PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Changes in Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction who Underwent Coronary Revascularization in the Past Two Decades: Cohort Study
AUTHORS	Takeji, Yasuaki; Shiomi, Hiroki; Morimoto, Takeshi; Yoshikawa, Yusuke; Taniguchi, Ryoji; Mutsumura-Nakano, Yukiko; Yamamoto, Ko; Yamaji, Kyohei; Tazaki, Junichi; Kato, Eri; Watanabe, Hirotoshi; Yamamoto, Erika; Yamashita, Yugo; Fuki, Masayuki; Suwa, Satoru; Inoko, Moriaki; Takeda, Teruki; Shirotani, Manabu; Ehara, Natsuhiko; Ishii, Katsuhisa; Inada, Tsukasa; Tamura, Toshihiro; Onodera, Tomoya; Shinoda, Eiji; Yamamoto, Takashi; Watanabe, Hiroki; Yaku, Hidenori; Nakatsuma, Kenji; Sakamoto, Hiroki; Ando, Kenji; Soga, Yoshiharu; Furukawa, Yutaka; Sato, Yukihito; Nakagawa, Yoshihisa; Kadota, Kazushige; Komiya, Tatsuhiko; Minatoya, Kenji; Kimura, Takeshi

VERSION 1 – REVIEW

REVIEWER	Mario Gramegna Cardiac Intensive Care Unit - IRCCS San Raffaele Scientific Institute - Milan, Italy
REVIEW RETURNED	22-Sep-2020

GENERAL COMMENTS	In this large, multi-centre registries-based study, Takeji et al. investigated demographics, clinical practices and 3-year outcomes in STEMI patients treated before and after 2010. By analyzing 9001 patients with STEMI, they did not demonstrate an improvement in 3-year mortality, but they found a mortality reduction beyond 30 days in patients treated after 2010. Moreover, they showed a stent thrombosis and any coronary revascularization reduction, but an increase for major bleeding after 2010. The strength of this study is the large sample size. Nevertheless, there are some major and minor issues. Major issues: 1- The authors should better specify in the introduction why they chose 2010 as the “turning” year. Apparently, they have chosen 2010 not only because it is straddling the two registries but also because it is the year of the introduction of the new-generation DES, as stated in the methods. 2- The focus of the paper is on patients with ST-segment-elevation Myocardial Infarction, but in the definitions paragraph it is mentioned the definition of myocardial infarction. The authors should better define how they identified STEMI patients.

	3- Despite patients in Wave-2 were older, sicker, with more incidence of cardiogenic shock, Killip class III/IV and multivessel disease, left ventricle ejection fraction was less often ≤ 40% compared to Wave-1 population. How do the authors explain it? 4- The authors should try to explain deeply the reason why the 30-day mortality rate did not change even if there has been an improvement in the clinical practices. One of the reasons could be that the population of Wave-2 was sicker than Wave-1, so despite the improvement in clinical practice, the primary outcome did not change. 5- One interesting point of the study is the very low use of high-intensity statin. According to the authors, why are high-intensity statins used so little in Japanese population? Minor issues: 1- There are some typos in the text, please double-check the text (e.g. page 5, lines 11-12: “This study was a historical comparison should result in systematic differences in selection of patients and acqisition of outcomes”)

REVIEWER	Sivabaskari Pasupathy The University of Australia, Australia
REVIEW RETURNED	02-Oct-2020

GENERAL COMMENTS	Takeji et al aimed to compare the changes in demographics, clinical practices, and long-term clinical outcomes of STEMI patients before and after 2010. This registry-based study compared all-cause death and other secondary endpoints cardiovascular death, non- cardiovascular death, myocardial infarction, etc at 3 year. The study did not demonstrate improvement in 3-year mortality risk however they demonstrated reduction in risks for definite stent thrombosis and PCI and increase in bleeding. This study is a retrospective analysis utilising well established registry and the results are well presented and article is well written. The study, while did not demonstrate any historical change withing the time frames assessed, it provides some insights into utility of DES. The article is well written and presented.

