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Management and outcomes over time of acute coronary syndrome patients at particularly high cardiovascular risk : the ACSIS registry-based retrospective study

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ABSTRACT

Objective Some patients following acute coronary syndrome (ACS) are at particularly increased risk for recurrent cardiovascular events. We aimed to examine temporal trends in the management and outcomes across the spectrum of these particularly high-risk patients.

Design and setting A retrospective study based on the ACS Israeli survey (ACSIS) registry, a multicentre prospective national registry, taking place biennially in 25 cardiology departments in Israel. Temporal trends were examined in the early (2002–2008) and late (2010–2018) time periods.

Participants Consecutive patients with ACS enrolled in the ACSIS registry were stratified according to the Thrombolysis in Myocardial Infarction Risk Score for secondary prevention (TRS2°P) to high (TRS2°p=3), very high (TRS2°p=4) or extremely high risk (TRS2°p=5–9). Patients with TRS2°p<3 were excluded. From the initial 15 196 patients enrolled, 5359 patients were eventually included.

Clinical outcome measures included 30-day major adverse cardiovascular events (MACE) and 1-year mortality.

Results Among 5359 patients (50% high risk, 30% very high risk and 20% extremely high risk), those with a higher risk were older, had more comorbidities, presented more with non-ST elevation myocardial infarction, and were treated less often with guideline-recommended pharmacotherapy and percutaneous coronary intervention. Over time, treatment has improved in all risk strata, and the rate of 30-day MACE has significantly decreased in all risk groups (from 21% to 10%, from 22% to 15%, and from 26% to 16%, in high, very high and extremely high-risk groups, respectively, p<0.001 for each). However, 1-year mortality decreased only among high and very high-risk patients, and not among extremely high-risk patients in whom 1-year mortality rates remained very high (28.7% vs 28.9%, p=1).

Conclusion Within a particularly high-risk cohort of patients with ACS, treatment has significantly progressed over almost 2 decades. While short-term outcomes have improved in all risk groups, 1-year mortality has remained unchanged in extremely high-risk patients with ACS.

Strengths and limitations of this study

- ► A multicentre prospective national registry-based retrospective study examining over two decades the treatment and outcome of consecutive acute coronary syndrome patients at particularly high cardiovascular risk .
- ► The cohort at focus is unique and rarely included in clinical trials.
- ► Data are complete and well documented.
- ► Data on cardiovascular mortality and treatment adverse effects were lacking.
- ► A causal relationship between improved treatment and a favourable cardiovascular outcome cannot be inferred due to the study's observational nature.

INTRODUCTION

Patients with acute coronary syndrome (ACS) are at increased risk for recurrent cardiovascular (CV) events.[1–3] However, some patients are at particularly high, at times at the highest, CV risk.[4–6] These patients are often those with a multitude of comorbidities, such as complex coronary artery disease, polyvascular disease, chronic kidney disease (CKD), diabetes and advanced age, but are also frequently the most debilitated and frail.[7 8] They are also at an increased risk of having adverse events from medical or invasive treatments.[9 10] Accordingly, these patients are often undertreated, although they might benefit the most from guideline-directed medical treatment (GDMT). Hence, therapeutic decision-making in these very high-risk patients is often challenging, especially in view of the paucity of guiding data, in part due to the scarce enrollment of these patients in clinical trials.[11 12]

It has been previously demonstrated[13–17] that patients who were at a higher baseline risk for major adverse cardiovascular events (MACE) according to the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for Secondary Prevention (TRS2°P) derived proportionally greater benefit from improved treatment over time compared with low and intermediate-risk patients. When appropriate secondary prevention treatment and cardiac rehabilitation were provided to high-risk patients (TRS2°p≥3), a larger relative risk reduction in clinical outcomes was observed compared with lower-risk patients, despite the fact theformer were oftentimes relatively undertreated .[18 19] The inverse association between patients' CV risk and the delivery of GDMT has long been acknowledged and referred to as the 'risk-treatment paradox'.[20 21]

It is still unclear whether over the years intensive treatment has been used more often in ACS patients at the highest risk for CV events and whether their clinical outcomes have improved. We aimed to examine temporal trends over almost two decades in the management and outcome across the spectrum of high-risk post ACS patients according to the TRS2°P.

