


# Heart failure and atrial flutter: a systematic review of current knowledge and practices

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## Abstract

While the interplay between heart failure (HF) and atrial fibrillation (AF) has been extensively studied, little is known regarding HF and atrial flutter (AFL), which may be managed differently. We reviewed the incidence, prevalence, and predictors of HF in AFL and vice versa, and the outcomes of treatment of AFL in HF. A systematic literature review of PubMed/Medline and EMBASE yielded 65 studies for inclusion and qualitative synthesis. No study described the incidence or prevalence of AFL in unselected patients with HF. Most cohorts enrolled patients with AF/AFL as interchangeable diagnoses, or highly selected patients with tachycardia-induced cardiomyopathy. The prevalence of HF in AFL ranged from 6% to 56%. However, the phenotype of HF was never defined by left ventricular ejection fraction (LVEF). No studies reported the predictors, phenotype, and prognostic implications of AFL in HF. There was significant variation in treatments studied, including the proportion that underwent ablation. When systolic dysfunction was tachycardia-mediated, catheter ablation demonstrated LVEF normalization in up to 88%, as well as reduced cardiovascular mortality. In summary, AFL and HF often coexist but are understudied, with no randomized trial data to inform care. Further research is warranted to define the epidemiology and establish optimal management.

**Keywords** Heart failure; Left ventricular systolic dysfunction; Atrial flutter; Arrhythmia; Catheter ablation; Systematic review

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## Introduction

Atrial flutter (AFL) is an atrial macro-reentrant tachyarrhythmia,<sup>1</sup> further subcategorized as cavotricuspid isthmus (CTI)-dependent and non-CTI-dependent atypical flutter.<sup>2</sup> Atrial fibrillation (AF) and AFL often coexist due to shared risk factors and precipitants. Both rhythms may be a cause or consequence of heart failure (HF) and are associated with stroke and increased mortality.<sup>3–6</sup> Treatment options for both rhythms include pharmacologic rate control<sup>7,8</sup> and rhythm control (anti-arrhythmic drugs,<sup>8,9</sup> cardioversion,<sup>9,10</sup> and catheter ablation<sup>11–13</sup>).

Most studies treat AFL and AF as interchangeable diagnoses.<sup>5,14</sup> However, more than 70% of patients with AFL do not experience AF, and less than 10% with AF are also diagnosed with AFL.<sup>15,16</sup> Furthermore, the distinction

between AF, typical, and atypical AFL is important, as the risks and success of catheter ablation are markedly different. For AF, long-term freedom from all recurrent atrial arrhythmias exceeds 50% with a single procedure, and approximately 70–80% with multiple procedures, acknowledging selected cohorts and expertise.<sup>17</sup> In small randomized trials, AF ablation reduced the composite of death and hospitalization in patients with HF with reduced ejection fraction.<sup>10,11</sup> By contrast, single-procedure ablation success rates exceed 90% for typical and atypical AFL,<sup>2</sup> with associated acute complication rates of 3–11%.<sup>12,13</sup> Ablation of AFL in unselected patients is associated with decreased hospitalizations, emergency department visits, development of subsequent AF,<sup>18</sup> and improved quality of life.<sup>1,19</sup> Guidelines therefore recommend it as first-line therapy.<sup>20</sup> However, few studies included patients with HF, and there

are no randomized controlled trials in patients with AFL and HF.

We therefore conducted a systematic review to define the following: (i) incidence, prevalence, and predictors of HF in AFL; (ii) incidence, prevalence, predictors, and phenotype of AFL in HF; (iii) overlap of AFL with AF in HF; (iv) prognosis of patients with HF and AFL compared with HF and no AFL; and (v) evidence for treatments of AFL in HF.

## Methods

### Search strategy

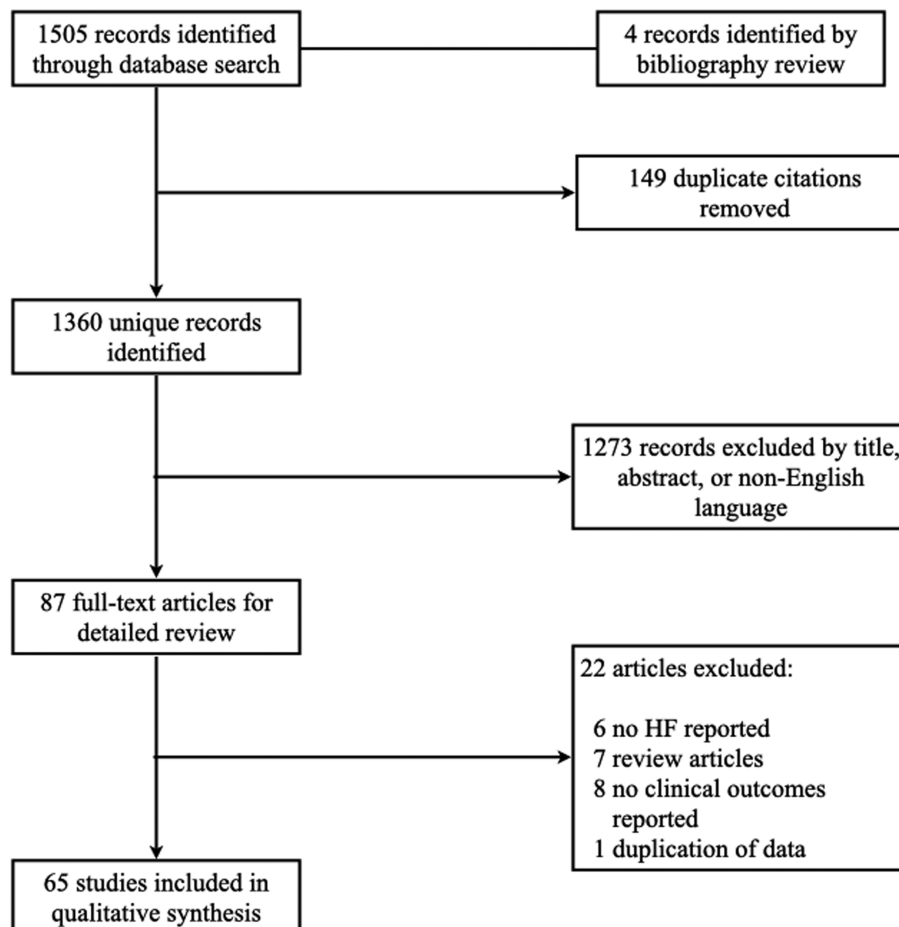
PubMed and EMBASE were searched without date restriction, limited to adult humans and English language, excluding case studies, reviews, and conference abstracts. The search strategy combined Medical Subject Headings terms and keywords in title and abstract to identify HF and AFL (Supporting Information). Reference lists of included articles

