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Is There a Cardiotoxicity Associated With Metallic Head Hip Prostheses? A Cohort Study in the French National Health Insurance Databases

Marion Lassalle PharmD, MPH, Sandrine Colas MSc, PhD, Annie Rudnichi MD, Mahmoud Zureik MD, PhD, Rosemary Dray-Spira MD, PhD

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Abstract

Background There are four distinguishable types of THA devices in wide use, as defined by the femoral and acetabular bearing surfaces: metal-on-polyethylene (MoP), ceramic-on-polyethylene (CoP), metal-on-metal (MoM), and ceramic-on-ceramic (CoC). Metallic head THAs (MoP and MoM) can potentially induce cardiac toxicity because cobalt species, generated at the head-neck trunnion, and in the case of MoM devices, at the articular surface as well, can be absorbed systemically. However, studies have provided inconsistent results.

Questions/purposes The purpose of this study was to assess the risk of dilated cardiomyopathy (DCM) or heart failure (HF) associated with metallic head THAs using data from the French national health insurance databases.

Methods Between 2008 and 2011 in France, 399,968 patients ≥ 55 years had a first THA. A total of 127,481 were excluded after we applied the exclusion criteria regarding arthroplasty and 17,137 as a result of a history of DCM/HF, recorded in the French national health insurance reimbursement databases, between January 1, 2006, and the date of inclusion. The final cohort included 255,350 individuals (43% men; mean age 72 ± 9 years). Of them, 93,581 (37%) had been implanted with MoP, 58,095 (23%) with CoP, 11,298 (4%) with MoM, and 92,376 (36%) with CoC THAs. Patients were followed until December 2015. Patients with incident DCM/HF were identified by a new entitlement to the long-term disease scheme or a first hospitalization with a diagnosis of DCM or HF. MoP and CoP THAs are generally implanted in old patients, whereas MoM and CoC are mostly indicated in young, active male patients. Thus, to consider the specific indications of the bearing couples, analyses were separately performed in two distinct subcohorts, one comprising patients with MoP or CoP and one comprising patients with MoM or CoC THA. In each subcohort, the DCM/HF risk was compared between patients with metallic head versus nonmetallic head THAs (MoP versus CoP, MoM versus CoC). Hazard ratios (adjusted HRs) of incident DCM/HF were estimated using Cox models adjusted for baseline sex,

One of the authors (ML) completed a 6-month paid internship at Janssen Pharmaceuticals (Johnson & Johnson, Issy-les-Moulineaux, France) that was relevant to but outside the scope of this study.

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Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

French National Agency for Medicines and Health Products Safety (ANSM), Department of Epidemiology of Health Products, Saint-Denis, France

M. Lassalle (✉), French National Agency for Medicines and Health Products Safety, Department of Epidemiology of Health Products, 143-147 Boulevard Anatole France, 93285 Saint-Denis, France, email: marion.lassalle@ansm.sante.fr

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age, THA characteristics (fixation technique with cement, use of a modular femoral neck), and comorbidities at baseline. Cox models were stratified by sex and age.

Results The crude incidence of DCM/HF per 100 person-years was 2.4 in patients with MoP, 1.8 with CoP, 1.2 with MoM, and 1.1 with CoC THAs. Overall, metallic head THAs were associated with a slight increase in DCM/HF risk (MoP versus CoP: adjusted HR, 1.08; 95% confidence interval [CI], 1.05-1.12; $p < 0.001$; MoM versus CoC: adjusted HR, 1.11; 95% CI, 1.03-1.19; $p = 0.007$). In the MoM-CoC subcohort, the risk tended to be more pronounced with MoM versus CoC THAs in women (MoM versus CoC: adjusted HR, 1.20; 95% CI, 1.07-1.35; $p = 0.002$) and patients aged ≥ 75 years (MoM versus CoC: adjusted HR, 1.16; 95% CI, 1.04-1.29; $p = 0.009$).

Conclusions Metallic head THAs were associated with a slightly increased DCM/HF risk, especially with MoM in women and older patients. Some caveats should be mentioned: severity of DCM or HF was not available and residual confounding cannot be ruled out despite considering many covariates. Our findings suggest that cardiac function should be regularly monitored in patients with metallic head THAs. Further investigations should be planned on large international cohorts.

Level of Evidence Level III, therapeutic study.

Introduction

More than 1 million THAs are done every year worldwide [30]. There are four main bearing couples in THAs, depending on the materials used for the prosthetic head and acetabular cup: metal-on-polyethylene (MoP), ceramic-on-polyethylene (CoP), metal-on-metal (MoM), and ceramic-on-ceramic (CoC). As a result of expected lower wear rate and greater implant longevity, hard-on-hard bearings, MoM and CoC, are specifically indicated in young, active male patients [40].

