Why is the clinical response to cardiac resynchronization better in LBBB patients?

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Abstract

Aims The improved clinical response in patients with left bundle branch block (LBBB) over LBBB-free patients treated with cardiac resynchronization therapy with a defibrillator (CRT-D) is commonly attributed to an LBBB abnormality. We aimed to find an alternative explanation.

Methods and results We analysed an immediate effect of selecting the LBBB group of patients in a cohort of 63 non-ischaemic cardiomyopathy (non-ICM) and 83 ischaemic cardiomyopathy (ICM) patients treated with CRT-D; 75% of non-ICM and 51% of ICM patients had an LBBB abnormality on the electrocardiogram, with a significant difference ($P = 0.0032$ by $\chi^2$). As a result of this difference, the proportion of non-ICM patients increased from 43% in the primary cohort to 53% in LBBB selection and decreased to 28% in non-LBBB group. By nonparametric survival analysis, the hazard ratio in non-ICM patients in the LBBB selection decreased from 0.48 ($P = 0.0488$) to 0.36 ($P = 0.0251$) and increased in the non-LBBB group to 0.75 ($P = 0.6496$). Any comparison of LBBB and non-LBBB groups must compare sets with a significantly altered proportion of patients of different aetiologies. Most publications on LBBB patients are erroneous because they compare LBBB with non-LBBB groups, not taking into account that the groups have been substantially changed by the selection process.

Conclusions The declared outcome of the LBBB groups reflects inevitably the survival outcome of their non-ICM patients and not the intended outcome of patients with LBBB. CRT-D in patients with different aetiologies of cardiomyopathy calls for separate evaluation.

Keywords Cardiac resynchronization therapy; Heart failure; Left bundle branch block; Risk factors; Co-morbidity burden

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Introduction

It is standard knowledge that patients with heart failure, low left ventricular ejection fraction (LVEF), and a wide QRS complex with left bundle branch block (LBBB) benefit from the so-called cardiac resynchronization therapy (CRT).1–5 The benefit ‘may reflect more LV dyssynchrony in LBBB than in non-LBBB patients’.1

CRT cohorts are generally composed of two types of patients: ischaemic cardiomyopathy (ICM) patients whose ventricular dysfunction is related to coronary heart disease and non-ICM patients in whom no such relation can be proved. In both groups, the low LVEF is the essential prerequisite for CRT. An ischaemic origin and complications of coronary heart disease may be perhaps regarded as mere co-morbidities of left ventricular dysfunction.6 The current, routine approach is to view the two groups as one and to treat them accordingly. LBBB patients are selected from cohorts including patients with both aetiologically different cardiomyopathies.

However, genuinely different aetiologies may affect the analysis of the outcome of treatment. More specifically, owing to differences in LBBB prevalence in patients of different aetiologies, the composition of the selected LBBB and non-LBBB groups differs from that of the original cohort in the proportion of non-ICM vs. ICM patients and in the

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proportions of patients burdened by differing numbers of co-morbidities. These changes in composition have not been studied to date, although they may significantly affect the declared outcome of patients with LBBB.

