PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from Heart but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received two reviews from its previous journal and two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Management and Outcomes Over Time of Patients After a Particularly High Cardiovascular Risk Acute Coronary Syndrome - The ACSIS registry-based retrospective study
AUTHORS	Grinberg, Tzlil; Hammer, Yoav; Wiessman, Maya; Perl, Leor; Ovdat, Tal; Or, Tsafrir; Kogan, Yoni; Beigel, Roy; Orvin, Katia; Kornowski, Ran; Eisen, Alon

VERSION 1 – REVIEW

REVIEWER	Duffy, Stephen

GENERAL COMMENTS	Comments for the Authors Grinberg, et al. Management & Outcomes of High-Risk Patients After an ACS - The ACSIS Registry heartjnl-2021-320484 Grinberg and colleagues report the findings of a study in which they examined the trends in management and outcomes of patients with high-risk features who presented with an acute coronary syndrome (ACS). Data were analysed from the ACS Israeli Survey (ACSIS). This group have published a series of articles from this registry on a similar theme. To classify patient risk, they used the TIMI Risk-Score for Secondary Prevention (TRS2˚P), and included patients with a TRS2˚P ≥3. Amongst 5,359 patients, there was a graded elevated risk associated with higher co-morbidities (some by definition, as they were included in the risk score). There was a graded increase in 30-day major cardiovascular events (MACE) and 1-year mortality. The highest risk patients ('extremely high-risk') also had less interventions and medical therapy. Over time, treatment improved, which was associated with less MACE in all three groups and 1-year mortality (though not for the extremely high-risk cohort). Major Comments 1. The methodology of the study appears sound, the analyses are appropriate (though a multivariable analysis for outcomes would be useful…see below).

	2. The improvements seen in treatment and outcomes for these high-risk patients over time is good, though it is unclear why this would occur given increasing high-risk features over time. Is feedback on treatments and outcomes provided to clinicians by the registry periodically? 3. Other than focusing only on the high-risk groups (TRS2˚P ≥3) and excluding the low- and intermediate-risk groups in the same registry, how are the findings different from the JAHA (doi:10.1161/JAHA.118.009885) and the American Journal of Medicine (The American Journal of Medicine 2020;133:839-847 doi:10.1016/j.amjmed.2019.12.027) papers? The findings appear to be similar. 4. It is recommended that the investigators perform a multivariable analysis for the predictors of 30-day MACE and 1-year mortality in the first time period (including the three risk categories in the MVA model), as it is likely that the poor outcomes are purely associated with risk. 5. While it seems counterintuitive that the highest risk patients have less secondary prevention therapy, it is likely that this group had contraindications to some of these therapies. For example, less ACE-inhibitors/ARBs and fewer coronary angiograms because of their (by definition) higher incidence of chronic kidney disease; less antiplatelets and/or DAPT because of their higher incidence of AF (thus, more oral anticoagulants). Are contraindications to medications collected in the registry? 6. I couldn't see the frequency of oral anticoagulant use in the tables. This would likely be higher in the very- and extreme-risk groups owing to the higher incidence of AF, resulting in less antiplatelet use. Are these data collected? 7. In the time-based analysis, the lack of increase in use of antiplatelets and ACE-inhibitors/ARBs over time is likely related to the issues noted in points 5 & 6). 8. Although noted by the investigators, the lack of information regarding cardiovascular death versus non-cardiovascular death at 1 year is important, as many of the extremely high-risk patients may have died of non-cardiovascular causes (given their significant comorbidities), so changes in cardiovascular therapy may not impact their outcome. Minor Comments 1. The tables are presented within the text (thesis style) 2. I suggest combining clopidogrel, prasugrel and ticagrelor in the tables, as the latter two agents were not available in the first time period. 3. Please review the details in the references. 4. On page 5, lines 35-40, the impact might be to develop strategies to intensify treatment with closer follow up in the highest risk patients.

