LETTERS TO THE EDITOR

Risk profile and benefits from Gp Ibb–Ill a inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials

We read with interest the work by De Luca et al.,1 which reported that the meta-analysis shows a significant relationship between benefits from Gp Ibb–Ill a inhibitors in terms of mortality at 30-day follow-up and patient’s risk profile for primary angioplasty in ST-segment elevation myocardial infarction (STEMI). In their discussion, the authors debated on the contrasting results of several recent large randomized trials conducted to explore the benefits from adjunctive Gp Ibb–Ill a inhibitors on the top of clopidogrel.

The reason for the ineffectiveness of adding a Gp Ibb–Ill a inhibitor to aspirin and clopidogrel with contemporary anticoagulation regimens was ascribed to a relatively low-risk population at baseline in both the BRAVE-3 and the HORIZONS trials.2,3 On the contrary, the authors emphasized the reduction in mortality of early tirofiban administration (2.3 vs. 4%) according to the result of the On-Time-2 trial.4

To the best of our knowledge, the Killip classifications and risk profiles of patients with acute myocardial infarction proportionally determined the majority of death overwhelming the additional benefits of medical intervention on standard dual antiplatelet (aspirin 250–324 mg and clopidogrel 300 mg) and anticoagulation therapy for primary angioplasty. Therefore, we collected the patients with STEMI undergoing primary angioplasty on dual antiplatelet (aspirin and clopidogrel) and anticoagulation therapy enrolled in the drug trials from Medline (Table 1).2–6 Since Killip classification may be the most powerful predictor to survival outcome, we adjusted the death rate in each clinical trial by 0.36 hazard ratio of major cardiac events of Killip class I calculated from the HORIZON trial5 in reference to the Killip class I ration of 13.4% in the controls of the On-Time-2 trial.6 As a result, the death rate ranged from 2.0 to 3.2% after adjustment which was far less than that of 4.0% in the control arm of the On-Time-2 trial. We noticed that there may be a bias for physicians making the decision to select the procedures of percutaneous angioplasty or coronary bypass surgery on both arms [1/477 (0.2%) vs. 7/473 (1.5%), P = 0.038] when urgent target vessel revascularization occurred in the On-Time-2 trial.6 Apparently, the mortality rate at 30-day follow-up for patients with STEMI undergoing coronary bypass surgery after primary angioplasty was a too short period to be counted.

In conclusion, we believed that the effect of Gp Ibb–Ill a inhibitors were similar to some antiplatelet agents like cilostazol and higher dosing of clopidogrel (>600 mg) especially for patients with STEMI and higher risk profiles. However, whether adding a Gp Ibb–Ill a inhibitor superior to currently high loading

| Table 1 | Comparison of 30-day mortality rates among trials of primary angioplasty for ST-segment elevation myocardial infarction in use of anticoagulation agents, aspirin, and clopidogrel with or without a Gp Ibb–Ill a inhibitor |
|---|---|---|---|---|
| Controlled antiplatelet agents/loading dose | Antiplatelet agents in study/loading dose | Anti-coagulation/loading dose | Killip class >1 | Death rate at 30-day origin/adjustment |
| CADILLA 3,5 | 1052 | Ab: 0.25 mg/kg UFH: 5000 U | 11.2% | 1.9%/2.0% |
| | 1030 | None | 10.6% | 2.3%/2.4% |
| BRAVE-3 2,6 | 401 | Ab: 0.25 mg/kg UFH: 60 U/kg | 24% | 3.2%/2.7% |
| | 399 | None | 23% | 2.5%/2.2% |
| KAMIR 6 | 1634 | Ci: 200 mg; Ab: 22.6% UFH: 50–70 U/kg | 19.6% | 2.2%/2.0% |
| | 2569 | Ab: 11.3% | 21.4% | 3.4%/3.0% |
| HORIZONS-AMI 3 | 2158 | Ci: 600 mg p.o. or Tic: 500 mg p.o. UFH plus a GPI: 50% and Bi: 50% | 6.9% | 2.0%/2.2% |
| | 1153 | Ci: 300 mg p.o. | 11.5% | 3.1%/3.2% |
| On-TIME 2 4 | 491 | Tir: 25 mg/kg UFH: 5000 U | 11.3% | 2.3%/2.4% |
| | 493 | None (bail-out Tir: 28.5%) | 13.4% | 4.0% |

Ab, abiciximab; As, aspirin; Bi, bivalirudin; Cl, cilostazol; Ci, clopidogrel; GPI, glycoprotein Ibb–Ill a inhibitor; UFH, unfractionated heparin; Tic, ticlopidine; Tir, tirofiban.
dose of clopidogrel (600 mg) before primary angioplasty is still uncertain and a further investigation according to the stratified risk of patients should be worked up.

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Chi-Lu Han
Division of Cardiology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China

doi:10.1093/eurheartj/ehq004
Online publish-ahead-of-print 27 January 2010

Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period

We have read with great interest the paper by Schulz et al.1 recently published in the European Heart Journal.

In this study, discontinuation of clopidogrel therapy was significantly associated with drug-eluting stents (DES) thrombosis (ST) only in the first 6 months after the procedure, with no significant effect thereafter. As the authors acknowledge, delayed healing is the most important pathophysiological mechanism for DES ST.2 Time course of arterial healing is rather different in bare-metal stents (BMS) and DES. After BMS implantation, endothelialization is near-complete by 3–4 months, but it reaches approximately 60% at 2 years after DES implantation. This remarks the importance of dual antiplatelet therapy early after DES implantation.

Although clopidogrel discontinuation is a strong predictor of DES thrombosis,2 the existing relationship between antplatelet therapy and stent thrombosis is complex and could not be limited to clopidogrel cessation. In fact, in this registry, only 37 of 73 thrombotic events (51%) were related to clopidogrel interruption.1,3 Aspirin 100 mg twice daily was recommended for an indefinite period after percutaneous coronary intervention. In previous studies, withdrawal from long-term antiplatelet monotherapy (the interruption of aspirin monotherapy after completing the 6-month of combined antiplatelet therapy) has been linked to DES thrombosis.3 However, the authors failed to provide data on the interruption of aspirin monotherapy and whether this impacted the occurrence of DES thrombosis. We would really appreciate if the investigators could provide information on this issue.

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Xacobe Flores-Rios
Department of Cardiology
Complexo Hospitalario Universitario A Coruña
As Xubias SN, A Coruña 15009
Spain
Tel: +34-981178184
Fax: +34-981178258
Email: xacobeflores@yahoo.es

Guillermo Aldama-López
Department of Cardiology
Complexo Hospitalario Universitario A Coruña
As Xubias SN, A Coruña 1509
Spain

Ramón A. Calviño-Santos
Department of Cardiology
Complexo Hospitalario Universitario A Coruña
As Xubias SN, A Coruña 1509
Spain

Nicolas Vázquez-González
Department of Cardiology
Complexo Hospitalario Universitario A Coruña
As Xubias SN, A Coruña 1509
Spain

Alfonso Castro-Beiras
Department of Cardiology
Complexo Hospitalario Universitario A Coruña
As Xubias SN, A Coruña 1509
Spain

doi:10.1093/eurheartj/ehq004
Online publish-ahead-of-print 27 January 2010

Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period: reply

We highly appreciate the interest of Flores-Rios et al. in our article ‘Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period’.1