Original research

Risk of myocardial infarction after invasive outpatient procedures

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ABSTRACT

Objective To assess the short-term risk of acute myocardial infarction (AMI) associated with procedures performed at outpatient specialised hospital clinics.

Methods In this case-crossover, population-based study, we identified first-time AMI cases aged ≥40 years via patient registries and linked them to their surgical intervention in Norway (2008–2016) and Sweden (2001–2014), respectively. The number of individuals with AMI who underwent procedures 0–7 days (hazard period) prior to the AMI diagnosis was compared with cases who were exposed 29–36 days (control period) before the AMI. A total of 6176 patients with AMI who underwent a procedure either during the defined hazard or control period contributed to the analyses. ORs with 95% CIs were computed using conditional logistic regression.

Results The mean age of the total population was 74.7 years and 64.6% were male. The relative risk was higher following procedures performed under general/regional anaesthesia for gastrointestinal endoscopy (OR$_{summary}$, 4.23, 95% CI 1.58 to 11.31), vascular (OR$_{summary}$, 3.12, 95% CI 1.10 to 8.90), urological/gynaecological (OR$_{summary}$, 2.30, 95% CI 1.50 to 3.53) and orthopaedic (OR$_{summary}$,1.78, 95% CI 1.30 to 2.44) procedures, and for ENT (ear, nose and throat) and mouth procedures (OR$_{summary}$, 1.53, 95% CI 1.19 to 1.99) performed under local anaesthesia.

Conclusion This large population-based register study from two countries suggests that outpatient procedures are generally safe with regard to the postoperative risk of AMI. However, some procedures, such as gastrointestinal endoscopy, vascular procedures and urological/gynaecological procedures may increase the risk of AMI by twofold or threefold within the first 8 days after the procedures. Further studies are warranted to assess whether the effect is modified by cardiovascular medication or other clinical factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous observational studies have reported temporal associations between some non-cardiac procedures and risk of acute myocardial infarction (AMI).
⇒ Studies were not based on study designs specifically developed to study the short-term effect of transient exposures.
⇒ It is not known whether and to what extent invasive outpatient procedures can trigger AMI and whether the risk differs by anaesthesia type.

WHAT THIS STUDY ADDS

⇒ There was no evidence for a substantial excess risk regarding AMI.
⇒ The short-term risk was apparently higher after surgical procedures performed under general/regional anaesthesia, with increased risk particularly for gastrointestinal endoscopy, vascular, urological/gynaecological and orthopaedic procedures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This knowledge is imperative for proper clinician–patient communication before undergoing surgical procedures.
⇒ It is important that clinicians, while performing particularly highly invasive and risk-prone procedures, consider every possible preventive strategy to decrease excess risk by following preoperative health assessment or risk stratification before planning a procedure.

INTRODUCTION

Acute myocardial infarction (AMI) is the most common cause of death in the world.[1 2] A common underlying pathophysiology is rupture of an atherosclerotic plaque with superimposed thrombosis which obstructs coronary blood flow.[2] Evidence suggests that outbursts of anger, acute stress, acute infections, circadian disruptions and sexual activity might trigger the onset of AMI in a vulnerable person.[3 4] Invasive procedures encompass a considerable amount of stress for a patient, which may cause inflammation and result in plaque rupture

and increased platelet aggregability, leading to AMI.[5–7] The induction time for this process could range from several hours to a few days.

