Instructions to authors

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2) The full list of authors and their academic affiliation
3) Corresponding author and contact details including email address
4) List of up to 5 keywords separated by semicolons

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Discussion should be directly related to the study being reported rather than a general review of the topic. It should cover the following subheadings: Findings, Data interpretation, Clinical implications (if relevant), Limitations and Conclusions.

References style used by ICFJ journal is Vancouver Numbered. They must include author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume and issue/book chapter, page numbers and where one exists the DOI.

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Figures should ideally be submitted in high-resolution TIF format, or alternatively in GIF, JPEG/JPG, or EPS format. The figures should be placed in separate files, named only with the figure numbers (e.g. "Figure1.tif"). Please ensure figures have the appropriate resolution: Line art: 1000 dpi Halftones; 300 dpi Combinations; 500 dpi Colour: 300 dpi Colour combinations; 500 dpi. Legends for Figures should be typed with double-spacing on a separate sheet.

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Acute Pulmonary Embolism and Paradoxical Embolism in Patients with Patent Foramen Ovale: To Close or Not to Close… That is the Question!

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Abstract

Nowadays, the treatment of patent foramen ovale (PFO) after acute pulmonary embolism (PE) remains matter of speculation. Absence of both randomized trials and recommendations in current international guidelines complicate the decisions making in such patients. In the present manuscript we discuss about the reasons for which PFO should be closed after acute PE.

Keywords: Patent Foramen Ovale; Pulmonary Embolism; Endovascular treatment

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Introduction

Several studies have already proposed and analysed the role of patent foramen ovale (PFO) in different clinical settings; cryptogenic stroke, peripheral and coronary paradoxical embolism, migraine with aura, and others. However, the PFO closure in pulmonary embolism (PE) patients remains one of the most intriguing for different reasons. Firstly, current international guidelines on acute PE no takes into account neither PFO or others atrial septum defects. Secondly, previous data were obtained from studies based on different PE classifications, as the Miller’s index, which is not currently used in the medical practice. Obviously, also the absence of any studies and/or trial on the role of PFO closure in PE patients contributes to this uncertainty. Because PFO is often asymptomatic, PE patients could receive the diagnosis during the management of the acute event [1]. In this manuscript, we review the reasons for which PFO should be closed after PE also presented a clinical case.

Evidence from the literature

As well known, stroke and PE are currently the second and third leading causes of cardiovascular mortality in western countries. For these reasons, it is quite intuitive that the presence of PFO in PE patients could be a serious problem both in the short- and long-term periods. If PE appears concomitantly with PFO, the abrupt elevation of pulmonary artery pressure (PAP) and also the increase in pulmonary vascular resistance can promote an inverse shunting across the PFO [2], resulting in an increased risk of systemic paradoxical embolization (PDE) [3]. Indeed, in this respect, Thomas et al. observed that PDE complicate PE in 67% of cases [4]. In PE patients, PFO are generally detected with transthoracic echocardiography (TTE) [5]. However, the clinical suspicion could arise also from the patient’s medical history. Further investigation in PE patients should be performed in the presence of previous suggestive signs and/or symptoms, as migraine, migraine-like symptoms, previous stroke or transient ischemic event of undefined etiology and previous systemic
embolism of undefined origin [6]. Because PFO could be often asymptomatic a depth TTE evaluation is recommended in case of inconclusive results at TTE. Moreover, the use of trans-esophageal echocardiography (TEE) has been shown to be more sensitive improving the PFO diagnostic accuracy. Nowadays, a simple venous contrast study, called “bubble test”, which is based on the injection of a shaken saline solutions into a peripheral vein, have demonstrated a higher sensitivity and specificity versus the traditional Doppler techniques in detecting PFO. Transcranial Doppler with bubble test is considered the most sensitive non-invasive diagnostic tool for PFO detection and quantitative assessment.

Previous studies, which analysed the relationship between PFO and PE, assessed that echocardiographic PFO detection signifies a higher risk of death and/or thromboembolic complications [6]. In particular, patients with a PFO greater than 4mm have 10-fold risks of death and 5-fold risks of systemic embolism compared to patients without PFO [7]. A recent study, which considered PE patients classified as intermediate-risk, revealed a PFO prevalence of 17.7 % [8]. On the contrary, a lower percentage have been found from Clergeau et al. in PE patients classified as low-risk PE [8]. Nowadays, despite seems that the prevalence of PFO increases with the severity of PE, due to the absence of definitive results, the real prevalence of PFO among the different PE risk groups remains matter of speculation.

PE implies an imbalance between the ventilation/perfusion ratio of the lungs. In particular, hypoxaemia in PE is due to the increased V/Q mismatch which is not associates with increased shunt. Generally, patients with hypoxaemia are not refractory to oxygen administration, apart in case of high risk (or massive) PE, which is associated with a severe ventilation/perfusion mismatch. In the other cases, a refractory hypoxaemia could contribute to raise the suspicion of the presence of alternative or complementary causes as PFO.

The latest European Society of Cardiology (ESC) guidelines on acute PE marginally takes into account the presence of PFO in PE patients. Indeed, it is only recommended to consider the presence of PFO when thrombolytic treatment must be performed. More in general, current international guidelines and consensus paper on PE reveal a lack of recommendation about the clinical and/or interventional management of PFO in PE patients. On the contrary, an interesting recommendation comes from Doyen at al. which suggested that PFO screening should be integrated into the decision algorithm for thrombolysis in PE patients [8]. However, the main question remains: “Should these patients be treated only with medical therapy after the acute event?” Is percutaneous PFO closure recommended? Answers are actually controversial. In the real world, although the majority of patients after acute PE are treated with oral anticoagulation, only few patients underwent to PFO closure. Why? Probably because most physician believed that the oral anticoagulation could be enough as secondary stroke prevention in these patients, despite some of those already presented single or multiple previous ischemic events at the time of PFO diagnosis. As general rule, before clinicians decide if PFO closure it is necessary to consider the risk-to-benefit ratio. A recent review of non-randomized trials suggested that the rate of recurrence of stroke was lower with PFO closure compared to medical treatment [10]. For this purpose, PFO percutaneous catheter closure can be proposed in patients with recurrent stroke therapy to avoid future PDE. The magnitude of the problem posed by PDE in patients with PE and PFO, coupled with the continued uncertainty regarding the optimal approach to secondary prevention underscores the critical need for a general consensus on the best treatment.

Role of hypercoagulable state:
A hypercoagulable state has been described both in patients with previous CS stroke and/or PE. About thirty-one percent of patients with CS have a hypercoagulable state; on the contrary, the real prevalence of thrombophilic mutations in PE has not been defined, because thrombophilic screening is actually not recommended as a part of the work-up in all patients with PE. The thrombophilic assessment could be another useful parameter to evaluate whether to close or not to close PFO and/or to start anti-thrombotic regimen. In clinical practice, the presence of known hypercoagulable states with recognised increased risks of thrombosis/embolism despite recommended warfarin treatment (lupus anticoagulant/antiphospholipid antibody syndrome) is an indication for primary PFO closure. In patients with PFO, thrombophilic states may increase the occurrence of venous clots that can paradoxically embolize to the systemic circulation.

Suggested Recommendations:
We believe that the choice to close the PFO should be recommended and also individualized at the same time. Obviously, the potential benefits of endovascular treatment should be weighed against the procedure risks and patient’s comorbidities. Generally, patients with cryptogenic cerebral ischemic events are at higher risk of silent PE [11]. Moreover, PE, especially if temporally correlated with an ischemic event, could influence the patient treatment (anticoagulation ± closing PFO). Based on these observations, we would recommend that patients with PFO and thrombophilia be strongly considered for Transcatheter PFO closure and then for chronic oral anticoagulation.

Declarations of Interest:
The authors declare no conflicts of interest.

Acknowledgements:
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [12]

References:
with right-to-left shunting. Cardiol Young. 2015;25:47-55 DOI: 10.1017/S1047951113001480;


Cardiovascular Risk Factor Burden in the United Arab Emirates (UAE): The Africa Middle East (AfME) Cardiovascular Epidemiological (ACE) Study Sub-Analysis

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Introduction
There has been a widespread global increase in modifiable risk factors for cardiovascular disease (CVD), which has contributed globally towards a growing burden of non-communicable diseases [1,2]. Even though it is estimated that up to 80% of deaths in developing countries are secondary to CVD, there is an absence
of systematic epidemiological data on cardiovascular (CV) risk factors from these developing countries [3,4]. The majority of epidemiological studies from the developing world pre-date recent socioeconomic developments and are either too country-specific or only recruited patients from specific healthcare settings (outpatients, specialist or acute care settings) [5-7].

As a result of considerable urbanization in recent years, an epidemiological transition has occurred in countries such as Africa and the Middle East (AfME) similar to that seen in other developing regions [4,5]. For example, the proportion of individuals living in urban centers in developing countries doubled between 1970 and 1994, and it is expected to double again by 2025 [8]. This rapid increase in urbanization has been paralleled by a rising burden of chronic diseases that has not been matched by the development of national preventive health systems and screening programs. In the absence of an infrastructure for universal CV screening in many developing countries, targeted screening strategies may be a useful solution for improving early detection of CV risk factors, particularly if screening is targeted at adults who attend general practice clinics [9-11].

The United Arab Emirates (UAE) in the AfME region has a population growth that is among the highest in the world, mostly due to job-related migration (expatriate); for example there was a seven-fold increase between 1975 and 2005 [12]. Furthermore, the UAE has a unique model of population growth and an urban population contributing to 85.5% of the total population [13]. Therefore, the contribution of CV risk from the UAE into the AfME region is quite significant, and therefore warrants specific analysis. The Africa Middle East Cardiovascular Epidemiological (ACE) study was undertaken to estimate the prevalence of CV risk factors in outpatients attending general practice and non-specialist clinics in urban and rural communities across the AfME region [14]. We sought to conduct a sub-analysis of UAE data collected in the ACE cross-sectional study, in order to determine the prevalence of CV risk factors in outpatients attending urban and rural general practice clinics specifically in the UAE. Our study provides an excellent opportunity to examine shifting patterns of CV risk in this region.

Methods

Study design and objectives

The ACE study has been described in full elsewhere [14]. Briefly, it was a cross-sectional epidemiological study conducted in clinics across the AfME region between July 2011 and April 2012 [14]. This sub-analysis evaluated only data generated from the UAE region. Site selection in the UAE, was based on the ability of a site to conduct clinical studies and the availability of clinical research expertise, infrastructure and ethical oversight, as designated in the ACE protocol [14].

The objective of this analysis was to conduct an in-depth sub-analysis of data generated from the UAE region of the ACE study, in order to estimate the prevalence of CV risk factors in outpatients attending general practice, and other non-specialist outpatient clinics in urban and rural communities. Additionally, for patients with a pre-existing diagnosis of hypertension or dyslipidemia, the ACE study and our sub-analysis aimed to assess the degree of control of these risk factors. The ACE study defined rural areas according to Chadhi (1998), as “those isolated from urban centers by a distance of >50 km, or those with a lack of easy access to commuter transportation” [15]. Ethical approval was obtained from all participating centers and appropriate regulatory bodies in each country of the ACE study. The study protocol therefore conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee. The ACE study was registered on clinicaltrials.gov under the identifier: NCT01243138 [14].

Patient population

Only subjects presenting to sites in the UAE were taken into consideration from the parent ACE study [14]. Male and female outpatients aged >18 years were enrolled after signing an informed consent form. Pregnant women, lactating mothers and outpatients with life-threatening illnesses were excluded from the study. In order to minimize selection bias, every fifth outpatient seen by a physician was included in the sub-analysis. Physicians evaluated outpatients via history taking, physical examination and carrying out laboratory investigations. Evaluations were typically undertaken during the same clinic visit; however, for patients who were non-fasting during the first clinic visit, a second visit was arranged to obtain fasting blood samples.

Definitions

In the ACE study [14] - and therefore the UAE sub-analysis - dyslipidemia was recorded if the patient was receiving lipid-regulating drugs, or if the patient had a high fasting lipid sample documented, according to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guidelines [16]: high low-density lipoprotein (LDL) cholesterol; high total cholesterol; low high-density lipoprotein (HDL) cholesterol; or high triglyceride level. Outpatients on lipid-regulating therapy were considered to have controlled LDL cholesterol if their values were at goal according to their CV risk category, based on the NCEP ATP III recommendations [16], mentioned below:

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>LDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD Risk Equivalent*</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Multiple (2+) Risk Factors</td>
<td>&lt;130 mg/dL (LDL-C goal for multiple-risk-factor persons with 10-year risk &gt;20% = &lt;100 mg/dL)</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td>&lt;160 mg/dL</td>
</tr>
</tbody>
</table>

*CHD Risk Equivalent, included are those with peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease (symptomatic [e.g., transient ischemic attack or stroke of carotid origin] or >50 percent stenosis on angiography or ultrasound), and likely other forms of clinical atherosclerotic disease (e.g., renal artery disease).

Blood pressure (BP) was recorded as the higher of two consecutive seated BP measurements, which were taken once from each arm using a standardized BP monitoring device, and after the outpatient had been sitting quietly for at least 5 minutes. Hypertension was defined as currently receiving antihypertensive drugs, or having a high BP reading according to the European Society of Cardiology (ESC) Cardiovascular Prevention guidelines [17]. Outpatients receiving antihypertensive drugs were considered to have controlled BP if recorded as below 140/90 mmHg (as defined by the ESC guidelines [17]).
The following modifiable CV risk factors were captured in the ACE study [14]: diabetes mellitus (diabetes), according to the American Diabetes Association criteria [18]; smoking, either current or past consumption of cigarettes, a pipe or water pipe (shisha); obesity, defined as body mass index (BMI) ≥30 kg/m²; and abdominal obesity, defined as a waist circumference ≥94 cm in male and ≥80 cm in female outpatients, according to the International Diabetes Federation (IDF) harmonized criteria [19].

Outpatients were also analyzed by age group (younger [aged <40 years], middle aged [aged 40-60 years], older [aged >60 years], by gender (male vs female), and according to reported nationality (national vs non-UAE national).

### Statistical methods

The same statistical methodology used in the principal ACE study [14] was extended to evaluate the UAE sub-group. Categorical data are summarized using percentages and 95% confidence intervals. Continuous data are reported using n, mean ± standard deviation or median [25th, 75th percentiles] as appropriate.

In order to minimize data acquisition bias, data from every fifth outpatient seen by a physician was included in the sub-analysis. Data analysis was done by a statistician and interpreted by the authors, who were then put together in the final manuscript.

### Results

In total, 495 subjects from general practice outpatient clinics across the UAE were analyzed. Approximately one-quarter (26.1%) were enrolled from centers in rural communities. The mean age of the overall cohort was 45.1 years, with near-equal representation of genders (Table 1). Half of the outpatients (50.5%) were younger than 45 years, and only 9.5% aged ≥65 years. The majority of outpatients (92.9%) had at least one of the six modifiable CV risk factors (Figures 1 and 2). Three-quarters (74.9%) had two or more risk factors, and more than half (59.7%) had three or more CV risk factors (Figure 1).

### Dyslipidemia: prevalence and risk-factor control

Dyslipidemia was the most prevalent CV risk factor, recorded in nearly three out of every four outpatients (74.0%) (Figure 2). For the overall cohort, median [25th, 75th percentiles] lipid values were: 181.5 [152.0, 208.5] mg/dl (total cholesterol), 110.0 [84.9, 135.5] mg/dl (LDL cholesterol), 46.0 [37.0, 54.8] mg/dl (HDL cholesterol), and 109.0 [79.7, 148.0] mg/dl (triglycerides) (Table 1).

Despite the high prevalence of dyslipidemia, less than one-third (29.5%) of outpatients were on a lipid-altering drug, which was predominantly a statin. The most common component of dyslipidemia was presence of low HDL cholesterol, recorded in 30.3% of the whole study cohort. The majority of outpatients who were on lipid-lowering agents were not at their LDL cholesterol goal, particularly those in the moderate and high CV risk categories (defined by NCEP ATP III [16]). Overall, 11.1% of low-risk, 66.7% of moderate-risk and 40.4% of high-risk outpatients were not at their LDL cholesterol goals. For every one outpatient without a prior diagnosis of dyslipidemia, screening identified one new dyslipidemia diagnosis.

### Hypertension: prevalence and risk-factor control

Hypertension was identified in 43.0% of outpatients (Figure 2) and 34.1% of the study cohort had a previous history of hypertension. In the overall cohort, median [25th, 75th percentiles] systolic and diastolic BPs were 130.0 [120.0, 144.0] mmHg and 81.0 [74.0, 90.0] mmHg (Table 1). Among outpatients with an abnormal BP reading at study entry, 36.0% had an isolated elevation in systolic BP, 25.9% had an isolated elevation in diastolic BP and 18.8% had elevations in both systolic and diastolic BP readings. Of the 182 outpatients with a pre-existing diagnosis of hypertension and currently on antihypertensive therapy, more than one-

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**Table 1. Baseline parameters of outpatients across the UAE, by gender, unspecified and overall.**

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Unspecified</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Subjects</td>
<td>279</td>
<td>215</td>
<td>1</td>
<td>495</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18-44</td>
<td>142 (50.9)</td>
<td>107 (49.8)</td>
<td>1 (100.0)</td>
<td>250 (50.5)</td>
</tr>
<tr>
<td>≥65</td>
<td>107 (38.4)</td>
<td>90 (41.9)</td>
<td>0</td>
<td>197 (39.8)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1 (0.4)</td>
<td>0</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Mean age, years (range)</td>
<td>45.6 (19.0-84.0)</td>
<td>44.5 (18.0-88.0)</td>
<td>31.0 (31.0-31.0)</td>
<td>45.1 (18.0-88.0)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg),</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>132.0 (120.0, 144.0)</td>
<td>130.0 (120.0, 143.0)</td>
<td>131.0 (131.0, 131.0)</td>
<td>130.0 (120.0, 144.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg),</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>80.0 (74.0, 90.0)</td>
<td>81.0 (75.0, 90.0)</td>
<td>73.0 (73.0, 73.0)</td>
<td>81.0 (74.0, 90.0)</td>
</tr>
<tr>
<td>Waist circumference (cm),</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>98.0 (88.0, 106.0)</td>
<td>94.0 (86.0, 104.0)</td>
<td>99.0 (99.0, 99.0)</td>
<td>96.0 (87.0, 105.0)</td>
</tr>
<tr>
<td>BMI (kg/m²),</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>27.9 (25.5, 31.3)</td>
<td>30.2 (25.4, 35.1)</td>
<td>30 (30.0, 30.0)</td>
<td>28.7 (25.5, 32.9)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl),</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>181.5 (149.0, 207.0)</td>
<td>181.0 (154.4, 209.0)</td>
<td>173.0 (173.0, 173.0)</td>
<td>181.5 (152.0, 208.5)</td>
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<tr>
<td>LDL-C (mg/dl),</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>median (25th, 75th percentile)</td>
<td>111.0 (83.4, 136.0)</td>
<td>106.6 (86.0, 130.0)</td>
<td>130.0 (130.0, 130.0)</td>
<td>110.0 (84.9, 135.0)</td>
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<td>HDL-C (mg/dl),</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>41.4 (35.0, 51.0)</td>
<td>49.0 (40.9, 59.0)</td>
<td>25.0 (25.0, 25.0)</td>
<td>46.0 (37.0, 54.8)</td>
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<tr>
<td>Triglycerides (mg/dl),</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>5.7 (5.2, 6.7)</td>
<td>5.5 (5.0, 6.6)</td>
<td>4.9 (4.9, 4.9)</td>
<td>5.6 (5.1, 6.6)</td>
</tr>
</tbody>
</table>

Legend: BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol.

---
third (34.1%) had BP readings above ESC-defined levels [17]. Screening identified 14.5% of patients (n=31) who were newly diagnosed with hypertension.

Obesity: prevalence
The overall prevalence of abdominal obesity, defined by waist circumference, was nearly twice as common compared with obesity defined by BMI ≥30 kg/m² (Figure 2). Of the total outpatients screened (N=495), 71.5% (n=354) had abdominal obesity and 40.4% (n=200) had BMI obesity.

Diabetes: prevalence
Nearly one-third of the eligible population had diabetes (32.4%), the majority of whom (58.6%) were aged >60 years. Overall, the median fasting plasma glucose level for the whole cohort was 5.6 [5.1, 6.6] mmol/l (Table 1). Of outpatients with diabetes (n=133), 89.9% had a pre-existing diabetes diagnosis. An additional 10.1% (n=15) were diagnosed at the time of study entry (based on a single fasting plasma glucose measurement of ≥7 mmol/l).

Smoking: prevalence
The overall prevalence of smoking was 26.6%, where 13.7% were current smokers and 12.9% were past smokers (Figure 2). Smoking was most common in younger outpatients, with only 3.6% of those aged >60 years being a current smoker (Figure 3A).

The prevalence of cardiovascular risk factors by age, gender, community (urban vs rural) and nationality
Dyslipidaemia, hypertension and obesity were present in a notable proportion of younger outpatients (Figure 3A). For example, approximately one in every two outpatients aged <40 years had dyslipidaemia or abdominal obesity, but the prevalence of these risk factors was higher still in middle aged/older patients (aged ≥40 years) (Figure 3A).

Male outpatients had a larger waist circumference (98.0 [88.0, 106.0] cm) but lower median BMI (27.9 kg/m²) compared with female outpatients (waist circumference: 94.0 [86.0, 104.0] cm, BMI: 30.2 kg/m²) (Table 1). Regardless of criteria used, obesity was more common in female than male outpatients (Figure 3B).

Female outpatients exhibited a higher prevalence of obesity (50.7%) and even higher prevalence of abdominal obesity (85.1%), whereas male outpatients had higher prevalence of dyslipidaemia (80.5%), hypertension (45.5%), diabetes (35.6%) and smoking (22.9%) (Figure 3B).

Rural areas recorded higher rates of most CV risk factors compared with urban areas. However, smoking was notably more prevalent in urban than rural areas (15.0% vs 10.1%) (Figure 3C).
UAE nationals exhibited slightly higher prevalence of obesity and diabetes compared with non-nationals (Figure 3D). For example, the percentage of nationals with obesity (BMI ≥30 kg/m²) was 47.8% (vs 32.0% of non-nationals), while the prevalence rates for abdominal obesity and diabetes were higher for UAE nationals versus non-nationals (77.2% vs 64.9% and 35.9% vs 28.6%, respectively). Smoking and dyslipidemia were notably more prevalent in non-nationals (16.7% and 78.4%) compared with nationals (11.2% and 70.0%). Hypertension was comparable between both nationals and non-nationals (Figure 3D).

After the initiation of the primary ACE study, US dyslipidemia guidelines were revised by the ACC/AHA (2013) [20], and the approach to dyslipidemia management was changed from a target-based approach to a risk based approach, therefore targets of therapy changed from those used in the ACE protocol (NCEP ATP III, 2002). The ACC/AHA (2013) Guidelines [20] identified four statin benefit groups; namely 1) Atherosclerotic Cardiovascular Disease (ASCVD), 2) Untreated LDL-C ≥190 mg/dL, 3) Diabetes Mellitus (40-75 years, LDL-C 70-189 mg/dL) and 4) Without clinical ASCVD, unlike the NCEP ATP III, 2002 guideline [16], which defined LDL-C goals based on number of risk factors, as outlined above.

An analysis of the NCEP ATP III guidelines versus the ACC/AHA guidelines showed a considerable increase in the proportion of patients eligible for statin therapy based on the updated ACC/AHA 2013 recommendations. According to the NCEP ATP III guidelines, 19.6% patients (n=97) were eligible for statin therapy, but this increased to 35.2% of outpatients (n=174) being eligible for statin therapy based on the 2013 recommendations from the ACC/AHA; this was an increase of 79.6%, or 77 outpatients (Figures 3E and 3F).

Discussion
This analysis of 495 outpatients from across the UAE demonstrates a high prevalence of CV risk factor clustering, in line with observations from the larger ACE study across the whole AfME region [14]. In our UAE sub-analysis, nine out of 10 screened outpatients had at least one conventional risk factor for CVD, with dyslipidemia and abdominal obesity being the most prevalent, affecting more than two-thirds of screened outpatients. Diabetes, hypertension and smoking followed closely in terms of overall prevalence. Although some specific differences were noted, similar observations were seen across gender, age, and for urban and rural communities, highlighting the unmet need for CV risk factor management in the UAE as a whole.

In order to tackle the global burden of CVD, some regions of the world have adopted critical measures, including primary prevention strategies that include early detection and targeted control of conventional modifiable risk factors [10,21,22]. In the Middle East, nine modifiable CV risk factors, including the six risk factors analyzed in the present study, almost completely explain the risk of acute myocardial infarction in this region [21]. In the INTERHEART Study, CV risk from these factors combined was higher in the Middle East compared with other regions of the world, perhaps highlighting the need for more aggressive preventive measures to be adopted than in these other regions [23]. Nonetheless, CVD prevention is dependent on early detection, but the majority of developing countries have deficiencies in their national infrastructure to set up and run a comprehensive screening program [24]. The findings of our study from the under-studied UAE region provides a compelling rationale for targeted screening of CV risk factors at general practice primary care clinics across the UAE, to act as a substitute, or rather an alternative, to more expensive and comprehensive population-wide screening approaches. Our findings demonstrate that targeted screening at the general practice consultation is able to provide significant results when identifying individuals at risk, who may then be able to make good use of primary preventive measures.

Given the relative young age of the current study population (mean age 45 years), the CV burden observed is quite alarming: half (50.9%) of the cohort were younger than 45 years of age and 89.6 % were younger than 65 years. In many recent studies conducted in the Middle East region, patients who exhibited manifestations of CVD, including acute coronary syndrome or atrial fibrillation, appeared at least 10 years younger than their age-matched counterparts in developed countries [25-28]. In other words, complications associated with atherosclerosis (target organ damage) have been temporally shifted backwards by a decade, which may negatively influence preventive strategies aimed to start after a given age. It is unclear whether our observations simply reflect differences in population demographics (e.g., a generally younger population in developing countries) or whether they are indicative of a predisposition to premature CVD in developing countries [29]. The prevalence of undiagnosed and uncontrolled CV risk factors observed in our relatively young adult population in the UAE appears consistent with other observations [30]; in addition, our study underscores a pathophysiological substrate for the predisposition towards early onset of CVD.

Social and economic structures have appeared to condition disease profiles in societies throughout history. Certain developments have been directly linked to alterations in disease patterns [31,32], and population movement from rural to urban areas has led to an increase in the burden of CV risk factors [2,33]. In the present study the more recognizable observation, in our opinion, is the discreet difference between urban and rural communities in the prevalence of most of these modifiable risk factors, in comparison with a conventional pattern that often displays more prevalent risk factors in urban communities [2,33]. Moreover, rural communities may be reaching prevalence rates for CV risk that are similar to their urban counterparts. Although we accept that our study cannot fully explain the discreet gap in CV risk factors between rural and urban communities; it does indicate that perhaps adoption of an “urban” lifestyle in rural communities may be a contributing factor to this shift in CV risk. It has been noted in this study (Figure 3C) that in rural communities, 76.7% had abdominal obesity, and smoking frequency appeared to be similar in both urban and rural cohorts. Therefore, rural communities need to receive as much attention as their urban counterparts in efforts to fight CVD in developing countries [34,35]. We found that obesity and abdominal obesity were particularly widespread in this UAE cohort, with a substantially higher prevalence in female than male outpatients, regardless of
obesity definition used. The prevalence of obesity was relatively consistent across age groups, and in both urban and rural communities. When using waist circumference as a measure of obesity, as suggested by the IDF [19] and other international organizations, a 31% higher prevalence was noted in those classified as ‘obese’ compared with if using BMI ≥30 kg/m² (71.5% vs 40.4%, respectively). Studies of acute myocardial infarction in multiethnic cohorts of patients, such as in INTERHEART [23], have demonstrated the limited value of BMI as a measure of obesity, and a close link between waist and hip circumference, and their ratios, with the risk for myocardial infarction, even after adjustment for BMI and other risk factors. Furthermore, an INTERHEART sub-analysis also observed a significant link between the risk of myocardial infarction and abdominal obesity (which accounted for ~25.0% of the population-attributable risk) in a Middle East cohort [7]. Since the prevalence of obesity appears to be epidemic in our study cohort, this emphasizes the necessity of devising new strategies to control the increasing prevalence of obesity in order to reduce the long-term burden on CV health.

