Review Article

Is low cardiac ejection fraction a risk factor for stroke?

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Abstract

Background and Purpose: Reduced ejection fraction (EF) ≤35% has been suggested as a criterion for anticoagulation in persons with heart failure in sinus rhythm, but the literature supporting EF as an independent stroke risk factor is conflicting. We here review the status of reduced EF as a stroke risk factor.

Methods: We performed a Medline search combining terms for stroke and heart failure (HF) or cardiac left ventricular systolic dysfunction and reviewed evidence that reduced EF increases the risk of stroke. We also reviewed clinical and epidemiological HF studies that included data on stroke and EF.

Results: Two of three longitudinal cohort studies found reduced EF (<50%) to be a stroke risk factor but did not find an inverse relationship between EF level and degree of stroke risk. Exploratory analyses of three clinical studies found an inverse relationship between EF level and degree of stroke risk but only in specific subgroups and vascular risk factors appeared to attenuate this relationship. Three analyses suggested an increased stroke risk with EF ≤20%.

Conclusion: Reduced EF (<50%) probably increases stroke risk but this is not consistently demonstrated in all populations studied. Reduced EF of any degree may be a surrogate for atherosclerotic cerebrovascular disease and in these patients traditional vascular risk factors may be more important for stroke risk than EF. There is no evidence to support EF ≤35% as a specific stroke risk factor. Research is needed to determine if very reduced EF (≤20%) is a specific stroke risk factor.

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Introduction

Ejection fraction (EF) is the percentage of cardiac left ventricular volume emptied in systole and is a reliable measure of left ventricular systolic dysfunction (LVSD). The prevalence of asymptomatic LVSD in the general population is about 3% to 6%[1-3] and about 37% of patients with heart failure (HF) in the United States have a reduced EF.[4] Reduced EF is one of the principal indications for anticoagulation in dilated cardiomyopathy,[5] and in 2006 the Heart Failure Society of America recommended that warfarin anticoagulation merits consideration in all patients with dilated cardiomyopathy and EF≤35%.[6] The most recent American College of Cardiology Foundation/American Heart Association Guidelines for the Management of Heart Failure[7] however do not recommend anticoagulation in patients with chronic HF without atrial fibrillation and specifically do not mention a level of EF as an indication for anticoagulation. The data supporting a connection between reduced EF and an increased risk of stroke is therefore conflicting,[8] and EF might not be the best criterion for selection of patients with LVSD for anticoagulation. Here we review the data supporting reduced EF as a risk factor for stroke.

Methods

We performed a Medline database search to identify potential studies. For cardiac dysfunction (left ventricular dysfunction) we used the exploded terms ‘‘heart failure’’ ‘‘ventricular dysfunction, left,’’ and ‘‘cardiac output, low’’ combined with the ‘‘or’’ operator. The stroke terms used were ‘‘brain infarction,’’ ‘‘brain ischaemia,’’ ‘‘stroke,’’ and ‘‘intracranial embolism’’ combined with the ‘‘or’’ operator. Cardiac dysfunction terms were combined with the stroke terms using the “and” operator. The search was conducted during the week of July 22, 2013. Articles were included regardless of year of publication. Additional articles were identified by hand-searching the reference lists of included articles identified by electronic search. Initial inclusion criteria were that the study contained a population with both EF data and reported the number (or percent) of persons with HF who experienced an ischemic stroke during follow-up, irrespective of heart

rhythm. Studies were excluded if the article did not separate ischemic strokes from hemorrhagic strokes, if >50% of the study population required artificial support with a ventricular assist device, or parenteral inotropic medications. Case reports, case series, reviews and non-original research articles were not included.