The health effects of metal-implanted medical devices, including those used in THA, are a growing matter of concern [6]. Cobalt-chromium alloys are largely used to manufacture metallic head THAs (MoM and MoP) [22, 26, 31]. Fretting and corrosion at the head-neck trunnion, and in the case of MoM devices, at the articular surface as well, result in metal ion release. Cobalt particles can disseminate in the body and accumulate in the heart [9, 35]. Cobalt cardiac toxicity was first reported in the mid-1960s [23]. More recently, case reports described heart symptoms consistent with the effects of cobalt cardiac toxicity in patients with metal prostheses [5, 14, 27]. However, to date, only two epidemiologic studies, based on small patient samples, have explored the cardiac effects of MoM hip prostheses [16, 32].

National medicoadministrative databases can help us assess risk pertaining to uncommon but potentially serious health effects of arthroplasty such as cardiac complications from corrosion products, as a result of the large number of included patients, to the individual recorded data and to the broad range of available information. In particular, the power of the French national health insurance information system is great, and its representativeness is high, because it almost includes the whole country's population [2, 25].

We therefore sought to assess the risk of dilated cardiomyopathy (DCM) or heart failure (HF) associated with metallic head THAs using data from the French national health insurance databases.

Patients and Methods

The study was based on the French national health insurance information system, Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM) [21, 25, 37]. The SNIIRAM databases have been used in previous epidemiologic studies [3, 4, 10, 11, 20, 33]. These databases cover > 95% of the French population with various programs based on the individual's employment situation. It also includes students, foreigners, and unemployed individuals. The SNIIRAM contains records since 2006, with dates, on outpatient drugs, laboratory tests, and medical devices as well as reimbursed services and procedures. The databases do not stipulate the medical indication for each reimbursement but contain the patients' demographic, administrative, and medical details (including severe and costly long-term diseases [LTDs] with full reimbursement of care) and the date of death. An anonymous, unique identifier for each patient links SNIIRAM information to the national hospital discharge database (Programme de médicalisation des systems d'information [PMSI]), which covers all public and private hospitals.

For this study, we obtained approval from the French data protection agency, the Commission Nationale de l'Informatique et des Libertés. Informed consent was not required because information was collected anonymously.

Participants

The eligible population was patients ≥ 55 years of age who had an initial THA between January 1, 2008, and December 31, 2011, and who were alive at the time of discharge. The identification algorithm for patients with THA has been used in previous studies [3, 10, 11]. The date of inclusion was the inpatient admission date for the first THA. Patients were excluded if they had a bilateral THA or underwent the first THA because of hip trauma, received a nontotal hip prosthesis, or if data characterizing the prosthesis or the bearing couple were missing or inconsistent. Patients were also excluded if they had a history of cardiomyopathy or HF or

a known cause of DCM/HF [1, 7, 24, 29] recorded in the SNIIRAM-PMSI databases between January 1, 2006, and the date of inclusion: myopathy, myocarditis, HIV infection, Lyme disease, or Chagas disease.

Exposure

The exposure of interest was the bearing couple: MoP, CoP, MoM, or CoC.

Total hip prosthesis is not recorded as a whole in the PMSI databases, but each of the component elements is recorded individually according to its List of Products and Services (LPS) code. For each patient, various LPS codes were used to identify the bearing surface of the implanted prosthesis.

MoP and CoP bearings are common options for THA in old female patients, whereas MoM and CoC are preferentially used in young, male active patients. Because age and sex are highly associated with the outcome, it was necessary to compare patients of homogeneous profiles, with the exception of the bearing couple, to study the association between metallic head THAs and DCM/HF risk. Thus, to take into consideration the specific indications of the bearing couples, we divided the study population into two distinct subcohorts of comparable patients: one comprising patients with MoP or CoP and one comprising patients with MoM or CoC.

Outcome

Patients with incident DCM/HF were identified by a new entitlement to the LTD scheme or a first hospitalization with a diagnosis of DCM (International Statistical Classification of Diseases, 10th Revision [ICD-10] code I42.0) or HF (ICD-10 code I50.x) or a diagnosis of a HF complication (ICD-10 codes I11.0, I11.9, I13.0, I13.1, I13.2, I13.9, K76.1, J81.x).

Covariates

Sociodemographic characteristics included sex, age at baseline, and affiliation with the Couverture Maladie Universelle Complémentaire (CMUc), a free healthcare insurance program in France that is available for people with low annual income [38].

The characteristics of the initial THA were fixation technique with cement, use of a modular femoral neck, and other metal medical devices implanted before inclusion such as a total knee arthroplasty or coronary stent.

Conditions known to be or suspected of being associated with DCM or HF [1, 7, 24, 28, 29] were considered at baseline, namely cardiovascular comorbidities, psychiatric comorbidities, endocrinal and metabolic comorbidities, other comorbidities, drugs, and lifestyle factors. Cardiovascular comorbidities were ischemic cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, valvular disease, and high blood pressure. Psychiatric comorbidities were depression and sleep disorders (using the reimbursement of prescribed hypnotic drugs as a proxy). Endocrinal and metabolic comorbidities were diabetes mellitus, measurable morbid obesity, dyslipidemia, other endocrinal diseases (including thyroid disorders), and hemochromatosis. Other comorbidities were cancer, chronic respiratory disease, sleep apnea, serious infection, chronic kidney disease, and chronic inflammatory conditions (such as rheumatoid arthritis). Drug reimbursement included prescription-only nonsteroidal antiinflammatory drugs and some psychiatric drugs. Lifestyle factors were a measurable history of chronic alcoholism or tobacco smoking. These conditions were identified based on a hospital discharge or LTD diagnosis recorded between January 1, 2006, and the date of inclusion together with, if pertinent, relevant prescriptions, specific laboratory tests, reimbursed services, and procedures. Drug treatments were identified with prescriptions reimbursed at least six times within 1 year before inclusion.