Decreasing the obesity burden will likely require more than a silo approach of interventional pharmaceutical or surgical efforts, or sporadic weight loss campaigns, since none of these strategies individually will likely have a sustained effect on weight control [36]. A more promising approach would seem to be a behavioral strategy that concentrates on encouraging and maintaining a healthy and active lifestyle, starting as early as childhood [37]. Strategies such as these require the reinforcement of wide-ranging public policies that specifically focus on definitions of healthy dietary intake, as well as considering more general aspects of urban planning and workplace environments in efforts to promote communities focused on healthy living [38,39].

Limitations

We focused this sub-analysis of the ACE study on the UAE, due to the paucity of data on CV risk factors from this region. Unlike past studies that focused on inpatients or subspecialty settings, our data are more representative of the general population since it comprises a cohort recruited from the outpatient/primary care setting. However, the UAE sub-analysis was limited by the design of the primary ACE study [14]. The cross-sectional design and obligatory reliance on one-time measurements of risk factors in addition to the lack of data on other variables that may have an effect on CV risk, such as social class and health insurance status, restricted the outcomes of the sub-analysis. Therefore, this analysis should provide the foundation for larger prospective studies, with a longitudinal and more comprehensive design to overcome these limitations. Moreover, selection bias may have occurred since this cohort of patients had access to primary care; therefore, may be representative of a wealthier UAE cohort, compared with the general more representative expatriate population.

Conclusions

Young male and female adults attending general practice outpatient clinics across urban and rural communities in the UAE appear to have a high incidence of CV risk factors. This study adds to pre-existing literature of CV epidemiology in developing countries by providing new insights into the risk associated with modifiable CV risk factors in the UAE. Our findings support the view that multiple CV risk factors are clustering earlier than traditionally understood for atherosclerotic risk, thus conditioning future preventive strategy. Put simply, earlier screening initiatives may be a crucial factor in the reduction of CV burden. Indeed, the concept of targeted screening of CV risk by general practitioners is greatly supported by the findings of this study, since it demonstrates a good opportunity for early detection as well as management that includes lifestyle interventions. Extending the concept of a healthy lifestyle is essential, and should be undertaken as a serious commitment by governments, policymakers, healthcare professionals and all other stakeholders in the UAE, in order to ensure CVD prevention. The adoption of such measures should aid a decrease in the rates of stroke and myocardial infarction, both of which have become so prevalent in developing nations.

Declarations of Interest

Dr. Ghazi Radaideh has acted as a consultant to Pfizer, Bayer, Amgen, Sanofi, MSD, AstraZeneca, Takeda and Novartis. Dr Nikolaos Tzemos has acted as a consultant to Pfizer, Sanofi and Amgen. Yasser Eldershaby, Jean Joury and Paula Abreu are employees of Pfizer.

Acknowledgments

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References


Early or Delayed Surgery for Infective Endocarditis Complicated by Cerebral Embolism: A Meta-Analysis

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Introduction
Cerebral embolism complicates 15-30% of infective endocarditis, and is an indication for surgery alongside severe valvular regurgitation, heart failure and uncontrolled infection[1]. Early surgery is effective and advocated in infective endocarditis with large vegetations for primary prevention of embolic events in one randomised trial and international guidelines [1,2], but the optimal timing of surgery remains controversial in those with cerebral embolism, due to the sparse literature and absence of randomised studies. In this meta-analysis, outcomes of early or deferred infective endocarditis surgery with cerebral embolism was pooled and compared.

Methods
PubMed, MEDLINE, Embase, Cochrane and Scopus databases from 1 January 1980 to 30 June 2016 were searched for original studies. Two authors evaluated these studies for inclusion independently, then extracted and pooled data using random-effects models.

Results
Amongst 2,423 papers obtained from the search, 23 full-texts were reviewed, and 6 studies totalling 701 patients were included for analyses. Rates and pooled odds ratio (95% confidence interval) for operative mortality of early or late surgery set at 7 days were 13.5% vs 10.8%, 1.40 (0.61-3.02); 14 days were 20.7% vs 13.0%, 1.95 (0.95-4.01). Pooled odds ratio of early surgery for long-term mortality was 2.95 (0.35-25.0); and for neurological events, embolic event was 1.22 (0.33-4.56) and intracranial bleeding 1.55 (0.16-15.32).

Conclusions
Although early surgery was not associated with statistically higher rates of mortality or neurological events it does need to be cautiously performed. Data is limited and larger and randomised studies would help to determine the optimal timing.

Keywords:
endocarditis, stroke, valve surgery, embolism

Citation:
Characteristics and outcomes from included studies were recorded using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). Pooled odds ratios of outcomes by timing of surgery was calculated using the Review Manager 5.3 (Cochrane Collaboration, London, UK) program.

Results
The search yielded 2,423 papers, and after initial screening and exclusions, 23 full-texts were reviewed, with the final 6 studies involving 701 patients were included for analyses. Reasons of exclusions after initial screening include not reporting outcomes of both early or late surgery, and deferred group including both patients with delayed surgery or purely medical management, and having only intracranial bleed patients and case reports or reviews. Early surgery was defined as <7 days from diagnosis in 2 studies and <14 days in 4 studies. Table 1 lists the characteristics of the 6 included studies.

In terms of neurological events, rates and pooled odds ratios of ischaemic stroke or transient ischaemic attack for early versus late surgery were 3.5% vs 2.0%, 1.22 (0.33-4.56) in 3 studies. For intracranial haemorrhage, these were 5.0% vs 2.2%, 1.55 (0.33-4.56) in 3 studies. Long-term mortality was 2.95 (0.35-25.0), reported in 2 studies, both using 14 days as cutpoint.

Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study period</th>
<th>Country</th>
<th>Centre</th>
<th>N</th>
<th>Early surgery (days)</th>
<th>Age (years)</th>
<th>Male</th>
<th>Prosthetic valve</th>
<th>Operative mortality</th>
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<tr>
<td>Basic[3]</td>
<td>2013</td>
<td>June 2000-December 2006</td>
<td>28</td>
<td>64</td>
<td>58</td>
<td>&lt;7</td>
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<td>69.0% (40)</td>
<td>22.4% (13)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>140</td>
<td>57</td>
<td>67.9% (95)</td>
<td>22.9% (32)</td>
<td>12.1% (17)</td>
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<td>Funakoshi[4]</td>
<td>2010</td>
<td>1990-2009</td>
<td>Japan</td>
<td>1</td>
<td>34</td>
<td>&lt;14</td>
<td>5.8% (2)</td>
<td></td>
<td>7.4% (2)</td>
<td></td>
</tr>
<tr>
<td>Garcia[5]</td>
<td>2013</td>
<td>1984-2009</td>
<td>Spain</td>
<td>7</td>
<td>43</td>
<td>&lt;14</td>
<td>46.5% (20)</td>
<td></td>
<td>38.5% (10)</td>
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<tr>
<td>Kim[8]</td>
<td>2011</td>
<td>1992-2007</td>
<td>Korea</td>
<td>1</td>
<td>34</td>
<td>&lt;14</td>
<td>43.5</td>
<td>67.6% (23)</td>
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<td>22</td>
<td>49.0</td>
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<td>27.3% (6)</td>
<td>0.0% (0)</td>
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<tr>
<td>Morita[7]</td>
<td>2015</td>
<td>July 2010-March 2013</td>
<td>Japan</td>
<td>82</td>
<td>105</td>
<td>&lt;7</td>
<td>57</td>
<td>69.5% (73)</td>
<td>1.0% (1)</td>
<td>8.6% (9)</td>
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<td></td>
<td></td>
<td>148</td>
<td>62.5</td>
<td>66.2% (98)</td>
<td>1.4% (2)</td>
<td>9.5% (14)</td>
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<tr>
<td>Yoshioka[8]</td>
<td>2012</td>
<td>2005-2010</td>
<td>Japan</td>
<td>1</td>
<td>34</td>
<td>&lt;14</td>
<td>64.2</td>
<td>61.8% (21)</td>
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<td></td>
<td>30</td>
<td>58.8</td>
<td>66.7% (20)</td>
<td>6.7% (2)</td>
<td>10.0% (3)</td>
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</table>

Our meta-analysis found no statistically significant differences for the main outcomes evaluated for early versus late surgery. In the current era when urgent early surgery is recommended including by the guidelines [1,2], our finding is reassuring that early surgery is safe. There still needs to be caution because numerically higher pooled adverse event rates (P>0.05), when surgery is performed very soon after cerebral embolism particular those with significant symptoms, at theoretical risk of neurological deterioration.

Beyond timing of surgery, there are a number of other approaches to try and reduce neurological complications in endocarditis patients[1]. Early diagnosis and initiation of antibiotic therapy is critical. Urgent surgery should be considered for those with high risk such as large vegetations for primary prevention of cerebral embolism [1,2]. Multidisciplinary heart team discussion and clinical judgement remains cornerstone to the management also.

This study has several limitations to highlight. There is no randomised data with all the studies being observational, and therefore significant differences in baseline characteristics exist and would affect the pooled results which were unadjusted. The numbers of patients were low for all studies, giving only a modest pooled sample power and inability to look at subgroups. The studies had wide heterogeneity from definitions of early and late surgery to being 7 or 14 days (and none used the 48 hours cutpoint of the randomised trial for primary embolic prevention as cutpoint), of outcomes like neurological events, of follow-up duration amongst others.

In conclusion, there were no significant differences in mortality and neurological outcomes between early and late surgery;
which while confirms the safety of early surgery, there should still be a caution undertaking. Further studies especially larger and/or randomised trials are required to address this important clinical problem.

**Conflicts of Interests**
The authors declare no conflicts of interest.

**Acknowledgements**
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [9].

**References**

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**Figure 1.** Pooled odds ratios of operative mortality for early versus delayed surgery for studies defining (a) 7 days and (b) 14 days as cutpoint.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early surgery</th>
<th>Late surgery</th>
<th>Odds Ratio</th>
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</thead>
<tbody>
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<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Kim 2011</td>
<td>4 34</td>
<td>2 22</td>
<td>54.3%</td>
</tr>
<tr>
<td>Morta 2015</td>
<td>0 105</td>
<td>1 148</td>
<td>10.9%</td>
</tr>
<tr>
<td>Yoshioka 2012</td>
<td>2 34</td>
<td>1 30</td>
<td>28.9%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>6 173</td>
<td>0 200</td>
<td>1.22 [0.33, 4.56]</td>
</tr>
</tbody>
</table>

**Figure 2.** Pooled odds ratios of neurological events for early versus delayed surgery for (a) ischaemic stroke or transient ischaemic attack, and (b) intracranial bleed.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Surgery &lt;7 days</th>
<th>Surgery ≥7 days</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events Total</td>
<td>Events Total</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Barsic 2013</td>
<td>13 58</td>
<td>17 140</td>
<td>52.4%</td>
</tr>
<tr>
<td>Morta 2015</td>
<td>9 105</td>
<td>14 148</td>
<td>47.6%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>22 163</td>
<td>31 288</td>
<td>1.40 [0.61, 3.20]</td>
</tr>
</tbody>
</table>

**References**
Preferential Vasodilator Effects of Levosimendan in Resistance Pulmonary Arteries in a Rodent Pulmonary Embolism Model

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Highlights

Background
We compared the vasoactive effects of levosimendan on isolated conduit (CPA) and resistance (RPA) pulmonary arteries versus mesenteric arteries and we assessed the PA vascular function and the PA vasoactive effects of levosimendan in a rodent PE model.

Methods
One group of male Wistar rats (200-300 g) was killed by decapitation to obtain pulmonary and mesenteric rings. Another group was assigned to a massive PE or saline solution infusion. After euthanasia mesenteric arteries and CPA (i.d. 1-2 mm) and RPA (≤ 0.5 mm) were dissected and cut into 2-3 mm wide rings recording contractile tension. We obtained the concentration-response curves of cumulative doses of levosimendan on pre-contracted arterial rings from decapitated and sham/embolized animals. A set of RPA rings was exposed to acute hypoxia. The effect of PE on the pulmonary vasoactive function was assessed by dose-response curves of acetylcholine (ACh) and endothelin-1 (ET-1) of PA rings from sham/embolized animals.

Results
Levosimendan relaxant potency of RPA was similar to mesenteric arteries and higher than CPA, while mesenteric rings showed the maximal relaxant effect, followed by RPA and CPA, respectively. PE did not affect the vasoactive response of PA rings either to ACh or to ET-1, and the relaxant effects of CPA and RPA to levosimendan were also preserved. Acute hypoxia reduced (P<0.05) but did not avoid the RPA relaxant effect of levosimendan.

Conclusions
Levosimendan is a more specific vasodilator of RPA with a similar relaxant potency as mesenteric arteries, which is preserved after PE but significantly reduced during hypoxia.

Keywords: levosimendan; pulmonary embolism; pulmonary arteries; vasodilation; hypoxia

Citation: Bedo C, Grignola JC. Preferential Vasodilator Effects of Levosimendan in Resistance Pulmonary Arteries in a Rodent Pulmonary Embolism Model. International Cardiovascular Forum Journal. 2017; 11: 16-22. DOI: 10.17987/icfj.v11i0.433

Introduction
The pulmonary vasculature consists of large, elastic, extra-parenchymal conduit pulmonary arteries (CPA, order 1 to 2) that arise from the sixth aortic arch and small, muscular resistance intrapulmonary arteries (RPA, ≥ 4th order), that originate from the mesenchymal lung bud by capillary plexus expansion [1]. This subdivision is associated with different response to several stimuli. While CPA dilates or fails to constrict to hypoxia, RPA is responsible for hypoxic pulmonary vasoconstriction, control the regional distribution of blood flow and largely determine pulmonary vascular resistance. This functional difference mainly depends on the distribution of electrophysiologically distinct myocytes in CPAs and RPAs arteries [1, 2].

Levosimendan is a positive inotropic agent (by increasing the sensitivity of troponin C to calcium) with vasodilating properties (by lowering of intracellular free Ca++, opening of different potassium channels and the inhibition of phosphodiesterase type III), also termed inodilator [3, 4]. There are several animals studies in different acute pulmonary hypertension (PH) models secondary to thromboxane A2 infusion [5], endotoxemia [6], acute pulmonary embolism (PE) [7, 8], and hypoxia [9] and some clinical studies that demonstrated the vasodilator effect of levosimendan on the pulmonary circulation, restoring right ventricular-arterial coupling as it increased right ventricular contractility concomitantly [10, 11]. Acute PE-induced PH results from two main mechanisms:
the mechanical obstruction of pulmonary vessels (passive mechanism) and the arterial vasoconstriction secondary to pulmonary neurohumoral activation (e.g. thromboxane A2, serotonin), neurogenic reflex, increased oxidative stress and hypoxemia (active mechanism) [12]. There is experimental evidence that secondary pulmonary vasoconstriction is the major contributor to the potentially fatal increase in pulmonary dynamic afterload in PE. Therefore the treatment should not only focus on removing the obstructing blood clot but also on reducing this vasoconstrictor response [13]. We have previously reported a significant decrease of the dynamic afterload despite the persistence of mechanical obstruction by clots during levosimendan infusion in a PE-induced PH ovine model [14]. The concomitant decrease of total pulmonary vascular resistance with the preservation of the pulmonary arterial characteristic impedance suggests a predominant vasodilator effect on distal arterial vessels [14].

We hypothesized that levosimendan would have a different vasodilator potency between CPA and RPA, with a predominant distal vasodilatation effect. The aims of the present work were: to compare the vasoactive effects of levosimendan on isolated CPA and RPA versus mesenteric arteries of rats; to assess the pulmonary arterial vasoconstriction and vasodilatation response and the pulmonary arteries vasoactive effects of levosimendan in a rodent PE model and to assess the effects of hypoxia on the RPA relaxant responses to levosimendan.

**Methods**

This study was approved by the Institutional Animal Care and Use Committee (CHEA, Facultad de Medicina, Universidad de la República. N° 070153-000611-13, http://www.chea.udelar.edu.uy/). We rigidly performed all institutional protocols to handle animals under experimentation according to Guide for Care and Use of Laboratory Animals (NIH Publication N° 85–23, revised 1996), prepared by the National Academy of Sciences’ Institute for Laboratory Animal Research.

Male Wistar rats (200-300 g) were used in this study. Rats fasted overnight with free access to water. One group of animals was killed by decapitation, and the lungs and mesenteric beds were rapidly immersed in Krebs solution to obtain pulmonary and mesenteric rings. Another group of animals was anesthetized with pentobarbital (40 mg/kg, i.p.) and fentanyl (50 mg/kg, i.p.). Both were maintained with pentobarbital (10 mg/kg/h), and fentanyl (1-2 mg/kg/h) administered intravenously throughout an infusion pump (Syringe pump, GRASEBY 3400, Smiths-Medical, Ohio, USA). Normothermia was kept using a heating pad. The animals were tracheotomized and mechanically ventilated (ServoVentilator model 300, SIEMENS AG, Munich, Germany). The tidal volume and the fraction of inspired oxygen were set in 8 mL/Kg and 60%, respectively. Respiratory rate was adjusted to maintain a baseline physiologic arterial oxygen and carbon dioxide tension. Blood samples were taken regularly (every 30 min) to analyze arterial oxygen and carbon dioxide tension (Blood gas analyzer, Radiometer, ABL520, Denmark).

We placed two 22G fluid-filled catheters into both external jugular veins for blood withdrawal and drug infusion, respectively. Another fluid-filled catheter was positioned into the common carotid artery to monitor systemic arterial pressure. We performed a sternotomy and placed a 22G fluid-filled catheter into the PA through a minimal stab in the right ventricular outflow. The distal tip of the catheter was positioned in the main PA before its bifurcation. All pressure transducers (P23Db Gould Statham) were zeroed to atmospheric pressure at the mid-axillary level. Once we completed the instrumentation, the animals allowed stabilizing for 15 minutes. Baseline hemodynamic data were obtained. Animals were divided into two groups:

- a) Sham group (saline solution, n = 8): infusion of 1 ml of saline infusion. Animals were euthanized once reached 60 minutes.
- b) Embolized group (PE, n = 8): one milliliter of blood was collected and allowed to clot at room temperature for five minutes. Clots were mechanically disaggregated achieving a diameter ~ 0.5 mm, and venous embolization was carried out progressively through the right jugular vein every 15 minutes over 60 minutes until systemic hypotension was reached, ensuring to produce a massive PE. Once hypotension developed, the animal was euthanized with an overdose of pentobarbital.

After euthanasia, heart and lungs were removed, and lungs were rapidly placed in Krebs solution.

**Tissue preparation and contractile tension recording**

Mesenteric arteries (i.d. 1-2 mm), CPA (i.d. 1-2 mm, second order) and RPA (i.d. ≤ 0.5 mm, fifth order) were carefully dissected from surrounding tissue and cut into 2-3 mm wide rings for studies on intact preparations [15]. During manipulation of the arteries, care was taken not to touch their intimal surface to preserve the endothelium layer.

The rings were suspended between two wire hooks in 5 ml organ baths for contractile tension recording with an isometric transducer (Myograph model 610M, Danish Myo Technology, Aarhus-Denmark for mesenteric arteries and RPA rings and KG-20 force transducers, World Precision Instruments, Sarasota-USA for CPA rings) [16]. The organ baths contained Krebs solution maintained at 37°C and continuously bubbled with a 95% O2-5% CO2 mixture as previously described. Tissues were stretched to a predetermined optimal resting tension of 0.5 g for pulmonary rings and 2.0 g for mesenteric rings [15]. The presence of functional endothelium was tested by the assessment of the relaxant response to ACh (10-6 M) in rings pre-contracted with 5HT (10-5 M). The ability of ACh to induce relaxation was taken as an indicator of the presence of functional endothelium. We discarded those rings with a relaxant response ≤ 20% of maximal tension. Total time of the experiments never exceeded 120 minutes. Based on previous experiments there was no spontaneous relaxation in pre-contracted rings during this period.

**Experimental protocol**

Six to eight mesenteric and PA rings were obtained from each animal. The rings were first stimulated by raising the K+ concentration of the buffer to 80 mM and then washing three times, allowing to recover the resting tension.

Comparative analysis of the effects of levosimendan on mesenteric arteries, RPA and CPA rings: after reaching a stable tension, the rings were contracted with the mixture of 3´10-9 M ET-1, 3´10-8 M thromboxane A2 mimetic U46619 and 3´10-6 M 5HT.
This mixture allowed us to avoid possible vasoactive response differences among arteries depending on the vasoconstrictor used [15], and mimics several forms of PH including PE, achieving a high vascular tone that presumably reflects what happens in massive PE [17]. Once equilibration (about 25 min), a concentration-response curve to levosimendan (10-9 M to 3´10-5 M) was carried out by cumulative addition of drug after a steady-state relaxant response was reached after each increment. The range of levosimendan doses and the interval between doses (7 min) are based on previous experiments.

Assessment of the PA vascular vasoconstriction and vasodilatation properties: the analysis of the endothelium function was performed through concentration-response curves of cumulative doses of acetylcholine (ACh, 10-9 to 10-5 M) in rings previously contracted by serotonin (5HT, 10-5 M). The vascular smooth muscle function was assessed by concentration-response curves of cumulative doses of endothelin-1 (ET-1, 10-11 to 10-8 M).

Assessment of the effects of hypoxia on levosimendan RPA relaxant responses: a set of RPA rings extracted from euthanized rats by decapitation was exposed to acute hypoxia. Hypoxia was induced by aerating the organ bath with 95% N2-5% CO2 (PO2 24 ± 1 mm Hg) [18] and then we obtained the dose-response curve to levosimendan.

**Drugs and reagents**
Acetylcholine chloride, serotonin hydrochloride, endothelin-1 and thromboxane A2 mimetic U46619 and Dimethyl Sulphoxide (DMSO) were obtained from Sigma-Aldrich, SPAIN. Levosimendan was obtained from Sigma Chemical Co, USA. They were dissolved in distilled deionized water except for levosimendan which was dissolved in DMSO. The final concentration of DMSO in the organ bath was less than 0.1 % and had no effect on the vessel reactivity. The concentration of drugs was expressed as a final molar concentration in the tissue chamber.

**Data analysis**
The maximal vasoactive effect (Emax, expressed as a percentage of the initial contractile response), which is an index of the efficacy of the vasoactive drug, and the drug concentration exhibiting 50% of the Emax (EC50, expressed as negative logarithmic concentration, -log EC50: pD2), which is an index of the potency of the vasoactive drug, were calculated from the fitted concentration-response curves for each ring. Data were averaged for each animal in all experiments. Relaxation responses to levosimendan are expressed as percentages of tension developed with KCl 80 mM.

**Statistical analysis**
Results are expressed as mean ± SEM, with n equal to the number of animals. Individual cumulative concentration-response curves were fitted assuming the sigmoid dose-response curves (Levenberg-Marquardt algorithm) by using Origin Pro Software (version 9.1, San Diego, CA, USA). For multiple comparisons (e.g. the vasoactive effects of levosimendan on the mesenteric arteries, CPA and RPA), statistical analysis was performed using a one-way ANOVA followed by a Bonferroni post hoc test, otherwise (e.g. rings from sham versus PE rats, CPA versus RPA rings and normoxic versus hypoxic RPA rings) we used a two-tailed unpaired Student’s t-test. Differences were considered statistically significant when P < 0.05.

**Results**

**Vasodilator effects of levosimendan**
Levosimendan induced a concentration-dependent relaxation, but was unable to fully relax 3´10-9 M ET-1, 3´10-8 M thromboxane A2 mimetic U46619 and 3´10-6 M 5HT-induced contractions in mesenteric as pulmonary rings. The highest concentration tested (3´10-4) produced a maximal relaxation of 85 ± 6% of the mesenteric arteries.

RPA and mesenteric rings showed the maximal relaxant potency, while the highest maximal relaxant effect was obtained in mesenteric arteries followed by RPA and CPA, respectively (P < 0.05) (Table 1, Figure 1).

**Effects of pulmonary embolism on pulmonary artery vasodilatation and vasoconstriction response**
Table 2 shows systemic and pulmonary arterial pressures of sham and embolized animals. Neither the endothelium function (Sham: pD2 6.9 ± 0.07 and Emax 20 ± 7% vs. PE: pD2 7.1 ± 0.09 and Emax 21 ± 17%) nor the vascular smooth muscle function (Sham: pD2 8.4 ± 0.2 and Emax 94 ± 11% vs. PE: pD2 8.6 ± 0.2 and Emax 90 ± 17%) of the PA rings from embolized rats was changed in comparison of PA rings from sham animals (Figure 2A, B).

**Effects of levosimendan on conduit and resistance PAs from embolized rats**
The relaxant effect of levosimendan was not significantly affected by PE. Like in the sham group, rings from embolized rats showed a significant higher levosimendan potency in RPA rings in comparison to CPA rings (Table 3, Figure 3).

**Effects of hypoxia on the RPA relaxant responses to levosimendan**
Figure 4 shows the effects of hypoxia on the RPA relaxant responses to levosimendan. Exposure to hypoxia induced a significant decrease of relaxant potency of levosimendan in RPA rings with similar efficacy (Emax) (normoxia: pD2 7.11 ± 0.06 and Emax 65 ± 5% vs. hypoxia: pD2 6.03 ± 0.09 and Emax 65 ± 7%).

**Discussion**
In the present study, we compared the effect of levosimendan, a new class of inodilator drug, in isolated mesenteric and conduit and resistance pulmonary arteries of adult rats. We evaluated the effect of PE on the vascular smooth muscle vasoconstriction, and endothelial vasodilatation response through the concentration-response curves to accumulating doses of ET-1 and ACh, respectively in PA rings from pulmonary embolized versus sham rats. Finally, we analyzed the relaxant effects of levosimendan on the proximal conduit PA versus distal resistance PA rings from sham and embolized rats, assessing the effect of hypoxia to the RPA relaxant effect of levosimendan, concomitantly. Our results indicate that: 1) Levosimendan produced different relaxant effects depending on the artery. Relaxant potency was higher in RPA and mesenteric arteries than CPA, while mesenteric rings showed the maximal relaxant effect (efficacy), followed by RPA and CPA, respectively. 2) PE did not affect the in vitro response of PA rings either to ACh (endothelial function) or ET-1 (vascular function).
smooth muscle function), and the relaxant effects of CPA and RPA to levosimendan were also preserved. 3) Hypoxia reduced but did not avoid the RPA relaxant effect of levosimendan.

The higher vasodilatation potency of levosimendan on RPA versus CPA is consistent with our previously results in an ovine model of blood clot PE-induced PH. Briefly, we have demonstrated that levosimendan reduced the dynamic afterload increase in PE-induced PH with a decrease in total pulmonary vascular resistance (input impedance) and relative preservation of main PA impedance (characteristic impedance), suggesting a predominant vasodilator effect over distal resistive pulmonary vessels [14].

