Clinical characteristics, treatment and 2-year outcomes in Malaysian and Bruneian patients with stable coronary artery within the worldwide CLARIFY registry

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ABSTRACT

Introduction: The on-going, international, prospective, observational, longitudinal CLARIFY registry is investigating the demographics, clinical profiles, management and outcomes of patients with stable coronary artery disease (CAD). This paper assesses baseline characteristics, treatment, and clinical outcomes at two years’ follow-up of Malaysian/Bruneian patients compared with the overall registry population.

Method: Between November 2009 and July 2010, outpatients from 45 countries who met the criteria for stable CAD were recruited into the registry. Baseline characteristics were documented at enrolment, and patients were reassessed during their annual visits over a five-year follow-up period. Key outcomes measured were sudden death and cardiovascular (CV) death, non-CV death and CV morbidity.

Results: At baseline, 33,283 patients were available for analysis within the registry; 380 and 27 were Malaysians and Bruneians, respectively. The mean ages of Malaysian/Bruneian patients and the rest of the world (RoW) were 57.83 (29.98 years) and 64.23 ± 10.46 years, respectively (p<0.001). The median body mass index values were 26.6 (24.4-29.6) kg/m² and 27.3 (24.8-30.3) kg/m², respectively (p=0.014). Malaysian/Bruneian patients had lower rates of myocardial infarction (54.55% versus 59.76%, p=0.033) and higher rates of diabetes (43.24% versus 28.99%, p<0.001) and dyslipidaemia (90.42% versus 74.66%, p<0.001) compared with the RoW. Measured clinical outcomes in Malaysian and Bruneian patients at 2-years follow-up were low and generally comparable to the RoW.

Conclusion: Malaysian/Bruneian patients with stable CAD tend to be younger with poorer diabetic control compared with the RoW. However, they had similar outcomes as the main registry following two years of treatment.

KEY WORDS:
Coronary artery disease; Malaysia; Brunei; demographics; registry, ischaemic heart disease, heart rate

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of mortality in Malaysian Ministry of Health hospitals, accounting for 25.19% of all reported deaths.¹ This is most likely a result of high prevalence of cardiovascular (CV) risk factors such as hypertension, diabetes mellitus, smoking and hyperlipidaemia. In fact, 63% of the Malaysian population had one or more CV risk factors in the Third National Health and Morbidity Survey (NHMS III).² A more recent survey of 3,722 low-income relatively young urban dwellers (mean age 41.5 years) also found that 35.1% had hypercholesterolemia, 32.7% had hypertension and 15.2% had diabetes mellitus.³ Despite the high prevalence of risk factors, we do not have prospective information on clinical characteristic, management and outcome in stable coronary artery disease (CAD) patients in Malaysia. Indeed, in a recent review of coronary artery disease research in Malaysia, most publications instable angina management were either retrospective or limited in a single centre.⁴

The international prospective observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) registry was designed to describe the demographics, clinical profiles, management and outcomes of contemporary CAD patients in participating countries, with the intention of identifying gaps between treatment and evidence.⁵ The registry protocol further recommended that each investigator enrolled between 10-15 consecutive, eligible patients to minimise the risk of selection bias. The rationale, design, and baseline characteristics of CLARIFY have been described previously.⁶⁷

In this publication, we present the clinical characteristics, management and two-year outcomes of Malaysian and Bruneian patients enrolled in CLARIFY in relation to the rest of the CLARIFY population. We included these two countries in this publication as they share similar geographical and demographical characteristics.

MATERIALS AND METHODS

Patients with stable CAD receiving standard management were enrolled in 45 countries in Africa, Asia, Australia,
Europe, the Middle East, and North, Central, and South America. Patients were treated according to the standard clinical practice of each institution, with no specific tests or therapies defined in the study protocol. In Malaysia and Brunei, the centres include general hospitals, private hospitals and university hospitals. Treating physicians included both cardiologists and internal physicians.