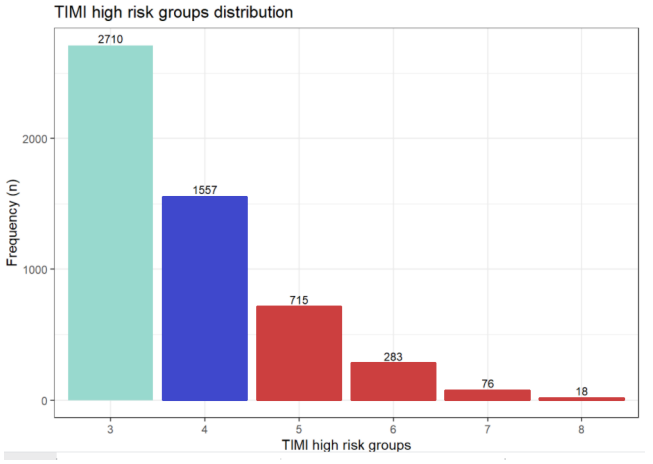

Figure 1 Patient distribution by the TIMI risk score for secondary prevention (TRS2°P). Risk factors: age ≥75 years, diabetes mellitus, hypertension, current smoking, peripheral arterial disease, prior stroke, prior coronary artery bypass graft surgery, chronic heart failure and chronic kidney disease (eGFR by MDRD <60 mL/min). High risk=3 risk factors; Very high risk=4 risk factors; extremely high risk ≥5 risk factors. eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; TIMI, Thrombolysis in Myocardial Infarction.

METHODS

A multicentre study from the ACS Israel Survey (ACSIS), a biennial prospective national registry of all patients with ACS hospitalised over a 2-month period (March to April) in 25 coronary care units and cardiology departments in all general hospitals in Israel. This registry entails demographic, clinical and angiographic data of all consecutive patients included in the survey. Data were recorded on prespecified forms for all admitted patients diagnosed with ACS. Admission and discharge diagnoses were documented by the attending physicians based on standard electrocardiographic, clinical and biochemical criteria.

Included in the study were all patients enrolled in the ACSIS registry during the years 2002–2018 who had available TRS2°P data. Excluded were patients with TRS2°p<3, considered to be at low or intermediate risk. All patients in each of the medical centres involved signed an informed consent form.

The TRS2°P is a simple risk score incorporating nine clinical characteristics, each assigned one point in the total count. These characteristics include age ≥75, diabetes mellitus, hypertension, current smoking, peripheral vascular disease (PVD), prior stroke, prior coronary artery bypass graft surgery (CABG), chronic heart failure (CHF), and CKD (defined by Modification of Diet in Renal Disease (MDRD) as <60 mL/min). This score was introduced relatively recently[14] and was originally designed to predict a graded risk for MACE at 3 years postmyocardial infarction (MI). It was later validated for secondary prevention in other studies[13 18 19 22–24] as an effective risk stratification tool that can distinguish a pattern of increasing benefit with the application of GDMT. In this study we suggested further stratification of this score pertaining specifically to the high-risk spectrum of patients; Patients were stratified for recurrent CV events by the TRS2°P into three groups: high-risk (TRS2°p=3), very high risk (TRS2°p=4) and extremely high risk (TRS2°p≥5).

Temporal trends were examined in the early (2002–2008) and late (2010–2018) time periods. This time partition was chosen to reflect the advancement in patients' care after an ACS brought about by the later era, when percutaneous coronary intervention (PCI), radial approach, more efficacious antiplatelets, high-potency statins, and cardiac rehabilitation have become the standard of care. Temporal trends in management were examined by referring to all aspects of secondary prevention therapy over time, including pharmacotherapy, PCI, and cardiac rehabilitation. Another analysis of temporal trends in treatment and outcome by survey years was additionally performed (online supplemental appendix table S1) to underscore the general direction and trend of the results.

Clinical outcomes included 30-day MACE and 1-year mortality from the index hospitalisation with ACS. MACE was a composite of death, MI, unstable angina pectoris, stroke, stent thrombosis or urgent revascularisation. In-hospital and 30-day outcome data were ascertained by hospital chart review, telephone contact and clinical follow-up data. Mortality data during hospitalisation, at 30 days and 1 year were determined for all patients based on hospital charts and by matching patients' identification numbers with the Israeli National Population Register.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of the study.