Optimal study requirements to identify reduced EF as a stroke risk factor were: a) Stroke must be a pre-specified endpoint and EF measured in all participants, b) It should only include patients in sinus rhythm or include a multivariable analysis including atrial fibrillation as an independent variable. Desirable criteria include a) a multivariable analysis that includes prior stroke (or use only first ever stroke), and HF as independent variables, b) it should be a cohort study rather than an exploratory analysis of a clinical study, c) it should also look for increasing risk with decreasing levels of EF, d) it should include both ischemic and non-ischemic cardiomyopathy (which should be analysed separately). Studies were reviewed against these criteria. We reviewed in detail those studies where the stroke or thromboembolism rate and EF were documented that were performed in patients in sinus rhythm or in whom a multivariable analysis including atrial fibrillation had been performed.

Results

The Medline search revealed 938 papers. Thirty-five of these met initial study inclusion criteria. Hand searching of the references listed in these included articles and of the American College of Cardiology and American Heart Association meeting proceedings yielded an additional 20 papers that met initial inclusion criteria.

We reviewed the remaining 55 papers in detail and selected those giving information relating EF to risk of stroke and thromboembolism. From these only 15[9-23]met one or more desirable criteria.(Table 1) No studies fulfilled the optimal or all of the desirable criteria.

Studies were mainly either cohort studies, exploratory analyses of clinical studies or primarily echocardiographic studies. It was difficult to compare results between studies as there was no standard way of giving EF results: Most frequently results were expressed as the Relative Risk or Odds Ratio [10,13] of stroke or thromboembolism between normal and reduced EF (usually <50%) or EF strata. Frequency of patients with reduced EF with and without stroke were given in other papers,[16] but others gave mean EF in the stroke and control groups[23] or an odds ratio of an abnormal EF comparing stroke and control groups[19]. Individual EF results were only occasionally provided.

We found only two cohort studies which fit desirable criteria[9,11]and one case control analysis of a subset from a cohort study.[10] There were seven exploratory analyses of clinical studies that met desirable criteria.[12-16,18,21] Two of three cohort studies found reduced EF (<50%) to be a risk factor for stroke but did not find an inverse relationship between EF level and degree of stroke risk.[9,10] The three exploratory analyses found an inverse relationship between EF level and degree of stroke risk but only in specific subgroups and vascular risk factors appeared to attenuate this relationship. Three exploratory analyses suggested an increased stroke risk with EF ≤20%.[13-15] Of eight other studies showing data on EF and stroke, two found an association between EF and stroke[16,23]and six[17-22]did not. These papers varied in sample size and methodology and all were exploratory analyses.

Discussion

The largest cohort study to date that looks at the relationship of LVSD and stroke is the *Cardiovascular Health Study*.[9] This study used Cox proportional hazard regression after adjustment for covariates to examine time to stroke in a community study of 5888 persons 65 years or older. All patients had EF estimation by two-dimensional echocardiography at baseline. They divided persons into three categories of left ventricular function (normal [EF ≥55%], borderline [45%-54%] and impaired [<45%] without HF and the same three categories of left ventricular function with HF. They found that the hazard ratio of stroke was 2.41 (95%CI:1.3,4.5) (event rate 5.07 per 100 patient years) in persons with HF and borderline left ventricular systolic function and 1.91 (1.3,2.7) (event rate 4.52 per 100 patient years) in persons with HF and impaired left ventricular systolic function but hazard ratio for stroke was not significantly increased or of marginal significance in the other groups. Two negative aspects of this study are that it did not include prior stroke in the multivariable analysis and did not separate out persons with nonischaemic cardiomyopathy. Although the study found EF to be a risk factor for stroke in HF, the fact that there was no increasing hazard with decreasing EF would appear to go against the theory that stasis in a dilating ventricle increases thromboembolic risk. It suggests that decreased EF at any level is a non-specific risk factor for stroke. Reduced EF at any level might therefore be a surrogate for the presence of atherosclerotic cerebrovascular disease. The cut off for LVSD in this study was however very high at 45% and does not preclude a pro-thromboembolic effect at lower EF

levels.