**Inclusion criteria.** Patients had to have documented stable CAD based on one of the following criteria: (1) myocardial infarction (MI), more than three months prior to enrolment; (2) coronary stenosis greater than 50%, based on coronary angiography; (3) chest pain with evidence of MI on stress echocardiogram (EGC); or (4) percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), more than three months prior to enrolment.

**Exclusion criteria.** Patients were not eligible for registry enrolment if they were: (1) hospitalised for CV disease reasons (including revascularisation) in the last three months prior to enrolment; (2) scheduled for revascularisation; or (3) afflicted by conditions that would limit participation/5-year follow-up. These conditions included limited cooperation, limited legal capacity, serious non-CVD impacting on life expectancy (cancer or substance abuse) or severe CVD (advanced heart failure, severe valve disease and/or history of valve repair/replacement).

The study was conducted in accordance with the principles in the Declaration of Helsinki and local ethical approvals were obtained prior to recruitment of patients (Institute Jantung Negara: IJNEC Ref. No: IJNEC/02110 (1); Negara Brunei Darussalam MHREC: MHREC/MOH/2010/14(S); Sime Darby Medical Centre: EC2010.04.1; University Malaya Medical Centre: MEC Ref. No: 764.4; Ministry of Health Malaysia: KKM/NIHSEC/08/0804/P10-194). All patients gave written informed consent for the collection of their data.

**Data collection.** At enrolment, investigators completed standardised electronic case report forms that documented patients' baseline data on demographics, employment status, medical history, risk factors, physical examination, heart rate, laboratory values that were available and current chronic medical treatment. There were no mandated tests or assessments required at baseline.

During the annual follow-up visits, patients were evaluated for clinical events that occurred since the last follow-up visit, and were reassessed for employment status, medical history, physical examination, heart rate, laboratory values and current chronic medical treatment. At each stage of data collection, data was anonymised via a patient identification code system that was maintained by a third-party data management centre.

**Measured outcomes.** The registry monitored patients for the following outcomes: (1) sudden death and CV death (fatal MI, fatal stroke, heart failure, ruptured aneurysm, pulmonary embolism, cardiac investigation/procedure/operation); (2) non-CV death and (3) CV morbidity (hospitalisation for nonfatal myocardial (re)infarction, unstable angina, new-onset/worsening heart failure, coronary revascularisation, nonfatal stroke and other vascular events/procedures, surgery, stenting, amputation)

**Statistical analysis.** All data collected and analysed at the Robertson Centre for Biostatistics, University of Glasgow, UK. Data analysis was performed based on the SAS statistical programme, version 9.2 or higher.

Baseline characteristics were presented using descriptive statistics with mean (standard deviation [SD]) or median for continuous variables, depending on the distribution of the data, and using numbers for categorical variables. Normality assumptions was satisfied and parametric statistical test (chi-square and Student’s T-test) were mainly used. All tests performed were two-sided and a significance level of 0.05 was adopted to confirm statistical differences between parameters.

**RESULTS**

Out of the 33,283 patients available for analysis at baseline, a total of 380 Malaysians and 27 Bruneians were enrolled. These two countries contributed about 1.12% of total CLARIFY population.

**Clinical characteristics**

Patients' baseline demographics, medical history, lifestyle parameters and vital signs and symptoms are listed in Table I while their baseline medical treatment for CV conditions are reported in Table II.

The mean age of patients in the Malaysian/Bruneian cohort was $57.83 \pm 9.98$ years, which was significantly younger than patients from the rest of the world (RoW) ($64.23 \pm 10.46$ years), $p<0.001$. The percentage of men in the Malaysian/Bruneian cohort was higher than in the RoW ($89.19\%$ versus $77.34\%$, $p<0.001$). Malaysians/Bruneians cohort were more likely to have received at least a secondary school / level education, to be fully employed and less likely to be retired that the rest of the overall registry population. The Malaysian/Bruneian patient cohort had comparable rates of current smokers as the RoW registry population ($11.06\%$ and $12.43\%$) and comparable rates of former smokers ($45.95\%$ and $45.39\%$) respectively ($p=0.705$ for smoking status). The rates of physical activity were also comparable: $35.38\%$ and $32.30\%$, respectively had at least 20 minutes of vigorous physical activity one or more times a week, and $14.50\%$ and $16.32\%$ respectively performed no physical activity at all ($p=0.384$).

