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Bueno, H., Rossello, X., Pocock, S. J., Van de Werf, F., Chin, C. T., Danchin, N., . . . Huo, Y. (2019). In-Hospital Coronary Revascularization Rates and Post-Discharge Mortality Risk in Non-ST-Segment Elevation Acute Coronary Syndrome. *Journal of the American College of Cardiology*, 74(11), 1454-1461. doi:10.1016/j.jacc.2019.06.068

which has been published in final form at: <https://doi.org/10.1016/j.jacc.2019.06.068>

In-hospital Coronary Revascularization Rates and Post-discharge Mortality Risk in Non-ST-segment Elevation Acute Coronary Syndrome

Brief title: Revascularization and post-discharge mortality in ACS

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Funding: The EPICOR and EPICOR Asia studies were funded by AstraZeneca.

Disclosures: H Bueno receives research funding from the Instituto de Salud Carlos III, Spain (PIE16/00021 & PI17/01799), AstraZeneca, BMS, Janssen and Novartis, has received consulting fees from AstraZeneca, Bayer, BMS-Pfizer, Novartis, and speaking fees or support for attending scientific meetings from AstraZeneca, Bayer, BMS-Pfizer, Ferrer, Novartis, and MEDSCAPE-the heart.org. X Rossello has nothing to disclose. S Pocock has received research funding from AstraZeneca. F Van de Werf has received consulting fees and research grants from Boehringer Ingelheim, Merck and Sanofi, and consulting and speaking fees from Boehringer Ingelheim, Roche, Sanofi, AstraZeneca, and The Medicines Company. CT Chin has received consulting or speaking fees from AstraZeneca, Merck, Servier, and Medtronic. N Danchin has received consulting or speaking fees from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, MSD, NovoNordisk, Pfizer, Sanofi-Aventis, and Servier. SW-L Lee has nothing to disclose. J Medina is an employee of AstraZeneca. Y Huo has nothing to disclose.

Acknowledgements: Editorial assistance was provided by Carl V Felton PhD, Paragon (Knutsford, Cheshire, UK), funded by AstraZeneca. CNIC is supported by the Spanish Ministry of Economy and Competitiveness (MINECO) and the Pro-CNIC Foundation and is a Severo Ochoa Center of Excellence (MINECO award SEV-2015-0505). X.R. has received support from the SEC-CNIC CARDIOJOVEN fellowship program.

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ABSTRACT

Background: The relationship between in-hospital coronary revascularization rate (CRR) and post-discharge mortality rates in survivors of non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) at a system level is unclear.

Objectives: To evaluate CRR and 2-year post-discharge mortality rate (2YMR) in NSTEMI-ACS.

Methods: CRR and 2YMR were analyzed by hospital rate of CRR (in deciles), by country and by world region in 11,931 patients with NSTEMI-ACS who survived to discharge and were enrolled in the EPICOR and EPICOR-Asia registries, twin multinational, observational, prospective cohort studies.

Results: Significant differences in patient baseline characteristics, medical therapies, CRR and 2YMR were found. Mean CRR ranged from 0.0%–96.8% in the first and tenth decile, respectively ($p < 0.001$), from 12.3% in Romania to 92.4% in Slovenia ($p < 0.001$), and from 53.9% in South East Asia (SEAsia) to 90.4% in South Korea-Singapore-Hong Kong. 2YMR varied significantly between hospital deciles of CRR (3.6% in tenth decile vs 9.2% in first decile; $p < 0.001$), countries (lowest 1.5% in Slovenia; highest 19.4% in Malaysia, $p < 0.001$), and regions (lowest South Korea-Singapore-Hong Kong, 3.8%; highest SEAsia, 11.7%; $p < 0.001$). Poisson regression models, adjusted for 15 mortality predictors showed a significant inverse association between CRR and 2YMR for hospitals ($r = -0.90$, $p < 0.001$), countries ($r = -0.65$, $p < 0.001$), regions ($r = -0.87$, $p = 0.005$).

