Brief Report

Exercise-based cardiac rehabilitation associates with lower major adverse cardiovascular events in people following a stroke

Running title: Buckley et al. Cardiac rehabilitation for stroke survivors

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Abstract

Background

The risk of major adverse cardiovascular events is substantially increased following a stroke. Although exercise-based cardiac rehabilitation has been shown to improve prognosis following cardiac events, it is not part of routine care for people following a stroke. We therefore investigated the association between cardiac rehabilitation and major adverse cardiovascular events for people following a stroke.

Methods

This retrospective analysis was conducted on June 20, 2021 using anonymised data within TriNetX, a global federated health research network with access to electronic medical records from participating healthcare organizations, predominantly in the United States. All patients were aged ≥18 years with cerebrovascular disease and at least 2-years of follow up. People with stroke and an electronic medical record of exercise-based cardiac rehabilitation were 1:1 propensity score-matched to people with stroke but without cardiac rehabilitation using patient characteristics, comorbidities, cardiovascular procedures, and cardiovascular medications.

Results

Of 836,923 people with stroke and 2-year follow-up, 2,909 met the inclusion for the exercise-based cardiac rehabilitation cohort. Following propensity score matching (*n*=5,818), exercise-based cardiac rehabilitation associated with 53% lower odds of all-cause mortality (odds ratio 0.47, 95% confidence interval: 0.40-0.56), 12% lower odds of recurrent stroke (0.88, 0.79-0.98), and 36% lower odds of rehospitalisation (0.64, 0.58-0.71), compared to controls. No significant association between cardiac rehabilitation and incident atrial fibrillation was observed.

Conclusion

Exercise-based cardiac rehabilitation prescribed for people following a stroke associated with significantly lower odds of major adverse cardiovascular events at 2-years, compared to usual care.

Key words

Exercise; Cardiac Rehabilitation; Secondary Prevention; Stroke; MACE; Preventive Cardiology

Introduction

Physical inactivity is a primary concern among the >7 million people living with cerebrovascular disease in the United States and >9 million stroke survivors in the European union, who have significantly increased risk of major adverse cardiovascular events.[1, 2] Exercise-based cardiac rehabilitation promotes secondary prevention of cardiovascular disease and has been associated with reduced long-term major adverse cardiovascular events in patients with various cardiac diseases.[3, 4] Cardiac rehabilitation is therefore an essential component of routine care for patients with acute coronary syndrome, heart failure, and those undergoing revascularisation.[5] However, despite similar cardiovascular risk factors, people following a stroke are not typically referred for exercise-based cardiac rehabilitation and the impact of such interventions on long-term clinical outcomes has not been previously investigated.

Remarkably, previous work suggests exercise interventions are superior to drug treatment in lowering mortality risk for people who survive a cerebrovascular event.[6] Therefore, outpatient exercise interventions may be beneficial for such populations. The aim of the present study was to investigate the association between exercise-based cardiac rehabilitation and long-term major adverse cardiovascular events in patients following a stroke.

Methods

This retrospective observational study utilised anonymised data within TriNetX, a global federated health research network with access to electronic medical records from participating academic medical centres, specialty physician practices, and community hospitals, predominantly in the United States. The TriNetX network was searched on June 20, 2021 and de-identified datasets were analysed that included data from 2002-2019 with at least 2-years of follow-up (i.e. index event was at least two years ago). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (eTable 1).

Patients with incident stroke or transient ischaemic attack (TIA) were identified from International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes I63 (Cerebral infarction) and G45 (TIA). All patients were aged ≥18 years with an incident cerebrovascular event recorded in EMRs at least 2-years ago (allowing for two-year follow up).

Exercise-based cardiac rehabilitation was identified (within 6-months of incident stroke) from ICD-10-CM code Z71.82 (Exercise counselling), Healthcare Common Procedure Coding System (HCPCS) codes S9451 (Exercise classes, non-physician provider) and S9472 (cardiac rehabilitation program, non-physician provider), or Current Procedural Terminology (CPT) codes 93797/93798/1013171 (Outpatient cardiac rehabilitation, with/without ECG). Correspondingly, these cardiac rehabilitation-related codes were excluded in the propensity matched controls. At the time of the search, 51 participating healthcare organisations had data available for patients who met the study inclusion criteria.

