

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Impact on Percutaneous Coronary Intervention for Acute Coronary Syndromes during the COVID-19 outbreak in a non-overwhelmed European health care system: COVID ACS-PCI Experience in Ireland
<b>AUTHORS</b>	Connolly, Niall; Simpkin, Andrew; Mylotte, Darren; Crowley, James; O'Connor, Stephen; AlHarbi, Khalid; Kiernan, Thomas; Arockiam, Sacchin; Owens, Patrick; John, Amal; Blake, Gavin; Fitzgerald, Sean; Cadogan, Diarmaid; Rosseel, Liesbeth

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Derek Chew Flinders University, Adelaide , South Australia
<b>REVIEW RETURNED</b>	22-Oct-2020

<b>GENERAL COMMENTS</b>	<p>This analysis of the PCI rates for ACS in Ireland is a relatively simple observational analysis describing a phenomenon/change in hospital attendance pattern that is consistent with what has been reported in many centres around the world.</p> <p>It is suggested that the authors may enhance the analysis by including outcome data for this cohort, such as the 30 day mortality rate for ACS receiving PCI, propensity matched for study period, and or the mortality rate for ACS in Ireland in these contrasting periods.</p>
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<b>REVIEWER</b>	Lloyd Evans Public Health Wales, Wales
<b>REVIEW RETURNED</b>	26-Oct-2020

<b>GENERAL COMMENTS</b>	<p>Dear Authors</p> <p>This is a very well written, timely and interesting paper. I only have some general observations as the study objectives are straightforward. These mainly surround what else could have incorporated to try to gain more insight into the reduction in PCI procedures during the initial two months of Covid-19.</p> <ol style="list-style-type: none"><li>1. Introduction – I understand the objectives of the study by reading the introduction but my personal preference would be to have a sentence at the end of the introduction that clearly demonstrates the aim of the study. For example, if people scan read a paper they can pick out a sentence that summarises what the study aims to do.</li><li>2. Method – To help with replicating the study elsewhere would be beneficial to explain how Acute Coronary Syndrome patients were identified. i.e. ICD-10 codes used?</li><li>3. Results – The discussion explains that additional demographic, clinical or mortality data was not collected. Is this not available or simply the study decided not to incorporate it? Would like this to be</li></ol>
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	<p>made clearer. I think all studies of this nature should have a clear understanding of the study cohort in terms of age, gender, deprivation status etc.</p> <p>4. Following from the above point, the modelling process should then account for these potential confounding factors. Is there a particular group of people that didn't present and therefore receive PCI that did in the past?</p> <p>5. Whilst the study makes it clear it is concentrating on the number of PCI procedures following ACS, I would like to know if the proportion of admissions of ACS that end with a PCI have changed too or has his remained stable? i.e. has there been a change in those being referred to a PCI treatment rather than just the number of people presenting changing? Whilst in the early stages of Covid-19, despite not being "overwhelmed" could there still be an apprehension over what could happen and therefore quickly become "overwhelmed"? Therefore, would be interesting to see what the figures are after the initial two months? Has there been some return to "normality" or has this trend continued? The latter would be very worrying.</p> <p>6. Following from the above, the biggest reduction in IRR was for the treatment of NSTEMI-ACS. From my understanding, there is less urgency around NSTEMI compared to STEMI, which has to be done immediately. Therefore, unlikely maybe, but could part of the reduction in NSTEMI-ACS be potentially down to oversubscribing in the past rather than undersubscribing now? This is why demographic information on understanding the people who did receive PCI, those admitted that didn't receive PCI, and those that didn't present at all is crucial.</p> <p>Many thanks Lloyd</p>
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<b>REVIEWER</b>	Giovanni Esposito University of Naples Federico II, Naples.
<b>REVIEW RETURNED</b>	14-Dec-2020