The *Northern Manhattan study* population was used for a case-control study in a subpopulation comparing 270 first stroke patients with 288 controls.[10] This study compared the frequency and severity of LVSD (mild: EF 41-50%, moderate: EF31-40% and severe: ≤30%) in a multivariable analysis and found that the odds ratio of LVSD of any degree was 3.92 (95%CI 1.93,7.97) in patients with stroke compared to controls.(Table 2) As in the *Cardiovascular Health Study*, there was no relationship between degree of EF reduction and stroke risk. All stroke risk factors including clinical HF were adjusted for, although the frequency of HF in the groups was not stated. These results reinforce the possibility that reduced EF at any level may be a non-specific surrogate of cerebro-vascular disease. One interesting finding however was that in the subset (20%) of strokes that were cardioembolic, LVSD was more strongly related to stroke risk than in the other stroke subtypes. This suggests that decreased EF may impart a small pro-thromboembolic risk that is not apparent when all stroke subtypes are pooled.

A further cohort study that included an analysis of EF was the *Olmsted County study* of ischemic stroke after HF.[11] 630 persons with incident HF were studied over a median of 4.3 years for the frequency of incident stroke. Baseline data comparing persons with (*n*=102) and without (*n*=528) subsequent stroke showed no significant difference in the frequency of EF<50% between the groups. In a very high stroke risk subgroup (19.8 per 100 patient years) within the first 30 days after HF diagnosis, the mean EF was >40%. A multivariable analysis of significant predictors of stroke >30 days after HF also showed that EF was not a significant risk factor for stroke. The drawbacks of this study are that EF was only available in about 50% of persons and there was no classification into ischemic and nonischaemic cardiomyopathy. Severity of HF by NYHA class was not given. This result does not support the *Cardiovascular Health Study* analysis linking EF to stroke risk in patients with HF. The finding that even in a very high stroke risk subgroup, the mean EF was only marginally decreased suggests that other risk factors for stroke are likely more important than reduced EF in stroke occurring in acute HF.

The Survival and Ventricular Enlargement (SAVE)[12] was the first exploratory analysis of a clinical trial of patients with LVSD to be published. SAVE was a study of 2,231 patients with EF ≤40% but without HF, enrolled a mean of 11 days after myocardial infarction. The patients were followed up for a mean of 42 months and had a low annual incidence of stroke of 1.5%. Patients with EF ≤28% had a relative risk of stroke of 1.86 compared with patients with EF of >35% (*p*=0.01). Age and decreased EF were significant risk factors for stroke in a multivariable analysis. Atrial fibrillation was not a risk factor for stroke but up to 31% of patients were on anticoagulation and this significantly reduced stroke risk. Neither hypertension nor diabetes was a risk factor for stroke. The SAVE study found that EF (especially EF ≤28%) was the most important independent predictor of stroke in patients after MI.(Figure 1) In addition, the risk of stroke increased by 1.18 times for every absolute decrease of 5% in the EF. Men made up 83% of the study sample. A concern about this study is that prior stroke was not included in the multivariable analysis and since prior stroke is a known strong risk factor for stroke,[11] its exclusion might have allowed LVSD to become a significant risk factor. This criticism could also be levelled at the *Cardiovascular Health Study* results for stroke discussed above and at the *Sudden Cardiac Death in Heart Failure* (SCD-Heft) trial outlined below.

The Studies of Left Ventricular Dysfunction (SOLVD) thromboembolism analysis[13] included 6,378 patients with EF≤35% in sinus rhythm, half of whom had symptomatic HF. All thromboembolic events: strokes, pulmonary and peripheral emboli were included together in the main analysis. Separate analyses were performed for men and women since a significant interaction between EF and gender was found (*p*=0.04). In an average follow up time of 40 months there were 1.82 events per 100 participant years of follow up in men and 2.42 events per 100 participant years in women. The SOLVD trial found that EF was independently related to thromboembolic risk, in women but not in men (fig 3). Multivariable analysis of the relative risk for a thromboembolic event per 10% decrease in EF was 1.53 (95%CI:1.06,2.20) in women and 1.08 (95%CI:0.89,2.20) in men. In SOLVD, multivariable risk factors for thromboembolism were dominated by prior stroke, diabetes and age in men, and EF did not reach significance. In women diabetes was the strongest, and only vascular, risk factor and EF was also a risk factor for thromboembolism. Sex differences in pathogenesis of thromboembolism are also suggested by the finding that in women but not in men, the relative risk of thromboembolic events was 2.17 [95%CI:1.10-4.30] times the risk with EF 11-20% than with EF ≥30%. Since a high percentage of endpoints were pulmonary emboli, a repeat multivariable analysis was performed excluding these cases to look at risk factors for stroke alone.