Conclusions: Higher CRRs at hospital, country and world region level are strongly associated with higher post-discharge survival, suggesting CRR as a marker of higher system quality.

Condensed Abstract

The relationship between in-hospital coronary revascularization rates (CRR) and 2-year post-discharge mortality rates (2YMR) was evaluated at a system level in 11,931 NSTEMI-ACS hospital survivors enrolled in the EPICOR and EPICOR-Asia registries. CRR and 2YMR varied between hospitals, countries and regions. Multivariable Poisson regression models adjusted for 15 mortality predictors showed a significant inverse association between CRR and 2YMR at a hospital level ($r = -0.90$, $p < 0.001$), country level ($r = -0.65$, $p < 0.001$), and region level ($r = -0.87$, $p = 0.005$). These findings suggest that CRR may be a marker of higher system quality.

Keywords: Acute coronary syndrome; coronary revascularization; mortality; risk, country, region

Abbreviations and Acronyms

2YMR = 2-year post-discharge mortality rate

CABG = coronary artery bypass grafting

CI = confidence interval

CRR = coronary revascularization rate

EPICOR = long-term follow up of antithrombotic management patterns in acute coronary syndrome patients

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

NSTEMI = non-ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

SD = standard deviation

STEMI = ST-segment elevation myocardial infarction

Introduction

Patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are, in general, at high risk of recurrent coronary events and mortality (1). Guidelines recommend an early invasive strategy – that is, coronary angiography and coronary revascularization when feasible – for a majority of these patients, in particular those at high or intermediate risk (2,3). Although there has been progress in recent years (4), there is still significant variation between hospitals, countries and regions in coronary revascularization rate (CRR) for these patients (1,5). Further, the long-term prognostic implications of differences in clinical practice regarding early coronary revascularization for NSTE-ACS patients are largely unknown. The present work was, therefore, designed to assess whether the rate of coronary revascularization performed during index admission in patients with NSTE-ACS, measured at a healthcare system level (hospital, country, region) is independently associated with post-discharge survival. This represents a post-hoc analysis of the long-term follow up of antithrombotic management patterns in acute coronary syndrome patients (EPICOR) and EPICOR Asia studies.

Methods

Patients

All patients with a final diagnosis of NSTEMI-ACS enrolled in 2 twin prospective studies: EPICOR (NCT01171404, 5,625 patients from 555 hospitals in 20 countries across Europe and Latin America between September 2010 and March 2011), and EPICOR Asia (NCT01361386, 6,306 patients from 219 hospitals from 8 Asian countries between June 2011 and May 2012) (6,7), were considered.

Site Selection

National coordinators in each country were responsible for site selection according to the national proportion of patients treated at hospitals with and without invasive cardiac intervention facilities, with the intention of achieving a fair representation of real-life practice at a country level.

Definitions

NSTEMI-ACS comprised non-ST-segment elevation myocardial infarction (NSTEMI) (chest pain/discomfort, lack of persistent ST-segment elevation, left bundle branch block or intraventricular conduction disturbances, and elevation of cardiac biomarkers [creatinine kinase-isoenzyme MB or troponins] with at least 1 value above the 99th percentile of the upper reference limit) and unstable angina (clinical presentation consistent with rest angina or on minimal exercise, with transient ST-T changes in the electrocardiogram and no significant increase in biomarkers of necrosis, but objective evidence of ischemia by non-invasive imaging, or significant coronary stenosis on angiography). Coronary revascularization was defined as the performance of any kind of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) performed during index hospitalization for NSTEMI-ACS (6).

Data Collection

Patient characteristics, pre-hospital care, hospital features, in-hospital care, including medical therapy, invasive and noninvasive interventions, coronary angiography results and coronary revascularization, were collected. Follow-up was prospectively performed through periodically scheduled, structured telephone calls assessing medical therapy continuation, the occurrence of cardiovascular events, and mortality up to 2 years after discharge (6).