REVIEWER	Kristin Kvakkestad, MD, PhD Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway I have a corresponding interest in and am currently working on a manuscript with results from an acute myocardial infarction registry, studying long-term survival in STEMI patients
REVIEW RETURNED	27-Nov-2020

GENERAL COMMENTS	I read with interest your manuscript entitled "Demographics, clinical practices, and long-term outcomes of patients with ST-segment-elevation myocardial infarction in the past two decades: CREDO-Kyoto Acute Myocardial Infarction Registry Wave-1 and Wave-2", written by Takeji Y et al. (Correspondence author: Kimura T., Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan).

	Clinical characteristics and long-term outcomes of STEMI patients treated after 2010 are of interest, since newer treatments have evolved and guidelines for treatment of STEMI patients have been updated. Real-life clinical data from registries after 2010 are sparse. I complement on your work to evaluate changes in demographics, clinical practices and long-term outcomes in STEMI patients before and after 2010. However, I have some comments to your manuscript, especially some methodological concerns. Please see the attached word-file for my questions/comments, and the attached manuscript for minor comments. PEER REVIEW – BMJ Open 2020 – 043683 Title: «Demographics, clinical practices, and long-term outcomes of patients with ST-segment-elevation myocardial infarction in the past two decades: CREDO-Kyoto Acute Myocardial Infarction Registry Wave-1 and Wave-2». By Takeji Y et al. (Correspondence author: Kimura T, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan) Major concerns: Title: - The title does not refer correctly to the study population. This should be changed to state that the study population consists of revascularized STEMI patients. Introduction: - Can you explain why this cohort of revascularized STEMI patients is suitable to evaluate changes in clinical practice before and after 2010? - Why did you include only patients from 2005-07 and 2011-13? It would have been interesting to include data from patients treated in 2008-2010. Methods: - Study population: Did any of the patients receive fibrinolysis before inclusion, or were all patients treated with primary PCI? I cannot find any data on fibrinolytic therapy. - Definitions and clinical outcome measures: At what time point were the baseline characteristics recorded? Was it upon admission to first hospital (around 40% had an inter facility transfer) or at the hospital where the patients were revascularized?

	- Why did you chose so many different secondary outcomes? Some of the outcomes are with competing risks that needs to be considered in the analysis and presentation of your results. How was the clinical distinction between target vessel revascularization (TVR) and ischemia-driven target vessel revascularization, as well as any coronary revascularization versus ischemia driven any coronary revascularization? Please consider to reduce number of outcomes, to avoid multiple testing. - Data collection and follow-up: When was the time for inclusion of the patients? (at the time of the STEMI diagnosis, at the time of admission to first hospital, to the PCI/CABG-centre, at the time of coronary revascularization, or at discharge) - At what time were the follow-up investigations carried out? - Please include in the study flow-chart number of patients were contacted for follow-up, and how many refused to participate, and how many were lost to follow-up because of other causes. - You state that follow-up was censored at 3 years to ensure >90% follow-up. I am concerned that this has affected your results. You need to account for patients at risk at every time point, that possibly can experience the event (i.e include patients who were lost to follow-up, and censore them at the time of last contact) Statistical analysis - Competing risks: You have defined several secondary outcomes with competing risk. I.e. the risk of stents thrombosis mights be lower and major bleeding higher in wave-2, because of competing risks. Please show graphically in the same figure the event free survival/hazard (i.e. Kaplan-Meier) for each of the end-points. (Ref: Cleves M, Gould W, Marchenko YV: Chapter 17 Competing risks. In: An introduction to survival analysis using STATA. 3rd ed: Stata press; 2016. ISBN 13: 978-1-59718-179-2. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999;94(446):496.) - Could you also, for all the end-points, give the median follow-up time for wave-2 versus wave-1? - Proportional hazards assumption: The authors provide assessment of proportional hazards of the included covariates for the whole 3-year period. Please provide evaluation of the global proportional hazards assumption, for the full Cox models for all end-points. Can you explain why a landmark analysis was performed, if it is correct that the proportional hazards assumption was fulfilled for the full Cox models? If you need a landmark analysis because the hazards were not proportional, you also need to build a Cox model for multivariate adjustment for the period 30 days to 3 years. I cannot read from the methods if you have performed such Cox regression models. Discussion