Previous epidemiological studies have reported temporal associations between some non-cardiac procedures and AMI.[8–10] However, these studies were not based on study designs specifically developed to study the short-term effect of transient exposures. Recently, we published a study suggesting no increased risk for AMI following ophthalmological procedures based on a case-crossover design.[11] However, the short-term risk associated with other types of procedures performed in the outpatient setting has not been investigated. Such knowledge on invasive procedures would be imperative for
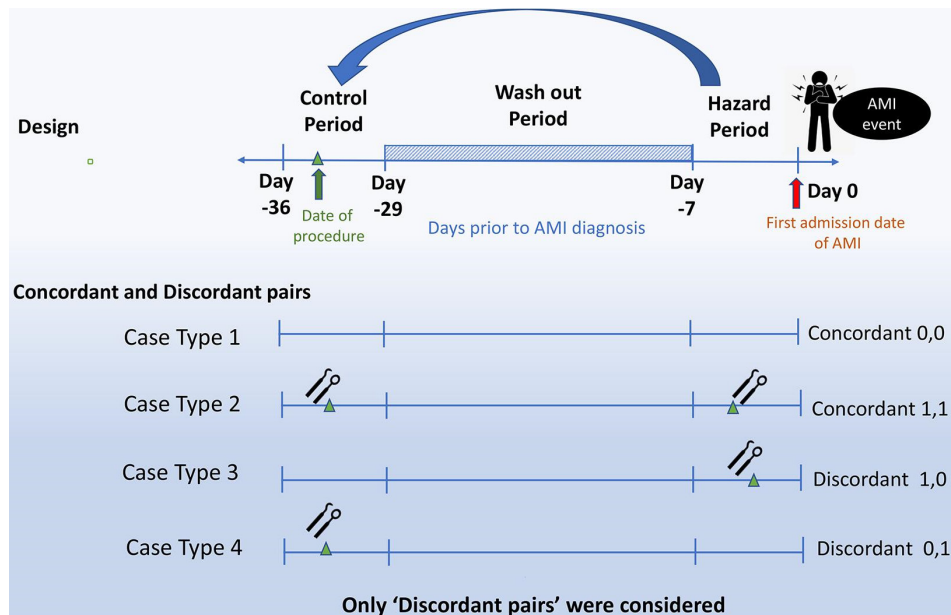
Figure 1 Schematic representation of the case-crossover study design. The 0–7 days window was defined as the hazard period and the 29–36 days window as the control period prior to the diagnosis date of AMI. Only discordant cases were included for analyses. AMI, acute myocardial infarction.

proper presurgical doctor–patient communication and risk–benefit considerations before planning invasive procedures. Therefore, the aim of the present study was to determine whether outpatient invasive procedures trigger the onset of AMI and whether the risk differs by anaesthesia type.

METHODS

This study is part of a larger project investigating the association between outpatient procedures and the short-term risk for cardiovascular events using Norwegian and Swedish data.[11 12]

Study design and setting

A case-crossover design was applied.[13 14] This study design is appropriate to assess the transient effects of intermittent exposures on the onset of AMI.[15] This design is somewhat analogous to conventional matched case–control study design. Only individuals with first-time AMI were included. The likelihood of being exposed to the procedures of interest during the hazard period was compared with the likelihood of being exposed to the procedures during the control period for the same subjects. Hence, each subject served as his/her own control and therefore by design we controlled for stable patient characteristics such as age, genetics, comorbidities and lifestyle factors. Based on the assumed induction time,[14] 0–7 days was defined as the hazard period before the onset of AMI and 29–36 days as the control period before AMI (see figure 1). If procedures do not increase the risk of an AMI within the first 8 days after the procedure, we would expect individuals to be just as likely to have had a procedure during the control period as they would during the hazard period.

Study population

We used the Norwegian Patient Register and the Swedish National Patient Register[16] to identify all AMI cases, and cause of death registers for cases that were not admitted to hospital before death. AMI diagnoses in the registers from both countries have high sensitivity and high specificity.[17 18] All patients over 40 years with a primary diagnosis of International Classification of Diseases-10 codes I21 or I22 occurring between 1 March 2008 and 31 December 2016 in Norway and between 1 March 2001 and 31 December 2014 in Sweden were included. The individual's first recorded diagnosis of AMI from the respective register during the study period was included in the analyses. The date of admission to the hospital was considered and used as the time of onset of AMI. Figure 2 illustrates the flow chart of the selection of the study population.