REVIEWER	Bing, Rong

GENERAL COMMENTS	The authors used a national registry of all ACS patients hospitalised in March-April for the years 2002-2018 to examine temporal trends in treatments and outcomes in a high-risk group of patients. 5459 of 15196 had TRS2P ≥3 and were included in this analysis. The strength of the data is the detailed collection of routine data in consecutive patients over time and the presentation of these descriptive data. The basic logistic regression and Cox models presented add a little additional interest but the reported associations are subject to substantial confounding. I have minor comments only: Ultimately this study describes 'real-world' practice but does not inform us about whether we should be treating patients differently. GDMT should not be followed unthinkingly, and, as the authors identify, the evidence upon which these therapies are based may not include very comorbid patients. High-risk for future events (as per the TRS2P score) does not imply that the risk is modifiable with GDMT. On this point, I would suggest modifying this sentence, which implies causality: "nonetheless, under better implementation of GDMT at discharge over two consecutive time-periods (that is in line with prior studies), they exhibited improved clinical outcomes, mainly lower 30-day MACE, 30-day mortality and 1-year mortality." Were 30-day bleeding events captured? What was the uptake of high-sensitivity troponin? The decreased MACE in the later time period might be due in part to ACS diagnoses made on the basis of small hsTn rises in the absence of other acute high-risk features. How were missing data handled? This is not specified in methods

VERSION 1 – AUTHOR RESPONSE

Dear reviewers,
Thank you for your helpful comments and suggestions. Below please find the response sand references incorporated into the manuscript.

Reviewer 1- major comments
Comment #1: The methodology of the study appears sound, the analyses are appropriate (though a multivariable analysis for outcomes would be useful…see below).
Response: Following the reviewer's comment a multivariate analysis was conducted. Please refer to comment #4 for further details.

Comment #2: The improvements seen in treatment and outcomes for these high-risk patients over time is good, though it is unclear why this would occur given increasing high-risk features over time. Is feedback on treatments and outcomes provided to clinicians by the registry periodically?

Response: The ACSIS registry is a biennial prospective national survey taking place over a two-month period with follow-up data collected at 30 days and 1-year post ACS. Although its overall findings are published periodically by the Israel Heart Society, no reporting or feedback on treatment and outcomes is provided to clinicians between the surveys. However, the improved treatment over time in high-risk patients despite their increasing high-risk features is perhaps attributed to its expanded use given such factors as better PCI techniques to reduce periprocedural adverse events (that higher-risk patients are more prone to), and closer patient community monitoring for adverse effects. Many of the study patients continued their follow-up in the hospital clinics, which may have facilitated their adherence to guideline directed medical treatment (GDMT) and provided an opportunity to address associated comorbidities. This in turn may have been associated with better clinical outcomes over time, particularly in higher-risk patients who (given their higher cardiovascular risk) have a higher relative risk reduction and thus may gain the most benefit from the greater implementation of GDMT.

Comment #3: Other than focusing only on the high-risk groups (TRS2˚P ≥3) and excluding the low- and intermediate-risk groups in the same registry, how are the findings different from the JAHA (doi:10.1161/JAHA.118.009885) and the American Journal of Medicine (The American Journal of Medicine 2020;133:839-847 doi:10.1016/j.amjmed.2019.12.027) papers? The findings appear to be similar

Response: We thank the reviewer for directing this question. The previous papers have added to the existing literature showing the validity of the TRS2˚P to risk-stratify patients for recurrent cardiovascular events and distinguish a pattern of increasing benefit with increased risk when considering the entire risk spectrum. The present study demonstrated this to be valid also when applied specifically to the high-risk spectrum of patients, suggesting further stratification of this score pertaining to a high-risk cohort. This multi-center study focused specifically on a high-risk post ACS population who has yet to be examined directly in clinical trials and observational studies. This is contrary to the single-center based, post PCI-MI patients who were included in the previous papers cited. Our findings strengthen and substantiate the findings of the prior studies with a reduced 30-day MACE over time also in the extremely high-risk patients, and yet, no advantage over time in 1-year survival (the latter finding explained elaborately in the text. page 17, last paragraph).

Comment #4: It is recommended that the investigators perform a multivariable analysis for the predictors of 30-day MACE and 1-year mortality in the first time period (including the three risk categories in the MVA model), as it is likely that the poor outcomes are purely associated with risk.

Response: We thank the reviewer for his suggestion to conduct a multivariate analysis for the predictors of 30-day and 1-year outcomes in the early time period. Below are the analysis' results that were incorporated into the manuscript.