Duration of Followup

Patients were followed from the date of inclusion to the date of incident DCM/HF. Those without DCM/HF were censored on the date of the following events, whichever came first: onset of a known cause of DCM/HF (myopathy, myocarditis, HIV infection, Lyme disease, Chagas disease), lost to followup (absence of healthcare reimbursement for 18 months), death, or December 31, 2015.

The duration of followup was expected to be long enough to detect incident DCM/HF; like in previous case reports [5, 14], cardiac symptoms appeared between 3 months and 6 years after implantation of metallic head THAs.

Baseline Characteristics of the Study Population

The eligible population comprised 399,968 patients. First, 127,481 patients were excluded after we applied the exclusion criteria regarding arthroplasty; then 17,137 were excluded as a result of a history of DCM/HF or having a known cause of DCM/HF. The final cohort included 255,350 individuals (42.7% men; mean patient age 72.0 ± 8.8 years); 93,581 (36.6%) had been implanted with MoP, 58,095 (22.8%) with CoP, 11,298 (4.4%) with MoM, and 92,376 (36.2%) with CoC THA (Fig. 1). The median followup was 5.4 years, accounting for 799,037 person-years

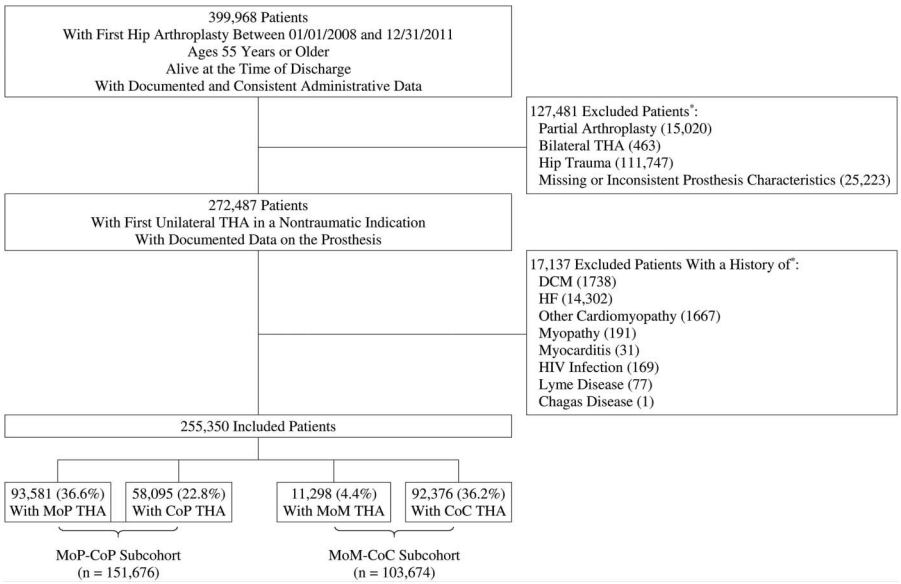

Fig. 1 The study flowchart shows the number of included patients and the repartition by bearing couples. *Patients can present more than one exclusion criterion.

(PYs) in the MoP-CoP subcohort, and 5.7 years, accounting for 578,851 PYs in the MoM-CoC subcohort.

We observed disparities between the MoP-CoP (n = 151,676) and MoM-CoC (n = 103,674) subcohorts. Compared with the MoM or CoC group, patients in the MoP or CoP group were more likely to be women (49.4% versus 38.2%; $p < 0.001$), be older (74.8 ± 8.2 years versus 67.9 ± 8.0 years; $p < 0.001$), and to present with cardiovascular comorbidities at baseline, including high blood pressure (62.4% versus 51.1%; $p < 0.001$) and ischemic cardiovascular disease (9.0% versus 6.4%; $p < 0.001$).

Within each subcohort, we observed slight differences between patients with metallic and nonmetallic head THAs. Within the MoP-CoP subcohort, fewer of the patients with MoP were men (36.3% versus 41.2%; $p < 0.001$), and these patients were older (75.9 ± 8.0 years versus 73.0 ± 8.1 years; $p < 0.001$) than those with CoP THAs. Cemented or modular neck MoP THAs were more common. Patients with MoP THAs had more psychiatric and cardiovascular comorbidities, except for valvular disease, which was less frequent in the MoP group. Although these patients presented less frequently with morbid obesity, we observed no difference among the other endocrinal or metabolic comorbidities. Cancers, chronic respiratory diseases, serious infections, chronic kidney diseases, and chronic inflammatory conditions were more common in patients with MoP THAs. We noted no differences in lifestyle factors. Within the MoM-CoC subcohort, patients with MoM THAs were more likely to be men (54.0% versus 48.9%; $p < 0.001$) and be younger (67.7 ± 8.1 years versus 67.9 ± 8.0 years; $p = 0.020$) than those with CoC THAs. More MoM THAs were cemented or had a modular neck. Patients with MoM THAs presented more often with high arterial blood pressure or ischemic cardiovascular diseases; however, we observed no major differences for the other cardiovascular comorbidities. Patients with MoM THAs had lower depression rates. We noted no differences in the rates of diabetes mellitus, measurable morbid obesity, or dyslipidemia, but other endocrinal diseases, including thyroid disorders, were less frequent in the MoM group. We observed no differences in the other comorbidities studied. Patients with MoM THAs were more likely to have a history of tobacco smoking, but we noted no difference in rates of chronic alcoholism (Table 1).

