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Ethnic differences in acute heart failure outcomes in Ontario☆

Louise Y. Sun [a,b,*], Antoine Kimmoun [c,d], Koji Takagi [d], Peter P. Liu [e], Anan Bader Eddeen [b], Alexandre Mebazaa [f,g]

[a] Division of Cardiac Anesthesiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada
[b] Institute for Clinical Evaluative Sciences, Ottawa, Ontario, Canada
[c] Medical Intensive Care Unit Brabois, Institut Lorrain du Cœur et des Vaisseaux, CHRU de Nancy, Vandoeuvre-les-Nancy, France
[d] Inserm U942, Lariboisière University Hospital, Paris, France
[e] Division of Cardiology, University of Ottawa Heart Institute, Ottawa, Ontario, Canada
[f] Department of Anaesthesia, Burn, and Critical Care, Saint-Louis Lariboisière University Hospital, Paris, France
[g] Université de Paris, France

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ABSTRACT

Background: Previous studies have identified ethnic differences in outcomes after episodes of acute heart failure in natives of Asia as compared to those of Europe. Whether these ethnic differences in outcomes would still exist, years after migration to a different geographical and cultural setting remain unclear. We investigated the one-year mortality after an episode of acute heart failure admission in Ontario residents of South Asian and Chinese descent as compared to the General Population.

Methods: We conducted a population-based, retrospective cohort study of adult Ontarions who were hospitalized for AHF between April 1, 2010 and March 31, 2016. Ethnicity was categorized using validated surname-based algorithms. The primary outcome was all-cause one-year mortality. Mortality rates were calculated using the Kaplan–Meier method. The relative hazard of death was assessed using a multivariable Cox proportional hazard model.

Results: Of 82,125 patients, 1287 (1.6%) were Chinese, 1662 (2.0%) were South Asians, and the remaining 79,176 (96.4%) were of the General Population. The risk of mortality was markedly lower amongst South Asians (adjusted HR 0.81, 95% CI [0.73–0.89]) relative to the General Population. There was no statistically significant difference in the risk of mortality between Chinese and the General Population (adjusted HR 1.00 [0.91–1.10]). In addition, guideline-directed medical therapies were associated with similar survival benefit in patients of all three ethnic origins.

Conclusions: We found a lower risk of one-year mortality after acute heart failure hospitalization amongst South Asians compared to Chinese and the General Population, and similar benefit of medical therapy in all three groups. Further studies are needed to explore the etiologies of these ethnic disparities to truly improve outcomes at the population level.

1. Introduction

Acute heart failure (AHF) is a growing health problem and a leading cause of mortality and hospitalization worldwide [1–3]. Evidence-based medical therapies such as β-blockers (BB), angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and mineralocorticoid receptor antagonists (MRA) have led to improved survival after AHF hospitalization in developed countries [4]. However, the impact of ethnic differences in health, health care and health-seeking behavior on outcomes remains unclear in this patient group [5]. Indeed, several key ethnic groups including Chinese and South Asians have not been widely examined in cardiovascular trials or large observational studies [6–9].

There appears to be an association between ethnicity and health that goes beyond medical care, culture and country of residence. For instance, while native South Asians have a higher burden of cardiovascular risk factors that predispose them to myocardial infarction (MI) earlier in life, the same burden of cardiovascular risk factors have been observed in South Asian emigrants presenting with acute MI, who have been long-term residents of Canada [10]. In addition to differences in baseline health status, the implementation of AHF management guidelines may also differ across ethnic groups. The recent ASIAN-HF study, a prospective multinational registry of patients with HF with reduced ejection fraction (HFrEF) in Asia, demonstrated considerable

☆ Each author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Room H2410, 40 Ruskin Street, Ottawa, ON K1Y 4W7, Canada.
E-mail address: lsun@ottawaheart.ca (L.Y. Sun).

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heterogeneity across the continent in terms of guideline-directed AHF therapies [11]. As these evidence-based medications were tested predominantly in Caucasian populations, the influence of ethnicity has yet to be established [12,13]. Moreover, the impact of ethnicity on outcomes after AHF admission has not yet been evaluated in people who have been long-term emigrants from their respective nations, who have had to some degree adapt to new dietary and cultural practices.

