

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Retrospective cohort analysis of Spanish national trends of coronary artery bypass grafting and percutaneous coronary intervention from 1998 to 2017
<b>AUTHORS</b>	CARNERO ALCAZAR, MANUEL; Hernandez-Vaquero, Daniel; Cubero-Gallego, Hector; Lopez Menendez, Jose; Piñon, Miguel; Albors Martin, Jose; Cuerpo Caballero, Gregorio; Cobiella Carnicer, Javier; Villamor, Cristina; Forteza, Alberto; Pascual, Isaac; Maroto Castellanos, Luis

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Kristen Tecson Baylor Heart and Vascular Institute, USA
<b>REVIEW RETURNED</b>	14-Dec-2020

<b>GENERAL COMMENTS</b>	<p>Title: Descriptive analysis of Spanish national trends of coronary artery bypass grafting and percutaneous coronary intervention from 1998 to 2017. bmjopen-2020-046141</p> <p>Summary: The authors utilized a nationwide Spanish database of revascularization procedures to evaluate trends over 20 years. The authors determined that revascularization, overall, increased over time; however, this was driven solely by PCI, as CABG use declined. The authors also found that while patients became increasingly more burdened by comorbidities, the (adjusted) in-hospital mortality rates declined over time.</p> <p>Strengths: Great database – nationwide, mandatory/complete. 20 years. Excluded AMI patients to increase comparability between treatment groups. No concomitant procedures included.</p> <p>Weaknesses: 39% of the database was excluded; I would be interested to know the trend/volume of exclusion by year.</p> <p>Major points:</p> <p>Abstract: The observed increase in (raw) volume does not account for changes in the nation's population – this needs to be standardized to the census demographics (per 100,000 persons, for example). After writing this comment, I see that the authors did so in the main text in terms of 1 million inhabitants – was this in terms of adult inhabitants? Please clarify.</p> <p>Please comment on the choice to exclude “Patients discharged alive earlier than two days after the procedure.” For uncomplicated PCI recipients, 1 overnight stay should be reasonable.</p> <p>It is noteworthy that elective revascularizations declined; please discuss further.</p> <p>It is odd that hospital volume had differential associations with mortality rates by revascularization method. Can you please provide additional commentary on that?</p>
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	<p>Minor points:  Abstract Line 26: please add “)” after “p&lt;0.001”.  Intro Line 19: please change “and the risk profiles” to “nor the risk profiles”</p> <p>I know that this is not the purpose of the manuscript, but it could be an interesting addition to include the trend of individuals who have CAD (and then to observe the revascularization trends in terms of rates).  While I agree with the observed increase in age and comorbidity burden, is it also possible that the documentation of comorbidities changed in 20 years (for example, the # of POAs that could be coded may have increased)?</p> <p>Page 6/8 Line 43: “increase” to “increased”  Line 47: “on addition” to “in addition”  Line 47-54: when talking about the differences in estimated CABGs per center – an additional explanation is the use of median vs means, which are and are not robust to skew, respectively.</p> <p>Conclusions line 13: “intensity of the reduction has been particularly intense” to “the reduction has been more pronounced”</p> <p>Conclusions line 14: I’m not sure that ‘atomization’ is the correct word here.</p> <p>Table 1: please change “global” to “overall” or “combined” or “total”</p> <p>Is it possible that patients are counted multiple times (throughout the years and also across revascularization groups)?</p> <p>Table 3 line 26: “data is shown” to “data are shown”</p> <p>Table 3 could be supplementary since this information is already implied by the results in tables 1 and 2.</p> <p>Figure 1. Please use commas instead of periods</p> <p>Figure 2. Please change ‘global’ to ‘overall’ or ‘combined’ or ‘total’</p> <p>RAMR Figure and supplemental figure 1: please change ‘Ano’ to ‘year’ and change the triangle marker to a circle, to be consistent with the other figures. Similarly, please use consistent line styles throughout (e.g., because figure 1 has 3 lines in it, including the overall, the line styles do not match the remaining graphs – CABG is a solid line in figures 2 and 3, but dashed in figure 1).</p> <p>For supplemental figure 1, is it possible to add a marker for the years when new hospitals were opened? I am wondering if the addition of the hospitals explains the dips in the lines for PCI.</p>
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<b>REVIEWER</b>	Mamas Mamas keele university, UK
<b>REVIEW RETURNED</b>	06-Jan-2021

