PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Temporal trends in cardiovascular risk factors, lifestyle, and secondary preventive medication for patients with myocardial infarction attending cardiac rehabilitation in Sweden 2006-2019: a registry-based cohort study
AUTHORS	Leosdottir, Margret; Hagstrom, Emil; Hadziosmanovic, Nermin; Norhammar, Anna; Lindahl, Bertil; Hambraeus, Kristina; Jernberg, Tomas; Bäck, Maria

VERSION 1 – REVIEW

REVIEWER	García García, Cosme Hospital Universitari Germans Trias i Pujol, Cardiology. Critical Cardiac Care Unit
REVIEW RETURNED	30-Nov-2022

GENERAL COMMENTS	This is an interesting retrospective registry-based cohort study performed in Sweden between 2006-2019. This is the National Swedeheart registry that described temporal trends (2006-2019) in risk factor prevalence, lifestyle, and prescription of secondary preventive medication at one-year after AMI for patients attending cardiac rehabilitation (CR) in Sweden. The study concludes there are an increasing proportion of patients in Sweden reaching secondary prevention goals for blood pressure and LDL cholesterol one year after an AMI. Major comments: - The study had a broad representability of Sweden population, although patients over 75 years old were not included in this registry. Is there any information about the proportion of AMI patients over 75 yo in Sweden?. This proportion could reach nearly 20% in some registries. - The use of statins has increased over the years, but there is any information about the statin dose? How many patients were taking high-intensity statins? - Is there any information about the use of iPCSK9? How is the use of these drugs in Sweden? - The increase in ACE inhibitors or the reduction in the use of beta-blockers could be related to the ejection fraction after AMI. The EF is available in the registry? The decrease in the use of beta-blockers was mainly observed in those patients with preserved EF?

REVIEWER	Tousoulis, Dimitris Athens University, Cardiology
REVIEW RETURNED	23-Jan-2023

GENERAL COMMENTS	In this interesting study temporal trends in cardiovascular risk factors, lifestyle, and secondary preventive medication for patients with myocardial infarction attending cardiac rehabilitation in Sweden 2006-2019: a registry-based cohort study In this an interesting study. However my concerns are the following 1. Please clarify what is the main message of the study? 2. How the changes in the medical treatment affect the results? 3. What you propose after this study? 4. What about the revacsularization PTCA or CABG. How affect the results? 5. What about the type of exercise. How affect the results?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Cosme García García, Hospital Universitari Germans Trias i Pujol

Comments to the Author:
General Comments:
This is an interesting retrospective registry-based cohort study performed in Sweden between 2006-2019. This is the National Swedeheart registry that described temporal trends (2006-2019) in risk factor prevalence, lifestyle, and prescription of secondary preventive medication at one-year after AMI for patients attending cardiac rehabilitation (CR) in Sweden.
The study concludes there are an increasing proportion of patients in Sweden reaching secondary prevention goals for blood pressure and LDL cholesterol one year after an AMI.

Major comments:
- The study had a broad representability of Sweden population, although patients over 75 years old were not included in this registry. Is there any information about the proportion of AMI patients over 75 yo in Sweden? This proportion could reach nearly 20% in some registries.
Answer: According to the National Board of Health and Welfare Statistics (public data source: www.socialstyrelsen.se/en/statistics-and-data/statistics/) approximately 55% of all AMI cases in the years 2006-2019 occurred in patients 75 years or older, with as much as 26% in the oldest age group (85 years or older). The case fatality increased with age, with 25% of the oldest group (85 years or older) dying before reaching hospital and 40% being dead within 28 days. Additionally, a large part of AMI patients >80 years of age who are admitted to hospital in Sweden receive care at internal medicine or geriatric wards. These patients are generally not included in SWEDEHEART. For those <80 years of age, however, the coverage in SWEDEHEART (the proportion of patients registered in SWEDEHEART out of all patients hospitalised with a discharge diagnosis of AMI registered in the mandatory National Patient Registry) is high, in 2020 being 92%.
Follow-up data has been registered for 75-80% of all AMI cases in SWEDEHEART since 2016. Up until 2018 it was only mandatory to register follow-up data on patients <75 years of age, while this age limit was increased to <80 years in 2018. Since then, patients 75-79 years represent approximately 20% of cases with follow-up data in the registry. To minimize the age-based case mix in our dataset for these two last years, however, we decided to apply the age limit of <75 years to all the years included (2006-2019).
In summary, the representability for patients in the <75 age group in our data is high, and the case mix is similar to EUROASPIRE, justifying comparisons. Representability for the total AMI population in the country is however lower, similar to most other AMI registries around the world. This limitation has been further highlighted in the Limitations section, page 17 (marked copy):

At the same time, a major limitation is the lack of data describing MI patients not attending CR and on those ≥75 years of age and results cannot be generalized to these groups. Even though the mean age in our data was similar to EUROASPIRE, the age range differed somewhat (our data 18-74 years vs 18-79 years in EUROASPIRE), which may have led to slight overestimation of the results.