Statistical Analysis

We conducted statistical analyses separately for MoP versus CoP and MoM versus CoC.

Kaplan-Meier curves were plotted and log-rank tests were performed to compare crude differences in cumulative DCM/HF risk. Hazard ratios (adjusted HRs) and their 95% confidence intervals (CIs) were obtained from multivariate Cox proportional hazard models adjusted for all baseline covariates. The proportional hazard assumption was met, meaning that the effect is constant over time. Cox models were also stratified by sex or age. Interactions between the bearing couple and sex as well as age, in association with DCM/HF, were investigated.

We performed sensitivity analyses. First, two time-dependent covariates were added to complete Cox models,

Table 1. Baseline characteristics by subcohort

Covariates	MoP-CoP subcohort (n = 151,676)			MoM-CoC subcohort (n = 103,674)		
	MoP (n = 93,581)	CoP (n = 58,095)	p value*	MoM (n = 11,298)	CoC (n = 92,376)	p value*
Sociodemographic characteristics						
Male sex	33,967 (36.3%)	23,920 (41.2%)	< 0.001	6104 (54.0%)	45,149 (48.9%)	< 0.001
Age (years), mean (SD) [range]	75.9 (8.0), [55-106]	73.0 (8.1), [55-98]	< 0.001	67.7 (8.1), [55-96]	67.9 (8.0), [55-102]	0.020
≤ 65	11,757 (12.6%)	12,043 (20.7%)		4969 (44.0%)	40,278 (43.6%)	
66-75	28,655 (30.6%)	21,790 (37.5%)		4217 (37.3%)	34,279 (37.1%)	
> 75	53,169 (56.8%)	24,262 (41.8%)		2112 (18.7%)	17,819 (19.3%)	
THA characteristics						
THA fixation with cement	41,158 (44.0%)	19,032 (32.8%)	< 0.001	3122 (27.6%)	12,788 (13.8%)	< 0.001
Modular neck	2089 (2.2%)	1032 (1.8%)	< 0.001	780 (6.9%)	3310 (3.6%)	< 0.001
Other metallic devices						
Total knee arthroplasty	2960 (3.2%)	1809 (3.1%)	0.594	240 (2.1%)	2080 (2.3%)	0.388
Cardiovascular comorbidities						
Ischemic cardiovascular disease	8873 (9.5%)	4837 (8.3%)	< 0.001	774 (6.9%)	5830 (6.3%)	0.027
Atrial fibrillation	6508 (7.0%)	3214 (5.5%)	< 0.001	466 (4.1%)	3555 (3.9%)	0.151
Valvular disease	3375 (3.6%)	2222 (3.8%)	0.028	244 (2.1%)	2266 (2.5%)	0.056
High arterial blood pressure	59,561 (63.7%)	35,021 (60.3%)	< 0.001	5892 (52.2%)	47,055 (50.9%)	0.015
Psychiatric comorbidities						
Depression	12,122 (13.0%)	6502 (11.2%)	< 0.001	1041 (9.2%)	9558 (10.4%)	< 0.001
Sleep disorders	7775 (8.3%)	4449 (7.7%)	< 0.001	720 (6.4%)	5974 (6.5%)	0.700
Endocrinal or metabolic comorbidities						
Diabetes mellitus	11,301 (12.1%)	6855 (11.8%)	0.107	1196 (10.6%)	9672 (10.5%)	0.705
Measurable morbid obesity	10,457 (11.2%)	7030 (12.1%)	< 0.001	1361 (12.1%)	10,701 (11.6%)	0.148
Dyslipidemia	34,518 (36.9%)	21,225 (36.5%)	0.169	3690 (32.7%)	30,878 (33.4%)	0.103
Other endocrinal diseases	9363 (10.0%)	5737 (9.9%)	0.411	914 (8.1%)	8256 (8.9%)	0.003
Other comorbidities						
Cancer	10,132 (10.8%)	5312 (9.1%)	< 0.001	832 (7.36%)	7228 (7.8%)	0.085
Chronic respiratory disease	9105 (9.7%)	5252 (9.0%)	< 0.001	955 (8.5%)	7473 (8.1%)	0.183
Sleep apnea	2000 (2.1%)	1412 (2.4%)	< 0.001	317 (2.8%)	2342 (2.5%)	0.086
Serious infection	12,587 (13.5%)	6341 (10.9%)	< 0.001	952 (8.4%)	8189 (8.9%)	0.121
Chronic kidney disease	2078 (2.2%)	1129 (1.9%)	< 0.001	108 (1.0%)	940 (1.0%)	0.536
Chronic inflammatory condition	2878 (3.2%)	1513 (2.6%)	< 0.001	284 (2.5%)	2066 (2.2%)	0.062
Drug reimbursement						
Prescription-only nonsteroidal antiinflammatory drugs	15,107 (16.1%)	10,339 (17.8%)	< 0.001	2086 (18.5%)	18,950 (20.5%)	< 0.001
Lifestyle factors						
History of chronic alcoholism	1909 (2.0%)	1112 (1.9%)	0.088	258 (2.3%)	1931 (2.1%)	0.178
History of tobacco smoking	6731 (7.2%)	4323 (7.4%)	0.070	975 (8.6%)	7346 (8.0%)	0.012

