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Diagnosing type 2 myocardial infarction in clinical routine. A validation study

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\textbf{ABSTRACT}

Objective. Since 2010, myocardial infarction (MI) patients reported to the Swedish registry for MI (SWEDEHEART) are routinely classified into MI subtypes. The registry has been used to study the type 2 MI population but the MI-classification in the registry has not previously been validated. The aim of this study was to validate the type 2 MI classification in the registry. Design. A total of 772 patients diagnosed with MI in 2011 and reported to the SWEDEHEART registry were included in the study. All patients were retrospectively classified into MI type 1–5 or myocardial injury by independent reviewers strictly adhering to the \textit{Third Universal Definition of MI}. This gold standard classification was compared with the classification in the registry. \textbf{Results.} Forty-eight (6.2\%) patients were classified as type 2 MI in the registry compared with 93 (12.0\%) according to the gold standard classification. A type 2 MI diagnosis was confirmed in 30 out of the 48 type 2 MI patients in the registry (PPV: 62.5\%). There was a moderate rate of agreement ($\kappa$: 0.43) between the gold standard classification and the classification in SWEDEHEART in deciding a type 2 MI diagnosis. \textbf{Conclusion.} The SWEDEHEART registry agreed moderately with the gold standard in classifying patients with type 2 MI diagnosis. Thus, studies on patients with type 2 MI in the registry should be interpreted with caution. Since the prevalence of type 2 MI is substantially underestimated in SWEDEHEART, the registry should not be used to study the prevalence of type 2 MI.

\textbf{Introduction}

A classification of myocardial infarction (MI), based on the underlying pathophysiological mechanism leading to the ischemic necrosis, was introduced in the \textit{Universal definition of myocardial infarction 2007} [1] and updated in the \textit{Third Universal definition of myocardial infarction 2012} [2]. Unlike a “classic” type 1 MI, caused by a coronary thrombo-embolic event, a type 2 MI occurs secondary to other conditions causing a mismatch in cardiac oxygen supply and demand. Further, a type 3 MI is described as a highly presumed MI where death occurs before biomarkers are elevated or collected. Type 4 and 5 MIs are related to coronary artery procedures [2].

Examples of conditions causing the ischemic imbalance in type 2 MI are tachycardia, anemia, shock and respiratory failure [2]. It is challenging to distinguish type 2 MI from type 1 MI and especially from myocardial injuries commonly occurring in patients with conditions such as heart failure, sepsis, renal failure and stroke [3].

Most MI patients in Sweden are registered in a national registry of coronary artery disease care and valvular interventions – the SWEDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies). During the study period, in 2011, all Swedish hospitals took part in SWEDEHEART and the registry had a median coverage among the reporting sites of 88\% concerning MI patients below the age of 80 years and 60\% concerning patients aged above 80 years [4,5]. A total of 19 647 patients were registered due to MI in 2011 [5]. Since 2010, registered MI patients are classified into type 1–5 by the reporting physician [5]. The registry contains a large number of patients reported as type 2 MI. In 2011 alone, 1403 patients (7.1\%) were registered as type 2 MI [6]. Several studies on type 2 MI have been published based on this population [6,7]. However, the MI classification in SWEDEHEART has not been validated, which makes it unclear how reliable studies on type 2 MI are when based on this registry. Therefore, the aim of this study was to validate the type 2 MI classification in the SWEDEHEART registry.

\textbf{Materials and methods}

\textbf{Study population}

The aim was to include the first 100 consecutive patients, treated at eight Swedish hospitals of different sizes in year
2011, diagnosed with acute MI (ICD-code I.21) at discharge and reported to the SWEDEHEART registry. Twenty-eight patients were excluded, leaving 772 patients which were included in the present study, see Figure 1 for details.

**Collection of data**

Detailed patient information such as age, sex, comorbidities, medications on admission, clinical parameters, laboratory results, electrocardiograms, results from invasive and non-invasive investigations, treatments in-hospital and medications on discharge was retrospectively collected from the electronic patient records of each hospital, using a pre-specified case report form. Relevant notes in medical records such as the discharge summary of the care event were also collected.

The reported MI classification, the MI diagnosis (ICD code I.21) and the date of admission connected to the diagnosis, were retrieved from the SWEDEHEART registry in each patient case.

