PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Heartwatch: an Irish Cardiovascular Secondary Prevention programme in primary care, a secondary analysis of patient outcomes.
AUTHORS	Homeniuk, Robyn; Stanley, Fintan; Gallagher, Joseph; Collins, Claire

VERSION 1 – REVIEW

REVIEWER	Tobias N. Bonten Leids Universitair Medisch Centrum, Public Health and primary Care
REVIEW RETURNED	11-May-2022

GENERAL COMMENTS	Abstract: starts with " The objective of this secondary analysis" . For a first time reader this is a bit of a strange start. Maybe change in something like " to investigate patient follow-up data from Heartwatch" Abstract ,results: " achieved more targets" : I would recommend to add an effect measure (number / percentage/ odds ratio) here. Methods: " The Heartwatch data is a highly dimensional dataset with a large number of records, therefore to avoid overfitted and complex models, a variable selection approach was taken to identify variables of interest, which would then be further investigated. " : to me it is unclear what happened here with selection of data for analysis in this paper. Please clarify. Methods: " That model was then applied to all patients with complete records for the selected variables" : I understand that the analyses were carried out on the ' complete case' dataset only. This is also presented in the results " To assess the progress of patients, we identified a cohort of 5,700 patients with at least 8 years in the programme" . : in my opinion this analysis seriously impacts on the validity of the results. Survival bias (only analyses on patients who stay in the programme) could seriously affect the outcome measures here. I would recommend to perform a proper survival analysis method, like Cox regression or a subtype of this method. Methods: outcomes are only presented in percentages in the complete case dataset. Sometimes it is unclear on which dataset results are presented (complete case 8 years, or other years). This negatively affects the readability and understanding of the results. Methods: prediction is being performed. But to me it is unclear which models are being used, which steps have been taken during the analyses. Furthermore, no prediction outcomes (like AUC's, Beta's,

	odds ratios) are being presented, only percentages of BIC's. Please change / clarify.

REVIEWER	Guy De Backer University of Ghent
REVIEW RETURNED	31-May-2022

GENERAL COMMENTS	In this manuscript entitled " Heartwatch: an Irish Cardiovascular Secondary Prevention programme in primary care, a secondary analysis of patient outcomes." results are presented on how a program of secondary prevention of ASCVD resulted in the control of conventional risk factors over a period of 8 years in patients with established ASCVD. Standardized protocols were used by the GP's who were selected in the study but the internal validity of the study variables is hard to evaluate. How well standardized were blood pressure measurements, lipid analyses, questionnaires on smoking, physical activity? Were patients without known diabetes screened for undetected diabetes? Was the secondary prevention program personalized in accordance with the residual risk of each patient? The external validity of the study is also difficult to assess. How representative were the GP's who participate? How were patients selected (consecutively, randomly?). The results also depend on the existing primary care Health care system in Ireland that may be very different from what exists in other countries . Results on secondary prevention of ASCVD strongly depend on the participation in comprehensive cardiac rehab programs. Were all these patients after an AMI or after revascularization not offered rehab programs?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Tobias N. Bonten, Leids Universitair Medisch Centrum Comments to the Author:

1. Abstract: starts with " The objective of this secondary analysis" . For a first time reader this is a bit of a strange start. Maybe change in something like " to investigate patient follow-up data from Heartwatch"

   The abstract has been changed to reflect this suggestion.

2. Abstract ,results: " achieved more targets" : I would recommend to add an effect measure (number / percentage/ odds ratio) here.

   The results section has been updated to include this feedback as follows:

   'After one year, 37% of the 8-year cohort had achieved a CCare score >5 increasing to 44% after year-8. Patient sex was predictive of better scores; male patients had almost a half-point advantage (0.432, CI: 0.335-0.509). Patients who enrolled earlier following their qualifying event and patients with more frequent visits were also more likely to achieve higher CCare scores.'

3. Methods: " The Heartwatch data is a highly dimensional dataset with a large number of records, therefore to avoid overfitted and complex models, a variable selection approach was taken to identify variables of interest, which would then be further investigated. " : to me it is unclear what happened here with selection of data for analysis in this paper. Please clarify.

   We have changed the statistical approach. See response to point 4 for details.

