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Characteristics and outcomes of medically managed patients with non-ST-segment elevation acute coronary syndromes: insights from the multinational EPICOR Asia study

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ABSTRACT

Background: Many patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) are medically managed without coronary revascularization. The reasons vary and may impact prognosis.

Methods: EPICOR Asia (NCT01361386) is a prospective study of hospital survivors post-ACS enrolled in 218 hospitals from 8 countries/regions in Asia (06/2011–05/2012). All medically managed NSTE-ACS patients were classified into 3 groups: 1) no coronary angiography (CAG–); 2) non-significant coronary artery disease (CAD) on angiogram (CAG+ CAD–); and 3) significant CAD (CAG+ CAD+). We compared baseline differences between patients medically managed and patients undergoing revascularization, and also between the medically managed groups. Adverse events were reported and compared up to 2 years.

Results: Of 6163 NSTE-ACS patients, 2272 (37%) were medically managed, with 1339 (59%), 254 (11%), and 679 (30%) in the CAG–, CAG+ CAD–, and CAG+ CAD+ groups, respectively. There were marked differences in the proportion of medically managed patients among the 8 countries/regions (13–81%). Medically managed patients had higher mortality at 2 years compared with revascularization (8.7% vs. 3.0%, $p < 0.001$). Among medically managed patients, CAG– patients were older, more likely to have pre-existing cardiovascular disease, and had the highest 2-year mortality (10.5% vs. 4.3% [CAG+ CAD–] and 6.6% [CAG+ CAD+], $p < 0.001$). Mortality differences persisted after adjusting for other patient risk factors.

Conclusions: Medically managed NSTE-ACS patients are a heterogeneous group with different risk stratification and variable prognosis. Identification of reasons underlying different management strategies, and key factors adversely influencing long-term prognosis, may improve outcomes.

Introduction

Much evidence suggests that patients admitted to hospital with non-ST-segment elevation acute coronary syndromes (NSTE-ACS), comprising non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina, will likely benefit from a strategy of early invasive management (coronary angiography within 48–72 h with a view to revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery) [1-3]. Therefore, current international guidelines for the management of patients with NSTE-ACS endorse optimal medical therapy and early invasive management for patients at intermediate- to high-risk [4,5].

Nevertheless, around half of patients admitted worldwide with NSTE-ACS do not undergo coronary revascularization and are managed only medically [6-8]. There are multiple reasons for not offering or performing revascularization for these patients, commonly related to the perceived high-risk nature of the revascularization procedure due to associated comorbidities or technical issues such as complex coronary anatomy [7-9]. However, these patients who are managed only medically are also more likely to not receive guideline-recommended medications, including dual antiplatelet therapy [8].

To further compound this, data from clinical trials and registries data have consistently shown that patients with NSTE-ACS who are treated only medically tend to have poorer long-term cardiovascular outcomes compared with patients who are able to undergo revascularization [7]. The degree to which outcomes may be improved for medically managed patients with NSTE-ACS is currently limited as there exist only a few large-scale randomized trials specifically examining newer

therapies for these patients and most data available have been obtained from sub-studies of larger trials [10-12].

More than half the population of the world live in Asia, and with current rising standards of living in Asian countries, the burden of cardiovascular disease (CVD) is expected to increase steadily in Asia. This will in turn be anticipated to have a significant effect on the global health burden and resources. However, there is a paucity of data from Asia with regard to patients with NSTE-ACS, especially those that are medically managed only. Therefore, the EPICOR (long-t**E**rm follow-u**P** of anti-thrombotic management patterns **I**n acute **COR**onary syndrome patients) Asia study afforded us the unique opportunity to investigate the extent to which patients with NSTE-ACS are treated only medically in Asia, to examine management patterns in different regions of Asia, and to describe the impact that this has on long-term outcomes.

Methods

The study design and baseline characteristics of the study participants in the EPICOR Asia study (NCT01361386) have previously been described [13]. In brief, this is a prospective study of 12,922 patients with ACS who were enrolled in 218 hospitals from 8 countries/regions in Asia between June 2011 and May 2012 and who survived until hospital discharge. They were followed-up for 2 years after discharge, and study endpoints were reviewed by independent adjudicators. The steering committee, which included academic investigators, along with representatives of the sponsor (AstraZeneca), designed the study and supervised its conduct. Statistical analyses were performed by a joint team comprising statisticians from the sponsor and an independent academic center. The study was approved by the local ethics committee or institutional review board at each study center, and written informed consent was obtained from all participants.

Patients

The attending physician at the individual study centers was entirely responsible for the in-hospital management of the study participants. Therefore, all management decisions, including pharmacotherapy and the decision to perform coronary angiography and whether to proceed with coronary revascularization, were entirely at the discretion of the attending physician.