The fact that PA rings without functional endothelium (≤ 20% of tension decrease during ACh exposition) showed similar dose-response curves of an accumulative addition of levosimendan, would make the levosimendan relaxant effects endothelium-independent, like in others vascular beds [19, 20]. Mesenteric rings relaxation to levosimendan showed similar dose-response parameters of other systemic vascular beds as the human internal mammary arteries (pD2 6.8 ± 0.1 and Emax 75 ± 5%) [20].

PE is associated with the release of vasoconstrictors and secondary pulmonary vasoconstriction, which add to the mechanical obstruction. This vasoconstriction is at least partially reversed by different vasodilator therapy that attenuates PE-induced PH [21]. De Witt et al. [5] showed that levosimendan induces vasodilation in the pulmonary vascular bed of the cat in thromboxane A2-induced PH. Furthermore, levosimendan has been shown to prevent endotoxin-induced PH [6]. Wiklund et al. [9] showed that levosimendan attenuated hypoxic pulmonary vasoconstriction in a porcine model, suggesting that the pulmonary vasodilatation effect of the drug is apparent when PH is present. To the best of our knowledge, this is the first study on the comparative effects of levosimendan in isolated CPA and RPA rings in a rodent PE model.

The predominant distal vasodilator effect (RPA) of levosimendan with mild vasodilatory effect on CPA in the vessels from the PE animals could preserve the ventricular-arterial coupling and the

Table 1. Parameters (pD2 and Emax) of the concentration-response curves of mesenteric arteries, conduit and resistance pulmonary arteries (PA) to levosimendan calculated from Figure 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conduit PA</th>
<th>Resistance PA</th>
<th>Mesenteric artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emax (%)</td>
<td>55 ± 5</td>
<td>70 ± 6*</td>
<td>85 ± 6**</td>
</tr>
<tr>
<td>pD2</td>
<td>5.71 ± 0.22</td>
<td>7.00 ± 0.21*</td>
<td>6.57 ± 0.13*</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

pD2 is the negative logarithm of concentration which relaxed 50% and Emax is the maximal relaxant effect achieved with the highest concentration of levosimendan tested. *P < 0.05 vs. Conduit PA; **P < 0.05 vs. Resistance PA.

Table 2. Hemodynamic data of sham and pulmonary embolized rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham (n = 8)</th>
<th>Pulmonary Embolism (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP, mm Hg</td>
<td>13 ± 2</td>
<td>26 ± 3*</td>
</tr>
<tr>
<td>mPAo, mm Hg</td>
<td>96 ± 12</td>
<td>43 ± 11*</td>
</tr>
</tbody>
</table>

Mean ± SEM. *P < 0.05 vs sham. mPAP: mean pulmonary arterial pressure; mPAo: mean aortic pressure.

Figure 1. Relaxant effects of cumulative doses of levosimendan on mesenteric arteries (triangles), conduit (squares) and resistance (circles) pulmonary arteries pre-contracted with a mixture of 3x10-9 M endothelin-1, 3x10-8 M thromboxane A2 mimetic U46619 and 3x10-6 M serotonin. Results are expressed as the mean ± SEM (n = 3 for mesenteric rings, and n = 8 for pulmonary arteries).

Figure 2. Effects of acetylcholine (endothelium function) (A) and endothelin-1 (vascular smooth muscle function) (B) on pulmonary arterial rings of sham (open circles) and pulmonary embolized (filled circles) rats. The acetylcholine concentration-response curves correspond to pre-contracted rings by 10-5 M serotonin (% of tension developed with KCl 80 mM). Results are expressed as the mean ± SEM (n = 8).
proximal-distal PA coupling during the treatment of PE-induced PH through avoiding the increase of proximal arterial stiffness [7, 22]. We have previously shown that proximal PA vasoconstriction induced by vascular smooth muscle activation improves both buffering and conduit function of the PA during acute PH mainly due to the increase in wall viscosity, preventing increased wall stiffness secondary to the recruitment of collagen fibers [23]. This different response to levosimendan could be linked to the differential distribution of electrophysiologically distinct smooth muscle cells in CPAs and RPAs arteries [1]. It is well known the role of smooth muscle contractile phenotypic diversity in the vascular system in determining the unique properties of selected regional circulations and its potential influence on drug targeting in disease [24].

It is noteworthy that neither endothelium nor vascular smooth muscle dysfunction was observed in PA rings from rats embolized since both, the increased oxidative stress and alterations in the availability of nitric oxide are implicated in the pathogenesis of PH associated with PE [25, 26]. The lack of vascular dysfunction observed would be attributable to at least two considerations. One explanation would be that vascular dysfunction is observed in vivo and once PA rings are isolated their response in vitro to the diverse stimulus was similar to vessels from sham animals. Another explanation would be related with the lower time spent to the PE-induced PH on other PE models (from 180 min to several hours) [27, 28]. Anyway, if the activation of the inflammatory response with the release of vasoactive mediators and increase of oxidative stress play some role in the pathogenesis of PH associated with PE [21, 29], levosimendan would also have the advantage of attenuating the PE-induced PH through mechanisms involving antioxidant effects [30, 31].

Lowering pulmonary arterial pressure while maintaining systemic vascular resistance and adequate cardiac output is crucial for several clinical scenarios like submassive and massive PE. Although levosimendan showed similar relaxant potency of both mesenteric and resistance pulmonary arteries which it could be disadvantageous in clinical settings, there are different strategies to ameliorate the appearance of hypotension as to not use the loading dose [14] and use in combination with other vasopressor agents [32].

Limitations

Some limitations of our study should be taken into consideration. We used the same concentrations of the mixture of vasoconstrictors
in pulmonary and mesenteric arteries, and therefore, the vasodilator response of levosimendan was not evaluated under equi-effective concentrations of endothelin-1, U46619, and serotonin for a given artery. The effect of levosimendan on the whole systemic arterial tree is the sum of the effects in all vascular beds and, thus, extrapolation of mesenteric arteries to the whole systemic circulation has to be done with caution. We have not measured any oxidative stress parameters like plasma nitrite/nitrate concentrations and plasma lipid peroxide concentrations to demonstrate the presence of an increase in oxidative stress after lung embolization in PE group. Although we employed a relatively short period to embolize the lungs, a significant increase in plasma nitrite/nitrate concentrations were observed after 60 min of lung embolization in a canine PE model [29]. We were careful to analyze several PA rings from different lobes of both lungs of each animal to obtain a representative sample beyond the final distribution of blood clots.

Conclusions
The results of the present study suggest that levosimendan is a more specific vasodilator of resistance PA with a similar relaxant potency as mesenteric arteries, which is preserved after PE but significantly reduced during hypoxia.

Thus, levosimendan could reduce pulmonary dynamic afterload with lesser effects on conduit PA and the hypoxic vasoconstriction, improving the right ventricular-arterial coupling and proximal-distal vascular coupling, and preserve an adequate ventilation/perfusion ratio, respectively, during PH treatment.

Further studies are required to demonstrate the mechanisms of action of levosimendan in conduit and resistance pulmonary arteries.

Declarations of interest
The authors declare no conflicts of interest.

Acknowledgments
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References


Long-Term Non-Invasive ECG-Based Risk Stratification of Sudden Cardiac Death: Extended 5-Year Results

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Introduction
Sudden cardiac death (SCD) remains the leading cause of mortality (up to 60%) in patients with coronary heart disease (CHD) [1,2] and especially with history of myocardial infarction (MI). SCD is reported in approximately 12% of this population during the first year after MI. [1, 2] The majority of SCD cases are due to ventricular arrhythmias - ventricular tachycardia (VT) and ventricular fibrillation (VF).

Left ventricular ejection fraction (LVEF) is still the most important instrumental factor determining the nature of the primary SCD prevention. However, current SCD risk assessment criteria based on the LVEF only are being criticized. The risk of SCD in patients with CHD and the single criterion “LVEF < 30%” is 2.5% annually. [3] In this situation, 80-90% of ICD implantations for primary prevention of SCD are futile during the device lifetime. However, 40% of SCD cases are reported in patients with cardiac diseases and LVEF > 40%. [4, 5] The use of ICDs for primary prevention in these patients is not covered by the current guidelines. Therefore, cost-effective identification of the risk of life-threatening arrhythmias and predictors of SCD is extremely important to administer appropriate preventive treatment. [6] Several non-invasive ECG-based methods have been proposed to determine predictors of life-threatening arrhythmias and SCD,

Highlights
Background
To evaluate predictive value of heart rate turbulence (HRT), deceleration capacity (DC) and microvolt T-wave alternans (mTWA) for risk stratification for sudden cardiac death (SCD) in patients after myocardial infarction (MI) during 60 months of follow-up.

Methods
We studied 111 patients after MI occurred > 60 days (27 [9; 84] months) before enrollment (84 men; mean age 64.1±10.5 years). All subjects had 24-hour ambulatory ECG monitoring with HRT, DC and mTWA evaluation. Follow-up period was 60 months; primary endpoint was SCD, secondary endpoint included all non-sudden cardiovascular deaths.

Results
During follow-up, we registered 19 cases of SCD and 11 cases of non-sudden cardiovascular deaths (including 7 fatal MI and 3 fatal strokes). DC had high negative predictive value (97.4% for all-cause mortality and 93.7% for SCD). DC values below 4.15 for all-cause mortality and 2.0 for SCD significantly increased risk of all-cause mortality (OR 8.5, 95% CI 2.9 to 24.6, <0.001) and SCD (OR 9.6, 95% CI 3.2 to 28.5, <0.001). Combined risk assessment at 12 months revealed that the most significant combination was HRT2 and mTWA100 > 53 mcV, which increased risk both of all-cause mortality (30.7-fold) and SCD (63.3-fold); however, at 60 months this predictive value for SCD decreased (OR = 20.8 (95% CI 2.8 to 114.0), p <0.001).

Conclusions
Evaluation of HRT, DC and mTWA during 24-hour ECG monitoring may define the high risk of cardiovascular mortality and SCD in post-MI patients especially during the first 12 months after the baseline examination.

Keywords: Sudden cardiac death; Risk stratification; T-wave alternans; Heart rate turbulence; Deceleration capacity

Citation:
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including heart rate turbulence (HRT) and microvolt T-wave alternans (mTWA). [1, 7, 8-10] Microvolt TWA has been described as a useful predictor of cardiac events in patients with various ischemic and nonischemic pathologies with or without low ejection fraction including acute coronary syndrome. [8, 9] However, there is lack of evidence concerning the use of these methods for SCD risk stratification in the post-MI patients, and they have not been included in the ESC 2015 Guidelines for management of patients with ventricular arrhythmias and the prevention of SCD, [11] despite the inclusion into ACC/AHA/ESC 2006 Guidelines for patients with severe LV dysfunction (classes of recommendations: mTWA – IIa, HRT – IIb). In recent years, deceleration capacity (DC) – parameter reflecting the ability of sinus rhythm to slow down - has also being investigated. Bauer et al. evaluated two-year mortality after MI and showed that predictive value of DC was higher than that of the LVEF and HRV. [7]

We have previously shown significantly high predictive value of HRT and mTWA during short-term follow-up (12 months). [12] Due to the relatively short follow-up (1-3 years) in most studies, we decided to investigate the long-term value of aforementioned predictors as well as DC in post-MI patients, both independently and in combination with other SCD risk factors (depressed LVEF, HRV, QRS duration, the number of premature ventricular contractions (PVCs) and the presence of VT).

**Methods**

**Design**

Single-center, prospective observational cohort study with retrospective DC evaluation.

**Patient groups**

Between 2008 to 2010, 111 patients (age 64.1±10.5 years; 84 males and 27 females) with history of MI occurred 2 months to 36 years (median 27 [9; 84] months) previously were enrolled into the study. Inclusion criteria were: MI more than 60 days prior to study entry, aged 18 years and over. Exclusion criteria were: permanent atrial flutter or atrial fibrillation, implanted pacemaker, II-III degree atrioventricular block, concomitant malignancies, hyperthyroidism, severe anemia (hemoglobin less than 90 g/l); co-administration of ivabradin or glycosides. Nineteen (17.1%) patients had percutaneous transluminal coronary angioplasty in the acute MI phase; and 45 (40.5%) had thrombolysis. Thirteen patients with Q-MI had not received revascularization treatment due to late admittance. Baseline characteristics are presented in Table 1. Detailed characteristics of the study population have been published previously. [12] Comparable control group included 60 individuals (44 males and 16 females, age 62.5±11.6 years) with no cardiovascular comorbidity.

The study complied with the Declaration of Helsinki. Study protocol was approved by the local ethics committee. All subjects signed informed consent prior to any study procedures.

**Methods**

All subjects had baseline examination including medical history, 12-channel ECG, echocardiography (EchoCG) with LVEF measurement, and 24-hour ambulatory ECG monitoring with HRV (SDNN and pNN50), HRT and mTWA evaluation, recording of PVCs number and episodes of sustained/unsustained VT.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Male/female</td>
<td>84 (75.7%)/ 27 (24.3%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.1±10.5</td>
</tr>
<tr>
<td>Months after MI</td>
<td>27 [9; 84]</td>
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**Type of MI**

<table>
<thead>
<tr>
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</tr>
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<tr>
<td>Q-MI</td>
<td>77 (69.4%)</td>
</tr>
<tr>
<td>Non-Q-MI</td>
<td>34 (30.6%)</td>
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**Hypertension, stage (ESH/ESC)**

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<td>2</td>
<td>20 (18.0%)</td>
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<td>69 (62.1%)</td>
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**Functional class of angina, Canadian classification**

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<tr>
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<td>54 (48.6%)</td>
</tr>
<tr>
<td>III</td>
<td>25 (22.5%)</td>
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<td>IV</td>
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**Diabetes, type**

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<tbody>
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<td>1 (0.9%)</td>
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<tr>
<td>2</td>
<td>2 (17.1%)</td>
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**Functional class of heart failure, NYHA**

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<th>Functional class</th>
<th>Number of patients (%)</th>
</tr>
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<td>23 (20.7%)</td>
</tr>
<tr>
<td>I</td>
<td>23 (20.7%)</td>
</tr>
<tr>
<td>II</td>
<td>31 (27.9%)</td>
</tr>
<tr>
<td>III</td>
<td>28 (25.2%)</td>
</tr>
<tr>
<td>IV</td>
<td>6 (5.4%)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>46.6±12.2</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>27 (24.3%)</td>
</tr>
<tr>
<td>LVEF ≥40%</td>
<td>84 (75.7%)</td>
</tr>
</tbody>
</table>

**Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>75 (67.6%)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>86 (77.4%)*</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>25 (22.5%)</td>
</tr>
<tr>
<td>Statins</td>
<td>105 (94.5%)</td>
</tr>
<tr>
<td>ASA</td>
<td>111 (100%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>28 (25.2%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>19 (17.1%)</td>
</tr>
</tbody>
</table>

Note: MI, myocardial infarction; LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid. *25 patients (22.5%) had contraindications to beta-blockers, such as asthma, chronic obstructive lung disease (n=16), marked bradycardia (n=7), transient AV-block 2 degree (n=2).
MTWA

MTWA was measured by modified moving average method [13] in two Holter leads with GE Healthcare (GE Healthcare, Fairfield, Connecticut, U.S.) GETEMED CardioDay Holter system, ie, recorder CardioMem CM3000 and software CardioDay® v. 2.2.0.3. The detailed technique has been described previously. [13] Absolute maximum value in 24 hours (mTWAmax), mTWA values at heart rate (HR) 100 bpm and at 05.00 AM were assessed in order to standardize measurement conditions.

HRT

Regarding HRT, turbulence onset (TO) (magnitude of sinus rhythm acceleration after PVC) and turbulence slope (TS) (intensity of subsequent sinus rhythm deceleration) were evaluated. Abnormal HRT values were considered as TO≥0%, and TS≤2.5 ms/RR.

DC

DC was calculated by appropriate software via the technique based on the determination of the difference between adjacent RR intervals described by Bauer et al. [7] According to the authors, DC reflects the influence of the parasympathetic autonomic nervous system on the heart. DC > 4.5 ms corresponds to the low SCD risk; DC 2.6 to 4.5 ms corresponds to the average risk; DC ≤ 2.5 ms reflects high risk. [7]

Duration of follow-up was 60 months. Primary endpoint was SCD; secondary endpoint included all non-sudden cardiovascular deaths; tertiary endpoints included non-fatal cardiovascular events and VTs. SCD was defined as death from an unexpected circulatory arrest usually due to cardiac arrhythmia occurring within an hour of the onset of symptoms. The cause of death outside the hospital was established based on the interview with relatives of the patients (personal or via telephone); all efforts were made to collect relevant medical documents.

Statistical analysis.

Data are presented as means ± standard deviations (SD) or as medians [25th; 75th percentiles]. Significance was assessed by two-sided t-test, Wilcoxon test or Mann-Whitney test with α=0.05. To assess sensitivity and specificity of absolute HRT, DC and mTWA values, and to define threshold values for the high risk group, ROC-analysis was performed. Significance of HRT, DC and mTWA values as independent risk factors was determined by univariate and multivariate Cox-regression analysis including clinical and ECG-based parameters with established risk predictive values. The relative risk was determined by Cox regression analysis. Due to the method of selection, risk of predefined outcomes was estimated using odds ratios adjusted for mTWA values. Survival was determined by Kaplan-Meier analysis. All calculations were performed with SPSS v21.0 (SPSS, Chicago, IL,USA).

Results

During the 60 months of follow-up, 19 cases of SCD (17.1%) and 11 cases of deaths from other causes (including 7 (6.3%) repeated fatal MIs and 3 (2.7%) fatal strokes) were recorded in post-MI patients. Among all-causes deaths, one case was not related to cardiovascular causes (death due to multiple organ failure after gastrectomy related to the ulcer bleeding; the cause of death was confirmed by autopsy). Four patients died in the hospital; autopsy revealed no structural changes that could be fatal. In other SCD cases, no autopsy was performed; these were deaths occurring within 60 minutes of the onset of symptoms, as well as cases of death during sleep, i.e. events that met SCD criteria. Information about these deaths was obtained from the relatives of patients; all SCD cases were qualified by the pathologists and appropriate documents were collected. All fatal MIs and fatal strokes occurred in hospital and were confirmed by medical records. In addition, tertiary endpoints were recorded in several patients including nonfatal MIs and the new-onset VT (Table 2). Three patients received pacemakers (DDD mode) during follow-up due to onset of different cardiac blockades. All cases of implantation were performed within 3 months after the enrollment making impossible to assess the trends of mTWA, HRT and DC. However, clinical monitoring for these patients continued; two patients remained stable until the end of the follow-up. The third patient developed nonsustained VT 14 months after pacemaker implantation (confirmed by pacemaker’s records), which caused a loss of consciousness and fall. VT self-terminated within 30 seconds; further patient’s condition was stable. In the control group during the follow-up no deaths were recorded, and mTWA, DC and HRT showed no significant changes.

To evaluate the prognostic value of SCD predictors, all patients were divided into subgroups of survivors, all-causes deaths, and SCDs. HRT, mTWA, and DC values by subgroups shown in Table 3. The majority of deaths (11 of 19 in the SCD subgroup and 6 of 10 in the all-causes subgroup) occurred within the first 3 months after enrollment that did not allow us to assess the trends of SCD predictors. In 6 patients who completed at least one study visit before death, a progressive insignificant decrease in LVEF from 40.7 ± 17.0% to 36.8 ± 15.7% (p = 0.097), and no significant HRT, mTWA, or DC changes were observed. According to Cox regression analysis, factors that significantly influenced the risk of overall mortality included LVEF, DC, HRT, HRV (SDNN, pNN50), mTWA at 05.00 AM and the daily number of PVCs (Table 4).

Regarding SCD, the cut-off prognostic value of mTWA at 100 bpm was 52.5 µV (sensitivity 68.4%, specificity 60.0%) that was practically identical to the 12-months value (53.5 µV) (sensitivity 73.3%, specificity 64.6%), but the sensitivity and specificity...
decreased. [12] Analysis of the 60-months data revealed that mTWA at 100 bpm > 52.5 µV 3-fold increased the SCD risk (OR = 3.1 (95% CI 1.1-8.8), p = 0.03). Thus, mTWA at 100 bpm retained its significance during long-term follow-up.

The cut-off prognostic value of mTWA at 05.00 AM was 18.5 µV that was identical to the 12-months value with comparable sensitivity (56.7% and 60.0%, respectively) and specificity (60.8% and 63.8% respectively). The mTWA at 05.00 AM > 18.5 µV 2-fold increased the risk of death from cardiovascular causes (OR 2.3 (95% CI 1.1-5.5), p = 0.04) but not the risk of SCD, consistent with analysis of short-term data.

Analysis of the combinations of several risk factors revealed that at 60 months of follow-up the risk of cardiovascular mortality was the highest in patients with LVEF <40% + VT during 24-hour ECG monitoring (OR 22.9 (95% CI: 2.6-200.4), p = 0.0001), while SCD risk was the highest in patients with LVEF <40%, impaired HRT and mTWA at 100 bpm > 53 µV (OR 24.8 (95 CI 2.6-237.2%) p = 0.002) compared with any of these parameters alone (Fig. 1 and 2). Of note, the combination of LVEF <40% and VT during 24-hour ECG monitoring was only slightly inferior to the combination of LVEF <40%, impaired HRT and mTWA at 100 bpm > 53 µV. DC in combination with other non-invasive parameters moderately increased risk of both cardiovascular mortality and SCD.

Significance of various combinations of risk factors regarding overall mortality and SCD risk after adjustment for clinical covariates is shown in Fig. 1 and 2. Survival curves are shown in Fig. 3 and ROC-curves for impaired HRT and mTWA combinations are shown in Fig. 4.

**Discussion**

To our knowledge, this is the first investigation of long-term risk stratification for mortality using mTWA, HRT and DC in post-MI patients.

In prospective clinical studies of >10,000 patients, mTWA identified patients at risk for fatal arrhythmia and cardiovascular Table 3. HRT, DC and mTWA values in the study population by outcomes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall group (n = 111)</th>
<th>Survivors (n = 81)</th>
<th>All-cause deaths (n = 30)</th>
<th>CV deaths (without SCD) (n = 11)</th>
<th>SCD (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTWAmax (WF 1/8), µV</td>
<td>89 [72;114]</td>
<td>88.0 [66.5;114.3]</td>
<td>88.0 [73;111.5]</td>
<td>78.5 [70;91.3]</td>
<td>95 [74;146]</td>
</tr>
<tr>
<td>mTWAmax (WF 1/32), µV</td>
<td>40 [29;49]</td>
<td>37.0 [28.8;47]</td>
<td>41.5 [28;56]</td>
<td>35.5 [28;47.3]</td>
<td>42 [29;67]</td>
</tr>
<tr>
<td>mTWA100 (WF 1/8), µV</td>
<td>50 [30;69]</td>
<td>49.5 [31.5;72]</td>
<td>52.0 [19.5;64.5]</td>
<td>38.5 [18;51.5]</td>
<td>54 [18;78]</td>
</tr>
<tr>
<td>mTWA5:00 (WF 1/8), µV</td>
<td>15 [6;27]</td>
<td>15.5 [6;8.27]</td>
<td>20 [8.8;28.8]</td>
<td>20 [6.3;33.8]</td>
<td>19 [9;28]</td>
</tr>
<tr>
<td>mTWA5:00 (WF 1/32), µV</td>
<td>6 [2;9]</td>
<td>6.0 [2.8;9.3]</td>
<td>7.5 [2;10]</td>
<td>7 [1;9;3]</td>
<td>7 [3;10]</td>
</tr>
<tr>
<td>Absolute TO value, %</td>
<td>-0.01 [-0.02; 0]</td>
<td>-0.01 [-0.02;0]</td>
<td>0 [-0.01;0.1]**</td>
<td>-0.01 [-0.02;0]</td>
<td>0 [-0.01;0.1]**</td>
</tr>
<tr>
<td>Absolute TS value, ms/RR</td>
<td>3.67 [1.95; 6.53]</td>
<td>4.0 [2.2;7.2]</td>
<td>2.9 [0.9;4.2]**</td>
<td>3.5 [1.0;6.6]</td>
<td>2.6 [0.3;3.8]*</td>
</tr>
<tr>
<td>DC, ms</td>
<td>4.2 [2.2;6.0]</td>
<td>4.95 [2.95;6.1]</td>
<td>1.75 [0.63;7]**</td>
<td>3.6 [0.7;4.4]</td>
<td>1.5 [0.5;3.2]*</td>
</tr>
</tbody>
</table>

Note: mTWA, microvolt T-wave alternans; mTWAmax, maximal microvolt T-wave alternans; HR, heart rate; WF, weighing factor; HRT, heart rate turbulence; TO, turbulence onset; TS, turbulence slope, SCD, sudden cardiac death.

*p<0.05 for SCD compared with other outcomes, ** p<0.05 for main group compared with control group, *** p <0.05 for the subgroup of survivors compared with overall mortality subgroup. All mTWA values are for the first lead.

**Figure 1.** Relative risk of overall mortality at 60 months for different risk factors combinations.

Note: DC, deceleration capacity; mTWA, microvolt T-wave alternans; HRT, heart rate turbulence; TO, turbulence onset; TS, turbulence slope; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; VT, ventricular tachycardia; OR, odds ratio; CI, confidence interval.

**Figure 2.** Relative risk of SCD at 60 months for different risk factors combinations.

Note: DC, deceleration capacity; mTWA, microvolt T-wave alternans; HRT, heart rate turbulence; TO, turbulence onset; TS, turbulence slope; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; VT, ventricular tachycardia; OR, odds ratio; CI, confidence interval.
and total mortality [8] and met American Heart Association, American College of Cardiology, European Society of Cardiology, and/or Heart Rhythm Society requirements for class I (level of evidence A) and class IIa (level of evidence A) indications for arrhythmia risk assessment. [4] Goldberger et al. [1] stated that mTWA provides valuable information regarding the risk of cardiovascular mortality and SCD among patients with ischemic, dilated, and hypertrophic cardiomyopathies. Thus, a recent consensus guideline recommended mTWA monitoring in any suspected risk for fatal arrhythmia [8] but it has not been included in the ESC 2015 Guidelines for management of patients with ventricular arrhythmias and the prevention of SCD [11] due to the lack of evidence-based information.

