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Sex-specific difference in outcome after cardiac resynchronization therapy

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Aims Observation of better outcome in women after cardiac resynchronization therapy (CRT) has led to controversies about a potential sex-specific response. In this study, we investigated to which extent this sex-specific difference in CRT outcome could be explained by differences in baseline characteristics between both sexes.

Methods and results We retrospectively analysed data from a multicentre registry of 1058 patients who received CRT. Patients were examined by echocardiography before and 12 ± 6 months after implantation. Response was defined as ≥15% reduction of left ventricular end-systolic volume at follow-up. Patient's characteristics at baseline, including New York Heart Association class, ejection fraction, QRS width and morphology, ischaemic aetiology of cardiomyopathy (ICM), number of scarred segments, age at implantation, atrial fibrillation, and mechanical dyssynchrony (Dyss) were analysed. Patients were followed for a median duration of 59 months. Primary end point was all-cause mortality. Women (24% of the population) had less ICM (23% vs. 49%, $P < 0.0001$), less scarred segments (0.4 ± 1.3 vs. 1.0 ± 2.1, $P < 0.0001$), more left bundle branch block (LBBB; 87% vs. 80%, $P = 0.01$), and more Dyss at baseline (78% vs. 57%, $P < 0.0001$). Without matching baseline differences, women showed better survival (log rank $P < 0.0001$). After matching, survival was similar (log rank $P = 0.58$). In multivariable analysis, female sex was no independent predictor of neither volumetric response ($P = 0.06$) nor survival ($P = 0.31$).

Conclusion Our data suggest that the repeatedly observed better outcome in women after CRT is mainly due to the lower rate ICM and smaller scars. When comparing patients with similar baseline characteristics, the response of both sexes to CRT is similar.

Keywords sex • gender • CRT • mechanical dyssynchrony • apical rocking

Introduction

Cardiac resynchronization therapy (CRT) has become an accepted treatment for patients with symptomatic systolic heart failure and prolonged QRS duration. It is associated with improvement of functional status and reduction in both hospitalization and mortality.[1,2] Nevertheless, a relevant fraction of the treated patients does not respond to therapy,[3] which has triggered various studies attempting to better characterize potential predictors of a successful CRT. Patient's sex has been suggested as one of these predictors.

While only few studies have shown similar outcome between men and women after CRT,[2,4] most authors found evidence for relevant

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sex-based differences. Furthermore, CRT seems to be under-utilized in women,[5] and the implantation has more complications.[6] Women have also been reported to have a lower frequency of ischaemic aetiology of heart failure[7] and more frequently a typical LBBB configuration of the QRS complex in electrocardiogram (ECG).[8] In spite of these obvious differences in male and female patient characteristics, most studies have concluded that female sex—*per se*—is an independent predictor of better outcome.[9,10]

LBBB and QRS width have been suggested to have a better prognostic value in women,[11] potentially due to their smaller heart. On the other hand, ECG criteria are associated with considerable variability in both identifying true LBBB[12] and measuring the QRS duration.[13]

Baseline assessment of mechanical dyssynchrony (Dyss) has been associated with better outcome and response to therapy.[14,15] However, only few studies included Dyss assessment in their analysis of CRT outcome in both sexes.[16]

In our study, we, therefore, aimed at investigating whether women have a better survival and volumetric response to CRT compared with men. For this, we investigated the impact of the potential confounding factors that may explain the difference in outcome between both sexes. We further analysed specific markers of Dyss which can be observed on echocardiographic images as a short septal contraction pulling the apex septally ['septal flash' (SF)] followed by a delayed lateral wall contraction which causes a lateral motion of the apex ['apical rocking' (ApRock)]. These markers have been shown to be associated with better outcome and volumetric response to CRT.[17] However, their potential relation to the phenomenon of a sex-specific CRT outcome had not been studied so far.

Methods

We retrospectively analysed data of 1058 patients who received CRT between 1999 and 2012 in six European centres,[15] detailed data of the contributing centres may be found in the Supplementary data online. The indication for CRT implantation was based on clinical considerations and left to the discretion of the treating physician. All patients were on optimized pharmacologic therapy for at least 3 months before CRT. Ischaemic origin of heart failure was proven by coronary angiography and/or records of myocardial infarction. At the time of inclusion, none of the candidates required interventional or surgical treatment for coronary disease. Patients were followed for a median duration of 59 months (interquartile range 37–86 months). Data on mortality were collected from medical records, by interviews with the patient's general practitioner or relatives, and/or from national death registries.

