A meta-analysis of ECG abnormalities (arrhythmia) in cardiomyopathies

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Abstract
An electrocardiogram (ECG) is an important diagnostic test recommended for individuals with a clinical suspicion of heart disease. The primary diagnostic role is the assessment of the strength and time of electrical activity in the heart. It is also the most common test for the diagnosis of arrhythmias, which are disturbances in the heart rhythm and rate. An ECG test is recommended for patients with cardiomyopathy (CM) and heart failure (HF). The two are distinct but related cardiac disease entities, in which HF is the final sequela to CM, which is a progressive heart muscle disease. Although arrhythmias are prevalent in both CM and HF, few studies have investigated them as the primary objective. In the present pooled analysis of 66 studies (HF=26; CM=40), atrial fibrillation (AF), ventricular tachycardia (VT) and premature ventricular contractions (PVC) are the most common arrhythmias. The prevalence of AF is higher in HF (32.7%) compared to CM (19.2%) possible due to higher mean age in HF patients (71.8 years) compared to CM (42.7 years) because AF correlates with age. However, the prevalence of VT and PVC is much higher in CM patients (38.0% and 56.6%) compared to HF (3.7% and 13.3%). In both HF and CM, the ECG test is more useful on the differential diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC), where it can differentiate ARVC from right ventricular outflow tract induced VT. In addition to diagnostic value, ECG-assessed arrhythmias can guide therapeutic intervention since AF and VT can be life-threatening and may require specific antiarrhythmic therapy.

Introduction
The electrocardiogram (ECG) is an important initial test used to detect and record the strength and time of the activation and propagation of cardiac electrical signals. It produces a graphical output that depicts each phase of the electrical signal as it travels throughout the heart. The graphical output provides information about cardiac rhythm and rate, and any aberration of the cardiac electrical conduction system [1]. Besides assessing electrical activity, the ECG is the mainstay of initial diagnostic tests for arrhythmias, which are disorders of the cardiac rhythm and rate. The detection of arrhythmias has important prognostic and therapeutic implications for patients with heart problems [2]. They are associated with an ominous prognosis and challenges in the efficacy of guideline-directed heart failure therapies. The ECG is one of the initial tests recommended for patients suspected or confirmed with cardiomyopathies (CM) and heart failure (HF).

Clinical distinction between CM and HF within the context of diagnosis and therapy has not been elucidated, and within the same context, the two terms have been used interchangeably. However, CM and HF are two very distinct, but related cardiac disease entities. On the one hand, CM is a spectrum of heterogeneous myocardial disorders that can potentially impair the normal functioning of the heart. In CM, the myocardium can become thin and stretched (dilated CM [D CM]), thickened (hypertrophy CM [HCM]), rigid and stiffened (restrictive CM [RCM]), thickened and spongy (left ventricular non-compaction CM [LVNC]), and fibrous and fatty (arrhythmogenic right ventricular CM [ARVC]) [2,3]. These variations of the structure of the myocardium form the basis of its primary classifications into DCM, HCM, RCM, LVNC, and ARVC. Each of these primary forms can be further subclassified into familial and non-familial forms, or into aetiological forms [2,3].

On the other hand, HF is the final and most severe sequelae to CM. Typically, CM affects the myocardium and progressively limits cardiac ability to contract and/or relax normally. When CM progresses, it compromises the pumping function of the heart leading to the development of HF, where the heart is unable to pump sufficient blood to meet the metabolic demands of tissues. The European Society of Cardiology (ESC) defines HF as a clinical syndrome characterized by typical symptoms of dyspnoea, oedema and fatigue, accompanied by signs of elevated jugular venous pressure, pulmonary crackles and peripheral oedema in the setting of structural and/or functional cardiac abnormalities [4]. The definition restricts itself within the symptomatic stages of HF and excludes the pre-clinical stage, which may manifest with asymptomatic systolic or diastolic LV dysfunction. Since HF is a sequela to CM, the pre-clinical stage may even suggest CM, further complicating the clinical distinction between the two disease entities.

In both CM and HF, ECG-detected arrhythmias are common, and usually portend an ominous prognosis, and in most cases, may require targeted preventive or curative therapies. However, differences in the prevalence, frequency, and types of arrhythmias in CM and HF have not been well-documented possibly because both disease entities rely on similar diagnostic and therapeutic approaches [3,4]. Nonetheless, the awareness of the prevalence of certain types of arrhythmias in the two disease entities is important to refine diagnostic tests and therapy, in turn, contributing to cost-efficient use of scarce clinical resources.
resources [2]. Thus, the present meta-analysis seeks to compare the use of ECG for the detection of arrhythmias in CM and HF patients. Unfortunately, due to a lack of studies that directly compare CM and HF, this meta-analysis compares findings from studies evaluating HF and studies evaluating CM. The intention is to get an insight into the commonly studied types of arrhythmias and their prevalence in both disease entities. The awareness of arrhythmias affecting the two disease entities has important clinical implications since it will deepen our understanding about them, and consequently guide in the selection of the most efficacious interventions and an overall improvement in the management of CM and/or HF.