<b>GENERAL COMMENTS</b>	<p>In this retrospective registry, the authors examined the daily rates of PCI performed for the treatment of ACS, during three different time periods, in relation to the COVID-19 outbreak in Ireland. A total of 490 ACS-PCI in the 2020-PreCOVID period (the two months preceding the first confirmed COVID-19 case) was performed for the treatment of all categories of ACS. On the other hand, only a total of 387 ACS-PCI cases were performed during the 2020-COVID period (the succeeding two months). During the two months since the first confirmed COVID-19 case, PCI rates for the treatment of all ACS, NSTEMI-ACS and STEMI dropped by 24%, 29% and 18%, respectively. As compared to the 2019 Reference period (436 PCI cases), there was a 22% reduction of PCI performed for the treatment of STEMI during the 2020-COVID period.</p> <p>This reviewer has the following comments:</p> <ul style="list-style-type: none"> <li>- The retrospective design and the non-inclusion of all PCI centers in Ireland represent two important limitations.</li> <li>- Please provide the area and the population served by the centers included in the analysis.</li> <li>- The statistical analysis section should be improved because it is quite succinct in its present form. Please amend this section by improving the explanation of IRR for the busy readers.</li> <li>- It is unclear to this reviewer, the denominators used to calculate the IRR (Reference 2019?).</li> </ul>
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	<ul style="list-style-type: none"> <li>- Table 1 and 2 are in the text and at the end. This is redundant and the number of Tables/Figures for this journal is up to 5. Can authors delete a copy?</li> <li>- The overall STEMI rate in January/February 2019 with that of March/April 2019 aren't shown in the table, can authors add them?</li> <li>- In the discussion section the authors reported: "It is also unlikely that the observed reduction in ACS treatments could be fully explained by changes in lifestyle or environmental factors, such as workplace stressors or exposure to air pollution, factors that have previously been associated with ACS". Of course, the reduction in PCI rates due to ACS could not be only explained by changes in lifestyle or environmental factors. However, we cannot exclude a true reduction of MI rate due to a paradoxical beneficial effect of social containment, which leads to a more relaxed lifestyle. As such, a sedentary lifestyle may be acutely protective in those carrying vulnerable plaques. Furthermore, the reduction of air pollution might represent another important protective factor. Recent data show that major cities that suffer from the world's worst air pollution have seen reductions of deadly particulate matter by up to 60% from the previous year, during lockdown period. It is well recognized that one of the triggering factors of STEMI is the presence of air pollutants including sulfur dioxide, nitric dioxide, carbon monoxide, ozone, and particulate matter (including PM2.5 and PM10). The authors may wish to expand this part in the discussion section.</li> <li>- The authors may wish also to discuss the decline in PCI rates observed in other countries (doi: 10.1161/CIRCULATIONAHA.120.046928; doi: 10.1161/CIRCINTERVENTIONS.120.009654).</li> <li>- The authors may wish to emphasize that the lack of data for Ireland on this topic.</li> <li>- In Figure 1, the orange dotted line represents the national closure of schools on 13th March, while the red dotted line represents the date of full implementation of the block on 28th March. But, in the figure, the orange dotted line is 12th March and the red dotted line is 26th March. Please revise.</li> <li>- The reduction for non-ST-segment-elevation ACS was greater than STEMI.</li> <li>- Did the authors collect information about age and gender?</li> </ul>
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**VERSION 1 – AUTHOR RESPONSE**

**Reviewer: 1**

**Dr. Derek Chew, Flinders Medical Centre**

Comments to the Author:

This analysis of the PCI rates for ACS in Ireland is a relatively simple observational analysis describing a phenomenon/change in hospital attendance pattern that is consistent with what has been reported in many centres around the world.

It is suggested that the authors may enhance the analysis by including outcome data for this cohort, such as the 30 day mortality rate for ACS receiving PCI, propensity matched for study period, and or the mortality rate for ACS in Ireland in these contrasting periods.

Many thanks for your comments. We are aware of the simplicity of our study, unfortunately specific data on mortality is not available at this juncture in this retrospective study owing to the complexities of the medical system, a predominantly paper based record system and the lack of a unified IT system or patient identifier between referring hospitals. We accept this as a limitation but believe the data presented still gives novel information on the repercussions of COVID in Ireland not previously published.

**Reviewer: 2**

**Mr. Lloyd Evans, Public Health Wales**

Comments to the Author:

Dear Authors

This is a very well written, timely and interesting paper. I only have some general observations as the study objectives are straightforward. These mainly surround what else could have incorporated to try to gain more insight into the reduction in PCI procedures during the initial two months of Covid-19.

1. Introduction – I understand the objectives of the study by reading the introduction but my personal preference would be to have a sentence at the end of the introduction that clearly demonstrates the aim of the study. For example, if people scan read a paper they can pick out a sentence that summarises what the study aims to do.

