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# ALternate Site Cardiac ResYNChronization (ALSYNC): a prospective and multicentre study of left ventricular endocardial pacing for cardiac resynchronization therapy

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**Aims** The ALternate Site Cardiac ResYNChronization (ALSYNC) study evaluated the feasibility and safety of left ventricular endocardial pacing (LVEP) using a market-released pacing lead implanted via a single pectoral access by a novel atrial transseptal lead delivery system.

**Methods and results** ALSYNC was a prospective clinical investigation with a minimum of 12-month follow-up in 18 centres of cardiac resynchronization therapy (CRT)-indicated patients, who had failed or were unsuitable for conventional CRT. The ALSYNC system comprises the investigational lead delivery system and LVEP lead. Patients required warfarin therapy post-implant. The primary study objective was safety at 6-month follow-up, which was defined as freedom from complications related to the lead delivery system, implant procedure, or the lead $\geq$70%. The ALSYNC study enrolled 138 patients. The LVEP lead implant success rate was 89.4%. Freedom from complications meeting the definition of primary endpoint was 82.2% at 6 months (95% CI 75.6–88.8%). In the study, 14 transient ischaemic attacks (9 patients, 6.8%), 5 non-disabling strokes (5 patients, 3.8%), and 23 deaths (17.4%) were observed. No death was from a primary endpoint complication. At 6 months, the New York Heart Association class improved in 59% of patients, and 55% had LV end-systolic volume reduction of 15% or greater. Those patients enrolled after CRT non-response showed similar improvement with LVEP.

**Conclusions** The ALSYNC study demonstrates clinical feasibility, and provides an early indication of possible benefit and risk of LVEP.

**Clinical trial** NCT01277783.

**Keywords** Prospective clinical trial • Left ventricular endocardial pacing • Heart failure • Safety

## Introduction

Cardiac resynchronization therapy (CRT) is a well-established treatment for heart failure patients with left ventricular (LV) systolic dysfunction and asynchronous LV contraction, restoring LV mechanical efficiency, improving patients' quality of life, and reducing heart failure-related hospitalizations/mortality.[1,2]

However, the clinical effectiveness of 'conventional' CRT is limited by the need to access to the LV epicardial surface via the coronary sinus (CS) and cardiac venous tributaries.[3] Anatomy dictates

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the choice of pacing site, leading to possible suboptimal electrical pacing parameters and phrenic nerve stimulation. Therefore, the choice of LV pacing site is often a matter of implant expediency rather than physiological imperative and can result in suboptimal clinical outcome.[4] Surgical LV epicardial lead implant may be an alternative to CS LV lead implant, but it requires an invasive surgical procedure. In contrast, LV endocardial pacing (LVEP) is less invasive and not restricted by access limitation.[5] ALternate Site Cardiac ResYNChronization (ALSYNC) is an international multicentre prospective study to evaluate the clinical feasibility and safety of LVEP using a single-incision, pectoral, atrial transseptal approach to LVEP lead delivery.

# Methods

The ALSYNC study enrolled 138 patients. All patients provided written consent. Each participating institution received local Ethics Committee approval.

## Inclusion/exclusion criteria

Patients, who had either a failed previous conventional LV lead implantation, or a suboptimal CS anatomy, or a CRT non-responder, who had worsened or unchanged HF status after at least 6 months of optimal CRT therapy, were eligible for enrolment when indicated for CRT. In addition, patients had to take oral vitamin K antagonist to maintain an international normalized ratio (INR) of 3, with a recommended range of 2–4. Patients were not eligible if they had a left superior vena cava (LSVC), a previous stroke, or mural thrombus, had an atrial septal defect closure device, or had atrial fibrillation (AF) and a $CHA_2DS_2$-VASc score of $\geq 5$.

## Patient evaluation

Eligible patients underwent the following evaluations at baseline and follow-up visits: New York Heart Association (NYHA) class; six-minute walk; two-dimensional Doppler echocardiography (LV systolic and diastolic volumes, ejection fraction, and degree of mitral regurgitation); and questionnaire for verifying stroke-free status (QVSFS).

## Implant procedure

Left pectoral vein access was achieved using standard methods. The ALSYNC system comprised investigational steerable guide (6227ATS, Medtronic, Minneapolis, MN, USA) and lead delivery (6248HS, 6248JS, or 6248JL, Medtronic) catheters, and a market-released transseptal RF powered wire with dilator (Model SAK-35-76, Baylis Medical Co., Montreal, Canada).

The steerable guide catheter acted as a delivery platform against the interatrial septum (*Figure 1A*) to facilitate transseptal puncture. The powered RF wire (2s@25W) punctured the *fossa ovalis* guided by intracardiac or transoesophageal echocardiography (TOE; *Figure 1B*); thereafter, the RF wire/dilator was advanced into the left atrium (*Figure 1C*). Crossing the septum, the RF wire assumed its pigtail conformation, and supported advancement of the lead delivery catheter across the septum and mitral valve to the LV cavity (*Figure 1D*). At the end, the LVEP lead (Model 3830, Medtronic) was advanced through the lead delivery catheter (*Figure 1E*) and the lead tip was fixed to the appropriate LV endocardial site (*Figure 1F*). *Figure 2* shows X-rays in the anteroposterior and left anterior oblique view after the implant. Intraoperative anticoagulation was managed by the administration of intravenous heparin to maintain a target activated clotting time of $>250$ s from the transseptal puncture until the catheters were removed after lead fixation.