Methods

We undertook a post hoc analysis of the medical records of patients who were eligible for treatment with CRT with a defibrillator (CRT-D device): all had heart failure symptoms in New York Heart Association functional class II or III, LVEF ≤ 35%, and QRS interval ≥ 120 ms according to contemporary guidelines. These patients had undergone implantations between February 2006 and December 2013. Our cohort ended up consisting of 146 patients (our primary cohort). All patients underwent coronary angiography, many of them more than once. Eighty-three patients were ICM patients; all suffered myocardial infarction in the past. All ICM patients were appropriately revascularized (either surgically or by a catheter intervention) >3 months before any required implantation. Sixty-three patients had non-ICM confirmed by coronary angiography. Implantations took place at the Invasive Arrhythmology Unit of the Cardiac Centre AGEL of the Pardubice District Hospital. All therapy was carried out according to previous and current European Society of Cardiology guidelines. The patients provided informed consent according to national and institutional regulations. Ethical approval of the study was obtained from the institutional ethics committee. All patients underwent a follow-up at 1 month after implantation and subsequently every 6 months. The time from implantation to death was recorded. Information on survival status was obtained from the Czech Institute of Health Information and Statistics. Standard baseline 12-lead electrocardiograms (ECGs) were recorded at a paper speed of 25 mm/s. Patients with right BBB or intraventricular conduction defect were grouped as having a non-LBBB morphology. Clinical and ultrasound data were stored in a purpose-made Excel database. For ‘potentially beneficial’ clinical parameters, we decided on LBBB (defined by classic criteria), QRS duration ≥ 150 ms, non-ICM aetiology of CMP, female gender, age ≤ 70 years, and absence of co-morbidities (CB0). For ‘potentially risky’ (harmful) clinical parameters, we chose non-LBBB, QRS duration < 150 ms, ischaemic aetiology of cardiomyopathy, male gender, age > 70 years, and CB ≥ 1 co-morbidity. To assess the changes in composition induced in the selection of patients with LBBB and non-LBBB group, we calculated increases or decreases in the number of patients in the various categories as described in detail in Table 2. As co-morbidities, we selected diabetes mellitus8,9 (when treated by oral antidiabetics or insulin), renal failure8,9 (serum creatinine levels ≥ 135 mmol measured repeatedly before implantation for patients of both aetiologies), atrial fibrillation, and BMI < 25 for ICM patients.10,11 Patients without co-morbidities were labelled as CB0 patients, CB ≥ 1 specified patients with one or more co-morbidities, CB1 patients with one co-morbidity, and CB ≥ 2 patients with two or more co-morbidities. QRS ≥ 150 ms was considered long and <150 ms short. A prevalence or proportion is defined as a portion in its relation to the whole in per cent. For Cox analysis, all the non-continuous parameters were categorized.

Statistical data analysis

Descriptive statistics were used to characterize the patient population. Continuous data were expressed as means ± SD and compared by a two-sample t-test assuming unequal variance. Categorical variables used in the study were defined according to the literature. Data were presented as number and percentage, and comparisons were based on a χ² or on Fisher’s exact test. No data adjustment was performed. Relative risk and 95% confidence intervals were calculated for each categorical variable as a predictor of all-cause mortality in the Cox regression model. Kaplan–Meier estimate of the time from baseline to endpoints were computed, as was the hazard ratio (HR) with corresponding confidence limits. Different patient subgroups characterized by different settings of categorical variables unique for each subgroup were compared using Kaplan–Meier curves, logrank tests, and the HR, with follow-up time as the underlying time scale. Multivariable Cox proportional hazard models were used to evaluate associations between defined covariates at the time of implantation and the risk of all-cause death. A P value < 0.05 was considered significant. Most of the data were analysed using NCSS 11 Statistical Software (2016) (NCSS, LLC, Kaysville, Utah, USA, ncss.com/software/ncss).

Results

The baseline characteristics for patients of different cardiomyopathies are presented in Table 1. Non-ICM patients differ notably from ICM patients in terms of LBBB—their LBBBs are longer. From our point of view, the prevalence of LBBB is more important: it occurs in 75% of non-ICM patients and in 51% of patients with ICM. Patients with different aetiologies also differ significantly in co-morbidity burden. The mean number of co-morbidities per patient was 1.08 in ICM and 0.32 in non-ICM patients. Prevalence of patients without co-morbidities was higher in non-ICM (71%) than in ICM patients (25%), whereas patients with one or more co-morbidities were more frequent in ICM (75%) than in non-ICM patients (29%). Of all the positive factors in the primary cohort, only patients without co-morbidities (n = 66) displayed a significant effect on outcome on the basis
Table 1  Basic data on patients treated with cardiac resynchronization therapy with a defibrillator