were reviewed for additional citations. English language studies fulfilling the participant, outcome, and study design criteria were included. Titles and abstracts were screened for inclusion, and full texts reviewed by the primary author (M.J.D.), with confirmation by the supervising author (N.M.H.). Articles were excluded during full-text review if they did not report on HF patients, were narrative review articles, did not report either clinical outcomes or epidemiological estimates, or duplicated previously published data. Results are synthesized qualitatively due to heterogeneity in objectives, design, and results.

## Results

The search identified 1404 articles in PubMed, 101 unique articles in EMBASE, and 4 articles added via bibliography review, totalling 1509 records (*Figure 1*). Of these, 65 met inclusion criteria. Only 10 studies included patients exclusively with AFL. The remaining 55 studies included both AF and

**Figure 1** Flow diagram of study selection. HF, heart failure



AFL, of which 21 studies reported the proportion with AFL separately. No study specifically described atypical AFL, and so all further discussion of AFL relates to either the typical phenotype or undifferentiated AFL only.

### Heart failure in atrial flutter: epidemiology overview

Twenty-five studies reported the epidemiology of HF in patients with AFL alone ( $n = 16$ ) or AFL/AF as a combined diagnosis ( $n = 9$ ) (*Tables 1 and S1*). In all 25 studies, HF was defined clinically based on the development of typical symptoms and signs, an existing clinical diagnosis, or administrative database coding. No study definition specified left ventricular ejection fraction (LVEF). The prevalence of HF in hospital or ambulatory populations with AFL ranged from 8% to 56%. The prevalence of HF was higher in patients with established AFL (14% to 56%) compared with newly diagnosed AFL (6% to 28%) (*Table 1 and Figure 2*). The incidence rate was between 0.9 and 3.6 per 100 person-years. Potential factors contributing to the diverse estimates include differences in arrhythmia duration, setting (inpatient vs. outpatient), study design (e.g. retrospective vs. prospective), cohort inclusion criteria, case ascertainment methods, coding, and indication bias among patients referred for catheter ablation. Nine studies (*Table S1*) combined AF and AFL diagnoses without disclosing the proportion of patients with AFL, and are not discussed further.<sup>5,14,33–39</sup>

### Heart failure in established atrial flutter

Only three studies examined HF patients solely with AFL.<sup>12,21,22</sup> In a large contemporary US cohort with AFL undergoing ablation ( $n = 5552$ ), 31% had concurrent HF defined using administrative data.<sup>12</sup> The prevalence of HF in AFL was even higher in two small historic cohorts: 40% in 110 patients undergoing ablation (1994–1997) and 56% in 71 patients hospitalized in Atlanta (1966–1970).<sup>21,22</sup>

Twelve studies included patients with both AF and AFL but separately reported characteristics of patients with AFL. The largest study reported HF in 30% of patients with AFL ( $n = 20\,298$ ), defining the cohort and comorbidities using International Classification of Disease (ICD) 9 codes in the US MarketScan claims database.<sup>26</sup>

### Heart failure in newly diagnosed atrial flutter

In patients with newly diagnosed AFL, a higher prevalence of HF (22% and 28%) was reported in two studies ( $n = 76$  and  $n = 181$ ) from the Marshfield Epidemiologic Study Area in Wisconsin, a comprehensive population-based cohort

defined using inpatient, outpatient, and electrocardiogram records.<sup>28,32</sup> A similar prevalence of comorbid HF (23%) was observed in 121 patients developing AFL in the Framingham Heart Study.<sup>30</sup> However, another Framingham study using a nested case-control design reported a lower prevalence of 8% in 112 individuals, the reason for the discrepancy being unclear.<sup>4</sup> Finally, a large Taiwanese national study ( $n = 6121$ ) and Canadian provincial registry ( $n = 9339$ ) of incident AFL cases identified using administrative records reported lower rates of HF at 13% and 6%, respectively.<sup>15,16</sup>

### Heart failure in atrial flutter: incidence and prevalence of heart failure in atrial flutter compared with atrial fibrillation

Eight studies reported prevalent HF in AFL and AF separately but within the same cohort and provide insights to their comparative frequency (*Table 1*). The prevalence of HF was similar in AFL compared with AF in five studies, and notably higher in three studies (45% vs. 35%,<sup>24</sup> 14% vs. 6%,<sup>23</sup> and 28% vs. 17%<sup>28</sup>). The two studies from Wisconsin confirmed the higher prevalence of HF in AFL vs. AF, with adjusted odds ratios ranging from 1.87 to 3.5.<sup>28,32</sup> By contrast, in three studies reporting long-term outcomes, AFL had similar<sup>4</sup> or even lower<sup>16,31</sup> adjusted risk of incident HF or HF hospitalization compared with AF. However, the latter two studies used administrative data to define the cohort and outcomes in Taiwan.