In all implants, the right atrial and ventricular leads were positioned prior to LVEP lead implant.

## Follow-up

Patients were followed at 1, 3, 6, and 12 months (minimum) and biannually thereafter.

## Primary objective

The primary objective of the ALSYNC study was to achieve LVEP while demonstrating a $\geq 70\%$ freedom from complications meeting the definition of primary endpoint at 6-month post-implant.[6] Primary endpoint complications were defined as follows: any transseptal implant tool, transseptal implant procedure, or LVEP lead-related adverse event resulting in patient death, confirmed stroke, termination of significant device function, or any invasive intervention (including administration of intramuscular and parental fluids). Stroke was defined as a neurological deficit of cerebrovascular cause with focal symptoms and signs lasting for $>24$ h with or without findings on imaging studies, or $<24$ h with appropriate findings on an imaging study.

All adverse events were adjudicated by an independent Adverse Event Adjudication Committee. An independent Data Monitoring Committee reviewed and monitored incidence of cerebrovascular events, procedure risk, and therapeutic benefit. Both committees had expertise in the diagnosis and classification of cerebrovascular events (Appendix A).

## Statistical methods

Two patients with major eligibility violations were excluded from analysis. The analysis of procedural success and safety, including the primary objective, includes all patients with an implant attempt. The analysis of follow-up experience includes all successfully implanted patients.

The primary objective was to compare endpoint-free survival at 6-month post-implant against the pre-defined level of 70%. The Kaplan–Meier estimate was used and the objective was met when its one-sided 97.5% confidence interval (CI) was above 70%. Time zero in the analysis was the date of first implant attempt. Patients were censored at the last documented contact with the investigational centres. For patients with a second implant attempt and one or more primary endpoints, the shortest time between implant attempt and subsequent endpoint was used in analysis. The study required 109 patients to achieve 80% power for the primary objective assuming a true complication-free rate of 81%.

Rates for stroke and transient ischaemic attack (TIA) were calculated as total number of events divided by cumulative time at risk, with CIs calculated from a Poisson regression model for stroke and a negative binomial regression model for TIA, respectively. It was not possible to fit a negative binomial model for stroke due to the low number of events. Baseline and follow-up values of outcome parameters were compared using repeated-measures linear and ordinal regression models.

Continuous variables are presented with mean and standard deviation, and categorical variables with count and percentage. *P*-values $<0.05$ are considered significant. All analyses were done using SAS versions 9.3 and 9.4 (SAS Institute, Inc., Cary, USA).

# Results

## Study population

A total of 138 patients were recruited between March 2011 and July 2013 by 16 European and 2 Canadian centres (Appendix B). Two patients were excluded from the analysis because of retained LSVC. Seventeen patients with minor eligibility breaches were included in the analysis, including 13 patients with prior AF and a $CHA_2DS_2$-VASc score of $\geq 5$.

