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INVITED COMMENTARY

ONLINE FIRST

Risk of Acute Myocardial Infarction in Patients With Total Hip or Knee Replacement

Lalmohamed et al[1] used epidemiologic analysis to test the association between total hip replacement (THR) or total knee replacement (TKR) and acute myocardial infarction (AMI). Not surprisingly, during the first 2 postoperative weeks, the risk of AMI was elevated in both populations of patients undergoing THR or TKR. The risk was elevated for 6 weeks in patients undergoing THR but only for 2 weeks in those undergoing TKR. It has been previously established that patients undergoing surgical procedures have an increased risk of MI.[1] The risk factors for perioperative cardiac morbidity and mortality have been established for many years, and although different studies[2,3] find slightly different risk factors, there is remarkable consistency over time: age older than 60 years, coronary artery disease, peripheral vascular disease, congestive heart failure, recent MI, and the standard risk factors for coronary artery disease, including diabetes mellitus, hypertension, smoking, and hyperlipidemia. Occasionally, an investigator will suggest that one risk factor or another is no longer important, such as MI in the last 30 days, but subsequent studies will identify once again that recent MI, MI in the last 6 months, or MI in the last year remains a risk factor for subsequent MI. Epidemiologic studies are limited by the population of patients in the database. If no one performs elective surgery on a patient within 30 days of an AMI, then that variable will not be significant in epidemiologic analysis. Recent MI is still a risk factor for cardiac morbidity; it simply is not a significant risk factor identified in the study because there are no patients with that risk profile in the database. Failure to demonstrate that a risk factor is significant does not imply the risk factor is not still a clinical issue; it simply implies one could not demonstrate the effect with the database. Infrequently, a new perioperative risk factor is identified, such as erectile dysfunction.[4] It is highly likely that these "new" risk factors are caused by peripheral vascular disease, which is highly associated with coronary artery disease rather than being a new independent perioperative risk factor.

The perioperative period is stressful to patients. A total of 5% to 15% of patients with cardiac risk have myocardial ischemia in the 24 hours before surgery.[2,5-7] Thinking about surgery increases cardiac risk. A total of 20% to 40% of patients at risk have an episode of myocardial ischemia in the first perioperative week. Perioperative myocardial ischemia is associated with an increased risk of short- and long-term cardiac morbidity and mortality.[2,5-8] In the present study, Lalmohamed et al[1] confirmed that major surgery is a risk for AMI and the risk factors of age of 60 years or older, age of 80 years or older, male sex, previous AMI, heart failure, and cerebrovascular disease increased that risk. The age when preoperative risk begins to increase is remarkably stable at approximately 60 years of age.[2,5-8] The risk of prior MI decreased with time since the MI. There were a number of medications that also appeared to increase risk, including nonsteroidal anti-inflammatory drugs, β-blockers, potassium-sparing diuretics, organic nitrates, and antiplatelet drugs. Each of these medications is likely a surrogate marker for either older age or the presence of coronary artery disease rather than a causal risk factor. It is not surprising that patients taking β-blockers, for instance, have a higher risk of MI.[9] Because β-blockers are a primary therapy for coronary artery disease, patients taking these medications have a much higher risk of having coronary artery disease.[9] In epidemiologic studies, it is critical to realize that causality is difficult or impossible to establish and many factors are surrogate markers for increased preexisting risk rather than causal factors.

The present study once again confirms that the perioperative period increases cardiac risk. Physicians must go further than establishing risk factors; physicians must actively work to reduce perioperative risk. The appropriate use of preoperative β-blockers,[5,6] clonidine,[7] statins, and aspirin reduces perioperative cardiac risk. There is a high risk of discontinuation of therapy with antiischemic agents in the perioperative period, despite level I evidence for continuation, with significant cardiac morbidity from discontinuation.[9] Physicians must carefully review perioperative medications and ensure they are appropriately managed in this critical perioperative period of high cardiac risk. It is important for physicians caring for patients in the perioperative period to recognize the potential for cardiac morbidity and mortality and then appropriately use the armamentarium of medical therapies we now have to reduce cardiac risk, prevent perioperative MIs, and prevent cardiac deaths. In their present study, Lalmohamed et al[1] clearly reinforce the importance and significance of the cardiac risk and the need to prevent perioperative cardiac morbidity and mortality.