Previously [12] we have demonstrated the significant predictive value of HRT and mTWA both in the general population of post-MI patients and in patients with preserved left ventricular function at 12 months of follow-up. No baseline characteristic typically linked with poor outcomes was associated with high mTWA, suggesting that mTWA offers complementary prognostic information. However, the subgroup analysis of patients with different LVEF at 60 months of follow-up virtually all investigated predictors showed no significant difference between subjects with preserved and reduced LV function, except low DC that remained significance in the subgroup of patients with LVEF > 40% (cardiovascular mortality: OR 8.5, 95% CI 2.9-24.6; p <0.0001 for all patients, and OR 16.1, 95% CI: 3.3-78.2, p <0.0001 in patients with LVEF > 40%; SCD: OR 9.6, 95% CI 3.2-28.5; p <0.0001 for all patients, and OR 21.3, 95% CI 3.7-122.3, p <0.0001 in patients with LVEF > 40%). This finding may suggest the high importance of these predictors for SCD and cardiovascular mortality risk stratification in the short-term perspective, indicating the need for more close monitoring and more aggressive therapy in these patients, as well as optimization of antiarrhythmic therapy to improve myocardial electrical stability. This is consistent with the findings of MERLIN-TIMI study. [9]

**Table 4. Significance of independent risk factors**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Overall mortality risk</th>
<th>Sudden cardiac death risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC</td>
<td>Threshold value</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>0.720</td>
<td>46.5%</td>
</tr>
<tr>
<td>DC, ms</td>
<td>0.749</td>
<td>4.15</td>
</tr>
<tr>
<td>TO, %</td>
<td>0.675</td>
<td>-0.005</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>0.664</td>
<td>3.5%</td>
</tr>
<tr>
<td>TS, ms/RR</td>
<td>0.663</td>
<td>1.21</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>0.624</td>
<td>134 ms</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>0.604</td>
<td>99 ms</td>
</tr>
<tr>
<td>mTWA at 05.00 AM, µV</td>
<td>0.568</td>
<td>18.5 µV</td>
</tr>
<tr>
<td>mTWA max, µV</td>
<td>0.523</td>
<td>67.5</td>
</tr>
<tr>
<td>mTWA at HR 100/min, µV</td>
<td>0.463</td>
<td>52.5 µV</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>0.643</td>
<td>9.5%</td>
</tr>
<tr>
<td>mTWA max, µV</td>
<td>0.617</td>
<td>72.5</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>0.608</td>
<td>134 ms</td>
</tr>
<tr>
<td>mTWA at 05.00 AM, µV</td>
<td>0.546</td>
<td>8.5 µV</td>
</tr>
</tbody>
</table>

Note: AUC, area under the ROC-curve; DC, deceleration capacity; LVEF, left ventricular ejection fraction; SDNN, standard deviation of normal to normal RR intervals; pNN50, proportion of the number of pairs of successive NNs that differ by more than 50 ms divided by total number of NNs; mTWA, microvolt T-wave alternans; HR, heart rate; TO, turbulence onset; TS, turbulence slope; PVC, premature ventricular contraction.

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**Figure 3a.** Cox regression for combination of HRT 2 and mTWA at HR 100 bpm > 53 mcV as a predictor of SCD at 12 months (A) [12] and 60 months (B). P values are for the log rank test.

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**Figure 3b.**
Threshold values obtained in our study differed from findings in other studies [8, 14] that may be explained by differences in measurement and in characteristics of study populations, but cut-offs for mTWA at 05.00 AM (CV mortality) and mTWA at 100 bpm (SCD) at 12 and 60 months of follow-up were similar suggesting the good reproducibility of mTWA measurement during short-term and long-term monitoring; it is consistent with the results of Chan et al. [15] who showed that the predictive value of the baseline mTWA evaluation persists during 2-3 years, and therefore re-measurement mTWA is reasonable only every 2 years. In this study, duration of follow-up was 18 ± 11 months; our results for the follow-up period of 60 months confirm the conclusions of the authors [15] as repeated measurements at 3, 6 and 12 months were not significantly different.

Combined risk stratification at 60 months revealed that the risk of cardiovascular mortality was the highest in patients with LVEF <40% and the presence of VT, and the maximum risk of SCD was similar in patients with LVEF <40%, HRT 2 and mTWA at 100 bpm > 53 μV and patients with LVEF <40% and VT detection during ECG monitoring. This differs from the findings at 12 months, when the combination of HRT 2 and mTWA at 100 bpm > 53 μV defined the subgroup of the highest risk compared both with an isolated impairment of any indicator and other combinations, including those with LVEF < 40%. [12] This may be explained by the fact that most patients (15 of 19 in the SCD subgroup and 8 of 10 in the group of cardiovascular mortality) died within the first 12 months after enrollment. These patients were characterized by the maximum impairment of the studied parameters, and these dropouts resulted in the elimination of the highest-risk groups according to a combination of non-invasive predictors; in the remaining patients, “conventional” risk factors - the low LVEF and myocardial ectopic activity – became important. Again, this finding support the high short-term importance of these predictors.

In our study, the new predictors were more accurate than the conventional ones. While HRT has been used for over 10 years and is included in the International Guidelines for risk stratification in patients after myocardial infarction, data about the use of DC to predict adverse outcomes in high-risk groups are limited. [7, 16, 17, 18] However, DC has a number of advantages compared with conventional HRV: independent evaluation of parasympathetic (DC) and sympathetic system (acceleration capacity is used to assess the activity of the sympathetic system, but its prognostic value has not been demonstrated); simplicity of data presentation (only one component instead of multiple HRV parameters) and direct focus on the risk assessment, with a clear staging by the low, medium and high. [7] Several studies have shown prognostic significance of HRT 2 and DC (“severe autonomic failure”) for the SCD risk stratification in the post-MI patients and preserved LVEF [16, 17] as well as in patients with CAD and diabetes. [18] In our study, this combination also was quite good for assessment of the risk of both overall mortality (4.3-fold), and SCD (4.4-fold) at 60 months.

Combined risk assessment with HRT and mTWA was first used by the REFINE study authors, [14] and subsequently by the other two study groups [19, 20] published later than our 12-months results. [12] Despite the fact that these studies had relatively long follow-ups (1.5 to 4 years) and the number of patients (173 to 322), included patients early after MI, differences in mTWA measurement and cut-off values, [19, 20] their findings of high prognostic significance of HRT 2 + mTWA confirm our data. Our study was the first one that used DC in a combined assessment of the risk of adverse outcomes and had the long follow-up up to 5 years.

Thus, our findings support high predictive value of HRT, DC and mTWA values for SCD and CV mortality risk stratification. Of course, the main questions are the following: “What should physician do with the patient who has non-invasive electrophysiological SCD predictors” and “Whether these data affect the choice of treatment strategy?” Based on the high negative predictive value of mTWA, T.Ikeda (Ikeda T. Combination of Tests in Risk Stratification. Report for Cardiostim 2014 on behalf of ISHNE-International Society for Holter and Noninvasive Electrocardiology (oral presentation).-19.06.2014, Nice) proposed a new algorithm for selection of patients for ICD implantation. According to this algorithm, the standard LVEF evaluation should be followed by the mTWA measurement; if the test is negative drug therapy should be continued, otherwise, (positive or indeterminate test)
additional non-invasive examinations are performed (ventricular late potentials, HRV, unstable VT detection etc.), and in some cases invasive electrophysiological study. There author considers ICD implantation justified only in case of positive result of the any additional tests. The more definitive answer may be received after the completion of a prospective REFINE-ICD study, which design includes randomization of patients with LVEF 36-50% and combined mTWA + HRT impairment for the standard treatment or ICD therapy. [5] In addition, long-term significance of noninvasive SCD predictors requires further confirmation in larger prospective studies.

Limitations

The single-center design, size of the study and number of events are limited; therefore, the findings require confirmation in a larger prospective study of high-risk subjects. This limitation was attenuated by adjustment for the well-known clinical and ECG risk factors. Despite the fact that post-MI population in our study was heterogenous and included patients with MI occurred from 2 months to about 30 years before enrollment, we analyzed possible effect of the MI onset on the noninvasive parameters; no significant influence was found; the heterogeneity of the previous MI treatment (invasive and non-invasive) was analyzed as well, and no significant impact was found. In addition, DC was evaluated retrospectively since this technique was unavailable at the study initiation.

Conclusions

Evaluation of HRT, DC and mTWA during 24-hour ECG monitoring may define the high risk of cardiovascular mortality and SCD in post-MI patients. The combination of abnormal HRT and mTWA100 > 53 μV is associated with the most significant increase in the risk of SCD during the first 12 months after the baseline examination. At 5 years of follow-up, value of noninvasive mortality predictors of the risk stratification is reduced compared with the importance of low LVEF and VT, but their contribution to a combined risk assessment remains significant. This suggest the high importance of these predictors for the short-term SCD and cardiovascular mortality risk stratification, indicating the need for more close monitoring and more aggressive therapy in these patients, as well as optimization of antiarrhythmic therapy to improve myocardial electrical stability or the selection of candidates for ICD implantation.

Declarations of Interest

V.S.: lectures and research work for Solvay Pharma, Sanofi, Nycomed, General Electric, Cordis a Johnson & Johnson; lectures for Boehringer Ingelheim, Bayer, Astra Zeneka. Elly Lilly; D.T.: lectures and research work for General Electric and Sanofi; E.O. received travel fees by General Electric, Boehringer Ingelheim and Sanofi.

Acknowledgements

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals”. [21] This study received no grant from any funding agency in the public, commercial or not-for-profit sectors.

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Long-Term Survival Following Aortic Valve Replacement: The Influence of Age, Prosthesis-Patient Mismatch and Indexed Effective Orifice Area

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Highlights

Background
Prosthesis-patient mismatch (PPM) has been linked to reduced long-term survival after aortic valve replacement. We studied the influence of age, PPM and indexed effective orifice area (iEOA) in this setting.

Methods
Patients (n=586) subjected to aortic valve replacement were followed up for a mean of 7.8 (maximum 20) years. The study population was divided into four equivalent groups by age. Mortality data was extracted from the National Statistics database. Data pertaining to patient body surface area and valve effective orifice area was collected prospectively and mismatch (moderate or severe) was defined according to established values. The Cox proportional hazard model was used to study the effect of age, mismatch and iEOA on survival. The Log Rank test was used to compare survival curves by age groups and date of surgery.

Results
The incidence of moderate PPM was 24.6%, and of severe PPM 3.9%. Mismatch increased the hazard of death by 31.2% for moderate PPM and 70.3% for severe PPM but did not reach statistical significance. Mean age of patients with mismatch (n=167) was 2.52 years less than in those without (63.35±10.61 versus 65.87±11.69, p=0.016). Age significantly affected survival, increasing the risk of death by 7.3% for every incremental year. Mean iEOA was 0.94±0.15cm²/m²; for every 0.1unit increase in iEOA the risk of death decreased by 8.8%.

Conclusions
Long-term survival was significantly affected by age at operation. Although mismatch increased hazard of death the effect did not reach statistical significance. A larger iEOA had a significant beneficial effect on survival.

Keywords: long-term survival; aortic valve replacement; age; prosthesis-patient mismatch; indexed effective orifice area

Citation:

Introduction
The concept of prosthesis-patient mismatch was introduced in 1978.[¹] PPM occurs when the effective orifice area (EOA) of a prosthesis is too small for the patient’s body size, resulting in excessively high postoperative valve gradients.[²] Independent researchers evaluating valve performance in vivo by echocardiography have underlined the overestimation of EOA in tables[³,⁴] issued by valve manufacturers (based on in-vitro testing)[⁵,⁶] and this has resulted in revised valve specifications.[⁷] Valve design has evolved from intra-annular implantation where the internal orifice diameter is smaller than the tissue annular diameter (TAD) to the introduction of supra-annular implantation where these diameters are equivalent.[⁸] This feature allows for
supra-annular implantation of a larger valve for a fixed TAD, often of the magnitude of one valve size. Various additional design features such as the TopHat design,[4] a lower-profile sewing ring and external mounting of pericardial tissue contribute to a larger EOA.[9]

The improvements in EOA are based on the premise that inferior haemodynamics result in suboptimal clinical outcomes. Studies have linked PPM with persistent left ventricular hypertrophy, diastolic dysfunction and curtailed functional improvement.[10] Late cardiac complications [11] and accelerated degeneration of bioprostheses have also been reported.[12] However, in the setting of advancing age, the combined effects of these factors on survival remains unclear.[13,14]

Although age undoubtedly increases early and late mortality after aortic valve replacement, the direct effect of mismatch remains debatable.[15-17] We studied the effect of the interaction of age and mismatch as well as the influence of iEOA on long-term survival both as a continuous variable, and as a categorical determinant of moderate or severe PPM.

Methods

586 consecutive patients (61.6% male, mean age 63.6±12.0) undergoing AVR ±CABG between January 1995 and December 2016 in a single-surgeon’s practice were enrolled in the study and grouped according to age: 15-59 (n=148), 60-67 (n=145), 68-74 (n=149), 74 or more (n=144). Patients were excluded if they underwent transcatheter valve implantation or other procedures. Baseline patient characteristics as well as postoperative complications were recorded in the presence or absence of PPM (table 1). Mortality data was obtained from the National Statistics database. Patients were followed up for a mean of 7.8 years (median 7.3) up to a maximum of 20 years. The Hospital Scientific Ethical Committee waived the necessity for consent as the study was retrospective and patient data was anonymized. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Surgery was performed in a standard fashion under normothermic bypass with antegrade cold cardioplegia. We used the internal thoracic artery supplemented by saphenous vein grafts when additional coronary bypass was necessary. No patient included in this series underwent root enlargement. Ninety three percent of patients over 70 received a bioprosthesis. The choice of valves implanted evolved with the introduction of models with a larger EOA.[9]

Table 1. Baseline patient characteristics and postoperative complications

<table>
<thead>
<tr>
<th>parameter</th>
<th>No PPM</th>
<th>Yes PPM</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>419</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>65.87±1.169</td>
<td>63.35±10.61</td>
<td>0.016</td>
</tr>
<tr>
<td>female</td>
<td>155 (36.9%)</td>
<td>72 (42.9%)</td>
<td>0.180</td>
</tr>
<tr>
<td>urgent surgery</td>
<td>48 (11.4%)</td>
<td>21 (12.5%)</td>
<td>0.715</td>
</tr>
<tr>
<td>concomitant CABG</td>
<td>139 (33.1%)</td>
<td>59 (35.1%)</td>
<td>0.639</td>
</tr>
<tr>
<td>ejection fraction (%)</td>
<td>70.4±14.31</td>
<td>69.7±13.59</td>
<td>0.717</td>
</tr>
<tr>
<td>mean Parsonnet score</td>
<td>13.96±7.17</td>
<td>13.40±6.61</td>
<td>0.375</td>
</tr>
<tr>
<td>mean EuroScore</td>
<td>5.31±2.07</td>
<td>4.87±1.99</td>
<td>0.037</td>
</tr>
<tr>
<td>mean logistic EuroScore</td>
<td>5.02±3.94</td>
<td>4.26±3.00</td>
<td>0.046</td>
</tr>
<tr>
<td>mean hospital stay (survivors)</td>
<td>6.20±3.62</td>
<td>6.30±4.87</td>
<td>0.797</td>
</tr>
<tr>
<td>median ventilation time (hours)</td>
<td>8</td>
<td>7</td>
<td>0.387</td>
</tr>
<tr>
<td>patients transfused</td>
<td>118 (28.1%)</td>
<td>53 (31.5%)</td>
<td>0.405</td>
</tr>
<tr>
<td>mean transfusion volume (units)</td>
<td>1.26±2.41</td>
<td>1.11±2.20</td>
<td>0.576</td>
</tr>
<tr>
<td>mean haemorrhage volume (ml)</td>
<td>459.8±311.0</td>
<td>476.4±348.1</td>
<td>0.617</td>
</tr>
<tr>
<td>IABP usage</td>
<td>18 (4.3%)</td>
<td>4 (2.4%)</td>
<td>0.272</td>
</tr>
<tr>
<td>&gt;24 hours inotropic support</td>
<td>116 (27.6%)</td>
<td>43 (25.6%)</td>
<td>0.618</td>
</tr>
<tr>
<td>atrial fibrillation/flutter</td>
<td>97 (23.1%)</td>
<td>47 (28.0%)</td>
<td>0.214</td>
</tr>
</tbody>
</table>

Table 2. Valves implanted during the study period

<table>
<thead>
<tr>
<th>valve size</th>
<th>1995-2001*</th>
<th>2002-2015**</th>
</tr>
</thead>
<tbody>
<tr>
<td>mechanical</td>
<td>CarboMedics Reduced</td>
<td>CarboMedics TopHat</td>
</tr>
<tr>
<td>19, 21</td>
<td>CarboMedics Standard</td>
<td>CarboMedics TopHat</td>
</tr>
<tr>
<td>23</td>
<td>CarboMedics Standard</td>
<td>CarboMedics Standard</td>
</tr>
<tr>
<td>bioprosthetic</td>
<td>Carpentier Edwards Perimount</td>
<td>Sorin Mitroflow</td>
</tr>
<tr>
<td>19, 21, 23</td>
<td>Carpentier Edwards Perimount</td>
<td>Carpentier Edwards Perimount/Magna</td>
</tr>
<tr>
<td>25</td>
<td>Carpentier Edwards Perimount</td>
<td>Carpentier Edwards Perimount/Magna</td>
</tr>
</tbody>
</table>

*1 St Jude Medical Toronto SPV valves inserted during this period
**7 Perceval valves inserted during this period

No PPM was defined as an indexed effective orifice area (iEOA) of >0.85cm²/m², moderate PPM as 0.65-0.85cm²/m² and severe as <0.65cm²/m², and was calculated according to published operative echocardiographic studies (table 3).

Statistical Methods

The student’s t-test was used to compare age groups with or without PPM. The Cox proportional hazard model was used to study the impact of age, iEOA and PPM category on long-term survival. Survival analysis was performed using the facilities of the Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL) by using both a non-parametric approach (Kaplan-Meier estimates) and semi-parametric approach (Cox regression analysis). The Log-Rank (Mantel-Cox) test was used to determine whether the Kaplan Meier survival curves for different age-groups differed significantly at the 0.05 level.

Results

Baseline characteristics and postoperative complications in patients without or with PPM did not differ, except for logistic/EuroSCORE risk, which was affected by age (table 1).
412 of 586 patients were alive at the completion of the study. The survival curves display the Kaplan-Meier survival probabilities for each age group against survival duration (figure 1). The log-rank test show that the Kaplan Meier survival curves of the four age-groups differ significantly when compared pairwise (table 4).

Survival was also plotted and analysed in relation to operative date, in five-year quartiles (figure 2). There was no influence on survival and the incidence of PPM within these quartiles was similar (p = 0.965) (table 5).

140 patients received a size 25 valve, 202 patients received a size 23, 195 patients received a size 21, and 49 patients received a size 19 valve. The incidence of moderate PPM was 24.6% and severe PPM was 3.9% (figure 3). Mismatch was present in 167 patients and was more prevalent in younger patients. In fact, the mean age of patients with mismatch (63.35±10.61) was 2.52 years lower than their counterparts with no mismatch (65.87±11.69) and this difference is significant (p=0.016) (figure 4).

There was no correlation between PPM and perioperative mortality. There were 11 early deaths (1.9%), and of these, 10 patients had no PPM and one had moderate PPM. Seven patients who died underwent concomitant coronary grafting and 8 were over 70 years old, both recognized risk factors for increased perioperative mortality.

Survival probability was significantly affected by patient’s age with the hazard of dying increasing by around 7.3% for every incremental year. In patients with severe and moderate mismatch the hazards of dying were respectively 70.3% and 31.2% higher compared to patients with no PPM, but the increase was not statistically significant. In patients with mismatch the hazards of dying were 86.5% higher for 19mm valves, 68.7% for 21mm valves and 13.7% for 23mm valves compared to 25mm valves. These hazard ratios are not significant mainly because the incidence of mismatch was low, particularly for the larger valves. (table 6).

---

<table>
<thead>
<tr>
<th>Table 3. EOA values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve model</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>CarboMedics</td>
</tr>
<tr>
<td>Carpentier Edwards</td>
</tr>
<tr>
<td>Sorin Mitroflow</td>
</tr>
<tr>
<td>St Jude Medical Toronto SPV</td>
</tr>
</tbody>
</table>

*reference source refers to the publications quoting the EOA values used in this study

| Table 4. Log-Rank (Mantel-Cox) test relating survival time to age |
|----------------------|------------------|-----------------|
| age groups | Chi-Square | df  | p value |
| group 1 versus group 2 | 11.607 | 1    | 0.001  |
| group 1 versus group 3 | 30.722 | 1    | 0.000  |
| group 1 versus group 4 | 66.560 | 1    | 0.000  |
| group 2 versus group 3 | 4.360  | 1    | 0.037  |
| group 2 versus group 4 | 28.157 | 1    | 0.000  |
| group 3 versus group 4 | 13.345 | 1    | 0.000  |
| four groups collectively | 80.057 | 3    | 0.000  |

df: degrees of freedom

<table>
<thead>
<tr>
<th>Table 5. PPM incidence in five-year quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period</td>
</tr>
<tr>
<td>1995-1999</td>
</tr>
<tr>
<td>2000-2004</td>
</tr>
<tr>
<td>2005-2009</td>
</tr>
<tr>
<td>2010-2015</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>X2(3) = 0.275, p = 0.965</td>
</tr>
</tbody>
</table>

---

Figure 1. Kaplan-Meier survival curves for the four age groups

Figure 2. Kaplan-Meier survival curves versus date of surgery (in five-year quartiles)

Figure 3. Kaplan-Meier survival curves for the four age groups

---
Mean iEOA was 0.94±0.15cm²/m². When iEOA was analysed as a continuous parameter rather than a categorical parameter, a higher iEOA was associated with a significantly reduced hazard ratio of dying. The chance of survival increased by 8.8% for every 0.1 unit increment in iEOA (table 7).

In conclusion, age was a significant predictor of long-term survival whereas prosthesis-patient mismatch failed to exert a statistically significant effect. This situation applied for both moderate and severe mismatch and for all valve sizes used. In contrast long-term survival was affected by iEOA when this was analyzed as a continuous variable.

Discussion
Cardiac-related mortality was shown to be increased by prosthesis-patient mismatch in a meta-analysis of 34 observational studies published in 2012.[26] This analysis included a number of studies that failed to demonstrate a significant effect of PPM, amongst which were one study [27] with a longer mean follow-up (9.1 vs. 7.8 years) and a second [28] with a comparable follow-up (median of 7.3 vs. 7.3 years) to our study. Both these studies failed to show a significant effect on survival, raising the possibility that a longer follow-up may be salient. The authors stressed the value of preventing PPM, particularly in younger patients in whom long-term survival may be impacted to a greater extent.

The incidence of common postoperative complications was similar in patients with or without PPM. Certain complications have been shown, by multivariate analysis, to affect long-term outcome. [29] In this study risk stratification was higher by logistic (p=0.046) and additive EuroSCORE (p=0.037) in patients without PPM because this group was older by 2.52 years, age being a contributor to the score. The incidence of mismatch is higher in younger patients and this may attenuate its effect on survival. Follow-up duration is inversely proportional to advancing age at operation. Studies with a longer follow-up have failed to demonstrate a deleterious effect of mismatch. The combined effect of a younger age and a longer follow-up may overshadow the importance of mismatch in determining long-term survival. Although mismatch leads to adverse cardiac events its effect on survival is reduced by advancing age.[29] Our results suggest that age, and its direct effect on follow-up duration, significantly affects survival whereas mismatch does not.

A long follow-up necessarily entails evolving practices including the implantation of novel valves that may significantly affect survival. Analysis of survival by operative date, in four five-year quartiles, showed no significant difference in survival in these groups.

When valve haemodynamics are translated into a continuum of iEOA a significant effect on long-term survival becomes evident. This relationship failed to reach statistical significance with mismatch because of the low incidence of moderate PPM, and the very low incidence of severe PPM. All data pertaining to valve EOA was obtained from published studies and not from our own post-operative measurements. These values should be readily available in theatre and act as a guide to the surgeon implanting an aortic prosthesis with the goal of avoiding mismatch. Our study suggests that the largest size valve with the best possible EOA should always be implanted. In extreme circumstances of a small aortic root, enlargement may be performed. However, the increased operative risk of this procedure has not been shown to benefit long-term survival.[30]
Limitations
The data was derived from a single surgeon’s practice and may not be representative of a wider population. A change in the use of certain valve models during the study period may have influenced the outcome. The low incidence of mismatch may have been a factor limiting statistical significance.

Conclusion
PPM, whether moderate or severe, did not significantly curtail long-term survival. A larger EOA increased survival by 8.8% per 0.1 unit increase. Age exerted a significant effect on survival, reducing it by 7.3% for each incremental year.

Declarations of interests
The authors declare no conflict of interest.

Acknowledgements
The authors agree to abide by the requirements of the “Statement of publishing ethics of the International Cardiovascular Forum Journal.”

References
3. Hemodynamic evaluation by Doppler echocardiography of small (≤21mm) mechanical-heart-valves/aortic-and-mitral-valves


31. Shewan LG, Coats AJS, Henein M. Requirements for ethical publishing in biomedical journals. International Cardiovascular Forum Journal 2015;2:2. DOI:10.17987/icfj.v2i1.4
Mortality and Co-Morbidities Among Hospitalised Hypertensives in Nigeria

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Introduction
Hypertension is the most important risk factor for cardiovascular diseases (CVD), accounting for about 54% of strokes, 47% of ischemic heart disease (IHD), 25% of other CVD, 13.5% of all deaths and 6% of all disability-adjusted life-years (DALYs) (the sum of years lived with disability and years of life lost) worldwide.[1] It is of note that about 80% of the burden occurred in low and middle-income countries, and a greater proportion of the burden was in young people of working age in low and middle-income regions than it was in high-income regions.[1] In a recent meta-analysis, the overall prevalence of hypertension in Nigeria was estimated at 28.9%, with a prevalence of 29.5% among men and 25.0% among women, and of 30.6% and 26.4% among urban and rural dwellers respectively.[2] In addition, the pooled awareness rate of hypertension at admission increased its odds by 7.5 fold.

Highlights
Background
There is paucity of data on the burden of morbidities, clinical characteristics and mortality related to systemic hypertension in Nigeria. The present study therefore aimed to systematically assess the co-morbidities and in-hospital outcomes among hypertensives admitted to 3 Teaching Hospitals in Nigeria.

Methods
Medical records of all subjects admitted to the medical wards of the study centres with an established diagnosis of hypertension in 2013 were reviewed. Admission, discharge and mortality registers of the medical wards were used to identify the cases, those discharged and those who died. The records of the patients were then reviewed and included if the inclusion criteria were satisfied.

Results
288 hypertensive patients were consecutively admitted in the medical wards of the 3 centres in 2013, of whom 146 (59.8%) were males. 88.4% of males and 87.8% of females had 1 or more co-morbidities at admission, and the commonest among all patients was heart failure (HF) followed by stroke/transient ischemic attack (TIA), in 76 (31.2%) and 69 (28.3%) patients respectively. The most frequent co-morbidity among males was HF in 34.3% of them, while stroke/TIA was more common among female patients, in 34.7% of them. Non-cardiovascular co-morbidities were uncommon, and the most frequent was community acquired pneumonia in 7.4% of all patients. 7.8% of all patients (13 males and 6 females; p=0.427) died in-hospital. The deceased had higher systolic blood pressure than the survivors, and majority of them (52.6%) were not on any antihypertensive medications at admission, which was the only predictor of mortality in the present study, increasing its odds by 7.5 fold (odds ratio=7.5; 95%confidence interval=2.8-20.0; p<0.001).

Conclusions
Co-morbidities were found in more than four-fifths of male and female patients, and the most frequent among males was HF while stroke and TIA were most common among female patients. Non-cardiovascular co-morbidities were uncommon. The prevalence of in-hospital mortality was relatively low, and not being on antihypertensive treatment at admission increased its odds by 7.5 fold.