Only baseline characteristics whose prevalence was ≥ 2% or over, in one or both subcohorts, are presented in this table.
*Mann-Whitney test for age, chi square tests for the other variables; MoP = metal-on-polyethylene; CoP = ceramic-on-polyethylene; MoM = metal-on-metal; CoC = ceramic-on-ceramic.

namely revision surgery with a MoM THA or contralateral MoM THA during followup, because these procedures may increase metal exposure. Second, to account for calendar period, Cox proportional hazard models considering age as the time-scale, and stratified by birth cohort (in 5-year intervals), were performed [19, 36]. Third, a propensity score was calculated for the assignment of either a metallic head or nonmetallic head THA using inverse probability of treatment weighted logistic regression models [18]. Fourth, Fine-Gray models [15] were used to estimate the association of metallic head THA with the incidence of DCM/HF with death as the competing event. Fifth, patients experiencing an outcome within 1 month, 3 months, or 6 months after their first THA were excluded, because these early events could be a marker of preexisting DCM/HF. Finally, we used a more stringent definition for the outcome without identification of HF complications: patients with incident DCM/HF were identified by a new entitlement to the LTD scheme or a first hospitalization with a diagnosis of DCM (ICD-10 code I42.0) or HF (ICD-10 code I50.x).

Statistical tests were two-tailed with 5% α risk. Analyses were performed using SAS Enterprise Guide 4.3 software (SAS Institute, Cary, NC, USA).

Results

DCM/HF Risk in the MoP-CoP Subcohort

Incidence rates of DCM/HF were 2.4/100 PYs in the MoP group and 1.8/100 PYs in the CoP group (Table 2). Crude cumulative DCM/HF risk was higher in patients with MoP than in those with CoP THAs (19.6% and 14.4%, respectively; $p < 0.001$; Fig. 2).

After controlling for potential confounding variables such as sex, age, comorbidities at baseline, and implant-related factors other than the bearing couple itself, MoP THAs were associated with a slight increase in DCM/HF risk compared with CoP THAs (adjusted HR, 1.08; 95% CI, 1.05–1.12; $p < 0.001$). This increased risk associated with MoP THAs was consistent regardless of sex (men: adjusted HR, 1.07; 95% CI, 1.02–1.12; $p = 0.008$; women: adjusted HR, 1.09; 95% CI, 1.04–1.14; $p < 0.001$) and age (≤ 65 years: adjusted HR, 1.08; 95% CI, 0.94–1.24; $p = 0.268$; 66-75 years: adjusted HR, 1.13; 95% CI, 1.05–1.21; $p < 0.001$; > 75 years: adjusted HR, 1.14; 95% CI, 1.10–1.18; $p < 0.001$) (Table 2).

In sensitivity analyses, the HR estimates were consistent with the main results when adding the two time-dependent covariates to the model (revision surgery with a MoM THA and contralateral MoM THA during followup) (adjusted HR, 1.08; 95% CI, 1.04–1.11; $p < 0.001$), accounting for calendar period (adjusted HR, 1.08; 95% CI, 1.05–1.12; $p < 0.001$), adjusting for the propensity score (adjusted HR, 1.06; 95% CI, 1.03–1.10; $p < 0.001$), or using a Fine-Gray model (adjusted HR, 1.06; 95% CI, 1.03–1.10; $p < 0.001$). Exclusion of patients with events within 1 month (adjusted HR, 1.08; 95% CI, 1.04–1.11; $p < 0.001$), 3 months (adjusted HR, 1.08; 95% CI, 1.04–1.11; $p < 0.001$), or 6 months (adjusted HR, 1.07; 95% CI, 1.04–1.11; $p < 0.001$) after the date of first THA did not modify the HR estimates. When using more stringent criteria for the outcome (new entitlement to the LTD scheme or first hospitalization with a diagnosis of DCM [ICD-10 code I42.0] or HF [ICD-10

Table 2. DCM/HF risk associated with MoP versus CoP THA, overall, by sex and by age