### Heart failure in atrial flutter: phenotype and predictors

Only one study characterized the phenotype of HF in patients with AFL. In a small post-ablation cohort from Boston ( $n = 36$ ), patients who developed ‘symptomatic HF’ had slightly lower mean LVEF at baseline (43 vs. 55%,  $P = 0.071$ ).<sup>23</sup> No study examined independent predictors of HF in AFL.

### Atrial flutter in heart failure: incidence and prevalence

No study described the incidence or prevalence of AFL in unselected patients with HF (*Table 2*), including any of the major HF registries.

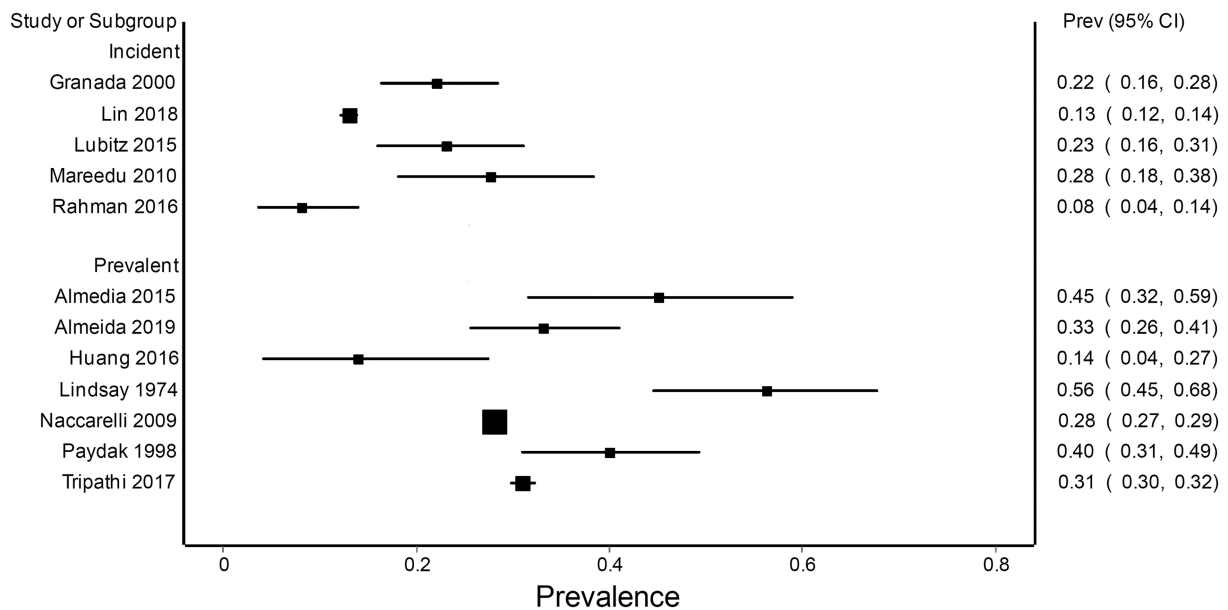
### Atrial flutter in heart failure: phenotype and predictors

No study reported the frequency of AFL phenotype (i.e. typical or atypical AFL) in HF. However, among the 181 individuals with new AFL in the Marshfield Epidemiologic Study

**Table 1** Characteristics of studies reporting incidence, prevalence, and predictors of HF in AFL

Study (first author, year)	Design	Population	LVEF (%)	Years	Mean/median f/up (years)	Cohort, n	AFL, n (%)	Prevalence HF in AFL (%)	Incidence HF in AFL (%)	Prevalence HF in AF (%)
<b>Established AFL</b>										
Lindsay, <sup>21</sup> 74	Case series	Hospitalization	Any	66–70	nr	71	71 (100)	56	nr	23
Paydak, <sup>22</sup> 98	Prospective cohort	Ablation	Any	94–97	20.1 m	110	110 (100)	40	nr	0
Tripathi, <sup>12</sup> 17	National registry	Ablation	Any	13–14	90 d	5552	5552 (100)	31	12	n/a
Huang, <sup>23</sup> 16	Prospective cohort	Ablation	Any	13–14	30 d	156	36 (23)	14	17	77
Almeida, <sup>24</sup> 15	Cross-sectional	Emergency department	Any	12	n/a	407	51 (13)	45	nr	87
Almeida, <sup>25</sup> 19	Retrospective cohort	Emergency department	Any	12	863 d	112	142 (13)	33	nr	87
Naccarelli, <sup>09</sup>	Registry national	Hospital or two outpatients	Any	04–05	n/a	242 903	20 298 (4)	28	nr	49
<b>Newly diagnosed AFL</b>										
Gula, <sup>15</sup> 18	Registry provincial	Hospital or emergency department	Any	03–11	3	9339	9339 (100)	5.8	nr	Excluded
Skjøth, <sup>27</sup> 18	Registry national	Ablation	No HF	00–16	5.5	5807	1517 (26)	n/a	1.1 PY	62
Maredu, <sup>28</sup> 10	Population cohort	Population MESA	Any	91–95	n/a	472	76 (16)	28	nr	84
Stiell, <sup>29</sup> 17	Prospective cohort	Emergency department	Any	10–12	30 d	1091	167 (15)	nr	nr	85
Rahman, <sup>4</sup> 16	Nested case-control	Outpatients Framingham	Any	48–02	10	1090	112 (10)	8	3.6 PY	39
Lubitz, <sup>30</sup> 15	Prospective cohort	Population Framingham	Any	49–12	5.4	1530	121 (8)	23	18	92
Lin, <sup>31</sup> 17	Registry national	Hospital and outpatient	No HF	01–13	13	175 420	6239 (3)	n/a	0.9 PY	97
Lin, <sup>16</sup> 18	Registry national	Hospital or two outpatients	Any	01–12	3.1	219 416	6121 (3)	13	1.1 PY	86
Granada, <sup>32</sup> 00	Population case control	Population MESA	Any	91–95	n/a	58 820	181 (1)	22	nr	nr