The end of our introduction has been modified to restate the aim as a summarising sentence.

*‘Our goal is to evaluate temporal trends of acute coronary syndromes treated via percutaneous coronary intervention during and before the COVID-19 outbreak in a European healthcare system affected but not overwhelmed by COVID-19 related pathology.’*

2. Method – To help with replicating the study elsewhere would be beneficial to explain how Acute Coronary Syndrome patients were identified. i.e. ICD-10 codes used?

This information has been provided in the methods section as below.

*'Cases were identified by combining cardiac catheterisation laboratory records showing performed PCI and hospital admission records. The data was cross-referenced with patient's paper and electronic records to provide accurate descriptors of the indication for PCI based on ESC defined diagnoses.'*

*'The overall PCI group ('All ACS') was dichotomised into two groups, as defined by the European Society of Cardiology guidelines: (1) 'STEMI', and, (2) 'NSTEMI-ACS', with the latter representing PCI performed for non-ST elevation myocardial Infarction (NSTEMI) and unstable angina (UA)[14,15].'*

3. Results – The discussion explains that additional demographic, clinical or mortality data was not collected. Is this not available or simply the study decided not to incorporate it? Would like this to be made clearer. I think all studies of this nature should have a clear understanding of the study cohort in terms of age, gender, deprivation status etc.

We agree fully with this major limitation. Unfortunately, the complexity of the system did not make it possible to add clinical outcome data. This has been acknowledged in the limitation section.

*'Additional complete clinical and mortality data were not available for all centres participating and therefore were not analysed.'*

4. Following from the above point, the modelling process should then account for these potential confounding factors. Is there a particular group of people that didn't present and therefore receive PCI that did in the past?

In this study we describe the overall effect of reduced numbers of PCI. There are less presentations of STEMI, but also less PCI for NSTEMI-ACS. The cause for that is potentially multifold: a decrease in prevalence of ACS, and on the other hand, patients not seeking medical attention. There are no indications from our experience that specific groups of patients were not referred to a cathlab or deferred from stenting because the system was overwhelmed during these initial phases of the

pandemic surge. However we have not specifically studied this in our analysis as demographic data were not fully available. We have acknowledged this as a limitation in the discussion paragraph as seen here.

*'Additional complete clinical and mortality data were not available for all centres participating and therefore were not analysed.'*

5. Whilst the study makes it clear it is concentrating on the number of PCI procedures following ACS, I would like to know if the proportion of admissions of ACS that end with a PCI have changed too or has his remained stable? i.e. has there been a change in those being referred to a PCI treatment rather than just the number of people presenting changing?