Echocardiography

Patients were scanned by echocardiography before and 12 ± 6 months after CRT implantation. Dyss was assessed by echocardiography at baseline examination and was defined visually by the presence of ApRock or SF[15] (Supplementary data online, *Videos S1* and *S2*). Left ventricular (LV) volumes and ejection fraction (EF) were measured using the modified biplane Simpson's method. Patients with LV end-systolic volume (LVESV) decrease of ≥15% at the follow-up visit were considered as volumetric responders. All echocardiographic readings were initially performed by two experienced readers in echocardiography. A blinded third reader was asked in case of disagreement.

For estimation of scar burden of the left ventricle, the extent and location of myocardial scars were visually assessed by analysis of echocardiographic images. Using an 18-segment model of the left ventricle, a myocardial segment which is thin, hyper-echogenic and akinetic or dyskinetic was considered as scarred. The mean number of scarred segments identified by the two readers was used. A validation of this approach is provided in the Supplementary data online.

Resynchronization therapy

All patients received a biventricular pacemaker. LV pacing leads were positioned, guided by coronary venography, preferably in lateral and posterolateral venous branches. Device settings were optimized after implantation based on surface ECG and Doppler echocardiography as deemed clinically appropriate.[18]

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Normally distributed data were compared between groups using the unpaired *t*-test for continuous variables and the χ^2 test for categorical variables. In case of serious deviations from the normal distribution Mann–Whitney *U* test was used for comparison. Survival rates were expressed using Kaplan–Meier's curves with the corresponding 95% confidence limits, while differences in survival were compared between groups using a Log-rank test. Predictors of long-term survival were analysed in Cox proportional hazards models, while predictors of volumetric response to therapy were analysed in logistic regression models. LV volumes were investigated in an earlier analysis of this database[15] and found to be not predictive of outcome in the univariable analysis; therefore, they were not included in the multivariable regression models of the current work. Furthermore, to determine whether the prognostic value of baseline comorbidities would differ based on sex, the statistical interaction between female sex and each of them was analysed separately in univariate analysis. However, the interaction terms were not entered in multivariable analysis to avoid complicated models with an inappropriately high number of variables. To compensate for the marked discrepancy in both numbers and baseline characteristics of men and women in the study, cohort matching was performed using the 'case–control matching' function of SPSS (see Supplementary data online for details). With this, we created a male and female subgroup, matched in both number of patients and all baseline parameters (*Table 1*). Using Kappa statistics, interobserver variability for ApRock and SF was tested in the whole study population, while intraobserver variability was tested in 100 randomly selected patients. Data analysis was performed using SPSS.[19] Two-sided *P*-value of <0.05 was considered significant.

Results

Baseline characteristics of both sexes are shown in *Table 2*. In women (24% of the population), the frequency of ischaemic aetiology of cardiomyopathy (ICM) was lower (23% vs. 49%, $P < 0.0001$), they had lower number of scarred segments (0.4 ± 1.3 vs. 1.0 ± 2.1, $P < 0.0001$), more frequently a LBBB like pattern in baseline ECG (87% vs. 80%, $P = 0.01$), and more Dyss at baseline (78% vs. 57%, $P < 0.0001$). Other characteristics did not differ from men.

Volumetric response to therapy

There was no significant difference between both sexes in the time from CRT implantation till the follow-up echocardiography when

Table 1 Clinical and echocardiographic characteristics of the study population after matching of all different baseline confounders between both sexes

	Female ($n = 172$)	Male ($n = 172$)	*P*-value
Dyss, *n* (%)	154 (89)	154 (89)	1.0
LVEF (%)	26 ± 6	25 ± 6	0.41
LBBB, *n* (%)	166 (96)	166 (96)	1.0
QRS width (ms)	168 ± 23	171 ± 23	0.33
AF, *n* (%)	30 (17)	30 (17)	1.0
NYHA	3.0 ± 0.5	2.9 ± 0.5	0.73
ICM, *n* (%)	35 (20)	35 (20)	1.0
Age at implantation (years)	64 ± 10	63 ± 11	0.20
Scarred segments, *n*	0.2 ± 0.9	0.2 ± 0.8	0.66

AF, atrial fibrillation; Dyss, mechanical dyssynchrony; ICM, ischaemic origin of cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 2 Baseline clinical and echocardiographic characteristics of the study population