<b>GENERAL COMMENTS</b>	The authors have undertaken an analysis from the Spanish NHS to report on temporal trends in coronary revascularisation over a 20 year period, and have described changes in case mix and
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	<p>clinical outcomes. the paper represents an important area of research, particularly in an arena where there is little robust national data from Spain.</p> <p>I think that the manuscript can be substantially improved however- the manuscript is written from a surgical perspective which is unsurprising given that author group are predominantly cardiac surgeons. i think that the paper would be significantly strengthened through inclusion of interventional cardiologists, and would improve quality of paper through giving incite into changes in interventional practice</p> <p>specific comments:</p> <p>1) figure 2 is number of procedures. this will be determined by population changes too. the authors should plot changes in activity per 100,000 or million population. Please can they also present graphs by: 1) sex 2) age groups 3) stable vs ACS. i think that this would be particualrly interesting and would be relevant from a national practice perspective to see whether the changes they describe are seen in all / some pt groups</p> <p>2) whilst a lot of detail has been added around surgery, there is very little detail around PCI that is important and can be derived from ICD9/10 codes- again involving interventional colleagues will help you capture this such as IVUS/OCT use, DES/BMS, no of stents, etc etc.</p> <p>3) why have authors excluded pts where length of stay is less than 2 days? much of europe has moved to day case PCI where LOS will be shorter than 2 days. this will result in exclusion (inappropriately) of a large number of cases.</p> <p>4) please add a figure in changes in charlson comorbidity index over time for PCI and CABG- this will be informative</p> <p>5) have the authors included pts that underwent CABG and a valve procedure ie SAVR/ MVR? they should do, as otherwise this will grossly undereport surgical revasc rates. They may wish to include this as a third group (ie PCI, CABG, CABG +Valve)</p> <p>6) i agree with their view taht comparison of outcomes between pci vs cabg shouldnt be made- these are very different cohorts</p> <p>7) the discussion should be framed around how developments in PCI/ CABG practice have resulted in the changes that they decscribe, and how guidelines may have driven this0- again why it is important to involve interventional cardiologists</p>
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<b>REVIEWER</b>	Akash Kataruka University of Washington Seattle, WA
<b>REVIEW RETURNED</b>	19-Jan-2021

<b>GENERAL COMMENTS</b>	<p>The authors present interesting analysis from the Spanish national database regarding the temporal trend in coronary revascularization, risk profiles and outcomes. Interesting observations emerged from the analysis including an increase in PCI volume and decrease in CABG volume, along with reduction in risk adjusted inpatient mortality.</p> <p>MAJOR comments:</p> <p>1. The authors state in the abstract that acute myocardial infarction was excluded in the analysis. It is unclear to me if the authors meant all MI (STEMI and NSTEMI) or simply STEMI. Table 1 includes NSTEMI so I presume it is only STEMI. The authors need to clarify their exclusion and provide justification for the exclusion</p>
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	<p>2. The authors used the Charlston Comorbidity index to capture overall risk profile. I agree with the use of a composite risk score to capture risk rather than individual risk factors. Can the authors provide justification regarding the Charlston index rather than the Framingham risk score or NCDR CathPCI Mortality risk?</p> <p>3. For overall revascularization volume in Figure 2 - can the authors stratify by indication (stable ischemic heart disease and NSTEMI-ACS)?</p> <p>4. The significant increase in PCI volume is different than the observation in the United States where PCI volume has decreased in light of randomized trials demonstrating similar outcomes between invasive and medical management. Can the authors provide additional information why PCI volume may have increased - more PCI centers, change in policy unique to Spain, change in insurance/reimbursement. I think the discussion would be important to contextualize the findings for international readers.</p> <p>5. The authors performed a stepwise logistic regression and display the coefficients from the multivariate logistic regression. It is unclear to me why the odds of death would be higher at higher volume center compared with low volume center adjusting for the remaining variables. One explanation would be more complex disease at higher volume center.</p> <p>6. The authors provide interesting descriptive analysis regarding number of vessels treated. Can the authors investigate the number of diabetic patients underlying multivessel revascularization. This would be important to describe as these patients would benefit more from CABG.</p> <p>MINOR</p> <p>1. Are additional descriptive variables regarding PCI available - atherectomy, left main revascularization etc.?</p> <p>2. Surgical turndowns are known to have higher risk despite risk adjustment. If description for turndown is available it should be described; if not then include as limitation</p> <p>3. Missing data is common in administrative/billing data. Can the authors comment on the missigness of the data and if imputation was used for risk adjustment variables?</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