4. Methods: " That model was then applied to all patients with complete records for the selected variables" : I understand that the analyses were carried out on the ' complete case' dataset only. This is also presented in the results " To assess the progress of patients, we identified a cohort of 5,700 patients with at least 8 years in the programme" . : in my opinion this analysis seriously impacts on the validity of the results. Survival bias (only analyses on patients who stay in the programme) could seriously affect the outcome measures here. I would recommend to perform a proper survival analysis method, like Cox regression or a subtype of this method.

   Survival Bias:

   We acknowledge the limitation of a potential survivor bias in our strengths and limitations:

   > *"Another possible limitation could be a survivor bias on the available long-term information, as those with worse scores may have exited the programme earlier than 8 years."*

   We also provide descriptive statistics of the overall participant group in the opening section of our results so that they can be compared to the 8-year cohort.

   Our decision to select the cohort in the main reflects our aim to evaluate the program over a longer period then previous report. [1-2] Using data only from participants with valid annual data is consistent with the methods of those previous reports, permitting more reasonable comparisons.

   1. Bennett K, Jennings S, Collins C et al. Heartwatch: A secondary prevention programme in primary care in Ireland. Eur J Prev Cardiol 2008;15:651–6.

   2. Fitzpatrick P, Fitz-Simon N, Lonergan M et al. Heartwatch: The effect of a primary care-delivered secondary prevention programme for cardiovascular disease on medication use and risk factor profiles. Eur J Prev Cardiol 2011;18:129–35.

   Survival Analysis:

   Unfortunately, no data on outcomes such as death, subsequent cardiac event or hospitalisation is available for analysis within the dataset. As such a survival analysis is not possible.

   Overall Model Interpretability & explanation

   To improve communication of the results we have changed the approach to use a single linear regression analysis. Details of the model have replaced the original approach in the methods section, results section and throughout as necessary.

   The method of the new statistical approach differs from the previous approach in two key ways:

   - In contrast to the previous approach, we have not used model selection to reduce the number of variables.

- Additionally, to address the lack of independence from repeated measures of the same patients over many visits we have used a mixed effects model approach, as opposed to separate models for different years.

The results of the new statistical approaches agree with the previous approach:

- variables selected for inclusion in the first model reach significance in the new model
- Effects are in the same direction and of similar sizes

We stand by the validity of the previous statistical approach but concede it might not have best communicated the point. Given the agreement of the two approaches and published support for multiple approaches to clarify the stability or sensitivity of effect estimates [3-4], we hope that the updated approach is acceptable.

3. Steegen S, Tuerlinckx F, Gelman A et al. Increasing Transparency Through a Multiverse Analysis. Perspect Psychol Sci 2016;11:702–12. https://doi.org/10.1177/1745691616658637

4. Lotte Meteyard, Robert A.I. Davies, Best practice guidance for linear mixed-effects models in psychological science, J Mem Lang, https://doi.org/10.1016/j.jml.2020.104092.

5. Methods: outcomes are only presented in percentages in the complete case dataset. Sometimes it is unclear on which dataset results are presented (complete case 8 years, or other years). This negatively affects the readability and understanding of the results.

   The manuscript refers to the overall demographics of the program in the first section of the results but does not refer to the group of all participants as a cohort. We believe this provides valuable and necessary context.

   The next section then introduces the 8-year cohort. Thereafter all results refer exclusively to the 8-year cohort, and this is stated in the text just after the cohort in introduced:

   “The remainder of the analyses presented here pertains to this cohort.”

6. Methods: prediction is being performed. But to me it is unclear which models are being used, which steps have been taken during the analyses. Furthermore, no prediction outcomes (like AUC's, Beta's, odds ratios) are being presented, only percentages of BIC's. Please change / clarify.

   We have changed the statistical approach and now include effect estimates and 99% confidence intervals in the text. See response to point 4 for additional details.

Reviewer: 2

Dr. Guy De Backer, University of Ghent

Comments to the Author:

In this manuscript entitled " Heartwatch: an Irish Cardiovascular Secondary Prevention programme in primary care, a secondary analysis of patient outcomes." results are presented on how a program of secondary prevention of ASCVD resulted in the control of conventional risk factors over a period of 8 years in patients with established ASCVD.

1. Standardized protocols were used by the GP's who were selected in the study but the internal validity of the study variables is hard to evaluate. How well standardized were blood pressure measurements, lipid analyses, questionnaires on smoking, physical activity? –

   All GPs were given the same training and care protocol and expected to carry out the program's activities in a standardised way. To address this concern, we have added the following to the methods sections.