We examined in a large multiethnic cohort from Ontario, Canada, the ethnic differences in one-year mortality following index AHF admission, as well as the impact of guideline-directed HF therapies on this outcome.

2. Methods

2.1. Design and study population

We conducted a population-based, retrospective cohort study in Ontario, Canada using linked administrative databases. The Research Ethics Board of Sunnybrook Health Sciences, Toronto, Canada approved this study and waived the need for informed consent. Included were patients ≥18 years of age, who were non-electively hospitalized in Ontario with HF as the primary admitting diagnosis between April 1, 2010 and March 31, 2016. For those with multiple HF admissions during the study period, the first non-elective HF admission was considered the index admission. We excluded non-Ontario residents and those who were <18 years of age. During the study period, Ontario was Canada's most populous province accounting for nearly 40% of the Canadian population, with a public funded, universal healthcare system that reimbursed all medically necessary healthcare and hospital services.

2.2. Data sources

Databases were linked deterministically using unique encoded identifiers. We used the Canadian Institute for Health Information's Discharge Abstract Database (DAD) to identify patients who were non-electively admitted to hospital with HF as the most responsible diagnosis (International Classification of Diseases 10th Revision [ICD-10-CA] I50 class of codes).

The DAD has 96% accuracy in the coding of HF based on the Framingham criteria [14]. Analyses were conducted by linking the DAD with the Registered Persons Database (RPDB) for demographics and vital statistics, the Ontario Health Insurance Plan (OHIP) database for physician fee-for-service claims, and the Ontario Drug Benefit (ODB) database (all prescription drug claims for Ontario residents over 64 years of age). These databases have been validated for the measurement of many outcomes, exposures, and comorbidities [15–18].

2.3. Classification of ethnicity

We used validated lists of 1133 Chinese surnames and 9950 South Asian surnames to identify patients of Chinese and South Asian ethnicities [19]. These lists have positive predictive values of 92% and 89%, respectively, in classifying individuals who previously identified themselves as Chinese and South Asian from primary data sources. The rest of the study cohort, who were mostly Caucasians, was classified as the "General Population" (GP).

2.4. Outcome

The primary outcome was all-cause mortality within one-year of index AHF hospital admission. Mortality was ascertained by using the RPDB.

2.5. Patient characteristics

Demographic variables (age, sex) were obtained from the RPDB. We estimated socioeconomic status based on patients' neighbourhood median income in the Canadian census, and determined their residence (rural versus urban) using Statistics Canada definitions [20]. We identified hypertension [17], asthma [21], chronic obstructive pulmonary disease (COPD) [22] and diabetes mellitus [16] using validated algorithms. Other comorbidities were identified using DAD and OHIP databases based on ICD codes within five years before AHF diagnosis, using previously described methods [23,24].

2.6. Medication and adherence

As universal medication reimbursement is only available to Ontario residents who are 65 years of age or older, we determined the proportion of patients within each ethnic group who were ≥65 years of age, who filled at least one prescription for BB, ACEi/ARB, or spironolactone within 90 days prior to the index admission and within 90 days of discharge.

We compared medication adherence amongst ethnic groups, by determining the proportion of days each of the medications was supplied within 6- and 12-months following discharge amongst those who had the medication prescribed within 30 days from discharge. We defined a high level of adherence as prescription covering ≥80% of days, which is a commonly used cut-off in clinical trials and other population-based studies in Ontario [25]. For patients who died before the 6- or 12-month end-points, the proportion of days of drug coverage supplied was calculated until the date of death.

2.7. Statistical analysis

Analyses were stratified by sex when appropriate. Continuous variables were analyzed using student's *t*-test and expressed as mean (SD). Categorical variables were analyzed using chi-square test and expressed as number (proportion). Survival time was defined from the date of AHF admission until death or last follow-up. Patients were censored when they lost possession of valid Ontario health insurance (i.e., assumed to have left Ontario). The probability of death was calculated using the Kaplan-Meier method. We assessed for the significance of the difference between ethnicity groups using the log-rank test. Rates were directly standardized by age and sex using the 2013 Canadian population as the reference. The relative hazard of death was assessed using a multivariable Cox proportional hazard model with adjustment for all risk factors listed in eTable 1. To identify ethnicity-specific risk factors, we tested for the presence of any interaction between ethnicity and each of the mortality risk factors using multiplicative interaction terms. The measure of association was hazard ratios (HR) with 95% CI. Analyses were performed using SAS 9.4 (Cary, NC), with statistical significance defined by a two-sided *P*-value <0.05.

