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Electrical Cardioversion-Associated Takotsubo Cardiomyopathy: A National Readmission Database 2018 Analysis and Systematic Review

ABSTRACT

The incidence of cardioversion-associated takotsubo cardiomyopathy in patients with atrial fibrillation undergoing electrical cardioversion is unknown. We aimed to determine the incidence of cardioversion-associated takotsubo cardiomyopathy using a National Readmission Database 2018 and a systematic review. We identified all patients with the index diagnosis of atrial fibrillation who underwent electrical cardioversion and were readmitted within 30 days with a primary diagnosis of takotsubo cardiomyopathy by International Classification of Diseases, Tenth Revision, Clinical Modification codes to find the incidence and risk factors of the disease. A systematic review was performed by searching PubMed and Embase for patients with atrial fibrillation who underwent electrical cardioversion and developed takotsubo cardiomyopathy from inception to February 2022. Baseline characteristics and clinical presentation were displayed. Among 154 919 patients admitted with atrial fibrillation who underwent electrical cardioversion in National Readmission Database 2018, 0.027% were readmitted with takotsubo cardiomyopathy (mean age of 71.0 ± 3.5 years and 96.7% were female). Female sex is an independent predictor of electrical cardioversion-associated takotsubo cardiomyopathy [adjusted odds ratio = 49.77 (95% CI: 5.90-419.87)], while diabetes mellitus is associated with less risk of electrical cardioversion-associated takotsubo cardiomyopathy [adjusted odds ratio = 0.31 (95% CI: 0.10-0.99)]. The systematic review included 13 patients (mean age of 74.8 ± 9.6 years and 77% were female). Acute heart failure due to apical type takotsubo cardiomyopathy is the most common presentation within 48 hours. The recovery time is less than 1 week in milder cases but can take up to 2 weeks in severe cases. Cardioversion-associated takotsubo cardiomyopathy is a rare complication in patients with atrial fibrillation who underwent electrical cardioversion. Female patients have a 50-fold increased risk, but DM is associated with a 3-fold risk reduction. The majority of patients recover within 2 weeks with supportive care.

Keywords: Electric countershock, cardioversion, atrial fibrillation, takotsubo cardiomyopathy, takotsubo syndrome

REVIEW

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia worldwide, with prevalence increasing with age.[1] Rhythm control is an essential strategy in symptomatic patients. Electrical cardioversion (ECV) is the fastest way to establish sinus rhythm compared to antiarrhythmic medications and ablation. Complications after ECV are uncommon. Skin irritation, pain, and burn are the most common morbidities, with moderate-to-severe pain occurring in up to 23%.[2] Transient hypotension is another benign complication that can resolve with intravenous fluid administration. Other complications include arrhythmias, myocardial dysfunction, thromboembolism, and esophageal injury related to transesophageal echocardiography (TEE). Takotsubo cardiomyopathy (TCM) is one of the reported causes of myocardial dysfunction after cardioversion. The mechanism of this disease is still unknown. Catecholamine-induced cardiotoxicity is one of the supported theories. Physical or emotional triggers increased the catecholamine significantly, causing myocardial dysfunction.[3,4]

To date, ECV-associated TCM was considered a rare complication of ECV in patients with AF undergoing ECV. This presentation's literature is limited and exists mainly

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in case reports, making estimating incidence impractical. Therefore, we aim to identify the incidence and risk factors of ECV-associated TCM in patients with AF undergoing ECV.

METHODS

We conducted a retrospective cohort study using data from the National Readmission Database (NRD) of the year 2018 and a systematic review to identify the incidence and baseline characteristics of patients who were readmitted with a diagnosis of TCM after ECV. We also used data from NRD to find predictors of ECV-associated TCM.

National Readmission Database 2018

The NRD is a unique and powerful database developed for the Healthcare Cost and Utilization Project (HCUP) and designed to support various analyses of national readmission rates for all patients, regardless of expected payer for hospital stay.[5] In 2018, the NRD contained data from 28 states, accounting for 58.7% of all US hospitalizations. It contains de-identified clinical and nonclinical data that support readmission analysis, such as verified patient linkage number that identifies discharges belonging to the same patient, length of stay, and up to 40 diagnoses and 25 procedures collected for each patient using the International Classification of Diseases, Tenth Revision, Clinical Modification, ICD-10-CM. (see Supplementary Table 1 for ICD-10 codes used in this study). Each discharge is weighted (weight = total number of discharges from all acute care hospitals in the USA divided by the number of discharges included in the 20% sample) to help calculate the national estimates.