   "Practices from each health board area were recruited with the aim of having national coverage of the program. Each area employed a regional GP co-ordinator and nurse facilitator to assist with the deployment of Heartwatch care protocol. Upon agreeing to become a Heartwatch practice, the clinical staff underwent specific training to enable a standardised approach to following the care protocol and performing the required checks at each visit."

2. Were patients without known diabetes screened for undetected diabetes?

   Yes, the standard protocol indicates that patients fasting glucose be monitored in all situations irrespective of diabetes diagnosis. The prevalence of diabetes increased overtime – this is mentioned in the results.

   "The number of patients with co-morbid diabetes that had HbA1c readings within target increased over time. However, this occurred in tandem with an increased new diagnosis of diabetes in the rest of the cohort"

3. Was the secondary prevention program personalized in accordance with the residual risk of each patient?

   The care given to patients by the practices had to be in line with the Heartwatch care protocols in terms of a maximum of four visits per year with a minimum of 10 weeks between visits and allowed for personalisation in terms of treatment while continuing to aim for the targets outlined in ESC guidelines. In the methods section, we mention that the content of each visit is driven by previous results.

   "Whether all factors were measured at every visit was dependent on whether the value was within target or not at the previous visit. For example, the target for total cholesterol is <5mmol/l – if a patient is within target, their GP only needed to measure at every other visit whereas if they were outside of the target their GP must repeat the test at the subsequent visit. However, the practice may choose to repeat all tests at each visit.[22]"

4. The external validity of the study is also difficult to assess. How representative were the GP's who participate? How were patients selected (consecutively, randomly?). The results also depend on the existing primary care Health care system in Ireland that may be very different from what exists in other countries .

   We have added further context to the Irish health system and the program's position within the system. Patients were selected from each practice based on recruitment criteria for the programme by practice staff based on need and willingness to participate.

   "In Ireland, GPs work as private healthcare professionals charging private patients per visit and receiving government payments on a capitation basis for eligible public patients. Around 43% of people in Ireland qualify for free GP care, either through the General Medical Scheme card (32.4%) or GP-visit card(10.4%).[14] GPs have a central role in the Irish health system, and they are critical in the management of long-term conditions with 80% of all GP visits relating to chronic disease management.[14] A fifth of Irish general practices were recruited to deploy the specially developed secondary prevention program, which enabled patients to attend up to four specialised visits per year, with a payment made per visit to the GP from the State."

5. Results on secondary prevention of ASCVD strongly depend on the participation in comprehensive cardiac rehab programs. Were all these patients after an AMI or after revascularization not offered rehab programs?

   We do not know whether the patients in Heartwatch were offered/attended cardiac rehabilitation prior to their sign up to Heartwatch. In an effort to address this issue, we had added some information about cardiac rehabilitation compliance to the introduction.

   "As of 2013, nearly 80% of Irish patients were compliant with cardiac rehabilitation recommendations.[10]"

VERSION 2 – REVIEW

REVIEWER	Tobias N. Bonten Leids Universitair Medisch Centrum, Public Health and primary Care
REVIEW RETURNED	26-Aug-2022

GENERAL COMMENTS	The authors have addressed my comments accordingly and have adapted the paper, which is now acceptable for publication in my opinion.

REVIEWER	Guy De Backer University of Ghent
REVIEW RETURNED	26-Aug-2022

GENERAL COMMENTS	I thank the authors for having considered my comments and I do accept most of the replies and adaptations that were made. My only remaining comment relates to the external validity of the study. How well can the results be extrapolated to promote secondary prevention of CVD in Ireland as a whole and in other countries? Can Heartwatch as a model be recommended to other countries with other primary care system?

VERSION 2 – AUTHOR RESPONSE

Reviewer response - External validity

My only remaining comment relates to the external validity of the study. How well can the results be extrapolated to promote secondary prevention of CVD in Ireland as a whole and in other countries? Can Heartwatch as a model be recommended to other countries with other primary care system?

Thank you – we have added to the discussion to try to directly address the external validity of the programme and highlight where our findings correspond with others (see end of the Discussion - Implications for policy and practice section)

Given the question we are trying to answer, we have employed the best workable methods with the quality and granularity of data we have available. Rigorously assessing validity is not possible without performing further investigations to confirm that our results are in fact externally valid. We don't have population level data for Ireland or details such as socioeconomic status for Heartwatch patients – which impacts how much our findings would be generalisable across a larger population.