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ONLINE FIRST

Timing of Acute Myocardial Infarction in Patients Undergoing Total Hip or Knee Replacement

A Nationwide Cohort Study

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Background: Limited evidence suggests that the risk of acute myocardial infarction (AMI) may be increased shortly after total hip replacement (THR) and total knee replacement (TKR) surgery. However, risk of AMI in these patients has not been compared against matched controls who have not undergone surgery. The objective of this study was to evaluate the timing of AMI in patients undergoing THR or TKR surgery compared with matched controls.

Methods: Retrospective, nationwide cohort study within the Danish national registries. All patients who underwent a primary THR or TKR (n=95 227) surgery from January 1, 1998, through December 31, 2007, were selected and matched to 3 controls (no THR or TKR) by age, sex, and geographic region. All study participants were followed up for AMI, and disease- and medication history–adjusted hazard ratios (HRs) were calculated.

Results: During the first 2 postoperative weeks, the risk of AMI was substantially increased in THR patients compared with controls (adjusted HR, 25.5; 95% CI, 17.1-37.9). The risk remained elevated for 2 to 6 weeks after surgery (adjusted HR, 5.05; 95% CI, 3.58-7.13) and then decreased to baseline levels. For TKR patients, AMI risk was also increased during the first 2 weeks (adjusted HR, 30.9; 95% CI, 11.1-85.5) but did not differ from controls after the first 2 weeks. The absolute 6-week risk of AMI was 0.51% in THR patients and 0.21% in TKR patients.

Conclusions: Risk of AMI is substantially increased in the first 2 weeks after THR (25-fold) and TKR (31-fold) surgery compared with controls. Risk assessment of AMI should be considered during the first 6 weeks after THR surgery and during the first 2 weeks after TKR surgery.

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TOTAL HIP REPLACEMENT (THR) and total knee replacement (TKR) are highly effective in patients with moderate to severe osteoarthritis.[1] These surgical procedures are frequently performed, yielding an estimated annual number of 1.8 million procedures worldwide.[2,3] Among patients undergoing THR or TKR surgery, acute myocardial infarction (AMI) has been identified as an important perioperative complication.[4,5] In the general population, AMI is a major cause of morbidity and mortality worldwide,[6] and each year more than 7 million patients are estimated to sustain an AMI.[6] In THR or TKR patients, the risk of AMI may be decreased or increased shortly after surgery. On one hand, the surgery itself may result in ischemic complications caused by marrow embolization.[7,8] On the other hand, antithrombotic agents are commonly used in these patients during hospitalization and have the potential to decrease the risk of AMI.[9] Epidemiologic studies[4,10-15] have reported 90-day AMI rates of up to 1.8%, of which most occurred within the first week.

See Invited Commentary at end of article

Timing of AMI after THR or TKR surgery has become of increasing interest.[14] Although early hospital discharge has been promoted in these patients, perioperative complications, including AMI, may argue against this practice.[16] Because no previous studies included a large control cohort for reference, it is thus difficult to interpret the magnitude of increased AMI risk after THR or TKR surgery compared with the general population. Differences in baseline characteristics among the studies further add to this difficulty. More important, previous studies have only focused

on short-term AMI risk (ie, <90 days) and did not investigate long-term risk for AMI.

Furthermore, data are limited on individual risk factors for AMI after THR or TKR surgery. This drawback is of particular importance given the number of comorbidities often present in these elderly patients. Previous studies[4,10-15] were limited by several design issues, such as small sample sizes and lack of matched control cohorts who did not undergo THR or TKR surgery. Moreover, none of these studies provided analyses adjusted for medication. For example, use of pain relievers (in particular, nonsteroidal anti-inflammatory drugs [NSAIDs]) is common among THR and TKR patients and might increase the risk of AMI.[17,18] The objectives of this study were to evaluate the timing of AMI after THR and TKR surgery, to evaluate potential effect modifiers of this relationship, and to identify determinants of AMI in THR and TKR patients.

METHODS

DATA SOURCES

Using Danish national registries, we conducted a nationwide retrospective cohort study. The total population from which the study participants were drawn was 5.5 million. Detailed information was available for all Danish residents, including data on second-line visits (hospitals, outpatient clinics, and emergency departments; from 1977 onward), drugs sold at retail pharmacies (from 1996 onward), citizen status (vital status, date of death, residence, migration, and socioeconomic status; from 1968 onward), and causes of death (1 underlying cause and up to 3 additional immediate causes; from 1970 onward). In Denmark, all residents have free access to health services, including hospital services and visits to general practitioners (tax funded). Previous reports demonstrated high quality, completeness, and validity rates, and these registries have been used in numerous recent epidemiologic studies.[19]

STUDY POPULATION

All patients 18 years or older who underwent a primary THR or primary TKR from January 1, 1998, through December 31, 2007, were included in the study. Both THR and TKR were identified using hospital discharge records and were classified by the *International Classification of Diseases, 10th revision (ICD-10)*[20] (*ICD-10* code NFB for THR and *ICD-10* code NGB for TKR). Each THR and TKR patient was matched with 3 controls of the same age and sex without a history of THR and TKR. The index date was defined as the date of primary THR and TKR hospital admission for THR and TKR patients and similarly for matched controls. We excluded individuals with a prior AMI within 6 weeks before or on the index date.