All patients hospitalized with a primary index diagnosis of AF who received ECV were included. Patients who developed ECV-associated TCM were identified by readmission within 30 days after the ECV for AF with a primary diagnosis of TCM. We excluded patients initially admitted in December as the NRD captured admission based on a calendar year without a link to the previous or following year (see Figure 1). We used the variables available in the NRD to identify patients' baseline characteristics, including age, gender, and comorbidities. Due to the de-identified nature of the data, institutional review board approval was not required.

Systematic Review

The systematic review was conducted following published PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance 2020[6] (see Supplementary Table 2). We performed a systematic search of the Medline and Embase databases (inception through February 2022) for patients with AF who underwent ECV and then developed TCM. Our search strings were ("atrial fibrillation"[Mesh] OR "atrial fibrillation"[tiab]) AND ("electric countershock"[Mesh] OR "cardioversion"[tiab]) AND ("takotsubo cardiomyopathy"[Mesh] OR "takotsubo"[tiab] OR "stress-induced cardiomyopathy"[tiab]) for PubMed. For Embase, search strings were ("cardioversion"/exp OR cardioversion) AND ("takotsubo cardiomyopathy"/exp OR "takotsubo cardiomyopathy" OR "stress-induced cardiomyopathy") AND ("atrial fibrillation"/exp OR "atrial fibrillation"). We hand-searched the bibliographies of selected studies to identify further eligible studies. Abstracts were reviewed for suitability and articles were accordingly retrieved.

Two authors (S.T. and A.T.) independently abstracted the data from included studies. All articles were screened using the inclusion criteria of (1) patients with AF who underwent ECV and (2) TCM that occurred after the ECV. Then, full articles were assessed with disputes resolved by consensus following discussion with a third author (J.K.). Assessment for risk of bias in included studies was done using The Joanna Briggs Institute (JBI) critical appraisal checklist for case reports.[7]

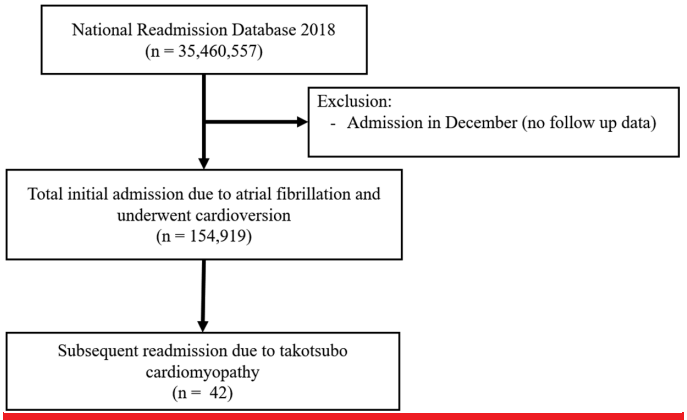

Figure 1. National Readmission Database 2018 diagram of included patients.

Statistical Analysis

The NRD data related to this analysis were downloaded from the HCUP central distributor. We adhered to the methodological standard of HCUP and followed the checklist provided by the HCUP. National estimates were calculated from the NRD variables by using the STATA function "discwt." Standard error calculations were made considering stratification (nrd_stratum) and hospitals defining the clusters (hosp_nrd). Categorical data were presented as frequency (%) and were compared using the chi-square test. Continuous data were presented as mean ± SD and were compared using the Student's *t*-test if normally distributed, determined by Shapiro–Wilk test. Median and interquartile range were used for non-normal distribution data and compared using the Mann–Whitney *U*-test. The univariate logistic regression was used to calculate an unadjusted odds ratio (OR) for primary and secondary

HIGHLIGHTS

- The incidence of cardioversion-associated takotsubo is rare, with 2.7 events per 10,000 procedures.
- Female patients had a 50-fold increased risk of developing this condition, while diabetes mellitus is associated with a decreased risk by 3-fold.
- Acute heart failure is the most common presentation, with an onset within 24 hours after the cardioversion.
- Supportive treatment with medical management is the mainstay of therapy, with most patients recovering within 2 weeks.

outcomes. Multiple logistic regression was performed to calculate the adjusted OR (Adj.OR) using all variables in the baseline characteristics. A 2-tailed *P*-value of .05 was designated as statistically significant. Statistical analyses were performed using STATA, version 16 (StataCorp, College Station, TX, USA).