	Female ($n = 254$)	Male ($n = 804$)	*P*-value
Dyss, *n* (%)	197 (78)	455 (57)	<0.0001
LVEF (%)	26 ± 6	27 ± 7	0.16
LBBB, *n* (%)	222 (87)	640 (80)	0.01
QRS width (ms)	168 ± 27	170 ± 29	0.25
AF, *n* (%)	56 (22)	205 (25)	0.20
NYHA	2.9 ± 0.5	2.9 ± 0.6	0.20
ICM, *n* (%)	58 (23)	397 (49)	<0.0001
Age at implantation (years)	64 ± 11	64 ± 11	0.57
Scarred segments, *n*	0.4 ± 1.3	1.0 ± 2.1	<0.0001

AF, atrial fibrillation; Dyss, mechanical dyssynchrony; ICM, ischaemic origin of cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

volume response was assessed (12.0 ± 4.0 months vs. 11.9 ± 3.7 months, for men and women, respectively, $P = 0.69$).

In the entire cohort, volume response rates were significantly higher in women compared to men (74% vs. 53%, $P < 0.0001$, *Figure 1A*). However, we found no significant difference in volumetric response between the matched groups (76% vs. 68%, $P = 0.13$, *Figure 1B*).

Univariate logistic regression analysis showed that women had a two and a half times higher probability for volumetric response to therapy than men [odds ratio (OR) 2.55, 95% confidence interval (CI): 1.75–3.71; $P < 0.0001$]. However, in multivariable analysis, female sex was not independently associated with volumetric response to therapy ($P = 0.06$). Independent predictors of volumetric response to therapy were only Dyss (OR: 16.31, 95% CI: 9.5–28.08; $P < 0.0001$), LVEF (OR: 0.96, 95% CI: 0.93–0.99; $P = 0.008$), and New York Heart Association (NYHA) functional class (OR: 0.55, 95% CI: 0.35–0.86; $P = 0.009$, *Figure 2A*).

Investigating predictors of volumetric response to therapy per-sex separately, our data showed that Dyss was the only variable that was highly associated with volumetric response to therapy regardless of sex, both in women (OR: 20.9, 95% CI: 5.15–84.58; $P < 0.0001$) and men (OR: 16.5, 95% CI: 9.01–30.03; $P < 0.0001$, *Figure 2B*).

Survival analysis

During follow-up, the survival rate of women was significantly higher in the entire cohort (Log- rank $P < 0.0001$, *Figure 3A*). However, between the matched groups, survival rates were similar (log rank $P = 0.58$, *Figure 3B*).

In univariate cox proportional hazards analysis with an end point of all-cause mortality, women had more favourable survival compared with men after CRT (OR: 3.12, 95% CI: 2.51–3.98; $P < 0.0001$). However, in multivariable analysis, female sex was not independently associated with better survival ($P = 0.31$). Independent predictors of survival were Dyss at baseline (OR: 2.93, 95% CI: 2.21–3.98; $P < 0.0001$), NYHA class (OR: 0.62, 95% CI: 0.48–0.79; $P < 0.0001$), and age at implantation (OR: 0.97, 95% CI: 0.95–0.98; $P < 0.0001$, *Figure 4A*).

Investigating predictors of survival per-sex separately, similar to the finding of the corresponding logistic regression analysis, our data showed that Dyss was the only variable that was associated with better survival regardless of sex (OR: 5.88, 95% CI: 2.63–13.15; $P < 0.0001$ in women and OR: 2.56, 95% CI: 2.08–3.70; $P < 0.0001$ in men, *Figure 4B*).

Evaluating the statistical interaction between sex and baseline comorbidities in prediction of volumetric response and survival after CRT, our data showed a significant interaction between female sex and most of the baseline variables including Dyss and ICM for the prediction of both volumetric response and survival (*Table 3*).

Relation between Dyss and ICM

In our data, patients with ischaemic aetiology of heart failure showed significantly less Dyss compared with patients with non-ischaemic aetiology (58% vs. 79%, $P < 0.001$). Furthermore, in a multivariable regression analysis for identifying predictors of Dyss, ICM was strongly and independently associated with less Dyss (OR: 0.54, 95% CI: 0.36–0.81; $P = 0.003$, Supplementary data online, *Table S1*).

Reproducibility of Dyss assessment

The intraobserver agreement for visual assessment of ApRock and SF had been reported earlier[15] and was 93% (*k*: 0.81, 95% CI: 0.66–0.95) and 93% (*k*: 0.80, 95% CI: 0.66–0.95), respectively. The interobserver agreement was 86% (*k*: 0.71, 95% CI: 0.67–0.76) for both ApRock and SF.

Discussion

In this multicentre study, we investigated to which extent the differences in baseline characteristics between both sexes can explain the common observation of better CRT outcome in women.