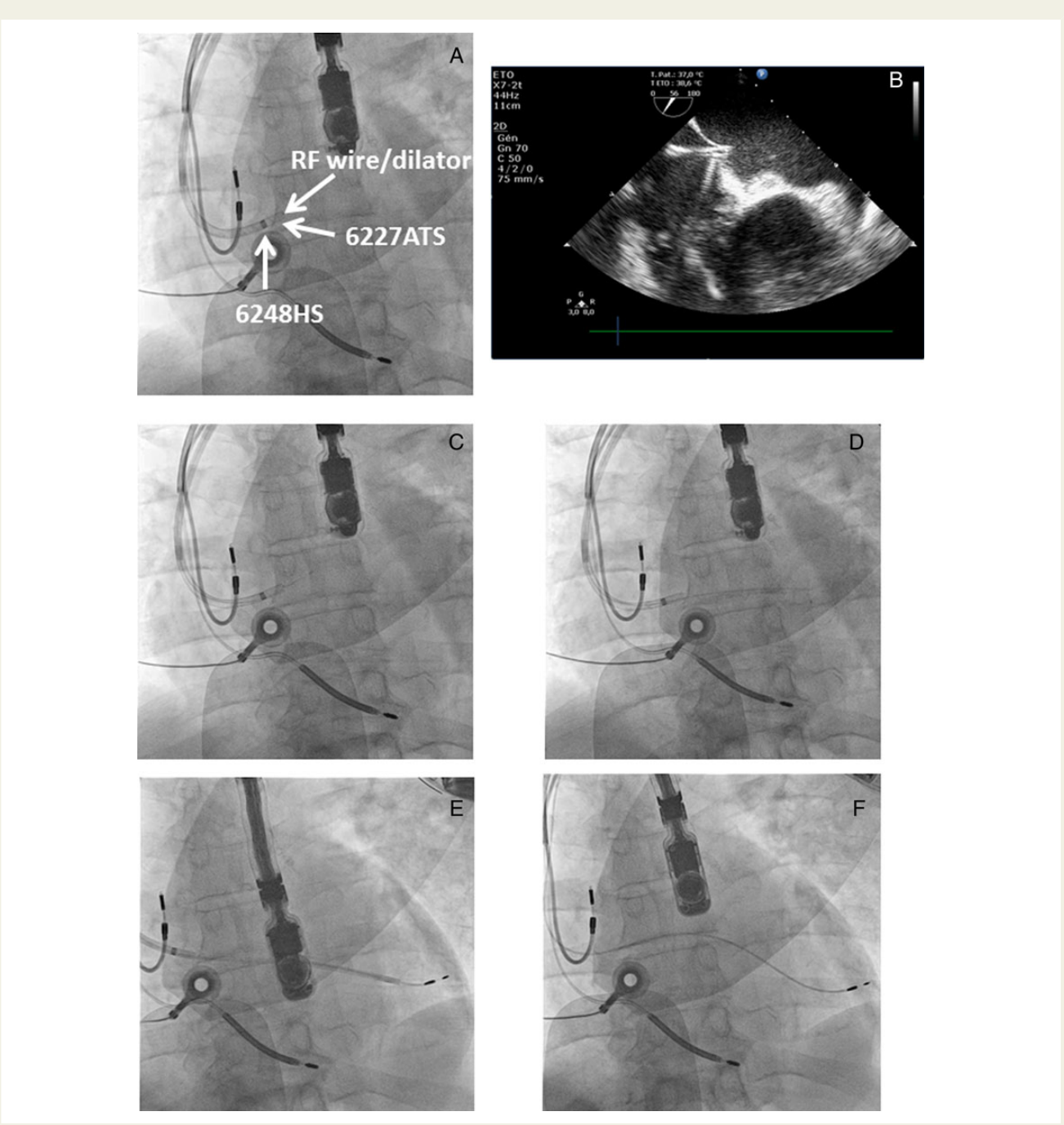


**Figure 1** Fluoroscopy and echo images illustrating the implant procedure.

Patient characteristics are summarized in *Table 1*. Of note, 50% of the patients had prior AF and 76% were on anticoagulation at enrolment. Thirty-one CRT non-responders (23%) were enrolled. In total, 23 patients (17%) required a *de novo* implant, 74 patients (54%) had a prior CRT device, and 39 patients (29%) had a non-CRT device implanted.

## Implant procedure

Left ventricular endocardial pacing lead implantation was attempted in 132 patients. Of four patients without an attempt, one patient died before the planned implant, and in three patients implant was not attempted because TOE showed thrombus in the left atrium. Left ventricular endocardial pacing lead implantation was successful in 118 (89%; 95% CI 83–94%) patients, with 2 patients requiring a second attempt. In 15 cases, a balloon catheter (9 cases) or a femoral Brockenbrough needle puncture (6 cases) facilitated the transseptal cannulation of the lead delivery catheter. Among 14 failed implant attempts, 2 were related to atrial thrombus identification during the procedure, 1 was related to aortic perforation after femoral Brockenbrough needle puncture, and 11 were related to a failed

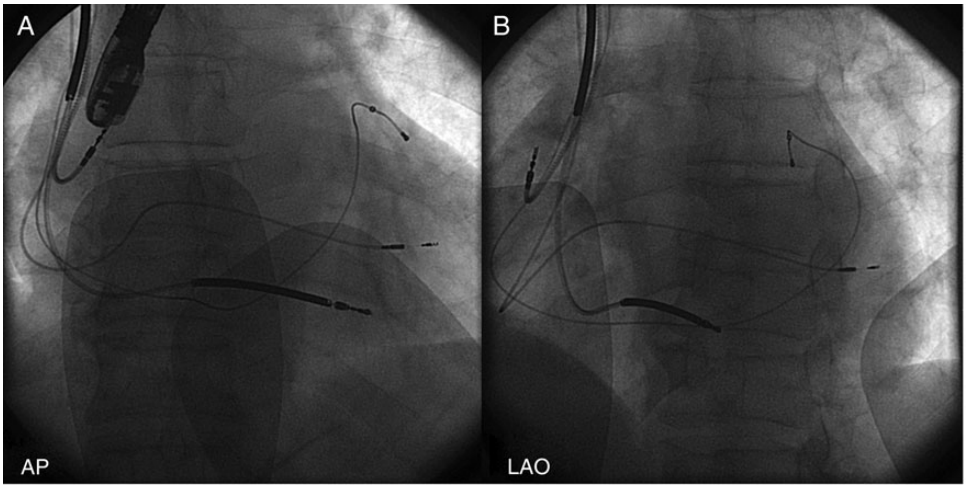


**Figure 2** X-rays in the anteroposterior and left anterior oblique view of the implant. The left ventricular endocardial pacing lead was located at the basal lateral site, different from the previous left ventricular coronary sinus lead.

atrial transseptal crossing. The total procedure time for successful implants was 132 ± 54 min, of which 61 ± 36 min were consumed for to the implantation of the LVEP lead. Fluoroscopy time was 27 ± 14 min. *Figure 3* shows the final LVEP lead positions in LV. The LVEP lead could be fixated at the desired endocardial site for 81% of the implants.

There were six LVEP lead dislodgements (at 0, 1, 1, 3, 37, and 43 days post-implant, respectively). These patients received a new LVEP lead (five immediately and one after 4 months), without further complications. In five patients, system infection required CRT system explant, two of which were classified as primary endpoints. All LVEP leads that needed removal could be extracted without further complications.

## Follow-up

Patients with successful LVEP lead implantation were followed for at least 12 months, with a mean follow-up of 17 ± 10 months.

## Electrical performance

Electrical performance at implant and during follow-up is illustrated in *Figure 4*.