Title: Descriptive analysis of Spanish national trends of coronary artery bypass grafting and percutaneous coronary intervention from 1998 to 2017.

bmjopen-2020-046141

Summary: The authors utilized a nationwide Spanish database of revascularization procedures to evaluate trends over 20 years. The authors determined that revascularization, overall, increased over time; however, this was driven solely by PCI, as CABG use declined. The authors also found that while patients became increasingly more burdened by comorbidities, the (adjusted) in-hospital mortality rates declined over time.

Strengths: Great database – nationwide, mandatory/complete. 20 years. Excluded AMI patients to increase comparability between treatment groups. No concomitant procedures included.

Weaknesses: 39% of the database was excluded; I would be interested to know the trend/volume of exclusion by year.

\*\*\* Comment

Thanks for the comment. Perhaps we, the authors, see it as a strength. First, we searched the national database for procedural codes. Next, we excluded all concomitant procedures and patients with acute myocardial infarction to define a group of patients where the evolution of both techniques could be analyzed. For example, it would have been of little interest to include patients undergoing coronary and aortic valve surgery or TAVR with PCI. Furthermore, the mortality analysis would have been highly biased if concomitant procedures had been included. In the same way, we understand that acute myocardial infarction as an admission diagnosis had to be excluded because the indication of surgery in this entity is marginal.

We have included Figure 1 and a Table 2 in the supplementary material to represent the variation of the excluded volume and the main reasons of exclusion throughout the study period. It can be seen that the volume of excluded episodes increased linearly between the first and the last period. This variation was mainly explained by an increase in the volume of patients in whom an acute myocardial infarction with ST elevation was coded as the main diagnosis on admission. There was also an increase in the proportion of patients excluded for coding reasons (consolidation of episodes, coding errors, etc.)

Major points:

1. Abstract: The observed increase in (raw) volume does not account for changes in the nation's population – this needs to be standardized to the census demographics (per 100,000 persons, for example). After writing this comment, I see that the authors did so in the main text in terms of 1 million inhabitants – was this in terms of adult inhabitants? Please clarify.

\*\* Comment

In the abstract, we have changed the total volume of patients for the rate of revascularization per million inhabitants per year, following the recommendations of the reviewer.

Change: Lines 51-52: "We observed a 2.2-fold increase in the rate of any type of myocardial revascularization/million inhabitants-year: 357(1998) to 776(2017). 93,682(15.5%) had a coronary surgery. PCI to CABG ratio rose from 2.2 (1998-2002) to 8.1 (2013-2017)."

The population to which the article refers is the total population, not only adults. We have decided to do so in order to replicate the information given in other articles and provided in the OECD or EuroStat reports, so that they can be compared. We have added figures 3A and 3B representing the indexed volume of procedures by age range.

2. Please comment on the choice to exclude "Patients discharged alive earlier than two days after the procedure." For uncomplicated PCI recipients, 1 overnight stay should be reasonable.

We fully agree with the reviewer's comment. Obviously, this is a writing error. We only excluded patients who were discharged two days after CABG, not PCI. In Spain, discharge so early after coronary surgery is marginal, and we consider it a coding error to be cautious. We have changed the text.