Danish guidelines recommend thromboprophylaxis (mostly low-molecular-weight heparin [LMWH]; started 12 hours before surgery or 12-24 hours after surgery) for all THR and TKR patients while in the hospital, which can be extended up to 35 days.[21] Previous Danish data revealed that 99.1% of THR and TKR patients had indeed received thromboprophylactic agents (of which 93% included LMWHs).[22]

OUTCOME ASSESSMENT

All patients were followed up from the index date until death, migration, THR or TKR revision, or the end of the study period (December 31, 2007) or AMI, whichever came first. Acute myocardial infarction was assessed using the National Hospital Discharge Registry and the Danish Causes of Death Registry (both classified using *ICD-10* code I21). Acute myocardial infarction was divided into fatal and nonfatal events based on death certificates.

POTENTIAL RISK FACTORS

We reviewed the literature to define potential (general) risk factors and confounders for this study.[23,24] These factors included age, sex, socioeconomic status, indication for surgery, a history of AMI (stratified by time between most recent AMI and THR or TKR surgery), history of other ischemic heart disease, heart failure, and cerebrovascular disease. Furthermore, a drug dispensing for β-blockers, renin-angiotensin-aldosterone system inhibitors, thiazide diuretics, calcium channel blockers, organic nitrates, statins, nonselective NSAIDs (including high-dose aspirin), cyclooxygenase 2 selective inhibitors, antiplatelet drugs, vitamin K antagonists, estrogen-containing drugs, antidiabetic drugs, and inhaled β_2-agonists within 6 months were considered as potential confounders for AMI.

STATISTICAL ANALYSIS

Using the PHREG procedure from SAS statistical software, version 9.2 (SAS Institute, Inc), we calculated hazard ratios (HRs) for the risk of AMI with THR and TKR and compared them with age- and sex-matched controls (stratified on matched pairs). Total follow-up time was divided into 6-week periods and the first 6 weeks into 1-week periods. Information on potential confounders and risk factors was collected during follow-up; before the start of each period, we evaluated the presence of these covariates. Potential confounders were included in the final model if they independently changed the β-coefficient for THR or TKR by at least 5%.

To assess the timing of AMI after THR and TKR surgery, we included period interaction terms (period × surgery) in the model for the following periods: less than 2 weeks, 2 to 6 weeks, 6 to 12 weeks, 3 to 6 months, 6 to 12 months, and 1 year or more after surgery. For each period, AMI risk was plotted against the median time since THR or TKR surgery and visualized using smoothing spline regression,[25-28] which has been advocated as an alternative to categorical analysis.[29] In addition, we used Kaplan-Meier plots to present the cumulative incidence rates of AMI over time (divided into fatal and nonfatal events).

To compare AMI risk after THR or TKR surgery with other elective operations, we performed a sensitivity analysis. Within THR matched controls, we selected patients who underwent hernia surgery. For these controls, the index date was reset at time of elective surgery hospital admission. The THR patients whose matched controls did not undergo these elective operations were excluded, and the analyses were further adjusted for calendar year, sex, and age at surgery.

For potential effect modifiers and determinants, we evaluated 2 periods by restricting follow-up to less than 6 weeks or 6 to 52 weeks after surgery. Potential effect modifiers were screened by entering an interaction term (risk factor × surgery) into the model. To identify determinants of AMI within THR and TKR patients only, we excluded controls and used stepwise backward elimination to determine the final regression model after entering all previously mentioned risk factors ($P < .05$) into the model. This study was approved by the National Board of Health and the Danish Data Protection Agency.