	In general, the discussion is good and well formulated. - There are other studies evaluating clinical practice and outcomes in STEMI patients after the year 2010: Szummer K et al. Eur Heart J. 2017;38:3056-3065, Puymirat E et al. Circulation 2017;136:1908-1919 PubMed . - You should include studies of revascularized STEMI patients for comparison of your results, as we know that a large proportion of STEMI patients still do not receive reperfusion (Widimsky P et al Eur Heart J 2010;31:943-957 PubMed , and Cenko E et al, Eur Heart J – Quality of Care and Clin Outc 2016;2:45-51). - Please discuss the implications of reduced renal function in wave-2 compared to wave-1, and the higher risk of bleeding in wave-2 vs wave 1. - Please discuss the internal and external validity of your results. - Please discuss the limitations of not performing a competing risk analysis, multiple endpoints (the multiple testing problem), and selection bias (only revascularized STEMI patients) Conclusion: Well formulated Minor comments: Please see the full manuscript for implemented comments and corrections

VERSION 1 – AUTHOR RESPONSE

<Response to the comments of the reviewer #1>
Reviewer #1:
#1. The authors should better specify in the introduction why they chose 2010 as the “turning” year. Apparently, they have chosen 2010 not only because it is straddling the two registries but also because it is the year of the introduction of the new-generation DES, as stated in the methods.

We appreciate your valuable comment. As you mentioned, 2010 was the year when the new-generation DES was approved in Japan, and we considered it is important to compare the clinical outcomes between before and after approval of the new-generation DES. Therefore, we modified and added the following statement in the introduction section.

Introduction (Page 7, Line 9 to Page 7, Line 14)
It is currently unknown whether the changes in the guidelines have contributed to change real-world clinical practice and to improve clinical outcomes; in particular, there is a scarcity of data evaluating the long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010, when the new-generation DES was approved in Japan.

#2. The focus of the paper is on patients with ST-segment-elevation Myocardial Infarction, but in the definitions paragraph it is mentioned the definition of myocardial infarction. The authors should better define how they identified STEMI patients.
We appreciate your comment. We added the following statement indicating the definition of STEMI in the methods section.

Methods (Page 9, Line 1 to Page 9, Line 4)
STEMI patients were defined by the electrocardiograms as patients with ≥0.1 mV of ST-segment elevation in ≥2 limb leads or ≥0.2 mV in ≥2 contiguous precordial leads, accompanied by chest pain lasting at least 30 minutes or increased serum levels of cardiac biomarkers such as troponin and/or creatine kinase MB fraction.

#3. Despite patients in Wave-2 were older, sicker, with more incidence of cardiogenic shock, Killip class III/IV and multivessel disease, left ventricle ejection fraction was less often ≤ 40% compared to Wave-1 population. How do the authors explain it?

Thanks for comment. One of the reasons for the lower LVEF in the Wave-1 than in Wave-2 might be related to the larger infarct size as measured by creatine kinase in the Wave-1 than in Wave-2, which could be related to the longer onset-to-balloon time in the Wave-1 than in Wave-2.

#4. The authors should try to explain deeply the reason why the 30-day mortality rate did not change even if there has been an improvement in the clinical practices. One of the reasons could be that the population of Wave-2 was sicker than Wave-1, so despite the improvement in clinical practice, the primary outcome did not change.

We appreciate your valuable comments. As you mentioned, we consider one of the reasons for no improvement in 30-day mortality from Wave-1 to Wave-2 was that the population of Wave-2 was older and had more comorbidities compared to Wave-1. Another reason might be the higher prevalence of hemodynamically unstable patients such as out-of-hospital cardiac arrest or cardiogenic shock in Wave-2. In addition, 30 days may be too short a period to see a survival benefit as a result of improvements in PCI techniques or STEMI systems of care. Indeed, long-term mortality risk had a trend toward improvement in Wave-2.

#5. One interesting point of the study is the very low use of high-intensity statin. According to the authors, why are high-intensity statins used so little in Japanese population?