3. Results

3.1. Baseline characteristics in the overall cohort

A total of 82,125 patients developed an index episode of AHF necessitating hospital admission. Of these patients, 1287 (1.6%) were of Chinese origin, 1662 (2.0%) were of South Asian origin, and 79,176 (96.4%) were of the GP.

Table 1 summarizes the baseline characteristics of the overall cohort and in subgroups according to ethnicity. The mean age of the overall cohort was 78 ± 12.0 years and 54% were women. In terms of common cardiovascular risk factors, hypertension was present in 89%, atrial fibrillation in 30%, prior MI in 27% and diabetes in 52% of the overall cohort.

3.2. Patient characteristics by ethnicity

South Asians were youngest at AHF hospitalization (75.0 ± 11.9 years) as compared to Chinese (79.6 ± 12.3 years) and the GP (78.0 ± 12.0 years) ($p < 0.001$). The prevalence of atrial fibrillation was lowest in South Asians (18%), followed by Chinese (24%) and the GP (31%) ($p < 0.001$). Conversely, more South Asians had a history of MI and diabetes (32% and 70%, respectively) than Chinese (18% and 51%, respectively) and the GP (28% and 51%, respectively) ($p < 0.001$). Furthermore, South Asians were more often treated with guideline-directed HF therapies before and after their AHF episode than other ethnic groups (Table 2). There were small between-group differences in medication adherence, with the Chinese being slightly less adherent to BB at 6 months and to spironolactone at 6 and 12 months post-discharge as compared to other ethnic groups (eTable 2).

3.3. One-year mortality

After standardization by age and sex, the standardized mortality rate was lowest in South Asians at one-year (134.6 [94.4–186.2] per 1000 person-years, vs. 220.5 [106.3–404.0] in Chinese and 205.2 [192.9–218.1] in the GP; $p = 0.01$). eTable 1 illustrates the multivariable risk factors for one-year mortality. In addition, the Kaplan-Meier survival curves for each ethnic group are presented in Fig. 1. The unadjusted and adjusted HRs of one-year mortality are also presented in Fig. 1, with the GP as the reference group. Compared to the GP, a lower risk of one-year mortality was observed in South Asians (unadjusted HR 0.68, 95% CI [0.62–0.75]; adjusted HR 0.81 [0.73–0.89]) but not in the Chinese (unadjusted HR 0.99 [0.9–1.1]; adjusted HR 1.00 [0.91–1.10]).

Table 1
Patient characteristics by ethnicity.