We identified medically managed patients for this pre-specified subgroup analysis of the EPICOR Asia study as patients who did not have either PCI or CABG during their index admission for NSTE-ACS. These medically managed patients were then classified into 3 medical management sub-groups: 1) no coronary angiography performed (CAG–); 2) non-significant coronary artery disease (CAD) on angiogram

(CAG+ CAD–); and 3) significant CAD on angiogram (CAG+ CAD+). Significant CAD was defined as coronary lumen stenosis of any coronary vessel >50% and non-significant CAD was defined as coronary stenosis ≤50%. We also identified all patients with NSTE-ACS who underwent revascularization as a comparator group.

Endpoints

Outcomes recorded up to 2 years post-discharge included mortality (overall and cardiovascular), myocardial infarction (MI), stroke, a composite endpoint (comprising death, MI or ischemic stroke), heart failure, ventricular arrhythmia, atrial fibrillation/flutter, and bleeding events.

Statistical analyses

We used mean values and standard deviations to summarize continuous variables and percentages for categorical variables. Baseline differences between groups (patients undergoing coronary revascularization versus medical management only, and between patients in the 3 different medical management groups) and regional differences in management strategy were analyzed according to classification group by the chi-square test. We then described and compared post-discharge outcomes over 2 years between patients undergoing coronary revascularization versus medical management only, and between patients in the 3 different medical management groups with a test of equality between groups by log-rank test. Kaplan–Meier curves were generated to estimate the unadjusted probability of mortality stratified by management strategy.

Because of the anticipated difference in baseline characteristics among different medically managed groups, the medically managed NSTE-ACS cohort was divided into 4 different risk categories based on the previously described EPICOR 1-year

mortality score [14]. In brief, the risk score can be calculated based on 11 contributory factors: age, ejection fraction, no coronary revascularization or thrombosis, EQ-5D score at discharge, prior cardiac disease, prior chronic obstructive pulmonary disease, serum creatinine, blood glucose ≥160 mg/dL, hemoglobin <13 g/dL, male sex, and diagnosis of STEMI. Specifically, the risk score can be calculated as; 0.043 x age (years) + 0.62 x 30% ≤ejection fraction <40% (1: yes, 0: no) + 1.35 x ejection fraction <30% (1: yes, 0: no) + 0.15 x EQ-5D score + 0.22 x max (serum creatinine [mg/dL] – 1.2, 0) + 0.41 x cardiac complications in hospital (1: yes, 0: no) + 0.39 x blood glucose ≥160 mg/dL (1: yes, 0: no) + 0.52 x chronic obstructive pulmonary disease (1: yes, 0: no) + 0.40 x gender (1: male, 0: female) + 0.39 x NSTE-ACS with medications only (1: yes, 0: no) − 0.22 x NSTE-ACS with PCI/CABG (1: yes, 0: no) + 0.35 x hemoglobin <13 g/dL (1: yes, 0: no) + 0.45 x peripheral vascular disease (1: yes, 0: no) + 0.30 x on diuretics at discharge (1: yes, 0: no). In general, any missing or unknown category was considered to belong in the ‘no’ category. For serum creatinine, missing values or values <1.2 were set to 1.2; other values remained unchanged. Total EQ-5D score was rescaled to the range of 0–10. Prior to risk score calculation, missing EQ-5D01–EQ-5D05 values were set to 0, and non-missing EQ-5D01–EQ-5D05 values were set to (EQ-5D01 -1) – (EQ-5D05 -1).

Patients were categorized into 4 categories: low risk (risk score ≤60 percentile); intermediate risk (60th percentile < risk score ≤80th percentile); high risk (80th percentile < risk score ≤90th percentile); and very high risk (90th percentile < risk score ≤100th percentile).

Kaplan–Meier mortality curves were generated for each medically managed subgroup in the very high-risk and low-risk categories. The estimated hazard ratio (HR), 2-sided 95% confidence interval (CI) and p-value for the comparisons among the medically managed subgroups within each risk category were calculated; the reference group being patients in the CAG– group.

Analyses were performed using SAS VER. 9.3 for MS Windows server.

Results

From 12,922 patients with ACS enrolled in EPICOR Asia, 6163 (48%) had NSTE-ACS and evaluable data for analysis of management strategy. The majority of patients with NSTE-ACS were enrolled in China (68.6%, 106 centers), followed by India (14.2%, 45 centers), South Korea (6.9%, 23 centers), Thailand (5.9%, 25 centers), Vietnam (1.3%, 8 centers), Hong Kong (1.1%, 5 centers), Malaysia (1.1%, 2 centers), and Singapore (0.9%, 1 center).

Patient characteristics

From 6163 patients with NSTE-ACS with evaluable data, 3891 (63.1%) underwent coronary revascularization and 2272 (36.9%) were medically managed (Fig. 1). Among the medically managed patients, 1339 (58.9%) were classified as not having had coronary angiography performed (CAG–). Among the rest who underwent coronary angiography, 254 (11.2%) were reported to have non-significant CAD (CAG+ CAD–), while 679 (29.9%) had CAD on angiogram (CAG+ CAD+).