Linea 124-125: "Patients discharged alive earlier than two days after CABG were also considered as coding errors"

3. It is noteworthy that elective revascularizations declined; please discuss further.

We appreciate your comment. Indeed, the evolution of the increase in unplanned admissions caught our attention. Reviewing the records of the administrative datastes, we observed that in 2016 and 2017 there was a significant amount of missing data. In addition, there may be an error when classifying transfers from one center to another as urgent or planned admissions. Due to both biases, we decided to withdraw the analysis of the type of admission from the study and consider

Furthermore, we consider that the variable acute coronary syndrome without ST elevation on admission may be more relevant, given that most patients with NSTEMI will have an unplanned admission and it has a direct impact on the therapeutic strategy and its results. It will be, therefore less affected by the biases previously described. Table 1 has been changed.

4. It is odd that hospital volume had differential associations with mortality rates by revascularization method. Can you please provide additional commentary on that?

Our hypothesis is that the most complex patients are referred to high-volume centers. Therefore, it is not so much that being treated on in a high-volume center increases the risk, but rather patients' comorbidities. We believe that these possible comorbidities that may explain this increased mortality may not be adequately collected in the administrative databases, and, therefore, it is difficult to adjust the mortality for them. We have explained this issue in lines 293-296.

Changes. Line 324-325:

The latter can be explained by the fact that patients referred to centers with greater activity may have anatomical characteristics or comorbidities that confer a greater risk, and which have not been adequately contemplated in this study (i.e.: left main disease, severely calcified coronary arteries, poor left ventricular function...).

Minor points:

5. Abstract Line 26: please add ")" after "p<0.001".

Thank you very much for detail. Corrected.

6. Intro Line 19: please change "and the risk profiles" to "nor the risk profiles"

Corrected.

Line 86: nor the risk profile of CABG and PCI patients in the Spanish National Health System (NHS)

7. I know that this is not the purpose of the manuscript, but it could be an interesting addition to include the trend of individuals who have CAD (and then to observe the revascularization trends in terms of rates).

We agree with the reviewer. In fact, it would be very interesting to carry out this study in Spain, taking into account the low rate of revascularization per 100,000 inhabitants. Is it due to a lower incidence of coronary artery disease or is it due to a lower indication for revascularization? Regardless of the fact that, indeed, it would be the subject of a different study, the problem is that the administrative database only collects information on admissions and outpatient procedures, so that we could only evaluate the number of patients with coronary disease admitted and not all who have coronary heart disease. This would make the analysis very complicated and biased. Beyond that, it would be difficult to know if a patient has one or more admissions, since the data is anonymized, so that if, for example, a patient were admitted 5 times for angina, we would be wrongly adding n +4 to the denominator.

8. While I agree with the observed increase in age and comorbidity burden, is it also possible that the documentation of comorbidities changed in 20 years (for example, the # of POAs that could be coded may have increased)?

We agree that variations in the prevalence of comorbidities may be due to errors or changes in coding. We had included a comment on the limitations, but have expanded it to draw the reader's attention to it.

Change: Limitations. Line 339-347: These conclusions have to be taken with caution due to possible coding biases and others inherent to administrative databases analyses. Beyond a real change, the variation in the prevalence of comorbidities can be also partially explained by changes and errors in coding throughout the study period. Surgical turndowns are known to have higher risk despite risk adjustment, but they could not be identified in this dataset. We could not estimate operative or cardiovascular risks according to validated clinical scores in cardiac surgery or cardiology (such as

EuroSCORE, Framingham Risk Score or NCDR CathPCI Mortality risk) given that the items of these scores are not available in the MBDS. The MBDS does not contain information on private activity in Spain.

9. Page 6/8 Line 43: “increase” to “increased”  
Corrected.

10. Line 47: “on addition” to “in addition”  
Corrected. Thank you.

11. Line 47-54: when talking about the differences in estimated CABGs per center – an additional explanation is the use of median vs means, which are and are not robust to skew, respectively. We decided to use the median instead of the mean to express the number of interventions per center because the size of the sample, in this case, is the number of hospitals per year or period, and the study variable is the number of interventions per center and year. Thus, this is a much smaller sample, and we thought it would be more appropriate to use a more robust position statistic such as the median which is less sensitive to extreme values. Thanks for the question.

