogrel drug therapy during the first year after successful coronary stenting

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BACKGROUND: Because clopidogrel is converted to its active metabolite by P450 isoenzymes, which are also involved in the metabolism of omeprazole, there is concern regarding whether the action of clopidogrel would be reduced in patients also taking omeprazole.

OBJECTIVE: To evaluate the impact of omeprazole administration on the effectiveness of clopidogrel drug therapy during the first year following successful coronary stenting (CS).

METHODS: A total of 588 consecutive patients who underwent successful CS for stable or unstable coronary artery disease were studied. Patients were classified into those who were treated (group A, n=340) or not treated (group B, n=248) with omeprazole for seven or more consecutive days during the entire observation period. The composite of cardiac death or rehospitalization for nonfatal myocardial infarction during the first year was the prespecified primary study end point.

RESULTS: Baseline characteristics, and dual clopidogrel and acetylsalicylic acid drug therapy were well balanced between the study groups. By one year, the primary end point was reached by 58 (9.9%) patients, including 20 (3.4%) who died due to cardiac reasons and 38 (6.5%) who were rehospitalized because of a nonfatal myocardial infarction. Patients in groups A and B, respectively, were at similar risk of the primary composite end point (10% versus 9.7%, hazard ratio 1.1 [95% CI 0.6 to 1.8]; P=0.89).

CONCLUSIONS: According to the results of the present study, treatment with omeprazole had no impact on the clinical efficacy of clopidogrel drug therapy during the first year after successful CS.

Key Words: Clopidogrel; Omeprazole; Prognosis; Stents

Dual antiplatelet drug therapy with acetylsalicylic acid and clopidogrel has become the standard therapy following coronary stenting (CS) for stable or unstable coronary artery disease (1). This dual antiplatelet drug therapy is accompanied by an increased risk of gastrointestinal bleeding; thus, it often necessitates the concomitant use of oral proton pump inhibitors as a means of bleeding prophylaxis, a strategy that was recently supported by data from clinical trials (2) and clinical guidelines (3).

Resistance to clopidogrel-induced platelet aggregation has been reported and appears to be associated with adverse clinical outcomes following CS (4-6). This lack of response to clopidogrel drug therapy has been attributed to various factors, including the interaction of certain drugs with its hepatic metabolism at the level of cytochrome P450 and its isoforms, where clopidogrel is transformed into its active metabolite (7-9). Omeprazole, one of the most widely

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HISTORIQUE : Puisque le clopidogrel est converti en métabolite actif par les isoenzymes P450, qui participent également au métabolisme de l'oméprazole, on craint que l'action du clopidogrel soit réduite chez les patients qui prennent également de l'oméprazole.

OBJECTIF : Évaluer les effets de l'administration d'oméprazole sur l'efficacité d'une pharmacothérapie au clopidogrel pendant la première année suivant l'installation d'une endoprothèse coronaire (EC).

MÉTHODOLOGIE : Au total, les auteurs ont étudié 588 patients consécutifs à qui on avait installé avec succès une EC en raison d'une coronaropathie stable ou instable. Les patients étaient classés parmi ceux qui recevaient (groupe A, n=340) ou non (groupe B, n=248) de l'oméprazole pendant au moins sept jours consécutifs, soit toute la période d'observation. Le résultat composite de décès cardiaque ou de réhospitalisation en raison d'un infarctus du myocarde non fatal pendant la première année constituait le paramètre ultime primaire prédéterminé de l'étude.

RÉSULTATS : Les caractéristiques de départ et une bithérapie au clopidogrel et à l'acide acétylsalicylique étaient bien équilibrées entre les groupes à l'étude. Au bout d'un an, 58 (9,9 %) patients avaient été affligés par le paramètre ultime primaire, y compris 20 décès (3,4 %) pour des raisons cardiaques et 38 réhospitalisations (6,5 %) pour un infarctus du myocarde non fatal. Les patients des groupes A et B, respectivement, couraient un risque similaire d'être affligés par le paramètre ultime primaire composite (10 % par rapport à 9,7 %, risque relatif 1,1 [95 % IC 0,6 à 1,8]; P=0,89).