## Primary endpoints

Thirty events met the endpoint definition in 27 of the 132 patients who underwent an LVEP implant procedure (primary endpoint, *Table 2*). The events happened on average 80 days after the implant procedure (median 2 days, range 0–682 days). The Kaplan–Meier estimate for freedom from primary endpoints at 6 months was 82.2% (95% CI 75.6–88.8%). The lower confidence limit was greater than 70%, so that the study's primary objective was met (*Figure 5*).

## Thromboembolic events

Five post-procedure strokes were reported (2.6 events per 100 patient-years; 95% CI 1.1–6.3). One stroke occurred after a failed LVEP implant attempt without transseptal puncture. Another was retinal artery thrombosis after right atrial lead repositioning at 6-month post-implant. None of the affected patients suffered moderate or severe persisting disability as indicated by modified Rankin Scale values between 0 and 2.

There were 14 TIA episodes observed in 9 patients (7.4 events per 100 patient-years; 95% CI 3.6–17.6), of which 4 were classified as primary endpoints due to invasive diagnostic or therapeutic actions. One patient experienced six TIA episodes. International normalized ratio measurements were available after seven thromboembolic events. In six cases (86%), the INR was below 2.5.

## Mitral valve regurgitation

There were no confirmed system-related mitral valve complications. In fact, echocardiographic findings suggested reduced mitral regurgitation (MR) as a consequence of improved LV function. After 6 months, 33% of patients showed improvement of MR by ≥1 class. One patient was hospitalized due to severe MR after 1-year post-implant, but the mechanism of this was unclear. The patient had moderate MR pre-implant. Mitral valve echocardiographic indices at baseline and at follow-up are summarized in *Table 3*.

## Clinical outcomes

Follow-up assessments are summarized in *Table 3*. At 6 months, 55% of patients had a reduction in LV end-systolic volume (LVESV) of at least 15%, and 59% of patients achieved an improvement of at least one NYHA class. In previous non-responders, the response rate, in terms of LVESV reduction of at least 15%, was 47%.

## Deaths

Twenty-three patients died during study follow-up. Fifteen deaths were due to heart failure or related renal or pulmonary failure, two from cancer, and one each from sudden cardiac death, gastrointestinal haemorrhage, pneumonia, and septic shock. One patient died from cardiac arrest after a haemothorax due to subclavian vascular perforation at the introducer incision site, 1-week

**Table 1 Patient baseline characteristics**

| Patient characteristics | All patients (*N* = 136) |
|---|---|
| General | |
| Gender (male) | 106 (78%) |
| Age (years) | 66 ± 10 |
| Body mass index (kg/m$^2$) | 28 ± 5 |
| Failed implant | 75 (55%) |
| Suboptimal CS anatomy | 30 (22%) |
| CRT non-responders | 31 (23%) |
| Cardiovascular and medical history | |
| Aetiology (ischaemic) | 56 (41%) |
| Myocardial infarction | 55 (40%) |
| Diabetes | 43 (32%) |
| AF | 68 (50%) |
| LBBB | 94 (69%) |
| $CHA_2DS_2$-VASc score[a] | 3.4 ± 1.3 |
| Baseline assessment | |
| NYHA class | |
| Class I | 4 (3%) |
| Class II | 29 (21%) |
| Class III | 93 (68%) |
| Class IV | 10 (7%) |
| QRS duration (ms) | 165 ± 32 |
| LVEF (%) | 29 ± 9 |
| LVESV (mL) | 151 ± 79 |
| LVEDD (mm) | 67 ± 10 |
| Mitral regurgitation, moderate or severe | 56 (41%) |
| BNP (pg/mL, *n* = 49) | 602 ± 843 |
| NT-proBNP (pg/mL, *n* = 78) | 3561 ± 4707 |
| INR | 1.7 ± 0.7 |
| Six-minute walk (m) | 326 ± 120 |
| Medication use | |
| Beta-blocker | 121 (89%) |
| ACEI/ARB | 120 (88%) |
| Diuretic | 120 (88%) |
| Aspirin | 50 (37%) |
| Anti-platelets other than aspirin | 17 (13%) |
| Anticoagulants | 104 (76%) |
| Implanted device | |
| CRT-D | 110 (81%) |
| CRT-P | 19 (14%) |
| ICD | 1 (1%) |
| None, failed implant | 6 (4%) |

LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; INR: international normalized ratio; CRT: cardiac resynchronization therapy; CS: coronary sinus; AF: atrial fibrillation; ICD: implantable defibrillator; CRT-P: cardiac resynchonization pacemaker; CRT-D: cardiac resynchronization defibrillator; ACEI: acetylconverting enzyme inhibitor; ARB: angiotensin receptor blocker; NT-proBNP: N-terminal of the prohormone brain natriuretic peptide; BNP: brain natriuretic peptide; LVEDD: left ventricular end diastolic dimension; LBBB: left bundle branch block.
[a]$CHA_2DS_2$-VASc score also calculated for patients without history of AF.

post-implant, and 1 patient died from a pulmonary artery perforation during a standard cardiac diagnostic catheterization 3-month post-implant. These deaths were not related to the transseptal implant tools, transseptal implant procedure, or/and LVEP lead.

*Figure 6* shows a Kaplan–Meier curve for mortality in the patients who had an LVEP implant attempt. Estimated mortality rates at 6, 12, and 24 months after first implant attempt were 8.3, 14.4, and 18.4%, respectively.