12. Conclusions line 13: “intensity of the reduction has been particularly intense” to “the reduction has been more pronounced”

We have changed the conclusion according to your suggestion.

Change. Line 332: Risk-adjusted mortality has been significantly reduced in both arms, although the reduction has been particularly pronounced among surgically revascularized patients

13. Conclusions line 14: I’m not sure that ‘atomization’ is the correct word here.

We have changed the sentence to: Line 333-334 “ in Spain, there is not an adequate balance between the volume of revascularizations and the number of hospitals, with centers with a low number of CABG procedures and a great proportion of hospitals with PCI programs but without CABG onsite.

14. Table 1: please change “global” to “overall” or “combined” or “total”  
We have changed it according to your suggestion in table 1. Thank you.

15. Is it possible that patients are counted multiple times (throughout the years and also across revascularization groups)?

Yes. For this reason, we have changed “patients” by “episodes” in Figure 1 and we have included previous CABG and/or PCI variables to adjust outcomes and comparisons. We have added further explanations: Lines 128-131: “Each episode corresponds to a single patient, but a patient might have more than one episode. Given that we analyzed in-hospital outcomes, different consolidated episodes will be considered as different patients for the purpose of this study.”

16. Table 3 line 26: “data is shown” to “data are shown”  
Corrected. Sorry for the mistake.

17. Table 3 could be supplementary since this information is already implied by the results in tables 1 and 2.

We have moved the table to supplementary material following the suggestion of the reviewer.

18. Figure 1. Please use commas instead of periods  
Corrected. Thank you.

19. Figure 2. Please change 'global' to 'overall' or 'combined' or 'total'  
Corrected. Thank you,

20. RAMR Figure and supplemental figure 1: please change 'Ano' to 'year' and change the triangle marker to a circle, to be consistent with the other figures. Similarly, please use consistent line styles throughout (e.g., because figure 1 has 3 lines in it, including the overall, the line styles do not match the remaining graphs – CABG is a solid line in figures 2 and 3, but dashed in figure 1). We have changed figures all throughout the text accordingly. Thank you very much for the comment.

21. For supplemental figure 1, is it possible to add a marker for the years when new hospitals were opened? I am wondering if the addition of the hospitals explains the dips in the lines for PCI. We have added two additional lines showing the number of hospitals of each type that submitted data to the MBDS each year. Supplementary Figure 1 is now Supplementary Figure 5.

Reviewer:2

Comments to the Author:

The authors have undertaken an analysis from the Spanish NHS to report on temporal trends in coronary revascularisation over a 20 year period, and have described changes in case mix and clinical outcomes. the paper represents an important area of research, particularly in an arena where there is little robust national data from Spain.

I think that the manuscript can be substantially improved however- the manuscript is written from a surgical perspective which is unsurprising given that author group are predominantly cardiac surgeons. i think that the paper would be significantly strengthened through inclusion of interventional cardiologists, and would improve quality of paper through giving incite into changes in interventional practice.

According to the reviewer's suggestion, we have included two cardiologists among the authors (third and 11th author). There are two interventional cardiologists and one specialist in internal medicine among the authors.

After reviewing the manuscript with them we have performed some major changes:

1) We have included more episodes of patients undergoing PCI: specifically, we have included those episodes in which ICD-10 procedure codes 02C0xxx, 02C1xxx, 02C2xxx, 02C3xxx, 02C4xxx were performed. Table 1 in supplementary appendix has changed. This has increased the sample size by 1.2%. We have changed the abstract (results section: lines 52-59), results (main text): lines 187-194, lines 259-260 in discussion, table 1 and 2, supplementary figure 2.

2) We have also investigated the type of stent (if any) implanted and if IVUS was performed. We have changed table 1 and 2, results (lines 209-214.)