Table 1. Baseline Characteristics of Patients Undergoing THR or TKR and Matched Controls

Characteristic	THR Patients		TKR Patients	
	Exposed (n = 66 524)	Unexposed (n = 200 001)	Exposed (n = 28 703)	Unexposed (n = 86 164)
Follow-up time, mean (SD), y	3.9 (2.8)	4.1 (2.7)	3.9 (2.6)	3.7 (2.6)
Male sex, %	36.9	36.9	37.6	37.6
Age, mean (SD), y	71.9 (12.5)	71.9 (12.5)	67.2 (10.8)	67.2 (10.8)
THR or TKR hospital stay, mean (SD), d	10.8 (9.4)		9.3 (6.3)	
Disease history (ever before), %				
Ischemic heart disease	12.5	10.5	11.8	9.4
Congestive heart failure	7.9	6.5	5.0	4.5
Drug use (within previous 6 mo), %				
NSAIDs	50.7	16.4	60.9	16.6
RAAS inhibitors	19.1	16.6	24.8	16.7
β-Blockers	13.2	12.1	14.9	11.9
Antiplatelet drugs	22.3	20.9	19.5	17.1
Vitamin K antagonists	3.3	3.0	3.1	2.8
Thiazide diuretics	17.9	14.2	20.4	12.6
Calcium channel blockers	14.4	12.6	16.0	11.4
Antidiabetic drugs	5.6	5.5	7.1	5.4
Statins	8.7	8.7	13.1	11.0

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone; THR, total hip replacement; TKR, total knee replacement.

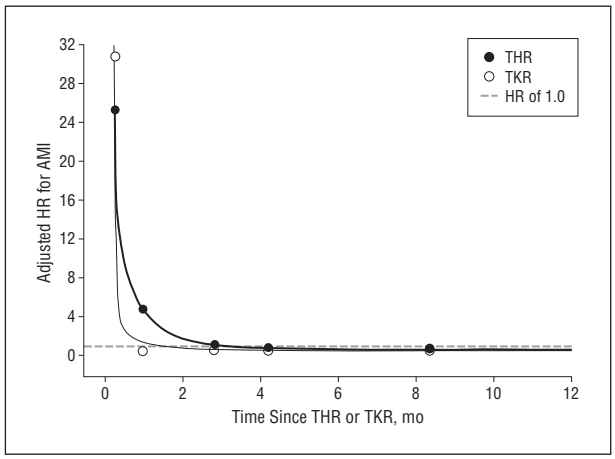

Figure 1. Adjusted hazard ratios (HRs) for acute myocardial infarction (AMI). THR indicates total hip replacement; TKR, total knee replacement.

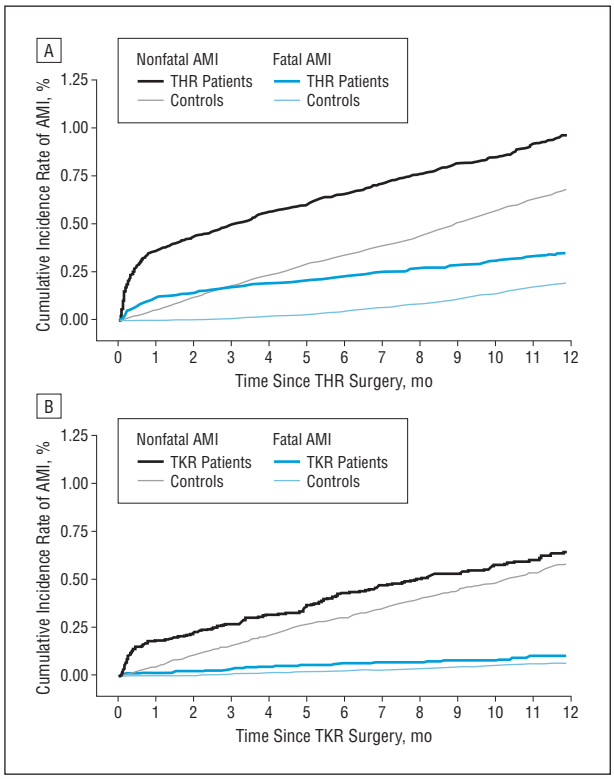

Figure 2. Cumulative incidence rates of acute myocardial infarction (AMI). A, Patients undergoing total hip replacement (THR); B, patients undergoing total knee replacement (TKR).

RESULTS

After exclusion of 437 patients with an AMI in the 6 weeks before or on the index date, 66 524 THR patients, 28 703 TKR patients, and 286 165 matched controls were enrolled in the study (**Table 1**). Because of matching, patients had a similar distribution of age (THR: mean age, 71.9 years; TKR: mean age, 67.2 years) and sex (THR: 36.9% male; TKR: 37.6% male) compared with matched controls. The THR and TKR patients were more likely to have used NSAIDs compared with controls and had slightly more often been diagnosed as having ischemic heart disease before surgery.