Keywords: mortality; co-morbidities; hypertension; anti-hypertensives; Nigeria

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Fulani rural population, among whom we recently reported a prevalence of hypertension of 28.5% in a rural settlement in Kano, North-West Nigeria.[3] In this Fulani population, 39.3% of the hypertensives were aware of it, and only 25% of the known hypertensives were on treatment. Age was the only independent predictor of hypertension, and for every increase in age by 1 year, the odds of developing hypertension was increased by 6.6%.[3]

Among hypertensive in-patients, Kolo et al retrospectively studied hypertension-related admissions and their outcome over 1 year, and reported that hypertension-related admissions represented 23.7% of the total, while mortality attributed to complications of hypertension was as high as 42.9% of the total.[4] Arodiwe et al similarly reviewed hypertension-related admissions over 5 years, and reported that hypertension-related admissions represented 6.2% of the total, with a case fatality rate of also 42.9%.[5]

The morbidities and mortality in hypertension impact negatively on many outcome measures among hypertensive subjects. Ukoh VA reported that the most common hypertensive complication was stroke followed by heart failure (HF) and chronic renal failure (RF), and 10.5% of all medical admissions was due to hypertensive complications.[6] Furthermore, Onwuchekwa et al reported that among admitted hypertensives, stroke was responsible for 39.9%, HF for 22% and RF for 9.4% of hypertensive complications, while 51.5% of deaths were due to stroke, 14.1% due to HF, and 12.1% due to RF.[7]

The above-mentioned studies were single centre based and of modest sizes; hence not representative.[5-7] It is therefore clear that comprehensive information is needed on the burden of morbidities, clinical characteristics and mortality related to systemic hypertension in a multicentre study, which can fill the knowledge gaps on hypertension in Nigeria. The present study therefore aimed to systematically assess the cardiovascular and other co-morbidities and in-hospital outcomes among hypertensives admitted to Teaching Hospitals in three large metropolitan cities within two geographic zones in Nigeria.

Methods
This was a retrospective study carried out in Departments of Medicine, Aminu Kano Teaching Hospital (AKTH), Kano, Ladoke Akintola University of Technology Teaching Hospital (LAUTECH TH), Ogbomoso, and Lagos University Teaching Hospital (LUTH), Lagos, Nigeria.

Approvals to carry out the study were sought from the Ethics Committees of the 3 study centres before the commencement of the study.

Medical records of all subjects admitted to the medical wards of the study centres with an established diagnosis of hypertension in 2013 were reviewed. Admission, discharge and mortality registers of the medical wards were used to identify the cases, those discharged and those who died. The records of the patients were then reviewed and included if the following inclusion criteria were satisfied: (1) established diagnosis of systemic hypertension, (2) availability of all admission notes, (3) availability of results of investigations that could confirm clinical diagnoses, and (4) documentation of required information for the study. Hypertension was defined as presence of sustained systolic and or diastolic blood pressure (SBP and DBP respectively) of ≥140 and or 90mmHg respectively, or its documented history, or if a patient was on any antihypertensive medication even if BP was normal.

The retrieved data for the study included demographic and clinical characteristics, clinical diagnoses, results of confirmatory and supporting investigations, duration of hospitalisation (in days) and information on whether patients had died or survived hospitalisation and were discharged or referred.

The data was explored for skewness and analysed using SPSS version 17.0 software. Proportions, medians with interquartile ranges and means with standard deviations were used to summarise patients’ characteristics, as appropriate. Chi-square, Fisher’s exact probability, Student’s t and Mann-Whitney tests were used to compare categorical and continuous variables, as appropriate. Regression models were used to determine predictors of mortality, and results were expressed as Odds ratio (OR) with 95% confidence intervals (95%CI). Survival analysis was conducted using Kaplan-Meier curves and Log rank test obtained for all-cause mortality between male and female patients. A p-value of <0.05 was considered statistically significant.

Results
In 2013, the number of beds in the medical wards of AKTH, LAUTH and LUTH were 88, 100 and 120 respectively. The admission records showed that a total of 288 hypertensive patients were consecutively admitted in the medical wards of the 3 centres in 2013, but 44 of them had incomplete medical records. The remaining 244 hypertensive patients satisfied the inclusion criteria and were included. Of these, 146 (59.8%) were males and 98 (40.2%) were females. The mean age of all patients was 58.4±15.9 years with a range of 20-93 years, mean SBP was 150±37mmHg and mean DBP was 94±24mmHg. In addition, 64 (26.2%) were unemployed, 154 (63.1%) were gainfully employed and the remaining 26 (10.7%) were retirees.

The baseline characteristics of males were compared with those of female subjects in Table 1, which shows that majority of males (67.1%) were urban dwellers and majority of females (60.2%) were rural dwellers, and males spent significantly more days on admission than females, with a median of 15 vs 9 days respectively. However, the mean age, blood pressures, heart rate and other variables in the Table were not significantly different between the 2 groups.

The pattern of antihypertensive prescriptions at admission is presented in Figure 1, which shows that 31.7% of the patients were not on any antihypertensive drug while the majority (62.3%) was on either 1 or 2 antihypertensive drugs. Further analysis showed that the prescription pattern did not differ by gender among the subjects (p=0.436).

Co-morbidities among male and female patients are presented in Table 2 and Figure 2. The commonest co-morbidity among all patients was HF followed by stroke/TIA, seen in 76 (31.2%) and 69 (28.3%) patients respectively. The most frequent co-morbidity among males was HF seen in 34.3% of them, while stroke and TIA were more common among female patients, seen in 34.7% of them. Stroke and TIA was also the 3rd most
common among males while HF was the 2nd among females. In addition, excess alcohol, cigarettes smoking and peripheral artery disease were significantly more common among males, while dyslipidemia and DM were significantly more common among females. Atrial fibrillation was the commonest arrhythmia seen in 5 (3.4%) male and 1 (1%) female, junctional rhythm in 2 (1.4%) male and 2 (2%) female, atrial flutter in only 1 female (1%), supraventricular tachycardia in 1 male (1.7%) and 1 female (1%) patients, and ventricular tachycardia in only 1 (1%) female patient. Non-cardiovascular co-morbidities were uncommon, but the most frequent among both males and females was CAP seen in 7.4%, followed by chronic liver disease in 3.7% and neoplastic diseases in 2.9%, of all patients. Overall, 88.4% of males and 87.8% of females had 1 or more co-morbidities at admission, as illustrated in Figure 2.

A total of 19 patients (7.8%) comprising of 13 (8.9%) males and 6 (6.1%) females (p=0.427) died in-hospital while others were discharged or referred. The survival curves for male and female patients were constructed and data was censored at 50 days (Log Rank (Mantel-Cox) p= 0.970) (Figure 3). The characteristics of the deceased were compared with those of the discharged patients in Table 3, which shows significantly higher mean SBP and prevalence of those not on antihypertensive treatment at admission among the former than the latter group (p=0.045), while other variables were not significantly different between the 2 groups. In addition, prevalence of stroke tended to be higher among the deceased while that for HF and DM tended to be higher among the discharged patients, although the differences were not statistically significant. Further analysis showed that not being on antihypertensive treatment at admission increased the odds of mortality by 7.5 fold (OR=7.5; 95%CI=2.8-20.0; p<0.001) in the regression models.

### Discussion

In the present multicentre retrospective study involving consecutively admitted hypertensive patients in 2013, data was complete for inclusion for only 244 patients. Two-thirds of the patients were on antihypertensive medications at admission, and males spent more days on the admission than females, with a median of 15 vs 9 days respectively. Various co-morbidities were found among 88.4% of males and 87.8% of females, and the most frequent among males was HF while stroke and TIA were most common among female patients. Arrhythmias were

### Table 1. Baseline characteristics of male and female patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Males N=146 (59.8%)</th>
<th>Females N=98 (40.2%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.9±15.9</td>
<td>57.6±15.9</td>
<td>0.549</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>148±37</td>
<td>154±38</td>
<td>0.189</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>92±23</td>
<td>97±24</td>
<td>0.123</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>96±17</td>
<td>100±15</td>
<td>0.130</td>
</tr>
<tr>
<td>RBS, mmol/l</td>
<td>6.9(6.1-8.1)</td>
<td>8.2(6.3-12.4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Sodium, mmol/l</td>
<td>135.3±13.3</td>
<td>135.3±7.6</td>
<td>0.995</td>
</tr>
<tr>
<td>Creatinine, µmol/l</td>
<td>116.6(89.3-169.3)</td>
<td>105.0(74.0-149.0)</td>
<td>0.604</td>
</tr>
<tr>
<td>PCV, %</td>
<td>34.2±8.8</td>
<td>33.7±8.1</td>
<td>0.772</td>
</tr>
<tr>
<td>Urban residence</td>
<td>98(67.1%)</td>
<td>90(90.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days on admission</td>
<td>15(9-27)</td>
<td>9(4-14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Key: BP, blood pressure; bpm, beats per minute; PCV, packed cell volume. Results are presented as means ± standard deviations, median with interquartile ranges or as proportions.

### Table 2. Co-morbidities among male and female patients.

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Males N=146 (59.8%)</th>
<th>Females N=98 (40.2%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>8(5.5%)</td>
<td>6(6.1%)</td>
<td>0.832</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50(34.3%)</td>
<td>26(26.5%)</td>
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</tr>
<tr>
<td>Stroke</td>
<td>35(24.0%)</td>
<td>34(34.7%)</td>
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<tr>
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<td>21(21.4%)</td>
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<tr>
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<td>10(6.9%)</td>
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<tr>
<td>Hypertensive encephalopathy</td>
<td>4(2.7%)</td>
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</tr>
<tr>
<td>Valvular heart disease</td>
<td>9(6.1%)</td>
<td>8(8.2%)</td>
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<tr>
<td>Deep vein thrombosis</td>
<td>2(1.4%)</td>
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<tr>
<td>Dyslipidemia</td>
<td>18(12.3%)</td>
<td>24(24.5%)</td>
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<td>Excess alcohol</td>
<td>46(31.5%)</td>
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<td>Cigarette smoking</td>
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<tr>
<td>Diabetes mellitus</td>
<td>20(13.7%)</td>
<td>23(23.5%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Non-cardiovascular co-morbidities</td>
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<td></td>
</tr>
<tr>
<td>Community acquired pneumonia</td>
<td>12(8.2%)</td>
<td>6(6.1%)</td>
<td>0.539</td>
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<tr>
<td>Chronic obstructive airway disease</td>
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<tr>
<td>Bronchial asthma</td>
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<td>1(1.0%)</td>
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<td>Urinary tract infection</td>
<td>2(1.4%)</td>
<td>2(2.0%)</td>
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<tr>
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<td>1(1.0%)</td>
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<td>0.070</td>
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<td>Thyroid disease</td>
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</tr>
<tr>
<td>Neoplasm</td>
<td>6(4.1%)</td>
<td>1(1.0%)</td>
<td>0.156</td>
</tr>
</tbody>
</table>

Key: Results are presented as means ± standard deviations or as proportions.
found in only 5.7%, and the most frequent was atrial fibrillation in 2.5% of the patients. Non-cardiovascular co-morbidities were uncommon, and the most frequent among all patients was CAP. The prevalence of in-hospital mortality was 8.9% among male and 6.1% among female patients (p=0.427), which was mainly predicted by not being on antihypertensive treatment at admission.

Firstly, this study has revealed the degree to which medical records were being kept in the study centres in 2013. The results show that 15.3% of the admitted hypertensive patients were not eligible for inclusion in the study because of incomplete records. Although this is significantly better than the observation made in a similar study where only 54.4% of the records had complete data for inclusion, our finding is still worrying.[7] These observations reveal the weaknesses of manual medical record keeping, and call for a shift towards computerised medical records keeping which was not available at all the study centres in 2013, which would have substantially reduced the challenges of missing or incomplete medical records. The unexpectedly low admission rates for patients including hypertensives in the study centres in 2013 could have been due to closures of the hospitals because of frequent strike actions by health workers.

Secondly, the prevalence of co-morbidities was high in both males and females, and 88.4% of males and 87.8% of females had 1 or more co-morbidities at admission. The commonest co-morbidity among all patients was HF (31.2%) followed by stroke/TIA (28.3%); the former being commonest among males (34.3%) and the latter among females (34.7%). As mentioned earlier, systemic hypertension is the most important risk factor for CVD, associated with important morbidities and mortality.[1] It has also been reported that 75.6% of hypertensive patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Discharged/ Referred N=225 (92.2%)</th>
<th>Deceased N=19 (7.8%)</th>
<th>p-value</th>
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<tr>
<td>Age, years</td>
<td>58.0±15.4</td>
<td>62.4±20.8</td>
<td>0.245</td>
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<tr>
<td>Systolic BP, mmHg</td>
<td>149±37</td>
<td>165±32</td>
<td>0.045</td>
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<tr>
<td>Diastolic BP, mmHg</td>
<td>94±24</td>
<td>94±18</td>
<td>0.918</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>97±17</td>
<td>100±15</td>
<td>0.472</td>
</tr>
<tr>
<td>Males</td>
<td>133(59.1%)</td>
<td>13(68.4%)</td>
<td>0.427</td>
</tr>
<tr>
<td>Co-morbidities ≥1</td>
<td>200(88.9%)</td>
<td>15(79.0%)</td>
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<td>Arrhythmias</td>
<td>14(6.2%)</td>
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<td>Heart failure</td>
<td>73(32.4%)</td>
<td>3(15.8%)</td>
<td>0.196</td>
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<tr>
<td>Stroke</td>
<td>63(24.0%)</td>
<td>7(36.8%)</td>
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<td>Renal failure</td>
<td>38(16.9%)</td>
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<td></td>
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<tr>
<td>Hypertensive encephalopathy</td>
<td>4(1.8%)</td>
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<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>17(7.6%)</td>
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<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>42(18.7%)</td>
<td>1(5.3%)</td>
<td>0.211</td>
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<tr>
<td>Community acquired pneumonia</td>
<td>17(7.6%)</td>
<td>1(5.3%)</td>
<td>0.999</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>7(3.1%)</td>
<td>2(10.5%)</td>
<td>0.157</td>
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<tr>
<td>Neoplasia</td>
<td>7(3.1%)</td>
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<td></td>
</tr>
<tr>
<td>No antihypertensive</td>
<td>29(12.9%)</td>
<td>10(52.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Key: BP, blood pressure; bpm, beats per minute. Results are presented as proportions.

Figure 2. Pattern of co-morbidities among male and female patients Legend: Number of patients admitted with various co-morbidities described according to gender.

Figure 3. Kaplan-Meier curves of survival among male and female subjects. Legend: Kaplan-Meier curves of overall survival among hospitalised male (green line) and female (blue line) hypertensive subjects, constructed after excluding subjects who spent >50 days on admission. Log Rank p=0.970
in Nigeria tend to be at very high risk for CVD events even if on treatment.[8] As such, it is not surprising that over 80% of the admitted patients in the study centres had such high prevalence of cardiovascular morbidities, including HF, stroke, DM, dyslipidemia and renal failure. Previous studies in Nigeria have shown similar morbidity pattern among hypertensives, with stroke as the most common complication followed by HF, whereas ischemic heart disease (IHD) is rare.[4-7] The rarity of IHD could be related to the pattern of the other CVD risk factors among our patients, because high blood pressure, heavy alcohol use, and advanced age are stronger predictors for stroke than for IHD, whereas dyslipidemia, diabetes mellitus, and smoking are more strongly linked to IHD.[8] Among 192 World Health Organization member countries, stroke burden was disproportionately higher in China, Africa, and South America, whereas IHD burden was higher in the Middle East, North America, Australia, and much of Europe.[10]

It is of note that the non-CVD co-morbidities were uncommon among patients in the present study, and hence not likely to be the reasons for the hospitalisations. Our observations therefore suggest that hypertensive patients in Nigeria tend to suffer mostly from cardiovascular complications than from other illnesses. The third important observation in the present study is that in spite of the high prevalence of co-morbidities of hypertension, including HF, stroke, DM and renal failure, the in-hospital mortality was relatively low (7.8%), without significant gender difference. In comparison, reported mortality rates among admitted hypertensive patients in other Teaching Hospitals in Nigeria were 34.3%, 23.3% and 22.1% respectively.[4,6,7] In agreement however, most deaths were consistently caused by stroke, followed by HF or RF.[4,6,7] The deceased had higher SBP than the survivors, and majority of them (52.6%) were not on any antihypertensive medications at admission, which was the only predictor of mortality in the present study, with odds of dying increased to 7.5. Unfortunately, data on treatment patterns was not provided in the 3 other studies from Nigeria for comparison with ours.[4,6,7] However, it is possible that the differences in treatment patterns between the studies could explain the variability in the mortality rates. It is well-documented that high BP bears an independent continuous relationship with the incidence of several CV events including stroke, myocardial infarction, sudden death, HF, peripheral artery disease and end-stage renal disease, at all ages and in all ethnic groups.[11] Clinical trials of antihypertensive therapies have demonstrated their benefits in terms of progressive reduction of death and morbidity from strokes as well as from coronary heart disease in the order of approximately 70% and 55%, respectively.[12]

Limitations
Incomplete medical record is one of the inherent limitations of retrospective studies, including the present study. In addition, data on the direct causes of deaths was not available to us and was not presented.

Conclusion
The present multicentre retrospective study involving consecutively admitted hypertensive patients has described the cardiovascular and other co-morbidities and in-hospital outcomes among hypertensives admitted to 3 Teaching Hospitals in 2 geographic zones in Nigeria. Two-thirds of the patients were on antihypertensive medications at admission, and co-morbidities were found among 88.4% of males and 87.8% of females. The most frequent co-morbidity among males was HF while stroke and TIA were most common among female patients. Non-cardiovascular co-morbidities were uncommon, and the most frequent among all patients was CAP. The prevalence of in-hospital mortality was relatively low, and not being on antihypertensive treatment at admission increased its odds by 7.5 fold.

Declarations of interest
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals.”[13]

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7. Ukoh VA. Admission of hypertensive patients at the University of Benin Teaching Hospital, Nigeria, East Afr Med J 2007; 84(7): 329-335.
The Impact of Maternal Congenital Heart Disease on Pregnancy Outcomes in Malta – A Retrospective Study

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Introduction

Advances in the management of congenital heart disease (CHD) have led to most patients reaching child-bearing age, with an increasing number of such women becoming pregnant. [1] The physiological changes that occur during pregnancy, including increases in blood volume, heart rate and cardiac output, represent an added cardiovascular burden which may be poorly tolerated by women with CHD, especially those with haemodynamically significant residua.[2] Such pregnancies are also at higher risk of neonatal complications.[3,4] Three main tools have been proposed for risk stratification of maternal cardiovascular complications among women with heart disease.[5] The CARPREG score [4] and modified World Health Organisation (WHO) classification [6,7] can be applied to women

Highlights

Background
Most female patients with congenital heart disease (CHD) are becoming pregnant. Maternal CHD can have a negative impact on mother and foetus. This is the first study investigating pregnancy outcomes in Maltese grown-up congenital heart disease (GUCH) patients and one of few to compare these with outcomes in women without heart disease.

Methods
Known GUCH pregnancies for the period of 2007-2014 were extracted from our database (GUCH cohort) and cardiovascular outcomes retrieved from hospital notes. A control cohort of 540 pregnancies in women without cardiovascular disease was generated through twenty-fold random matching based on subject age from among all pregnancies in Maltese nationals for the same 8-year period. Obstetric and offspring outcomes were compared between the two cohorts.

Results
The GUCH cohort consisted of 27 pregnancies in 24 women. Cardiovascular complications occurred in only 1/27 (3.7%) pregnancies. Elective Caesarean sections were commoner (29.6% vs. 15.4%) and unassisted vaginal deliveries less frequent (51.9% vs. 64.6%) in the GUCH cohort (p=0.02). Obstetric complication rates were similar. GUCH women had smaller babies (median 3030g vs. 3230g; p=0.045) and showed a trend towards more small-for-gestational age babies (18.5% vs. 8.4%; p=0.08) and congenital malformations (7.4% vs. 2.4%; p=0.06).

Conclusions
Despite the potential adverse effects of maternal CHD on mother and foetus, most pregnancies are uncomplicated and outcomes comparable to those in women without heart disease, particularly if baseline clinical status is good. Based on our findings, it is being proposed that prospective mothers be counselled about the possibility of having smaller infants.

Keywords: Congenital Heart Defects; Pregnancy; Cardiovascular Pregnancy Complications

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with both CHD and acquired heart disease (AHD), while the ZAHARA score [8] is designed specifically for women with CHD. CARPREG and ZAHARA scores consider the maternal clinical cardiac status to calculate risk of cardiovascular complications. In the modified WHO classification, pregnancies are classified into four risk groups based on specific heart lesions, with maternal risk ranging from very low in WHO class I to extremely high and warranting advice against pregnancy in class IV.[6,7]

Malta has a population of around 425,000 and the main religion is Roman Catholic.[9] Termination of pregnancy is illegal up to the time of writing of this manuscript. Malta's health care system is funded through taxation and national insurance, and specialised services, including a dedicated service for grow-ups with congenital heart disease (GUCH) are provided in one main teaching hospital. Obstetric data covering all deliveries to residents and non-residents taking place on the Maltese islands is collected and administered by the National Obstetric Information System (NOIS), which was launched by the Department of Health Information and Research in 1999.[10] There has been a trend of increasing maternal age over the past decade, with the 30-34 years' age bracket being the one with most reported deliveries (36.3%) in 2015. There were 3544 reported deliveries in women of Maltese nationality in 2015, 92.7% of all babies were born at term and the average birth weight was 3217g. Two maternal deaths were reported in the last decade.[10]

The overall incidence of CHD in Malta has been reported at around 0.8%, which is similar to that in other European countries.[11] Virtually all congenital cardiac surgery on children and adults born in Malta is carried out in overseas tertiary referral centres, in the United Kingdom, through a reciprocal National Health Service agreement. A number of structural cardiac interventions are carried out locally by visiting specialists. A GUCH service was initiated in the late 1990s and expanded considerably over the last decade. It includes a specific service for the provision of preconceptual counselling to female patients who want to get pregnant and for their management during pregnancy through close collaboration with obstetricians and anaesthetists.

The aims of this retrospective study were (a) to describe maternal outcomes among women with CHD in Malta and (b) to investigate the potential impact of maternal CHD on obstetric and offspring outcomes through comparison with reported outcomes in age-matched women with no history of cardiovascular disease in the general Maltese population.

**Methods**

All known pregnancies in women of Maltese nationality with CHD for the 8-year period 2007 – 2014 were retrieved from our institutional database (“GUCH pregnancy cohort”). Baseline characteristics, cardiac events and obstetric and offspring outcomes for these women were obtained retrospectively from hospital paper notes and digital investigation reports. An individual twenty-fold random matching based on subject age was performed out of all 29,349 pregnancies in Maltese women with no documented cardiovascular disease as collected by NOIS for the same study period. This generated the age-matched control cohort of 540 pregnancies referred to in the manuscript as “non-CVD pregnancy cohort”. NOIS pregnancy entries for women of non-Maltese nationality were excluded primarily to avoid any bias related to potentially differing epidemiological and/or genetic characteristics, as well as due to the possibility of their medical data leading up to the index pregnancy being incomplete. Maltese pregnancies with incomplete obstetric and/or offspring outcome data were also excluded during the matching process.

The term “tachyarrhythmias” refers to any symptomatic sustained and non-sustained tachyarrhythmia and excludes incidental asymptomatic atrial/ventricular ectopy. Ventricular and valvular function was based on echocardiographic findings and follows international guidelines.[12] Left ventricular systolic dysfunction is defined as an ejection fraction <55% and right ventricular systolic dysfunction is defined as a tricuspid annular plane systolic excursion (TAPSE) <16mm and fractional area change <35%. Aortic outflow tract obstruction is referred to as moderate if peak velocity is 3.0-3.9m/s and mean pressure drop is 25-40mmHg and severe if peak velocity is >4.0m/s and mean pressure drop is >40mmHg. Pulmonary outflow tract obstruction is defined as moderate if peak velocity is 3.0-4.0m/s and severe if >4.0m/s. Mitral regurgitation is defined as more than mild if proximal isovelocity surface area (PISA) is >0.4cm and vena contracta >0.3cm. Aortic regurgitation is defined as more than mild if pressure half time is <500ms and vena contracta is >0.3cm. Pulmonary regurgitation is referred to as severe if pressure half-time is <100ms and colour flow Doppler origin of the regurgitant jet is from the bifurcation of the branch pulmonary arteries. Severity of tricuspid regurgitation is based mostly on visual assessment.

The outcomes compared between the subjects in the two study cohorts were based on those collected by NOIS. Obstetric outcomes studied were threatened abortion, threatened premature labour, antepartum haemorrhage, placenta praevia, placental abruption, suspected intrauterine growth retardation (IUGR), maternal infections, hypertensive diseases of pregnancy, gestational diabetes, need for hysterectomy within 24 hours of delivery, retained placenta, severe haemorrhage (defined as blood loss of 1 litre in 2 hours), need for blood transfusion, dystocia and maternal death. Offspring outcomes studied were number of offspring per pregnancy, offspring gender, pregnancy duration, prematurity (pregnancy duration < 37 weeks), small-for-gestational age (SGA) births (birth weight <10th centile for gestational age), birth weight, presence of congenital malformations diagnosed at birth and occurrence of stillbirths and neonatal death. Informed consent was obtained from all participants. The study protocol was approved by the University of Malta Research Ethics Committee and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

**Statistical methods**

Categorical variables were analysed using Chi-squared tests. Fisher's Exact test was applied in the case of smaller sample sizes. Shapiro-Wilk test applied to numerical variables (pregnancy duration and birth weight) showed a non-normal distribution. Subsequently, Mann-Whitney U test was used for comparison of these variables between the two study cohorts. Analyses were performed using SPSS 21 (IBM® SPSS® 21, SPSS Inc., Chicago IL, USA). All statistical analyses were two-sided and statistical significance was defined as p≤0.05.
Results

The GUCH pregnancy cohort consisted of 27 pregnancies in 24 women, with 9 pregnancies belonging to modified WHO class I, 15 pregnancies to modified WHO class II/II-III and 3 pregnancies to modified WHO class III (Table 1). Maternal baseline characteristics are summarised in Table 2. Repaired tetralogy of Fallot was the commonest congenital heart lesion, featuring in 6/27 (22.2%) GUCH pregnancies. Mean maternal age was 27.44 ± 5.24 years (range 15–41 years). All women were in New York Heart Association (NYHA) class I prior to the index pregnancy and none had cyanosis at baseline. Three patients were on cardiac medications prior to pregnancy: two women were on aspirin and one patient was on warfarin. Only one patient – a case of atrio-pulmonary (AP) Fontan surgery for tricuspid atresia – had a history of prior arrhythmias in the form of sustained atrial flutter needing direct current cardioversion in the past. Complete echocardiographic data was available for 23/27 GUCH pregnancies. In all these cases, there was no systemic ventricular function at baseline. One patient had moderate congenital aortic stenosis (AS) and another patient had moderate right ventricular outflow tract obstruction (RVOTO) at branch pulmonary artery level but no patients had severe outflow tract obstruction.

Cardiac events and cardiac medication use in pregnancy in the GUCH cohort is summarised in Table 3. Cardiac events were uncommon with only one patient, with a history of tricuspid atresia and atrio-pulmonary (AP) Fontan surgery, developing paroxysmal atrial arrhythmias and heart failure. The same patient was also the only one to require antiarrhythmic therapy, low-dose diuretics and anticoagulation during pregnancy. Two other women, one with total cavopulmonary connection (TCPC) and one with recent percutaneous closure of an atrial septal defect (ASD) remained on low-dose aspirin during pregnancy.

