Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry

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Aims
Our aim is to determine mortality and morbidity in Asian patients under clinical management for heart failure (HF). Specifically, we will define the incidence of, and risk factors for, sudden cardiac death, as well as the socio-cultural factors influencing therapeutic choices in these patients.

Methods
This is a prospective observational multinational Asian registry of 5000 patients with symptomatic HF (stage C) and LV systolic dysfunction (EF ≤ 40%) involving 44 centres across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand). Data collection includes demographic variables, clinical symptoms, functional status, date of HF diagnosis and prior cardiovascular investigations, clinical risk factors, lifestyle factors, socio-economic status, and survey of cultural beliefs, health practices, and attitudes towards device therapy. Centre-level characteristics (case load, referral pattern, specialization, and infrastructure) are also obtained. Patients uniformly undergo standard 12-lead ECG and transthoracic echocardiography at baseline, and are followed over 3 years for outcomes of death or hospitalization. The mode of death and cause of hospitalization are adjudicated by a central event adjudication committee using pre-specified criteria.

Perspective
By providing prospective data regarding the demographics, risk factors, and outcomes of Asian patients under treatment for HF, the ASIAN-HF registry is expected to advance fundamental understanding of the burden and predictors of death and hospitalization among these patients. The knowledge gained will be important for guiding resource allocation and planning preventive strategies to address the unmet and growing clinical needs of patients with cardiovascular disease in Asia.

Trial registration
NCT01633398

Keywords
Heart failure • Death • Sudden • Outcomes • Asia

Introduction
Heart failure (HF) is a major public health problem worldwide. As the final common pathway of a myriad of heart diseases, HF burden increases with increasing prevalence of cardiovascular disease in a community, as patients survive their acute cardiac injuries and progress to chronic HF. The World Health Organization has projected that the largest increases in cardiovascular disease worldwide are occurring in Asia, due to rapidly increasing rates of smoking, obesity, dyslipidaemia, and diabetes among Asians. Thus the burden of HF is expected to reach epidemic proportions in Asia. In the multiethnic Asian city of Singapore alone,
the age-adjusted HF admission rate rose by $\sim 40\%$ over the last decade, making HF the most common cardiac cause of hospitalization (representing $\sim 24\%$ of all cardiac admissions), with only $32\%$ surviving 5 years. These alarming statistics reflect the global shift in cardiovascular disease burden to developing countries in Asia. Yet in sharp contrast to the wealth of data regarding HF in Western nations, epidemiological data are scarce in Asian patients with HF. The limited available evidence suggests that there are important ethnic-related differences specific to this region, and a large treatment gap exists with regards to proven therapies that may contribute to the high mortality and morbidity rates of HF in Asia.

The lack of data regarding the mortality burden of HF in Asians has contributed to underuse of potentially life-saving therapies. Sudden cardiac death (SCD) accounts for $\sim 50\%$ of deaths in HF according to Western statistics, with risk of death increasing particularly with LVEF $< 40\%$. The prophylactic implantation of a defibrillator in at-risk patients with reduced LVEF has been shown to reduce SCD and, therefore, has become standard practice in Western nations. However, in Asia there is resistance to uniform adoption of similar preventive measures and continued controversy regarding the risk of SCD among Asians. In a subgroup analysis of US data, the incidence of SCD appeared to be lower among Asian Americans than Caucasian Americans, contributing to the perception that Asians may be at lower risk of SCD and thus less likely to benefit from preventive interventions. Very few studies have been performed in Asia, and these have been limited by retrospective design, referral and selection bias, variability in the definition of SCD, or lack of adjudication of outcomes. Conflicting results have been reported, fueling the ongoing debate. Socio-economic barriers also exist in Asian nations, where socialized medicine is largely practised, and patients, medical communities, governments, and the society at large need to be convinced of the burden of preventable HF mortality specifically in Asians, before accepting this practice. Finally, ill-defined cultural differences may play a role in limiting the application of device therapy in Asia. Cultural norms in ageing, conservative value systems, and ethnicity- or religion-specific health beliefs may contribute to clinical decisions regarding the prophylactic insertion of a defibrillator, even in the face of proven outcome benefits.

Given the public health importance of HF, the epidemic of cardiovascular disease in Asia, and the availability of potentially life-saving drugs and devices, but ill-defined barriers to their application in Asians, there is an urgent need to fill the knowledge gaps regarding the mortality burden of HF, as well as to understand the barriers to preventive drug and device therapy, among Asian patients with HF. Such knowledge is critical to define the unmet clinical needs among Asian patients with HF, and to guide clinical decisions as well as healthcare resource planning to meet these needs. The Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry is being initiated to meet these manifest needs. This is a fundamental step towards the long-term goal of improving outcomes among the large and growing population of patients with HF in Asia.

