Analysis of gender and race reporting in randomized controlled trials for heart failure

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UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE

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Diploma thesis

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1. INTRODUCTION

1.1. Definition of heart failure

Heart failure (HF) is an important cardiovascular disease due to its increasing prevalence and high mortality rate. According to the American College of Cardiology, HF is defined as a clinical syndrome which results in abnormal heart function or increase in the subsequent risk of, clinical symptoms and signs of reduced cardiac output and/or pulmonary or systemic congestion at rest or with stress. It is characterised by a constellation of symptoms (dyspnoea, orthopnoea, lower limb swelling) and signs (elevated jugular venous pressure, pulmonary congestion). It is caused by a structural and functional defect in myocardium resulting in diminishing of ventricular filling or the ejection of blood. Some of the major pathogenic mechanisms contributing to HF are ischemia-related dysfunction, increased hemodynamic overload, ventricular remodelling and accelerated apoptosis and genetic mutations (1).

The most common cause for HF is reduced left ventricular myocardial function, where the patients present with dyspnea, fatigue limiting exercise tolerance and fluid retention depicted by pulmonary and peripheral edema (2).

HF can be classified as predominantly left ventricular, right ventricular or biventricular based on the location of the deficit. HF due to left ventricular dysfunction is divided according to the left ventricular ejection fraction (LVEF). HF with normal LVEF (>50%) is defined as HF with preserved ejection fraction (HFpEF) and HF with decreased LVEF (<40%) as HF with reduced ejection fraction (HFrEF). The patients with LVEF in the range of 40-49% are defined as HF with mid-range ejection fraction (HFmrEF) (2).

Moreover, depending on the time of the onset, HF is categorized as acute, subacute, chronic or chronic with acute decompensation. Acute heart failure (AHF) is broadly defined as a rapid onset of new or worsening signs and symptoms of HF. On the other hand, chronic HF is complicated by multiple co-morbidities that are progressive in nature (3).

Furthermore, patients can be categorized based on signs and symptoms which are used to describe the status of HF patients. Patients with low LVEF, presenting no signs or symptoms of HF are described as having asymptomatic left ventricular systolic function. Patients experiencing HF symptoms or signs are described as having chronic HF whereas patients whose disease status does not change for at least 1 month are described as having stable HF (3,4). The New York Heart Association (NYHA) function classification is used to classify HF based on symptoms severity and the amount of exertion needed to provoke symptoms (5).

1.2. Epidemiology of heart failure

HF is a widespread global issue. Ischemic cardiomyopathy is the most common cause of HF in the industrialized countries. The prevalence of HF has been estimated to be approximately 1% to 2% in developed countries which tends to increase with age, and it is >10% among people >70 years old (2).

According to the American Heart Association (AHA) and American College of Cardiology (ACC), HFpEF is more prevalent in women compared with men, no difference has been found in HFpEF incidence between the sexes, and HFpEF was the most common subtype in women with HF. The patients with HFpEF often show hypertension and atrial fibrillation (AF) with a lower rate of myocardial infarction (MI) while coronary artery disease (CAD) is the main determinant of HFrEF (4,6).

AHA also states that HF prevalence has increased from 5.7 million to 6.5 million in Americans ≥ 20 years of age. Black males had the highest proportion of hospitalized HFrEF whereas white females had the highest proportion of hospitalized HFpEF. HF is continuing to increase due to better survival from MI and aging population (7).

The prevalence, incidence, morbidity and mortality show geographic variations, depending on the different aetiologies and clinical characteristics observed among patients with HF (8). AHA estimates that more than 8 million Americans above the age of 18 years will suffer from HF by 2030. The total economic cost is expected to reach 70 billion dollars by 2030 (9).

Various laboratory and clinical parameters have been used to aid prognosis and outcomes in HF patients with preserved and reduced systolic function. S2PLiT-UG score is an example of such score that is based on independent predictors of 1-year all-cause mortality following discharge after an AHF event. The score divides the patients into three categories, namely, low, intermediate and high which could be used for facilitating risk stratification and therapeutic decision-making (10).

A study conducted by Borovac et al. showed that among all AHF patients, the HFmrEF phenotype was related to higher all-cause mortality compared to patients with HFrEF, during the 1-year follow-up (11).

1.3. Etiology of heart failure

The underlying diseases that can cause HF are very different and their detection is of great importance. The etiology of the HF can be divided into three types of causes: predisposing, determining and precipitating (12).

Predisposing causes are also known as risk factors, which can be identified in the population without any symptoms of HF. These include structural alterations, congenital or acquired, disorders of the peripheral vessels or cardiac valves that produce alterations in the normal physiology of the heart. CAD is responsible for more than 50% of HF cases in United States, mainly in males (13). Dilated cardiomyopathy and congenital cardiac abnormalities are other less prevalent factors contributing to HF (8,14). Arterial hypertension (AHT) has an indirect influence on the progressive deterioration of ventricular function, especially in women and black individuals with HF (15). This has been supported by Framingham study, which states that HF risk is double in the population with mild AHT and four-fold when the arterial pressure goes above 160/95 mmHg. Over time AHT leads to left ventricular hypertrophy which is also a risk factor for the development of HF. The risk of HF in diabetic women is 5 times higher compared to non-diabetic women, and higher than in diabetic men (16).

The determining causes of HF are the factors that alter the regulating mechanisms of the ventricular function, hemodynamic load conditions and heart rate. Idiopathic dilated cardiomyopathy affects both sexes and is characterized by prominent left ventricle (LV) systolic dysfunction. Restrictive cardiomyopathy is depicted by an alteration in cardiac compliance with rapid early diastolic filling. Hypertrophic cardiomyopathy is a genetic disorder, characterized by hypertrophy of the LV without apparent cause (17,18). Right ventricle has complex morphology due to its noncylindrical form and demonstrates different hemodynamic qualities compared to LV. Right ventricle free wall longitudinal strain (RV FWS) is an echocardiographic method used to measure right ventricle systolic function and its mechanics. Since the RV consists mainly of longitudinal and oblique myofibers and shared interventricular septum with LV, it is considered that RV FWS corresponds predominantly to right ventricle mechanical function. Therefore, RV FWS is used as a potent predictor, independent of LV systolic function, for cardiovascular and all-cause mortality among patients with HFrEF and pulmonary arterial hypertension (19).

Other secondary myocardial modification that causes HF is CAD. Some of the less frequent causes include cardiomyopathies which have infectious origin, toxic and metabolic cardiomyopathies (20).

In addition to this, hemodynamic overload can be due to a pressure or volume overload. Aortic stenosis and AHT are examples of increase in afterload that causes a pressure overload in LV. Pulmonary artery hypertension and pulmonary stenosis lead to the same consequences in the right ventricle. HF caused by volume overload can be caused by hypervolemia, mitral, tricuspid and aortic insufficiency (21).

Furthermore, the precipitating causes are factors that lead to decompensation in a stable patient with or without previous diagnosis of HF, but with an underlying structural cardiac abnormality. These factors are divided into cardiac and extracardiac causes (22). Cardiac causes include arrythmias and acute myocardial infarction (AMI) whereas extracardiac causes include infections of the respiratory tract, drugs that cause sodium retention, pulmonary embolism, physical or psychological stress, anemia and toxic habits (12,23).

Additionally, occlusive CAD is the most common reason for symptomatic HF in the US. With time, one or both ventricles become spherical and demonstrate atrioventricular valve incompetence, leading to annular dilation over time. The result is combined systolic and diastolic HF, with systolic dysfunction predominating in the majority of patients (24).

Regardless of the primary causes, HF is a progressive disease worsened by increased hemodynamic burden or a reduction in oxygen delivery to the increased myocardium demands. The majority of underlying causes of HF depend on gender, age, ethnicity and comorbidities (25).

1.4. Pathophysiology of heart failure

Since HF is a complex clinical syndrome, the understanding of the pathophysiology is crucial for the optimal treatment of the condition. However, this is often neglected by the physicians (24).

Pathophysiology of HF is considered to be a damaged state of systolic function of the heart followed by a state of low cardiac output (CO), that is, systolic failure. Eventually, left ventricular filling in diastole can be delayed which results in elevation of filling pressure and symptoms of HF, that is, diastolic failure (21).

Stroke volume (SV) is the amount of blood ejected by the ventricle per heartbeat and is affected by three main factors: preload, defined by the amount of myocardial fiber stretch at the end of diastole; afterload, defined by the resistance needed by the ventricles to overcome the force to eject blood; and contractility, which is the inotropic state of the heart. Optimization of these factors need to be maintained in order for the heart to function effectively. Imbalance of

this hemodynamic, between the cardiac ejection and filling capabilities leads to the presence of symptoms of HF (24,26).

1.4.1. Ventricular dysfunction

This can be divided into two categories: systolic dysfunction (impaired ventricular contraction and ejection) and diastolic dysfunction (impaired relaxation and ventricular filling), accounting for 70% and 30%, respectively. Systolic dysfunction may result from impaired cardiac contractile function, increased LV afterload or structural abnormalities of the left heart. This impairment can be caused by ischemic disease, infarction, uncontrolled hypertension or valvular incompetence. On the other hand, diastolic dysfunction results from increase in the amount of blood in the ventricle, causing an increase in both end-systolic and end-diastolic volumes (27). This in turn leads to an increase in left ventricle end-diastolic pressure (LVEDP) which causes elevation in pulmonary venous pressure. In other words, diastolic dysfunction is clinically manifested as pulmonary congestion. Similarly, the common cause of right ventricular failure is left ventricular failure (28,29).

The Frank-starling mechanism explains the compensatory role in the early stages of HF (Figure 1). It also explains how several compensatory mechanisms try to sustain adequate tissue perfusion by maintaining the mean arterial pressure (MAP) in a patient with HF. The figure shows how CO is a function of LVEDP which is directly related to left ventricle end-diastolic volume (LVEDV) or preload. However, these mechanisms are beneficial initially but worsen HF in a vicious cycle in the long-term (29).
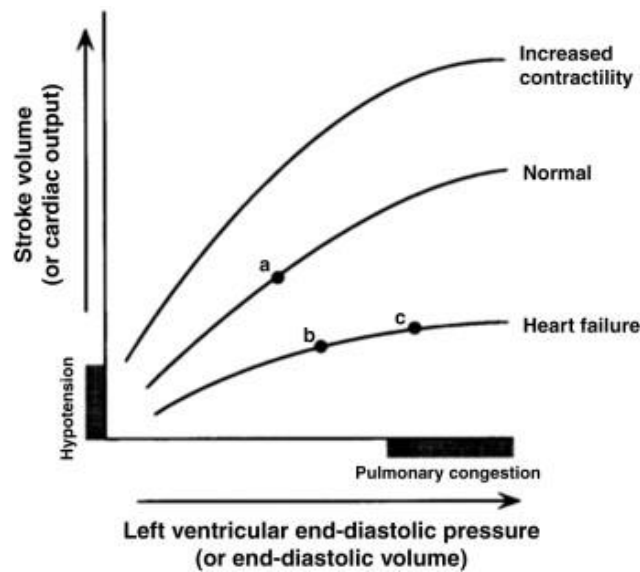
Figure 1. The Frank-Starling mechanism.

Taken from: Kemp C, Conte J. The pathophysiology of heart failure. Cardiovasc Pathol.2012;21(5):365-71.