In a logistic regression analysis adjusted only to TRS2˚P level (which, in fact, represents a multivariate analysis considering it consists of nine clinical characteristics), the odds for 30-day MACE in the early period were 35% higher in extremely high versus high-risk patients (OR 1.35, 95% CI 1.07-1.7, P=0.01). However, this was not the case with very high-risk patients, who demonstrated a comparable risk for MACE as their high-risk counterparts (OR 1.34, 95% CI 0.9-1.37, P=0.34). When the regression model was adjusted for additional covariates (that were found statistically significant for MACE in a univariate analysis) the results were similar with a 61% higher risk for MACE in the early period among extremely high compared to high-risk patients (OR 1.61, 95% CI 1.15-2.26, P=0.01) but no such increased risk among very high-risk patients (OR 1.14, 95% CI 0.9-1.45, P=0.29).

In a Cox regression analysis, the probability for 1-year mortality was 97% higher in extremely high versus high-risk patients (HR 1.97, 95% CI 1.61-2.42, P<0.001) and 44% (HR 1.44, 95% CI 1.18-1.76, P<0.001) higher in very high versus high-risk patients. When a multivariate analysis adjusted for the variables found to be significant in the univariate model was performed, similar results were obtained with 88% (HR 1.88, 95% CI 1.35-2.62, P=0.00031) and 27% (HR 1.27, 95% CI 0.99-1.62, P=0.06) greater 1-year mortality in extremely high and very high-risk compared to high-risk patients,

respectively.
These analyses are summarized below and added as Table S3 in the supplemental material.

		Very high-Risk	Extremely high-Risk
30-day MACE	Model 1*	OR 1.34 95% CI 0.9-1.37 P=0.34	OR 1.35 95% CI 1.07-1.7 P=0.01
	Model 2‡	OR 1.14 95% CI 0.9-1.45 P=0.29	OR 1.61 95% CI 1.15-2.26 P=0.01
1-year mortality	Model 1*	HR 1.44 95% CI 1.18-1.76 P<0.001	HR 1.97 95% CI 1.61-2.42 P<0.001
	Model 2#	HR 1.27 95% CI 0.99-1.62 P=0.06	HR 1.88 95% CI 1.35-2.62 P=0.00031

Multivariate analysis for the predictors of 30-day MACE and 1-year mortality in the early time period. The OR and HR are in comparison to high-risk patients.
*Adjusted to TRS2˚P level only.
‡Adjusted to TRS2˚P, age, gender, dyslipidemia, diabetes mellitus, hypertension, smoking status, history of congestive heart failure, chronic renal failure, family history of coronary artery disease, prior coronary artery bypass graft surgery, prior percutaneous coronary intervention.
#Adjusted to the above variables plus body mass index.

Comment #5: While it seems counterintuitive that the highest risk patients have less secondary prevention therapy, it is likely that this group had contraindications to some of these therapies. For example, less ACE-inhibitors/ARBs and fewer coronary angiograms because of their (by definition) higher incidence of chronic kidney disease; less antiplatelets and/or DAPT because of their higher incidence of AF (thus, more oral anticoagulants). Are contraindications to medications collected in the registry?
Response: We thank the reviewer for this comment. Data on contra-indications to medications are not collected routinely by the registry. However, indirect data on contra-indications is provided by the creatinine values on presentation, in case of renal contra-indications to treatment, and by the proportion of patients discharged with anticoagulants, in case of contra-indications to DAPT. Indeed, the creatinine on presentation was the highest among extremely high-risk patients (Mean 1.08 mg/dL [0.88, 1.37], 1.30 mg/dL [1.02, 1.68], 1.52 mg/dL [1.25, 2.14] in high, very high and extremely high-risk patients, respectively, p<0.001). Similarly, they were more commonly prescribed anticoagulants on hospital discharge (6.7%, 10.2%, 13.5%, respectively, p<0.001). As the reviewer noted, these factors probably explain, in part, the under-treatment with ACEi/ARB's and DAPT in the highest-risk patients. Data on the above percentages of anticoagulation use were added to Table 3 of the manuscript.

Comment #6: I couldn't see the frequency of oral anticoagulant use in the tables. This would likely be higher in the very- and extreme-risk groups owing to the higher incidence of AF, resulting in less antiplatelet use. Are these data collected?
Response: This issue was addressed in the former comment.

Comment #7: In the time-based analysis, the lack of increase in use of antiplatelets and ACE-inhibitors/ARBs over time is likely related to the issues noted in points 5 & 6).
Response: Further to the response to comment #5, we added to the time-based analysis the percentage of discharge anticoagulation stratified by the risk level and time period (Table 4). Anticoagulants on discharge were prescribed more often in the late than the early period among all high-risk groups with higher absolute values in higher-risk patients. This did probably affect the prescription of antiplatelets (or lack of) as mentioned.