**Study design**

This is the first prospective multinational Asian registry of patients with symptomatic HF (stage C) and LV systolic dysfunction (EF $\leq 40\%$), established with the broad purpose of determining the burden of morbidity and mortality in Asian patients under care for HF, and, more specifically, the incidence of, and risk factors for, SCD.

**Hypotheses and specific objectives**

**Central hypothesis**

In Asian patients with HF, the age- and co-morbidity-adjusted burden of SCD, as well as all-cause death, other cause-specific cardiovascular deaths, and HF hospitalizations, are as high as those reported in Western patients using standardized definitions, while the unadjusted burden is even higher due to greater prevalence of cardiovascular risk factors among Asians compared with Western populations. The Acute Decompensated Heart Failure Registry International-Asia Pacific study (ADHERE-AP) found that Asian patients were younger, but had more clinically severe HF, compared with similar registries in the USA and Europe, and in-hospital mortality was higher for patients enrolled in ADHERE-AP compared with the US-based ADHERE.

**Specific objectives**

(i) The primary objective of this study is to determine the incidence of SCD in Asian patients diagnosed with HF and followed in representative Asian cardiovascular centres.

We will explore the magnitude and distribution of the centre-specific burden of SCD, and consider relevant subgroup estimates of the burden of SCD based on relevant centre characteristics. We will also estimate an overall burden of SCD across all centres depending on the level of clinical (qualitative) and statistical (quantitative) heterogeneity. In addition, the incidence of all-cause death and other cause-specific cardiovascular deaths will also be determined.

(ii) To determine the incidence of all-cause and cause-specific hospitalization among Asian patients with HF.

(iii) To determine the risk factors for SCD, all-cause death, other cause-specific death, and hospitalization among Asian patients with HF.

Risk factors for these outcomes established in Western studies will be analysed. In addition, we will study factors that are found to be highly prevalent in Asian patients, as well as assess the thresholds of traditional risk factors (e.g. EF, QRS duration) that are associated with increased risk in Asian patients.

(iv) To understand the socio-cultural barriers to device therapy among Asian patients.

The use of devices will be captured and the reason why a device was not implanted in appropriate patients will be identified. We hypothesize that perceived state of health, cultural norms in ageing, and ethnicity- or religion-specific health beliefs and economic factors will influence receptivity to device therapy among Asian patients with HF.
Overall study design
This is a prospective observational multinational registry of Asian patients with symptomatic HF (stage C) and LV systolic dysfunction (EF ≤ 40%). The study involves medical centres across Asia (Figure 1). Data collection includes demographic variables, clinical symptoms, functional status, date of HF diagnosis and prior cardiovascular investigations, clinical risk factors, lifestyle factors, socio-economic status, and survey of cultural beliefs, health practices, and attitudes towards device therapy. Centre-level characteristics (case load, referral pattern, specialization, and infrastructure) are also obtained. Patients uniformly undergo standard 12-lead ECG and transthoracic echocardiography at baseline, and are followed over 3 years for outcomes of death or hospitalization. The mode of death and cause of hospitalization are adjudicated by a central event adjudication committee using pre-specified criteria.

Site selection
The study involves 44 medical centres across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand) constituting a novel network of Asian centres of cardiovascular expertise (Figure 1). Eligible sites were centres covering a broad spectrum of medical, cardiology, and HF specialty units that regularly admit patients with acute HF and follow patients with chronic HF in outpatient clinics. Site selection was based on size of the country, geographic location of the site within the country, patient population served, HF patient volume, and availability of expertise in echocardiography. For instance, in large countries such as India and China, sites from all areas of the country were selected to obtain a reasonable sample size from each of the ethnic groups.

Study population
Consecutive patients are screened for eligibility according to the following inclusion and exclusion criteria.

Inclusion criteria
(i) Adults (>18 years)
(ii) A diagnosis of symptomatic HF (stage C HF regardless of functional status) with at least one episode of decompensated HF in the previous 6 months that:
   (a) resulted in a hospital admission (primary diagnosis) or
   (b) was treated in an outpatient clinic
(iii) LV systolic dysfunction (EF ≤ 40% on baseline echocardiography)
(iv) Available for follow-up over 3 years.

These inclusion criteria were selected in recognition of current recommendations emphasizing that HF is a progressive, staged disease, in acknowledgement of the subjective nature of NYHA functional classification; and are also supported by a recent meta-analysis showing that risk of death in HF increases as the EF falls below 40%.