AF, atrial fibrillation; AFL, atrial flutter; d, days; HF, heart failure; f/up, follow-up; m, months; MESA, Marshfield Epidemiologic Study Area; nr, not reported; PY, per 100 person-years

**Figure 2** Prevalence of heart failure in patients with incident or prevalent atrial flutter. CI, confidence interval; Prev, prevalence.**Table 2** Characteristics of studies reporting incidence, prevalence, and predictors of AFL/AF in HF

Study (first author, year)	Cohort	Dates	Design	n	LVEF Inclusion (%)	% with AFL
<b>Tachycardia-induced cardiomyopathy</b>						
Brembilla-Perrot, <sup>40</sup> 16	AFL ablation	96–14	Retro cohort	1269	Any	100
Pizzale, <sup>41</sup> 09	AFL ablation	98–06	Prospect cohort	111	Any	100
Luchsinger, <sup>42</sup> 98	AFL ablation	nr	Case series	11	<50%	100
Nerheim, <sup>43</sup> 04	HF outpatients	nr	Case series	24	≤40%	16.7
Jeong, <sup>44</sup> 08	TICM	nr	Case control	42	≤45%	50
Nia, <sup>45</sup> 11	AF/AFL and LVSD outpatients	09–10	Case control	387	<40%	15
<b>Hospitalized HF</b>						
Wang, <sup>46</sup> 19	Hospitalized	01–15	Pro cohort	5588	Any	nr
Devkota, <sup>47</sup> 16	Hospitalized	14	Retro cohort	157	<50%	nr
von Scheidt, <sup>48</sup> 14	Hospitalized	09–11	Registry	1853	≤40%	nr
Lund, <sup>49</sup> 14	KaRen cohort	07–11	Registry multinational	539	≥45%	nr
Sulaiman, <sup>50</sup> 15	Hospitalized	12	Registry multinational	5005	Any	nr
Sasaki, <sup>51</sup> 13	Hospitalized	10–11	Registry national	8620	Any	nr
Sulaiman, <sup>52</sup> 20	Hospitalized	07–14	Registry national	75 430	Any	nr
<b>alcoholic CM</b>						
Dai, <sup>53</sup> 12	Hospitalized	05–06	Registry national	42 399	Any	nr
	ROSE, DOSE, CARRESS-HF	08–13	Trial substudy	750	Any	nr
Patel, <sup>54</sup> 18	ASTRONAUT	09–12	Trial substudy	1358	≤40%	nr
Greene, <sup>55</sup> 17	EVEREST	03–06	Trial substudy	4133	≤40%	nr
Mentz, <sup>56</sup> 12	TRACE	90–92	Trial substudy	6676	Any	nr
Pedersen, <sup>57</sup> 05	OPTIME-CHF	97–99	Trial substudy	949	LVSD	nr
Benza, <sup>58</sup> 04	DIAMOND	93–97	Trial substudy	506	≤35%	nr
Pedersen, <sup>9</sup> 01						
<b>Chronic HF</b>						
Hummel, <sup>6</sup> 13	Outpatients	09–10	Validation study	2467	Any	nr
Ibrahim, <sup>59</sup> 19	Outpatients	08–18	Registry national	1 103 386	Any	nr
Gurwitz, <sup>60</sup> 13	In/outpatient	05–08	Registry national	11 994	Any	nr
Zambito 05 <sup>61</sup>	AFL ablation	01–05	Retro cohort	90	<55%	100
Kalscheur, <sup>62</sup> 17	COMPANION	00–02	Trial substudy	293	≤35%	nr
Swedberg, <sup>63</sup> 12	EMPHASIS-HF	06–12	Trial substudy	2737	≤30%/35%	nr
Vermes, <sup>64</sup> 03	SOLVD	86–91	Trial substudy	391	≤35%	nr

AF, atrial fibrillation; AFL, atrial flutter; HF, heart failure; LVSD, left ventricular systolic dysfunction; ms, milliseconds; nr, not reported; pro, prospective; retro, retrospective; TICM, tachycardia-induced cardiomyopathy.