Grinberg T, *et al*. *BMJ Open* 2022;**12**:e060953. doi:10.1136/bmjopen-2022-060953

Statistical analysis

Patients' characteristics were presented as n (%) for categorical variables, and as median (IQR) for continuous variables. The three groups (high, very high, and extremely high) were tested with a χ^2 test for trend for comparison of categorical variables, and with Kendall rank correlation for continuous variables. The two groups (early vs late period) were tested with χ^2 for categorical variables and with Mann-Whitney-Wilcoxon test for continuous variables. Survival curves were presented, and the Kaplan-Meier log-rank test was used to test the variable of interest on survival. To evaluate the probability of 30-day MACE a logistic regression model was performed adjusted for TRS2°P study group, time period, and their interaction (risk group * Period). Using the same adjustments, the probability of 1-year mortality was evaluated with a Cox proportional hazard model. Multivariate analyses for the outcomes of interest were performed for the first time period. Covariates that were found statistically significant in the univariate analysis and had less than 10% missing data were selected for the model. All tests were conducted at a two-sided alpha level of 0.05 which was considered statistically significant. No statistical adjustments were performed to compensate for missing data. Statistical analysis was performed using R software (Vienna, Austria, 2020).

RESULTS

A total of 15 196 patients were enrolled in the ACSIS registry during the years 2002 to 2018. Among them, 14 427 patients had available TRS2°P data and 5359 patients had TRS2°p≥3 and were included in the study (online supplemental appendix figure S1). Of the patients included, approximately 50% (n=2710) were classified as high risk, 30% (n=1557) as very high risk and 20% (n=1092) as extremely high risk (figure 1). Baseline characteristics of patients are presented in table 1. Compared with high-risk and very

Table 1 Baseline characteristics by TIMI risk score for secondary prevention (TRS2°P)

	TRS2°P			
n (%)	High-risk TRS2°P=3 (n=2710)	Very high-risk TRS2°P=4 (n=1557)	Extremely high-risk TRS2P≥5 (n=1092)	P-value
Age, years (median (IQR))	69 (60–78)	75 (65–81)	77 (69–82)	<0.001
Gender (male)	1889 (69.7)	1076 (69.1)	784 (71.8)	0.3
Higher education	249 (27.8)	135 (25.4)	68 (19.4)	0.003
Hypertension	2377 (87.7)	1438 (92.4)	1062 (97.3)	<0.001
Diabetes mellitus	1548 (57.1)	1080 (69.4)	881 (80.7)	<0.001
Dyslipidaemia	2005 (74.1)	1206 (77.5)	897 (82.3)	<0.001
Current smoker	990 (36.5)	483 (31)	345 (31.6)	<0.001
PVD	224 (8.3)	322 (20.7)	523 (47.9)	<0.001
CKD*	371 (13.7)	466 (30)	592 (54.3)	<0.001
Family history of CAD	514 (20.9)	262 (18.9)	145 (15.5)	<0.001
Prior MI	1029 (38.1)	806 (51.9)	715 (65.5)	<0.001
Prior CABG	328 (12.1)	343 (22)	510 (46.7)	<0.001
Prior PCI	971 (35.9)	646 (41.6)	568 (52.3)	<0.001
Prior CHF	195 (7.2)	312 (20)	558 (51.1)	<0.001
Prior stroke	296 (10.9)	342 (22)	422 (38.6)	<0.001
Prior medications				
Aspirin	1641 (62.1)	1090 (71.7)	807 (76.3)	<0.001
Clopidogrel	325 (12.6)	229 (15.3)	250 (23.7)	<0.001
Statins	1486 (58.3)	960 (65.4)	747 (72.5)	<0.001
ACEi	839 (44.9)	532 (48.9)	365 (49.4)	0.016
ARBs	313 (17.3)	218 (20.7)	163 (23)	0.001
Beta blockers	1267 (48.7)	889 (59.3)	698 (67.1)	<0.001
Nitrates	366 (14.8)	330 (23)	328 (33.4)	<0.001

*CKD was defined as eGFR< 60 mL/min by MDRD formula.
ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIMI, Thrombolysis in Myocardial Infarction.