All the analysis has been re-performed considering these changes.

specific comments:

1) figure 2 is number of procedures. this will be determined by population changes too. the authors should plot changes in activity per 100,000 or million population. Please can they also present graphs by: 1) sex 2) age groups 3) stable vs ACS. i think that this would be particularly interesting and would be relevant from a national practice perspective to see whether the changes they describe are seen in all / some pt groups

Activity data were already represented per million inhabitants in the original text. We have changed



the abstract to make it clear anyway (lines 52-54). Thank you very much for the comment. We have added additional graphs showing the information the reviewer requested. We have moved the figure of the total number of procedures to the supplementary material (supplementary figure 1) We have added three figures to the main text: volume per million inhabitant and sex of each procedure and volume per million inhabitant and age range of each type of procedure (Figures 2A, 2B, 3A & 3B). In addition, we have added in the supplementary material the total number of procedures according to the type of coronary syndrome. (Supplemental Figure 3)

We have added:

Results: line 196-203: "We observe relevant differences in the volume of procedures by sex. Overall, more PCI and CABG were performed in men than in women, but the difference increased more markedly in PCI (Figure 2B). Regarding the type of procedure by age range, PCI increased in all age ranges, although the increase was more pronounced in those over 60 years of age. On the contrary, CABG significantly decreased among those over 70 years of age and experienced a slight decrease in the younger population strata (Figure 3). Absolute number of procedures and according to type of coronary syndrome is shown in supplementary figures 2 and 3."

Discussion: lines 281-283: "Furthermore, we detected large and increasing differences between men and women depending on the type of revascularization (see figure 2), which probably denotes a limited access of women to the healthcare system."

2) whilst a lot of detail has been added around surgery, there is very little detail around PCI that is important and can be derived from ICD9/10 codes- again involving interventional colleagues will help you capture this such as IVUS/OCT use, DES/BMS, no of stents, etc etc.

We have included the type of stents implanted and the use of IVUS in the text, in Table 1, in the analysis of factors associated with mortality and in the predictive models of mortality.

Changes: Table 1, table 2, results (line 209-215)

3) why have authors excluded pts where length of stay is less than 2 days? much of europe has moved to day case PCI where LOS will be shorter than 2 days. this will result in exclusion (inappropriately) of a large number of cases.

This is a writing error. We only excluded patients who were discharged two days after CABG, not PCI. In Spain, discharge so early after coronary surgery is marginal, and we consider it a coding error to be cautious. We have changed the text.

Line 124-125: "Patients discharged alive earlier than two days after CABG were also considered as coding errors"

4) please add a figure in changes in charlson comorbidity index over time for PCI and CABG- this will be informative.

We have added an additional supplementary figure (Figure 4) showing the changes in Charlson's Index.

5) have the authors included pts that underwent CABG and a valve procedure ie SAVR/ MVR? they should do, as otherwise this will grossly underreport surgical revasc rates. They may wish to include this as a third group (ie PCI, CABG, CABG +Valve)

The purpose of our study was to study the trend of isolated coronary procedures and we expressly excluded concomitant procedures. We understand that a valve or thoracic aorta disease combined with coronary stenosis are completely different nosological entities from an isolated coronary disease. Similarly, we understand that a valve replacement or a repair of the thoracic aorta combined with a surgical revascularization are not the same surgical procedure as an isolated coronary surgery. In our humble opinion, it is mixing apples and oranges. Similarly, it would have been incongruous to analyze combined percutaneous procedures (such as TAVR, atrial appendage exclusions, mitraclips, etc ...). In any case, we have reported the proportion of episodes that were excluded due to concomitant

procedures (4.7%) in Table 2 of the supplementary material and in Figure 1.

6) I agree with their view taht comparison of outcomes between pci vs cabg shouldnt be made- these are very different cohorts.

We completely agree. It was not the aim of the study. Thank you.

7) the discussion should be framed around how developments in PCI/ CABG practice have resulted in the changes that they decscribe, and how guidelines may have driven this0- again why it is important to involve interventional cardiologists.