Type of analyses	Number of incident DCM/HF (incidence rate per 100 PYs)		Multivariate analyses*	
	MoP	CoP	HR (95% CI)	p value
Overall	11,540 (2.4)	5552 (1.8)	1.08 (1.05-1.12)	< 0.001
Stratified by sex				
Men	4817 (2.8)	2676 (2.1)	1.07 (1.02-1.12)	0.008
Women	6723 (2.2)	2876 (1.5)	1.09 (1.04-1.14)	< 0.001
Stratified by age				
≤ 65 years old	441 (0.7)	398 (0.6)	1.08 (0.94-1.24)	0.268
66-75 years old	2102 (1.3)	1428 (1.2)	1.13 (1.05-1.21)	< 0.001
> 75 years old	8997 (3.4)	3726 (3.0)	1.14 (1.10-1.18)	< 0.001

*Cox models adjusted for: sex and age at baseline, affiliation with the CMUc (free healthcare insurance program in France), THA fixation with cement, use of a modular neck, history of implantation with total knee arthroplasty, coronary stent, ischemic cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, valvular disease, high blood pressure, depression, sleep disorders, diabetes mellitus, measurable morbid obesity, dyslipidemia, other endocrinal diseases, hemochromatosis, cancer, chronic respiratory disease, sleep apnea, serious infection, chronic kidney disease, chronic inflammatory condition, reimbursement of prescription-only nonsteroidal antiinflammatory drugs, reimbursement of specific psychiatric drugs, measurable history of chronic alcoholism or tobacco smoking; DCM = dilated cardiomyopathy; HF = heart failure; MoP = metal-on-polyethylene; CoP = ceramic-on-polyethylene; PYs = person-years; HR = hazard ratio; CI = confidence interval.

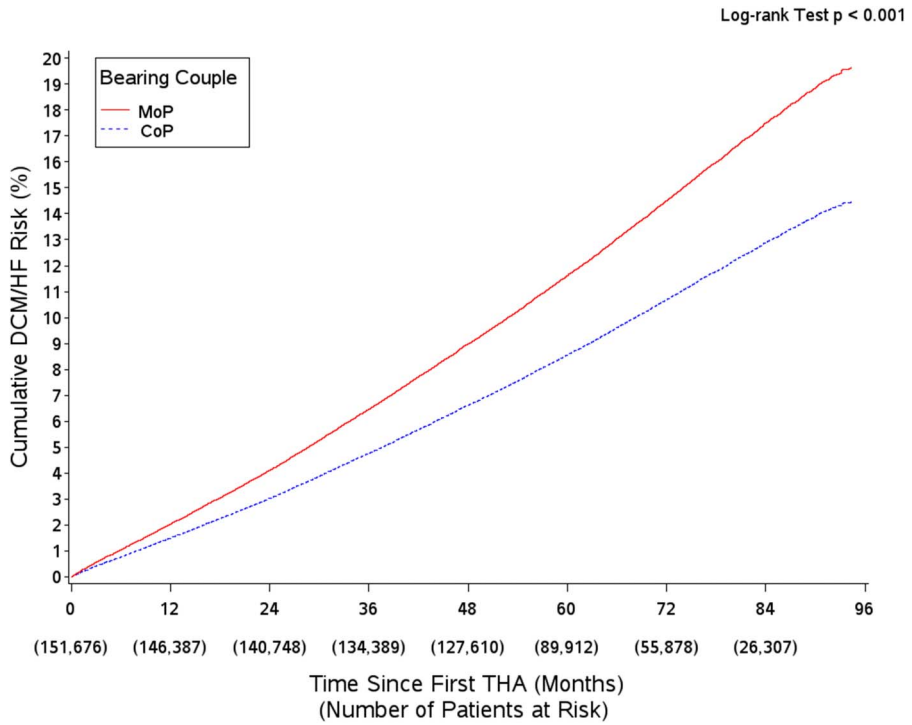

Fig. 2 The cumulative DCM/HF risk according to the bearing couple in the MoP-CoP subcohort is shown.

code I50.x]), MoP THAs remained associated with a slight increase in DCM/HF risk compared with CoP THAs (adjusted HR, 1.09; 95% CI, 1.05–1.13; p < 0.001; see Table, Supplemental Digital Content 1).

DCM/HF Risk in the MoM-CoC Subcohort

Incidence rates were 1.2/100 PYs in the MoM group and 1.1/100 PYs in the CoC group. Crude cumulative DCM/HF risk was higher in patients with MoM than in those with CoC THAs (9.9% and 8.7%, respectively; p < 0.001; Fig. 3).

After controlling for potential confounding variables such as sex, age, comorbidities at baseline, and implant-related factors other than the bearing couple itself, MoM THAs were associated with a slight increase in DCM/HF risk compared with CoC THAs (adjusted HR, 1.11; 95% CI, 1.03–1.19; p = 0.007). Models stratified by sex or age showed that this risk tended to be more pronounced in women (men: adjusted HR, 1.04; 95% CI, 0.94–1.15; p = 0.429; women: adjusted HR, 1.20; 95% CI, 1.07–1.35; p = 0.002) and among patients > 75 years (≤ 65 years: adjusted HR, 1.04; 95% CI, 0.88–1.23; p = 0.634; 66-75 years: adjusted HR, 1.03; 95% CI, 0.91–1.17; p = 0.658; > 75 years: adjusted HR, 1.16; 95% CI, 1.04–1.29; p = 0.009), although the interaction tests were not significant (Table 3).