# Discussion

The ALSYNC study demonstrates clinical feasibility, and provides an early indication of possible risk and benefit of LVEP for CRT patients who would not otherwise benefit from conventional CRT. The implant procedure was successful in 89% of the patients. At 6-month post-implant, 82.2% of the patients remained free of complications related to implantation or presence of an LVEP lead. The LVESV was reduced by at least 15% in 55% of patients, and 59% achieved an improvement of at least one NYHA class.

## Left ventricular endocardial pacing

Cardiac resynchronization therapy offers appropriately selected heart failure patients improvement in quality of life with reduction in hospitalizations and mortality.[1,2]

However, CRT has important limitations. Between 5 and 10% of implant attempts result in failure to institute the therapy and ~30% of patients who are successfully implanted show no clinical improvement —so-called non-responders.[1] CRT device reprogramming to optimize atrioventricular as well as interventricular pacing output timing has been disappointing with large studies failing to demonstrate any enhanced clinical effectiveness.[7]

There is evidence that the LV pacing site may be of critical importance in defining patient response,[4] although there is debate as to how best to determine the optimal pacing site. Nevertheless, with conventional CRT therapy, it is the anatomy of the coronary sinus and its tributaries, poor lead electrical performance, and phrenic nerve stimulation that limit LV epicardial pacing site selection. Such limitations are essentially resolved by accessing the LV endocardial landscape for the delivery of CRT.[5] Garrigue *et al.*[8] studied 15 patients who had an epicardial lead implanted through the coronary sinus and compared them with 8 patients with LVEP leads placed by transseptal puncture following identification of unsuitable coronary sinus anatomy. They reported a significant improvement in the echocardiographic and Doppler variables in the patients who had LVEP. Bracke *et al.*[9] reported that LVEP improved the clinical efficacy in a non-responder to CRT. However, LVEP is difficult to achieve using conventional tools and techniques and may be associated with important morbidity risks related to thromboembolic events in the systemic circulation or functional mitral valve impairment related to a transmitral pacing lead system.[5]

## Feasibility of the pectoral transseptal left ventricular endocardial pacing lead implant

Cardiac resynchronization therapy with LVEP using the 3830 lead and an atrial transseptal LVEP lead placement has been reported using vari-