Approximately twice as many patients were resident in metropolitan versus rural areas, with subsequent management strategy appearing unrelated to residency (Table 1A). Patients who had no form of insurance cover were more likely to not undergo coronary revascularization compared with those patients who were insured.

Compared with patients who underwent coronary revascularization, those medically managed tended to be older, more likely female, more likely to have a prior history of CVD, and to have more CVD risk factors, mainly hypertension and diabetes. However, smokers were more likely to undergo coronary revascularization.

There also existed significant differences in baseline characteristics between the medically managed patient groups. Compared with patients in the other 2 groups, the CAG– group were older, more were female, and were less likely to be treated in a center with catheterization lab facilities (Table 1B). Among the 2 groups of medically managed patients who underwent coronary angiography, the patients in the CAG+ CAD+ group had a higher burden of CVD risk factors compared with patients in the CAG+ CAD– group.

Country/regional differences in management strategy

There was a marked variability in the proportion of patients with NSTE-ACS who were medically managed among the 8 countries/regions studied, ranging from 13.3% in South Korea to 80.6% in Malaysia (Fig. 2).

Clinical outcomes

At 2 years post-discharge, compared with those who underwent coronary revascularization, medically managed patients had significantly poorer outcomes with higher overall mortality, cardiovascular mortality, and rates of MI, stroke, heart failure (all $p < 0.001$) and atrial fibrillation/flutter ($p < 0.05$) (Table 2A). With regard to bleeding events, there was no significant difference between patients who underwent coronary revascularization and medically managed patients.

Among those medically managed, patients who did not have angiography performed (CAG–) had the worst outcomes, with significantly higher event rates for overall mortality, MI, and the composite of death, MI or ischemic stroke (Table 2B). Mortality was lowest among patients in the CAG+ CAD– group (4.3%) and was generally comparable with that of patients who had coronary revascularization. Moreover,

2-year cumulative mortality was lower in both CAG+ groups compared with CAG–, the CAG+ CAD– group generally having comparable cumulative mortality with the coronary revascularization group (Fig. 3). For the composite endpoint of death, MI or primary ischemic stroke, patients in the CAG+ CAD– group had the lowest rates (5.9%), compared with patients in the CAG+ CAD+ group (11.6%) and patients in the CAG– group (17.3%).

Comparisons stratified by risk category

Because of the significant differences in baseline characteristics between the 3 medical management groups, we performed comparisons as stratified by risk categories to better understand differences in outcomes. As anticipated, patients in the higher risk categories (high and very high) had higher observed mortality rates compared with those in the lower risk (low and intermediate) categories, regardless of medical management group (Table 3 and Supplementary Fig. I). Notably, for the low-risk category, patients classified as CAG– had a 2-year mortality risk of only 1.7%. Strikingly, within the very high-risk category, patient mortality rate in the CAG+ CAD– group (11.5%) was markedly lower than for patients in the other 2 groups (CAG– 24.6%; CAG+ CAD+ 21.2%). Mortality risk was significantly lower both for the CAG+ CAD– (HR [unadjusted], 0.40) and the CAG+ CAD+ (HR [unadjusted], 0.61) groups when compared with CAG– (each $p < 0.01$); this significant difference was not evident when adjusted for risk classification (Supplementary Table I).

Discussion

This analysis using data from EPICOR Asia, a large international cohort study, is one of the first reports on the characteristics and outcomes of medically managed patients with NSTE-ACS across Asia. Furthermore, as it studies patients who have survived to hospital discharge, it also offers a unique opportunity to understand long-term outcomes post-discharge. Our study highlights several observations and raises important issues to consider in the hope of further improving our healthcare systems. First, despite guideline recommendations, only about 60% of patients in our cohort underwent coronary revascularization during hospitalization for NSTE-ACS, with broad inter-regional variability (19–87%) [4,5]. Second, even among this relatively low-risk patient population of patients with NSTE-ACS who successfully survived to hospital discharge, the patients who were able to have successful coronary revascularization had better long-term outcomes compared with patients who were only medically managed. Third, among medically managed patients with NSTE-ACS, there was a trend towards differential outcomes when stratified by whether coronary angiography was performed or if significant CAD was present.

The proportion of patients in our study not undergoing coronary revascularization is broadly similar to previously reported studies [6-8]. Medically managed patients with NSTE-ACS may have comorbidities that are contraindications to coronary angiography or may have complex anatomy that precludes revascularization.

Interestingly, in our study, we also demonstrated a wide variability among Asian countries in the proportion of patients who were only medically managed. This may be related to variations in local customs and beliefs insofar as there are regions in Asia where patients are reluctant to have invasive procedures performed.