Diastolic and systolic HF are not separate entities (21). HF is a result of a single continuous disease spectrum, where systolic and diastolic HF are phenotypes at two extremes (Figure 2). Hence, heart dysfunction occurs as a result of heart disease which cause diastolic dysfunction. It should be widely viewed as an element of pathophysiology in HF.
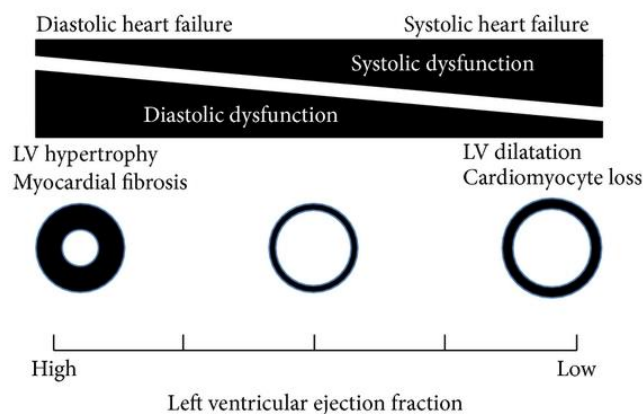

Figure 2. Single syndrome hypothesis of heart failure

Taken from: Komamura K. Similarities and Differences between the Pathogenesis and Pathophysiology of Diastolic and Systolic Heart Failure. Cardiol Res Pract. 2013; 2013:1-6.

1.4.2. Neurohormonal dysregulation

The neurohormonal model is the foundation of chronic systolic HF therapy. Neurohormonal activation is crucial for the maintenance of MAP and in the compensation during early stages of HF. Hemodynamic and neurohormonal derangement leads to baroreceptor-mediated sympathetic nervous activity causing elevation in heart rate, blood pressure and vasoconstriction. Increased adrenergic tone leads to the activation of the renin-angiotensin-aldosterone system (RAAS) (30). Consequently, the release of catecholamines has direct effect on the heart to increase the heart rate and contractility; on the peripheral vasculature leading to vasoconstriction. Subsequently, these changes lead to increase in SV and total peripheral resistance (TPR), increasing MAP. Increase in the release of renin leads an increase in vascular tone and pressure overload on a heart susceptible to hemodynamic injury. Additionally, angiotensin II stimulates the secretion of aldosterone, which reduces renal excretion of water and sodium, leading to excessive preload (24,29).

Patients with ischemic HF demonstrate a higher resting muscle sympathetic nerve activity compared to patients with non-ischemic HF. Certain circulating biomarkers can be measured in a patient with acute decompensation heart failure (ADHF). One example of such biomarker present in HF is catestatin (CST) which is cardioprotective peptide that counterbalances the negative effects of sympathetic nervous system by causing vasodilation and inhibiting the release of catecholamines. Research has shown positive correlation between high levels of CST, disease severity and mortality in HF patients. The levels of CST were found to be similar in patients with HFpEF and HFrEF (31).

Endothelial dysfunction known to be induced by oxidation stress, further contributes to the development of HF. A distorted endothelium dependent vasodilation, causing repeated episodes of ischemia/reperfusion, can have a decremental effect on myocardium. These changes not only induce systolic dysfunction, but also increased diastolic stiffness with diastolic dysfunction (32).

Overtime, aforementioned adaptions diminish the CO by the downregulation and uncoupling of contractility from normal stimuli. Long term consequences of this compensation result in ventricular remodelling which further accelerates myocardial dysfunction (29).

1.4.3. Ischemic injury

Ischemic injuries after myocardial infarction (MI) leads to several structural changes such as permanent injury, remodelling and ischemic replacement fibrosis. The subendocardium is susceptible to acute injury caused by hypoperfusion (24). During mild ischemia, heart adapts between supply and the energy utilization over which myocardial viability can be maintained, known as "short-term hibernation".

The "stunned myocardium" recovers over a period of hours to days whereas in chronic repetitive ischemia, the heart is incapable to recover between episodes of spontaneous ischemia. With increasing severity of ischemia, the heart downregulates metabolism to maintain myocyte viability at the expense of contractile function. As a compensatory response to ischemia, "hibernating myocardium" develops regional myocyte cellular hypertrophy, similar to the changes found in advanced HF (33).

It is crucial to differentiate between ischemic fibrosis and hibernating myocardium, as revascularization in viable myocardium result in improved left ventricular systolic function, exercise capacity and survival in comparison with medical therapy alone (24,33).

1.4.4. Ventricular remodelling

Left ventricular stress and injury leads to ventricular remodelling in untreated patients after large MI (34). Along with the chronic hemodynamic stresses on the heart, the size, shape, structure and function of the ventricle is modified. As the HF progresses, the overall changes in the shape are identified, with heart becoming less elliptical and more spherical. The histologic presentation demonstrates myocyte hypertrophy, apoptosis and increased interstitial collagen. The failing heart enlarges to increase ventricular volume to maintain the SV and CO. Increased contractility is achieved at the expense of increased myocardial wall thickness and ventricular mass. These changes become detrimental in the long-term process of remodelling which eventually impair contractility (29).

Cardiomyocyte hypertrophy and interstitial fibrosis are structural changes, whereas myocardial strips and increased cardiomyocyte stiffness are functional changes (Table 1). The table shows that myocardial dysfunction results from a sequence of events that causes myocardial remodelling, eventually HF (35,36).

Table 1. Factors responsible for myocardial remodelling (35,36)

HFpEF remodelling	HFrEF remodelling
Comorbidities (obesity)	Progressive loss of cardiomyocytes
Proinflammatory state	Autophagy
Reactive oxygen species	Apoptosis
Limited NO bioavailability	Necrosis (ischemia)
Low PKG activity	Fibrosis
Concentric LV thickness	Eccentric LV thickening
Intracellular collagen deposition	Extracellular collagen deposition

Abbreviations: HFpEF- heart failure with preserved ejection fraction, HFrEF- heart failure with reserved ejection fraction, NO- nitric oxide, PKG- protein kinase G, LV- left ventricle.

1.4.5. Genetic mutations

The significance of genetic mutation in HF is very important. Genetic predisposition increases the risk of HF depending upon the genomic variation and mutations (14). Framingham Offspring study proposed that parental HF was linked with asymptomatic left ventricular dysfunction, with an increased risk for overt HF in the offspring (37).

In 2006, AHA described cardiomyopathies that are mainly genetic and linked with mechanical and electrical dysfunction (29). The groups were based upon morphological and functional phenotypes: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathy such as left ventricular non-compaction cardiomyopathy. The genetic understanding of HF at the molecular level may lead to the development of new and specific individual treatment options in the future (37).

1.5. Diagnostics of heart failure

Clinical history and physical examination are the bases for the diagnosis of HF. During clinical history taking, the physician should include cardiovascular risk factors, toxic habits and noncardiac diseases that might contribute to HF. The symptoms belong to two groups: tachycardia, pulmonary rales and pitting edema, which are not very specific whereas the

specific signs include displacement of the apical beat, jugular venous distension and gallop rhythm which present in serious forms of HF (3).

Several criteria have been proposed to diagnose HF. The first model to systematize HF arise from the Framingham study. This criterion included the presence of two main or one main and two minor criteria (Table 2) (16).

Table 2. The Framingham study criteria (16)

Major criteria	Minor criteria
Paroxysmal nocturnal dyspnea or orthopnea	Ankle edema
Distended neck vein	Night cough
Rales	Dyspnea on exertion
Cardiomegaly	Hepatomegaly
Acute pulmonary edema	Pleural effusion
S3 gallop	Vital capacity decreased by 1/3
Increased venous pressure $\geq$ 16 cm water	Tachycardia rate of $\geq$ 120/min
Circulation time $\geq$ 25 sec	
Hepatojugular reflux	

Another criterion used to diagnose HF is defined by European Society of Cardiology (ESC) (Table 3). It includes symptoms present at rest or during exercise and objective evidence of cardiac dysfunction at rest. Cardiac function is also uniformly evaluated by appropriate tests, which in most cases are obtained from the echocardiogram (38). Diagnostic criteria 1 and 2 that appear in Table 3 should be met in all cases (39).

Table 3. European Society of Cardiology 2016 Guidelines (39)

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms +/- Signs*	Symptoms +/- Signs*	Symptoms +/- Signs*
	2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
	3	-	1. Elevated levels of natriuretic peptides$_a$; 2.At least one additional criterion: Relevant structural heart disease (LVH and/or LAE), Diastolic dysfunction	

Abbreviations: HFpEF- heart failure with preserved ejection fraction, HFrEF- heart failure with reserved ejection fraction, HFmrEF- heart failure with mid-range ejection fraction, HF- heart failure, LVEF- left ventricular ejection fraction, LAE- left atrial enlargement, LVH- left ventricular hypertrophy, BNP- b-type natriuretic peptide

* Signs may not present in the early stages of HF (especially in HFpEF) and in patients being treated with diuretics.

$_a$BNP > 35 pg/ml

In comparison to the above diagnostic criteria, Boston criteria is used in older adults due to its validity and improved prediction of adverse outcome (Table 4) (38). Although Framingham criteria provided greater sensitivity to diagnose HF, the specificity and positive predictive value was higher when using Boston criteria (38).

Table 4. Boston Criteria for diagnosing HF (38)

Category	Diagnosis	Score (points)
I History	Rest dyspnea	4
	Orthopnea	4
	Paroxysmal nocturnal dyspnea	3
	Dyspnea on walking on level	2
	Dyspnea on climbing	1
II Physical examination	Heart rate abnormality	1-2
	Jugular venous pressure elevation	1-2
	Lung crackles	1-2
	Wheezing	3
	Third heart sound	3
III Chest radiography	Alveolar pulmonary edema	4
	Interstitial pulmonary edema	3
	Bilateral pleural effusions	3
	Cardiothoracic ratio ≥ 0.50	3
	Upper-zone flow redistribution	2

Definite heart failure 8-12 points, possible 5-7 points, unlikely 4 points or less

The diagnosis or exclusion of HF is supported by various other examinations and tests to provide prognostic value. The initial clinical evaluation is focused at confirming HF, determining risk factors and identifying comorbid illnesses (38). B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NI-proBNP) are used for immediate diagnosis of both HFpEF and HFrEF, even in situations when echocardiography is not available. Echocardiography provides urgent information, including the function of the ventricles, chamber size, wall thickness and valve abnormalities (2).

After diagnosis, HF is organised into classification system that allows prediction of mortality and can be used for monitoring treatment response (1).

The NYHA classification system is the most widely used method to measure symptom severity. It defines four functional classes as (1,2):

- Class I: HF does not cause limitations to physical activity; no HF symptoms
- Class II: HF causes slight limitations to physical activity; symptoms with significant exertion but comfortable at rest or with mild activity
- Class III: HF causes marked limitations of physical activity; symptoms with mild exertion and only comfortable at rest
- Class IV: HF patients are unable to carry on any physical activity, symptoms occurs even at rest

Furthermore, AHA/ACC propose a staging of HF as (1):

- Stage A: High risk of HF but no structural heart disease or symptoms of HF
- Stage B: Structural heart disease but without symptoms of HF
- Stage C: Structural heart disease and symptoms of HF
- Stage D: Refractory HF requiring special interventions

1.6. Ethnicity associated risk factors for heart failure

The differences in outcomes between black and white patients are widening while the hospitalization and short-term mortality are decreasing (40).