Variable	Overall	Chinese	South Asians	General Population	P-value
	$N = 82,125$	$N = 1287$	$N = 1662$	$N = 79,176$	
Age, Mean ± SD	78.2 ± 12.1	79.6 ± 12.3	75.2 ± 11.9	78.2 ± 12.0	<0.001
Female	41,371 (50%)	694 (54%)	871 (52%)	39,806 (50%)	0.008
Rural residence	10,742 (13%)	13 (1%)	12 (1%)	10,717 (14%)	<0.001
Income quintile					
1 (Lowest)	19,110 (23%)	362 (28%)	394 (24%)	18,354 (23%)	<0.001
2	17,729 (22%)	273 (21%)	437 (26%)	17,019 (22%)	
3	16,098 (20%)	215 (17%)	381 (23%)	15,502 (20%)	
4	15,220 (19%)	239 (19%)	262 (16%)	14,719 (19%)	
5 (Highest)	13,463 (16%)	163 (13%)	186 (11%)	13,114 (17%)	
Hypertension	72,971 (89%)	1160 (90%)	1543 (93%)	70,268 (89%)	<0.001
Atrial fibrillation	24,844 (30%)	310 (24%)	306 (18%)	24,228 (31%)	<0.001
Myocardial infarction	22,536 (27%)	228 (18%)	529 (32%)	21,779 (28%)	<0.001
Valvular heart disease	8783 (11%)	103 (8%)	110 (7%)	8570 (11%)	<0.001
Peripheral vascular disease	5963 (7%)	55 (4%)	54 (3%)	5854 (7%)	<0.001
Cerebrovascular disease	7503 (9%)	102 (8%)	136 (8%)	7265 (9%)	0.12
Pulmonary circulation disorder	3971 (5%)	52 (4%)	53 (3%)	3866 (5%)	0.003
COPD/Asthma	39,165 (48%)	442 (34%)	660 (40%)	38,063 (48%)	<0.001
Alcohol abuse	1536 (2%)	≤5 (0%)	18 (1%)	1516 (2%)	<0.001
Renal disease	11,436 (14%)	192 (15%)	269 (16%)	10,975 (14%)	0.02
Diabetes	42,346 (52%)	660 (51%)	1156 (70%)	40,530 (51%)	<0.001
Hypothyroidism	3494 (4%)	38 (3%)	76 (5%)	3380 (4%)	0.06
Liver disease	1703 (2%)	27 (2%)	30 (2%)	1646 (2%)	0.74
Dementia	4724 (6%)	79 (6%)	55 (3%)	4590 (6%)	<0.001
Depression	2931 (4%)	24 (2%)	32 (2%)	2875 (4%)	<0.001
Psychosis	519 (1%)	≤5 (0%)	8 (1%)	506 (1%)	0.39
Primary tumor	7505 (9%)	101 (8%)	88 (5%)	7316 (9%)	<0.001
Metastatic cancer	1283 (2%)	22 (2%)	20 (1%)	1241 (2%)	0.45
Paraplegia	1044 (1%)	25 (2%)	30 (2%)	989 (1%)	0.01
Venous thromboembolism	1256 (2%)	14 (1%)	18 (1%)	1224 (2%)	0.14
Overall 1-year mortality rate					
Crude rate	28,460 (35%)	444 (36%)	417 (25%)	27,599 (35%)	–
Age-sex standardized rate/1000 PY (95%CI)	203.2 [191.3–215.7]	220.5 [106.3–404.0]	134.6 [94.4–186.2]	205.2 [192.9–218.1]	0.01
Age-standardized mortality rate/1000 PY (95%CI)					
Women	200.6 [182.8–219.7]	307.7 [104.1–701.5]	107.4 [75.7–147.8]	202.0 [183.7–221.6]	<0.001
Men	207.8 [192.1–224.4]	134.6 [68.6–237.2]	163.0 [92.9–265.2]	210.3 [194.0–227.7]	0.13

SD = standard deviation; COPD = chronic obstructive pulmonary disease; PY = person-years; CI = confidence interval.

3.4. Oral guideline-directed therapy

Post discharge prescription of ACEi/ARB/MRA and/or BB was associated with similarly lower risk of one-year mortality in all three ethnic groups (Fig. 2). Fig. 2 further shows that post-discharge use of an MRA (i.e., spironolactone) was also associated with lower one-year all-cause mortality in the GP (unadjusted HR 0.82 [0.79–0.84]; adjusted HR 0.82 [0.79–0.84]). This trend was however not statistically significant in the South Asian (unadjusted HR 0.84 [0.66–1.07]; adjusted HR 0.87 [0.68–1.13]) and Chinese groups (unadjusted HR 0.82 [0.65–1.03]; adjusted HR 0.82 [0.65–1.04]).

4. Discussion

We demonstrated in a large multiethnic cohort that 1) the risk of death within one-year after an AHF hospitalization is influenced by ethnicity and 2) guideline-directed medical therapies were associated with similar survival benefit in AHF patients of all three ethnic groups.

Ethnic differences in survival have been demonstrated following a variety of acute cardiovascular events [13]. A previous Canadian report demonstrated that in the context of a universal healthcare system, South Asian patients had better long-term survival after acute MI as compared to Chinese and the GP [26]. In contrast, a similar study performed in the United Kingdom found no difference in post-MI survival between South Asians and the GP [27]. This observed difference in survival may be explained by the fact that a higher proportion of South Asian Canadians are of Indian origin whereas the majority of South Asians residing in the U.K. are of Pakistani and Bangladeshi origin [27]. This difference in sub-ethnic mix highlights the crucial impact of ethnic origin on cardiovascular disease outcomes [5]. Recent work by our group found that native East Asians living in China, Korea, and Japan had better one-year survival following an AHF episode compared to native Europeans [28]. Here, we hypothesized that the better post-AHF

Table 2
Medication prescription pre- and post-acute heart failure admission, stratified by ethnicity.