Tables 4 and 5 summarise the results of comparison of obstetric and offspring outcomes respectively. There were no significant differences in the frequency of pregnancy and delivery-related complications between the two cohorts. Unassisted vaginal delivery was the commonest mode of delivery in both cohorts, however it was less common among subjects in the GUCH cohort (GUCH 51.9% vs. non-CVD 64.6%). Conversely, elective pre-labour Caesarean section was employed more frequently among women in the GUCH cohort (8/27; 29.6%) when compared to those in the non-CVD cohort (83/540; 15.4%). Four of the 8 Caesarean sections (50%) in the GUCH pregnancy cohort were performed for cardiac indications, 3/8 (37.5%) had obstetric indications and one was performed based on patient preference. Instrumental delivery was used for 2/27 (5.4%) GUCH pregnancies and for 20/540 (3.7%) non-CVD pregnancies. The differences in delivery methods between the two cohorts were statistically significant (p=0.02). There were more premature births in the GUCH cohort (11.1% vs. 4.1%) though this difference did not reach statistical significance (p=0.11). Overall pregnancy duration in the two cohorts was not significantly different (median duration GUCH 38 weeks vs. non-CVD 39 weeks; p=0.14). Women in the GUCH cohort gave birth to significantly smaller babies (median birth weight: GUCH 3030g vs. non-CVD 3230g; p=0.045) and showed a trend towards having more SGA babies (GUCH 18.5% vs. non-CVD 8.4%; p=0.08). There was also a trend towards more frequent congenital malformations among offspring born to GUCH women (7.4% vs. 2.4%; p=0.06).

Discussion

Maternal CHD is traditionally associated with poorer pregnancy outcomes, mainly through increased risk of cardiac events in the mother and complications in the foetus.[6] Neonatal complication rates of 20-28% and neonatal mortality of 1-4% have been reported among women with all forms of heart disease.[3,4,8,13,14] The commonest reported complications are premature births, small-for-gestational-age birthweights and respiratory distress syndrome. The maternal predictors of neonatal events are baseline NYHA class >II or cyanosis, maternal left heart obstruction, smoking during pregnancy, multiple gestation, use of oral anticoagulation during pregnancy and the presence of a mechanical valve prosthesis.[6] Hypertensive diseases of pregnancy and postpartum haemorrhage (PPH) are the commonest obstetric complications reported in women with heart disease.[3,13] Contrary to maternal and neonatal complications, the reported experience with obstetric complications is more variable. Whereas the CARPREG found coarctation of the aorta as an independent predictor for pregnancy-induced hypertension and use of anticoagulants in the peripartum period and cyanosis as independent predictors for PPH [4], the ZAHARA investigators found no such associations in their cohort.[8]

Adverse maternal cardiac events were only observed in one of the 27 GUCH pregnancies (3.7%) in our cohort, with the same patient developing symptomatic paroxysmal atrial arrhythmia as well as heart failure. This pregnancy was the one with the highest predicted risk in our cohort (CARPREG risk = 27%; ZAHARA risk = 70%; modified WHO class III). Arrhythmias and heart failure have been consistently reported as the commonest maternal cardiovascular complications.[3,4,8,15] Our cardiac event rate of 3.7% is lower than what has been reported in most large studies concentrating on pregnancy in women with CHD, where cardiac event rates ranged from 4% to 25%.[1,3,5,8,13,16,17] Although this finding is reassuring, it should be interpreted with caution as it is likely to be, at least partly, due to fewer women with more complex forms of CHD and poorer baseline cardiac status in the Maltese GUCH cohort when compared to other studies referred to earlier. In fact, both CARPREG and ZAHARA risk scores for the 23/27 patients in the Maltese GUCH cohort with complete pre-pregnancy echocardiographic data were low, with an overall CARPREG mean risk of 6.91 ± 6.34% (median 5%) and an overall ZAHARA mean risk of 8.25 ± 13.89% (median 2.9%). Similarly, only three pregnancies occurred in women considered to be at high risk of maternal cardiac complications by modified WHO classification, with all other pregnancies being in lower risk categories (Table 1).

The commonest primary cardiac lesion in our series was tetralogy of Fallot (TOF) (6/27 in 6 patients; 22.2% pregnancies), followed by coarctation of the aorta (4/27 in 3 patients; 14.8% pregnancies). No maternal cardiac events were reported in either of these groups. RV dysfunction and/or moderate to severe PR have been reported as the main risk factors for cardiac complications in pregnancies in women with TOF.[6,18-20] All our TOF patients had undergone complete repair in infancy or early childhood. Although two women had moderate pulmonary regurgitation
(PR) and one had severe PR, all 6 patients were asymptomatic and all had normal right ventricular (RV) function at baseline. All three coarctation patients in our cohort had undergone surgical repair, and none had significant residual hypertension prior to pregnancy. Consequently, they were all at low risk of aortic rupture and cerebral aneurysm rupture, which are the maternal complications mostly reported in this patient group.[6]

Three women went through a high-risk pregnancy: one patient with atrial switch (Mustard repair) for transposition of the great arteries (TGA) and two patients with Fontan-type palliation. Our only atrial switch patient had good systemic RV function, no significant TR and no previous arrhythmias, putting her in a more advantageous position for a good maternal outcome.[6,21-23] Both women with Fontan palliation had good NYHA status, retained ventricular function and no significant atrioventricular valve regurgitation at baseline, all factors considered favorable with this type of circulation.[6] However, a previous history of atrial arrhythmias requiring treatment and a possibly less efficient type of Fontan circuit (classical Fontan with right atrium to pulmonary artery conduit) in the patient with AP Fontan resulted in a difference in occurrence of cardiac events between the pregnancies.[24] Thus, even when assessed by cardiac lesion, most of our patients tolerated pregnancy without maternal complications, largely because their anatomy and function at baseline put them at the more favourable end of the spectrum.

Our study is one of few in the literature to compare pregnancy outcomes in GUCH patients with those in contemporary women without heart disease from the same population.[1,14,17,25] There were significantly more deliveries by Caesarean section and fewer normal vaginal deliveries in our GUCH cohort, which compares to the reported literature.[1,14,17,25] There was no excess of obstetric complications in our GUCH pregnancy cohort when compared to non-CVD women (Table 4). These findings are similar to those reported in the Canadian study by Siu et al[14], the German study by Hrycyk et al[25] and those stemming from the Registry Of Pregnancy And Cardiac disease (ROPAC).[17] Conversely, in their nationwide U.S. study from 2015, Thompson et al found the odds of several obstetric complications, including gestational diabetes, preterm labour, placental abruption and postpartum haemorrhage, to be significantly higher among delivery hospitalisations for women with CHD.[1]

Overall, neonatal outcomes in our GUCH cohort were good and, in the main, not significantly worse than those in the non-CVD cohort. Although there was a higher rate of premature

### Table 1.

<table>
<thead>
<tr>
<th>Modified WHO class I (n=9)</th>
<th>Number of pregnancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaired ASD</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Repaired PS</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Repaired pAVSD</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td><strong>Modified WHO class II / II-III (n=15)</strong></td>
<td></td>
</tr>
<tr>
<td>Repaired CoA</td>
<td>4 (14.8%)</td>
</tr>
<tr>
<td>Unoperated VSD</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Repaired TOF</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>SAS</td>
<td>3 (11.1%)</td>
</tr>
<tr>
<td>Congenital AS</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td><strong>Modified WHO class III (n=3)</strong></td>
<td></td>
</tr>
<tr>
<td>Fontan-type palliation</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>TGA-Mustard</td>
<td>1 (3.7%)</td>
</tr>
</tbody>
</table>

Congenital heart lesions in the 27 GUCH pregnancies divided by modified WHO classification of maternal cardiovascular risk [6,7]. Abbreviations: ASD = atrial septal defect; VSD = ventricular septal defect; PDA = patent ductus arteriosus; CoA = coarctation of the aorta; TOF = tetralogy of Fallot; PS = pulmonary stenosis; TAPVD = total anomalous pulmonary venous drainage; SAS = subaortic stenosis; TGA = transposition of great arteries; AS = aortic stenosis; pAVSD = partial atrioventricular septal defect; WHO = World Health Organisation

### Table 2.

<table>
<thead>
<tr>
<th>(a) Clinical characteristics (N = 27)</th>
<th>Number of pregnancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>NYHA functional class I</td>
<td>27 (100)</td>
</tr>
<tr>
<td>History of atrial arrhythmias</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>History of ventricular arrhythmias</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Permanent pacemaker / ICD in situ</td>
<td>0 (0)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Cardiac medications (N = 27)</th>
<th>Number of pregnancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelets</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Oral anticoagulant</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antihtypertensive agent</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(c) Echocardiographic parameters (N = 23)*</th>
<th>Number of pregnancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic ventricular dysfunction</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Subpulmonary ventricular dysfunction</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Moderate aortic outflow tract obstruction</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Severe aortic outflow tract obstruction</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Moderate pulmonary outflow tract obstruction</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Severe pulmonary outflow tract obstruction</td>
<td>0 (0)</td>
</tr>
<tr>
<td>More than mild mitral regurgitation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>More than mild aortic regurgitation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>More than mild tricuspid regurgitation</td>
<td>0 (0)</td>
</tr>
<tr>
<td>More than mild pulmonary regurgitation</td>
<td>3 (13)</td>
</tr>
</tbody>
</table>

Maternal baseline cardiac characteristics for the 27 pregnancies in the GUCH cohort.

* Complete echocardiographic data was available for 23/27 pregnancies.

Abbreviations: ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association
Comparison of obstetric complications between GUCH and non-Maternal death 0/27 (0%)
Dystocia 0/27 (0%)
Blood transfusion 0/27 (0%)
(1l in 2hrs) 0/27 (0%)
Haemorrhage
Retained placenta 0/27 (0%)
24hrs 0/27 (0%)
Hysterectomy within
Gestational diabetes 0/27 (0%)
eclampsia 0/27 (0.0%)
Pre-eclampsia/hypertension 0/27 (0.0%)
Gestational Infections 0/27 (0%)
Suspected IUGR 2/27 (7.4%)
Placental abruption 0/27 (0.0%)
Placenta praevia 0/27 (0.0%)
Antepartum labour 0/27 (0%)
Threatened premature labour 0/27 (0%)
Antepartum haemorrhage 0/27 (0.0%)
Peripartum haemorrhage 0/27 (0%)
Preeclampsia 0/27 (0%)
Eclampsia 0/27 (0.0%)
Gestational hypertension 0/27 (0%)
Infections 0/27 (0%)
Suspected IUGR 2/27 (7.4%)
singleton pregnancies)
Male infant gender 14/27 (51.9%)
Pregnancy duration (weeks)+ 38 (range 36 - 41)
Premature birth§ 3/27 (11.1%)
Small for gestational age$ 5/27 (18.5%)
Birth weight (grams)# 3027 [2821, 3232] [3030]
Congenital malformations 2/27 (7.4%)
Still births / neonatal deaths 0/27 (0%)
Cardiac events and need for cardiac medication use during pregnancy in the 27-patient GUCH pregnancy cohort
+ The only patient to develop significant cardiac events during pregnancy and to require anticoagulation, antiarrhythmic therapy and a diuretic was a patient with atrio pulmonary Fontan for tricuspid atresia.
Cardiac events
Heart failure
Atrial arrhythmias requiring treatment
Ventricular arrhythmias requiring treatment
Thromboembolic events
Infected endocarditis
Need for urgent percutaneous / surgical intervention
Cardiac medications used during pregnancy
Antihypertensive agent
Diuretic
Antiarrhythmic agent/s
Low-molecular weight heparin
Anticoagulant agent
Antithrombotic agent/s
Low-molecular weight heparin
Antiplatelets
Comparison of offspring outcomes between pregnancies in the two study cohorts
+ Pregnancy duration is expressed as median followed by range in weeks
§ Rates of premature birth and small for gestational age babies (<10th centile for gestational age) are expressed as percentages out of all live births
# Birth weight is expressed as mean with 95% confidence intervals followed by median in square brackets.
+* Statistically significant differences are shown in bold

<table>
<thead>
<tr>
<th>Table 3.</th>
<th>Number of pregnancies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac events</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (3.7)+</td>
</tr>
<tr>
<td>Atrial arrhythmias requiring treatment</td>
<td>1 (3.7) +</td>
</tr>
<tr>
<td>Ventricular arrhythmias requiring treatment</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infected endocarditis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Need for urgent percutaneous / surgical intervention</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Cardiac medications used during pregnancy</strong></td>
<td></td>
</tr>
<tr>
<td>Antithrombotic agent</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1 (3.7)*</td>
</tr>
<tr>
<td>Antiarrhythmic agent</td>
<td>1 (3.7)*</td>
</tr>
<tr>
<td>Low-molecular weight heparin</td>
<td>1 (3.7)*</td>
</tr>
<tr>
<td>Anticoagulant agent</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 4.

<table>
<thead>
<tr>
<th>Complication</th>
<th>GUCH pregnancies</th>
<th>Non-CVD pregnancies</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened abortion</td>
<td>1/27 (3.7%)</td>
<td>28/540 (5.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Threatened premature labour</td>
<td>0/27 (0%)</td>
<td>13/539 (2.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>0/27 (0.0%)</td>
<td>9/540 (1.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Placenta praevia</td>
<td>0/27 (0.0%)</td>
<td>2/539 (0.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>0/27 (0.0%)</td>
<td>3/540 (0.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Suspected IUGR</td>
<td>2/27 (7.4%)</td>
<td>28/539 (5.2%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Infections</td>
<td>0/27 (0%)</td>
<td>32/540 (5.9%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>0/27 (0.0%)</td>
<td>37/540 (6.9%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Pre-eclampsia/eclampsia</td>
<td>0/27 (0.0%)</td>
<td>3/540 (0.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>0/27 (0%)</td>
<td>25/539 (4.6%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hysterectomy within 24hrs</td>
<td>0/27 (0%)</td>
<td>0/540 (0%)</td>
<td>/</td>
</tr>
<tr>
<td>Retained placenta</td>
<td>0/27 (0%)</td>
<td>3/540 (0.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Haemorrhage (11 in 2hrs)</td>
<td>0/27 (0%)</td>
<td>0/540 (0%)</td>
<td>/</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0/27 (0%)</td>
<td>2/539 (0.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dystocia</td>
<td>0/27 (0%)</td>
<td>1/540 (0.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Maternal death</td>
<td>0/27 (0%)</td>
<td>0/540 (0%)</td>
<td>/</td>
</tr>
</tbody>
</table>

Comparison of obstetric complications between GUCH and non-CVD cohorts
Abbreviations: IUGR = intrauterine growth retardation

Births in our GUCH cohort (11.1% vs. 4.1%), this difference did not reach statistical significance (p=0.11). Furthermore, the lowest pregnancy duration observed was only 36 weeks and there were no cases of severe prematurity. This contrasts with the observations made by other studies where higher rates of premature births in GUCH pregnancies [4,26], as well as significantly more premature births when compared to women without heart disease, were reported.[14,17] However, it should be noted that some of these studies included other forms of heart disease apart from CHD and had a higher proportion of women with a less favourable baseline maternal status and thus a higher propensity for poorer neonatal outcomes.

The main difference in offspring outcomes observed between patient and control cohorts related to significantly smaller babies born to women with CHD (median birth weight GUCH 3030g vs. non-CVD 3230g; p=0.045). There was also a trend towards more babies being small-for-gestational age in the GUCH cohort (18.5% vs. 8.4%; p=0.08). This observation has been documented by several other studies.[17,25,27] Maternal cyanosis and poor cardiac output are recognized as the main risk factors for foetal growth restriction and lower birth weights.[27] The fact that, on the whole, our GUCH cohort consisted of women with good saturations and satisfactory cardiac output at baseline, and that use of medications linked with IUGR was minimal, suggests that there might be other less well-recognized factors coming into play to interfere with foetal growth in mothers with CHD. It could also be argued that the “cardiologist’s definition” of good cardiac output based on imaging and functional status might not necessarily translate into equally good utero-placental flow.
Limitations

The small Maltese GUCH population and the even smaller numbers of female patients that became pregnant during the study period, which in themselves are an inevitable consequence of the small size of the country, represent the main limitation of this study. It is possible that some women with CHD of mild complexity who were not under regular specialist follow-up and were deemed to be at very low risk in pregnancy might have delivered in private centres and thus failed to be included due to lack of documentation in hospital records. Notwithstanding, the fact that most Maltese deliveries on the islands take place in state-run hospitals irrespective of maternal or obstetric risk makes it likely that missed GUCH pregnancies were few and that only women with mild or trivial lesions were selected out. A further limitation is the retrospective nature of the study which resulted in some patients having incomplete data, though this was limited to few patients who were not under regular specialist clinical follow-up. The comparison of outcomes between GUCH and non-CVD cohorts relied on outcomes routinely collected by NOIS. Because NOIS only captures pregnancies that end in the birth of a baby of ≥22 completed weeks, comparison of miscarriage rates could not be performed.

Conclusions

Although pregnancy in the presence of maternal CHD can be of higher risk to mother and foetus, our findings reinforce the fact that, with careful preconceptual counselling and close monitoring by a specialist team of cardiologists, obstetricians and anaesthetists, pregnancy outcomes can be comparable to those in women without heart disease. The presence of maternal CHD appears to predispose to lower infant birth weight, even in women with less complex disease and good baseline functional status. While risk-predicting tools are a helpful guide, advice to prospective mothers needs to be tailored to the individual patient’s case, taking into account not only the woman’s functional status but also the services and infrastructure of the institution where the pregnancy will be followed and delivery performed so as to ensure safety at all stages.[28] Finally, large multi-centre collaborations like the European Society of Cardiology’s ROPAC [29] which also include data about follow-up after pregnancy, will help shed more light on the long-term impact that pregnancy could have on cardiac function in women with CHD, particularly in an era where access to assisted reproductive technology, often with use of hormonal therapy and a higher possibility of multiple pregnancies, is increasing in many countries.

Declarations of interest:
The authors declare no conflicts of interest.

Acknowledgements

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals.” [30]

References


Estimation of Risk Factors for Cardiogenic Shock in Takotsubo Cardiomyopathy: A Retrospective Study

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Highlights

Background
Presentation of Takotsubo cardiomyopathy (TCM) widely varies amongst the patients, ranging from asymptomatic patients to cardiogenic shock or even cardiac arrest. The underlying risk factors inherent to the patient that predispose to a catastrophic presentation have not been delineated well in the past. Objective: To distinguish risk factors and presenting characteristics of patients diagnosed with cardiogenic shock from TCM.

Methods
Total 51 angiography-confirmed TCM patients admitted in Upstate Hospital from 2010 – 2014 were compared retrospectively, 13 presenting with cardiogenic shock.

Results
While TCM was predominantly common in elderly females, four of the total six male TCM patients presented with shock (Odds ratio= 8.0, p=0.027). TSH was higher in cardiogenic shock group. Patients with shock had significantly higher incidence of ST elevations on EKG and higher peak troponins. Moreover, ST elevations were predominantly in the inferior, anteroseptal and lateral leads in the shock group as compared to only the septal leads in the control group. Echocardiography revealed lower LV ejection fraction, LV outflow tract obstruction and concomitant significant mitral regurgitation in shock patients. No correlation was found with age, BMI, coronary disease risk factors (diabetes, hypertension, smoking), coincident infection, electrolyte imbalance, QTc interval length.

Conclusions
Risk factors and pathophysiology for cardiogenic shock in TCM were identified. TCM in males is rare, but male gender is a risk factor for shock.

Keywords: Takotsubo; cardiogenic shock; echocardiography

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Estimation of Risk Factors for Cardiogenic Shock in Takotsubo Cardiomyopathy: A Retrospective Study

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Background/Objectives:
Takotsubo cardiomyopathy (TCM) is characterized by acute transient ischemic left ventricular dysfunction usually accompanied by electrocardiographic (EKG) changes and elevated cardiac biomarkers in the absence of significant coronary artery disease. TCM can have a fairly complex and catastrophic presentation but early diagnosis and appropriate treatment results in very low mortality. The severity of TCM presentation varies between patients and is likely related to the variable degree of myocardial ischemic damage, ventricular systolic dysfunction and circulatory failure. Prevalence of complications including cardiogenic shock is reported to be as high as 20% patients (1-4) though the pathogenesis remains elusive and under-estimation can be disastrous. Pre-existent literature has attempted to identify various risk factors that may predispose to cardiogenic shock in such patients, including the role of gender, age, BMI, coronary disease risk factors (diabetes, hypertension or smoking), electrolyte imbalance, extent of ischemic damage and pathological changes in myocardium identified on echocardiography(5-8). An understanding of the risk factors inherent to the patient as well as the disease related manifestations linked to presentation with shock can help early risk-stratification, assessment of severity, anticipation of the future course and guide appropriate therapy. The premise of the
present study was to determine the factors that were linked to presentation with shock in our hospital, further the understanding of the pathogenesis and early, accurate estimation of poor outcome. The hypothesis was to test the previously proven risk factors and define new factors. This study would be most clinically relevant in emergency department during the initial triage of TCM patients.

Methods

Study population
We did a retrospective case control study with age matched cohort selected from patients admitted in a single tertiary facility- SUNY Upstate Hospital, Syracuse, NY. Appropriate Institutional Review Board exemption was obtained (IRB exemption number 719685-1). Inclusion criteria was based on the proposed Mayo Clinic criteria (9): Adults(>18 years) with presentation mimicking myocardial infarction with ST-T wave changes in electrocardiogram(EKG) and/or elevation of troponins, typical echocardiographic picture of acute onset regional wall motion abnormalities with or without apical ballooning and or insignificant(<50% stenosis) coronary artery disease(CAD) on catheterization. Patients with pre-existent heart failure with left ventricular ejection fraction(LVEF)<45% were excluded from the study. A total of 51 patients were discharged with a diagnosis of TCM between January 2010 and December 2014 meeting the above mentioned criteria.

Definitions

Cardiogenic shock(CS) was defined as systolic blood pressure<90 mm Hg requiring inotropic/vasopressor support or presentation with cardiac arrest/ventricular arrhythmia requiring resuscitation. LV outflow tract obstruction(LVOTO) was defined as outflow tract peak instantaneous pressure gradient >=30 mmHg on continuous wave Doppler and systolic anterior motion of mitral leaflet on 2D-images and confirmed via Doppler, occurring prior to the use of inotropic agents. ST elevation was defined as ≥2 mm in leads V2–V3 and ≥1 mm in other leads in two or more contiguous leads, significant inverted T wave as ≥0.5 mm. Concomitant infection was defined as patients meeting sepsis criteria at presentation with a known source of infection at discharge or death.

Study protocol

Commonly ordered, relevant and widely available laboratory studies were included in the study- Serum potassium, magnesium, cardiac enzymes, thyroid stimulating hormone (TSH) and pro-brain natriuretic peptide (pro-BNP). Cardiac enzymes [creatine kinase (CK), creatine kinase MB fraction (CK-MB) and troponin T] were followed until normalization or death. Only the levels checked at the time of presentation were used in the study. Unfortunately, free T4 was not available for most patients so it was excluded from the study.

Modified Simpson’s biplane method was used for calculation of LVEF. Echocardiographic color Doppler was used for quantification of mitral regurgitation. QTc length was calculated using the Bazett’s formula and QTc prolongation was defined as QTc> 450ms for males and >460ms for females. Only patients who underwent cardiac catheterization to confirm the diagnosis of TCM were included.

Statistical analysis

IBM SPSS (version 19.0, SPSS Corp, Chicago, IL, USA) was used for statistical analysis. Qualitative data is presented as frequencies and quantitative data as mean ± standard deviation. Categorical variables were compared by using Chi-square test, and continuous variables were compared using Student’s t-test. The statistical analysis was performed individually on all the studied variables using the above mentioned tests as appropriate and they were categorized as below:

1. Clinical characteristics at presentation: age, gender, body mass index (BMI), presence of hypertension (HTN), diabetes (DM), smoking history, β-blocker use, TSH, electrolyte levels, proBNP. (Table 1)
2. Clinical indicators of TCM on laboratory, EKG and echocardiography: Peak troponin value, QTc interval length, LVEF, left ventricular end-diastolic pressure (LVEDP), presence of tachycardia, new bundle branch block, ST elevation, new significant (moderate or severe) mitral regurgitation and LVOTO. (Table 2)

The factors with significant association then underwent multivariate logistic analysis in their groups. P value < 0.05 was considered significant.

Outcome/Follow-up

Echocardiography was obtained at the time of presentation and only patients with documented significant resolution of wall motion abnormality in follow up imaging within 6 months were included. Outcome data was obtained up to 6 months from discharge, including- follow up imaging, recurrence of TCM or death.

Results

A total of 45 patients (88.2%) were females while 6 patients (11.8%) were males. Thirteen patients(25.5%) presented with cardiogenic shock as defined above. The rest of the patients with normal hemodynamic status or those that did not fit the definition of cardiogenic shock were added as controls. The mean age between the groups was not significantly different (65.9 vs 61.2 years, p=0.226). The most common presenting symptom in TCM was chest pain (43%) followed by shortness of breath (20%), altered mental status most commonly from drug overdose (16%) and gastrointestinal symptoms like nausea, abdominal pain (6%). Previous psychiatric illness history such as depression or anxiety disorder was present in 49% patients and a preceding stress was identified in 47% patients. Among the other characteristics, 55% had history of alcohol use, 73% had smoking history and 39% had chronic pain issue with prescription opioid use, 29% were diabetic and 71% were hypertensive.

Comparison of clinical characteristics at presentation:

Of the clinical characteristics named in the ‘Statistical analysis’ section, only gender and TSH exhibited statistical significance (table 1). On multivariate logistic regression analysis of gender and TSH, only gender had a significant value (p= 0.027) with males having an odds ratio of 8 to present with cardiogenic shock as compared to females (95% confidence interval: 1.26 to 50.7, p= 0.027).
Comparison of clinical indicators of TCM:

EKG comparison revealed diffuse T wave inversion and absence of reciprocal changes uniformly in both groups. ST elevation was present in 17 patients (33.3%), and was statistically more common in the shock group (p=0.012). No significant difference was found in terms of incidence of tachycardia, new bundle branch block or QTc interval length (table 2). ST elevations were predominantly in the inferior, anteroseptal and lateral leads in the shock group as compared to only septal leads in the control group, while leads V1 and aVR remained the least involved in both the groups together (figure 1). Inferior lead ST elevation was significantly more common in the shock group (p=0.012). No significant difference was present in 17 patients (33.3%), and was statistically more common in shock group (75% vs 61.5%) but this was not a significant finding (p=0.523). Heart rate for ST elevation was 5.12 ± 10.85 vs 4.15 ± 1.12 which was not a significant finding (p=0.083). The pathogenesis of Takotsubo cardiomyopathy remains elusive but the suggested mechanisms include widespread coronary vasospasms, catecholamine or neurogenic stunning of myocardium as a result of sympathetic overstimulation from intense and sudden stress, impairment of microvascular perfusion or less likely transient myocarditis (10,11). In the present study an attempt was made to improve our understanding about TCM through identification of factors that may precede or coincide with cardiogenic shock presentation, understanding about TCM through identification of factors that may precede or coincide with cardiogenic shock presentation, allowing us to use the information in clinical practice for risk stratification and anticipation of possible catastrophic change in patient’s clinical course.

Discussion

The presentation of TCM may closely mimic myocardial infarction and the severity of ventricular dysfunction may be variable resulting in a spectrum of symptoms and signs. The pathogenesis of Takotsubo cardiomyopathy remains elusive but the suggested mechanisms include widespread coronary vasospasms, catecholamine or neurogenic stunning of myocardium as a result of sympathetic overstimulation from intense and sudden stress, impairment of microvascular perfusion or less likely transient myocarditis (10,11). In the present study an attempt was made to improve our understanding about TCM through identification of factors that may precede or coincide with cardiogenic shock presentation, allowing us to use the information in clinical practice for risk stratification and anticipation of possible catastrophic change in patient’s clinical course.

Table 1.