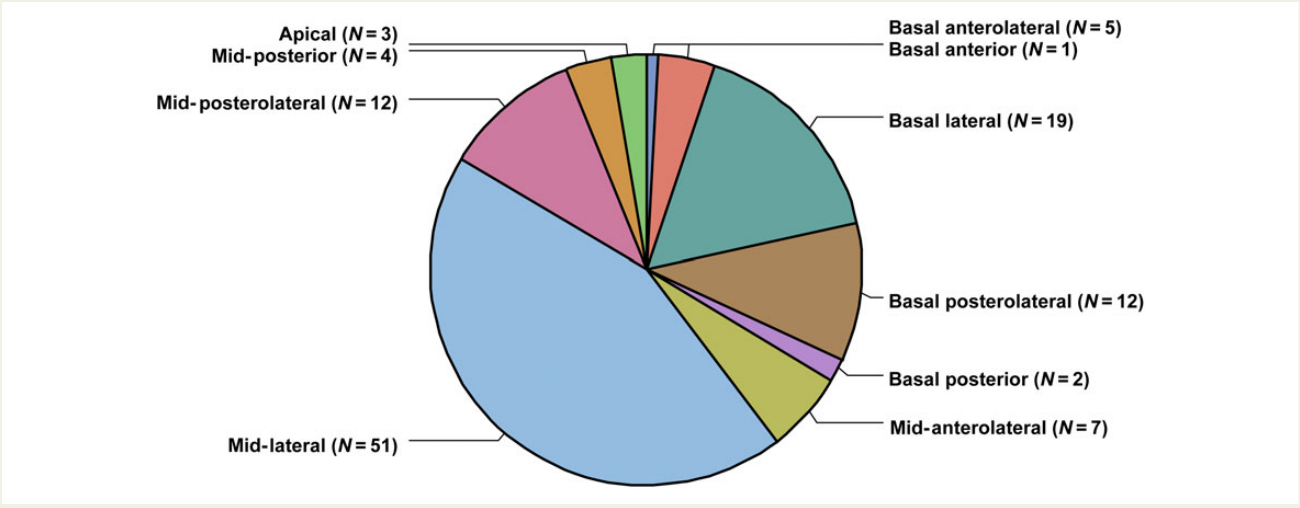


**Figure 3** Final left ventricular endocardial pacing lead position (for two patients not reported).

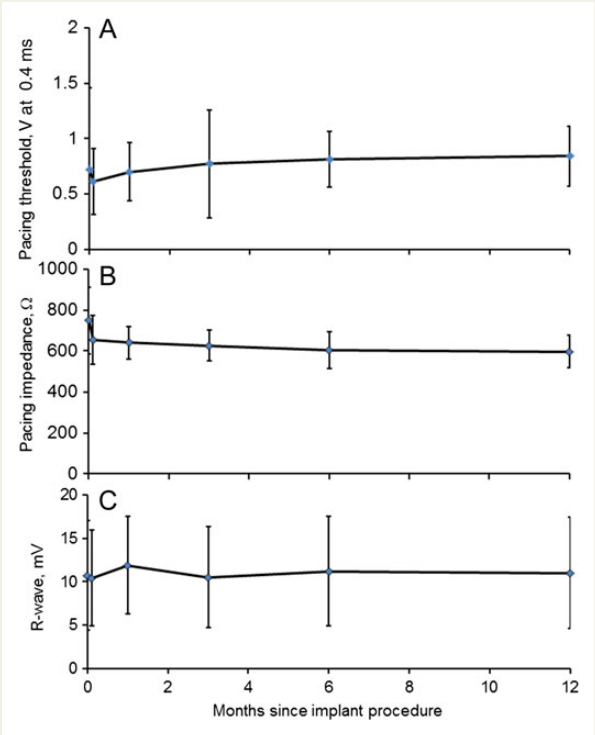


**Figure 4** Bipolar electrical performance of the left ventricular endocardial pacing lead: (*A*) pacing threshold, (*B*) pacing impedance, and (*C*) R-wave.

ous combinations of inferior transseptal catheterization and superior lead placement,[10] but there has been no previous human clinical evaluation of a purpose-designed lead delivery system and procedure.

The ALSYNC study was a prospective and multicentre study evaluating clinical performance of an investigational telescopic atrial transseptal LVEP lead implant system and the SelectSecure® Model 3830 lead. The system allows an LVEP lead to be implanted via a single-incision pectoral approach independent of patient anatomy and it was used in patients with no viable access to the CS or with a worsened or unchanged symptomatic status after a previous CRT implant. The implant success rate of 89% and 95% CI (83–94%) demonstrated feasibility of the procedure.

## Complications and major risks

HF without AF is associated with risks of stroke and thromboembolism with reported clinically apparent stroke rates of 1.3–3.5% per year.[11] Atrial fibrillation increases thromboembolic risk in heart failure, presumably in part by causing chaotic contraction of the cardiac atria.[12] Warfarin therapy reduces the risk of ischaemic stroke (0.72 events per 100 patient-years), but is offset by an increased risk of major haemorrhage (1.78 events per 100 patient-years).[13] Implantation of an LVEP lead may increase this risk. There are numerous reports in the literature of 'inadvertent' LVEP with associated thromboembolic events.[14] A retrospective review of 51 LVEP patients with a median of 24-month follow-up reported 4.6 stroke events per 100 patient-years and the risk seemed to be strongly correlated with a sub-therapeutic level of anticoagulation.[15]

In this study, the incidence of mild strokes was 2.6 events per 100 patient-years. Stroke detection was an important element in the study protocol. The QVSFS was used which has high sensitivity but only moderate specificity.[16] It could be argued that the ability to precisely diagnose stroke vs. TIA was limited in the study by the inability to perform magnetic resonance imaging (MRI). However, the standard of care for diagnosing a neurological thromboembolic event is not MRI but computed tomography scanning and neurological assessment. It is a challenge to compare the observed thromboembolic events in the ALSYNC study to the existing published literature because of differences in patient population and stroke/TIA definition. The ALSYNC study included sicker HF patients (failed CRT implant or CRT non-responders) who were mostly in NYHA class III and IV and had a high prevalence of AF at baseline.

Anticoagulation, particularly warfarin, appears to be effective in mitigating thromboembolic risk for LVEP,[10,15] but is limited by the ability to maintain effective therapeutic levels of anticoagulation.[15]

**Table 2 Primary endpoint details**

| Cohort Time frame (*n* patients at risk) | Implant failed Implant (14) | Implant success | | | | All patients Total (132) |
|---|---|---|---|---|---|---|
| | | Implant (118) | PHD (118) | 6 months (105) | >6 months (94) | |
| Procedure complication | | | | | | 6 |
| Intracardiac thrombus | 3 | | | | | |
| Aorta puncture | 1 | | | | | |
| Pericardial effusion | | 1 | | | | |
| Pneumothorax | 1 | | | | | |
| Bleeding | | | | | | 7 |
| Pocket haematoma | | 2 | 3 | | | |
| Nose bleeding | | 1 | | | | |
| Retroperitoneal haematoma | | | | 1 | | |
| Lead dislodgement | | 1 | 3 | 2 | | 6 |
| Confirmed stroke | | | | | | 5 |
| Stroke | 1 | | | 1 | 2 | |
| Retinal artery thrombus | | | | | 1 | |
| Transient ischaemic attack* | | 1 | | 2 | 1 | 4 |
| Infection | | | | 1 | 1 | 2 |
| Total | 6 | 6 | 6 | 7 | 5 | 30 |

PHD: pre-hospital discharge.
*Adjudicated by Adverse Event Adjudication Committee.

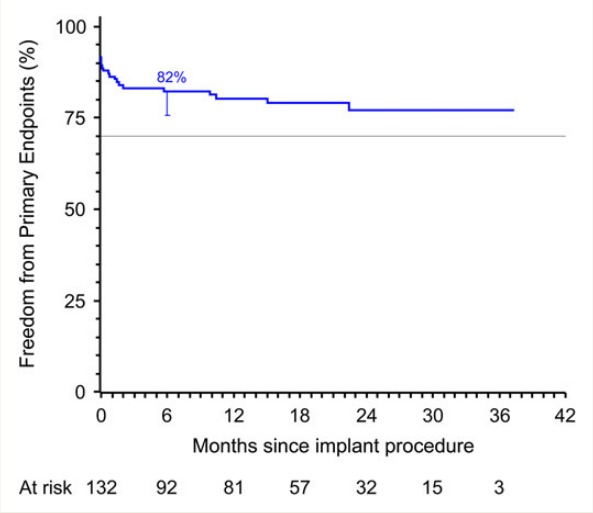


**Figure 5** Kaplan–Meier estimate for the percentage of patients free from primary endpoints. The horizontal reference line corresponds to the pre-specified lower limit for acceptable performance. Numbers under the figure are the number of patients at risk.