Procedures

All medical and surgical procedures performed at outpatient clinics are registered in the Norwegian Patient Register and the Swedish National Patient Register. The dates of outpatient procedure registration were available from 1 January 2008 and 1 January 2001 in Norway and Sweden, respectively. The surgical procedures conducted in both countries were coded according to the Nordic Medico-Statistical Committee (NOMESCO) classification of surgical procedures.[16] For some procedures, the coding system of the Swedish National Board of Health and Welfare was used.[19] Procedures conducted due to prodromal conditions of AMI or being related to treatment of AMI were excluded to minimise confounding by indication or reverse causation. Also, some procedures such as partial resection of small intestine, loop enterostomy and terminal enterostomy, which cannot be performed in outpatient settings, were excluded. The list of excluded procedures is presented in online supplemental table S2. The transient effect of ophthalmological-related procedures triggering AMI has been published elsewhere[11] and thus not included here. The number with the corresponding proportion of procedures performed within the defined period is presented in online supplemental table S5.

Anaesthesia

Since anaesthesia types were not available at the individual level, our experts assigned each procedure as 'general', 'regional' or 'local' anaesthesia on what is believed to be standard of care for that procedure. For analyses, we categorised the procedures by 'regional/general' or 'local' anaesthesia. We grouped regional
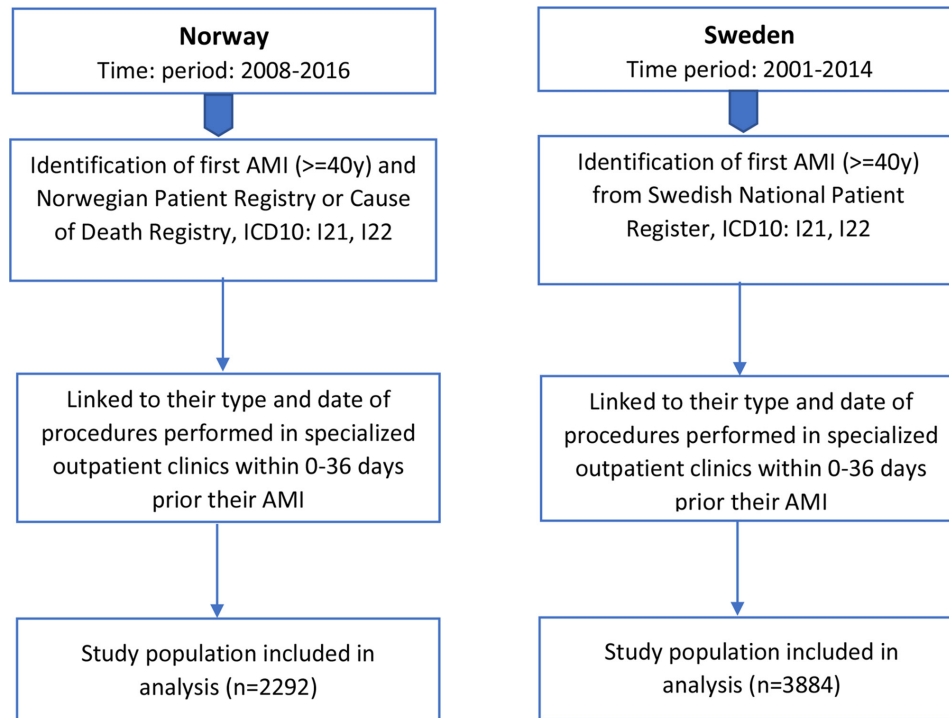
Figure 2 Flow chart of the selection of the study population for analyses. AMI, acute myocardial infarction; ICD-10, International Classification of Diseases-10.

with general anaesthesia together because procedures performed under regional anaesthesia were not many. All procedures included in the analysis are presented in online supplemental table S1.

Statistical analysis
For each individual, the status of exposure to any procedure was assessed using a hazard period (0–7 days before the onset of the first AMI) and compared with the control period (29–36 days before AMI) of the same duration. Only discordant cases (ie, those exposed either during the hazard period or the control period) were included in the analyses as concordant cases (i.e, who were exposed during both or neither of the hazard nor the control period) do not provide information. This is similar to matched-pair, case–control studies, where only discordant pairs, that is, pairs having a different value for the exposure, contribute to the statistical analysis.[20] The odds ratios (ORs) with their corresponding 95% CIs were computed using conditional logistic regression models. Separate analyses for Norway and Sweden were conducted and the results for both country-specific and summary estimates of procedure types according to anaesthesia types were presented. The summary estimates were computed using a fixed-effect model.[21] In some instances, data on exposed cases and the estimated effects were only from one of the countries. To assess how long the increased risk persisted after the procedures, secondary analyses were conducted using different hazard periods of 8–14 days, 22–28 days with the corresponding control period defined as 37–43 days, and 51–57 days prior to date of AMI diagnosis, respectively.