Figure 1 shows that the risk of AMI was substantially increased during the first 2 weeks after THR or TKR surgery compared with controls. Adjusted HRs were 25.5 (95% CI, 17.1-37.9) for THR and 30.9 (95% CI, 11.1-85.5) for TKR. Compared with patients who underwent hernia surgery, the 2-week AMI risk remained significantly elevated (adjusted HR, 21.9; 95% CI, 2.94-163.2). In TKR patients, the risk reached baseline levels after the first 2 weeks (2-6 weeks: adjusted HR, 0.81; 95% CI, 0.37-1.77), whereas in THR patients, the risk remained elevated during the first 6 weeks after surgery (2-6 weeks: adjusted HR, 5.05; 95% CI, 3.58-7.13). Kaplan-Meier plots revealed the same timing patterns (**Figure 2**).

Table 2. Effect Modifiers of AMI Risk After THR or TKR vs Matched Controls

Stratum	Adjusted HR (95% CI)[a]			
	Risk of AMI After THR		Risk of AMI After TKR	
	6-wk Risk	6- to 52-wk Risk	6-wk Risk	6- to 52-wk Risk
All patients	17.8 (13.5-23.4)	0.95 (0.82-1.10)	8.69 (4.73-16.0)	0.70 (0.53-0.92)
By age, y				
18-59	2.41 (0.68-8.57)	1.14 (0.56-2.30)	2.26 (0.45-11.3)	2.68 (1.27-5.67)
60-79	12.4 (8.35-18.5)	0.95 (0.78-1.17)	9.20 (4.13-20.5)	0.60 (0.42-0.84)
≥80	25.3 (17.7-36.2)	0.94 (0.76-1.15)	11.2 (4.83-25.8)	0.58 (0.34-1.01)
By sex				
Male	12.8 (8.56-19.3)	0.98 (0.79-1.23)	7.86 (3.59-17.2)	1.02 (0.70-1.46)
Female	21.7 (15.4-30.4)	0.93 (0.77-1.12)	9.50 (4.47-20.2)	0.45 (0.30-0.69)
By any previous history of disease				
No previous AMI	18.8 (13.9-25.5)	1.00 (0.85-1.17)	8.63 (4.44-16.7)	0.68 (0.50-0.92)
Previous AMI	12.5 (5.54-28.4)	0.72 (0.48-1.09)	9.03 (1.89-43.1)	0.84 (0.37-1.88)
No heart failure	14.9 (10.9-20.4)	1.03 (0.87-1.21)	6.51 (3.28-12.9)	0.85 (0.63-1.15)
Heart failure	37.2 (17.8-78.0)	0.64 (0.45-0.93)	29.9 (6.25-143.5)	0.23 (0.11-0.48)
No cerebrovascular disease	15.7 (11.6-21.2)	1.04 (0.89-1.21)	9.73 (4.96-19.1)	0.82 (0.62-1.10)
Cerebrovascular disease	30.3 (12.8-71.6)	0.49 (0.30-0.79)	2.35 (0.45-12.2)	0.12 (0.04-0.36)
By outpatient use of antithrombotic drugs in previous 6 mo[b]				
None	13.8 (9.49-20.1)	1.13 (0.94-1.36)		0.81 (0.58-1.15)
Vitamin K antagonists only	25.3 (4.41-145.5)	1.36 (0.58-3.18)		1.31 (0.33-5.15)
Antiplatelet drugs only	24.9 (15.4-40.3)	0.67 (0.51-0.88)		0.51 (0.31-0.87)
Combined use or other	-	1.00 (0.31-3.16)		0.16 (0.01-2.48)

Abbreviations: AMI, acute myocardial infarction; HR, hazard ratio; THR, total hip replacement; TKR, total knee replacement.
[a] Adjusted for any previous ischemic heart disease and use of antithrombotic drugs, loop diuretics, nonselective nonsteroidal anti-inflammatory disease, or selective serotonin reuptake inhibitors within the previous 6 months.
[b] For TKR patients, number of observations was too low to calculate 6-week HRs for antithrombotic drug use strata.

Absolute 6-week rates of AMI were 0.51% for THR patients and 0.21% for TKR patients.

For both THR and TKR, we found a strong effect modification by age (**Table 2**). During the first 6 weeks, the effect of THR on AMI risk was highest in the oldest patients (≥80 years old; adjusted HR, 25.3; 95% CI, 17.7-36.2), whereas we could not detect a significantly increased risk in patients younger than 60 years (adjusted HR, 2.41; 95% CI, 0.68-8.57). We found a similar, albeit less substantial, age trend with TKR surgery. No other significant effect modifiers for the relationship between THR or TKR and AMI during the first 6 postoperative weeks were identified.

