The Risk of Ischemic Cardiovascular Events Associated with Targin® Use

Abstract

Background: Targin® is an oral fixed combination of the extended-release (ER) high potency opioid (HPO) oxycodone and the opioid antagonist naloxone. It is approved in Germany for the treatment of severe pain and has demonstrated to provide comparable analgesic efficacy to that of oxycodone, while improving opioid-induced constipation (OIC). Since approval a large rise in Targin® use could be observed in Germany. In November 2012, several US articles were published regarding the Food and Drug Administration's (FDA) concerns over potential cardiac safety risks associated with use of opioid antagonists discussing withdrawal as possible cause for these risks. Furthermore, some recent epidemiological studies hinted at a potential relation between opioids themselves and cardiovascular (CV) outcomes.

In July 2014, the FDA approved Targiniq ER® (oxycodone/naloxone ER tablets) to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Targiniq ER® was the second ER/long-acting opioid analgesic with FDA-approved labeling describing the product's abuse-deterrent properties consistent with the FDA's 2013 draft guidance for industry.

Objectives: The main objective of this study was to estimate the risk of major ischemic CV events in patients prescribed Targin® compared to those being prescribed ER oxycodone or another ER HPO. Additionally, the occurrence of withdrawal symptoms associated with the use of Targin® or other ER HPOs was explored. Furthermore predictive factors for (i) the choice of ER HPO and (ii) the occurrence of ischemic CV events were explored.

Methods: Source of data for this study was the German Pharmacoepidemiological Research Database (GePaRD), which consists of claims data from four German statutory health insurance providers covering over 17 million insured members throughout Germany. A cohort of users of ER HPO was established during the study period from January 01, 2006 to December 31, 2011. Cohort entry was defined as the first dispensation of an ER HPO. Baseline covariates were assessed in the year preceding cohort entry. The primary outcome was the combined endpoint of acute myocardial infarction (MI) and ischemic stroke (IS), whereas a secondary outcome also examined additional ischemic CV events such as angina pectoris (AP) and transient ischemic attacks (TIAs). The occurrence of withdrawal symptoms was explored as an additional outcome. In the cohort analyses, first a drug utilization part including characteristics of HPO users as well as patterns of opioid use was conducted. Furthermore two separate logistic regression models were used to, first, identify predictors

for the treatment choice and, second, for the occurrence of the primary outcome. Following this, incidence rates (IRs) were calculated for the outcomes in users of Targin®, ER oxycodone, ER morphine and other ER HPO, including patches. Additionally, a nested case-control analysis within this user cohort was conducted to obtain confounder-adjusted estimates for the risk of MI and IS associated with (i) current ER HPO treatment or (ii) recent discontinuation or (iii) recent switch of ER HPO therapy.

Results: During the study period 309,936 patients received at least one ER HPO. Mean age at cohort entry was 70.2 years and 67% of patients were female. The most common ER HPO leading to cohort entry was fentanyl (38.4%), followed by oxycodone (16.3%) and morphine (13.2%). Overall, 12,384 CV events fulfilled our definition of MI or IS resulting in an overall IR of 19.48 (95% confidence interval (CI): 19.14-19.82) per 1,000 person years (PY). The highest IR was found for fentanyl (IR: 24.99; 95% CI: 24.03-25.98), followed by buprenorphine (IR: 21.27; 95% CI: 19.51-23.14). Use of oxycodone/naloxone revealed a lower risk (19.03; 95% CI: 17.41-20.76). The overall cumulative incidence for MI/IS after discontinuation of ER HPO treatment was 11.29 (95% CI: 10.61-12.01) per 10,000 discontinuation periods (DISCP). The risk was highest for buprenorphine, followed by fentanyl. The overall IR for the secondary outcome including MI, IS, AP and TIA was 72.41 (95% CI: 71.72-73.11) per 1,000 PY. The highest IR was found for AP, followed by TIA, IS and MI. The overall cumulative incidence for the additional outcome defined as withdrawal symptoms after discontinuing ER HPO therapy was 1.19 (95% CI: 0.98-1.44) per 10,000 DISCP. It was highest for hydromorphone and morphine (1.74 and 1.71 per 10,000 DISCP, respectively) and lowest after discontinuing treatment with oxycodone/naloxone (0.82; 95% CI: 0.44-1.50).

Predictors of an ER HPO treatment with oxycodone/naloxone compared to oxycodone alone in incident HPO users were female sex, older age and a diagnosis of cancer. Additionally, a later calendar year of cohort entry revealed increasing odds to be treated with the combination product. In the prediction model for MI/IS male sex and increasing age were associated with high risks for MI/IS. Among the examined co-morbidity cerebrovascular disease, TIAs and diabetes were found to be strong predictors.

In the case-control analyses only current morphine use yielded a small but significantly elevated adjusted odds ratio (aOR) of 1.12 (95% CI: 1.04-1.22) for MI/IS. Recent discontinuation and recent switch of substance had a statistically significant impact on the outcome as well (aOR: 1.12, 95% CI: 1.04-1.21 and 1.25; 95% CI: 1.03-1.52, respectively). Among the included co-morbidity, highest aORs were found for TIAs and cerebrovascular disease. Recent discontinuation of HPO ER treatment compared to a recent discontinuation of oxycodone yielded a statistically significant aOR only for buprenorphine (aOR: 1.69; 95% CI: 1.09-2.63). A recent switch of substance to oxycodone/naloxone was rare. Compared to

no switch a recent switch of substance among current users of oxycodone/naloxone revealed an aOR of 0.91 (95% CI: 0.23-3.67).

Discussion: In this study we examined the risk of ischemic CV events in a large cohort of nearly 310,000 users of ER HPOs. In the cohort analyses current use or discontinuation of oxycodone/naloxone revealed comparably low risks for the examined outcomes of MI/IS, the broader definition of ischemic CV events and the occurrence of withdrawal symptoms. In the adjusted analyses only current use of morphine was significantly associated with an increased risk of MI or IS. Additionally a recent discontinuation or a recent switch of ER HPO treatment elevated the risk for these ischemic CV events. On a substance basis no increased risks were observed for MI/IS when examining recent discontinuation of or a recent switch to oxycodone/naloxone.

Both prediction models yielded plausible results reflecting important risk factors for the occurrence of MI/IS as well as expected predictors regarding treatment with oxycodone/naloxone compared to oxycodone alone. Though older age, female sex and a diagnosis of cancer were found to be significant predictors of starting treatment with the combination product instead of oxycodone alone, CV co-morbidity had no significant influence, which indicates that channeling based on CV risk factors was of less importance. Our findings were consistent and robust and also comparable to recent literature. By not restricting our study population with respect to indication or treatment time our results might be generalized. Overall, no elevated risks for major ischemic CV events associated with use of oxycodone/naloxone compared to other ER HPOs were observed.