System-level Analysis

The relationship between CRR during index hospitalization and 2-year post-discharge all-cause mortality rate (2YMR) was assessed at a system level using 3 different approaches: individual hospital level, country level and region level. The 743 participating hospitals that recruited NSTEMI-ACS patients were divided according to the decile of in-hospital CRR, and these were correlated with 2YMRs. Across the 28 participating countries, the national CRR were correlated with the national 2YMRs. Finally, 8 geographical regions were defined: Southern Europe (France, Greece, Italy and Spain), Northern Europe (Belgium, Denmark, Finland, Germany, Luxembourg, the Netherlands, Norway, and the United Kingdom [UK]), Eastern Europe (Poland, Romania, Slovenia, and Turkey), Latin America (Argentina, Brazil, Mexico, and Venezuela), China, India, South East Asia (Malaysia, Vietnam and Thailand) and South Korea-Singapore-Hong Kong (1,8), and regional CRR were correlated with average regional 2YMRs.

Statistical Analysis

Continuous parameters are mostly presented as mean (standard deviation [SD]) and groups. Categorical data are expressed as percentages and compared across deciles, countries and regions using Chi-square tests.

Poisson regression models were used to estimate 2YMR according to the revascularization status, adjusted for 15 known predictors of 2-year mortality in the overall study population. These predictors were previously obtained from a risk scoring system using Cox regression to estimate 2YMR in individual patients with acute coronary syndrome and with well reported goodness-of-fit, discriminatory power and internal validation (9). Predictors, ranked by predictive strength, were: age, low left ventricular ejection fraction, elevated serum creatinine at admission, poor EuroQol-5 Dimensions score, low hemoglobin at admission, previous cardiac disease, previous chronic obstructive pulmonary disease, elevated blood glucose at admission, prescription of diuretics at discharge, male sex, lower educational level, prescription of an aldosterone inhibitor at discharge, low body mass index, in-hospital cardiac complications, and Killip class. After obtaining the patient-level adjusted 2YMR, the data were collapsed to obtain the mean adjusted 2YMR for each level of analysis (i.e., by hospital deciles, countries and regions). We then plotted them against their corresponding percentage of revascularization, and estimated the Pearson's correlation coefficient, weighted by group size, to determine the strength of the association between 2YMR and CRR. All probability values were 2-sided and p values of <0.05 were considered as statistically significant. All statistical analyses were performed using STATA software, version 13.1 (Stata Corp, College Station, TX, USA).

Results

The study cohort comprised 11,931 patients recruited in 743 hospitals from 28 countries of 8 world regions. The mean age was 62.8 years (SD, 11.6), 70.5% male, with high prevalence of risk factors: 7,530 (63.7%) hypertensive, 4,746 (42.5%) currently smoking, 4,242 (37%) with hypercholesterolemia, 3,234 (27.4%) with diabetes mellitus; and high prevalence of prior cardiovascular disease (5,039, 43%). A majority of patients were admitted in Killip class I (6,173, 82.9%), 3,602 (31.9%) presented with hemoglobin <13 mg/dl, 2,815 (24.6%) with creatinine \geq 1.2 mg/dl, and 2,135 (20.3%) with blood glucose >160 mg/dl. There were substantial differences in patient baseline profiles and medical management across hospital deciles of CRR (**Table 1** and **Supplementary Table 1**), countries (data not shown), and regions (**Supplementary Table 2**). The in-hospital CRRs were 0% in hospitals belonging to the first decile, 56.8% for hospitals in the fifth decile and 96.8% in hospitals of the tenth decile (**Table 1**). Compared with other hospitals, those from the lowest decile of CRR were less frequently tertiary/university centers (26%), and less often had catheterization laboratories (31%) or participated in a 24/7 primary PCI network (70%).