**Definition of MI types**

The definition of MI types and myocardial injury used in this study, is the MI classification presented in the Third Universal Definition of Myocardial Infarction. Type 1 MI was defined as MI caused by a verified or highly suspected coronary artery plaque rupture, ulceration, fissuring or dissection resulting in an intracoronary thrombus formation. Type 2 MI was defined as MI without intracoronary thrombus formation where conditions other than atherosclerotic CAD contributed to a cardiac oxygen supply/demand imbalance. Myocardial injury was defined as evidence of myocardial necrosis in form of elevated cTn with or without a rising or falling pattern and without clear clinical evidence of ischemia. For details, see supplementary file.

**Adjudication process**

MI classification was done retrospectively by two independent reviewers using a pre-specified form based on the Third Universal Definition of MI. All patients were classified as MI type 1–5 or myocardial injury. The classification was done without knowledge of the classification in the SWEDEHEART registry. In case of classification disagreement between the initial two reviewers, a third independent reviewer was needed to make a majority decision. In a few cases with disagreement between all three reviewers a relative majority decision was reached using a fourth independent reviewer. The final classification was considered as the “Gold standard” for the MI type. All reviewers (AG, TB, GB, MH, KS, BL) were physicians, specially trained on the classification presented in the Third Universal Definition of MI.

In case of a type 2 MI or a myocardial injury classification, reviewers also assessed the triggering mechanisms or underlying conditions contributing to the ischemic or non-ischemic myocardial injury. Several contributing triggering mechanisms or underlying conditions were possible in each case.

**Ethics**

This study has been approved by the Regional Ethical Review Board Uppsala, reference number 2012/208.
Statistics

The positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity for a type 1 and 2 MI classification in the SWEDEHEART registry were calculated. Binomial option in the tables and exact statements was used to obtain asymptotic and exact tests and confidence intervals.

Agreement between the gold standard classification and the classification in the SWEDEHEART registry, as well as agreement between the gold standard reviewers, was calculated using both Cohen’s Kappa statistics [8], and Gwet’s AC1 (first order agreement coefficient) [9]. Kappa- (k) and Gwet’s AC1 values <0 were interpreted as no agreement, 0–0.2 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement and 0.81–1 as almost perfect agreement [10].

PPV, NPV and Gwet’s AC1 analyses were performed with SAS Software, version 9.4 (SAS Institute Inc., Cary, NC, USA), while Cohen’s Kappa analyses were performed with IBM SPSS Statistics 24.0 (SPSS, IBM Corporation, Armonk, NY).

Results

According to the gold standard classification, a MI diagnosis was confirmed in 728 (94.3%) of the 772 patients. The remaining 44 patients were classified as myocardial injury. Further, a total of 625 patients were classified as type 1 MI, 93 as type 2 MI and 10 as type 3, 4 or 5 MI (Figure 2).

According to the SWEDEHEART registry, 609 patients were reported as type 1 MI, 48 as type 2 MI and 5 as type 3, 4 or 5 MI. In 86 cases the MI type were reported as “unknown” and in 24 cases the classification variable was missing (Figure 2).

The prevalence of type 1 MI in the SWEDEHEART registry was similar in comparison to the gold standard classification (78.9 vs 81.0%) while the prevalence of type 2 MI was lower (6.2 vs. 12.0%).

Classification agreement analyzes

The relation between the gold standard classification and the reported classification in SWEDEHEART is shown in Table 1. The MI diagnosis in the registry was confirmed in 728 (94.3%) of the cases. A type 1 MI diagnosis in the registry was correct in 523 out of 609 cases (PPV 85.9%; 95%CI 82.9–88.5). Out of 48 patients reported to the registry as type 2 MI, 30 were correctly classified, while 10 of the patients had a type 1 MI and 8 patients a myocardial injury according to the gold standard classification. Thus, the PPV for a type 2 MI diagnosis in the SWEDEHEART registry was 62.5% (95% CI 47.3–76.0). The PPV, NPV, sensitivity and specificity for a type 1 and type 2 MI diagnosis in the registry are shown in Table 2.

PPV, NPV, sensitivity and specificity for type 1 and type 2 MI diagnosis in the registry are shown in Table 2. Among the 625 patients with a true type 1 MI, 523 were reported as type 1 MI in the registry. Less than one third of the 93 patients with a true type 2 MI, were reported as type 2 MI in the registry. Among the 44 patients with a myocardial injury according to the gold standard classification, 33 patients were reported as type 1 MI, 8 as type 2 MI and in 3 cases the classification was missing or reported as “unknown” in the registry.