- The use of statins has increased over the years, but there is any information about the statin dose? How many patients were taking high-intensity statins?
Answer: Unfortunately, data on statin intensity and dose is not included in SWEDEHEART. In another publication using data from the Swedish National Patient Register and Prescribed Drug Register, prescription of lipid-lowering therapy for patients with a recent MI (<365 days) in 2010-2016 was analysed. The proportion receiving high-intensity statin increased from 31.7% in 2010-2013 to 91.3% in 2014-2016 (Svensson M et al Ups J Med Sci. 2022;127). This is considerably higher than what was reported in EUROASPIRE V, where 50% of those on lipid-lowering drugs were taking high-intensity lipid-lowering drugs or drug combinations. This information has been added to the Discussion section, page 13 (marked copy):

Another possible explanation could be the higher proportion of patients being prescribed lipid lowering therapies in our study as compared to EUROASPIRE. Between 2015 and 2019 94-95% of patients were prescribed statins and/or ezetimibe, with the corresponding proportion in EUROASPIRE V (2016-2017) being 84%, out of which only 50% were prescribed high-intensity lipid lowering drugs (5). In a study using Swedish registry data, the proportion of AMI patients receiving high-intensity statins post-MI during 2014-2016 was 91.3% (21).

- Is there any information about the use of iPCSK9? How is the use of these drugs in Sweden?
Answer: Registration of the use of PCSK9i started in SWEDEHEART in 2017. As information on use prior to 2017 was not available, as well as the use being minimal in the first years (0.5-1.5%) we decided to include only statins and ezetimibe in the definition of lipid lowering therapy. We have added this information to the Methods section, page 8 (marked copy):

Registration of the use of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors started in SWEDEHEART in 2017. As information on use prior to 2017 was not available, as well as the use being minimal in the first years (0.5-1.5%) we decided to include only statins and ezetimibe in the definition of lipid lowering therapy (15).

- The increase in ACE inhibitors or the reduction in the use of beta-blockers could be related to the ejection fraction after AMI. The EF is available in the registry? The decrease in the use of beta-blockers was mainly observed in those patients with preserved EF?
Answer: The decreased use of beta blockers was most prominent in patients with preserved EF, with 70.5% of patients with preserved EF being treated with beta blockers in 2019 compared to 88.6% in those with reduced EF. This information has been added to the Results section, page 12 (marked copy):

The decrease was mostly driven by a decrease in use among patients with preserved ejection fraction (from 85.1% in 2006 to 70.5% in 2019, p for difference <0.0001), while the use in patients with reduced ejection fraction was unchanged (87.8% in 2006 compared to 88.6% in 2019, p for difference = 0.540).

Reviewer: 2
Dr. Dimitris Tousoulis, Athens University

Comments to the Author:
in this interesting study temporal trends in cardiovascular risk factors, lifestyle, and secondary preventive medication for patients with myocardial infarction attending cardiac rehabilitation in Sweden 2006-2019: a registry-based cohort study.

In this an interesting study. However, my concerns are the following:
1. Please clarify what is the main message of the study?
Answer: The main message is that large improvements have been observed in treatment of key risk factors (first and foremost LDL-C and BP) as well as prescription of preventive medication among post-MI patients in Sweden between 2006-2019. Compared to EUROASPIRE results from the

same period, these improvements are considerably larger, but are in line with reports from other quality registries in Europe. We argue that continuous auditing and open comparisons of CR outcomes may explain some of the observed improvements and differences. Meanwhile, similar to the rest of Europe, changes directed towards a healthier lifestyle were less encouraging. The main message is conveyed in the Abstract and the revised Conclusions:

Abstract (pages 2-3, marked copy):
While little change was observed for persistent smoking and overweight/obesity, large improvements were observed for LDL-C and BP target achievements and prescription of preventive medication for Swedish patients after MI 2006-2019. Compared to published results from patients with coronary artery disease in Europe during the same period, these improvements were considerably larger. Continuous auditing and open comparisons of CR outcomes might possibly explain some of the observed improvements and differences.

