Regional variations in hospital management and post-discharge mortality in patients with non–ST-segment elevation acute coronary syndrome

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Abstract

Background: Therapeutic variability not explained by patient clinical characteristics is a potential source of avoidable morbidity and mortality. We aimed to explore regional variability in the management and mortality of patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS).

Methods and Results: 11,931 NSTE-ACS hospital survivors enrolled in two prospective registries: EPICOR (5625 patients, 555 hospitals, 20 countries in Europe (E) and Latin America (LA), September 2010–March 2011) and EPICOR Asia (6306 patients, 218 hospitals, 8 countries, June 2011–May 2012) were compared among eight pre-defined regions: Northern E (NE), Southern E (SE), Eastern E (EE); LA; China (CN), India (IN), South-East Asia (SA), and Hong Kong, Singapore and South Korea (KS). Patient characteristics differed between regions: mean age (lowest 59 years, IN; highest 65.9 years, SE), diabetes (21.4% NE; 35.5% IN) and smoking (32% NE; 62% IN). Variations in dual antiplatelet therapy at discharge (lowest 83.1%, IN; highest 97.5%, SA), coronary angiography (53.9% SA; 90.6% KS), percutaneous coronary intervention (35.8% SA; 78.6% KS) and coronary artery bypass graft (0.7% KS; 5.7% NE) were observed. Unadjusted 2-year mortality ranged between 3.8% in KS and 11.7% in SE. Two-year, risk-adjusted mortality rates ranged between 5.1% (95% confidence interval 2.9%–7.3%) in KS to 10.5% (8.3%–12.7%) in LA.

Conclusion: Wide regional variations in patient features, hospital care, coronary revascularization and post-discharge mortality are present among patients

hospitalized for NSTE-ACS. Focused regional interventions to improve the quality of care for NSTE-ACS patients are still needed.

Introduction

Variations in hospital and post-discharge mortality related to the quality of hospital care have been described for patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS) [1-4]. The increase in the use of coronary angiography and revascularization in these patients, for instance, seems to explain part of the reduction in 6-month mortality observed in the United Kingdom (UK) during recent years [5]. Despite this fact, wide regional variations in hospital care of these patients have been described at national and international levels, including medical therapies and invasive strategy [6-12]. We aimed to better understand the relationship between different geographic patterns in hospital care of patients with NSTE-ACS in general and the rates of use of coronary revascularization in particular, and the risk of death after hospital discharge.

Methods

In total, 23,490 patients with non-fatal NSTE-ACS were enrolled between September 2010 and March 2011 from 555 hospitals in 20 countries across Europe and Latin America (LA) (EPICOR [long-tErm follow uP of antithrombotic management patterns In acute CORonary syndrome patients], NCT01171404, n = 10,568), and between June 2011 and May 2012 from 219 hospitals across eight countries in Asia (EPICOR Asia, NCT01361386, n = 12,922). The protocol and case record form of both studies were almost identical and their rationale and designs have been described elsewhere [13, 14]. The current study is a pre-defined secondary objective of both studies. Of these patients, only those with NSTE-ACS were included in the present analysis; 5625 from EPICOR and 6306 from EPICOR Asia.

Definitions used in EPICOR have been presented elsewhere [13, 14]. Diagnosis of NSTE-ACS included non–ST-segment elevation myocardial infarction (diagnosis based on the presence of chest pain or discomfort, lack of persistent ST-segment elevation, left bundle branch block or intraventricular conduction disturbances, and elevation of cardiac biomarkers [creatinine kinase-isoenzyme MB and troponins] with at least one value above the 99th percentile of the upper reference limit), and unstable angina (diagnosis based on the presence of angina symptoms at rest or on minimal exercise, and transient ST-T changes, with no significant increase in biomarkers of necrosis but objective evidence of ischemia by non-invasive imaging or significant coronary stenosis on angiography). An invasive management was defined as the realization of at least a diagnostic coronary angiography during index hospitalization with or without further coronary revascularization.