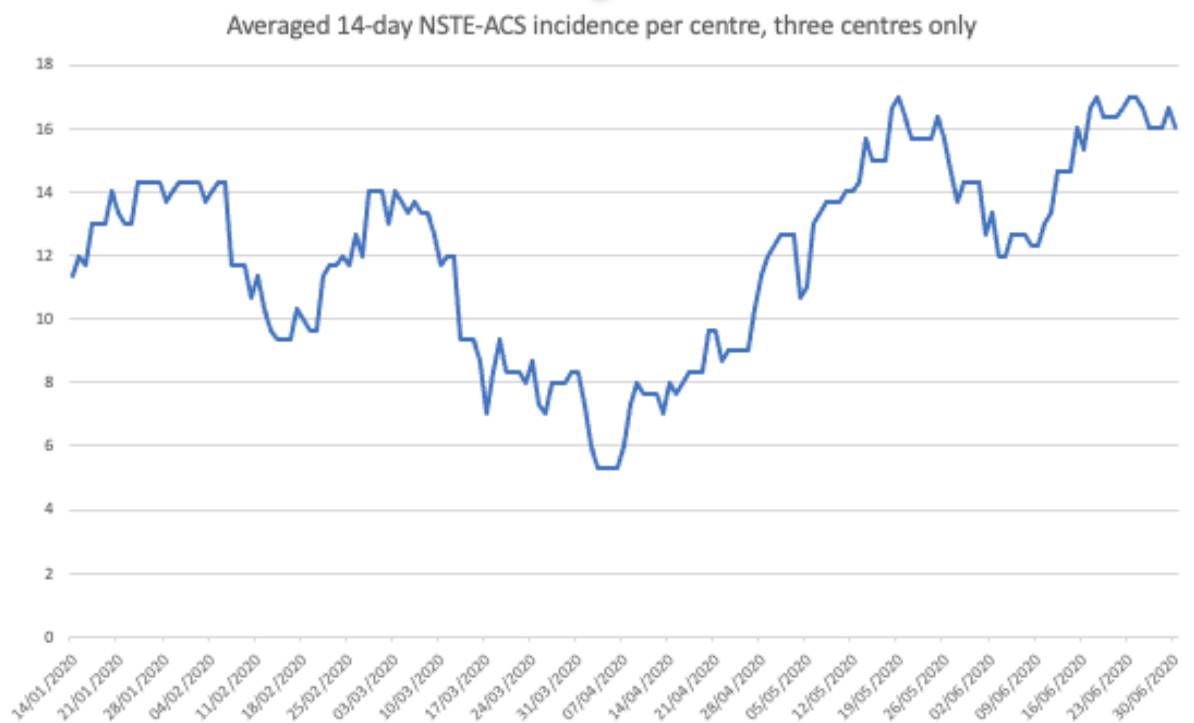
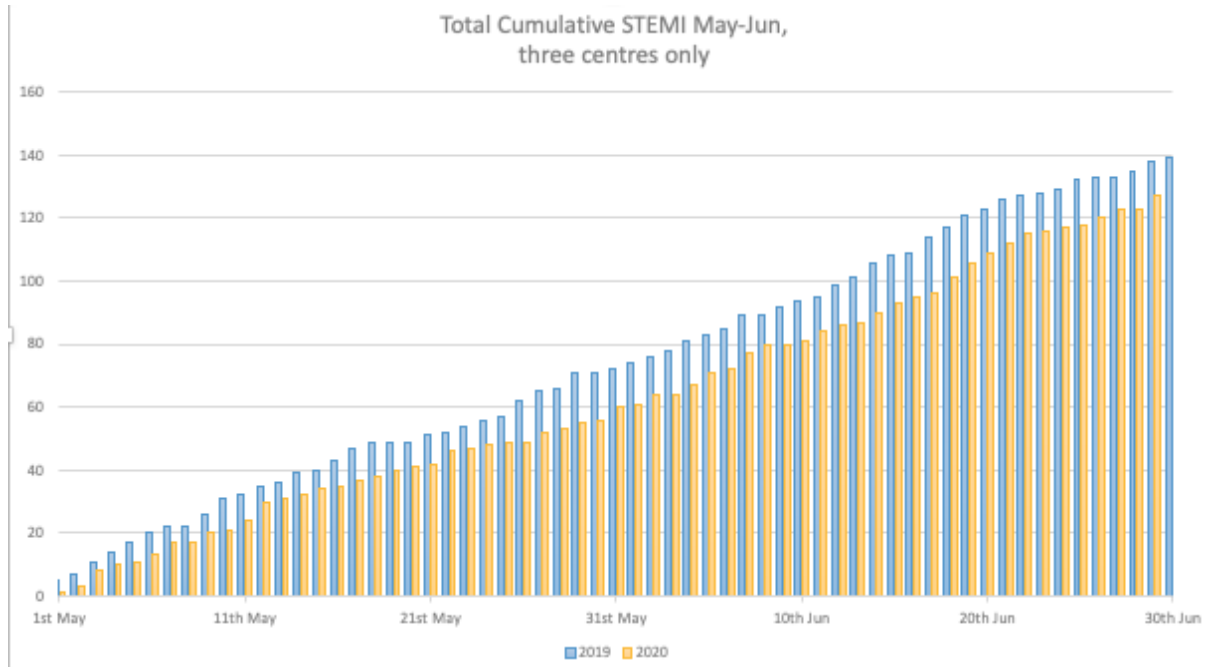
The authors agree that this would be very interesting. The choice for using patients who have had PCI performed as the basis of the study was taken on the basis that Cath Lab records represented the most readily identifiable patient cohort on which to provide an accurate comparison (there is image based confirmation of intervention as well as accurate legal logs given the patients received radiation). Given the study is based on patients referred to the specialist centre it is not possible to analyse the proportion of patients treated in non-specialist centres which were not referred as these centres could not be included and the data would not be complete. We have acknowledged this limitation in the limitation section as below.