Conclusion (page 18, marked copy):
Between 2006-2019, an increasing proportion of patients in Sweden reached secondary preventive goals for BP and LDL-C one year after an MI. The proportion of patients treated with evidence-based secondary preventive medication also increased. Both levels of BP and LDL-C, as well as use of pharmacological treatment were comparable with data from other similar European quality registries and national level audits used for benchmarking. The trends were more favourable than those observed in EUROASPIRE, data from which represents several European countries where audits were not widely available. The results may indicate that national quality registries can contribute to improving outcomes in CR and add evidence to the importance of auditing and benchmarking as means to improve quality of care. Less encouraging, no changes were seen the proportion of current smokers at the time of the MI who are abstinent at one-year, more patients reported inadequate levels of physical activity, and the proportion of patients with central obesity and diabetes increased, as was observed in EUROASPIRE. These observations bare witness of a large unmet need to prioritize patient lifestyle support after an MI, which should be improved to provide patients with adequate risk reduction.

2. How the changes in the medical treatment affect the results?
Answer: Thank you for this important comment. Indeed, a more prevalent use of potent lipid-lowering therapy and ACEi/ARB could have contributed to the higher proportion of patients reaching treatment targets for LDL-C and BP. A more widespread use of intensive secondary preventive treatment may also partly be explained by the national benchmarking between centres that SWEDEHEART facilitates. This is elaborated on in the Discussion sections, page 13 (marked copy):

Another possible explanation could be the higher proportion of patients being prescribed lipid lowering therapies in our study as compared to EUROASPIRE. Between 2015 and 2019 94-95% of patients were prescribed statins and/or ezetimibe, with the corresponding proportion in EUROASPIRE V (2016-2017) being 84%, out of which only 50% were prescribed high-intensity lipid lowering drugs (5). In a study using Swedish registry data, the proportion of AMI patients receiving high-intensity statins post-MI during 2014-2016 was 91.3% (21). An additional explanation for the more pronounced improvement in target attainment in SWEDEHEART compared to EUROASPIRE, as well as a more pronounced use of potent lipid-lowering therapy, might be the possibility of continuous self-audit of publicly available data for CR centres reporting to SWEDEHEART, as only a minority of the countries participating in EUROASPIRE had quality registries or audits comparable to SWEDEHEART.

3. What you propose after this study?
Answer: Our results add evidence to the importance of auditing and benchmarking as means to improve quality of care and as such strengthen the incentive for more countries to implement audit systems. This has been clarified in the Conclusions. Also, our less encouraging observations on lifestyle bare witness of a large unmet need to prioritize patient lifestyle support after an MI. This should be improved, to provide patients with adequate risk reduction. The following has been added to the Conclusion, Discussion section, page 18 (marked copy):

The results may indicate that national quality registries can contribute to improving outcomes in CR, and add evidence to the importance of auditing and benchmarking as means to improve quality of care. Less encouraging, no changes were seen the proportion of current smokers at the time of the MI who are abstinent at one-year, more patients reported inadequate levels of physical activity, and the proportion of patients with central obesity and diabetes increased, as was observed in EUROASPIRE. These observations bare witness of a large unmet need to prioritize patient lifestyle support after an MI, which should be improved to provide patients with adequate risk reduction.

4. What about the revascularization PTCA or CABG. How affect the results?
Answer: As shown in Supplementary Table S3 the rate of revascularization increased from 65.1% in 2006 to 90.3% in 2019. Apart from a higher proportion being treated with dual antiplatelet therapy, it is unlikely that revascularization has affected the use of secondary preventive treatment or lifestyle interventions.

5. What about the type of exercise. How affect the results?
Answer: Unfortunately, we do not have information on type of exercise in the SWEDEHEART registry. However, we only observed minor changes in median number of days that the patients were physically active during the study, differences that would not affect the study results.

VERSION 2 – REVIEW

REVIEWER	García García, Cosme Hospital Universitari Germans Trias i Pujol, Cardiology. Critical Cardiac Care Unit
REVIEW RETURNED	04-Apr-2023

GENERAL COMMENTS	Authors have resolved most of comments I suggested in my first revision, including the limitations in the right section

REVIEWER	Tousoulis, Dimitris Athens University, Cardiology
REVIEW RETURNED	09-Mar-2023

GENERAL COMMENTS	The authors answered all the queries satisfactory

VERSION 2 – AUTHOR RESPONSE