In sensitivity analyses, the transient effect of outpatient procedures on AMI onset was assessed among individuals who had undergone (1) percutaneous transluminal coronary angioplasty with insertion of stent during the last 12 months prior to AMI occurrence or (2) primary percutaneous coronary intervention (PCI) as a treatment within 90 days after the diagnosis of AMI.

Also, sensitivity analyses were conducted using a hazard period of 0–6 days with a corresponding control period of 28–34 days prior to the date of AMI diagnosis to ensure that the same week-days were compared between the two periods. Furthermore, we also excluded cases where either the hazard or the control period happened between 24 December and 2 January as outpatient procedures can be less common during and between Christmas and New Year.

Statistical analyses in Norway were performed using STATA/IC V.16.1, while analyses in Sweden were performed using SAS V.9.3 for Windows.

Patient or public involvement
No patients or the public were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design or implementation of the study. No patients were asked to advise on the interpretation or writing up the results. There are plans to disseminate the results of the research to the relevant patient community.

RESULTS
In total, 6176 patients with AMI were identified, 3884 from Sweden and 2292 from Norway. Table 1 presents the characteristics of all first-time cases of AMI included in the analyses. In total, majority were older-adults, were more men than women, and more often had a history of hospitalisation due to malignant cancer (15%) and ischaemic heart diseases (11.5%). The highest proportion of outpatient procedures performed within the specified period (ie, within 0–36 days prior to AMI) was dermatological procedures (31.4%), followed by urological/gynaecological (23.6%), gastrointestinal endoscopy (15.8%) and ENT (ear, nose and throat) and mouth procedures (10.3%).

Table 1 Baseline characteristics of the study samples

	Sweden*	Norway*	Total
Individuals with first-time AMI†	3884	2292	6176
Preoperative factors			
Male, n (%)	2459 (63.3)	1530 (66.8)	3989 (64.6)
Age, mean±SD	74.2±11.4	74.7±11.94	74.7±11.67
Age groups (years), n (%)			
40–49	109 (2.8)	63 (2.8)	172 (2.8)
50–59	338 (8.7)	210 (9.2)	548 (8.9)
60–69	800 (20.6)	474 (20.7)	1274 (20.6)
70–79	1186 (30.0)	610 (26.6)	1796 (29.1)
80–89	1198 (30.6)	735 (32.1)	1933 (31.3)
>90	254 (6.5)	200 (8.7)	454 (7.4)
Comorbidities (ICD-10 codes), history‡, n (%)			
Chronic rheumatic heart diseases, I05–I09	8 (0.2)	2 (0.1)	10 (0.2)
Ischaemic heart diseases, I20, I23, I24 and I25	512 (13.2)	196 (8.6)	708 (11.5)
Heart failure, I50	349 (8.9)	127 (5.5)	476 (7.7)
Pulmonary heart diseases and diseases of pulmonary circulation, I26–I28	384 (9.9)	16 (0.7)	400 (6.5)
Cerebrovascular diseases, I60–I69	212 (5.4)	74 (3.2)	286 (4.6)
Diseases of arteries, arterioles and capillaries, I70–I79	181 (4.6)	184 (8)	365 (5.9)
Chronic obstructive pulmonary disease (COPD), J44	177 (4.5)	62 (2.7)	239 (3.9)
Diabetes mellitus, E08–E13	485 (12.4)	128 (5.6)	613 (9.9)
Malignant cancer, C00–C96	498 (12.8)	427 (18.6)	925 (15)
Acute kidney failure and chronic kidney disease, N17–N19	206 (5.3)	88 (3.8)	294 (4.8)
Procedures§, n (%)	n=4669	n=3379	n=8048
ENT/mouth	572 (12.3)	256 (7.6)	828 (10.3)
Dermatology	1190 (25.5)	1341 (39.7)	2541 (31.4)
Lung/thorax	36 (0.8)	50 (1.5)	86 (1.1)
Abdominal	66 (1.4)	20 (0.6)	86 (1.1)
Gastrointestinal endoscopy	770 (16.5)	502 (14.9)	1272 (15.8)
Urology/gynaecology	1140 (24.4)	762 (22.6)	1902 (23.6)
Vascular	195 (4.2)	54 (1.6)	249 (3.1)
Orthopaedics	591 (12.7)	261 (7.7)	852 (10.6)
Others	109 (2.3)	133 (3.9)	242 (3.0)
Mode of anaesthesia, n (%)	n=4669	n=3379	n=8048
local	3969 (85)	3007 (89)	6976 (86.7)
regional/general	700 (15)	372 (11)	1072 (33.3)