Eight geographical regions were defined for regional analyses (Fig. 1): Southern Europe (SE) (France, Greece, Italy and Spain), Northern Europe (NE) (Belgium, Denmark, Finland, Germany, Luxembourg, The Netherlands, Norway, and UK), Eastern Europe (EE) (Poland, Romania, Slovenia and Turkey), LA (Argentina, Brazil, Mexico and Venezuela), China (CN), India (IN), South-East Asia (SA) (Malaysia, Vietnam and Thailand) and South Korea-Singapore-Hong Kong (KS) [15]. Supplementary Table S1 shows the number of patients enrolled per country and region.

Statistical analysis

Continuous parameters are mostly presented as mean (SD) and regions are compared using one-way analysis of variance. Ordinal and continuous highly skewed distributed variables are presented by median and inter-quartile range, and regions are compared using the nonparametric Kruskal-Wallis test. Categorical data is expressed as percentages and compared between regions using Chi-square tests. Cumulative probability of all-cause post-discharge mortality by region was plotted using the Kaplan-Meier method.

We used a Poisson regression model to estimate 2-year mortality rates for each region. Poisson regression modelling is used for count outcomes during a given interval of time (i.e., number of deaths in 2-year follow-up) and provides an estimation of incidence rates. In this study, we obtained both crude and adjusted estimates of 2-year mortality for each region. The latter was adjusted for 16 known predictors of 2-year mortality in the overall study population, which were obtained from the same cohort in our EPICOR 2-year risk [16] and were (ranked by the

strength of its association with 2-year mortality): older age (fitted as continuous), low left ventricular ejection fraction (≥40, 39–30 and <30%), lack of coronary revascularization or reperfusion therapy during hospitalization, elevated serum creatinine at admission (fitted as continuous if ≥1.2 mg/dL), poor EuroQol Five Dimensions score (0, 1, ≥2), low hemoglobin at admission (≥13, 12–11 and <11 g/dL), previous cardiac disease, previous chronic obstructive pulmonary disease, elevated blood glucose at admission (fitted as continuous if ≥140 mg/dL), diuretics prescribed at discharge, male sex, lower educational level (no formal, primary, secondary, university), aldosterone inhibitor prescribed at discharge, body mass index <20 kg/m^2, in-hospital cardiac complications, and Killip class (I, II and III–IV). To allow for missing values for each co-variate, multiple imputation was used, as described in the EPICOR 2-year mortality risk score publication [16], which included the Von Hippel method of transformation then imputation for continuous variables [17].

All probability (p-)values were 2-sided and 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). GraphPad Prism version 6.00 (GraphPad Software, La Jolla California) was used to produce the figures.

Results

The study cohort comprised a total of 11,931 consecutive NSTE-ACS patients who survived to hospital discharge. Supplementary Fig. 1 depicts the distribution of patients across the eight regions. Substantial differences in patient baseline profiles across regions were observed (Table 1, Fig. 1). Mean patient age ranged between 59.0 years (IN) and 65.9 years (SE) and the proportion of men between 66.2% in SA and 79.1% in IN. The prevalence of risk factors also varied by region, with current smoking ranging between 32.0% (NE) and 62.0% (IN), and diabetes between 21.4% (NE) and 35.5% (IN). Although Killip class I was more frequently reported in E and LA compared with the Asian regions, the rate of missing values for this parameter among the latter was high (CN 70.4%, IN 46.9%, KS 44.3%, SA 31.9%).

There were also regional differences in the characteristics of the participating hospitals where these patients were treated (Supplementary Table S2). In general, a higher proportion of Asian participants were initially admitted to hospitals with catheterization laboratory facilities compared to E and LA patients. The percentage of on-site cardiac surgery was also higher in Asian and LA enrolling hospitals compared to E. Many centers had a coronary or intensive care unit, ranging from 87.9% (SA) to 100% in IN and KS.

In-hospital management

Medication prescription patterns at discharge (Table 2) differed between regions. Dual antiplatelet therapy was prescribed at discharge in most patients in each region, ranging between 77.5% (IN) and 89.7% (SA), with aspirin and clopidogrel

used in the majority of cases. Prescription of statins at discharge was high, between 80.4% in KS and 93.3% in CN. IN showed the lowest prescription rates for beta-blockers (58.0%) and angiotensin converting enzyme inhibitors (45.1%) and EE the highest (91.3% and 82.7%, respectively).

Assessment of left ventricular ejection fraction before discharge was not universal, ranging from 51.6% in IN to 84.8% in SE (Supplementary Table S2). The proportion of patients with severely depressed left ventricular ejection fraction also varied, being the lowest in CN (3.1%) and the highest in SA (12.8%).