CRRs also differed among countries, ranging from 12.3% in Romania to 92.4% in Slovenia, $p < 0.001$; **Supplemental Table 3**), and regions, ranging from 53.9% in South East Asia to 90.4% in South Korea-Singapore-Hong Kong ($p < 0.001$). Complete 2-year follow-up was achieved in 10,275 patients (86.1%). The mean follow-up time for the rest of patients ($n=1,656$, 13.9%) was 385 ± 222 days. Two-year post-discharge mortality rates also varied significantly between hospital deciles (3.6% for decile 10, 9.2% for decile 1; $p < 0.001$), countries (lowest 1.5% in Slovenia, highest 19.4% in Malaysia, $p < 0.001$), and regions (lowest 3.8% in South Korea-Singapore-Hong Kong, highest, 11.7% in South East Asia, $p < 0.001$).

Using Poisson regression models that adjust for the 15 previously identified independent predictors of post-discharge mortality (**Figure 1**) (9), we showed a significant difference in the estimated 2YMR between revascularized and non-revascularized patients: 5.2% (95% confidence interval [CI] 4.5–5.8%) versus 9.5% (95% CI 8.5–10.4%), respectively ($p < 0.001$). Moreover, a significant correlation exists between average in-hospital CRR and adjusted 2YMR at hospital level ($r = -0.90$, $p < 0.001$), country level ($r = -0.65$, $p < 0.001$) and region level ($r = -0.87$, $p = 0.005$) (**Central illustration**).

Discussion

This large, prospective, international cohort study of patients who were discharged alive from hospital after NSTEMI-ACS shows that the rate of coronary revascularization performed during index hospitalization is inversely associated with 2-year covariate-adjusted mortality rates measured at a hospital, national or regional level. Our findings align well with and support guideline recommendations for coronary revascularization if significant coronary artery disease is present in patients presenting with NSTEMI-ACS (2,3). They also support the suggestion of considering early invasive strategy as a hospital quality indicator for patients with NSTEMI (10).

We, and others, have previously shown that there are marked regional differences in the management and prognosis of patients with ST-segment elevation myocardial infarction (STEMI) (1) and NSTEMI-ACS (5,8,11-13), which cannot be explained by baseline patients characteristics alone. In this study, we show that important differences in revascularization rates exist not only at a regional but at a country and hospital level, and that these differences are associated with long-term survival at any level of analysis. This consistent association is relevant as it suggests that patients admitted to facilities offering early coronary revascularization have better long-term outcomes. However, this does not necessarily mean that the mortality benefit is explained only by coronary revascularization itself. Other aspects of care associated with providing early intensive care in these hospitals may also play a role.

A number of other studies, mostly observational, support the hypothesis of a survival benefit associated with coronary revascularization in the early phase of NSTEMI-ACS. A recent study showed a significant risk-adjusted reduction in 6-month mortality in the UK during the last decade, following a marked increase in the use of coronary angiography and revascularization (4). We, and others, had previously described that NSTEMI-ACS patients undergoing an invasive

strategy and coronary revascularization, either PCI or CABG, showed improved survival compared with medically treated patients (14-16). A recent analysis of the Atherosclerosis Risk in Communities (ARIC) surveillance study showed that early PCI (under 24 h after symptom onset) in hospitalized NSTEMI patients was associated with improved 28-day survival, especially in high-risk patients, but not at 1 year (17). Although using a wider time frame (1 month) for revascularization, a large Canadian cohort study assessing the relationship between coronary revascularization and 1-year prognosis showed consistent results, with a lower risk of death or cardiovascular hospitalization among those undergoing revascularization (18).