RESULTS

National Readmission Database 2018

The NRD 2018 had 35,460,557 hospitalizations, with 154,919 index admissions of AF patients who underwent ECV. Of this, 42 patients (0.027%) subsequently developed TCM and were readmitted within 30 days, as shown in Figure 1. From NRD 2018, the majority of patients who developed TCM after ECV were female compared to those who did not have TCM (96.7% vs. 39.4%, $P < .001$). The age of the TCM group was not significantly different from the control group, with a mean age of 71.0 ± 3.5 vs. 67.8 ± 0.3 years, respectively. Patients who developed TCM had significantly fewer comorbidities of diabetes mellitus (DM) (10.5% vs. 32.7%. $P = .028$). Coronary artery disease was found in 55.3% in the TCM group and 46.6% in the control group. Prevalence of anxiety and depression was not significantly higher in patients with TCM (23.9% vs. 11.7% and 16.6% vs. 9.3%, respectively). The full detail of baseline characteristics is shown in Table 1.

Independent predictors of cardioversion-associated TCM were female sex (Adj.OR 49.77; $P < .001$; 95% CI: 5.90-419.87) and DM (Adj.OR 0.31; $P = .049$; 95% CI: 0.10-0.99). Coronary artery disease, anxiety, and depression were not independently associated with ECV-associated TCM, as shown in Table 2.

Systematic Review

The literature search identified 25 articles from Embase and 15 studies from Medline. We found 1 additional article from a manual search. Sixteen studies were relevant for evaluation. Three studies were excluded because patients with AF did not receive cardioversion but developed TCM following AF ablation in 2 studies[8,9] and a pacemaker placement in 1 study.[10] A total of 13 articles were included. All of them were case reports. The type of publication included was 7 case reports,[11-17] 1 letter to the editor,[18] and 5 poster presentation abstracts.19-23 The flow diagram of the systematic review is shown in Figure 2. Quality assessment was performed using the JBI critical appraisal checklist for case reports. All 13 studies were deemed appropriate after being critically appraised and were included (see Supplementary Table 3).

Baseline characteristics of the included studies in the first analysis are shown in Table 3. The mean age was 74.8 ± 9.6 years, 77% were female, and 77% had hypertension. Six studies reported the type of anticoagulation used, all of which used vitamin K antagonists. Sotalol was used in 46% of participants as a rhythm control agent before cardioversion from the available reported data. Eleven patients had normal left ventricular ejection fraction before ECV, while 2 studies did not report this parameter. The indication of cardioversion was symptomatic AF (9 studies), atrial flutter (1 study), AF with heart failure (2 studies), and persistent AF after AF ablation (1 study). Energy used in electrical cardioversion was reported in 7 studies with a range of 70 J to 200 J. The onset of TCM occurred within 48 hours after the procedure in all reports. Presentation of cardioversion-associated TCM included acute respiratory distress with pulmonary edema due to heart failure (84.6%), chest pain (15.4%), pulseless electrical activity cardiac arrest (15.4%), and cardiogenic shock (30.8%). Electrocardiography (ECG) findings included new T wave inversion in 53.8%, new left bundle block in 15.4%, and no ECG changes in 15.4%. All studies used transthoracic echocardiography (TTE) to diagnose TCM. Most cardioversion-associated TCM had an apical type (12 from 13 studies), and 1 study found an atypical focal type of TCM. Eight patients from 13 included studies underwent cardiac catheterization, which showed non-obstructive coronary artery disease. The disease severity ranged from mild to severe, with a recovery period of 1-20 days. All patients were treated conservatively. Most patients had normalized