The Malaysians/Bruneian cohort was smaller in size compared with the RoW. The median body mass index values for the Malaysian/Bruneian cohort and the RoW patient cohorts were $26.6$ ($24.4-29.6$) $kg/m^2$ and $27.3$ ($24.8-30.3$) $kg/m^2$, respectively ($p=0.014$). The median waist circumference values were $94.0$ ($88-101$) cm and $96.52$ ($88-105$) cm respectively ($p<0.001$).

Malaysian/Bruneian patients in the CLARIFY registry were less likely to have experienced an MI ($54.55\%$ versus $59.76\%$, $p=0.033$) and were more likely to have undergone PCI ($63.64\%$ versus $58.61\%$, $p=0.040$) compared with rates...
reported in RoW. However, the rates of CABG between both cohorts were comparable (21.87% in the Malaysia/Brunei cohort and 23.43% in the RoW cohort, p=0.459). A higher percentage of Malaysian and Bruneian patients had coronary arteries with stenosis exceeding 50.0%, specifically at the left anterior descending artery (p=0.0001), circumflex artery (p=0.0001), and bypass graft conduits (p=0.0001).

The rate of angina was much lower in the Malaysian/Brunei cohort (4.91% versus 22.21% in the RoW, p=0.001), as well as the rate of congestive heart failure symptoms (2.95% versus 15.02%, p=0.001). A smaller percentage of patients in the Malaysians/Bruneian cohort had atrial fibrillation/flutter than the rest of the CLARIFY registry (3.69% versus 7.04%, p=0.008). The incidence of stroke was comparable between the cohorts (p=0.408).

In terms of chronic comorbidities, Malaysian and Bruneian patients had comparable rates of treated hypertension as the rest of the CLARIFY registry (71.74% and 70.95% respectively, p=0.725), but significantly higher rates of diabetes (43.24% vs 28.99% respectively, p=0.001) and dyslipidaemia (90.42% vs 74.66%, p=0.001). Glycaemic control among Malaysian/Bruneian patients with hyperglycaemia was poorer than the rest of the cohort, as mean HbA1c levels were 7.23% and 6.83%, respectively.

Baseline management of CV risk factors
Prescriptions rates for aspirin, oral anticoagulants, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs), long-acting nitrates, amiodarone/dronedarone and diuretics were lower among Malaysian and Bruneian patients compared with the RoW registry population (Table II). However, a significantly higher percentage of Malaysian/Bruneian patients were prescribed thienopyridine and lipid-lowering agents (p=0.001). The rate of calcium antagonist usage was comparable between the two cohorts although verapamil/diltiazem appeared to be less favoured in the Malaysian/Brunei cohort (2.7% vs 5.85% in RoW, p=0.006).

Outcomes at 2-years follow-up
Broadly, the rates of measured outcomes (included all-cause death including cardiovascular death, fatal and non-fatal MI, fatal and non-fatal stroke, and major bleeding) in Malaysian and Bruneian patients were low and similar to that in the rest of the CLARIFY registry cohort (Table III). The rate of all-cause death was 2.5%, fatal and non-fatal stroke was 1.2%, and fatal and non-fatal MI was 1.0% among Malaysian/Bruneian patients compared with rates of 2.0% (p=0.393), 0.9% (p=0.357) and 1.3% (p=0.769), respectively in the overall patient population. The exception to this observation was that there was significant more unstable angina in Malaysia/Brunei cohort (2.3% vs 6.5%; p=0.005).