Study selection

The present meta-analysis is a comparison of the findings of two previous unrelated meta-analyses on ECG-detected arrhythmias in HF and CM patients, respectively. The comparison is expected to give an insight into the differences in arrhythmic manifestations in the two cardiac disease entities in the absence of randomized controlled trials (RCTs) that directly compare the two diseases. In a synopsis, studies included in the two previous meta-analyses were searched in PubMed, and key journals in the field of cardiology, and complemented with a review of the top 100 results from Google Scholar, and references of articles and review papers. The inclusion criteria were studies that specifically recruited patients with CM or HF as per the current diagnostic guidelines, used ECG in the initial assessment, and reported the overall number, frequency or percentage of patients with arrhythmias. In both studies, the outcome of interest was the frequency of the different types of arrhythmias in different structural forms of CM and HF, respectively.

Study findings

Study characteristics

The total number of studies included in the two meta-analyses was 66, consisting of 26 studies [5-30] evaluating arrhythmias in HF and 40 studies [31-70] evaluating arrhythmias in CM. The HF studies had a total patient population of 147,318 with an equal gender representation (male=65.3%, female=34.7%) and an average age=61.7±15.03 years. The main types of HF evaluated were thyrotoxic HF, HFrEF, ischemic HF, HfPEF, HfMfE, hypertensive, right HF, and systolic HF. In the other hand, the CM studies had a smaller total population of 6,601 patients, relatively younger (42.7±15.3 years) and with a male preponderance (male=65.3%). Unlike HF studies that comprised of prospective, retrospective and registry, CM studies comprised of prospective, retrospective, and cross-sectional. In both meta-analyses, the most common ECG-detected arrhythmias were atrial fibrillation (AF), ventricular tachycardia (VT) and premature ventricular contraction (PVC), also known as ventricular extrasystoles or ventricular premature beats. Although other arrhythmias types were also mentioned, the data was insufficient to support a pooled analysis. Besides, arrhythmias that do not have significant implications on prognosis and therapy have not attracted sufficient studies compared to AF, VT and PVCs.

ECG-detected arrhythmias

Atrial fibrillation: In HF studies, AF was the most studied arrhythmia, with all the 26 studies listing the presence of AF in the initial ECG-based cardiac evaluation. The overall prevalence of AF was about a third (32.7%; 95% CI: 32.5% to 33.0%; Figure 1) of all the patients presenting with HF. The highest prevalence was among hypertensive HF (46.5%; 95% CI: 44.4% to 48.6%), and HFrEF patients (40.3%; 95 CI: 39.7% to 41.0%) while the least was in Thyrotoxic HF (6.7%; 95% CI: 5.1% to 8.8%) and high output HF (19.0%; 95% CI: 13.9% to 25.4%). Table 1 presents a summary of the prevalence of AF in different types of HF.

Similarly, in CM studies, AF was the most common reported arrhythmia in 67.5% of the included studies but with a much lower overall prevalence relative to HF (12.8%; 95% CI: 9.9% to 16.3%; Figure 2). In the primary types of CM, the highest prevalence was among RCM patients (19.2%; 95% CI: 7.3% to 41.8%) followed by DCM (15.2%; 95% CI 11.4% to 20.1%). The lowest prevalence was among ARVC patients (3.3%; 95% CI 1.2% to 9.1%) and LVNC (7.7% (95% CI 2.3% to 22.9%). Table 2 presents a summary of AF prevalence among primary structural forms of CM.

Ventricular tachycardia: Although VT is a potentially lethal arrhythmia, it was reported in only two HF studies [20,30] recruiting 3,360 patients, of which 94 had ECG-detected VT, a prevalence rate of 3.7% (95% CI: 3.0 to 4.5%). The prevalence could be higher since the majority of studies reported VAs in general without listing the specific clinical types. In the two studies, VT was f in patients with HFrEF, hypertensive HF and right HF (Figure 3).

In contrast, more studies, 72.5% reported VT in 1,107 CM patients out of 3,079, translating into a prevalence of 38.0% (95% CI: 33.5% to 42.7%), which is ten-fold higher than that reported in HF patients. Unlike HF, VT in CM was detected in all the five primary types of CM – ARVC, DCM, HCM, LVNC and RCM. The prevalence was the highest in ARVC (59.4%; 95% CI: 47.5% to 70.3%), followed by DCM (53.4%; 95% CI 24.8% to 41.2%), HCM (22.9%; 95% CI 15.4% to 32.8%), LVNC (20.2%; 95% CI 13.0% to 30.1%), and RCM (10.1%; 95% CI 0.1% to 9.2%) (Figure 4).

Premature ventricular contractions: In HF patients, only five (5) studies (19.2%) reported ECG-detected cases of PVCs on index admission [7,13,23,26,30]. Overall, PVCs were confirmed in 150 out of 1,389 HF patients diagnosed with HfPEF, hypertensive HF, ischemic HF, systolic HF and thyrotoxic HF. The overall prevalence was 13.3% (95% CI: 11.4% to 15.4%) (Figure 5).