Ethnic and racial differences exist for the outcome of HF in patients within a diverse municipal health system, even after adjusting the risk factors and comorbidities (40). These differences could be due to the underlying etiology and pathophysiology of HF that contribute to the outcome. In black patients, HF is associated with diabetes and hypertension, while white patients have higher incidence of coronary disease leading to ischemic cardiomyopathy (41).

Although, black people are more likely to seek care for emergency department for HF, but this may be related to poorer health literacy, absence of medical home and cost-barriers. On the other hand, white patients had lower clinic utilization which could lead to higher mortality (40). This raises a question whether the disparities exist due to underlying biological, genetic and epigenetics differences or due to inequalities.

The influence of race on HFpEF and HFrEF have been investigated on postmenopausal women (4,42). The study by Eaton et al. proposed that white race and not African American and Hispanic groups correlated with both, HFpEF and HFrEF. This was supported by Pandey

et al., who reported that the lifetime risk of HFpEF development was 1.5-fold higher in non-blacks when compared with blacks (4,43).

1.7. Gender associated risk factors for heart failure

The overall lifetime risk of HF is fairly comparable between sexes; with an estimation of 21% for men and 20% for women at age of 40 years in the Framingham Heart Study. Patients with HFpEF are older and show female predominance whereas men are more likely to be subjected to HFrEF (2). Gender differences were found in ADHF for the clinical characteristics at presentation including age and comorbidities. Women are known to less commonly report the symptoms of chest pain compared with men; this could lead to gender disparities in the outcome of AMI (4,44).

HFpEF is more common in women compared with men and contributes to at least half of the cases of HF in women. Women develop HF at an older age compared to men. However, over the past 50 years, the incidence of HF has declined among women while survival after the onset of HF has improved in both sexes (2,4).

The importance of heart failure in women has been underappreciated. Women with heart disease tend to have worse outcomes and less likely to benefit from treatment compared to men. In many mixed-gender cardiovascular clinical trials, women are often underrepresented. As a consequence, women do not benefit from gender-specific cardiology evidence-based medicine which has resulted in more deaths in women compared to men in the past 3 decades (45).

A study conducted by Gulati et al. found that women differ to men in terms of prevalence, symptoms and pathophysiology of MI. Less anatomical obstructive CAD and relatively more preserved left ventricular function have been reported in women, despite higher rates of MI and mortality compared with men. Data from the National Institutes of Health implicate adverse coronary reactivity, microvascular dysfunction and plaque erosion /distal microembolization as key factors that lead to female-specific MI pathophysiology. Women with ischemic heart disease (IHD) often have more persistent symptoms than men, frequent hospitalizations and lower rates of general well-being (46).

Few factors that contribute to high prevalence of IHD in women are elevated levels of triglycerides, obesity and diabetes (3-fold greater risk of IHD than non-diabetic women). Furthermore, metabolic syndrome (combination of central obesity, glucose intolerance, hypertension and dyslipidemia) which is a predisposition to cardiac risk factors is more common after menopause, likely related to hormonal-mediated changes. Other factors that

predispose women is ovulation dysfunction that is linked to premature coronary atherosclerosis and polycystic ovarian syndrome (46,47).

Novel risk marker such as high-sensitivity C-reactive protein (hsCRP) may improve the risk detection in women. It is consistently higher in women compared to men, from puberty onwards. An elevation in hsCRP is associated with a greater risk of IHD than traditional risk factors would predict. On the other hand, endothelial response is adversely affected by traditional cardiac risk factors such as tobacco abuse, hyperlipidemia, diabetes and hypertension which tends to worsen after menopause. This contributes to ischemic changes in women (46).

Since men have higher risk of HFrEF, this attributes to their predisposition to macrovascular CAD and MI, whereas coronary microvascular dysfunction has been postulated to play a key role in women with HFpEF, hence predisposing them to heart failure syndromes such as Takotsubo and peripartum cardiomyopathy. Recent trends (2005-2014) in the Atherosclerosis Risk in Communities study showed that both first and recurrent hospitalizations for acute HF were more likely to be HFrEF in men than women, and in blacks than whites (48). Lam et al. found that young HFpEF patients were predominantly non-white males with obesity, while older patients with HFpEF tend to be predominantly hypertensive females. Echocardiographic studies have shown that women with HFpEF are more likely to have concentric LV remodelling, more severe diastolic dysfunction including impaired LV relaxation, higher diastolic stiffness and high LV filling pressures compared to men with HFpEF. To effectively investigate the underlying cardiovascular disease development, biological sex is an important experimental variable that needs to be better addressed both in basic and clinical research studies (49).

According to Leigh et al. the age-adjusted death rate from CHD is higher among non-Hispanic blacks than any other ethnic group. It was also found that African Americans with confirmed acute coronary syndrome were younger, poorer, less educated and had a longer pre-hospital delay than white counterparts, with black women outpacing white men. CHD disparities exist for ethnic minorities which range from differences in treatment and outcomes to a lack of epidemiological studies. It is important to address both gender and sex disparities in order to guide effective diagnosis and treatment of heart failure in patients (50).

1.8. Randomized controlled trials

Randomized controlled trials (RCTs) are quantitative, comparative, controlled experiments in which the researcher studies two or more interventions in a series of individuals who receive them in random order. RCTs are gold standard and are simplest and most powerful tools in clinical research to study the safety and efficacy of new treatments or interventions. This methodological approach is used to answer patient-related questions and provides highest quality evidence with low-risk of systemic error (bias). However, RCTs cannot yield robust data unless they are planned, conducted and analysed in ways that are methodologically sound and appropriate to the question being asked. This can be achieved by sample size calculation and pilot study to achieve appropriate planning in terms of time and money that should be employed. The study sample must be representative of the target population for the findings from the study to be generalisable (51).

2. AIM

The aim of this study is to determine the reporting of data on gender and ethnicity in RCTs of interventions for heart failure treatment in the major journals from the field of cardiology from 2017 to 2019.

Hypotheses of this study are:

1. Majority of analysed studies will include stratification based on gender and ethnicity
2. There will be low frequency of papers that report on sex/gender and race/ethnicity specific results
3. There will be low frequency of papers that mentioned specific sex/gender or race/ethnicity results in discussion section
4. Majority of the research will be based on white ethnic background compared to other ethnicities

3. MATERIALS AND METHODS

3.1. Study design

The analysis consisted of cross-sectional meta-epidemiological study of RCTs published between January 2017 to December 2019 in five major cardiology journals. We examined RCTs on heart failure for reporting on sex/ gender and race/ethnicity. The analysis was conducted on publicly available data and personal patient data were not included and therefore approval of an Ethics committee was not necessary.

3.2. Inclusion and exclusion criteria

The inclusion criteria specified that the study being investigated had to be designed as an RCT and involve studies published on heart failure. Five journals included in the study were selected as highest-ranking journals in their categories in Journal Citation Reports (JCR) according to Journal Impact Factor (JIF) of 2019. They were, namely, European Heart Journal, Circulation, Journal of the American College of Cardiology, Circulation Research and European journal of Heart Failure.

We excluded RCTs that were not full-length articles such as research letters or brief reports or protocols.

3.3. Search

We searched PubMed using advanced search feature with a MeSH term and the names of the journals with the composition: (heart failure [MeSH Terms]) AND ("European heart journal"[Journal]) OR ("Circulation"[Journal]) OR ("Journal of the American College of Cardiology"[Journal]) OR ("Circulation research"[Journal]) OR ("European journal of heart failure"[Journal]). Additional filter for obtaining only the RCT papers was used, along with the publication date limited only from January 2017 to December 2019. This search helped to obtain 371 journals out of which 27 short forms with incomplete information were excluded. The remaining 344 journals with full texts were downloaded for data extraction on sex and race integration across six article sections: title, abstract, introduction, method, results and discussion.

3.4. Data extraction

To record the data, we used Microsoft Excel, version 2020 (Microsoft Inc, Canada). We extracted the data for: journal name, year of publication, study name, sex or race detailed terminology explained, sex or race mentioning in the title, abstract or introduction, number of study participants, number of male and female subjects, list of different ethnic backgrounds, sex and race specific analyses planned in the methods and results, differences in the sex and race specific results, sex and race specific results mentioned in the discussion section and centre of the study. To ensure that no reference to sex was missed, each journal was searched electronically using terms such as sex, gender, male, female, male and men using search function. The data extracted for each section was coded as either absent (0) or present (1). Additional codes were added depending upon the findings for difference in race and sex specific results. While analysing the data for the number of males and females included in the studies, only the exact number or figure was used, and the percentages listed in brackets were disregarded.

3.5. Data analysis

We used MedCalc statistical software, version 19.1.2 (MedCalc Software, Ostend, Belgium) to conduct data analysis. Categorical variables were expressed as whole numbers and percentages, while continuous data were shown as median and interquartile range. Normality of continuous data distribution was assessed with Kolmogorov-Smirnov test, while Kruskal-Wallis test with *post-hoc* Conover analysis was used to test their differences. Furthermore, differences between categorical variables were assessed with chi-square test. Statistical significance was set at $P<0.05$.

4. RESULTS

The study identified RCTs published between January 2017 and December 2019, accounting for a total of 344 manuscripts. Majority of the RCTs were published in the year 2018 (151; 43.9%), followed by 2017 (115; 33.4%) and 2019 (78; 22.7%) (Figure 3).
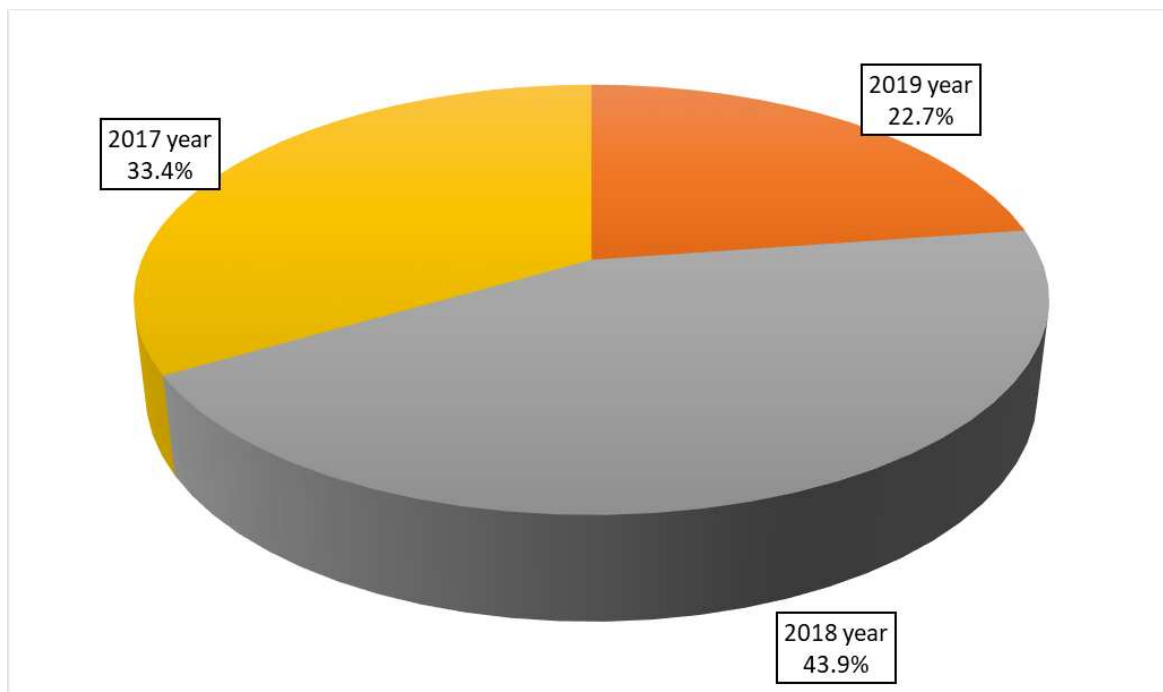