We have included a comment regarding the uneven evolution of PCI and CABG and its relationship with the changes in the indications of the clinical guidelines in the second paragraph of the discussion: Lines 261-269. “In addition, there was, over the past 20 years, a 27.7% reduction in the volume of CABG (5506 in 1998 Vs 3872 in 2017) and a 3.7-fold increase of PCI volume (8735 in 1998 Vs 32272 in 2017). During such a long period of time, the indications for CABG and PCI have varied, mainly in patients with stable 1 or 2-vessel coronary artery disease, with percutaneous revascularization being the most frequently indicated nowadays. In patients with left main or three-vessel disease, the indication for PCI is also gaining strength, although with less intensity. These changes have been mainly due to the development of new percutaneous devices and the optimization of medical treatment. (1,19). Even so, different studies have consistently continued to detect the benefit of CABG in patients with more complex coronary disease (2,20).”

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Kristen M Tecson Baylor Scott & White Research Institute
<b>REVIEW RETURNED</b>	07-Feb-2021

<b>GENERAL COMMENTS</b>	Thank you for your revision, which addresses all of my prior comments. No further suggestions
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<b>REVIEWER</b>	Mamas Mamas Keele University, England
<b>REVIEW RETURNED</b>	04-Feb-2021

<b>GENERAL COMMENTS</b>	The authors have done an excellent job in answering my queries, and i believe that the manuscript has improved. One final analysis that should be included which i think would represent important data for the community (and could be presented as figures is) 1) Growth of CABG in pts with prior PCI 2) Growth of PCI in pts with prior CABG this is important data and shows that often clinically atherosclerosis is a dynamic process and often pts will require different means of revascularisation. there is little data ijn this space and the authors should add a paragraph to their discussion re this.
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<b>REVIEWER</b>	Akash Kataruka University of Washington Seattle, WA, United States
<b>REVIEW RETURNED</b>	11-Feb-2021

<b>GENERAL COMMENTS</b>	The authors have made major revisions to strengthen the manuscript. The additional details about the patient population and description of revascularization volume by indication is insightful.
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

Thank you for your revision, which addresses all of my prior comments. No further suggestions

\*\*\* Comment

Thank you for your comment.

Reviewer:2

Comments to the Author:

The authors have done an excellent job in answering my queries, and i believe that the manuscript has improved. One final analysis that should be included which i think would represent important data for the community (and could be presented as figures is)

1) Growth of CABG in pts with prior PCI

2) Growth of PCI in pts with prior CABG

this is important data and shows that often clinically atherosclerosis is a dynamic process and often pts will require different means of revascularisation. there is little data in this space and the authors should add a paragraph to their discussion re this.

\*\* Comment

According to the reviewer's suggestion, we have added a comment in the results (lines 220-225) and a paragraph in the discussion (lines 304-309) on the variation in the proportion of patients with previous revascularizations. In addition, we have added a supplementary figure showing these findings. Thank you very much for your comment-

Line 220-225: The proportion of patients with previous revascularization increased linearly throughout the study: (1998-2002: 13.9%;2003-2007: 19.4%; 2008-2012:25.3%; 2013-2017:29.4%;  $p < 0.001$ ). Most of this increase was due to a growth of revascularized patients with previous PCI, while the number of patients undergoing CABG or PCI with a history of previous surgery decreased or increased minimally, respectively (Table 1 and Supplementary Figure 5).

Line 304-309: The increase in the proportion of patients requiring a new revascularization increased throughout the study (see Table 1 and Supplementary material). This increase was more notable in PCI and, above all, at the expense of a previous percutaneous revascularization. This finding is consistent with the sustained increase in revascularizations over time, the lower need for re-intervention after CABG, and the preference for percutaneous approaches in the global series (1,2,6,8, 19, 20) (Table 1 and Supplementary Figure 5).

Supplementary Figure 5.

Reviewer: 3

Comments to the Author:

The authors have made major revisions to strengthen the manuscript. The additional details about the patient population and description of revascularization volume by indication is insightful.

**\*\*Comment**

Thank you very much for your comment. Your review has been of great help to improve the paper.

**VERSION 3 – REVIEW**

<b>REVIEWER</b>	Mamas Mamas keele university, UK
<b>REVIEW RETURNED</b>	18-Feb-2021
<b>GENERAL COMMENTS</b>	thank you for making changes- no further comments from me