In the THR patients, the 6-week risk of AMI was higher among older patients; men; patients with a previous AMI, heart failure, or cerebrovascular disease; and users of NSAIDs, β-blockers, potassium-sparing diuretics, organic nitrates, and antiplatelet drugs during follow-up compared with THR patients without these characteristics (**Table 3**). The elevated risk caused by a previous AMI before THR or TKR surgery diminished with an increasing time since most recent AMI before surgery (Table 3).

COMMENT

This study demonstrated an increased risk of AMI during the first 2 weeks after THR (25-fold) and TKR (31-fold) surgery compared with matched controls. The risk of AMI sharply decreased after this period, although it remained significantly elevated in the first 6 weeks for THR patients. The association was strongest in patients 80 years or older, whereas we could not detect a significantly increased risk in patients younger than 60 years. Furthermore, a previous AMI in the 6 months before surgery increased the risk of new AMI during the first 6 weeks after THR and TKR (4-fold increase) surgery but did not modify the relationship between THR or TKR and AMI.

To our knowledge, this is the first study comparing AMI risk after THR or TKR surgery with the risk of matched controls not undergoing surgery. Previous studies were limited to reports on (primarily perioperative) incidence rates only and showed somewhat conflicting results. For example, Khatod et al[11] demonstrated a 0.1% incidence rate of AMI within 90 days after TKR surgery, whereas Gandhi et al[14] found a 1.8% incidence rate in the first 18 days after THR or TKR surgery. This discrepancy may partially be explained by differences in diagnosing AMI because the latter study used serum troponin levels in addition to electrocardiogram changes for diagnosis. Most other studies[4,12,13,15] found an AMI incidence rate of 0.3% to 0.8%, which is well in line with our findings. Because most of these studies included perioperative events only (typically <20 days), our incidence rates tended to be more toward 0.8% rather than the lower end. Alternatively, the discrepancy may be explained by differences in baseline characteristics among the studies, including comorbid cardiovascular disease and characteristics of the orthopedic center performing the surgical procedure. An American study[30] thus showed that high-volume hospitals had a lower 30-day mortality rate after major orthopedic surgery, although no adjustments were made for comorbidities or surgical complexity.

Evidence on timing of AMI after THR and TKR surgery is scarce. Previous studies have only found an el-

Table 3. Determinants of AMI Risk in Patients Undergoing THR or TKR

	Adjusted HR (95% CI)[a]			
	Risk of AMI in THR Patients Only		Risk of AMI in TKR Patients Only	
Determinant	6-wk Risk	6- to 52-wk Risk	6-wk Risk	6- to 52-wk Risk
By age (reference: 18-59 y), y				
60-79	5.46 (2.22-13.39)	3.26 (1.85-5.76)	2.55 (0.77-8.42)	1.27 (0.73-2.22)
≥80	11.08 (4.48-27.41)	5.04 (2.80-9.07)	8.20 (2.38-28.22)	2.35 (1.21-4.57)
Female sex (reference: male sex)	0.70 (0.55-0.88)	0.70 (0.56-0.88)	0.57 (0.33-0.98)	0.28 (0.18-0.44)
By any previous history of diseases, unless stated otherwise (reference: no history)				
Previous AMI[b]	2.12 (1.59-2.83)	2.72 (2.02-3.66)	1.15 (0.55-2.42)	2.79 (1.60-4.86)
1½-6 mo before	4.25 (2.24-8.05)	5.23 (2.51-10.87)	4.14 (0.91-18.87)	2.55 (0.34-19.16)
6-12 mo before	3.82 (1.90-7.67)	3.32 (1.34-8.24)	2.18 (0.28-16.79)	
>12 mo before	1.91 (1.40-2.59)	2.56 (1.88-3.49)	0.96 (0.43-2.17)	2.92 (1.66-5.11)
Heart failure	2.47 (1.90-3.20)	2.76 (2.11-3.61)	3.75 (2.01-6.98)	2.34 (1.37-4.02)
Cerebrovascular disease	2.06 (1.57-2.70)	1.26 (0.92-1.74)	2.09 (1.05-4.15)	0.82 (0.35-1.91)
By use of drugs in previous 6 mo (reference: no use in previous 6 mo)				
NSAIDs[c]	1.80 (1.31-2.47)	3.37 (2.43-4.67)	1.64 (0.78-3.42)	2.39 (1.31-4.37)
By cumulative previous DDD exposure				
<30 DDDs	1.33 (0.66-2.71)	3.33 (1.81-6.13)	2.61 (1.09-6.24)	2.06 (0.83-5.16)
30-180 DDDs	2.22 (1.45-3.41)	3.20 (1.97-5.19)		
>180 DDDs	1.63 (0.99-2.68)	3.62 (2.17-6.05)	1.29 (0.39-4.20)	3.91 (1.86-8.22)
β-Blockers	1.45 (1.11-1.88)	1.00 (0.75-1.32)	1.49 (0.82-2.67)	1.53 (0.96-2.44)
Potassium-sparing diuretics	1.61 (1.10-2.36)	1.49 (1.01-2.22)	0.60 (0.14-2.55)	0.81 (0.29-2.30)
Organic nitrates	2.68 (2.02-3.55)	1.64 (1.19-2.27)	1.45 (0.68-3.10)	2.60 (1.45-4.64)
By outpatient use of anticoagulant drugs in previous 6 mo (reference: no use in previous 6 mo)				
Vitamin K antagonists only	0.83 (0.46-1.49)	0.83 (0.49-1.40)	1.86 (0.65-5.36)	1.03 (0.43-2.49)
Platelet inhibitors only	1.33 (1.03-1.73)	0.92 (0.71-1.19)	2.30 (1.21-4.37)	1.11 (0.67-1.83)
Combined use or other	0.23 (0.06-0.94)	0.90 (0.45-1.81)		0.33 (0.04-2.42)