Additionally, this may reflect the different healthcare and reimbursement systems throughout the region. We noted in our study that patients who had no form of insurance cover were more likely to not undergo coronary revascularization. Also, compared with patients who had coronary revascularization, medically managed patients were more likely to have been hospitalized in a center without catheterization laboratory facilities. Similarly, among the medically managed patients, the group who did not undergo angiography were more likely to have been at a center with no catheterization laboratory facilities. Such observations, as in this study, highlight potentially actionable targets for healthcare administrators who may be hoping to increase the proportion of patients who undergo coronary revascularization in the future.

Consistent with prior reports, our study showed that patients with NSTE-ACS who are only medically managed tend to have poorer long-term outcomes [7]. Furthermore, because all of our patients survived to hospital discharge, this excess in adverse events that persists beyond the acute phase likely reflects that medically managed patients have more high-risk features than patients undergoing revascularization.

The extent to which this can be modified remains an important unmet clinical need. We know that, contrary to guideline recommendations, the use of coronary angiography and subsequent revascularization in patients with NSTE-ACS is less prevalent in patients with high-risk features [9]. Furthermore, the evidence for the use of newer therapies for medically managed patients with NSTE-ACS has been inferred from substudies of larger trials, and therefore has to be interpreted appropriately. Trials involving only medically managed patients with NSTE-ACS are

few, and to date, have not suggested any specific management regimen for this group of high-risk patients.

Furthermore, despite published societal guidelines there continues to be variation in physician practice in regard to medications prescribed for individual patients. In addition, patients may have contraindications to, or may not be able to tolerate specific medications, which may prove significant. For example, in our study population comprising survivors of NSTE-ACS, and hence likely 'lower-risk', dual antiplatelet therapy was used at discharge in the majority (~88%) of patients [15]. While this is a relatively high usage rate, this needs to be considered in the context of current guidelines that recommend the use of dual antiplatelet therapy for all NSTE-ACS patients in the absence of contraindications. Also, medication compliance and adherence is a significant issue, especially in chronic diseases such as ischemic heart disease. This coupled with changes in medical therapy and perhaps subsequent revascularization during follow-up highlight the challenges in understanding what determines outcomes among these patients.

The difficulty in treating medically managed patients with NSTE-ACS is further complicated as this is a heterogeneous group of patients who have different long-term prognoses, as demonstrated in our study. Among patients who had coronary angiography performed but were not revascularized, about a quarter did not have significant CAD. As anticipated, these patients had fewer events over follow-up compared with patients with significant CAD. This therefore supports the use of angiography as a risk-stratifying tool to better inform patients and physicians.

We noted that patients in our study who did not have coronary angiography performed had the highest rate of adverse outcomes over the follow-up period. This

is likely because most of these patients would have been deemed by the attending physician as too high-risk for even undergoing angiography. However, when we divided this group by risk categories, we noted that patients in the low-risk category had an excellent prognosis. This reinforces the utility of risk assessment in deciding which patients should be sent to the catheterization laboratory, and who can be safely treated only medically. In addition to benefit with regard to patient outcomes, the use of risk stratification to guide catheterization laboratory utilization may lead to better use of limited healthcare resources, especially in Asia.

Importantly, systems to monitor interventions designed to improve healthcare outcomes need to be developed concurrently. For example, setting up new cardiac catheterization laboratories should be coupled with reporting of patient outcomes and resource use, not only for the acute encounter but for subsequent follow-up. Establishing nationwide patient registries that mandate complete patient reporting would provide data on temporal trends and assess the impact of specific interventions. With the increasing availability of mobile devices and decentralized data storage using ‘cloud servers’, this may be an achievable goal for even the less developed countries over time.

Medically managed patients with NSTE-ACS represent a heterogeneous group with variable clinical features and mortality risk. There remains an urgent unmet clinical need to further identify the factors determining why particular management strategies are employed, to be able to identify the patients most at risk, and to define and implement strategies to improve prognosis.

Limitations

Interpretation of the study findings should consider several potential limitations, for example, despite a comprehensive data collection effort, there may exist unknown factors that could impact on either the management strategies or outcomes examined in our study. As this was an observational study and no specific medical management strategies were mandated, there likely exists variation with regards to medical therapy between sites and countries, and there may have also been changes to medications post discharge the investigators were unable to track. In addition, data relating to rates of revascularization performed after discharge were not available, thus, it was not possible to fully assess the extent to which differences in individual treatment strategies at discharge, or over follow-up, may have influenced study outcomes. While representativeness in current practice per country was attempted through local center selection, the findings should be generalized with caution, particularly for those countries with relatively few local centers and, although independent adjudicators reviewed the reported endpoints, the quality of source documentation was variable due to many centers involved across different regions.