Table 2 Characteristics of the index ACS and in-hospital complications by TIMI risk score for secondary prevention (TRS2°P)

TRS2°P n (%)	High-risk TRS2°P=3 (n=2710)	Very high-risk TRS2°P=4 (n=1557)	Extremely high-risk TRS2°P≥5 (n=1092)	P-value
STEMI on presentation	1058 (39.1)	510 (32.8)	261 (23.9)	<0.001
Grace score >140	354 (19.4)	383 (37.4)	494 (65.2)	<0.001
Peak Troponin I elevated	984 (74.8)	583 (77.8)	438 (82)	<0.001
Admission Killip class I	2128 (80)	1077 (70.3)	596 (56.1)	<0.001
Admission Killip class II	293 (11)	256 (16.7)	266 (25)	<0.001
Admission Killip class III	183 (6.9)	169 (11)	172 (16.2)	<0.001
Admission Killip class IV	56 (2.1)	30 (2)	29 (2.7)	0.34
HR (BPM) (median (IQR))	80(68, 94)	80(68, 96)	83(70, 100)	<0.001
SBP (mm Hg) (median (IQR))	144(125, 163)	144(123, 165)	141.5(122, 165)	0.222
DBP (mm Hg) (median (IQR))	80(70, 90)	79(68, 90)	77(66, 90)	<0.001
NSR	2329 (85.9)	1272 (81.7)	852 (78)	<0.001
AF/ SVT	169 (7.1)	131 (9.6)	107 (11.7)	<0.001
Normal EF (>50%)	875 (41)	392 (32.6)	213 (26)	<0.001
Mild EF (40%–50%)	605 (28.3)	349 (29)	205 (25)	0.143
Moderate EF (30%–40%)	422 (19.8)	280 (23.3)	215 (26.3)	<0.001
Severe EF (<30%)	233 (10.9)	182 (15.1)	186 (22.7)	<0.001
In-hospital complications				
CHF mild-moderate (Killip-2)	254 (9.4)	203 (13.1)	238 (21.9)	<0.001
Pulmonary oedema (Killip-3)	240 (8.9)	213 (13.7)	190 (17.4)	<0.001
Cardiogenic shock (Killip-4)	135 (5)	88 (5.7)	67 (6.1)	0.13
Post-MI angina/reischaemia	114 (4.2)	75 (4.8)	54 (4.9)	0.265
MR moderate-severe	60 (2.2)	45 (2.9)	44 (4)	0.002
New atrial fibrillation	197 (7.3)	129 (8.3)	119 (10.9)	<0.001
Asystole	54 (2)	56 (3.6)	51 (4.7)	<0.001
Stroke	14 (0.5)	16 (1)	12 (1.1)	0.035
Acute renal failure	242 (9)	220 (14.2)	214 (19.7)	<0.001
Bleeding	44 (1.6)	43 (2.8)	34 (3.1)	0.002
Blood transfusions	38 (3.8)	31 (5.3)	44 (10.6)	<0.001

ACS, acute coronary syndrome; AF/SVT, atrial fibrillation/supraventricular tachycardia; BPM, beats per minute; CHF, congestive heart failure; CVA, cerebrovascular accident; DBP, diastolic blood pressure; EF, ejection fraction; HR, heart rate; MI, myocardial infarction; MR, mitral regurgitation; NSR, normal sinus rhythm; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

high-risk patients, extremely high-risk patients were older (mean age 77 years vs 69 years and 75 years, respectively), from a lower educational background, and had more comorbidities including hypertension (97%), diabetes mellitus (81%), dyslipidaemia (82%), CHF (51%), CKD (54%), PVD (48%), prior MI (65%), prior revascularisation by CABG or PCI (47% and 52%, respectively) and prior stroke (39%).

Extremely high-risk patients had already been taking secondary prevention pharmacotherapy to a larger extent compared with the other groups. Concerning the index ACS (table 2), on hospital admission, extremely high-risk patients presented more often with non-ST elevation MI. They also presented with a higher heart rate and a lower blood pressure, a higher Killip class with a reduced ejection fraction, a higher GRACE score and peak troponin I level, and a greater proportion of atrial fibrillation on ECG.

Still, they had undergone fewer coronary angiographies and PCI's (66% vs 86% and 41% vs 59% in extremely high vs high-risk patients, respectively, table 3).