Area general population study, 22% of whom had HF, 90% had electrocardiograms consistent with typical CTI-dependent AFL.<sup>32</sup> Similarly, 84% of 1269 patients referred to a French centre for AFL ablation, 15% of which had prior HF, presented with 'counter-clockwise' AFL.<sup>40</sup>

### Atrial flutter in heart failure: concomitant diagnosis and subsequent development of atrial fibrillation

The overlap between AFL and AF in HF is poorly described. Without specific studies in unselected patients with HF, several indirect observations merit consideration. In a US national outpatient database derived from insurance claims ( $n = 484\,537$ ), isolated AFL was least common (0.03%), dual diagnosis AF/AFL more frequent (0.1%), and lone AF most common (1.4%).<sup>26</sup> However, only a minority of patients in each group (28–30%) had concurrent HF, defined by ICD-9 codes.

In four studies of highly selected patients with HF/ left ventricular systolic dysfunction (LVSD) and AFL referred for ablation, 33% overall (range 25% to 57%) had concurrent AF (Table 2).<sup>22,43,44,61</sup> Following AFL ablation, AF developed in 17–30% of patients over 350 days to 2 years.<sup>22,61</sup> De novo AF was strongly associated with LVSD following AFL ablation: 43% vs. 14% comparing LVEF < 50% vs. >50%, and 31% vs. 7% for LVEF < 35% vs. 36–55% in two US single-centre cohorts.<sup>22,61</sup> In the remaining cohort and case series studying tachycardia-induced cardiomyopathy, the small sample sizes limit meaningful conclusions regarding the overlap.<sup>43,44</sup>

### Atrial flutter in heart failure: prognosis

While 13 studies examined mortality and/or rehospitalization in AF/AFL as a combined diagnosis, the prognostic implications

of AFL in HF relative to either sinus rhythm or AF have never been investigated (Table 3; additional details in Table S2).

### Atrial flutter in heart failure: treatment

Thirty-one studies described treatment of patients with AF or AFL, some or all having pre-existing HF or LVSD (Table 4). From these, 14 studies described the management separately for AF and AFL patients, of which 5 described electrical cardioversion, 10 catheter ablation,<sup>8,22,40–45,61,68</sup> and 9 drug therapy.<sup>8,21,24,41,42,65,68,69</sup>

For cardioversion, among 19 825 US inpatients with AFL (16% with existing HF), concurrent HF was associated with an increased odds of receiving electrical cardioversion during hospitalization.<sup>8</sup> Potential explanations include that decompensated HF prompted cardioversion, anti-arrhythmic drug options are limited in HF, and greater cardiology specialist involvement in care. Across all studies, early and long-term maintenance of sinus rhythm after cardioversion ranged from 89% to 96% and 42% to 90%, respectively.<sup>36,65,69</sup> The highest long-term success rate was achieved in 50 Dutch patients, of whom 16% had 'cardiomyopathy' not otherwise defined, using cardioversion and progressive anti-arrhythmic drugs with repeat cardioversion if needed.<sup>69</sup> Cardioversion had similar short-term success (96%) among New Zealand patients admitted with HF and LVEF ≤ 40%, of whom 46 of 77 had concurrent AFL.<sup>68</sup> This was the only study reporting outcomes after cardioversion or pharmacologic treatment of AFL in unselected HF patients, with a 1 year all-cause mortality or rehospitalization rate of 23% following cardioversion. Only four other studies reported outcomes after cardioversion or pharmacologic treatment in subgroups with AFL, although only 16% to 56% had concurrent HF (Table 4).<sup>8,21,24,69</sup>

In the 10 catheter ablation studies, immediate procedural success ranged from 87% to 100%, with AFL recurrence of

**Table 3** Mortality and hospitalization rates among studies with HF and concurrent AF/AFL

Study (first author, year)	AFL (%)	All-cause mortality (%)	All-cause admission (%)	All-cause mortality or HFH (%)	HFH (%)	Follow-up
Mentz, <sup>56</sup> 12	nr	26 <sup>a</sup>	nr	nr	30 <sup>a</sup>	24 months
Pedersen, <sup>57</sup> 05	nr	25 <sup>a</sup>	nr	nr	nr	30 days
Greene, <sup>55</sup> 17	nr	17	53 <sup>a</sup>	nr	31 <sup>a</sup>	12 months
Patel, <sup>54</sup> 18	nr	nr	nr	40	nr	60 days
Kalscheur, <sup>62</sup> 17	nr	nr	nr	50 at 120 days <sup>a</sup>	nr	990 days
Swedberg, <sup>63</sup> 12	nr	nr <sup>c</sup>	nr <sup>c</sup>	nr <sup>c</sup>	nr <sup>c</sup>	4 years
Pederson, <sup>9</sup> 01	nr	nr <sup>b</sup>	nr	nr	nr	42 months
Rodriguez, <sup>65</sup> 16	28	12	nr	nr	nr	nr
Ueberham, <sup>66</sup> 20	nr	1.3	nr	nr	nr	In-hospital (6.2 days)
Aoyama, <sup>67</sup> 20	nr	nr	5	nr	5	20.3 months
Tripathi, <sup>12</sup> 17	100	nr	18	nr	2	90 days
Lund, <sup>49</sup> 14	nr	nr <sup>c</sup>	nr	nr	nr	18 months
Hummel, <sup>6</sup> 13	nr	nr	nr	nr <sup>b</sup>	nr	6 months

AF, atrial fibrillation; AFL, atrial flutter; HF, heart failure; nr, not reported; LVSD, LV systolic dysfunction.