DISCUSSION
This is the first prospective registry looking into stable CAD in Malaysia and Brunei. Overall, Malaysian and Bruneian patients appeared to be younger compared with the rest of the registry. The younger mean age implied that the Malaysian/Bruneian cohort developed co-morbidities at an earlier age that the rest of the registry. Indeed, the registry reported higher prevalence of dyslipidaemia and diabetes among Malaysians/Bruneian patients than the RoW cohort, which appeared to mirror prior findings that CV risk factors are prevalent in the Malaysian population.3,8 For example, a higher percentage of patients in the Malaysian/Brunei cohort suffered from diabetes and had poorer HbA1c control than the rest of the CLARIFY registry. The high prevalence of CV risk factors in the two developing countries of interest likely reflects the insufficient emphasis and effort in primary prevention strategies at a national level.

Healthy lifestyle such as good dietary choices, increasing physical activities as well as health screening programs may need to target younger populations in these countries. The mean age of the patients in both countries was around 58 ± 10 years old, the relatively high CV disease burden in this young, productive age group carries significant economic impact and thus, early, effective interventions should bring major cost-savings to these nations, besides the positive implications to the overall human costs.

In terms of treatment, there was a high prescription rate of prophylactically important drugs such as anti-platelets and statins in the overall CLARIFY registry population, including the current cohort of interest. Unfortunately, effective risk factor management of stable CAD patients in Malaysia and Brunei is still lacking compared with the RoW. For example, the Malaysian/Brunei cohort had poorer HbA1C control. Compliance of patients to lifestyle changes and medications may be the main cause of these observations. However, the CLARIFY registry is not designed to look at patients’ compliance to medications and lifestyle modifications. The future focus of intervention should be on better control of risk factors. Newer medications such as empagliflozin and liraglutide which has been shown to reduced cardiac death and events in stable CAD patients may be beneficial to these patients.10,11

Heart rate-limiting agents such as beta blockers are first-line agents to reduce angina in patients with stable angina but the usage in Malaysia and Brunei was low compared with the RoW cohort. There was no significant difference in the prevalence of asthma or bradycardia (which could be the contraindication for beta blocker therapy) in these two cohorts. The usage of beta blocker was reportedly low in Malaysia. Indeed, Ong et al. noted that only 77.5% of patients were given beta blockers after a myocardial infarct but the dose was not optimised in 60.7% of these patients.12 Further studies into the prescribing behaviour of beta blockers in the region would be useful.

Despite the differences in baseline characteristics and disease management, Malaysian/Bruneian patients had broadly similar clinical outcomes as the rest of the CLARIFY cohort. However, the former cohort had a lower incidence of unstable angina versus the RoW cohort. It is difficult to postulate the reasons for this trend, due to various confounders such as different baseline demographics and co-morbidities, and to insufficient information regarding treatment intensities. It would be interesting to see the result of the planned analysis.
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of 5-year data to see the impact of these difference in baseline characteristic on clinical outcome.

It is hoped that nation-specific prospective data such as that provided by the CLARIFY registry will help to identify knowledge gaps in patient characteristics and their management to allow the development of remedial strategies.

LIMITATIONS
Several limitations in the design impacted the results analysis. The Malaysian/Bruneian patient cohort is significantly smaller than the RoW population in the CLARIFY registry, which limits interpretation of the analysis. The appropriateness of prescribed treatment, at baseline and during follow-up, could not be assessed because data collection did not assess the use of medication according to guideline recommendations. The data collection process also did not gather information on the doses prescribed and adverse events associated with treatment. Finally, despite steps to ensure that patient selection was representative of the population, the risk of selection bias could not be entirely removed.

CONCLUSION
Malaysian/Bruneian patients with stable CAD had low rates of clinical events at two years’ follow-up that were comparable with the rest of the CLARIFY registry.

REFERENCES