

Dear Dr. Merino,

We thank the reviewers for their comments on our manuscript.

* We need more information about the nature of patients being missed by registries and in particular whether the missing groups in both countries are similar. Can you reassure us that missed patients are indeed similar to those included and that there are no differences between countries?

Yes, we can provide reassurance both from previous literature and from new analyses. We agree that understanding patients missed by registry is vital for interpretation. Patients missed by MINAP are more likely to have NSTEMI,[1] be older, female, and having a greater use of blood pressure and lipid lowering medication .[2] Similarly, patients missed by SWEDEHEART/RIKS-HIA were more likely to have NSTEMI,[3]be older (80 years old and above), and have greater use of blood pressure lowering medication[4]

This evidence of consistency between the UK and Sweden in characteristics of missed patients (older, more NSTEMI) allows us to directly examine whether the older patients and NSTEMI patients who were included had similar case mix, and therefore are reasonable to compare in new sensitivity analyses (Table). The result show similar casemix differences comparing all patients and patients with a greater risk of being missed by the registries in the two countries.

Change in the manuscript

We have edited the manuscript (discussion), and have included the sensitivity analysis comparing the case mix in all AMI patients and subgroups of patients aged 80 years and above, and NSTEMI patients in Sweden and the UK (Table S5).

* Sweden has 1.5 times higher admission rates for AMI, but the registries include two times more Swedish patients as UK patients, suggesting that there is still a substantial portion of UK patients left out of the comparison. Do you have more info on the higher admission rates in Sweden? Is this really based on higher AMIs, or are there more hospital beds in Sweden and thus more (and healthier) patients are admitted to the hospital?

Yes, the reviewer is correct that the rate of AMI admission was higher in Sweden, compared to the UK. The estimated AMI admission rate was 2766.0 per million population in Sweden,[8 9] and 1518.3 per million population in England and Wales (MINAP population).[10]¹ The estimated rate was 1.8 times greater in Sweden than in England and Wales.

¹ The 2010 AMI admission rate in Sweden is derived based on estimated 26000 hospitalized AMI patients (SWEDEHEART 2012 annual report), divided by Sweden population in 2010 (9.4 million). In 2010, the estimated AMI admission in England and Wales was 79,863, in the population of 52.6 million.

This is unlikely to be the consequence of difference in hospital beds, as Sweden had fewer hospital beds for acute care than the UK.[7] We agree that patients included in the registry may be healthier, as we demonstrated in the reply to the first comment that patients not included in the registries were older and more frequently had a history of cardiovascular diseases. However, this was unlikely to explain the difference in the admission rate between countries, as we demonstrated the case mix differences comparing all patients and patients with a greater risk of being missed by the registries in the two countries were similar.

Change in the manuscript

We have edited the manuscript (discussion), including additional references for higher AMI admission rate in Sweden than the UK.

* In your latest response to reviewers you mention that "The key point is that patients not included in the registries usually have more comorbidities with a worse outcome, thus the nature of any bias is conservative: the true difference in hospital outcome and variation may be greater in the UK than Sweden than is reported in the manuscript." Can you please provide a reference or other evidence to back up this claim?

Yes, the key reference is our previous study published in the Lancet, which demonstrates that older patients and patients with NSTEMI – those patients more likely to be missed - had a greater 30-day mortality in the UK than in Sweden.[11] In Present study also shows that among patients who have a higher likelihood of being missed from the registry (for example, NSTEMI patients), hospital variation in 30-day mortality was greater in the UK than in Sweden.

Based on the evidence, the true hospital mortality and variation is estimated to be greater in the UK than in Sweden.

Table S5: Case-mix and treatment for patients with acute MI in Sweden (n=119,786) and the UK (n=391,077), comparing all patients to patient subgroups (age ≥ 80 years old, NSTEMI). Values are % (95% confidence interval) unless otherwise indicated