Table 1. Baseline Characteristics

Baseline Characteristics	Takotsubo Cardiomyopathy (n = 42) %	No Takotsubo Cardiomyopathy (n = 154 877) %	*P*
Female sex	96.7	39.4	<.001
Age, years (median, IQR)	72 (67-78)	69 (60-78)	.093
Hypertension	70.8	69.7	.960
Coronary artery disease	55.3	46.6	.368
Diabetes mellitus	10.5	32.7	.028
Hyperlipidemia	38.1	51.3	.164
Stroke	12.2	9.0	.656
Peripheral vascular disease	23.2	16.1	.388
COPD	33.3	21.6	.189
Obesity	15.2	27.7	.144
Anemia	18.3	23.5	.714
CKD stage 3 and above	11.3	21.9	.246
Systolic heart failure	35.6	31.5	.687
Diastolic heart failure	27.3	17.2	.273
Obstructive sleep apnea	4.3	16.8	.124
Anxiety	23.9	11.7	.082
Depression	16.6	9.3	.237
Nicotine dependence	0	10.3	n/a
Alcohol-related disorder	7.8	0.6	.704
Charlson index (median, IQR)	2.4 (0-12)	2.6 (0-16)	.872

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; n/a, not applicable.

Table 2. Logistic Regression Analysis Showing Association Between Baseline Characteristics and Takotsubo Cardiomyopathy after Cardioversion

Baseline Characteristics	Univariate Analysis Odds Ratio (95% CI)	*P*	Multiple Analysis* Adjusted Odds Ratio (95% CI)	*P*
Female sex	45.00 (6.05-334.06)	<.001	49.77 (5.90-419.87)	<.001
Age	1.02 (0.99-1.05)	.093	0.99 (0.98-1.01)	.594
Hypertension	1.02 (0.40-2.59)	.960	1.17 (0.49-2.79)	.731
Coronary artery disease	1.46 (0.64-3.33)	.368	2.04 (0.70-5.91)	.189
Diabetes mellitus	0.25 (0.07-0.86)	.028	0.31 (0.10-0.99)	.049
Hyperlipidemia	0.54 (0.23-1.28)	.164	0.55 (0.24-1.27)	.161
Stroke	1.41 (0.31-6.42)	.656	1.15 (0.27-4.91)	.850
Peripheral vascular disease	1.61 (0.57-4.58)	.368	1.82 (0.45-7.36)	.402
COPD	1.86 (0.74-4.68)	.189	1.53 (0.50-4.70)	.456
Obesity	0.45 (0.15-1.31)	.144	0.59 (0.18-1.97)	.390
Anemia	0.83 (0.30-2.26)	.714	0.68 (0.25-1.83)	.449
CKD stage 3 and above	0.48 (0.14-1.65)	.246	0.55 (0.17-1.78)	.318
Systolic heart failure	1.19 (0.50-2.84)	.687	1.76 (0.56-5.58)	.335
Diastolic heart failure	1.71 (0.65-4.50)	.273	1.54 (0.35-6.70)	.563
Obstructive sleep apnea	0.21 (0.03-1.55)	.124	0.37 (0.46-2.90)	.341
Anxiety	2.28 (0.90-5.79)	.082	1.46 (0.52-4.08)	.468
Depression	1.88 (0.66-5.23)	.237	1.26 (0.42-3.74)	.683
Nicotine dependence	n/a	n/a	n/a	n/a
Alcohol-related disorder	1.48 (0.20-11.00)	.704	3.03 (0.43-31.44)	.266
Charlson index	0.98 (0.76-1.26)	.872	1.06 (0.70-1.62)	.777

*Multiple logistic regression analysis was adjusted by all the baseline characteristics.
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; n/a, not applicable.

LVEF during the follow-up TTE at 6 days to 8 weeks. One patient whose LVEF did not recover before discharge died suddenly from sudden cardiac death during the follow-up period.