Figure 3. Publication of RCTs in terms of years

Figure 4 shows that the highest number of RCTs were published in the Journal of the American College of Cardiology (121; 35.2%) and Circulation (118; 34.3%), whereas lowest numbers were published in the European Heart Journal (10; 2.9%).
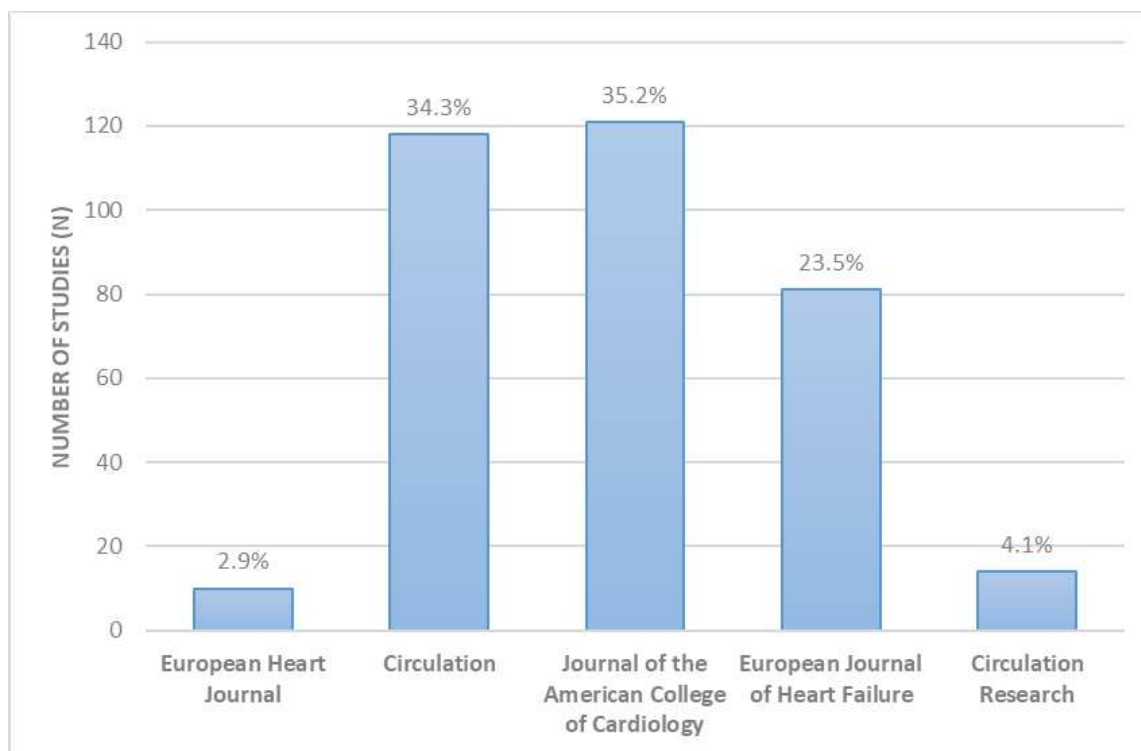
Figure 4. Number of RCTs published in five major Cardiology journals

The overall percentage of sex and race were rarely mentioned in the title of the RCTs, 1.2% and 1.7%, respectively.

There was no statistically significant difference in the number of RCTs that included sex/gender in abstract section between different journals (P=0.502). Circulation accounted for the highest number of RCTs that stated this parameter, whereas Circulation Research accounted for the least, 26 and 1, respectively (Figure 5). Overall, 63 (18.3%) of published RCTs reported sex/gender in the abstract section (Figure 5).
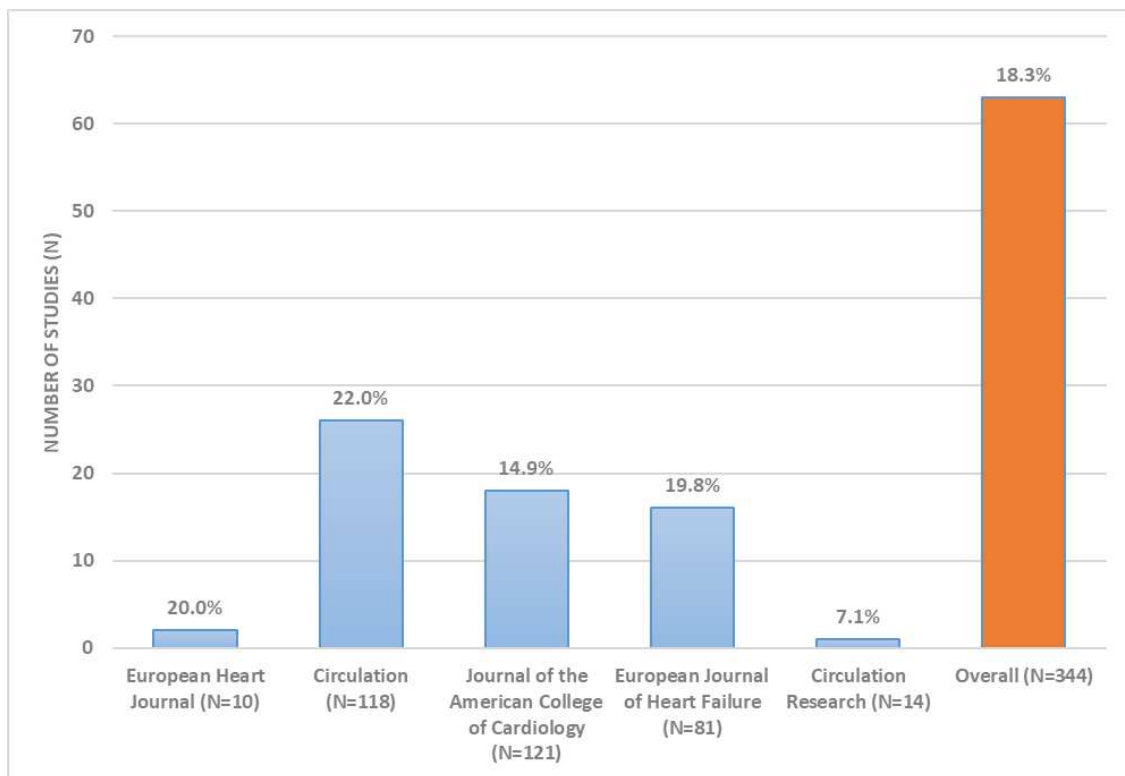

Figure 5. Sex/gender reported in the Abstract section of the RCTs

In comparison to the sex/gender, race/ethnicity was mentioned only in 16 (4.65%) of the overall RCTs (Figure 6).
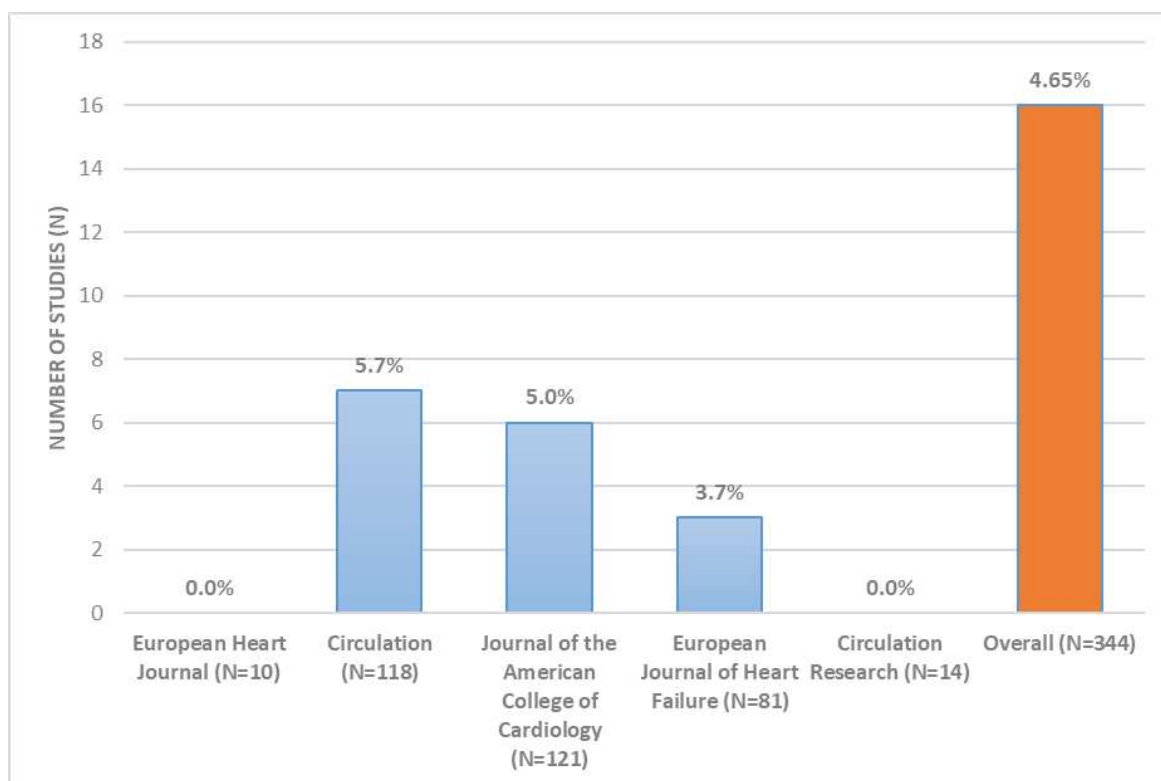