Thanks for valuable comment. As we described in manuscript, we defined high-intensity statins therapy as the statin doses greater than or equal to atorvastatin 20 mg, pitavastatin 4 mg, or rosuvastatin 10 mg. However, Standard
dose from Japan Phamaceutical Reference was atorvastatin 10 mg, pitavastatin 1-2 mg, or rosuvastatin 5 mg, and therefore, intensive lipid lowering strategy using high-dose statins have not widely been implemented in Wave-1 and Wave-2.
Minor issues:

#6. There are some typos in the text, please double-check the text (e.g. page 5, lines 11-12: “This study was a historical comparison should result in systematic differences in selection of patients and acqisition of outcomes”)

We appreciate your valuable comment. We checked and modified typo.

<Response to the comments of the reviewer #2>

Reviewer: 2
This study is a retrospective analysis utilising well established registry and the results are well presented and article is well written. The study, while did not demonstrate any historical change withing the time frames assessed, it provides some insights into utility of DES. The article is well written and presented.

We deeply appreciate your valuable comment.

<Response to the comments of the reviewer #3>
Reviewer #3:
#1.
Title:
The title does not refer correctly to the study population. This should be changed to state that the study population consists of revascularized STEMI patients.

We appreciate your comment. According to your suggestion, we modified our manuscript title as follows.

Title (Page 1, Line 1 to Page 1, Line 4)
Title: Changes of Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction who Underwent Coronary Revascularization in the Past Two Decades: Cohort Study

#2. Introduction:
Can you explain why this cohort of revascularized STEMI patients is suitable to evaluate changes in clinical practice before and after 2010? Why did you include only patients from 2005-07 and 2011-13? It would have been interesting to include data from patients treated in 2008-2010.

We appreciate your valuable comment. In Japan, 2011 was the year when the new-generation DES was approved, and we considered it is important to compare the clinical outcomes between before and after approval of the new-generation DES among patients who underwent revascularization. Therefore, the Wave-2 was planned to enroll patients between 20111 and 2013. Unfortunately, we did not have data between 2008-2010.

#3. Study population: Did any of the patients receive fibrinolysis before inclusion, or were all patients treated with primary PCI? I cannot find any data on fibrinolytic therapy.

Thanks for your question. This study enrolled consecutive patients who underwent coronary revascularization for AMI within 7 days from the onset. We did not have detailed data about fibrinolysis. However, in Japan, it is quite rare to implement fibrinolysis before revascularization.

#4. Definitions and clinical outcome measures: At what time point were the baseline characteristics recorded? Was it upon admission to first hospital (around 40% had an inter-facility transfer) or at the hospital where the patients were revascularized?

Thanks for your question. Baseline characteristics were recorded at the time of admission in the participating centers. Therefore, information was obtained from the record of the hospitals where patients underwent coronary revascularization.

#5. Why did you chose so many different secondary outcomes? Some of the outcomes are with competing risks that needs to be considered in the analysis and presentation of your results. How was the clinical distinction between target vessel revascularization (TVR) and ischemia driven target vessel revascularization, as well as any coronary revascularization versus ischemia driven any coronary revascularization? Please consider to reduce number of outcomes, to avoid multiple testing.

We appreciate your valuable comment.
The aim of this study was descriptions of incidences of clinical outcomes from the view of historical comparison. Therefore, we prefer to provide the results of various clinical outcomes for practicing physicians who were interested in. However, we deleted P values for cardiac death, sudden cardiac death, non-cardiac death, TVR, ischemia driven TVR, any coronary revascularization and ischemia driven any coronary revascularization to avoid the potential risk of alpha error. To avoid the competing risks between the non-fatal outcomes, we determinedthe follow-up periods separately for each outcome with censoring due to death or the last visit. We thus calculated the survival functions irrespective to other non-fatal outcomes. According to the valuable comments from the reviewer, we clarified this issue in the revised manuscript.
Ischemia-driven TVR and ischemia-driven any coronary revascularization were defined according to the ARC definition (Cutlip DE, Windecker S, Mehran R et al. Circulation. 2007;115:2344-2351 PubMed . doi: 10.1161/CIRCULATIONAHA.106.685313.)..

We added the following sentence in the methods section.

Methods (Page 11, Line 14 to Page 11, Line 17)
To calculate the survival functions, follow-up periods were separately calculated for each outcome with censoring due to death or the last visit. The non-fatal outcomes other than the analyzed outcomes in the survival analyses were ignored.