Exclusion criteria
Severe valve disease as the primary cause of HF:
(i) Life-threatening co-morbidity with life expectancy of <1 year
(ii) Unable or unwilling to give consent
(iii) Concurrent participation in a clinical therapeutic trial which requires patient consent.

Study schedule
Patients will be recruited over 2 years and followed at 6 months (+ 4 weeks), 1 year (+8 weeks), 2 years (+8 weeks), and 3 years (+8 weeks) according to the schedule in Table 1.

Data collection
Details of clinical data points collected at each study visit are provided in Table 2. In addition to the standard patient profile questionnaire, a health perception visual analogue scale (VAS) and the standardized language-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) will be administered. All questionnaires will be made available in the local languages and completed by the patients at the specified visit schedules. To understand further the socio-cultural factors that influence Asian patients in making decisions regarding device therapy, a qualitative interpretative approach will be used. This Device Therapy Perception Questionnaire will include the following four questions with semi-structured response options as well as open text responses that will be captured in the patient’s native language and translated for subsequent analysis. These questions were derived from pilot studies in Asian populations, and designed to be as open ended as possible to minimize bias.

Electrocardiography
Standard resting 12-lead ECG will be performed at each centre and analysed for rate, rhythm, axes, intervals, conduction abnormalities and arrhythmias, and evidence of prior myocardial infarction or chamber enlargement (Table 2). In addition, each ECG will be scanned and captured electronically for future detailed measurements at a central laboratory (W.S.).

Echocardiography
Standard transthoracic echocardiography will be performed at each centre according to internationally accepted guidelines and will include assessment of LVEF and dimensions, left atrial dimension, LV diastolic function, stroke volume, and cardiac output (Table 3). The Cardiovascular Imaging Core Laboratory of the National University Health System, Singapore (L.H.L.) is responsible for oversight of imaging protocol guidelines to provide quality assurance of echocardiograms and the associated data. All echocardiographic data will be stored digitally and made accessible to the Core Laboratory. The Core Laboratory will ensure accuracy and reproducibility of interpreted results through consistent training and systematic analytical processes according to international standards.
Outcome determination and adjudication

The outcomes of interest are all-cause and cause-specific death and hospitalizations (see definitions below). HF events are diagnosed according to Framingham criteria for the clinical diagnosis of congestive HF. Each outcome event and its cause are adjudicated using pre-specified criteria by a central event adjudication.

Figure 1 Map showing geographic distribution of study sites across Asia. Stars indicate the cities across 11 Asian regions (China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan and Thailand) where participating medical centres of the ASIAN-HF study are located. Investigators at these 44 participating centres constitute a novel network of Asian cardiovascular investigators.
committee comprising members of the Steering Committee. Their decisions will be based on independent physician review of the data from the case report forms, death certificates, hospital discharge summaries, and any other relevant information requested by members of the event adjudication committee and based on criteria outlined in the event adjudication committee charter. Briefly, all deaths and hospitalizations are classified as cardiac or non-cardiac, with more specific categories assigned as permitted by the circumstances of the clinical event. SCD is defined as unexpected observed or unobserved and, when sufficient information regarding preceding symptoms is available, SCD is defined as a death that occurs within 1 h of onset of cardiac symptoms in a person without any previous condition that would explain the fatality.

Biomarker substudy
Blood sample collection will be performed at selected sites (Singapore and Hong Kong) for biomarker measurements, as previously published, and as described in the Supplementary material.

Study management
The ASIAN-HF Steering Committee, chaired by the Director of the Cardiovascular Research Institute, National University of Singapore (A.M.R), and consisting of leading investigators from each region [China (S.Z.); Japan (W.S.); India (C.N.); Korea (S.W.P.); Hong Kong (C-M.Y.); Thailand (T.N.); Malaysia (R.O.); Philippines (E.B.R.); Indonesia (B.S.)], key independent international experts (I.A.), the Core Laboratory Director (L.H.L.), and the principle investigator (C.S.P.L.), is responsible for the overall conduct of the study. The study is funded by the Investigator-Sponsored Research Program of Boston Scientific, via a grant for investigator-initiated studies awarded to the Cardiovascular Research Institute, Singapore after competitive application. The protocol design and execution of the ASIAN-HF study are entirely under the oversight of the ASIAN-HF Steering Committee, and the grant sponsor has no access to patient-specific data or practice site data or performance information. The Cardiovascular Research Institute has recruited an independent contract research organization, Quintiles Outcome, for data management and overall study management.

The study is approved by the local institutional review board at each site. Details are available in the Supplementary material.