The prevalence of MI types among the patients with a missing or “unknown” classification in the SWEDEHEART registry was similar to the overall prevalence in the study population according to the gold standard classification; with 88 patients (80%) classified as type 1 MI, 16 (14.5%) as

| Table 1. SWDEHEART Reported classification vs. Gold standard classification. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Type 1 MI       | Type 2 MI       | Type 3–5 MI     | Myocardial injury | Total |
| SWDEHEART       |                 |                 |                 |                 |       |
| Type 1 MI       | 523             | 47              | 6               | 33              | 609   |
| Type 2 MI       | 10              | 30              | 0               | 8               | 48    |
| Type 3–5 MI     | 4               | 0               | 1               | 0               | 5     |
| Missing/unknown | 88              | 16              | 3               | 3               | 110   |
| Total           | 625             | 93              | 10              | 44              | 772   |

Reported MI-types in the SWEDEHEART registry in relation to the gold standard classification. MI: myocardial infarction.
type 2 MI, 3 (2.5%) as type 3–5 MI and 3 (2.5%) as myocardial injury.

A comparison in clinical characteristics between patients reported as type 2 MI in the SWEDEHEART registry and patients with a type 2 MI according to Gold standard can be found in Supplementary Table 1.

After exclusion of all missing and “unknown” cases, kappa statistics gave a moderate level of agreement (K 0.43; 95% CI 0.31–0.54) while Gwet’s AC1 gave an almost perfect level of agreement (AC1 0.88; 95% CI 0.85–0.91) between the gold standard classification and the classification in the SWEDEHEART registry in deciding a type 2 MI diagnosis (Table 3). Analyzed with Kappa, the rate of agreement between the gold standard reviewers was also moderate, both in the overall classification (κ: 0.51) and in deciding a type 2 MI diagnosis (κ: 0.53) (Supplementary Table 2).

**Variation in type 2 MI reporting between hospitals**

The prevalence of type 2 MI reported to SWEDEHEART as well as the prevalence of true type 2 MIs varied between different hospitals (Table 4). Site no 3 reported zero patients as Type 2 MI while site no 2 reported 17 patients. In general, all hospitals underreported type 2 MI. There was also a variation in the diagnostic accuracy concerning the patients reported to the registry as type 2 MI. Five out of six reported type 2 MI patients from site no 1 were true type 2 MIs compared to one out of four reported from site no 7.

**Triggering mechanisms**

The most common triggering mechanisms contributing to a type 2 MI according to the gold standard classification were tachycardia followed by anemia and hypertension. While almost half of the patients with an anemia triggered type 2 MI were reported as a type 2 MI in the SWEDEHEART registry, only three out of 24 patients with a hypertension triggered type 2 MI were registered as type 2 MI (Figure 3).

Among the eight patients with a myocardial injury according to the gold standard classification, but incorrectly reported as type 2 MI to the registry, heart failure was assessed to contribute to the myocardial injury in six cases, renal failure in three cases, sepsis in two cases and critical illness, stroke, Takotsubo syndrome and infection in one case each.

**Discussion**

This study aimed to validate the type 2 MI classification in the SWEDEHEART registry, which has not previously been done. The main findings are that the PPV of a type 2 MI diagnosis in SWEDEHEART was 62.5%, and that the prevalence of type 2 MI was underestimated in the registry, using a gold standard classification based on the Third Universal Definition of Myocardial Infarction. Further, the rate of agreement between the registry and the gold standard classification in deciding a type 2 MI diagnosis was moderate analyzed with Cohen’s Kappa (κ: 0.43) and almost perfect analyzed with Gwet’s AC1 (AC1: 0.88).

According to the results of the present study, there is an underreporting of type 2 MI in the SWEDEHEART registry. Overall, there was a variation between Swedish hospitals in reported prevalence of type 2 MI in 2011 ranging from 0 to 25%, whereof most hospitals reported a prevalence of 5–10% [5]. The present study found underreporting of type 2 MI in all eight investigated hospitals. Among the total number of 772 included MI patients in the present study, 6.2% were reported as type 2 MI compared with a true prevalence of 12%. In addition, the prevalence of type 2 MI among MI patients not registered in SWEDEHEART was 28% in 2011 [3], indicating that patients with type 2 MI are less often reported in the registry. Further, type 2 MI patients, compared with type 1 MI patients, are more often treated outside the cardiology department [3,11] which likely entails a certain risk of not getting a MI diagnosis. Accordingly, the prevalence of type 2 MI in the SWEDEHEART registry is underestimated.

### Table 3. Agreement on type 2 diagnosis.

<table>
<thead>
<tr>
<th>SWEDHEART</th>
<th>Gold standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 MI</td>
<td>Other</td>
</tr>
<tr>
<td>Type 2 MI</td>
<td>30</td>
</tr>
<tr>
<td>Other</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>77</td>
</tr>
</tbody>
</table>

Agreement on type 2 MI diagnosis between gold standard and SWEDEHEART (K 0.43; AC1 0.88, 90.2%). MI: myocardial infarction.