*Patients over 40 years who had undergone procedures in outpatient clinics within 36 days prior to their first-time AMI diagnosis are presented.
†In Norway, date of hospital admission with first-time AMI was from 1 March 2008 through 31 December 2016, and in Sweden it was from 1 March 2001 through 31 December 2014.
‡History of comorbidities diagnosed based on hospitalisations in the 2-year period prior to the onset of AMI.
§The number of procedures performed within 36 days prior to their first AMI diagnosis.
AMI, acute myocardial infarction; ENT, ear, nose and throat; ICD-10, International Classification of Diseases-10.

General/regional anaesthesia

Orthopaedic, gastrointestinal endoscopy, urological/gynaecological and vascular procedures were associated with short-term increased risk of AMI, with summary ORs ranging from 1.78 to 4.23. Either weak or no associations were found in relation to other procedural groups (see figure 3).

Local anaesthesia

Generally, the ORs were lower for procedures performed under local anaesthesia compared with 'general/regional' anaesthesia (see figure 3). There was an increased risk of AMI in relation to ENT and mouth procedures (OR_summary, 1.53, 95% CI 1.19 to 1.99), urological/gynaecological procedures (OR_summary, 1.44, 95% CI 1.24 to 1.66) and vascular procedures (OR_summary, 2.01, 95% CI 1.34 to 3.03).

Overall, with increasing time since the procedures, the association with AMI decreased (see online supplemental tables S3 and

S4). In the sensitivity analyses, the results were largely similar when restricting to AMIs followed by primary PCI treatment within 90 days, except for orthopaedics and urological/gynaecological procedures performed under general/regional anaesthesia, which conferred a slightly higher risk of AMI compared with the main analyses (see online supplemental table S6). Furthermore, based on Norwegian data, urological/gynaecological and vascular procedures performed under general/regional and local anaesthesia, respectively, were associated with a slightly higher risk of AMI among those who have undergone percutaneous transluminal coronary angioplasty with insertion of stent during the last 12 months prior to AMI onset (see online supplemental table S7). The results did not materially change when a hazard period of 0–6 days with a corresponding control period of 28–36 days was used and when cases who were exposed during the Christmas and New Year holidays were excluded (online supplemental table S8).
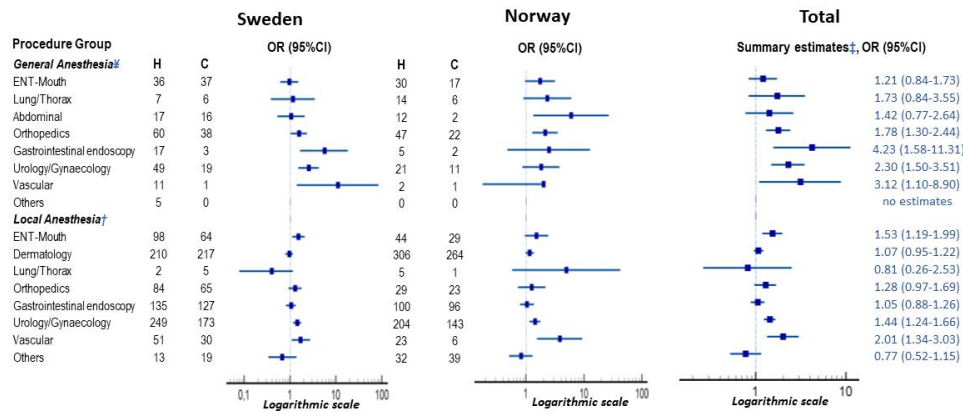
Figure 3 Forest plot of ORs for AMI in the week following procedures. A case-crossover analysis using hazard period (0–7 days) and control period (29–36 days) before the index date for the diagnosis of AMI. AMI, acute myocardial infarction; C, individuals exposed only in the control period; ENT, ear, nose and throat; H, individuals exposed only in the hazard period.‡Summary estimates of Norwegian and Swedish data calculated using inverse-variance method (fixed-effect model). ¥General anaesthesia: For ENT or mouth, lung/thorax, orthopaedics, abdominal, gastrointestinal endoscopy, urologic or gynaecological, and vascular related procedures, please see online supplemental table S1. Others procedure group include suture of peripheral nerve in unspecified region, control before and after allogeneic bone marrow transplantation, control before and after high-dose treatment with autologous stem cell. †Local anaesthesia: For ENT-mouth, lung/thorax, dermatology, orthopaedics, gastrointestinal endoscopy, urologic or gynaecological, and vascular related procedures, please see online supplemental table S1. Others procedure group include decompression and freeing of adhesions of median nerve or Ulnar nerve; laparocentes, aspiration of bone marrow for example, sternal puncture, needle biopsy of lymph node, lumbar puncture, change of gastrostomy tube, percutaneous needle biopsy of liver, aspiration or drill biopsy of bone marrow-unspecified, external traction of spine and neck, Other minor procedure in gastroenterological surgery, puncture or needle biopsy of soft tissue - unspecified region.