CONCLUSIONS : D'après les résultats de la présente étude, le traitement à l'oméprazole n'avait aucune effet sur l'efficacité clinique de la pharmacothérapie au clopidogrel pendant la première année suivant l'installation réussie d'une EC.

prescribed proton pump inhibitor, was recently shown to attenuate the antiplatelet effects of clopidogrel, as a result of competitive inhibition of the cytochrome P450 2C19 isoform (10).

The database of one recently published study from our own study group (11) afforded us the opportunity to examine the impact of treatment with omeprazole on the clinical effectiveness of clopidogrel drug therapy during the first year after successful CS.

PATIENTS AND METHODS

Patients

The present analysis is part of one prospectively designed study that investigated the impact of platelet responsiveness to dual oral antiplatelet drug therapy on the one-year morbidity and mortality after successful CS. Details concerning study design, inclusion and exclusion criteria,

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and the results on one-year outcome were previously published (11). In summary, from April 2003 through January 2005, 612 consecutive patients who underwent successful CS in the catheterization laboratory of Tzanio Hospital (Piraeus, Greece) due to stable angina or a recent acute coronary syndrome, were studied. All patients were treated with both acetylsalicylic acid (100 mg/day to 325 mg/day) and clopidogrel (300 mg or 600 mg as a loading dose and then 75 mg/day) for at least 12 h before CS.

The composite of cardiac death or rehospitalization for nonfatal myocardial infarction during the first year after CS was the prespecified primary study end point. Prespecified secondary end points included the one-year incidence of cardiac death and the one-year incidence of rehospitalization for nonfatal myocardial infarction. Cardiac death was defined as sudden unexplained death, death due to fatal myocardial infarction, or death after rehospitalization because of heart failure or possible acute myocardial ischemia. New nonfatal myocardial infarction after patient discharge was defined as a new episode of chest pain, resulting in rehospitalization, with new electrocardiogram changes (ST-T changes, new Q waves or both, in two or more contiguous leads) and an increase in plasma levels of either creatine kinase MB isoenzyme (two or more times the normal level) or cardiac troponin (I or T) (higher than the 99th percentile of normal). The diagnosis of cardiac death or nonfatal myocardial infarction was verified by review of death certificates, discharge medical reports and hospital records, or contact with the attending physicians. In-hospital and postdischarge follow-up data were prospectively collected on predesigned case report forms. After discharge, patients were followed up at one, six, nine and 12 months, on an outpatient basis or by telephone interview. In particular, detailed information pertaining to concomitant drug therapy, including omeprazole, was obtained on patient presentation at the catheterization laboratory, and was updated during the hospital stay and at the predefined follow-up intervals. All patient drug therapy, including omeprazole, was left to the discretion of the attending physician.

For the purpose of the present analysis, the study patients were classified into those who were treated (group A) or not treated (group B) with omeprazole for seven or more consecutive days during the entire observation period. The local ethics committee approved the study protocol, and informed consent was obtained from all participants.

Statistical analysis

Values were expressed as mean $\pm$ SD. Comparisons of continuous variables were made by use of the *t* test or Mann-Whitney U test as appropriate. Dichotomous variables were presented as percentages. Associations between dichotomous variables were tested by use of χ^2 or Fisher's exact testing as appropriate. Event-free survival between the study groups was analyzed with the Kaplan-Meier method and the log-rank test was used for comparisons between the curves. Differences between the study groups in the risk of the primary or secondary study end points were evaluated by Cox regression analysis. Patients who died because of noncardiac causes were censored at the time of death. All tests were two-tailed and $P < 0.05$ was considered to be statistically significant. Statistical analysis was performed with SPSS statistical software (release 11.0, SPSS Inc, USA).

RESULTS

Baseline characteristics and in-hospital course

Of the 612 patients in the original study, 24 (3.9%) who were treated with a proton pump inhibitor other than omeprazole were excluded; thus, 588 (96.1%) were included in the present analysis. Of the 588 analyzed patients, 340 (57.8%) and 248 (42.2%) comprised groups A and B, respectively. Omeprazole was started in 237 (69.7%) group A patients before CS and was started in 103 (30.3%) patients following the procedure. In 210 (61.7%) group A patients, omeprazole was administered for the entire observation period. In 130 (38.2%) patients, omeprazole was administered for a median period of 229 days (range seven to 362 days).