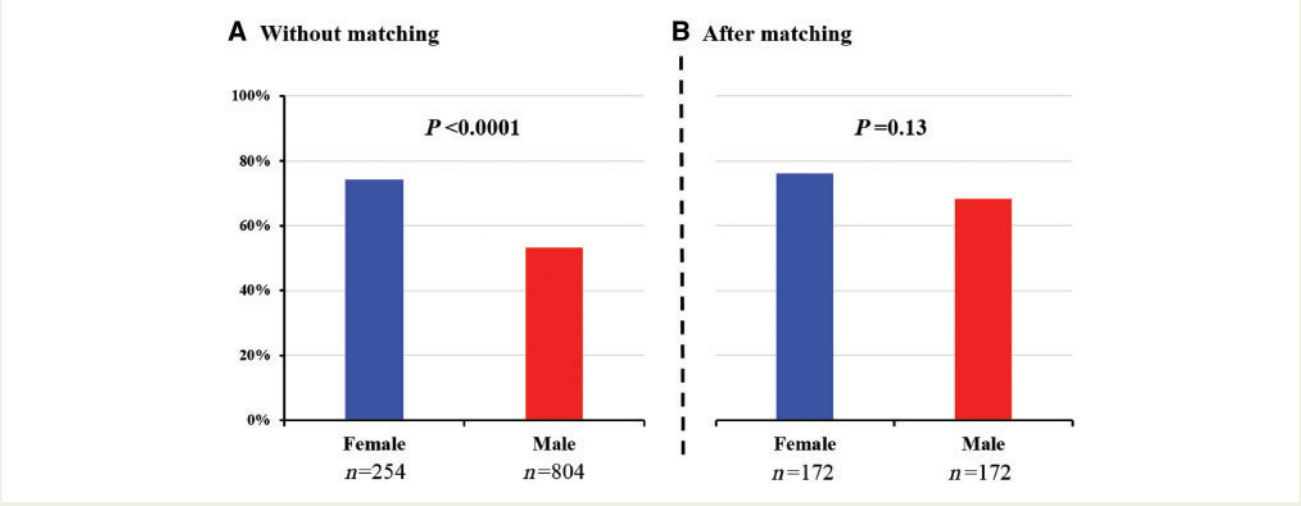

Figure 1 Long-term volumetric response rates to CRT in both sexes without matching of baseline characteristics (*A*) and after matching (*B*).