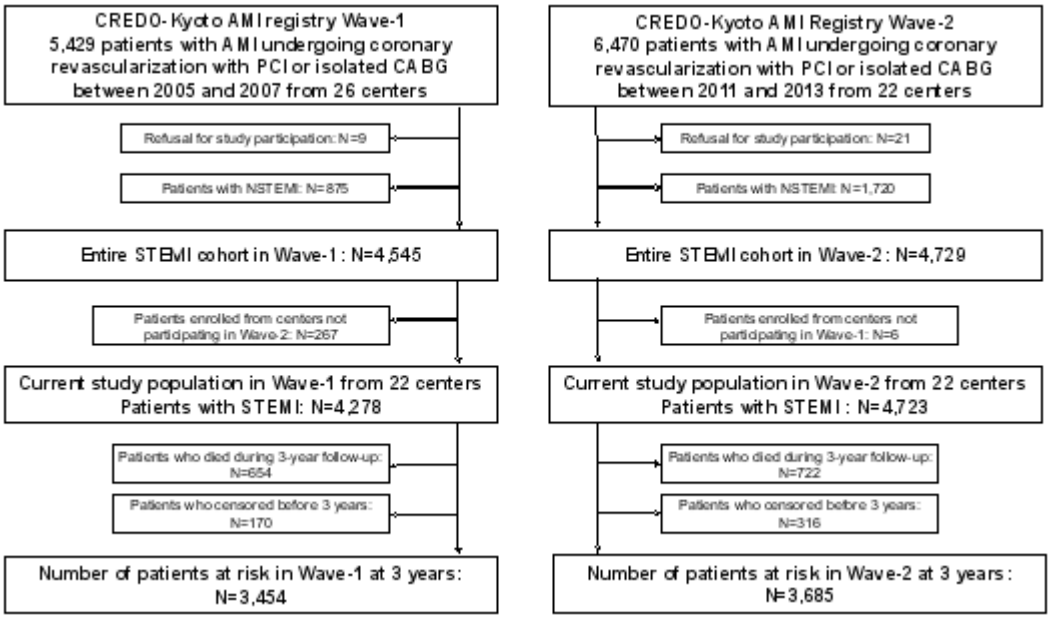
#6. When was the time for inclusion of the patients? (at the time of the STEMI diagnosis, at the time of admission to first hospital, to the PCI/CABG-centre, at the time of coronary revascularization, or at discharge)

Thanks for your question. This study was a retrospective registry, but time zero for clinical follow-up was the day of coronary revascularization.

#7. At what time were the follow-up investigations carried out?

Thanks for your question. The observation started from the index date until the date of death or last contact. As described above, the follow-up periods were separately calculated for each outcome with censoring due to death or the last contact, and the non-fatal outcomes other than the analyzed outcomes in the survival analyses were ignored. We clarified these issues in the revised manuscript accordingly.

#8. Please include in the study flow-chart number of patients were contacted for follow-up, and how many refused to participate, and how many were lost to follow-up because of other causes.



Thanks for your comments. We added following information as you make advice in Figure 1 (study flow-chart).

#9. You state that follow-up was censored at 3 years to ensure >90% follow-up. I am concerned that this has affected your results. You need to account for patients at risk at every time point, that possibly can experience the event (i.e include patients who were lost to follow-up, and censore them at the time of last contact)