***Table 1**: Details of 15 studies examined. EF ejection fraction; HF: heart failure; HR: hazard ratio, RR: Relative risk; OR: Odds ratio; MVA: multivariable analysis.*

Reference	% with HF (NYHA class)	Stroke rate (no of strokes/total no of patients)	EF cut-offs	How EF compared	Atrial Fibrillation % excluded/ MVA	EF Risk of stroke? And level	Prior stroke included in MVA
9 Gottdiener *CHS*	4.9%	12.5-50.7 per 1000 pt. yrs. 5532 total patients	Borderline <55%, impaired 45%	HR for stroke in normal vs low EF groups	2%	HR:Borderline: +HF:2.41; Impaired: -HF: 1.27; +HF: 1.91	No
10 Hays *NOMASS*	Not stated	277 strokes 288 controls	mild 41-50%; mod 31-40%; severe ≤30	OR for mild, mod or severe ↓EF in strokes vs controls	10% of strokes	OR: mild: 4.0; mod/severe 3.9; All ↓EF: 3.9	Not relevant
11 Witt *Olmsted County Study*	100%	102/630	<50% (EF missing in 50% of strokes)	RR of stroke with↓EF	47% of strokes (adjusted for in MVA)	P 0.014 (but EF lower in non-stroke)	Yes
12 Loh *SAVE*	0% "overt HF"	103/2231	All pts : <40%: 3 gps:<28% ; 29-35%; >35%	RR of stroke in MVA	16% of strokes (adjusted in MVA)	RR: 1.18: 18% increase in stroke for 5% ↓EF	No
13 Dries *SOLVD*	38%	226/6378	All pts: ≤35%: 4 gps:≥30%; 21-30%; 11-20%; ≤10%	RR of thrombo-embolic events	excluded	RR: 1.53 per 10% ↓EF	Yes
14 Freuden-berger *SCD-Heft*	(All pts NYHA II or III)	56/2114	All pts: ≤35%:	HR for thrombo-embolic events	excluded	HR 0.82 per 5% ↑EF	Yes
15 Falk *PROMISE*	(All pts NYHA III or IV)	22/1088	All pts: ≤35%: 1 subgp	% with stroke EF≤20% vs EF>20%	Not stated	Warfarin reduced stroke in EF≤20%: p<0.05	No MVA
16 Fox *ARIC*	0.04%	98/1792	50%	% with low EF: stroke vs no-stroke	Not stated	P<0.0001	No MVA
17 Siachos	100% (NYHA III or IV)	34/168	20%	EF in stroke vs no-stroke	Excluded	P=0.82	excluded
18 Mujib *DIG*	100%	222/7788	<35%	OR for stroke in ↓EF	excluded	P=0.85	No

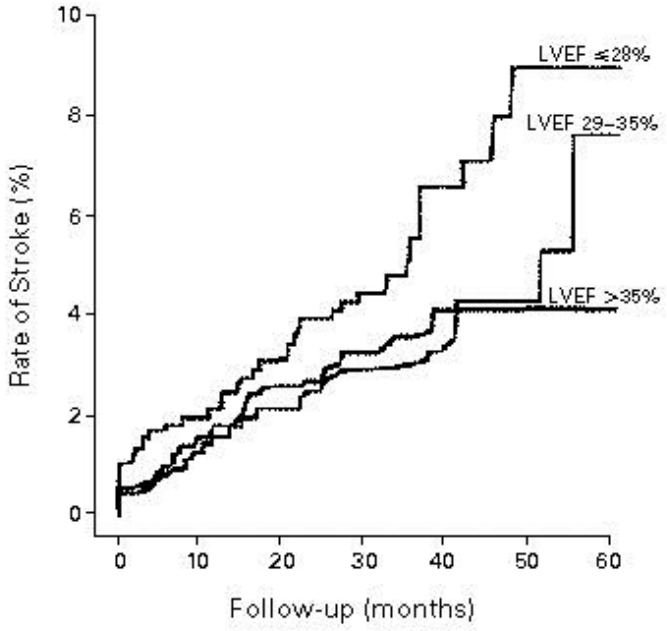
***Table 1**: Details of 15 studies examined. EF ejection fraction; HF: heart failure; HR: hazard ratio, RR: Relative risk; OR: Odds ratio; MVA: multivariable analysis (cont.).*