An invasive strategy was employed in a majority of patients but ranged between 53.9% in SA and 90.6% in KS. Coronary revascularization before discharge basically followed the same trend (Supplementary Table S2, Fig. 1), ranging between 38.6% in SA and 79.3% in KS. The type of revascularization also differed but less importantly. The majority of patients (58.7%) were treated with percutaneous coronary angioplasty (between 35.1% in LA and 78.6% in KS) and 2.4% (from 0.7% in KS to 5.7% in NE) underwent surgical revascularization. The median length of hospital stay was 6 days (4–10 days) but varied widely between the 3 days observed in IN and 9 days in CN.

Post-discharge mortality risk

After discharge, 81 patients (0.7%) died by any cause during the first 30 days and 684 within the first 2 years, so the all-cause, 2-year post-discharge mortality risk was 5.7% (95% confidence interval [CI], 5.3% to 6.2%), ranging between 3.8% in KS and 11.7% in SA (Fig. 2, Supplementary Table S3). After comprehensive adjustment for baseline characteristics, comorbidities and therapies employed in hospital with a

validated model (http://www.acsrisk.org/) [16], differences between regions in adjusted all-cause, 2-year mortality risk remained significant ($p < 0.001$) (Fig. 2, Supplementary Table S3), with the lowest rate observed in KS (5.1%; 95% CI, 2.9%–7.3%) and the highest in LA (10.5%; 95% CI, 8.3%–12.7%).

Discussion

The present study, evaluating a large geographic area from the world, shows an important variability in the hospital management of NSTE-ACS patients, which is not explained only by differences in the clinical profile of the patients, and is associated with differences as high as two-fold between some regions in post-discharge adjusted survival.

Important regional variations were described in medical therapy for acute coronary syndrome several years ago [7, 8, 11, 12, 18]. Our study shows that, although some general progression has occurred, important regional differences in the management of NSTE-ACS persist worldwide. The rates in the use of dual antiplatelet therapy, statins, angiotensin converting enzyme inhibitors is higher than previously described, and the variability is lower. However, very important differences in the use of an invasive strategy and coronary revascularization during initial hospitalization remain. This seems to be relevant as regions with the highest rate of use of evidence-based therapies — medications and coronary revascularization — show the lowest rate of 2-year mortality, while regions with higher rates of medical management show higher 2-year mortality rates.

Although previous studies performed by us [6, 16] and others [5, 19] showed that early revascularization is associated with a significantly lower post-discharge mortality risk in NSTE-ACS patients even after adjustment for confounders, and the current results of the study are consistent with these studies, our results also point out that other factors matter. Indeed, after extensive adjustment for baseline characteristics and treatments, there still are significant residual regional differences

in mortality risk. Whether this is due to uncontrolled intrinsic patient differences, other differences in management or unmeasured confounders needs further study. We speculate that the regional differences observed in a number of performance measures, such as use of dual antiplatelet therapy, statins, or other drugs, and the use of an invasive strategy and coronary revascularization, which have been described as quality indicators [20], and validated as prognostic markers [2, 3], may be a reflection of wider differences in the quality of care provided by the different healthcare systems. The influence of limited health resources in poor performing countries also needs to be considered.

One interesting observation from our study is the discrepancy between the immediate availability of coronary angiography (i.e., proportion of patients admitted to centers with catheterization laboratory facility) and the actual access to treatment. The extreme examples are NE with the lowest proportion of hospitals with on-site catheterization laboratory or on-site cardiac surgery on one hand and the highest levels of coronary angiography, percutaneous coronary intervention and coronary artery bypass graft, as well as with the lowest 2-year adjusted mortality rates on the other hand. On the opposite side, a number of regions, mostly from Asia, where only hospitals with catheterization laboratory facility participated in the registry, showed much lower rates of coronary angiography or revascularization and also some of the highest post-discharge mortality rates. This discrepancy highlights that quality of care is not only a matter of availability of resources but also depends on knowledge of guidelines and application of its recommendations, organization of care, including effective referral systems from secondary centers to tertiary centers with full coronary revascularization facilities, and issues related to social security coverage

and/or need for reimbursement for procedures. Therefore, revascularization rates are probably not the only cause for the better survival of patients with NSTE-ACS in some regions but rather a surrogate for a higher quality of the healthcare system. This comprises factors such as other issues related to acute care, quality of revascularization, post-discharge compliance with lifestyle changes, secondary prevention therapies or cardiac rehabilitation. In fact, a number of other critical issues related to access of care must be considered when such different healthcare systems are compared, including public insurance coverage, public versus private health, reimbursement for procedures (i.e., coronary angiography and/or revascularization), devices (i.e., coronary stents) or drugs (i.e., secondary prevention drugs). Local healthcare authorities should be aware of this fact.