Baseline characteristics were compared using chi-squared tests or independent-sample t-tests. Given cardiac rehabilitation provision is typically reserved for cardiovascular patients following an acute coronary syndrome, revascularisation, and heart failure, referral of patients in this database was likely due to cardiovascular comorbidities. Thus, propensity score matching was used to control for these potential confounders. Patients following a stroke/TIA and an electronic medical record of exercise-based cardiac rehabilitation were 1:1 propensity score-matched[7] to patients following a stroke but without cardiac rehabilitation based on age, sex, ethnicity, hypertensive diseases, ischaemic heart diseases, heart failure, diabetes mellitus, chronic kidney disease, cardiovascular procedures (including electrocardiography, echocardiography, catheterization, cardiac devices, and electrophysiological procedures), and cardiovascular medications (including beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and ACE inhibitors). These variables were chosen because they are established risk factors for cardiovascular disease and mortality or represent differences in quality of care.

Using logistic regression [LogisticRegression of the scikit-learn package in Python (version 3.7)], TriNetX performs a 1:1 greedy nearest neighbour matching model,[7] with a caliper of 0.1 pooled standard deviations. In order to eliminate bias resulting from nearest neighbour algorithms, the orders of rows are randomized. Any baseline characteristic with a standardised mean difference between cohorts lower than 0.1 is deemed well matched.[8]

To prevent inadvertent disclosure of protected health information, patient counts for demographics, clinical characteristics, and outcomes of less than 10 are reported as ≤10. Following propensity score matching, logistic regression produced odds ratios (OR) with 95% confidence intervals (CIs) for 2-year incidence of major adverse cardiovascular events (defined in this study as all-cause mortality, recurrent stroke, rehospitalisation, and incident atrial fibrillation), comparing exercise-based cardiac rehabilitation with propensity matched non-cardiac rehabilitation controls. Statistical significance was set at $P<0.05$.

Results

In total, 836,923 patients with new-onset stroke/TIA were identified from 51 US healthcare organisations with at least 2-years of follow-up. Of which, 2,909 (0.3%) met the inclusion criteria for the exercise-based cardiac rehabilitation cohort. Following propensity score matching, there were 2,909 patients in each cohort (*n*=5,818 in total), which were well-matched for age, ethnicity, sex, included comorbidities, cardiovascular procedures, and cardiovascular medications (Table 1).

Using the propensity score-matched cohorts, 2-year mortality was proportionally lower with 8.5% (*n*=247 of 2,903 patients) in the exercise-based cardiac rehabilitation cohort compared to 16.5% (n=473 of 2,873 patients) in the controls (OR 0.47, 95% CI 0.40-0.56). Two-year recurrent stroke was proportionally lower with 39.2% (n=1,141 of 2,909 patients) in the exercise-based cardiac rehabilitation cohort compared to 42.3% (n=1,231 of 2,909 patients) in the controls (OR 0.88, 95% CI 0.79-0.98). Rehospitalisation at 2-years was proportionally lower with 40.7% (n=1,185 of 2,909 patients) in the exercise-based cardiac rehabilitation cohort compared to 51.8% (n=1,507 of 2,909 patients) in the controls (OR 0.64, 95% CI 0.58-0.71). No significant association was observed between cardiac rehabilitation and incident atrial fibrillation (10.7% (n=190 of 1,775 patients) in the exercise-based cardiac rehabilitation cohort compared to 10.6% (n=208 of 1,955 patients) in the controls (OR 1.01, 95% CI 0.82-1.20).

Discussion

Collectively, this real-world data analysis suggests exercise-based cardiac rehabilitation for people following a stroke associates with significantly lower odds of major adverse cardiovascular events at 2-years, compared to matched controls. Specifically, in 5,818 people following a stroke, exercise-based cardiac rehabilitation (n=2,909) associated with 53% lower odds of all-cause mortality, 12% lower odds of recurrent stroke, and 36% lower odds of rehospitalisation, compared to matched controls without cardiac rehabilitation (Figure 1).

Exercise-based cardiac rehabilitation is recommended (with the highest level of scientific evidence - class I) by the European Society of Cardiology[5] and the American College of Cardiology[9] for patients with acute coronary syndrome, heart failure, and those undergoing revascularisation. These international recommendations are supported by evidence of improved prognosis. However, exercise-based cardiac rehabilitation is not part of routine care for patients following a stroke.

As cerebrovascular disease and cardiac disease share similar risk factors and comorbidities, it seems logical that exercise-based cardiac rehabilitation, proven to work for the heart, should also work for the brain. Especially, since only 18% of stroke survivors meet the weekly physical activity guidelines.[10] Indeed, a network meta-analysis demonstrated that when compared with controls, exercise interventions were associated with lower odds of mortality for stroke survivors compared to drug therapies.[6] One important caveat, however, is that only three trials with 227 patients represented exercise interventions, whereas 24 trials with 65,827 patients represented pharmacology. Highlighting the timely need for more research into non-pharmacological interventions for people following a stroke.

A more recent systematic review and meta-analysis (n=19 studies) investigated the impact of exercise interventions *similar* in design to exercise-based cardiac rehabilitation for people following a stroke and demonstrated significant improvements in aerobic capacity.[11] However, no previous trials have examined long-term clinical outcomes of cardiac rehabilitation for patients with cerebrovascular disease. Although an electronic medical record of cardiac rehabilitation does not provide information as to the intervention type, dose, or adherence, prior work has demonstrated that patients following a stroke are able to meet or even exceed minimal recommendations for exercise intensity and duration during a typical exercise session (consisting of 60 minutes of aerobic and resistance training) after completing cardiac rehabilitation.[12] Further, integrating survivors of stroke into exercise-based cardiac rehabilitation may improve endurance and functional strength.[13] This is promising, given physical activity, which has not received adequate attention in secondary stroke prevention trials, was the strongest predictor of a good outcome in a secondary analysis[14] of the SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) study.[15] These preliminary data contribute to the evidence promoting the efficacy and feasibility of cardiac rehabilitation for people following stroke.

Given, the American Heart Association have called for exercise prescription to be incorporated into routine management of stroke survivors,[16] the promising findings of the present study warrant subsequent controlled trials to investigate the impact of exercise-based cardiac rehabilitation for patients with cerebrovascular disease.

Limitations

It is of note that cardiac rehabilitation is not provided as part of usual care for patients following a stroke, but for other cardiovascular conditions, such as acute cardiac syndrome, revascularisation procedures, and heart failure, which were therefore included in the propensity score matching. The data were collected from health care organization electronic medical record databases without information regarding stroke severity or stroke type, which may have impacted the findings. Although only one follow-up time point is presented (2-years; to balance long-term follow-up and sample size), there was no meaningful difference in findings when looking at 1-year or 5-year follow-up time points (i.e., the direction of effect estimates did not change). Furthermore, 52% of the sample were female, and when analysing the data stratified for sex, there was no difference in impact i.e., cardiac rehabilitation associated with lower mortality, recurrent stroke, and rehospitalisation for both males and females. We included an electronic medical record of 'Exercise counselling' as an inclusion in the exercise-based cardiac rehabilitation cohort. However, as exercise counselling does not necessarily correspond to an exercise intervention, inclusion may have contributed to more conservative effect estimates of cardiac rehabilitation within our study. It is not clear if a beneficial effect of cardiac rehabilitation is mediated via cardiac or cerebral improvements (or both), and this warrants future mechanistic investigation. Other residual confounding may have impacted our results, including pre-stroke physical activity levels, lifestyle factors and socioeconomic status. Finally, further mechanistic work is needed that investigates the individual exercise responses in subtypes of cerebrovascular disease and potential mediators of benefit.

Conclusions

In 5,818 people following a stroke, exercise-based cardiac rehabilitation was associated with lower odds of 2-year major adverse cardiovascular events, compared to matched controls. These findings are encouraging for exercise as medicine for people following a stroke and highlight the need for subsequent trials, considering stroke severity and subtype.

Acknowledgement

Not applicable.

Statement of ethics

The paper is exempt from ethical committee approval. This retrospective review of real-world patient data did not require ethical approval in accordance with national guidelines. Written informed consent from participants was not required in accordance with national guidelines. As a federated network, research studies using the TriNetX network do not require ethical approval or patient informed consent as no patient identifiable information is received.

Conflicts of Interest

BJRB has received research funding from Bristol-Myers Squibb (BMS)/Pfizer. SLH has received research funding from BMS. EF-E and PU are employees of TriNetX LLC. DAL has received investigator-initiated educational grants from BMS, has been a speaker for Boehringer Ingeheim, and BMS/Pfizer and has consulted for BMS, Boehringer Ingelheim, and Daiichi-Sankyo. GYHL is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. In addition, GYHL is an Associate Editor of *Cerebrovascular Diseases*.

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Author Contributions

BJRB conceived, analysed the data, and drafted the manuscript. SLH, EF-E,PU, DAL, DHJT, GYHL all revised and approved the final manuscript.

Data Availability Statement

To gain access to the data in the TriNetX research network, a request can be made to TriNetX (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained.

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Figure Legends

Figure 1. Two-year incidence of major adverse cardiovascular events from new-onset cerebrovascular disease; comparing patients who received exercise-based cardiac rehabilitation (*n*=2,909) to propensity matched patients who received usual care only (*n*=2,909).