<sup>a</sup>Significantly increased from patients in sinus rhythm.

<sup>b</sup>nr = value not reported, but significant difference from sinus rhythm.

<sup>c</sup>nr = value not reported, but no significant difference from sinus rhythm.

Table 4 Characteristics of included studies reporting on treatment of AFL in HF

Study (first author, year)	Cohort	Dates	Design	Consecutive	n	LVEF (%)	% with AFL	% with prior HF	% with LVEF normalization	% with partial LVEF recovery
Tachycardia-induced cardiomyopathy										
Pizzale, <sup>41</sup> 09	AFL ablation	98–06	Prospect cohort	Yes	111	Any	100	25	57	89 <sup>a</sup>
Brembilla-Perrot, <sup>40</sup> 16	AFL ablation	96–14	Retro cohort	Yes	1269	Any	100	15	56	nr
Brembilla-Perrot, <sup>70</sup> 15	AFL ablation	99–04	Retro cohort	Yes	1187	Any	100	12	nr	nr
Luchinger, <sup>42</sup> 98	AFL ablation	nr	Case series	Yes	11	<50%	100	100	55	73 <sup>a</sup>
Jeong, <sup>44</sup> 08	TICM	nr	Case control	No	42	≤45%	50	100	81	100 <sup>b</sup>
Nerheim, <sup>43</sup> 04	HF outpatients	nr	Case series	No	24	≤40%	16.7	100	33	100 <sup>d</sup>
Nia, <sup>45</sup> 11	AF/AFL and LVEF < 40% outpatients	09–10	Case control	Yes	387	<40%	15	100	88	nr
Left ventricular systolic dysfunction										
Zambito, <sup>65</sup> 05	AFL ablation	01–05	Retro cohort	Yes	90	<55%	100	100	nr	nr
Foo, <sup>68</sup> 19	New AF/AFL and HF	15–16	Retro cohort	Yes	79	≤40%	58	100	nr	75 <sup>a</sup>
Rodriguez, <sup>65</sup> 16	New AF/AFL and HF	09–14	Retro cohort	Yes	25	≤40%	28	100	40	84 <sup>a</sup>
Shiga, <sup>71</sup> 02	AF/AFL and HF outpatient	88–01	Retro cohort	No	108	<50%	nr	100	nr	nr
Aoyama, <sup>67</sup> 20	AF/AFL ablation	14–18	Retro cohort	No	40	<50%	nr	100	75%	nr
Greene, <sup>35</sup> 17	ASTRONAUT trial	09–12	Trial substudy	Yes	1358	≤40%	nr	100	nr	nr
von Scheidt, <sup>48</sup> 14	HF inpatients	09–11	Regional registry	Yes	1853	≤40%	nr	100	nr	nr
Mentz, <sup>56</sup> 12	EVEREST trial	03–06	Trial substudy	Yes	4133	≤40%	nr	100	nr	nr
Kalscheur, <sup>62</sup> 17	COMPANION trial	00–02	Trial substudy	Yes	293	≤35%	nr	100	nr	nr
Swedberg, <sup>63</sup> 12	EMPHASIS-HF trial	06–12	Trial substudy	Yes	2737	≤30/35%	nr	100	nr	nr
Any LVEF										
Lindsay, <sup>21</sup> 74	New AFL hospitalization	66–70	Case series	Yes	71	Any	100	56	nr	nr
Paydak, <sup>22</sup> 98	AFL ablation	94–97	Prospect cohort	Yes	110	Any	100	40	nr	nr
Crijns, <sup>69</sup> 97	Chronic AFL	86–93	Case series	Yes	50	Any	100	16	nr	nr
LaPointe, <sup>8</sup> 10	AFL inpatients	00–04	Retro cohort	Yes	19 825	Any	100	16	nr	nr
Almeida, <sup>24</sup> 15	AF/AFL presenting to ED	2012	Cross-sectional	Yes	407	Any	13	36	nr	nr
Stiell, <sup>7</sup> 11	AF/AFL ED visit	2008	Retro cohort	Yes	1068	Any	12	4	nr	nr
Santini, <sup>72</sup> 04	AF/AFL inpatients	2000	Prospect cohort	Yes	2838	Any	10	11	nr	nr
Zhang, <sup>73</sup> 14	AF/AFL ED visit	08–11	Regional registry	Yes	2016	Any	3	37	nr	nr
Sulaiman, <sup>52</sup> 20	Hospitalized alcoholic CM	07–14	Registry national	No	75 430	Any	nr	100	nr	nr
Ueberham, <sup>66</sup> 20	AFL and AF ablation	10–18	Registry national	Yes	54 645	Any	nr	100	nr	nr
Patel, <sup>54</sup> 18	ROSE, DOSE, and CARRESS-HF trials	08–13	Trial substudy	Yes	750	Any	nr	100	nr	nr
Scheuermeyer, <sup>38</sup> 15	AF/AFL ED visit	09	Retro cohort	Yes	416	Any	nr	36	nr	nr
Naccarelli, <sup>33</sup> 12	AF/AFL one hospitalization or two outpatient visits	03–09	Retro cohort	Yes	377 808	Any	nr	31	nr	nr
Barbic, <sup>74</sup> 18	AF/AFL ED visit	13	Pre-post evaluation	Yes	301	HF excluded	nr	nr	nr	nr

Percentage of LVEF normalization and partial recovery reflects that of cohorts with HF/LVSD at baseline.