DISCUSSION

In this study, there was no evidence of increased risk of AMI for most of the outpatient procedures. However, for some procedures, especially for those performed under general/regional anaesthesia, there was a short-term increased risk of AMI. The highest risk was observed in relation to orthopaedic, urological/gynaecological, gastrointestinal endoscopic and vascular procedures, which were performed under general/regional anaesthesia. Further, there was evidence of increased risk of AMI in relation to some ENT-mouth, urological/gynaecological and vascular procedures performed under local anaesthesia.

To the best of our knowledge, this is the first study to investigate general outpatient procedures as triggers of AMI. Prior studies have mostly investigated the risk of AMI following non-cardiac surgery in the inpatient setting.[8–10 22] However, the findings from these earlier studies cannot be generalised to outpatient procedures as those tend to be less invasive and generally safer than inpatient procedures.

Anaesthesia, in general, is believed to be very safe and poses very low risk for elective patients, regardless of whether it is general/regional or local anaesthesia. The typical AMI (type 2) caused by anaesthesia is generally due to myocardial ischaemia related to drop in blood pressure in vulnerable patients. Probably, it is the type of surgical procedure and the patient's physical health which pose the most risk, rather than anaesthesia per se.[23] Thus, the short-term increased risk for procedures performed under general/regional anaesthesia might be due to an extensive procedure leading to significant inflammation, altering the balance between coagulation and fibrinolysis and thereby causing myocardial infarction through atherothrombosis. Another possible explanation is that the secondary preventive antiplatelet medication has been stopped before some surgeries to reduce bleeding, thereby increasing the risk of AMI.[6 7 24–26]

Furthermore, an increased risk observed in relation to procedures involving gastrointestinal endoscopy and ENT-mouth might be due to autonomic stress caused by the investigation, leading to a surge of catecholamines and cortisol and to coronary vasoconstriction and plaque instability, which in turn might trigger an AMI in vulnerable patients.