*'Further information on the number of ACS presentations to the participating hospitals as well as referrals for intervention from district hospitals that were treated non-invasively were not available.'*

5a. Whilst in the early stages of Covid-19, despite not being “overwhelmed” could there still be an apprehension over what could happen and therefore quickly become “overwhelmed”? Therefore, would be interesting to see what the figures are after the initial two months? Has there been some return to “normality” or has this trend continued? The latter would be very worrying.

The authors agree that follow-up trends would be very interesting to assess for a return to normality and recovery of PCI rates. Initial assessment on incomplete data suggested a sustained reduction in STEMI but a recovery in NSTEMI-ACS presentations see graphs for illustrative purposes

only below. However these trends are based on data only available from three centres of the five participating centres, leaving a substantial gap in data and as a result this has not been included in the paper.



6. Following from the above, the biggest reduction in IRR was for the treatment of NSTEMI-ACS. From my understanding, there is less urgency around NSTEMI compared to STEMI, which has to be done immediately. Therefore, unlikely maybe, but could part of the reduction in NSTEMI-ACS be potentially down to oversubscribing in the past rather than undersubscribing now? This is why demographic information on understanding the people who did receive PCI, those admitted that didn't receive PCI, and those that didn't present at all is crucial.

The definition for including PCI subjects in this study for STEMI and NSTEMI-ACS is the same in pre-COVID period versus COVID period. Unfortunately we lack data on patients that had STEMI or NSTEMI-ACS that presented to the hospital but did not receive PCI as well as patients that did not present to the hospital. We agree with the reviewer that this could help identify why PCI numbers have decreased. Unfortunately we do not have these data available, this is highlighted in the limitation section and we have discussed potential mechanisms further in the text also.

*'Using ACS-related PCI activity could underestimate the true incidence of ACS presenting to hospitals due to alterations in clinical practice patterns, such as an increased use of non-invasive strategies.'*

*'Further information on the number of ACS presentations to the participating hospitals as well as referrals for intervention from district hospitals that were treated non-invasively were not available'*

*'We must also consider the potential effect of physician selection of patients for intervention on PCI rates. A more conservative approach to patient selection could contribute to a fall in invasive intervention with more patients being managed non-invasively. Misconceptions in the required acuity of management of STEMI vs NSTEMI-ACS could also lead to differences in referral patterns from non-specialist centres. Assuming a tendency towards a more conservative approach to management of NSTEMI-ACS could explain why the drop in procedures was more exaggerated in this group. Indeed a suggestion of a move to a lower risk profile of patient has been seen during the pandemic in other jurisdictions that also showed drops in PCI rates for STEMI and NSTEMI-ACS[23].'*



Many thanks

Lloyd

**Reviewer: 3**

**Dr. Giovanni Esposito, Univ Naples Federico II**

Comments to the Author:

In this retrospective registry, the authors examined the daily rates of PCI performed for the treatment of ACS, during three different time periods, in relation to the COVID-19 outbreak in Ireland. A total of 490 ACS-PCI in the 2020-PreCOVID period (the two months preceding the first confirmed COVID-19 case) was performed for the treatment of all categories of ACS. On the other hand, only a total of 387 ACS-PCI cases were performed during the 2020-COVID period (the succeeding two months). During the two months since the first confirmed COVID-19 case, PCI rates for the treatment of all ACS, NSTEMI-ACS and STEMI dropped by 24%, 29% and 18%, respectively. As compared to the 2019 Reference period (436 PCI cases), there was a 22% reduction of PCI performed for the treatment of STEMI during the 2020-COVID period.

This reviewer has the following comments:

- The retrospective design and the non-inclusion of all PCI centres in Ireland represent two important limitations.

We agree with the reviewer. That this represents an important limitation and this has been highlighted in the limitation section. Due to the timely data collection at that time, we could only collect data from 5 of 6 primary PCI centres. Our study covers 79.7% of PCI for STEMI in non-COVID years, so we do represent a significant part of PCI performed in Ireland.

- Please provide the area and the population served by the centres included in the analysis.

This has been clarified further in the study population paragraph of the methods as below.

*'The five participating centres in this study account for 79.7% of all STEMI presentations in Ireland (est. population 4.90 million in 2020) based on the latest published national data[12,13].'*

- The statistical analysis section should be improved because it is quite succinct in its present form. Please amend this section by improving the explanation of IRR for the busy readers. - It is unclear to this reviewer, the denominators used to calculate the IRR (Reference 2019?).