|                | Cohort 146 | ICM | Non-ICM | P   |
|----------------|------------|-----|---------|-----|
| n              | 146        | 83  | 63      |     |
| Age, years, Ø ± SD | 69.8 ± 8.6 | 71.5 ± 7.8 | 67.5 ± 9.0 | 0.0059 |
| QRSD ms, Ø ± SD   | 160.6 ± 21.3 | 157.3 ± 20.6 | 165.1 ± 21.6 | 0.0254 |
| LBBB ms, Ø ± SD   | 164.9 ± 21.3 | 160.0 ± 22.0 | 169.3 ± 19.9 | 0.0471 |
| Men             | 113 ± 25 | 77  | 71 ± 25 | 86  | 42 | 67  | 0.0069 |
| Age > 70 years   | 49          | 48  | 48      | 58  | 24  | 38  | 0.0182 |
| QRS < 150 ms     | 25          | 25  | 25      | 25  | 12  | 19  | 0.1276 |
| Non-LBBBB       | 39          | 41  | 49      | 16  | 25  | 0.0032 |
| CB ≥ 1          | 50          | 62  | 75      | 18  | 29  | 0.0001 |
| CB1             | 36          | 37  | 45      | 16  | 25  | 0.0176 |
| CB ≥ 2          | 18          | 25  | 30      | 2   | 3   | <0.000 |
| øCB             | 0.75 ± 0.80 | 1.08 ± 0.81 | 0.32 ± 0.53 | <0.0001 |
| BMI < 25        | 30          | 21  | 14      | 17  | 16  | 25  | 0.2065 |
| Atrial fibrillation | 41        | 28  | 28      | 34  | 13  | 21  | 0.0811 |
| Diabetes mellitus | 48         | 33  | 33      | 40  | 15  | 24  | 0.0422 |
| Renal failure    | 20          | 14  | 15      | 18  | 1   | 5   | 0.0777 |
| Women            | 33          | 23  | 12      | 14  | 21  | 33  | 0.0069 |
| Age > 70 years   | 74          | 51  | 35      | 42  | 39  | 62  | 0.0182 |
| QRS < 150 ms     | 109         | 75  | 58      | 70  | 51  | 81  | 0.1276 |
| LBBB             | 89          | 61  | 42      | 51  | 47  | 75  | 0.0032 |
| QRS ≥ 150 ms     | 72          | 49  | 29      | 35  | 43  | 68  | <0.0001 |
| CB0              | 66          | 52  | 21      | 25  | 45  | 71  | <0.0001 |

ICM, ischaemic cardiomyopathy patients; Non-ICM, non-ischaemic cardiomyopathy patients; %, proportions in per cent; CB, co-morbidity burden; P, statistical significance assessed by t-test, figures in italics by χ²; QRSD, duration of QR complex on ECG; CB1, number of patients with one co-morbidity; CB ≥ 1, number of patients with one or more co-morbidities; CB ≥ 2, number of patients with two or more co-morbidities; øCB, mean number of co-morbidities per patient.

Note the same level of significance when the difference between the prevalence of LBBB in non-ischaemics vs. ischaemics is compared with the difference between the proportions of non-ischaemics in the non-LBBB vs. LBBB groups (Table 2). The highlighted data shows the same statistical significance of the difference between the frequency of LBBB and non-LBBB patients in ischemic and non-ischemic cardiomyopathy.

Table 2  Compositional changes induced by selection of patients with left bundle branch block

|                | Cohort 146 | Peterson |
|----------------|------------|----------|
| n or q         | Non-ICM n | ICN n | CB non-ICM n | CB ICM n | CB0 non-ICM n | CB0 ICM n |
| LBBB n         | 16 556    | 6872    | 89          | 47       | 42       | 14       | 45       | 34       | 10          |
| Virtual n      | 5935       | 38      | 51          | 12       | 55       | 27       | 13       |
| ~/− %          | 0.67       | +16%    | +24%        | −18%     | +17%     | −18%     | +26%     | −25%     |
| Non-LBBB n     | 8042       | 1987    | 57          | 16       | 41       | 6        | 45       | 11       | 11          |
| Virtual n      | 2923       | 26      | 32          | 8        | 35       | 18       | 8        |
| ~/− %          | 0.33       | −32%    | 0.39        | −38%     | +28%     | −25%     | +29%     | −39%     | +38%        |

