

Trends in evidence-based treatment and mortality for ST elevation myocardial infarction in Malaysia from 2006 to 2013: time for real change

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BACKGROUND: The administration of evidence-based pharmacotherapy and timely primary percutaneous coronary intervention have been shown to improve outcome in ST elevation myocardial infarction (STEMI). However, implementation remains a challenge due to the limitations in facilities, expertise and funding.

OBJECTIVES: To investigate adherence to guideline-based management and mortality of STEMI patients in Malaysia.

DESIGN: Retrospective analysis.

SETTINGS: STEMI patients from 18 participating hospital across Malaysia included in the National Cardiovascular Database-Acute coronary syndrome (NCVD-ACS) registry year 2006 to 2013.

PATIENTS AND METHODS: Patients were categorized into four subgroups based on the year of admission (2006 to 2007, 2008 to 2009, 2010 to 2011 and 2012 to 2013). Baseline characteristics and clinical presentation, in-hospital pharmacotherapy, invasive revascularization and in-hospital/30-day mortality were analysed and compared between the subgroups.

MAIN OUTCOME MEASURE(S): Rate of in-hospital catheterization/percutaneous coronary intervention.

RESULTS: The registry contained data on 19483 patients. Intravenous thrombolysis was the main reperfusion therapy. Although the overall rate of in-hospital catheterisation/PCI more than doubled over the study period, while the use of primary PCI only slowly increased from 7.6% in 2006/2007 to 13.6% in 2012/2013. The use of evidence-based oral therapies increased steadily over the years except for ACE-inhibitors and angiotensin-receptor blockers. The adjusted risk ratios (RR) for in-hospital mortality for the four sub-groups have not shown any significant improvement. The 30-day adjusted risk ratios however showed a significant albeit gradual risk reduction (RR 0.773 95% CI 0.679-0.881, $P < .001$).

CONCLUSION: Adherence to evidence-based treatment in STEMI in Malaysia is still poor especially in terms of the rate of primary PCI. Although there is a general trend toward reduced 30-day mortality, the reduction was only slight over the study period. Drastic effort is needed to improve adherence and clinical outcomes.

LIMITATION: Retrospective registry data with inter-hospital variation.

Acute ST elevation myocardial infarction (STEMI) is the leading cause of mortality and morbidity in Malaysia and is the most deadly type of acute coronary syndrome.¹ Urgent invasive or non-invasive reperfusion therapy followed by evidence-based phar-

macotherapy are the mainstay of treatment. However, timely invasive percutaneous coronary intervention (PCI) and the adherence to evidence-based pharmacotherapy are still a huge challenge in developing countries. Our population has a high burden of cardiovas-

cular risk factors.² Local data shows that around 16% of patients undergoing PCI are younger than the age of 45;³ the elderly tend to be undertreated both pharmacologically and invasively.⁴ Improving clinical outcomes is of utmost importance and adherence to guideline-based treatment is crucial in determining the outcome.⁵

The Malaysian National Cardiovascular Disease -Acute Coronary Syndrome (NCVD-ACS) Registry is an ongoing prospective registry first established in 2006. It started with 8 hospitals in 2006, but currently involves 18 hospitals across Malaysia. The registry was initiated to collect clinical data including in-hospital management and clinical outcome. The NCVD-ACS Registry is sponsored by the Ministry of Health Malaysia and co-sponsored by National Heart Association of Malaysia. The Clinical Research Centre of Malaysia provides technical support in the form of clinical epidemiology expertise, biostatistics and information and communication technology services. Through this concerted effort, we were able to analyse changes in demographic and clinical characteristics as well as the quality of hospital management and clinical outcomes. We used the NCVD-ACS Registry to analyse adherence to guideline-based STEMI treatment and assess how clinical outcomes have changed over recent years.

PATIENTS AND METHODS

Source of data

Anonymised patient data were obtained from the Malaysian NCVD-ACS registry for years 2006 to 2013. The NCVD-ACS registry is sponsored by the Ministry of Health Malaysia and co-sponsored by the National Heart Association of Malaysia. Selected patients were those diagnosed with ST-elevation MI from 18 participating hospitals across Malaysia. Data was collected upon admission and throughout the patient stay using a standardized case report form. A unique national identification number was given to each patient to avoid duplication. Follow-up was done at 30 days through phone calls or when patients came to the clinic review. A cross check with the national death registry was also done to verify mortality status. Records were taken of baseline characteristics and clinical presentation, in-hospital treatment, procedural details and clinical outcome. Data was then entered into the NCVD-ACS website after verification. The operation of the NCVD-ACS is supported by a comprehensive ICT system to ensure functional efficacy and effectiveness.