AFL, atrial flutter; AF, atrial fibrillation; ED, emergency department; HF, heart failure; LVEF, left ventricular ejection fraction; nr, not reported; TICM, tachycardia-induced cardiomyopathy.

<sup>a</sup>Defined as LVEF > 40%.

<sup>b</sup>Defined as LVEF increase ≥ 5%.

<sup>c</sup>Defined as LVEF increase ≥ 15%.

<sup>d</sup>LVEF improvement not explicitly defined.

5–30% up to 2.3 years.<sup>22,45,68</sup> Only the aforementioned non-randomized New Zealand study described clinical outcomes in unselected HF patients undergoing ablation, with lower 1 year all-cause mortality or rehospitalization than patients undergoing cardioversion (8 vs. 23%,  $P = 0.57$ ).<sup>68</sup>

Seven studies specifically reported outcomes after treatment in tachycardia-induced cardiomyopathy (with or without ablation or LVSD control groups) — five after catheter ablation,<sup>40–44</sup> and two with pharmacologic rate or rhythm control (Table 4).<sup>43,44</sup> Tachycardia induced cardiomyopathy was typically defined as LVEF < 40–50% with concurrent tachyarrhythmia, no alternate aetiology identified, and subsequent improvement with arrhythmia control.<sup>75</sup> The rates of LVEF improvement (57% to 100%) or normalization (33% to 88%) appear greater than in unselected patients with HF, with improvement variably defined as LVEF increase of 5% to 15%, or to above 40% (Table 4). Factors associated with failed LVEF recovery included age,<sup>40</sup> ischaemic heart disease,<sup>40</sup> prior anti-arrhythmic use,<sup>40</sup> lack of heart rate reduction,<sup>41,43</sup> and increasing left ventricular end-diastolic diameter.<sup>44</sup> AFL-related tachycardia-induced cardiomyopathy was associated with lower cardiovascular mortality compared with LVSD unrelated to AFL among French patients undergoing catheter ablation; this was the only study that described survival after treatment of tachycardia-induced cardiomyopathy.<sup>40</sup>

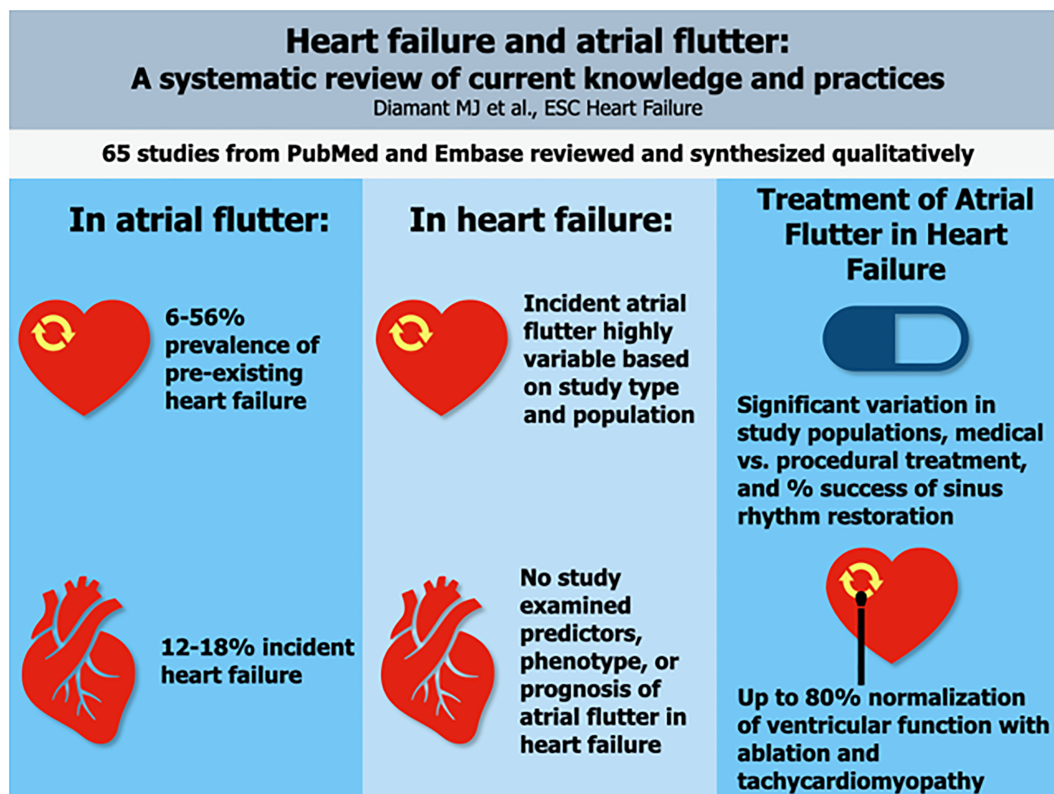
## Discussion

This systematic review has several key findings. First, the incidence and prevalence of HF in patients with AFL is high. Second, in unselected patients with HF, remarkably little is known about AFL—the incidence, prevalence, predictors, phenotype, overlap with AF, role of imaging, prognostic implications, and pharmacological treatment have not been described. Finally, ablation has mainly been studied in selected cohorts with tachycardia-induced cardiomyopathy, so the effectiveness in patients with AFL and HF due to other aetiologies is unknown. Figure 3 provides a summary of key findings.