Our results have also implications for research, emphasizing the importance of having diverse regional representation in randomized clinical trials towards testing therapies or strategies for NSTE-ACS patients; results may be modulated by local practice patterns as evident from a number of trials [21, 22]. There is also the need to try and reasonably standardize treatment practice across regions to avoid excessive confounding associated with regional variation in clinical practice and outcomes.

Several limitations should be considered in this study. 1) 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) but interestingly, the regions with highest baseline risk did not show the highest post-discharge mortality rate. 2) The

lack of information on the cause of death precludes the inference of a potential mechanism for a survival advantage. 3) There might be unexplored variability both within and between countries, rather than regions. 4) While both registries were designed to recruit representative patients from centers also representative of the type of hospitals (i.e., tertiary) within each country, regional differences in center characteristics suggests that some bias in regard to the type of hospitals recruiting patients from EPICOR and EPICOR Asia may play a role. Hence, some caution is needed to extrapolate our findings since these centers might not be fully representative of the reality of each country. 5) Despite its wide representation, this is not a global study as important regions are not represented. However, it is likely that similar findings would have been found had more regions been included in the study.

In conclusion, important geographic variations in patient features, initial medical care, coronary revascularization and post-discharge mortality are present among patients hospitalized for NSTE-ACS, which remain after extensive adjustment for confounders. More research is needed to define the best opportunities to improve the quality of care for these patients at each healthcare system.

Acknowledgements

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Table 1 Patient characteristics by region

	All patients	Southern Europe	Northern Europe	Eastern Europe	Latin America	China	SK, HK & Singapore	India	South-East Asia
N, (%)	11,931 (100)	1213 (10.2)	2174 (18.2)	1235 (10.4)	1003 (8.4)	4253 (35.7)	553 (4.6)	986 (8.3)	514 (4.3)
Baseline characteristics									
Age, mean (SD)	62.8 (11.6)	65.9 (12.5)	64.6 (12.3)	61.0 (10.9)	63.2 (11.6)	61.9 (10.8)	63.7 (11.8)	59.0 (11.4)	63.8 (12.3)
Age ≥75, *n* (%)	2094 (17.6)	351 (28.9)	523 (24.1)	158 (12.8)	188 (18.7)	562 (13.2)	110 (19.9)	89 (9.0)	113 (22.0)
Male, *n* (%)	8407 (70.5)	903 (74.4)	1559 (71.7)	868 (70.3)	666 (66.4)	2904 (68.3)	387 (70.0)	780 (79.1)	340 (66.2)
Hypertension, *n* (%)	7530 (63.7)	797 (66.6)	1294 (60.4)	859 (70.2)	759 (76.5)	2667 (63.1)	318 (57.5)	485 (49.5)	351 (68.3)
Hypercholesterolemia, *n* (%)	4242 (37.0)	720 (60.9)	1150 (54.6)	586 (49.5)	497 (53.6)	855 (21.1)	143 (26.1)	52 (5.5)	239 (47.0)
Diabetes mellitus, *n* (%)	3234 (27.4)	408 (34.1)	460 (21.4)	307 (25.2)	336 (34.1)	1046 (25.0)	169 (30.6)	348 (35.5)	160 (31.1)
Currently smoking, *n* (%)	4746 (42.5)	384 (34.7)	649 (32.0)	475 (40.8)	350 (37.8)	1901 (46.5)	243 (46.7)	508 (62.0)	236 (47.1)
Prior cardiovascular disease, *n* (%)	5039 (43.0)	553 (46.0)	979 (45.2)	642 (52.3)	498 (50.7)	1805 (43.2)	171 (31.2)	192 (21.2)	199 (38.7)
Clinical status on admission									
Killip class, *n* (%)									
I	6173 (82.9)	981 (86.7)	1597 (88.4)	1022 (88.0)	764 (84.7)	983 (78.0)	224 (72.7)	368 (70.2)	234 (66.9)