Patients were categorized into four groups based on the year of admission (2006 to 2007, 2008 to 2009, 2010 to 2011 and 2012 to 2013). Determination of

patient ethnicity was based on self-reporting and the national identity card. STEMI is defined as a persistent ST-segment elevation of ≥ 1 mm in two contiguous electrocardiographic leads or the presence of a new left bundle branch block in the setting of positive cardiac markers.

Statistical method and analysis

Continuous variables were expressed as mean and standard deviation and differences between the years were analysed using the *t* test. Categorical variables were described as numbers (percentages), and differences were analysed using the chi-square test or the Fisher exact test. To avert biases in the estimates and loss of power, missing data for explanatory variables were assumed to be missing at random. In the analysis of in-hospital and 30-day all-cause mortalities, all significant variables from a univariate analysis were adjusted to produce a final result for in-hospital and 30-day adjusted risk ratios comparing all sub-groups. A generalized linear model with a log link, binomial distribution, and a robust variance estimator was used to estimate the risk ratios. The risk ratios represent the relative risk for mortality of the patients in year 2006 -2007 compared to the other three groups. Variables that were statistically significantly different (a two-sided *P* value of less than .05) between the years, that were of clinical importance, and that had sufficient outcomes in the respective sub-categories were adjusted for in the model. All analyses were conducted using SPSS statistical software (version 21, IBM SPSS Statistics, USA).

RESULTS

The patient population was predominantly ethnic Malay (more than 50%) with a strong male dominance (more than 85%) (**Table 1**). The majority of patients fell into the 41 to 60 year- old age group. The prevalence of Malay ethnics and young patients (<40 years old) trended upward over the study period. Smoking was the most prevalent risk factor followed by hypertension and diabetes mellitus. This pattern remained consistent throughout the years with no clear changes. Among the relevant comorbidities, previous myocardial infarction (MI) was most common followed by chronic renal disease and cerebrovascular disease. All conventional cardiovascular risk factors and related comorbidities remained stable with no marked changes over the years. A large majority of STEMI patients were in Killip class 1 or 2 on presentation. However, there was a steady increase in Killip 4 (cardiogenic shock) presentations.

Intravenous thrombolysis was the main mode of reperfusion therapy throughout the study years (**Table 1**).

Table 1. Demographics, risk factors and premorbid conditions.

	2006-2007	2008-2009	2010-2011	2012-2013	P
Age					
<40	227 (7.7)	262 (8.6)	400 (8.5)	750 (9.5)	
41-<60	1692 (57.1)	1667 (54.5)	2653 (56.5)	4416 (55.9)	.013
61<80	978 (33.0)	1051 (34.3)	1519 (32.3)	2569 (32.5)	
>80	68 (2.3)	81 (2.6)	124 (2.6)	159 (2.0)	
Gender					
Male	2663 (85.5)	2731 (85.0)	4169 (85.3)	7109 (86.0)	.493
Female	451 (14.5)	482 (15.0)	720 (14.7)	1158 (14.0)	
Ethnicity					
Malay	1661 (53.3)	1786 (55.6)	2795 (57.2)	5034 (60.9)	
Chinese	657 (21.1)	618 (19.2)	898 (18.4)	1281 (15.5)	<.001
Indians	605 (19.4)	600 (18.7)	808 (16.5)	1257 (15.2)	
Others	191 (6.1)	209 (6.5)	388 (7.9)	695 (8.4)	
Diabetes mellitus	1133 (36.4)	1136 (35.4)	1816 (37.1)	2980 (36.0)	<.001
Hypertension	1517 (48.7)	1584 (49.3)	2454 (50.2)	4151 (50.2)	<.001
Smoking					
Active/former	2111 (70.3)	2087 (68.6)	3234 (68.6)	5553 (70.2)	.142
Never	892 (29.7)	955(31.4)	1478 (31.4)	2359 (29.8)	
Dyslipidaemia	656 (21.1)	851 (26.5)	1335 (27.3)	2085 (25.2)	<.001
FHx Premature CAD	372 (11.9)	345 (10.7)	598 (12.2)	880 (10.6)	<.001
Previous MI	329 (10.6)	377 (11.7)	530 (10.8)	890 (10.8)	<.001
Chronic Lung Ds	67 (2.2)	78 (2.4)	118 (2.4)	137 (1.7)	<.001
Cerebrovascular Ds	95 (3.1)	72 (2.2)	120 (2.5)	227 (2.7)	<.001
Peripheral Vascular Ds	11 (0.4)	10 (0.3)	22 (0.5)	12 (0.1)	<.001
Chronic Renal Ds	106 (3.4)	103 (3.2)	174 (3.6)	263 (3.2)	<.001
Killip Class					
Class I	1699 (65.9)	1725 (64.4)	2643 (64.6)	4396 (61.3)	
Class II	593 (23.0)	653 (24.4)	843 (20.6)	1452 (20.3)	<.001
Class III	125 (4.8)	110 (4.1)	201 (4.9)	324 (4.5)	
Class IV	161 (6.2)	189 (7.1)	406 (9.9)	997 (13.9)	
Urgent reperfusion therapy					
Thrombolysis	2235(74.0)	2400 (77.6)	3628 (76.5)	5712 (70.6)	
Primary PCI	229 (7.6)	180 (5.8)	408 (8.6)	1099 (13.6)	<.001
Not Given (missed/contraindicated/others)	557 (18.)	514 (16.7)	731 (14.9)	1285(15.6)	
Door to needle time (median minutes)	55	48	41	45	<.001