We thank the reviewer for the comment and have rewritten the statistical analysis paragraph with excerpt below with further clarification of the IRR.

*'The '2019-Reference' and the '2020-PreCOVID' periods are compared with the more recent '2020-COVID' time period, results are presented as incidence rate ratios (IRR) along with corresponding 95% confidence intervals and p-values. The IRR represents the ratio of the current rate of PCI relative to the preceding rate. IRR values below 1.0 suggest a reduction in PCI over time, whereas values above 1.0 would suggest an increase in PCI.'*

- Table 1 and 2 are in the text and at the end. This is redundant and the number of Tables/Figures for this journal is up to 5. Can authors delete a copy?

We have deleted the relevant documents and the tables now only appear in the text.

- The overall STEMI rate in January/February 2019 with that of March/April 2019 aren't shown in the table, can authors add them?

We have updated the tables accordingly as can be seen below.

Table 1. Mean and standard deviation of daily PCI procedures per centre for All ACS, NSTEMI-ACS and STEMI cases.

<b>Period</b>	<b>Total</b>	<b>Daily mean per centre</b>	<b>±SD</b>
<i>All ACS</i>			
<i>2020-COVID<sup>a</sup></i>	<i>387</i>	<i>1.25</i>	<i>1.34</i>
<i>2020-PreCOVID<sup>b</sup></i>	<i>490</i>	<i>1.66</i>	<i>1.66</i>

<i>NSTE-ACS</i>			
<i>2020-COVID<sup>a</sup></i>	<i>212</i>	<i>0.68</i>	<i>1.07</i>
<i>2020-PreCOVID<sup>b</sup></i>	<i>288</i>	<i>0.98</i>	<i>1.29</i>
<i>STEMI</i>			
<i>2020-COVID<sup>a</sup></i>	<i>175</i>	<i>0.56</i>	<i>0.77</i>
<i>2020-PreCOVID<sup>b</sup></i>	<i>202</i>	<i>0.68</i>	<i>0.86</i>
<i>2019-Reference<sup>c</sup></i>	<i>436</i>	<i>0.73</i>	<i>0.92</i>
<i>2019-Jan/Feb<sup>d</sup></i>	<i>207</i>	<i>0.70</i>	<i>0.91</i>
<i>2019-Mar/Apr<sup>e</sup></i>	<i>229</i>	<i>0.75</i>	<i>0.94</i>

<sup>a</sup>*2020-COVID is February 29<sup>th</sup> - April 30<sup>th</sup>, 2020 (62 days);*

<sup>b</sup>*2020-PreCOVID is January 1<sup>st</sup> - February 28<sup>th</sup>, 2020 (59 days);*

<sup>c</sup>*2019-Reference is January 1<sup>st</sup> - April 30<sup>th</sup>, 2019 (120 days);*

<sup>d</sup>*2019-Jan/Feb is January 1<sup>st</sup> - Feb 28<sup>th</sup>, 2019 (59 days);*

<sup>e</sup>*2019-Mar/Apr is March 1<sup>st</sup> - April 30<sup>th</sup>, 2019 (61 days).*

- In the discussion section the authors reported: "It is also unlikely that the observed reduction in ACS treatments could be fully explained by changes in lifestyle or environmental factors, such as workplace stressors or exposure to air pollution, factors that have previously been associated with ACS". Of course, the reduction in PCI rates due to ACS could not be only explained by changes in

lifestyle or environmental factors. However, we cannot exclude a true reduction of MI rate due to a paradoxical beneficial effect of social containment, which leads to a more relaxed lifestyle. As such, a sedentary lifestyle may be acutely protective in those carrying vulnerable plaques. Furthermore, the reduction of air pollution might represent another important protective factor. Recent data show that major cities that suffer from the world's worst air pollution have seen reductions of deadly particulate matter by up to 60% from the previous year, during lockdown period. It is well recognized that one of the triggering factors of STEMI is the presence of air pollutants including sulfur dioxide, nitric dioxide, carbon monoxide, ozone, and particulate matter (including PM<sub>2.5</sub> and PM<sub>10</sub>). The authors may wish to expand this part in the discussion section.