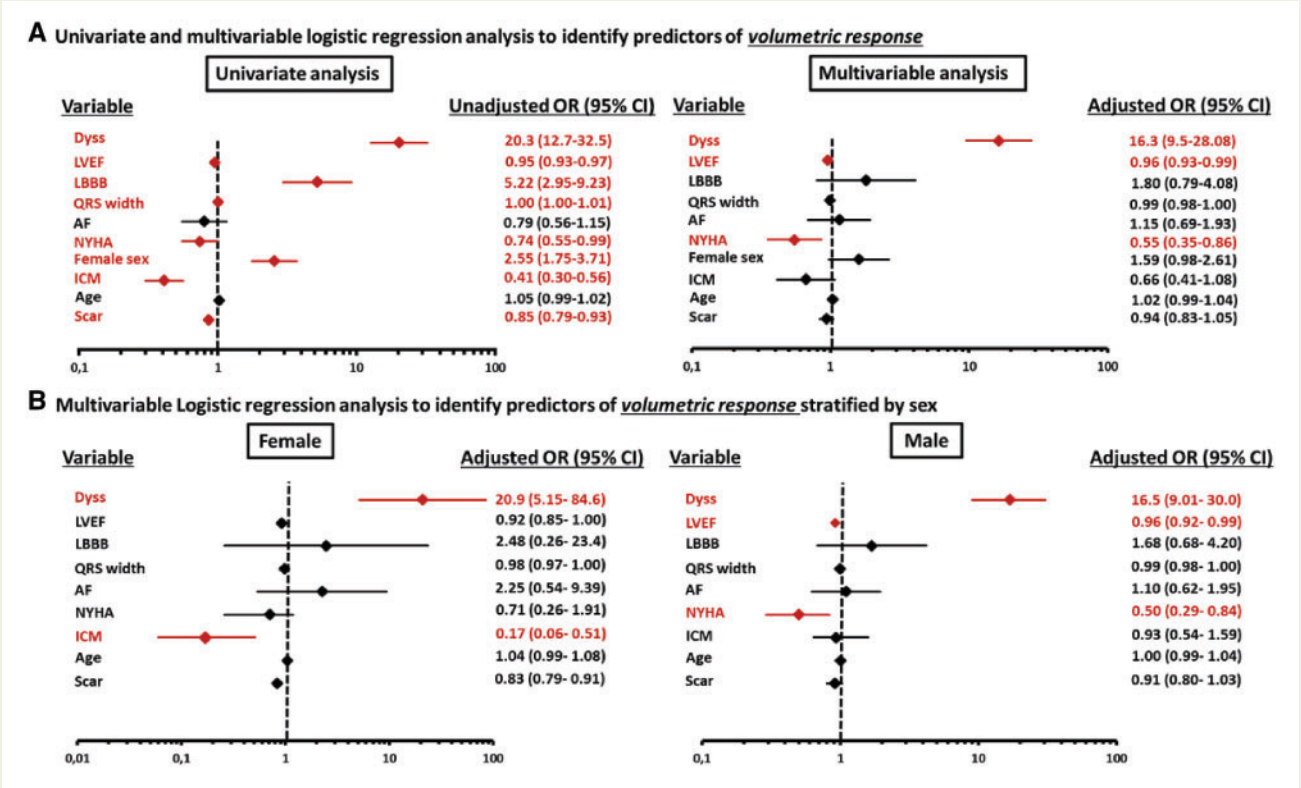

Figure 2 Univariate and multivariable logistic regression analyses for identifying predictors of volumetric response in the entire study population (*A*) and multivariable analysis stratified by sex (*B*). ORs are presented with 95% CI in parentheses. Significant associations are marked in red ($P < 0.05$). AF, atrial fibrillation; Dyss, mechanical dyssynchrony; ICM, ischaemic origin of cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Our main findings were (i) baseline characteristics of men and women differed significantly; (ii) female sex was associated with better survival and favourable volumetric response to therapy; (iii) after adjustment for baseline characteristics, both survival and volumetric response to therapy of men and women proved to be equal; and (iv) Dyss at baseline showed, regardless of sex, the strongest association with both, volumetric response and better survival.

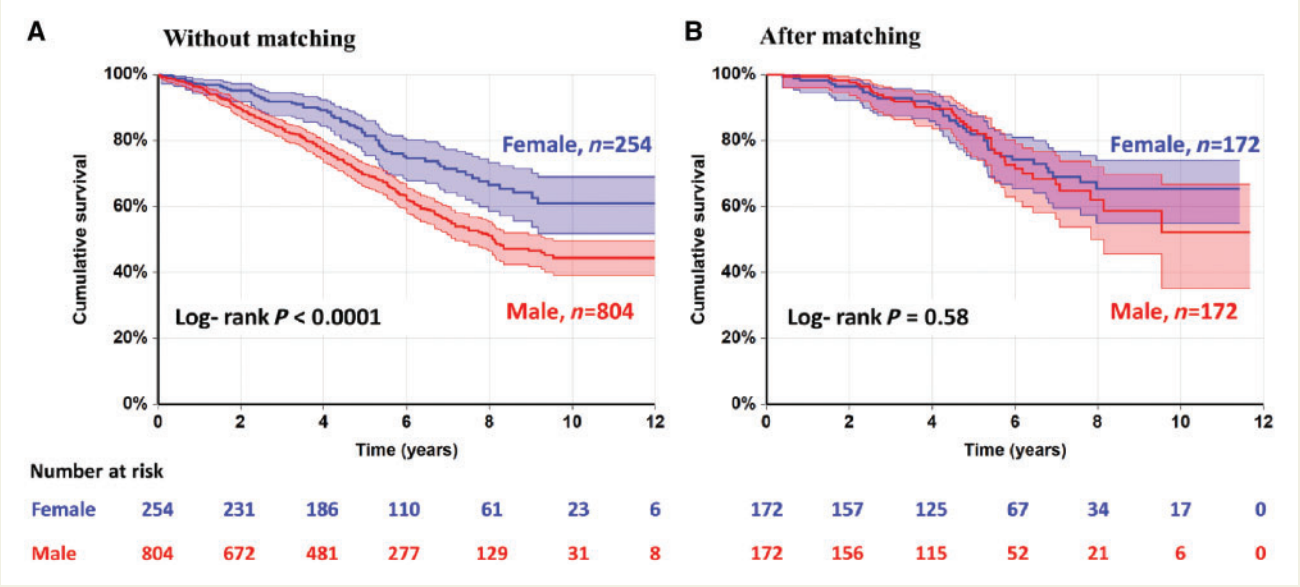

Figure 3 Kaplan–Meier survival curves (solid lines) with the corresponding 95% confidence limits (semi-transparent thick lines) depicting long-term survival for women (in blue) and men (in red) without (*A*) and after (*B*) matching of all baseline characteristics.