Data are n (%) unless otherwise noted.

The median door-to-needle time shortened slightly from 55 minutes in 2006/2007 to 45 minutes in 2012/2013. The use of primary PCI also increased but rather slowly from 7.6% in 2006/2007 to 13.6% in 2012/2013.

The overall invasive and pharmacological treatments are presented in **Table 2**. Even though the rate of primary PCI did not drastically change over the study period, we observed a significant increase in in-hospital cardiac catheterisations and PCI (including primary PCI) over the study period (**Table 2**). The percentage of cardiac catheterisation/PCI more than doubled from 2006/2007 (catheterisation 20.6%, PCI 19.2%) to 2012/2013 (catheterisation 47.7%, PCI 41.2%).

The use of evidence-based oral therapies steadily increased over the years, achieving rates of more than 85% in aspirin, adenosine diphosphate receptor antagonist and statin use. The use of ADP-antagonist showed the biggest improvement with an increase from 63.8% (2006/2007 group) to 86.1% (2012/2013 group). The use other pharmacotherapies all showed a gradual improvement except for ACE/ARB where the rate was about the same throughout.

No significant changes were seen in the in-hospital mortality through the years except for the drop in mortality in 2010-2011 group (**Tables 3 and 4**). The mortality rate then slightly increased in 2012-2013 although still lower than the 2006/2007 and 2008/2009 groups. When compared to the 30-day mortality rate in 2006/2007, we observed a generalised decrease in mortality and achieved a significant drop in adjusted risk ratios for the 2010/2011 (RR 0.777 95% CI 0.673-0.897, $P=.001$) and 2012/2013 groups (RR 0.773 95% CI 0.679-0.881, $P<.001$) (**Table 5**).

DISCUSSION

In developed western countries, the adoption of timely coronary reperfusion as well as guideline-based pharmacotherapy over the last decade has correlated with an up to 25% reduction in both in-hospital and post-discharge ACS-related mortality.⁶⁻⁸ Although there is an encouraging increase in the rate of in-hospital catheterization/PCI for STEMI patients, we are still behind in terms of the actual primary PCIs. In-hospital mortality remained constant throughout these years. The

Table 2. Evidence-based pharmacotherapy and invasive coronary intervention (coronary catheterisation).

	2006-2007	2008-2009	2010-2011	2012-2013	P
Catheterisation	642 (20.6%)	723 (22.5%)	1172 (25.7%)	3761 (47.7%)	<.001
PCI	599 (19.2%)	598 (18.6%)	990 (23.5%)	3151 (41.2%)	<.001
Caspirin	2335 (89.0%)	2524 (88.9%)	4013 (92.5%)	6786 (92.7%)	<.001
ADP antagonist	1630 (63.8%)	1996 (71.7%)	3574 (84.2%)	3152 (86.1%)	<.001
Beta blocker	1708 (66.4%)	1750 (64.1%)	2801 (68.5%)	5084 (71.9%)	<.001
ACE-I/ARB	1595 (52.4%)	1519 (49.0%)	2536 (52.4%)	4334 (52.4%)	<.001
Statin	2290 (88.1%)	2351 (83.7%)	3835 (89.2%)	6567 (89.7%)	<.001

Table 3. Clinical outcomes (unadjusted all-cause mortality).