There are, however, alternative explanations to a direct beneficial effect of coronary revascularization. The first is selection bias. It is known that patients undergoing an invasive strategy and receiving coronary revascularization are usually younger, show less comorbidity and are at lower risk than medically managed patients (14,19,20). Although this is true, the comprehensive adjustment of our model and the consistency of the effect found at any level of CRR (i.e., hospital deciles) suggest that the effect cannot fully be explained by differences in baseline characteristics. One study comparing the differences in management and outcomes of acute myocardial infarction between all UK and Swedish hospitals reported that coronary revascularization in patients with NSTEMI was associated with a lower 1-year mortality risk difference between hospitals in the highest and lowest revascularization quarter when adjusted for patient case mix (9%; 95% CI, -1% to 14%, in Sweden, and 14%; 95% CI, 8% to 20%, in the UK) (21). A second alternative explanation is that the differences observed in revascularization rates may be a reflection of differences in the quality of care seen from a wider perspective provided by the different healthcare systems or hospitals. In fact, our study shows significant differences in the use of dual antiplatelet therapy, beta-blockers or statins across hospitals from

different deciles of CRR, as well as between countries and regions. The use of these treatments is a quality indicator for the management of myocardial infarction (10), which has been validated as a prognostic factor as well (10,22). However, although there is some degree of association between quality indicators for the management of myocardial infarction, this association is, at best, modest (22).

At the hospital level, despite the important differences between hospitals within different deciles of CRR (i.e. those in the first decile less frequently tertiary centers, less often with catheterization laboratories or participating in STEMI networks), we cannot say that hospitals with the lowest CRRs were either spoke or hub hospitals as there was a large variation in their characteristics, ranging from hospitals without catheterization laboratory to hospitals with catheterization laboratory and 24/7 PCI programs. In fact, although Northern Europe participated with the lowest proportion of hospitals with on-site catheterization laboratory, they had the highest levels of CRR, indicating a highly efficient referral network. On the contrary, a number of countries, mostly from Asia, participated only with hospitals with catheterization laboratory facility but showed much lower rates of coronary angiography or revascularization (8). The fact that the hospitals with zero CRRs were the ones enrolling the lowest number of patients (mean 8 patients, 53% recruited ≤ 5 patients) may explain in part this finding.

Limitations

A number of limitations should be considered in this study: 1) It is important to highlight that a causal relationship between initial coronary revascularization and post-discharge mortality risk cannot be concluded from these findings. Despite the thorough risk adjustment, its proven value as a quality indicator, and the reasoning as a wider marker of system quality, the causal

effect of coronary revascularization remains hypothetical. 2) It is not possible to rule out the possibility that differences in post-discharge mortality may be explained in part by differences in hospital mortality (i.e., initial survival of higher risk patients may translate into higher post-discharge mortality). Also, mortality related to elective post-discharge revascularization procedures is not considered, which may be particularly relevant for CABG. However, interestingly, the regions with highest baseline risk did not show the highest post-discharge mortality rate. 3) The lack of information on the cause of death precludes the inference of a potential mechanism for a survival advantage. 4) While both registries were designed to recruit representative patients from representative centers in each country, we cannot rule out a bias in regard to the type of hospitals recruiting patients. Hence, some caution is needed to extrapolate our findings regarding geographic differences, since these centers might not be fully representative of the whole country. 5) Despite its wide representation, this is not a global study as important regions are not included. However, it is likely that similar findings would have been found had more regions been included in the study.

In conclusion, higher average rates of coronary revascularization performed during index hospitalization in patients presenting with NSTEMI-ACS, measured at a hospital, country and world region level, are independently associated with lower adjusted 2-year mortality rates.

PERSPECTIVES

Competency in medical knowledge: Despite international guidelines recommendations, there is huge variability in the rates of in-hospital coronary revascularization rates among hospitals, countries and world regions. Higher coronary revascularization rates are inversely correlated with lower adjusted post-discharge mortality risks at all levels of analysis.

Competency in patient care: Interventions to ensure that a majority of NSTEMI-ACS patients undergo coronary angiography and, if needed, coronary revascularization during index hospitalization, regardless of the location of initial admission or healthcare setting, are needed. This may include the expansion of more agile networks for patient transfers when these are not readily available.