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Conflicts of interest

Y. Huo, S.W-L. Lee, J.P.S. Sawhney, H-S. Kim, and A.A. Garcia have nothing to disclose. C.T. Chin has received research support from Eli Lilly, honoraria from Medtronic, and has been a consultant or advisory board member for AstraZeneca. T.K. Ong has acted as a consultant or advisory board member for Sanofi-Aventis, Abbott Vascular, Boston Scientific, Boehringer Ingelheim, Novartis, and AstraZeneca. H. Bueno has received advisory/consulting fees from AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, Novartis, Roche, and AstraZeneca, and research grants from AstraZeneca. R. Krittayaphong has been a consultant or advisory board member for AstraZeneca and Boehringer Ingelheim. S.J. Pocock receives research funds from AstraZeneca. V.T. Nhan has received research grants from AstraZeneca, Servier, Sanofi, and Boston Scientific, and has been a consultant or advisory board member for AstraZeneca, Pfizer, Sanofi, Boehringer Ingelheim, Servier, MSD, Abbott, Bayer, Novartis, Merck Serono, Biosensor, Biotronic, Boston Scientific, Terumo, and Medtronic. A. Vega and N. Hayashi are employees of AstraZeneca.

Table 1A

Baseline characteristics of patients with NSTE-ACS by management strategy.

	Coronary revascularization (n = 3891)	Medically managed (n = 2272)	p[a]
Age, mean (SD), years	61 (10.7)	63 (11.8)	<0.001
Age ≥75 years, n (%)	427 (11.0)	437 (19.2)	<0.001
Index event diagnosis, n (%)			<0.01
NSTEMI	1543 (39.7)	981 (43.2)	
Unstable angina	2348 (60.3)	1291 (56.8)	
Male, n (%)	2847 (73.2)	1457 (64.1)	<0.001
Residence, n (%)			0.98
Rural	1265 (32.5)	738 (32.5)	
Metropolitan	2626 (67.5)	1534 (67.5)	
Insurance, n (%)			
Government	2987 (76.8)	1606 (70.7)	<0.001
Private	387 (9.9)	196 (8.6)	0.09
Employer	67 (1.7)	25 (1.1)	0.05
Other	151 (3.9)	69 (3.0)	0.09
None	386 (9.9)	393 (17.3)	<0.001
Country/region, n (%[b])			<0.001
China	2792 (34.0)	1433 (17.4)	
Hong Kong	29 (16.4)	40 (22.6)	
India	464 (18.8)	408 (16.5)	
Malaysia	13 (13.0)	54 (54.0)	
Singapore	37 (39.8)	18 (19.4)	
South Korea	371 (52.6)	57 (8.1)	
Thailand	142 (14.8)	225 (23.5)	
Vietnam	43 (20.7)	37 (17.8)	
Hypertension	2308 (59.3)	1447 (63.7)	<0.001

Diabetes mellitus	994 (25.5)	679 (29.9)	<0.001
Family history of CAD	359 (9.2)	210 (9.2)	0.98
Current smoking	1113 (28.6)	503 (22.1)	<0.001
Obesity (BMI >30 kg/m^2)	259 (6.7)	144 (6.3)	0.77
Previous CVD, n (%)	1408 (36.2)	928 (40.8)	<0.001
Prior MI	451 (11.6)	316 (13.9)	<0.01
Prior PCI	442 (11.4)	286 (12.6)	0.15
Prior CABG	58 (1.5)	65 (2.9)	<0.001
Chronic renal failure, n (%)	59 (1.5)	90 (4.0)	<0.001
Initial creatinine >1.2 mg/dL	420 (11.1)	415 (18.3)	<0.001
Discharge hospital type, n (%)			<0.001
Community/other	542 (13.9)	509 (2.4)	
Non-university general	974 (25.0)	509 (22.4)	
University general	2375 (61.0)	1254 (55.2)	
Cath lab facilities[c], n (%)	3886 (99.9)	2115 (93.1)	<0.001

Table 1B

Characteristics of medically managed patients with NSTE-ACS.

	CAG– (n = 1339)	CAG+ CAD– (n = 254)	CAG+ CAD+ (n = 679)	p[a]
Age, mean (SD), years	65 (12.0)	59 (12.0)	62 (10.7)	<0.001
Age ≥75 years, n (%)	327 (24.4)	30 (11.8)	80 (11.8)	<0.001
Index event diagnosis, n (%)				0.11
NSTEMI	596 (44.5)	95 (37.4)	290 (42.7)	
Unstable angina	743 (55.5)	159 (62.6)	389 (57.3)	
Male, n (%)	829 (61.9)	160 (63.0)	468 (68.9)	<0.01
Residence, n (%)				0.84
Rural	434 (32.4)	79 (31.1)	225 (33.1)	
Metropolitan	905 (67.6)	175 (66.9)	454 (66.9)	
Insurance, n (%)				
Government	969 (72.4)	148 (58.3)	489 (72.0)	<0.001
Private	105 (7.8)	25 (9.8)	66 (9.7)	0.28
Employer	12 (0.9)	9 (3.5)	4 (0.6)	<0.001
Other	42 (3.1)	9 (3.5)	18 (2.7)	0.74
None	217 (16.2)	65 (25.6)	111 (16.3)	<0.01
Country/region, n (%[b])				<0.001
China	833 (10.1)	144 (1.8)	456 (5.6)	
Hong Kong	27 (15.3)	6 (3.4)	7 (4.0)	
India	219 (8.9)	64 (2.6)	125 (5.1)	
Malaysia	39 (39.0)	3 (3.0)	12 (12.0)	
Singapore	4 (4.3)	6 (6.5)	8 (8.6)	
South Korea	21 (3.0)	18 (2.6)	18 (2.6)	
Thailand	175 (18.3)	11 (1.1)	39 (4.1)	
Vietnam	21 (10.1)	2 (1.0)	14 (6.7)	
Hypertension	867 (64.7)	135 (53.1)	445 (65.5)	0.001