Abbreviations: AMI, acute myocardial infarction; DDD, daily defined dosage; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug; THR, total hip replacement; TKR, total knee replacement.

[a] The following covariates were retained in the final model after stepwise backward elimination: age, sex, previous AMI, a history of heart failure, cerebrovascular disease ever before, use of NSAIDs in the previous 3 months, and use of β-blockers, potassium-sparing diuretics, organic nitrates, and antithrombotic agents in the previous 6 months.

[b] For TKR patients (6- to 52-week risk), previous AMI recency categories were merged (too few observations): previous 1½ to 12 months and longer than the previous 12 months.

[c] At least 1 prescription in the previous 3 months (reference: no use in the previous 3 months). For TKR patients, the cumulative DDD categories of less than 30 DDDs and 30 to 180 DDDs were merged (too few observations).

evated risk during the first 4 to 5 postoperative days. Gandhi et al[14] found that within 5 days after THR or TKR surgery, 91% of all in-hospital AMI events had occurred. Similarly, Parvizi et al[13] found that perioperative AMIs were most likely to occur within 4 days after THR or TKR surgery. Our findings confirm this increased risk of AMI and suggest that the risk is actually increased for an even longer period (THR: first 6 weeks; TKR: first 2 weeks).

The biological mechanism explaining the increased risk of AMI may be related to marrow embolization because surgical invasion of the medullary canal of the femur potentially causes marrow embolization and cardiac stress.[14] This embolization process occurs primarily with THR and to a lesser extent with TKR.[7,8] This fact may explain the differences in AMI risk between THR and TKR observed in our study. Among THR patients, the increase in AMI risk lasted for a longer period compared with TKR patients. Furthermore, hemodynamic stressors associated with the surgery (eg, effects of anesthesia on the cardiovascular system, blood loss, fluid shifts, arrhythmias, and hypoxia) can further contribute to the observed increased risk of AMI after THR and TKR surgery.

It is unlikely that the use of inpatient antithrombotic agents will explain the observed elevated risk of AMI after THR and TKR surgery. Most Danish THR and TKR patients are treated with LMWHs,[22] which have been shown to lower the risk of death and myocardial infarction during the first 6 days of therapy in patients with unstable coronary artery disease.[9] This finding would imply that we may have underestimated the risk of AMI and that the actual association between THR or TKR and risk of AMI would be even stronger. There is conflicting evidence about the association between dabigatran etexilate and an increased risk of AMI.[31] However, dabigatran was not available during the entire study period and should therefore not have influenced our results. As a further note, patients taking (outpatient) antithrombotic agents may represent a higher-risk population (eg, use of low-dose aspirin to prevent secondary events). This may have cancelled our effect modification and is most likely the reason why antiplatelet drugs were identified as a significant determinant of AMI during the first 6 weeks after THR and TKR surgery.