DISCUSSION

To the best of our knowledge, this is the first study to identify the incidence of ECV-associated TCM in patients with AF. We found that ECV-associated TCM occurred 2.7 times per 10,000 ECV events for AF. The common complications of cardioversion that physicians inform the patient of are skin injury, esophageal injury with TEE, and perioperative thromboembolic events. The incidence of thromboembolic events ranges from 0% to 6.8%, and esophageal injury related to TEE is up to 0.2%-0.5%.[24,25] Compared to other complications of cardioversion, ECV-associated TCM is quite rare. The mean age of the patients with ECV-associated TCM was 71 years in the NRD and 74.8 years in the systematic review. The age range of patients with ECV-associated TCM is slightly higher than that reported in the International Takotsubo Registry, which reported a mean age of 66.8 years but not significantly different from the control group.[26] The female gender was the predominant gender, with a prevalence of 96.7% in the NRD 2018 compared to 89.8% in the International Takotsubo Registry.[26] In our analysis, the female gender increased the risk of ECV-associated TCM by 50-fold.

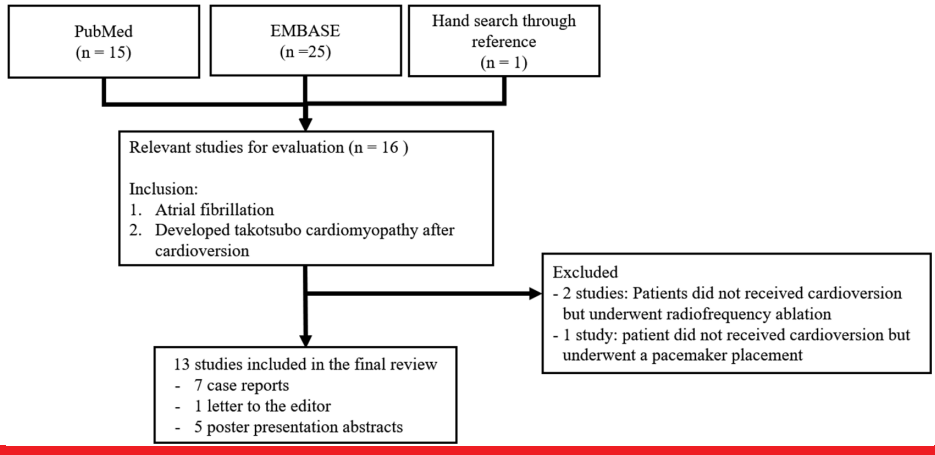

Figure 2. Flow diagram of the study selection process for the systematic review.