We agree with the reviewer and have expanded our discussion in that regard with particular reference to Ireland.

*'Potential factors for an observed reduction in ACS treatments include changes in lifestyle or environmental factors, such as workplace stressors or exposure to air pollution. The link between environmental pollution and cardiovascular outcomes is long established with both short and long term exposures to pollutants such as PM<sub>2.5</sub> (fine particulate matter  $\leq 2.5 \mu\text{m}$  in aerodynamic diameter), Nitrogen Dioxide and Ozone linked with ACS[17,18]. Indeed, there have been changes in air quality recorded during lockdowns for COVID-19, both in Ireland and abroad with Nitrogen Dioxide levels in Ireland well-below expected levels compared to previous years[19-21]. In contrast to findings in major industrial cities worldwide there was not a significant drop in PM<sub>2.5</sub> in Ireland[22]. However, it remains plausible that a rapid reduction in particulate and other environmental pollutants could contribute to a reduction in ACS incidence and mortality.'*

- The authors may wish also to discuss the decline in PCI rates observed in other countries (doi: 10.1161/CIRCULATIONAHA.120.046928; doi: 10.1161/CIRCINTERVENTIONS.120.009654).

This is a relevant comment. During the course of this submission process, data of other countries have become available. This has been added in the discussion, see sample excerpts below.

*'It has been shown in other jurisdictions that the hospital admission rate for ACS itself has declined and the reduction in admissions is also mirrored in a downward trend in PCI rates[16].'*

*'Indeed a suggestion of a move to a lower risk profile of patient has been seen during the pandemic in other jurisdictions that also showed drops in PCI rates for STEMI and NSTEMI-ACS[21].'*

- The authors may wish to emphasize that the lack of data for Ireland on this topic.

We agree with the reviewer and have emphasized this further in the discussion and limitations paragraphs.

*' Using ACS-related PCI activity could underestimate the true incidence of ACS presenting to hospitals due to alterations in clinical practice patterns, such as an increased use of non-invasive strategies.'*

*'Further information on the number of ACS presentations to the participating hospitals as well as referrals for intervention from district hospitals that were treated non-invasively were not available.'*

- In Figure 1, the orange dotted line represents the national closure of schools on 13th March, while the red dotted line represents the date of full implementation of the block on 28th March. But, in the figure, the orange dotted line is 12th March and the red dotted line is 26th March. Please revise.

Thank you for this observation, we have made corrective changes accordingly in Figure 1.



- The reduction for non-ST-segment-elevation ACS was greater than STEMI.

This is an important point and factors which likely play a significant part of this have been discussed further in the text.

*'We must also consider the potential effect of physician selection of patients for intervention on PCI rates. A more conservative approach to patient selection could contribute to a fall in invasive intervention with more patients being managed non-invasively. Misconceptions in the required acuity of management of STEMI vs NSTEMI-ACS could also lead to differences in referral patterns from non-*

*specialist centres. Assuming a tendency towards a more conservative approach to management of NSTEMI-ACS could explain why the drop in procedures was more exaggerated in this group. Indeed a suggestion of a move to a lower risk profile of patient has been seen during the pandemic in other jurisdictions that also showed drops in PCI rates for STEMI and NSTEMI-ACS[23].'*

- Did the authors collect information about age and gender?

Unfortunately we do not have any demographic data available. Due to the timely collection of data at that time we opted to look at net effects of COVID on PCI numbers. We have highlighted this in the limitation section.

*'Additional complete clinical and mortality data were not available for all centres participating and therefore were not collated.'*

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Derek Chew Flinders University Australia
<b>REVIEW RETURNED</b>	28-Feb-2021
<b>GENERAL COMMENTS</b>	No new comments
<b>REVIEWER</b>	Lloyd Evans Public Health Wales, Wales
<b>REVIEW RETURNED</b>	08-Mar-2021
<b>GENERAL COMMENTS</b>	Dear Author I'm happy that my comments from the first review have been addressed, particularly acknowledging the limitations of the availability of data that would allow a more comprehensive statistical analysis. Many thanks Lloyd
<b>REVIEWER</b>	Giovanni Esposito Federico II University of Naples. Italy.
<b>REVIEW RETURNED</b>	14-Mar-2021
<b>GENERAL COMMENTS</b>	The authors have adequately addressed all comments.