<table>
<thead>
<tr>
<th>Findings</th>
<th>Cardiogenic shock</th>
<th>Stable Hemodynamics</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age(years)</td>
<td>65.92</td>
<td>61.29</td>
<td>0.226</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4(30.8%) (96.2%)</td>
<td>2(5.3%) 36(94.7%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI(kg/m2)</td>
<td>36.61</td>
<td>29.72</td>
<td>0.096</td>
</tr>
<tr>
<td>Diabetes(n)</td>
<td>6(46.2%)</td>
<td>9(23.7%)</td>
<td>0.125</td>
</tr>
<tr>
<td>Hypertension(n)</td>
<td>10(76.9%)</td>
<td>26(68.4%)</td>
<td>0.561</td>
</tr>
<tr>
<td>Smoking(n)</td>
<td>8(61.5%)</td>
<td>29(76.3%)</td>
<td>0.303</td>
</tr>
<tr>
<td>Prior β-blocker use(n)</td>
<td>4(30.8%)</td>
<td>4(10.5%)</td>
<td>0.083</td>
</tr>
<tr>
<td>Coincident infection(n)</td>
<td>5(38.5%)</td>
<td>11(28.9%)</td>
<td>0.523</td>
</tr>
<tr>
<td>TSH(mIU/L)</td>
<td>5.52 ± 10.85</td>
<td>1.43 ± 1.23</td>
<td>0.050</td>
</tr>
<tr>
<td>proBNP (pg/mL)</td>
<td>4928 ± 4227</td>
<td>2696 ± 1995</td>
<td>0.143</td>
</tr>
<tr>
<td>Potassium(mmol/L)</td>
<td>3.8 ± 0.6</td>
<td>3.9 ± 0.5</td>
<td>0.703</td>
</tr>
<tr>
<td>Magnesium(meq/L)</td>
<td>1.49 ± 0.20</td>
<td>1.49 ± 0.27</td>
<td>0.971</td>
</tr>
</tbody>
</table>

Clinical characteristics of patients. In parentheses: percentage of patients with the finding among shock and normal hemodynamic group respectively.

Table 2.

<table>
<thead>
<tr>
<th>Findings</th>
<th>Cardiogenic shock</th>
<th>Stable hemodynamics</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak troponin T (ng/ml)</td>
<td>2.32 ± 4.20</td>
<td>0.74 ± 1.01</td>
<td>0.035</td>
</tr>
<tr>
<td>Time for troponins to peak(hours)</td>
<td>6.6 ± 6.2</td>
<td>4.6 ± 3.7</td>
<td>0.179</td>
</tr>
<tr>
<td>Tachycardia(n)</td>
<td>8(61.5%)</td>
<td>16(42.1%)</td>
<td>0.226</td>
</tr>
<tr>
<td>ST elevation(n)</td>
<td>8(61.5%)</td>
<td>9(23.7%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Inferior lead ST elevation(n)</td>
<td>6(75%)</td>
<td>1(11.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>459.69 ± 47.08</td>
<td>473.05 ± 40.72</td>
<td>0.331</td>
</tr>
<tr>
<td>Moderate or severe mitral regurgitation(n)</td>
<td>9(69.2%)</td>
<td>8(21.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>New bundle branch block(n)</td>
<td>3(23.1%)</td>
<td>6(15.8%)</td>
<td>0.552</td>
</tr>
<tr>
<td>LVOTO(n)</td>
<td>9(69.2%)</td>
<td>5(13.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF(%)</td>
<td>26.9 ± 9.0</td>
<td>33.0 ± 8.6</td>
<td>0.035</td>
</tr>
<tr>
<td>LVEDP(mm Hg)</td>
<td>35.0 ± 22.2</td>
<td>26.3 ± 7.0</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Clinical indicators coincident with TCM. In parentheses: percentage of patients with the finding among shock and normal hemodynamic group respectively.
It has been reported that TCM patients are more likely to develop cardiogenic shock as compared to their ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI) counterparts(12) and the prevalence of cardiogenic shock in TCM varies from 4 to 20%(2,3). In-hospital cardiac mortality from TCM ranges from 0 to 2% (3,13) while all-cause mortality ranges from 0 to 9% (2,6,13,14). A diagnosis of TCM as a cause of cardiac arrest and shock can only be made if the patient survives the initial insult(15). Such patients may get misdiagnosed as myocardial infarction in the absence of catheterization, thus possibly underestimating the prevalence and mortality associated with TCM.

In the present study, males were seen to have eight times the risk to have cardiogenic shock but the number of males in our study was small. A similar higher risk, however, was also found in a National Inpatient Sample (NIS) database study of 24,701 TCM patients(6). Murakami et al(16) documented an odds ratio of 4.32 amongst males to have in-hospital composite cardiac events as compared to females as well as a higher incidence of Killip Class >= 3 ventricular failure and ventricular arrhythmia. In a follow-up study of 286 TCM patients (17), male sex was found to be an independent predictor of mortality. Similarly, in a study on Medicare beneficiaries, males were seen to have worst outcomes (18) amongst TCM patients. The cause of this gender disparity is difficult to ascertain but the hypotheses could include: higher overall coronary disease burden in males, higher rate of coincident precipitating illness such as sepsis (6) and a greater influence of physical rather than emotional stress amongst males(16,19)

Anatomically, TCM is characterized by wall motion abnormalities that span beyond the territory of a single coronary artery (9). Apical involvement is a feature of TCM possibly from the limited blood supply to the apex making it vulnerable to ischemia and hypofunction. It is also proposed that apex is sensitive to adrenergic overstimulation(10). Higher troponin T levels in cardiogenic shock group found in our study could mean a bigger infarct size(20-22), indicating a bigger ischemic burden. This finding was also supported by the lower LVEF in shock patients. The time required for the troponins to peak was comparable in both groups. proBNP was higher in the shock group but lacked statistical significance due to low power.

ST-elevations in EKG were statistically more common in the shock group. Comparison of leads involving ST-elevation in both the groups gave an interesting outlook into the pathogenesis. In patients with cardiogenic shock, ST elevations were present uniformly in inferior, anteroseptal and lateral leads- II, III, aVF, I, aVL, V3-V6 (figure 1). On the other hand, the control group had ST elevations predominantly in the anteroseptal leads V2-V4 while both the groups predominantly spared leads V1 and aVR. This contrasting finding may again support the hypothesis of extensive infarct size among shock patients and possible simultaneous involvement of left anterior descending and left circumflex arteries. The relative sparing of leads V1 and aVR has been discussed in the past and is possibly related to non-extension of wall motion abnormalities to the areas represented by these leads (23,24).

Left ventricular tract obstruction(LVOTO) results from basal LV wall hyperkinesis and systolic anterior motion of the mitral leaflet(25) and the incidence is estimated between 20 to 50% of TCM patients(5,26,27). In the present study, LVOTO was significantly more common in the cardiogenic shock group and this is in agreement with previous reports (5). In fact, LVOTO along with ST elevation on EKG, were significant predictors of underlying cardiogenic shock(table 3). Treatment of these patients with inotropic agents can exacerbate the underlying obstruction through stimulation of the already hyperdynamic basal segment and worsen the shock(2,7,25). In addition, cardiogenic shock patients had higher incidence of significant mitral regurgitation and LVEDP, likely as a consequence of the underlying systolic dysfunction and LVOTO(5).

The role of early β-blocker in TCM has been controversial. Their use in cardiogenic shock associated with LVOTO has been suggested to allow better diastolic relaxation, better forward flow and improvement in systolic pressure(2,27,28), conversely, their role in improving short term mortality has been questioned recently (29). Similarly, the use of β-blockers to prevent recurrence has not been proven beyond doubt (2,25,30,31). Of the three patients with recurrence of TCM in our study, two had been started on β-blockers as outpatient prior to the recurrence. On the other hand, the prescription of β-blockers as outpatient jumped from 16% to 61% patients after the diagnosis of TCM and only 5% of the patients experienced recurrence. The recurrence rate of TCM is estimated to be up to 11.4% in previous studies (32,33), thus the recurrence rate was much lower in this study. Other medications like aspirin, angiotensin-converting enzyme inhibitors, statins have not been shown to prevent recurrence (31).

Another highlight of the study was the presence of significantly higher TSH in cardiogenic shock patients. This phenomenon can
be difficult to explain based on the currently available literature with reports incriminating hypothyroidism (8,34) as well as hyperthyroidism (35-37) as the cause of TCM. The proposed mechanisms in hypothyroid patients include higher level of circulating catecholamine (38), coronary artery vasospasms (34,39), increased sympathetic reactivity(8) or pre-existent dilated cardiomyopathy(40), while similar number of hypotheses exist for hyperthyroidism. Nevertheless, hypothyroidism was not a significant clinical risk predictor in our multivariable regression analysis. This underlines the fact that very little is known of the pathogenesis of TCM.

Published literature has attempted to identify various risk factors that may pre-dispose to cardiogenic shock in TCM patients and an understanding of these factors can help early estimation of worse outcome and initiation of aggressive approach to treatment. This study aimed to further substantiate the understanding of potential comorbidities that are associated and can be hypothesized to influence the outcome in TCM patients. Future research should be directed towards understanding the role of the identified comorbidities which may result in determination of potentially modifiable factors through prevention or early intervention in the course of the disease. Research on takotsubo cardiomyopathy is always faced with the hurdle of low power, as is the case with this study, but this should not deter future researchers as such manuscripts help in understanding the disease one step at a time.

Conclusion
In conclusion, this study highlights gender bias in prevalence of TCM among females but also identifies the possibility of males at a higher risk for cardiogenic shock, confirmation would be needed through a larger study. Left ventricular tract obstruction and diffuse ST elevations were proven to be relatively strong predictors of underlying cardiogenic shock and a suggestion was made for possible role in pathogenesis. The controversy surrounding the role of β-blocker and thyroid hormonal imbalance in pathogenesis and/or prevention of TCM was discussed. The role of some of the previously suggested risk modifying factors such as age, diabetes, coincident infection, QTc length were not substantiated.

Study limitations
The limitations of the study included the retrospective design and single facility patient selection. TCM is a rare disease and the sample size was small to moderate compared to previous studies. Very small number of male patients in the study limited the possibility of making any conclusive statements about gender bias in the severity of presentations. In order to reduce any false positive results, we employed a strict inclusion and exclusion criteria and this resulted in inability to extrapolate the results to patients with kidney disease and heart failure. Cardiogenic shock is a relatively rare manifestation in TCM which further reduced the power of some of the tests. Power of certain lab values including proBNP were low to achieve statistical significance.

Declarations of interest
The authors declare no conflicts of interest.

Acknowledgments
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals”[41]

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Angina In Patients with Non-Obstructive Coronary Angiograms: Six-Years Follow-up

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Introduction
Flow-limiting atherosclerotic lesions in the epicardial coronary arteries have long been recognized as the underlying pathological mechanism for myocardial ischemia in patients with angina [1,2]. However, approximately one third of patients undergoing coronary angiography for angina have no significant coronary artery stenosis [3]. In these patients a number of mechanisms for chest pain have been proposed including microvascular disease, diffuse arterial wall calcification and non-cardiac causes [4-8], but little is known about related cardiovascular (CV) events. Conventional management of these patients used to be only reassurance based on the perceived good prognosis [9-11]. Such approach resulted in frequent clinical visits, repeated investigations without satisfactory explanation of symptoms, development of depression and a shift towards alternative medical assistance [12-14]. Recent studies have shown such patients to have increased risk of major CV events compared with asymptomatic reference population [15-18].

This study aims at evaluating the long term persistence of angina and occurrence of major CV events in patients with stable angina and non-obstructive coronary angiograms.

Methods
We retrospectively evaluated all patients presented between 1st July 2008 and 31st December 2009, who received elective cardiac assessment and coronary angiography at the Cardiovascular Unit.
of the University of Catania, Sicily, because of clinical suspicion of obstructive coronary artery disease as a cause for chest pain. All patients had a positive stress test defined as >1 mm ST shift in more than one lead or already existing ECG changes at rest (ST depression or T wave inversion). Typical angina was defined as exertional chest pain relieved by rest or nitrates. All patients received a diagnostic coronary angiography through the femoral artery, using conventional Judkins procedure. Non-obstructive coronary disease was defined as <50% stenosis of the left main stem artery or <70% in any of the epicardial coronary arteries [19]. Patients were excluded if they had recent or previous myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft, heart failure with reduced left ventricular ejection fraction, ≤40% on echocardiography, aortic stenosis or hypertrophic cardiomyopathy.

For each patient, name, gender, age, address, telephone number and CV risk factors details were collected from the clinical records. Systemic arterial hypertension was defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or taking treatment of hypertension. Dyslipidaemia was defined as total cholesterol >240 mg/dl, HDL-cholesterol <40 mg/dl (men) or <50 mg/dl (women), LDL-cholesterol >115 mg/dl, or taking treatment for dyslipidemia. Diabetes was defined as fasting blood glucose level >126 mg/dl or use of hypoglycemic medications. Smoking was defined as current or never. Family history of coronary artery disease (CAD) was defined as the presence of first-degree family member with CAD before 60 years of age. The burden of these CV risk factors for each patient was calculated as a score, counting 1 for each risk factor. Patients with previous myocardial infarction and obstructive coronary disease were excluded from the calculation of the score.

The patients included in the study had telephone medical consultation by one of the authors (SV) in 2015, to collect information about persistence of angina and/or occurrence of CV events defined as acute myocardial infarction or stroke.

Statistical analysis
Continuous variables are expressed as mean (SD) and categorical variables as frequencies. Differences between means were tested using unpaired two-sample Student t-test and differences between frequencies using Chi-square. The mean value of the CV risk factor score for each group of patients was calculated as the sum of the scores divided by the number of patients. The relationship between CV risk factors and the persistence of symptoms at follow-up was estimated with a logistic regression, using persistence of symptoms as a response and CV risk factors as independent variables. Statistical analyses were carried out using STATA 11.

Results
At baseline:
During the study period, 2574 patients (2025 men and 549 women) were referred for diagnostic coronary angiography because of exertional angina. Non-obstructive CAD was found in 151 (5.8%). These patients formed the study group. Compared to the rest of the population found to have significant coronary stenosis, the patients with non-obstructive disease were younger and a greater proportion were women. Also, the prevalence of diabetes and smoking was significantly less frequent in the non-obstructive group compared to those with significant coronary stenosis (Table 1). Hypertension and dyslipidaemia were almost equally present in about half of the two groups of patients. Only few patients did not have any of the conventional CV risk factors, however their proportion was almost double in the non-obstructive group, although the difference was not statistically significant.

Of the non-obstructive coronary disease, 79 were men (52.3%) and 72 women (47.7%) and the proportion of women was significantly higher than in the coronary obstructive group (Table 1). Women in the non-obstructive coronary disease group were older (63.3 (9.6) vs. 59.5 (12.1) years, p=0.03) and had higher prevalence of dyslipidaemia than men. In the same group, more men smoked than women. The prevalence of hypertension, diabetes and family history of CAD was not different between genders (Table 2).

The mean value of the CV risk factors score was significantly greater in the obstructive coronary stenosis group compared to the non-obstructive group [2.6 (1.0) vs. 2.3 (1.0), p=0.04].

At follow-up:
Follow-up data were available in 127/151 patients (63 men and 64 women) with non-obstructive CAD. The remaining 24 patients could not be contacted for several reasons, including change of address, wrong telephone number or they refused to give information. In this subgroup of patients, there was no age difference between women and men (63.7 (9.1) vs. 60.4 (12.6) years, p=0.09). Persistence of exertional chest pain was reported in one fifth of patients, again with no gender difference (Table 3). Overall, an acute CV event occurred in 4.7% at follow-up, 2 - 5 years after the initial angiogram. Four patients (3.1%) had acute myocardial infarction (one of whom died) and two (1.6%) had stroke. Persistence of symptoms did not correlate with the class of antianginal drugs that patients were taking or with withdrawal of treatment. Patients with persistent angina had lower mean value of CV risk scores than those without angina (1.9 (1.0) vs. 2.4 (1.1), p=0.04). No difference was found between the CV risk score of these patients and those who had cardiovascular events (2.1 (0.4), p=0.6). Dyslipidaemia was less frequent in patients with

| Table 1 Comparison of baseline demographic characteristics and CV risk factors between patients with obstructive and non-obstructive coronary artery stenosis |
|------------------------|-----------------|-----------------|-----------------|
|                        | non-obstructive n=151 | obstructive n=2423 | p               |
| Age y (SD)             | 61.3 (11.1)      | 64.5 (10.9)      | 0.0005          |
| Women (%)              | 72 (47.7)        | 549 (21.3)       | <0.0001         |
| Hypertension (%)       | 93 (61.6)        | 1512 (58.7)      | 0.48            |
| Diabetes (%)           | 30 (19.8)        | 765 (29.7)       | 0.009           |
| Dyslipidemia (%)       | 66 (43.7)        | 1296 (50.3)      | 0.11            |
| Smoking (%)            | 34 (22.5)        | 846 (32.8)       | 0.008           |
| Family history of CAD  | 51 (33.7)        | 945 (36.7)       | 0.45            |
| No risk factor         | 5 (3.3)          | 45 (1.7)         | 0.14            |

Data are expressed as mean (SD) or proportions. Comparisons are made using independent t-test or Chi2 test. Each patient may present one or more risk factors.
consistent with previous reports [21].

Despite the centres with some more proactive in offering direct anatomical diagnosis of the coronary status than others [20]. This raises the question about the nature of the angina like chest pain that patients complain of, which could be explained by either calcified epicardial vessels or microcirculation disease [4,23-26] or else non-cardiac in origin, e.g. gastroesophageal reflux, psychiatric disorders or musculoskeletal [27].

Aside from the angina symptoms, the overall acute CV event rate during the 6 year follow-up was low, which support the current perception that patients with non-obstructive coronary disease have good prognosis [22,28]. But the prevalence of acute events in our group seem to be higher than the respective rates in the general population in Italy, being 2.2% for myocardial infarction and 1.4% for stroke [29].

Such comparisons cannot be fully justified, since our patients were symptomatic and many were found to have coronary disease, even in the absence of significant stenoses. Furthermore, our patients with acute events did not show any relationship between events and conventional risk factors of atherosclerosis and they developed the events while on full risk controlling medications. Likewise, patients with consistent angina at follow-up were not different in the extent of risk factors they carried, except for a lower rate of dyslipidaemia, when compared to the asymptomatic patients. This finding to some extent contradicts the relevant use of risk factors for predicting symptoms or events, well established in the Framingham Study [30].

Another variability is the percentage of patients who continued to complain of angina at follow-up. While 20% of our patients fell in this category, a significant higher percentage has been reported by others, even at shorter follow-up [14,22]. This raises the question about the nature of the angina like chest pain that patients complain of, which could be explained by either calcified epicardial vessels or microcirculation disease [4,23-26] or else non-cardiac in origin, e.g. gastroesophageal reflux, psychiatric disorders or musculoskeletal [27].

Finally, compared to our patients with non-obstructive coronary disease, those with significant stenosis had higher rates of diabetes and smoking and overall CV risk burden, thus confirming the potential relevance of risk factors in the development of obstructive coronary disease. This however, remains to be retested in a larger sample of patients.

Discussion

Findings

Our results show that about 6% of patients with stable angina have non-obstructive coronary disease on conventional routine angiography. These patients were younger and had a lower prevalence of diabetes, smoking and an overall lower risk factors score than those with obstructive disease. After six-years follow-up, one in five of the patients with non-obstructive coronary disease continued to experience angina and one in twenty had an acute CV event. Compared to patients who remained asymptomatic after six-years follow-up, those who experienced angina had lower cholesterol and overall CV risk factor burden. Finally, those who developed acute CV events (4.7%) did not have any specific risk factors pattern or relationship between risk factors and events.

Data interpretation

Previous studies have reported large variability in the rate of anatomically non-obstructive coronary disease in patients undergoing elective non-invasive diagnostic coronary angiography, ranging from 2% to 62% [3,9,11,14,16]. Such large variability reflects differences in the strategic management of patients between centres with some more proactive in offering direct anatomical diagnosis of the coronary status than others [20]. Despite the low percentage of such patients in our cohort, the prevalence of women was as twice as in those with significant stenosis, thus consistent with previous reports [21].

persistent angina at follow-up than in patients without angina. The other CV risk factors did not show any significant difference (Tables 4). Diabetes increased three times the risk of persistent angina at follow-up (Table 5).

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Limitations

This study has several potential limitations. First, it is a relatively small-, single-centre study. Therefore our results may not be applicable to other patients in different geographical areas.

Table 2 CV risk factors in the non-obstructive coronary artery stenosis group (n= 151)

<table>
<thead>
<tr>
<th></th>
<th>men (n= 79)</th>
<th>women (n= 72)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (56.9)</td>
<td>48 (66.7)</td>
<td>0.21</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (16.4)</td>
<td>17 (23.6)</td>
<td>0.26</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>27 (34.1)</td>
<td>39 (54.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>27 (34.1)</td>
<td>7 (9.7)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>22 (27.8)</td>
<td>29 (40.2)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Each patient may present one or more risk factors

Table 3 Six-years follow-up (n=127)

<table>
<thead>
<tr>
<th></th>
<th>men (n=63)</th>
<th>women (n=64)</th>
<th>all (n=127)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistence of angina(%)</td>
<td>12 (19.0)</td>
<td>14 (21.8)</td>
<td>26 (20.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>Major CV events (%)</td>
<td>4 (6.3)</td>
<td>2 (3.1)</td>
<td>6 (4.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>All (%)</td>
<td>16 (25.4)</td>
<td>16 (25.0)</td>
<td>32 (25.2)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 CV risk factors according to the persistence of angina at follow-up (n=127)

<table>
<thead>
<tr>
<th></th>
<th>no angina (n=101)</th>
<th>angina (n=26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>62.6 (10.6)</td>
<td>60.0 (12.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Men</td>
<td>50.5</td>
<td>46.1</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80.2</td>
<td>69.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28.7</td>
<td>34.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>58.4</td>
<td>26.9</td>
<td>0.004</td>
</tr>
<tr>
<td>Smoking</td>
<td>28.7</td>
<td>26.9</td>
<td>0.85</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>44.5</td>
<td>30.7</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) or proportions. Comparisons are made using independent t-test or chi2 test. Each patient may present one or more risk factors.
Second, because the study was retrospective and dependent upon the hospital clinical records, there is the possibility of some inaccuracies of the information coded into the database. Third, the persistence of angina at follow-up was dependent upon the subjective judgment of patients. Therefore, the non-cardiac origin of the chest pain in some patients cannot be excluded. Fourth, we did not perform coronary angiograms at follow-up. Hence, it is possible that some patients might have had a progression of coronary lesions without symptoms as has previously been shown [31]. Sixth, occult coronary abnormalities and microvascular dysfunction leading to abnormal myocardial perfusion were not investigated.

Clinical implications
Although the population sample we studied was relatively small, our observations suggest that patients with angina, even in the absence of obstructive coronary stenosis, cannot be considered at low CV risk and need to be fully investigated for better assessment of angina and atherosclerosis risk factors control, since a minority might continue to develop symptoms or acute events.

Conclusions
A significant proportion of patients with stable angina and non-obstructive coronary stenosis continue complaining of persistent chest pain after six years after the initial coronary angiogram, and carry risk for acute events higher than the general population. CV risk factors burden in these patients was lower than in those with obstructive coronary stenosis. Furthermore, persisting angina and acute major CV events were not related to a greater CV risk factors burden. This seems to indicate that in patients with insignificant coronary stenosis the degree and the extension of coronary obstruction is unrelated to the persistence of symptoms and to the occurrence of CV events.

Declarations of Interest
The authors declare no conflicts of interest.

Acknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [32].

Table 5 Relationship between CV risk factors and persist- ence of symptoms at follow-up

| Table 5 Relationship between CV risk factors and persistence of symptoms at follow-up |
|-----------------------------------------|-----------------|------------------|------------------|
| Diabetes  | 3.29  | 0.01  | 1.22-8.81  |
| Hypertension  | 1.82  | 0.18  | 0.74-4.43  |
| Family history of CAD  | 1.48  | 0.52  | 0.43-5.11  |
| Previous myocardial infarction  | 1.21  | 0.86  | 0.12-11.4  |
| Sex  | 1.19  | 0.68  | 0.50-2.82  |
| Age  | 0.97  | 0.27  | 0.94-1.01  |
| Smoking  | 0.96  | 0.95  | 0.29-3.18  |
| Dyslipidemia  | 0.83  | 0.77  | 0.25-2.73  |

References


Preliminary Short-term Results of a Population of Patients Treated with MitraClip therapy: one Center Experience

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Introduction

Functional mitral regurgitation (FMR) is increasingly common in elderly patients of real-world clinical experience with a large rate of comorbidities, almost all not suitable for surgical mitral valve repair. Morbidity and mortality are related to MR severity [1,2], and benefits from MitraClip therapy can often be seen through a reverse LV remodelling with LV dimension reductions [3]. Transcatheter implantation of the MitraClip device (Abbott, Abbott Park, IL, USA) is an important therapeutic strategy for patients with moderate-severe MR of functional etiology with a high surgical risk [4,5]. We sought to assess the feasibility, acute effectiveness, safety and short-term durability of MitraClip therapy in MR reduction and global clinical improvement in a population of 62 patients who underwent the percutaneous...
procedures.

Materials and Methods
The MitraClip system
MitraClip is a catheter-based system made of a steerable 24-F guide catheter and the clip delivery system, which conducts the MitraClip polyester-covered mechanical device at its distal end [4]. Each clip has two arms and a ‘gripper’ adjacent to each arm. The procedure is performed in the cardiac catheterization laboratory with continuous echocardiographic and fluoroscopic guidance with the patient under general anesthesia. The distal end of the guide catheter reaches the left atrium through a transseptal-puncture approach. MitraClip effective position is held at the origin of main regurgitant jet, assessing the adequacy of the grasp, and if necessary placing a second device.

Patients
Data were collected retrospectively from one center in Italy between January 2011 and December 2016. A total of 62 patients [mean age 74±11 years, 43 men (69%)] underwent MitraClip therapy for MR of at least grade 3+, often with a poor clinical status [53 patients in NYHA functional class III-IV (85.5%)]. All patients had functional MR, with a high STS (Society of Thoracic Surgeons) risk score and EuroScore II during the baseline evaluation of the management of the valvular disease. As regards STS risk score, the lowest value was: Risk of Mortality: 0.33% and Morbidity or Mortality: 7.6% (Long Length of Stay: 2.31%, Short Length of Stay: 2.3%); Permanent Stroke: 0.45%; Prolonged Ventilation: 3.25%; DSW Infection: 0.1%; Renal Failure: 0.9%; Reoperation: 2.13% while the highest value was: Risk of Mortality: 35% (mean ± standard deviation 3.73 ± 4.7) and Morbidity or Mortality: 68.73% (mean ± standard deviation 25.1 ± 12) (Long Length of Stay: 53.2% (mean ± standard deviation 11.34 ± 8.3); Short Length of Stay: 64.2% (mean ± standard deviation 25.6 ± 14.8); Permanent Stroke: 5.2% (mean ± standard deviation 2.2 ± 1.04); Prolonged Ventilation: 54.2% (mean ± standard deviation 14.5 ± 9.5); DSW Infection: 1.04% (mean ± standard deviation 0.3 ± 0.16); Renal Failure: 47.4% (mean ± standard deviation 8.04 ± 8.7); Reoperation: 29.3% (mean ± standard deviation 9.8 ± 3.15)]. As concerns EuroScore II, the lowest value of Risk of In-Hospital Mortality was 3.4% while the highest value was 70.3% (mean ± standard deviation 32.1 ± 17.1). Due to the high surgical risk of the patients, MitraClip therapy was almost the only way to treat Mitral Regurgitation. Patients underwent transthoracic and transesophageal echocardiography to quantify MR and to evaluate the morphologic suitability for MitraClip implantation. All patients received optimal medical and device treatment, in respect of their comorbidities. Baseline demographic characteristics are shown in Table 1. The informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee.