There was a relatively high incidence of implant site haematomas compared with that observed in conventional CRT implants. This was expected given the in-procedure and life-time anticoagulation requirements. Implant site bleeding issues were mitigated by careful pocket management.

The protocol required lifelong anticoagulation with vitamin K antagonists targeting an INR of 3 with a recommended range of 2–4, based on the existing literature. Given the incidence of stroke and bleeding complications in the study, a narrower INR range of 2.5–3.5 is recommended for LVEP patients (similar to those with a mechanical valve).[17]

Mitral valve function was not adversely impacted by the chronic presence of the 3830 lead, consistent with the finding by Rademakers *et al.*[15] Only one adverse event was reported with worsening mitral regurgitation. It is not possible to exclude any deleterious effect in all patients, although there was no direct evidence for lead-related change in mitral valve function in any given study patient. Indeed, in the study population as a whole there was notable improvement in mitral valve function. The observed mortality was 14.4% at 12-month post-implant, mainly caused by progression of HF. A comparative study is warranted to assess survival benefit of LVEP, although ALSYNC included a relatively sicker patient population, with 76% of patients in NYHA class III or IV, 23% non-responder to conventional CRT, 50% having a history of AF, and 76% on oral anticoagulation at enrolment.

## Clinical outcome of left ventricular endocardial pacing

Haemodynamic benefit of LVEP vs. LV epicardial pacing has been considered, but not in a controlled or prospective manner.[18] Given that limitation, there is evidence that LVEP offers greater LV functional benefit than does epicardial LV pacing.[8] That so many patients

**Table 3 Echocardiographic indices and clinical outcomes**

| | Baseline ($n = 118$) | 6 months ($n = 105$) | Change | *P*-value* | Response definition | Response rate for all patients ($n = 118$) | Response rate for non-responders with prior CRT ($n = 31$) |
|---|---|---|---|---|---|---|---|
| LVESV | 149 ± 79 mL | 121 ± 74 mL | 29 ± 60 mL reduction | <0.0001 | ≥15% relative reduction | 55% | 47% |
| | | | | | ≥30% relative reduction | 33% | 5% |
| LVEF | 29 ± 10% | 36 ± 12% | 7 ± 10% increase | <0.0001 | ≥5% absolute increase | 64% | 61% |
| Mitral regurgitation | Moderate/ severe: 41% | Moderate/ severe: 30% | | 0.035 | ≥1 class improvement | 33% | 43% |
| NYHA class | I/II/III/IV: 3%/ 20%/69%/7% | I/II/III/IV: 19%/ 51%/28%/2% | | <0.0001 | ≥1 class improvement | 59% | 52% |
| Six-minute walking test | 332 ± 117 m | 388 ± 135 m | 47 ± 87 m increase | 0.004 | ≥60 m increase | 44% | 42% |

LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; CRT: cardiac resynchronization therapy.
**P*-value from repeated-measures linear or multinomial regression model.

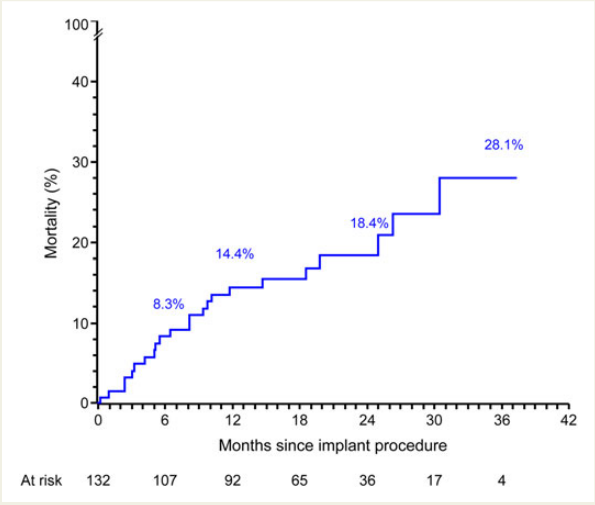


**Figure 6** Kaplan–Meier curve for mortality in the patients who had a left ventricular endocardial pacing implant attempt.

fail to respond to conventional LV epicardial pacing for CRT provides further impetus for exploration of the LVEP approach.

Although the study was not designed to assess the impact of LVEP on LV function and clinical status and the protocol did not require optimization of the pacing site, there were signals of potential benefit. Left ventricular systolic function, as measured by multiple transthoracic echocardiographic indices, as well as six-minute walking test and NYHA class, showed improvement with LVEP. Of note, 33% of the patients showed 'super-response' at 6 months, as defined by an LVESV reduction of 30% or greater.[19] It was also noteworthy that patients who were non-responders to conventional epicardial CRT showed response to LVEP CRT. Other investigators have demonstrated both acute and chronic differential haemodynamic response to LVEP and LV epicardial pacing CRT with the potential for greater response at LVEP sites. If our findings are confirmed by prospective randomized studies, then it would further reinforce the expectation that LVEP may offer better long-term clinical outcomes. That the ALSYNC patient population seemed to indicate the potential for CRT response, when a conventional CRT approach had not achieved benefit, is tantalizing, but again requires testing by an adequately powered, randomized prospective clinical trial to show the effectiveness of LVEP compared with conventional therapy.