n, number of patients in the primary cohort or in the chosen selection; q, quotient, ∑ of patients in the selected group/∑ of patients in the original cohort; Virtual n, number of patients, provided that the reduction in the number of patients is proportional to the reduced number of patients in the selected group; ~/− %, increments or decrements expressed as a percentage of the corresponding virtual value; non-ICM n, number of non-ischaemic cardiomyopathy patients; ICM n, number of ischaemic cardiomyopathy patients; CB non-ICM n, sum of co-morbidities in non-ischaemic cardiomyopathy patients; CB ICM n, sum of co-morbidities in ischaemic cardiomyopathy patients; CB0 non-ICM n, number of non-ischaemic cardiomyopathy patients without co-morbidities; CB0 ICM n, number of ischaemic co-morbidity patients without co-morbidities.

All figures (apart from ratios and quotients) represent numbers of patients.

Proportion of non-ICM patients (non-ICM% NSLBB (n)) in the LBBB group can be calculated from the primary cohort in advance: non-ICM% NSLBB = (non-ICM LBBB n − non-ICM LBBB n (n)) / non-ICM LBBB n (n), where non-ICM LBBB n (n) is the number of non-ischaemic cardiomyopathy patients with LBBB in the primary cohort and LBBB n (n) is the number of all LBBB patients in the primary cohort.

From the data in bold and italics in Tables 1 and 2, the significance of the difference in LBBB prevalence between non-ICM and ICM patients and the significance of the difference between the prevalence of non-ICM patients in the LBBB and no LBBB groups are calculated. The table shows the conflicting changes in the number of patients with different aetiologies of cardiomyopathies (non-ICM n and ICM n) and the conflicting changes in the sum of co-morbidities (CB non-ICM and CB ICM) and in the number of patients without co-morbidities (CB0 non-ICM and CB0 ICM) in relation to aetiology. The highlighted data shows how profoundly different the composition of the LBBB and non-LBBB patient groups is.

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of the Cox regression report \((P = 0.0081)\). If patients without co-morbidities were not taken into account, non-ICM patients had the best scores in both the original cohort \((P = 0.1604)\) and the LBBB selection \((P = 0.0709)\). The second best were young patients. Patients with LBBB had only a negligible effect. Of all the ‘negative factors’, patients who had one or more co-morbidities \((n = 80)\) displayed a significant negative effect \((P = 0.0049)\).

The selection of LBBB patients for CRT-D is associated with an increased proportion of non-ICM patients. As a result, the group of patients without LBBB has a reduced proportion of non-ICM patients. The statistical significance of the difference between the prevalence of LBBB in patients with ischaemic and non-ischaemic CMP in other authors’ cohorts differs from our findings, we reduced the size of their primary cohorts to the size of our cohort and adjusted the LBBB prevalence accordingly. The \(P\) values for our cohort, Peterson et al. cohort, and Barsheshet et al. cohort were 0.0032, 0.0408, and <0.0001.

Table 2 demonstrates the conflicting changes in the number of patients with different aetiologies (non-ICM \(n\) and ICM \(n\)) in the LBBB selection and in the LBBB-free group. Similar changes in aetologically different patients are also present in the number of patients without and with co-morbidities \((CB0 \text{ and } CB \geq 1)\). The table also shows comparable changes in the number of patients with non-ischaemic aetiology in Peterson et al. cohort.3

Table 3 shows the numerical relations of ICM and non-ICM patients in terms of the number of co-morbidities. The relationship is particularly evident when the number of patients

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Survival results of patients different in aetiology.

| Survival of patients different in etiology |
|------------------------------------------|
| ![Survival Graph](https://example.com/survival_graph.png) |
| IS......Ischemic cardiomyopathy patients. |
| nonIS......Non-ischemic cardiomyopathy patients HR 0.48 (CI 0.25 – 0.92), \(P = 0.0488\). |

The figure shows a better survival result of patients with non-ischemic aetiology of cardiomyopathy in our primary cohort.
with different numbers of co-morbidities is expressed as a percentage of the total number of patients with a defined number of co-morbidities (numbers in red). Note also that CB0 vs. CB ≥ 1 = 25% vs. 75% in ICM patients and 71% vs. 29% in non-ICM patients, a difference significant at P ≤ 0.0001.