### Heart failure in atrial flutter

The incidence and prevalence of HF in AFL was high, particularly in patients with prevalent AFL (28% to 56% in six studies). Because many studies enrolled patients undergoing catheter ablation, the most generalizable estimate of HF prevalence in patients with established AFL was 28% observed in the US MarketScan claims database.<sup>26</sup> The prevalence of HF in newly diagnosed AFL is likely lower, reported to be 6–13% in large contemporary cohorts.<sup>15,16</sup>

Figure 3 Summary of key findings (visual abstract).





How much of this high prevalence relates to tachyarrhythmia vs. shared risk factors is unclear. The phenotype of HF including LVEF and aetiology is also uncertain. The finding of similar or higher risk of developing HF in AFL relative to AF requires further confirmation. Yet, if the prevalence of LVSD in AFL is high, then routine assessment of cardiac function may be appropriate to ensure timely initiation of guideline-directed medical therapies. The diagnostic yield and cost effectiveness of such a strategy would require evaluation. Additionally, if AFL conveys significantly increased risk of HF, and this risk is modifiable, then earlier and more aggressive intervention may be warranted. Therapeutic strategies that could be compared include electrical cardioversion or AFL ablation.

### Atrial flutter in heart failure

In the general population, the prevalence of both HF and AF/AFL is increasing.<sup>14,76,77</sup> AFL concurrent with HF will accordingly increase. The implications for health systems need defining, starting with the burden of disease and associated healthcare utilization including ambulatory and hospital care. If the prognostic implications of AFL are similar to AF/AFL considered as a combined diagnosis, then HF hospitalization may be a marker of further adverse events, and an opportune time to intervene. Whether arrhythmia is an indicator of risk, such as a consequence of increasing filling pressures leading to atrial remodelling and subsequent AFL, or a target for specific interventions, warrants investigation. It also remains unclear whether typical AFL may be a consequence of right-sided HF. While the studies included in this review do not report phenotype of HF nor right-sided involvement, studies examining atrial arrhythmias in arrhythmogenic cardiomyopathy with predominant right ventricular involvement may provide further insight. Among four studies of arrhythmogenic cardiomyopathy patients ( $n = 36$  to 294),<sup>78–81</sup> 2–11% had documented AFL compared with 8–11% with AF, and 2–19% with both AF and AFL. Atrial arrhythmias were associated with either right-sided or left-sided ventricular dysfunction or chamber enlargement, but analyses among patients specifically with AFL were never reported.

There is insufficient evidence to comment on specific elements of a rate control strategy. However, the early success of cardioversion was high, as was longer term rhythm control using anti-arrhythmic drugs in selected studies. Whether the benefits of ablation in tachycardia-induced cardiomyopathy extend to HF due to alternate aetiologies also merits study. This is particularly relevant given the high success rates and reduction in de novo AF resulting from CTI ablation,<sup>18</sup> as well as the accruing evidence to suggest prognostic benefit from PVI ablation for concurrent AF and HF.<sup>10,11,82</sup> The CAMERA-MRI trial demonstrated greater improvement in ventricular function after PVI ablation in the absence of ventricular

fibrosis on cardiac MRI.<sup>83</sup> Similar studies are warranted in patients with AFL to develop more personalized treatment pathways.

### Overlap of atrial fibrillation with atrial flutter

The intersection between AF and AFL has two distinct perspectives: (i) the prevalence of AFL in patients with AF and (ii) the prevalence of AF in patients with AFL. Because AF is approximately 10-fold more common than AFL in the general population,<sup>26</sup> if even a small proportion of patients with AF have concurrent AFL (e.g. 10%), then a large proportion of patients with AFL have concurrent AF. The trials of AF in HF offer another potential view of the overlap between AF and AFL.<sup>82</sup> However, only one study described the proportion of patients with concomitant AFL (9%).<sup>84</sup>

The overlap between AFL and AF also merits consideration when planning ablation for AFL in patients with LVSD, as up to 43% of whom subsequently develop AF.<sup>22</sup> Concurrent PVI and CTI ablation could be considered without documented AF in those deemed high risk for future AF. Alternatively, pulmonary vein triggers for both arrhythmias could be targeted, as currently being studied in the CRAFT trial.<sup>85</sup> However, randomized controlled trials are needed to examine these strategies in patients with HF before adoption into clinical practice. Further, in those with multiple arrhythmias amenable to ablation, personalized ablation strategies chosen from a combination of presenting arrhythmias, clinical and treatment history, imaging, and mapping may ultimately yield the best clinical outcomes.

### Limitations

Several limitations merit consideration and highlight areas for further research. Many studies considered AF and AFL as an interchangeable diagnosis, reflecting the limited accuracy of ICD coding to distinguish AFL in administrative databases.<sup>86</sup> Many HF trials require elevated natriuretic peptide levels for inclusion, so these patients may be distinct from patients with AF/AFL enrolled in community-based cohorts or registries. The significant heterogeneity in study design, populations, and outcomes prevented quantitative synthesis.

### Conclusion

There is limited evidence in all aspects of the intersection between AFL and HF. Outcomes for these patients are unknown, and the treatments and processes of care provided are poorly defined. While previous efforts have largely focused on AF and HF, future studies need to characterize the burden of disease and contemporary management of AFL

and other atrial arrhythmias, compare treatment strategies, and delineate subgroups that may benefit from more intensive or invasive therapy.

## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Studies of heart failure in atrial flutter or fibrillation as combined diagnosis.

**Table S2.** Characteristics of studies reporting outcomes of patients with HF and concurrent AF/AFL.

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