In sensitivity analyses, the HR estimates were consistent when adding the two time-dependent covariates (adjusted HR, 1.10; 95% CI, 1.02–1.19; p = 0.013), accounting for calendar period (adjusted HR, 1.09; 95% CI, 1.01–1.18; p = 0.024), adjusting for the propensity score (adjusted HR, 1.08; 95% CI, 1.00–1.17; p = 0.037), or using a Fine-Gray model (adjusted HR, 1.12; 95% CI, 1.04–1.21; p = 0.004). The HR estimates were not modified after excluding patients who had events within 1 month (adjusted HR, 1.11; 95% CI, 1.03–1.19; p = 0.008), 3 months (adjusted HR, 1.11; 95% CI, 1.03–1.20; p = 0.007), or 6 months (adjusted HR, 1.11; 95% CI, 1.03–1.20; p = 0.007) after the date of their first THA. When using more stringent criteria for the outcome (new entitlement to the LTD scheme or first hospitalization with a diagnosis of DCM [ICD-10 code I42.0] or HF [ICD-10 code I50.x]), the HR estimate of the association between DCM/HF risk and MoM (versus CoC) THAs remained consistent with the main results (adjusted HR, 1.01; 95% CI, 0.93-1.10; p = 0.756; see Table, Supplemental Digital Content 2).

Discussion

Metallic head THAs (MoP and MoM) are suspected to be associated with an increased risk of cardiac toxicity as a result

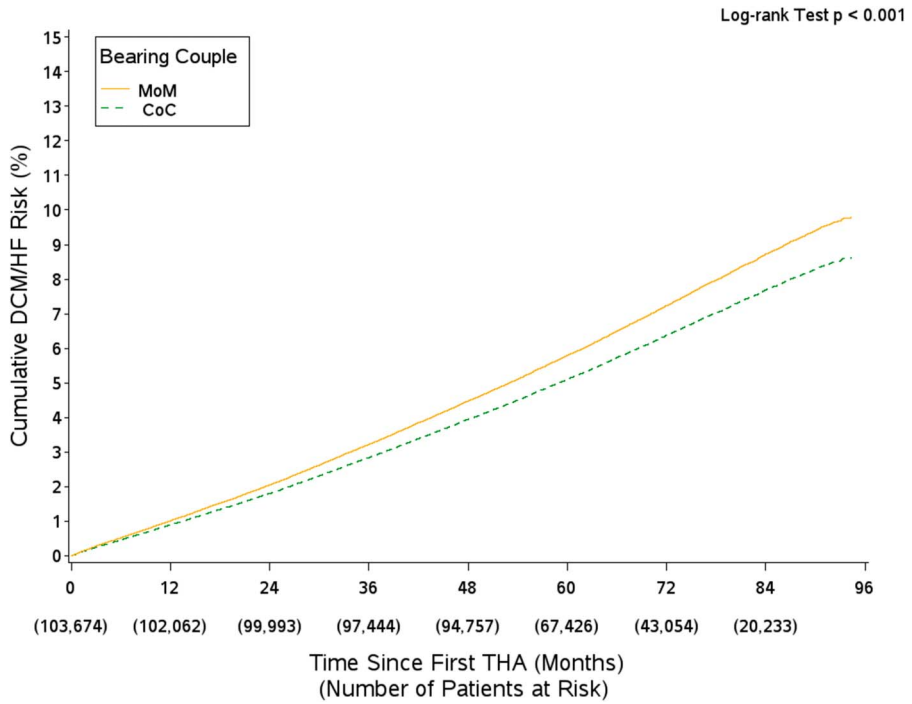

Fig. 3 The cumulative DCM/HF risk according to the bearing couple in the MoM-CoC subcohort is shown.

of potential systemic cobalt dissemination related to fretting and corrosion arising from the head-neck junction and, for the MoM bearing, from the articular surface as well, although the reported findings have been inconsistent [16, 32]. The French national health insurance databases are a powerful tool to assess cardiac risk related to metallic head THAs. In this study, MoP (versus CoP) and MoM (versus CoC) THAs were associated with a slight increase in incident DCM/HF

Table 3. DCM/HF risk associated with MoM versus CoC THA, overall, by sex and by age

Type of analyses	Number of incident DCM/HF (incidence rate per 100 PYs)		Multivariate analyses*	
	MoM	CoC	HR (95% CI)	p value
Overall	815 (1.2)	5379 (1.1)	1.11 (1.03-1.19)	0.007
Stratified by sex				
Men	461 (1.3)	3067 (1.2)	1.04 (0.94-1.15)	0.429
Women	354 (1.1)	2312 (0.9)	1.20 (1.07-1.35)	0.002
Stratified by age				
≤ 65 years old	156 (0.5)	960 (0.4)	1.04 (0.88-1.23)	0.634
66-75 years old	277 (1.1)	1939 (1.0)	1.03 (0.91-1.17)	0.658
> 75 years old	382 (3.3)	2480 (2.7)	1.16 (1.04-1.29)	0.009