Reference	% with HF (NYHA class)	Stroke rate (no of strokes/total no of patients)	EF cut-offs	How EF compared	Atrial Fibrillation % excluded/ MVA	EF Risk of stroke? And level	Prior stroke included in MVA
19 Mahajan	Not stated	73 strokes 73 controls	All pts: ≤35%:	EF in stroke gp vs EF in controls	excluded	P0.38	No MVA
20 Komori	100% (70% NYHA III or IV)	10/111	43%-45%	EF in stroke gp vs EF in no-stroke	10% of strokes	P 0.7	No
21 Szummer *VALIANT*	26%	81/5573	43%-49%	EF in stroke gp vs EF in no-stroke	16% of strokes	0.081	Yes
22 Deleu	Not stated	72 strokes 79 controls	37%-50%	EF in stroke gp vs EF in no-stroke	Not stated	Not significant	No
23 Kozdag	Mean NYHA class III	18 strokes 28 no stroke	29%-34%	EF in stroke gp vs EF in no-stroke	Not stated	P 0.03. Not significant in MVA	No

***Table 2**: LV function in stroke patients and control subjects in the Northern Manhattan Study[10]. Normal LVEF >50%, mild LV dysfunction 41-50%, moderate 31-40% and severe <30%. ±Adjusted for age, gender, AF, diabetes mellitus, hypertension, hypercholesterolemia, current smoking, CAD, HF and LV mass index.*

	Stroke patients, n (%)	Control subjects, n (%)	Unadjusted Odds Ratio (CI)	±Adjusted Odds Ratio (CI)
Normal LV function	205 (75.9)	274 (95.1)		
LV dysfunction Any degree	65 (24.1)	14 (4.9)	6.21 (3.39-11.37)	3.92 (1.93-7.97)
Mild LV dysfunction	29 (10.7)	7 (2.4)	5.54 (2.38-12.89)	3.96 (1.56-10.0)
Moderate/Severe LV dysfunction	36 (13.3)	7 (2.4)	6.87 (3.00-15.75)	3.88 (1.45-10.39)

***Figure 1**: Cumulative rate of stroke in the SAVE trial according to left ventricular EF* [12]



In these results, in women, EF was no longer a significant risk factor, and prior stroke and smoking became significant. This suggests that the pathogenesis of thromboembolism is different from that of stroke, and that EF is less important as a risk factor for stroke than for thromboembolism. The reason for this is likely that the risk of a clinical ischemic event in the brain is increased by pre-existing vascular disease risk factors, which may not be the case for other locations of embolism. SOLVD also appears to show that the pathogenesis of thromboembolism is more likely to be related to reduced EF in women than in men, possibly because in men multiple strong vascular risk factors override any effect of reduced EF and make it undetectable.

A third trial analysis that showed an inverse relationship between thromboembolism risk and EF was that of the *SCD-Heft Trial*.[14] 2114 patients in sinus rhythm enrolled in this implanted cardiac defibrillator study were followed over a median 45.5 months for stroke and peripheral or pulmonary embolism. Hypertension (Hazard Ratio [HR] 1.86 [95%CI:1.10,3.13]) and EF (HR 0.82[0.69,0.97] for every 5% decrease) were the only risk factors for thromboembolism. Two concerns about these results however are that the multivariable analysis did not include prior stroke, even though up to 7% of patients had prior stroke.