Figure 6. Race/ethnicity reported in the Abstract of the RCTs

Figures 7 and 8 demonstrate the use of investigated parameters in the Introduction section of the RCTs. RCTs that reported sex/gender in the Introduction were only 12 (3.5%) overall, with no contribution at all from RCTs published in two journals (European Heart Journal and Circulation Research). Likewise, same RCTs contributed nothing to the number of the race/ethnicity mentioned in the Introduction section, with the overall of 10 (2.91%).
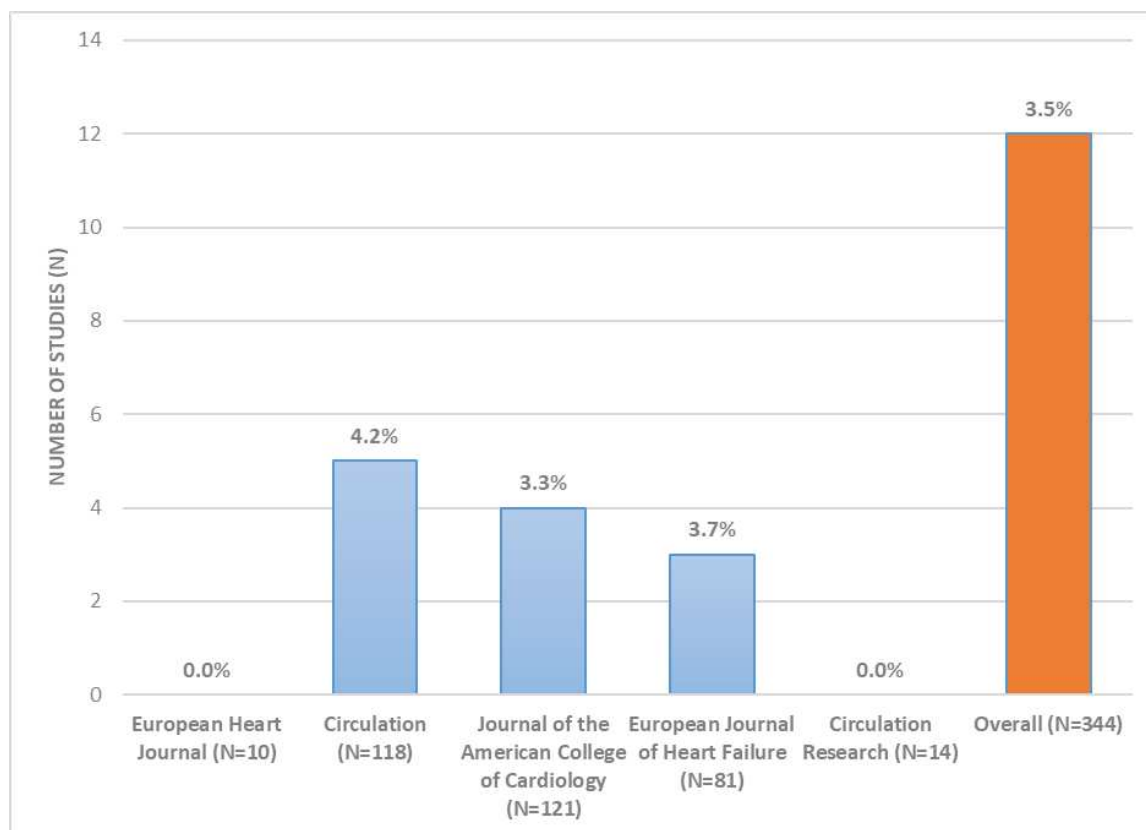

Figure 7. Sex/gender differences from previous studies mentioned in the Introduction
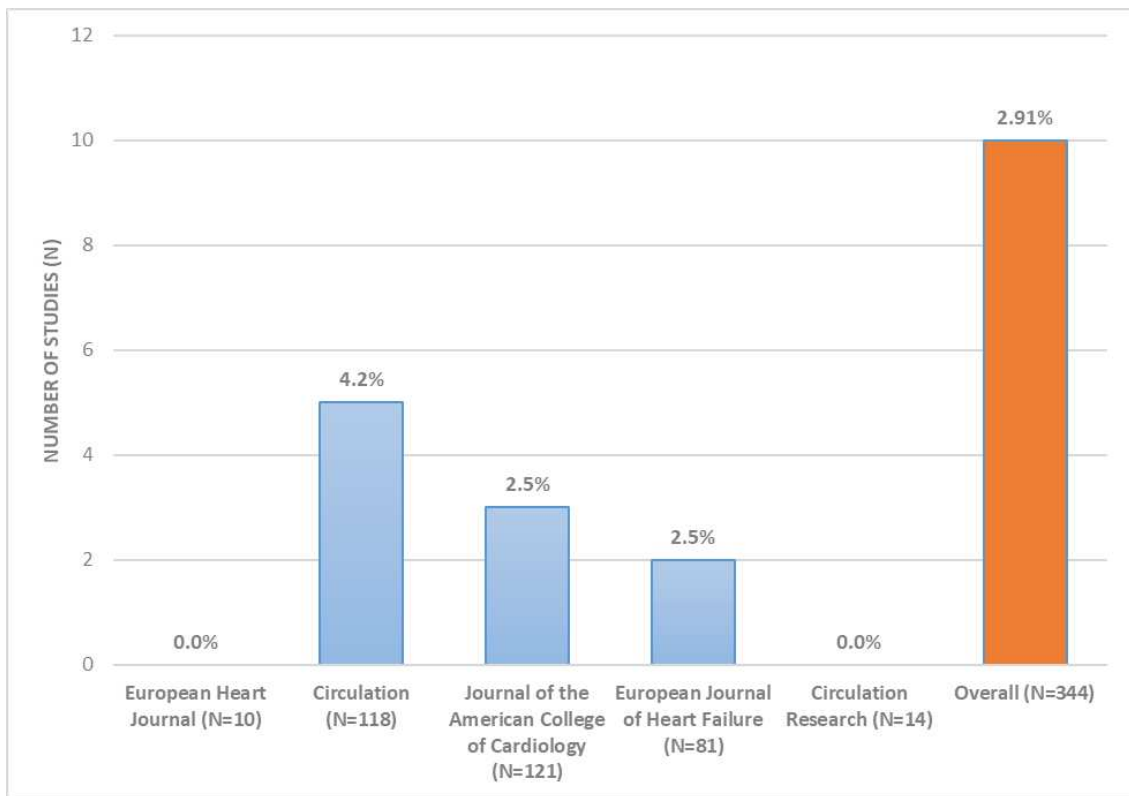
Figure 8. Race/ethnicity differences from previous studies mentioned in the Introduction

Most of the papers in this study (N=305; 88.6%) mentioned sex/gender in any of the sections, while race/ethnicity was mentioned in a total of 212 papers (61.6%). Furthermore, Circulation journal accounted for the highest number of RCTs for stating sex/gender, 107 (90.7%) while race/ethnicity was reported highest in the Journal of the American College of Cardiology, 82 (67.8%). None of these parameters showed significant differences according to all included journals (P=0.419 for sex/gender; P=0.187 for race/ethnicity) (Figures 9 and 10).
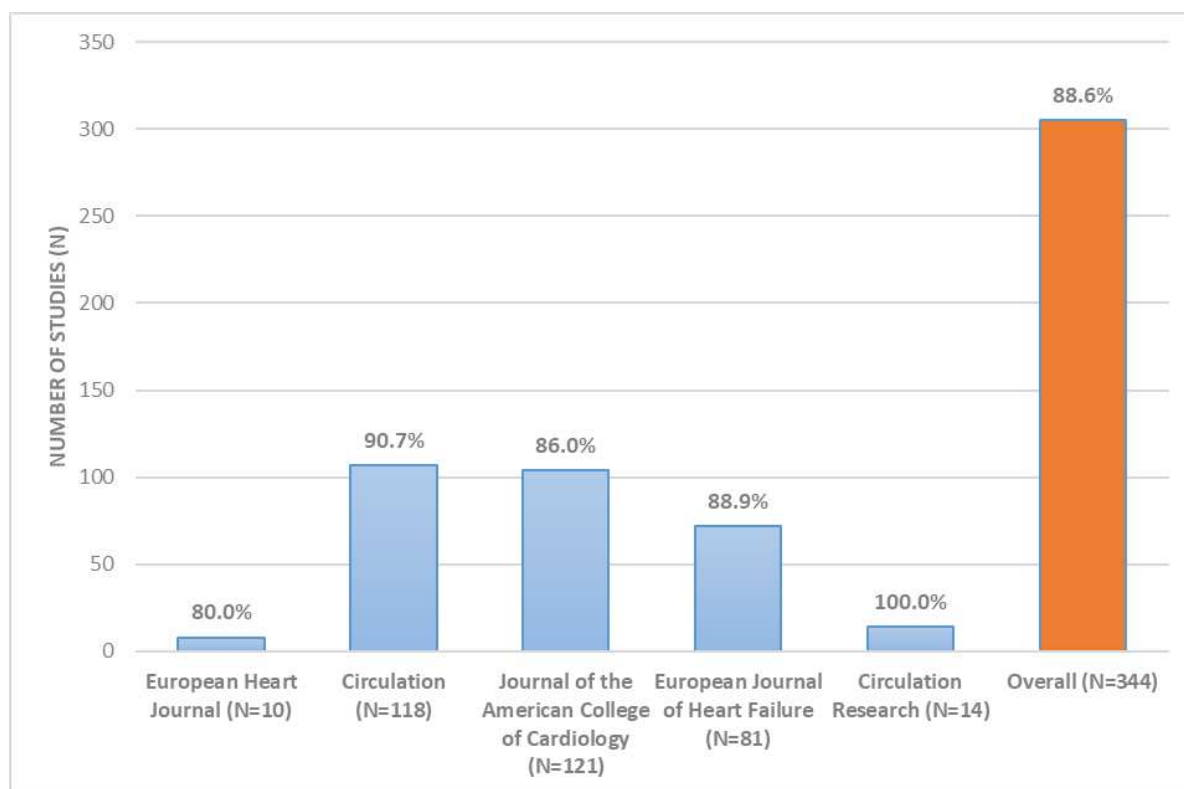

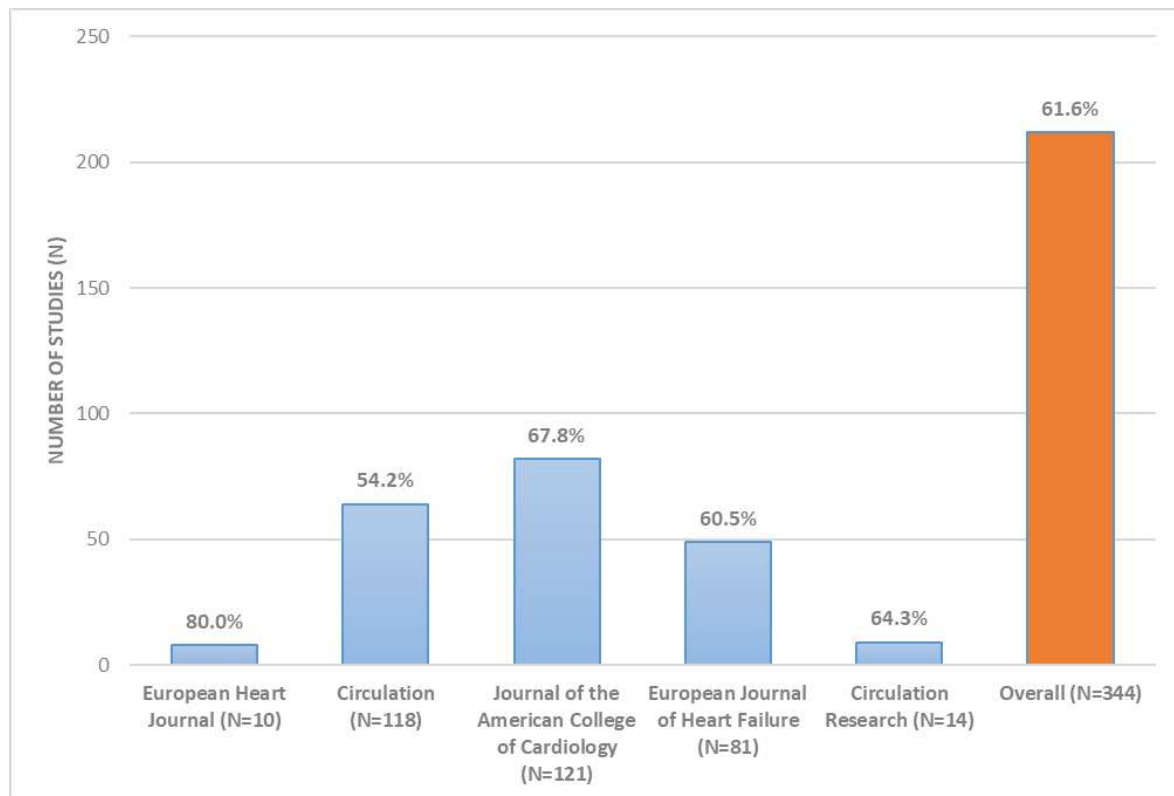**Figure 9.** Reporting of sex/gender in the article

Figure 10. Reporting of race/ethnicity in the article

Majority of the investigated papers did not include any terminology based on sex/gender or race/ethnicity.