Diabetes mellitus	392 (29.3)	65 (25.6)	222 (32.7)	0.08
Family history of CAD	123 (9.2)	19 (7.5)	68 (10.0)	0.49
Current smoking	298 (22.3)	44 (17.3)	161 (23.7)	0.11
Obesity (BMI >30 kg/m^2)	87 (6.5)	19 (7.5)	38 (5.6)	0.45
Previous CVD, n (%)	577 (43.1)	79 (31.1)	272 (40.1)	0.002
Prior MI	222 (16.6)	14 (5.5)	80 (11.8)	<0.001
Prior PCI	175 (13.1)	33 (13.0)	78 (11.5)	0.59
Prior CABG	46 (3.4)	2 (0.8)	17 (2.5)	0.05
Chronic renal failure, n (%)	79 (5.9)	2 (0.8)	9 (1.3)	<0.001
Initial creatinine >1.2 mg/dL	303 (22.6)	25 (9.8)	87 (12.8)	<0.001
Discharge hospital type, n (%)				<0.001
Community/other	219 (23.8)	75 (29.5)	115 (17.0)	
Non-university general	316 (23.6)	30 (11.8)	163 (24.0)	
University general	704 (52.6)	149 (58.7)	401 (59.1)	
Cath lab facilities[c], n (%)	1186 (88.6)	254 (100.0)	675 (99.4)	<0.0001

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CAG = coronary angiogram; CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram; cath lab = catheterization laboratory; CVD = cardiovascular disease; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation. Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%. Non-significant CAD defined as coronary stenosis ≤50%.

[a] Chi-square test.

[b] Percentage values shown as percentage of all patients recruited in that country.

[c] Primary treatment hospital.

Table 2A

Outcomes by 2 years post-discharge for patients with NSTE-ACS by management strategy.

Patients, n (%)	Coronary revascularization (n = 3891)	Medically managed (n = 2272)	p[a]
All-cause death	117 (3.0)	197 (8.7)	<0.001
Cardiovascular death	45 (1.2)	82 (3.6)	<0.001
MI	74 (1.9)	119 (5.2)	<0.001
Stroke	47 (1.2)	51 (2.2)	<0.001
Composite of death, MI or IS	222 (5.7)	325 (14.3)	<0.001
Heart failure	70 (1.8)	79 (3.5)	<0.001
Atrial fibrillation/flutter	11 (0.3)	14 (0.6)	<0.05
Clinically relevant bleed	256 (6.6)	128 (5.6)	0.27

Table 2B

Outcomes by 2 years post-discharge for patients with NSTE-ACS by medical management sub-group.

Patients, n (%)	CAG– (n = 1339)	CAG+ CAD– (n = 254)	CAG+ CAD+ (n = 679)	p[a]
All-cause death	141 (10.5)	11 (4.3)	45 (6.6)	<0.001
Cardiovascular death	56 (4.2)	5 (2.0)	21 (3.1)	0.12
MI	84 (6.3)	5 (2.0)	30 (4.4)	<0.01
Stroke	34 (2.5)	1 (0.4)	16 (2.4)	0.09
Composite of death, MI or IS	231 (17.3)	15 (5.9)	79 (11.6)	<0.001
Heart failure	53 (4.0)	4 (1.6)	22 (3.2)	0.13
Atrial fibrillation/flutter	11 (0.8)	1 (0.4)	2 (0.3)	0.29
Clinically relevant bleed	77 (5.8)	8 (3.1)	43 (6.3)	0.15

CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram; IS = ischemic stroke; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome.

Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%. Non-significant CAD defined as coronary stenosis ≤50%.

[a] Test of heterogeneity between groups based on log-rank test.

Table 3

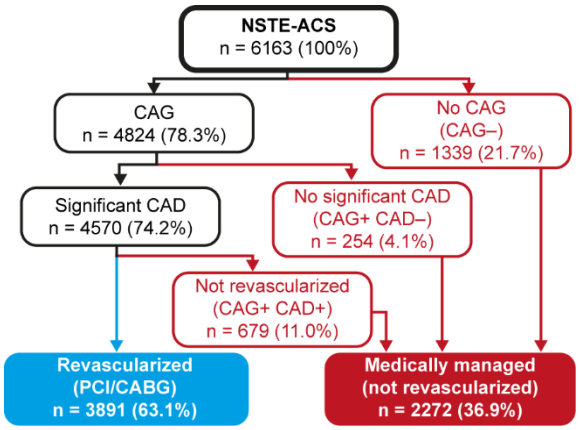
2-year mortality rates stratified by risk score and medical management subgroup.