Procedure
All the percutaneous interventions were performed using the protocol described above4,5. Briefly, the MitraClip system is carried to the left atrium by means of transseptal puncture, through the transfemoral venous route. The MitraClip polyester-covered mechanical device has 2 arms opened and closed thanks to the delivery catheter. The MitraClip system is positioned at the origin of the main regurgitant jet, and the device is grasped orthogonally to the plane of the mitral valve annulus. During the procedure, once the reduction of MR and the assessment of the diastolic transmitral gradient are detected with the use of transesophageal echocardiography, the clip can be deployed. The patient is under general anaesthesia throughout the intervention, monitoring the procedure by fluoroscopy and transesophageal 2- and 3-dimensional echocardiography. Procedural success was fixed as the implantation of at least one clip. The day before procedure, each patient was treated with a 300 mg clopidogrel loading dose and 100mg aspirin, while during procedure we used heparin and for the following 6 months patients were treated with clopidogrel (at a dose of 75 mg daily, for 30 days after procedure) and aspirin (at a dose of 100 mg daily).

Echocardiography
The severity of MR at baseline was graded according to the American Society of Echocardiography guidelines[6]. Post-intervention, the severity of MR was detected trough a quantitative assessment with the technique reported by Foster et al [7]. Left ventricular ejection fraction (LVEF) was assessed according to the biplane Simpson’s method. The mitral valve orifice area was performed using the pressure half-time method.

Statistical Methods
Continuous variables are presented as mean ± standard deviation. Despite MR, TR and Aortic Regurgitation (AR) are ordinal variables, we took a comparison as continuous variables (just hypothetically), calculating the mean ± standard deviation grade of reduction of MR, TR, AR to quantify the mean grade of improvement of valvular regurgitations after MitraClip therapy. Categorical variables are presented as counts and percentages. Comparisons of continuous variables were performed by T test for paired samples; comparisons of categorical variables were performed by χ2 (chi-square) Test or McNemar Test, where appropriate, using SPSS software. A two-tailed p-value < 0.05 was regarded as statistically significant. Degenerative MR was defined as the presence of leaflet pathology (either anterior, or posterior or both), and functional MR was defined as the absence of leaflet pathology. No one of the patients had MR of degenerative etiology, while 23 patients (37%) had FMR with ischaemic aspects and 6 patients (9.7%) had FMR with degenerative aspects.

Ethics
All patients included in the study were fully informed about the MitraClip procedure and signed a written consent form.

Results
Objectives
The primary objective of this study was to assess acute reduction of MR severity, TR severity, AR severity and the patients’ clinical status at 1 month, as reflected by NYHA functional class (study primary effectiveness endpoint).

1-month (short term) outcomes
The 62 patients underwent a total of 67 interventions, with repeated procedures performed at 2018, 1537, 779, 693, and 446 days in 5 patients. 67 of 67 interventions (100%), were successful in 62 patients, with 2 nonprocedural deaths at 1 month. A single clip was implanted in 43 successful procedures (69%), whereas two clips per procedure were implanted in 19 successful procedures.
Successful clip implantation was associated with a reduction in MR severity by 1, 2, and 3 grades in 61% (n=37), 28% (n=17), and 8% (n=5) of procedures respectively, with an average reduction of 1.5 grades. Mitral regurgitation of grade 2+ or less was achieved in 54 successful procedures (90%). Five (8%) of the 62 successfully treated patients were discharged with MR severity reduced from 4+ to 3+.

The total device time, i.e. the time from septal puncture to withdrawal of the guide catheter from the left atrium, averaged ± standard deviation, minutes 254± 59.

A significant improvement in TR was observed with a reduction in TR severity of grade 2+ or less in 54 patients (92%). AR severity (100% mild-to-moderate before procedures) had neither great improvement nor significant worsening at 1 month.

Overall distributions of MR severity, TR severity, AR severity at baseline and at 1-month follow-up are shown respectively in Table 2. MR severity is also showed in Figure 1.

The patients successfully treated with MitraClip system showed an improvement in clinical status with a reduction in NYHA functional class to I-II class in 42 patients (70%). The overall distribution of NYHA functional class at baseline and at 1-month follow-up is shown in Figure 2.

Despite MR severity is an ordinal variable, if we take a comparison

---

**Table 1. Baseline patient characteristics**

<table>
<thead>
<tr>
<th>Baseline patient characteristics</th>
<th>n = 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean ± SD</td>
<td>73.8 ± 10.7</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (69.4)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (30.6)</td>
</tr>
<tr>
<td>BMI classes, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>[18.5 - 25)</td>
<td>24 (38.7)</td>
</tr>
<tr>
<td>[25 - 30)</td>
<td>30 (48.4)</td>
</tr>
<tr>
<td>≥30</td>
<td>6 (9.7)</td>
</tr>
</tbody>
</table>

**Comorbidities and Risk Factors**

Family history of cardiovascular diseases, n (%) | 19 (30.6) |

**Smoke, n (%)**

| Yes | 9 (14.5) |
| Former | 3 (4.8) |
| Diabetes mellitus | 23 (37.1) |
| Insulin therapy, n (%) | 12 (19.4) |
| Hypertension, n (%) | 45 (72.6) |
| Atrial fibrillation, n (%) | 22 (37) |
| Congestive heart failure, n (%) | 23 (38) |
| Hypercholesterolemia, n (%) | 29 (46.8) |

**Chronic pulmonary disease (COPD), n (%)** | 8 (12.9) |

**GFR MDRD** | 58.0 ± 27.1 |

**GFR < 60, ml/min, n (%)** | 33 (53.2) |

**Anemia, n (%)** | 32 (51.6) |

**Charlson Comorbidity Index > 1, n (%)** | 48 (77.4) |

**Prior myocardial infarction, n (%)** | 26 (41.9) |

**Prior PTCA, n (%)** | 25 (40.3) |

**Prior CABG, n (%)** | 14 (22) |

**Cerebrovascular Disease, n (%)** | 9 (14.5) |

**MR etiology, n (%)**

| functional with ischaemic aspects | 23 (37.1) |
| functional with degenerative aspects | 6 (9.7) |

**MR severity, n (%)**

| 1+ to 2+, mild-to-moderate | 0 (0) |
| 2+, moderate | 0 (0) |
| 3+, moderate-to-severe | 8 (13) |
| 4+, severe | 54 (87) |

**TR severity, n (%)**

| 1+ to 2+, mild-to-moderate | 27 (43) |
| 2+, moderate | 21 (34) |
| 3+, moderate-to-severe | 11 (18) |
| 4+, severe | 3 (5) |

**AR severity, n (%)**

| 1+ to 2+, mild-to-moderate | 57 (92) |
| 2+, moderate | 5 (8) |
| 3+, moderate-to-severe | 0 (0) |
| 4+, severe | 0 (0) |

**LV ejection fraction (%)± SD** | 60 ± 17 |

**LV end-diastolic volume, mL (mL± SD)** | 175 ± 60 |

**Regurgitant Volume, mL/beat (mL± SD)** | 54 ± 9 |

**Effective Regurgitant Orifice Area (EROA), cm² (cm²± SD)** | 0.35 ± 0.06 |

**LA anterior-posterior diameter, mm (mm± SD)** | 45 ± 7.6 |

**LA end-systolic Volume, mL (mL± SD)** | 93 ± 23 |

**Vena Contracta, cm (cm± SD)** | 0.64 ± 0.08 |

**PAPs, mmHg (mmHg± SD)** | 41 ± 9.6 |

**NYHA functional class, n (%)**

| I-II | 9 (14.5) |
| III-IV | 53 (85.5) |

**Electrical therapy, n (%)**

| ICD | 17 (27.4) |
| CRT | 10 (16.1) |

BMI, Body Mass Index; eGFR, estimating Glomerular Filtration Rate; MDRD, Modification of Diet in Renal Disease; CABG, coronary artery bypass graft surgery; MR, Mitral Regurgitation; TR, Tricuspid Regurgitation; AR, Aortic Regurgitation; PAPs, estimated Pulmonary Artery Pressure; LV, Left ventricular; LA, Left atrial; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.
as a continuous variable (just hypothetically) using mean ± standard deviation, we find a decrease from 3.9 ± 0.3 at baseline to 1.5 ± 0.8 at 1-month follow-up (<0.001) in MR grade in 60 successfully treated patients. A statistically significant reduction was also noted in TR severity, with the same comparison, with a decrease from 1.8 ± 0.9 at baseline to 1.3 ± 0.8 at 1-month follow-up (<0.001) in these patients.

Of the 60 patients with clinical follow-up data, 42 (70%) had improved from NYHA functional class III or IV at baseline to NYHA functional class I or II, while 18 (30%) remained in NYHA functional class III or IV with no great functional improvement, despite MR being reduced by 1 and even 2 grades.

**Discussion**

**Main findings**

This observational, retrospective one-center investigation of 62 patients with severe MR showed that MitraClip therapy is feasible and effective in these patients. Acutely, clip implantation achieved MR grades of ≤ 2+ in the vast majority of patients. At 1-month follow-up, 40 of the 60 successfully treated patients followed clinically, had improved by at least one NYHA functional class. The preliminary results of these findings satisfy our primary efficacy endpoint.

Our study suggests that the majority of patients with severe FMR will experience a clinical benefit from MR reduction by MitraClip therapy, particularly important for the severity of both ischaemic and non-ischaemic cardiomyopathy often present in these patients. Clinical benefits are expressed for both the mitral valvular disease and the underlying heart failure disease.

**Treatmet options for severe functional mitral regurgitation**

The management of current real-world patients with severe FMR, is an hard challenge, because of their high STS risk score and EuroScore II, together with their old age and several comorbidities. When optimized medical, and, where appropriate, cardiac resynchronization therapy, fail to reduce MR in these patients, MitraClip is almost the only way to treat them [8]. However, we wait for new insights on safety and effectiveness of MitraClip system during long-term follow-up, to highlight, if true, long-term durability of MR reduction, functional improvement, survival and quality of life of these patients. In the present study, concordant with other observational MitraClip studies,[5,9] MR grades of 2+ or less were acutely achieved in 90% of successful procedures. This rate is noticeably higher than the 74% reported in EVEREST (Endovascular Valve Edge-to-Edge REpair Study) [4] and suggests the hypothesis that FMR may be treated with MitraClip with a greater effectiveness than degenerative MR. The chance to reverse maladaptive remodelling is a major determinant of long-term prognosis in these patients [10,11]. 4-year outcomes from EVEREST II trial showed no difference in the prevalence of moderate-severe and severe MR or mortality at 4 years between surgical mitral repair and percutaneous approach, despite a number of cases treated with MitraClip required surgery to treat residual MR [13]. Clearly, the acute reduction in MR severity in our patients was accompanied at 1 month by significant improvement in NYHA functional class.
Survival
Considering the adverse baseline characteristics of our patients, particularly focusing on age, NYHA functional class, LV ejection fraction, the presence of coronary artery disease and ischaemic cardiomyopathy, it is a good result to observe a 30-day mortality rate of 3.2% (1-month follow-up changes in echocardiographic variables, electrocardiographic parameters and postprocedural rate of complications will be discussed in a forthcoming analysis about secondary safety endpoint). 26 patients (42%) had a prior myocardial infarction, 14 patients (22%) underwent a coronary artery bypass grafting (CABG) surgery and 25 patients (40%) underwent a percutaneous transluminal coronary angioplasty (PTCA) in their past medical history; this was relevant in their comorbidities, global clinical status, baseline evaluation of the surgical risk, and also for a prediction of survival and prognosis during the long-term follow-up. Fransen et al [3] in a group of patients with severe LVEF reduction heart failure treated with MitraClip reported a 30-day mortality rate of 6%. Braun et al [12] observed in a group of patients with coronary artery disease who underwent MitraClip therapy a perioperative mortality of 8%. In our population 33 patients (53%) had annular dilation of mitral valve while 25 patients (39.7%) had papillary muscle dysfunction, complicating the functional etiology and the management of these patients. Post-procedural close haemodynamic monitoring of each individual patient in Coronary Intensive Care Unit is mandatory because MitraClip therapy can alter the balance of preload and afterload [3].

Limitations
We recognize the retrospective nature of this study, the bit small number of patients and short-term follow-up at 1-month as major limitations. As a consequence, there were no study protocol strictly adhered at the enrollement of different patients, together with logistic limitations inside the hospital. The echocardiographic assessment of MR severity was performed only at rest, and there wasn’t an independent dedicated core laboratory. Furthermore, a complete insight on our study will be provided with the secondary safety endpoint analysis.

Conclusions
This study suggests that severe FMR can be successfully reduced by MitraClip implantation, with clinical benefits at 1 month. We need to integrate our results, with present and future national and multinational registries (including the Italian GIOTTO, in which our hospital is a participant center), to validate our outcomes and to assess the long-term durability of MR reduction, long-term survival and of quality of life of patients treated with MitraClip therapy during the following scheduled follow-up visits.

Declarations of Interest
The authors declare no conflict of interest.

Acknowledgements
There’s no funding source. The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [14].

References
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Effectiveness Evaluation of ICDs Implanted in the Right Side vs. Left Side

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Abstract

Background
The implantation of ICDs left pectorally is the conventional normal practice, but pathological reasons may obly to insert the devices on the right side. The aim of our evaluation was to define the outcome of right-sided implantation (n=52) on defibrillation effectiveness in comparison to the left-sided ICD implantation (n=210).

Methods
A cohort of patients received standard therapy for primary or secondary prevention of sudden cardiac death (SCD) in patients with the structural cardiac disease, lay open to the ICD-DR implantation. The 262 individuals who had all the inclusion criteria were comprised in the assessment.

Results
The defibrillation threshold testing (DFT), at the end of implantation showed that the mean energy to revert a programmed induced sustained ventricular tachycardia/ventricular fibrillation was 33.4±6.3 J for the patients that had the ICD implanted on the right side, and 23.9±5.3 J for the ones that presented the ICD positioned on the left side, P<0.0001. However the mean and the sum of shock events recorded by ICD during 1 year of monitoring, according to the side of ICD implantation, did not show any difference.

Conclusions
Our results show that ICD implantation on the right side caused an elevated DFT in comparison to the left side insertion. This study also reported that there is no difference regarding safety and effectiveness about the amount of appropriate and inappropriate shock therapies, the mean and the sum of shock events recorded by ICD during 1 year of monitoring, according to the side of ICD implantation.

Keywords: Ventricular arrhythmia; Automatic implantable cardioverter-defibrillator; Right-sided implantation; Intraoperative test.

Citation: Kiuchi MG, Chen S, Paz LMR, Pürerfellner H. Effectiveness evaluation of ICDs implanted in the right side vs. left side. International Cardiovascular Forum Journal 2017;11:65-68, DOI: 10.17987/icfj.v11i0.443

Introduction
Implantation of automatic implantable cardioverter-defibrillators (ICD) in subjects with elevated danger for life threatening ventricular arrhythmias is the normal therapeutic technique [1]. The implantation of ICDs left pectorally is the conventional normal practice, which has significantly enhanced at the time by the progress of new ICD leads, shock algorithms, high energy defibrillators, and fast energy supply succeeding the introduction of new compeers of capacitors. Yet, pathological reasons like thrombosis, infection and reckless leads on the left side may obly to insert the devices on the right side, as well upgrade systems from the pacemaker to ICD previously implanted on the right side. With growing implantations of ICDs, the number of system revisions due to lead dysfunction and/or infections will rise and the number of rights sided implantations will upsurge successively. The consistency of devices implanted on the right pectoral side remnants controversially debated. The few studies presenting right-sided implants have totally set up important higher thresholds as matched to devices inserted on
left pectoral site, but none of the studies have reported of failing initial intraoperative tests [2-8]. The aim of our evaluation was to define the outcome of right-sided implantation on defibrillation effectiveness in comparison to the left-sided ICD implantation.

Materials And Methods

Study design

This prospective study was conducted at the Department of Cardiac Artificial Stimulation and Cardiac Surgery of the Hospital e Clínica São Gonçalo, São Gonçalo, Rio de Janeiro, Brazil in partnership with Elisabethinen Krankenhaus, Linz, Austria. A cohort of patients received standard therapy for primary or secondary prevention of sudden cardiac death (SCD) in patients with the structural cardiac disease, lay open to to the ICD-DR implantation in accordance with the “Guidelines for Implantable Electronic Cardiac Devices of the Brazilian Society of Cardiology” [9].

Patients were followed for one year after the implant procedure. Inclusion criteria were the following: (i) individuals with structural cardiac illness and ICD implant warning for primary or secondary avoidance of SCD; (ii) left ventricular ejection fraction ≤35%; (iii) subjects who are providing documentation not showing cardiac ischemia previously ICD implant evinced by myocardial scintigraphy at rest and during stress, by cardiac magnetic resonance imaging at rest and during stress, or coronary angiography; (iv) upgrade from pacemaker to ICD system implantation. Exclusion criteria were the following: (i) ischemic cardiac disease; (ii) LVEF> 35%; (iii) nonexistence of structural cardiac disease; (iv) valvar heart disease that might lead to arrhythmias; (v) left atrial or ventricular thrombi were to decrease the hazard of embolization regrading to the intraoperative testing procedure; (vi) patients necessitating epicardial defibrillator patches also were left out as they were not treated with endocardial defibrillator leads.

The goal line of our evaluation was to define the outcome of right-sided implantation on defibrillation effectiveness in comparison to the left-sided ICD implantation. The enrollment of the patients began in January 2011 and ended in January 2016. We enrolled 262 patients that meet the criteria to receive an ICD. They were monitored till 12 months after ICD implantation, and they were recognized in our headquarters. The study was shepherded in covenant with the Declaration of Helsinki and was permitted by the Ethics Committee of our hospital. All individuals delivered written informed consent before their inclusion in the study.

Implantation and programming of the ICDs, twenty-four hour ABPM, and transthoracic echocardiography

These procedures were previously reported in detail in our previously manuscript [10]. After initial lead and device placement, ventricular fibrillation was induced, and an initial shock at an energy of 20 or 24 J was delivered. If successful, the energy was decreased by 5 or 6 J steps until failure to convert ventricular fibrillation occurred, or a 5 or 6 J shock was successful. Starting energy and decremental steps depended on the specific defibrillator being implanted. The lowest energy to successfully terminate ventricular fibrillation was taken as the defibrillation threshold testing (DFT). In systems with two intravascular leads, the proximal defibrillation coil was placed in the high superior vena cava (SVC) or left innominate vein in patients with a left-sided approach. Right-sided implantation necessitated lower SVC positioning of the proximal coil due to anatomical constraints [11].

Follow-up patients

The patients were evaluated 15 days after ICD implantation to observe the pocket, the site of the surgical incision, and to adjust the device programming. Fifteen days later, the patients returned for further evaluation (one month after ICD implantation). The data were obtained from the day of the device implant to 12 months after implantation. Subsequently, patients were evaluated every 3 months till the complete total period of follow-up. At each follow-up visit, we achieved a record (stored on a USB device and then transferred to a computer) of the ICD memory data that has accumulated since the last reset of memory. The occurrence and duration of therapy events were recorded.

Statistical analysis

All patients enrolled were included in the analysis. The results were expressed as the mean and standard deviation (mean ± SD) in the case of normal distribution and as median with interquartile range otherwise. Statistical tests were all of two sides. Comparisons between the two paired values were performed by paired t-test in case of a Gaussian distribution or alternatively, by Wilcoxon test. The comparisons between more than two values paired values were performed by analysis of variance for repeated measures ANOVA or Kruskal-Wallis test, as appropriate, complemented by a post hoc test. Frequencies were compared with x² or Fisher’s exact tests. P values <0.05 were considered significant. Correlations between two variables were performed by Pearson in the case of a Gaussian distribution or, alternatively, with the Spearman correlation test. Kaplan-Meier analysis was performed to determine the probability of success, assessed as the percentage of patients free of therapies. Differences in free survival therapies were evaluated with the log-rank/Mantel-Haenszel test. The Cox regression analysis was applied to explore triggering factors of ATP and shock events. All statistical analyses were performed using the program Graphpad Prism v 7.0 (Graphpad software, La Jolla, CA, USA).

Results

Patients

The 262 individuals who had all the inclusion criteria were comprised in the assessment. The baseline features divided into two groups according to the side of ICD implantation, are displayed meticulously in Table 1.

Therapy events

The acute defibrillation threshold testing (DFT), at the end of implantation showed that the mean energy to revert a programmed induced sustained ventricular tachycardia/ventricular fibrillation was 33.4±6.3 J for the patients that had the ICD implanted on the right side, and 23.9±5.3 J for the ones that presented the ICD positioned on the left side, P<0.0001 (Figure 1). Table 2 shows the mean and the sum of shock events recorded by ICD during 1 year of monitoring, according to the side of ICD implantation. After 12 months of monitoring, 15 individuals bearing the ICD implanted on the right side (37%) experienced appropriate shock events, and 40 patients bearing the ICD implanted on the left side (19%) received the appropriate shock therapy, P=0.0948, by log-rank/Mantel-Haenszel test (Figure 2). During this same
time of follow-up, 11 individuals bearing the ICD implanted on the right side (21%) experienced inappropriate shock events, and 24 patients bearing the ICD implanted on the left side (11%) received inappropriate shock therapy, P=0.0677, by log-rank/Mantel-Haenszel test (Figure 3).

Discussion

We demonstrated that an ICD implantation on the right side caused an elevated DFT in comparison to the left side insertion. This study also showed that there is no difference regarding the amount of appropriate and inappropriate shock therapies, the mean and the sum of shock events recorded by ICD during 1 year of monitoring, according to the side of ICD implantation.

Markewitz and colleagues [12] confirmed that the DFT in a two-lead system was lower when the proximal coil was positioned in the left subclavian vein than when it was located in the SVC. Our finding that the right-sided DFT is augmented in bipolar systems is consistent with this statement, given that right-sided vascular access requires an SVC location in single lead systems, and favors such a place in two-lead systems. Likewise, in a study by Epstein and colleagues [13] right-sided implant of biphasic non active can systems occasioned in a high DFT in those systems that lacked subcutaneous leads. These authors also suggested that the boost in DFT resulted from a defibrillating electrical field that was minus auspiciously dispersed over the myocardium due to the anatomical limitations of right-sided venous access. We demonstrated that despite the benefit of a large surface area, right-sided active can DFTs were significantly increased matched with the left-sided implant. An acceptable ventricular sensing of >6 mV and a pacing threshold of <1 V @ 0.5 ms were succeeded in all subjects, prior to testing. As all our patients reached these values, we must question whether right ventricular stimulation threshold alone has sufficient proof for suitable device function [14]. The inappropriate shock events were triggered by any kind of supraventricular tachycardia or atrial fibrillation with high conduction to the ventricles, as well some sustained noising in one or both intra-cardiac channels. However, no difference was reported regarding the amount of appropriate and inappropriate shock therapies, the mean and the sum of appropriate and inappropriate shock events recorded by ICD during the 12 months of follow-up, according to the side of ICD implantation, demonstrating that the implant of ICD in any side is safety for the patients.

Limitations

Although our data showed favorable results about the effectiveness of the ICDs implanted in the left side, our group of patients was small. This relatively small sample size can be seen as a limitation.

Conclusion

Our results show that ICD implantation on the right side caused an elevated DFT in comparison to the left side insertion. This study also reported that there is no difference regarding safety and effectiveness about the amount of appropriate and inappropriate shock therapies, the mean and the sum of shock events recorded by ICD during 1 year of monitoring, according to the side of ICD implantation.

Conflict of Interests

The authors declare no conflict of interest. The study was sponsored by health plans in the state of Rio de Janeiro and the Pacemed (US$ 400,000).
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References
Surgical Treatment for Floating Right Heart Thrombus in High Risk Patients

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Highlights
Right heart floating thrombus or “embolus in transit” can be a very dangerous condition, usually associated to pulmonary thromboembolism. Even though many treatment options have been considered, nowadays, the recommended approach remains unclear. Surgical embolectomy has been used as an option, usually less preferred than thrombolysis or percutaneous approach, but it can be a safe and effective procedure in patients with high risk of embolization.

Keywords: right heart thrombus; surgical embolectomy


Introduction
Right heart thrombus is a potentially threatening condition, with a described mortality up to 40% when it’s related to massive pulmonary embolism [1]. In some cases, these thrombi are “floating” inside the right atrium, with a significant increase of the embolization risk and, therefore, require an emergent therapeutic decision. So far, this question has been discussed in many occasions, considering both options, thrombolysis and surgical embolectomy, equally valid for these patients considering their clinical context, but the evidence available concerning this matter is still weak [2].

Case presentation
We present the case of a 70-year-old man, without any cardiovascular risk factor, with a recent history of a long period of immobility due to a cranial trauma.

He presented with an episode of pain and swelling of the right lower limb, being diagnosed of an iliofemoral venous thrombosis by echocardiography. Therefore, he was treated with low-molecular-weight heparin. After 24 hours, he presented with sudden shortness of breath, chest pain and loss of consciousness. A computed tomographic pulmonary angiography revealed a massive bilateral acute pulmonary thromboembolism. (Fig 1)

In order to determine the right heart involvement, a transthoracic echocardiogram was performed, showing a floating mass inside the right atrium, trespassing the tricuspid valve and entering the right ventricle, compatible with a recently formed thrombus (Fig 2).

After discussing all the possible therapeutic options, surgical treatment was considered due to the high risk of embolization. Therefore, right atrium embolectomy was performed through median sternotomy and with cardiopulmonary bypass. Right atrium and both pulmonary veins were opened and reviewed, obtaining a 20-cm long thrombus from the right heart chambers and the right pulmonary vein, with the shape of the iliofemoral venous axis (Fig 3). The procedure was uneventful and the patient had a non-complicated postoperative course. An inferior vena
The cava filter was placed right after the procedure, being removed 3 days later, once the anticoagulant treatment was settled. He was discharged 7 days later with long-term treatment with LMWH during 6 months.

Discussion
Although it has been widely reviewed in scientific literature, the treatment for the floating right thrombus or “embolus in transit” is still a matter for discussion.

Most published evidence consists on isolated case reports or small case series. Rose P et al. analyzed in 2002 all reported cases in English of right heart thromboembolism, getting a 177 patient series. They determined the effects of the different treatment options and the patients baseline characteristics on the mortality rate, determining that thrombolysis was the best option with the lowest mortality. Nevertheless, a prospective randomized trial needs to be done in order to establish clear recommendations. [3]

In this case we presented, surgical embolectomy was considered as the best option, since the patient was already under treatment with heparin, and the echocardiographical findings pointed towards a high risk of embolization, and, therefore, a high mortality risk. In the last published guidelines, surgery remains as the last option for pulmonary embolism treatment, only recommended for patients with hemodynamic instability, any contraindications for thrombolysis or catheter removal of the thrombus or, like in this case, evidence of the thrombus inside the right heart chambers.

Echocardiographical diagnosis is unavoidable due to the need for ruling out any septal abnormalities, such as patent foramen ovale, that would lead to paradoxical embolism and a wider range of complications. Surgical approach to this entity also allows atrial septal defect repair [4]. In the case we have described also defined the high mobility of the thrombus inside the right atrium, which forced to take the decision of getting the patient under surgical embolectomy.

Conclusion
Right heart floating thrombus or “embolus in transit” is a rare but life-threatening condition, with high mortality when emergency treatment is not administered. Surgical approach, with cardipulmonary bypass and right atrium embolectomy can be a safe and effective procedure, with a low complication rate.

Declarations of interest
The authors declare no conflicts of interest

Aknowledgements
The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [5]

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