Sample size considerations
The sample size of the study, to address the primary objective of assessing the burden of SCD in Asian patients with HF, is the largest achievable with the allocated resources (available patients, finance, and time). Each of the selected sites confirmed that they had a sufficient HF patient load to recruit 100–200 patients per year that would satisfy the inclusion and exclusion criteria. Using a conservative estimate of 60 recruited patients per year for each site, we estimate that over the recruitment period of 2 years, we will enrol (60 patients × 44 centres × 2 years =) 5280 patients. Allowing a 5% dropout, we are aiming for a final n of approximately 5000 patients in the registry. The recruited patients will be followed-up for at least 3 years. Initial estimates based on results from previous Western studies indicate that an adequate number of patients are expected to experience the outcomes of interest within the 3-year follow-up period:

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)10 enrolled 2521 symptomatic patients with HF and reduced LVEF of either ischaemic or non-ischaemic aetiology. In the placebo arm, the overall mortality rate was ≤30% over 5 years (≤6% annual all-cause mortality). We therefore estimate an overall mortality burden of ≤18% (n = 900 all-cause deaths) over 3 years in our cohort. In SCD-HeFT, defibrillator therapy was associated with a decreased risk of death compared with placebo, with a hazard ratio of 0.77 and a 97.5% confidence interval of 0.62–0.96; *P = 0.007. Using the conservative assumption that only SCD deaths were prevented by defibrillator therapy, we assume that 23% of deaths were due to SCD, and that the SCD burden in the SCD-HeFT population was ≤7% over 5 years (1.4% annual SCD rate) with a 97.5% confidence interval of 1.2–11.4% over 5 years (0.24–2.28% annually). Thus, a conservative estimate of the burden of SCD in our cohort is 4.2% (n = 210) over 3 years. In the MADIT-CRT study of 1820 patients with ischaemic or non-ischaemic HF with reduced EF, the primary endpoint of all-cause death or HF event occurred in 25.3% of patients at 2.4 years in the defibrillator-only arm. In the absence of defibrillator therapy, we estimate that the burden of all-cause mortality and HF

Table I Study visit schedule

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>Visit 2: 6 months (±4 weeks)</th>
<th>Visit 3: 1 year (±8 weeks)</th>
<th>Visit 4: 2 years (±8 weeks)</th>
<th>Visit 5: 3 years (±8 weeks)</th>
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</thead>
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<tr>
<td>Echocardiography</td>
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<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*The following questionnaires will be administered during the study. Visit 1: Patient Profile Questionnaire; Visual Analogue Scale for Current Health Perception; Kansas City Cardiomyopathy Questionnaire; Device Therapy Perception Questionnaire. Visits 2–5: Visual Analogue Scale for Health Perception; Kansas City Cardiomyopathy Questionnaire.
hospitalizations will be \( \approx 35\% \) over 3 years (\( n = 1750 \) events) in our cohort.

**Discussion**

The ASIAN-HF registry is the first prospective study of 5000 Asian patients with symptomatic HF (stage C) and LV systolic dysfunction (EF \( \leq 40\% \)) from 44 centres in 11 Asian nations. The broad purpose of this registry is to determine the mortality and morbidity (incidence) burden of HF in Asian patients, and more specifically to define the burden and risk factors of SCD, as well as the sociocultural barriers to preventive device therapy. We expect that this registry will advance our fundamental understanding of the burden and predictors of death and hospitalization among Asian patients with HF. The knowledge gained will be important for guiding resource allocation and planning preventive strategies to address the unmet and growing clinical needs of patients with cardiovascular disease in Asia.

**Burden of cardiovascular disease in Asia**

The burgeoning problem of cardiovascular disease in developing countries was recently highlighted at the United Nations High-Level Meeting on Prevention and Control of Non-Communicable Diseases (NCDs). According to the World Health Organization,
deaths from NCDs will increase by 17% overall in the next decade, and the World Economic Forum estimates that losses related to disease treatment and lost productivity will exceed US$47 trillion over the next 20 years. Of great concern is the large and growing burden of cardiovascular disease in Asia, due to the ‘globalization of unhealthy lifestyles’, including tobacco use, excess alcohol consumption, poor-quality food, and lack of exercise. HF, the ultimate manifestation of various cardiovascular diseases, is a chief contributor to these alarming statistics and is a critical public health problem to address in Asia.