Risk category	CAG– (n = 1339)	CAG+ CAD– (n = 254)	CAG+ CAD+ (n = 679)	All (n = 2272)
Low	7/412 (1.7)	5/117 (4.3)	5/244 (2.0)	17/773 (2.2)
Intermediate	22/340 (6.5)	1/68 (1.5)	9/204 (4.4)	32/612 (5.2)
High	25/234 (10.7)	2/43 (4.7)	7/118 (5.9)	34/395 (8.6)
Very high	87/353 (24.6)	3/26 (11.5)	24/113 (21.2)	114/492 (23.2)

CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram.

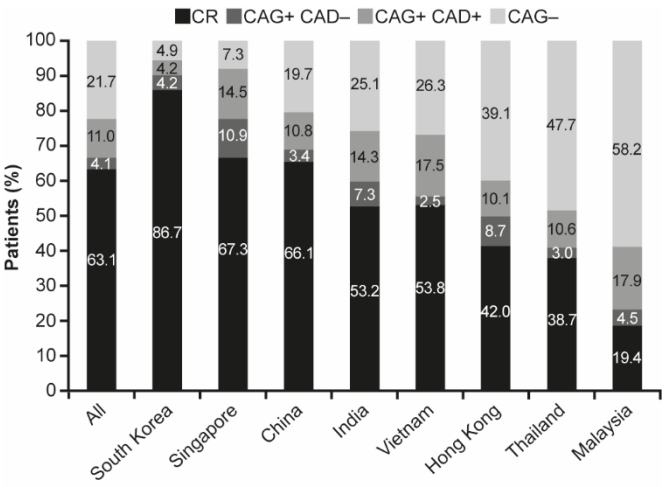
Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%. Non-significant CAD defined as coronary stenosis ≤50%.

Fig. 1. Management strategy for patients with NSTE-ACS.



Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%. Non-significant CAD defined as coronary stenosis ≤50%. CABG = coronary artery bypass graft; CAD = coronary artery disease; CAG = coronary angiogram; CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram; PCI = percutaneous coronary intervention; NSTE-ACS = non-ST-segment elevation acute coronary syndrome.

Fig. 2. Country/regional differences in management strategy.

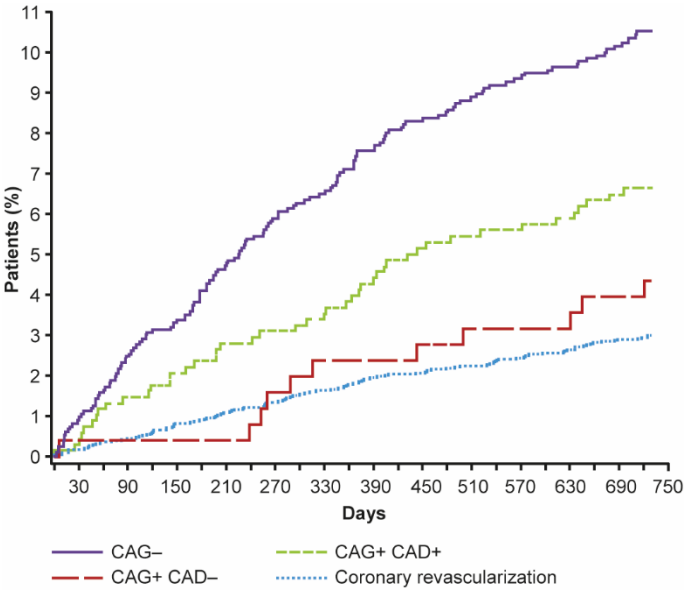


CAD = coronary artery disease; CAG = coronary angiogram; CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram; CR = coronary revascularization.

Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%. Non-significant CAD defined as coronary stenosis ≤50%.

Number of patients (sites) % of patients: All = 6163 (218) 100%; South Korea = 428 (23) 6.9%; Singapore = 55 (1) 1.1%; China = 4225 (106) 68.6%; India = 872 (45) 14.2%; Vietnam = 80 (8) 1.3%; Hong Kong = 69 (5) 1.1%; Thailand = 367 (25) 5.9%; Malaysia = 67 (2) 1.1%.

Fig. 3. 2-year cumulative mortality by management strategy (unadjusted).



CAD = coronary artery disease; CAG = coronary angiography; CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram.

Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%; non-significant CAD defined as coronary stenosis ≤50%.

Supplementary material

Supplementary Table I. Cumulative mortality among medically managed groups relative to CAG– (unadjusted, and adjusted, for risk category).