	2006-2007	2008-2009	2010-2011	2012-2013	P
In-hospital	295 (9.8%)	272 (8.8%)	383 (8.0%)	696 (8.6%)	.052
30-day	378 (12.1%)	362 (11.3%)	474 (9.7%)	798 (9.7%)	<.001

Table 4. Adjusted relative mortality risk compared to the 2006/2007 sub-group In Hospital.

Variables	No. of patients	No. (%) of deaths	P	Adjusted risk ratio* (95%CI)
STEMI (n=19483)				
2006-2007	3114	295 (9.5%)		1.00
2008-2009	3213	272 (8.5%)	.182	0.889 (0.748-1.057)
2010-2011	4889	383 (7.8%)	.006	0.799 (0.682-0.937)
2012-2013	8267	696 (8.4%)	.052	0.868 (0.752-1.001)

Table 5. Adjusted 30-day relative mortality risk compared with 2006/2007 subgroup.

Variables	No. of patients	No. (%) of deaths	P	Adjusted risk ratio* (95%CI)
STEMI (n=19483)				
2006-2007	3114	378 (12.1%)		1.00
2008-2009	3213	362 (11.3%)	.281	0.919 (0.788-1.071)
2010-2011	4889	474 (9.7%)	.001	0.777 (0.673-0.897)
2012-2013	8267	798 (9.7%)	<.001	0.773 (0.679-0.881)

cumulative mortality at 30 days postdischarge showed a steady decrease but could have been better.

Realising this issue, the Ministry of Health, in conjunction with Ministry of Education and National Heart institute, initiated a greater Kuala Lumpur STEMI network in late 2015. This network between government hospitals, academic university hospitals and the National Heart institute refers acute STEMI patients directly to PCI capable centres for primary PCI. The aim is to provide access to primary PCI for all patients with STEMI. The network is still at an early stage of development, and due to limitations in supporting staff and facilities, is only active during office hours. Nevertheless we hope to develop this network into a 24-hour service within the next few years.

According to the multinational Global Registry of Acute Coronary Events (GRACE), the use of optimal revascularization and statin use could prevent up to 32% and 10% of death by 6 months, respectively, which clearly demonstrates the additional mortality benefits of pharmacotherapy. Although our cohort shows that rates of aspirin, ADP-antagonist and statin use are all more than 85%, a poor prescribing rate for ACE-I/ARB and beta-blocker persists. Unfortunately, pharmacotherapy costs to patients remains a significant barrier. Hence there is ongoing nationwide effort to increase the availability of generic formulations to ease the cost strain to patients.

Analysis of several other acute coronary syndrome registries around the Asia Pacific region shows some discrepancies. Even though local guidelines in Australia and New Zealand are generally comparable to those of Western countries⁹⁻¹⁵ there are variabilities in the guidelines in other countries.¹⁶⁻¹⁸ These registries suggest that there is still much room for improvement. A recent effort was the Asia-Pacific real world evidence on outcome and treatment of ACS (APRICOT) project

which assembled leading academic teams from several countries across the Asia Pacific region.¹⁹ The APRICOT working group has recommended a few key strategic steps towards improvement in outcome: longer-term patient surveillance, greater patient education (pain awareness, compliance, primary/secondary prevention), overcoming geographical challenges to pre-hospital and post-discharge care, and adoption of a value-based over cost-based healthcare system.¹⁸ A limitation of the study is that it used retrospective registry data that varies among hospitals.

In conclusion, the standard of in-hospital management of STEMI is still sub-optimal in Malaysia and the mortality rate remains high. The rate of primary PCI as the reperfusion strategy is very low as well. Although IV thrombolysis is still relevant in our clinical setting, it should not continue to be the default reperfusion treatment as it has been shown to be inferior to primary PCI. On-going efforts are now being done to improve STEMI care. The greater KL STEMI network started in late 2015 and we look forward to see how it will improve STEMI care and overall clinical outcomes. Treating physicians need to be more aware of the importance of evidence-based pharmacotherapy and more generic based medications need to be introduced to ease the cost burden to our patients.

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This NCVD registry study was approved by the Medical Review & Ethics Committee (MREC), Ministry Of Health (MOH) Malaysia in 2007 (Approval Code: NMRR-07-20-250). MREC waived informed consent for NCVD.

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