Figure 2 shows the survival outcome in our patients with different numbers of co-morbidities in relation to the aetiology of cardiomyopathy.

Table 4 summarizes some data in the LBBB selection and in five patient groups from our primary cohort. Significant changes in the proportions of patients in different groups are evident especially in aetiollogically defined patients: in non-ICM and ICM patients (non-ICM patients % = 100 − ICM patients %). Significant differences in patients categorized by aetiology occur in the proportions of patients without co-morbidities (CB0): in the non-LBBB group, they include 19% in both non-ICM and ICM patients, while in the LBBB selection, they include 38% non-ICM and 11% ICM patients. Similar ‘discrepancies’ can be observed in patients with co-morbidities: in the group of patients without LBBB, there are 9% CB ≥ 1 non-ICM patients and 53% CB ≥ 1 ICM patients, while in the LBBB selection, there are 15% CB ≥ 1 non-ICM patients and 36% CB ≥ 1 ICM patients.

Discussion

We must first emphasize that the aim of this study was not to multiply the number of studies comparing the survival outcomes of patients with ICM and non-ICM. We were particularly interested in how the selection process of patients with LBBB changes the composition of the selection and the consequences that follow.

Left bundle branch block abnormality in patients of different aetiologies

LBBB is a strong predictor of mortality in heart failure patients who are not treated by resynchronization and have LVEF ≤ 39%. In cohorts selected for CRT, the opposite is true: clinical outcome of patients with LBBB, in comparison with the patients without LBBB, is better. There are two possible explanations. First, resynchronization therapy is more effective in patients with LBBB. Second, the group of LBBB patients includes more patients with a good prognosis.

In our primary cohort, the prevalence of LBBB in non-ICM patients is significantly higher (75%) than in ICM patients (25%, Table 1). A similar difference was found in the majority of published CRT cohorts. In fact, we could not find a single cohort where it was the other way around. In the Peterson et al. cohort, the ratio was 78%:62%; in the MADIT-CRT cohort, 88%:58%. The immediate positive effect of CRT in an individual patient with LBBB can be explained by the technique through which the impaired activation of the ventricle is corrected. The pacing catheter, routinely positioned in a posterolateral coronary vein, delivers the stimulating impulse at the site of the latest ventricular activation and yields the greatest immediate improvement in LV systolic function. However, by selecting patients with LBBB, the prevalence of non-ischaemic patients in the LBBB and non-LBBB groups changes in the opposite direction, and the changes are significantly different. The LBBB selection process determines the composition of both the selected LBBB group and the non-LBBB group. Similar changes in composition in the proportions of patients with non-ICM can be calculated from data from the studies in Peterson et al.3 (Table 2) and MADIT-CRT12 (Table 4).

Ischaemic aetiology as a risk factor in cardiac resynchronization therapy

The effect of aetiology on the outcome of CRT or CRT-D has been widely discussed. In the often quoted study by Wikstrom et al., the clinical gains were found to be the same in both aetiology-different groups. Nevertheless, when applying Kaplan–Meier estimates of endpoint death from any cause, there was still some inconsistency among patients of different aetiologies. The apparent differences in outcome found in the COMPANION, CARE-HF, and MADIT-CRT5 studies were statistically insignificant in the interaction-term analysis. However, Bart et al.18 (in 3112 prospectively collected patients), Bilchick et al.2 (registry, 14 946

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Figure 2 Survival results of patients with varying numbers of co-morbidities.

Survival results of patients with varying numbers of comorbidities

![Survival graph](image)

CB0... patients with no comorbidities. $N = 66$.
CB1... patients with 1 comorbidity. $N = 53$.
CB≥2... patients with 2 or more comorbidities. $N = 27$.