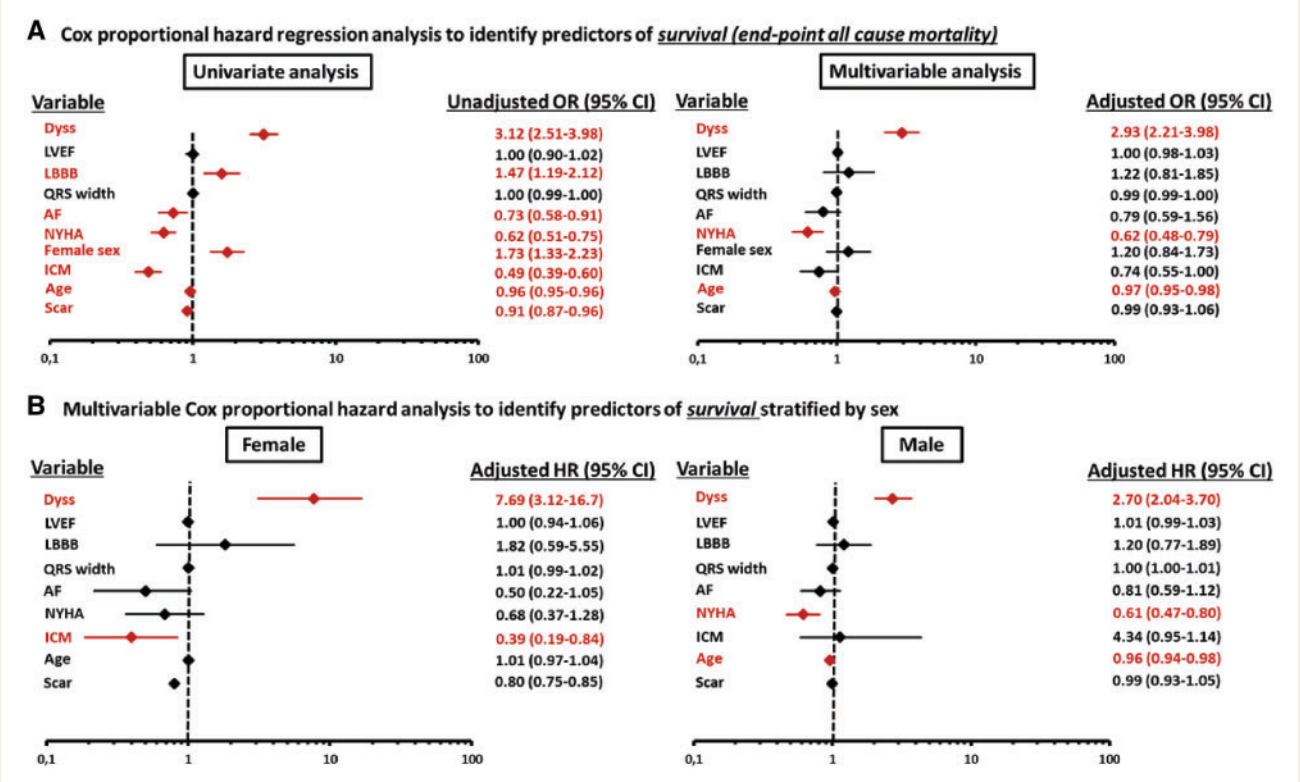

Figure 4 Univariable and multivariable cox regression analyses for identifying predictors of survival (end point: all-cause mortality) in the entire study population (*A*) and multivariable analysis stratified by sex (*B*). ORs are presented with 95% CI in parentheses. Significant association are marked in red ($P = 0.05$). AF, atrial fibrillation; Dyss, mechanical dyssynchrony; ICM, ischaemic origin of cardiomyopathy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 3 Statistical interactions between female sex and baseline comorbidities

P-value for volumetric response		*P*-value for survival (end point is all-cause mortality)	
Interaction	***P*-value**	**Interaction**	***P*-value**
Female sex × Dyss	<0.0001	Female sex × Dyss	<0.0001
Female sex × LVEF	<0.0001	Female sex × LVEF	<0.0001
Female sex × LBBB	<0.0001	Female sex × LBBB	0.45
Female sex × QRS	<0.0001	Female sex × QRS	0.99
Female sex × AF	0.007	Female sex × AF	0.75
Female sex × NYHA	<0.0001	Female sex × NYHA	<0.0001
Female sex × ICM	<0.0001	Female sex × ICM	<0.0001
Female sex × age	<0.0001	Female sex × age	<0.0001
Female sex × scar	0.01	Female sex × scar	0.02