Medication	Adherence	Prescription (%)			P-value
		Chinese ($N = 1127$)	South Asians ($N = 1386$)	General Population ($N = 68,327$)	
ACEi/ARB	Within 90 days prior to admission	57	64	55	<0.001
	Within 90 days after discharge	56	64	57	<0.001
Beta-blocker	Within 90 days prior to admission	51	60	55	<0.001
	Within 90 days after discharge	61	69	61	<0.001
Spironolactone	Within 90 days prior to admission	54	62	65	<0.001
	Within 90 days after discharge	79	85	82	0.004

ACEi = Angiotensin Converting Enzyme inhibitors; ARB = Angiotensin II Receptor blockers.

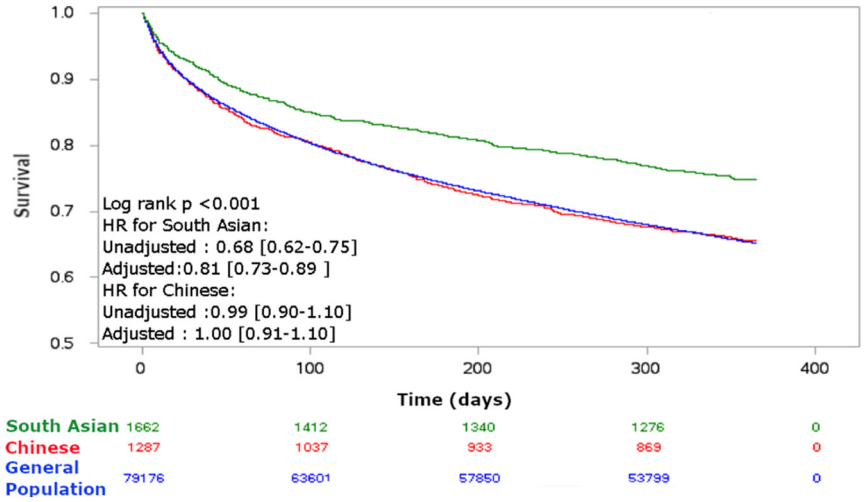

Fig. 1. Unadjusted estimated one-year survival after index hospital admission for acute heart failure, stratified by ethnicity. Adjusted hazard ratios (HRs) are provided in the figure. The General Population was used as the reference group for the calculation of HRs.

outcomes observed in native Asians may be related to environmental factors, genetic differences, and geographic variations in disease severity, management, and co-morbidity burden. In the present study, we also found better one-year survival after AHF hospitalization in South Asians but not Chinese, when compared to the GP. In the context of a universal health care system, our findings suggest that genetics, HF severity and co-morbidity burden, rather than environmental and geographical factors, are important determinants of survival post-discharge survival in patients with AHF [28].

We also found that for all ethnic groups studied, medical HF therapy was associated with a lower risk of one-year mortality. These guideline-directed therapies are prescribed according to ejection fraction (EF). Specifically, in HFrEF, neuro-hormonal antagonists (i.e., ACEi/ARB, MRA and BB) are associated with improved survival. However, recommended therapy for HF with preserved EF (HFpEF) is etiology-specific and focuses on the treatment of comorbid conditions such as hypertension [29]. While long-term survival of HFpEF compared to HFrEF is still debated, some data might suggest that HFpEF might be associated with better long-term outcome [30–35]. Thus, even though, in this study, information concerning left ventricular EF is lacking, higher rates of survival in South Asians might be possibly attributed to a higher prevalence of hypertension (and subsequently HFpEF), as well as younger age at AHF presentation in this ethnic group [36–38].

Few studies have assessed the impact of spironolactone therapy on AHF outcomes and none have examined ethnicity-related differences [39]. A recent randomized control trial assessing the effect of spironolactone in patients with AHF showed no difference on the state of circulatory congestion (defined by NT-proBNP levels, clinical congestion score, dyspnea, urine output, and changes in weight) between the spironolactone and placebo groups [40]. Although this study was not stratified by ethnicity, it is to be noted that 42% of included patients were African Americans. The present study demonstrated a clear one-year survival benefit of spironolactone in the GP and a trend towards benefit in Chinese and South Asians.

