Preventive Medicine 93 (2016) 121–127

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

The risks of pulmonary embolism and upper gastrointestinal bleeding beyond 35 days after total hip replacement for coxarthrosis among middle-aged patients: A cross-over cohort

Grégoire Ficheur, MD, PhD [a,*], Alexandre Caron, MD [a], Jean-Baptiste Beuscart, MD, PhD [b], Laurie Ferret, PharmD, PhD [c], Sophie Putman, MD [d], Régis Beuscart, MD, PhD [a], Emmanuel Chazard, MD, PhD [a]

[a] Univ. Lille EA 2694, CHU Lille, Department of Public Health, F-59000 Lille, France
[b] Univ. Lille EA 2694, CHU Lille, Department of Geriatric Medicine, F-59000 Lille, France
[c] CHU Lille, Department of Pharmacy, F-59000 Lille, France
[d] CHU Lille, Department of Orthopedic Surgery, F-59000 Lille, France

ARTICLE INFO

Article history:
Received 5 May 2016
Received in revised form 3 August 2016
Accepted 5 September 2016
Available online 6 September 2016

Keywords:
Patient safety
Venous thromboembolic event
Bleeding event
Total hip arthroplasty
Total hip replacement

ABSTRACT

Prophylactic anticoagulation is recommended up to 35 days after total hip replacement (THR). Although several observational studies have assessed the incidence of thrombotic events or bleeding events after THR, the corresponding measures of association have never been studied concomitantly. Here, we evaluated the duration of the elevated risks (relative to the baseline risk) of both venous thromboembolic events and bleeding events after THR for coxarthrosis among middle-aged patients.

This was a population-based, cross-over cohort study of data extracted from the French national inpatient database between 2007 and 2013. We included middle-aged patients (aged 45 to 69) having undergone THR for coxarthrosis. We compared the numbers of pulmonary embolisms (PEs) (respectively upper gastrointestinal bleedings (UGIBs)) following the THR with the numbers occurring during three unexposed periods one year later. This enabled us to estimate the odds ratio (OR) [95% confidence interval (CI)] for each of six successive 35-day intervals.

The study included 108,099 patients. The ORs for PE were respectively 12.4 (95% CI, 8.6–17.8) (absolute risk difference rate per 100,000 (ARD/100,000) = 130) and 5.0 (95% CI, 3.4–7.4) (ARD/100,000 = 52) for the first two 35-day intervals, and the risk was close to 1 thereafter. The risk of UGIB fell quickly, with an OR of 6.5 (95% CI, 4.6–9.1) (ARD/100,000 = 83) and 0.8 (95% CI, 0.4–1.6) for the first two 35-day intervals, respectively. The majority of UGIBs occurred during the inpatient stay for THR.

Among middle-aged patients, the risk of a PE remains elevated beyond 35 days after THR for coxarthrosis, whereas the risk of a UGIB remains elevated for the first 35 days only.

1. Introduction

The American College of Chest Physicians' guidelines (Falck-Ytter et al., 2012; Guyatt et al., 2012) recommend the administration of antithrombotic agents for at least 10 to 14 days after major orthopedic surgery (Grade 1B). The continuation of anticoagulation therapy on an outpatient basis is recommended for the 35 days following surgery (Grade 2B). These guidelines are based on randomized clinical trials (RCTs), the results of which must be complemented by population-based studies (Rothwell, 2005) for three main reasons: (i) population-based studies evaluate the effectiveness and safety on real data; (ii) the rarity of the event means that a population-based study (with greater statistical power than an RCT) is required to estimate the corresponding risk - especially since RCTs in similar populations report different major bleeding rates (Dahl et al., 2010); and (iii) RCTs have limited follow-up periods and cannot calculate the risk relative to the baseline risk (outside the context of surgery and prophylactic anticoagulation).

To the best of our knowledge, three population-based studies (Lalmohamed et al., 2013a; Pedersen et al., 2012; Sweetland et al., 2009) have assessed the risk (relative to baseline risk) of a venous thromboembolic event (VTE) for >35 days after total hip replacement (THR), and only one study has assessed the risk (relative to baseline risk) of a bleeding event (Lalmohamed et al., 2013b). However, none of the studies cited above simultaneously assessed the corresponding measures of association for both types of events. In contrast, several studies have assessed the incidence of both thrombotic events and bleeding events (Guijarro et al., 2011; Lanes et al., 2011; Pedersen et al., 2014).

* Corresponding author at: Department of Public Health, Lille University Hospital, 2 avenue Oscar Lambret, F-59037 Lille cedex, France.
E-mail address: gregoire.ficheur@univ-lille2.fr (G. Ficheur).

http://dx.doi.org/10.1016/j.ypmed.2016.09.010
0091-7435/

Historically, THR was only performed on elderly, relatively inactive patients. Progressively, this procedure has been extended to middle-aged patients, who now account for over half of all THRs. The increasing proportion of middle-aged patients is also due to aging of the "baby-boomer generation", and is forecast to continue until 2030 (Kurtz et al., 2009). Even though THR in these patients raises specific issues (including the fact that the prosthesis will be present for a longer period and that they are at higher risk for revision (Malchau et al., 2002)), there are currently very few literature data on this population.