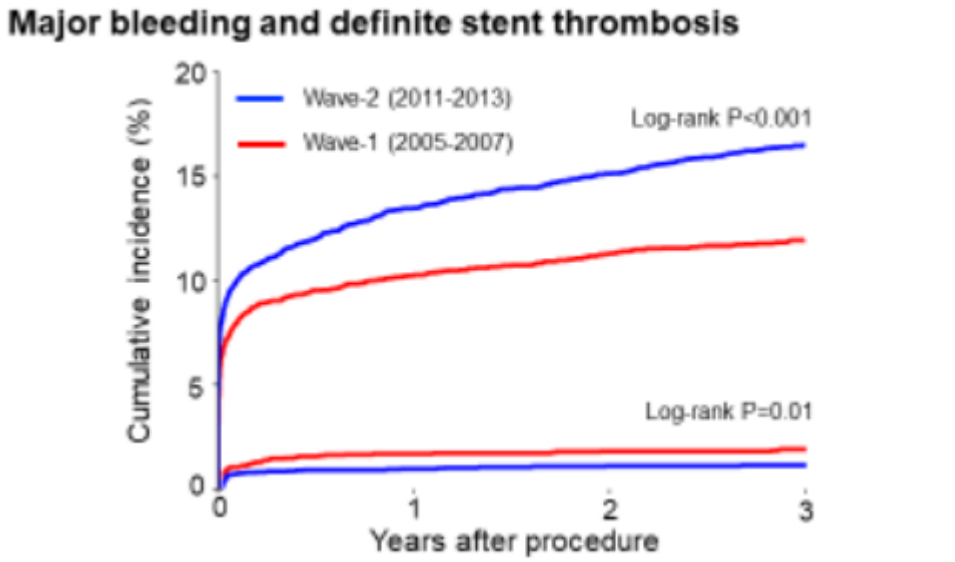
We appreciate your clarifications. We censored at 3 years for only patients who had more than 3-years follow-up duration. In contrast, patients who lost follow-up before 3-years were censored at the last contact or death. As described above, the follow-up periods were separately calculated for each outcome with censoring due to death or the last contact, and we conducted the survival analyses based on these data.

#10. You have defined several secondary outcomes with competing risk. I.e. the risk of stents thrombosis mights be lower and major bleeding higher in wave-2, because of competing risks. Please show graphically in the same figure the event free survival/hazard (i.e. Kaplan-Meier) for each of the end-points.

We appreciate your relevant comment. As we mentioned above, the follow-up periods were separately calculated for each outcome with censoring due to death or the last contact. The non-fatal outcomes other than the analyzed outcomes in the survival analyses were ignored, and thus, cause-specific Kaplan-meier curve and Cox proportional hazard model should be considered appropriate. Of course, we recognize that any non-fatal event might influence the following events as the reviewer pointed out. However, we did not stop the observations at the first non-fatal event as described above, in which the competing risk should become problem.
We showed graphically the Kaplan-Meier curve for major bleeding and stent thrombosis in the same figure (Reference Figure 2).
We considered the higher risk of the Wave-2 compared to the Wave-1 for major bleeding could be explained by the longer DAPT duration and difference in the types of thienopyridine, and the lower risk for stent thrombosis could largely be explained by the introduction of new-generation DES, which was demonstrated by prior meta-analysis (Toyota T, Shiomi H, Morimoto T, et

al. Meta-analysis of long-term clinical outcomes of everolimus-eluting stents. Am J Cardiol. 2015;116:187-94.).
We are happy to conduct other additional analysis if the editors and reviewers consider it necessary to publish this manuscript.

<Reference Figure 2>



Interval	0 day	30 days	1 year	2 years	3 years
<Major bleeding>					
Wave-2					
N of patients at risk	4723	4067	3665	3453	3276
N of patients with event		457	618	686	741
Cumulative incidence		9.8%	13.5%	15.1%	16.5%
Wave-1					
N of patients at risk	4278	3773	3485	3333	3189
N of patients with event		331	428	467	492
Cumulative incidence		7.8%	10.3%	11.3%	12.0%
<Stent thrombosis>					
Wave-2					
N of patients at risk	4241	3945	3642	3476	3335
N of patients with event		45	54	59	60
Cumulative incidence		1.1%	1.3%	1.5%	1.5%
Wave-1					
N of patients at risk	3739	3494	3257	3137	3012
N of patients with event		52	74	78	81
Cumulative incidence		1.4%	2.0%	2.2%	2.3%

#11. Could you also, for all the end-points, give the median follow-up time for wave-2 versus wave-1?

Thanks for your comments. We showed the median follow-up time for all endpoints in the table below.