NIS... proportion of patients with non-ischemic cardiomyopathy.

CB0 vs CB1 patients HR 0.30, $P = 0.0167$.
CB0 vs CB≥2 patients HR 0.22, $P = 0.0001$.

The figure summarizes the relationship of the number of comorbidities to the aetiology of cardiomyopathy.

Table 4 Some data from five patient selections chosen from the primary cohort

| Selection   | $n$ | Peterson non-ICM % | MADIT-CRT non-ICM % | Non-ICM % | CB0 non-ICM % | CB0 ICM % | CB ≥ 1 non-ICM % | CB ≥ 1 ICM % |
|-------------|-----|---------------------|---------------------|----------|---------------|-----------|-----------------|--------------|
| ICM patients | 83  | 0                   | 0                   | 0        | 0             | 25        | 0               | 75           |
| Non-LBBB    | 57  | 25                  | 17                  | 19       | 19            | 9         | 53              |
| Cohort 146  | 146 | 36                  | 43                  | 31       | 14            | 12        | 42              |
| QRS ≥ 150 ms109 | 39   | 47                  | 33                  | 15       | 14            | 14        | 39              |
| LBBB        | 89  | 42                  | 53                  | 38       | 11            | 15        | 36              |
| Non-ICM pts | 63  | 100                 | 100                 | 71       | 0             | 29        | 0               |

$n$, number of patients in the selection; Peterson non-ICM %, proportions of non-ischaemics in the Peterson study (calculated from the data given in the publication); MADIT-CRT non-ICM %, proportions of non-ischaemics in the MADIT-CRT study (calculated from data given in the publication); non-ICM %, proportion of patients with non-ischaemic cardiomyopathy; CB0 non-ICM %, proportion of patients with non-ischaemic aetiology without co-morbidities; CB0 ICM %, proportion of patients with ischaemic cardiomyopathy without co-morbidities; CB ≥ 1 non-ICM %, proportion of ischaemic patients with one or more co-morbidities; CB ≥ 1 ICM %, proportion of non-ischaemic patients with 1 or more co-morbidities.

Proportions of patients with non-ischaemic cardiomyopathy (non-ICM %) calculated from the data published by Peterson et al. correlate with our data at $r = 0.9809$ and $P < 0.00001$.

The table shows the order of selections according to the proportion of non-ischaemic patients (red). Note the conflicting sequences of patients without co-morbidities (CB0) or with co-morbidities (CB ≥ 1), differing in aetiology. The highlighted data shows how profoundly different the composition of the LBBB and non-LBBB patient groups is.
patients), Khidir et al.4 (registry, 973 patients) and others found ICM to be a powerful predictor of poor outcome.

In our cohort, outcome of non-ICM patients was significantly better than in ICM patients in the nonparametric survival assessment (Figure 1). The result was not unexpected: ICM patients were significantly older and had significantly more co-morbidities. In addition, myocardial infarction as such worsens the patients prognosis.19,20 Similar differences in mean age, prevalence of diabetics, and patients with kidney disease were observed by Barsheeshet et al.12

The deviance of patients with non-ischaemic CMP was evident in the Cox regression report. Unless co-morbidity was considered, of the patients with ‘potentially beneficial factors’, patients with non-ICM had the most pronounced effect, followed by young patients. The relationships were even more pronounced in the selection of LBBB.

In the non-LBBB group, patients with non-ICM differed from patients with ischaemic CMP in their small proportion (28%), but not in their effect on survival. The difference in survival between patients with non-ischaemic and ischaemic CMP, as assessed by nonparametric survival analysis, was negligible—probably owing to the strong positive effect of non-ICM aetiology. In contrast, in the LBBB selection, the proportion of patients with non-ICM cardiomopathy was only slightly higher (53%), but the mortality rate was even lower than in the primary cohort. The question may arise under which conditions a comparison of survival outcomes in a group of patients with LBBB with a group of patients without LBBB can provide reliable evidence that an LBBB abnormality as such is responsible for a better clinical outcome. We believe that a valid demonstration of the significant effect of the LBBB abnormality alone could only be achieved in circumstances if there was no difference in survival between patients of different aetiologies.

