RATIONAL

Oral antiplatelet (OAP) medication is essential in treatment and prevention of myocardial infarction (MI) [1-2]. In Finland clopidogrel has shown to be the drug of choice [3]. Excessive drug effect and subsequent bleedings are known drawbacks of this OAP [4]. Warfarin is an anticoagulant known to cause severe bleedings. Combination of warfarin and clopidogrel is best to be avoided due to their pharmacodynamic drug-drug interaction [5], but only few studies about real-life evidence on this topic have been published [6].

OBJECTIVES

The aim of this real-world data linking study was to examine risk of major bleedings and factors associated with it in clopidogrel-treated MI patients in Finland.

METHODS

All Finnish adult patients discharged from hospitals (and alive 7 days after discharge) after their first MI (ICD-10 I21) during 2009-2012, and treated with clopidogrel, were included in the study. Study end points were hospitalization due to major bleeding and bleeding mortality. Follow-up time was from clopidogrel initiation until clopidogrel discontinuation, end point, death, or end of year 2013. Cox proportional hazards model was used to assess the association of risk between preselected covariates (listed in Table 1) and incidence of outcomes. Clopidogrel exposure and concomitant warfarin use, as well as comorbidities were handled time-dependently in the analyses. Warfarin purchase had to occur during ongoing clopidogrel course to be considered as a potential interaction. Cohort entry year was used as strata in the model.

REFERENCES


RESULTS

The cohort consisted of 18,762 MI patients treated with clopidogrel. Risk of bleeding requiring hospitalization was increased by more than 3.5-fold by older age and by history of major bleeding (Table 1). Warfarin use together with clopidogrel was associated with a 2.4-fold increase of this risk. The number of warfarin users was 2,205 (11.8%). Only 18 (0.1%) patients had major bleeding as the primary cause of death. The overall mortality rate in the cohort receiving clopidogrel was 4.6%.

| Table 1. Adjusted hazard ratios (HR) for predictors of hospitalization due to major bleeding in patients receiving clopidogrel |
|---------------------------------|-----------------|----------------|
| Age (as cty)                    | HR              | 95% CI         |
| 70-74                           | 1.69            | 0.87-3.27      |
| 75-79                           | 3.49            | 1.79-6.82      |
| 80+                             | 7.38            | 3.85-14.97     |
| Diabetes mellitus               | 0.97            | 0.79-1.21      |
| Chronic renal failure           | 1.75            | 1.10-2.84      |
| Dementia/Alzheimer’s disease    | 1.88            | 0.98-3.74      |
| Ischemic stroke or TIA          | 1.40            | 1.05-1.87      |
| Hyper tension                   | 0.37            | 0.18-0.74      |
| Hypertension                    | 0.85            | 0.56-1.37      |
| Congestive heart failure        | 1.36            | 0.83-2.26      |
| Severe liver disease            | 0.75            | 0.11-5.36      |
| Malignancy                      | 1.49            | 1.02-2.04      |
| Clopidogrel use                 | 3.85            | 2.45-8.33      |

The multivariate model included all the variables listed in this table simultaneously.

STUDY REGISTRATION

The study was registered into the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) e-register of studies (EUPAS@205).

CONCLUSIONS

In post-MI patients treated with clopidogrel aging increased the risk of severe bleedings remarkably already at age of 65 years. Patients with bleeding history are vulnerable for a new event and must be carefully monitored. Atrial fibrillation diagnosis was not associated with remarkably increased bleeding risk but concomitant use of warfarin with clopidogrel was found to increase this risk by more than 2-fold.

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- Social Insurance Institution (Kela 41/522/2015)
- Statistics Finland (TKS-617-15)

CONFLICT OF INTEREST STATEMENT

T.P. and H.K. are CFO employees and thus in continual collaboration with Pharma companies. P.H. works for the sponsor, AstraZeneca Nordic Baltic, E.R., J.A. and V.K. have received consultancy fees from Pharma industry.

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