Risk score vs. CAG–	Hazard ratio	95% CI	p value[a] (Log rank)
Unadjusted[b]			
CAG+ CAD–	0.40	0.21, 0.73	<0.01
CAG+ CAD+	0.61	0.44, 0.85	<0.01
Adjusted[b]			
CAG+ CAD–	0.59	0.32, 1.10	0.10
CAG+ CAD+	0.76	0.54, 1.06	0.11

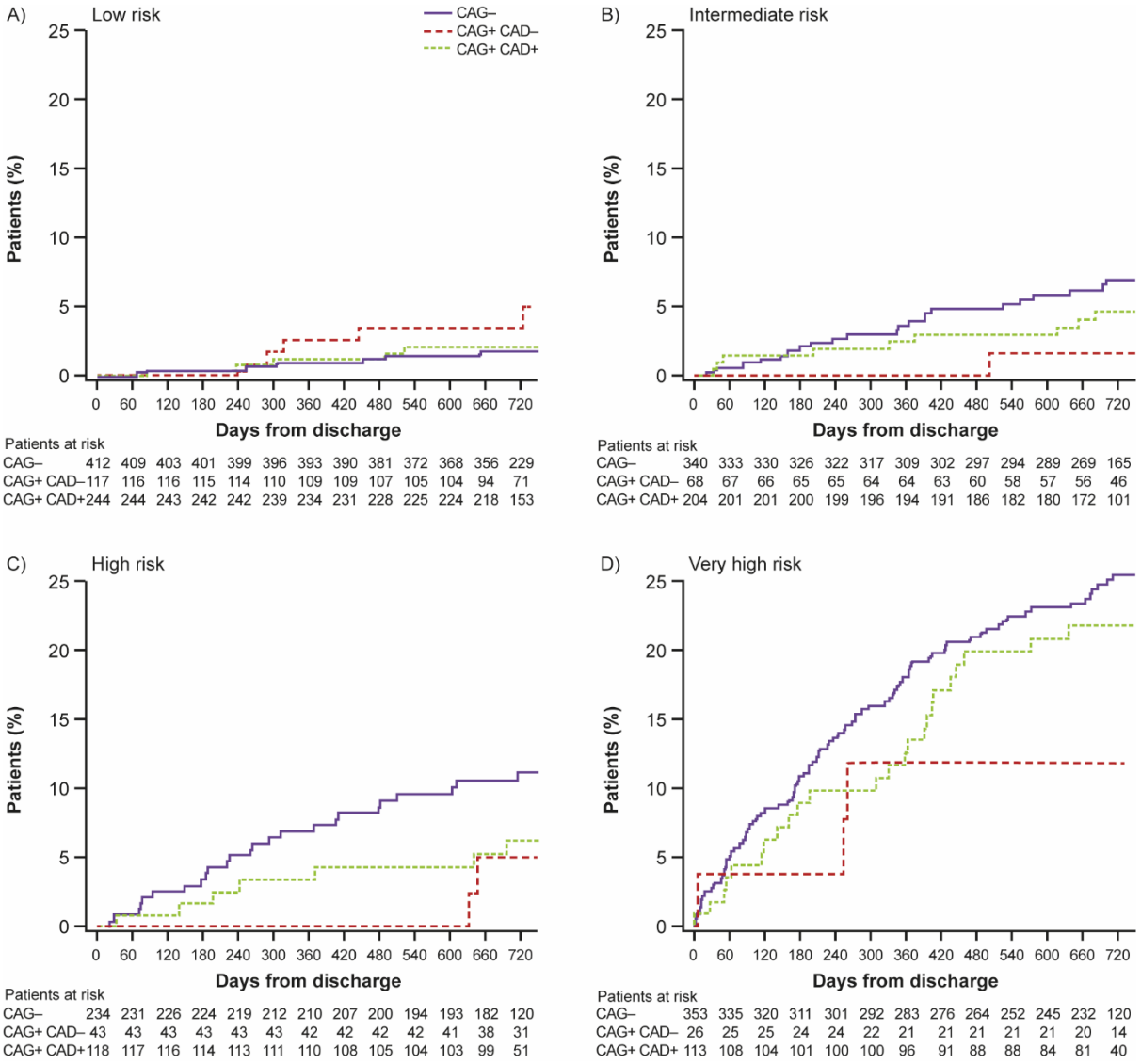
CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram; CI = confidence interval.

Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%. Non-significant CAD defined as coronary stenosis ≤50%.

[a] Log rank.

[b] For risk score (low, intermediate, high and very high).

Supplementary Fig. I. 2-year cumulative mortality by management strategy in (A) low risk, (B) intermediate risk, (C) high risk, and (D) very high risk groups.



CAD = coronary artery disease; CAG = coronary angiography; CAG– = no coronary angiography; CAG+ CAD– = non-significant CAD on angiogram; CAG+ CAD+ = significant CAD on angiogram.

Significant CAD defined as coronary lumen stenosis of any coronary vessel >50%; non-significant CAD defined as coronary stenosis ≤50%.