Translational outlook. The performance of in-hospital coronary revascularization rates should be prospectively evaluated as a system quality measure for the management of NSTEMI-ACS.

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FIGURE LEGENDS

Figure 1. Incidence rate ratios (IRR) in the univariate and multivariate Poisson regression models for the 15 predictors of 2-year all-cause mortality for which coronary revascularization rates were adjusted for.

Poisson regression models were performed at individual-patient level to obtain each subject's adjusted 2-year mortality rate. After obtaining the estimates, data was collapsed to obtain the mean adjusted 2-year mortality rate for each level of analysis (hospital deciles, countries and world regions) and make correlations between the average revascularization rate for each group in each level of analysis and 2-year adjusted mortality rate.

Central Illustration: Correlation between in-hospital coronary revascularization rate (percutaneous coronary intervention and/or coronary artery bypass grafting) and 2-year, risk-adjusted, all-cause mortality rate, according to hospital decile, country and region. The figures are weighed-data scatter plots illustrating the relationship between 2-year risk-adjusted mortality rates (adjusted for 15 known predictive factors (9)) and coronary revascularization rates by either predefined region (panel A), country (panel B), and hospital decile (panel C). Each circle represents a population group (region, country or hospital decile) and its size is scaled according to its size. The regression lines demonstrate a strong inverse association across the 3 comparisons.

TABLE 1: Baseline patient characteristics, in-hospital treatment and mortality by hospital level according to coronary revascularization rate (in deciles 1, 5 and 10)*

	Hospitals in Decile 1	Hospitals in Decile 5	Hospitals in Decile 10
Number of patients in each decile (%)	845 (7.1)	1,289 (10.8)	1,477 (12.4)
Baseline characteristics			
Age (years), mean (SD)	62.9 (12.0)	62.7 (11.3)	62.4 (11.5)
Male, n (%)	563 (66.6)	907 (70.4)	1,128 (76.4)
Hypertension, n (%)	585 (70.1)	798 (62.6)	874 (59.5)
Hypercholesterolemia, n (%)	324 (41.5)	396 (33.1)	461 (32.0)
Diabetes mellitus, n (%)	289 (34.7)	309 (24.3)	363 (24.8)
Currently smoking, n (%)	350 (45.2)	546 (45.7)	564 (40.2)
Prior CVD, n (%)	373 (47.1)	545 (44.0)	514 (35.0)
Clinical status on admission, n (%)			
LVEF <40%	64 (8.7)	59 (5.1)	80 (5.6)
Creatinine ≥1.2 mg/dl	269 (35.5)	305 (24.5)	335 (23.4)
Glucose >160 g/dl	211 (28.4)	232 (20.5)	255 (18.6)
Hemoglobin <13 mg/dl	263 (35.4)	381 (30.7)	388 (26.8)
Patient management, n (%)			
Coronary revascularization	0 (0)	724 (56.8)	1,428 (96.8)
PCI	0 (0)	694 (54.3)	1,411 (95.6)
CABG	0 (0)	34 (2.7)	18 (1.2)
DAPT at discharge	650 (76.9)	1,025 (79.5)	1,393 (94.3)
Statin at discharge	712 (85.2)	1,150 (89.8)	1,382 (93.8)
BB at discharge	632 (75.5)	958 (74.5)	1,143 (77.4)
ACEI/ARB at discharge	601 (71.7)	794 (61.9)	964 (65.3)
MRA at discharge	67 (8.0)	78 (6.1)	109 (7.4)
2-year mortality	78 (9.2)	79 (6.1)	53 (3.6)

*For a simpler presentation, this table only shows deciles 1, 5 and 10. Data for all 10 deciles are shown in Supplementary Table 1.

ACEI/ARB angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BB, beta-blocker; CABG, coronary artery bypass grafting; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; SD, standard deviation.