Extremely high-risk patients developed more in-hospital complications including pulmonary oedema, new-onset atrial fibrillation, acute renal failure, bleeding requiring blood transfusions, and moderate-to-severe mitral regurgitation (table 2). At hospital discharge, extremely high-risk patients were prescribed secondary

Table 3 Interventional treatment and pharmacotherapy of index ACS and clinical outcomes at 30 days and 1 year

TIMI risk score for secondary prevention (TRS2°P)				
n (%)	High-risk TRS2°P=3 (n=2710)	Very high-risk TRS2°P=4 (n=1557)	Extremely high-risk TRS2P≥5 (n=1092)	P-value
PCI	1608 (59.3)	785 (50.4)	446 (40.8)	<0.001
PCI in NSTEMI patients‡	782 (56.7)	409 (49.3)	286 (41)	<0.001
Time from symptom onset to PPCI (median [IQR])*	210 [141,380)	210 [150,360]	260 [180,510]	0.18
Total angiographies	1998 (85.6)	1012 (74.9)	645 (65.9)	<0.001
Medications at discharge				
Aspirin	2462 (92.7)	1372 (91.4)	916 (87.9)	<0.001
Prasugrel	218 (8.1)	85 (5.5)	20 (1.9)	<0.001
Ticagrelor	344 (12.8)	177 (11.4)	94 (8.8)	0.001
Clopidogrel	1700 (63)	969 (62.4)	732 (68.2)	0.012
No P2Y12 inhibitors	435 (16.1)	322 (20.7)	228 (21.2)	<0.001
DAPT (in PCI patients)†	1346 (91.1)	644 (89.3)	361 (85.5)	0.001
Anticoagulation	170 (6.7)	148 (10.2)	134 (13.5)	<0.001
Statins	2287 (86.7)	1271 (85.4)	875 (84.3)	0.049
ACEi/ARBs	2099 (80.5)	1164 (79)	723 (71.3)	<0.001
Beta blockers	2072 (79.1)	1186 (80)	807 (78.6)	0.91
Cardiac rehabilitation referral at 30-day FUP	728 (43.2)	381 (41.3)	210 (31.2)	<0.001
Clinical outcomes				
30-day re-hospitalisation	470 (19.7)	278 (20.9)	209 (22.9)	0.04
30-day angina	45 (3.1)	49 (6.2)	35 (6.1)	0.001
30-day MACE	419 (15.5)	287 (18.6)	231 (21.3)	<0.001
30-day Mortality	166 (6.2)	139 (9)	127 (11.7)	<0.001
30-day UAP/MI	229 (8.5)	141 (9.1)	106 (9.7)	0.45
30-day CVA	13 (0.5)	15 (1)	9 (0.8)	0.16
30-day stent thrombosis	16 (1.2)	6 (0.8)	6 (1.2)	0.68
30-day urgent revascularisation	122 (4.5)	71 (4.6)	49 (4.5)	0.99
1-year mortality	337 (12.8)	286 (18.9)	306 (28.8)	<0.001

MACE was defined as death/MI/UAP/CVA/stent thrombosis/urgent revascularisation
*In STEMI patients only, measured in minutes.
†n=1478, n=721 and n=422 for high risk, very high risk and extremely high risk, respectively.
‡n=1651, n=1046 and n=829 for high risk, very high risk and extremely high risk, respectively.
ACEi, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; FUP, follow-up; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; UAP, unstable angina pectoris.

prevention therapy to a lesser extent (table 3), with less aspirin, fewer potent P2Y12 inhibitors (merely 2% received prasugrel and 9% ticagrelor), and slightly fewer statins and ACE inhibitors (ACEi)/ angiotensin receptor blockers (ARBs). Referral to cardiac rehabilitation at 30-day post-MI was also lower accordingly.

Compared with high and very high-risk patients, the clinical outcomes of extremely high-risk patients were worse (table 3), with a higher 30-day MACE (15.5%, 18.6% and 21.3%, respectively), and 1-year mortality (12.8%, 18.9% and 28.8%, figure 2).

Comparing the early and late time periods (online supplemental appendix table S2), patients in the late period had more comorbidities, yet presented less often with heart failure and an advanced Killip class. They underwent significantly more coronary angiographies and PCI's and experienced fewer in-hospital complications. The utilisation of guideline-recommended