Although some procedures were associated with a high relative risk, it does not necessarily infer a high absolute risk. Absolute risk cannot be estimated using this data at hand. However, the average yearly absolute risk for an AMI was estimated and also to what extent this risk would increase due to the respective procedures. The estimated annual risk of AMI in the population aged ≥40 years was 0.73% in Sweden and 0.63% in Norway in 2008 (National Board of Health and Welfare; https://www.socialstyrelsen.se/) and in 2012 (http://statistikkbank.fhi.no/hkr/), respectively, that is, during the middle of the studied time period in each country. According to our estimations, in Sweden, if an individual undergoes gastrointestinal endoscopy or vascular procedure, it could increase his/her annual risk for AMI from 0.73% to 0.80% and 0.87%, respectively. Correspondingly, if an individual was to undergo an orthopaedic procedure, it could increase his/her annual risk for AMI from 0.73% to 0.74% in Sweden and from 0.63% to 0.64% in Norway. Given the rarity of the exposure and the short effect period, these procedures are unlikely to play a major role in the total burden of cardiovascular disease morbidity. However, some particularly risky, specific procedures in vulnerable individuals might require attention.

Strength and limitations

This study has several strengths. First, when assessing the association between invasive outpatient procedures and risk of AMI, a conventional cohort or case–control approach might encounter strong confounding by stable patient characteristics, such as lifestyle-related factors or chronic underlying comorbid conditions.[27] Therefore, by employing a case-crossover design, our results are inherently adjusted for time-invariant confounders.

Second, both the Norwegian and Swedish healthcare systems are universal and provide the same access to care to all residents. Thus, by exploiting the mandatory registration of hospital admissions and invasive procedures in both countries, we eliminated the possibility of self-selection or recall bias in this study. Third, previous validation studies affirmed that the external validity of AMI diagnosis in the Norwegian Patient Register and the Swedish National Patient Register is very high.[17] [18]

This study is not without limitations. First, case-crossover studies can imply time-dependent bias arising due to differences between the hazard and the control period. Acute medical conditions associated with a higher risk for AMI might be an indication for several medical or surgical procedures. Therefore, procedures conducted due to prodromal conditions and diagnosis of AMI or related to treatment of AMI were excluded (see online supplemental table S2). Nevertheless, it is a limitation that the indication of invasive medical and surgical procedures and the effects of these procedures performed due to these conditions were not separable in the present study. For example, we might have somewhat overestimated the effects of gastrointestinal endoscopies as these procedures can be performed in patients where coronary symptoms mimic gastrointestinal problems. Second, it might be possible that the dates and diagnostic codes of some procedures were incorrectly recorded in the outpatient registers. Although codes from the register of the outpatient procedures were included, it is also possible that some procedures were done in patients while being hospitalised for other reasons. Further, it is possible that some procedures performed might be missing since private hospitals in Sweden did not report to the same extent in the beginning of the register. However, it is important to recognise that such uncertainties generally lead to underestimation but not overestimation of effects in a case-crossover setting. Third, we had no information about the symptoms or the type or severity of the AMI. The cardiac event could be a result of myocardial injury after a non-cardiac surgery.[28] Both could be type 1 or type 2 AMI, where type 1 is caused by atherothrombosis triggered by a surgery, whereas type 2 is caused by an imbalance in oxygen supply demand due to the anaesthesia.[6] Fourth, information on anaesthesia was not available on an individual level, and therefore for each procedure a qualified assessment was performed by an anaesthesiologist based on routine clinical practice. Fifth, we could not determine effect modifications by use of cardiovascular medications due to unavailability of data. In addition, no data on procedural sedation and analgesia were available. As the latter may relieve anxiety, discomfort or pain,[29] we might underestimate both the number of AMIs and the association of the procedures with risk of AMI in this study. Lastly, the findings from this study might not be readily generalisable to other countries and populations because some outpatient procedures included in this study might be practised as inpatient procedures and preprocedure evaluations may differ in other contexts.

In conclusion, the risk increase was small on the absolute scale, and thus most of the outpatient procedures appeared to be generally safe. However, there was an increased relative risk seen over a short term for procedures using general/regional anaesthesia (orthopaedic, gastrointestinal endoscopies, urological/gynaecological, vascular procedures) or using local anaesthesia (ENT-mouth and urological/gynaecological). These associations decreased with increasing time since the procedure. Although AMI in relation to outpatient procedures seems rare, it is still a life-threatening event. Hence, it is important that clinicians, while performing particularly highly invasive and therefore risk-prone procedures, consider every possible preventive strategy to decrease excess risk by following preoperative health assessment or risk stratification before planning a procedure and also when monitoring after the procedure.

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