II	841 (11.3)	100 (8.8)	156 (8.6)	109 (9.4)	72 (8.0)	194 (15.4)	40 (13.0)	95 (18.1)	75 (21.4)
III-IV	431 (5.8)	51 (4.5)	53 (2.9)	31 (2.7)	66 (7.3)	84 (6.7)	44 (14.3)	61 (11.6)	41 (11.7)
Creatinine ≥1.2 mg/dL, *n* (%)	2815 (24.6)	249 (22.5)	604 (28.8)	238 (19.7)	236 (26.1)	911 (21.7)	141 (26.1)	219 (25.6)	217 (42.7)
Blood glucose >160 g/dL, *n* (%)	2135 (20.3)	239 (22.4)	331 (18.0)	240 (21.3)	216 (25.6)	664 (16.1)	134 (28.2)	212 (34.3)	99 (22.5)
Hemoglobin <13 mg/dL, *n* (%)	3602 (31.9)	318 (28.6)	482 (23.2)	266 (21.9)	264 (31.6)	1428 (34.0)	181 (33.3)	393 (49.4)	270 (53.2)

P-value <0.001 for all comparisons between regions.

Red colour depicts the highest and blue colour the lowest value for each row.

Number of patients (%) with missing values: age 3 (0.03%), gender 0 (0%), hypertension 102 (0.9%), hypercholesterolemia 467 (3.9%), diabetes 139 (1.2%) smoking status 772 (6.5%), prior cardiovascular disease 210 (1.8%), Killip class 1393 (11.7%), creatinine 504 (4.2%), blood glucose 636 (5.3%), hemoglobin 313 (1.0%).

Abbreviations. HK, Hong Kong; SK, South Korea.

Table 2 Medications used at discharge

	All patients	Southern Europe	Northern Europe	Eastern Europe	Latin America	China	SK, HK & Singapore	India	South-East Asia
Anti-thrombotics*									
DAPT, *n* (%)	9914 (83.1)	1017 (83.8)	1717 (79.0)	979 (79.3)	789 (78.7)	3700 (87.0)	487 (88.1)	764 (77.5)	461 (89.7)
Aspirin + clopidogrel	9539 (80.0)	939 (77.4)	1609 (74.1)	961 (77.8)	747 (74.5)	3698 (87.0)	485 (87.7)	643 (65.2)	457 (88.9)
Aspirin + prasugrel	347 (2.9)	70 (5.8)	103 (4.7)	11 (0.9)	41 (4.1)	0 (0.0)	2 (0.4)	119 (12.1)	1 (0.2)
SAPT, *n* (%)	1483 (12.4)	121 (10.0)	257 (11.8)	189 (15.3)	167 (16.7)	481 (11.3)	44 (8.0)	186 (18.9)	38 (7.4)
Statin, *n* (%)	10,783 (90.4)	1117 (92.1)	1998 (92.0)	1113 (90.3)	899 (91.5)	3951 (93.3)	442 (80.4)	794 (81.9)	469 (91.3)
Beta blockers, *n* (%)	9145 (76.7)	985 (81.2)	1860 (85.6)	1127 (91.3)	801 (79.9)	3033 (71.3)	420 (76.0)	572 (58.0)	347 (67.5)
ACEI/ARB, *n* (%)	7954 (66.7)	916 (75.5)	1500 (69.0)	1021 (82.7)	734 (73.2)	2636 (62.0)	356 (64.4)	445 (45.1)	346 (67.3)
MRA, *n* (%)	733 (6.1)	66 (5.4)	97 (4.5)	119 (9.6)	88 (8.8)	256 (6.0)	28 (5.1)	61 (6.2)	18 (3.5)