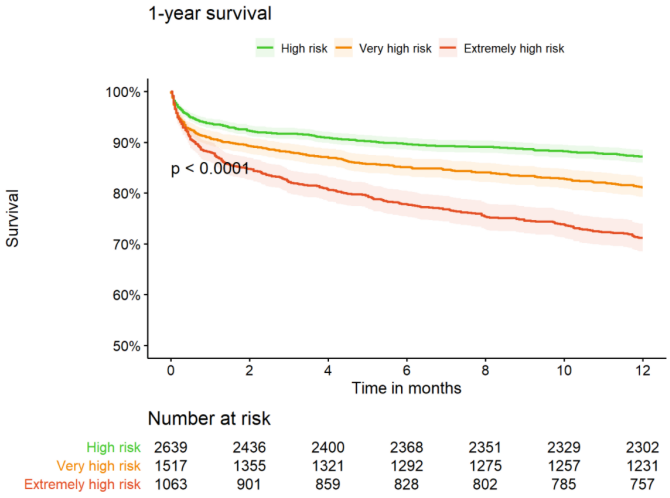

Figure 2 Kaplan-Meier curves for 1-year survival by the TIMI risk score for secondary prevention (TRS2°P). TIMI, Thrombolysis in Myocardial Infarction.

pharmacotherapy at hospital discharge across all TRS2°P groups has become more prevalent over time, including potent P2Y12 inhibitors (which were entirely not in use in the early period), statins, and beta-blockers, and so has cardiac rehabilitation referral at 30-day follow-up (table 4). Yet, for the most part, the absolute percent of these GDMT measures was still lower with higher TRS2°P scores. It is noteworthy that contrary to the other risk groups, extremely high-risk patients did not demonstrate enhanced use of aspirin and ACEi/ARBs over time.

With respect to clinical outcomes over time (table 5), the rate of 30-day MACE has decreased among all high-risk-strata comparing the early to the late period (20.5% to 10.5%, 22.3% to 14.8% and 25.9% to 16.4%, in high risk, very high risk and extremely high-risk groups, p<0.001 for each, respectively), driven by almost all of its individual components. One-year mortality rate has decreased as well (online supplemental appendix figure S2), however, exclusively among high and very high-risk patients (15.5% to 9.8%, p<0.001; 21.7% to 15.9%, p=0.005) but not among extremely high-risk patients (28.7% to 28.9%, p=1, figure 3). The rates of 30-day rehospitalisation, recurrent MI, and angina have also declined over time.

In a logistic regression analysis adjusted to the risk level and time period, the odds for 30-day MACE decreased by 49% between the early and late time periods (adjusted OR 0.51, 95% CI 0.44 to 0.60, p<0.001), with no significant interaction between risk-level (TRS2°P) and time period. In a Cox regression analysis, the probability of 1-year mortality decreased by 25% between the early and late time periods (HR 0.75, 95% CI 0.66 to 0.86, p<0.001). The interaction between risk level and time period was significant only for the extremely high-risk group (p=0.002). When Cox regression analysis was performed for each risk level, 1-year mortality was lower over the late period among both high and very high-risk but not among extremely high-risk patients (online supplemental appendix table S3). Multivariate analysis for the predictors of 30-day MACE and 1-year mortality in the early time

Table 4 Temporal trends in GDMT by discharge among the entire cohort and by TIMI risk score for secondary prevention (TRS2°P)