### Table 4. Variation in type 2 MI prevalence between sites.

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients (total n)</th>
<th>Type 2 MI according to gold standard, n</th>
<th>Type 2 MI reported in SWEDEHEART, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>98</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
<td>9</td>
<td>0</td>
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<tr>
<td>4</td>
<td>98</td>
<td>9</td>
<td>6</td>
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<td>5</td>
<td>92</td>
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<td>6</td>
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<td>7</td>
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<td>4</td>
</tr>
<tr>
<td>8</td>
<td>98</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

Type 2 MI classification in different hospitals according to gold standard, according to the SWEDEHEART registry and according to both. MI: myocardial infarction; n: number.
The PPV of a type 2 MI diagnosis in the SWEDEHEART registry was 62.5% which was lower than the PPV of a type 1 MI diagnosis. It is also low compared with the PPV of most diagnoses in the Swedish National Inpatient Register [12], as well as for all major cardiovascular diagnoses in the Danish National Patient Registry [13]. To conclude that the type 2 MI population in the SWEDEHEART registry is valid for epidemiological studies, a higher PPV would be desirable. However, to the best of our knowledge, there is no consensus what level is necessary. Furthermore, the PPV is highly dependent on the prevalence of a disease. Hence, a high PPV may not be expected for a sub-diagnosis constituting a minority of the investigated population, as in the case of type 2 MI. Validation studies on sub-diagnoses tend to report low PPVs, especially for rare sub-diagnoses, as has been shown for other conditions like dementia [14].

Kappa statistics is seldom used in diagnosis validation studies although it has been proposed for diagnose validation in Swedish quality registers [15]. The advantage of Kappa statistics is that it corrects for chance agreement [8]. In the present study, there was a moderate rate of agreement ($\kappa$: 0.43) in deciding a type 2 MI diagnosis between the SWEDEHEART registry and the gold standard classification. A better agreement would be desirable. However, the few existing clinical criteria for a type 2 MI diagnosis are not very specific [2] and publications on type 2 MI display an inconsistency in the type 2 MI definition [11,16,17], signaling that there is a disagreement in this classification also in the research community. Further, a moderate rate of agreement was also seen between the gold standard reviewers in the present study, even though they were specially trained to follow the MI classification presented in the Third Universal Definition of Myocardial Infarction. This indicates that these criteria are open to interpretations and are very challenging to apply in clinical routine.

If analyzed in detail, the rate of agreement in the current analysis was mainly affected by a high number of false negative type 2 MIs (47 cases), while the number of false positive type 2 MIs were fewer (18 cases). This supports the interpretation that underreporting of type 2 MIs in the registry is a greater problem than the diagnostic inaccuracy of reported type 2 MIs.

In contrast to the results of the Kappa analysis, an almost perfect agreement (0.88) was calculated with Gwet’s AC1. An advantage of Gwet’s AC1 over Cohen’s Kappa is that it is not affected by trait prevalence. While it is difficult to reach a high Kappa value when one reviewer alternative is much more common than the other, Gwet’s AC1 is more stable [9]. Since the prevalence of type 2 MI is low in the SWEDEHEART registry, it is motivated to use Gwet’s AC1 as a complement to Cohen’s Kappa when analyzing the agreement between the registry and a Gold standard.

Validation of type 2 MI diagnosis made in clinical routine has previously been done in two Israeli studies by Stein et al. [18] and by Landes et al. [19] as part of studies comparing type 1 and type 2 MI. The former could confirm the diagnosis in 127 of 178 (71%) type 2 MI patients in a national registry for acute coronary syndrome (the ACSIS registry), according to the Second Universal Definition of MI. The latter confirmed, according to study specific type 2 MI criteria, the diagnosis in 107 of 148 (72%) patients with a clinical type 2 MI diagnosis. These figures are comparable with the 63% type 2 MI diagnosis that could be confirmed in the present study. However, in the two Israelis studies, they only validated the type 2 MI diagnosis, not the type 1 MI diagnosis. The present study is, to the best of our knowledge, the first study designed specifically to validate all types of MI in a population derived from routine clinical care and the first study to strictly adhere to the Third Universal Definition of MI.