Case-mix N	Sweden			UK		
	All AMI 119786	Age ≥ 80 years 35903	NSTEMI 81354	All AMI 391077	Age ≥ 80 years 101711	NSTEMI 233659
STEMI	32.1 (31.8, 32.3)	24.9 (24.5, 25.3)	--	40.3 (40.1,40.4)	27.3 (27, 27.6)	--
Age, year, mean, SD	71.2, 12.3	85.0, 3.8	72.4, 12.0	69.5, 13.6	85.8, 4.3	71.8, 13.3
Female	36.3 (36.1, 36.6)	51 (50.5, 51.5)	37.6 (37.3, 37.9)	34.8 (34.7,34.9)	53.4 (53, 53.7)	38 (37.8, 38.2)
MI severity, median (Q1, Q3)						
Systolic blood pressure, mmHg	145 (125, 165)	140 (120, 163)	148 (130, 167)	139 (120, 158)	137 (117, 158)	140 (121, 160)
Heart rate, beat per minute	78 (65, 93)	80 (68, 100)	79 (66, 95)	79 (66, 94)	83 (70, 100)	80 (68, 97)
Troponin I, µg/L	4.2 (0.8, 18.0)	4.3 (0.94, 17.1)	2.6 (0.63, 9.69)	4.4 (0.8, 21.7)	3.52 (0.68, 15.9)	2.18 (0.46, 8.36)
Troponin T, µg/L	0.7 (0.2, 2.3)	0.7 (0.21, 2.2)	0.45 (0.17, 1.3)	0.65 (0.2, 2.3)	0.53 (0.176, 1.82)	0.356 (0.14, 0.96)
Risk factor						
Current smoking	23.3 (23.0,23.5)	6.7 (6.4, 7)	19.9 (19.6, 20.2)	29.5 (29.3,29.6)	8 (7.8, 8.2)	23.5 (23.3, 23.7)
History of diabetes	22.7 (22.4,22.9)	22.4 (21.9, 22.8)	24.7 (24.4, 25)	17.6 (17.4,17.7)	17.4 (17.2, 17.7)	20.7 (20.5, 20.8)
History of hypertension	45.2 (44.9,45.5)	50.6 (50.1, 51.1)	47.8 (47.4, 48.1)	47.3 (47.2,47.5)	54.4 (54.1, 54.7)	51 (50.8, 51.2)
Cardiovascular disease history						
Heart Failure	9.7 (9.5,9.8)	18.3 (17.9, 18.8)	12.3 (12.1, 12.5)	5.3 (5.2,5.4)	10.9 (10.7, 11.1)	7.4 (7.3, 7.5)
Cardiac arrest prior to admission	1.3 (1.3,1.4)	0.8 (0.7, 0.9)	0.8 (0.8, 0.9)	2.3 (2.2,2.3)	1.3 (1.3, 1.4)	1.3 (1.2, 1.3)
Cerebrovascular disease	10.1 (9.9,10.3)	16.1 (15.7, 16.5)	11.4 (11.1, 11.6)	8.5 (8.4,8.5)	14.4 (14.2, 14.7)	10.2 (10.1, 10.3)
MI	22.4 (22.1,22.6)	31.9 (31.4, 32.4)	26.5 (26.2, 26.8)	18.3 (18.1,18.4)	24 (23.8, 24.3)	22.9 (22.7, 23.1)
Pre-hospital treatment						
Antiplatelet mono-therapy	36.6 (36.3,36.6)	51.7 (51.1, 52.2)	42 (41.7, 42.4)	26.4 (26.3,26.6)	33.5 (33.2, 33.8)	31.2 (31, 31.4)
Antiplatelet dual-therapy	4.0 (3.9,4.1)	4.4 (4.2, 4.6)	4.8 (4.7, 5)	2.9 (2.9,3)	3.4 (3.3, 3.5)	3.7 (3.6, 3.8)
PCI	8.0 (7.8,8.2)	5.7 (5.4, 5.9)	9.2 (9, 9.4)	5.4 (5.4,5.5)	3.1 (3, 3.2)	6.3 (6.2, 6.4)
CABG	7.7 (7.6,7.9)	7.8 (7.6, 8.1)	9.8 (9.6, 10)	4.8 (4.8,4.9)	4.1 (3.9, 4.2)	6.5 (6.4, 6.6)

Abbreviations: STEMI, ST-elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery;

Reference

1. Herrett E, Smeeth L, Walker L, et al. The Myocardial Ischaemia National Audit Project (MINAP). *Heart* 2010;**96**(16):1264-67
2. Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *Bmj* 2013;**346**:f2350 doi: 10.1136/bmj.f2350[published Online First: Epub Date]].
3. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart* 2010;**96**(20):1617-21
4. Harnek J, Nilsson J, Friberg O, et al. The 2011 outcome from the Swedish Health Care Registry on Heart Disease (SWEDEHEART). *Scandinavian cardiovascular journal : SCJ* 2013;**47 Suppl 62**:1-10 doi: 10.3109/14017431.2013.780389[published Online First: Epub Date]].
5. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014;**383**(9932):1899-911
6. Pujades-Rodriguez M, Timmis A, Stogiannis D, et al. Socioeconomic deprivation and the incidence of 12 cardiovascular diseases in 1.9 million women and men: implications for risk prediction and prevention. *PloS one* 2014;**9**(8):e104671 doi: 10.1371/journal.pone.0104671[published Online First: Epub Date]].
7. WHO Europe. Health for All Database (HFA-DB). <http://data.euro.who.int/hfad/>.
8. Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease. SWEDEHEART 2011 Annual Report. .
9. OECD. OECD.StatExtracts. <http://stats.oecd.org/>.
10. Myocardial Ischaemia National Audit Project (MINAP). Tenth Public Report.
11. Chung S-C, Gedeberg R, Nicholas O, et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet* 2014;**383**(9925):1305-12