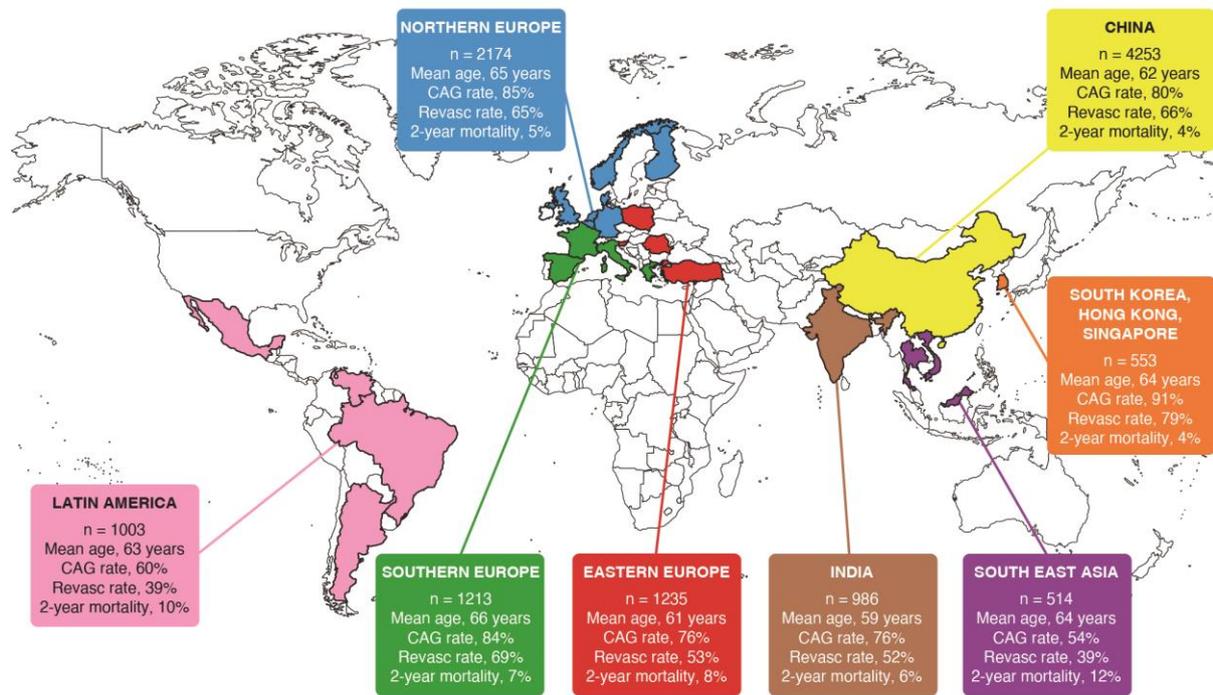*P*-value < 0.001 for all comparisons between regions.

Any P2Y$_{12}$ inhibitor includes clopidogrel, prasugrel or ticlopidine. Cilostazol was prescribed in 95 patients from SK, HK and Singapore (17.5%), 35 patients from China (0.8%) and eight from India (0.8%). DAPT was defined as aspirin plus another oral antiplatelet agent, such as clopidogrel, prasugrel or ticlopidine.

Red colour depicts the highest and blue colour the lowest value for each row.

Number of patients (%) with missing values: antithrombotics 98 (0.8%), statin 70 (0.6%), β-blockers 44 (0.4%), ACEI/ARB 45 (0.4%), MRA 73 (0.6%).

Abbreviations. *ACEI*, angiotensin-converting-enzyme inhibitor; *ARB*, Angiotensin receptor blocker; *DAPT*, dual antiplatelet therapy; *HK*, Hong Kong; *MRA*, mineralocorticoid receptor antagonist; *SAPT*, single antiplatelet therapy; *SK*, South Korea.

Fig. 1 World map with countries participant in the EPICOR registries with main characteristics and outcomes by region

NORTHERN EUROPE
n = 2174
Mean age, 65 years
CAG rate, 85%
Revasc rate, 65%
2-year mortality, 5%

CHINA
n = 4253
Mean age, 62 years
CAG rate, 80%
Revasc rate, 66%
2-year mortality, 4%

SOUTH KOREA, HONG KONG, SINGAPORE
n = 553
Mean age, 64 years
CAG rate, 91%
Revasc rate, 79%
2-year mortality, 4%

LATIN AMERICA
n = 1003
Mean age, 63 years
CAG rate, 60%
Revasc rate, 39%
2-year mortality, 10%

SOUTHERN EUROPE
n = 1213
Mean age, 66 years
CAG rate, 84%
Revasc rate, 69%
2-year mortality, 7%

EASTERN EUROPE
n = 1235
Mean age, 61 years
CAG rate, 76%
Revasc rate, 53%
2-year mortality, 8%

INDIA
n = 986
Mean age, 59 years
CAG rate, 76%
Revasc rate, 52%
2-year mortality, 6%

SOUTH EAST ASIA
n = 514
Mean age, 64 years
CAG rate, 54%
Revasc rate, 39%
2-year mortality, 12%

Abbreviations. CAG, coronary angiography; Revasc, revascularization.