TABLE 1

Baseline characteristics of patients treated (group A) and not treated (group B) with omeprazole

Characteristics	Group A (n=340)	Group B (n=248)	P
Age, years, mean $\pm$ SD	62.1 $\pm$ 10.5	61.7 $\pm$ 10.8	0.69
Male sex, %	82.4	81.9	0.88
Body mass index, kg/m ² , mean $\pm$ SD	27.6 $\pm$ 2.9	27.9 $\pm$ 2.9	0.19
Current smoker, %	49.7	50.8	0.79
Medical history, %			
Hypertension, %	50.9	46.4	0.28
Diabetes mellitus, %	30.0	26.2	0.31
Hypercholesterolemia, %	66.5	65.3	0.77
Familial coronary artery disease, %	27.4	28.2	0.82
Myocardial infarction, %	17.1	17.7	0.83
Coronary angioplasty, %	8.2	8.5	0.92
Coronary artery bypass grafting, %	4.4	5.2	0.64
Indication for coronary stenting, %			
Stable angina	22.6	23.8	
NSTEMI	42.4	36.3	0.31
STEMI	35.0	39.9	

NSTEMI Non-ST segment elevation acute coronary syndrome; *STEMI* ST segment elevation myocardial infarction

Baseline, angiographic and CS-related characteristics were well balanced between the study groups (Tables 1 and 2). In particular, a total of 98.4%, 96.2% and 91.9% of patients were treated with clopidogrel by the first, third and 12th month of follow-up, respectively, with no difference between the study groups.

Postprocedural coronary side branch closure, main treated vessel closure, major myonecrosis and in-hospital death were observed in 9.3%, 1.3%, 7.1% and 1.1% of patients, respectively. The rate of all these angiographic complications and adverse in-hospital events was similar between groups A and B (Table 2).

Primary and secondary end points

No patients were lost during the follow-up. During this period, drug therapy (other than omeprazole) was similar between the study groups (Table 2).

By the first year, the primary end point was reached by 58 (9.9%) patients, including 20 (3.4%) who died due to cardiac reasons and 38 (6.5%) who were rehospitalized because of a nonfatal myocardial infarction. Patients in groups A and B, respectively, were at similar risk of the primary composite end point (10% versus 9.7%, hazard ratio (HR) 1.1 [95% CI 0.6 to 1.8]; $P=0.89$), and the secondary end points of cardiac death (3.5% versus 3.2%, HR 1.1 [95% CI 0.4 to 2.7]; $P=0.84$) or rehospitalization for myocardial infarction (6.5% versus 6.5%, HR 1 [95% CI 0.5 to 1.9]; $P=0.99$) (Figure 1). Rates of one-year stent thrombosis (definite, probable and possible) according to the Academic Research Consortium (8.8% versus 8.5%, HR 1.1 [95% CI 0.7 to 1.8]; $P=0.88$), and of one-year repeat revascularization (9.4% versus 8.9%, HR 1 [95% CI 0.6 to 1.9]; $P=0.82$) were similar between groups A and B, respectively.

Among group A patients, there was no difference in the rate of composite primary end point between those who started the omeprazole before versus after CS, respectively (9.7% versus 10%, HR 0.9 [95% CI 0.4 to 2.1]; $P=0.91$), or between those who were treated with omeprazole for the entire period of observation versus those who were not, respectively (9% versus 11.5%, HR 0.8 [95% CI 0.4 to 1.6]; $P=0.46$).