Exclusion criteria was searched in all papers to identify whether sex/gender was excluded while selecting the study participants, which narrowed down the results to only one study, where no female participants were allowed to take part in the research. Similarly, 98.3% of the papers did not mention race/ethnicity as part of their exclusion criteria, apart from two studies that excluded only African Americans (0.6%).

In the description of the study methods, 35 (10.2%) papers described plans to examine results separately by sex/gender (Figure 11), and only 17 (4.9%) overall planned to examine differences in race/ethnicity in their research (Figure 12). Journal of the American College of Cardiology included 13 (10.7%) papers for investigating difference between gender, while it included only 6 (5%) journals for planning race specific analyses. There were no statically significant differences according to investigated journals for these parameters (P=0.808 for sex analysis; P=0.955 for race analysis).
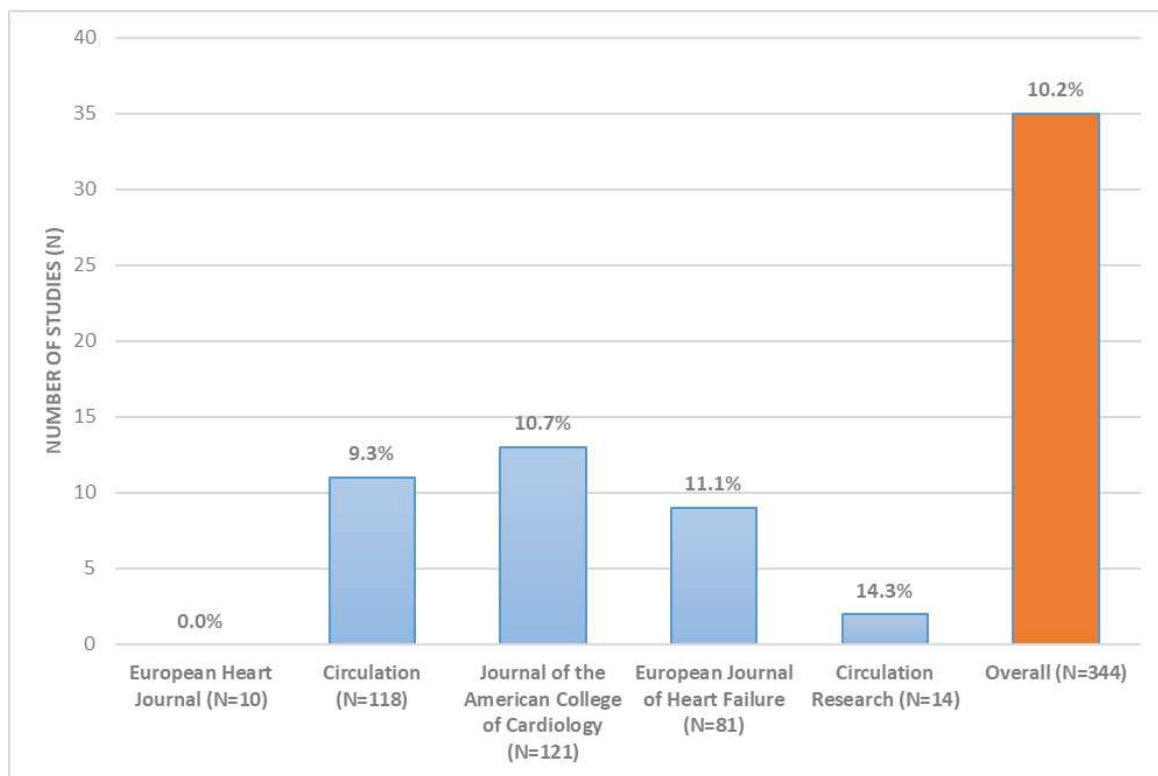
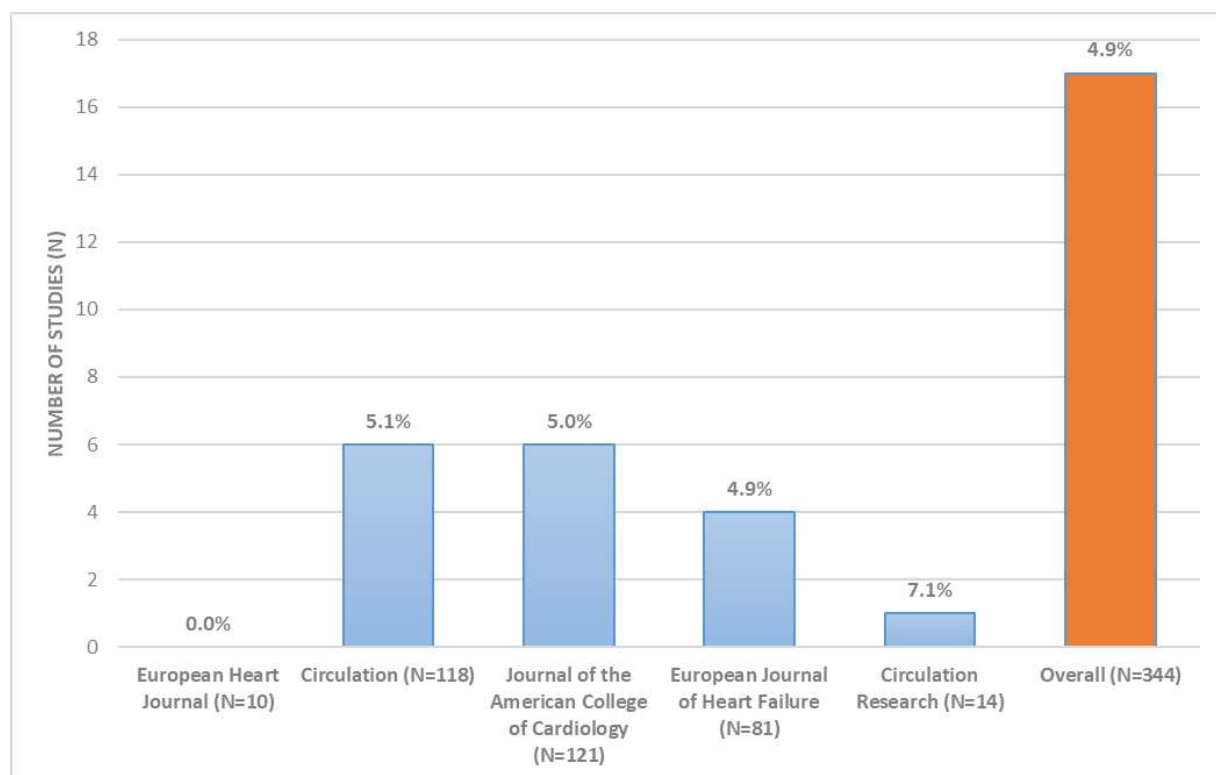**Figure 11.** Sex specific analyses planned in the methods

Figure 12. Race specific analyses planned in the methods

In a total of 180 (52.3%) papers, at least one analysis in results section was included based on gender, out of which, Circulation journal contributed for 69 (58.5%) studies (Figure 13). Furthermore, race specific results were less commonly reported, with 67 (19.4%) papers compared results between different races (Figure 14). There were no statistically significant differences in the reporting of specific data in result section of the papers according to included journals for both sex/gender and race/ethnicity parameters (P=0.337 and P=0.175, respectively). The further analyses of the results showed that very few papers included sex (N=26; 7.5%) or race (n=8; 2.3%) specific results differences mentioned as part of their discussion section.
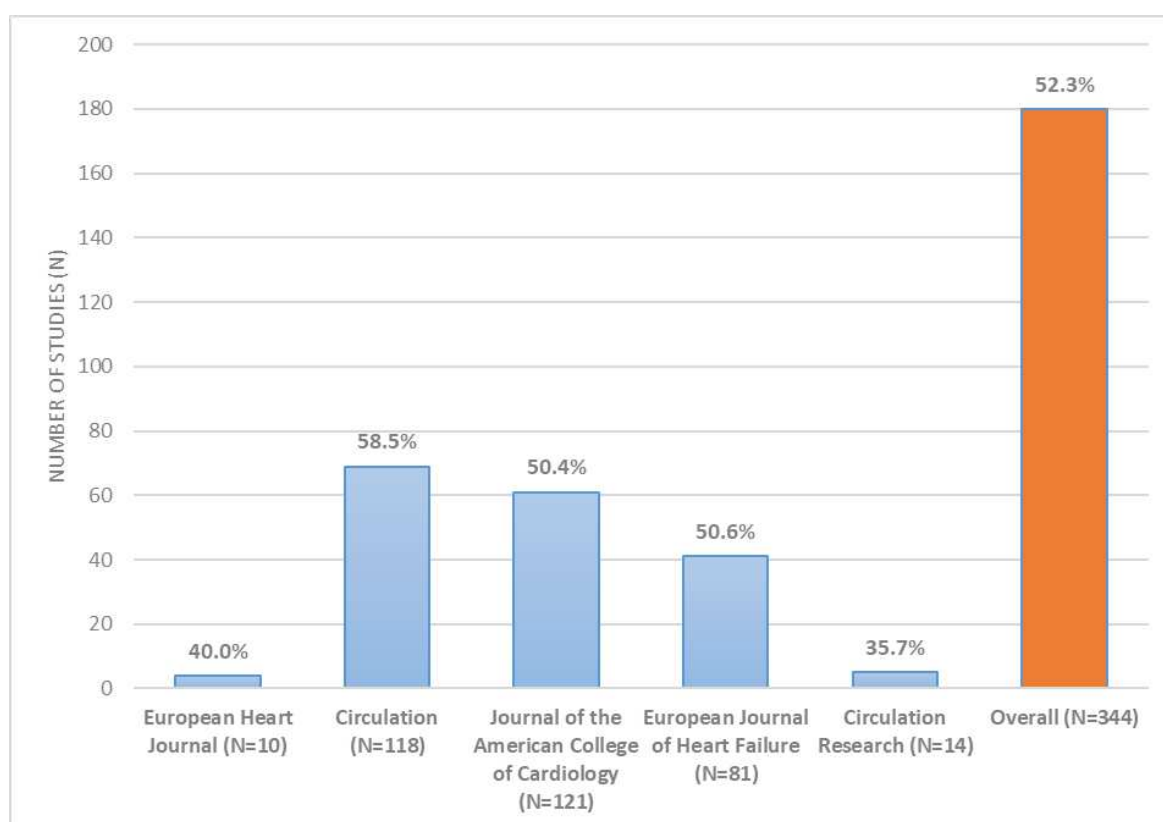