Fig. 2 Proportion of patients undergoing invasive strategy (panel A), and coronary revascularization (percutaneous coronary intervention and coronary artery bypass grafting [CABG], panel B) during index hospitalization by region
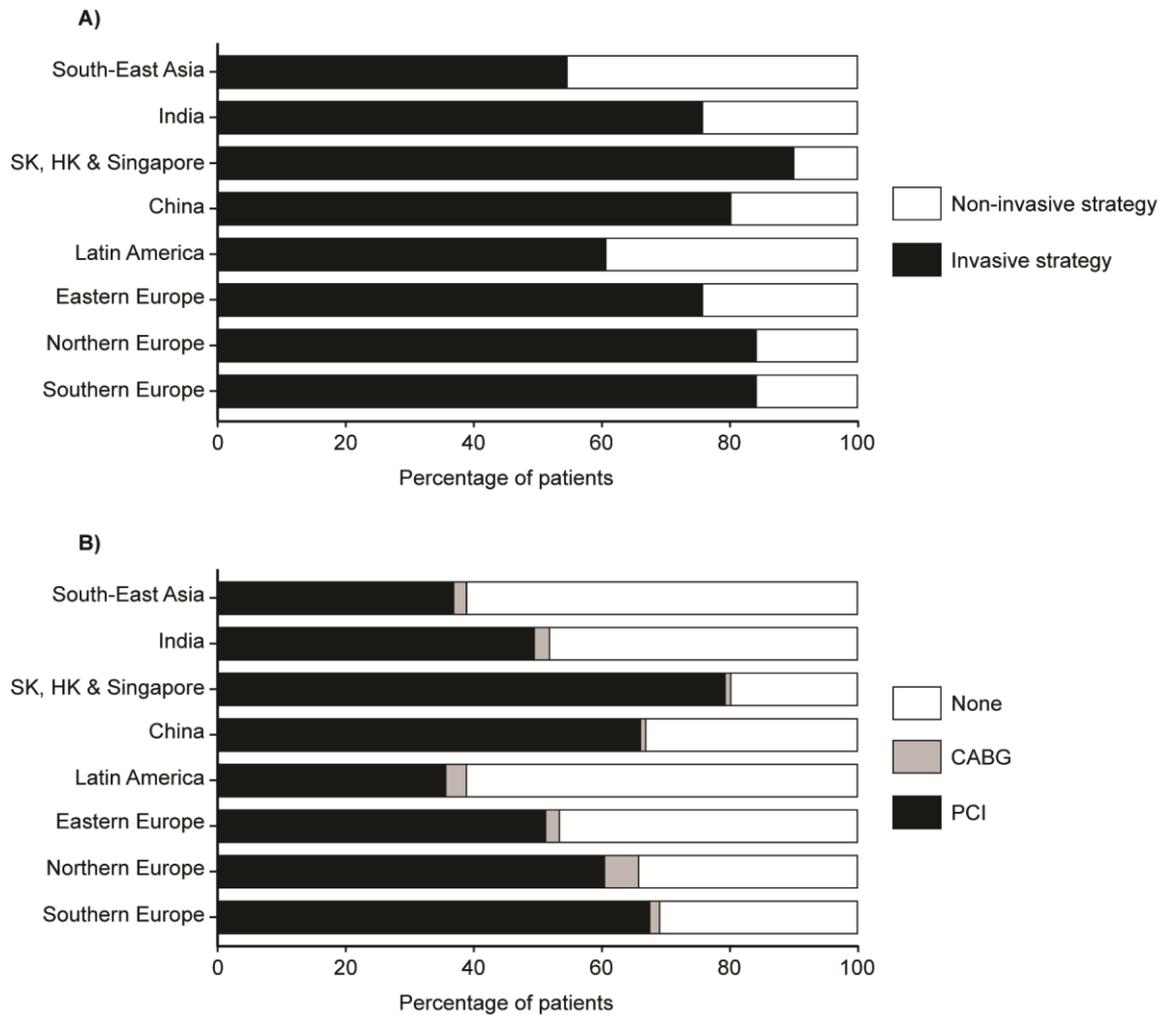
Abbreviations. HK, Hong Kong; PCI, percutaneous coronary intervention; SK, South Korea.