DISCUSSION

The present analysis demonstrated that in a relatively large cohort of patients undergoing successful CS, treatment with omeprazole was not

TABLE 2
Angiographic-, coronary stenting- and in-hospital
course-related characteristics of patients treated (group A)
and not treated (group B) with omeprazole

Characteristics	Group A (n=340)	Group B (n=248)	P
Multivessel coronary artery disease, %	57.6	52.4	0.21
LVEF, %, mean $\pm$ SD	49.4 $\pm$ 4.7	49.3 $\pm$ 4.6	0.64
Treated vessel, %			
Left main artery	0.3	1.6	0.09
Left anterior descending artery	63.5	63.3	0.96
Left circumflex artery	25.9	27.8	0.59
Right coronary artery	43.2	41.5	0.68
Graft	2.4	4.8	0.11
Treated lesions, n, mean $\pm$ SD	1.6 $\pm$ 0.7	1.6 $\pm$ 0.8	0.67
B2 or C treated lesions, %	87.8	86.1	0.71
Bifurcation treated lesion, %	26.2	25.4	0.83
Stent type, %			
Bare metal	81.5	80.2	0.71
Sirolimus-eluting	18.5	19.8	
Stents, n, mean $\pm$ SD	1.5 $\pm$ 0.6	1.5 $\pm$ 0.7	0.55
Total stent length, mm, mean $\pm$ SD	22.9 $\pm$ 11.3	24.1 $\pm$ 11.5	0.29
Preprocedural MLD, mm, mean $\pm$ SD	0.52 $\pm$ 0.26	0.53 $\pm$ 0.27	0.55
Postprocedural MLD, mm, mean $\pm$ SD	2.92 $\pm$ 0.39	2.94 $\pm$ 0.41	0.47
Periprocedural use of GP IIb/IIIa inhibitors, %	22.4	25.8	0.33
Side branch closure, %	10.0	8.9	0.65
Acute or subacute treated vessel closure, %	0.9	1.6	0.42
Postprocedural major myonecrosis, %*	6.8	6.5	0.89
In-hospital death, %	0.9	1.6	0.42
Drug therapy during the first year, %			
Acetylsalicylic acid	97.6	98.3	0.77
Clopidogrel	98.8	98.3	0.94
Statin	86.7	85.1	0.82
ACEI or ARBs	84.7	82.2	0.34

*An increase by at least three times the normal (in patients with normal preprocedural creatine phosphokinase MB values) or an increase by at least 50% over the preprocedural value (in patients with decreasing preprocedural creatine phosphokinase MB values). ACEI Angiotensin-converting enzyme inhibitors; ARBs Angiotensin receptor blockers; GP Glycoprotein; LVEF Left ventricular ejection fraction; MLD Minimal lumen diameter

associated with any excess risk of cardiac death or rehospitalization for myocardial infarction during the first year after the intervention.

To our knowledge, the present study was the first to show a lack of omeprazole and clopidogrel interaction in a real-life setting of patients undergoing successful CS for stable or unstable coronary artery disease. Gilard et al (10) recently demonstrated that omeprazole significantly attenuated the antiplatelet action of clopidogrel in a randomized clinical trial investigating 124 patients after CS. However, the impact of omeprazole was studied only on laboratory parameters measuring the antiaggregating properties of clopidogrel, and not on clinical outcomes. Moreover, in contrast to the results of the present study, two recently published large retrospective studies (12,13) have shown that, following an acute coronary syndrome, concomitant use of clopidogrel and proton pump inhibitors is associated with an increased risk of future fatal or nonfatal ischemic complications. However, patients in both of these studies, who were treated with proton pump inhibitors, were significantly older and sicker than those who were not treated with such drugs. Subsequently, the worse baseline risk profile of the former group, rather than the concomitant use of clopidogrel and proton pump inhibitors per se, could explain the worse prognosis of patients treated with proton pump inhibitors in these recently published studies. In the present study, no difference in baseline risk

Figure 1 Kaplan-Meier curves of patients who were treated (black line) or not treated (grey line) with omeprazole for the cumulative (Cum) incidence of the primary end point (A), cardiac death (B) and rehospitalization for nonfatal myocardial infarction (C)

profile or one-year outcome was observed between patients treated versus not treated with proton pump inhibitors.

The observed lack of difference in outcomes between omeprazole- and nonomeprazole-treated patients in the present study may be

because cytochrome P450, the site of hepatic activation of clopidogrel, has many isoforms; it is likely that not all of these isoforms are affected by omeprazole. Cytochrome P450 2C19 isoform was shown by Gilard et al (10) to be the target of competitive inhibition by omeprazole, but other isoforms, shown in various studies to be part of clopidogrel metabolism (7-9,14,15), may remain unaffected by omeprazole.