The basic difference between the LBBB and non-LBBB groups in cohorts, where the prevalence of LBBB in patients with different aetiologies of cardiomopathy is different, is not only in a significantly different proportion of patients with non-ICM. There is also the possibility that, in addition to a higher proportion, their aetiology may also contribute to a better result.

Co-morbidity burden in aetiologically different patients

Table 3 demonstrates an inverse relationship between patients with a normalized number of co-morbidities categorized according to aetiology (red numbers in brackets). There are probably a number of reasons for this inverse relationship: age, gender, and more, but above all, it is the aetiology. In CRT patients, Theuns et al.,19 Zeitler et al.,6 Biton et al.,21 and Wolks et al.22 demonstrated increasing risk of death with increasing co-morbidity burden or increasing ‘number of clinical risk factors’. Zeitler et al.6 and Biton et al.20 demonstrated that an increasing number of risk factors is associated with an increasing proportion of ischaemic patients (and thus, logically, an increasing number of risk factors is associated with a declining proportion of non-ischaemic patients). However, none of these studies explicitly addressed the relationship between co-morbidity burden and the aetiology of CMP.

Conflict sequences in the proportions of patients without (CBO) or with co-morbidities (CB ≥ 1), which differ according to the aetiology of the patients, are given in Table 4. The association of changes in the proportions of patients with non-ICM (non-ICM %) with changes in the proportions of patients with ICM and one or more co-morbidities (CB ≥ 1 ICM %) in all six groups suggests the interdependence between aetiology and co-morbidity.

Figure 2 shows the relationship between the increased risk of groups of patients with a defined incremental burden of non-cardiovascular disease and the proportion of non-ICM patients in each group. The mere fact that patients with co-morbidities are more at risk than patients without co-morbidity is nothing new. However, the demonstration of an inverse relationship between the number of co-morbidities and the number of patients with a non-ischaemic aetiology of CMP is new, at least in the sense that no one considered this relationship to be of any importance. Probably the most important observation is that patients without co-morbidities are predominantly (78% according to our data, 90% in Biton et al.20 study) patients with non-ICM.

Survival outcome of left bundle branch block populations: what does it reflect?

There is no doubt that in the long-term follow-up of CRT-D patients, death from any cause is less frequent in those patients with LBBB than those without.5 Many studies proved the LBBB patients to have better CRT response than the non-LBBB patients.1–5,23–25 However, it has never been fully analysed which factor is actually responsible for the ‘better CRT response’. In fact, the better response (demonstrated, e.g. by the Kaplan–Meier curves) in all these publications revealed the effect of a higher prevalence of patients with non-ICM, which occurred owing to the selection of patients with LBBB. Because LBBB selection is associated with the formation of a non-LBBB group in which the proportion of patients with non-ischaemic CMP is reduced, LBBB patients always have a better outcome than patients without LBBB. It may be appropriate to ask the authors of the MADIT-CRT studies4,5 what causes a better CRT result in their patients. Is it the presence or absence of an LBBB abnormality or a higher proportion of patients with non-ICM in the LBBB selection (53%)
compared with a much lower percentage (17%) in the LBBB-free group?

**Conclusions**

The question arises as to the clinical significance of our findings. It is true that patients with LBBB on ECG have a better response to CRT than patients without LBBB. However, it is far from true that this is simply due to the presence of an LBBB abnormality on the ECG. The better survival outcome of the LBBB population reflects its higher proportion of patients with non-ICM and not better resynchronization. In short, the better declared clinical outcomes of patients with LBBB in the above publications are flawed.

So the questions go even deeper. Would it not be more beneficial for patients if those treated with cardiac resynchronization and differing in the aetiology of cardiomyopathy were evaluated separately?

**Conflict of Interest**

None declared.

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