Table 3. Characteristics of Studies Included in the Systematic Review

Author, Year, Type of Article	Sex, Age (Years)	Comorbidities	Medication Before CV	AC	Indication for CV	LVEF Before CV/After CV, Takotsubo Type	Type of CV, Energy (J)	Onset After CV	Initial Presentation	Electrocardiogram	Angiogram	Treatment	Recovery/ Discharge (Days)
Eggleton, 2008, case report	Female, 76	HTN, CAD, HLP, nicotine dependence	Sotalol, perindopril, furosemide	Warfarin	AF	Normal/45%, apical	TEE-guided DCCV	10 hours	Acute respiratory distress, cardiogenic shock	Widespread TWI, QT prolongation	Yes, no obstructive CAD	Dopamine	6 days
Vizzardi, 2013, case report	Female, 81	HTN, HLP	Sotalol	Warfarin	Persistent AF	Normal/20%, apical	DCCV	24 hours	Acute chest pain and respiratory distress, cardiogenic shock	Widespread TWI	Yes, no obstructive CAD	Furosemide, antiplatelet and i.v. heparin, inotropic drugs	6 days
Siegfried, 2014, case report	Female, 67	HTN	Metoprolol succinate, spironolactone	Warfarin	Symptomatic AF	Normal/15%, apical	DCCV, 200	0 hours	Bradycardia, hypotension, cardiogenic shock	Widespread TWI, low-voltage, QT prolongation	No data	Intubation, dobutamine, norepinephrine, vasopressin	9 days
Muhammad, 2016, poster abstract	Male, 73	HTN, DM, CKD, giant cell arteritis	Sotalol, diltiazem	No data	AF	Normal (58%)/30%, apical	DCCV	24 hours	Acute respiratory distress, shock, PEA cardiac arrest	No data	No data	CPR, norepinephrine, intubation	7 days
McCutcheon, 2016, letter to the editor	Female, 87	HTN, HLP, CKD, asthma, MVP	No data	No data	AF and CHF	Normal (> 60%)/no data, apical	DCCV, 100	24 hours	Acute respiratory distress	New LBBB	Yes, no obstructive CAD	Intubation	14 days
Shah, 2018, Poster abstract	Female, 87	HTN, HLP, CHF	Furosemide	No data	AF	No data/apical	TEE-guided DCCV, 200	24 hours	Acute respiratory distress	New LBBB	Yes, no obstructive CAD	Diuresis	Sudden death during follow-up
Alishetti, 2018, Poster abstract	Female, 77	No data	Sotalol, beta-blocker	No data	AF	Normal/reduced, apical	DCCV, 150	1 hour	Bradycardia, cardiogenic shock	No data	No data	Atropine, dopamine, epinephrine	3 days
Pir, 2019, Poster abstract	Female, 81	HTN, CHF	No data	No data	AF	Normal/20%, apical—anteroinferior	TEE-guided DCCV, 150	48 hours	Acute respiratory distress	Widespread TWI	No data	Diuresis	No data
Zaghlol, 2019, case report	Male, 73	HTN, HLP	Olmesartan	No data	Symptomatic AF	Normal/25%, apical	DCCV, 120	5 hours	Sudden-onset retrosternal chest pain, respiratory distress	No ST-T change	Yes, no obstructive CAD	Furosemide, intubation	1 day
Kline, 2020, Poster abstract	Female, 83	DM	No data	No data	AF and CHF	Normal/20%, apical	TEE-guided DCCV	24 hours	Acute respiratory distress, acute heart failure	Widespread TWI, QT prolongation, NSVT	Yes, no obstructive CAD	No data	7 days
Mangion, 2020, case report	Female, 61	HTN	Sotalol, ramipril, bumetanide	Acenocoumarol	Atrial flutter 2:1	Normal/20%, apical	Electrical cardioversion, 70	24 hours	PEA cardiac arrest	Anterior lead TWI	Yes, no obstructive CAD	Intubation, CPR	20 days
Landi, 2021, case report	Female, 74	DM	Beta-blocker	Warfarin	AF and hypotension	No data/30%, apical	DCCV	2 hours	Acute respiratory distress	Widespread TWI, QT prolongation	Yes, no obstructive CAD	Lidocaine infusion	No data
Bae, 2022, case report	Male, 78	HTN, CAD, CKD, Gilbert syndrome	Sotalol, metoprolol tartrate, losartan, furosemide	Warfarin	AF during ablation	Normal/45%-50%, focal	DCCV	12 hours	Acute respiratory distress	No ST-T change	No data	Diuresis	6 days

AC, anticoagulation; AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CPR, cardiopulmonary resuscitation; CV, cardioversion; DCCV, direct current cardioversion; DM, diabetes mellitus; HLP, hyperlipidemia; HTN, hypertension; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MVP, mitral valve prolapse; PEA, pulseless electrical activity; TEE, transesophageal echocardiography; TWI, T wave inversion.

Interestingly, diabetic patients had a lower risk of ECV-associated TCM with an adjusted OR of 0.31. The prevalence of diabetes in patients with ECV-associated TCM was 10.5% compared to 21.1% in the International Multicenter GEIST (GErman Italian Spanish Takotsubo) registry. The mechanism of this protective effect is unclear. Autonomic dysfunction from DM may lead to a decreased response to catecholamine surge from the stress produced by ECV.[27]

All patients reported in the systematic review developed symptoms of TCM within 48 hours of ECV. This typical clinical feature of TCM occurs acutely after a trigger, either physical or emotional stress, as shown in the International Takotsubo Registry.[26] Majority of the patients presented with acute decompensated heart failure due to TCM and were treated supportively with diuretics, inotrope, and oxygen supplements. We found that widespread T wave inversion was a more common finding on 12-lead ECG than ST elevation, which is different from the International Takotsubo Registry, which reported a high prevalence of ST elevation of 43.7%. It is worth noting that TCM can be presented with normal ECG since 2 of 13 patients had normal ECG without ST-T changes. The majority of reported cardioversion-associated TCM were typical apical types. Patients with milder symptoms of heart failure recovered within 1 week, while patients who required mechanical respiratory support may have a longer hospital course lasting up to 2-3 weeks. The majority of patients' LVEF recovered after conservative treatment. However, 1 patient who did not have an LVEF recovery before discharge had sudden cardiac death during follow-up. Persistent decreased LVEF may portend a poor prognosis and may need close monitoring or intervention to prevent sudden death.