ECG-based response prediction

Previous studies have suggested that based on sex, ECG criteria of dyssynchrony assessment might have different prognostic value for men and women. In a study that included CRT patients with LBBB and non-ischaemic cardiomyopathy, Varma *et al.*[20] found that at any given QRS duration women would show more electrical dyssynchrony compared with men in particular for mid-range duration and consequently would show better response to CRT. Also, Biton *et al.*[21] showed, in an analysis of the MADIT-CRT database, a better outcome in women compared with men regardless of QRS width. Finally, it has been suggested by Loring *et al.*[11] that an LBBB like pattern in ECG carries a better prognostic effect for women than for men.

On the other hand, the variable diagnostic value of ECG for detecting true LBBB pattern of myocardial dyssynchrony,[8,22] and the observed variability in measuring QRS duration[13] would challenge these hypotheses. Additionally, identifying a common predictor in both men and women that is independently associated with better outcome and response to CRT regardless of sex would be more practical than adopting, based on sex, different cut-off values of QRS duration for CRT candidate selection.

Sex and Dyss

In the current study, we additionally studied Dyss which has been shown to be associated with better outcome in CRT patients.[14,23,24] Furthermore, It has been shown recently that baseline assessment of Dyss could be a valuable supplement to the current guidelines of CRT candidate selection resulting in better survival and higher response rates,[17] this finding is consistent with previous data that showed that Dyss is more accurate in reflecting true LBBB pattern of myocardial contraction compared to the standard ECG criteria of dyssynchrony.[12]

Our data showed that at baseline women had more Dyss compared with men (78% vs. 57%, $P < 0.0001$, *Table 2*), and female sex was associated with better survival and volumetric response to therapy. However, after adjustment of baseline differences, female sex was not independent predictor of outcome any more. Similarly, in a study where Dyss, assessed by tissue Doppler, was not different between both sexes, Bleeker *et al.*[16] observed non-significant difference between sexes neither in survival nor in response to therapy. Moreover, our data showed that regardless of sex, Dyss was the only variable that was independently and most strongly associated with volumetric response to therapy (*Figure 2B*) and better survival (*Figure 4B*) independent from other measures of dyssynchrony including QRS width and morphology.

Influence of interaction among ischaemic heart failure, Dyss, and sex in CRT outcome

In addition to the well-established negative impact of ischaemic cardiomyopathy on response to CRT,[25] recent studies have shown that both the extent and the distribution of myocardial scar[26] could mask true pattern of a LBBB-like myocardial contraction, and relates to worse outcome.[27,28] In our data, patients with ischaemic aetiology of heart failure showed significantly less Dyss compared with patients with non-ischaemic aetiology (58% vs. 79%, $P < 0.001$). Moreover, ICM was independently associated with less Dyss (Supplementary data online, *Table S1*).

In our cohort, women had less ischaemic cardiomyopathy (23% vs. 49%, $P < 0.0001$) and less extent of scarred myocardium (0.4 ± 1.3 vs. 1.0 ± 2.1, $P < 0.0001$, *Table 2*) which is consistent with the findings of previous studies. This suggests woman have more frequently uncomplicated patterns of LBBB-like contraction which are better amendable by CRT due to the absence of scar. Similar to our findings, Xu *et al.*[29] showed that after adjustment for ischaemic aetiology of the cardiomyopathy, female sex was not an independent predictor of better outcome. We, therefore, assume that ischaemic scar is a potent confounder that would lead to a lower rate of amendable Dyss and—consequently—to the observed worse CRT outcome of men compared with women. The significant interaction between female sex, ICM and scarred myocardium in relation to volumetric response and survival ($P < 0.05$ for all interactions) is shown in *Table 3*.

Limitations

Our study has an observational and retrospective design, and therefore, no control group. However, for a comparison of outcome with adjusted baseline conditions, it can be assumed that this design is

useful and allows valid conclusions. In the current analysis, we adjusted the statistical models for the most relevant cardiovascular risk factors. However, other risk factors which can influence cardiovascular outcome, such as diabetes mellitus, chronic kidney disease, and chronic obstructive pulmonary disease, were not available in the database and consequently could not be assessed.