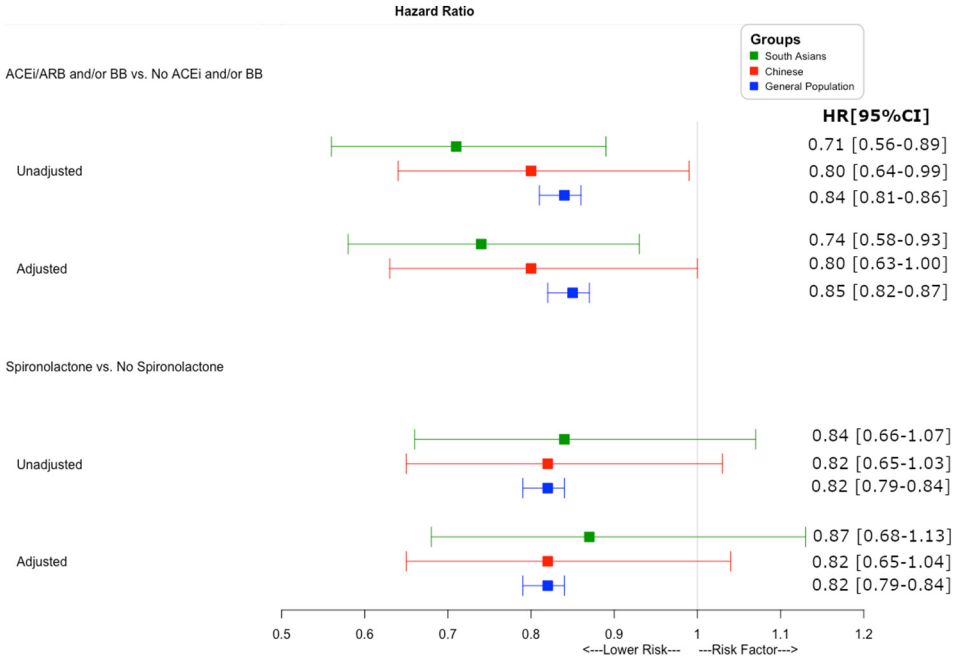

Fig. 2. The impact of medication type on one-year mortality after index hospital admission for acute heart failure, stratified by ethnicity.

Our study has several limitations. First, as self-reporting remains the gold standard for identifying ethnic origins [41], the use of a surname-based algorithm may have led to some degree of misclassification. Second, we were unable to examine the impact of the duration of immigration on the immigrants' perceptions of health and their health-seeking behavior [42]. Third, we observed a low proportion of AHF hospital admissions in Ontario. This may be attributed to the excellence of community-based HF care in Ontario, which is known to reduce admissions [25,43]. Population-based studies need to be conducted in other jurisdictions to verify the generalizability of our findings. Fourth, information concerning left ventricular EF was unavailable in the databases used, which limited our ability to examine the exact benefit of oral guideline-directed HF therapies by EF in each of the ethnic groups. Finally, our observations are to be interpreted in light of biases that are inherent to the retrospective design. Indeed, our data sources lacked some relevant detailed information such as smoking and body mass index. The inability to measure, and thereby adjust for, differences in such characteristics could have in part explained the differences in event rates observed in this study. However, we were able to use validated surrogate measures from the same databases, such as COPD as well as all other important comorbidities, in our rigorous multivariable risk adjustment models.

5. Conclusions

We found in a real world, multiethnic cohort, better one-year survival following an AHF hospitalization in South Asians as compared to Chinese and the General Population. In addition, we found that guideline-directed medical therapies were associated with similar survival benefit in AHF patients of all three ethnic groups. Our study identifies important ethnic disparities in outcomes within a universal health care system, the etiologies of which should be further explored in subsequent interventional and health services studies.

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Declaration of Competing Interest

Antoine Kimmoun. AK received speaker's honoraria from Baxter, MSD, Gilead, ASPEN. Alexandre Mebazaa. AM received speaker's honoraria from Orion, Otsuka, Philips, Roche and Servier. AM received fee as member of advisory board and/or Steering Committee and/or research grant from Adrenomed, Epygon, Neurotronik, Roche, Sanofi and Sphyngotec. AM owns shares in S-Form Pharma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.05.043.

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