Endpoints	Wave-1	Wave-2
	Median follow-up, days (IQR)	
All-cause death	1836 (1488-2152)	2029 (1324-2411)
Myocardial infarction	1801 (1356-2137)	1983 (1089-2379)

Definite stent thrombosis	1821 (1462-2143)	2014 (1253-2402)
Stroke	1796 (1342-2136)	1989 (1098-2388)
Hospitalization for heart failure	1791 (1256-2133)	1966 (968-2376)
Major bleeding	1763 (1048-2117)	1920 (565-2346)
Target vessel revascularization	1577 (222-2021)	1785 (277-2269)
Ischemia-driven target vessel revascularization	1736 (944-2106)	1931 (785-2348)
Any coronary revascularization	1426 (199-1959)	1599 (236-2219)
Ischemia-driven any coronary revascularization	1703 (772-2087)	1880 (599-2312)

#12. The authors provide assessment of proportional hazards of the included covariates for the whole 3-year period. Please provide evaluation of the global proportional hazards assumption, for the full Cox models for all end-points. Can you explain why a landmark analysis was performed, if it is correct that the proportional hazards assumption was fulfilled for the full Cox models? If you need a landmark analysis because the hazards were not proportional, you also need to build a Cox model for multivariate adjustment for the period 30 days to 3 years. I cannot read from the methods if you have performed such Cox regression models.

Thanks for your professional comments.

We confirmed that the proportional hazard assumption was verified for all the variables in the Cox proportional hazard models for primary outcome measure during the entire follow-up period. As we explained in method section, proportional hazard assumptions for the risk-adjusting variables were assessed on the plots of log (time) versus log [-log (survival)] stratified by the variable.

To make the analysis consistent for all the outcome measures, we used the Cox proportional hazard models for all the outcomes. Because we hypothesized the causes of all-cause death and major bleeding would be different between early and long-term periods from the clinical perspective, we conducted landmark analysis for all-cause death and major bleeding at 30 days . In the landmark analysis, we build multivariable Cox models within 30 days and beyond 30 days up to 3 years, and the results were described at Supplemental Figure I and II. The 30-day period was too short on the plots of log (time) versus log [-log (survival)] to affect the assessment of proportional hazard

assumption. We thus constructed the Cox proportional hazard models for both within 30 days and beyond 30 days up to 3 years, as well as entire follow-up.

#13. There are other studies evaluating clinical practice and outcomes in STEMI patients after the year 2010: Szummer K et al. Eur Heart J. 2017;38:3056-3065 PubMed , Puymirat E et al. Circulation 2017;136:1908-1919.

Thanks for your comment.
One of the strength of our study was that we compared “long-term” clinical outcomes in the 2 cohorts. Anyway, we modified the discussion section and added references as follows.

Discussion (Page 15, Line 12 to Page 15, Line 14)
There was scarce of data evaluating demographics, clinical practices, and long-term clinical outcomes in STEMI patients enrolled beyond 2010 compared with those enrolled before 2010. (Puymirat E, et al. Circulation. 2017;136:1908-1919., Szummer K, et al. Eur Heart J. 2017;38:3056-3065.)

#14. You should include studies of revascularized STEMI patients for comparison of your results, as we know that a large proportion of STEMI patients still do not receive reperfusion (Widimsky P et al Eur Heart J 2010;31:943-957 PubMed , and Cenko E et al, Eur Heart J – Quality of Care and Clin Outc 2016;2:45-51).

We appreciate your valuable comment. Regarding many studies included patient who did not undergo revascularization, we added references mentioned only for patients who underwent primary PCI. (Menees DS, et al. N Engl J Med. 2013;369:901-9. Biswas S, et al. Am J Cardiol. 2018;121:279-288.)
Menees, et al reported 30-day mortality was 5.2% in 2005 and 4.9% in 2013. Biswas, et al reporter 30-day mortality was 4.8% in 2005 and 4.7% in 2008.

These event rates were numerically similar to our study. Moreover, in these studies, although timely access to primary PCI has improved, early mortality rates have not changed from 2005 to 2009 and 2005 to 2016, which were consistent with our results.

Therefore, we added these references into the following statement in the discussion section.

Discussion (Page 15, Line 15 to Page 15, Line 16)

The mortality rates at 30 days were still around 5-6% in both Wave-1 and Wave-2, which was in line with the previous studies. (Menees DS, et al. N Engl J Med. 2013;369:901-9. Biswas S, et al. Am J Cardiol. 2018;121:279-288.)

#15. Please discuss the implications of reduced renal function in wave-2 compared to wave-1, and the higher risk of bleeding in wave-2 vs wave 1.