In the current data, one of the limitation is the absence of weights and heights of the study population, so LV volumes could not be indexed to body surface area. Nevertheless, response to therapy was defined as a reduction of at least 15% of LVESV at follow-up compared with baseline. This relative way of response assessment should not depend on the difference in body size between men and women and therefore should not affect our results.

It has been suggested in the literature that the underuse of CRT in women could be attributed to showing less specific symptoms. It is therefore possible, that comparable NYHA classes do not represent the same severity of heart failure in both sexes. One would expect, however, that such selection bias—if relevant—would lead to higher mortality in women which was not the case.

In the current work, data from cardiac magnetic resonance for assessment of myocardial scars were not available for all patients, so the assessment of scar location and extend was only possible based on visual assessment of the echocardiographic images. In a validation study to this approach in those patients of our data base where magnetic resonance imaging data were available, however, we could show that our approach was sufficiently accurate for the purpose of this analysis (see the Supplementary data online).

Conclusion

After adjustment of baseline characteristics, men and women show similar survival and volumetric response to CRT. Our data suggest that the repeatedly observed better outcome in women is mainly due to lower rate of ischaemic cardiomyopathy and, with this, more frequent occurrence of Dyss patterns which are amendable by CRT.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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IMAGE FOCUS

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Multiple arteriovenous fistulas after laser lead extraction in heart transplant patient

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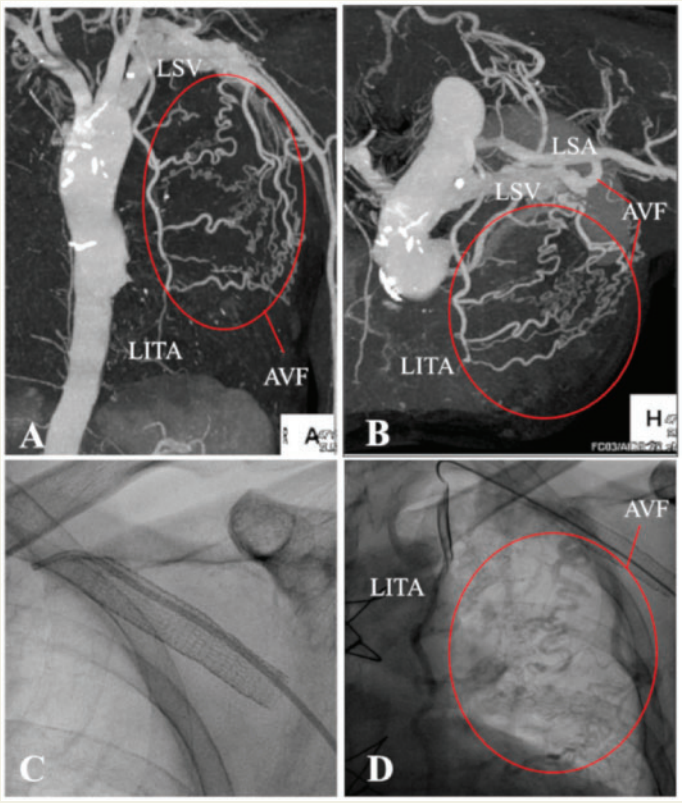
A 49-year-old man underwent orthotopic heart transplantation (HTx) for end-stage dilated cardiomyopathy with implanted cardiac resynchronization therapy defibrillator (CRT-D) removal. Laser lead extraction (LLE) was performed, but the procedure was difficult because of extensive adhesions within the vein and overcrowding.

Two years after HTx, physical examination revealed a new continuous murmur in the left subclavian area. Computed tomographic angiography showed multiple arteriovenous fistulas (AVFs) of the left subclavian vein (LSV) fed by the left internal thoracic artery (LITA) and left subclavian artery (LSA) (*Panels A* and *B*). We diagnosed iatrogenic AVFs and successfully performed endovascular repair for the AVF between the LSV and LSA with a 10 × 50 mm covered stent (*Panel C*; Supplementary data online, *Video S1*). The non-repaired AVF between LSV and LITA (*Panel D*, Supplementary data online, *Video S2*) was closely followed up.



CRT-D removal during HTx is a standard strategy because there is concern that lead retention could be associated with infection or venous thrombosis.

Long-term placement of CRT-D leads causes inflammation within the vein, resulting in adhesion formation. The proximity of the vessels allows scaring between the adjacent artery and vein. LLE could involve tearing of the venous wall communicating with the adjacent artery and vein.

It is important to recognize AVFs as a complication of LLE during HTx. Physical examination can help in the diagnosis of AVFs, and computed tomographic angiography is useful in detecting AVFs.

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.