Comment #8: Although noted by the investigators, the lack of information regarding cardiovascular death versus non-cardiovascular death at 1 year is important, as many of the extremely high-risk patients may have died of non-cardiovascular causes (given their significant comorbidities), so changes in cardiovascular therapy may not impact their outcome.
Response: We thank the reviewer for the comment. This is, indeed, an important limitation to our study that was mentioned as part of the study limitations and discussed in the manuscript in more details (page 17, last paragraph). We agree with the reviewer that the cardiovascular mortality of the highest-risk patients is possibly exceeded by their non-cardiovascular mortality. Still, their short-term outcome measured by 30-day MACE did improve over time in association with the more prevalent use of GDMT.

Reviewer 1- minor comments
Comment #1: The tables are presented within the text (thesis style)
Response: The tables were presented within the text according to the journal's submission guidelines: "the main document should contain your main text, references and editable tables", "Tables should be in Word format and placed in the main text where the table is first cited."

Comment #2: I suggest combining clopidogrel, prasugrel and ticagrelor in the tables, as the latter two agents were not available in the first time period.
Response: As suggested by the reviewer, we added the parameter "Any P2Y12 inhibitor" as part of the discharge GDMT (Table 4). We can see that prescription of a P2Y12 inhibitor by discharge was more common in the late rather than the early period across all risk groups but was still slightly lower in absolute terms in the higher-risk groups.

Comment #3: Please review the details in the references.
Response: Details have been reviewed and corrected.

Comment #4: On page 5, lines 35-40, the impact might be to develop strategies to intensify treatment with closer follow up in the highest risk
Response: We thank the reviewer for the comment. Following the reviewer's comment, the study's conclusion was rephrased as following: "...While a causal relation cannot be inferred, GDMT should not be denied in these high-risk patients, and efforts should be made to develop strategies to intensify treatment with closer follow-up". (page 19, first paragraph).

Reviewer 2- minor comments
Comment #1: On this point, I would suggest modifying this sentence, which implies causality: "nonetheless, under better implementation of GDMT at discharge over two consecutive time-periods (that is in line with prior studies), they exhibited improved clinical outcomes, mainly lower 30-day MACE, 30-day mortality and 1-year mortality."
Response: We thank the reviewer for pointing this out. The above sentence was rephrased accordingly: "Nonetheless, over two consecutive time-periods, they exhibited improved clinical outcomes, mainly lower 30-day MACE, 30-day mortality and 1-year mortality, in association with better implementation of discharge GDMT (page 17, paragraph 2).

Comment #2: Were 30-day bleeding events captured?
Response: Unfortunately, data on 30-day bleeding events is not routinely reported by the registry. Only in-hospital bleeding events and required blood transfusions are currently reported. This information, if available, would most definitely shed further light on the cost of enhanced GDMT implementation in the particularly high-risk patient spectrum.

Comment #3: What was the uptake of high-sensitivity troponin? The decreased MACE in the later time period might be due in part to ACS diagnoses made on the basis of small hsTn rises in the absence of other acute high-risk features.
Response: We thank the reviewer for directing this question. In the ACSIS registry troponin values reported were not of high-sensitivity (hs-cTn) during the first years of the survey. Only later, approximately since 2010 and coincident with its global use according to issued guideline, regular troponin was replaced with hs-cTn. Therefore, as the reviewer connoted, it is possible that some patients included in the late period had, in fact, more subtle or minor ACS events compared to early period-patients, and that this factor affected the resulted MACE. Supporting this inference is the lower rate of advanced Killip class and severe EF on hospital presentation over the late compared to the early period (Table S2, supplemental material).
Following the reviewer's comment, the lack of availability of hs-cTn during the early period was added to the study limitations (page 18, paragraph 2).

Comment #4: How were missing data handled? This is not specified in methods
Response: We thank the reviewer for the comment. No statistical adjustments were performed to compensate for missing data, which were not sizeable for the most part. For the multivariate analysis only covariates with less than 10% missing values were selected. All missing values were systematically recorded and detailed in Table S4 of the supplemental material.
This clarification was added to the statistical analysis description of the manuscript.