Thanks for your comment. We consider reduced renal function in wave-2 compared to wave-1 was explained by older age. Older age and reduced renal function lead to higher prevalence of ARC-HBR in wave-2 than in wave-1, which might be a reason for the higher risk of bleeding in wave-2 than in wave-1. Another reason for the higher risk of bleeding in wave-2 than in wave-1 might be the longer DAPT duration in wave-2 than in wave-1, and difference in the types of thienopyridine between the 2 cohorts.

#16. Please discuss the internal and external validity of your results.

We appreciate your valuable comment.

Our study was based on the multicenter registry with large sample size enrolled consecutive patients who underwent revascularization for AMI and the follow-up rate was high enough. In contrast, we should be careful to interpret the outcomes which had low event rate such as sudden cardiac death and definite stent thrombosis. Although we did our best to adjust the clinically relevant confounders, the primary interest of this study was comparison between 2 decades, and there might

be some residual unmeasured confounders, which might be related to the decades. We thus mentioned these issues in limitaiton section. We believe our findings should be applicable in Japan or other similar settings outside Japan, the changes in clinical pictures of STEMI should be investigated in other settings with different healthcare systems.

Therefore, we added these references into the following statement in the discussion section.

Discussion (Page 17, Line 13 to Page 17, Line 17)

Our study was based on the multicenter registry with large sample size enrolled consecutive patients who underwent revascularization for AMI and the follow-up rate was high enough. Threfore, we believe our findings should be applicable in Japan or other similar settings outside Japan, but the changes in clinical pictures of STEMI should be investigated in other settings with different healthcare systems.

#17. Please discuss the limitations of not performing a competing risk analysis, multiple endpoints (the multiple testing problem), and selection bias (only revascularized STEMI patients)

Thanks for your comments. We added the following statements in the limitation section according to your suggestions.

Discussion (Page 18, Line 12 to Page 18, Line 15)

Second, we chose several outcomes as secondary outcomes carrying the risk of multiple comparisons. Third, we only included patients who underwent coronary revascularization, which might have lead to selection bias. However, it is quite rare for a STEMI patient not undergoing primary PCI.

Finally, we modified all typo in our manuscript according to your advice.

VERSION 2 – REVIEW

REVIEWER	Dr Mario Gramegna IRCCS San Raffaele Scientific Institute - Milan
REVIEW RETURNED	15-Feb-2021

GENERAL COMMENTS	Thank you for your comments.

REVIEWER	Kristin Marie Kvakkestad Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway I am currently working on an article conserning STEMI patients included in a local quality registry and their long-term survival.
REVIEW RETURNED	18-Feb-2021

GENERAL COMMENTS	The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 2 – AUTHOR RESPONSE

<Response to the comments of the reviewer #3>

Reviewer #3:

#1. Title: (Page 1, Line 1 to Page 1, Line 4)

According to your suggestion, we modified our manuscript title as follows.

Title: Changes in Demographics, Clinical Practices, and Long-term Outcomes of Patients with ST-segment-elevation Myocardial Infarction who Underwent Coronary Revascularization in the Past Two Decades: Cohort Study

#2. Strengths and limitations of this study: (Page 6, Line 7)

According to your suggestion, we modified the word “outcomes” to “events”

#3. Introduction: (Page 7, Line 2)

According to your suggestion, we modified the word “appeared” to “appears”

#3. Study Population: (Page 8, Line 7)

According to your suggestion, we added “within 7 days from onset”.

#4. Data Collection and Follow-up: (Page 11, Line 4)

According to your suggestion, we added the following sentence.

“Follow-up started at the time of revascularisation for STEMI.”

#5. Statistical Analysis: (Page 11, Line 20)

According to your suggestion, we modified “adjusted hazard ratio” to “the overall and cause-specific hazard ratios”

#6. Limitation

According to your suggestion, we deleted following sentence.

“It is noteworthy that cumulative incidence of myocardial infarction was numerically higher in Wave-2 than in Wave-1, despite significantly lower incidence of definite stent thrombosis in Wave-2 than in Wave-1.”

#7. Limitation: (Page 18, Line 12 to Page 18, Line 13)

According to your suggestion, we added following limitation.

“Second, the incidence of various end-points during 3-year follow-up is probably overestimated, because not accounting for competing risks.”