Fig. 3 Adjusted 2-year, all-cause mortality rate by region
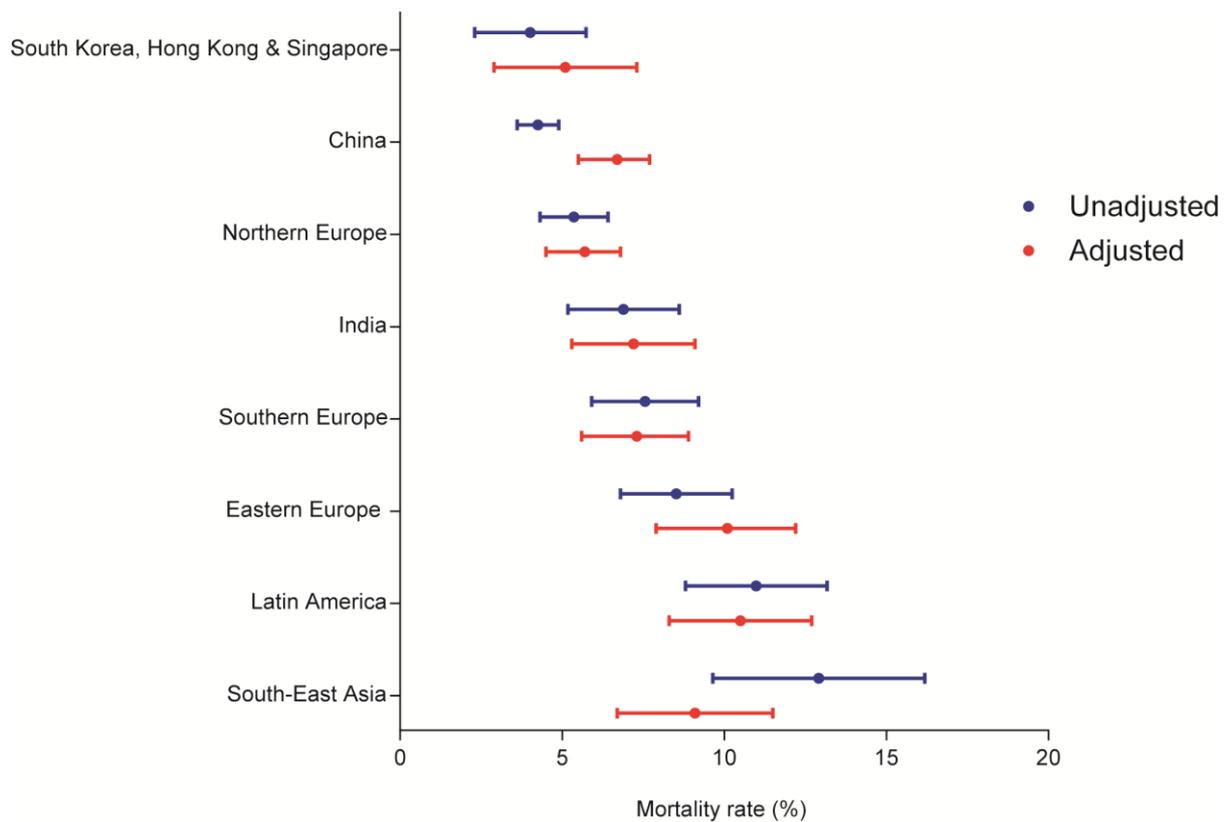
Two-year mortality risk adjusted for: age, sex, body mass index, Killip class; creatinine, hemoglobin, and blood glucose at admission; left ventricular ejection fraction; in-hospital cardiac complications; coronary revascularization; quality of life; prior cardiac disease or chronic obstructive pulmonary disease; educational level; diuretics or aldosterone inhibitors prescribed at discharge.

Abbreviations. *HK*, Hong Kong; *SK*, South Korea.