Our study implies that a recent AMI (within 1 year) should be a contraindication for those undergoing elective THR surgery. Previous literature confirmed AMI as

a risk factor for a new AMI in these patients.[14] However, no other study has evaluated the time since most recent AMI, but this is important when planning the performance of THR. We were able to show a sharp decrease in risk of a new AMI when the previous AMI had occurred more than 1 year before surgery. However, even beyond this period, the risk remained elevated compared with those without a previous AMI. These findings are indirectly supported by a Swedish retrospective cohort study[32] in patients with ST-elevation myocardial infarction. The authors of that study reported that the risk of reinfarction was highest within the first year of AMI.

Strengths of this study include the nationwide population-based design, the large sample size, information on matched controls, and completeness of follow-up. Unlike most other studies, we had access to outpatient prescription data (such as NSAIDs) and information from outpatient clinics. Because we had highly valid data on mortality, we were able to identify out-of-hospital fatal AMI events. The major drawback is the lack of information on other risk factors for AMI, such as smoking, blood pressure, biochemical variables, and body mass index. A higher body mass index is associated with an increased risk of coronary artery disease[33] and osteoarthritis, the main indication for THR and TKR. However, in a previous study[34] on patients undergoing THR, body mass index at the time of surgery was not associated with short- or long-term mortality. Furthermore, we did not have information on inpatient anticoagulant use. Because warfarin and LMWHs have been shown to reduce AMI incidence, this could have distorted our study findings.[9,35] As explained, this would mean an underestimation of our observed increased AMI risk. We cannot exclude the possibility that hospitalized patients may have been more likely to be diagnosed as having an AMI. However, we did not look at silent myocardial infarctions (which are more likely to be recorded as silent ischemic events rather than AMIs). Moreover, we also found an increased risk of fatal AMIs, for which the detection rate should be equal. Finally, we did not have information about general anesthesia, which may well be the cause of the increased risk of AMI after THR and TKR surgery. However, a previous study[36] that evaluated the influence of general anesthesia in surgical patients vs those who received regional anesthesia showed a trend toward only a 1.4-fold increased risk of AMI. This is well below the excess risk we observed in our study, suggesting that the increased risk in THR/TKR patients might not be fully explained by general anesthesia only. Furthermore, our sensitivity analysis demonstrated that the increased risk of AMI after THR surgery remained elevated when compared with other elective operations.

To our knowledge, this is the first study that found that THR (25-fold) and TKR patients (31-fold) are at increased risk of AMI during the first 2 weeks after surgery. The elevated risk was sustained for 6 weeks after THR and for 2 weeks after TKR. The effect of surgery on AMI risk was strongest in patients 80 years or older. The relationship was not more pronounced in those with well-known risk factors of AMI (such as heart failure, cerebrovascular disease, and previous AMI), although they increased the risk of AMI within THR and TKR patients. Finally, our data suggest that elective THR surgery should be contraindicated in patients with a previous AMI in the last 12 months before surgery.

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INVITED COMMENTARY

ONLINE FIRST

Risk of Acute Myocardial Infarction in Patients With Total Hip or Knee Replacement

Lalmohamed et al[1] used epidemiologic analysis to test the association between total hip replacement (THR) or total knee replacement (TKR) and acute myocardial infarction (AMI). Not surprisingly, during the first 2 postoperative weeks, the risk of AMI was elevated in both populations of patients undergoing THR or TKR. The risk was elevated for 6 weeks in patients undergoing THR but only for 2 weeks in those undergoing TKR. It has been previously established that patients undergoing surgical procedures have an increased risk of MI.[1] The risk factors for perioperative cardiac morbidity and mortality have been established for many years, and although different studies[2,3] find slightly different risk factors, there is remarkable consistency over time: age older than 60 years, coronary artery disease, peripheral vascular disease, congestive heart failure, recent MI, and the standard risk factors for coronary artery disease, including diabetes mellitus, hypertension, smoking, and hyperlipidemia. Occasionally, an investigator will suggest that one risk factor or another is no longer important, such as MI in the last 30 days, but subsequent studies will identify once again that recent MI, MI in the last 6 months, or MI in the last year remains a risk factor for subsequent MI. Epidemiologic studies are limited by the population of patients in the database. If no one performs elective surgery on a patient within 30 days of an AMI, then that variable will not be significant in epidemiologic analysis. Recent MI is still a risk factor for cardiac morbidity; it simply is not a significant risk factor identified in the study because there are no patients with that risk profile in the database. Failure to demonstrate that a risk factor is significant does not imply the risk factor is not still a clinical issue; it simply implies one could not demonstrate the effect with the database. Infrequently, a new perioperative risk factor is identified, such as erectile dysfunction.[4] It is highly likely that these "new" risk factors are caused by peripheral vascular disease, which is highly associated with coronary artery disease rather than being a new independent perioperative risk factor.