One has to be cautious about the way potential drug-to-drug interactions at the level of hepatic metabolism may translate into clinical outcomes. This was the case with lipophilic statins, namely atorvastatin, and clopidogrel: a metabolic interaction at the level of cytochrome P450 3A4 isoform had been proposed (16), quite similar to the one with omeprazole. However, the clinical relevance of this interaction has been questioned by recent studies (17-19) and until now, has remained highly controversial.

Limitations

Some limitations of the present study should be taken into account. First, it was not a randomized trial but a retrospective analysis of an observational study. Second, it was a relatively small study and third, it was substantially underpowered to address its hypothesis. Larger, prospective and higher-powered studies are needed to elucidate this issue.

CONCLUSIONS

According to the results of the present study, treatment with omeprazole had no impact on the clinical effectiveness of clopidogrel drug therapy during the first year after successful CS. While firm conclusions cannot be drawn due to the observational and retrospective design of the present study, it does provide preliminary evidence on little or no clinical relevance of the proposed omeprazole-clopidogrel interaction. Higher-powered studies are necessary to confirm that omeprazole has no clinical effect on patients concomitantly taking clopidogrel.

REFERENCES

1. Bassand JP, Hamm C, Ardissino D, et al. The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;28:1598-660.
2. Schreiner GC, Laine L, Murphy SA, et al. Evaluation of proton pump inhibitor use in patients with acute coronary syndromes based on risk factors for gastrointestinal bleed. *Crit Pathw Cardiol* 2007;6:169-72.
3. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008;118:1894-909.
4. Grossmann R, Sokolova O, Schnurr A, et al. Variable extent of clopidogrel responsiveness in patients after coronary stenting. *Thromb Haemost* 2004;92:1201-6.
5. Gurbel PA, Tantry US. Drug insight: Clopidogrel nonresponsiveness. *Nat Clin Pract Cardiovasc Med* 2006;3:387-95.
6. Lev EI, Patel RT, Maresh KJ, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: The role of dual drug resistance. *J Am Coll Cardiol* 2006;47:27-33.
7. Lau WC, Gurbel PA, Watkins PB, et al. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation* 2004;109:166-71.
8. Farid NA, Payne CD, Small DS, et al. Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007;81:735-41.
9. Suh JW, Koo BK, Zhang SY, et al. Increased risk of atherothrombotic events associated with cytochrome P450 3A5 polymorphism in patients taking clopidogrel. *Can Med Assoc J* 2006;174:1715-22.
10. Gilard M, Arnaud B, Cornily J-C, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: The randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008;51:256-60.
11. Foussas SG, Zairis MN, Patsourakos NG, et al. The impact of oral antiplatelet responsiveness on the long-term prognosis after coronary stenting. *Am Heart J* 2007;154:676-81.
12. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009;180:713-8.
13. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009;301:937-44.
14. Savi P, Combalbert J, Gaich C, et al. The antiaggregating activity of clopidogrel is due to a metabolic activation by the hepatic cytochrome P450-1A. *Thromb Haemost* 1994;72:313-7.
15. Hulot J, Bura A, Villard E, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood* 2006;108:2244-7.
16. Lau WC, Waskell LA, Watkins PB, et al. Atorvastatin reduces the ability of clopidogrel to inhibit platelet aggregation: A new drug-drug interaction. *Circulation* 2003;107:32-7.
17. Lotfi A, Schweiger MJ, Giugliano GR, et al; TIMI 22 Investigators. High-dose atorvastatin does not negatively influence clinical outcomes among clopidogrel treated acute coronary syndrome patients – a Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) analysis. *Am Heart J* 2008;155:954-8.
18. Trenk D, Hochholzer W, Frundi D, et al. Impact of cytochrome P450 3A4-metabolized statins on the antiplatelet effect of a 600-mg loading dose clopidogrel and on clinical outcome in patients undergoing elective coronary stent placement. *Thromb Haemost* 2008;99:174-81.
19. Saw J, Brennan DM, Steinhilb SR, et al; CHARISMA Investigators. Lack of evidence of a clopidogrel-statin interaction in the CHARISMA trial. *J Am Coll Cardiol* 2007;50:291-5.