*Cox models adjusted for: sex and age at baseline, affiliation with the CMUc (free healthcare insurance programs in France), THA fixation with cement, use of a modular neck, history of implantation with total knee arthroplasty, coronary stent, ischemic cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, valvular disease, high blood pressure, depression, sleep disorders, diabetes mellitus, measurable morbid obesity, dyslipidemia, other endocrinal diseases, hemochromatosis, cancer, chronic respiratory disease, sleep apnea, serious infection, chronic kidney disease, chronic inflammatory condition, reimbursement of prescription-only nonsteroidal antiinflammatory drugs, reimbursement of specific psychiatric drugs, measurable history of chronic alcoholism or tobacco smoking; DCM = dilated cardiomyopathy; HF = heart failure; MoM = metal-on-metal; CoC = ceramic-on-ceramic; PYs = person-years; HR = hazard ratio; CI = confidence interval.

risk overall. The risk tended to be more pronounced with MoM (versus CoC) THAs in women and patients aged ≥ 75 years.

Some limitations should be mentioned. First, this study showed a moderate effect size of the association between DCM/HF risk and metallic head THAs. These findings have public health relevance, however, as a result of the large and increasing number of implanted patients and the severity of the studied cardiac events. Overall, multiple sensitivity analyses were performed, showing results consistent with those in the main analyses, thus supporting the robustness of the findings. Although absolute risks were not different when using a restrictive definition of the outcome, the observed effect between DCM/HF risk and metallic head THAs was consistent with the main results with CIs overlapping. Absolute risks were not different in some subgroups either, in particular in patients aged 55 to 65 years, potentially as a result of an absence of an association in this population or as a result of a lack of power in this subgroup. Further investigations based on large international cohorts, with powered subgroups analyses, are needed to confirm our results about the association between DCM/HF risk and metallic head THAs. Second, the outcome was identified either by a new entitlement to the LTD scheme or a first hospitalization with a diagnosis of DCM, HF, or HF complication. Thus, our analyses focused on the most serious cases of DCM/HF. Moreover, changes in coding patterns of DCM/HF in discharge diagnoses, coding errors, or inappropriate coding practices could have occurred over time. However, such changes are likely to have occurred regardless of THA bearing couple and therefore are not expected to have biased our results. Third, although many confounding factors were considered, including the use of a modular femoral neck or revision with a MoM THA, the confounding effect of unmeasured and/or unknown risk factors of DCM/HF cannot be ruled out. Information on dietary, occupational, or environmental exposure to cobalt was not available. However, these factors were not expected to influence the choice of the bearing couple. MoM prostheses are suspected of inducing greater blood metal concentrations than MoP [8, 34, 39]. But biologic cobalt levels, when performed, were not recorded. Finally, causes of death were not available in the French national health insurance databases.

Previous epidemiologic studies have suggested an association between MoM THAs and cardiac toxicity. In a single-center, cross-sectional study based on 35 matched pairs of patients in the United Kingdom (31 men, four women), Prentice et al. [32] found a 7% lower cardiac ejection fraction in the MoM hip resurfacing group versus non-MoM THAs. Although they observed no difference in the New York Heart Association score for HF, that study was not powered to evaluate cardiac endpoints, which were assessed as a secondary outcome. In a cohort study using data from the Australian Government Department of Veterans' Affairs health claims database, Gillam et al. [16] found that, in men, Articular Surface Replacement XL large femoral head MoM THAs (DePuy Orthopaedics Inc, Warsaw, IN, USA) were associated with a higher rate of hospitalization for HF compared with MoP THAs with an adjusted HR of 3.21 (95% CI, 1.59-6.47). They found no difference in women, but, according to the authors, the male cohort was a more vulnerable group and as such was more susceptible to development of HF after exposure to MoM prostheses than the female cohort. Moreover, the choice of a potentially cardiotoxic comparator, MoP THA, could have led to an underestimation of the risk. In the present study, the DCM/HF risk tended to be more pronounced with MoM THAs compared with CoC in women and patients > 75 years. Theories about pharmacokinetic and immunologic factors may explain this finding. Sex and age differences in the metabolism of metal ions (such as different lean mass, cellular or extracellular storage, or renal excretion) may lead to higher metal levels in women [13] and in older individuals. In addition, an increased incidence of metal allergy has been observed in women [17] and is known to be involved in local reactions around the hip prosthesis [12]. However, to date, there is little evidence that metal hypersensitivity could contribute to cardiac toxicity.

This study showed a slightly increased DCM/HF risk associated with metallic head THAs, especially in women and older patients. Although moderate in size, these results have public health relevance as a result of the large and increasing number of implanted patients and to the severity of these cardiac events. Our findings suggest that cardiac function should be regularly monitored in patients with metallic head THAs. Moreover, occurrence of cardiac symptoms in patients with metallic head THAs should alert the physician to potential toxicity related to cobalt exposure. Further investigations on the potential harmful effects of metallic exposure related to medical devices should be considered in future research through international consortiums that integrate epidemiologic data from multiple sources.

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