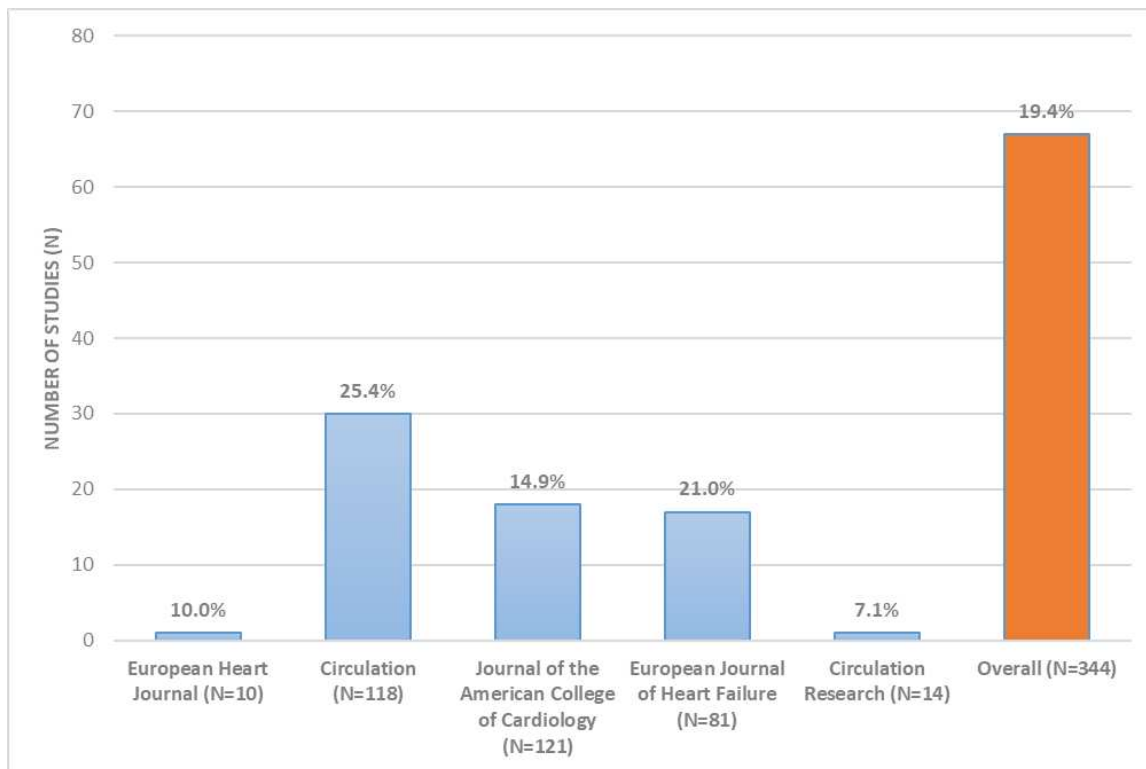**Figure 13.** Sex specific results described in results

Figure 14. Race specific results described in results

Out of 344 journals, 193 (56.1%) studies were multicentric. In addition to that, all the journals were also analysed for the number of males and females included in studies. The results were higher for females, 285 (63-2097) in comparison with males, 212 (39-972) (P=0.309).

White population was included in highest number of included papers (N=71), followed by black population (N=56), Asian population (N=33), Hispanic/Latin American (N=15) and other races (N=32). Also, studies with white population included significantly larger number of participants (1086 (103.5-3633)) in comparison with papers that investigated black population (176 (29-434)), Asian population (508 (13-1509)) and Hispanic/Latin American population (147 (13.5-764.5)) (P<0.001). Detailed differences in number of participants according to investigated race can be seen in Figure 15.
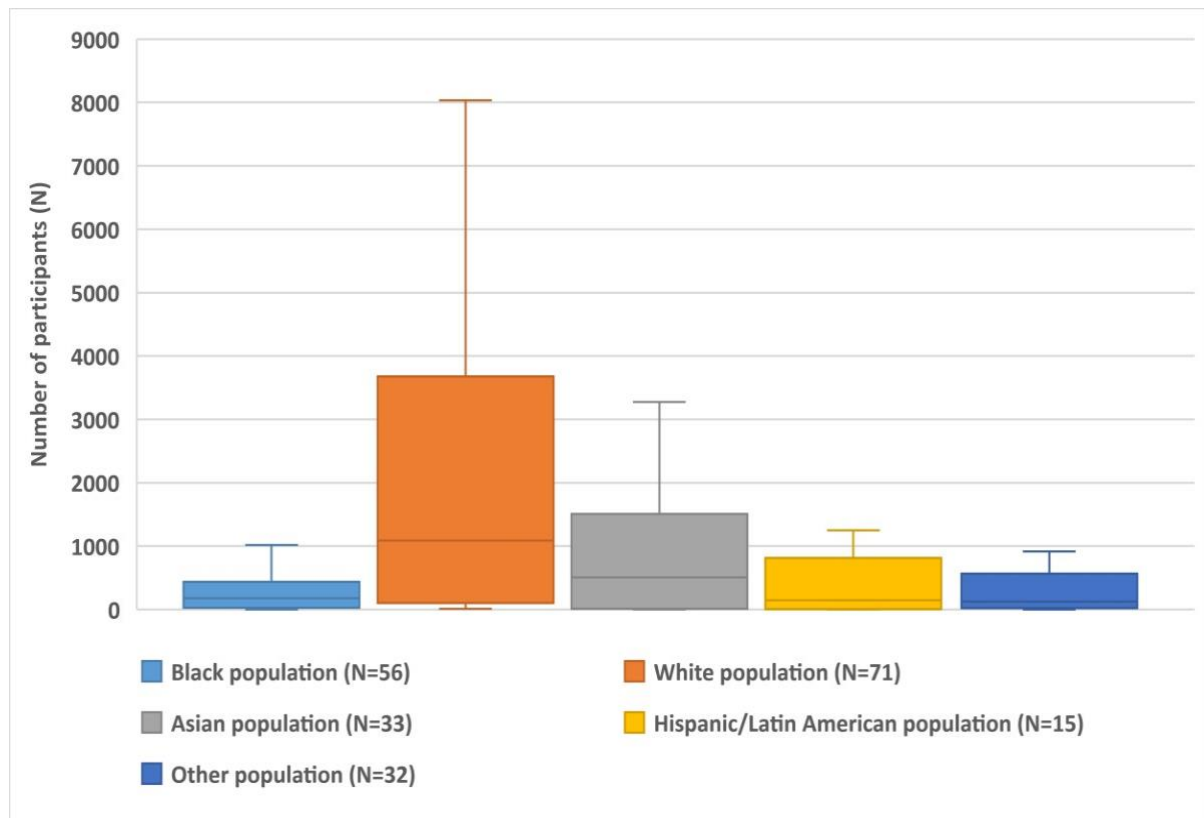
Figure 15. Difference in number of included study participants according to race

The highest number of study participants according to journals were included in the European Journal of Heart Failure, 1448 (399-3380), followed with Journal of the American College of Cardiology (1204 (424-7159)) and Circulation (1129 (222-9102)). Circulation Research had lowest number of included participants in its papers (60.5 (40-165)) (P=0.005). Detailed results can be seen in Figure 16.

Figure 16. Differences in the number of study participants according to different journal

5. DISCUSSION

The analysis of the published data demonstrates low levels of reporting on sex and race consideration in published RCTs on heart failure treatment interventions. While 88.6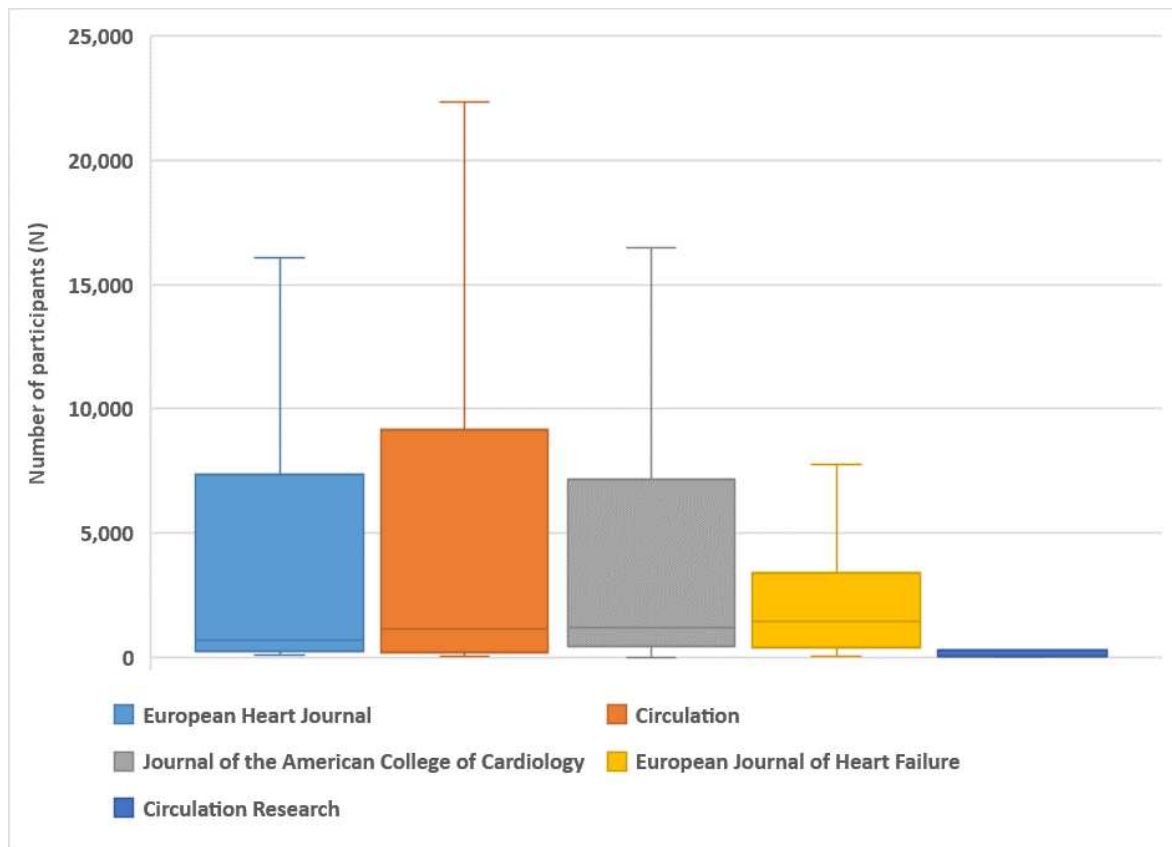% of the RCTs overall reported on sex/gender within article, only 52.3% reported at least one outcome by sex/gender. Similarly, 61.5% of the published RCTs extended their research based on race/ethnicity, only a mere 19.4% of these reported on race specific results. In other words, even though majority of the published RCTs included significant population, which included both males and females, only few studies included information that would allow the readers to compare results by race/ethnicity. Therefore, our study aimed to highlight possible clinical differences in terms of sex and race differences in the presentation of HF which could have clinical significance.

The highest number of papers based on HF were published in the Journal of the American College of Cardiology, followed by Circulation journal, with a difference of only about 1%. When taking the parameters of the study into consideration (sex and race described in different sections), Circulation journal had highest number of included papers. In majority of the parameters, no statistically significant difference was found, besides white race participants and number of participants included in different journals overall.

There has been an increase in the recognition of the importance of the role of sex and race in the pathology, diagnosis, prevention and treatment of various health conditions in the scientific community. This has led to a modest increase in the inclusion of both sexes and reporting of sex specific analyses in RCTs.

There is enormous evidence that biological sex affects the penetrance and pathology of genetic cardiomyopathies with males typically being more severely affected. Conversely, female specific stress factors such as pregnancy may trigger HF (49). Dewan et al. reported that although women with HFrEF lived longer than men, their additional years of life are of poor quality, along with greater self-reported psychological and physical disability (52). Women have a significantly higher risk of mortality in the first year after an acute MI, especially women with age <55 years. In addition to this, women who present with MI are less likely to receive fibrinolytic drugs, stents and related therapies (45). Therefore, inclusion criteria for HF studies should include women participants for the betterment of the advancements in the treatment outcomes.

Although discrepancies exist between the type of heart failure that men and women are predisposed to, few studies suggest that women and non-whites have higher chances of hypertension compared to men which is a risk factor for HF (4,53).

Clayton et al. reported that women are often underrepresented in clinical trial of cardiovascular diseases (45), but our study found that higher number of women were enrolled in the HF studies. However, there was no statistical significance for the numbers of males and females included.

Women are less likely to be admitted to the hospitals due to cardiovascular problems as they report chest pain less often compared to men (44). On the other hand, study by Gulati et al. report that women with IHD have persistent symptoms and more frequent hospitalization (46). This is contraindicated by research carried out by Greene et al. who reported higher number of females tend to suffer from nonischemic HF, and the same was true for Asian population. Patients to be diagnosed with nonischemic HF with etiology of preserved HF were more likely to be female, Asian, had higher baseline blood pressure, better baseline renal function and functional class and fewer comorbidities. There was stronger relationship between HF duration and mortality among female patients (54).

Patients with higher baseline concentration of lipoprotein are more likely to have a history of MI or peripheral artery disease. Furthermore, studies show that women are more predisposed to diabetes when compared with men. This is supported by Perrone-Filardi et al. who proved that IHD in women are mainly from the consequences of elevated triglycerides, obesity and diabetes. These factors tend to deteriorate after menopause in women (47).

Gender differences are found in the presentation of HF subtypes. Patients with HFpEF show female predominance whereas men show predisposition for HFrEF (2). This has been reinforced by other studies that included similar research and found that HFrEF were more common in black and white men, whereas HFpEF was most common in white women (48). Additionally, participants with a history of HF at baseline were more frequently white, hypertensive with previous cardiovascular diseases (55).

Along with the investigation of differences in the presentation of HF among different sex and race, attention needs to be paid to other contributing factors that can lead to HF. African Americans with acute coronary syndrome were reported to be younger, less educated and came from poorer backgrounds (50). This demands the necessity to include people from ethnic minorities, with detailed attention to their backgrounds. The analyses from our study showed that maximum number of participants according to race, were of white ethnicity. Out of 344 studies, 71 included white participants, 1086 (103.5-3633) compared to black participants, 176 (29-434) which were included in 56 papers. One of the reasons contributing to low number of participants of non-white ethnicity in clinical trials could be their unwillingness to engage in research. This has been supported by Periera et al. who examined willingness to participate in

clinical trials by ethnicity. It was found that African American and Hispanic-American participants had more negative attitudes towards clinical trials than white/non-Hispanics (56).

Our study did not find significant difference between the presentation of sex and race within RCTs published in different journals. There are several reasons to strive for balanced gender and race representation in clinical trials in order to increase generalizability of the data. Since heart diseases manifest differently in men and women, disease symptoms are often reported differently by men and women. Moreover, sex-based differences are common in the pharmacokinetics and pharmacodynamics of drugs, this states that men and women often respond to interventions differently (45,52). It is important to include sex and race considerations from point to point throughout the entire research paper.

Lower number of RCTs reported on race/ethnicity when compared to sex/gender. The data collected did not hold any statistically difference for these two parameters, stating that holistically approach needs to be employed while recruiting participants for the study. The enhanced sex focused approach will not only expand our knowledge base on female and male biology but minimize risk of harm to both genders (49,50). This will allow clinicians to practice truly evidence-based sex and race appropriate medicine and deliver individualized clinical care. There is a notable absence of sex and race criteria in guidelines to improve the quality of RCT reporting, such as the Consolidation Standards of Reporting Trial (CONSORT) Statement (57). Despite being the "gold standard" of scientific evidence, the results from our study suggests that the majority of RCTs in HF fall far short of providing sufficient information on sex and race perspective. Including sex and race specific data will provide high quality data as suggested by SAGER Guidelines for reporting on standardized criteria for sex and race (58).

This study has several limitations. Only 5 representative journals were investigated in this study, limited to 2017-2020 period. Additionally, for thesis purposes only one author performed data extraction, so this could influence results.

6. CONCLUSION

Based on the study results, we can conclude the following:

1. Overall, most of the RCTs in this study (N=305; 88.6%) mentioned sex/gender in any of the sections, while race/ethnicity was mentioned in a total of 212 papers (61.6%).

2. Analysed RCTs on average included more female participants than men.

3. White population was included in highest number of included RCTs with highest number of participants.

4. In a total of 180 (52.3%) RCTs, at least one analysis in Results section was included based on gender, while race specific results were less commonly reported in only 19.4% of studies.

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8. SUMMARY

Aim: The aim of this study is to determine the reporting of data on gender and ethnicity in RCTs of interventions for heart failure treatment in the major journals from the field of cardiology from 2017 to 2019.

Methods: We analysed 344 RCTs published between January 2017 to December 2019 in top five cardiology journals. Full-length papers on heart failure were analysed for reporting on sex/gender and race/ethnicity considerations. We extracted the data for: journal name, year of publication, study name, sex or race detailed terminology explained, sex or race mentioning in the title, abstract or introduction, number of study participants, number of male and female subjects, list of different ethnic backgrounds, sex and race specific analyses planned in the methods and results, differences in the sex and race specific results, sex and race specific results mentioned in the discussion section and centre of the study.

Results: Majority of the RCTs were published in the year 2018 (151; 43.9%), followed by 2017 (115; 33.4%) and 2019 (78; 22.7%). The highest number of RCTs were published in the Journal of the American College of Cardiology (121; 35.2%) and Circulation (118; 34.3%), whereas lowest numbers were published in the European Heart Journal (10; 2.9%). Overall, 63 (18.3%) of published RCTs reported sex/gender in the abstract section, and race/ethnicity was mentioned only in 16 (4.65%). Sex/gender differences from previous studies were mentioned in the Introduction section in 3.5% of the studies, while race differences in only 2.91%. Most of the papers in this study (N=305; 88.6%) mentioned sex/gender in any of the sections, while race/ethnicity was mentioned in a total of 212 papers (61.6%). In the methods section, 35 (10.2%) papers described plans to examine results separately by sex/gender, and only 17 (4.9%) overall planned to examine differences in race/ethnicity in their research. In a total of 180 (52.3%) papers, at least one analysis in results section was included based on gender, while race specific results were reported in 67 (19.4%) papers. White population was included in highest number of papers (N=71), and studies with white population included significantly larger number of participants (1086 (103.5-3633)) in comparison with others (P<0.001).

Conclusion: With sex/gender and race/ethnicity specific analyses neglected in majority of the included studies, researchers should invest more efforts to plan, conduct and report sex/gender and race/ethnicity outcomes in future RCTs.

9. CROATIAN SUMMARY

Naslov: Analiza izvještavanja o spolu i etničkoj pripadnosti u randomiziranim kontroliranim ispitivanjima u srčanom zatajenju

Cilj: Cilj ovog istraživanja bio je procijeniti izvještavanje o spolu i etničkoj pripadnosti u randomiziranim kontroliranim ispitivanjima (RCT) intervencija za liječenje srčanog zatajenja u časopisima iz područja kardiologije u razdoblju od 2017. do 2019. godine.

Metode: Analizirali smo 344 RCT-a objavljena u razdoblju od siječnja 2017. do prosinca 2020. u top pet časopisa iz kardiologije. Cjelokupni članci (radovi) o zatajenju srca analizirani su radi izvještavanja o spolu i etničkoj pripadnosti. Izdvojili smo podatke za: naziv časopisa, godinu publiciranja, naziv istraživanja, detaljno tumačenje termina spola ili rase, spominjanje spola i rase u naslovu, sažetku ili uvodu, broj sudionika u istraživanju, broj muškaraca i žena, popis različitih etničkih skupina, specifične analize planirane u metodama i rezultatima vezane za spol i rasu, razlike u rezultatima ovisno o spolu i rasi, rezultatima povezanima sa spolom i rasi u odjeljku rasprave i mjestu istraživanja.

Rezultati: Većina RCT-ova objavljena je u 2018. godini (151; 43,9%), a slijede 2017. (115; 33,4%) i 2019. (78; 22,7%). Najveći broj RCT-a objavljen je u časopisu *Journal of the American College of Cardiology* (121; 35,2%) i *Circulation* (118; 34,3%), dok je najmanji broj objavljen u *European Heart Journal* (10; 2,9%). Sveukupno, 63 (18,3%) objavljenih RCT-a prijavilo je spol u uvodu, a rasa / etnička pripadnost su spomenuti tek u 16 (4,65%). Razlike u spolu u odnosu na prethodne studije spomenute su u odjeljku uvoda u 3,5% studija, dok su razlike u rasama spomenute u samo 2,91% uvoda. Većina radova u ovom istraživanju (N = 305; 88,6%) spominjala je spol u barem nekom od odjeljka, dok je rasa/etnička pripadnost spomenuta u ukupno 212 radova (61,6%). U odjeljku o metodama, 35 (10,2%) radova opisalo je planove za ispitivanje rezultata odvojeno prema spolu, a samo 17 (4,9%) ukupno je planiralo ispitati razlike u rasi / etničkoj pripadnosti u svojim istraživanjima. U ukupno 180 (52,3%) radova, najmanje jedna analiza u odjeljku rezultata bila je vezana uz spol, dok su rezultati specifični za rasu prijavljeni u 67 (19,4%) radova. Bijela populacija bila je uključena u najveći broj radova (N = 71). Nadalje, studije s bijelom populacijom uključivale su značajno veći broj sudionika (1086 (103,5-3633)) u usporedbi s ostalim (P <0,001).

Zaključak: S obzirom na to da su analize spola i etničke pripadnosti zanemarene u većini uključenih studija, istraživači bi trebali uložiti više napora u planiranje, provođenje i izvještavanje o ishodima vezanima uz spol i etničku pripadnost u budućim RCT-ovima.

10. CURRICULUM VITAE

Personal Data:

Name: Kamaljeet Kaur Sandhu

Date of birth: 6th February 1992

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Education:

MD 2020 Split, Croatia

BSc (Hons) 2011-2014, England, United Kingdom

3 A-levels 2009-2011, England, United Kingdom

11 GCSE 2006-2009, England, United Kingdom

Languages:

English (fluent)

Punjabi (fluent)

Hindi (fluent)

Urdu (intermediate)

Croatian (basic)

Traineeships:

Dec 2019- Mar 2020; Merlyn Vas Health and Social Care, Leicester, UK

Jul - Oct 2019; Park Medical centre, GP practice, Peterborough, UK

Sep 2013; Oncology Department at Lincoln County Hospital, UK

Jan 2011-Jan 2012; Emergency Department at Peterborough District Hospital, UK

Jun 2010; Acute Elderly Ward at Peterborough and Stamford Hospital, Peterborough, UK

Jan 2008-Sep 2010; Florence Nightingale (Home Care), Peterborough, UK

Awards:

2014; University of Lincoln recognition of achievement award

Active member of ISA Split (International Student Association)