Study Limitations

We acknowledged several limitations in this study. First, the NRD used ICD-10 codes to identify the diagnosis and procedures. This can be heterogeneous as it heavily relies on the accuracy of the input data from the primary providers. Second, the NRD did not include several data points such as baseline medications, laboratory tests, imaging, significant emotional stress, and inhospital medication prescription. These missing data prevented investigators from exploring the association between TCM and these variables. Given these limitations, the authors labeled the findings as ECV-associated TCM rather than ECV-induced TCM to avoid misleading information. Third, the NRD did not include deaths outside of the hospital or data on elective outpatient procedures, which could lead to an underestimation of the incidence of ECV-associated TCM.

CONCLUSION

Cardioversion-associated TCM in AF patients who underwent ECV is a rare complication with an incidence of 2.7 events per 10,000 procedures. Female patients had a 50-fold increased risk of developing this condition, while DM is associated with a decreased risk by 3-fold. Acute heart failure is the most common presentation, with an onset within 24 hours after the ECV. Supportive treatment with medical management is the mainstay of therapy, with most patients recovering within 2 weeks.

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Supplementary Table 1. ICD-10 code used in the study	
Variables	**ICD-10 codes**
Atrial Fibrillation	I480, I4811, I4819, I4891, I482
Anemia	D50, D51, D52, D53, D55, D56, D57, D58, D59, D60, D61, D62, D63, D64, D460, D461, D462, D464, O990
Anxiety	F41
Alcohol-related disorders	F10
Chronic kidney disease ≥ stage 3	N183, N184, N185, E082, E132, I12, I13, N186, Z992, Z4931, Z4901
Coronary artery disease	I20, I21, I22, I23, I24, I25
Chronic obstructive pulmonary disease	J41, J42, J43, J44
Diabetes Mellitus	E08, E09, E10, E11, E13
Essential hypertension	I10, I11, I12, I13, I14, I15, I16
Heart failure, systolic	I501, I502, I504, I5082
Heart failure, diastolic	I503
Hyperlipidemia	E78
Major depressive disorder	F32, F33
Nicotine dependence	F17, Z87891
Obesity	E66, Z683, Z684
Obstructive sleep apnea	G4733
Peripheral vascular disease	E085, E095, E105, E115, E135, I73, T82856, Z9862, Z95820, I252, I2583
Takotsubo cardiomyopathy	I5181
Electrical cardioversion	5A2204Z

ICD-10 = International Classification of Diseases, Tenth Revision

Supplementary Table 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist 2020

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	n/a
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	n/a
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	n/a
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7
Study characteristics	17	Cite each included study and present its characteristics.	Page 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7 Supplementary table 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	n/a
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	n/a
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	n/a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	n/a
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	n/a
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9-10
	23b	Discuss any limitations of the evidence included in the review.	Page 9-10
	23c	Discuss any limitations of the review processes used.	Page 9-10
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9-10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	n/a
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	n/a
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	n/a
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	n/a
Competing interests	26	Declare any competing interests of review authors.	n/a
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	n/a

Supplementary Table 3. Assessment for risk of bias by The Joanna Briggs Institute critical appraisal checklist for case reports

Studies	year	1. Were patient's demographic characteristics clearly described?	2. Was the patient's history clearly described and presented as a timeline?	3. Was the current clinical condition of the patient on presentation clearly described?	4. Were diagnostic tests or assessment methods and the results clearly described?	5. Was the intervention(s) or treatment procedure(s) clearly described?	6. Was the post-intervention clinical condition clearly described?	7. Were adverse events (harms) or unanticipated events identified and described?	8. Does the case report provide takeaway lessons?
Eggleton	2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vizzardi	2013	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Siegfried	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Muhammad	2016	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear
McCutcheon	2016	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Shah	2018	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Alishetti	2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pir	2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zaghlol	2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kline	2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Landi	2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes