# ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

# Revivent TC Transcatheter Ventricular Enhancement System for Ischemic Heart Failure

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## Summary of Key Points

- Ischemia represents one of the main aetiologies of heart failure (HF) and can arise from myocardial infarction which may lead to myocardial scarring, left ventricular (LV) dilatation and dysfunction and progressive deterioration of cardiac function.
- Currently, for patients with ischemic HF who are refractory to pharmacotherapies, the main alternatives are cardiac implantable electronic devices to prevent sudden cardiac death and surgical ventricular reconstruction (SVR) to exclude the nonviable LV. SVR is not always preferred due to its highly invasive nature.
- The Revivent TC (BioVentrix, Inc.) consists of titanium anchor pairs implanted via the Less Invasive Ventricular Enhancement (LIVE) hybrid transcatheter procedure to exclude the scarred myocardium on the LV, allowing the viable portion of the LV to operate more efficiently. Compared to SVR, it offers a less invasive procedure to reshape the LV for patients with high surgical risks or comorbidities who are refractory to pharmacotherapies.
- Early evidence reported a high rate of major and minor adverse events up to 22% and 14% respectively, which may be partly due to procedural inexperience in early trials.
- Short-term outcomes supported the ability of Revivent TC to exclude the scarred LV, improve cardiac function, HF symptoms, exercise capacity and patient's quality-of-life up to 12 months.
    - Increased LV ejection fraction (LVEF; mean difference range, 5% to 12.2%)
    - Reduced LV end-systolic volume index below 60 mL/m$^2$
    - Increased 6-minute walk test distance (mean difference range, 53 to 92.7m)
    - Reduced Minnesota Living with Heart Failure Questionnaire score (mean difference, 13 points)
    - Reduced New York Heart Association (NYHA) functional class
- However, the long-term durability of these results remains uncertain.
- The early results have to be interpreted with caution due to the lack of controlled studies, limited long-term outcomes, small patient size and lack of procedural experience which may be addressed by ongoing trials.
- No studies reported on cost-effectiveness but the reduced re-hospitalisation rate with Revivent TC (13% with Revivent TC *vs.* ≥50% with optimal medical therapy at 6-month) may potentially bring cost savings to the healthcare system.
- Implementation considerations include the need for a well-trained multi-disciplinary heart team and proper selection of patients with appropriate anatomical features which may increase the demand for imaging services.
- At present, three other related LV restoration devices are in development.

## I. Background

Heart failure (HF) is a complex clinical syndrome that result in insufficient cardiac output and the inability of the heart to meet the demands of the body and can manifest from functional or structural impairment.[1] Ischemia represents one of the many aetiologies of HF, accounting for 65% of patients with HF.[2] It could arise from myocardial infarction (MI) which may not be reversed in 30% of patients despite successful revascularisation.[3] This can lead to myocardial scarring with a consequent left ventricular (LV) remodelling and ischemic cardiomyopathy,

which is characterised by LV dilatation, increasing ventricular wall stresses, LV end-systolic and diastolic volumes, sphericity and progressive deterioration of cardiac function.[3,4] In addition, the scar formation may also correlate with aneurysm formation that can further impair contractile function and lead to life threatening complications such as ventricular arrhythmia, ventricular rupture and systemic embolism.[1,5] Symptoms of HF are exacerbated with exertion and can arise from fluid accumulation (e.g., dyspnea, edema and orthopnea) or decreased cardiac output (e.g., fatigue and anorexia). Patients with advanced HF may experience tachycardia and peripheral vasoconstriction.[1]

Ischemic heart disease accounts for 18.8% of all deaths and is the third leading cause of death in Singapore in 2019.[6] It was reported that the odds of HF increased by 26% and 48% per decade in men and women respectively following MI.[2] In the SOLVD-T trial, MI patients had a two-fold higher rate of hospitalisation for chronic HF and a four-fold higher mortality rate compared to patients without MI.[2]

While it has long been recognised that scarred myocardial tissue plays a central role in affecting the heart function, there are challenges in designing new treatment modalities to address the scar structure.[7] At present, pharmacotherapies are the main treatment options but offer limited effectiveness as the one- to two-year mortality rate of patients with ischemic HF remained at 40 to 50%, likely due to minimal reduction in ventricular volume.[3] Surgical options for ventricular repair include surgical ventricular reconstruction (SVR) which is not always preferred due to high surgical risk, presence of comorbidities and induced cardioplegia.[8]

## II. Technology

The Revivent TC Transcatheter Ventricular Enhancement System[a] (BioVentrix, Inc.) is a LV restoration device that aims to exclude the nonviable scarred myocardium, reshape the LV and reduce ventricular volume through a less invasive procedure. It comprises a series of implantable titanium anchor pairs with an internal hinged anchor and an external locking anchor that are connected by a poly-ether-ether-ketone tether. These micro-anchors are implanted through the Less Invasive Ventricular Enhancement (LIVE) procedure and serve to exclude the scarred myocardial tissue on the LV, thereby reshaping the heart and reducing ventricular wall stresses (Figure 1).

Briefly, the internal hinged anchor can be deployed on the right of the ventricular septum with a transcatheter approach via the right internal jugular vein, while the paired external locking anchor is deployed on the LV epicardium through a left-sided mini-thoracotomy.[9] The scarred myocardium can be excluded by drawing both anchors together.[10] This reduces the LV size and allows the functional portion of the LV to operate more efficiently. An average of two to three anchor pairs are typically implanted for each patient in a single procedure. The Revivent TC is indicated for patients with LV dilatation post-MI with acontractile scar tissue in the anteroseptal or apical wall of the LV and a transmurality of more than 50% (see Table A1 in Appendix A).

[a] Hereinafter referred to as Revivent TC.

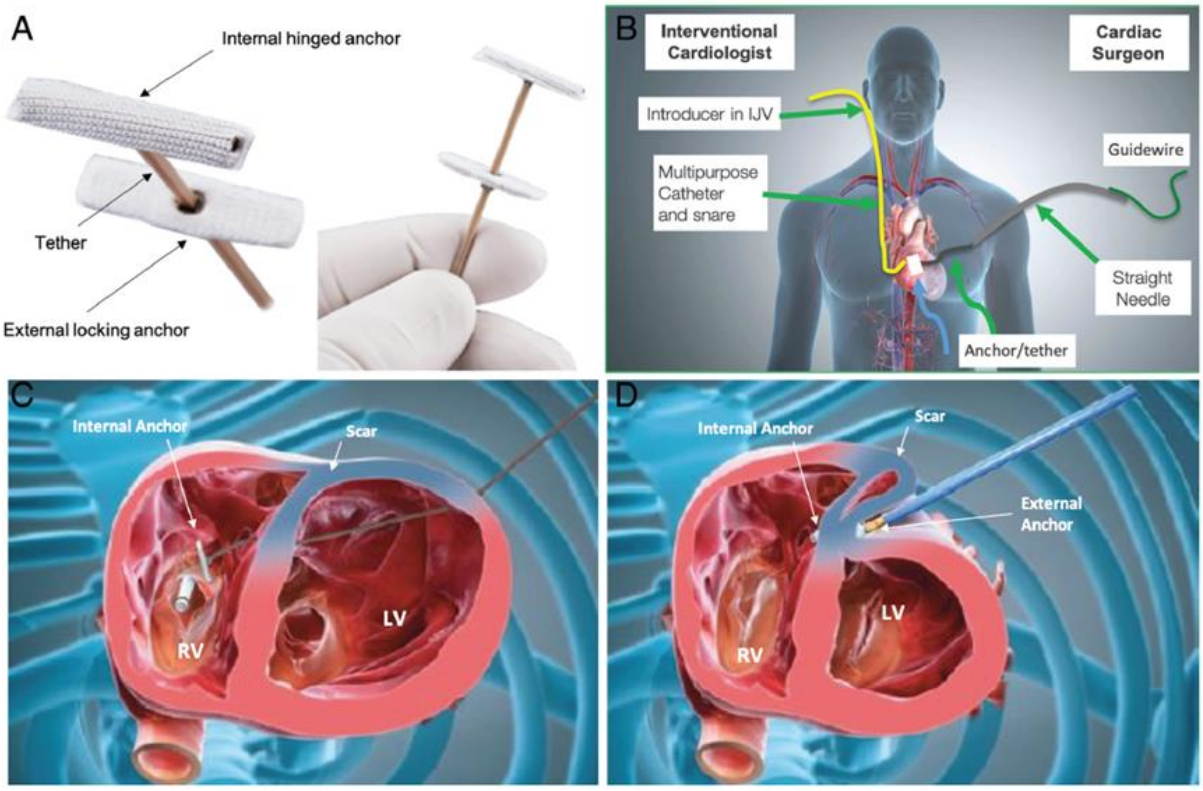


**Figure 1**. Schematic view of the Revivent TC System (A) and visualisation of the transcatheter hybrid LIVE procedure (B-D). *Image taken from Klein et al. (2019)*[10].

Before the development of Revivent TC, LV reshaping is performed by SVR which requires sternotomy, cardiopulmonary bypass and cardioplegic arrest. The invasive nature of SVR limits the number of patients who could benefit from the procedure. The hybrid transcatheter LIVE technique to implant the Revivent TC offers the advantage of a less invasive procedure to reshape the LV on the beating heart without the need for an open-heart surgery.

## III. Regulatory and Subsidy Status

The Revivent TC received the CE mark in 2016. The US Food and Drug Administration (FDA) granted Revivent TC the Breakthrough Device Designation in November 2019 for the treatment of HF. However, it is not yet approved for use in the United States by the FDA and is pending trial results.

## IV. Stage of Development in Singapore

| | | | |
|---|---|---|---|
| ☒ | Yet to emerge | ☐ | Established |
| ☐ | Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used) | ☐ | Established *but* modification in indication or technique |
| ☐ | Nearly established | ☐ | Established *but* should consider for reassessment (due to perceived no/low value) |

## V. Treatment Pathway

Based on the 2020 Clinical Practice Guidelines for HF published by the Heart Failure Society (Singapore), pharmacological management such as angiotensin-converting enzyme inhibitors and beta-blockers are recommended as first-line treatment for HF patients.[11] Angiotensin II receptor blockers, angiotensin receptor neprilysin inhibitor, ivabradine or vasodilators may be prescribed to patients refractory to first-line treatment or are experiencing worsening HF.[11] Patients who remain at risk of sudden cardiac death despite optimal medical therapy may be treated with cardiac implantable electronic devices such as implantable cardioverter-defibrillator therapy, which may be considered for patients with ischemic cardiomyopathy at least 40 days post-MI with New York Heart Association (NYHA) class II-III symptoms and LVEF ≤35%.[11] Surgical options such as coronary artery bypass graft (CABG) may be used as a revascularisation technique for patients with HF associated with ischemic heart disease, while SVR may be used to directly reshape the LV.[11]

At present, SVR is not a standard clinical treatment option in Singapore for patients with scarred tissue on the LV as it is not recommended for routine use in patients with ischaemic cardiomyopathy due to uncertainty in its value.[11] This is in line with guidelines by the European Society of Cardiology and European Association for Cardio-Thoracic Surgery, which highlight the uncertainty in the use of SVR and indicate that it may be considered in selected patients in centres with procedural expertise.[12]

Compared to SVR, the less invasive LIVE procedure with Revivent TC may lead to a change in practice as current guidelines do not address the scarred myocardium of adversely remodelled LV after MI.[10] It has the potential to offer an interventional treatment option for patients with high surgical risks or comorbidities who are refractory to pharmacotherapies.

## VI. Summary of Evidence

This assessment was based on the Population, Intervention, Comparison and Outcome (PICO) criteria presented in Table 1. The main body of evidence identified, and the inclusion and exclusion criteria were listed in Table A2 (Appendix A). One systematic review (SR)[8] of five case series, one additional case series[13] and a post-market registry study[14] were selected for inclusion in this brief. Of note, the post-market registry includes outcomes from both Revivent TC and its predicate device (Revivent).[14] Patients in the post-market registry may also overlap with the case series as it aggregated patients who received the device between 2012 to 2019.[14]

The five case series included in the SR had a short-term follow-up of up to 12 months. Of which, the study by Klein et al. (2019)[10] was a CE mark study with a larger sample size (n=86) while the remaining studies[9,15-17] had a smaller cohort sizes between 7 to 26 patients. The quality of the five case series in the SR were judged as fair based on the National Institutes of Health (NIH) tool for observational studies.[8] The study details of the included studies were summarised in Table B1 (Appendix B).

**Table 1: Summary of PICO criteria.**

| | |
|---|---|
| **Population** | Patients with heart failure and prior myocardial infarction, and have left ventricular scarring with dilatation or aneurysm |

| | |
|---|---|
| **Intervention** | Revivent TC |
| **Comparison** | Guideline-directed medical therapy or surgical ventricular reconstruction, if available |
| **Outcome** | Safety, clinical and cost effectiveness |

## Safety

Table 2 summarised the safety outcomes. A high number of major adverse events (AEs) were reported across the studies. In the CE mark study, the individual rate of major AE ranged from 1.2% to 8.1% while it ranged from 7.7% to 22.2% in the other studies.[9,10,13,15,16] The major AEs reported include bleeding, stroke, ventricular septal defect, right ventricular perforation and restriction, and mitral and tricuspid regurgitation.[8] Complications may persist in the long-term, where progressive worsening of tricuspid regurgitation was reported up to five years compared to baseline.[13]

Moreover, in-hospital mortality ranged from 0% to 4.5% which falls on the lower spectrum of 3% to 14% reported in various SVR studies.[10] Three out of the four in-hospital mortalities reported in the CE mark study were procedure-related due to LV injury, subendocardial necrosis, and pulmonary artery injury.[10] Median hospital and intensive care unit length of stay were 14.5 days and 92 hours respectively in the CE mark study (Table B2 in Appendix B).[10]

Minor AEs were only reported in the CE mark study, with the individual rate of minor AEs ranging from 3.5% to 14%.[10] Frequent minor AEs included ventricular arrhythmia which may be attributed to mechanical stimulation of the healthy myocardium during anchor implantation in the LIVE procedure.[8] Of note, 59.3% and 40.7% of patients in the CE mark study received the Revivent TC via the sternotomy and hybrid LIVE approach respectively, with no significant difference in major and minor AEs between both approaches (Table B3 in Appendix B).[10]

Overall, a high rate of major and minor AEs up to 22.2% and 14% were reported respectively. The high rate of AEs observed may be due to inadequate operator experience as the LIVE procedure presents a significant learning curve.[8] Subtle refinements made to the system since its CE mark approval in 2016 and increased procedural experience may possibly mitigate the safety concerns observed.[10] Notably in the recently published post-market registry study, in-hospital mortality was reported to be less than 1% in the past two years as compared to 2.5% from 2012 to 2019.[14]

**Table 2: Summary of safety outcomes of the included studies.**

| Author (year) | Safety outcome | Event rate(s) |
|---|---|---|
| Klein et al. (2019)[10] | Major adverse event, range (%) | 1.2 to 8.1 |
| | Minor adverse event, range (%) | 3.5 to 14.0 |
| | In-hospital mortality, n (%) | 4 (4.5) |
| Klein et al. (2019)[9] | Right ventricular perforation*, n (%) | 1 (11.1) |
| | Right ventricular restriction*, n (%) | 1 (11.1) |
| | Tricuspid regurgitation deterioration*, n (%) | 2 (22.2) |
| | In-hospital mortality, n (%) | 0 (0) |
| Wang et al. (2021)[16] | Major adverse cardiac event*, n (%) | 2 (7.7) |
| Loforte et al. (2019)[15] | Right ventricular perforation*, n (%) | 1 (14.3) |

| | | |
|---|---|---|
| Weschler et al. (2013)[17] | – | – |
| Naar et al. (2021)[13] | Acute mitral regurgitation*, n (%) | 1 (4.5) |
| | Tricuspid regurgitation deterioration*, n (%) | 2 (9.1) |
| Biffi et al. (2021)[14] | In-hospital mortality, n (%) | 5 (2.5) |
| * Safety outcome classified as major adverse event. | | |

**Effectiveness**

The SR showed that Revivent TC resulted in stable improvements in LV outcomes up to 12 months, where statistically significant improved LV ejection fraction (LVEF) and LV volume consisting of LV end-systolic volume index (LVESVI) and LV end-diastolic volume index (LVEDVI) were reported (Table 3).[8] The post-operative increases in LVEF (mean difference range, 5 to 12.2%) were clinically meaningful as it reached the minimal clinically important difference (MCID) of ≥5%.[8,18] All studies reported significant improvement between pre- and post-operative LVESVI and LVEDVI (p≤0.001). Of four studies that had a pre-operative LVESVI above 60 mL/m$^2$ which was associated with a five-fold increase in mortality, therapeutic post-operative volume reduction below 60 mL/m$^2$ was achieved in three studies.[3,8] These results were durable up to two years in the extended CE mark study reported in the post-market registry study (Figure B1 in Appendix B).[14] Further, LV size was also reported to be reduced (Figure B2 in Appendix B) while spherical index remained unchanged (Table B4 in Appendix B).[9,15,16] The structural improvements further led to a post-operative reduction in mitral regurgitation grade, pointing to potential alleviation of HF symptoms (Table B4 in Appendix B).[8] Taken together, improved LV outcomes indicate improved cardiac function while reduced LV dimension may indicate the ability of Revivent TC to exclude the scarred myocardium and reduce heart size. Overall, a 12-month survival rate of 90.6% (95% CI, 84.6% to 97.0%) was reported in the CE mark study.[8]

These LV improvements were augmented by studies that were only available in abstracts[19-24], as well as results from the post-market registry study, although no statistical analysis was reported and the follow-up period and potential patient overlap with the SR remain unclear (Figure B1 in Appendix B).[8,14]

The studies in the SR that reported on functional outcomes showed consistent post-operative improvements, with clinically meaningful improvement in exercise capacity (mean difference range of 6-minute walk test [6MWT] distance, 53 to 92.7m; p<0.001), based on the MCID of ≥30m,[25] and quality-of-life (QoL; mean difference of the Minnesota Living with Heart Failure Questionnaire score, 13 points; p<0.001) based on a MCID of 8.2 points.[26] In addition, HF symptoms were reduced as evident from the significant decrease in the NYHA functional class in all except one study[9], which may be attributed to early outcome measurements post-operatively. Notably, the MCID for NYHA functional class is a decrease in ≥1 class,[25] which was achieved in 2 smaller trials[15,16] but not the larger CE mark study,[10] which did report the proportion of patients with NYHA class III declined from 59% to 22%.[8] Out of 74 patients analysed in the CE mark study, 46 (62.2%) were classified as a 'responder' due to improvements in the 6MWT, QoL, or HF symptoms.[10]

**Table 3: Summary of key clinical outcomes from the systematic review by Brinza et al. (2021)[8].**

| | Klein et al. (2019)[10] | Klein et al. (2019)[9] | Wang et al. (2021)[16] | Loforte et al. (2019)[15] | Wechsler et al. (2013)[17] |
|---|---|---|---|---|---|
| Total patients, N | 86 | 9 | 26 | 7 | 11 |
| Follow-up | 12 months | 2.3 months† | 9 months | 6.3 months† | 12 months^ |
| **LVEF (%)** | | | | | |
| Baseline | 29 ± 8 | 28.8 ± 8 | 35.6 ± 8.8* | 22.8 ± 8.1 | |
| Follow-up | 34 ± 9 | 40 ± 10 | 45.9 ± 9.8* | 35 ± 7.2 | NR |
| Mean difference | +5 | +11.2 | +10.3 | +12.2 | |
| *P*-value | p<0.005 | p<0.001 | p<0.001 | p=0.001 | |
| **LVESVI (mL/m²)** | | | | | |
| Baseline | 74 ± 28 | 53 ± 8 | 84.8 ± 25.7 | 93.2 ± 10.5 | 72.6 ± 26.9 |
| Follow-up | 54 ± 23 | 30 ± 11 | 65.6 ± 24.4 | 52.1 ± 15.1 | 43.9 ± 223 |
| Mean difference | -20 | -23 | -19.2 | -41.1 | -28.7 |
| *P*-value | p<0.001 | p<0.001 | p<0.001 | p<0.001 | p<0.0001 |
| **LVEDVI (mL/m²)** | | | | | |
| Baseline | 106 ± 33 | 75 ± 23 | 107.8 ± 33.2 | 137.2 ± 20.1 | 102.5 ± 27.3 |
| Follow-up | 80 ± 26 | 45 ± 6 | 90.5 ± 31.8 | 78 ± 10.2 | 69.5 ± 27.2 |
| Mean difference | -26 | -30 | -17.3 | -59.2 | -33 |
| *P*-value | p<0.001 | p=0.001 | p<0.001 | p=0.001 | p<0.0002 |
| **NYHA class** | | | | | |
| Baseline | 2.6 ± 0.5 | 2.7 ± 0.4 | 2.7 ± 0.6 | 3.4 ± 0.6 | |
| Follow-up | 1.9 ± 0.8 | 2.3 ± 0.7 | 1.7 ± 0.7 | 1.4 ± 0.9 | NR |
| Mean difference | -0.7 | -0.4 | -1.0 | -2.0 | |
| *P*-value | p<0.001 | p=0.58 | p<0.001 | p=0.001 | |
| **6MWT (m)** | | | | | |
| Baseline | 363 ± 92 | | 368.8 ± 40.0 | | |
| Follow-up | 416 ± 106 | NR | 461.5 ± 61.2 | NR | NR |
| Mean difference | +53 | | +92.7 | | |
| *P*-value | p<0.001 | | p<0.001 | | |
| **QoL (MLHFQ)** | | | | | |
| Baseline | 39 ± 21 | | | | |
| Follow-up | 26 ± 22 | NR | NR | NR | NR |
| Mean difference | -13 | | | | |
| *P*-value | p<0.001 | | | | |

Note: Data, where available, were reported as mean ± S.D.

†Mean follow-up period across all patients; ^6 months follow-up was also conducted and LVESVI and LVEDVI were significantly reduced compared to baseline; *LVEF as measured by echocardiography.

Abbreviations: 6MWT, 6-minute walk test; LVEF, left ventricular ejection fraction, LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NR, not reported; NYHA, New York Heart Association; QoL, quality-of-life.

Although durable LV and functional outcomes up to 12 months were reported by the SR, it was not consistently observed in a small long-term case series by Naar et al. (2021)[13] with a follow-up of five years (Table 4). Improvements in LVESVI, LVEDVI and NYHA functional class were statistically significant at five-year follow-up compared to baseline, with no significant improvement in LVEF, 6MWT and QoL scores.[13] In addition, the five-year all-cause mortality of 24% reported was lower than the five-year mortality rate of 46% and 29% for patients with ischemic cardiomyopathy receiving medical therapy and CABG surgery respectively.[13,27]

However, given the observational nature of the study, uncertainties remain if the observed effects were largely due to the index intervention.[13] Overall, in a small patient cohort, durable long-term result of the Revivent TC remain uncertain from limited early studies.

**Table 4: Summary of long-term outcomes reported by Naar et al. (2021)[13].**

| | Baseline | 6 months | 2 years | 5 years |
|---|---|---|---|---|
| **Total N** | 23 | 20 | 18 | 11 |
| LVESVI (mL/m$^2$) | 73.2 ± 27 | 51.5 ± 22 (p<0.001) | 49.9 ± 20 (p<0.001) | 56.1 ± 16 (p=0.047) |
| LVEDVI (mL/m$^2$) | – | ↓ (p<0.001) | ↓ (p<0.001) | ↓ (p=0.04) |
| LVEF (%) | – | ↑ (p=0.13) | ↑ (p=0.01) | ↑ (p=0.46) |
| NYHA class | 2.3 ± 0.5 | ↓ (p=0.27) | ↓ (p=0.11) | 1.6 ± 0.7 (p=0.01) |
| 6MWT (m) | – | 392 ± 97 (NS) | 432 ± 77 (p=0.06) | ↑ (NS) |
| QoL (MLHFQ) | – | ↓ (p=0.82) | ↓ (p=0.61) | ↓ (p=0.91) |
| All-cause mortality | – | – | 13% | 24% |

Notes:

1) Data, where available, were presented as mean ± S.D.
2) *P*-values at follow-up are with respect to baseline.
3) ↑ denotes an increase and ↓ denotes a decrease in the respective parameters as numerical data were not reported.

Abbreviations: 6MWT, 6-minute walk test; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MLHFQ; Minnesota Living with Heart Failure Questionnaire; NS, not significant; NYHA; New York Heart Association; QoL, quality-of-life.

## Cost-effectiveness

There were no cost-effectiveness studies identified for Revivent TC. However, Revivent TC was reported to result in a six-month re-hospitalisation rate of 13% in the post-market registry study, as compared to ≥50% in patients with HF receiving optimal medical therapy.[14,28] This may potentially translate to significant cost savings to the healthcare system. In Singapore, frequent admitters including those with HF had an average cost per patient of S$29,547.[29]

## Ongoing clinical trials

Three ongoing clinical trials were identified from the ScanMedicine database (NIHR Innovation Observatory) (Table 5). Evaluation of Revivent TC with guideline-directed medical therapy (GDMT) compared to GDMT alone is assessed in the pivotal ALIVE IDE trial and the REVIVE-HF trial at multiple sites. Long-term safety and effectiveness of the Revivent TC is investigated in the post-market BRAVE-TC registry at multiple centres in Europe. Primary completion of the pivotal ALIVE IDE trial is expected in March 2022, but the company has not yet announced a timeline for regulatory submission to the FDA.

**Table 5: Summary of ongoing clinical trials for the Revivent TC.**

| Study name; Trial ID | Estimated enrolment | Study design, aim and follow-up period | Estimated study completion date |
|---|---|---|---|
| REVIVE-HF; NCT03845127 | 180 | Multi-center, open label, 2:1 RCT to assess the treatment of ischemic cardiomyopathy induced heart failure with the Revivent TC plus GDMT compared to GDMT alone over a 3- and 6-month follow-up period | December 2022 |
| ALIVE; NCT02931240 | 126 | Multi-center, open-label, 2:1 non-randomised controlled trial to assess the treatment of ventricular dysfunction with the Revivent TC plus GDMT | December 2025 |

| | | | |
|---|---|---|---|
| | | compared to GDMT alone over a 12-month follow-up period | |
| BRAVE-TC; ISRCTN89757315 | 100 | Multi-center prospective single-arm post-market registry to observe and record the results of the use of the Revivent TC in a commercial, post-approval environment and to observe long-term safety and performance of the device over a 5-year follow-up period | October 2022 |
| Abbreviations: GDMT, guideline-directed medical therapy; RCT, randomised controlled trial. | | | |

**Summary**

Early evidence showed significant safety issues from the high rate of major AEs reported which may be attributed to the relative lack of experience in early trials and the substantial learning curve required.[8,15] Furthermore, short-term outcomes reported in the SR supported the ability of Revivent TC to improve cardiac function, HF symptoms, exercise capacity and patient's QoL up to 12 months. However, uncertainties remain on the durability of these benefits in the long-term due to limited data available. No cost effectiveness study was identified, although there is some indication that Revivent TC may potentially lead to cost savings from reduced re-hospitalisation rates.

Results from the included studies have to be interpreted with caution due to lack of controlled studies, limited long-term outcomes and small patient cohorts. It remains ambiguous if the benefits observed were primarily due to Revivent TC or confounding factors such as background medical therapies for HF. Also, the initial learning curve may represent a source of variability in outcomes and complication rates in early studies.[8] The observed benefits need to be validated by controlled long-term studies with adequate sample size to assess if LV reshaping with Revivent TC can provide durable LV improvements and overall survival.

## VII. Estimated Costs

The cost of the Revivent TC was not available. It was claimed that the less invasive nature of the LIVE transcatheter procedure to implant the Revivent TC for LV reshaping can decrease the cost associated with conventional SVR treatment. The average total hospitalisation cost for patients receiving SVR and CABG surgery in the United States was reported to be US$70,717.[30]

## VIII. Implementation Considerations

The selection of patients with the appropriate anatomical features for the micro-anchor deployment is crucial for clinical benefits to be realised (see Table A1 in Appendix A). The localization, size, and transmural extent of the scar needs to be objectified by cardiac magnetic resonance imaging or dynamic computed tomography. The increase in demand for these imaging services need to be considered when introducing the procedure into the healthcare system.

Furthermore, complications from the procedure can be high in centres in the early stage of providing the procedure as the novel LIVE procedure requires a significant learning curve.[8] To ensure proper implantation, a well-trained and dedicated multidisciplinary 'heart team'

including an interventional cardiologist, cardiac surgeon and an echocardiographer is required.[8]

## IX. Concurrent Developments

There are several minimally invasive LV restoration devices in development that addresses the enlarged LV in patients with HF (Table 6). Instead of the epicardial approach used in the Revivent TC, these devices isolate the nonviable portion of the LV through other techniques.

**Table 6: Similar LV restoration devices in development.**

| Technology (Manufacturer) | Brief Description | Regulatory status | Current Development |
|---|---|---|---|
| AccuCinch Ventricular Restoration System (Ancora Heart, Inc.) | The AccuCinch implant is a percutaneous device developed to reshape the LV of the heart directly for the treatment of HF patients with or without FMR. It is deployed into the LV wall below the mitral valve through a transcatheter approach via the femoral artery. Once positioned, the implant will be cinched and locked in place to reduce the size of the LV and support and strengthen the heart wall. | - | Clinical studies to assess its safety and efficacy are ongoing in the United States and Europe. |
| Parachute Implant System (Cardiokinetix, Inc.) | The Parachute is a ventricular portioning device implanted by a catheter-based approach through the femoral artery into the LV. It consists of a fluoropolymer membrane stretched over a nitinol frame intended to isolate the akinetic or aneurysmatic portion of the LV in patients with ischemic HF. | • CE mark in 2011<br>• Approved by the Korean Ministry of Food and Drug Safety in South Korea in 2015 | It remains an investigational device in the United States and the IDE study was terminated in June 2017. Further investigation and device development remain unclear. |
| Heartech Left Ventricular Partitioning Device (Xinrui Medical Equipment Co. Ltd.) | The Heartech is a left ventricular partitioning device that has a similar design to Parachute® to allow percutaneous ventricular restoration. | - | One-year result from the first-in-human study was published in January 2021. Clinical studies to assess its safety and efficacy are ongoing in China. |

## X. Additional Information

Two studies[10,17] in the SR were funded by BioVentrix, Inc. while conflict of interest were reported in four studies[9,10,16,17] in the SR as well as the study by Naar et al. (2021)[13].

In addition, Revivent TC was highlighted by several overseas horizon scanning agencies. The National Institute for Health Research (NIHR) Horizon Scanning Centre published a Technology Alert report in August 2013 on Revivent, which is an earlier version of Revivent TC that requires an open-heart sternotomy to implant the micro-anchor pairs. It concluded that the Revivent may offer an additional treatment option for patients with HF and left ventricular scars if clinical and cost effectiveness can be demonstrated.[31]

It was also monitored by the Patient-Centered Outcomes Research Institute (PCORI) in its March 2020 issue of the Horizon Scanning Status Report (Volume 2, Issue 1)[32], and was subsequently archived in the June 2020 issue (Volume 2, Issue 2)[33] due to the high rate of serious AEs reported in early trials that may limit its use and hence curtail its disruptive potential.

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# Appendix

## Appendix A: Target patient population and studies identified.

**Table A1: Target patient population.**

| S/N | Indication |
|---|---|
| 1 | NYHA Class III to IV |
| 2 | Previous myocardial infarction (90 days or more) |
| 3 | Presence of ischemic scar<br>• Anteroseptal, apical and/or anterolateral region<br>• Discrete acontractile (akinetic and/or dyskinectic)<br>• Transmural (>50%) |
| 4 | Presence of LV dilation or aneurysm |
| 5 | Presence of viable myocardium at the base for implant |

**Table A2: List of identified and included studies.**

| Type of study | Number of studies identified | Number of studies included |
|---|---|---|
| Systematic review | 1 | 1 |
| Post-market registry | 1 | 1 |
| Case series | 6 (5 included in the systematic review) | 1 |
| Case report | 3 | – |
| Abstract | 6 | – |

Note:
1. Inclusion criteria
   a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
   a. Studies with a case-report study design.
   b. Studies only available in the abstract form.

## Appendix B: Supplementary tables and figures of studies included

**Table B1: Characteristics of included studies.**

| Author (year) | N | Follow-up reported | Study design | Recruitment sites | Population |
|---|---|---|---|---|---|
| Klein et al. (2019)[10] | 89 | 6 and 12 months | Observational, prospective, multicentre | Europe (22 sites) | HF patients (18 to 80 years) with LV dilatation and dysfunction due to MI that occurred 90 days prior to study enrolment, LVEF>15% and ≤45%, NYHA class II-IV, LVESVI ≥60 mL/m$^2$ and ≤120 mL/m$^2$, exhibit sufficient functional remote myocardium and sufficient transmural scar for anchor placement |
| Klein et al. (2019)[9] | 9 | Before hospital discharge (2 – 155 days) | Observational, multicentre | Netherlands (2 sites) | HF patients with NYHA class ≥II and ischaemic cardiomyopathy (EF <40%) after anteroseptal MI, dilated LV with either an akinetic or dyskinetic scar in the anteroseptal wall and apex with >50% transmurality |
| Wang et al. (2021)[16] | 26 | 1, 3, 6 and 9 months | Observational, prospective, single centre | China (1 site) | HF patients (18 to 80 years) with NYHA class II–IV, stable HF medication for >90 days, significantly enlarged left ventricle with aneurysm formation, LVESVI >60 mL/m$^2$, LVEF <40% and a life expectancy ≥1 year |

| | | | | | |
|---|---|---|---|---|---|
| Lorforte et al. (2019)[15] | 7 | 189.7 ± 104.5 days | Observational, retrospective, single centre | Italy (1 site) | Severe HF patients (18 to 75 years) with NYHA class III-IV despite optimal medical therapy for at least 90 days, LVEF <35%; LVESVI >60 mL/m$^2$ and ≤120 mL/m$^2$, no infarction within three months of operation; and referral for ventricular reshaping operation |
| Naar et al. (2021)[13] | 23 | 6 months, 2- and 5-years | Observational, prospective, single centre | Czech Republic (1 site) | HF patients aged 18–80 years, LVEF 15 to 45%, NYHA class II–IV, stable HF medication for >90 days, presence of ischemic LV dysfunction due to prior myocardial infarction leading to transmural scarring with akinesis or dyskinesis in the anteroseptal, apical, or apicolateral region |
| Biffi et al. (2021)[14] | 203 | – | Post-market registry study | Multiple | – |
| Abbreviations: HF, heart failure; LV, left ventricle; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; NYHA; New York Heart Association. | | | | | |

**Table B2: Hospital and intensive care unit length of stay.**

| Trial | Hospital LOS | ICU LOS |
|---|---|---|
| Klein et al. (2019)[10] | Median 14.5 days (Range: 5 to 51 days) | Median: 92h (Range: 0 to 1104h) |
| Klein et al. (2019)[9] | Median: 9 days (IQR: 3 to 57 days) | Median: 2 days (IQR: 1 to 46 days) |
| Wang et al. (2021)[16] | NR | NR |
| Loforte et al. (2019)[15] | Mean: 22.1 days (Range: 9 to 45 days) | Mean: 7.8 days (Range: 1 to 22 days) |
| Naar et al. (2021)[13] | NR | NR |
| Biffi et al. (2021)[14] | NR | NR |
| Abbreviation: ICU, intensive care unit; IQR, interquartile range; LOS, length of stay. | | |

**Table B3: Adverse events reported in the CE mark study by Klein et al. (2019)[10].**

| | Sternotomy approach (n=51), n (%) | Hybrid LIVE approach (n=35), n (%) | Total (n=86), n (%) | p-value (sternotomy *vs.* hybrid approach) |
|---|---|---|---|---|
| **Major adverse events** | | | | |
| Tricuspid valve insufficiency increase | 1 (2.0) | 4 (11.4) | 5 (5.8) | 0.0734 |
| Mitral valve insufficiency increase | 1 (2.0) | 1 (2.9) | 1 (1.2) | 0.79 |
| Pulmonary valve insufficiency increase | 3 (5.9) | 0 (0.0) | 3 (3.5) | 0.15 |
| Ventricular septal defect | 1 (2.0) | 1 (2.9) | 2 (2.3) | 0.79 |
| Bleeding | 3 (5.9) | 4 (11.4) | 7 (8.1) | 0.36 |
| Renal dysfunction | 3 (5.9) | 1 (2.9) | 4 (4.7) | 0.52 |
| Respiratory failure | 1 (2.0) | 1 (2.9) | 2 (2.3) | 0.79 |
| Stroke | 3 (5.9) | 1 (2.9) | 4 (4.7) | 0.52 |
| Late cardiac arrest | 0 (0.0) | 2 (5.9) | 2 (2.3) | 0.09 |
| **Minor adverse events** | | | | |
| Atrial fibrillation | 1 (1.9) | 2 (5.9) | 3 (3.5) | 0.72 |
| Pleural effusion | 3 (5.9) | 2 (5.9) | 5 (5.8) | 0.97 |
| Ventricular arrhythmia | 8 (15.7) | 4 (11.4) | 12 (14.0) | 0.58 |
| Low cardiac output | 4 (7.8) | 1 (2.9) | 5 (5.8) | 0.34 |
| Pulmonary infection | 2 (3.8) | 3 (8.6) | 5 (5.8) | 0.37 |

| | | | | |
|---|---|---|---|---|
| Sepsis | 4 (7.8) | 1 (2.9) | 5 (5.8) | 0.34 |

**Table B4: Summary of functional mitral regurgitation and spherical index outcomes.**

| | Klein et al. (2019)[10] | Klein et al. (2019)[9] | Wang et al. (2021)[16] | Loforte et al. (2019)[15] | Wechsler et al. (2013)[17] | Naar et al. (2021)[13] | Biffi et al. (2021)[14] |
|---|---|---|---|---|---|---|---|
| Total patients, N | 86 | 9 | 26 | 7 | 11 | 23 | 104 |
| Follow-up | 12 months | 2.3 months† | 9 months | 6.3 months† | 12 months | 5 years | NR |
| **FMR grade** | | | | | | | |
| Baseline | 1.12 ± 0.73 | | | – | | | |
| Follow-up | 0.86 ± 0.64 | NR | NR | ↓* | NR | NR | NR^ |
| Mean difference | -0.26 | | | – | | | |
| *P*-value | p=0.03 | | | p<0.05 | | | |
| **Spherical index** | | | | | | | |
| Baseline | | 0.5 ± 0.1 | | 0.5 ± 0.1 | | | |
| Follow-up | NR | 0.5 ± 0.1 | NR | 0.4 ± 0.1 | NR | NR | NR |
| Mean difference | | 0 | | -0.1 | | | |
| *P*-value | | p=0.7 | | p=0.621 | | | |

† Mean follow-up period across all patients.
* Numerical data not available, but it was reported that all patients had significantly decreased FMR post-operatively.
^ Numerical data not available, but it was reported that 63% of patients had ≥1 grade decrease in FMR.
Abbreviation: FMR, functional mitral regurgitation; NR, not reported.


**Figure B1.** Efficacy of the Revivent TC in the post-market registry study (n=104) compared to the CE mark study (n=86). LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index. Image taken from Biffi et al. (2021)[14].

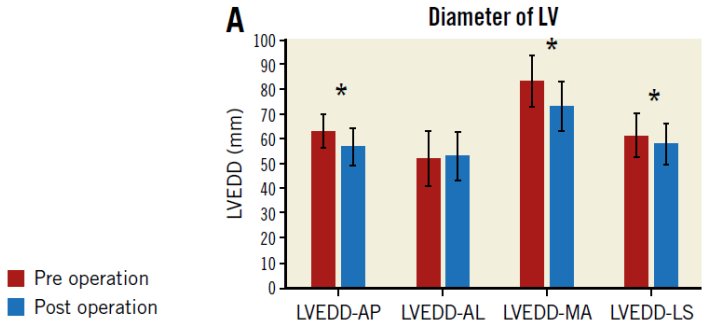


**Figure B2.** Reduced left ventricular end-diastolic diameter (LVEDD) in different views by echocardiography and cardiac magnetic resonance. LVEDD-AL: LV end-diastolic diameter (LVEDD) measured between the anterior and lateral walls in the four-chamber view by CMR; LVEDD-AP: LVEDD measured between the anterior and posterior dimension in the long-axis view on echocardiography; LVEDD-MA: LVEDD measured between the mitral valve and the apex in the four-chamber view by CMR; LVEDD-LS: distance between the lateral wall and the septum on the short-axis view at the papillary muscle level by CMR. Image taken from Wang et al. (2021)[16].