In terms of methodological aspects, the Observational Medical Outcomes Partnership (Ryan et al., 2013; Simpson et al., 2013) (OMOP, an empirical, strict, systematic evaluation of study designs) has shown that cross-over designs (Maclure, 1991; Maclure and Mittleman, 2000) (such as cross-over cohorts and case-crossover studies) are superior in the field of pharmacoepidemiology. These designs were not used in the above-cited population-based studies.

1.1. Objective

The primary objective of the present study was to simultaneously assess the duration of the elevated risks (relative to the baseline risk, outside the context of surgery) of a VTE and of a bleeding event following THR for coxarthrosis in a population of middle-aged patients.

2. Material and methods

2.1. Data sources

For the period from 2007 to 2013, the "acute care" section of the French national inpatient database contained information on 171,556,421 inpatient stays. Collection of these data has been approved by the French National Data Protection Commission (CNIL authorization number 1,754,053). The database contains a summary of each inpatient stay in France, including the ICD-10 diagnostic code ("WHO | International Classification of Diseases (ICD)"), the medical procedures performed (coded according to the French CCAM classification) and the patient's age, gender, and unique identifier. With regard to the quality of the data, 153 tests (Agence Technique de l'Information sur l'hospitalisation, 2015) are performed routinely when the information on the inpatient stay is sent to the French public health insurance agency. These include checks on the chronology of the inpatient stays, the format (missing, incorrect or imprecise values) of the demographic characteristics (gender, age, date and mode of entry, date and discharge mode), the format of procedure codes and diagnostic codes, and the agreement between procedure codes, diagnostic codes, the length of stay, age, and gender.

2.2. Definitions

For the avoidance of doubt concerning the terms used in the Methods and Results section, it should be noted that the term "venous thromboembolism (VTE)" includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The term "bleeding event" encompasses upper gastrointestinal bleeding (UGIB) and intracranial bleeding.

2.3. Study design

We carried out a population-based, crossover cohort study by analyzing the French national inpatient database from 2007 to 2013. Each patient served as his/her own control, which enabled us to control for certain personal, time-constant confounding factors. The patient is analyzed when he/she is "exposed" to the THR and is used as his/her own control 12 months later (when he/she is no longer exposed to the THR).

For the study population as a whole (Fig. 1), we compared the likelihood of a PE after THR with the likelihood of a PE during three unexposed periods around 12 months after THR. We then defined six successive, 35-day, high-risk intervals. The use of 35-day intervals allows to precisely address the risks beyond the recommended 35-day period of anticoagulation.

2.4. Patients

2.4.1. Inclusion criteria (definition of exposure)

We included middle-aged patients (aged 45 to 69) having undergone THR between July 1st, 2007, and March 31st, 2012. Inpatient stays with THR were identified by the procedure code NEKA020 (corresponding to "Hip joint replacement with total hip replacement") and one of the following ICD-10 diagnostic codes: M16.0, M16.1 or M16.9 ("osteoarthritis of hip").

2.4.2. Non-inclusion criteria

We did not include patients meeting one or more of the following criteria: those with THR and an S72.x diagnostic code ("fracture of femur") or a T84.x diagnostic code ("complications of internal orthopedic prosthetic devices, implants and grafts"), and those with a history (as recorded during previous hospitalizations) of thromboembolism: VTE (the I80.x diagnostic code "phlebitis and thrombophlebitis" or the I26.x diagnostic code "pulmonary embolism"), myocardial infarction (the I21.x code "ST elevation and non-ST elevation myocardial infarction" or the I22.x code "Subsequent ST elevation and non-ST elevation myocardial infarction", available from So (So et al., 2006)), ischemic stroke (the I63.x code "cerebral infarction"), "nonpyogenic thrombosis of intracranial venous system" (code I67.6) or "central retinal artery occlusion" (code H34.1)).

2.4.3. Exclusion criteria

We excluded patients having undergone another THR during the 21 months following the PE, since we wanted to assess the risk relative to an unexposed period.

2.5. Measurements

2.5.1. Outcome definition

We determined whether the included patients had suffered a PE in the 210 days following THR. If more than one PE was detected during a given exposed period or unexposed period, the first event in each period was selected.

Several algorithms for tracking VTEs within claims data have been developed and evaluated (Tamariz et al., 2012). Many of these refer to ICD-9. An evaluation of ICD-10 (using a database similar to our own) revealed that it was more difficult to identify inpatient stays with DVT than stays with PE (Casez et al., 2010). Furthermore, DVT does not necessarily require hospitalization.

In summary, we decided to use PE as a marker of the risk of a VTE in the present cross-over study. The ICD-10 codes used to identify PE are I26.0 ("pulmonary embolism with acute cor pulmonale") and I26.9 ("pulmonary embolism without acute cor pulmonale").

2.6. Statistical analysis

Firstly, we performed a descriptive analysis of the demographic characteristics of all inpatient stays meeting the inclusion criteria. Categorical data were expressed as the number (frequency). Quantitative data were expressed as the mean ± standard deviation (SD) or the median (interquartile range (IR)).

Secondly, we calculated the odds ratio (OR) [95% confidence interval (CI)] for each 35-day interval. We assessed the likelihood of a PE occurring from 0 to 34 days after THR, relative to the likelihood of a PE occurring during three 35-day unexposed intervals (respectively 330, 365 and 400 days later). A similar analysis was performed for the five other 35-day-long intervals. We used conditional logistic regression to calculate the OR [95% CI] for each interval. Then, we calculated the