	Entire cohort			High-risk (TRS2°P=3)			Very high-risk (TRS2°P=4)			Extremely high-risk (TRS2°P≥5)		
n (%)	Early (n=2737)	Late (n=2622)	P-value	Early (n=1404)	Late (n=1306)	P-value	Early (n=777)	Late (n=780)	P-value	Early (n=556)	Late (n=536)	P-value
PCI	1256 (45.9)	1583 (60.4)	<0.001	739 (52.6)	869 (66.5)	<0.001	324 (41.7)	461 (59.1)	<0.001	193 (34.7)	253 (47.2)	<0.001
Total angiographies	1427 (69.9)	2228 (85)	<0.001	806 (78.5)	1192 (91.3)	<0.001	366 (64)	646 (82.8)	<0.001	255 (57.6)	390 (72.8)	<0.001
Composite intervention*	829 (32.9)	1397 (53.8)	<0.001	492 (38.6)	781 (60.4)	<0.001	205 (28.7)	403 (52.3)	<0.001	132 (25)	213 (40)	<0.001
Aspirin	2385 (89.4)	2365 (93.4)	<0.001	1241 (90)	1221 (95.5)	<0.001	676 (89.7)	696 (93.2)	0.019	468 (87.3)	448 (88.5)	0.6
Prasugrel	0 (0)	323 (12.4)	<0.001	0 (0)	218 (16.8)	<0.001	0 (0)	85 (11)	<0.001	0 (0)	20 (3.8)	<0.001
Ticagrelor	0 (0)	615 (23.7)	<0.001	0 (0)	344 (26.5)	<0.001	0 (0)	177 (22.8)	<0.001	0 (0)	94 (18)	<0.001
Clopidogrel	1887 (69.2)	1514 (58.3)	<0.001	1021 (73)	679 (52.3)	<0.001	500 (64.4)	469 (60.4)	<0.001	366 (66.3)	366 (70.1)	<0.001
Any P2Y12 inhibitor	1887 (69.2)	2452 (94.4)	<0.001	1021 (73.0)	1241 (95.5)	<0.001	500 (64.4)	731 (94.2)	<0.001	366 (66.3)	480 (92.0)	<0.001
Anticoagulants	157 (5.9)	295 (12.8)	<0.001	64 (4.7)	106 (9.2)	<0.001	43 (5.7)	105 (15.0)	<0.001	50 (9.4)	84 (18.1)	<0.001
Statins	2063 (77.3)	2370 (95)	<0.001	1077 (78.2)	1210 (96)	<0.001	577 (76.5)	694 (94.4)	<0.001	409 (76.2)	466 (93)	<0.001
ACEi/ARBs	1997 (74.8)	1989 (82)	<0.001	1048 (76)	1051 (85.6)	<0.001	570 (75.6)	594 (82.6)	0.001	379 (70.7)	344 (72)	0.7
Beta blockers	2047 (76.6)	2018 (82.1)	<0.001	1046 (75.7)	1026 (82.8)	<0.001	594 (78.9)	592 (81.2)	0.29	407 (75.8)	400 (81.6)	0.028
Cardiac rehabilitation referral at 30-day FUP	338 (28.6)	981 (46.7)	<0.001	184 (30.4)	544 (50.5)	<0.001	89 (29)	292 (47.5)	<0.001	65 (24.3)	145 (35.6)	0.003

*Composite intervention was defined as DAPT and statins at discharge and PCI during hospitalisation.
ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; DAPT, dual antiplatelet therapy; FUP, follow-up; GDMT, guideline-directed medical treatment; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Table 5 Temporal trends in clinical outcomes among the entire cohort and by TIMI risk score for secondary prevention (TRS2°P)

n (%)	Entire cohort			High-risk (TRS2°P=3)			Very high-risk (TRS2°P=4)			Extremely high-risk (TRS2°P≥5)		
	Early (n=2737)	Late (n=2622)	P-value	Early (n=1404)	Late (n=1306)	P-value	Early (n=777)	Late (n=780)	P-value	Early (n=556)	Late (n=536)	P-value
30-day rehospitalisation	564 (22.7)	393 (18.3)	<0.001	279 (21.6)	191 (17.4)	0.012	154 (22.1)	124 (19.7)	0.3	131 (26.4)	78 (18.8)	0.008
30-day recurrent MI	95 (3.5)	38 (1.5)	<0.001	48 (3.4)	22 (1.8)	0.011	27 (3.5)	8 (1.1)	0.003	20 (3.6)	8 (1.6)	0.06
30-day angina	77 (6.6)	52 (3.2)	<0.001	30 (5)	15 (1.8)	0.001	25 (8.3)	24 (4.9)	0.07	22 (8.3)	13 (4.2)	0.06
30-day MACE	605 (22.1)	332 (12.8)	<0.001	288 (20.5)	131 (10.1)	<0.001	173 (22.3)	114 (14.8)	<0.001	144 (25.9)	87 (16.4)	<0.001
30-day Mortality	254 (9.3)	178 (6.9)	0.002	112 (8)	54 (4.2)	<0.001	78 (10)	61 (8)	0.18	64 (11.5)	63 (11.9)	0.9
1-year mortality	543 (19.9)	386 (15.5)	<0.001	216 (15.5)	121 (9.8)	<0.001	168 (21.7)	118 (15.9)	0.005	159 (28.7)	147 (28.9)	1

MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, non available; TIMI, Thrombolysis in Myocardial Infarction.

Figure 3 Kaplan-Meier curves for 1-year survival by time periods stratified by the TIMI risk score for secondary prevention (TRS2°P). TIMI, Thrombolysis in Myocardial Infarction.

period was additionally performed (online supplemental appendix table S3).