Evidence of a unique Asian phenotype

Results from HF studies in Western populations may not be generalizable to Asian populations. Evidence for ethnic-related differences in HF was recently provided in the ADHERE-AP study, where, compared with similar registries in the USA and Europe, Asian patients hospitalized for acute decompensated HF were found to be younger, and more likely to exhibit severe clinical symptoms and signs. While exact reasons for these differences could not be ascertained, this study importantly showed that in the vast majority of Asian patients, HF is a chronic disease (with a history of prior HF in two-thirds of patients), and that there is significant underutilization of echocardiography among patients in this region (with only 50% of patients undergoing the procedure). We therefore aim to extend the prior ADHERE-AP registry by studying patients in the chronic HF setting, providing planned resources to avoid high rates of missing echocardiographic data, and prospectively following patients to determine long-term outcomes and their risk factors.

Table 3  Echocardiography protocol

<table>
<thead>
<tr>
<th>2D</th>
<th>Col</th>
<th>PW</th>
<th>CW</th>
<th>TDI</th>
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</thead>
<tbody>
<tr>
<td>Parasternal long axis (2D, MV/AV colour)</td>
<td>1 clip</td>
<td>1 clip</td>
<td></td>
<td></td>
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<tr>
<td>Parasternal short axis (aortic valve)</td>
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<td>Parasternal short axis at mitral valve</td>
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<tr>
<td>Parasternal short axis at papillary muscle</td>
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<tr>
<td>Parasternal short axis at apex</td>
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<td>Doppler mitral valve inflow</td>
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<tr>
<td>Doppler pulmonary vein</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Doppler LVOT/aortic valve</td>
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<tr>
<td>Mitral annular TDI—medial (septal)</td>
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<td>Mitral Annular TDI—lateral</td>
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<tr>
<td>Tricuspid annular TDI</td>
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<tr>
<td>Apical 2Ch (including left atrium)</td>
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<td></td>
<td></td>
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<tr>
<td>Apical long axis (including left atrium)</td>
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<tr>
<td>IVC (with sniff)</td>
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</tbody>
</table>

Ao, aorta; AV, aortic valve; 2Ch, 2-chamber; 4Ch, 4-chamber; Col, colour; CW, continuous wave Doppler; 2D, two-dimensional; LA, left atrial; MM, M-mode; MV, mitral valve; PW, pulse wave Doppler; TDI, tissue Doppler imaging; TV, tricuspid valve.

*2D, frame rate 60–80 Hz. Store three cardiac cycles.

*CW, PW, TDI, adjust sweep speed to capture three cardiac cycles per clip. Store one clip if in sinus rhythm and three clips if AF or other irregular rhythms.

*TDI, frame rate >160 Hz.

Unanswered questions in Asian patients with heart failure

Ethnic differences in outcomes have been observed among patients enrolled in a HF management programme at two centres in Singapore, with Indians and Malays incurring a worse prognosis than ethnic Chinese. While the greater burden of diabetes and atherosclerotic vascular disease in Indians may explain their worse outcome, the reasons for the poorer prognosis in Malays are unclear. Whether ethnicity-specific risk factors exist, or whether known predictors (such as cardiovascular risk factors, echocardiographic LV measurements, or ECG parameters) require recalibration in different ethnic groups is unknown.

Furthermore, exact causes of death among Asian patients with HF remain poorly understood. In particular, the risk of SCD among Asians is an area of controversy. In the Second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) in Western patients, an implantable cardiac defibrillator (ICD) reduced mortality in patients with a history of myocardial infarction and LVEF <30%, largely due to a decrease in SCD. When the same MADIT-II criteria were applied to a Japanese cohort, patients who were eligible but did not undergo ICD implantation showed significantly lower risk of SCD and even better overall survival than the historical Western MADIT-II population. In contrast, when applied to a Chinese cohort, those satisfying the MADIT-II criteria were found to be at similar risk of SCD compared with the original Western MADIT-II population. Both previous Asian studies have been criticized for their small sample sizes, possible selection bias, and retrospective nature. However, they clearly demonstrate the ambiguity regarding the risk of SCD among Asian patients—an issue that may be depriving Asian
patients of potentially life-saving therapy, and one that needs to be urgently addressed so that patients, doctors, and policy-makers can make informed healthcare decisions.

**Conclusions**

The ASIAN-HF registry aims to fill the knowledge gaps regarding the mortality and morbidity burden of HF among Asian patients. Given that up to half of deaths and readmissions for HF may be preventable, a better understanding of the demographics, risk factors, and outcomes of such patients may provide opportunities to improve management and prognosis, guide healthcare resource allocation, and identify future areas of research in this large and growing population.

**Supplementary material**

Supplementary material is available at *European Journal of Heart Failure* online.

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Conflict of interest: C.S.P.L. is a member of the Scientific Steering Committee of the MADIT-Asia trial and receives limited travel support but no other honoraria or reimbursement related to this trial. All other authors have no conflict to declare.

References