It is arguable that the outcome of the ALSYNC study in terms of its risk and benefit profile paves the way for such a study.

## Limitations

The ALSYNC system requires visual guidance for locating the fossa ovalis and safe performance of a transseptal puncture. The ALSYNC study was not a comparative study; thus, the true benefit to risk ratio of LVEP compared with other alternatives for LV epicardial pacing cannot be estimated. Additionally, bias, including observer bias and regression to the mean, cannot be excluded for the secondary endpoints. There was no systematic experience of long-term LVEP lead extraction in the context of thromboembolic complication or system infection.

## Conclusion

The ALSYNC study demonstrates clinical feasibility, and provides an early indication of possible risks and benefits of LVEP. This approach to CRT warrants a comparative study designed to evaluate the clinical effectiveness and safety of LVEP to other alternatives for LV epicardial pacing.

# Authors' contributions

B.G., M.v.G.: performed statistical analysis; J.M., Z.Y.: handled funding and supervision; J.M., M.B., L.G., C.L., F.R., S.T., P.D., Z.Y., B.G., M.v.G., R.Y., P.J., on behalf of the ALSYNC Investigators: acquired the data; J.M., Z.Y.: conceived and designed the research; J.M., Z.Y., B.G., M.v.G.: drafted the manuscript; J.M., M.B., L.G., C.L., F.R., S.T., P.D.,

Z.Y., B.G., M.v.G., R.Y., P.J., on behalf of the ALSYNC Investigators: made critical revision of the manuscript for key intellectual content.

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**Conflict of interest:** J.M. reports consulting fees and honoraria from Medtronic, Inc. and speaker's bureau for Boston Scientific Corp. and Sorin Group; M.B. reports speaker's bureau for Medtronic, Inc., Boston Scientific Corp., and Biotronik; L.G. reports grants from Medtronic, Inc.; C.L. reports grants from Medtronic, Inc., St. Jude Medical, Inc., Boston Scientific Corp., and Sorin Group; S.T. reports grant from Medtronic, Inc.; P.D. reports grants from Medtronic, Inc., Boston Scientific Corp., St. Jude Medical, Inc., and Sorin Group; Z.Y. reports salary from Medtronic, Inc.; B.G. reports salary from Medtronic, Inc.; M.v.G. reports salary from Medtronic, Inc.; R.Y. reports consulting fees and honoraria from Medtronic, Inc.

# Appendix A

**Table A1 List of Adverse Event Adjudication Committee (AEAC) and Data Monitoring Committee (DMC) members**

| Name | Institute | Committee |
|---|---|---|
| Prof D. Böcker (chair) | St. Marienhospital, Hamm, Germany | AEAC |
| Prof D. Lacroix | University of Lille, France | AEAC |
| Dr T. Lawo | University Hospital Bergmannsheil, Bochum, Germany | AEAC |
| Dr A. Pietersen | KPLL, Copenhagen, Denmark | AEAC |
| Prof H. Pürerfellner | St. Elizabeth's Sisters Hospital, Linz, Austria | AEAC |
| Prof M. Rosenqvist | Karolinska Institutet, Stockholm, Sweden | AEAC |
| Prof V. Thijs | University Hospital Leuven, Belgium | AEAC |
| Dr John Fisher (chair) | Montefiore Medical Center, New York, USA | DMC |
| Dr Irfan Altafullah | Minneapolis Clinic of Neurology, USA | DMC |
| Dr Alan Bank | United Hospital, Saint Paul, USA | DMC |
| Andrew Mugglin, PhD | Division of Biostatistics, University of Minnesota, USA | DMC |

# Appendix B

**Table B1 List of principal investigators involved in the ALSYNC study**

| Principal investigator | Institute |
|---|---|
| M. Biffi | S Orsola-Malpighi University Hospital, Bologna, Italy |
| D. Connelly | Golden Jubilee National Hospital, Glasgow, UK |
| P. Defaye | University Hospital Grenoble, France |
| L. Gellér | Semmelweis University, Heart Center, Budapest, Hungary |
| D. Gras | Nouvelles Cliniques Nantaises, Nantes, France |
| J.M. Herzet | Centre Hospitalier Regional de la Citadelle, Liège, Belgium |
| P. Jais | Hôpital Cardiologique Haut-Lévêque, Bordeaux, France |
| E. Lau | Royal Victoria Hospital, Belfast, UK |
| C. Leclercq | University Hospital Rennes, France |
| J. Morgan | Southampton General, Hospital, Southampton, UK |
| H. Poty | Infirmerie Protestante, Lyon, France |
| F. Ruffa | *Alessandro* Manzoni Hospital, Lecco, Italy |
| M. Santini | San Filippo Neri Hospital, Rome, Italy |
| O. Segal | The Heart Hospital, London, UK |
| R. Tavernier | St John's Hospital Bruges, Brugge, Belgium |
| S. Tung | Saint Paul's Hospital, Vancouver, Canada |
| K. Vernooy | Maastricht University Medical Center, Maastricht, The Netherlands |
| R. Yee | London Health Sciences Centre, London, Canada |

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