The most common triggering mechanisms of a type 2 MI in the present study were tachyarrhythmia and anemia. This corresponds well to what has been reported in other studies, also using a more strict interpretation of the potential type 2 MI triggers presented in the Third Universal Definition of Myocardial Infarction [11]. The results suggest that the likeliness of a type 2 MI reporting in SWEDEHEART varies depending on the underlying trigger of the myocardial ischemia. Very few true type 2 MI patients with an ischemia triggered by hypertension were reported as type 2 MI in the

![Figure 3. Number of cases where a certain triggering mechanism contributed to a type 2 MI according to the gold standard classification (blue) in relation to the percentage of them being reported as type 2 MI in the SWEDEHEART registry (red). MI: myocardial infarction.](image-url)

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The PPV of a type 2 MI diagnosis in the SWEDEHEART registry was 62.5% which was lower than the PPV of a type 1 MI diagnosis. It is also low compared with the PPV of most diagnoses in the Swedish National Inpatient Register [12], as well as for all major cardiovascular diagnoses in the Danish National Patient Registry [13]. To conclude that the type 2 MI population in the SWEDEHEART registry is valid for epidemiological studies, a higher PPV would be desirable. However, to the best of our knowledge, there is no consensus what level is necessary. Furthermore, the PPV is highly dependent on the prevalence of a disease. Hence, a high PPV may not be expected for a sub-diagnosis constituting a minority of the investigated population, as in the case of type 2 MI. Validation studies on sub-diagnoses tend to report low PPVs, especially for rare sub-diagnoses, as has been shown for other conditions like dementia [14].

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registry. This indicates that hypertension is not a widely acknowledged cause of myocardial ischemia. Anemia, on the other hand, was the triggering mechanism most likely resulting in a type 2 MI diagnosis by the reporting physician. Hence, there seems to be a greater acceptance among physicians that anemia may cause myocardial ischemia. A type 2 MI diagnosis may also be perceived as more clinically relevant in the case of anemia, since it justifies a medical decision to abstain from using anticoagulants and platelet inhibitors.

Limitations

Patients registered in SWEDHEART in 2011 were included in the present study. This was only one year after the introduction of the classification variable in the registry. Hence, this is an early validation study and, as observed for other cardiovascular registry diagnoses [13], the accuracy of the MI classification in the registry may improve over time. Moreover, the Third Universal Definition of Myocardial Infarction, was published in 2012; thus, one year after the SWEDHEART reporting of the included patients. Yet, it was chosen as the basis for the gold standard classification since it was the current universal definition for the time of the adjudication process. This may be seen as unfair since the reporting physicians classified the patients according to the previous Universal Definition of Myocardial Infarction, published in 2007 [1]. The definition of type 2 MI does not really differ between the 2007 and the 2012 Universal Definition of Myocardial Infarction, although the distinction between type 2 MI and myocardial injury was less clear in the 2007 edition. The term myocardial injury was not used in the 2007 edition and this definition was more vague concerning which triggering mechanisms that can cause a type 2 MI. Consequently, this may negatively affect the agreement with the gold standard classification in the present study. These limitations suggest that a type 2 MI diagnosis in the SWEDHEART registry would be more accurate in a study including more recently reported patients.

The Fourth Universal Definition of Myocardial Infarction was published after the present study was performed. The MI classification presented in this latest update does not differ from the classification presented in the Third Universal Definition of Myocardial Infarction, but it contains some minor clarifications [20].

In 14% of the included patients, the classification variable was missing, or the patients were reported to have an “unknown” MI type in the registry. This group was excluded from the agreement analyses which may imply a situation of selection bias. However, the prevalence of MI types in this group was very similar to the overall prevalence in the total study population which indicates that the significance of a potential bias should be small with this procedure. The proportion of MI patients in SWEDHEART with a missing or “unknown” classification has decreased since 2011 [21].

The gold standard classification used in this study had a moderate rate of inter-reviewer agreement (k: 0.51) which may indicate a low quality. However, all reviewers were specially trained on, and strictly adhering to, the classification presented in the Third Universal Definition of Myocardial Infarction. Thus, this rather indicates that it is difficult to agree in the MI classification using these guidelines. In addition, disagreement between the reviewers in the present study was solved by a majority decision using a third and sometimes a fourth independent physician, which is a robust diagnosis adjudication process.

Conclusion

The SWEDHEART registry agreed moderately with a gold standard based on the Third Universal Definition of Myocardial Infarction in deciding a type 2 MI diagnosis. Hence, studies on the type 2 MI population in SWEDHEART should be interpreted with caution. A clear underreporting of type 2 MI to the SWEDHEART registry was found. The registry should therefore not be used to study the prevalence of Type 2 MI.

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Disclosure of interest

The authors report no conflict of interest.

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