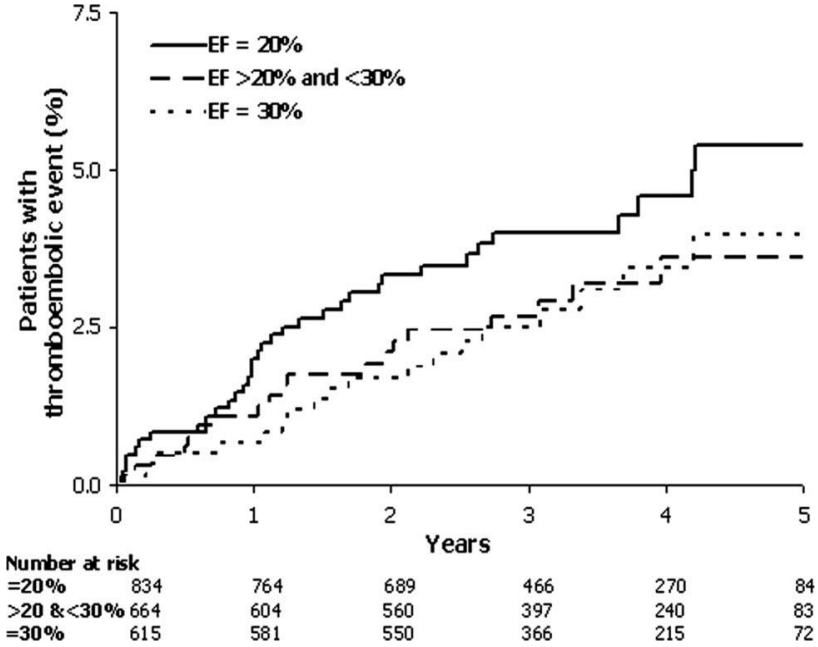
Secondly, stroke was not analysed separately from other thromboembolic events and when transient ischemic attack was included as an endpoint, EF was no longer a significant predictor of thromboembolism. The authors commented that ischemic stroke in LVSD may be related to severity of cerebral arterial disease rather than thromboembolism alone, echoing what several of the studies above appear to show.

The fact that these three trials have shown an inverse relationship between EF and thromboembolism/stroke risk does support a specific effect of severe LVSD on thromboembolism risk, independent of reduced EF of any level being a surrogate marker of cerebrovascular disease. The three trials that showed this relationship, all studied EF below 28%,[12-14] whereas those failing to show this relationship[9-11]had cutoffs for LVSD that were higher. SOLVD data show that the rate of thromboembolism increases significantly with an EF of 11-20% in women[13] (Table 3) and the SCD-Heft data also shows an increase in stroke with an EF of 20%.[14] (Figure 2) This is similar to an earlier finding that in severe HF in patients with an EF of 20% the stroke rate was increased and was reduced with warfarin.[15] These three analyses suggest that the left ventricle may only become a significant source of thromboembolism with very low EFs around 20%, and this may be one factor why the other studies above failed to show an inverse relationship between thromboembolism and stroke.

***Table 3**: Incidence and relative risk of thromboembolism according to gender and EF quartile from the SOLVD trial. CI = confidence interval. Adapted from Dries et al. (1997).*[13]

LVEF	Incidence	Relative Risk (95% CI)
Men, n=5457		
≤30%	1.70	1.00
21-30%	1.83	1.08 (0.83-1.41)
11-20%	2.01	1.21 (0.86-1.70)
≤10%	1.96	1.21 (0.30-4.92)
Women, n=921		
≤30%	1.78	1.00
21-30%	2.41	1.35 (0.74-2.47)
11-20%	3.80	2.17 (1.10-4.30)
≤10%	4.20	2.43 (0.32-18.26)

***Figure 4**: Proportion of patients with thromboembolic events in three strata of baseline Efs. SCD -Heft Study.*[14]



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