In CM patients, eleven (11) studies or 27.5% [31,32,38,34,56,59,61,45,64,65] reported cases of PVCs in 434 patients out of a total of 8,282 patients at index admission. The overall prevalence was 56.6% (95% CI: 49.9% to 63.1%) (Figure 6), which is more than four-fold the prevalence reported in HF patients.

Discussion

ECG-detected arrhythmias are a common manifestation in patients with CM and HF as well as in other forms of heart diseases [1]. However, current evidence does not support the broad application of ECG tests in the general population because of the high probability of misinterpretation [4]. In HF and CM patients, the detection of arrhythmias in these patients is important since they portend an unfavourable prognosis and usually require adjunctive therapy to the guideline-directed evidence-based HF treatment [5-7]. Despite the high prevalence and clinical implications of arrhythmias in CM and HF patients, studies with an original aim of evaluating arrhythmias in patients with CM or HF are lacking. Most studies only provide the frequency or percentage of patients presenting with arrhythmias at index admission or after follow-up in studies evaluating the therapeutic efficacy of various clinical interventions for arrhythmias. Other studies examine the prognostication in all patients presenting with arrhythmias, the effect of arrhythmias on the efficacy of HF therapies.
Atrial Fibrillation in HF: Event Rate and 95% CI

| Study name | Group by | Events/Total | Statistics for each study | Event rate and 95% CI |
|------------|----------|--------------|---------------------------|-----------------------|
|            | Subgroup within study | Total | Event rate | Lower limit | Upper limit |
| QWTO-HF (22) | HFmEF | 15/23 / 25083 | 0.020 | 0.267 | 0.284 |
| Karayes, 2005 [19] | HFmEF | 15/23 / 50083 | 0.020 | 0.270 | 0.284 |
| QWTO-HF (22) | HFpEF | 19 / 71 | 0.141 | 0.077 | 0.242 |
| Stegmayr, 1998 [16] | HFpEF | 19/72 / 40425 | 0.340 | 0.335 | 0.344 |
| Cullen, 2002 [11] | HFpEF | 502 / 949 | 0.518 | 0.529 | 0.549 |
| Karayes, 2005 [19] | HFpEF | 5 / 42 | 0.130 | 0.098 | 0.337 |
| Karmont, 2003 [14] | HFpEF | 1 / 3 | 0.297 | 0.132 | 0.398 |
| Karayes, 2005 [19] | HFpEF | 15 / 79 | 0.190 | 0.118 | 0.291 |
| Connolly, 2011 [16] | HFpEF | 58/66 / 5951 | 0.690 | 0.677 | 0.792 |
| Khandel, 2011 [17] | HFpEF | 43 / 207 | 0.206 | 0.158 | 0.259 |
| Daoud, 2014 [18] | HFpEF | 121 / 523 | 0.311 | 0.157 | 0.209 |
| EMRS II [20] | HFpEF | 833 / 2319 | 0.375 | 0.362 | 0.388 |
| AHEAD [21] | HFpEF | 524 / 2421 | 0.283 | 0.268 | 0.302 |
| QWTO-HF (22) | HFpEF | 5162 / 51814 | 0.340 | 0.332 | 0.348 |
| AHEAD [21] | High Output | 54 / 179 | 0.150 | 0.130 | 0.254 |
| ATTEND [19] | High Output | 96 / 279 | 0.284 | 0.350 | 0.428 |
| EMRS II [20] | High Output | 152 / 497 | 0.323 | 0.232 | 0.422 |
| Balleine, 2010 [20] | HFpEF | 9 / 38 | 0.231 | 0.157 | 0.309 |
| Balleine, 2010 [20] | HFpEF | 9 / 42 | 0.228 | 0.189 | 0.281 |
| Balleine, 2010 [20] | HFpEF | 9 / 103 | 0.230 | 0.210 | 0.259 |
| EMRS II [20] | Right HF | 60 / 113 | 0.694 | 0.491 | 0.671 |
| AHEAD [21] | Right HF | 50 / 151 | 0.330 | 0.138 | 0.262 |
| Hudelson, 2002 [24] | HFpEF | 50 / 209 | 0.145 | 0.117 | 0.199 |
| Khan, 2007 [25] | HFpEF | 248 / 1931 | 0.297 | 0.258 | 0.278 |
| Dukic, 2008 [26] | HFpEF | 21 / 147 | 0.143 | 0.124 | 0.163 |
| Oster, 2016 [27] | HFpEF | 17 / 400 | 0.326 | 0.237 | 0.415 |
| Amb, 2017 [28] | HFpEF | 30/59 / 3974 | 0.372 | 0.382 | 0.392 |
| Yen, 1995 [4] | HFpEF | 4 / 135 | 0.029 | 0.011 | 0.076 |
| Dorent, 2007 [29] | HFpEF | 22 / 383 | 0.057 | 0.034 | 0.084 |
| Seppala, 2013 [7] | HFpEF | 8 / 72 | 0.111 | 0.030 | 0.173 |
| Goyal, 2018 [8] | HFpEF | 3 / 50 | 0.060 | 0.019 | 0.170 |
| Balleine, 2018 [9] | HFpEF | 12 / 103 | 0.117 | 0.067 | 0.164 |
| Overall | HFpEF | 46917 / 147212 | 0.327 | 0.313 | 0.330 |

Heterogeneity: Q = 4453.435; df(Q) = 32(p=0.000); Inconsistency (I-Squared) = 99.281%

Figure 1. Prevalence of atrial fibrillation in heart failure

Table 1. Atrial fibrillation event rate in heart failure types

| HF Type          | Positive Cases | Total Cases | Event Rate (%) | 95% CI    | Studies |
|------------------|----------------|-------------|----------------|-----------|---------|
| Hypertensive HF  | 1,130          | 2,401       | 46.5           | 44.4 to 48.6 | 19-30   |
| HFmEF            | 11,197         | 27,504      | 40.3           | 39.7 to 41.0 | 10-22   |
| Right HF         | 96             | 269         | 37.9           | 31.8 to 44.5 | 20-21   |
| HFpEF            | 13,730         | 40,425      | 34.0           | 33.5 to 34.4 | 13-22   |
| SYSTOLIC HF      | 6,227          | 19,765      | 31.9           | 31.3 to 32.6 | 24-28   |
| HFmEF            | 15,423         | 55,683      | 28.0           | 27.6 to 28.4 | 22       |
| Ischemic HF      | 191            | 803         | 23.8           | 21.0 to 26.9 | 12-23   |
| High Output HF   | 34             | 179         | 19.0           | 13.9 to 25.4 | 21       |
| Thyrotoxic HF    | 47             | 753         | 6.7            | 5.1 to 8.8  | 5-9     |
| Overall          | 48,075         | 147,212     | 32.7           | 32.5 to 33.0 | 5-30    |

HF: Heart Failure; HFmEF: Heart Failure with Mid-range Ejection Fraction; HFpEF: Heart Failure with Reduced Ejection Fraction; HFmEF: Heart Failure with Preserved Ejection Fraction; HFpEF: Heart Failure with Reduced Ejection Fraction
Table 2. Atrial fibrillation event rate in cardiomyopathy types

| CM Type | Positive Cases | Total Cases | Event Rate (%) | 95% CI        | Studies |
|---------|----------------|-------------|----------------|--------------|---------|
| RCM     | 127            | 514         | 19.2           | 7.3 to 41.8  | 63-70   |
| DCM     | 151            | 870         | 15.2           | 11.4 to 20.1 | 31-35,37-39 |
| HCM     | 454            | 2,934       | 8.0            | 3.1 to 19.0  | 40,42,44,46 |
| LVNC    | 23             | 398         | 7.7            | 2.3 to 22.9  | 48-50,52 |
| ARVC    | 8              | 295         | 3.3            | 1.2 to 9.1   | 53,55   |
| Overall |                |             | 12.8           | 9.9 to 16.3  | 31-70   |

Atrial Fibrillation in CM: Event Rate and 95% CI

| Study name        | Comparison | Statistics for each study | Event rate and 95% CI |
|-------------------|------------|----------------------------|-----------------------|
| Roccu, 1996 [53]  | ARVC       |                            |                       |
| Peters, 2003 [55] | ARVC       |                            |                       |
| Von der Haarling, 1984 [31] | DCM       |                            |                       |
| Keil, 1986 [32]   | DCM        |                            |                       |
| Grannum, 2000 [33] | DCM       |                            |                       |
| Grannum, 2003 [34] | DCM       |                            |                       |
| Kuri, 2017 [35]   | DCM        |                            |                       |
| Kapoor, 2018 [37] | DCM        |                            |                       |
| Shaik, 2019 [38]  | DCM        |                            |                       |
| Boukila, 2019 [39] | DCM       |                            |                       |
| Saupe, 1978 [40]  | HCM        |                            |                       |
| Billiot, 2000 [42] | HCN       |                            |                       |
| Dumont, 2004 [44] | HCN        |                            |                       |
| Molend, 2009 [45] | HCN        |                            |                       |
| Geetha, 2010 [46] | LVNC       |                            |                       |
| Murphy, 2005 [48] | LUND       |                            |                       |
| Callester, 2011 [50] | LUND     |                            |                       |
| D’Arcy, 2012 [52] | LVNC       |                            |                       |
| Ben de, 1980 [53] | RCI        |                            |                       |
| Fait, 1984 [54]   | RCI        |                            |                       |
| Ambrus, 2008 [55] | RCI        |                            |                       |
| Rahman, 2004 [56] | RCI        |                            |                       |
| Khayesi, 2017 [57] | RCI       |                            |                       |
| Okimoto, 2019 [58] | RCI       |                            |                       |
| Cheng, 2013 [59]  | RCI        |                            |                       |
| Omir, 2019 [70]   | RCI        |                            |                       |

Heterogeneity: Q = 278.26; df(Q) = 26(p=0.000); Inconsistency (I-Squared) = 91.915%

Figure 2. Prevalence of atrial fibrillation in cardiomyopathy

Ventricular Tachycardia in HF: Event Rate and 95% CI

| Study name | Group by | Statistics for each study | Event rate and 95% CI |
|------------|----------|----------------------------|-----------------------|
| EHFS II [20] | HVEF    |                            |                       |
| EHFS II [20] | HVEF    |                            |                       |
| SUH, 2010 [30] | Hypertensive HF |                            |                       |
| SUH, 2010 [30] | Hypertensive HF |                            |                       |
| EHFS II [20] | Right HF |                            |                       |
| EHFS II [20] | Right HF |                            |                       |
| Overall    |          |                            |                       |

Heterogeneity: Q = 154.256; df(Q) = 3(p=0.000); Inconsistency (I-Squared) = 98.865%

Figure 3. Prevalence of ventricular tachycardia in heart failure
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**Ventricular Tachycardia in CM: Event Rate and 95% CI**

| Study name        | Comparison | Total Event rate | Lower limit  | Upper limit |
|-------------------|------------|------------------|--------------|-------------|
| Bases, 1996 [63]  | ARVC       | 15/20            | 0.500        | 0.328       | 0.672       |
| Harir, 2000 [54]  | ARVC       | 63/130           | 0.497        | 0.327       | 0.540       |
| Rieder, 2003 [55] | ARVC       | 112/205          | 0.548        | 0.450       | 0.658       |
| Neave, 2004 [66]  | ARVC       | 112/205          | 0.548        | 0.450       | 0.658       |
| De Cobelli, 2006 [57]| ARVC     | 14/23            | 0.093        | 0.042       | 0.192       |
| Gharbi, 2010 [59] | ARVC       | 30/168           | 0.441        | 0.325       | 0.558       |
| Kerem, 2011 [80]  | ARVC       | 59/59            | 0.992        | 0.980       | 0.999       |
| Hoffmayr, 2011 [81]| ARVC     | 41/60            | 0.594        | 0.475       | 0.705       |
| Seravelli, 2012 [82]| ARVC    | 41/60            | 0.594        | 0.475       | 0.705       |
| Von Ohlenhausen, 164 [51] | DCM | 25/50          | 0.417        | 0.290       | 0.544       |
| Nevi, 1986 [52]  | DCM       | 20/33            | 0.466        | 0.351       | 0.586       |
| Grima, 2000 [53]  | DCM       | 73/202           | 0.347        | 0.254       | 0.415       |
| Gramm, 2003 [44]  | DCM       | 111/243          | 0.324        | 0.276       | 0.375       |
| Kaberle, 2010 [57] | DCM     | 6/50             | 0.100        | 0.046       | 0.205       |
| Sahai, 2010 [36]  | DCM       | 3/10             | 0.100        | 0.033       | 0.200       |
| Breen, 2019 [58]  | DCM       | 28/189           | 0.467        | 0.345       | 0.592       |
| Corrado, 1999 [43]| DCM       | 27/202           | 0.282        | 0.208       | 0.356       |
| Blett, 2000 [42]  | DCM       | 30/168           | 0.441        | 0.325       | 0.558       |
| Suchard, 2006 [43]| DCM     | 17/102           | 0.346        | 0.254       | 0.435       |
| Duffield, 2005 [44]| DCM    | 6/70             | 0.093        | 0.042       | 0.192       |
| Ashcroft, 2006 [45]| DCM   | 5/70             | 0.071        | 0.025       | 0.126       |
| Chir, 1999 [47]   | DCM       | 20/153           | 0.109        | 0.046       | 0.205       |
| Gecckic, 2000 [48]| DCM      | 14/54            | 0.412        | 0.351       | 0.511       |
| Narang, 2005 [49] | DCM       | 10/45            | 0.222        | 0.154       | 0.300       |
| Calabrese, 2011 [60]| DCM    | 17/77            | 0.221        | 0.142       | 0.327       |
| Calabrese, 2012 [61]| DCM    | 5/20             | 0.100        | 0.046       | 0.192       |
| Desilets, 2013 [52]| DCM   | 42/242           | 0.174        | 0.113       | 0.232       |
| Calabrese, 2016 [60]| DCM    | 59/146           | 0.200        | 0.150       | 0.250       |
| Falk, 1986 [84]   | DCM       | 14/27            | 0.412        | 0.351       | 0.511       |
| Okamoto, 2011 [88]| DCM      | 1/104            | 0.010        | 0.001       | 0.005       |
| 151/131           |           | 0.430            | 0.355       | 0.501       |

**Heterogeneity: Q = 292.752; df(Q) = 28(p=0.000); Inconsistency (I-Squared) = 90.436%**

Figure 4. Prevalence of ventricular tachycardia in cardiomyopathy

**Ventricular Premature Contractions in HF: Event Rate and 95% CI**

| Study name        | Subgroup within study | Total Event rate | Lower limit  | Upper limit |
|-------------------|-----------------------|------------------|--------------|-------------|
| Karas, 2008 [13]  | HFpEF                 | 0.099            | 0.048        | 0.193       |
| Karas, 2008 [13]  | HFpHEF                | 0.099            | 0.048        | 0.193       |
| Karas, 2008 [13]  | HFpHEF                | 0.099            | 0.048        | 0.193       |
| Sultana, 2010 [30]| Hypertrophic HF       | 0.084            | 0.012        | 0.171       |
| Sultana, 2010 [30]| Hypertrophic HF       | 0.084            | 0.012        | 0.171       |
| Bocorets, 2005 [23]| Ischemic HF+DID      | 0.197            | 0.161        | 0.238       |
| Bocorets, 2005 [23]| Ischemic HF+DID      | 0.197            | 0.161        | 0.238       |
| Devkota, 2016 [26]| Systolic HF           | 0.172            | 0.121        | 0.239       |
| Devkota, 2016 [26]| Systolic HF           | 0.172            | 0.121        | 0.239       |
| Yen, 1990 [8]     | Thyroxic HF           | 0.010            | 0.004        | 0.027       |
| Yen, 1990 [8]     | Thyroxic HF           | 0.010            | 0.004        | 0.027       |
| Stal, 2013 [7]    | Thyroxic HF           | 0.026            | 0.009        | 0.055       |
| Stal, 2013 [7]    | Thyroxic HF           | 0.026            | 0.009        | 0.055       |
| 150/1389          |                       | 0.120            | 0.114        | 0.154       |

**Heterogeneity: Q = 58.247; df(Q) = 6(p=0.000); Inconsistency (I-Squared) = 89.699%**

Figure 5. Prevalence of premature ventricular contractions in heart failure
or the prevalence and prognosis of arrhythmias in generally critically ill patients.

On the other hand, studies that evaluate ECG as a diagnostic tool in CM or HF patients mainly emphasize on the presence of ECG abnormalities since it is very unlikely for CM and HF patients to have normal ECG findings [4-6]. The most important ECG features indicating problems in electrical activation or propagation are vector information – P, QRS and T waves – that may assist in detecting cardiac chamber enlargement and other related changes [71]. For instance, left atrial (LA) enlargement can cause characteristics P wave changes. In patients with cardiac enlargement that improves in a relatively short period, R wave height may first increase and then decrease. Tissue oedema may be the underlying reason for the first increase and the distance between the recording electrode and the heart for the subsequent decrease, but other factors may modify such findings. Minor electrical conduction disturbances secondary to myocardial stretch may contribute to changes in the QRS complex. A decrease in the variability of RR intervals may also help to characterize cardiac problems [71].

Atrial fibrillation

Both HF and CM are primary cardiac diseases whose progression has been associated with an elevated risk of developing arrhythmias, especially in patients with co-existing ischemic heart disease [7-10]. Although arrhythmias are mostly a consequence of the two diseases, they can also be the causative agent as in the case of tachycardia- and PVCs-induced CM. Among arrhythmias, AF has been prevalent in both HF and CM patients, and presents a challenge to the managing clinician because of the increased risk of thromboembolic stroke and cardiac death [2,4].

The present findings indicate AF is the most studied arrhythmia in both CM and HF patients. Research focus on AF increased significantly after the publication of the Framingham Heart Study (FHS), which associated AF with heart diseases such as hypertension, coronary heart disease and cardiac failure, which was significantly more prevalent in older patients aged 70 years or older. In turn, increased stroke incidence associated with AF results from cardiovascular abnormalities [72]. Therefore, early identification of AF in HF patients is critical to guide specific adjunctive therapy to manage or treat AF.

Although AF is commonly found, unexceptionally, in both HF and CM patients, the present findings show that the overall prevalence of AF in HF patients (32.7%) is about twice that found in CM (19.2%). The underlying reason for the marked difference in the prevalence of AF in the two clinically similar cardiac disease entities is unclear since they share the same mechanisms. Typically, the primary cause of AF is a disturbance in cardiac electrical signals resulting in the atria (upper chambers of the heart) contracting faster and out of sync, in turn causing the atrial walls to fibrillate [72]. What causes the disturbance in electrical signals remains to be elucidated. However, age, genetics, heart disease, sick sinus syndrome, heart attack, and hypertension have identified as risk factors for the development of AF as well as HF [73-81]. Since AF and HF share almost the same risk factors, it may contribute to the high incidence of AF among HF patients. In particular, age may be an independent risk factor potentially contributing to the difference in AF prevalence between HF and CM patients [81,82]. The average age of HF patients in the included studies was 71.8 years, and that of CM patients was 42.7 years. In support of the influence of age on the prevalence of both AF and FH, the Framingham Heart Study [72] reported the incidence of AF increases significantly with age, and with a disproportional percentage of patients aged 70 years of age or older affected by AF and FH.

The high prevalence of AF in hypertensive patients more than in other HF types suggests that the causative agent may contribute to the slight differences in the prevalence of AF between HF phenotypes, and between AF and CM [78,80]. In the present analysis, patients with hypertensive HF have the highest prevalence of AF (46.5%), possibly because hypertension is a causative agent of both HF and AF. Hypertension and AF are two prevalent and often co-existing conditions, especially in the North American population. Hypertension may result in LV hypertrophy (LVH), impaired ventricular filling, LA enlargement and slowed the velocity of atrial conduction. These changes in cardiac structure and physiology may induce the development of AF.
and increase the risk of thromboembolic complications [73]. In patients with hypertension-associated AF, aggressive treatment of hypertension may reverse the structural changes in the heart and reduce or prevent the occurrence of AF.

In the present findings, HFrEF has the second most prevalent rate of AF (40.3%) and has been associated with increased morbidity, mortality and hospitalization. In these patients, AF can be the consequence and cause of HF. On the one hand, AF is a consequence of HF through neurohormonal imbalance and the activation of the renin-angiotensin-aldosterone system (RAAS), leading to increased filling pressure and afterload. These maladaptive physiological changes can lead to increased LA stretch and fibrosis, which contribute to the development of conduction disturbance and the initiation of maintenance of AF [74-78]. The RAAS can also directly contribute to pro-arrhythmic remodelling with angiotensin II, causing atrial fibrosis and anisotropic conduction. HF patients can also exhibit altered calcium handling and calcium overload, leading to after-depolarisations and arrhythmias [73]. On the other hand, AF can contribute to the development of HF through several mechanisms. In AF patients, the loss of atrial systole can impair LV filling and decrease cardiac output by up to 25%, especially in patients with diastolic dysfunction [79]. Irregular of rapid ventricular conduction can result in LV dysfunction and in some patients, tachycardia-induced CM [79,80]. The restoration of sinus rhythm increases stroke volume and LV emptying prior to a notable improvement in contractile function, which explains why some HF patients gain rapid hemodynamic improvement with cardioversion [81].

In CM patients, the highest prevalence of AF (19.2%) was seen in RCM patients. The high prevalence may be attributed to the heterogeneity of the causes of RCM. More importantly, whereas the definition of DCM and HCM primarily depends on morphological criteria, RCM is a primary abnormality in the diastolic function secondary to derangement in the dynamics of ventricular filling leading to increase ventricular end-diastolic pressure and dilated atria. In most cases, the systolic function is preserved or slight abnormally [65]. Second, RCM can develop in the late stages of HCM, DCM, valvular, hypertensive and ischemic heart disease or a specific heart muscle disease such as amyloidosis [63,67]. All these factors are associated with an increased risk of developing AF and may explain the high prevalence of AF in RCM patients relative to other CM phenotypes. In addition to aetiological agents, the high prevalence may be associated with delayed diagnosis of the disease. Often, RCM patients are diagnosed at an advanced stage of the disease with pronounced cardiopulmonary symptoms. It is because of the delayed diagnosis when the disease is almost training into HF that may explain the high prevalence rates [65,67]. Thus, the findings suggest that although AF is prevalent in both HF and CM, it is more common in HF than in CM patients unless the diagnosis is belated, usually during the advanced phase of the disease.

Ventricular tachycardia

Ventricular tachycardia is another common arrhythmia in both CM and HF patients. Same to AF, non-sustained VT (duration < 30 sec) and sustained VT (duration > 30 sec) [61] have also received extensive research interest because of their potentially life-threatening characteristic. It is a fast heart rate arising from improper electrical activity in the ventricles. Non-sustained VT may be more common but very unlikely to cause any health problems, but sustained VT is less common but more life-threatening [80]. The present findings reveal that the prevalence of VTs is much lower in HF patients at index admission (3.7%) relative to AF in the same population and relative to CM patients, whose overall prevalence was 38.0%, more than ten-fold the prevalence in HF patients. However, among HF patients, fewer studies reported the incidence of VT compared to CM studies. The prevalence of VT was high in all structural forms of CM - ARVC (59.4%), DCM (32.4%), HCM (22.9%), LVNC (20.2%), and RCM (10.1%).

The occurrence of VT in HF patients increases with the clinical severity of HF. Large myocardial infarction (MI) and greater LV systolic dysfunction are likely to be associated with VTs, which are the most common electrical mechanisms that can lead to sudden cardiac death (SCD) [80]. HF patients with systolic dysfunction who develop VTs are more vulnerable to SCD, especially when VT degenerates to VF. Patients with comorbid HF and VT usually present with cardiac arrest to the emergency department or with palpitations, syncope, chest pain, or ICD shocks to cardiology outpatient clinics, which vary based on the hemodynamic stability of VT. Both non-sustained and sustained VT in HF patients can result in considerable morbidity and mortality [82]. The most complicated VT in HF patients is VT storm (≥3 more episodes of sustained VT), which may necessitate ICD shock or anti-tachycardia pacing within 24 hours [82]. However, HFpEF patients with VT lack any approved treatment regimen by either ICD or drugs, and thus, most studies tend to focus on HFrEF patients, which may explain the high prevalence of VTs among these patients.

Several pathological mechanisms have been associated with the development of VT in HF patients. The most common is electrical re-entry around islands of heterogeneous myocardial fibrosis, particularly in areas of scar post-MI. Scar-related VT manifests as monomorphic with single QRS morphology. The induction of monomorphic VT during the electrophysiologic study (EPS) can predict patients with an increased likelihood of spontaneous VT [82-84]. Polymorphic VTs, presenting as continuously changing QRS morphology, has been linked to acute ischemia, drugs-associated QT prolongation or electrolyte imbalance. Increased activation of the sympathetic nervous system (SNS) can be another trigger for the induction of CT. The activation of SNS through beta-adrenoreceptors activates ryanodine receptor on the sarcoplasmic reticulum inside the cardiomyocytes resulting in the eflux of calcium and increase of intracellular concentration, which is a trigger for VT [82,83]. This mechanism explains the effect of beta-blockers in suppressing VT, and SCD in HF patients. Primary VT, which occurs between 24 and 48 hours of acute MI, acute ischemic is the transient or correctable cause of VT. In this case, revascularization is the primary management of primary VT. In contract, secondary VT, occurring after 48 hours of acute MI has been linked with worse clinical outcomes [84]. Other pathogenic mechanisms for AF include increased diastolic calcium levels, early and delayed after depolarisations.

Therapy for HF can also contribute to the initiation and maintenance of VT. Anti-arrhythmic drugs are one of the leading medications implicated as a cause of VT in HF patients. Digoxin is an arrhythmogenic drug commonly used in the management of HF. Dobutamine therapy for acute decompensated HF is also another common cause of VT [2-4]. Because of the risk of VT, patients on dobutamine require continuous monitoring. In some patients with advanced HF, VT can also manifest as a complication of LV assist device, mostly occurring peri-operatively. It is advisable to determine the underlying mechanism of VT in HF patients to inform the most efficacious therapy [84]. For instance, the best therapy for VT secondary to inflammation is antiarrhythmic medication and immunosuppression, whereas VT secondary to myocardial scarring is antiarrhythmic medication and catheter ablation [4].
Premature ventricular contractions

Premature ventricular contractions (PVCs) are the most frequent type of arrhythmias encountered in clinical practice in both healthy individuals and those with structural heart disease [23,36]. They are extra heartbeats initiated in the ventricles and disrupt the normal heart rhythm, sometimes causing the sensation of fluttering or a skipped heartbeat. In healthy individuals, PVCs are considered a benign entity. They are asymptomatic and are not a source of clinical concern and often requires no treatment [7,13]. In contrast, patients with underlying heart disease may require treatment [13]. In patients with CM or HF, the present findings indicate the overall prevalence of PVC in HF patients is 13.3%. It was detected in HFrEF, hypertensive HF, ischemic HF, systolic HF and thyrotoxic HF. Patients with CM had more than four-fold prevalence (56.6%) compared to HF patients. The findings are consistent with reports in the literature, indicating that the incidence of PVCs is common to individuals with normal or diseased hearts. Their detection is incidental, and affect 1% of the general population on standard 12-lead ECG and rises to between 40% and 75% on 24-48 hour ambulatory ECG recording [85]. The prevalence of PVCs is also age-dependent, which ranges from <1% on children < 11 years to 69% in individuals >75 years [86].

The pathophysiology of PVCs is not well known although ventricular myocytes spontaneously depolarize to create extrasystoles that results in mechanical dys synchrony with cardiac cycle [87,88]. The affected myocytes are triggered by cyclic adenosine monophosphate mediated and calcium-dependent delays in after depolarization [87]. In the absence of structural heart disease, most PVCs originate from the LV/RV outflow tract (LVOT/RVOT) or the epicardial tissues immediately adjacent to the aortic sinuses of Valsalva, although most foci are found in the RVOT [87]. Fascicular PVCs originate from within the LV Hts-Purkinje system although the may also originate from ventricular tissues adjacent to the aortomitral continuity, the tricuspid annulus, the mitral valve annulus, papillary muscles and other Purkinje-adjacent structures [87,88]. PVCs in the presence of structural heart diseases such as coronary artery disease, non-ischemic CM, ARVC, HCM, amyloidosis and sarcoidosis may require adjunctive therapy in addition to HF therapy. A 24% PVC burden has the best sensitivity and specificity in predicting the development of CM, although individuals with an untreated PVC burden of 20% are at risk of developing PVC [87]. Other risk factors for the development of PVC-induced CM are high frequency of PVCs, longer duration of PVCs, broad QRS complex PVCs, interpolated PVCs, male sex, lack of short-term variability of the PVC burden, and PVCs in asymptomatic patients [89].

The high prevalence of VTs in CM patients and its prognostic implications makes the 12-lead ECG an important diagnostic tool. Unlike HF patients where ECG has non-specific findings, in CM patients, ECG can provide valuable diagnostic information such as the presence of LVH, the presence of myocardial scar resulting in Q wave or fragmentation changes, corrected QT interval, morphologies of VAs and other clues of structural heart disease [82]. However, ECG findings should be interpreted and correlated with clinical symptoms to exclude misdiagnosis or innocent findings. In particular, ECG is useful in CM patients to identify V1's morphologies, which can help to identify the arrhythmogenic substrates as well as distinguish epicardial from endocardial electrical circuits [74]. More importantly, ECG is a valuable diagnostic tool in ARVC phenotype. The ECG morphology of VT/PVCs can differentiate between RVOT-VT and VT due to ARVC. Multiple VT forms, including a left bundle branch block (LBBB)/superior axis, essentially excludes RVOT-VT, shifting the pre-test probability towards ARVC [83].

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