DISCUSSION

In this study from a national ACS registry, several findings were demonstrated. Within a population of ACS patients who were at particularly high risk for recurrent CV events, the higher the risk, the older and more comorbid were the patients, and these were treated less commonly with GDMT (angiography, pharmacotherapy and cardiac rehabilitation). Accordingly, a graded risk for worse clinical outcomes (30-day MACE and 1-year mortality) was evident with higher TRS2°P scores. Nevertheless, over time, the utilisation of GDMT at hospital discharge has become more prevalent in all high-risk groups. Clinical outcomes have similarly improved among all high-risk groups throughout time periods with a decrease in 30-day MACE and 1-year mortality, with the exclusion of extremely high-risk patients who did not demonstrate improved 1-year mortality over time. This benefit was observed despite the fact that compared with patients in the early period, patients included in the late period had more baseline comorbidities that were unadjusted for in the analysis, therefore implying an even larger positive trend in outcome.

The TRS2°P was designed originally in the TRA2°P-TIMI 50 trial[14] to predict CV death, MI or stroke at 3 years post-MI. Since then, several studies have validated its utility as a risk prediction model in other,[16 22 23 25] at times higher-risk populations,[4 24] as well as for other prespecified endpoints[13] and for a shorter term. It has been substantiated not only for risk-stratification but also for distinguishing a pattern of increasing benefit from optimal treatment with increasing TRS2°P scores.[18 19] In keeping with prior evidence, in this study, we demonstrated that for a particularly high-risk cohort of patients following ACS, further stratification of the TRS2°P was

predictive of not only a greater risk for recurrent CV events and death but also of which patients will develop hospital complications such as heart failure, atrial fibrillation, and bleeding.

This study focused on a population who is at the highest risk for secondary CV events, far exceeding the risk attributed to very/extremely high-risk patients reported in official guidelines,[26 27] and much higher than the 'average' ACS patients who are usually included in clinical trials. This patient cohort is of special interest since only sparse evidence[11 28] is available regarding the recommended optimal treatment of these patients, who pose a therapeutic challenge due to their complex comorbidities and who are frequently managed conservatively (angiography and high potency platelets abandoned).[29] In fact, we hardly found any studies addressing this patient group specifically, and the majority of data was derived from subgroup analyses of other populations.[18 19 30]

Indeed, the study patients had significant comorbidities, with the majority of patients having diabetes mellitus, about a half with prior MI, a third smokers, and almost all having hypertension. They developed considerable in-hospital complications and an overwhelming rate of MACE and mortality. 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.

While 30-day MACE has improved among all risk groups over time periods, 1-year mortality has not changed among extremely high-risk patients. Although there could be several plausible explanations for this finding, it is probably associated with the high burden of comorbidities, which outweighed the benefit GDMT might have had on their CV risk. Supporting this hypothesis is the aforementioned improvement in 30-day MACE. Still, this finding could simply be due to chance. Overall, for the entire high-risk patient cohort who is the subject of this study, clinical outcomes were favourable despite their multitude of CV risk factors.

Still, the question of whether GDMT should be more often applied in the post-ACS patients from the highest risk spectrum cannot be answered by this study, owing to its retrospective observational nature and the lack of consideration of net clinical benefit. Randomised controlled studies will be needed to bridge this knowledge gap. However, this study supports and serves as a starting point for such randomised trials to be conducted.

This study is multicentre and based on a large prospective national registry with pre-specified parameters and endpoints. Data are complete and well documented on prespecified forms by several teams from different medical centres. However, there are limitations to this study. First, data referring to medication use pertained only to discharge and 30-day follow-up, hence we cannot infer medication adherence. Second, no data were available with respect to the PCI procedure including the specific number, location, and type of stents deployed, coronary anatomy, and lesion severity. Third, high-sensitivity cardiac troponin was only available for the late time period, which may have affected the results. Forth, the proportion of missing values was significant for some of the variables (online supplemental appendix table S4). Fifth, no data were collected regarding the cause of death, thus CV mortality was not reported. Finally, based on this study we cannot deduce a causal association between increased GDMT and a favourable CV clinical outcome. Moreover, there are probably other important contributing factors not accounted for, such as enhanced treatment adherence, better pharmacological treatment of associated highly prevalent comorbidities, and a greater frequency of post-discharge community monitoring, among other factors.

CONCLUSION

Within a particularly high-risk cohort of patients with ACS, the use of GDMT has become more prevalent over almost two decades. While short-term outcomes have improved in all high-riskgroups, 1-year mortality has improved only in the high and very high-risk groups. 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.

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